Opening the psychological black box in genetic counseling

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Women from families in which many individuals have developed breast and/or ovarian cancer may request for DNA-testing. A DNA-test result may disclose their own risks to develop cancer (again), their relatives' risks and subsequent medical options. This thesis describes several nation-wide studies in the Netherlands about the psychological and medical impact of DNA-testing on the lives of these women and their relatives. Despite their general understanding of the DNA-test result, many participants interpreted the result differently from what the genetic-counselor had actually communicated. Like in a children's whisper game, their relatives also misinterpreted the information communicated by the first messenger. The messengers' misinterpretation was not only related to their rational ideas about heredity and cancer, but also to their unfulfilled need for certainty, sense of self and existential issues. Their misinterpretations predicted their distress and medical decisions after DNA-test result disclosure. The study results are described in their historical/theoretical context, followed by practical clinical suggestions for genetic-counselors and psychologists.

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Contents

Chapter 1

Introduction

1.1. The genetic-counseling context of this thesis

1.1.1. The motivation of counselees

> *Emma is a woman of 32 years old. She grew up in a family with many cancer patients. Her mother had developed breast cancer and died when Emma was 14. The sister of her mother had had ovarian cancer, and family myths tell that her mother's mother had had both breast- and ovarian cancer. Because of this familial background of cancer, Emma was worried about her own health, and frequently performed breast self-examination. Two years ago, she felt a lump in her left breast, which later showed to be a malignant tumor. The surgeon removed the tumor by breast conserving surgery. Follow-up treatment was successful, but Emma worried about the possible recurrence of cancer, and she was considering undergoing prophylactic surgical removal of her breasts and ovaries. She started feeling uncertain whether she would be able to live long enough to see her 10-year old daughter grow up. She wondered whether her daughter and her sister would also develop cancer one day like Emma and her mother. Emma felt distressed over these uncertainties. When she discussed this with her general practitioner, she was advised to visit the department of Clinical Genetics. She followed this suggestion, because she wanted to be released from the uncertainty about the possible recurrence of cancer and her relatives' cancer-risks. A genetic-counselor told her that her family history indicated that it was likely that she had developed cancer because of a genetic predisposition for hereditary breast- and ovarian cancer. At the end of this intake genetic-counseling session, a blood sample was taken to perform a DNA-test in the BRCA1/2-genes which are associated with hereditary breast- and/or ovarian cancer. She was explained that the result of this test may tell her what her risks are to develop ovarian cancer and to develop contralateral mamacarcinoma, and what the cancer-risks of her daughter and sister may be.* (Based on an anonymous example from the pilot study)

Emma underwent genetic-counseling, like many women from families with multiple cases of breast- and/or ovarian cancer. She was motivated to do so, because she wanted her uncertainties to be reduced. Counselees often report that they want to undergo genetic-counseling to receive certainty about their cancer-risks, their relatives' risks and the heredity of cancer in the family. Moreover, by means of genetic-counseling they want to regain personal control over their own cancer: they may use genetic knowledge as a guideline or basis to know what medical steps to take (1-6).

Genetic-counseling is not the simple process of genetic-counselors disclosing genetic-information to counselees, which automatically creates accurate perceptions of this information and well-informed medical decisions in the counselees. From the counselees' perspective, personal and existential motivations, such as their need for

certainty and control over cancer, are involved. Genetic-counseling seems to open in counselees a black-box full of medical, psychological, existential and family-relational themes.

The purpose of the research described in this thesis is to provide more insight in the psychological black box of counselees who undergo DNA-testing for hereditary breast- and/or ovarian cancer. More specifically, I will examine how counselees interpret the communicated DNA-test results, how this influences their psychological well-being and medical decisions, how they communicate with relatives, and what the role is of existential issues such as the counselees' need for certainty.

This thesis only describes the psychological aspects of DNA-testing in the BRCA1 and BRCA2-genes which are associated with hereditary breast- and ovarian cancer (7,8). Since the identification of these highly penetrant mutations in 1994 and 1995, a genetic revolution started: individuals from strongly affected families could request for individual BRCA1/2-testing. The large number of counselees enabled the performance of large psychological studies in genetic-counseling, such as in this thesis.

In this introduction chapter, I will first sketch the context of the research, that is: the procedure of genetic-counseling (1.1.2.), the communicated genetic-information (1.1.3.), medical implications (1.1.4.), and previous psychological research (1.2.). This leads to the purpose, research questions, design, method and overview of this thesis (1.3.).

1.1.2. First consultation session in genetic-counseling (T1)

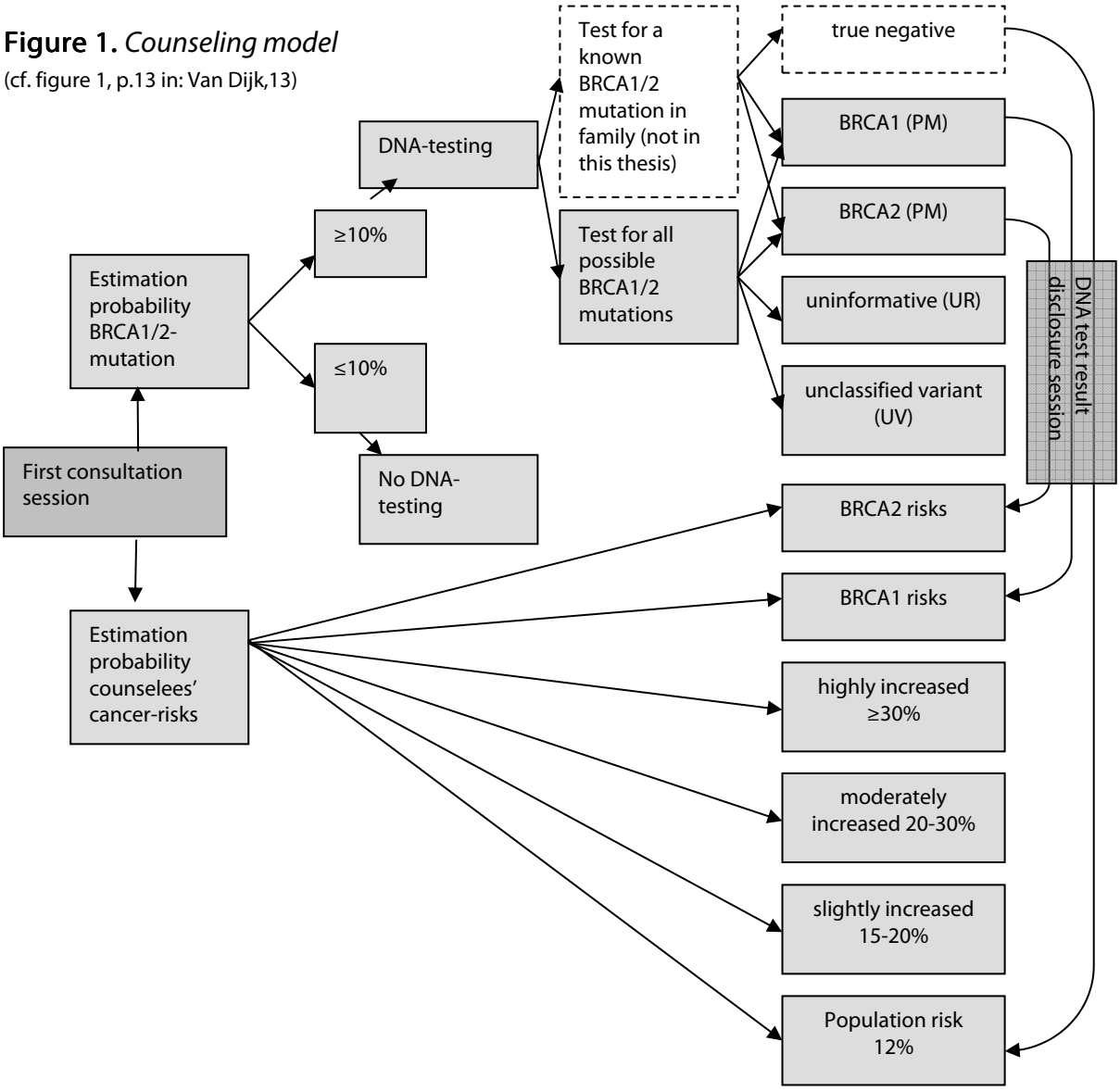
Individuals from families with many cases of breast and/or ovarian cancer may be referred to a department of Clinical Genetics or Familial Cancer Clinic in the Netherlands. The genetic-counselor or clinical-geneticist (in the following: 'genetic-counselor') follows a standard counseling protocol (9,10), as summarized in figure 1.

In a first (and sometimes only) consultation with the counselee, the genetic-counselor starts with explaining the procedure of genetic-counseling, describes the population-risks of developing breast and ovarian cancer, and explains the possible hereditary transmission and implications of high-risk genetic-mutations in genes such as BRCA1 and BRCA2 (BRCA= BReast CAncer). The genetic-counselor records the medical history of the counselee and her relatives, and examines their medical files for confirmation. Subsequently, the genetic-counselor makes a preliminary estimation of the counselees' lifetime risk of developing breast cancer on the basis of her pedigree/family history. Usually, one out of four risk categories is communicated: 1. population risks, i.e. nowadays 12% (11), 2. slightly increased risk, i.e. 10-20%, 3. moderately increased risk, i.e. 20-30%, 4. highly increased risk, i.e. 30% or over. On the basis of these risks and the medical history of the counselee, the genetic-counselor may also communicate options for risk-management, such as surgery and frequent surveillance of breasts and/or ovaries (see 1.1.4.).

Subsequently, the genetic-counselor may offer DNA-testing to the counselee, when there is a probability of at least10% of detecting a pathogenic mutation in this individual. This a priori probability is calculated on the basis of the medical history of the counselee and of her pedigree, that is the number of affected relatives with breast and/or ovarian cancer and their ages of diagnoses (9,10,12).

When a DNA-mutation is already known in the family, calculation is straightforward; for instance, a first-degree relative of an individual with a detected mutation has an average 50% probability of having inherited that mutation. This thesis does not cover DNA-testing in individuals from families in which a mutation has been detected previously, because nowadays most DNA-tests in the Netherlands are performed in counselees from families without a known mutation. In order to maximize the likelihood of detecting a new BRCA1/2 mutation in these families, usually the first individual tested is one who has already developed breast and/or ovarian cancer, i.e. the 'index patient'.

Figure 1. *Counseling model*
(cf. figure 1, p.13 in: Van Dijk,13)



1.1.3. Second consultation session: the actually communicated DNA-test result (T2)

At this moment, it takes two to six months before analysis of the BRCA1/2-genes of a counselee is completed. The genetic-counselor may communicate at least seven pieces of information about the BRCA1/2-result to the counselee: 1.One out of three DNA-test result categories. 2.The likelihood that cancer is heritable in the family. 3.Contralateral breast- and ovarian-cancer-risks for the counselee. 4.Lifetime breast- and ovarian-cancer-risks for healthy relatives. 5.Options for surveillance and/or risk-reducing/preventive surgery for counselees and relatives. 6.DNA-testing options for the relatives of counselees. 7.Reproductive options for the counselee.

1. One out of three DNA-test results in the BRCA1/2-genes is communicated: a pathogenic-mutation (PM), an uninformative result (UR) or an unclassified-variant (UV). The detection of a PM explains the occurrence of cancer in the family. A UR means that no mutation was detected, but the individual and/or relatives may still be at risk to develop cancer because of the high-risk pedigree. A UV, also called: variant-of-uncertain-clinical-significance, indicates that a mutation was found, but the contribution of this BRCA1/2 sequence variant to cancer risk and heredity remains largely undefined; future research may reveal the meaning of this unknown mutation for cancer risks and heredity. Chapter 2 describes the nomenclature in more detail; we have chosen for these terms, because they are most frequently used by genetic-counselors and researchers in the Netherlands.

2. The genetic-counselor may communicate the likelihood that cancer in the family is due to a genetic cause, i.e. heredity-likelihood. For instance, the genetic-counselor explains that the PM-result implies that it is very likely that cancer is heritable in the family. In case of UR/UV, heredity-likelihood is explained on the basis of the pedigree; the genetic-counselor may explain that the pedigree suggests that it is very likely, likely or unlikely that cancer is heritable in the family. Frequently, the genetic-counselor is not clear about the heredity-likelihood and only gives a general explanation of heredity-likelihood. See more details on heredity-likelihood in chapter 4.

3. The detection of a UR or a UV implies that the counselees' cancer-risks do not differ from the first consultation, thus the counselor merely repeats the cancer-risks as calculated on the basis of the pedigree.

When a PM is detected, more precise risks are communicated (10,14). A pathogenic BRCA1-mutation is associated with a range of risks from 65% to 85% of developing a primary breast cancer before the age of 70, and with a range of risks from 39% to 69% for developing ovarian cancer before the age of 70. A pathogenic BRCA2-mutation is associated with a range of risks from 45% to 84% of developing primary breast cancer before 70, and with a range of risks from 11% to 27% of developing ovarian cancer. A BRCA1- or a BRCA2-mutation is associated with a 60% risk of developing a second primary breast cancer when a counselee has already been diagnosed with cancer.

4. The genetic-counselor may communicate cancer-risks for untested relatives on the basis of the DNA-test result and the family history. This is communicated for either hypothetical healthy female relatives or specific relatives, such as their children.

5. On the basis of these communicated cancer-risks and the counselees' medical history, genetic-counselors may discuss several risk management options (see below) (15-17).

6. When a PM is detected, the possibility is offered to relatives of the counselee to undergo DNA-testing. When a UV is detected in the counselee and DNA-testing in relatives may be useful for creating a better understanding of the pathogeneity of the unknown mutation, a genetic-counselor may also request the counselees' relatives to participate in DNA-testing for co-segregation analysis. All counselees are advised to communicate the DNA-test result to their relatives. Currently, there is a lively debate among genetic-counselors whether relatives should be directly involved and informed by genetic-counselors, or not. This debate involves many legal and ethical questions.

7.Genetic-counselors may also discuss reproductive options with the counselee, such as having children with the 50% risk that their child inherits the cancer-predisposition, prenatal genetic diagnosis (PND) and preimplantation genetic diagnosis (PGD) (cf.18).

1.1.4. Implications for surveillance and surgery of the counselee and her relatives

Genetic-counselors may discuss several risk-management options with the counselee, i.e. surgery and/or surveillance of breasts and ovaries. Those recommendations are based on the cancer risk estimations in case of PM, the pedigree in case of UR/UV, combined with the counselees' medical history, such as previous surgery and surveillance. Usually, the options are communicated in a neutral way, and may include an explanation of the pros and cons for the counselee of each option. In case that a counselee has high risks and/or a PM-result, the genetic-counselor usually advises the counselee in stronger terms to undergo active surveillance or surgery. See more details in the national guideline for BRCA1/2-counseling (14).

Surveillance- Women without a previous cancer diagnosis with lifetime risks of at least 20% for developing breast cancer may opt for more intensive breast surveillance than women from the general population. Ovary screening may be offered to PM-carriers and/or if ovarian cancer runs in the family.

Surgery- Counselees with a high lifetime risk of developing breast or ovarian cancer, especially PM-carriers, can opt for preventive surgery. This may include surgical removal of the unaffected breast (i.e. prophylactic bilateral mastectomy, PBM) which may also include reconstruction of the breast, and/or removal of the unaffected ovaries (i.e. prophylactic bilateral salpingo oophorectomy, PBSO). Surgery significantly reduces the counselees' risks of developing cancer (19).

Which option is most suitable for a counselee depends on her personal situation. For instance, PBM is a mutilating irreversible procedure, which may involve medical complications and may significantly impact self-image, sexuality and well-being; this may partially be prevented by breast reconstruction (20-25). PBSO implies that menopause starts, which may be associated with several physical complaints (26,27). Counselees make their decision to undergo PBSO and/or PBM on the basis of many different medical, psychological, and social context factors (28). In this thesis (chapters 3, 5, 6, 8), I will describe how these medical decisions of counselees may be related to their recollections and interpretations of the communicated cancer-risks.

1.1.5. Uncertain issues in genetic-counseling

In the preceding text, I have described genetic-counseling from the perspective of the standard counseling protocol (9). This may have created the image of genetic-counseling as a consistent, clear procedure which involves few uncertainties. In practice, communication is not always consistent and counselees may experience uncertainties. The following uncertainties may occur.

Uncertainty is inherent to DNA-testing, because it involves the communication of risks for specific subgroups of counselees. Approximately 12% of all Dutch women develop breast cancer during their lifetime (11). The development of cancer could be attributed to a genetic predisposition in approximately 5% to 10% of all patients with breast cancer (10). Approximately 10% of all women with such a possible genetic predisposition are expected to be caused by a mutation in the BRCA1- or BRCA2-genes; the remaining 90% are expected to be caused by a mutation in other genes which are not known or which are not tested (15). Of all BRCA1- and BRCA2-test results, approximately 10% are PM, 80% UR and 10% an UV (29). By definition, the detection of UR/UV-result is associated with uncertainty for the counselee, because such a result means that another genetic cause may be present that is not known yet. Even the most conclusive outcome of testing, i.e. the detection of PM, does not imply certainty that a counselee will develop cancer, but it implies a strongly increased lifetime risk of developing cancer; this is presented in a broad range of risks and not in an exact risk figure.

It seems that somewhat different information is communicated by different genetic-counselors and to different counselees (see chapter 6, especially table 1). For instance, some genetic-counselors communicate UV-results and others do not(30). Genetic-counselors may adjust information to the situation and understanding skills of counselees, and the communicated risk management options may depend on the situation and preferences of the individual counselee. Genetic-counselors may also evoke uncertainty by non-verbal communication not consistent with the communicated information (31,32,33). Additionally, counselees are also confronted with other

uncertainties regarding cancer-risk estimates, such as missing data, limitations in testing accuracy, source credibility and conflicting information (34).

Uncertainties may also be inherent to the possible medical consequences of DNA-testing. Usually, risk management options are communicated in a neutral, non-coercive way, which leaves counselees with all freedom –and thus with many uncertainties- to make an autonomous decision to opt for surveillance and/or surgery. After detection of a PM, genetic-counselors often strongly recommend considering surveillance of breasts and/or ovaries, and PBSO, which may provide counselees with relative certainty about what medical steps to take. In case of UR/UV-results, recommendations are not strong. Although it is not very common, UR/UV-counselees with a cancer history may choose to undergo PBM and PBSO because of having had cancer; many of them seem to decide to undergo PBM and/or PBSO after disclosure of BRCA1/2-results, even when the UR/UV-result in combination with the pedigree does not strongly indicate such radical medical decisions (e.g.35; see chapters 2, 5).

In summary: disclosure of DNA-test results involves several uncertainties for counselees. In chapter 10, I examine how counselees cope with these uncertainties.

1.2. The historical and psychological context of this thesis

1.2.1. Information-oriented and counselee-oriented approaches in history

The psychological research that I describe in this thesis has to be understood from the context of previous psychological research on genetic-counseling. To explain this context of psychological literature, I will first shortly describe the history of how psychologists became involved in genetic-counseling. This description follows the articles from Resta, Biesecker and Kessler (36-38).

From its origination shortly after WWII (36), the discipline of clinical genetics seems to have been divided into two approaches that I call the information-oriented and the counselee-oriented approach. Other authors have used different terms to refer to such a difference in genetics: 'content-oriented and person-oriented approaches' (Kessler, in: 37), 'decontextualised and contextualized approaches' (Julian-Reynier et al, in: 38), 'traditional medical and biopsychosocial models' (Rolland in: 39), 'directive and non-directive approaches' and 'teacher-style and counseling-style' (Kessler in: 40-42). Generally speaking, the information-oriented approach focuses on the communication of genetic-information, and the impact on the medical decisions that counselees make. The counselee-oriented approach focuses on the psychological and personal needs of counselees, and on the way how counselees understand and adjust to the result and embed the DNA-test result in their lives. Both approaches can be seen in both the history of genetic-counseling in general and also in the psychological literature on genetic-counseling, as I will show in 1.2.2.

Generally speaking, genetic counseling has been dominated by a mainly information-oriented approach in its infancy until the 80s of the 20th century. Several authors describe that this approach was mainly caused by the eugenic ideals of the first genetic-counselors: although they criticized eugenic programs that were based on racism and coercion, many of them supported the ideal of improving the genetic composition of the population, and preventing 'harmful heredity to be continued or spread' (43,44). The information-oriented approach of the first decades of genetic-counseling may also be attributed to the relatively hierarchical, paternalistic role of physicians in general in that historical period. Moreover, psychologists and psychological perspectives were seldom involved in medicine in general. Few physicians would have felt comfortable acting like pseudo-psychologists (44).

The information-oriented approach was apparent in the most frequently quoted definition of genetic-counseling in the 70s which stated that its goal was 'providing people with an *understanding* of the genetic problems in the family' (44) as a means of 'enabling families to plan reproductive decisions' (37). Thus, there was an emphasis on the communication of genetic-information and the understanding of counselees. Practically, counselors frequently had a directive approach in their communication with patients, i.e. a form of persuasive communication involving 'various combinations of deception, coercion and threat' (42). Otherwise stated, they acted like teachers who 'educated' counselees (41). This approach had the advantage that genetic-counselors 'only' had to communicate and explain genetic information and give medical advise. They did not need to undergo an intensive training to become pseudo-psychologists who have to pay attention to the counselees' psychological and existential processes (41).

From as early as the 50s, there were also genetic-counselors who stressed the importance of psychosocial aspects of genetic counseling. However, it took many years before this psychological perspective became gradually recognized by more genetic-counselors. In the 70s, the number of criticisms on the directive, teaching-style approach increased. It was for instance stated that the information-oriented approach undermined the psychological self-directedness of counselees (40,41). This increasing influence of opponents to the information-oriented approach seems to have been influenced by the general societal development of the increasing importance of the autonomy and freedom of patients; the patient also gained a more central role in counseling and psychotherapy, which culminated in the client-centered psychotherapy of Carl Rogers. A general trend towards a counselee-oriented ethics was apparent in medicine (45,46).

These criticisms gradually caused significant changes in the practice of genetic-counseling (43). The teaching-style evolved into a counseling-style, meaning that counselees were helped by genetic-counselors to make autonomous medical decisions (41). Eugenic, societal goals were replaced by personal and family goals such as informed decision-making regarding cancer-risk management and reproductive options (44):

genetic-counselors acknowledged that 'families had little interest in eugenics, but instead were concerned about the effects of genetic disease on their lives, their children and their reproductive plans' (36). It was expected that a qualified counselor also had to be aware of 'the profound psychological effects which may have long-term consequences that may extend to relatives'; he/she also had to see and deal 'with the client's fears, hopes, defenses and rationalizations in order to help him/her deal with his/her problems in a realistic manner' (37). The counselees' needs were seen as central in deciding whether a directive or a nondirective approach was required in counseling (47-49). Thus, genetic-counseling was seen more and more as a process which was psychosocial by nature (50).

Despite this shift towards a more psychological paradigm (50), the formal goals of genetic-counselors continued to mainly reflect an information-approach (cf.37). For instance in 1975, a special committee of the American Society for Human Genetics defined the goals of genetic-counseling as 'a process to help the individual or family comprehend the medical facts, (…) appreciate how heredity contributes to the disorder (…), understand alternatives of dealing with the disorder (…), choose course of action'. Only the last goal stated a counselee-oriented goal, i.e. 'to make the best possible adjustment to the disorder' (51). In 2006, a new definition was developed by the American National Society of Genetic Counselors which includes a better balance between the information-oriented and counselee-oriented approaches: 'Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence. Education about inheritance, testing, management, prevention, resources and research. Counseling to promote informed choices and adaptation to the risk or condition' (52).

Thus from the 70s onwards, genetic-counseling gradually became more oriented towards the counselee, and had a more nondirective counseling-style approach of counselees. In this context, the need for psychological research on the goals of genetic-counseling arose. Studies in the 70s and 80s showed that genetic-counselors intended to have a counselee-oriented approach, but meanwhile the genetic-counseling sessions were often determined by the goals the counselor had in mind (37). In the 90s, research also focused on the expectations of counselees, who reported information provision and assistance with decision-making as the most beneficial aspects of genetic-counseling (53-56). However, this kind of research was criticized for being too information-oriented by mainly asking about knowledge, reproductive plans and behaviors (37).

The counselee-oriented approach started in reproductive genetics, and was in the 80s and 90s used in the counseling of counselees who had requested for a test for Huntington's Disease, a neurodegenerative dominantly heritable disease. During the genetic revolution of the 90s, this approach was applied in the counseling of counselees who underwent BRCA1/2-testing for hereditary breast- and ovarian-cancer (57,58).

1.2.2. Information-oriented and counselee-oriented approaches in psychological studies on genetic-counseling

There seems to be a remainder of the information-oriented approach of genetic-counseling in the psychological research on genetic-counseling. Many psychological studies on genetic-counseling have focused 'one-sidedly on the communication of probabilities, and have not fully taken into account the personal context and meaning of genetic-counseling for the counselee' (38). For instance, many studies examined how specific genetic-information is communicated by the genetic-counselor, how this specific information is specifically received, processed and reproduced by the counselee from a cognitive, decontextualised distance (38).

Since about ten years, more and more studies have emerged from a counselee-oriented perspective, especially qualitative and phenomenology studies. Still, the number of articles from this approach seems to remain behind the number of information-oriented articles.

For instance, relatively few studies have focused on the broad impact that DNA-test result disclosure may have on the counselees' lives: many studies focused on the impact on medical decisions and distress, but relatively few on the impact on the counselees' experience of their own body, main decisions in life, their relationships with relatives, etc. Thus, it is not completely clear how counselees integrate the DNA-test result in the general story of their life (59). It has been suggested that DNA-testing is inherently an existential process in the experience of counselees (60-62), but the role of existential processes has not systematically been studied in quantitative studies with large samples. Others have suggested that counselees do not simply take up genetic-information 'as value-neutral objective truth, but rather risk information is deeply subjective, interiorized against a pre-existing sense of self' (63). This hypothesis has not systematically been studied. There are studies about the counselees' cognitions about the genetic-information, but these do not really seem to provide a complete answer to the question how this subjective interiorization process takes place, that is: how counselees create their own interpretations of the DNA-test result, and how these may influence their lives. Moreover, it has been suggested that the picture of DNA-testing is not complete as long as family processes have not been included (64,65). For instance, the influence of social relationships on the way how families provide meaning to the DNA-test result is still unknown.

In summary, previous information-oriented studies did not seem to focus on the full width and depth of the impact of DNA-testing, the subjective interpretations of counselees and the influence that these interpretations may have on their lives, and the involvement of relatives. Studies that did focus on these counselee-oriented themes often had a qualitative and/or theoretical design, included relatively small samples and/or did not systematically examine counselee-oriented issues. In chapter 10, I will describe this

difference between the information-oriented and counselee-oriented approach in psychological research in more detail. Chapter 12 will summarize these results.

Our counselee-oriented, clinical psychological focus can also be found in the following paragraphs in which I will provide a general overview of psychological research on BRCA1/2-counseling. Its aim is to merely show which (mainly information-oriented) relevant studies have been performed on BRCA1/2-counseling and how our (mainly counselee-oriented) research is related to these. Thus, the following texts will not provide a complete review, but only roughly sketch general trends in psychological research on ***BRCA1/2-counseling***, and especially focuses on which information-oriented and counselee-oriented trends may be visible. Of course, there may be a large body of literature on the discussed topics outside of the field of BRCA1/2-counseling but I will not discuss that in the following paragraphs (where relevant, this literature will be cited in the chapters). This review is based on recent review articles on BRCA1/2-counseling or genetic counseling in general, as cited in the paragraphs.

1.2.3. A psychopathological perspective in genetic-counseling studies

> *Her genetic-counselor told Emma that a UV-result was detected. Emma was disappointed about this result, because the result left her with uncertainties about the likelihood that the genetic UV-mutation was pathogenic and about the likelihood that her relatives would develop cancer. She had also hoped that the DNA-test result would help her making decisions about preventive surgery. During the first months after the DNA-test result, she worried much and felt distressed.*

A psychopathological perspective of genetic counseling hypothesizes that the communicated results of genetic-counseling may evoke distress and psychopathology.

Is the experience of distress indeed inherent to genetic-counseling for counselees? Many studies have shown that counselees feel somewhat distressed after DNA-test result disclosure, but this distress seldomly reaches psychopathologic levels and it significantly decreases after a couple of months (66-71).

There is debate about the question whether genetic-counseling evokes psychopathology. It has been suggested that up to one-third of all counselees may experience significant distress after DNA-testing (72). High distress levels have been associated with several factors, such as having an inaccurate perception of the communicated risks, previous experiences with cancer in the family, recent breast-cancer life-events and neuroticism prior to DNA-testing (73). Research on psychopathology in counselees has been criticized for using insensitive, non-validated instruments, which may lead to either overestimation or underestimation of the observed proportions of

counselees with significant psychopathologic symptoms (74). Moreover, psychopathology and distress in BRCA1/2-counselees have often been discussed without taking into account the general context of having had cancer and/or living in a family with many cases of cancer; this counselee-oriented context of the counselees' general life has been suggested to be a better predictor of distress than the communicated genetic-information (74).

For these reasons, we have examined in our research how genetic-counseling predicts distress and psychopathology from the perspective of how counselees embed the DNA-test result in their lives; more specifically, we examined how the counselees' interpretation of the DNA-test result (and not the actually communicated DNA-test result) predicts their levels of distress (see chapters 5, 6, 8, 10). We have also developed more sensitive, genetics-specific distress-instruments in Dutch, such as Esplen's BRCA-Self Concept Scale (75, see chapters 5, 6), and the counselees' Unfulfilled Need for Certainty Scale (see chapters 9, 10). These new instruments focused at counselee-oriented aspects of their lived experience of genetic-counseling (i.e. uncertainty, vulnerability, stigma, mastery) instead of putting probably insensitive and information-focused labels on the counselees regarding psychopathology and distress.

1.2.4. Simple input-output models in genetic-counseling studies

> *Three months after the receipt of the UV-result, Emma discussed with her oncologist whether she could undergo PBM. Her oncologists told that this was possible because of her cancer-history, and Emma decided for this option. Emma attributed the final decision to undergo this radical surgery to genetic*-counseling*: 'the DNA-test result was the final straw'*.

Until recently, several studies in genetic-counseling assumed a simple input-output model, i.e. a model in which certain behavior is directly predicted by a certain input, possibly also in combination with a prediction by the expected consequences of certain behavior. For instance, it has frequently been assumed that the communication of the DNA-test result (i.e. input) has a direct impact on the medical decisions of counselees (i.e. output). For instance, it was expected that counselees would opt for PBM and PBSO after a PM-result, and would opt for frequent surveillance after a UR or UV-result. A similar simple model was hypothesized for the levels of distress and psychopathology which were expected to be directly predicted by the communication of the DNA-test result.

Indeed, several studies in the field of genetic-counseling failed to show a direct and consistent medical and psychosocial impact as a result of actually communicated genetic-information (66,69-71,76). We speculate that the lack of consistent large effects of the input on the output may be due to the underlying input-output model being too simple

and/or the range or selection of the included input-variables too small or irrelevant. For instance, many psychological studies only used the communication of the DNA-test result category (i.e. PM/UR/UV) and/or the counselees' cancer-risks as input-variables, but the genetic-counselor may communicate many other pieces of genetic-information which could also have been used as input-variables (see 1.1.3.).

In our studies, we have tested whether the simple input-output-model could accurately explain the medical and psychological impact of genetic-counseling. First, we tried to improve this input-output model, by including more input-variables and more sensitive output-variables than in previous studies (cf. chapter 6), and by focusing on specific subgroups of counselees instead of focusing on all counselees in general (see chapters 5, 6, 8). These improvements suggested that there were actually some relationships between input and output in our samples. Second, we created a more complex model, by creating and testing whether these input-output relationships were mediated by the 'counselees' psychological black-box in between the input and output of genetic-counseling'. That is, we examined which counselee-oriented, subjective processes were experienced by the counselees during the genetic-counseling process. We tried to predict the output by the input via mediation by these variables, (see explained in 1.2.2.3.; cf. chapters 5, 6, 8).

1.2.5. Perception, affect, cognition and appraisal in genetic-counseling studies

> *Emma told: 'I know that the genetic-counselor has communicated that a mutation was found for which the meaning is not known yet; thus this mutation could turn out to be pathogenic or to be unrelated to cancer. But I am convinced that this is actually a pathogenic mutation. I have decided to have my breasts removed, including my healthy breast, on the basis of my own belief.'*

Since decades, many psychologists have focused on cognitive processes in patients, such as their perception of their risk to develop a disease (again), i.e. risk-perception. Several risk-perception studies have also been performed in BRCA1/2-counseling. Here, we summarize these results regarding genetic-counseling, on the basis of recent reviews on risk-perception in this field (e.g.77-79,90). This information may not reflect the whole field of risk perception, for which the literature may be more elaborated on many topics.

Several studies have shown that many counselees do not have an accurate perception of their cancer-risks in genetic-counseling (77,78). As we know about the patients' perception in fields other than genetic-counseling, the psychological and medical impact/output of genetic-counseling seems to be better predicted by the counselees' risk-perception than by the actually communicated DNA-test result. However, many of these risk-perception studies still have inconsistent or even contradictory results in genetic-

counseling (79). In chapter 4, we suggest that these inconsistent results may be caused by the fact that the counselees' perception is often studied by non-valid instruments in genetic-counseling, and only included the counselees' perception of the cancer-risks and excluded other probably important variables such as their perception of heredity-likelihood. We have developed new variables to measure the counselees' perception of genetic-counseling and used these variables to predict the outcomes in chapters 5 and 6.

Another frequently studied theme in genetic-counseling is coping, such as described in the transactional model of stress and coping of Lazarus and Folkman. This model states that counselees may see a DNA-test result as a threat for their well-being on the basis of their *primary appraisals* of the personal significance of the stressor, and their *secondary appraisals* of their abilities to cope with the DNA-test result. Among many others, two main types of coping have been described: problem-focused coping –such as seeking information and undergoing medical surveillance- and emotion-focused coping – such as seeking social support. (80) For instance, previous research of our research groups has shown that passive reactions to genetic test results are associated with larger distress (87). In chapters 6, 9 and 10, we describe the counselees' copingstyle.

Studies about Leventhal's common-sense model of self-regulation (88,89) have shown that in genetic-counseling, the counselees' representation of the hereditary cancer consists of many different elements, such as cognitive representations, emotional representations, coping strategies, evaluation/appraisal, etc (87,90-92). For instance, emotional representations of hereditary cancer have shown to consistently predict higher levels of distress (87). Counselees seem to distort the communicated medical information by using their own heuristics and mental models of inheritance and disease causation to interpret and assimilate the risk information they have received (93,94). These representations may function independently from and/or parallel to rational, factual information (79,95), for instance due to biases of availability, representativeness, anchoring, influence of incidences on risk-perception, emotions and emotional forecasting (90,96). In chapter 4 we therefore suggest to distinguish the counselees' recollections from their interpretations. In chapter 9, we ask the question *why* counselees use such cognitive techniques and biases, and *how* these cognitive processes may influence their perception. We suggest that counselee-oriented variables –for instance about their selves, existence and needs for certainty- may provide an answer to these questions.

1.2.6. Communication theory and the family in genetic-counseling studies

> *The genetic-counselor had communicated Emma–on the basis of her pedigree- that she had a somewhat elevated risk of developing breast cancer. Emma recalled that she was communicated moderate to high risks, and she subsequently felt and thought (i.e. her interpretation) that she had a very high risk to develop cancer. Thus, Emma was*

communicated 'A', she recalled 'B', interpreted 'C' and made medical decisions on the basis of C. Subsequently, she told her relatives that she was communicated C, and her relatives recalled being communicated D, and interpreted this as E, and they based their medical decisions on the basis of E.

Communication theory of genetic-counseling focuses on the way in which a 'sender' (i.e. genetic-counselor) communicates information to a 'receiver' (i.e. counselee), and how 'noise' may occur in the communication of information. Several studies have described how the communication process, i.e. the way genetic-counselors communicate information (directly or indirectly addressing themes, choice of words, etc), may influence how counselees perceive the communicated information. Such studies often involve qualitative analyses of transcripts of genetic-counseling sessions (97-100). For instance, research from our research group has shown how different relatives may fulfill different roles within a family: one may be the messenger of the news, another one may be the first user of DNA-testing or medical risk-management (101).

Communication theory is implicitly present in many studies on genetic-counseling, for instance in studies that examine how accurate the perception of counselees is (77-79). It has been advised to genetic-counselors to use interventions based on communication theory (56,102).

Most communication studies have focused on the question whether the DNA-test result is communicated or not, to which relatives, and possible explanations of these results. For instance, research shows that most relatives are informed by the proband about the DNA-test result, mostly within four months after testing (103). Especially pathogenic-mutations are communicated, in particular to first-degree female relatives from cohesive families for whom DNA-test results may have medical consequences (103-108). These communicated DNA-test result have shown to subsequently cause distress in relatives (105,109-111), awaken familial conflicts and myths (112-114), and influence the relatives' well-being, medical-decisions and intention to request DNA-testing (109,115-120). The communication of DNA-tests results may interfere the natural cycle of individuals in these families (39, 65,112,121).

In chapters 7 and 8 we study how counselees recall and interpret the information communicated by genetic-counselor, how they communicate with their relatives, and how this influences the relatives' lives. This has not been systematically studied before.

1.2.7. Counselee-oriented approaches in genetic-counseling studies

On a superficial level, Emma seemed to adapt well to her cancer history and the DNA-test result. She had an active coping style, expressed her feelings to friends and relatives, acknowledged her physical limitations of lack of energy, generally felt happy about her

life, achieved good results in her job and was able to combine this with her role of being a mother. However, below the surface she felt uncertain about the possible recurrence of cancer and the heredity of cancer in the family. She found it difficult to deal with this uncertainty and unpredictability of her future: 'these feelings are always there, I cannot run away from them.' She described that uncertainty had become the basis of the way how she lived her life. Because of this general need for certainty in life, she had requested for DNA-testing, in the hope that she would receive more certainty. However, her need for certainty felt even more unsatisfied, when she had been communicated the UV-result. In response to this, she felt distressed. When she explored her distress in more detail she identified her existential needs and the receipt of uncertainty as the essence of this distress.

This section describes current counselee-oriented trends in psycho-oncology research. On the basis of these trends, we had expected similar trends in psychological research on genetic-counseling. But we did not find these. Psycho-oncology research may 'show us the way' in developing counselee-oriented studies on genetic-counseling.

In line with the dominant main theories in psychology as described above, the field of psycho-oncology in the past has often focused on information-processes, for instance on how patients cognitively process and adjust to medical information, and how psychopathology may be diagnosed and treated. During the last decades, attention has been growing for counselee-oriented processes in psycho-oncology (122-124). This counselee-oriented trend derives its origins from different psychological backgrounds, such as phenomenology, existential and humanistic psychotherapy (e.g.125,126), post-traumatic growth (127,128), positive psychology and spirituality (129,130). A large number of counselee-oriented studies is emerging on the personal and existential meaning of cancer for patients, which may also apply to the meaning of cancer-risks for counselees. For instance, studies describe how patients give a personal meaning to medical information (e.g.131) and relates it to their meaning in life and spirituality (132-138), and how this may evoke uncertainty and vulnerability (137). Improvement in finding positive meaning-making in cancer-patients have been suggested to help them adjust better to the cancer and to the communicated medical information (132,139-147).

It is remarkable that this trend in psycho-oncology is not paralleled by an equally large increase of the number of counselee-oriented studies in genetic-counseling. Because being or not being at risk for developing cancer –i.e. the essence of the communicated information in genetic-counseling- is also inherently about existential themes, similar to the existential nature of a cancer-diagnosis. To explain this: counselees do not ask for DNA-testing to understand probabilities accurately (1,5,6), but to fulfill existential needs: they want to receive information that provides them with certainty (6,93), e.g. about their own and their relatives' cancer-risks, to know which medical decisions to make and to find hope

(1,5,6,148,149). Genetic information is not simply 'taken up as value-neutral objective truth, but rather risk information is deeply subjective, interiorized against a pre-existing sense of self' (63), and has to be integrated flexibly by the counselees in the general story of their life (59). It has been suggested that the communication of cancer-risks may evoke questions in counselees about existential concerns in life, such as death, freedom, responsibility, isolation, meaninglessness (60). This is also suggested by several qualitative, theoretical and phenomenological studies (e.g.6,32,60,62,150,151).

Empirical counselee-oriented studies have shown that genetic-counseling may influence the counselees' self-identity (61,152) and may cause positive life changes (153). Genetics-specific existential feelings may be evoked, such as responsibility for undergoing and disclosing DNA-testing to provide relatives with risk-information (154-157), guilt about transmitting pathogenic genes to offspring (158), shame and stigma (75,159). The counselees' spirituality and religion have also shown to influence their perception and experience of genetic-information (150,160-162). However, most of these counselee-oriented studies in genetic-counseling were non-systematic and included small samples or had a non-empirical/theoretical nature.

1.3. This thesis

1.3.1. Purpose and research questions

The definitive formal purpose of current study was systematically investigating the counselees' perception and impact of BRCA1/2-test results from a counselee-oriented, integrative perspective.

The main research questions were:

(1) How do UV-counselees perceive the communicated DNA-test result from a counselee-oriented point of view?
(2) How is the actually communicated genetic-information related to the counselees' risk management strategies and well-being?
(3) How do counselees communicate the DNA-result to their untested relatives, and how does this influence the perception and medical and psychological impact of relatives?
(4) What role do counselee-oriented processes and traits play in these before-mentioned processes, such as need for certainty and personality?
(6) Given the answers to the previous questions: is UV-disclosure acceptable given the low informational value, and the possibly large psychological and medical impact of this result?

1.3.2. Method

1.3.2.1. General design

To answer our six research questions, this thesis includes six different studies which are described in the following chapters:

(1) A literature study on the BRCA1/2-nomenclature for UV/UR-results,
(2) A retrospective pilot study in UV-counselees with and without cancer,
(3) A retrospective study focusing on the long-term impact of PM, UR and UV-results in counselees with and without cancer,
(4) A family study in the relatives of the counselees who are included in the retrospective study,
(5) A prospective study focusing on the short-term impact of PM, UR and UV-results on counselees with cancer.

1.3.2.2. Motivation of instrument selection

The aim of all studies was to describe the current practice of genetic-counseling. Therefore, we developed a non-intervening study procedure that involved 'care as usual'. The studies were performed in the departments of Clinical Genetics in several Dutch university medical centers (and the peripheral medical centers where the genetic-counselors of these departments also counsel counselee): the Leiden University Medical Center (LUMC), the Maastricht University Medical Center (MUMC), the University Medical Central of University Groningen (UMCG), Erasmus Medical Center Rotterdam (EMCR), or the VU Medical Center Amsterdam (VUMC). We asked the counselees to fill-in one or multiple questionnaires by paper and pencil, or by the internet. Medical information was derived from the medical files, the summary letters send to counselees after genetic-counseling, and checklists filled-in by counselors after each session. Each questionnaire consisted of multiple psychometric instruments.

The selected instruments are described in the chapters. Our general motivation to select this combination of instruments was our wish to create an in-depth understanding of the broad impact that DNA-testing may have on the lives of counselees. First, we wished to make the results of our studies generalizable and comparable with previous studies in our field. Therefore, we have used several instruments which have shown to be reliable and valid in our field. Second, to study counselee-oriented topics in genetic-counseling, we used counselee-oriented instruments that have not been used before in genetic-counseling, but have shown to be reliable and valid in other fields. Third, we have developed new instruments to measure counselee-oriented phenomena that have not been studied before. Fourth, we have developed other questionnaires to collect general information about sociodemographics, medical behavior in the past and intentions for

future surveillance and/or surgery, and communication of the DNA-test result with relatives and friends.

1.3.2.3. Motivation of the selection of statistics, and explanation of difficult statistical issues
The chapters describe the specific statistic method and tests. However, four fundamental statistical choices return in many chapters. Therefore, we describe these topics here, to facilitate the readers' understanding.

Data reduction and data increase- To simplify the study results, we reduced the data where possible with Principle Component Analyses (PCA); in all cases, we have also performed the main analyses in the studies on the original data, and if these led to different conclusions, we have not used the PCA-factors.

Previous studies, and clinical experience of genetic-counselors, tell that many differences may exist in the counselees' perception and impact of different DNA-test results. Therefore, we tested differences between the three DNA-test result categories (PM, UV, UR) with Kruskal-Wallis tests (K-W). To reduce the loss of data not provided by counselees, we imputed values that were missing in less than 20% of all items of a scale, by means of multiple imputing techniques in SPSS. We did not impute a variable when it was not part of a scale, to avoid overestimation of the detected relationships; however, this caused a larger number of missing values.

Previous studies have been criticized for not taking into account the general context of genetic-counseling (74,68). Therefore, we either corrected analyses for several covariates or included more predictors in our models, in line with the literature: actually communicated genetic-information (163,164); elapsed time since DNA-test result disclosure (165,70); experiences with cancer and death in the family (164,166-168); cancer-history, current treatment (35,68,71,73,169); age, education, having-children, religion (170,164); risks measured in percentages (171-182). To simplify the texts, we only present these covariates or predictors when these significantly influenced the study results with moderate or large effect sizes, or lead to other conclusions or relevant nuances of the study results.

Mediation analyses - We used mediation analyses in chapters 5, 6, 8 and 9. Mediation means that variable Z 'explains' or 'mediates' the relationship between variables X an Y, either completely or partially. For instance, the communication of a PM-result (X) predicted distress (Y), but this relationship was completely mediated by the counselees' perception (Z). In that case, the PM-result predicted distress only indirectly via the counselees' perception. The counselees' perception of the DNA-test result (Z) explained why the PM-result (X) had influenced the distress (Y). All effects of the PM-result (X) on distress (Y) went

indirectly via the perception (Z). It was unthinkable that the PM-result (X) would directly have caused distress (Y) without the mediating role of the counselees' perception (Z).

When we would have only reported the simple regression results in which the PM-results (X) had caused distress (Y), we would have created an incomplete, false image of the situation, because the crucial mediating variables (Z) would have been omitted. This might have led to bold conclusions such as 'the communication of PM-results causes distress'. But in reality it is truer that counselees had created an inaccurate or frightening perception in response to the PM-results, which had caused distress. This would have led to completely different implications: the results from the simple regression analysis would imply that to avoid distress, PM-result should not be communicated. The mediation regression analysis would imply that to avoid distress, the counselees' perception of the PM-result should be changed. This example clarifies our statement in 1.2.4. that simple input-output models may be not be sufficient to explain the impact of genetic-counseling. As long as such complex mediation models are not tested and falsified, it seems unjustified that reviewers, such as Hamilton (183) and Coyne (74), have concluded that the disclosure of DNA-test results does not cause distress in counselees, or only causes a small amount of distress which varies over time. Their simple models only justified them to report that they could not find a *direct* impact of DNA-test result disclosure on a specific range of outcome-measures. Subgroups of counselees may actually experience significant distress(72), which may only become visible when mediating variables such as their perception of the DNA-test result are also examined.

To be able to speak about 'mediation', the relationships between X, Y and Z have to fulfill several steps (184): X → Z → Y. Step 1: X (e.g. communicated risks) and Z (e.g. interpreted risks) are significantly correlated to each other. Step 2: X is significantly correlated with Y. Step 3: Z is significantly correlated with Y. Step 4: the significance and/or effect size of the influence of X on Y has to decrease when Z is included in the analysis. We decided to present the mediation in a clinically relevant way in the chapters (e.g. chapter 5, 3.4., tables 6-9). We do not discuss step 1, i.e. the relationship between X and Y, because this step is already assumed in the subsequent steps ($R>.20$, $p<.01$). First, we may discuss a so-called *direct* relationship between X and Y. This means that X and Y are correlated, and this effect (its Beta) is *not* significantly influenced by the mediator Z (i.e. it is 'direct', there is no mediation). Second, we may only present an effect of Z on Y; this means that there are neither direct nor indirect relationships between X and Y (of course, in this situation there is no mediation, but only simple regression/correlation: Z is predicted by Y and not by X). Third, we may discuss a so-called *indirect* relationship between X and Y. This means that there is a significant relationship between X and Y (we report this effect as the figure before the slash, e.g. **.30**/.10); however, this effect (i.e. its Beta) is significantly influenced/mediated when we put Z in the equation (we report this changed significance/beta as the figure after the slash, e.g. .30/**.10**). We do not present not-

significant relationships between X and Y, and between Z and Y, and we also do not always present all mediation steps, because of length restrictions of our articles. Therefore, in some cases we only presented effects between the perception-variables (Z) and the outcome-variables (Y); that means that there were neither direct nor indirect/mediated effects between the DNA-test result (X) and the outcomes (Y). For instance, we did not find a relationship between Unclassified Variants (X) and outcomes (Y), but we did find and present a relationship between the perception (Z) and the outcomes (Y) (chapter 6, 3.5., table 10): in this case, only the perception predicted the outcomes, and the Unclassified Variant result did not predict these outcomes at all.

Mediation can formally be tested by means of a specific kind of regression analyses, as developed by Preacher and Hayes(185,186). Regression mediation analysis is statistically comparable with SEM, but the regression method has the advantage that it can easily be used and interpreted, even when values are missing, binary variables are included or normality is violated; it has good a priori power in relatively small and moderate sample sizes such as in our studies (187-190). We describe/formulate mediation results in terms of prediction (e.g. 'X predicted Y') to clarify our hypothesis; however, regression analyses may indicate the presence of mediation effects, but cannot definitely prove this, because we did not perform intervention studies. The design of our studies and the nature of the mediators made mediation likely, because the mediation results were in line with our theoretical expectations and previous studies, causality was suggested by the timeline of the study (e.g. T1-variables predicted T2-variables), and the mediators were flexible and changeable like an intervention(188). See more details on regression analyses in chapter 5.

Correlated but also different - In the retrospective study, the family study and the second prospective study (chapters 4, 7, 9), we analyzed the relationships between the cancer-risks actually communicated by the genetic-counselor on the one hand, and the counselees' recollections and interpretations of cancer-risks on the other hand. By means of t-tests, we tested whether these variables differed from each other. By means of Pearson's correlations, we tested whether these variables were related to each other.

It was possible that these variables differed from each other and at the same time correlated with each other. This means for example, that the counselees' interpretation was hypothetically different from what the genetic-counselor had actually communicated ($p(t)<.01$, $d>.2$). At the same time, there was a significant positive correlation ($p(R)<.01$, $R>.23$), which indicated that the higher the actually communicated cancer-risks were, the higher the perceived risks were. This co-existence of differences and correlations may be exemplified by the hypothetical relationship between the number of cigarettes that a person smokes per day and the amount of damage to the lungs: the number of cigarettes and the amount of damage are obviously two different phenomena, but they are also related with each other. Where possible in the chapters, we try to explain this co-existence,

for instance by examination of the scatterplot. This may reveal explanations for the patterns, such as outliers in the data (i.e. extreme scores). Another explanation may be that counselees consistently overestimate the actually communicated risks, so that hypothetically the following sum could be made: interpreted risk = actually communicated risk + 10%. The data could also have been grouped by the DNA-test result category: all counselees in the PM-group had high scores, and all counselees in UV/UR-groups had low scores, which caused the correlation.

Significance and effect size - In all chapters, we described both the significance levels and the effect sizes of each statistical relationship. A meaningful relationship is defined by both a significant p-value and a moderate or large effect size.

Except for our pilot study, we defined the significance level in all our studies by p-values <.01, and we did not use more strict criteria for correction of statistical errors such as Bonferroni. This decision was a balance between arguments. On the one hand, all studies had an explorative nature, which means that we wished to give an overview of possible statistical relationships and patterns, and not to determine precise figures. We also had rather specific expectations about the direction of most correlation tests. These two arguments would suggest using high p-values as definition of significance (e.g. p<.10), to avoid type-II statistical error, i.e. rejecting our hypothesis when the hypothesis is actually true. On the other hand, we performed many tests, which increased the possibility of type-I error, i.e. accepting our hypothesis when it is actually not true. To reduce this error, the p-value had to be reduced. Therefore, we decided to use p<.01 as criterion for significance.

The effect sizes for associations (e.g. χ^2) were Cramer's V: small effects were around .25, moderate around .50 and large around .75. The effect sizes for correlations (e.g. Pearson's R or std. ß in case of simple regression analyses) were Pearson's R: small effects are between .1 to .23, moderate .24 to .36 and large higher than .37. The effect sizes for differences (e.g. Student's t) were Cohen's d: small effects were between .2 to .3, moderate around .5 and large around .8. The effect sizes of multiple regression analyses (including mediation analyses by means of regression analyses) were Cohen's f^2: small effects were around .2, moderate around .15 and large around .35.

1.3.3. Overview of this thesis

This thesis has been built like a pyramid (figure 2). This means that later chapters are built upon previous chapters. It also implies that our theories develop over the chapters, so that the later chapters include more complex and detailed models. Some elements of the later chapters even 'overruled' elements in previous chapters. For instance, we hypothesized in chapter 3 that the uncertain UV-result directly causes distress in counselees, but in chapter 10 we hypothesized that the lack of fulfillment of the counselees' expectations of the UV causes distress.

In the first part of this thesis, we have built the foundations of this thesis by means of the nomenclature/literature study and the pilot study. In **chapter 2** on BRCA1/2-nomenclature, we examined and selected the terminology that we wished to use in the rest of my research. In the qualitative pilot study in **chapter 3**, we explained the theoretical basis of this thesis, and examined how counselees perceive UV-results. Central in this study was the distinction that counselees made between their recollections of the DNA-test result and their interpretations of that result, like Emma said to know that the counselor had communicated message 'A', but she believed in message 'B'.

In the second part, we developed a counselee-oriented, integrative approach on the perception and impact of genetic-counseling in counselees. In the first retrospective study in **chapter 4**, we developed a quantitative instrument on the basis of the insight from the pilot study that counselees make a distinction between their recollections and interpretations. We measured the relationships (i.e. differences and correlations) between the counselees' recollections and interpretations of both their own cancer-risks and of the heredity-likelihood. In the second retrospective study in **chapter 5**, we used these perception-variables to predict the medical and psychological impact of DNA-testing, like Emma, who made her medical decisions on the basis of her belief in 'B': her interpretation of B predicted her medical decisions. Mediation regression analyses was used to assess whether information-oriented and/or counselee-oriented variables predicted and/or mediated the medical and psychological impact of DNA-testing. The results from this retrospective study were subsequently confirmed in the first prospective study in **chapter 6** which focused on the short-term impact of DNA-test result disclosure. In that chapter, we discussed differences between the short-term impact in the prospective study and the long-term impact in the retrospective study. Moreover, we added new perception-variables to this study, i.e. the counselees' recollections and interpretations of their relatives' risks, and we tested whether these variables also predicted the medical and psychological impact of DNA-testing.

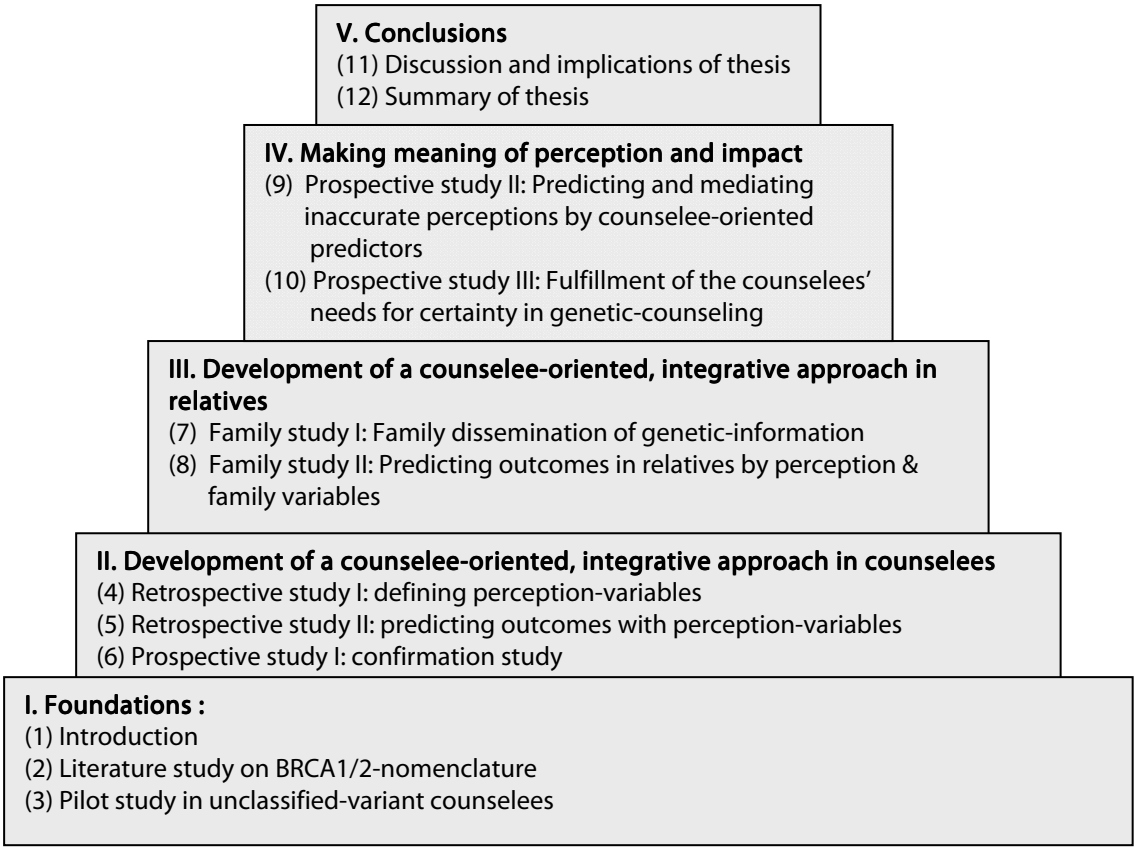
In the third part, we performed a study on the family communication of DNA-test results and its impact on the counselees' untested relatives. We used the counselee-oriented, integrative perspective that we had developed in part two of this thesis in this study. More specifically, the application of this perspective lead to our family-model that we call 'the whisper game of genetic counseling'. That is, we described in our studies how the genetic-counselor had communicated the DNA-test result to the counselee, who had subsequently recalled and interpreted this information and had communicated this result to her relative; finally, this relative had recalled and interpreted this information. In the first family study in **chapter 7**, we examined the steps of this model, and showed where 'noise' had occurred between these steps. In the second family study in **chapter 8**, we added another variable to the model, i.e. the communication process between the counselee and the relative. Finally, we explored the impact of DNA-testing on the lives of the relatives,

and tried to predict this by the actually communicated DNA-test result, the counselees' recollections and interpretations, and the relatives' recollections and interpretations.

In the fourth part, we tried to make sense of the relationships between information-oriented and counselee-oriented approaches, and we examined the meaning of DNA-test results for counselees at a deeper level than in the previous parts of this thesis. Previous chapters had shown that the counselees' and relatives' interpretation of the DNA-test result was important, but what this interpretation really meant for counselees was not clear yet. Therefore, we studied several counselee-oriented variables about the way how counselees give meaning to the DNA-test result, such as their need for certainty and their existential self-concept. In **chapter 9**, we use both information-oriented and counselee-oriented variables to predict and/or mediate how accurate counselees perceive the DNA-test result. In **chapter 10**, we assume that counselees may use genetic-counseling to fulfill their needs for certainty. We describe their need for certainty, the extent to which this need is fulfilled by the DNA-test result, and how the lack of fulfillment was related to their coping styles and distress.

In the fifth part, we concluded this thesis with discussions in **chapter 11**, and implications in **chapter 12**.

Figure 2. *Overview of the chapters in this thesis*



Frequently used abbrevations

	DNA-test results
BRCA1/2-test	DNA-test in both the BRCA1-gene and BRCA2-gene, which are associated with hereditary breast and/or ovarian cancer
UV	Unclassified Variant
PM	Pathogenic Mutation
UR	Uninformative DNA-test result
NPDTR	No Pathogenic DNA-test result, i.e. UV and UR
	Surgical options
(P)BM	(Prophylactic) Bilateral Mastectomy (Surgical removal of (un)affected breast)
(P)BSO	Prophylactic Bilateral Salpingo Oophorectomy (Surgical removal of (un)affected ovaries)
	Instruments
HADS	Hospital Anxiety and Depression Scale
IES	Impact of Events Scale
COPE	COPE, Coping styles questionnaire
LCQ	Life Changes Questionnaire (cf. chapter 2)
UNCS	Unfulfilled Need for Certainty Scale (cf. chapter 10)
	BRCA-related self-concept (cf. chapter 5): Scale developed by Esplen with three subscales: vulnerability, stigma and mastery
	Statistics
VAF	Variance Accounted For, i.e. R^2 (effect size)
PCA	Principal Component Analysis, i.e. factoranalysis
M, sd	Mean, standard deviation
	Terms used in mediation analyses
I	Information actually communicated by the genetic-counselor: e.g. UV, PM, UR, cancer-risks, heredity-likelihood
P	Perception of the counselee: e.g. recollections and interpretations of both cancer-risks and heredity-likelihood
O	outcomes e.g. HADS, IES, LCQ
	Other
	genetic-counselor: genetic-counselor (‘genetisch consulent’) or geneticist (‘klinisch geneticus’)
	cancer-risks (cf. chapter 4): the risk that an individual may develop cancer during her life-time
	heredity-likelihood (cf. chapter 4): the likelihood that the occurrence of cancer in the family is due to a genetic predisposition, i.e. ‘the extent to which cancer is heritable’

Chapter 2

Disentangling the Babylonian speech confusion in genetic counseling:

an analysis of the reliability and validity of the nomenclature for BRCA1/2 DNA-test results other than pathogenic

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Abstract

Purpose

Effective communication of DNA-test results requires a sound terminology. However, the variety of terms in literature for DNA-test results other than pathogenic, may create inconsistencies between professionals, and misunderstanding in patients. Therefore, we conducted a theoretical and empirical analysis of the terms most frequently used in articles between 2002 and 2007 for BRCA 1/2-test results other than pathogenic.

Design

We analyzed the content validity of the no-pathogenic DNA-test result-terms by comparing the literal and intended meaning of the terms and by examining their clarity and the inclusion of all relevant information. We analyzed the reliability of the terms by measuring the strength of association between terms and their meanings and the consistency among different authors over time.

Results

Two hundred twenty-seven articles with 361 no-pathogenic DNA-test result-terms were found. Only two terms seemed to have acceptable validity: variant of uncertain clinical significance and no-pathogenic-DNA-test-result. Only variant of uncertain clinical significance and true negative were found to be used reliably in the literature.

Conclusions

Current DNA nomenclature lacks validity and reliability. Transparent DNA-test result terminology should be developed covering both laboratory findings and clinical meaning.

1. Introduction

Because more and more genes are being identified, several guidelines have been developed to standardize the naming and symbolization of genes, changes in genes, and protein sequences. Guidelines for human gene nomenclature were first published in 1979 and were later updated (191). Several suggestions for further standardization have been made (192-195).

However, these guidelines only focused on naming changes in DNA and protein sequences. No guidelines have been developed for the communication of no-pathogenic DNA-test results (NPDTRs), i.e., when suspected pathogenic changes are not detected in mutation analysis in individual patients. Should we communicate such findings to patients as 'negative,' 'no-pathogenic,' or 'uninformative'?

These no-pathogenic DNA-test results (NPDTRs) are frequently found. For example, PM-results in the BRCA1 or BRCA2 genes for hereditary breast and ovarian cancer are only found in about 10% of tested probands from breast cancer families. In about 80% of all tested probands, no BRCA1/2 mutation is identified. In the remaining 10%, a BRCA1/2 variant, often a missense mutation, is detected for which the clinical significance regarding cancer risks is not known; future research may show this variant to be a disease-causing mutation or a benign polymorphism.

When a pathogenic BRCA1 mutation is found, lifetime cancer risks of 65% to 85% for breast and 39% to 69% for ovarian cancer are communicated to the counselee; when a pathogenic BRCA2 mutation is found, breast cancer risks of 45% to 84% and ovarian cancer risks of 11% to 27% are communicated (16,17,196-198). On the basis of these risks, possible risk management options are discussed, such as surveillance and prophylactic surgery of breasts and/or ovaries. However, in the NPDTR, decisions about surveillance and prophylactic surgery and DNA testing in relatives are based on the family pedigree and cancer history (30).

The communication of NPDTRs is often a difficult process because of the involvement of several groups of people. Molecular geneticists have to interpret DNA-test results correctly and convey these to clinicians. Subsequently, clinicians have to translate DNA-test results understandably to patients who have to recall DNA-tests outcomes correctly, act accordingly, and disclose these outcomes correctly to relatives. Moreover, molecular and clinical geneticists from different genetic centers should provide consistent information to their colleagues, patients, and relatives.

Indeed, NPDTRs seem to be regularly misunderstood by the patients (cf.199-202). Such misunderstandings may affect medical decisions, such as prophylactic surgery after disclosure of unclassified variants (203). Moreover, sound terminology is sine qua non for the unrestrained scientific development and dissemination of genetic knowledge, especially in the light of the persistent increase of the number of articles on NPDTRs.

Words are important instruments for the genetic counselor, whose main task is transmitting information about inheritance, DNA-test results, and possible management options. The specific wording may influence how patients and other professionals understand, interpret, memorize, and attach consequences to the result. This chapter analyzes the geneticist's linguistic instrument both theoretically (i.e., content validity) and empirically (i.e., reliability) in a similar way as each scientific instrument should be reviewed. The aim is to test current nomenclature, select sound terms, and suggest improvements.

2. Method

2.1. Preparatory literature study

We initially conducted a literature study to select relevant terms referring to NPDTRs and to identify all possible meanings that could be given to NPDTRs. We focused on the specific aspects of terms, like 'negative DNA-test result,' and not on general nouns like 'mutation' or 'DNA-change.'

A literature search was performed in the Pubmed for NPDTR terms used in the articles between 2002 and 2007 at April 5, 2008. This search entry was developed by a psychologist (J.V.), a clinical geneticist (C.J.v.A.), and a librarian (J.W.S.). This **chapter** is restricted to BRCA1/2 genes for hereditary breast and ovarian cancer, because most mutation analyses are requested for these genes. We did not include search criteria for polymorphism and noncarrier, because these terms were already often mentioned in the articles found by other search criteria. We marked all NPDTR terms in the title, abstract, and method section of each article. Subsequently, we identified clarifications and possible meanings of NPDTR terms.

The following search query was used in PubMed: 'Genes, BRCA2' [Mesh] OR 'Genes, BRCA1'[Mesh] OR BRCA1-gene OR BRCA1-genes OR BRCA2-gene OR BRCA2-genes OR BRCA 1-gene OR BRCA 1-genes OR BRCA 2-gene OR BRCA 2-genes OR BRCA-gene OR BRCA-genes OR 'BRCA gene' OR 'BRCA genes' OR BRCA1/2[tw] OR 'BRCA 1/2'[tw] OR ((brca OR brca*) AND (gene OR genes OR genetic OR genetic*))) AND (inconclusive[All Fields] OR nonconclusive[All Fields] OR 'non-conclusive'[All Fields] OR 'not conclusive'[All Fields] OR 'not-conclusive'[All Fields] OR 'uninformative'[All Fields] OR 'not informative'[All Fields] OR 'non-informative'[All Fields] OR 'non informative'[All Fields] OR 'non-informative'[All Fields] OR noninformative[All Fields] OR unclassified[All Fields] OR 'not classified'[All Fields] OR 'not-classified'[All Fields] OR 'true-negative'[All Fields] OR 'informative negative'[All Fields] OR 'not pathogenic'[All Fields] OR 'not-pathogenic'[All Fields] OR 'non-pathogenic' [All Fields] OR nonpathogenic[All Fields] OR 'without pathogenic'[All Fields] OR 'uncertain pathogenic'[All Fields] OR 'unknown pathogenic'[All Fields] OR 'indeterminate' OR 'uncertain significance' OR 'uncertain relevance' OR 'uncertain meaning' OR 'unknown

significance' OR 'unknown relevance' OR 'unknown meaning' OR 'uncertain clinical significance' OR 'uncertain clinical relevance' OR 'uncertain clinical meaning' OR 'unknown clinical significance' OR 'unknown clinical relevance' OR 'unknown clinical meaning' OR 'uncertain biological significance' OR 'uncertain biological relevance' OR 'uncertain biological meaning' OR 'unknown biological significance' OR 'unknown biological relevance' OR 'unknown biological meaning' OR 'uncertain pathological significance' OR 'uncertain pathological relevance' OR 'uncertain pathological meaning' OR 'unknown pathological significance' OR 'unknown pathological relevance' OR 'unknown pathological meaning' OR 'mutation negative' OR 'mutation-negative' OR 'negative test result' OR 'negative result' OR 'negative DNA test result' OR 'negative test-result' OR 'negative-result' OR 'negative DNA-test result' OR 'negative DNA-test-result'. The resulting reference list can be requested from the authors.

2.2. Analysis of content validity

Our theoretical analysis comprised an analysis of the content validity of NPDTRs. Content validity is often regarded as the most fundamental kind of validity and measures the degree to which an instrument (here: a term) is representative of the entire concept that the instrument is designed to measure: does the term 'say what we want it to say' and does it include all essential elements? Measuring content validity involves a nonstatistical analysis of the term in relationship to what the author means by this term followed by an evaluation of the validity in terms of 'strong,' 'acceptable,' or 'weak.' We evaluated each term on four aspects: a comparison of the literal and intended meaning, clarity of the subject, inclusion of relevant information, and potential misunderstanding by patients.

Firstly, a panel of a molecular geneticist (J.T.W.), a clinical geneticist (C.J.v.A), and two psychologists (J.V. and A.T.) discussed the literal meaning of each term, identified the underlying intended meaning of each term, and compared literal and intended meaning. To identify the literal meaning, we used dictionaries and internet engines, such as Van Dale English-Dutch, Oxford English Dictionary, Babylon English-English, Webster's Revised Unabridged Dictionary, Roget's Thesaurus, Google, and Wikipedia. To identify the intended meaning, we used the results from our literature study.

Secondly, we evaluated whether the subject of the term was specific enough to understand what the term precisely refers to, by means of a semantic analysis and with the help of the literature study. For instance, the concrete meaning of the expression 'clinical meaning' is unclear and cannot be derived from the term variant of uncertain clinical meaning.

Third, we discussed whether all relevant clinical information could be derived from the formulation of the term itself, e.g., the reference to the clinical meaning is absent in the term unclassified variant but is generally mentioned in the term variant of uncertain clinical meaning.

Fourth, we identified potential misunderstanding by patients resulting from the ambiguity of the term. For example, patients may experience false reassurance after disclosure of a so-called inconclusive DNA-test result, which does not provide information about the pedigree or possibility of a false-negative DNA test (204,86). Patients may also experience false alarm when a so-called unclassified variant is found, 'because something is found, thus there must be something wrong' (cf.203).

Each of these four aspects was evaluated in terms of 'weak,' 'acceptable,' or 'strong.' We combined these four evaluations in an assessment of the total validity of each term. Total validity was determined on basis of the sum of the evaluations of the four aspects. Differences in opinion were discussed until agreement was achieved.

2.3. Analysis of reliability

Our empirical analysis assessed how reliably NPDTR terms are used in the articles by different authors over time. Measuring the reliability of words requires other measures than measuring the reliability of a physical device or a questionnaire. In general, reliability describes the consistency of a measuring instrument with regard to different raters (interrater reliability) or to measurements at different moments (test-retest reliability). Applied to terms, reliability refers to how consistent different authors use a term by giving it one specific meaning (interauthor consistency) or how consistent a term receives the same meaning over time by different authors (temporal consistency).

To be able to measure reliability, each term was classified according to its meaning. *Firstly*, we assigned each term to one of the eight terminological groups and then grouped each term by its meaning (A–H in table 1). For example, the authors of Article 1 (cf.203) used the term unclassified clinical variant, which we assigned to Group 5 of 'unclassified-variants.' The authors used this term to refer to 'a mutation with unknown clinical meaning,' which led us to classify this term for Article 1 in Group A. Two raters (J.V. and C.J.v.A.) performed the classification after agreement was attained on differences in a consensus meeting. Terms and meanings were entered in SPSS14.

The interauthor consistency/agreement was calculated by dividing the number of articles that used a specific meaning by the total number of articles using this term (see table 3). Perfect interauthor consistency means that 100% of the authors give a term the same meaning. Some authors may have unintentionally given a different meaning to a term; however, if this is a complete coincidence, we expect at most 5% of all authors doing this and 95% of all authors giving one term the same meaning. Therefore, a term is called reliable if 95% of all authors give one term the same meaning.

Secondly, we calculated associations between terms and meanings with $[chi]^2$. Good reliability is operationalized as a significant $[chi]^2$ association of a term with its most frequently reported meaning and an insignificant $[chi]^2$ association with other meanings, e.g., the term unclassified variant most frequently means 'mutations with unknown clinical

meaning,' and this term should therefore have significant associations with this meaning and insignificant associations with other meanings such as 'pathogenic mutation.'

Third, perfect temporal consistency means that each term has the same meaning over several years. This is operationalized as a nonsignificant [chi]^2 test between meaning and year of publication.

3. Results

3.1. Preparatory literature study

The literature search yielded 227 articles, of which 16 articles did not show relevant terms and 9 articles were only retrievable as abstracts. No articles were found with search terms referring to 'not/non/uncertain/unknown pathogenic,' so these terms were removed from further analysis in the reliability study.

From the 202 remaining articles, 361 NPDTR terms were identified. We identified eight similar groups of terms, viz. inconclusive (non/not conclusive), uninformative (not/uninformative), true negative (informative negative), unclassified variant (not classified), variant of uncertain significance (variant of uncertain clinical significance/relevance/meaning/pathogeneity), polymorphism, negative, and noncarrier (points 1–8 in table 1).

Identification of meanings of the terms resulted in eight different groups (see letters A–H in table 1), e.g., the term noninformative was sometimes used to only refer to (B) 'absence of any mutations that has no clinical meaning for the patient,' but this term is sometimes used to refer (E) both to 'absence of any mutations, which either has or has no clinical meaning,' and 'absence of changes with clinical meaning.'

Table 1. *Results of preparatory literature study (n=227; 2002-07; see the search entry in the text); identified terms and possible meanings of no-pathogenic DNA-test results (followed by symbolic notation)*

Terminological groups

(1) inconclusive
(2) non-informative
(3) true-negative
(4) unclassified variant
(5) variant-of-uncertain-clinical-significance
(6) polymorphism
(7) negative
(8) non-carrier

Groups of terminological meanings

(A) Mutation with unknown clinical meaning
(B) Absence of any mutations, that has no clinical meaning for the patient (i.e. no mutation found in a patient of a family without a pre-identified pathogenic mutation)
(C) Absence of any mutations, that does have clinical meaning for the patient (i.e. no mutation found in a patient of a family with a pre-identified pathogenic mutation)
(D) A term refers to 2 kinds of DNA-test results:
    (b) absence of changes without clinical meaning
    (c) absence of changes with clinical meaning
(E) A term refers to 3 kinds of DNA-test results:
    (a) changes with unknown clinical meaning
    (b) absence of changes without clinical meaning
    (c) absence of changes with clinical meaning
(F) A term refers to 2 kinds of DNA-test results:
    (1) absence of changes without clinical meaning
    (2) changes with unknown clinical meaning
(G) Benign polymorphism
(H) A term refers to 2 kinds of DNA-test results:
    (g) benign polymorphism
    (h) disease-related polymorphism

3.2. Analysis of content validity

Table 2 shows the results of the content validity. The literal and intended meanings were largely similar for most terms: inconclusive and uninformative (both do not give definitive answers to the questions of patients and/or geneticists), variant of uncertain clinical significance (referring to the indefinite status of the clinical meaning of this DNA-variant), and NPDTR (referring to not having detected a pathogenic mutation).

The term non-pathogenic DNA-test result seemed less accurate than the term no-pathogenic DNA-test result (NPDTR), because the former term stresses the presence of a DNA-test result and the latter stresses the absence of a pathogenic mutation. Literal and intended meanings were slightly similar in the terms polymorphism and noncarrier but the former does not say that the DNA locus has 'multiple forms' and that this is found in >1% of the population; the latter does not cover the intended essence of not carrying a mutation of the specific gene. The term unclassified variant is incorrect, because many variants may be classified into categories of estimated potential pathogeneity (cf.205,206) and the intention is to cover the indefiniteness of the functional and/or clinical meaning of this DNA variant. The terms negative DNA-test results and true-negative DNA-test result are incorrect, because the intention is to refer to the absence of a mutation and not to the negation of a DNA-test result.

The subject to which most terms refer is rather unclear, except for the terms variant of uncertain clinical significance and nonpathogenic DNA-test result. The following subjects are indistinct: 'inconclusive,' 'uninformative,' 'reliably negated' (regarding true-negative results), 'unclassified,' 'negated' (negative result), 'has multiple forms' (polymorphism), or 'not-carried' (noncarrier). It is impossible to derive from the literal meanings of these terms what DNA-test results are intended: pathogenic mutation, family-specific mutation, variant with undetermined clinical meaning, benign, or disease-related polymorphism.

Except for the term true negative, much relevant clinical information could not be derived from the literal meaning of the terms. Lacking information was for e.g., risks and risk management should be based on the pedigree, possibility of a mutation in yet unknown genes, sensitivity and insensitivity of DNA testing, future research showing clinical meaning of unclassified variants and variants of uncertain clinical significance, and polymorphisms are found in >1% of the population.

All terms are to some extent ambiguous and may lead to misunderstandings in the patients, resulting in false reassurance (i.e., 'nothing is detected, so I'm not at risk') or false alarm (i.e., 'something is found, so I'm at risk'). The theoretical analysis was completed with a panel judgment of the total validity of each term. Validity was only judged as acceptable for the terms NPDTR and variant of uncertain clinical significance. The other terms have weak content validity.

Table 2. *Theoretical analysis of the validity of current terms for no-pathogenic DNA-test results.Because of similar results, terms 1 and 2 are combined. Evaluations (eval.) are based on previous column/columns. Three kinds of evaluation are possible: weak(-), acceptable(0), strong(+)*

Term	literal meaning	intended meaning (literature and praxis)	comparison of the literal and intended meaning	eval	clarity of the subject this term refers to	eval	relevant information unmentioned in the term	eval	potential misunderstandings by patients	eval	eval of total validity
1. inconclusive DNA-test result **2. uninformative DNA-test result**	1. a DNA-test result that does not lead to a definitive conclusion 2. a DNA-test result that does not give information	these DNA-test results do not yield definitive conclusions or information about the questions of the patients and/or geneticists (not considering the subject/content of these questions)	literal and intended meanings are similar (not considering the subject/content of the questions)	+	the subject which is 'inconclusive' or 'uninformative', is very unclair. possible subjects: a. functional meaning b. clinical meaning c. heredity d. cancer risks e. cancer risk management possible DNA-results covered by term: f. pathogenic mutation g. family-specific mutation h. unclassified-variant i. polymorphism	-	1. risks and risk management should be based on the counselee's pedigree 2. possible mutation in a yet unknown gene 3. sensitivity and insensitivity of DNA-testing	-	false reassurcance, i.e.'nothing is found, so I'm not at risk'	-	-
3. true-negative DNA-test result	a real, complete or reliable negation, rejection or contradiction of a DNA-test result	denial (negation) of the presence of a mutation	both literal and intended meaning concern a negation, but the intention is to refer to the negation of a mutation and not to the negation of a DNA-test result itself	-	the subject 'which is reliably negated', is unclair. possible DNA-results covered by term: f. pathogenic mutation g. family-specific mutation h. unclassified-variant i. polymorphism	-	idem 2 for affected counselees	+	interpretation of negative as 'bad', false reassurance	-	-
4. unclassified DNA-variant	a DNA-test result that cannot be classified	the meaning of this DNA-variant is not determined (yet)	the literal meaning refers to the classification of the DNA-variant. However, many variants are classified into categories of estimated potential pathogeneity. The intention is to refer to the meaning which is not determined (yet).	-	the subject which is 'unclassified' or 'undetermined' is unclair: possible domains: a. functional meaning b. clinical meaning j. estimated potential pathogeinity possible DNA-results covered by term: g. family-specific or new mutation	-	idem 1, 3 4. future research may show clinical meaning of DNA-test result	-	false alarm, i.e. something is found, thus there must be something bad'	-	-

Table 2. *Continued*

5. variant-of-uncertain-clinical-significance	a DNA-test result of which the clinical significance is uncertain (i.e. ambiguous, doubtful or undecided)	the clinical meaning of this DNA-test is not determined (yet)	both literal and intended meaning mention the indefinite status of the clinical meaning of this DNA-variant.	+	the subject is clair, viz. clinical genetics. the precise clinical content is not mentioned, e.g. heredity, risks, medical management, etc. The word 'insignificant' may be interpreted incorrectly as 'irrelevant' or 'unimportant', but patients/geneticists may perceive this as important. The subject is unclear when 'clinical' is omitted.	0	idem 1-4	-	false alarm	-	0
6. polymorphism	multiple (=poly-) forms (=morphe)	multiple variations at a DNA-locus found within more than 1% of a population	both intended and literal meaning concern multiplicity. However, the literal meaning does not include DNA-locus and percentage, which are essential in the intended meaning, but the genetic context in which this term is used may clarify this.	0	the subject which 'has multiple forms' is not stated, viz. DNA-locus, but the genetic context in which this term is used may clarify this. possible DNA-results covered by term: k. benign polymorphism l. disease-related polymorphism	-	idem 1-3 5. found in >1% of population	-	false alarm, false reassurance	-	-
7. negative DNA-test result	a negation, rejection or contradiction of a DNA-test result	denial (negation) of the presence of a mutation	both literal and intended meaning concern a negation, but the intention is to refer to the negation of a pathogenic mutation and not to the negation of a DNA-test result	-	the subject 'which is negated' is unclair. possible DNA-results covered by term: f. pathogenic mutation g. family-specific mutation h. unclassified-variant i. polymorphism	-	idem 1-4.	-	false alarm, false reassurance	-	-
8. non-carrier	a counselee does carry something	a counselee does not carry a mutation	both literal and intended meaning concern not-carrying something, but the literal meaning does not cover the intended essence of not-carrying a *mutation*	0	the subject which 'is not carried' is unclair. possible DNA-results covered by term: f. pathogenic mutation g. family-specific mutation h. unclassified-variant i. polymorphism	-	idem 1-4.	-	false reassurance, some patients use 'not-carrying' to refer to 'not-carrying a disease'	-	-
9. no-pathogenic DNA-test result	a DNA-result which is not pathogenic	no pathogenic mutation is detected	literal and intended are similar	+	subject is clear	+	idem 1-4	-	false reassurance	-	0

3.3. Analysis of reliability

Each term in each article was classified into a group of terms (1–8 in table 1) and into a group of meaning (A-H in table 1). Classification into a terminological group was uncomplicated.

Classification according to the meaning was difficult for the term noninformative in 25% of all articles, for polymorphism in 20%, for negative in 12.5%, and for the terms inconclusive and noncarrier in 5% of all articles (see table 3).

The following results were both found in the total literature study as in separate analysis in which only articles were included that were classified without difficulty. Articles about psychological topics written by psychologists did not show different results from articles about nonpsychological topics written by physicians and are therefore not separately presented.

Frequency analyses indicated that the terms unclassified variant, variant of uncertain significance, and true negative were given the same meaning by >95% of all authors, implicating strong interauthor consistency. Consistency among authors was more imperfect, and thus less reliable, for the terms noninformative (85% of all authors gave this term the same meaning), inconclusive (72%), negative (71%), and poor for polymorphism (53%), and noncarrier (52%).

Four terms related significantly to their relevant meaning: inconclusive and noninformative, true negative, unclassified variant, and variant of uncertain clinical significance. Three terms significantly related to irrelevant meanings: polymorphism, negative, and noncarrier.

Most terms seemed to express the same meaning over time, except for the terms polymorphism and negative: in articles since 2004, the term polymorphism has been more consistently used as a group name for benign and disease-related polymorphisms, and the term negative is more consistently used as 'absence of any mutation, with clinical meaning' ($X^2 = 30.0$, df = 16, P = 0.02; $X^2 = 75.9$, df = 40, P = 0.001, respectively).

Table 3. *Empirical analysis of the reliability of terms used in literature between 2002 and 2007 (n=227). Each term referring to no-pathogenic DNA-test results in BRCA1/2 (NPDTR) was identified and scored on: number of articles in which the term was difficult to classify, classification of each term by meaning, total frequency of each term, number of articles written by psychologists or topic about psychology, relationship between the meaning of each term and year of publication (χ^2-tests), and relationships between number of psychological articles and (a) meaning and (b) number of articles difficult to classify(χ^2-tests). Positive relationships between terms and meaning with significant X^2-tests are flagged.*

		N(%) of articles difficult to classify	**meanings**								**Total N per term (% of all terms)**	**Association (χ^2) between meaning and year of publication (2002-2007)**
			A. Mutation with unknown meaning	B. absence of Mutations, without clinical meaning	C. absence of Mutations, with clinical meaning	D. group name of several DNAresults: absence of changes without clinical meaning + absence of changes with clinical meaning	E. group name of several DNA-results: absence of changes without clinical meaning + absence of changes with clinical meaning + changes with unknown clinical meaning	F. group name of several DNAresults: absence of changes without clinical meaning + changes with unknown clinical meaning	G. benign polymorphism	H. group name of several DNA-results: benign polymorphism + disease-related polymorphism		
terms	**1. inconclusive**	1 (5.5)	1 (5.5)	13 (72.3)***	0	0	1 (5.5)	3 (16.7)	0	0	18 (4.7)	n.s.
	2. noninformative	5 (25.0)	1 (5.0)	17 (85.0)***	0	0	1 (5.0)	1 (5.0)	0	0	20 (5.5)	n.s.
	3. true-negative	0	0	1 (5.8)	16 (94.2)***	0	0	0	0	0	17 (4.7)	n.s.
	4. unclassified variant	0	55 (100)***	0	0	0	0	0	0	0	55 (15.2)	n.s.
	5. variant-of-uncertain-significance	0	87 (100)***	0	0	0	0	0	0	0	87 (24.1)	n.s.
	6. polymorphism	12 (19.5)	0	0	0	0	0	0	33 (53.2)**	29 (46.7)**	62 (17.2	χ^2=30.0, df=16, p=.02
	7. negative	10 (12.6)	1 (1.3)	56 (70.9)***	13 (16.4)***	8 (10.1)***	1 (1.3)	0	0	0	79 (21.9)	χ^2=75.9 df=40, p=.001
	8. non-carrier	1 (4.3)	0	8 (34.7)***	12 (52.1)***	1 (4.3)	1 (4.3)	1 (4.3)	0	0	23 (6.7)	n.s.
	N of column (% of total)	29 (8.0)	145 (40.1)	95 (26.3)	41 (11.3)	9 (2.4)	4 (1.1)	5 (1.4)	33 (9.1)	29 (8.0)	361 (100)	n.s.

* p<.05, ** p<.01, *** p<.001

4. Discussion

4.1. Conclusions

Effective communication of DNA-test results requires a sound DNA terminology given the often far-reaching consequences of test results for patients. Nomenclature has received much attention in the field of molecular genetics (191), in contrast with the communication of NPDTRs, which has received little attention in the field of genetic counseling. This has caused a multiplicity of words to have evolved over time.

Our analyses showed a lack of validity and reliability for most of the terms currently used for NPDTRs in BRCA1/2. The terms variant of uncertain clinical significance and no-pathogenic DNA-test result showed acceptable or strong validity. The terms unclassified variant, variant of uncertain significance, and true negative were used reliably among different authors over time. Other terms were difficult to classify and were used unreliably and the term no pathogenic was not found in our literature study.

The lack of sound terminology could be attributed to the absence of evidence-based guidelines and to the involvement of several specialisms. The inconsistency of genetic terminology in general may reflect the fast nonsystematic development of genetics as a rather young field. However, more recently some terminological consistency seems to have been developed, as shown by the terms polymorphism and negative, which are more consistently applied since 2004.

4.2. Suggestions for new DNA-terminology

To our knowledge, this is the first study examining the reliability and validity of nomenclature for NPDTRs systematically. Previous articles discussed the inconsistent use of several terms and the lack of content validity. The absence of previous studies may be due to the belief that terms are mere symbols to refer to phenomena. For instance, why should we worry about the precise formulation, when both the terms unclassified variant and variant of uncertain clinical significance superficially refer to the same phenomenon? This may be called a 'referential view on language.' We subscribe to the reverse view of constructivism: reality is, at least partially, cognitively constructed by the words and interpretations people use (207-211). Therefore, subtle differences in wording may influence the patient's understanding, interpretation, and memory of information. This may especially account for ambiguous and important information, such as NPDTRs, where patients seem to clutch at every straw of information (203).

To facilitate communication among professionals and with patients, we suggest to use or develop terms that have shown validity and reliability, like the terms variant of uncertain clinical significance and no-pathogenic DNA-test result.

Terms should have a complete correct literal meaning, like these two terms have. Incorrectness may obstruct effective communication between physicians and with patients.

The strength of the former term, variant of uncertain clinical significance, may lie in the combination of both molecular-genetic information (variant) and clinical information (uncertain significance). Other terms only mention molecular-genetic or clinical information, or neither as shown in table 2. Whether a term has to communicate all six aspects that we identified could be questioned. In any case, terms seem to be more unclear and ambiguous when they either exclusively cover molecular genetic information, e.g., unclassified variant or exclusively cover clinical meaning, e.g., uninformative. We suggest using terms that cover both functional/molecular-genetic and clinical meaning. The strength of the term no-pathogenic DNA-test result may lie in keeping close to the factual laboratory finding, i.e., not finding a pathogenic mutation and having a completely clear subject. Unambiguous, completely transparent expressions should be used. For example, 'absence/presence of a mutation,' 'with/without clinical meaning,' or 'the presence of a pathogenic-mutation is not-shown.' Which terms are preferred may depend on the knowledge level of both the messenger and the receiver of the information: molecular and clinical geneticists may speak among each other about 'positive/negative DNA-test results,' but this may be translated to a patient as 'presence/absence of a mutation.'

The term no-pathogenic DNA-test result is also paralleled by the term pathogenic DNA-test result in literature and in practice. The linguistic relationships between these two terms are clear and balanced, in contrast with most DNA-test result terminology, which has unclear unbalanced terminological relationships. For instance, the term unclassified variant might imply the use of the term classified variant in literature; however, the term classified variant is seldom used.

The most important argument to use either variant of uncertain clinical significance or NPDTR is that patients should be able to understand and correctly interpret genetic terms and communicate them reliably to their relatives. In our opinion, the patient's perception should be the gold standard in developing medical terminology, because experts often seem to overestimate the layperson's knowledge and understanding of specialist knowledge (212,213). Focus groups of both patients and professionals could be a useful tool for establishing a sound genetic terminology (cf.214) that could be the basis for unified guidelines. Both clinicians, molecular geneticists, and patients should be involved in the practical formulation of understandable unambiguous model test reports (215). We also suggest to confirm the results of our theoretical and literature study in praxis by analyzing how DNA-test results are actually and differently formulated by molecular geneticists, clinicians, patients, and others.

Chapter 3

The counselees' view of an Unclassified Variant in BRCA1/2: *recall, interpretation, and impact on life*

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Abstract

Background

Unclassified Variants (UVs, variants of uncertain clinical significance) are found in 13% of all BRCA1/2 mutation analyses. Little is known about the counselees' recollections and interpretations of a UV, and its psychosocial/medical impact.

Method

Retrospective semi-structured interviews with open questions and five-point Likert scales were carried out in 24 counselees who received a UV-result 3 years before (sd=1.9).

Results

Sixty-seven percent (16/24) recalled the UV-result as a non-informative DNA-result; 29% recalled a pathogenic result. However, 79% of all counselees interpreted the UV-result as a genetic predisposition for cancer. Variation in recall and interpretation were unexplained by demographics, cancer history of themselves and relatives, and communication aspects of UV-disclosure. Sixty-seven percent perceived genetic counseling as completed, whereas 71% expected to receive new DNA-information. Although most counselees reported that UV-disclosure had changed their lives in general little, one in three counselees reported large changes in specific life domains, especially in surveillance behavior and medical decisions. Ten out of 19 participants who interpreted the UV as pathogenic had undergone preventive surgery, against none of the 5 counselees who interpreted the UV as non-informative.

Implications

Counselors and researchers need to address discrepancies between the counselees' factual recall and their subjective interpretation of non-informative BRCA1/2-test results.

1. Introduction

1.1. Background

After the identification of the BRCA1- and BRCA2-genes in hereditary breast and ovarian cancer, many mutation analyses have been carried out in women at increased risk (7,8). The lifetime cancer risk associated with a BRCA-mutation is 39 to 85% for breast and 11 to 63% for ovarian cancer. The risk for affected women to develop a second primary breast cancer is 40 to 60% (17,196-198).

1.2. Need for certainty

The prime motives for women at increased breast/ovarian cancer risk to apply for genetic counseling and DNA-testing, are reducing uncertainty and the need for information on surveillance and surgery (1,5). Therefore, many counselees expect to receive a clear-cut result, either a positive (pathogenic) or a negative (no-mutation) result (216,217). However, about 90% of the test-applicants receive a DNA-test result, which does *not* provide certainty: the communicated cancer risks and risk management options remain solely based on family history, and DNA-testing is not offered to relatives. There are two kinds of uncertain DNA-test results: uncertain negative results (often called 'inconclusive') and uncertain positive results ('Unclassified Variant', or 'Variant of Uncertain Clinical Significance' detected). In uncertain negative results, no mutations have been found in affected counselees at high risk of breast and/or ovarian cancer. This accounts for about 80% of all BRCA1/2-results, and includes the possibility of a still undetected BRCA1/2 mutation (false negative) or a mutation in a yet unknown gene (30). Uncertain positive variants (UVs) are mutations for which the effect on the protein function of the gene is still unknown. These account for 12.5% of all BRCA1/2-results, that is, 32% of all BRCA1 and 53% of all BRCA2-mutations (30).

1.3. The genetic-uncertainty-causes-distress hypothesis

Some authors hypothesize that disclosure of uncertain DNA-results evoke more psychological distress than certain DNA-results, because these results would maintain uncertainty about the genetic status (86,199,218,219,220).

Some studies confirmed that individuals with an uncertain negative result experience more distress than those who received a certain negative result (i.e. exclusion of a known familial mutation), but less distress than those who received a certain positive result (a pathogenic mutation) (163,200,204,221,222). In two studies, uncertain positive results (UV) did not seem to cause more psychological distress than a certain DNA-result (223,224).

Authors do not always explicate their hypothesis that uncertainty about the genetic status would cause distress. Two studies mentioned the continuation or rise of uncertainty after UV-disclosure compared to the pre-disclosure situation (224,225), and two studies reported uncertainty to be an important issue for UV-counselees (225,226).

The hypothesis that genetic uncertainty causes distress seems too general and unspecific (227,228) to find high distress levels due to uncertain DNA-results and the genetic counseling in general (74,229). *Firstly*, other variables should be included, such as: demographics, family history and cancer history (222,230,231), coping style and personality (232,230,233,234), illness perception (235,87), and family communication (236). *Secondly*, the question could be raised whether current general distress measures are sensitive enough to measure the subtle impact of DNA-results on the various life domains of the counselees. Moreover, the contextual meaning of these measures is not always clear, due to the absence of comparison with other relevant stressors and reference groups (74). *Third*, the hypothesized relationship between uncertain DNA-results and distress assumes that the counselees correctly understand and interpret these DNA-results as uncertain.

1.4. The distorted perception hypothesis

Several authors hypothesize (86,201,237,238) that counselees may incorrectly interpret uncertain results as certain results. Uncertain negative results may be interpreted as the certain absence and UVs as the certain presence of a genetic predisposition for cancer. The few studies available on this issue mainly operationalized distorted perception as perceived cancer risks. Some researchers found that counselees mentioned lower risks of developing cancer, a lower likelihood of being a mutation carrier or the absence of genetic predisposition at all, after disclosure of uncertain negative results (compared to pre-disclosure measures) (199-202), but others did not (86,204). Studies on UV-disclosure seem to indicate that counselees have a good comprehension of UVs (223), and perceive their cancer risks as unchanged, lower (223,225) or increased (226) compared to pre-disclosure.

These contradictory results may be caused by a too limited operationalization of distorted perception. For this reason, some researchers broadened their focus to both cognitive and affective risks (239,240). However, risk perception itself is just one part of a complex interpretation process in which several intertwined aspects of genetic counseling are perceived and interpreted. One of these aspects is the counselees' possibility to correctly understand and recall the DNA-test result. Rao et al. (226) reported that only 41% of the counselees correctly reproduced a UV-test result as an uncertain positive variant while 59% reproduced a certain negative result. However, it remains unclear whether this 59% did not correctly reproduce the factual UV-information counseled to them or whether they subjectively interpreted this UV-information differently. The present study will disentangle these two aspects of objective recollection and subjective interpretation.

1.5. Research questions

I. To examine the distorted perception hypothesis, our study focuses on possible differences between factual recall and subjective interpretation in a retrospective group of UV-counselees. II. To explore other clinical relevant aspects of the interpretation process, we measure: subjective understanding, perception of the completion of genetic counseling, expectation to receive a UV-result, and uncertainty about the familial occurrence and possible genetic cause of cancer. To study the genetic-uncertainty-causes-distress hypothesis, we measure: (III) the impact of UV-disclosure upon life in general and upon several specific life domains, and (IV) the influence of other variables on the recall, interpretation, impact and distress: sociodemographics, *counselor*'s communication, family history, cancer history.

These questions are relevant because communication of DNA-results that do not provide complete certainty will be more common in the future, due to the proliferation of humane disease data bases (241). Moreover, the question is raised by clinicians whether low penetrance genes should be communicated to counselees or not.

2. Methods

2.1. Participants

The current retrospective study is part of a larger Dutch multicenter study on UVs, approved by the Medical Ethical Committees of the participating centers. Participants were adult women with breast and/or ovarian cancer who had received a UV-test result in the BRCA1 or BRCA2 gene at the Department of Clinical Genetics of the Leiden University Medical Center (LUMC) or the VU University Medical Center Amsterdam (VUMC) in the period 1998-2006. For reasons of relational nature, genetic testing was incidentally offered to unaffected relatives of counselees with a UV-test result.

2.2. Genetic counseling

Genetic counseling for breast/ovarian cancer consists of two or three sessions: intake, disclosure of the DNA-test result, and sometimes disclosure of new genetic information. In the intake session, moderate risks (20-30%) or high risks (>30%) for developing recurrent breast and ovarian cancer were communicated based on pedigree information, and corresponding surveillance options were discussed. Prophylactic surgery of breasts and/or ovaries was discussed, given that a PM would be found. A counselee was tested for BRCA1/2 in case of clinically presumed hereditary breast and/or ovarian cancer, when the mutation detection rate was about 10%, or if cancer was diagnosed at a relatively young age (242,29). Although figures are unavailable, some *counselor*s discussed the possibility of finding a UV-result. UV-test results were communicated face-to-face in the DNA-disclosure

session and afterwards summarized in a letter. In a third session, some counselees received information on the pathogenic (4/24) or non-pathogenic (5/24) meaning of their UV based on the latest scientific developments.

2.3. Instruments

Information on age, children, marital status, educational level, employment, time elapsed since UV-disclosure, and cancer history was collected in a questionnaire. The number and percentage of affected relatives were extracted from the medical files.

Information about the counselor's communication was derived from the *counselor*'s summary letter by means of content analysis: relevant aspects about DNA-disclosure were identified and coded as variables, and scored per letter; only variables mentioned in more than 10% of all letters (n≥3) were included.

Interview: In addition to an interview with open questions, 5-point Likert scales were used. Independently from heredity information about the familial occurrence and possible genetic cause of cancer, we asked specific questions about the UV-result and its meaning.

Firstly, the participants were asked to recall what the *counselor* had communicated about the UV-result (*'factual recall'*). *Secondly*, they were asked to describe their thoughts and feelings about the UV-result (*'subjective interpretation'*). Their perceived level of understanding of the UV-result was measured with a 5-point Likert scale, ranging from 1, no understanding, to 5, very good. Another item measured their perceived level of uncertainty about the heritability of cancer in general,i.e. familial occurrence and possible genetic cause of the cancer, based on both the DNA-result and the pedigree information (range from 1, 'very uncertain', to 5, 'very certain').

Three yes/no-questions were asked: 'before receiving the DNA-test result, had you taken into account the possibility of receiving this DNA-test result?', 'do you expect to receive more information about this DNA-test result?' and 'is the genetic counseling process completed in your opinion?'

The relative amount of *general* changes in life due to genetic counseling was studied by three questions: 'how much has your life changed due to (a) genetic counseling, (b) having cancer, and (c) other life events?' The level of life changes was rated on a scale ranging from 1 ('no change') to 5 ('complete change'). Similarly, the changes in eight *specific life domains* after UV-disclosure were assessed. The domains, constructed on the basis of our clinical experience, were: preventive risk management (surveillance and preventive mastectomy and/or oophorectomy), general physical complaints, body experience, emotional well-being, social relationships, personality, coping with uncertainty, and existential view on life (e.g. meaning of life, values, religion). *Finally*, participants were asked to attribute the changes in each domain on a scale ranging from 'completely due to genetic counseling' ('1') to 'completely due to the development of cancer' ('5').

2.4. Categorization and statistical analyses

Two psychologists (JV, AJ) categorized the answers on factual recall and subjective interpretation after UV-disclosure independently. Three categories emerged: non-informative, the DNA-test result is uncertain, meaning that no information can be given about cancer risks; pathogenic, a PM is found, implicating high cancer risks; and non-pathogenic, no mutation is found, implicating no/low cancer risks. Interrater reliability was good (Cohen's Kappa: .84, $p<.001$). Categorization of differences was discussed until agreement was reached.

Frequencies and t-tests were calculated. The influence of covariates (*counselor*'s letter, cancer history, family history, demographics) on outcome variables (factual recall, subjective interpretation, general impact, impact on life domains) was calculated. Because of the small n, non-parametric test statistics (Fisher's/X^2 exact, Mann Whitney U, Kruskal Wallis) were used for analysis.

3. Results

3.1. Patient characteristics

Forty-nine out of 64 eligible women who had received a UV-result were asked to participate in this study. Reasons for exclusion were: 6 had died due to cancer, 6 had received comorbid cancer diagnoses, and 3 were psychologically too stressed. Twenty-four out of the 49 women consented and completed participation; 19 persons declined, 4 did not respond, one died before having the interview, and one withdrew because of unresolved feelings (response rate: 51%).

Nineteen out of 24 participants (75%) had cancer, and five were unaffected. Seventeen had breast cancer, 5 had ovarian cancer, and 10 of them had recurrent cancer. Mean time between UV-disclosure and participation was 3.0 years (sd: 1.9 years)(see Table 1). Relevant communication aspects in the *counselor*'s summary letter were identified (see Table 2). Fifteen women were only communicated a UV-result, but four women later learned about the definitive pathogenic meaning of their UV and 5 about the non-pathogenic meaning. On all outcome measures, no significant differences were found between these groups.

Table 1. *Demographic variables and cancer history (n=24)*

Variable	N (%)	Mean (Sd)
Medical center		
LUMC	18 (75)	
VUMC	6 (25)	
Demographic variables		
High school or higher	13 (54)	
Being married	21 (88)	
Having children	21 (88)	
Having daughters	18 (75)	
Age (years)		54.4 (11.8)
Time since counseling (years)		3.0 (1.9)
Development of first cancer		
before counseling	18 (75)	
after counseling	1 (4)	
Kind of cancer, time since diagnosis (years)		
Breast cancer	17 (71)	9.5 (8.5)
Ovarian cancer	5 (21)	5.5 (6.4)
Recurrent breast cancer	4 (17)	11.7 (8.5)
Recurrent ovarian cancer	1 (4)	2.0 (--)
Metastatic cancer	5 (21)	9.3 (7.9)
Pedigree characteristics: mean number of relatives (% of all relatives who is affected); mean number of affected relatives (sd)		
1st degree relatives	6.8 (.21)	1.42 (1.1)
2nd degree relatives	17.2 (.15)	2.58 (2.1)
3rd degree relatives	10.7 (.07)	0.75 (1.2)

Figure 1. *The counselees' recollections and the subjective interpretations of the UV-disclosure*

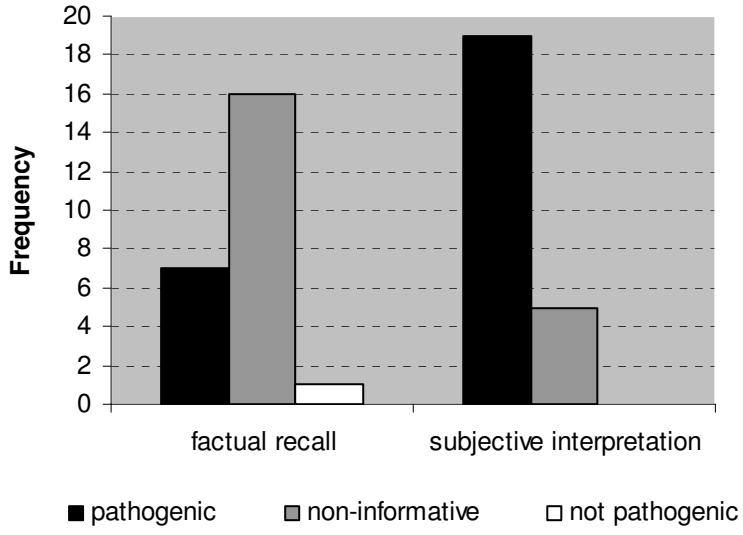

Table 2. *Communication variables in the counselor's letter; scored if mentioned in more than three (10%) of all letters*

Variables	N (%) of letters
Heredity information based on family history	7 (29.2)
Meaning of UV	
non-pathogenic	1 (4.2)
non-informative	20 (83.3)
possibly pathogenic	3 (12.5)
Meaning of family history	
not suspicious for hereditable cancer	2 (8.3)
hereditable cancer not mentioned	12 (50)
suspicious for hereditable cancer	10 (41.7)
This UV has been found before	3 (12.5)
Formulation of UV	
mutation	13 (54.2)
deviation	9 (37.5)
change	1 (4.2)
variant	1 (4.2)
Risk management options as if pathogenic BRCA results	21 (87.5)
Continuation of DNA-research	20 (83.3)

3.2. Question 1: factual recall and subjective interpretation of UV-disclosure

Factual recall - Sixteen participants (67%) recalled that the *counselor* had communicated the UV as a 'non-informative mutation', 7 (29%) recalled that a PM was communicated, and 1 (4%) recalled that she had received a non-pathogenic test result. (see Figure 1, Table 3)

Subjective interpretation - Nineteen women (79%) interpreted the UV-test result as carrying a PM, and only 5 women (21%) interpreted this as being non-informative.

Associations - The subjective interpretation of most women (17/24) was different from their factual recall about the UV-disclosure session; recall and interpretation were only identical in 7/24 persons, and were not associated with each other (X^2=4.02, df=2, p=.013).

Table 3. *Table of outcome variables regarding counseling sessions: n (%)*

Variables	Intake	UV-disclosure	Disclosure of new information about the UV-test result	
			pathogenic	non-pathogenic
total	24	24	3 (1 missing)	5
factual recall of genetic counseling	0 (0)	7 (29)	2 (67)	0 (0)
pathogenic	3 (13)	16 (67)	0 (0)	1 (20)
non-informative	0 (0)	1 (4)	0 (0)	5 (100)
not pathogenic	21 (87)	0 (0)	0 (0)	0 (0)
not mentioned				
subjective interpretation of genetic counseling	15 (63)	19 (79)	2 (67)	1 (20)
pathogenic	5 (21)	5 (21)	0 (0)	5 (100)
non-informative	3 (12)	0 (0)	0 (0)	0 (0)
not pathogenic	1 (4)	0 (0)	0 (0)	0 (0)
not mentioned				
subjective understanding of genetic counseling †	4.37 (71)	4.37 (82)	5.00 (0)	3.33 (1.21) *
subjective uncertainty about the heredity ‡	3.21 (1.18)	2.92 (1.39)	5.00 (.00) *	2.67 (1.5)

** Significant Kruskal-Wallis tests between columns at .05-level. † Means and sd. of scores on a 5-point scale ranging from 1 (no understanding) to 5 (complete understanding). ‡ Means/ sd. on a 5-point scale ranging from 1 (complete uncertainty) to 5 (complete certainty)*

3.3. Question 2: subjective level of understanding, expectations, completion of genetic counseling, and uncertainty

Participants reported to understand the UV-result well (m=4.37, sd=0.82). Fifteen participants (64%) reported to have realized beforehand that they might receive a UV-test result. Seventeen participants (71%) perceived genetic counseling as completed. However, 16 (67%) expected to receive new genetic information in the future (with the inclusion of 9 women who perceived the counseling as completed). Participants reported that UV-disclosure neither provided certainty nor uncertainty about the heredity, i.e. familial occurrence and possible genetic cause, of the cancer (mean=2.92, sd=1.39).

These outcome measures were unrelated with recall and interpretation, except for expectations and uncertainty. Those who *recalled* UV-disclosure as pathogenic instead of non-informative, less often expected to receive new information (n=17, n=4; t=2.58, df=16.00, p<.05). Participants who *interpreted* UV-disclosure as pathogenic instead of non-informative, perceived more uncertainty about the heredity (t=3.33,df=19.81, p<.005).

3.4. Question 3: the impact of disclosure of test results

Most participants reported that disclosure of the DNA-test result had changed their lives 'little' (m=2.48, sd=1.1.6), but 25% mentioned large life changes. Other life events, like change of work, cancer diagnosis or death of relatives, had changed their lives 'little' (m=2.95, sd=1.5), but having cancer had changed their lives significantly the most (m=3.95, sd=.97; respectively t=4.86, df=20. p<.001; t=2.96, df=20, p<.01). (see table 4)

The counselees who *recalled* the UV-test result as pathogenic instead of non-informative, reported significant less life changes due to cancer (respectively m=2.80, sd=.84; m=4.40, sd=.63; t=-4.64, df=18, p<.001) and did *not* report differences between life changes due to cancer and due to other life events (respectively m=2.75, sd=0.96; m=2.50, sd=1.05; m=3.10, sd=1.50). No association was found between the interpretation of the UV-test result and life changes due to DNA-disclosure.

All life domains had changed little after UV-disclosure, and these little changes were not related with recall and interpretation. Existential view on life and risk management changed the most (means = 3). However, in all life domains, about one in three counselees reported large changes (i.e., score higher than 3), especially in existential view on life (46%) and risk management (42%). All changes were attributed to having cancer and not to DNA-test results (i.e., attribution scores lower than 3), with exception of 'preventive risk management' (m=4.33, sd=.98) and 'body experience' (m=3.14, sd=2.38); changes in 'physical complaints' were as much attributed to the development of the cancer as to the DNA-result (m=3.0,sd=2.5).

Ten participants (41.7%) had undergone prophylactic surgery within one year after UV-disclosure, and before receiving new genetic information. Seven persons completely attributed this decision to UV-disclosure, and three attributed this to cancer developments

as well. Regarding recall of UV-disclosure, no differences in surgical decisions were found between those recalling pathogenic or non-informative information. However, ten out of 19 participants (53%) who *interpreted* the UV as pathogenic had undergone preventive surgery, against none of the 5 counselees who interpreted this as non-informative (X^2=4.51, df=1, p<.05; Fisher's p <.05).

Table 4. *Table of outcome variables: completion, expectations, impact on life*

Variable	N (%)	Mean (sd)
genetic counseling feels as being completed	17 (71)	
expectation of new genetic information	16 (67)	
changes in life *		
due to cancer		2.48 (1.16)
due to genetic counseling		3.95 (.97)
due to other life events		2.95 (1.50)
mean changes of life domains, number of counselees reporting changes larger than 3 *		
existential view on life	11 (46)	3.00 (1.53)
risk management (surveillance, operations)	10 (42)	2.75 (.156)
body experience	8 (33)	2.43 (1.41)
personality	8 (33)	2.46 (1.41)
emotional well-being	8 (33)	2.42 (1.44)
coping with uncertainty	7 (29)	2.21 (1.41)
relationships	6 (25)	2.21 (1.38)
physical complaints	4 (16)	1.67 (1.17)

** Means/sd. on a 5-point scale ranging from 1 (no changes in life) to 5 (complete change of life)*

3.5. Question 4: cancer history, family history and summary letter

Neither significant associations nor significant moderation effects were found between covariates and outcome measures. Only one aspect of the summary letter was associated with the outcome measures: the seven persons who received heredity information (familial occurrence/possible genetic cause of the cancer) on the basis of the pedigree during the UV-disclosure session, reported a higher certainty about the heredity of the cancer (m=3.86, sd=.69; m=2.38, sd=1.26; t=-2.91, df=21, p=<.01), interpreted the UV more often as non-informative (71% instead of 10.5%; X^2=15.34, df=1, p<.001, Fisher's p<.001), and did less often choose for BSO (46.6% instead of 100%; X^2=5.93, df=1, p<.05, Fisher's p<.05).

4. Discussion

4.1. Conclusions

The results from our study suggest the existence of two parallel processes in reaction to the disclosure of uncertain positive DNA-test results, Unclassified Variants, in BRCA1/2: factual recall and subjective interpretation. These processes are not associated with each other, and differences could not be explained by the counselee's cancer history, family history or sociodemographics. Medical decisions seem to be more associated with subjective interpretation than with factual recall.

4.2. The distorted perception hypothesis

This study gives evidence for and against the hypothesis that the perception of many counselees of uncertain DNA-test results is distorted. On the one hand, most counselees correctly *recalled* a UV-test result as non-informative. They also understood correctly that UV-disclosure does neither provide certainty nor uncertainty about the familial occurrence and possible genetic cause of cancer. On the other hand, perception was sometimes distorted: a minority incorrectly *recalled* UV-disclosure as disclosure of a pathogenic result, and most counselees *interpreted* the UV-test result as a genetic predisposition for cancer.

The most striking result was that the majority of the participants recalled UV-disclosure as non-informative, but interpreted this as pathogenic at the same time. When confronted with this paradox, some participants said that they 'knew better' than the *counselor*. Question is whether this interpretation has to be judged as distorted perception? If the medical meaning of the UV-result is the gold standard, then the answer is 'yes'. However, if one focuses on other elements in the counseling and the psychological coping process of the counselee, the answer may be 'no'.

The counselees' interpretation may be influenced by information, textual and framing effects (243), or accentuation of certainties in genetic counseling (31).
For instance, some counselees seem to base their interpretation of the DNA-result on their family history, because counselees interpreted the UV more often as non-informative when the *counselor* also communicated heredity information based on the pedigree during the UV-disclosure session.

Interpreting the UV-result as a pathogenic result could be a functional way to cope with uncertain information. *Firstly*, it lowers the cognitive load by transforming the grey colour of the DNA-test result into black or white. However, this does not explain the direction of the dichotomy, i.e. the main interpretation of a UV as pathogenic. This direction may be explained by a mental strategy of 'playing safe' by assuming the worst-case scenario. Another explanation is that many counselees have a strong wish for certainty and control (1,5,244,245). Recalling and interpreting the UV-test result as pathogenic, and undergoing prophylactic surgery, do fulfil this need.

These findings contradict previous studies, also from our center, showing that counselees have a good understanding of uncertain DNA-test results (196,85,223), but confirm one study which showed that many counselees recalled the UV-result as a pathogenic result (226). Further research should examine whether the 'distortion' in the interpretation of a UV-result stems from additional counseling elements, or from motives to cope with uncertain information.

4.3. The genetic-uncertainty-causes-distress-hypothesis

Some authors suggested that disclosure of uncertain DNA-test results might evoke uncertainty and distress (86,199,218,237). However, we found no associations between UV-disclosure, uncertainty and distress.

Disclosure of a UV-test result was neither associated with the feeling of certainty nor with the feeling of uncertainty about the heredity of the cancer. Several counselees explained this feeling of being in the middle of certainty and uncertainty as the balanced sum of the uncertainty of their factual recall and the certainty of their subjective interpretation.

The *general* impact of UV-disclosure on the counselee's life is limited; the cancer history has a much greater impact. This underlines Coyne's suggestion to frame the impact of genetic counseling in the context of other stressors and reference groups (74). However, this does not imply that the psychological impact of UV-disclosure can be ignored. About one in three counselees reported large changes in all *specific* life domains. Moreover, the interpretation of UV-results as pathogenic explains the decision for preventive surgery of breasts and/or ovari. These results emphasize that genetic counseling and scientific research about uncertain DNA-results should focus on identifying vulnerable subgroups that experience a strong impact of uncertain DNA-results.

4.4. Medical consequences

Factual recall and subjective interpretation of UV-disclosure were not equally important for medical decision making. Recall was not associated with preventive options and surgical decisions, but interpretation was. Participants interpreting the UV as pathogenic more often decided in favour of prophylactic surgery, without *counselor*'s advice. They opted for this operation to minimize their risk of developing a second primary breast and/or ovarian cancer. This decision could not be explained by cancer history, family history or sociodemographics, except for the communication of heredity information based on family history which was associated with more frequent adnectomy. The participants mainly attributed their decision for prophylactic surgery to UV-disclosure, meaning that the UV-result and not their family/cancer history motivated this decision.

The decision for prophylactic surgery is medically not completely unjustified because these women have cancer and belong to a high risk family. Their pedigree seems to suggest that either the UV-result will turn out to be pathogenic or that a PM exists in a yet unknown gene. On the other hand, it is medically incorrect to attribute surgery decisions to a non-informative DNA-result: a UV-result is itself not a medical indication for prophylactic surgery of healthy tissue. These medical decisions should be based on family history and personal cancer history. However, variation in the participants' medical decisions were not explained by family history and cancer history, but were explained by the subjective interpretation of the UV-result as pathogenic.

Other studies confirm that counselees opt for prophylactic surgery after UV-disclosure (163,246,247), and that surgery decisions after genetic counseling are not only determined by factual information (248). Studies in other fields also suggest that people react to risk information using two conceptually different processes: a more cognitive-deliberational system and a more intuitive-emotional system (82-84). The latter system seems to signal whether an individual is OK or in danger, and if the risk is interpreted as dangerous, the individual is motivated to behaviourally protect himself or herself.

UV-dislosure might be a difficult process for *counselor*s. On the one hand, the laboratory report does not indicate a certain genetic predisposition for cancer. On the other hand, the pedigree suggests heredity, and many counselees expect or ask for genetic certainty. Consequently, *counselor*s should be aware of transferring their own ambivalence toward the test results to the counselees.

We suggest some communication guidelines. In addition to the explanation that the family history of cancer may for instance be caused by coincidence or by a mutation in yet unknown genes, *counselor*s should help counselees to assimilate this information at a cognitive level in order to prevent incorrect understanding and interpretation. *Counselor*s could ask counselees to summarize the information, and to verbalize their interpretation, like 'how do you feel about your cancer risk?' Subsequently, medical decisions should not be based on a UV-test result, but on the total context. *Counselor*s should also keep in track

with the counselees' understanding and interpretation in follow-up sessions, to make corrections if necessary.

4.5. Limitations and conclusions

Before-mentioned interpretations should be read cautiously, because this study is limited by the small number of participants, the retrospective design, and the absence of validated questionnaires, e.g. about psychological distress. Mean age and mean education level seem to be a little higher than in previous studies in our center (222). We have addressed these limitations in an ongoing nation-wide prospective and retrospective study with control groups, validated measures and the inclusion of relatives.

This study shows that UV-results might evoke a factual recollection of an uncertain result, and a subjective interpretation that implies a genetic predisposition. Although a UV-result has a relatively small impact on their lives compared to cancer, counselees report that they base their risk management decisions mainly on their interpretation of the UV-test result.

Chapter 4

Perceiving cancer-risks and heredity-likelihood in genetic-counseling:

the analysis of the counselees' recollections and interpretations of BRCA1/2-test results

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Abstract

Background

Previous studies on the counselees' perception of DNA-test results did not clarify whether counselees were asked about their recollections or interpretations, and only focused on patients' own risks and not on the likelihood that cancer is heritable in the family. We tested differences and correlations of four perception aspects: recollections and interpretations of both cancer-risks and heredity-likelihood.

Method

In a retrospective study, women tested for BRCA1/2 on average 5 years ago completed questionnaires about their perception. Participants had received an unclassified-variant (n=76), uninformative (n=76) or pathogenic-mutation (n=51) result in BRCA1/2. Analyses included t-tests, correlations and Structural-Equation-Modelling.

Results

The counselees' perception showed to consist of four distinctive phenomena: recollections and interpretations of cancer-risks and of heredity-likelihood. This distinctiveness was suggested by significant differences between these perception-variables. Moderate to strong correlations were found between these variables, suggesting that these differences between variables were consistent. The relationships between these variables were not influenced by actually communicated DNA-test result, sociodemographics, medical and pedigree information, or framing of cancer-risk questions. The largest differences between recollections and interpretations were found in the unclassified-variant group and the smallest in uninformatives. Cancer-risks and heredity-likelihood correlated least in the pathogenic-mutation-group. Communication of ambiguous genetic-information enlarged the differences.

Discussion

To understand the counselees' perception of genetic-counseling, researchers should study recollections and interpretations of cancer-risks and heredity-likelihood. Genetic-counselors should explicitly address the counselees' recollections and interpretations, and be aware of possible inaccuracies.

1. Introduction

1.1. Background

Since the identification of the BRCA1 and BRCA2-genes in hereditary breast and ovarian cancer, many mutation analyses have been performed in women at increased risk. Usually, a BRCA1/2-test is performed in case of clinically presumed hereditary breast and/or ovarian cancer, primarily in an affected woman with a mutation detection rate of about 10%, or if she has developed cancer at a relatively young age (15).

A genetic-counselor may communicate six pieces of information about the BRCA1/2-result to an index-patient/proband. 1. The DNA-test result category, i.e. a pathogenic mutation in the breast and ovarian cancer–predisposition genes BRCA1 and BRCA2 (PM), Uninformative-Result, i.e. no mutation in the BRCA1/2 genes (UR), or Unclassified-Variant/variant-of-uncertain-clinical-significance, i.e. the contribution of BRCA1/2 sequence variants to cancer risk remains largely undefined (UV). 2. The likelihood that cancer is heritable in the family (i.e. heredity-likelihood; see below). 3. Contralateral breast- and ovarian-cancer-risks for the affected proband 4. Breast- and ovarian-cancer-risks for healthy relatives. The communicated heredity-likelihood and cancer-risks are based on the DNA-test result and cancer-history of the proband and relatives. In UV/UR-families, the counselor communicates cancer-risks mainly based on the pedigree. 5. Options for surveillance and/or preventive surgery (prophylactic bilateral mastectomy, PBM, and bilateral salpingo-oophorectomy, PBSO) of counselees and relatives. 6. Counselees are advised to communicate this DNA-test result to their relatives.

1.2. Assumptions in the literature

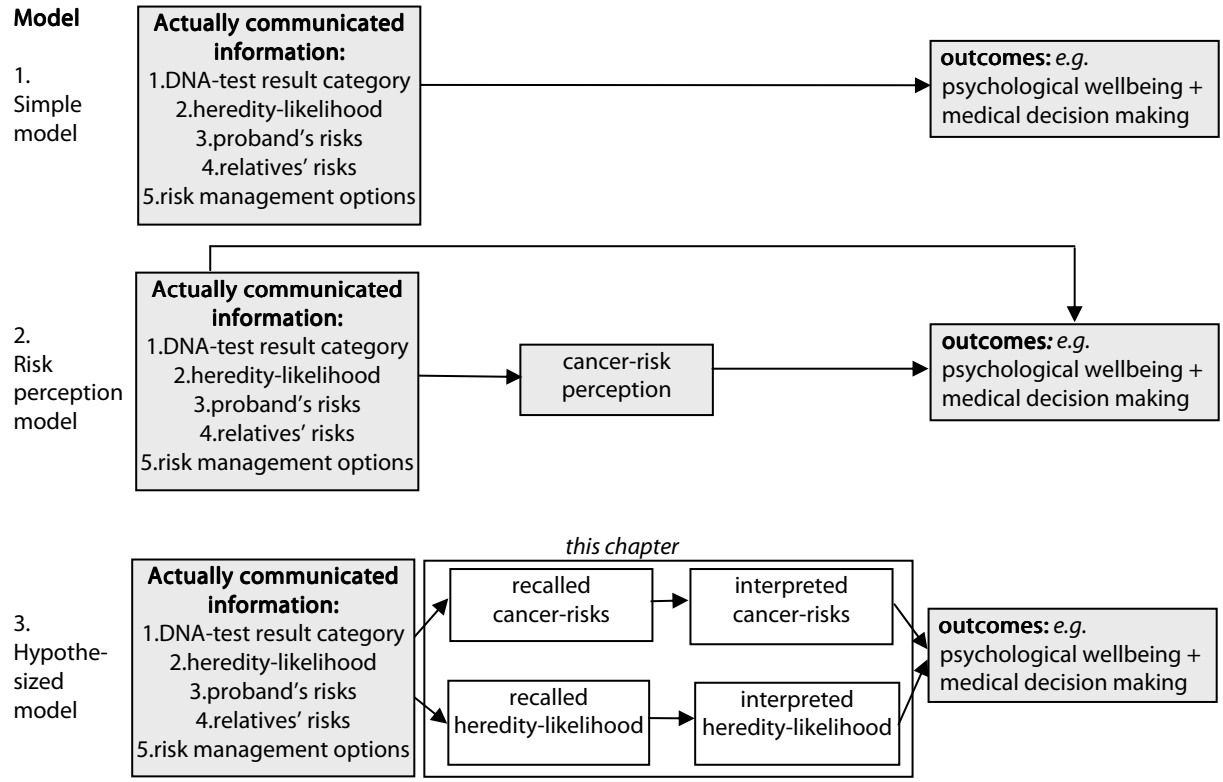
Many studies assume that the communication of a BRCA1/2-result has a direct impact on the counselees' psychological well-being and medical decisions. However, reviews suggested that such studies yielded inconsistent results and showed that DNA-test results rarely predict psychological impact (66,68,70, 71,76). For instance, several studies described disclosure as a stressful experience, mainly after PM communication, but studies differed in distress levels and decrease over time (169,182,199,321,249-255).(figure 1-1)

Not finding a clear direct relationship between the actually communicated DNA-test result and impact-measures caused researchers to turn their focus towards the counselees' perception of the BRCA1/2-results. Recent studies suggested that the receipt of a DNA-test result only has an indirect impact on the counselees' lives, via the mediation of the counselees' perception of cancer-risks (64). Results of these studies seem to be more consistent, and perception-variables explain more variance of the impact-variables. It is suggested that the higher the perceived cancer-risks reported by a counselee are, the more distressed she is (164,169,177-179,199,256-258), the more often she decides to

undergo surgery, and the better she adheres to surveillance of breasts and ovaries (177,257,259-262). Thus, perceived risks are suggested to be better predictors of the impact of genetic-counseling than objective information (cf.77-79). (see figure 1-2) Despite their improved explanation of the impact of genetic-counseling, these risk-perception studies still vary widely in their outcomes, and perception-variables only partially explain the impact (77-79). For example, reported accuracy of perception varies (239): after genetic-counseling, 4% to 37% of all counselees have an improved more accurate risk-perception, but 3-70% of all counselees overestimate their cancer-risks, and 0% to 85% of the counselees perceive their cancer-risks accurately (171-182,249,250,263). Therefore, several authors suggest that risk-perception has been operationalized too simply in previous studies. New measures should be developed to measure the perception of DNA-test results as a multidimensional construct (84,239,264), including personal interpretations of the DNA-test result, risk figures and inheritance (94,239,265).

In this chapter we test four new perception-measures: recollections and interpretations of both cancer-risks and heredity-likelihood (see figure 1-3). We only focus on the counselees' perception of their own cancer-risks and of heredity-likelihood. Other perception-variables are assumed to be implicitly included in these variables: e.g. understanding of the DNA-test result category may be reflected in the counselees' perception of cancer-risks and heredity-likelihood; perception of relatives' risks may overlap with perceived heredity-likelihood.

Figure 1. *Models (1,2) in previous studies and Complex Model of Genetic Counseling (3), as hypothesized in this chapter; in this chapter, only the relationships between recollections and interpretations, and between cancer-risks and heredity-likelihood are studied*



1.3. Recollections and interpretations

In previous qualitative studies, we asked patients to describe their risk to develop cancer (203,239). Several counselees indicated that they did not know whether our question referred to the actually communicated risks, or their own interpretation of that information. They spontaneously mentioned a discrepancy between their recollection of the objective risk, and their personal interpretation of that risk, e.g.: 'I know that the genetic-counselor communicated 'A', but I'm convinced 'B' is true. Therefore, I trust B when considering surgery and surveillance.'

We hypothesize that the counselees' perception combines the processes of recalling and interpreting the communicated DNA-test results. Recollection concerns memorizing and reconstructing what the genetic-counselor has said, Interpreting concerns giving meaning to the recalled information, for instance, by subjectively selecting, weighing and evaluating the information, e.g. as a form of meaning-based coping (131) or by integrating genetic-information in one's identity (61). Both recollections and interpretations may be biased due to selective listening and heuristic information-processing (cf.83), but interpreted information is more deeply processed and more connected with personal meanings than recalled information.

Previous perception studies may have yielded inconsistent results, because they measured either the counselees' recollections (174,172,182,263) or interpretations (169,257,266), or were unclear about this. Most studies operationalized the counselees' perception with aspecific formulations such as: 'what DNA-test result did you receive?' and 'what are your cancer-risks?' Other researchers asked counselees about their cognitions and feelings of risks (87,239,267), in line with the dual-process theory (81-84): 'how do you estimate your chance of developing breast cancer?'; 'what do you feel your chance is?' These questions are also ambiguous, because it is unclear whether the requested estimations are recollections of what the counselor had told, mere subjective interpretations of the communicated risks, or a combination of both. It is also unclear whether feelings about chance include only subjective interpretations or also factual recollections. Due to these ambiguous formulations, different counselees may have given different answers, which may have subsequently caused failure of predicting the impact of DNA-testing.

1.4. Cancer-risks and heredity-likelihood

In our qualitative study, many counselees differentiated between their own cancer-risks and the likelihood that cancer is heritable in the family: 'My own risks do not worry me; I have already had cancer. I worry about the heredity of cancer in my family, and its meaning for my children and sister.' (unpublished part of 203/study in chapter 3).

The sole use of the counselees' perception of their own cancer-risks may explain the poor prediction of outcomes in previous perception studies for two reasons. *Firstly*, only about 10% of all BRCA1/2-test results in affected cases prove pathogenic, and provide exact risk information for the counselee and her relatives. In all other cases, cancer-risks are mainly based on the pedigree and on cancer history, age at onset, and segregation analyses. In these cases, cancer-risks are in general not communicated.

Secondly, one of the main motivations of counselees to request genetic-testing is receiving information about their relatives' cancer-risks (1,5) and heredity-likelihood, i.e. the likelihood that cancer in the family is heritable. Heredity-likelihood is either communicated on the basis of the PM's, or of the pedigree in case of UV's/UR's.

1.5. Research questions

The purpose of this study was to examine relationships between recollections and interpretations, and between perceived cancer-risks and heredity-likelihood. 1.Is the counselees' recollection of genetic-information different from their interpretation? 2.Do recollections predict interpretations? Finding a difference does not imply that variables are unrelated; we expect that recollections and interpretations are correlated, because interpretations are reflections on the counselees' previous recollections of what was communicated. 3.Do counselees perceive heredity-likelihood and cancer-risks differently?

4.Are perceived cancer-risks and heredity-likelihood correlated? We expect these to correlate, because both cancer-risks and heredity-likelihood are high when PM is found, and both are lower in case of UV/UR. 5.Do the answers to the previous questions differ between PM, UV and UR?

2. Method

2.1. Population

This retrospective study was part of a larger Dutch multicenter study on UV's in BRCA1/2 approved by the Medical Ethical Committees of the participating centers. We sent an invitation letter with consent-form and questionnaire to all affected and unaffected adult first tested individuals with cancer (index-cases) from families with intermediate or high risk breast/ovarian-cancer who had received a BRCA1/2-test result in the period 1998-2008 at the Departments of Clinical Genetics of the Leiden University Medical Center, Maastricht University Medical Center, University Medical Central Groningen, and VU Medical Center Amsterdam. We included all index-patients (PM, UR, UV). All results had been communicated face-to-face and summarized in a letter for the counselee. We explicitly asked counselees to not re-read the letter before filling-in the questionnaire.

2.2. Instruments

We asked questions about the counselees' recollections and interpretations of cancer-risks, and of pedigree-based and test-based heredity-likelihood. Questions had been developed in a previous study (203). The presented perception-questions only focused at breast-cancer-risks, because 96% of all counselees reported that they did not experience their ovarian-cancer-risks as strongly influencing their lives, and experienced breast-cancer-risks as relatively more influential.

Recollection-questions were introduced as follows: 'we ask you to recall what your counselor has actually communicated to you, regardless of your own ideas and feelings'. Recollections of cancer-risks were measured by the question 'what cancer-risks did your counselor tell'. Recollections of heredity-likelihood based on the DNA-test result were asked as 'according to your counselor, what does the DNA-test result mean for the likelihood that the cancer in your family is heritable?' Recollections of heredity-likelihood based on the pedigree were asked as: 'regarding your pedigree, what did your counselor communicate about the likelihood that cancer in your family is heritable?' We asked participants to describe their 'own current thoughts and feelings about cancer-risks, test-based and pedigree-based heredity-likelihood regardless of what the counselor has communicated'.

In line with other studies (66,70,164), we asked counselees to rate cancer-risks and heredity-likelihood on a 7-point scale (not likely-very likely). People often use such broad

categories to translate detailed risk information (268-270). We also asked counselees to recall/interpret cancer-risks in percentages, as frequently used (171-182). These answers were excluded from analyses, because most counselees (153/204) did not recall the communicated percentage. Many (69/204) recalled or interpreted cancer-risk of precisely 50% (cf.216,217), indicating stochastic uncertainty; this caused a lack of variation in the counselees' perceptions of percentage-risks.

2.3. Statistical analyses

Analyses with non-parametric tests (not shown here) did not show large differences with parametric tests, and did not lead to different conclusions. Therefore parametric tests are presented. Effect sizes were described with Cohen's d, correlations and standardized B.

Question 1: Differences between recollections and interpretations of cancer-risks and of heredity-likelihood. were tested using the percentage of exact agreement as well as t-tests. Question 2: To test whether recollections predict interpretations, both regarding cancer-risks and heredity-likelihood, we used path-analyses/Structural Equation-Modeling, SEM, in LISREL 8.80 (271) (see final model in figure 2) (e.g.272,273). For evaluation of model fit, the matrix of discrepancies (i.e., the matrix of residual variances and covariances) was investigated (cf.274). We report the overall X^2 statistic with the associated p-value, and the root mean squared error of approximation (RMSEA) (275). Indicative of good model fit are a non-significant X^2 statistic ($\alpha>.05$), and RMSEA $\leq .06$ (276).

Question 3: Differences between cancer-risks and heredity-likelihood, regarding recollections or interpretations, were tested with t-tests. Question 4: The correlations between perceived cancer-risks and heredity-likelihood were estimated using SEM. Question 5: To assess differential effects for different DNA-test results, a separate multi-group analysis was performed using SEM.

Previous studies have been criticized for not taking into account the general context of genetic-counseling (68,74). Therefore, we corrected analyses for several covariates suggested by literature: actually communicated genetic-information (163,164); elapsed time since DNA-test result disclosure (70,165); experiences with cancer and death in the family (164,166-168); cancer history and treatment (35,68,69,71,73); age, education, having-children, religion (164,170); risks measured in percentages (171-182). Most covariates did not significantly influence the relationships between recollections and interpretations, and between cancer-risks and heredity-likelihood. An exception to this was additional explanation provided by the genetic-counselor in summary letters to counselees, such as 'future research may detect a pathogenic-mutation' and using the non-neutral terms 'mutation' or 'deviation'; each explanation predicted a larger difference between recollections and interpretations, but correlations were small (std.ß's<.20,p's<.01). Therefore, covariates are not presented. (see table 1)

Table 1. *Description of moderators/covariates (all showed to be not significant)*

Moderator/covariate name		Operationalisation [1]
actually communicated DNA-test result (derived from medical files, and confirmed by letters summarizing the counseling sessions sent to counselee)	result category[2]	Pathogenic-mutation (PM), unclassified-variant (UV), uninformative-result (UR)
	heredity-likelihood[3]	Low, medium, high
	counselee's cancer-risks[3]	Breast cancer(%); ovarian cancer(%)
	relatives' cancer-risks[3]	Breast cancer(%); ovarian cancer(%)
	counselee's options[3]	Mastectomy (PBM), oophorectomy (PBSO), frequency breast and ovarian surveillance, breast self-examination
	additional explanation in letter to counselee[3]	Explanation of genetics; possible involvement of non-BRCA1/2-genes; indications of heredity (pedigree, etc); future research may show pathogenic-mutation in non-BRCA1/2-genes; DNA-testing is not 100% sensitive to detect changes; use of the term 'deviation' or 'mutation' instead of the neutral term 'change' or 'variation'; autosomal dominant gene; about 10% of all breast-cancer cases are possibly caused to a heritable cause; about 10% of all heritable breast-cancers are detectable by BRCA1/2-testing; in non-pathogenic cases, mentioning of cancer-risk and/or heredity-likelihood if the DNA-test result had shown to be pathogenic
elapsed time	[3]	Years since disclosure of: DNA-test result; 1st, 2nd cancer diagnosis, metastases
pedigree (derived from medical file)	[3]	N and % for: affected, unaffected, deceased 1st degree, 2nd degree, 3rd degree, all relatives
	Cancer[3]	Breast-cancer, ovarian-cancer, unaffected, metastases
medical history	before testing[3]	Mastectomy (PBM), oophorectomy (PBSO),
	after testing[3]	Mastectomy (PBM), oophorectomy (PBSO), chemo, radio, hormone, other
	current [3]	Chemo, radio, hormone, other
sociodemographics	[3]	Age, marital status, having children, educational level, religious, employed
counselees' perception (other than already measured)	result category[3]	Recollection of category (multiple choice question); accuracy of perception (PM: 97%; UI: 97%; UV:75%)
	proband's ovarian cancer-risks[3]	Recollection and interpretation of ovarian-cancer-risks (1-7 Likert scale)
	relatives' cancer-risks[3]	Recollection and interpretation of breast-cancer and ovarian-cancer-risks (1-7 Likert scale)
perceived own cancer-risks in %	[4]	Recollection and interpretation of breast-cancer-risks (%)

[1]Variables with two levels were included as dichotomous variables (e.g. female 0, male 1); other variables were included on ratio/linear-level. [2]Covariate was included in analyses of research questions 1 and 3 by doing separate t-tests for each category; covariate was included in analyses of research questions 2 and 4 by doing multi-group analyses in SEM; [3]All analyses are corrected for the influence of the DNA-test result category. Inclusion of these covariates in SEM-analyses was impossible due to multicollinearity and small n; therefore, regression and correlation analyses were performed (cf.figure 2), in which one covariate at a time was used in predictions: recalled risks →interpreted risks; recalled heredity-likelihood →interpreted heredity-likelihood; partial-R between recalled cancer-risks and recalled heredity-likelihood, between interpreted cancer-risks and interpreted heredity-likelihood. Covariate was included in analyses of research questions 1 and 3 by doing a separate t-test, for each level of each covariate (e.g. 2 levels: mastectomy; no mastectomy). Covariate was included in analyses of research questions 2 and 4 by doing Separate ANCOVA (analyses of covariance) and partial correlation analyses, including each covariate; [4] Covariate was included in analyses of research questions 1 and 3 by doing separate t-tests, categorical-risks replaced by %-risks. Covariate was included in analyses of research questions 2 and 4 by doing separate ANCOVA; categorical-risks replaced by %-risks.

3. Results

3.1. Study sample

Four-hundred-and-twelve out of 484 eligible probands who had received a DNA-result in the past were invited to participate in our study. Reasons for exclusion were: being deceased, comorbid diagnoses or psychopathology (resp. 7%; 4%; 4%). Half of the probands consented (206/412=50%), and completed the questionnaire. Sixty-three women declined; 145 did not respond. Cited reasons for decline were: being too ill to participate, unresolved feelings, and lack of motivation (resp. 12%; 8%; 7%).

All participants were women, because DNA-testing had not been performed in male probands in our sample; this is in line with the Dutch policy of first testing individuals with breast and/or ovarian cancer from high-risk families, and the large majority of them are women. Mean time elapsed since DNA-test disclosure was 5 years (sd=2.0 yrs). UV was communicated to 76 women (36.8%), UR to 77 women (37.4%), and PM to 53 women (25.8%). As part of standard counseling, letters summarizing the disclosed genetic information were sent by the genetic counselor to all participants; exact cancer-risk information was written in 126 out of the 204 letters (62%), the remaining 78 letters did not include risk information. Most participants (n=57; 28%) belonged to a family with high cancer-risks (30 to 40%), 11(5%) belonged to a family with intermediate cancer-risks between (20-30%) and 10(5%) belonged to a family with low cancer-risks (10-20%). Mean communicated cancer-risk on the basis of the pedigree differed significantly between UV(m=32%,sd=14.0), UR(m=25%,sd=14.7) and cancer-risks on basis of PM(m=64%,sd=10.6).

The majority had a diagnosis of cancer before genetic-counseling (88.3%). Hundred-seventy-three had breast cancer (83.9%), 16 ovarian cancer (7.7%), 5 both (2.0%), and 34 metastatic cancer (16.7%). Table 2 presents sociodemographics. Medical variables and sociodemographics were equally distributed among specific groups of DNA-test results, participants, decliners and non-responders.

3.2.1. Question 1: recollections and interpretations differ

Tables 3-4 and figure 2 show the results for the counselees' recollections and interpretations of (1) cancer-risks and (2) heredity-likelihood.

Counselees recalled intermediate cancer-risks of 4.5 on a 7-point Likert scale (sd=1.4) and interpreted intermediate risks of 4.0(sd=1.6). Recollections and interpretations differed significantly t=-3.4,p<.01,d=.33), except for UR(p>.05,d=.13). 38% of all counselees recalled and interpreted cancer-risks identically, 31% interpreted cancer-risks as higher and 30% interpreted cancer-risks as lower compared to their recollections of the cancer-risks. (see table 3).

Counselees recalled an intermediate heredity-likelihood of 4.4(sd=1.4), and interpreted this as 4.8(sd=1.3). Recollections and interpretations differed significantly (t=-2.4,p<.05,d=.30), except for PM(p>.05,d=.00). 48% of all counselees recalled and interpreted heredity-likelihood identically, 35% interpreted this as higher, and 17% interpreted this as lower compared to their recollections.

Table 2. *Overview of sample*

Variable	N (%)	Mean(sd)
DNA-test result		
time since disclosure (years)		5.0 (2.0)
unclassified-variant(UV)	76(36.8)	
uninformative-result(UR)	77(37.4)	
pathogenic-mutation(PM)	53(25.8)	
Development of first cancer		
after counseling	22(10.8)	
before counseling	182(89.2)	
Cancer, time since diagnosis (years)		
breast cancer	173(83.9)	9.0 (7.6)
ovarian cancer	16(7.7)	11.0 (8.9)
metastatic cancer	34(16.7)	6.0 (4.9)
Percentage of female relatives with breast and/or ovarian cancer		
1st degree relatives	37(37.0)	
2nd degree relatives	5(16.0)	
3rd degree relatives	2(10.0)	
Demographic variables		
age (years)	54.0(10.5)	
being married	164(79.6)	
having children	189(91.7)	
having daughters		1.2(0.8)
having sons		1.0(0.8)
high school or higher		73(35.4)

3.2.2. Question 2: recollections predict interpretations

Figure 2 provides the path model testing all relationships simultaneously: The statistical model provided a good fit to the data (χ^2 (2) =.77, p=.67; RMSEA=.00). The recollection of cancer-risks and heredity-likelihood predicted their interpretation (resp. $\beta_{\text{cancer-risks}}$= .47, $\beta_{\text{heredity-likelihood}}$= .76), resulting in respectively medium and strong explained variances (22%; 58%).

Figure 2. *Statistical model for the recollections and interpretations of cancer-risks and heredity-likelihood: coefficients for the final Structural Equation Model, and for simple regression analyses (shown between brackets)*

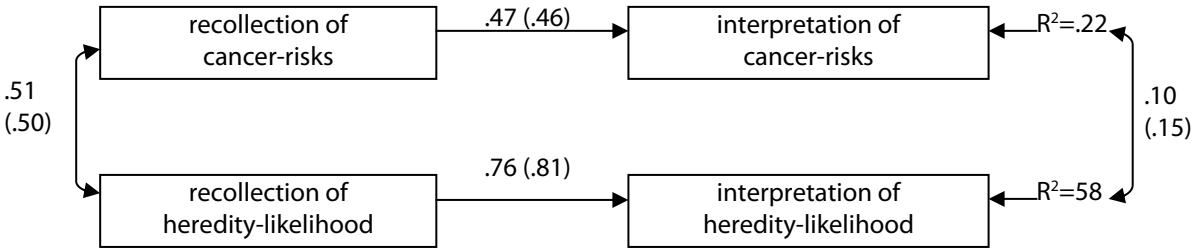


Table 3. *Results of recalled versus interpreted cancer-risks*

DNA-test result	recalled cancer-risks		interpreted cancer-risks		Relationship between recalled and interpreted cancer-risks			
	M (sd)	Median	M (sd)	Median	t (p)	% recalled > interpreted	% recalled < interpreted	% recalled = interpreted
mean	4.5 (1.4)	4	4.0 (1.6)	4	-.34 (.007)	30.4	31.3	38.3
unclassified variant	4.5[a] (1.5)	4	4.6[a] (1.8)	4	-3.25 (.002)	11.4 [a]	47.7 [a]	40.9 [a]
uninformative	3.8[a] (1.1)	4	3.4[a] (1.2)	4	ns	29.6 [a]	29.6 [a]	40.7 [a]
pathogenic mutation	4.9[a] (1.2)	5	4.2[a] (1.7)	5	2.94 (.005)	43.2 [a]	15.9 [a]	40.9 [a]

M=mean, sd=standard deviation, R=correlation, t=t-test, p=p-value, n.s.=not significant. Recollections and interpretations of cancer-risks measured on 7-points scale, ranging from 1 to 7 (not–complete at risk). A= significant column differences between scores of a measure between DNA-test results (Kruskal-Wallis, p<.01).

3.2.3. Question 3: cancer-risks and heredity-likelihood differ

Overall, counselees recalled intermediate cancer-risks of 4.5 (sd=1.4), and heredity-likelihood of 4.4 (sd=1.4; d=.07). Counselees interpreted intermediate cancer-risks of 4.0 (sd=1.6), and significantly higher heredity-likelihood of 4.8 (sd=1.3) with a strong effect size (t=-3.6, p<.0001, d=.55) (see tables 3-4). No differences were found between the DNA-test results (p (K-W)>.05).

3.2.4. Question 4: cancer-risks and heredity-likelihood correlate

The path model of question 2 also showed that recollection of cancer-risks and heredity-likelihood correlated quite strongly (R=.51, p<.001).

Table 4. *Results of recalled and interpreted test-based versus pedigree-based heredity-likelihood*

DNA-test result	recalled heredity-likelihood		interpreted heredity-likelihood		Relationship between recalled and interpreted heredity-likelihood			
	M (sd)	Median	M (sd)	Median	t (p)	% recalled > interpreted	% recalled < interpreted	% recalled = interpreted
mean	4.4 (1.4)	4	4.8 (1.3)	5	-2.41 (.017)	17.2	35.1	47.8
unclassified-variant	4.6[a] (1.6)	4	4.6[a] (1.6)	4	-4.85 (.000)	23.5	32.4	44.1
uninformative	3.0[a] (1.5)	3	3.4[a] (1.9)	4	-1.68 (.009)	20.8	41.5	37.7
pathogenic mutation	6.9[a] (0.4)	7	6.9[a] (0.4)	7	ns	5.9[a]	5.9[a]	88.2[a]

M=mean, sd=standard deviation, R=correlation, t=t-test, p=p-value, ns=not significant. Recollections and interpretations of heredity-likelihood measured on 7-points scale, ranging from 1 to 7 (not-certainly heritable). A= significant column differences between scores of a measure between DNA-test results (Kruskal-Wallis, p<.01)

3.2.5. Question 5: DNA-test result category

To investigate differences between UV, PM, and UN, a multigroup structural equation model was formulated and tested simultaneously in each group. This model provided a reasonably good fit to the data (χ^2 (6) =11.11, p=.09; RMSEA =.11). Although RMSEA was slightly higher than the threshold, X^2 was still non-significant. Results showed that in all three DNA-test result groups, recollections predicted interpretations of cancer-risks as well as heredity-likelihood. Recalled cancer-risks explained a smaller percentage of variance in interpreted cancer-risk for UV-counselees than PM/UR-counselees (resp. 13%, 31% and 40%). Recalled heredity-likelihood explained a small percentage of variance in interpreted heredity-likelihood in UV, a larger percentage for PM/UR (resp.9%, 45%, 42%). Correlations between cancer-risks and heredity-likelihood were small for PM and large for UV/UR (resp. .09, .54, .50) (see table 5).

Table 5. *Results of structural equation modeling*

	overall	unclassified-variant	pathogenic-mutation	uninformative-result
Prediction of interpreted cancer-risks by recalled cancer-risks (R^2)	.22	.13	.31	.40
Prediction of interpreted heredity-likelihood by recalled heredity-likelihood (R^2)	.58	.09	.45	.50
Correlation between cancer-risks and heredity-likelihood	.51	.54	.09	.50

4. Discussion

4.1. Conclusions

In previous studies on the impact of genetic-counseling on counselees' lives, risk-perception has been operationalized in unspecific ways. It remained unclear whether counselees reported their recollections or interpretations of the DNA-test result. Moreover, counselees were asked about their own cancer-risks, and not about heredity-likelihood, which is indicated by many counselees as a major reason to undergo DNA-testing (1,5). The use of these presumably non-valid perception-measures may explain the relatively small effect sizes and inconsistencies between those studies. We have showed that at least four new perception-measures are required to explain the impact of DNA-testing on the counselees' lives (277).

Our research shows a significant differentiation between perceived recollection and interpretion of the DNA-test result, and between cancer-risks and heredity-likelihood. This differentiation was not influenced by covariates: the actually communicated DNA-test result, elapsed time, experience with their own and relatives' cancer and treatment, sociodemographics and measuring cancer-risks in percentages.

4.2. Explanations

We suggest two explanations why most counselees differentiated between recollections and interpretations, and why almost half of them did not.

Firstly, counselees may interpret the DNA-test result differently compared to their recollection, due to ambiguity or uncertainty of the genetic-information (cf. 81-84). For instance, differences were larger when UV's were communicated Differences increased slightly when genetic-counselors provided additional explanations, e.g. 'future research may detect a pathogenic-mutation in yet unknown genes'. Counselees may react to such uncertain/ambiguous information by processing information in dual ways (cf.81-84).

Secondly, personality traits may explain individual differences. For instance, more autonomous individuals may be more likely to create their own interpretation, independently from their recollections of the counselors' message. Autonomous counselees may rely more on their own opinion and use other sources of information (suggested by unpresented a-posteriori analyses).

We did not only find differences, but also large correlations between recollections and interpretations, and between perceived cancer-risks and heredity-likelihood. This could be caused by the high risks and heredity-likelihood in PM. These strong/significant correlations may also suggest that the differences between the perception-variables were consistent, i.e. most counselees interpreted cancer-risks higher than in their recollections, which caused significant differences and strong correlations.

4.3. DNA-test results

Differences were found between the three groups of DNA-test results. First, PM-carriers recalled and interpreted heredity-likelihood identically, probably due to a ceiling effect caused by high cancer-risks communicated by the genetic-counselor. Cancer-risks were reported as much lower than heredity-likelihood, and correlations were small; this was not due to post-testing preventive mastectomy (PBM) or oophorectomy (PBSO), as shown by covariate-analyses.

Second, in line with our previous study (203), the counselees' interpretation of UV's was poorly predicted by their recollections. Thus, they did not base their interpretations on their recollections of what the genetic-counselor had communicated. This could be caused by the ambiguity of UV's.

Third, in UR-counselees, we found relatively strong correlations and lack of differences between both recollections and interpretations, and strong correlations between cancer-risks and heredity-likelihood. Thus, the four perception-variables were more strongly related than in PM/UV. This suggests a more balanced perception compared to the more 'dissociated' perception in PM/UV.

4.4. Limitations

The retrospective design of this study only allowed exploratively measuring the long-term impact of genetic-counseling, and not the short-term impact. Causal relationships were suggested, but could not be conclusively determined. Other limitations are: only genetic-counseling for BRCA1/2 was included, genetic-information was communicated in a non-standardized way, and the retrospective design only allowed studying the short-term impact of DNA-test result disclosure in patients who had been diagnosed with cancer with a mean of 9 years ago. We focused only on the counselees' recollections and interpretations of breast cancer risks, and not of ovarian cancer risks; new studies should also focus on the latter. We used four single items to measure the counselees' perception, which does not exclude the possibility that these variables are indicators of one underlying construct measured by slightly different scales; therefore, multiple-item-measures should be developed. We suggest developing more elaborate models on the basis of longitudinal studies, including several genetic-diseases.

4.5. Implications

We suggest genetic-counselors to avoid communication of ambiguous information, which counselees could misinterpret. Our study suggests that counselors should especially be careful in communicating UV's and additional explanations.

Many counselees had forgotten the communicated numerical risks, which suggests that cancer-risks are better measured in verbal categories than in percentages. This finding could explain the finding of previous studies that the use of percentage-scales causes

larger differences between subjective and objective lifetime risk than categorical scales (77). Moreover, percentage-risks were often interpreted as 50%, i.e. black-or-white: 'either I get cancer or I do not get cancer' (216,217). Categorical scales may be more in line with the counselees' own way of describing risks (239), and seem to lead to less overestimation (278). For these reasons, we suggest that future researchers operationalize cancer-risks as categories. Currently, empirical evidence lacks for the efficacy of the communication of risks in percentages, despite the genetic-counselors' preference for this communication format (279). More intervention studies are required to examine which format (categories, percentages, proportions, or a combination) lead to the most accurate perceptions, least distress and best informed medical decisions of counselees (243,280,281).

Genetic-counselors may contribute to diminishing the discrepancy between the counselees' recollections and interpretations, by tailoring the information to the counselees' own interpretations. Before and after disclosing DNA-test results, genetic-counselors could explicitly ask counselees about their perception of cancer-risks, heredity-likelihood, possible causes and treatments of cancer, reason for requesting DNA-testing, and possible medical consequences, and they could adjust their communication to these perceptions of counselees (cf.264). It has shown that counselees may indeed benefit from tailoring risk-information, as suggested by a pilot study showing that explicitly discussing the counselees' pre-existing interpretations increases the accuracy of their risk-perception (282).

Counselors could ask counselees to rephrase the DNA-test result in their own words, and reflect on their ideas and feelings, such as: 'did you expect this result?'; 'how do you feel about this result?'; 'what does this mean for your relatives?'; 'do you believe this result?'; 'what medical decisions are you reflecting upon after having received this information?' Additional explanation may be formulated in the terminology and metaphors of the counselees.

In summary, counseling should be a personal, two-directional/reciprocal process including tailoring of risk-information (283). This is also in line with Edwards et al (284) who suggested that the positive effects of interventions in genetic-counseling are not explained by the information elements, but by the emotional and psychosocial elements of these interventions. Thus, genetic-counseling should not only focus at merely disclosing genetic-information such as cancer-risks, but also on the context and personal meaning (i.e. interpretation) of this information for counselees (38). Intervention studies may focus on improving interaction and tailoring of information to the needs and personality of the counselees. This may help counselees to make well-informed medical decisions, improve well-being and communication to relatives.

Chapter 5

Opening the psychological black box in genetic-counseling:

The psychological impact of DNA-testing is predicted by the counselees' perception, the medical impact by the pathogenic or uninformative BRCA1/2-result

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Abstract

Background

It has been hypothesized that the Outcomes of DNA-testing (O) are better predicted and/or mediated by the counselees' Perception (P) than by the actually communicated genetic-Information (I). In this study we aimed at quantifying the effect that perception has in genetic counseling for hereditary breast/ovarian cancer.

Methods

204 women who had previously been tested for BRCA1/2, participated in a retrospective questionnaire study; 93% had had cancer. Communicated Information (I) consisted of cancer-risks and BRCA1/2-test result category: unclassified-variant(n=76), uninformative(n=76), pathogenic mutation(n=51). Four perception-variables (P) were included: the counselees' recollections and interpretations of both the cancer-risks and the likelihood that the cancer in their family is heritable. The outcome-variables (O) included life changes, counselees' medical decisions, BRCA-related self-concept, current psychological well-being, and quality-of-life. Bootstrap mediation analyses determined whether relationships were direct (I→O or P→O) or indirect through the mediation of perception (I→P→O).

Results

The actually communicated pathogenic mutation and uninformative-result directly predicted medical-decisions (I→O), i.e. intended and performed surgery of breasts/ovaries. All other outcomes were only directly predicted by the counselees' perception (recollection and interpretation) of their cancer-risks and heredity-likelihood (P→O), or this perception mediated the outcome (I→P→O). However, this perception was significantly different from the actually communicated cancer-risks (I→P). Unclassified-variants were inaccurately perceived (mostly overestimated); this misperception predicted both psychological outcomes and radical medical decisions.

Discussion

Genetic-counselors need to explicitly address the counselee's interpretations and intended medical decisions. In case of misinterpretations, additional counseling might be offered. Communication of unclassified-variants needs special attention given the pitfall of overestimation of risk.

1. Introduction

1.1. Background

Women with breast and/or ovarian cancer may request for genetic-counseling, to receive information about their own cancer-risks, their relative's cancer-risks and the likelihood that cancer is due to a genetic susceptibility in the family. A DNA-test may be performed, when there is a probability of at least 10% to find a pathogenic-mutation. Detection of such a mutation implies that cancer is very likely to be heritable in the family and that both the probands' and the relatives' cancer-risks are high. Cancer-risks and heredity-likelihood are based on the pedigree, when unclassified-variants or uninformative-results are detected (203,285).

How does disclosure of a DNA-test result influence the counselees' lives? It is often assumed that the communication of DNA-test results directly predict outcome-variables, such as the counselees' wellbeing and medical decisions. However, research data are inconsistent (66,68,76). Several authors suggest that this is caused by the fact, that the outcomes are mediated by the counselees' inaccurate perception of the DNA-test result. Indeed, studies including perception-measures seem to yield more consistent results and also explain more of the variance of the outcome measures (e.g.163,177,180,257).

Therefore we propose that, to fully understand the process and impact of genetic-counseling, three aspects of counseling should be studied simultaneously: 1.actually communicated genetic-information by the genetic-counselor; 2.the counselees' perception of the communicated information, and 3.impact of both on the counselees' lives (cf. figure 1). In previous studies (203,285), we subdivided the counselees' perception in four variables: the counselees' recollections and interpretations of both cancer-risks and heredity-likelihood. Recollection is the counselees' memory of the genetic-counselor's communication. Interpretation concerns the personal selection, weighting and evaluation of that information. Cancer-risks concern the counselees' own risk to develop cancer (again). Heredity-likelihood is the likelihood that cancer is due to a genetic susceptibility in the family, i.e. heredity. In pathogenic-mutation families, heredity is very likely. In non-pathogenic families, heredity-likelihood is based on the pedigree.

1.2. The current study

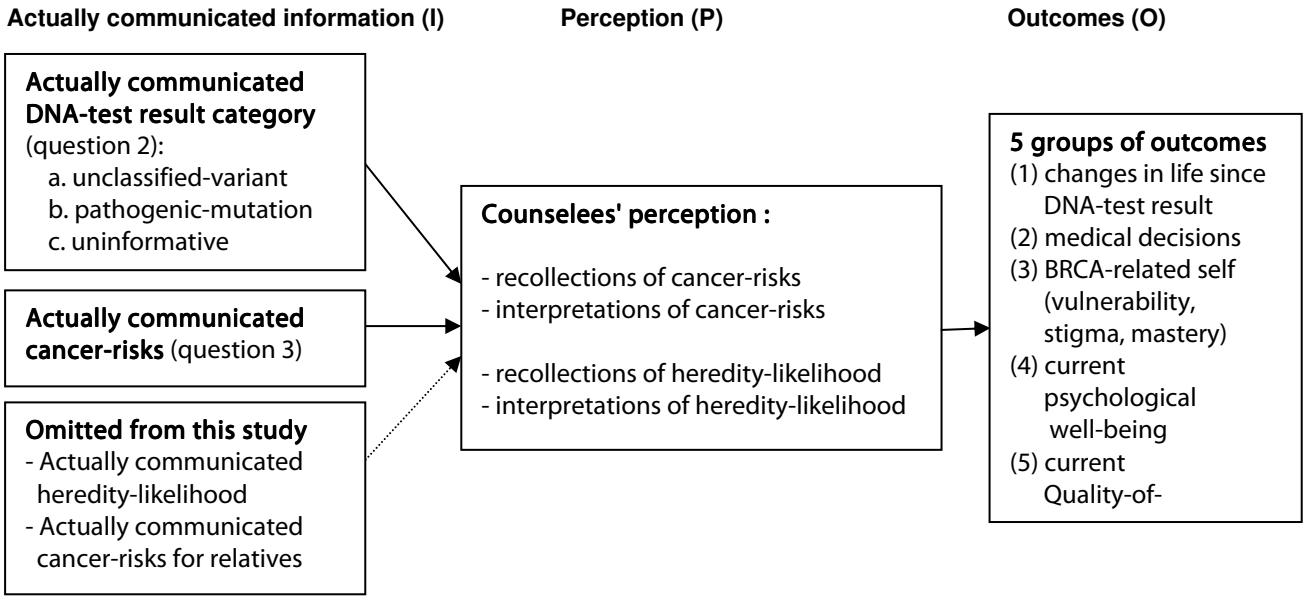
Our previous studies in chapters 3 and 4 only covered the counselees' perception. In current study, we tested all three parts of the model, by means of three research questions. *The first question* was: do counselees recall and interpret cancer-risks and heredity-likelihood differently from what the genetic-counselor has actually communicated to them? In line with previous studies, we hypothesize that most counselees have an inaccurate perception, i.e. they recall and interpret the cancer-risks and heredity-likelihood differently from what has actually been communicated.

We also wanted to test the influence of the actually communicated information on the outcomes. A genetic-counselor may communicate the proband's cancer-risks, the DNA-test-result category (unclassified-variant, UV, pathogenic-mutation, PM, uninformative result, UR), and information about heredity-likelihood and relatives' cancer-risks. In this study, we focused on communicated cancer-risks and heredity-likelihood, because the communication of other information was not consistently reported in the medical files.

Therefore, *the second question* was: are the outcomes of DNA-test result disclosure (a) directly predicted by the actually communicated cancer-risks, (b) mediated by the counselees' perception, or (c) only predicted by the counselees' perception? We hypothesize that the outcomes are either (c) solely predicted by the counselees' perception, or (b) the counselees' perception completely mediates the impact that the cancer-risks have on the outcomes. Thus, cancer-risks do not or do only indirectly predict the outcomes.

The third question was: are the outcomes of DNA-test result disclosure (a) directly predicted by the actually communicated DNA-test result category, (b) mediated by the counselees' perception, or (c) only predicted by the counselees' perception? We have three hypotheses. First, the actual communication of a pathogenic-mutation directly predicts medical outcomes, because this DNA-test result leads to unequivocal management options. Second, the actual communication of a UR is expected to directly predict the outcomes, because URs are expected to evoke false reassurance and therefore have a direct large negative impact on medical decisions (e.g. less likely to undergo preventive mastectomy, PBM) (86). Third, UVs are expected to not predict the outcomes, because this result often evokes ambiguity and uncertainty, which may cause an inconsistent or no direct impact on outcomes; the counselees' perception is expected to be the sole predictor in these cases (203).

Figure 1. *Complex Perception Model of Genetic Counseling including outcomes*



2. Method

2.1. Participants and procedure

We sent a questionnaire to all adult female probands affected and unaffected with breast and/or ovarian cancer who had received a DNA-test result in BRCA1/2-genes in the period 1998-2008 at the Departments of Clinical Genetics of the Leiden University Medical Center, the Maastricht University Medical Center, the University Medical Central of University Groningen, or the VU Medical Center Amsterdam. Counseling included an intake-session in which the counselees' cancer-risks had been calculated and communicated on the basis of the pedigree. A session followed in which the DNA-test result had been communicated. Only in case of PMs, the counselees' cancer-risks had been communicated on the basis of the DNA-test result. In non-pathogenic-results, pedigree-based cancer-risks remained unchanged. Women, who had already had breast cancer, had been communicated risks for contralateral breast cancer. Surveillance/surgery-options had been communicated on the basis of communicated risks and medical history. All results had been communicated face-to-face, and letters summarizing the sessions had been sent to the counselees. See more details elsewhere (203).

2.2. Instruments

Instruments included information actually communicated by the genetic-counselor, the counselees' perception, and outcome-variables (see table 1).

Information actually communicated by the genetic-counselor was derived from medical files and summary letters sent to counselees: DNA-test result category (PM, UR, UV) and (recurrence) cancer-risks for the counselee. Perception-variables are described previously (203,285). Outcomes included five domains, to create a broad picture.

1.Changes in eight life domains are developed elsewhere (203,285). To reduce the number of variables, we used principal component analyses with varimax-rotation, and decided the number of factors on basis of the eigenvalues, scree plot, explained variance (VAF/R^2), interpretability, and Cronbach's alpha. Two factors were shown: psychological changes and physical-medical changes. Both scales were normally distributed and had high reliability (resp. VAF=.90, .88; α=.83, .63).

2.Medical decision-making consisted of post-testing preventive surgery (mastectomy and/or bilateral salpingo-oophorectomy, BSO), and of the counselees' intention to undergo surveillance and/or surgery of breasts and/or ovaries within the next six months.

3.BRCA-related self concept was developed by Esplen (75) in PM-carriers, and consists of the subscales ‘stigma’, ‘vulnerability’ and ‘mastery’ (resp. 8, 5 and 4 items) and shows good reliability and validity. Consistency of translation was confirmed by formal translation into Dutch and satisfactorily backtranslation into English. Factor analyses yielded two factors with good reliability, normal distribution, and identical items as Esplen's original scale: stigma and vulnerability. Mastery was removed due to low reliability. Inter-item correlations of factors were larger than .65; reliability was good (resp. VAF=.86, .88; α= .81, 77).

4.Current psychological wellbeing included validated Dutch translations of the Hospital Anxiety and Depression Scale, Lerman's Cancer Worry Scale and Impact of Events Scale Revised (286). Norm groups are unavailable, but we regard depression, anxiety, avoidance and intrusions as clinically relevant when mean scores are 'much' or 'often' (resp.11, 11, 26, 24).

5.Quality-of-life was measured in general regarding the last two weeks (287), physically, psychologically and socially.

Table 1. *Overview of instruments and items*

		scaling	Items
Information communicated by the genetic-counselor	*cancer-risks*	cancer-risks in %, rescaled to a 1-7 scale to match counselees' recollections and interpretations	
	DNA-test result	scored as 3 dummy-items: communicated (1)/not (0)	pathogenic-mutation, unclassified-variant, uninformative
counselees' perception	*recollections of cancer-risks and heredity-likelihood*	2 items (1-7 scale: not-complete at risk/heritable)(203)	(1) what is your risk to develop cancer (again), according to your genetic-counselor; (2) according to your genetic-counselor, what does your pedigree/DNA-result mean for the likelihood that cancer is heritable in your family (pathogenic-mutation: result-based; other DNA-results: pedigree-based)
	interpretations of cancer-risks and heredity-likelihood	2 items (1-7 scale: not-complete at risk/heritable)(203,285)	What are your own thoughts and feelings about: (1) your risk to develop cancer (again), (2) the likelihood that cancer is heritable in your family.
outcomes	*changes in life since DNA-test result*	8 items (1-7 scale: not-completely changed). Explorative factor analyses showed two factors(203,285)	(1) psychological changes including the items: emotional well-being, social relationships, personality, coping with uncertainty, existential view on life. (2) physical-medical changes including the items: preventive risk management, physical complaints, body experience
	medical decision-making	(1) 2 dichotomic items; (2) 6 items (1-7 scale: very little-very much intention)	(1) mastectomy (PBM) or bilateral salpingo-oophorectomy (PBSO) after DNA-test result or not; (2) intention to undergo: breast self-examination, breast or ovaries surveillance by physician, mammography/MRI, PBM, PBSO
	BRCA-related self-concept *current psychological well-being*	17 items (1-7: completely disagree-completely agree), confirmative factor analyses showed two factors(75) (1) Hospital Anxiety and Depression Scale: 14 items (1-4 scales), 2 scales; (2) Lerman's Cancer-Worry Scale: 4 items (1-4 scale), 1 scale; (3) Impact of Events Scale: 15 items (1-4 scale), 2 scales; (4) intention to ask for psychological help within 6 months (1-7 scale: unlikely-likely)(288,289,290,291)	(1) stigma (2) vulnerability (1) anxiety, depression (2) cancer-worry (3) intrusions (4) avoidance (5) intention to ask for psychological help
	current quality-of-life	4 items (1-4 scale: bad-good)(287)	how did you feel the last week: overall, physically, psychologically, socially.

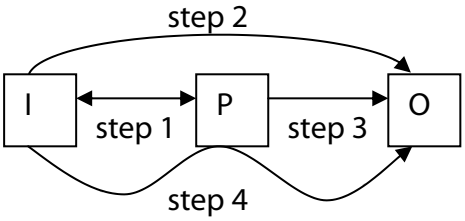
2.3. Statistical analyses

To answer the first research question, we present the percentages of counselees accurately recalling and interpreting cancer-risks and heredity-likelihood: these perception-variables were compared with the actually communicated categorical risk, which was derived from the verbal categories mentioned in the summary letter and medical-files, confirmed by the communicated percentage-risks rescaled to the 7-points Likert scale ranging from 1 (not at risk) to 7 (complete at risk) (cf.203). Subsequently, we performed t-tests to test whether the means of the counselees' perception, i.e. recollections and interpretations of cancer-risks and heredity-likelihood, differed significantly from the actually communicated cancer-risks.

Questions 2 and 3 were analyzed with mediation analyses. We followed mediation steps with bootstrap and SPSS-macro as described by Baron and Kenny (184), and Preacher and Hayes (185,cf.189). This technique is relatively robust against violations of normality and has an a priori power of .80 with medium effects at sample sizes larger than 70 (187).

Mediation is assumed to be present when the counselees' perception-variables (P) mediate the relationship between the actually communicated information(I) and the outcomes(O). Four mediation steps have to be fulfilled. 1. Actually communicated information and perception have to significantly correlate (I&P). 2. Actually communicated information significantly predicts outcomes (I→O). 3. Perception-variables significantly predict outcomes (P→O). 4. When the perception-variables are included in the bootstrap analyses, I explains O less accurate as compared with step 2 (I→P→O). Either the beta decreases but remains significant (i.e. 'partial mediation') or the beta becomes non-significant (i.e. 'complete mediation').

Figure 2. *Figure showing mediation steps*



I (predictor) = information actually communicated by the genetic-counselor
P (mediator) = perception of the counselee
O = outcomes

Mediation steps 2, 3 and 4 are presented together in one table. We use the expression 'direct effect' to indicate that the actually communicated information directly predicts the outcomes; the Beta is not influenced by the inclusion of perception-variables in analyses (i.e. mediation in step 4 is not significant). We use the expression 'indirect effect' to indicate that the actually communicated information indirectly predicts the outcomes, via the partial or complete mediation of perception-variables (i.e. mediation in step 4 is significant). The word 'effect' without adjective indicates analyses between variables I-P, I-O or P-O in steps 1, 2 and 3.

Due to restrictions of the applied SPSS-macro, step 1 is univariate, and other steps multivariate. Linear regression analysis was used to calculate standardized betas and logistic-regression in case of binary outcomes. To simplify analyses, recollections and interpretations of cancer-risks and heredity-likelihood were included as four independent mediators without taking into account possible causal relationships between these. The perception-variables correlated moderately and differed significantly from each other, but multicollinearity was not-significant. Sizes of significant effects were described with Pearson's correlation coefficients, Cohen's d in case of comparing means (.02 is small, .50 medium, .80 large), and f^2 in case of multiple regression (.02 is small, .15 medium, .35 large).

We used 5000 bootstrap resamples, which is considered as sufficient for final reporting (185). Confidence intervals were adjusted for possible bias due to the asymmetric distribution of bootstrap estimates (cf. Efron in 185). Alpha was set at .01 and confidence-intervals at .99, as a small correction for the number of four predictors of actually communicated information. We decided not to correct more conservatively, because of the explorative nature of this study, and to prevent relevant clinical information to be unobserved. Analyses had been corrected for elapsed time since DNA-result disclosure, surgery of breasts/ovaries before DNA-testing, having cancer or not, receiving radio/hormone/chemotherapy at time of DNA-testing and currently, and several sociodemographic-variables; however these variables did not significantly influence the results and are therefore not presented.

3. Results

3.1. Participants

We asked 412 women to participate, and 206 (50%) consented. Initially, we separated analyses for those individuals whose UV-result was changed in a pathogenic (n=9) or non-pathogenic (n=8) test result (not presented here). These separate analyses did not show significant differences (p(t)>.01), and therefore, we included all of them in the UV-group (presented here). The analyzed sample consisted of 76 UV's, 55 PM's and 77 UR's. (see table 2 in chapter 4)

Mean time elapsed since disclosure of the DNA-test result was 5 years (sd=2.0). Of all 204 counselees, 179 (88%) had had breast cancer, 17 (8%) ovarian cancer and 14 (7%) were unaffected (no differences between DNA-results). Before DNA-testing, 36 (18%) had undergone mastectomy and 11 (5%) BSO because of cancer. After DNA-testing, 90 (44%) had undergone prophylactic mastectomy (PBM) and 61(29%) prophylactic BSO (PBSO). No differences were found for pre-testing surgery among the DNA-test result groups, but differences were significant for post-testing surgery (K-W=17,p<001;K-W=44,p<.001). UR-counselees had least often undergone PBM and PBSO (25%, 4%), PM-carriers had most often undergone this (57%, 72%), and UV-counselees were in-between (50%, 25%). More details about sociodemographics and DNA-test results have been published elsewhere (285). Outcome-variables are described in table 3.

Table 3. *Description of outcomes*

Outcome-variable	m (sd) or n (%)
Medical	
post-testing mastectomy (PBM)*	90 (45%)
post-testing bilateral salpingo-oophorectomy (PBSO)*	61 (32%)
intention for breast self-examination*	1.74 (.96)
intention for surveillance of breasts*	6.47 (1.34)
intention to have a mammography/MRI*	6.45 (1.40)
intention for mastectomy (PBM)*	1.75 (1.40)
intention to have surveillance of ovaries*	4.28 (4.20)
intention for bilateral salpingo-oophorectomy (PBSO)*	2.17 (1.92)
BRCA-related self-concept	
BRCA-related stigma	14.41 (7.00)
BRCA-related vulnerability	22.83 (7.61)
Psychological	
cancer-worry	8.44 (2.99)
depression	2.30 (.23)
anxiety	2.96 (.42)
intrusion	13.62 (4.08)
avoidance	14.12 (4.67)
wish for psychological help*	2.05 (1.51)
Quality-of-life	
total quality-of-life**	5.53 (1.27)
physical quality-of-life***	3.07 (.97)
psychological quality-of-life***	3.16 (.96)
relational quality-of-life***	3.55 (.82)

*Life changes are not reported because these scales are resulted from factor analyses (m=.00, sd=1.00); * measured on a scale ranging between 1 and 7 (very unlikely/very likely); ** measured on a scale ranging between 1 and 7 (bad-very good); *** measured on a scale ranging between 1 and 5 (bad-very good); Other variable have broader scales (see 2.2.); n.s. = not significant.*

3.2. Question 1

The mean actually communicated cancer-risks was 5.3 on a 7-points scale (sd=1.1; see table 4). Counselees recalled and interpreted cancer-risks as 4.5 (sd=1.4) and 4.0 (sd=1.6) respectively. They recalled and interpreted heredity-likelihood as 4.4 (sd=1.4) and 4.8 (sd=1.3) respectively. Compared to actually communicated cancer-risks, only 22% had recalled similar cancer-risks, 24% interpreted similar cancer-risks, 8% recalled similar heredity-likelihood and 4% interpreted similar heredity-likelihood. We found significant differences between the recalled cancer-risks, interpreted cancer-risks, recalled heredity-likelihood and interpreted heredity-likelihood on the one hand, and the actually communicated cancer-risks of 5.3 (sd=1.1) on the other hand; effect sizes of these differences were medium to large (resp. t=3.4, -5.7, 4.7, -5.8; resp. d=.63, .94, .71, .41; all p's<.001). No differences were found between DNA-test results (p(K-W)>.01). (see table 4) In sum: the majority of counselees perceived cancer-risks and heredity-likelihood inaccurately; their perception differed significantly from the actually communicated cancer-risks.

Table 4. *Actually communicated and perceived cancer-risks*

	actually communicated cancer-risks m (sd)	**recalled cancer-risks m (sd); % accurate**	**interpreted cancer-risks m (sd); % accurate**	**recalled heredity-likelihood m (sd); % accurate**	**interpreted heredity-likelihood m (sd); % accurate**
overall	5.3 (1.1)	4.5 (1.4) 22%	4.0 (1.6) 24%	4.4 (1.4) 8%	4.8 (1.3) 4%
unclassified-variants	4.2 (.4)	4.5 (1.5) 20%	4.6 (1.8) 20%	4.6 (1.6) 10%	4.6 (1.6) 10%
pathogenic-mutations	6.0 (.0)	3.8 (1.1) 27%	3.4 (1.2) 24%	6.9 (0.4) 7%	6.9 (0.4) 2%
uninformative-results	3.4 (.5)	4.9 (1.2) 25%	4.2 (1.7) 29%	3.0 (1.5) 9%	3.4 (1.9) 0%

m: mean, sd: standard deviation, %accurate: % of counselees with scores identical to actually communicated cancer-risks; actually communicated cancer-risks and heredity-likelihood were measured on scales ranging from 1 to 7 without decimals.

3.3. Question 2

We used four mediation steps to investigate whether the actually communicated cancer-risks (I) predicted the outcomes (O), and whether this was mediated by the counselees' perception (P). Step 1 is presented in table 5, steps 2 - 4 in table 6.

Step 1 (I&P): The actually communicated cancer-risks correlated with the recollection of cancer-risks, and the recollection and interpretation of heredity-likelihood; effect sizes were large (resp. R=.33, .64, .78).

Step 2 (I→O): Actually communicated cancer-risks did not directly predict any outcomes.

Step 3 (P→O): The counselees' perception predicted all psychological and quality-of-life outcomes, stigma, and intended mammography/MRI. Effect sizes were medium.

Step 4 (I→P→O): Via the mediation of perception-variables, actually communicated cancer-risks predicted vulnerability, post-testing mastectomy and intended surveillance of ovaries. These effects were large.

In sum: analyzed over all participants, the actually communicated cancer-risks did not directly predict any outcomes, but perception-variables (especially interpreted cancer-risks) predicted and mediated most of the outcomes.

Table 5. *Pearson's correlations between actually communicated information and perception*

Actually communicated information	***perception***			
	recollections		**interpretations**	
	recalled cancer-risks ††	**recalled heredity-likelihood ††**	**interpreted cancer-risks ††**	**interpreted heredity-likelihood ††**
pathogenic-mutations †	.64***	.41***	.13*	.65***
uninformative †	-.29***	-.60***	-.28***	-.52***
unclassified-variant †	-.17*	Ns	.16*	Ns
cancer-risks ††	.33*	. 63***	ns	.78***

*P-values *<.05, **<.01, ***<.001, ns=not significant ; † values: 1= actually communicated, 0= actually not communicated; †† measured on 7-points scale (1=low-7=high).*

Table 6. *Results for question 2: actually communicated cancer-risks (acr)*

Predicted outcomes (O)	acr (I)	perception-variables (P)				total model statistics	
	acr	recalled cancer-risk	interpreted cancer-risk	recalled heredity-likelihood	interpreted heredity-likelihood	R^2	f^2
DIRECT EFFECT (I→ O)							
x	ns	ns	ns	ns	ns		
EFFECT (P→ O)							
Medical							
intended mammography/MRI	ns	ns	.79	ns	ns	.21	.27
Psychological							
wish for psychological help	ns	ns	.35	ns	ns	.10	.11
anxiety	ns	ns	.08	ns	ns	.10	.11
avoidance	ns	ns	1.10	ns	ns	.11	.13
BRCA-related self-concept							
BRCA-stigma	ns	ns	1.61	ns	ns	.21	.27
Quality-of-life							
total Quality of Life	ns	ns	.31	ns	ns	.12	.14
physical Quality of Life	ns	.30	.23	ns	ns	.10	.11
psychological Quality of Life	ns	.30	.36	ns	ns	.20	.25
relational Quality of Life	ns	.32	.22	ns	ns	.19	.23
INDIRECT EFFECT (I→ P→O)							
Medical							
post-testing mastectomy(PBM)	.81/ns	.84	ns	ns	ns	.83	4.88
intended ovaries surveillance	2.3/ns	2.2	2.3	ns	ns	.88	7.33
BRCA-related self-concept							
BRCA-vulnerability	2.7/ns	ns	1.8	ns	ns	.41	.69

Table shows standardized betas for outcome-variables (O) predicted directly by actually communicated information (I) or by the counselees' perception (P), or by mediation (I→P→O). Only significant predictors, mediators and total models are presented. P-values <.01. R^2 is explained variance of total model, f^2 the corresponding effect size. Constant and error terms are not presented to keep tables simple. The mediation rows show two betas for the actual communicated cancer-risks: prediction without/with inclusion of the mediator(s) in the regression equation; a reduction of the ß implies partial mediation (e.g. .81/.40); when ß becomes not significant (ns), this implies complete mediation (e.g. .81/ns). Outcomes not presented here were not significantly predicted by any variables.

3.4. Question 3

We used four mediation steps to investigate whether the actually communicated DNA-test result (I) predicted the outcomes (O), and whether this was mediated by the counselees' perception (P). The communicated DNA-test result consisted of three dummy-variables. Therefore, we had to perform separate analyses for UV's, PM's and UR's.

3.4.1. Unclassified-variants

Step 1(I→P): The actual communication of a UV only predicted recalled cancer-risks and interpreted cancer-risks, and not heredity-likelihood; effects were small with R's of -.18 and .17 respectively (see table 5).

Step 2 (I→O): The communication of a UV only directly predicted depression with a medium effect.

Step 3 (P→O): Perception-variables predicted all other outcomes. Effect sizes were large for medical outcomes and BRCA-related self-concept, and medium for quality-of-life, psychological changes and well-being.

Step 4 (I→P→O): Mediation was absent (see table 7).

In sum: the communication of a UV only directly predicted depression, and perception-variables (especially interpreted cancer-risks) predicted all other outcomes.

Table 7. *Results for question 3: unclassified-variants (UV)*

Predicted outcomes (O)	uv (I)	perception-variables (P)				total model statistics	
	uv	recalled cancer-risk	interpreted cancer-risk	recalled heredity-likelihood	interpreted heredity-likelihood	R^2	f^2
DIRECT EFFECT (I→ O) depression	.08	ns	ns	ns	ns	.12	.14
EFFECT (P→ O)							
Life-changes							
psychological-changes	ns	ns	.13	ns	ns	.16	.19
Medical							
posttesting mastectomy (PBM)	ns	.28	.27	ns	ns	.23	.30
post-testing oophorectomy (PBSO)	ns	ns	.14	ns	ns	.23	.30
intended PBM	ns	ns	.19	ns	ns	.24	.32
intended PBSO	ns	ns	.06	ns	ns	.24	.32
intended ovariessurveillance	ns	ns	.11	ns	ns	.24	.32
BRCA-related self-concept							
BRCA stigma	ns	ns	.10	ns	ns	.25	.33
BRCA vulnerability	ns	ns	.10	ns	ns	.24	.32
Psychological							
wish for psychological help	ns	ns	.29	ns	ns	.12	.14
anxiety	ns	ns	.11	ns	ns	.10	.11
intrusion	ns	ns	.05	ns	ns	.07	.07
avoidance	ns	.09	.35	ns	.05	.13	.15
Quality-of-life							
total Quality of Life	ns	ns	.20	ns	ns	.11	.13
physical Quality of Life	ns	65	.14	ns	ns	.09	.10
psychological Quality of Life	ns	ns	.21	ns	ns	.11	.13
relational Quality of Life	ns	.38	.03	ns	ns	.11	.13
INDIRECT EFFECT (I→ P→O)							
x	ns	ns	ns	ns	ns	ns	ns

See footnote in table 5.

3.4.2. Pathogenic-mutations

Step 1(I→P): The actual communication of a PM predicted recalled cancer-risks, interpreted heredity-likelihood and recalled heredity-likelihood with large effects, and predicted the interpreted cancer-risks with a small effect (R's are .64, .65, .41 and .13 respectively; see table 5)

Step 2(I→O): The communication of a PM directly predicted having undergone a PBM or PBSO after DNA-testing, or having the intention to undergo these surgeries the coming months, and the intention to undergo surveillance of breasts. Effect sizes were large for intended PBM and PBSO; other effects were medium.

Step 3(P→O): The counselees' perception predicted psychological outcomes, and quality-of-life. Effect sizes were medium.

Step 4(I→P→O): Via the mediation of perception-variables, the communication of a PM predicted stigma and vulnerability, psychological changes and intentions to have mammography/MRI and surveillance of ovaries. Effect sizes were large (see table 8).

In sum: the communication of a PM directly predicted several medical outcomes, and perception-variables (especially interpreted cancer-risks) predicted quality-of-life and psychological outcomes, and mediated the impact on medical intentions, stigma and vulnerability.

Table 8. *Results for for question 3: pathogenic-mutations (PM)*

Predicted outcomes (O)	PM (I)	perception-variables (P)				total model statistics	
	PM	recalled cancer-risk	interpreted cancer-risk	recalled heredity-likelihood	interpreted heredity-likelihood	R^2	f^2
DIRECT EFFECT (I→ O)							
post-testing mastectomy(PBM)	.08	ns	ns	ns	ns	.07	.07
post-testing oophorectomy(PBSO)	.10	ns	ns	ns	ns	.10	.11
intended mastectomy(PBM)	.12	ns	ns	ns	ns	.27	.37
intended PBSO	.34	ns	ns	ns	ns	.67	2.03
intended breast surveillance	.09	ns	ns	ns	ns	.09	.10
EFFECT (P→ O)							
Psychological							
wish for psychological help	ns	ns	.27	ns	ns	.12	.14
anxiety	ns	ns	.30	ns	ns	.09	.10
intrusion	ns	ns	.27	ns	ns	.07	.07
avoidance	ns	ns	.32	ns	ns	.13	.15
Quality-of-life							
total Quality of Life	ns	ns	.11	ns	ns	.11	.13
physical Quality of Life	ns	.02	.04	ns	ns	.09	.10
psychological Quality of Life	ns	ns	.18	ns	ns	.11	.13
INDIRECT EFFECT (I→ P→O)							
Life-changes							
psychological-changes	.01/ns	ns	.11	ns	ns	.21	.27
Medical							
intended mammography/MRI	.99/.21	ns	.06	ns	ns	.19	.24
intended ovaries surveillance	2.68/.53	.22	ns	ns	ns	.49	.96
BRCA-related self-concept							
BRCA-stigma	.54/.23	ns	.09	ns	ns	.21	.27
BRCA-vulnerability	3.3./ns	ns	.25	ns	ns	.24	.32

See footnote in table 5.

3.4.3. Uninformative DNA-test results

Step 1(I→P): The actual communication of an uninformative-result predicted recalled and interpreted heredity-likelihood negatively with large effect sizes (resp. R's=-.60, -.52), and correlated negatively with medium effect sizes with recalled and interpreted cancer-risks (resp. R's=-.29, -.28; see table 5)

Step 2(I→O): The communication of an UR predicted less physical-medical changes and PBM after DNA-testing, and a lower intention to undergo PBM and PBSO. Effect sizes were large for intended PBM and PBSO; other effects were medium.

Step 3(P→O): The counselees' perception predicted all psychological and quality-of-life outcomes and intended mammography/MRI. Effect sizes were medium.

Step 4(I→P→O): Via the mediation of perception-variables, the communication of an UR predicted, stigma, vulnerability, psychological changes and BSO after DNA-testing. Effect sizes were large (see table 9).

In sum: the communication of an UR directly predicted several medical outcomes, and perception-variables (especially interpreted cancer-risks) predicted quality-of-life and psychological outcomes, and mediated several outcomes, e.g. BRCA-related self-concept.

Table 9. *Results for question 3: uninformative DNA-test result (UR)*

Predicted outcomes (O)	UR (I)	perception-variables (P)				total model statistics	
	UR	recalled cancer-risk	interpreted cancer-risk	recalled heredity-likelihood	interpreted heredity-likelihood	R^2	f^2
DIRECT EFFECT (I→ O)							
Medical							
physical-medical changes	.29	ns	ns	ns	ns	.06	.06
post-testing mastectomy(PBM)	.11	ns	ns	ns	ns	.11	.13
intended mastectomy(PBM)	.30	ns	ns	ns	ns	.28	.39
intended oophorectomy(PBSO)	.34	ns	ns	ns	ns	.34	.51
EFFECT (P→ O)							
Medical							
intended mammography/MRI	ns	ns	.20	ns	ns	.17	.20
Psychological							
wish for psychological help	ns	ns	.05	ns	ns	.08	.09
anxiety	ns	ns	.33	ns	ns	.09	.10
intrusion	ns	ns	.17	ns	ns	.07	.07
avoidance	ns	.70	.69	ns	.30	.13	.15
Quality-of-life							
total Quality of Life	ns	ns	.20	ns	ns	.09	.10
physical Quality of Life	ns	ns.50	.12	ns	ns	.09	.10
psychological Quality of Life	ns	ns	.08	ns	ns	.11	.13
INDIRECT EFFECT (I→ P→O)							
Life changes							
psychological-changes	.52/ns	ns	.10	ns	ns	.16	.19
Medical							
post-testing PBSO	.27/.16	ns	.16	ns	ns	.19	.23
BRCA-related self-concept							
BRCA-stigma	5.9/.23	ns	.03	ns	ns	.27	.37
BRCA-vulnerability	5.0/ns	ns	.20	ns	ns	.25	.33

See footnote in table 5.

4. Discussion

4.1. Conclusions

Many authors have assumed that disclosure of DNA-test result category and/or cancer-risks by a genetic-counselor has direct, consistent influence on many aspects of the counselee's life (e.g.66,68,76). Here, however we showed that a direct influence only exists for the counselee's decision for surgery, which is directly predicted by the communication of a pathogenic or uninformative DNA-test result.

All other outcomes were not or only indirectly predicted by the cancer-risks and DNA-test result category that the genetic-counselor had actually communicated. Because these outcomes were predicted and/or mediated by the counselees' perception, and especially by their interpretation of their own cancer-risks. However, this perception of most counselees differed from what the genetic-counselor had actually communicated: thus, inaccurate perceptions predicted most outcomes.

Other authors also suggested that the inaccurate, subjective perception of counselees may explain the impact of genetic-counseling better than actually communicated information (292-295). For example, a person's representations of her illness and genetic condition predicted psychological well-being and medical decision-making better than communicated medical information (cf.89,202,296,297). Perception also showed to be an important predictor of outcomes (87,202,298). However, these studies did not include formal mediation analyses and genetics-specific scales.

4.2. Direct prediction

The communication of a PM directly predicted that counselees had undergone, or intended to undergo, PBM, PBSO and frequent surveillance (I→O). This was in line with our hypothesis that counselees show more radical medical behavior after pathogenic-results, because of its high cancer-risks and unequivocal management options.

The communication of an UR directly predicted that counselees had not undergone, or did not intend to undergo, PBM, BSO and frequent surveillance. They seem to have felt somewhat falsely reassured by the DNA-test result (cf.86,200,204), as confirmed by the finding that they recalled and interpreted cancer-risks and heredity-likelihood lower than other test results.

4.3. Perception

We hypothesized that all four perception-variables would predict and mediate the impact of DNA-testing on outcome-variables (P→O). However, we found that not all perception-variables predicted and mediated the same number of outcomes, nor did they effect the outcomes to the same extend. Interpreted cancer-risks predicted/mediated 54 outcomes,

recalled cancer-risks 18, interpreted heredity-likelihood 4 and recalled heredity-likelihood only 1(cf. tables 6-9).

The perception-variable that predicted and mediated most outcomes, was the counselees' interpretation of their own risk to develop cancer (again). Interpreted cancer-risks predicted many outcomes, possibly because they concern a direct threat to the counselees' personal health. This is in contrast with heredity-likelihood which did not predict many outcomes; the latter concerns a distant threat -for relatives- which influenced the probands' own lives less than the more personal threat of their own cancer-risks. It was also to be expected, that subjectively feeling and thinking to be at high risk to develop cancer predicts larger psychological impact, more radical medical-decisions and stronger wish for psychological help.

Counselees recalled higher cancer-risks when PMs and/or high cancer-risks were actually communicated. This was to be expected, because PMs actually imply high cancer-risks. The recollection of high risks explains why these counselees frequently decided for post-testing mastectomy and ovaries' surveillance, which has subsequently influenced quality-of-life.

Counselees interpreted high heredity-likelihood when PMs and/or high cancer-risks were communicated, and low heredity-likelihood when an UR was disclosed. Interpreted heredity-likelihood predicted surgery or surveillance of ovaries, possibly because PM carriers interpreted very high heredity-likelihood, which understandably predicted radical medical-decisions. Interpreted heredity-likelihood also predicted the tendency to avoid thoughts, feelings and images regarding genetic-testing, possibly because of intense emotions regarding relatives' cancer-risks.

Heredity-likelihood, especially as recalled by counselees, was an unimportant predictor of outcome-variables. Should we delete heredity-likelihood from our model? Not necessarily. The absence of predictions only means that the outcome-variables are better predicted by other variables. It does not say that heredity-likelihood is not important in the counselees' ideas and feelings regarding DNA-testing. From clinical experience, we know that counselees reflect a lot about consequences of DNA-testing for relatives. Apparently, their lives are less influenced by reflections on their relatives' risks than on their own cancer-risks.

4.4. Inaccuracy of perception

More than 75% of all counselees could correctly identify which of the three DNA-test result categories they had received (unpresented results,cf.1,2). However, despite this understanding, our current study showed that most counselees had an inaccurate perception of the communicated cancer-risks and heredity-likelihood. We found that counselees with UVs overestimated both cancer-risks and heredity-likelihood. Counselees with URs overestimated cancer-risks and underestimated heredity-likelihood. PM carriers

underestimated cancer-risks and overestimated heredity-likelihood. Only between 0% and 30% of all counselees recalled and interpreted cancer-risks and heredity-likelihood accurately.

4.5. Possible explanations

Why do counselees misperceive DNA-test results? Why is the inaccurate perception such an important predictor/mediator of outcomes?

The counselor may have communicated DNA-test results inaccurately. This explanation seems unlikely, because a summary letter with accurate information was sent to counselees.

Counselees may have difficulties understanding complex information, especially ambiguous information such as UVs. The summary letter may have been unclear or too complex. The counselor's formulation of genetic-risks may have created ambiguity, e.g. 'likely', 'rarely' (264). The counselor may have communicated her/his own interpretation/suggestions next to objective information, which resulted in the communication of incongruent information. Counselees misunderstood the relationship between the meaning of the pedigree and the DNA-test, as shown by mixing both in their perception of heredity-likelihood (285). Misunderstandings could also be caused by low education, innumeracy (299-301), black-or-white thinking (i.e. 'either I get cancer or I do not get cancer') (216,217), floor- and ceiling effects (264). Difficult information may also be more difficult to memorize. Counselees may listen selectively due to schematic and biased perception. They hear information confirming their perception and use heuristics, non-rational arguments and cognitive dissonance (cf.83). Some have optimistic biases (eg.302), or pessimistic biases (eg.303).

Counselees may have developed their own strong, independent opinion about cancer-risks and heredity-likelihood, due to their often life-long history with cancer in the family. They reconstruct communicated cancer-risks and heredity-likelihood according to personal and family experiences (304-307). They may personalize or exaggerate risk-information, because of the personal relevancy of genetic-information (cf.297,308). Peers and relatives may also influence interpretations.

Interpretations predicted/mediated more outcomes than recollections and actual information. Possibly, because in situations of personal threat, an individual may trust their own interpretations best. Subjective, emotional-loaded processes may be the relatively fastest way to evaluate threats and resources (81-84).

4.6. Unclassified-variants

Unclassified-variants were perceived more inaccurately than other DNA-test results. A quarter of all counselees with a UV inaccurately identified their result as pathogenic (16%) or uninformative (8%) (unpresented results,cf.1,2). All these counselees overestimated

cancer-risks and heredity-likelihood, compared to actually communicated cancer-risks. This suggests 'false alarm'.

Their perception was not predicted by any actually communicated information, but it did predict medical decisions and psychological impact. Post-hoc t-tests revealed that counselees with a UV reported almost as much physical-medical changes as mutation-carriers: 28% had BSO and 58% contralateral or bilateral mastectomy. They felt more stigmatized than uninformatives, and had lower quality-of-life than all other DNA-test results. The communication of a UV directly evoked feelings of depression, even on long-term in this retrospective study.

Thus, most counselees did not perceive the communicated UV accurately, and this inaccurate perception caused the relatively radical medical decisions that they had made. This could be explained by their selective understanding that 'a mutation was found', without equally valuing that this mutation 'does not have a clinical meaning (yet), and the future may show that it is either pathogenic or not harmful'. They may feel threatened and stigmatized by this DNA-test result without having the certainty and medical options that PMs provide.

Of course, most counselees are at moderate or high risk for developing cancer, as their pedigrees indicated. This possibility is not as high as they interpret. It is also remarkable, that almost the same large number of counselees with a UV decide for preventive surgery as PM-carriers.

From a psychological perspective, the counseling of UVs has to be improved. Genetic-counselors should pay more attention to the counselees' interpretations and medical decisions. Extra psychological tracking is recommended. As long as these measures are not taken, the question should be raised whether it is psychologically better justified to communicate UVs as uninformatives, i.e. 'we did not detect any mutations explaining the occurrence of cancer' instead of 'we detected a mutation/genetic-change with unknown clinical consequences'. On the other hand, a counselee has to be informed about the detection of an UV if additional investigation in the family is needed, such as cosegration-analysis and functional testing.

4.7. Methodological issues

This study is limited by its retrospective design, relatively small sample of women mainly affected with cancer, inclusion of only BRCA1/2-genes, and exclusion of other factors, e.g. coping and illness perceptions. A larger sample was practically not feasible in this retrospective nation-wide study. The sample size made structural-equation-modeling impossible. We suggest conducting larger, prospective studies, in affected and unaffected women and men, with use of structural equation modeling to include relationships between perception-variables. Detected effect sizes were mainly medium; therefore, the influence of other (non-counseling) variables predicting the outcomes may be studied.

4.8. Implications

The results could be summarized by a participant's comment: 'The genetic-counselor communicated 'A', but I'm convinced 'B' is true. Therefore, I trust on B when considering surgery and surveillance.' This shows how counselees interpret genetic information differently from facts and from their recollections. Thus, when a genetic-counselor asks the counselee whether she understands the information, she may accurately parrot the several pieces of information communicated by the genetic-counselor. This does not mean she accurately interprets information.

Genetic-counseling should become more interactive (cf.264). Before giving results and recommendations, counselors should assess the counselees' risk perceptions, illness models of cancer, ideas about treatment and surveillance, and other relevant factors such as family dynamics, current psychological and existential concerns. The communication of genetic-information should be tailored to the individual, to personalize and shape risk-information to be congruent with the counselees' views. After risk-communication, genetic-counselors should assess whether counselees understand the information, e.g. by asking to repeat the result in their own words. Counselees should be asked about their own ideas and feelings about the results and risks. *Finally*, they should be asked which medical consequences they have in mind and on which they base this information.

Genetic-counselors should provide counselees with feedback about inaccuracies in their interpretations, provide additional explanation and refer to psychologists if needed. Such empathic confrontations may foster tailoring of medical information and improve recollections (309-311). Explicitly addressing the counselees' perception lowers distress and raises satisfaction (cf.312,313). A study in 28 counselees suggested that explicitly discussing the counselees' perception may result in more accurate risk-estimation (282).

Psychological help should be offered to counselees who think or feel to be at high risk to develop cancer or to develop cancer again. Because their interpretation of cancer-risks correlated strongly with their wish to receive help. Correlations suggest the focus of psychological-help for counselees with high cancer-risk: feeling stigmatized, vulnerable, or considering undergoing surgery.

This study raises many questions. How many skills do counselees have to interpret DNA-test results accurately? How much information is good for them to know? Where should the cut-off line be drawn between psychological benefits and medical costs of misinterpretations? How should we balance naive autonomy of counselees and professional paternalism of genetic-counselors? Thus, what is the optimum amount of information to disclose?

Chapter 6

Explaining the short-term impact of DNA-testing in breast cancer patients:

the counselees' perception matters, but the actual BRCA1/2 result does not

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Abstract

Objective

Previous studies suggest that learning a DNA-test-result has no direct impact on the medical-decisions and psychological well-being of counselees. Their perception, especially their recollections and interpretations of their cancer-risks and heredity, predict and/or mediate this impact. These studies were criticized for their small range of predictors, mediators, outcomes and contextual factors. We studied the short-term impact of DNA-testing with an extended model.

Method

Three months after disclosure of BRCA1/2-test-results, we sent counselees a questionnaire about their perception, medical and psychological outcomes, and medical, familial and psychological contexts. 248 affected women participated; 30 had received pathogenic-mutations, 16 unclassified-variants and 202 uninformative-results.

Results

The actually communicated genetic-information and the contextual variables predicted the counselees' perception, but did not directly predict any outcomes. The counselees' perception predicted and/or completely mediated the counselees' medical intentions and behavior, physical and psychological life-changes, stigma, mastery, negativity and cancer-worries. Short-term distress was related to the perception of their own risks, but also of their relatives' risks and heredity-likelihood. Effect sizes were medium to large.

Conclusions & implications

The outcomes of DNA-testing were better predicted by the counselees' perception than by the actually given genetic-information. We recommend genetic-counselors to have tailored, interactive dialogues about the counselees' perception.

1. Introduction

1.1. Explaining the impact of DNA testing

Genetic counseling has been described as 'the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease' (52). This assumes that genetic counseling influences the counselees' lives, such as in their understanding and adapting to their possibly heritable disease. Many studies have indeed described changes in the counselees' lives. For instance, after the communication of DNA test results for hereditary breast and ovarian cancer (i.e. BRCA1/2 genes, 15), some counselees decided to change the frequency of surveillance of breasts/ovaries and/or underwent prophylactic mastectomy (PBM) or bilateral salingo-oophorectomy (PBSO) (35,70), and some experienced distress (66-69,71,183).

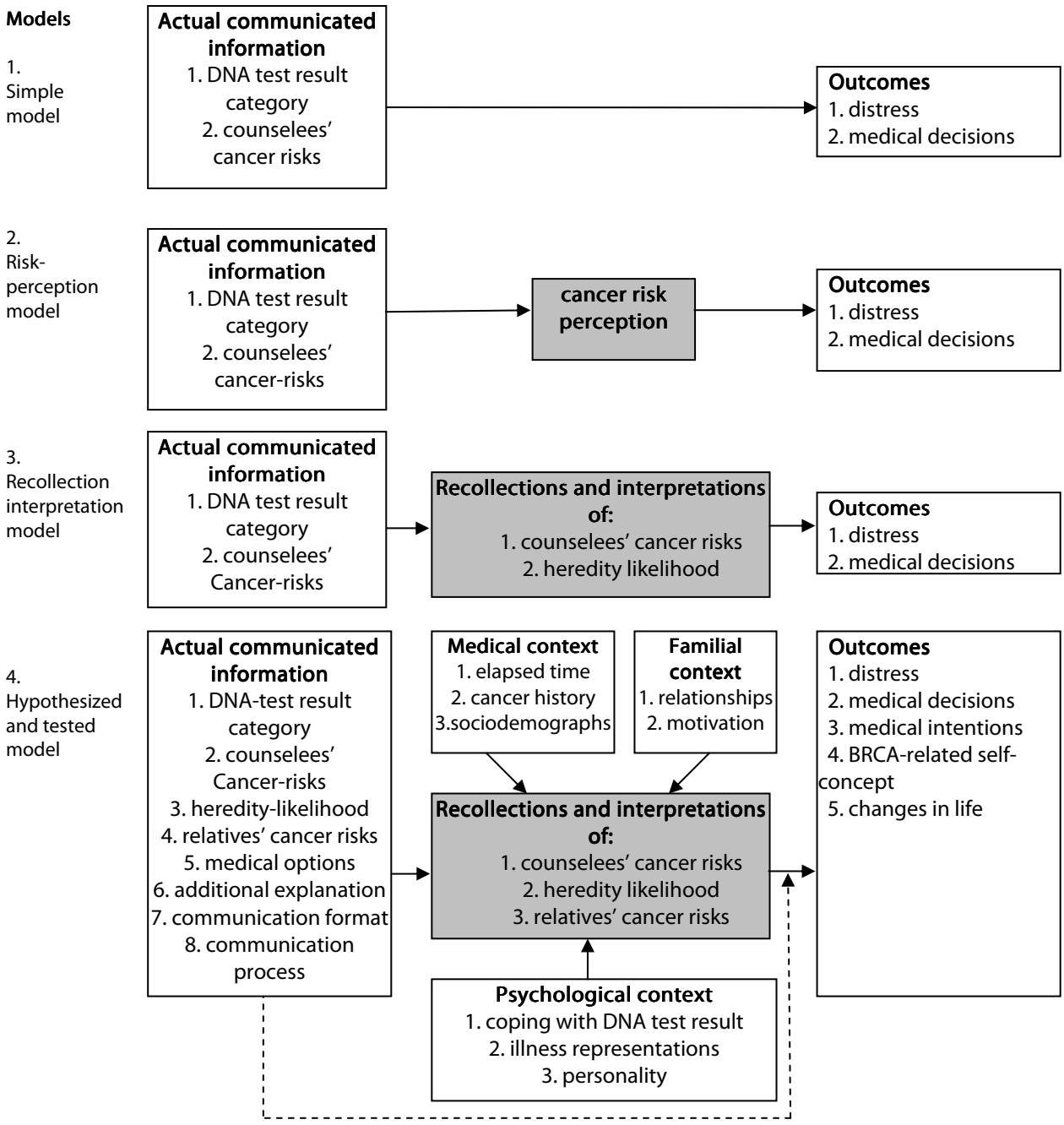
The majority of follow-up studies have addressed the impact of genetic counseling and test results, whereas only a few have explained how genetic counseling leads to the observed changes. Explanatory studies are important to help understand why genetic counseling sometimes has a negative impact on counselees (e.g.72), and may support counselors in optimizing 'the process of helping' (52). We therefore developed an explanatory model, which we will describe based on a short literature overview, and giving references as examples of general trends. We went on to empirically test our model. We focus on BRCA1/2 testing in cancer patients, because they are the majority of counselees who have DNA testing in the Netherlands but they are relatively understudied (68,71).

1.2. Simple input-output models

Many studies have described the general impact of BRCA1/2 testing on distress and medical decisions in counselees (see model 1, figure 1). Most showed that different DNA results are associated with different outcomes. A pathogenic mutation (PM) result implies a high cancer risk for the counselee and a high likelihood that cancer is heritable in the family; after learning of a PM, many counselees decide to undergo frequent surveillance and/or prophylactic surgery of breasts and/or ovaries (35,70), and feel somewhat distressed (183). An uninformative result (UR) implies that no mutation was found but that the counselee's pedigree suggests that cancer is likely to be heritable in this family and the counselee is at increased risk of developing cancer (again); this result is associated with infrequent surveillance behavior and little distress in counselees (35,70,183). An unclassified variant (UV) or variant-of-uncertain-clinical-significance is a genetic mutation for which the meaning is not known yet, i.e. it could be pathogenic or non-pathogenic, but the pedigree suggests heredity and high cancer risks for the counselee; this result is associated with many feelings of uncertainty, relatively high distress and the decision to undergo prophylactic surgery (203,277).

These studies reported small to moderate associations between the communicated DNA test result category (PM, UR, UV) and outcome variables. They were followed by prediction studies in which the authors tried to explain how genetic counseling predicts outcomes. For instance, they predicted the impact from other information communicated by genetic counselors, i.e. the counselees' cancer risks. Both the DNA test result category and the cancer risks do not seem to consistently and directly explain the medical and psychosocial impact of DNA testing (66,69-71,76).

Figure 1. *Three models from previous studies and the hypothesized model described in this paper*



1.3. The risk perception and recollection/interpretation models

Not finding a clear, direct relationship between the genetic information actually communicated and the outcomes caused previous researchers to look at the counselees' perception of the BRCA1/2 results (model 2, figure 1). Several studies have described how about half of all counselees have an inaccurate perception of the communicated cancer risks (78), i.e. their perception was not in line with the genetic counselor's message. Subsequently, their –often inaccurate– perception influences their medical decisions and distress (67,77,79).

However, there is a large variance in the reported perception variables and effect sizes (77-79). This may be because the counselees' perception is a multidimensional construct (84,239,264), which has often been measured by only asking counselees about their recollection of their own cancer risk, and not, for example, of their relatives' risks or likelihood of heredity (285). Moreover, most counselees were asked about their recollections of the factually communicated genetic information, and not about how they interpreted it (94,239,265). The latter aspect involves subjectively selected, weighed and evaluated information, provided with personal meaning (131,285), and seems to better reflect the counselees' subjective construction of their risk perception than their recollections, because many authors have suggested that counselees subjectively interpret the cancer risks by using heuristics, such as their own beliefs about inheritance, past experiences with cancer in the family, subjective motivations, social comparison, and need for control (79,90).

Our retrospective study (chapters 3-6) was the first to show that the counselees' recollections and interpretations of their own cancer risks and heredity likelihood strongly predicted their long-term medical decisions and psychological well-being (see model 3, figure 1). Neither the DNA test result category that was actually communicated nor the counselees' own cancer risks predicted any outcomes directly. The exceptions were PM results, which predicted the counselees' decision to undergo prophylactic surgery; this could be because prophylactic surgery is usually only performed in the Netherlands after detecting a PM (203,286,278; chapters 3-6) . Our earlier study could be criticized for its retrospective design, which may have caused recall bias and relatively low reported distress, so in this empirical study we measured the short-term impact.

1.4. Extending the model

The recollection/interpretation model in our previous studies was still a simplification of the reality of genetic counseling, in which more variables may be included in different parts of the model (model 4, figure 1).

Information actually communicated– Previous studies included the DNA test result category and/or the counselees' cancer risks as predictors of the outcome of genetic counseling. In reality, counselors also often report the likelihood that cancer is heritable in

the family (i.e. heredity likelihood, 285), the cancer risks for relatives, and the medical options (i.e. surveillance and/or surgery for breasts and/or ovaries), in line with Dutch counseling guidelines (9,10). They may also explain more about genetics (e.g. 'future research may show a PM in as yet unknown genes'), and may report the risks in many different ways, such as describing the risk verbally or giving percentages (243,280,281). Table 1 shows the possible pieces of information that can be communicated by Dutch counselors. All these subtle pieces of information may contribute to the counselees' perception and the impact of the genetic counseling. It is therefore quite understandable that previous studies that included only one or two predictors, did not strongly predict the outcomes.

Recollections and interpretations– The counselees' recollections and interpretations of their heredity likelihood did not strongly predict their distress in our retrospective studies (277). This may be explained by the long time that had passed since the DNA testing was performed in our previous study, by the fact that 'heredity likelihood' was too abstract for the counselees to understand, and by the cancer risks of individual relatives probably being more relevant. The current study therefore included recollections and interpretations of the relatives' cancer risks over a relatively short period, i.e. 3 months.

Outcomes– Previous studies showed that genetic counseling has a relatively small impact on the lives of counselees, possibly because of the relatively small range of impact measures used that had an insensitive or non-validated nature (314,315). The outcomes of genetic counseling may be more strongly predicted if genetic-specific instruments are used to measure how the counselees' lives have changed (203), and how they experience vulnerability, mastery, and stigma related to heritable cancer (159).

Context– Previous studies have been criticized for not taking into account the context of genetic counseling (68,74). The counselees' medical history of cancer(35,68,71,73,169) and several sociodemographic characteristics –e.g. whether they have children– may influence their perception and outcomes (164,170). The familial context may influence perceptions and outcomes, e.g. the communication style within the family, cancer experiences in the family (164,166-168) and the reason to undergo DNA testing (for themselves or relatives) (1). The psychological context may also influence perceptions and outcomes, e.g. the counselees' coping styles, cognitive representation of cancer and their personality (87,164,170,202).

Relationships– Our previous studies suggested that the counselees' recollections and interpretations play a crucial role as mediators between the information actually communicated and the outcomes (286,285). We assume that recollections and interpretations are important because they represent the fundamental 'process of flexibly integrating the communicated genetic information into the general context of their life'(59). We therefore hypothesize that both the information actually communicated and the contextual variables influence the recollections/interpretations, and indirectly

influence the outcomes via – and only via – the complete mediation of recollections/interpretations. We expect the strength of the causal relationships between the recollections/interpretations and the outcomes to differ between the category of DNA result (PM, UR or UV), as suggested by the simple input-output models (35,70,183) (i.e. moderated mediation (184); e dotted line in model 4, figure 1).

1.5. Research questions

In this explorative study, we wanted to predict the short-term outcome of giving a DNA test result to counselees who had already had cancer, by using an extended model (figure 1). We wanted to determine if the short-term outcomes of reporting a DNA test result are only directly predicted and/or completely mediated by the counselees' recollections/interpretations? That is, can these outcomes be directly predicted by the DNA test result actually communicated and the contextual factors?

2. Methods

2.1. Sample and procedure

Eligible participants were women with breast and/or ovarian cancer who had requested a BRCA1/2 test in the period 2006-2009 at the Departments of Clinical Genetics of Leiden University Medical Center, Maastricht University Medical Center, University Medical Central Groningen, Erasmus Medical Center Rotterdam, or the VU Medical Center Amsterdam. All these centers offer genetic counseling according to Dutch guidelines, although this did not prevent some variation (see table 3).

Eligible counselees were sent an informed consent letter and a questionnaire after the first counseling session (T1), when DNA testing was offered to those with a mutation detection rate of at least 10% based on the family cancer history and/or those who had had a cancer diagnosed at a relatively young age (29,316). A second questionnaire was sent three months after the second counseling session, in which the DNA test result was disclosed (T2). The counselor filled in a checklist after each session to report what information had actually been given to the patient. This was complemented with information from medical files. DNA test results were generally communicated face-to-face, but in 18 cases by phone. Within 3 months after the result, all the counselees were sent a letter which summarized the genetic information communicated. Tables 1 and 3 show the pieces of genetic information communicated.

Table 3. *Overview of the pieces of information most frequently given by the genetic counselor*

	All counselees (n=248)		Pathogenic mutation (n=30)		Non-pathogenic result (n=218)*	
Communicated information	**n (%)**	**M (sd)**	**n (%)**	**M (sd)**	**n (%)**	**M (sd)**
DNA test result category						
unclassified variant	16 (6%)					
pathogenic mutation	30 (12%)					
uninformative result	202 (82%)					
Cancer risk for healthy female relatives						
breast cancer	195 (78%)	29% (9%)	30 (100%)	45% (8%)	157 (78%)	26% (11%)
ovarian cancer	67 (27%)	17% (7%)	30 (100%)	21% (7%)	27 (14%)	13% (7%)
Cancer risk for counselees						
contralateral breast cancer	238 (96%)	36% (5%)	30 (100%)	45% (2%)	194 (96%)	35% (4%)
ovarian cancer	96 (39%)	11%(10%)	30 (100%)	28% (5%)	60 (30%)	2% (1%)
Likelihood of heredity						
very likely	30 (12%)		30 (100%)		0	
likely	64 (26%)		0		57 (28%)	
unlikely	58 (24%)		0		53 (26%)	
unclear	213 (4%)		0		42 (21%)	
general explanation	50 (20%)		0		202 (100%)	
Risk management options for counselees						
unchanged	107 (43%)		5 (17%)		94 (47%)	
option of surgery	76 (31%)		23 (77%)		42 (21%)	
option of frequent surveillance	149 (60%)		23 (77%)		118 (58%)	
Risk management options for relatives						
option of surgery	78 (31%)		29 (97%)		45 (22%)	
option of frequent surveillance	218 (88%)		29 (97%)		177 (88%)	
DNA testing	54 (22%)		28 (94%)		15 (7%)	

*M: mean, sd standard deviation; *unclassified variants and uninformative results were combined because no significant differences were found between these.*

2.2. Instruments

To answer the research questions, we tested mediation models at T2, consisting of predictors (I, information), mediators (P, perception), outcomes (O, outcomes) and contextual variables (C, context).

The predictors related to the information (I) actually communicated. Table 1 lists all the possible pieces of genetic information (we did not select specific pieces because of the exploratory nature of this study). These items were developed by analyzing counseling sessions, and by discussion with several counselors from different departments of clinical genetics.

The mediators were questions on perception (P), which were shown to be important predictors and mediators in previous studies (285; see table 2). We asked counselees about their recollections and interpretations of: their own risk for developing a contralateral breast tumor; their relatives' cancer risk for developing a primary breast cancer; the likelihood that cancer was heritable in the family. We did not ask about their perception of other pieces of genetic information to avoid making the questionnaire too long. We excluded perceived ovarian cancer risks as predictors, because 239 (97%) of all participants reported that their perception of ovarian cancer risks or their actual risk influenced their lives less than breast cancer risks.

Outcome measures (O) included medical decisions and psychological well-being, as in previous studies and for ease of comparison (see table 2). We not only asked counselees about past medical behavior, but also about their current medical intentions, because we did not expect to find large changes shortly after they learned their DNA test result, but we did expect to see changes in their intentions. We also added new genetic-specific questions about life changes and BRCA-related self-concept (see section 1.4.).

To reduce the number of outcomes, we created composite measures and/or used principal component analyses (PCA) with varimax rotation, and we decided on the number of factors on the basis of the eigenvalues, scree plot, Variance-Explained-For (VAF/R^2), interpretability, and Cronbach's alpha. PCA results are not presented here but can be requested from the authors. For each participant, we calculated scores on the created factors using regression analyses (m=0; sd=1.0).

Medical decisions during the past 6 months consisted of the composite variables: breast self-examination, surveillance of breasts and ovaries. Nobody had undergone a PBM and PBSO after DNA testing at the time of this study. PCA showed three intentions: for surveillance of breasts, PBM, and surveillance of ovaries/BSO.

PCA suggested negativity and worries as two factors underlying the scores on the Hospital Anxiety and Depression Scale, Positive Affect Negative Affect Scale, Lerman's Cancer Worry Scale, and Impact of Events Scale (288,290,291,286,289). Negativity measured general as well as cancer-specific negative emotions. Worries measured general and cancer-specific worries. PCA confirmed that Esplen's BRCA-related self-concept

consisted of feeling stigmatized, vulnerable to developing cancer, and reduced mastery over cancer (75,277). PCA confirmed two composite scores out of eight life domains: psychological changes and physical-medical changes due to DNA testing (203,285).

Contextual variables (C) were reliable and/or valid items from previous Dutch studies (see section 1.4.). The medical context considered cancer history and sociodemographics. The familial context was studied by the openness to discuss hereditary cancer in the family scale (168) and the counselees' reasons to undergo DNA testing (1). Adjusted items on the Illness Perception Questionnaire (IPQ) (317) examined whether other life events during the last six months had influenced their lives. The psychological context considered coping (318), illness representations (317), existential personality traits (319) and optimism (320).

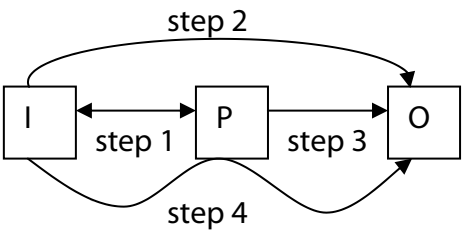
2.3. Statistics

Our analyses focused on T2, after the DNA test result was disclosed. Descriptives and t-tests were used to describe population-, perception- and outcome variables. Multiple imputing was used for missing values (<10% of one scale missing). As in our previous studies (277,321), questions were analyzed with bootstrapping mediation analyses, with 5000 bootstrap resamples because of its large power (185,187,189).

First, we performed mediation analyses on all the counselees together. Then we analyzed each of the three groups of DNA test result categories separately (i.e. moderated mediation).

The perception variables (P) mediate the relationship between the information actually communicated (I) and the outcomes (O) when four steps are fulfilled: 1. information actually communicated and perception correlate significantly (I&P); 2. information actually communicated significantly predicts outcomes (I→O); 3. perception variables significantly predict outcomes (P→O); and 4. when the perception variables are included in the bootstrap analyses, I explains O less accurately than step 2 (I→P→O). Either the beta decreases but remains significant (i.e. 'partial mediation') or the beta becomes non-significant (i.e. 'complete mediation'). Steps 2, 3 and 4 are presented together in one table: step 1 is assumed by the table and is therefore excluded.

Figure 2. *Schema of mediation steps, as explained in the method section*



I (predictor) = information actually communicated by the genetic-counselor (see table 1)
P (mediator) = perception of the counselee (see table 2)
O = outcomes (see table 2)

Table 1. *Overview of predictors and contextual factors, including instruments used in our analyses*

Group		Operationalization
Information actually communicated by the genetic-counselor (derived from medical file, summary letter and checklist filled in by genetic counselor)	*DNA test result category (T1 & T2) **	pathogenic mutation, unclassified variant, uninformative
	Cancer risks relatives (T1 & T2)	cancer risks in %; cancer risks rescaled to a 1-7 scale (not at risk-completely at risk) to match the counselees' perception items
	Cancer risks counselees(T1 & T2)	cancer risks in %; cancer risks rescaled to a 1-7 (not at risk-completely at risk) scale to match the counselees' perception items
	Heredity likelihood (T1 & T2)	1-7 scale (not likely to be heritable–very likely to be heritable)
	*Risk-management options counselees (T1 & T2) **	1. not changed, 2. mastectomy (PBM), 3. oophorectomy (PBSO), 4. frequent surveillance, 5. surveillance frequency comparable with population
	*Risk-management options relatives (T1 & T2) **	1. not changed, 2. mastectomy (PBM), 3. oophorectomy (PBSO), 4. frequent surveillance, 5. surveillance frequency comparable with population
	*Additional information ** *(T2)*	1. explanation of population breast/ovarian cancer risks, 11. explanation of part of breast/ovarian cancers caused by heredity, 12. risk of finding a pathogenic mutation, 13. risk of transmitting a pathogenic mutation, 14. additional explanation of the detected mutation, 15. communication of mutations –also benign ones- are frequently found in DNA, 16. being at-risk does not mean developing cancer, 17. cancer is not likely to be heritable in your family, 18. other untested mutations may explain cancer, 19. extra explanation of genetics in general, 20. explanation of the possibilities of DNA testing, 21. possibility of future research and new findings, 22. at T1: possibility of finding an unclassified variant.
	*Communication format **	1. in words; 2. in percentage; 3. in words and percentage, 4. mirroring of risks (e.g.10%at risk and 90% not at risk), 5. exact cancer risk versus range of cancer risks, 6. using the neutral terms 'genetic change' or 'variation' instead of 'mutation' or 'deviation'
	Communication process	Factual aspects: 1. DNA test result disclosure face-to-face or by phone*, 2. provision of a flyer explaining genetic testing and results*; Self-reflection by genetic counselor on 1-7 semantic differentials: 4. stressing the indefiniteness of the non-pathogenic result, 5. attentive to emotions, 6. clearness, 7. difficulty, 8. uncertain, 9. to-the-point.

Table 1. *Continued*

Medical context (derived from questionnaire; medical file confirmation)	*Cancer history (T1 & T2)*	1. breast or ovarian cancer*, 2. metastases*, 3. kind of cancer treatment: mastectomy*, BSO*, chemotherapy*, radiotherapy*, other therapy*, 4. years since disclosure of cancer diagnoses, metastases, treatment and of genetic counseling
	Sociodemographics (T1)	1. living together with a partner*, 2. having children*, 3. number of children, 4. number of children at home, 5. being religious*, 6. having a job*, 7. number of hours of job, 8. educational level ranging from none (0) – university (7), 9. age.
Familial context (derived from questionnaire + medical file)	*Family relationships (T1)*	In questionnaire: 1. openness to discuss hereditary cancer in the family scale (scores ranges from 7=closed to 35=open) (168); 2. In medical file: pedigree information, i.e. numbers and percentages of with-cancer-affected and deceased 1st, 2nd and/or 3rd degree relatives.
	Motivation (T1)	In questionnaire: 1. self as motivation to undergo DNA testing (not much,1-7), 2. relatives as motivation to undergo DNA testing (1=not – 7=much)
	Other life events (T2)	In questionnaire: Perceived influence on life from other life events, as measured by adjusted IPQ questions (1=few – 10=many changes) (317)
Psychological context (derived from questionnaire)	*Coping with DNA test result (T2)*	COPE: 1. active, 2. acceptance, 3. distraction, 4. denial, 5. priority taking, 6. ask for help, 7. turn towards God, 8. renaming, 9. expression of emotions, 10. waiting, 11. surrender, 12. making plans, 13. using drugs, 14. asking moral support (4=not – 8=much) (318)
	Illness representations (T2)	IPQ R: 1.timeline, time cycle, consequences, personal control, treatment control, illness coherence (1=few – 10=many changes) (317,87,202)
	Personality (T2)	Ryff's conceptual well-being scales: 1. environmental mastery, 2. purpose in life, 3. self-acceptance, 4. autonomy, 5. personal growth, 6. enjoying relationships, 7. vitality, 8. inner strength (6, little-36, much)(319); Revised life orientation scale measuring (10=not optimistic – 50=very optimistic) (320)

**measured on a binary scale (not communicated = 0; communicated = 1)*

Table 2. *Overview of mediators and outcomes; single items, composite scales, or factors resulting from principal component analyses*

	Group	Scaling	Range of total scores	Explained variance if PCA; Alpha	References	Items
Mediators	*recollections of cancer risks and heredity likelihood* (single items)	2 items	1-7 (not completely at risk/heritable)		(203,285)	(1) According to your genetic counselor what is your risk of developing cancer (again); (2) according to your genetic counselor, what does your pedigree/DNA result mean for the likelihood that cancer is heritable in your family (pathogenic mutation: result-based; other DNA results: pedigree-based)
	interpretations of cancer risks and heredity likelihood (single items)	2 items	1-7 (not completely at risk/heritable)		(203,285)	What are your own thoughts and feelings about: (1) your risk of developing cancer (again), (2) the likelihood that cancer is heritable in your family, (3) the risk for healthy relatives
Outcomes	*medical decisions last 6 months* (composite measure)	(1) breast self-examination (1 item) (2) breast surveillance (2 items) (3) ovaries' surveillance (2 items)	1-5 (not at all-every day) 0-1 (no-yes) 0-1 (no-yes)			During the 6 last months have you performed or had: (1) breast self-examination; (2) surveillance of breasts by physician; mammography; (3) surveillance by physician; blood sample
	medical decisions intended in the next 6 months (PCA)	(1) intended breast surveillance (3 items) (2) intended mastectomy (PBM) (2 items) (3) intended surveillance/surgery of ovaries (PBSO) (3 items)	Individual regression scores (overall: m=0, sd=1)	.27; .87 .27; .87 .19; .90		In the next 6 months do you intend to perform: (1) breast self-examination; surveillance of breasts by physician; mammography; (2) mastectomy (PBM); (3)surveillance by physician; blood sample; PBSO
	BRCA-related self-	(1) stigma (7 items)	7-49 (none-a lot)	.30; .75	(75,277)	See scales in references

Table 2. *Continued*

	concept (composite measure, PCA-confirmed)	(2) vulnerability (5 items) (3) mastery (4 items)	5-35 (none-a lot) 4-28 (none-a lot)	.22; .73 .19; .59		
	current psychological well-being (PCA)	Hospital Anxiety and Depression Scale; Impact of Events Scale; Positive Affect Negative Affect Scale; Lerman's Cancer Worry Scale (1) negativity (2) worries	individual scores calculated with regression (overall: m=0, sd=1)	.40; .90 .37; .87	1: (288,290) 2: (291) 3: (286)	See scales in references: (1) anxiety, depression, positive and negative affects (2) cancer worry, avoidance, intrusions, anxiety
	changes in life since DNA test result (composite measure, PCA-confirmed)	(1) psychological changes (3 items) (2) physical-medical changes (5 items)	3-15 (none-a lot) 7-35 (none-a lot)	.20; .67 .40; .83	(203,277)	(1) emotional well-being, social relationships, personality, coping with uncertainty, existential view on life. (2) preventive risk management, physical complaints, body experience

We use the expression 'direct effect' to indicate that I directly predicts O (I→O); its beta is not influenced by P (i.e. mediation in step 4 is not significant). 'Indirect effect' indicates that I indirectly predicts O, via the partial or complete mediation of P (i.e. mediation in step 4 is significant). 'Effect' (without an adjective) indicates analyses between the variables I-P or P-O in steps 1, 2 and 3.

Similarly, perception variables (P) mediate the relationship between the contextual variables (C) and the outcomes (O) when 4 similar steps are fulfilled: C&P; C→O; P→O; and C→P→O.

Linear regression analysis was used to calculate standardized betas and logistic regression for binary outcomes. To keep analyses simple, the counselees' recollections and interpretations of their own cancer risks, their relatives' cancer risks, and heredity likelihood were included as independent mediators without taking into account any possible mutual relationships. Sizes of significant effects were described with simple correlation coefficients, Cohen's d and f^2. PBM/BSO after DNA testing were not described, because no counselees had undergone such surgery after testing at the time of this study.

We decided to define the significance level by $p<.01$ as a balance between arguments. On the one hand, our study had an exploratory nature, which suggested we should take a high p-value to avoid a type II statistical error. On the other hand, the large number of tests increased the possibility of a type I error, which we had to reduce by lowering the p-value.

3. Results

3.1. Description

467 counselees filled in the first questionnaire after the intake session (T1), and 248 (54%) of them returned the second questionnaire after the DNA test result (T2). At T1 decliners showed more negativity, worries, coped more often by denial and taking drugs (all d's=.2), and recalled a lower own cancer risks (d=.4).

The mean time since cancer diagnosis was 5 years; 94% had had breast cancer and 6% ovarian cancer. Metastases were detected in 26% of them. Before DNA testing, 56% had undergone symptomatic mastectomy, 6% symptomatic BSO, and 5% presymptomatic BSO. Their mean age was 56 years, 42% had attended high school/higher education, 84% were married, and 87% had children (see table 4).

Table 5 shows the outcome variables and shows that many participants had recently undergone surveillance of breasts and/or ovaries, or intended to do so during the next six months. None of them had undergone prophylactic surgery after DNA testing, but several PM carriers intended to do so. Counselees reported 'some' changes in their lives after DNA testing, currently experienced little negativity and worries, but felt little mastery over their cancer. Table 6 shows that all the perception variables differed from the information actually communicated, and that relatives' risks were interpreted as higher than own

cancer risk. Cancer risks and the likelihood of heredity were perceived as high by PM counselees, as low by UR counselees, and as intermediate by UV counselees.

Table 4. *Description of study population*

	Variable	n	%	Mean	sd
Participation	Returned questionnaire after intake	458	68		
	Returned questionnaire after DNA-result	248	54		
Cancer history	Time since diagnosis (years)			5	5
	Breast cancer	234	94		
	Ovarian cancer	14	6		
	Metastatic cancer	64	26		
	Mastectomy (BM)	139	56		
	Bilateral salpingo oophorectomy (BSO)	53	11		
Sociodemographics	Age			56	23
	Attended high school or higher	105	42		
	Being married	207	84		
	Having children	216	87		
	Having daughter(s)	171	69		
	Having son(s)	151	61		

3.2. Overall

Step 2 (I→O): The actually communicated cancer risks for counselees and for relatives did not directly predict any outcomes (see indirect predictions in step 4.)
Step 3 (P→O): The counselee's interpretations of her own and her relatives' cancer risks and heredity likelihood predicted breast self-examination, performed surveillance of breasts and ovaries, and intended breast surveillance and mastectomy with small effects. The counselee's recollections and interpretations of her own and her relatives' cancer risks and heredity likelihood also predicted stigma, mastery, worries, negativity, medical-physical and medical changes to a large extent (see table 6).
Step 4 (I→P→O): Via the complete mediation of interpreted heredity likelihood, the actually communicated cancer risks for counselees and relatives indirectly predicted the intention to undergo surveillance and/or surgery of ovaries. Via the complete mediation of recalled and interpreted cancer risks, the actually communicated counselee's cancer risks predicted vulnerability. Mediation effects were large.

Thus, in sum, the actually communicated cancer risks for counselees and relatives did not directly predict any outcomes. The counselees' perception did predict these outcomes and completely mediated the effect of the communicated risks on the intention to undergo surveillance/surgery of ovaries.

Table 5. *Description of outcome variables*

	Outcome variable	Overall (n=248)				Pathogenic mutation (n=30)		Uninformative result (n=202)		Unclassified variant (n=16)	
		M	sd	High scorers		M	sd	M	sd	M	sd
				n	%						
Medical	breast self-examination	2.3	1.1	74	30	2.5*	.8	2.0*	.8	2.0*	.9
	breast surveillance	.82	.3	n/a		.89*	.3	.68*	.5	.82*	.3
	ovaries surveillance	.35	.4	n/a		.47*	.5	.33*	.5	.38*	.5
	intention for surveillance of breasts	5.0	.8	144	58	5.3*	.4	4.9*	.8	5.2*	.7
	intention for mastectomy	2.5	1.2	32	13	4.5*	.6	1.6*	.7	2.3*	.9
	intention for surveillance/surgery ovaries	2.6	1.5	50	20	4.3*	.8	1.6*	.7	2.3*	1.3
BRCA-related self-concept	BRCA-related stigma	19.2	7.0	20	8	22.8*	5.4	17.8*	5.6	18.7*	7.2
	BRCA-related vulnerability	16.5	6.4	65	26	20.3*	6.8	15.1*	6.9	16.1*	6.1
	BRCA-related mastery	11.0	3.1	30	12	12.4*	2.7	10.6*	2.5	10.8*	3.1
Psychological	negativity	.04	3.5	12	5	.67	3.3	0.0	3.5	.64*	.2
	worries	.00	2.6	12	5	.16	1.9	0.0	2.7	.58*	2.3
Life changes after DNA testing	medical-physical	5.4	2.4	12	5	6.7*	2.0	5.1*	2.3	5.4*	.4
	psychological	9.6	4.1	11	4	11.2*	4.0	9.5*	4.2	9.6*	3.5

*See table 2 for description of scales. *Differences between pathogenic mutations and non-pathogenic results (t-test; Cohen's d>.30). See explanation of 'high scores' in the Methods section.*

Table 6. *Overview of perception variables.*

	Actually communicated breast cancer risk for counselee[1]		Actually communicated breast cancer risks for relatives[1]		Recalled own breast cancer risk		Interpreted own breast cancer risk		Recalled heredity likelihood		Interpreted heredity likelihood		Interpreted relatives' cancer risks	
	M	sd	M	sd	M	sd	M	sd	M	sd	M	sd	M	sd
T2: overall	4.2	1.4	3.7	1.0	3.8 2367	1.2	3.9 2367	1.3	3.7 2367	1.8	3.3 2367	2.0	4.7 2367	1.5
T2: pathogenic mutation	5.8	.5	4.6	.7	5.2 2367	.8	5.2 2367	1.2	6.0 2367	1.5	6.8 2367	.6	6.6 2367	1.0
T2: uninformative result	4.4	.9	2.9	1.2	3.4 2367	1.2	3.6 2367	1.2	3.3 2367	1.6	2.8 2367	1.6	4.4 2367	1.4

Means and (standard deviations).[1] Actually communicated percentages re-categorized to 1-7 Likert scales, to match the scale of all perception variables: 1 (very low risk/not likely heritable)-7 (very high risk/very likely heritable). Perception compared with actually communicated cancer risks: [2] difference (Cohen's d>.30), [3]low correlation (R<.23). Interpretations compared with recollections: [4] difference (d>.30), [5]low correlation (R<.23) (NB: recollections and interpretations differed significantly and all R<.23 for counselees with an independent personality, see table 2; differences were not significant and all R>.50 for dependent personalities). Perception of own cancer risks, relatives' cancer risks and heredity likelihood compared with each other: [6]difference (d>.30), [7]low correlation (R<.23). Significant influence from having undergone mastectomy and/or BSO on perception variable: [8]difference between undergone/not undergone (d>.30), [9]correlation (R>.23)

Table 7. *Mediation analyses for counselee's and relatives' cancer risks (T2), (n=248)*

Predicted outcomes (O)	Information (I) (std. ß)		Perception (P) (std. ß)					Total model statistics	
	Counselee's cancer risks	Relatives' cancer risks	Recalled cancer risk	Recalled heredity likelihood	Interpreted cancer risk	Interpreted heredity likelihood	Interpreted relatives' risks	R^2	f^2/n
EFFECT (P→ O)									
Medical									
breast self-examination	ns	ns	ns	ns	ns	ns	.22	.05	.05
breast surveillance	ns	ns	ns	ns	.21	.20	ns	ns	.05[n]
ovaries surveillance	ns	ns	ns	ns	.22	ns	ns	ns	.05[n]
intention breast surveillance	ns	ns	ns	.17	ns	.08	ns	.04	.04
intention mastectomy	ns	ns	ns	ns	.16	.14	ns	.08	.09
Psychological									
stigma	ns	ns	-.24	ns	.43	ns	.21	.17	.20
mastery	ns	ns	ns	ns	.43	.19	.21	.22	.28
worries	ns	ns	.64	ns	.98	ns	.75	.50	1.00
negativity	ns	ns	ns	ns	.10	.37	.24	.33	.49
Life changes									
medical-physical changes	ns	ns	-.33	ns	.52	ns	ns	.21	.27
psychological changes	ns	ns	-.31	.18	.58	ns	ns	.17	.20
INDIRECT EFFECT (I→ P→O)									
intention surveillance/surgery ovaries (PBSO)	.02/ns	ns	ns	ns	ns	.36	ns	.13	.15
intention surveillance/surgery ovaries (PBSO)	ns	.03/ns	ns	ns	ns	.33	ns	.22	.28
vulnerability	.12/ns	ns	.37	ns	.45	ns	ns	.27	.37

Table shows standardized betas for outcome variables (O) predicted directly by actual information communicated (I) or by the counselees' perception (P), or by mediation (I→P→O). Only significant predictors, mediators and total models are presented. P-values <.01. R^2 is explained variance of total model, f^2 the corresponding effect size. Constant and error terms are not given and can be requested from the authors. The mediation rows show two betas for the actually communicated cancer risks: prediction without/with inclusion of the mediator(s) in the regression. equation; a reduction of the ß implies partial mediation (e.g. .02/.05); when ß become not significant (.02/ns), this implies complete mediation. Outcomes not presented here were not significantly predicted by any variables. n=Nagelkerke ns not significant.

3.3. Pathogenic mutations

Step 2 (I→O): The actually communicated PM and cancer risks did not directly predict any outcomes (see indirect predictions in step 4).
Step 3 (P→O): The interpretations of cancer risks predicted, together with recalled cancer risks, interpreted heredity likelihood and relatives' risks, breast self-examination, surveillance of ovaries/breasts and intended mastectomy. All the perception variables predicted stigma, mastery, negativity, medical-physical and psychological life changes. All effects were large (see table 7).
Step 4 (I→P→O): Via the complete mediation of recalled cancer risks, the actually communicated PM indirectly predicted the intention to undergo surveillance/surgery of the ovaries. Via the complete mediation of interpreted counselee's cancer risks, recalled counselee's cancer risks and interpreted relatives' cancer risks, the actually communicated PM indirectly predicted vulnerability and worries. Mediation effects were large.

Thus, in sum, the actually communicated PM did not directly predict any outcomes. The counselees' perceptions did predict these outcomes and completely mediated the effect of communicated risks on the intention to undergo surveillance/surgery of ovaries, vulnerability and worries.

3.4. Uninformative results

Step 2 (I→O): The actually communicated UR and cancer risks did not directly predict any outcomes (see indirect predictions in step 4).
Step 3 (P→O): The interpreted cancer risks and heredity likelihood predicted performed and intended surveillance of ovaries, with a small effect. The recollections and interpretations of counselee's and relatives' cancer risks and heredity likelihood predicted stigma, mastery, vulnerability, negativity, medical physical and psychological changes, with a large effect (see table 9).
Step 4 (I→P→O): Via the complete mediation of the recalled and interpreted counselees' and relatives' cancer risks, the actually communicated UR indirectly predicted the intention to undergo surveillance/surgery of ovaries and worries.
Thus, in sum, the actually communicated UR did not directly predict any outcomes. The counselees' perceptions did predict these outcomes and completely mediated the effect of the communicated risks on the intention to undergo surveillance/surgery of ovaries, and worries. Most medical outcomes were not predicted at all.

Table 8. *Mediation analyses for pathogenic-mutations (T2), (n=30)*

Predicted outcomes (O)	Information (I) (std. ß)	Perception (P) (std. ß)					Total model statistics	
	Pathogenic mutation result	Recalled cancer risk	Recalled heredity likelihood	Interpreted cancer risk	Interpreted heredity likelihood	Interpreted relatives' cancer risks	R^2	f^2/n
EFFECT (P→ O)								
Medical								
breast self-examination	ns	ns	ns	.69	ns	.35	.41	.69
breast surveillance	ns	ns	ns	.71	1.9	ns	ns	.20 [n]
ovaries surveillance	ns	4.8	ns	2.9	ns	ns	ns	.62 [n]
intention mastectomy (PBM)	ns	ns	ns	.25	ns	ns	.06	.06
Psychological								
stigma	ns	.77	ns	.85	ns	ns	.21	.27
mastery	ns	ns	-.42	ns	-.37	ns	.27	.37
negativity	ns	ns	ns	.20	.30	.30	.28	.39
Life changes								
medical-physical changes	ns	.84	ns	1.2	.49	ns	.50	1.00
psychological changes	ns	.13	ns	1.6	.62	ns	.59	1.44
INDIRECT EFFECT (I→ P→O)								
Medical								
intention surveillance/surgery ovaries (PBSO)	1.2/ns	2.4	ns	ns	ns	ns	.25	.33
Psychological								
vulnerability	3.2/ns	2.4	ns	3.4	ns	ns	.32	.47
worries	1.22/ns	ns	ns	.54	ns	.13	.52	1.08

See footnote for table 7

Table 9. *Mediation analyses for uninformative results (T2)*

Predicted outcomes (O)	Information (I) (std. ß)	Perception (P) (std. ß)					Total model statistics	
	Uninfor-mative result	Recalled cancer risk	Recalled heredity likelihood	Interpreted cancer risk	Interpreted heredity likelihood	Interpreted relatives' cancer risks	R^2	f^2/n
EFFECT (P→ O)								
Medical								
ovaries surveillance	ns	ns	ns	.47	ns	ns	ns	.17[n]
intention breast surveillance	ns	ns	ns	.18	.18	ns	.08	.09
Psychological								
stigma	ns	ns	ns	.27	ns	.23	.16	.19
mastery	ns	.08	ns	.40	ns	.16	.23	.30
vulnerability	ns	.48	ns	.66	ns	.23	.21	.27
negativity	ns	ns	.25	.20	.20	ns	.39	.64
Life changes								
medical-physical changes	ns	.31	.25	.39	ns	ns	.15	.18
psychological changes	ns	.23	.12	.51	ns	ns	.17	.20
INDIRECT EFFECT (I→ P→O)								
intention surveillance/surgery ovaries (PBSO)	-.88/ns	.25	ns	.18	ns	ns	.20	.25
worries	1.50/ns	ns	ns	.45	ns	.15	.52	1.08

See footnote in table 7

Table 10. *Mediation analyses for unclassified variants (T2)*

Predicted outcomes (O)	Perception (P) (std. ß)					Total model statistics	
	recalled cancer risk	recalled heredity likelihood	interpreted cancer risk	interpreted heredity likelihood	interpreted relatives' cancer risks	R^2	f^2/n
EFFECT (P→ O)							
Medical							
breast self-examination	ns	ns	ns	ns	.47	.22	.28
breast surveillance	ns	ns	ns	.41	ns	ns	.17[n]
ovaries surveillance	ns	ns	.36	.40	ns	ns	.14[n]
intention breast surveillance	ns	.45	ns	.21	ns	.41	.69
intention mastectomy (PBM)	ns	ns	.19	.37	.18	.40	.67
intention surveillance/surgery ovaries (PBSO)	ns	.57	ns	ns	ns	.32	.47
Psychological							
stigma	ns	ns	1.2	.62	ns	.95	19.0
mastery	ns	ns	-.58	ns	ns	.34	5.1
vulnerability	ns	ns	.96	ns	ns	.93	13.3
negativity	ns	ns	.53	.50	ns	.26	.35
worries	ns	ns	1.30	.54	ns	.99	99.0
Life changes							
medical-physical changes	ns	.31	.24	.97	ns	.79	3.8
psychological changes	.39	ns	.86	ns	ns	.99	99.0

See footnote in table 7

3.5. Unclassified variants

Step 2 (I→O): The actually communicated UV and cancer risks did not directly predict any outcomes (see indirect predictions in step 4).
Step 3 (P→O): The recollections and interpretations of heredity likelihood and the interpretations of cancer risks for counselees and relatives predicted breast self-examination, surveillance of ovaries/breasts, and the intentions to undergo surveillance or surgery. The interpretations of cancer risks and heredity likelihood predicted stigma, mastery, vulnerability, negativity and worries, medical physical and psychological life changes. All effects were large (see table 10).
Step 4 (I→P→O): There were no significant mediation effects.
Thus, in sum, the actually communicated UV did not directly predict any outcomes. All outcomes were strongly predicted by their perception.

3.6. Contextual variables

Step 2 (C→O): The contextual variables did not directly predict any outcomes, neither in the overall analyses nor in the specific PM/UR/UV groups (see indirect predictions in step 4).
Step 3 (C→O): See sections 3.2.-3.6.
Step 4 (C→P→O): Via the complete mediation of the recalled and interpreted counselees' and relatives' cancer risks, most of the variables regarding the counselees' medical, familial and psychological context predicted the intention to undergo surveillance/surgery of ovaries and worries. Because of their small effect sizes, these are not presented.

Thus, in sum, the medical, familial and psychological context of the counselees predicted their recollections/interpretations, but did not directly predict any outcomes strongly.

4. Discussion

4.1. Conclusion

This study has confirmed (278,285) the crucial role of the counselees' perception, that is, their recollections and interpretations of the communicated cancer risks for themselves and for their relatives, and of the likelihood of heredity being involved. These perception variables were influenced by both the genetic information actually communicated, and the medical, familial and psychological context of the counselee. Subsequently, these perceptions predicted the counselees' medical intentions and decisions, psychological well-being, and genetic-specific vulnerability, stigma, mastery and life changes. These outcomes had not directly been predicted by the genetic information communicated or the contextual variables: the context only influenced the outcomes via the complete mediation of the counselees' recollections and interpretations. Effect sizes were larger than most other perception studies, probably because we used both more and specific perception variables (285). This important role of the counselees' perception suggests that genetic information is not 'simply taken up as value-neutral objective truth' (63), but is flexibly embedded in the general context of the counselees' lives (59) and 'interiorized against a pre-existing sense of self' (63).

4.2. Outcomes

In line with previous studies, we found the overall psychological impact of genetic testing was relatively small (69,74,322-324). Subgroups reported high scores (see table 5). The higher the counselees recalled and interpreted their heredity likelihood and cancer risks for themselves and their relatives, the greater were their distress scores (independent of whether they had a PM, UV or UR test result). This suggests that some counselees may struggle with genetic and cancer-specific issues, but most do not experience pathological levels of distress.

The counselees' distress in the short-term was not only predicted by their perception of their own cancer risks, but also by their relatives' cancer risks and heredity likelihood. Thus, in contrast with long-term results (277), the counselees' distress shortly after learning their DNA test result was partly due to their ideas and feelings of what the result would mean for their relatives and the consequences. These worries may disappear over time when it is more likely that the counselee has communicated the result to her relatives and they have also undergone DNA testing and/or had medical surveillance.

No counselees had undergone (contralateral) prophylactic surgery after DNA testing, probably due to the short period since the result was known, but the recent uptake of surveillance of breasts and/or ovaries was high. Intentions to undergo medical surveillance of breasts/ovaries in the next six months were also high, and several PM carriers intended to undergo prophylactic (contralateral) surgery. Counselees seemed motivated to undergo

surveillance and/or surgery because of their own recollections and interpretations of the DNA test result. Thus, feeling at-risk predicted their medical behavior and intentions better than objective levels of risk.

4.3. DNA test results

Comparing the relationships and effect sizes between tables 7 to 10 shows different relationships between the perception variables and outcome variables for different DNA test results, i.e. moderated mediation. We also found significant differences between the DNA test results, in interaction tests with dummy labeling (data not shown).

PM carriers perceived their cancer risks and heredity likelihood as high. Their perceptions predicted all outcomes, and these counselees experienced a larger medical and psychological impact from genetic counseling than those with a UR result. Counselees with a UR result perceived relatively low cancer risks and heredity likelihood, experienced a small impact on their lives, and many outcomes were not predicted at all. This suggests that PM carriers perceived and reacted to their DNA test result fairly adequately, but those with a UR result experienced some 'false reassurance' and their medical decisions were neither based on the actual DNA test result nor on their own perception. UV counselees perceived their own and their relatives' cancer risks and heredity likelihood as relatively high, and when we compare their perception with the risks actually communicated in table 1, their overall perception seems to be inaccurate. They also had a strong intention to undergo mastectomy/BSO (almost as strong as mutation carriers) and they experienced more negativity and worries than the other test result groups. All outcomes were predicted by their own – probably inaccurate – perception with very large effects, although the large effects could also be due to the small sample size.

4.4. Tailoring information

In contrast with previous studies, we have described many different items of genetic information communicated by the genetic counselor. From all these items, only the following directly predicted the counselees' perceptions and indirectly predicted outcomes: the DNA test result category (PM/UR/UV), the counselees' own cancer risk and that for their relatives. Other items were not significant, probably because these were seldom communicated, and may reflect how genetic counselors tailor risk information to the counselees' context. Another possible explanation for the non-significance of information variables is that counselors did not consistently follow the Dutch counseling guidelines. We suggest the balance between standardized and tailored communication in genetic counseling should be studied.

4.5. Limitations

This study may be biased by the relatively large number of decliners at T2, and the fact that decliners had more negative symptoms than participants, which is line with other Dutch studies showing large decline[37]. There was a wide variation in the communication of the DNA test results, and not all the information was communicated to all counselees. There was no baseline measurement before intake for logistic reasons. Only cancer patients were included, and there were no control groups of healthy individuals or untested cancer patients, but our results are in line with other studies in these groups (321,325,326). We only included correlations larger than .20 and p values smaller than .01, so this may have caused us to miss clinically relevant relationships. The range of mediation, context, outcome variables and multivariate interactions may be further broadened in future studies. We have only presented contextual variables as predictors, since interaction analyses (data not presented) did not yield a different result.

4.6. Practical implications

The communication of UVs caused false alarm, poorly informed medical decisions, and distress, suggesting that UVs should only be communicated when necessary, e.g. if additional investigation in the family is needed (203,277).

The outcomes of DNA testing were only predicted and/or completely mediated by the counselees' perceptions. This suggests that counselees create their own interpretation of their DNA test result, and make medical decisions based on information from other sources in addition to their genetic counselor.

More studies are needed to better understand why counselees give subjective meaning to genetic disorders, and why many of them subjectively interpret the DNA test result communicated to them in such a way that their perception differs from the information actually given (78). Researchers should not only focus on genetic information, cognitive biases, schemas and heuristics that may predict the inaccuracy of the counselees' perception (cf.83,79,90,302,303,), but also on the qualitative/existential meaning that cancer risks may have for counselees (60,63,137,152,164).

Genetic counselors could help counselees in this interpretation process, for instance, by asking questions about their ideas and feelings about the DNA test result category, heredity likelihood, their own and their relatives' cancer risks, and the possible medical consequences (cf.264). Thus, counseling should be interactive and tailored to the individual, as suggested by a pilot study showing that explicitly discussing the counselees' pre-existing interpretations increases the accuracy of their risk perception (282). Such interventions could be effective because of their broad focus on the counselee and her subjective meaning-making instead of the mere information transfer (327).

Chapter 7

A whisper-game perspective on the family communication of DNA-test results:

A retrospective study on the communication process of BRCA1/2-test results between proband and relatives

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Abstract

Objective

The objective was to study how DNA-test result information was communicated and perceived within families.

Method

A retrospective descriptive study in 13 probands with a BRCA1/2 unclassified variant, 7 with a pathogenic mutation, 5 with an uninformative result, and in 44, 14, and 12 of their 1st and 2nd degree relatives respectively. We examined differences and correlations between: (a) information actually communicated (b) probands' perception, (c) relatives' perception. The perception consisted of recollections and interpretations of both their own and their relatives' cancer-risks, and heredity-likelihood (i.e. likelihood that cancer is heritable in the family).

Results

Differences and low correlations suggested few similarities between the actually communicated information, the probands' and the relatives' perception. More specifically, probands recalled the communicated information differently compared with the actually communicated information (R=.40), and reinterpreted this information differently (R=.30). The relatives' perception was best correlated with the proband's interpretation (R=.08), but this perception differed significantly from their proband's perception. Finally, relatives reinterpreted the information they received from their proband differently (R=.25), and this interpretation was only slightly related with the original message communicated by the genetic-counselor (R=.15). Unclassified-variants were most frequently misinterpreted by probands and relatives, and had the largest differences between probands' and relatives' perceptions.

Discussion

Like in a children's whisper-game, many errors occur in the transmission of DNA-test result information in families. More attention is required for how probands disseminate information to relatives. Genetic-*counselor*s may help by supporting the probands in communicating to relatives, e.g. by providing clear summary letters for relatives.

1.Introduction

1.1. Background

Having multiple family members with breast and ovarian cancer may lead an individual to request for DNA-testing. Usually, a DNA-test is first performed in an individual with cancer, a proband. The detection of a pathogenic BRCA1/2 mutation provides probands with precise information about their own cancer-risks. Contralateral breast-cancer recurrence risks for affected women are 30-60%, primary breast and ovarian-cancer risks for unaffected women are respectively 60-80% and 30-60% (BRCA1) / 5-20% (BRCA2). The majority of probands receives an uninformative-result (UR), and about 10% an unclassified-variant/variant-of-uncertain-clinical-significance (UV). In these cases, cancer-risks are primarily calculated on the basis of the pedigree.Vinket al, 2004 Subsequently, risk management options, such as surveillance and prophylactic surgery of ovaries and breasts depend on the pathogenic-result or the pedigree.

Many studies showed that probands may experience a significant influence of DNA-testing on their psychological wellbeing and medical decisions (66,76). Fewer studies have examined how probands communicate DNA-test results to untested relatives, and how a test result influences their relatives' lives. The perception and impact of relatives has not been studied from the relatives' own perspective (109), despite the fact that relatives are often closely involved in genetic-counseling.

First, many relatives provide medical information on the proband's request to complete pedigree information, which is the basis for DNA-testing and risk-estimation.

Second, many probands undergo DNA-testing for the reason of receiving genetic-information for their relatives (1,154,200). Detection of a pathogenic-result enables relatives to request for DNA-testing, and other DNA-results allow calculation of a priori cancer-risks for relatives on the basis of the pedigree.

Third, most relatives are informed by the proband about the DNA-test result, mostly within four months after testing (103). Especially pathogenic-mutations are communicated, in particular to first-degree female relatives from cohesive families for whom DNA-test results may have medical consequences (103-108). The communicated DNA-test result may subsequently cause distress in relatives (105,109-111), awaken familial conflicts and myths (112-114), and influence the relatives' well-being, medical-decisions and intention to request DNA-testing (109,115-120).

1.2. Family communication timeline

We examined the relatives' perception as a part of the family communication timeline of genetic counseling. Family communication of genetic-counseling involves two senders of genetic-information, viz. the genetic-counselor and the proband, and two receivers, viz. the proband and the relative. The communication of genetic-information may involve

'noise', either caused by genetic-*counselor*s and probands who disclose information inaccurately, and/or the probands and relatives who receive information inaccurately.

First, noise may occur in the receipt of information. We showed in previous studies that probands may recall the DNA-test result differently compared to what had actually been communicated (285). Subsequently, these probands did not interpret the risk-information result identical to how they recalled it. Hence, the receival of information – either by probands or relatives- consists of three different processes: actual communicated information, recollections and interpretations.

Second, noise may occur due to ineffective disclosure of genetic-information. In this family study, we focus on the proband, who is not only receiver, but also sender of information. It is unclear how the proband makes this role transformation, and whether she communicates what she recalls or whether she mainly communicates her own interpretation and makes a selection of the information when disclosing to relatives. We expect that the probands' main message is their subjective interpretation because the interpretation has been reported as the most important aspect of their perception, and strongly influences well-being and decision-making (285).

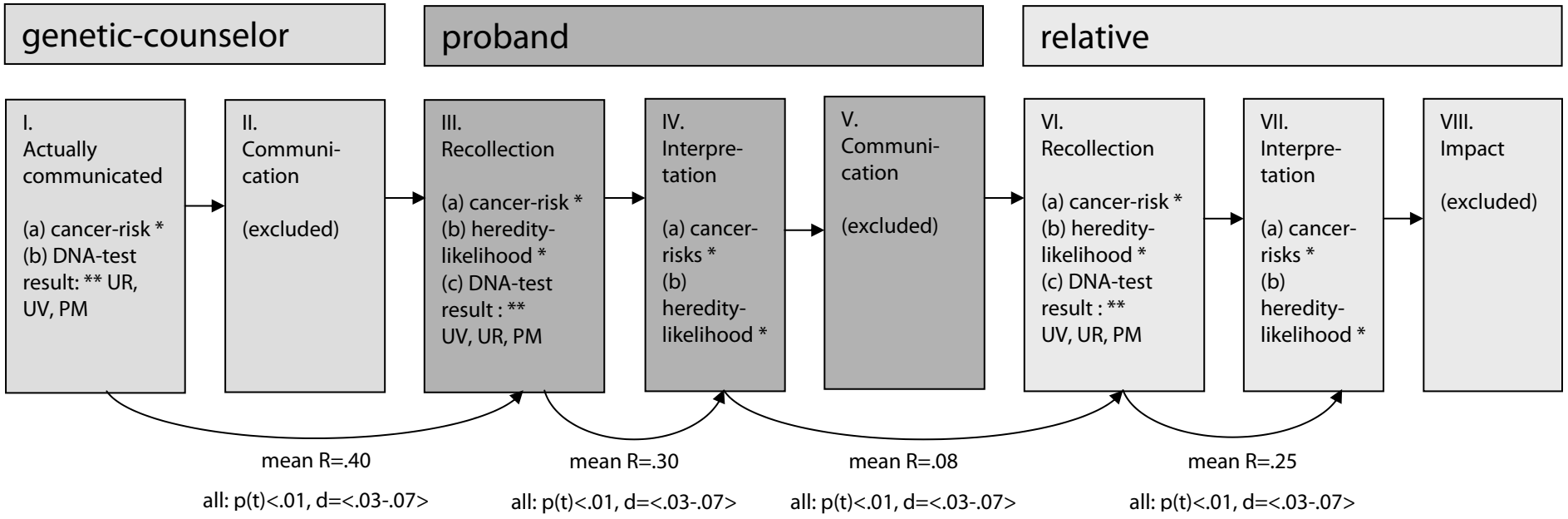
Figure 1 depicts our hypothesized family communication timeline of genetic counseling. I.A DNA-test result and cancer-risks are obtained; II.the genetic-*counselor* communicates this to a proband. III.The proband recalls and IV.interprets this information. V.The proband communicates her interpretation of the DNA-test result to the relative, which is VI.recalled and VII.interpreted by the relative, and VIII.may have consequences for the relatives' lives. Because of logistic reasons, II, V and VIII were excluded from this study.

1.3.Hypotheses and research questions

The difficulty of communicating information accurately can be illustrated by children's whisper games, in which one child whispers a word to another child who subsequently whispers the word to another child. In most cases, the last child in the line of whisperers understands another word than the initial word.

We hypothesized that the family communication of a DNA-test result functions like a whisper game, in which the originally communicated information fades out more at every step in the communication timeline. More specifically, we asked: 1.Is there a significant difference between each step in the family communication timeline of genetic-counseling? The steps in the family communication timeline of genetic-counseling consist of the genetic-information actually communicated by the genetic-*counselor* (i.e. DNA-test result category and cancer-risks), and the recollections and interpretations that probands and relatives have regarding this genetic-information (cf.figure 1). We expected to find significant differences between all variables of respectively steps I-III, III-IV, IV-VI, and VI-VII.

Figure 1. *Family communication timeline of genetic counseling, showing variables included in this article, and the found correlations and differences.*



'Excluded' boxes were not studied in this article;
R= mean Pearson's correlations between all variables of two steps; all= results (t/d) regard all tested variables of two steps;
p(t)=significance of t-tests between variables of two steps; d=value-range of Cohen's d of differences between variables of two steps;
**=measured on Likert scale ranging from 1 (not at risk/heritable) to 7 (complete at risk/heritable);*
***=each DNA-test result is included as dichotomous variable: communicated/recalled/interpreted (1) or not (0).*

2.Does the initially communicated genetic-information fade out more and more at every next step in the communication model? More specifically: does the information transmitted at the first step correlate less and less with each step further away from the first step? We expected that the correlations would decrease between the following steps, i.e.: I-III>I-IV>I-VI >I-VII; III-IV>III-VI>III-VII; IV-VI>IV-VII; small correlations between VI-VII.

3.Are there differences in the information transfer (i.e. correlations and decrease in correlations) between unclassified-variants (UV), pathogenic-mutations (PM) and unformative-results (UR)? 4.Do the following covariates influence the information transfer: sociodemographics, pedigree, familial relationship, cancer-history of proband and relative? We expected that the whispergame-effect would be stronger than the communicated DNA-test result and covariates.

2. Method

2.1. Procedure

Eligible participants in current study were probands from families with intermediate or high cancer-risks who had received a BRCA1/2 DNA-test result in the period 1998-2008 at the Leiden University Medical Center or the VU Medical Center Amsterdam (203). Because the primary focus of our study concerns unclassified-variants, we first approached probands with an unclassified-variant, communicated as 'a mutation/genetic-change for which the clinical meaning is not known (yet)'. In addition, we approached women with a PM or UR, with matching year of result-disclosure.

We asked all 89 probands in this study for their approval to contact their 1st and 2nd degree relatives in the affected branch of the family. Subsequently, in line with the proband's preference, we either sent our invitation letter to relatives directly, or to the proband who distributed the letters. We administered the relatives' questionnaire both in a paper-and-pencil-version as in an Internet version. The study was approved by the medical ethical committees of the participating medical centers.

2.2 .Instruments

Development and description of the questions about the probands' and relatives' recollections and interpretations of both cancer-risks and heredity-likelihood have been described elsewhere (203,277,285).(see figure 1;table 1)

Table 1. *Overview of instruments and items*

	Instruments	scaling	Items
Actually communicated information	cancer-risks	cancer-risks in %, rescaled to a 1-7 scale to match counselees' recollections and interpretations (derived from medical file and summary letter sent to proband)	
	DNA-test result	scored as 3 dummy-items: communicated (1) or not (0)	pathogenic-mutation, unclassified-variant, uninformative
Proband's perception	recollection of DNA-test result	1 item with 3 options (see chapters 4 & 5)	options: (a) 'no genetic change detected', (b) 'a genetic change was detected meaning that cancer is heritable in my family', (c) 'a genetic change was detected for which the meaning for breast/ovarian cancer is unknown at this moment, and therefore tells nothing about the heredity of cancer in my family'
	recollections of own cancer-risks and heredity-likelihood	2 items (1-7 scale: not-complete at risk/heritable) (see chapters 4 & 5)	(1) what is your risk to develop cancer (again), according to your genetic-*counselor*; (2) according to your genetic-*counselor*, what does your pedigree/DNA-result mean for the likelihood that cancer is heritable in your family (pathogenic-mutation: result-based; other DNA-results: pedigree-based)
	interpretations of own cancer-risks and heredity-likelihood	2 items (1-7 scale: not-complete at risk/heritable)(see chapters 4 & 5)	What are your own thoughts and feelings about: (1) your risk to develop cancer (again), (2) the likelihood that cancer is heritable in your family
	interpretations of healthy relatives' cancer-risks	1items (1-7 scale: not-complete at risk) (see chapters 4 & 5)	What are your own thoughts and feelings about the risk for a healthy female relative in your family to develop cancer?
Relatives' perception		relative's questionnaire: identical to proband's perception, except 'healthy relatives' risks'	'genetic-*counselor*' was replaced for 'your relative' (i.e. proband)
Covariates		(1) 3 items derived from medical files (%);(2) 6 binary items in questionnaire (yes/no); (3) 8 items (several scales)	(1) percentage of affected 1st, 2nd and 3rd degree relatives; (2) gender: woman, children, married, religiously active, employed, high school and higher, or lower educated; (3) age, breast or ovarian or other cancer, metastases, year of diagnoses, mastectomy, adnexextirpation, radio/chemotherapy in past or now

2.3. Statistical analysis

Research question 1 was answered by performing t-tests to calculate differences: a.between all variables of steps I and III, b.between all variables of steps III and IV, c.between all variables of steps IV and VI, d.and between all variables of steps VI and VII. Figure 1 shows which variables are included in each step. To facilitate presentation of the large number of t-tests, we only present an overview of the results; details can be requested from the authors.

Research question 2 was analyzed in two phases. In phase 1, all applicable correlations between all variables of all steps were calculated (figure 1 shows all variables). In phase 2, mean correlations were calculated between all variables of the steps required for answering research question 2: I-III, I-IV, I-VI, I-VII; III-IV, III-VI, III-VII; IV-VI, IV-VII; VI-VII. To facilitate data presentation, we only present phase 2; data from phase 1 can be requested from the authors.

Research question 3 was answered by calculating mean correlations regarding research question 2 separately for each of the three DNA-test results. Research question 4 was explored by calculating partial correlations for research question 2, corrected for covariates.

Missing values (<2%) were imputed by multiple imputing within each step. To correct for three DNA-test-result categories, p-values smaller than .01 were regarded as significant. Effect sizes were calculated with Cohen's d and correlations.

3. Results

3.1. Sample

Table 2 shows sample information. We approached 89 probands, but were unable to contact 44 of them (mainly due to deceased, too ill to participate and moved to another address). Twenty-five (56%) out of the remaining 45 probands participated, and 20 (44%) probands did not want that we asked their relatives; the main reported reasons for decline were: 'I do not know whether my relatives would accept me providing you with their private addresses'; 'I do not have contact with relatives'; 'I do not want to burden them'; 'I have not communicated the result' and 'I want to keep the genetic-counseling process closed and completed'. We approached 157 of their relatives, of whom 60 (38%) did not react, mainly due to organizational issues such as inaccurate address. Seventy out of the remaining 97 (72%) agreed up participation. Twenty-seven relatives (28%) declined; the most frequently reported reason was wanting to keep the genetic counseling process psychologically closed and being afraid that participation could remind them of painful memories. Statistical analysis of participation/decline rates did not reveal other significant patterns. In sum: the large non-response in probands and relatives was due to the retrospective design which caused high rates of decease and inaccurate addresses of

eligible individuals; analyses of decliners showed that participation in this study was regarded as a sensitive theme, involving ethical issues and wanting to keep counseling psychologically closed.

Included relatives were mainly first-degree (64%), especially daughters (32%) or sisters (29%). Fifty-four (77%) relatives were women, 15 (21%) had had breast cancer, none ovarian cancer and 5 (7%) another kind of cancer. Six of the affected and none of the unaffected women had undergone prophylactic mastectomy, and one affected woman prophylactic bilateral salpingo-oophorectomy (BSO). Perception did not differ between affected and unaffected participants.

Thirteen (52%) probands had actually received a UV, 7 (28%) a PM and 5 (20%) an UR. Of the 70 relatives, 44 (63%) belonged to a family in which an unclassified-variant was communicated, 14 (20%) in a mutation-family and 12 (17%) in an uninformative-family.

Table 2. *Information about procedure and sample*

Variable	M(sd)	N(%)
Probands		
Total number of contacted probands		45(100%)
Probands declining		20(44%)
Probands agreeing to approach their relatives		25(56%)
Relatives		
Total number of contacted relatives		97(100%)
Relatives declining		27(28%)
Participating relatives		70(72%)
Relationship of relative to proband		
1st degree		45(64%)
2nd degree		12(17%)
3rd degree		12(17%)
4th degree		1(2%)
Sociodemographics of relatives		
women		54(77%)
high-school or higher		26(37%)
employed		50(71%)
Cancer-history of relatives		
breast cancer		15(21%)
ovarian cancer		0
another kind of cancer		5(7%)
year of cancer diagnosis	2002(4.0)	
mastectomy/affected women		6/15(40%)
mastectomy/unaffected women		0/55
bilateral salpingo-oophorectomy/unaffected women		1/70(1%)
Pedigree		
% affected 1st degree relatives/all relatives	37%(10%)	
% affected 2nd degree relatives/all relatives	7%(7%)	
% affected 3rd degree relatives/all relatives	7%(2%)	

Table 3. *Overview of variables*

Step	Description	actually communicated DNA-test result (means, sd)			
		overall	**unclassified-variant**	**pathogenic-mutation**	**uninformative-result**
I actually communicated	communicated to proband: unclassified-variant, pathogenic-mutation, uninformative (n,%)		13(1.0)	7(1.0)	5(1.0)
	cancer-risks (% rescaled to 1-7 scale)	4.9(1.2)	4.0(1.0)	6.0(0.0)	3.0(0.0)
III probands' recollections	recollection of unclassified-variant, pathogenic-mutation, uninformative (n,%)		11(.45)	11(.45)	2(.1)
	recalled own cancer-risks	4.7(1.4)	4.6 (1.5)	5.2 (.4)	3.5 (.6)
	recalled heredity-likelihood	4.6(1.9)	4.5 (.7)	6.2 (1.2)	2.3 (.8)
IV probands' interpretations	interpreted own cancer-risks	6.0(1.7)	6.5 (1.2)	4.1(1.7)	4.1(.9)
	interpreted heredity-likelihood	6.4(1.3)	5.5 (.7)	7.0 (.0)	4.7(2.3)
	interpreted relatives' cancer-risks	5.5(1.2)	5.3 (1.4)	6.7(.8)	5.3(.8)
VI relatives' recollections	recollection of: unclassified-variant, pathogenic-mutation, uninformative (n,%)		19(.3)	35(.5)	14(.2)
	recalled own cancer-risks	4.9(1.0)	4.9 (.9)	5.7(.7)	3.9 (1.1)
	recalled heredity-likelihood	3.4(1.4)	3.9(1.2)	5.0(.0)	2.4(1.2)
VII relatives' interpretations	interpreted own cancer-risks	3.8(1.4)	4.3(1.0)	5.0(.0)	2.9(1.3)
	interpreted heredity-likelihood	3.8(1.3)	4.0(1.4)	3.0(1.2)	4.1(.8)

3.2. Question 1: differences between steps

All variables differed significantly between steps I-III, III-IV, IV-VI, and VI-VII. Al p-values were smaller than .01, and Cohen's d's varied between 0.3 and 0.7, which is regarded as medium effects. (see figure 1)

3.3. Question 2: fading-out

Table 4 shows mean correlations between the steps. First, when we examined the four communicated aspects as depicted in the left columns of the geneticist, we found that the correlations decreased at every step downwards: correlations I-III>I-IV>I-VI>I-VII. Thus, the actually communicated information by the genetic-*counselor* faded out more and more in respectively the proband's recollections and interpretations and the relatives' recollections and interpretations. Second, we found that the correlations of the proband's recollections decreased at every step downwards in table 4: correlations III-VI>III-VI>III-VII. Thus, the proband's recollections faded out more and more in respectively the proband's

interpretations and the relatives' recollections and interpretations. Third, the correlations of the probands' interpretations with other variables decreased in each step: IV-VI>IV-VII. Thus, the proband's interpretations faded out more and more in the relatives' recollections and interpretations. Fourth, the relatives' recollections VI correlated only for .25 with interpretations. Thus, the relatives' recollections faded out in the relatives' interpretations.

The mean correlations between the main steps as depicted in figure 1 are: .40 between the information actually communicated by the genetic-*counselor* and the proband's recollections(I-III); .30 between the proband's recollections and interpretations(III-IV); .08 between the proband's interpretations and the relatives' recollections(IV-VI); and .25 between the relatives' recollections and interpretations.

3.4. Question 3: DNA-test results

We calculated all correlations of research questions 2 and 3 separately for three different DNA-test results. The number of participants for PMs was too small to calculate correlations in steps III, IV and VI. Similar to overall results, the genetic-information from the first communication steps faded out in each DNA-test result group. Exceptions were the high correlations of the information actually communicated by the genetic-*counselor* and the relatives' recollections of UVs and URs (R's=.44, .49). Unclassified-variants were recalled worse by probands compared to other results (R=.16), and the proband's interpretations of an unclassified-variant did not correlate with the relatives' recollections and interpretations.

3.5. Covariates

No significant effects of covariates were found, except for the proband's mothers who interpreted higher cancer-risks, and the probands' daughters who less often recalled having received PMs (R's=.25, -.29, -24, p's<.01).

Table 4. *Mean correlations between steps: overall and specified for different DNA-test results*

		From this step (e.g. I → III)												
		I. geneticist				***III. proband: recollections***			***IV. proband: interpretations***			***VI. relative: recollections***		
	DNA-test result	***overall***	*UV*	*UR*	*PM*	***overall***	*UV*	*UR*	***overall***	*UV*	*UR*	***overall***	*UV*	*UR*
To this step (e.g. I → III)	***III. proband: recollections***	**.40**	.16	.40	.58									
	IV. proband: interpretations	**.33**	.22	.33	.48	**.30**	.34	.64						
	VI. relative: Recollections	**.29**	.44	.49	.29	**.07**	.16	.09	**.08**	0	.06			
	VII. relative: Interpretations	**.15**	.20	.26	.05	**.03**	.09	.06	**0**	0	0	**.25**	.13	.07

All correlations: p<.01; UV=unclassified-variant, UR=uninformative-result, PM=pathogenic mutation; several cells contained too little pathogenic-mutation carriers to calculate mean correlations, therefore only correlations with step I are presented.

4. Discussion

4.1. Conclusion

This study is the first to examine the relatives' perception of genetic-counseling as part of the family communication timeline of genetic-counseling. We compared the communication of genetic-information between probands and relatives with a children's whisper game. Our expectation was confirmed that errors would accumulate in the communication of genetic-information from step to step: from information actually communicated by the genetic-*counselor* to the proband's recollection, and from that to the proband's interpretation, and from that to the relatives' recollection, and from that to the relatives' interpretation.

First, all steps differed significantly from each other, implying that noise occurred in all transfers of information between genetic-*counselor*, proband and relatives. This also means that the recollections and interpretations of both probands and relatives were inaccurate, when compared with the information that was actually communicated to them.

Second, the information originally communicated by the genetic-*counselor* faded out at every step in the communication timeline, like a whisper game. The final step, the relatives' interpretation, showed a correlation of no more than .15 with the originally communicated information.

4.2. Noise

The least noise (R=.40) had arisen in the communication between genetic-*counselor* and proband, and the largest noise (R=.08) between the proband's and relatives' perception. The correlations between recollections and interpretations were relatively low, both for probands and relatives (R's=.30, .25), which was comparable to previous studies (203,285).

Why did noise arise? First, probands and relatives may have difficulties understanding the meaning of DNA-test results and pedigree (277,285). Their inaccurate perceptions could also be caused by the time passed since communication of the DNA-test result, low education, innumeracy (299-301), and black-or-white thinking, i.e. 'either I get cancer or I do not get cancer' (83,88).

Second, probands and relatives may have selectively listened to the communicated information, and may have used heuristics, such as representativeness and availability biases and illusion of control (328). They may have been stuck in specific family communication patterns (329), and have developed their own opinion about cancer-risks and heredity-likelihood on the basis of their experiences with cancer in the family (304-307).

Third, probands may only have disclosed information which they perceived as most likely to be true and as most relevant for their relatives. Particularly in situations of personal threat, an individual may trust their own interpretations most (81-84).

Fourth, the largest part of the noise remained unexplained by the variables in this study. This suggests involvement of other variables.

4.3. Actually communicated information

The information communicated by the genetic-*counselor* did not completely fade-out, because it correlated with the relatives' recollections and interpretations (I-VI/VII). However, these remaining correlations were small (R's=.29, .15).This suggests that the largest part of the relatives' perception was not directly predicted by the actually communicated information, which confirms the whisper-game phenomenon.

Analyses yielded two results: 1.the actually communicated information predicted the relatives' perception to some extent; 2.the relatives' perception differed significantly from the actually communicated information. This is comparable with the results of a children's whisper-game: 1.the first and the last communicated words may be somewhat related; 2.there may be a difference between the first and last words. Thus, the relatives' perception was inaccurate/different compared to what was actually communicated by genetic-*counselor*s, but was also somewhat related. Finding significant correlations between the first and last steps suggest that the first step (slightly) predicts the last step; this suggests that the actually communicated information consistently predicted the counselees' inaccurate perception.

We hypothesize that the influence from the actually communicated information on the relatives' perception is completely explained/mediated by the way how probands communicate DNA-test results to relatives (321).

4.4. DNA-test results

We found large correlations between the genetic-*counselor* communication and the relatives' recollection in families with unclassified-variants and uninformatives. The genetic-*counselor*'s information predicted the relatives' recollections even better than the proband's recollections. Probands with these DNA-test results largely overestimated the cancer-risks and heredity-likelihood in their recollections and interpretations (277,285), but relatives reduced the extent of this overestimation, so that the relatives' perception was more in line with what the genetic-*counselor* had actually communicated.

Possibly, relatives understood the actual meaning of the DNA-test result better. Or they deduced from nonverbal communication that their proband was exaggerating. Or the answers of the relatives showed a tendency towards the mean. Or the relatives had read the summary letter that probands had received from their genetic-*counselor*; we have no

information whether relatives have read this letter, but only less than 20% of the letters included explicit risk-information for relatives.

Compared to other DNA-test results, unclassified-variants were recalled and interpreted the most inaccurate, and the probands' perception also correlated the worst with the relatives' perception.

4.5. Implications

Large noise occured in the family communication timeline of genetic counseling. Therefore, genetic-*counselor*s should not only be aware of the proband in their consultation room, but also of the absent relatives to whom the proband will disclose the DNA-test result.

Genetic-*counselor*s should explicitly help probands in disclosing DNA-test results to their relatives (108,330), especially regarding unclassified-variants and possible medical consequences for relatives (331). Probands often perceive the disclosure process as difficult and stressful (106,108,332), especially when children are involved (110,333-335) or when DNA-test results are negative (336). This could be achieved by improving the summary letters for probands, especially by including more explicit information for relatives (cf.337).

Direct communication between *counselor* and relatives may contribute in improving family communication (cf.338). For instance, genetic-*counselor*s might send letters to relatives, summarizing the DNA-test result and providing the possibility for private consultation by phone or face-to-face. This raises ethical questions. Are genetic-*counselor*s obliged to inform high-risk relatives? Are they allowed to inform a non-patient population who has not requested for genetic-information? Are they allowed to violate the proband's privacy? Is communication beneficial, when relatives do not receive risk-management options, but may feel 'alarmed'? Guidelines should be developed for genetic-*counselor*s if, when and how they should communicate DNA-test results to relatives (339).

4.6. Methodological issues

This study is limited by its small sample size and retrospective design. Therefore, causal relationships remain theoretically assumed. There may have been sampling bias, because probands decided which relatives we could ask to participate, and the relatives' participation percentage was low. The communication timeline assumes a linear feed-forward process, but feedback loops may have been present. All variables were assumed to be linear, to enable calculating mean correlations and t-tests. Non-presented analyses showed identical results with Spearman-correlations, Fisher-exact-tests and corrections for family-dynamics, second/changed DNA-test result, DNA-test-request by relatives, mastectomy and adnexextirpation/BSO. Mediation analyses including communication

processes are described elsewhere (321). Future studies should be prospective and include more variables.

Despite these limitations, this study 'taps from the richness of family responses to create a more complete picture of the effects of genetic testing' (64). It underlines studies on risk-perception in probands (203,277,285), and suggests a broader focus on the family domain, which is both 'critical and relatively neglected' in the science and practice of genetic-counseling (65).

Chapter 8

Family communication matters:

the impact of telling relatives about Unclassified-Variants and Uninformative DNA-test results depends on the proband's communication processes and the relatives' subjective perception

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Abstract

Background

Unclassified-variant and uninformative BRCA1/2-results are not only relevant for probands to whom results are disclosed, but also for untested relatives. Previous studies have seldomly included relatives and have not explained how their lives were influenced by these results. We explored the family communication timeline of genetic-counseling: 1. genetic-counselors communicate the relatives' cancer-risk, 2. probands perceive this risk and 3. communicate this to relatives; 4. relatives perceive this information, and 5.experience an impact on their lives.

Methods

We conducted a retrospective descriptive study in 13 probands with an unclassified variant and 5 with an uninformative result, and in respectively 27 and 12 of their untested female relatives from moderate cancer-risk families. In questionnaires, probands described their perception of the DNA-test result (i.e. recollections and interpretations of cancer-risks and heredity-likelihood). Relatives described the communication process, their perception and impact (i.e. medical-decisions, distress, quality-of-life, life-changes). Bootstrap analysis was used to analyze mediation-effects.

Results

The relatives' own perception strongly predicted breast self-examination, breast/ovarian-surveillance or surgery, levels of distress and quality-of-life, and amount of reported life-changes. The extent to which the proband had communicated the DNA-test result in an understandable, direct, reassuring way, predicted the relatives' perception. The actually communicated relatives' cancer-risks or the proband's perception did not predict relatives' perception and impact-measures. Family characteristics influenced the communication process, but not the relatives' perception and outcomes.

Discussion

Relatives seem to make poorly informed decisions on the basis of their own perception, which was unrelated to the information that probands had communicated on the basis of the actually communicated result. Therefore, genetic-counselors may guide probands in the communication process, and may directly inform relatives, if possible.

1. Introduction

1.1. Background

Results of genetic-counseling and testing are not only relevant for the tested proband, but also for her relatives (166,168). The detection of a pathogenic-mutation (PM) in a proband, i.e. the first tested in the family, has unequivocal implications: the deleterious mutation in the proband suggest that cancer in the family is caused by a genetic predisposition, and relatives have high a priori cancer-risks. Subsequently, a relative could be tested for the PM that was detected in the proband, and on the basis of this DNA-test result, the genetic-counselor could advise her to undergo surveillance or surgery of breasts/ovaries. When no pathogenic mutation (PM) is detected in the proband, the genetic-counselor may calculate a priori cancer risks for relatives, and relatives could be advised to undergo frequent surveillance of breasts/ovaries, but DNA-testing is not an option.

What does the literature say about the impact of DNA-testing in untested relatives? The few studies in this field have not directly asked relatives about the impact of DNA-testing on their lives; only probands were asked about the impact on their relatives (109). These studies suggest that the communication of a DNA-test result may cause distress in relatives, especially in children (105,109-111), and may revive unresolved family myths, loyalty conflicts and family-relational problems (112-114). Relatives seem more likely to undergo DNA-testing after communication of a PM, and are influenced by the emotional and behavioral characteristics of the communication process by the proband (109,116,120). One study showed relationships of the cancer-risk perceptions among sisters within pathogenic-families (111).

Most studies focused on the impact of PM results on relatives. It is unclear how families without a PM communicate about the DNA-test result, and how this communication process relates to the medical-decisions and well-being of relatives. When no PM is found, either an uninformative-result (UR) or unclassified-variant (UV), may be difficult for probands to communicate and difficult for relatives to understand. In contrast with PMs, UR/UV-results do not imply clear information about the likelihood that cancer is heritable in the family and about the relatives' risks to develop cancer. The communicated heredity-likelihood and cancer-risks are calculated on the basis of the pedigree, and are therefore less clear/unequivocal than PMs. Due to this unclearness of UR/UV-results, relatives may not base their perception and medical-decisions on the actual content of the result, but on their own perception of the result and on communication processes between proband and relative (326).

1.2. General family communication timeline

In this study, the impact of UR/UV-results on relatives' lives is explored by describing the relatives' relatives' perception, medical decision-making, psychological-distress, quality-of-

life and amount of life-changes. The family communication timeline of genetic counseling consists of 5 steps (cf.figure 1) (326).

First, a genetic-counselor communicates genetic-information to the proband: 1. DNA-test result category in this study: an unclassified-variant (a DNA-mutation for which the clinical meaning is not known) or an uninformative-result (no mutation was found in a family with high cancer-risks); 2.risk for developing ovarian-cancer and/or contralateral breast cancer for the proband; 3.life-time cancer-risks for relatives of the proband; 4.the likelihood that cancer is heritable in the family, i.e. heredity-likelihood. The current study only included UR/UV-results, and focused on the communicated cancer-risks for relatives.

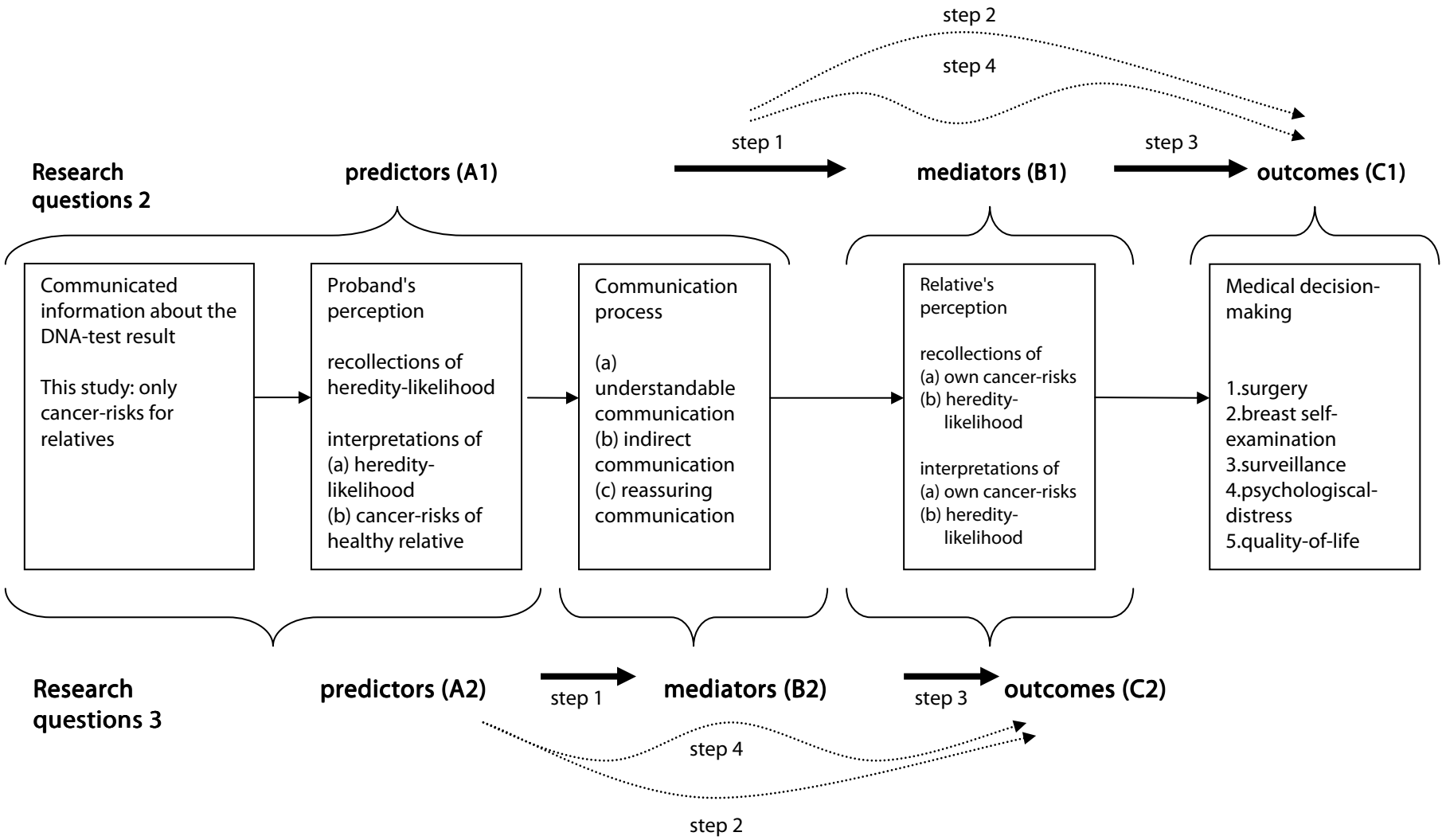
Second, the proband perceives the communicated information. We operationalize 'perception' as a person's recollections and interpretations of DNA-test result category, cancer-risks and heredity-likelihood (277,285). This perception has shown to be inaccurate in many probands, and significant differences exist between the actually communicated information and the proband's perception of the DNA-test result (277,326,340).

Third, the proband may communicate the DNA-test result to their relatives. This communication process can be described in two ways. First, she may communicate facts, such as cancer-risks and heredity-likelihood. Second, she may communicate emotional and psychosocial processes. For instance probands and relatives may discuss their worries and feelings of uncertainty about the cancer-risks for all involved and their feelings about inheritance and cancer (338). A proband may provide social support and be open, or instead be closed, non-supportive and avoidant in the communication (109,338,341,342). These communication processes between proband and relative could be influenced by family-relational characteristics such as level of openness to discuss cancer (166-168).

Fourth, relatives recall and interpret the information that the proband has communicated about her cancer-risks and heredity-likelihood. Our previous study showed that the relatives' perception differed significantly from their proband's perception, and correlated poorly with their proband's perception (326). This finding suggests that genetic-information is generally not accurately transferred between proband and relatives like a children's whisper-game.

Fifth, the relatives' perception may influence outcome-variables of relatives: medical-decisions, psychological-distress, quality-of-life, and life-changes.

Figure 1. *The communication timeline of genetic-counseling, showing all included variables and research questions of this article. Steps and dotted lines are mediation steps as explained in the method-section*



1.3. Research questions

1. What is the impact of DNA-test result disclosure on the lives of untested relatives from UR/UV-families, i.e. medical-decisions, psychological-distress, quality-of-life and number of life-changes?
2. In UR/UV-families, is the impact on relatives: a.directly predicted by the actually communicated relatives' cancer-risks and the proband's perception; b.mediated by the relatives' perception; c.only predicted by the relatives' perception?
3. In UR/UV-families, is the relatives' perception: a.directly predicted by the actually communicated relatives' cancer-risks and the proband's perception; b.mediated by the communication process; c.only predicted by the communication process?
4. Do family characteristics (openness to discuss hereditary cancer in the family, relationship/involvement between proband and relative, pedigree) predict the communication process, but not the perception and outcomes of relatives?

2. Method

2.1. Procedure

Eligible participants in the current study were probands from families with intermediate or high cancer-risks who had received a BRCA1/2 DNA-test result in the period 1998-2008 at the Leiden University Medical Center or the VU Medical Center Amsterdam (277,285). Because the primary focus of our study concerns UVs, we first approached probands with UVs, communicated as 'a mutation/genetic-change for which the clinical meaning is not known (yet)'. In addition, we approached women with UR-results, with matching year of result-disclosure.

Eighteen out of 55 contacted probands with UR/UV-results agreed that we approached their 1st-degree and/or 2nd-degree relatives in the affected branch of the family (33%), 24 probands (44%) did not respond, and 13 (23%) declined. Subsequently, in line with the proband's preference, we either sent our invitation letter to relatives directly, or to the proband who distributed the letters. We approached 91 relatives; 49 of them participated (54%), 30 (33%) did not respond, and 12 declined (13%); 8 participants were excluded because they had requested for a DNA-test in themselves or were male. Analysis of which probands declined, did not react or agreed upon participation did not show significant predictors; familial characteristics did also not predict which relatives declined, reacted or agreed (i.e. all instruments in table 1 in the proband's questionnaire).

The study was approved by the medical ethical committees of the participating medical centers. Details on procedure and sample are described elsewhere (285,326).

2.2. Instruments and analyses

Questions about the proband's and relatives' perception were developed in previous studies (277,326) and are depicted in table 1.

Communication process variables were developed on the basis of clinical experience (343,239). To reduce the number of variables, principal component analyses (PCA) with multiple imputing for missing values were performed on the communication process. Varimax rotation was performed for interpretability of components. Number of components was decided on the basis of the eigenvalues, scree plot, interpretability, and good Cronbach's alpha. Psychological-outcomes (291)(3), quality-of-life (287) and total amount of life-changes (203,277) were measured with valid, reliable scales; reliability was confirmed with Cronbach's alphas.

Question 1: sample and outcome-variables were described with frequencies and means(m,sd). In line with our previous studies (277), questions 2, 3 and 4 were analyzed with mediation analyses via bootstrapping (185), which is a relatively robust technique (187). Mediation is present when variable B mediates the relationship between variable A and C, and four mediation steps are fulfilled. 1.Variables A and B significantly correlate (A&B). 2.Variable B significantly predicts variable C (B→C). 3.Variable A significantly predicts variable C (A→C). 4.When variable B is included in bootstrapping analyses, A explains C to a lesser extent as compared with step 3 (A→B→C). Either the Beta decreases but remains significant (i.e. 'partial mediation') or the beta becomes non-significant (i.e. 'complete mediation'). Mediation step 1 is not presented but assumed in each table in which steps 2, 3 and 4 are presented together.

We use the expression 'direct effect' to indicate that A directly predicts C; the Beta is not influenced by the inclusion of Beta in analyses (p-value step 4>.01). We use the expression 'indirect effect' to indicate that A indirectly predicts C, via partial or complete mediation by Beta (p-value step 4<.01). We use the expression 'effect' without adjective to indicate analyses between variables A-B, A-C or B-C in steps 1, 2 and 3. Linear regression analyses were used to calculate standardized betas, logistic-regression in case of binary outcomes. Alpha was set at .01 and 5000 bootstrap resamples were performed (185). Effect-sizes were described with Nagelkerke (<.20 moderate; .20 - .40 good; >.40 strong) or f^2 (.02 small; .15 medium; .35 large).

Table 1. *Overview of instruments*

variable	number of items (scoring)	scale	Reference	Description/example of questions
Actually communicated cancer-risks for relative	1 item	%		
proband's recollections of heredity-likelihood	2 items	1-7 scale: not-complete at risk/heritable	(285,277)	'according to your genetic-counselor, what is the likelihood that cancer is heritable in your family'
proband's interpretations of heredity-likelihood and of relatives' cancer-risks	2 items (1-7 scale: not-complete at risk/heritable)	idem	(285,277)	'What are your own thoughts and feelings about:' (a) the likelihood that cancer is heritable in the family, (b) the risk for a healthy female relative in your family to develop cancer?
communication process	11 items (1-7 scale with names at poles), reduced to 3 factors with factor analyses (see 3.2.2.): (a) understandable communication, (b) indirect communication, (c) reassuring communication	Individual scores based on regression: m=0.0 sd=1.0	New	high factor loading on a: short/extensively; difficult/easy to understand; not-clear/clear; proband not-understanding/ understanding herself; bad/good explanation; b: calm/upset; tell facts/facts-and-in-conciseness; not-reassuring/reassuring; c: not/attentive to my questions; not/tell everything she knows
relative's perception	relative's questionnaire: identical to proband's perception		(285,277)	'genetic-counselor' was replaced for 'your relative' (i.e. proband)
medical decisions	4 items: surgery, breast self-examination, surveillance	No (0) - Yes (1)	New	having had surgery of breasts and/or ovaries after DNA-test result disclosure by proband; having peformed breast self examination the last 6 months; having surveillance of breasts and/or ovaries the last 6 months by a physician

Table 1. *Continued*

Psychological-outcomes	19 items, original 3 scales : avoidance and intrusions from the Impact of Events Scale, Lerman's Cancer Worry Scale; reduced to one scale in this study (3.2.2.)	19 (lowest total score)-76 (highest)	(291) * (3)*	
Quality-of-life	General quality-of-life, and specific psychological, relational and physical distress	4 (lowest total score)-20 (highest)	(287)*	
Life-changes-questionnaire	7 items (scores:1,not-7, completely changed), reduced to 1 total score (3.2.2.)	7 (not changed)-28 (completely changed)	(285,277)*	Seven life domains: surveillance/surgery, physical complaints, bodily experience, emotional life, relationships, personality, existential view-on-life.
Family characteristics	1.openness to discuss hereditary cancer in the nuclear family; 2.relationship of relative towards proband;3.relational-ethics; 4.Pedigree information; 5.perceived total involvement of relative in a. genetic-counseling process and b. in cancer-process of proband, c. general relationship with proband; 6.having discussed the DNA-test result with other relatives, and their reaction	1:7(closed)-35(open); 2.rank number; binary (0,not,1,yes); 3.trust&justice:6-30, loyalty:3-15, entitlement: 3-15; 4.%,n; 5.1-3; 6.n, 1-7	1:(168)*; 3:(344)*	2. age ranking of the relative in the nuclear family (i.e.: relative is 1st, 2nd, nth child); relative is: sister, mother, daughter of uncle/aunt, daughter of sister/brother, grandmother, 1st degree, 2nd degree, 3rd degree; 3. loyalty, trust/justice, negative entitlement of relative towards nuclear family; 4. affected, deceased 1st, 2nd, 3rd-degree relatives (%, n);5.three categories:closely involved1,involved from a distance,2,not involved,3; 7.number of relatives; reaction of negative/positive, not/encouraging, not/understanding, not/satisfying on1-7-semantic-differential-scales.

**Instruments have been translated into Dutch, and all Cronbach's α's>.70 as shown in previous publications in Dutch samples*

3. Results

3.1. Population

We included 13 probands with UV-results and 5 with UR-results, and respectively 27 (65%) and 12(35%) of their untested female relatives. Of the 41 relatives, 8 (21%) had had breast-cancer, diagnosed around 2002 (sd=4 years). Twenty-eight (72%) had had higher education, 27 (69%) had a job, 9 (23%) were religious; no significant differences were found between URs and UVs in demographics and cancer-histories of probands and relatives (326).

The originally communicated cancer-risks were substracted for 32 relatives (81%) from their proband's medical-file; mean communicated relatives' risks were 20.4% (sd=15.3%); for comparison reasons only, we transformed this into 3.7 (sd=1.0) on a 1-7 point-scale. On 7-point-scales, probands recalled mean heredity-likelihood and relatives' cancer-risks as 4.1 and 5.2 respectively, and interpreted heredity-likelihood higher as 5.8. Relatives recalled mean cancer-risks of 4.6 and heredity-likelihood of 3.0; they interpreted both higher as 4.5 and 3.6. (table 2).

Table 2. *Overview of variables in the family communication timeline*

	Variable	M (sd)	N (%)
actually communicated information	relatives' cancer-risks	20.4 (15.3)	
	unclassified-variant		27(63%)
	uninformative-result		14(37%)
proband's perception	recalled heredity-likelihood	4.1 (1.7)	
	interpreted heredity-likelihood	5.8 (1.5)	
	interpreted relatives' cancer-risks	5.2 (1.1)	
relatives' perception	recalled cancer-risks	4.6 (1.0)	
	recalled heredity-likelihood	3.0 (1.3)	
	interpreted cancer-risks	4.5 (.9)	
	interpreted heredity-likelihood	3.6 (1.2)	

3.2. Preparatory analyses

PCA yielded three components for the communication process (resp. VAF's=.44, .15, .11; α=.90, .70, .85). Component 1 (4 items) measured 'understandable communication', i.e. the extent to which the proband explained the DNA-test result in an understandable way to the relative. Component 2 (4 items) measured 'indirect communication', i.e. the extent to which the proband communicated the DNA-test result indirectly to the relative. Component 3 (3 items) measured 'reassuring communication', i.e. the extent to which the proband communicated the DNA-test result in a reassuring or soothing way. The variable 'poor/good explanation' loaded high on both indirect and reassuring communication, and low on understanding, which suggests that relatives base their total evaluation of the quality of the explanation more on the process of communication than on the content of communication. Interpretation of these three components was confirmed by correlations with other variables (not described here; table 3)

The scales for psychological-distress, quality-of-life and number of life-changes resulted from PCA-analysis; which showed good reliability of .81, .92 and .85 (cf. table 1).

Table 3. *Results of Principal Component Analyses, Varimax rotation with Kaiser normalization*

	Component		
	1: understandable communication	**2: indirect communication**	**3: reassuring communication**
Short-extensive	.35	.58	.10
Difficult-easy to understand	.93	.04	.05
Calm-Upset	-.25	.52	-.64
Not clear-clear	.88	.21	.17
Proband did not understand–did understand the result herself	.84	.26	.09
Only tell facts-tell facts and in-conciseness	.11	.68	-.16
Not reassuring-reassuring	.06	.10	.90
Not attentive-attentive to my questions	.41	.64	.25
She seemed not to tell everything-seemed to tell everything	.65	.36	.19
Bad-good explanation	.25	.59	.54

3.3. Question 1: outcomes

Four out of the 8 affected relatives(50%) had undergone contralateral prophylactic mastectomy after the proband's DNA-testing, and 4 of the 33 unaffected relatives(12%) had undergone prophylactic mastectomy. Thirty-two (82%) of both affected and unaffected women had performed breast-self examination during the last six months and 21(54%) surveillance of breasts and/or ovaries by a physician. Mean psychological-distress was 29.3, which is low on the scale-range of 19 to 76; 3 relatives (8%) reported large distress larger than 57. Mean quality-of-life was 15.3, which is moderately high on the scale-range of 4 to 20; 8 relatives (21%) reported low quality-of-life lower than 10. Relatives reported that their lives had somewhat changed regarding medical and psychological aspects (13.5); 11(28%) reported large changes larger than 15. Outcomes did not significantly differ between affected and unaffected relatives (table 4).

Table 4. *Description of outcome-variables in relatives*

	N (%)	M (sd)
	39 (1.00)	
surgery		
general	8 (.21)	
presymptomatic	4/31 (.13)	
symptomatic	4/8 (.50)	
breast self examination	32 (.82)	
surveillance by physician	21 (.54)	
Psychological distress		29.3 (10.0)
quality-of-life		15.3 (3.3)
Total amount of life-changes		13.5 (5.8)

See table 1 for description of the scales

3.4. Question 2: prediction of medical decisions

Only significant correlations between A and B from step 1 were used in mediation steps 2-4, which are presented in table 5 (cf. figure 1).

Step 2(B1→ C1): The relatives' perception predicted all outcome-measures with moderate to strong effect-sizes. Interpreted heredity-likelihood predicted surgery, and recalled and interpreted heredity-likelihood predicted breast self-examination. Recalled and interpreted cancer-risks and interpreted heredity-likelihood predicted surveillance. Recalled and interpreted cancer-risks predicted psychological-distress and life-changes. Recalled and interpreted heredity-likelihood predicted quality-of-life.

Step 3(A1→C1): The actually-communicated relatives' cancer-risks and proband's perception did not predict any outcomes.

Step 4(A1→B1→ C1): There was no mediation.

In summary: the relatives' own perception was the only predictor of outcome-variables.

Table 5. *Results for research question 2*

predicted outcome variables C1	Predictors A1	Mediator(s) B1				total model statistics	
		recalled cancer-risk	interpreted cancer-risk	recalled heredity-likelihood	interpreted heredity-likelihood	Nagelkerke	f^2
DIRECT EFFECT: A1→C1							
X	ns	ns	ns	ns	ns	ns	ns
EFFECT: B1→C1							
surgery	ns	ns	ns	ns	1.1	.32	ns
breast self examination	ns	ns	ns	11.3	6.5	.69	ns
surveillance	ns	2.0	5.4	ns	.7	.55	ns
psychological-distress	ns	.3	.1	ns	ns	ns	.13
quality-of-life	ns	ns	.5	ns	-.3	ns	.44
total amount life-changes	ns	ns	ns	.4	.7	ns	1.1
INDIRECT EFFECT: A1→ B1 →C1							
x	ns	ns	ns	ns	ns	ns	ns

3.5. Question 3: prediction of relatives' perceptions

Only significant correlations between A and B from step 1 were used in mediation steps 2-4, which are presented in table 6.

Step 2(B2→C2): The communication-process predicted all perception-variables with large effect-sizes. Understandable, indirect and reassuring communication together predicted the relatives' recollection of cancer-risks. Reassuring communication was the only predictor of both recollections and interpretations of heredity-likelihood. Understandable and reassuring communication predicted the interpretation of cancer-risks.

Step 3(A2→C2): The actually-communicated relatives' cancer-risks and proband's perception did not predict any perception-variables of the relatives.

Step 4(A2→B2→C2): There was no mediation.

In summary: the communication process was the only, strong predictor of the relatives' perception.

Table 6. *Results for research question 3*

predicted outcome variables C2	Predictor A2	Mediator(s) B2			total model statistics
		understandable communication	indirect communication	reassuring communication	f^2
DIRECT EFFECT: A2→C2					
x	ns	ns	ns	ns	ns
EFFECT: B2→C2					
recalled cancer-risks	ns	-.42	.53	-.35	1.00
recalled heredity-likelihood	ns	ns	ns	-.59	.52
interpreted cancer-risks	ns	-.47	ns	-.26	.42
interpreted heredity-likelihood	ns	ns	ns	-.49	.27
INDIRECT EFFECT: A→ B→C					
x	ns	ns	ns	ns	ns

See footnote table 5 for explanation

3.7. Question 4: family characteristics

Family characteristics did neither directly nor indirectly predict the relatives' perception and outcomes. The directness of the communication from proband to relative was predicted by: the relative's perception of the family communication about hereditary cancer as open, when she was a relatively younger sibling in the nuclear family, was the sister of the proband and felt more loyal to the nuclear family, and was more closely involved with the genetic-counseling-process, cancer-process and in general relationship with the proband. The extent to which the communication was experienced as reassuring was predicted by the relative's perception of the family communication about hereditary cancer as open, and the percentage of affected 1st, 2nd and 3rd degree relatives (see table 7).

Table 7. *Results for research question 4*

	Understandable communication	Indirect communication	Reassuring communication
Openness to discuss hereditary cancer in the nuclear family	ns	-.42	-.33
Age ranking in the nuclear family, i.e.: relative is 1st, 2nd, nth child	ns	-.36	ns
Relative is sister of proband	ns	-.28	ns
Loyalty of relative towards nuclear family	ns	.44	ns
% affected 1st degree relatives	ns	ns	-.34
% affected 2nd degree relatives	ns	ns	-.53
% affected 3rd degree relatives	ns	ns	-.31
Involvement of relative in genetic-counseling process of proband	ns	-.50	ns
Involvement of relative in cancer-process of proband	ns	-.32	ns
Closeness of relationship of relative towards proband	ns	-.47	ns

Figures are regression analysis-results: std.ß, p<.01

4. Discussion

4.1. Conclusion

This is the first systematic study on the impact of DNA-testing on the lives of untested relatives from UR/UV-families. The impact on the medical-decisions of relatives was remarkably high, given that most relatives were unaffected and were at moderate risk to develop cancer. They reported that their lives had somewhat changed regarding medical and psychological aspects. Eighty-two percent had performed breast-self examination and 54% surveillance by a physician. Twenty percent of all relatives had undergone mastectomy. Distress was low and quality-of-life moderately high; however, subgroups reported large distress and low quality-of-life.

The impact of the DNA-test outcome was strongly predicted by the relatives' own perception: the higher cancer-risks and heredity-likelihood were in the recollections/interpretations of relatives, the more radical were the medical-decisions and the more negative the psychological distress and quality-of-life. The relatives' perception was strongly predicted by the way in which the proband had communicated the DNA-test result: the less understandable, direct and reassuring the communication was, the higher the cancer-risks and heredity-likelihood were in the relatives' perception. The actually communicated cancer-risks of relatives and the proband's perception were not predictive of the relatives' perception and the impact in the relatives.

Family characteristics only predicted the way in which the proband had communicated the DNA-test result to the relative, and did not predict the relatives' perception and outcomes. This suggests that family dynamics only influences how a family communicates about a DNA-test result, but not how an individual relative feels and thinks about this result and its consequences. This could be explained by the fact, that relatives may have developed their own strong, independent opinion about cancer-risks and heredity-likelihood, due to their often life-long history with cancer in the family (285,304-307).

4.2. Communication matters

The results indicate that, as we hypothesized, relatives from UR/UV-families do not rely their medical decisions and psychological impact on communicated facts, but on the communication process and their own perception. This is probably due to the complexity and lack of clarity of the UR/UV-result.

The understandability and directness in which the proband had communicated the result, predicted some aspects of the relatives' perception. However, the extent of reassurance provided by the proband predicted all aspects of the relatives' perception. This means that probands gave reassurance, independently from the content of the DNA-test result (confirmed by the fact that these variables were uncorrelated with the actually

communicated cancer-risks; unpresented data). This reassurance could either have been accurate or inaccurate, from a genetic-counselors' perspective. Probands are for instance accurate when they provide reassurance after a true-negative result (i.e. no-mutation detected in a family with a known mutation), or when no reassurance is provided after a PM. They are inaccurate when they give false reassurance after a PM, or when they provide no reassurance after a true-negative result.

On the one hand, communication by probands could have been expected to be neutral in our study, i.e. neither reassuring nor its opposite, because our sample consisted of mainly unaffected relatives from at-moderate risk families without a PM. On the other hand, the genetic-counselor may not have communicated neutral information. Previous studies have shown that genetic-counselors may feel uncertain about DNA-test results and may also non-verbally show their uncertainty to the counselees (31-33,345). This may especially be the case when no PM (UR/UV) is found, as was the case in our sample. We found that the proband's perception of their own and/or their relatives' cancer-risk was often not in line with the objectively communicated facts, as reported in summary letters and medical files; however, their perception may be in line with the non-verbal communication of the genetic-counselors. Probands may also have interpreted the uncertainty of the genetic-counselor as a possibility to trust their own ideas and feelings instead of trusting the objectively communicated information. This may have led to a variety in the perceptions of both the probands and the relatives. However, we do not have data on these hypotheses.

Ad hoc analyses showed that, compared to URs, relatives perceived the communication of UVs as more indirectly and less reassuring (shown by unpresented, significant t-tests). Moreover, UVs were recalled/interpreted with somewhat higher cancer-risks/heredity-likelihood; much more relatives underwent surveillance and surgery (71% and 26% versus 36% and 8%), which was comparable with relatives who had been disclosed a PM (85% and 50%) (326). This seems to suggest that relatives perceived UVs as more pathogenic than URs, which is in line with the proband's perception (277,285,340).

4.3. Limitations

This study is limited by its relatively small sample size, retrospective design and relatively large number of hypothesized parameters. Causal relationships remain theoretically assumed and are not definitely proven. There may have been sample bias, because probands decided which relatives we were allowed to approach, and the relatives' participation percentage was low.

Selection bias could have occurred, because especially relatives who experienced a large impact of DNA-testing on their medical behavior may have wanted to participate in this study. Only 33% of the probands and 54% of the relatives participated, which may

limit representativeness of our sample; however, analyses of decline, non-response and participation did not show significant predictors.

We did not present results for the relatives' sociodemographics and cancer-history (affected, unaffected, breast and/or ovarian cancer, metastases; kind of treatment and surveillance; years of diagnoses), because these showed to be not-significant predictors, mediators and moderators in analyses of perception and outcomes.

4.4. Implications

We give the following suggestions for genetic-counselors, on the basis of the findings of our current study which need to be confirmed in larger studies. DNA-testing is often relevant for relatives. Therefore, genetic-counselors are advised to calculate and discuss cancer-risks for specific relatives, report this specifically in medical-files and in the letters that they send to the proband and relatives. Of course, this may raise ethical and legal questions in countries where genetic-information is expected to be restricted to the communication of the probands' risks only.

In this Dutch study, we discovered that specific cancer-risks were infrequently reported in medical-files and letters, and it was often unclear whose cancer-risks were calculated (e.g. sister, daughter, cousin, and niece). This may have contributed to the inaccurate perceptions and impact of both probands and relatives.

Genetic-counselors may explicitly support probands in disclosing DNA-test results and cancer-risks accurately to relatives (108,346), especially in communicating this information in an understandable, direct way without giving false reassurance. Direct communication between counselor and relative may facilitate this process, and may contribute to improving the recollections and interpretations of relatives. For instance, genetic-counselors could send a letter to all relatives with a summary of the DNA-test result and with the possibility for a personal consultation by phone or face-to-face.

Chapter 9

A counselee-oriented perspective on risk-communication in genetic-counseling:

explaining the inaccuracy of the counselees' risk-perception shortly after BRCA1/2-test result disclosure

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Abstract

Purpose

An important aim of genetic-counseling is helping counselees to understand the genetic contributions to their disease, such as their genetic risk to develop breast or ovarian cancer. However, many psychological studies show that their perception of their risks is often inaccurate. Previous studies showed that several information-oriented variables predict the level of accuracy, focusing on specific processes of receiving and processing risks. We choose to examine counselee-oriented predictors about how counselees embed cancer-risks in their lives. These predictors reflect the personal meaning of genetic-risks and are expected to explain/mediate the impact of genetic-counseling on risk-perception-accuracy.

Method

We analyzed 248 questionnaires of a prospective study, filled-in by probands with breast/ovarian cancer who had received pathogenic mutations, unclassified-variants or uninformative-results (resp. n=30, 16, 202). Several hypothesized predictors were used to predict the absolute level of accuracy of the counselees' risk-perception. Mediation-regression-analyses were performed to examine whether counselee-predictors mediated/explained the influence of information-predictors on the accuracy. Information-oriented predictors regarded: presentation format and communicated information, question format, education, pedigree-information, cancer experience and cognitive processes/heuristics. Counselee-oriented predictors regarded the self/personality, their life/existence in general and their need for certainty about the DNA-test, heredity and cancer.

Results

Both information-oriented and counselee-oriented variables significantly predicted the accuracy of the counselees' risk-perception, with moderate to large effect sizes. Counselee-oriented variables completely mediated/explained the effects of information-oriented variables on the accuracy.

Discussion

Counselees seem to transform the objective cancer-risks into personally relevant information. Only through this personal meaning of the genetic-information, the information-oriented processes cause inaccurate perceptions. Genetic-counselors are suggested to focus on these personal processes when communicating genetic-information.

1.Introduction

1.1. Inaccuracy of risk perception

Genetic counseling can be described as the 'process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease' (52). This includes the communication of risk information and medical options based on these risks. These risks are calculated on the basis of a PM DNA-test result, or on the basis of pedigree-information, in combination with the counselees' cancer-history.

On the basis of current literature, we can conclude that genetic-counseling slightly improves the counselees' understanding of cancer-risks. Overall, counselees seem to have a better perception after counseling than before counseling (66,67,78). Yet Smerecnik et al concluded in their review that only approximately 25% (range: 2–55%) of all counselees estimated their risk more correctly after counseling; from an average of 42% pre-counseling to an average of 58% post-counseling. However, on average 25% (range: 5–76%) continued to overestimate and 19.5% (range: 7–55%) continued to underestimate their risk even after counseling (78). Other reviewers concluded that women often have an inaccurate perception when their risk estimates are compared with objective estimate of their risk (77).

Thus, many counselees do not bring their own subjective ideas and feelings about their own cancer-risks in agreement with the actually communicated genetic-information, i.e. the former differs from what has been communicated. Despite being inaccurate in many counselees, the perception of the communicated risks seems to be a better predictor of their medical decisions and distress than the actually communicated risks (277,321,340). Overestimations lead in some individuals to inappropriate uptake of medical surveillance and preventive measures (79,77,203,277,340), and poorer psychological functioning (79,277,321,340).

1.2. Predictors of understanding

Because of the important role of risk-perception and its importance in predicting the impact of genetic-counseling, it is relevant to understand how counselees create their own perception, and especially why it deviates from the actually communicated risks. We differentiate between two kinds of possible causes of the inaccuracy: information-oriented and counselee-oriented predictors. Most previous studies have been information-oriented. Several studies suggest that this orientation should be broadened with counselee-oriented predictors(see 1.4.).

Information-oriented predictors focus on how specific genetic-information is communicated by the genetic-counselor, how it is received, processed and reproduced by the counselee, and how these processes are influenced by knowledge-related variables

such as education and numeracy skills. These predictors focus on the specific processing of specific genetic-information, and not on broad and fundamental processes such as the counselees' personality, and integration of the DNA-test result in their lives in general. In 1.3. we describe the following information-oriented predictors: what information is communicated, levels of education and innumeracy, presence of specific information about cancer in relatives and in counselees, and specific cognitive processes regarding the processing of specific information.

Counselee-oriented predictors focus on how the genetic-information is experienced and fundamentally embedded in the life of the counselee. In 1.4., we describe variables about the self, existential concerns and need for certainty.

Counselee-oriented variables may be important in explaining why counselees have an inaccurate perception of their cancer-risks. Counselees do not perceive their cancer-risks from a cognitive, decontextualised distance, but experience cancer-risks as meaningful for themselves. We suggest that person-oriented predictors about the self, existence and need for certainty influence their risk-perception and its accuracy.

The difference between information-oriented and counselee-oriented predictors could also be described with the difference between the 'function' and 'meaning' of a process. Information-oriented predictors describe how the communication/receipt/inner-processes function in counselees, and the counselee-oriented predictors provide an understanding of the existential meaning of this information for the counselee (cf. difference between the spelling/grammar and the meaning of a sentence). In 1.5. we will hypothesize that counselee-oriented predictors explain (i.e. in statistical terms: 'mediate', cf. 1.5.) *why* information-oriented variables influence the counselees' perception.

1.3. Information-oriented approach: an overview of variables

Presentation format-The format in which cancer-risks are presented by the genetic-counselor may influence the accuracy of the counselees' perception (243,280,281). Genetic risks can be presented as proportions (X out of Y), percentages, and/or in graphical format; risks can be communicated as life-time risks, or related to the current age of the counselee (residual risk, risk over the next 10 years), and can be mirrored (e.g. 80% at-risk implies 20% not-at-risk) (280). Genetic-counselors prefer communication of numerical formats, but few studies provide empirical evidence for its efficacy (279). Explaining general figures of population risks may cause overestimation (278), counselees may feel at fifty-fifty risk (90), and the denominator of proportions are often inaccurately understood (90).Verbal labels or categories are interpreted too subjectively (90).

Communicated information-Cancer-risks may be perceived more accurately when a pathogenic-mutation (PM) is communicated and not an uninformative result (UR) or unclassified-variant (UV), but results are inconsistent (70,86,203,204). There is a large variation in the information communicated during genetic-counseling sessions, which may

influence risk-perception (78). When family-history, heredity and personal risk estimates are all communicated, the counselees' perception of these risks (risk-perception) is more accurate than when only thefamily history, heredity of personal risk is communicated (78). However, we found that counselees may not be able to distinguish the meaning of the DNA-test result from pedigree-information (285), especially after the communication of ambiguous DNA-test results such as unclassified-variants (203).

Question format-In line with the presentation format as described above, also the way how risk-perceptions are measured/formulated by the reseaacher (i.e. the instrument) may influence their accuracy (77). Katapodi et al. (77) concluded in their review that the use of percentage-scales causes larger differences between subjective and objective lifetime risk than Likert-type scales (77). This could be explained by the fact that categorical or Likert-type scales may be more in line with the counselees' own way of describing risks (239). However, percentage-scales may result in the measurement of more accurate perception of 5-years risk (347). The accuracy could be improved by using scales with 7 categories instead of visual analogue scales (348), comparing own risks with general population risks (349,350,348), timing (79) and ordering risk-items in the questionnaire correctly (351). Recent studies suggested that the counselees' medical decisions and distress are better predicted, confirm the counselees' own experiences, when the risk-instruments do not only include cognitive items but also affective items (239), and focus on their interpretations (285,277,203).

Information-related sociodemographics- Lower educated counselees are more unaware of their risks (77), and innumeracy may lead to misunderstanding (79,90,352,353).

Family history-The majority of studies showed that counselees with a positive family history, defined as having at least one first or second degree relative with breast cancer, were more likely to recall/interpret higher cancer-risks than other women, irrespective of their communicated risks (77,354). It has been suggested that family history functions like an 'availability heuristic' (354). Several risk-perception studied included the number/percentage of affected and deceased relatives as predictors. In contrast, the counselee-centered 'lived experience' and personal meaning of being a member of a family with many cancer patients has received little attention (355,328).

Cancer-experience-Affected women seem to interpret their genetic risk in the context of their previous cancer experiences (221), such as recurrence of cancer, surgery and current surveillance. The influence of the counselee-centered meaning of these medical facts on the counselees' perception has hardly been studied.

Cognitive processes-Risk-perception accuracy has also been suggested to be influenced by cognitive information-processes of counselees, such as appraisal, coping and personal theories of inheritance (86,164). Many individuals think in non-Mendelian terms about genetics (354), and use their own rule-of-thumb/heuristics and mental models of inheritance and causes of disease to interpret and assimilate the risk information they

have received (93,94). Counselees have shown to create their own cognitive and emotional representation of the causes, identity, timeline, cure/controllability and consequences of hereditary breast/ovarian cancer (79). These representations may function independently from and/or parallel to rational, factual information (79,95), for instance due to biases of availability, representativeness, anchoring, influence of incidences on risk-perception, emotions and emotional forecasting (90,96). Biases may help people to process information faster (164), cope with health problems, reduce stress (235,298), defend themselves and their self-worth and self-integrity (95). However, the extent to which illness representations in counselees at increased risk differ from healthy individuals may be small (356).

1.4. Counselee-oriented approach

Possibly, previous studies have focused one-sidedly on the communication of probabilities, and have not sufficiently taken into account the personal context and meaning of genetic-counseling for the counselee (38). When confronted with risk-information, counselees have to translate the probabilistic statements into terms with personal meaning (62). 'Taken together (…) risk information is rarely taken up as value-neutral objective truth, but rather risk information is deeply subjective, interiorized against a pre-existing sense of self' (63).

In our previous studies, we developed questions to measure risk-perception that reflected the counselees' own meaning-making process better, instead of risk-perception questions that merely focused on the communication and linear psychological processing of probabilities. We asked counselees about their own interpretations of the meaning of the DNA-test result for their cancer-risks, regardless of what the genetic-counselor has actually communicated (277,285,321,326,340). These interpretations were better predictors of their medical decisions and well-being than their recollections of what the genetic-counselor had actually communicated.

Sense of self : Counselees have to integrate the DNA-test result flexibly in the general life story of who they are (63). They may ask questions about their sense of self such as: Am I a mutation-carrier or not? Am I a potential-cancer-patient or not? And what does this mean? Does this change who I am? Communication of risks may influence/change their identity, and their identity may influence/change risk-perception (61,152). A study in elderly showed that their perception of genetic-risks had been influenced by affect-related personality traits, such as extraversion, optimism, and locus of control (357). Other studies showed that trait-optimism influenced risk-perception (358).

Existence: The counselees' self may be fundamentally involved in risk-perception. Risk-communication may evoke questions about existential concerns in life, such as death, freedom, responsibility, isolation, and meaninglessness (60). Existential feelings may be evoked, such as responsibility for undergoing and disclosing DNA-testing to provide

relatives with risk-information (154-157), guilt about transmitting pathogenic genes to offspring (158), shame and stigma (159,75). As secondary appraisal process, counselees have to integrate, adjust or accommodate the risk-information in their general sense of meaning (131). Counselees have reported that obtaining certainty during the genetic-counseling process had enhanced their lives (6); 83% experienced at least one positive life change (153), and 42% of counselees with unclassified-variant-results reported large changes in their existential view on life (203).

Need for certainty: Counselees do not ask for DNA-testing to understand probabilities accurately (1,5,6), but they want to receive information that provides them with certainty (6,93), e.g. about their own and their relatives' cancer-risks, to know which medical decisions to make (1,5,6,148,149). However, DNA-testing does not provide immediate certainty on demand. Counselees often have to wait for the results for a long time. DNA-test result may be ambiguous, such as UV/URs. Surgery of ovaries and breasts may not be offered after UR/UV. Indeed, counselees have reported that many expectations about genetic-counseling are not met (216,359-361). The counselees' need for certainty often collides with their perceived lack of certainty in the actual situation, causing uncertainty (3,31,164,362-366).

The counselees' need for certainty seem to reflect how the DNA-test result is embedded in their lives. Their unfulfilled need for certainty regarding the DNA-test result, heredity-likelihood and cancer may influence the way how they perceive cancer-risks. Counselees who do not receive certain genetic-information may re-interpret this information in such ways that they do perceive certainty. Therefore, many counselees seem to attach more value to their own opinion than to the genetic-counselor's (285,203).

These counselee-oriented processes may also explain why the information-oriented processes influence their perception. That is, the presentation and question format, the communicated information, sociodemographics and family history may influence the counselees' perception, because of the meaning of this information for their selves, their existence and fulfillment of their needs for certainty. The counselee-oriented processes may motivate them to use cognitive techniques; for instance, counselees with a large need for certainty but who perceived uncertainty over the DNA-test result may distort the information in their perception to perceive certainty. In summary, we expect that counselee-oriented variables predict the accuracy of their perception with equal or larger effect sizes than information-oriented variables, and completely mediate the effects of information-oriented variables on this accuracy.

1.5. Research questions

1. Do counselee-oriented variables regarding the self, existence and the unfulfilled need for certainty significantly predict the accuracy of the counselees' perception?
2. Is perception-accuracy also significantly predicted by information-oriented predictors?

3. Do counselee-oriented variables significantly explain the effect of information-oriented variables on the accuracy of the counselees' perception; more specifically: when counselee-oriented variables are included in the analyses, do the effects of the information-oriented variables on the accuracy of the counselees' risk-perception become non-significant?

2. Method

2.1. Procedure and design

Eligible participants were women with breast and/or ovarian cancer who had requested for a BRCA1/2-test in the period 2006-2009 at the departments of Clinical Genetics of the Leiden University Medical Center, the Maastricht University Medical Center, the University Medical Central Groningen, Erasmus Medical Center Rotterdam, or the VU Medical Center Amsterdam. Eligible counselees received two questionnaires: immediately after the first genetic-counseling session (T1), and 3 months after the second genetic-counseling session in which the DNA-test result was disclosed (T2). Usually, genetic-counselors disclosed the following information: DNA-test result category, heredity-likelihood, cancer-risks for female relatives and for the counselee, risk management options (surgery, surveillance) for relatives and counselees, including the possibility for relatives to undergo DNA-testing when applicable. Table 3 in chapter 6 shows the most frequently communicated information; more details on procedure, design and population are described elsewhere (340).

2.2. Instruments

All instruments are presented for T2 only. Using counselee-oriented and/or information-oriented predictors at T1 yielded similar results (not presented).

The accuracy of the counselees' risk-perception was measured as difference between the counselees' interpretation of their own cancer-risks and the cancer-risks actually communicated by the genetic-counselor. We decided to use their interpretations and not their recollections of cancer-risks (285), because previous analyses in the same sample showed that their interpretations did not differ significantly from and correlated strongly with their recollections (340), but did predict psychological and medical outcomes better than recollections (340,277). Interpreted cancer-risks were measured by the question 'regardless of what your genetic-counselor has communicated, what are your own thoughts and ideas of your risks to develop cancer?' Counselees could answer on a 1-7 Likert-scale ranging from 1 (not at risk) to 7 (complete at risk), which had the least number of missing values compared with percentage scales and showed the most accurate perception(285,277). Actually communicated risks had been derived from a checklist filled-in after each session by the genetic-counselor, medical-files and summary letters that

counselees received within 3 months after the DNA-result; actual risks were rescaled to the 1-7 Likert-scale to match the counselees' interpretation. We used absolute-difference scores (i.e. regardless of the direction of the difference), because of the explorative nature of the study, the small sample size and missing values; moreover, unpresented data analyses did not show different results when we did not use absolute differences.

Items about the self were measured by the Ryff-well-being questionnaire, which was shown to be a reliable and valid scale to measure positive, existential well-being; we used the scales: autonomy, mastery, vitality, inner strength, and self-acceptance (319,367,368). In addition, we used the Revised Life Optimism Scale to measure trait optimism, which was shown to be a reliable, valid instrument (320,369).

Existential items were measured with the purpose-in-life-scale of the Ryff well-being scale (319,367,368). Further, we asked counselees to rate on three 1-7 Likert-scales (1, very seldom, 7-very often): how often they had been wondering how many years they still have to live, what the meaning of their life is, and how often they actually experienced their life as meaningful during the last two weeks.

Need for certainty was measured with the Need for Structure Scale, which is a reliable, valid instrument to measure one's desire for structure and response to lack of structure (370). We asked them about the number of experiences with uncertainties in life before genetic-counseling, and the number of certainties; answers were given on 1-7 semantic differentials (1, little experiences, 7, many experiences). In chapter 10, we describe how we developed items about the Unfulfilled Need for Certainty regarding the domains of DNA-test result, heredity, cancer and self (371). We asked counselees to rate on 7-point scales to what extent they wished to receive certainty about these domains; from this need for certainty we subtracted the level of certainty that they perceived during last two weeks.

Information-oriented variables were developed on the basis of literature and of the experience of involved genetic-counselors. Table 2 describes instruments for presentation format, communicated information, sociodemographics, family history, cancer-experience, cognitive processes. Specific coping styles were measured with the COPE (318) regarding coping with the DNA-test result. Regarding the question-format we only present Likert-scales in this article. We have also asked counselees to recall and interpret their risks in percentage-scales and we compared this with actually communicated cancer-risks; this did not result in different study outcomes.

Table 2. *Overview of information-oriented instruments*

Information-oriented group of variables	Variable description	Items/scales
Presentation format		**Risks communicated in words**, graphics, percentage, proportion or **in a combination of formats**; **mirroring of risks**; exact cancer-risk versus range of cancer-risks; using the term 'genetic change' or using other terms (all binary items)*
Communicated information	DNA-test result category	**Pathogenic-mutation; uninformative-result (i.e. no mutation is found, but counselee is at risk because of pedigree); unclassified-variant (i.e. mutation is found for which the pathogenic meaning is not know yet, and counselee is at risk because of pedigree).**(all binary items) *;**
	Cancer-risks and heredity	**Cancer-risks for proband(%); cancer-risks for relatives(%);** likelihood that cancer is heritable in the family (heredity-likelihood; verbal) *; ** (285)
	Additional counseling aspects	**Counseling was face-to-face; a flyer explaining genetic-testing/results was provided. During the intake: possibility of finding an unclassified-variant mentioned**; explanation of population breast/ovarian cancer-risks; explanation of part of breast/ovarian cancers caused by heredity; risk of finding a pathogenic-mutation; risk of transmitting a pathogenic-mutation when detected. Communicated during result-disclosure: additional explanation of the detected mutation; mutations –also benign ones- are frequently found in DNA; being-at-risk does not mean developing cancer; cancer is not likely to be heritable in your family; other untested mutations may explain cancer; extra explanation of genetics in general; (im)possibilities of DNA-testing; start of family-research of DNA-test result in relatives; possibility of future research and new findings. (all binary items, except for risks measured in %) *
Knowledge-related sociodemographics		educational level (both measured binary, i.e. higher/lower than high school, and on 7-points scale) ***
Family history		Pedigree-information: high cancer-risk; moderate cancer-risk; low cancer-risk *;**
Cancer experience	Medical history	Binary items: breast cancer, ovarian cancer, metastases, preventive bilateral mastectomy (PBM), bilateral salpingo-oophorectomy (PBSO), chemotherapy, radiotherapy, other therapy; elapsed years since cancer diagnoses, metastases, treatment and DNA-test result***
Cognitive processes	Recollections and expectations	Measured at intake: 'Before genetic-counseling, to what extent did you expect to receive a pathogenic-mutation'; measured after result-disclosure: to what extent was this DNA-test result in line with your expectations; **do you expect to receive a new DNA-test result in the future; what extent of heredity-likelihood do you expect this future result to imply?***
	Illness representation	Influence on life; **duration**; control; helpfulness of treatment; **severity/physical limitations**; worries; understanding; influence on mood (semantic differentials, 0, not, 10, completely)***(372)
	Coping	Scales of COPE: **Active, acceptance, priority-taking, planning, renaming,** denial, distraction, turn to God, waiting, taking drugs. Scale of IES: **avoidance***(318,286)

*Instrument: *Filled-in by genetic-counselors in a checklist after each genetic-*counseling *session; **derived from medical-file and/or summary letter sent to the counselee by the genetic-counselor; ***counselees' questionnaire. Social variables are not included (see discussion-section);* ***Bold:*** *significant predictors of the inaccuracy of perception (see table 3)*

2.3. Statistics

Missing values were imputed by multiple imputing. Population variables are described with frequencies and means.

Question 1: We performed regression-analyses with one counselee-oriented predictor (X) at a time (standardized ß=R) to predict the perception-accuracy (Y); due to multicollinearity and the relatively small sample, we could not use multiple-predictor-analyses.

Question 2: We did the same for information-oriented variables (X). Differences in X and Y between DNA-test results were tested with Kruskal-Wallis tests (K-W); DNA-test results were included as moderators in regression analyses to test differences in the relationships between X and Y; only significant differences between DNA-test results are presented in this chapter, and otherwise we show overall results.

Question 3: We did mediation analyses (184,185) as we described elsewhere (277,340). We did one analysis for each information-oriented variable. The information-oriented variable was the predictor (X), the predicted variable was the perception-accuracy (Y). Mediators were the counselee-oriented variables (M). Mediation is assumed to be present when four criteria are met. 1. X and M correlate. 2. X predicts Y. 3. M predicts Y. 4. When both X and M are included in prediction of Y, and we compare these results with criterion 2, the predictive value of X decreases (i.e. partial mediation) or becomes non-significant (i.e. complete mediation). For example, the communication of a UV-result instead of PM/UR-relates correlates with a strong unfulfilled need for certainty about the DNA-test result (step 1); both the UV-result and the unfulfilled need for certainty predict a more inaccurate perception (steps 2 and 3); when the unfulfilled need for certainty is included in analyses, the UV-result does not significantly predict the accuracy anymore which suggests complete mediation (step 4).

We did multiple mediation analyses.

*Firstl*y, we did mediation analyses with all counselee-oriented variables together as mediators, but for some information-oriented variables this resulted in a very small number of participants per analysis due to missing values or multicollinearity.

Secondly, we did mediation analyses with only autonomy, purpose in life and unfulfilled need for certainty about the DNA-test result together as mediators; these variables correlated strongest with both the significant information-oriented predictors and the accuracy; the number of participants per cells was large enough to calculate this.

Third, we did analysis for each of these three counselee-oriented variables separately, to make the number of participants in each analysis as large as possible. For presentation purpose, we only present data with p-values<.01 and std.ß>.20, and only show tables for mediation criteria 2 and 3. Criterion 4 is not presented because we only found complete mediation. Significance level was defined as p<.01. This level reflected a balance between

the explorative nature of this study (suggesting to set a high p-value to avoid type-II error), and the large number of tests (suggesting a low p-value to avoid type-I error).

3. Results

3.1. Population

We approached 654 women who had undergone BRCA1/2-testing. Of them, 467(71%) filled-in the T1-questionnaire and 248(53%) the T2-questionnaire. Mean time since cancer-diagnosis was 5 years; 94% had had breast cancer and 6% ovarian cancer. Metastases were present in 26% of all participants. Before DNA-testing, 56% had undergone symptomatic mastectomy, 6% symptomatic bilateral salpingo oophorectomy (BSO) and 5% preventive/presymptomatic (PBSO). Mean age was 56 years, 42% had visited high school or higher, 84% was married, 87% had children. More information is published elsewhere (340). Missing value-analyses did not show significant results.

3.2.Counselee-oriented predictors

Self: Counselees had a more accurate perception when they were more autonomous, felt more mastery, vitality, self-acceptance, optimism, and inner strength. Effect sizes were moderate to large (see table 3).

Existence: Counselees perceived their cancer-risks as more accurate when they had a stronger experience of purpose in life, less frequently wondered how many years they still can live and what the meaning in their life is, and currently experienced living a more meaningful life. Effect sizes were moderate to large.

Need for certainty: Counselees perceived their cancer-risks as more accurate when they were more experienced with uncertainties in life, desired less structure and reacted more positively to a lack of structure. Accuracy was also higher when counselees reported less needs for certainty, perceived more certainty and experienced more fulfillment of their needs for certainty about cancer, DNA-test result and heredity. Effect sizes were moderate to large.

Table 3. *Results for counselee-oriented predictors*

	Counselee-oriented predictors	Inaccuracy of perception (std.ß)
Self	-Autonomy	-.24
	-Mastery	-.35
	-Vitality	-.24
	-Self-acceptance	-.23
	-Optimism	-.28
	-Inner strength	-.20
Existence	-Purpose in life	-.20
	-Wondering about how many remaining years	.35
	-Wondering about meaning in life	.43
	-Experiencing meaning in life	-.39
Need for certainty	-Desire for structure	.39
	-Reaction to lack of structure	.39
	-Previous experiences with uncertainties in life	-.25
	-Need for certainty about DNA-test result	.20*
	-Need for certainty about heredity	.48
	-Need for certainty about cancer	.22*
	-Need for certainty about the self	.20*
	-Perceived certainty about DNA-test result	-.34
	-Perceived certainty about heredity	-.40
	-Perceived certainty about cancer	-.40
	-Perceived certainty about the self	-.35
	-Unfulfilled need for certainty about cancer	.40
	-Unfulfilled need for certainty about DNA-test result	.36
	-Unfulfilled need for certainty about heredity	.55
	-Unfulfilled need for certainty about the self	.39

*All p<.01, std.ß>.20; *p<.07; results regard the total sample because no significant differences were found between DNA-test results (pathogenic-mutation; uninformative-result; unclassified-variant; not-significant Kruskal-Wallis tests); a positive ß means that the counselee-oriented predictor had caused a more inaccurate perception, and a negative ß means a more accurate perception.*

3.3. Information-oriented predictors

Table 4 presents the significant information-oriented predictors (P<.01; std.ß>.20). About half of the tested information-oriented variables were significant predictors (cf. table 2). All significant effects were moderate to large.

Presentation format: The counselees' perception was more accurate when: risks for UV/URs had not been communicated in words or in multiple formats. The perception was also more accurate when the cancer-risks for UV/URs had not been mirrored (e.g. 80% at risk = 20% not at risk), and when these risks for PM results had been mirrored.

Communicated information: The counselees' perception was more accurate when a PM and not an UR or UV had been communicated, when cancer-risks were higher, when counseling was face-to-face and a flyer had been provided, and when the possibility of finding an unclassified-variant had been mentioned during the intake.

*Cognitive processes:*The higher the cancer-risks and heredity-likelihood were in the counselee's recollections and/or expectations, the more accurate was their risk-perception. The perception was more accurate when counselees expected that the duration of their cancer would be shorter, cancer was less severe, and when they used active, accepting, priority-taking and planning coping styles, and did not use renaming or avoidance as coping.

3.4. Mediation analyses

When we included counselee-oriented variables as mediators (M) in regression-analyses, information-oriented variables (X) did not significantly predict the level of accuracy of the counselees' perception anymore (Y), and the counselee-oriented variables were the only significant predictors of Y (cf. table 3). Information-oriented variables became non-significant when we used them as mediators: all counselee-oriented variables, the three strongest variables (autonomy, purpose, unfulfilled need for certainty about DNA-test result) and each of these variables separately.

Table 4. *Results for information-oriented predictors*

Information-oriented predictors		Inaccuracy of perception (std.ß)
Presented format	Counseling format: in words	.29(UV/UR)/ns(PM)
	Counseling format: combination of formats	.30 (UV/UR)/ns(PM)
	Mirroring of risks	.40 (UV/UR)/-.58(PM)
Communicated information	Actual pathogenic-mutation	-.23
	Actual uninformative-result	.24
	Actual unclassified-variant	.20
	Actual cancer-risks proband	-.38
	Actual cancer-risks relatives	-.30
	Face-to-face counseling	-.20
	Provision of flyer explaining genetic-counseling	-.33
	Possibility of finding an unclassified-variant mentioned during the intake	-.42
Cognitive processes	Recalled own cancer-risk (1-7 Likertscale)	-.35
	Recalled own cancer-risk (% scale)	-.35
	Recalled relatives' risk (1-7 Likertscale)	-.46
	Recalled heredity-likelihood (1-7 Likertscale)	-.34
	Expectation of a new result in future	.40
	Expectation of a pathogenic-result in future	.47
	Expected duration of cancer	.33
	Experienced physical symptoms/severity of cancer	.35
	Active coping with DNA-test result	-.41
	Acceptance coping with DNA-test result	-.28
	Priority coping with DNA-test result	-.39
	Planning coping with DNA-test result	-.34
	Renaming coping with DNA-test result	.38
	Avoidance coping with DNA-test result	.29

P<.01; std.ß>.20 Non-significant results not presented; T=t-test is significant (p<.01) with medium or large effect; N=n<50; ns=not significant; results regard the total sample, except were reported, because no significant differences were found between DNA-test results (pathogenic-mutation (PM); uninformative-result (UR); unclassified-variant(UV); not-significant Kruskal-Wallis tests); a positive ß means that the counselee-oriented predictor had caused a more inaccurate perception, and a negative ß means a more accurate perception.

4. Discussion

4.1. Conclusions

This study showed that both counselee-oriented and information-oriented variables predicted the accuracy of the counselees' risk-perception. The amounts of variance explained by counselee-oriented and by information-oriented variables were similar (cf. tables 3 and 4).

We found that several information-oriented variables influenced the accuracy of the counselees' risk-perception. Counselees with UV/UR's were less accurate than PM-carriers, possibly because this information was less clear; communication of additional information in words and/or in multiple formats seemed to have confused these counselees even more (cf. 203). PM-carriers and counselees with high risks (actually communicated and recalled) had a more accurate perception, possibly due to the clarity of pathogenic results which may be easier to perceive accurately. As expected, their perception was more accurate when counselees were younger (77), counseling was face-to-face, and flyers were provided (327). Moreover, counselees had a more accurate perception when they had active coping styles, and did not have passive coping styles, negative expectations and distress, which confirms other studies (90,284).

The influence of information-oriented variables was completely mediated/explained by counselee-oriented variables. We found that the counselees' risk-perception was directly influenced, and was completely mediated, by the following variables: positive-existential personality characteristics, experience of meaning/purpose in life, previous experiences with uncertainties in life, their general need for structure, and their specific needs for certainty about the DNA-test result, about heredity of cancer in their family, and about their own cancer. These counselee-oriented variables completely explained the effect of the information-oriented variables.

The information-oriented variables influenced the counselees' perception *because* they evoked a personal process in the counselee, which involved her self/personality, her existential concerns in life and her needs regarding the DNA-test result, her cancer and the heredity of cancer in the family. For instance, the presentation format and the actually communicated DNA-test result have influenced the counselees' risk-perception, *only via* (i.e. through the mediation of) the personal and existential meaning that this information inherently has for the counselees. More specifically, the communication of a PM (i.e. information-oriented) created a feeling of certainty over the genetic cause of cancer in the counselee (i.e. counselee-oriented); subsequently this feeling of certainty influenced the counselees' perception, and created an *indirect* relationship between the communication of the PM and the perception.

The results also suggest that the counselees' cognitions, such as their cognitive illness representations, influence their risk-perception *through* the personal and existential

meaning of these cognitions. Thus, the counselees' risk-perception is not determined by merely rationally knowing 'I am at risk', but by the personal and existential meaning of knowing this. Thus, when counselees are confronted with risk-information, they translate the probabilistic statements into terms with personal meaning (62), and try to embed this information in the general story of their lives (59). By subjectively translating and embedding this information, counselees seem to distort the originally communicated cancer-risks, i.e. creating their inaccurate perception.

4.2. Counselee-oriented approach

The counselee-oriented predictors that we propose in this chapter are not intended to replace the information-oriented predictors. Our approach is integrative and is intended to understand/explain how information-oriented processes do influence the accuracy of the counselees' risk-perception. First, we described the impact of actually communicated genetic-information on the counselees' perception, and described how counselees function psychologically, such as using biases and heuristics. Subsequently, we explained by mediation analyses why counselees experienced these information-oriented influences.

We suggest that the perception of cancer-risks is not a sum of 'decontextualized' (38) representations, biases, rules or schemas. Risk-perception is the result of a counselee putting the communicated risks in the lived experience and broad context of her life, which includes how she manages existential concerns and needs, and what kind of person she is. Because of her fundamental needs, she may use cognitive techniques and misinterpret the communicated risks.

The counselee-oriented approach seems to be a less normative approach than the information-oriented approach. To be in line with other studies, we used the term 'inaccurate perception'. However, words such as 'inaccuracy' and 'inadequate counseling' seem to suggest that the counselee and/or genetic-counselor are 'wrong'. But even if a counselee may be 'inaccurate' from an information-oriented point-of-view, she could feel justified from her own point-of-view and from her own needs and drives. Thus, having an inaccurate perception may not necessarily mean that counselees want to be provided with additional 'correct information'. It could be argued that letting counselees have their own inaccurate perception – i.e. respecting their autonomy - may sometimes be more ethically justified than paternalistically forcing them 'to think adequately'.

The counselee-oriented approach is in line with the general trend in psycho-oncology to pay more attention to the role of meaning and spirituality in cancer-patients (122). For instance, cancer-patients who experience meaning in life seem to be better adjusted to cancer (132,144,146,147). They also experience a better quality-of-life and well-being, and up to 50% less depression (132,133,139-141).Terminal patients with high spiritual well-being also experience a lower desire for hastened death, less depression and less suicidal ideation (133,142). Moreover, patients who are able to reengage in meaningful

goals and focus on pleasant issues, experience more positive affect (143). These meaning-making processes may be influenced by the way that physicians communicate with patients (373,374).

4.3. Limitations and implications

Our study is based on a relatively small sample size in the moderately short follow-up time after DNA-test result disclosure. The study may be biased by the fact that we have only included women affected with cancer. However, elements in their cancer-history –such as having metastases- did not predict the level of accuracy of the counselees' perception, and were also not-significant as moderators in unpresented interaction analyses. We suggest replicating this study in other genetic disorders, in both sexes and in patients affected and unaffected with cancer.

Subsequent studies should also focus on the social construction of the meaning of genetic-information, because friends and relatives are part of the counselees' context, and may influence their interpretations (90,375,376). Such social studies should not focus on the open communication of genetic-information per se (168), but on the experience and the meaning of this communication for the counselee, such as perceived social support. More counselee-oriented instruments could be developed and used. For instance, interview studies could be performed to ask counselees what the communicated information fundamentally means to them, like in before-mentioned qualitative studies. Moreover, future studies may also examine which variables (dynamically) limit the counselee from sharing her subjective ideas and feelings in an information driven counseling session.

Regression mediation analyses strongly indicated the presence of mediation effects, but did not definitely prove this, because this was not an intervention study (188). However, the design of the study and the nature of the mediators made mediation likely (188). These mediation results confirmed our theoretical expectations and previous qualitative studies. T2-accuracy was predicted by T1-predictors. The communication of DNA-test results did actually influence the mediators like an intervention (as described elsewhere, i.e. 371). Questionnaires/items about the self also showed to be flexible instead of being an unchangeable trait which would suggest moderation instead of mediation; because we found significant differences between T1 and T2 in the self-items ($d>.4$), suggesting that the DNA-test result may have altered the counselees' self-experience which is in line with our hypotheses (60,cf.61-62). We suggest performing intervention studies to determine and influence these mediation effects.

From our counselee-oriented perspective, we suggest to focus on developing assessment instruments and interventions regarding the psychological/existential needs and motivations of counselees to undergo genetic-counseling. Genetic-counselors could

explicitly ask counselees about their reasons to request DNA-testing, and assess the role of this request in their actual life situation.

Subsequently, genetic-counselors could use this counselee-oriented assessment to explore together with counselees the decision to undergo DNA-testing or not. DNA-testing may not be suitable for all counselees in all personal/existential situations, and some counselees may first need psychological counseling. Different stages of readiness to undergo DNA-testing may exist (377). For instance, does a counselee have (too) high expectations of DNA-testing as a way to cope with her cancer? Could some of them benefit more from first referring them for intensive medical and/or psychological help to learn to live with cancer, instead of immediately undergoing DNA-testing? When counselees receive counseling at an optimal stage, their perception of genetic-information and its consequences may be better adjusted to the actual medical situation. Current theories and instruments about stages-of-readiness should be developed to include counselee-oriented elements.

The counselee-oriented assessment could also be used in tailoring the format of risk-communication, for instance by focusing on the personal consequences of the DNA-test result (38). Such assessments before DNA-testing could include the question how counselees think and feel about their cancer-risks; the actual risks could be tailored to this pre-testing risk-perception. Such interventions seem to make the counselees' risk-perception more accurate (282). To assess their understanding after DNA-test result disclosure, counselees could be asked to repeat the communicated information in their own words. To explore their interpretations, counselees could be asked about 'their own ideas and feelings, regardless of the communicated information' and about the medical consequences they have in mind (277,285,340).

Counselees could be provided with additional information if necessary. But as our study suggests, information-provision alone cannot be expected to improve their perception much. Therefore tailored risk-communication may also include discussion of the fundamental subjective meaning that the DNA-test result may have for counselees, and the ways how they can embed the result in their lives. For instance, a counselee could explore together with her genetic-counselor what she can do with this risk-information, what she can tell their relatives, and how this information feels, and how she copes with uncertainty and vulnerability related to this result.

To help counselees in creating a realistic meaning of the DNA-test result, it may be explained beforehand what counselees can realistically expect from genetic-counseling and what not. This regards both medical and psychological aspects, including both certainties and uncertainties. Currently, patient-information is often unbalanced in the Netherlands, because flyers and websites seem to pay much attention to certainties and little to uncertainties that may arise after DNA-testing. Nuanced patient-information could

help counselees to have realistic expectations of the certainties they may obtain, which may subsequently improve their perception of the communicated information.

More rigorous interventions to improve the counselees-oriented variables include training in coping with hereditary cancer (331), and (continue) finding meaning in life despite one's cancer-experience, physical limitations and (genetic) uncertainties (378). Several existential psychotherapeutic interventions for cancer-patients have been developed, showing moderate effects on distress and well-being (138,379); these effect sizes are comparable with other psychological interventions for cancer-patients (380-382). More recent meaning-oriented interventions have shown to have large effects (378,383,384).

Our advice to develop counselee-oriented interventions is in line with the review of Edwards et al (327). They showed that previous interventions, both information-oriented and counselee-oriented, have not been effective because of their information-oriented elements, but because of their counselee-oriented elements, i.e. focus on emotions and support (327). It has been advised to develop genetic-counseling into a personal, two-directional/reciprocal process (283) with explicit focus on the counselee. This may help counselees in their search for certainty, may improve their perception of genetic-information and make their medical decisions more well-informed.

Chapter 10

Genetic counseling as fulfillment of the cancer-patient's need for certainty:

Description of perceived certainty, need for certainty, and reactions to unfulfilled need for certainty in a prospective study in BRCA1/2-counselees

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Submitted

Abstract

Objective

Many cancer-patients undergo DNA-testing in the BRCA1/2-genes to receive information about the likelihood that cancer is heritable. Previous studies suggested that DNA-testing often does not fulfill the counselees' needs for certainty. We systematically examined the balance between the counselees' Need-for-Certainty and Perceived-Certainty (NfC-PC, i.e. level of fulfillment of NfC) regarding the specific domains of DNA-test result, heredity and cancer. We also examined relationships of NfC-PC with coping styles and distress.

Method

Before disclosure of BRCA1/2-test results for hereditary breast/ovarian cancer (T1), questionnaires were filled-in by 467 cancer-patients. Another questionnaire (T2) was filled-in after disclosure of pathogenic-mutation results (n=30), uninformative results (n=202) or unclassified-variants (n=16).

Results

Before and after DNA-test result disclosure, overall 58% to 94% of all counselees experienced unfulfilled NfC regarding the DNA-test result, heredity and cancer. Compared to T1, the communication of pathogenic-mutations (T2) caused more fulfillment of their need for certainty about the DNA-result, but less about cancer and heredity. Compared to T1, unclassified-variants (T2) did not change the extent of fulfillment of all counselees' needs for certainty (NfC>PC). Compared to T1, uninformative-results (T2) caused more fulfillment of all needs than before disclosure. Counselees differentiated NfC and PC between the domains of DNA-result, heredity and cancer. The unfulfilled needs for certainty (NfC-PC) were uncorrelated with cognitive understanding of the DNA-test result, but correlated strongly with distress, misinterpretation of information and passive coping, correlated moderately with active-coping and barely with acceptance.

Conclusions

The counselees' NfC needs more attention in research and practice, e.g. when the potential uncertainties of testing are discussed. The counselees' NfC should be assessed and used in tailored, mutual communication of DNA-test results.

1. Introduction

1.1. Certain uncertainty

Since the identification of the BRCA1- and BRCA2-genes for hereditary cancer, many cancer-patients have undergone DNA-testing (15). Reduction of uncertainty is an important goal of genetic counseling for women from families with a strong history of breast and/or ovarian cancer. Counselees report that they want to undergo DNA-testing, to receive certainty about their cancer-risks, their relatives' risks, the role of a possible genetic predisposition of cancer in the family to obtain access to periodic screening, and to regain personal control over their own cancer (1-6).

Genetic-counseling and mutation testing in index patients (i.e. the first tested in the family) do not always provide certainty. Even the most conclusive outcome of testing, i.e. the detection of a pathogenic-mutation (PM), does not imply certainty that a counselee will develop cancer (again). In these cases, contralateral breast-cancer risks are communicated for affected women as 30-60%, and primary breast and ovarian-cancer risks for unaffected carriers as respectively 60-80% and 30-60% (BRCA1) / 5-20% (BRCA2). These are population risks and not individual risks, i.e. a PM is generally associated with these risks but does not tell whether this specific counselee will develop cancer. Moreover, a PM-result may evoke new uncertainties in other domains of the counselees' lives, for instance regarding medical-decisions, telling the family, family planning, and DNA-testing and medical-decisions of relatives.

About 85% of all DNA-test results in index cases do not show a PM, but show either an 'uninformative result' (UR), i.e. no mutation in the BRCA1/2 genes, or an 'Unclassified-Variant'/'variant-of-uncertain-clinical-significance' (UV), i.e. a mutation for which the clinical meaning is not known yet (UV). These non-informative -results include even more uncertainty than PM's, because no precise risk-figures are available in these cases but only general risk estimations on the basis of the counselee's pedigree. Counselees are also confronted with other uncertainties regarding cancer-risk estimates, such as limitations in the sensitivity and specificity of the DNA-tests, source credibility and ambiguous information (34). Genetic-counselors and other physicians may also evoke uncertainty by non-verbal communication not consistent with the communicated information (31-33,345,385,386).

Many studies show that counselees experience much uncertainty and lack of personal control regarding the DNA-test result (3,31,164,244,245,362-366,387,388). Reported levels of uncertainty vary considerably, and depend on instruments and samples.

Thus, many counselees ask for genetic-counseling because of a strong need to obtain certainty, but this need often remains partially or completely unfulfilled. It has been suggested, that this unfilled need for certainty is the essence of the experience of being-at-

high-risk-for-cancer and may explain how counselees cope in general with the DNA-test result and distress. (6,62,389,390)

This chapter describes an empirical study about the extent to which the counselees' need for certainty is fulfilled by DNA-test result disclosure, and how this is related to copingstyles and distress. This study has four points which differ from previous studies on uncertainty in genetic-counseling. First, we focus on specific experiences of uncertainty. Second, we focus on the balance between the counselees' need for certainty and their perception of certainty. Third, we describe the relation between uncertainty, copingstyles and distress. Fourth, we focus both on cognitive and affective elements of uncertainty, and not only on cognitive processes as in many previous studies.

1.2. Specific domains of uncertainty

Previous studies on the counselees' experience of uncertainty have used unspecific instruments (391,227) or have only measured traits (244,366,392,393). Instruments that measure the counselees' need for certainty (NfC) as a trait, or measure the global experience of perceived certainty or uncertainty (PC), may not grasp the counselees' subtle, ever changing experience of different certainties in different situations. For instance, a cancer-patient may feel certain about her cancer –because the tumor is under control- but may feel uncertain about the role of the genetic-predisposition of cancer in the family. A counselee may feel certain about the heredity during the intake-session of genetic-counseling, but after disclosure of the DNA-test result, she may suddenly experience uncertainty. Thus, we suggest that the counselees' experience of certainty should be operationalized specifically in different domains of uncertainty (376,394). Although traits may influence the experience of certainty in specific domains, global trait-instruments may be less useful than specific state-instruments to really understand how counselees experience a specific situation.

We categorized the kinds of uncertainty as described in literature into three groups, and use this categorization in the operationalization of NfC and PC in our study. We have omitted literature on NfC/PC about one's self, personality or life (e.g.137,138,395), to focus on NfC/PC regarding genetic-counseling.

1.DNA-test result: Many studies suggest that uncertainty may be an important part of the counselees' lived experience of being-at-risk to develop cancer (again) (3,6,31,62, 164,244,245,362-366,270,388-390). Counselees feel uncertain about waiting for a long time for the result, and about the possible unclear meaning of the DNA-test result, especially of UR/UV-results. UV-counselees report much uncertainty (203,217,224-226).

2.Heredity: Counselees do not only undergo DNA-testing to receive information for themselves, but also for their relatives, in particular their offspring (1,5). Counselees seem to experience distress because of the (uncertain) meaning of the DNA-result for the

likelihood that cancer is heritable in their family and for their relatives' cancer-risks (e.g.217,277,340).

3.Cancer: Many patients experience uncertainty regarding the diagnosis, the prognosis (376,396), and making medical decisions (35,376,397,398). For example, they decide to undergo surgery to reduce uncertainty (397), and request DNA-testing to receive certainty about their cancer, recurrence risk, and what decisions to make (1,5,35). Genetic-testing may answer the existential question regarding cancer 'why did I have to become ill?', and may be regarded as a way to regain personal control (399,245).

1.3. Need-for-Certainty and Perceived-Certainty

Previous studies have either described NfC or PC in counselees. Both may be required to understand the variety of reactions that different counselees have to a specific situation. For instance, two counselees may perceive the same high level of uncertainty regarding the DNA-test result. The counselee who has a high need to receive certainty about the DNA-test result will experience the situation as more distressful than the counselee who does not strongly need to receive certainty. Thus, the assumption that genetic-information, cognitions, or PC directly lead to distress is too simplistic (227). It is the imbalance between NfC and PC that seems to matter, not NfC or PC *per se*.

NfC implies an awareness of the ideal situation (optimal certainty) and PC implies the perception of the situation in reality. The ideal and realistic perceptions of situations may clash in genetic-counseling.

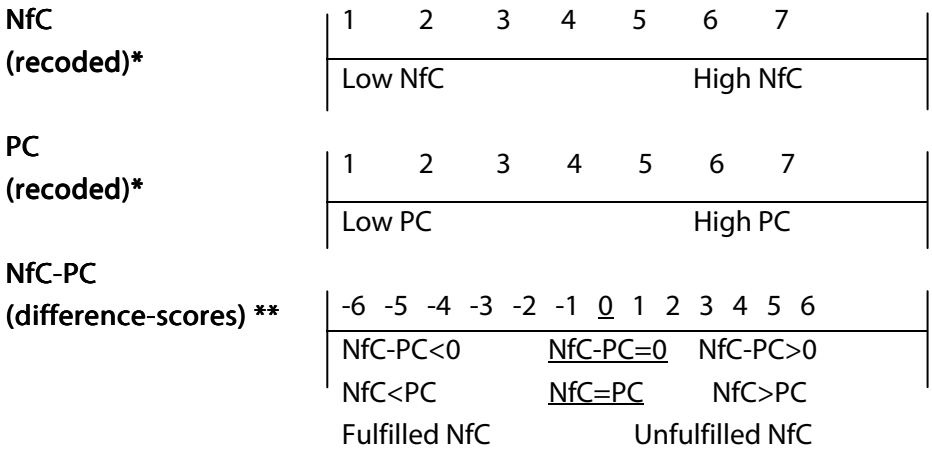
Ideal: Counselees undergo DNA-testing to receive certainty (1,5,6), hope and mastery over their cancer and over their relatives' cancer-risks (148,216,359-361).

Reality: However, DNA-testing does not provide immediate certainty on demand. Counselees have to wait for the results, the result may be ambiguous, may not provide them with the desired options for control, and the communicated cancer-risks may be imprecise and not in line with their own prior interpretations (400). Counselees report that many expectations about genetic-counseling are not met (216,359-361). Confrontation with this uncertain reality of DNA-testing may lead to disappointment and uncertainty (3,31,164,362-366). Thus, the counselees' NfC often collides with the actual PC after genetic-counseling (which is possibly similar to the communication of medical information in other situations).

PC and NfC can be expected to influence each other. Counselees may use their needs and expectations (NfC) as a heuristic background against which they perceive the current situation (PC); thus, NfC may influence PC. Counselees may also adjust their needs and expectations (NfC) in reaction to the actual level of certainty (PC) in this situation. Despite the mutual influence of NfC and PC, we assume that counselees are able to differentiate the actual level of certainty (PC) from their preferred level of certainty (NfC) in a situation, because NfC and PC can be described as fundamentally different processes.

In our study, we measured both NfC and PC, which were assumed to be continuous variables with uncertainty and certainty as end points of one axis. We focused on the balance/relationship between NfC and PC, which was operationalized by the difference between both (NfC-PC); we refer to this difference as 'fulfillment of the counselees' need for certainty'. That is: the counselees' perceived level of certainty fulfills their need for certainty to a lower or higher extent (see figure 1). It is this level of fulfillment, and not NfC or PC per se, that we expect to explain fundamental copingstyles.

Figure 1. *Explanation of the scales of the Unfulfilled Need for Certainty Scale: Need for Certainty (NfC), Perceived Certainty (PC), and level of fulfillment of the need for certainty (NfC-PC)*



**Reverse scaling of the semantic differential in the questionnaire (see table 1); recoding: 1=7, 2=6, 3=5, 4=4, 5=4, 6=2, 7=1; **NfC=PC regards score '0' only; NfC is assumed to be mainly fulfilled when NfC-PC<0 and NfC<PC; NfC is assumed to be mainly unfulfilled when NfC-PC>0 and NfC>PC*

1.4. Coping and distress related to unfulfilled Need for Certainty

We examined the extent to which the counselees' specific needs for certainty are fulfilled in genetic-counseling in this study, because we assumed that counselees experience NfC and PC as important in coping with DNA-test results and with cancer, and unfulfilled NfC may lead to distress (6). In line with the literature, we can identify several ways of coping with the uncertainty of the DNA-test result, of heredity and/or of cancer.

Cancer-patients are assumed to cope optimally with the cancer-experience, when they are able to acknowledge and/or integrate the co-existence of two processes or 'dual realities' (401). This may be understood from the theoretical assumption that two simultaneous positions on certainty are possible (391). First, humans can recognize that the possibility of certainty or complete predictability is an illusion, because the world is fundamentally unpredictable. Second, there is a human drive to reduce uncertainty, to explain the world, and to render it predictable. Both positions may not be mutually exclusive. It has been assumed that patients cope optimally with cancer when they are able to have both positions at the same time, i.e. positively accepting the objective reality of uncertainty, risks and limitations, and at the same time acknowledging and living-out the subjective reality of desires, dreams and needs to reduce uncertainty (138,395,401). Thus, they have to reconcile their perceived lack of certainty/control with their wish for mastery and responsibility (152), and to let uncertainty and hope go hand-in-hand (393,394).

However, unfulfilled NfC may not always go hand-in-hand with acceptance. Counselees may also deny one of the dual realities, i.e. decrease of PC and/or increase of NfC, as suggested by previous studies in cancer-patients (402-404). For instance, cancer-patients may cope by doubting, engaging, denying or by experiencing distress (60); we may apply these copingstyles to the situation of cancer-patients in genetic-counseling, as indicated by previous studies. Counselees may doubt the PC by reinterpreting the actually communicated DNA-test result (221,400). They may actively engage in behaviors to change the situation by undergoing frequent surveillance and/or surgery of breasts and/or ovaries (35,77). They may cope with the DNA-test result by using passive copingstyles such as denial, renaming and/or avoidance (87,405). When uncertainty is not reduced but other copingstyles are unavailable, counselees may experience distress (228). This distress can be described as meta-uncertainty (391), i.e. uncertainty resulting from the question whether PC or NfC is most applicable.

Thus, we assume that counselees may cope with their unfulfilled need for certainty in the ways described above: acceptance, reinterpretation, active coping, passive coping, and/or distress. More specifically, we expect that the more unfulfilled the need for certainty is, the more counselees will report these copingstyles/distress.

1.5. Unfulfilled need for certainty as an affective evaluative process

Previous studies have often operationalized NfC and PC as information-oriented, mainly cognitive processes, such as fulfillment of the counselees' cognitive needs and expectations for information and structure (54,55,406). However, NfC and PC seem to depend on many psychological, appraisal and coping processes and not only on information-oriented processes (see 1.4.); NfC-PC seems to be a general evaluation of a situation in its totality, which includes both cognitive and affective elements (cf.391).

1.6. Research questions

These three points lead to the following research questions in this study. 1.How many counselees experience an unfulfilled need for certainty? 2.Is there a change in the level of fulfillment of NfC after disclosure of test results, and do different DNA-test results cause different changes? 3.Do the domains of unfulfilled need for certainty (i.e. cancer, heredity, DNA-test result) differ from each other? 4.Is the extent to which the counselees' NfC remains unfulfilled after DNA-test result disclosure related to acceptance, reinterpretation, active coping, passive coping, and distress? Each of these questions will be answered separately for PM, UV and UR, because we assume that differences exist between these groups regarding NfC and PC, as described before. 5.Is the extent to which the counselees' NfC is fulfilled independent from the counselees' cognitive understanding of the DNA-test result, cognitive need for structure and the actually communicated DNA-test result?

2. Method

2.1.Study procedure

We decided to include only BRCA1/2-testing in counselees who have (had) cancer, because they are the majority of counselees receiving DNA-test results in the Netherlands. Eligible participants were women with previous or current breast and/or ovarian cancer who had requested a BRCA1/2-test in the period 2006-2009 at the departments of Clinical Genetics of the Leiden University Medical Center, the Maastricht University Medical Center, the University Medical Center Groningen, Erasmus Medical Center Rotterdam, or the VU Medical Center Amsterdam. Eligible counselees received two questionnaires: one after the first genetic-counseling session (T1), one 3 months after the second genetic-counseling session in which the DNA-test result was disclosed (T2).

Actually communicated information was derived from a checklist filled-in after each session completed by the genetic-counselor, from medical files and from summary letters that counselees received within 3 months after the result.

Usually, genetic-counselors disclosed the following information: DNA-test result category, the likelihood that cancer is due to a genetic predisposition in this family (i.e. heredity-likelihood), cancer-risks for female relatives and for the counselee, risk management options (surgery, surveillance) for relatives/counselee and the possibility for relatives to undergo DNA-testing (340).

2.2. Instruments

We developed the Unfilled-Need-for-Certainty-Scale (UNCS) on the basis of our model of four domains (DNA-test result, heredity, cancer, self), and differences between NfC and PC. The initial 80-item UNCS was based on literature and tested in a pilot study, and the number of items was reduced by factor-analyses which *Finally* showed good reliability and validity (e.g.203).

This resulted in a 19-item UNCS administered at T1 and at T2. Both at T1 and T2, we measured 6 subscales: NfC and PC about the DNA-test result, heredity-likelihood and cancer (see table 1). Counselees were asked to rate items 'for the preceding month' on semantic differentials, ranging from 1, high, to 7, low, NfC. For instance: 'I did not feel much uncertainty' to 'I felt much uncertainty', and 'I need certainty' to 'I do not necessarily need certainty'. To facilitate interpretation of the scores, we recoded these items so that '1' indicates low NfC/PC and '7' high NfC/PC. PC was measured with multiple items on each domain, and all PC-scales showed good reliability (see table 1). NfC was measured with only one item on each domain; we selected this item from the initial 80-item UNCS because of its general formulation and strong correlations with other initial items.

Unfulfilled need for certainty (NfC-PC) for a domain was measured by substracting the mean of all PC-questions on that domain from the NfC on that domain (see table 1); using Z-scores yielded similar results and is not shown. We assumed that NfC and PC can be substracted because the items had been formulated similarly, and both PC and NfC seemed to measure comparable concepts as shown by large overall Cronbach's α (see table 1) and strong correlations between PC and NfC (R's=.60-.80). Study results did not differ when we measured NfC-PC with only one item for NfC and one item for PC.

Other instruments are shown in table 2. For validation purpose, we used multiple instruments to operationalize each phenomenon under study.

Table 1. *Description of items (semantic differentials) and their reliability of the 19-items Unfulfilled Need for Certainty Scale (UNCS) administered at T1 and T2*

After intake-session ***(overall α=.78)***		**After DNA-test result disclosure session** ***(overall α=.78)***	
Need for certainty (NfC)* *(overall α=.74)*	Perceived certainty (PC) * *(overall α=.79)*	Need for certainty (NfC)* *(overall α=.75)*	Perceived certainty (PC)* *(overall α=.78)*
T1 NfC Cancer I need/do not necessarily need certainty about cancer	**T1 PC cancer (c): α=.85** *I did not feel(1)-I felt (7)…* 1.uncertainty about c. in general 2.certainty about c. in general** *I felt uncertain (1)/certain(7) about…* 3. treatment/surveillance of c. 4. daily life coping with c. 5. the development of c. in future	**T2 NfC Cancer** I need/do not necessarily need certainty about cancer	**T2 PC cancer (c): α=.87** *I did not feel(1)-I felt (7)…* 1.uncertainty about c. in general 2.certainty about c. in general** *I felt uncertain (1)/certain(7) about…* 3.treatment/surveillance 4. daily life coping with cancer 5.development of cancer in future
T1 NfC DNA-test result I need/do not necessarily need certainty about the DNA-test result	**T1 PC DNA-test result (tr) : α=.88** *I did not feel(1)-I felt (7)…* 1.uncertainty about tr in general 2.certainty about tr in general** *I felt uncertain (1)/certain(7) about…* 3.consequences of tr for myself 4.consequences of tr for relatives 5.meaning of tr for my future 6.unchangeability of tr	**T2 NfC DNA-test result** I need/do not necessarily need certainty about the DNA-test result	**T1 PC DNA-test result (tr) : α=.85** *I did not feel(1)-I felt (7)…* 1.uncertainty about tr in general 2.certainty about tr in general** *I felt uncertain (1)/certain(7) about…* 3.consequences of tr for myself 4.consequences of tr for relatives 5.meaning of tr for my future 6.unchangeability of tr
T1 NfC heredity I need/do not necessarily need certainty about the heredity of cancer in the family	**T1 PC heredity (her) : α=.86** *I did not feel(1)-I felt (7)…* 1.uncertainty about her in general 2.certainty about her in general** *I felt uncertain (1)/certain(7) about…* 3.consequences of her for my cancer 4.consequences of her for my future 5.consequences of her for relatives	**T2 NfC heredity** I need/do not necessarily need certainty about the heredity of cancer in the family	**T1 PC heredity (her) : α=.89** *I did not feel(1)-I felt (7)…* 1.uncertainty about her in general 2.certainty about her in general** *I felt uncertain (1)/certain(7) about…* 3.consequences of her for my cancer 4.consequences of her for my future 5.consequences of her for relatives

All items were measured with semantic differentials ranging from 1, high PC/high NfC, to 7, low PC/low NfC; for presentation purpose, all items are reverse-coded in this chapter so that '1' means low PC/NfC and '7' high PC/NfC (see figure 1); **reverse coded to match the scale of the other items (1=low PC/NfC-7=high PC/NfC); * All items had been formulated like states, i.e. counselees were asked to rate the items regarding 'the last month', except for questions regarding the self which had been formulated like traits, i.e. 'in general I'm a person who…'; the self-items are not presented in this chapter because we want to focus on state-items; α=Cronbach's α; c=cancer, tr=DNA-test result, her=heredity*

Table 2. *Overview of instruments other than the UNCS*

Research question	Theme	Scales	Range of total scores(low/high)	Cronbach's Alpha
1, 2	**Actual DNA-test result**	Actually communicated DNA-test result categories: PM, UR, UV*	0-1 (not/ communicated)	
4	**Level of cognitive understanding and actually communicated cancer-risks**	1.Level of understanding according to the counselee; 2. counselees' level of understanding according to the genetic-counselor*; 3.actually communicated DNA-test result: counselees' own cancer-risks, relatives' cancer-risks*; 4.Need-for-structure: 12-items, subscales 'desire for structure' and 'reaction to lack of structure' (407,370,406)	1&2:1-7 (bad-good understanding); 3:%; 4: scales: 4-24, 7-42	4: .82; .83
5	**Acceptance**	1.COPE:acceptance-copingstyle, 2 items (318); 2.uncertainty is bearable, i.e. sum of the answers to the question 'uncertainty is unbearable' on the domains of cancer, DNA-test result, heredity and self <12	1:2-8; 2:4-28	1:.79
	Reinterpre-tation	difference score between actually communicated own cancer-risks* and counselees' interpretation of their own cancer-risks (correlated and square-root); scales are measured in 1-7 verbal categories (285)	0-6	
	Active coping	1.COPE:active-copingstyle, 2 items (318); 2.changes in life: 2 scales, i.e. psycholo-gical, medical-physical (203,277); 3.intention to undergo: a.surveillance/surgery of ovaries (PBSO), b.mastectomy (PBM), c. breast surveillance	1:2-8; 2: scales: 7-35, 3-15 3:1-7	1: .85, .84 2: .87, .86
	Passive coping	1.COPE:denial and renaming copingstyle, 2 items (318); 2.Impact of Events Scale: avoidance (408)	1:2-8; 2:8-32	1: .79 2: .81
	Distress	1. uncertainty is unbearable' on the domains of cancer, DNA-test result, heredity and self; 2. two distress-factors 'negativity' and 'worries' (m=0), resulting from principal-component-analyses (prosp-2) on the following general-distress and cancer-specific distress scales: Hospital Anxiety and Depression Scale, Positive Affect Negative Affect Scale, Lerman's Cancer-Worry Scale and Impact of Events Scale(1)(288,290)(2)(291)(3)(286,289); 3. Esplen's BRCA-specific distress, subscales: feeling stigmatized, vulnerable to develop cancer, mastery over cancer (75,277).	1:1-7; 3: 7-49, 5-35, 4-28	2: .90, .87 3: .75, .73, .59

Table 2. *Continued*

Covariates and moderators	**Cancer history**	1. breast or ovarian cancer, 2. metastases, 3. kind of cancer treatment (binary items: PBM, PBSO, chemotherapy, radiotherapy, other therapy), 4. months since disclosure of cancer diagnoses, metastases, treatment and of genetic-counseling	1-3: 0-1 (not/applicable); 4: months	
	Inner resources	Personality: 1.Ryff's conceptual well-being scales (319): mastery, purpose in life, self-acceptance, autonomy, vitality, inner strength 2. Optimism (320); 3.experience with few/much uncertainty in life until now	1: 7-42, except autonomy=8-56; 2:10-50; 3: 1-7	1:.81, .82,.80 .84, .86, .83 2: .79
	Social resources	1. openness to discuss hereditary cancer in the family (409) in nuclear family, and in current family; 2. Dutch Relational Ethics Scale (344) in nuclear family, and in current family: trust/justice, loyalty, negative entitlement	1:7-28 2:6-30; 3-15; 3-15	1: .82, .83 2: .84, .82,.81 .79, .80, .81
	Family characteristics	pedigree information**, i.e.: number and percentage of with-cancer-affected and deceased 1st, 2nd and/or 3rd degree relatives.	n,%	
	Socio-demographics	1.living together with a partner, 2. having children, 3.being religious, 4. having a job, 5.educational level (0, no-7, university)	1-4: 0-1 (not/applicable)	

***derived from the checklist filled-in by the genetic-counselor; **derived from medical-file; all other items derived from the questionnaire filled-in by the counselee*

Table 3. *Results of questions 1 and 2*

Domain	Need for certainty = NfC (1, low - 7, high)				Perceived certainty = PC (1, low – 7, high)				Unfulfilled need for certainty = NfC-PC (<0, fulfilled - >0, unfulfilled)			
	Intake (n=467)	PM (n=30)	UR (n=202)	UV (n=16)	Intake (n=467)	PM (n=30)	UR (n=202)	UV (n=16)	Intake (n=467)	PM (n=30)	UR (n=202)	UV (n=16)
Cancer	5.9 (1.5) [2]	6.3 (1.3) [12]	5.6 (1.7) [12]	6.1(1.2) [2]	4.5 (1.3) [2]	4.3 (1.2) [23]	5.0 (1.3) [123]	5.1 (1.2) [123]	1.4 (2.2) 76% [4]	2.0 (1.7) 73% [134]	.6 (2.4) 77% [134]	1.0 (1.6) 87% [34]
DNA-result	5.9 (1.3) [2]	5.5 (2.1) [1]	5.5 (1.8) [1]	6.3 (1.4) [2]	3.9 (1.4) [2]	4.6 (1.8) [13]	5.4 (1.3) [13]	4.6 (1.5) [123]	2.0 (2.1) 86% [4]	.9 (2.9) 67% [134]	.1 (2.4) 64% [134]	1.7 (2.0) 88% [34]
Heredity	6.2 (1.2) [2]	6.7 (.5) [13]	6.2 (1.4) [3]	6.2 (.8) [3]	4.2 (1.3) [2]	3.7 (1.7) [123]	4.7 (1.3) [123]	4.3 (1.3) [23]	2.0 (1.8) 91% [4]	2.5 (1.9) 89% [134]	1.5 (2.1) 82% [134]	1.9 (1.6) 94% [34]

Cells show the results for the questionnaire filled-in by counselees after the intake (T1) and after one of the three possible DNA-test results (T2: PM, UR or UV). Figures are means (standard deviations), and % of counselees with NfC-PC<0; see figure 1 for explanation of the scores.[1]Difference between intake and DNA-test result as shown by t-tests with p<.01 and Cohen's d>.14 (i.e. medium effects or larger); [2]Difference between NfC and PC (either at intake or at PM/UR/UV) as shown by t-tests with p<.01 and Cohen's d>.14 (i.e. medium effects or larger); [3]Difference between PM, UR, UV measured with Kruskal-Wallis test, either for NfC or PC (p<.01);[4]Difference from 0 as shown by one-sample t-tests with p<.01 and Cohen's d>.14 (i.e. medium effects or larger).

2.3. Statistics

1. We described the percentage of counselees who experienced an unfulfilled need for certainty (i.e. NfC>PC; see figure 1); t-tests were used to show whether NfC was mainly unfulfilled, i.e. larger than PC. 2. Differences between intake(T1) and PM/UR/UV(T2) were calculated with t-tests (effect sizes are shown with Cohen's d), and differences between the disclosure of PM, UR and UV with Kruskal-Wallis-tests and t-tests(t/d). 3. We calculated differences in NfC-PC-scores between the domains of cancer, DNA-test result and heredity with t-tests (t/Cohen's d). 4. Relationships between NfC, PC, NfC-PC and cognitive-understanding-variables were calculated with correlations, corrected for PM/UR. 5. For each domain, we calculated correlations between NfC-PC and the coping- and distress-variables.

Inclusion of other variables as either covariates or moderators in analyses did not substantially change answers to the research questions and are therefore not presented (see table 2; see selection of variables in 340). Significance level was defined as $p<.01$. This level reflected a balance between the explorative nature of this study (suggesting to set a high p-value to avoid type-II error), and the large number of tests (suggesting a low p-value to avoid type-I error).

3. Results

3.1. Population

We approached 654 cancer patients who had undergone BRCA1/2-testing. Of them, 467(71%) filled-in the T1-questionnaire and 248(54%) the T2-questionnaire. Mean time since cancer-diagnosis was 5 years (sd=2); 94% had had breast cancer and 6% ovarian cancer. Metastases were detected in 26% of all participants. Before DNA-testing, 56% had undergone therapeutic mastectomy, 6% therapeutic and 5% preventive bilateral salpingo-oophorectomy (PBSO). Mean age was 56 years, 42% had visited high school or higher, 84% were married, 87% had children (see chapter 6).

3.2.1. Question 1: description of unfulfilled need for certainty

On all domains, after intake and after DNA-test result disclosure, NfC was always significantly larger than PC (all $p(t)<.01$, $d>.14$; see [2] in table 3). On each domain, between 58% and 94% of all counselees experienced NfC as mainly unfulfilled (NfC>PC; see percentages in table 3).

3.2.2. Question 2: change in unfulfilled need for certainty after DNA-test result

Compared to T1, PM-counselees experienced more fulfillment of their NfC about the DNA-test result, but less fulfillment of their NfC about cancer and heredity (p(t)'s<.01, d's>.14). (see table 3) Compared to T1, UV-counselees experienced no changes in fulfillment of NfC in all domains (p(t)'s >.05). Compared to T1, UR-counselees experienced more fulfillment of their NfC in all domains.

PM-counselees experienced less fulfillment of their NfC regarding cancer and heredity than counselees with an UV/UR (p(t)'s<.01, d>.14). Compared to PM/UR-counselees, a larger percentage of UV-counselees experienced unfulfilled NfC on all domains, and their mean unfulfilled NfC was larger than UR-counselees on all domains (p(t)'s<.01, d>.14). Compared to PM/UV-counselees, UR-counselees experienced more fulfillment on all domains (p(t)'s<.01, d>.14).

3.2.3. Question 3: differences between domains

The counselees' scores on the unfulfilled NfC (NfC-PC) differed significantly between all domains. More specifically: scores differed between cancer and DNA-test result (d's: intake:.41; PM:.29, UR:.25, UV:.16; p(t)'s<.01), between cancer and heredity (d's: intake:.14; PM:.72, UR:.35, UV:.56; p(t)'s<.01), DNA-test result and heredity (d's: intake:.15; PM:.81, UR:.62 , UV:.33; p(t)'s<.01).

3.2.4.Question 5: correlations with coping and distress

Table 4 shows how the level to which the counselees' NfC remained unfulfilled (NfC-PC) correlated with coping styles and distress. NfC-PC correlated barely with the extent to which counselees had an accepting-coping style, but correlated moderately with another operationalization of acceptance, i.e. experiencing the uncertainty as bearable. NfC-PC correlated strongly with reinterpretations of cancer-risks, i.e. with the level to which the risks were perceived inaccurately. NfC-PC correlated moderately with active-coping, i.e. with an active-coping style, psychological and medical changes, intention to undergo surveillance/surgery of ovaries (PBSO), mastectomy (PBM), and breast surveillance. NfC-PC correlated moderately with passive coping styles, i.e. with the level of avoidance, denial and renaming. NfC-PC correlated strongly with distress, i.e. with the level of uncertainty about cancer, DNA-test result and heredity perceived as unbearable, and with negative emotions, worries, feeling stigmatized, low mastery over cancer and large vulnerability to develop cancer.

Table 4. *Results for question 5*

Coping and distress related to the level of unfulfilled need for certainty (NfC-PC)			Level of unfulfilled need for certainty after DNA-test result disclosure (NfC-PC)					
	Measurement	Subscales	NfC-PC-cancer		NfC-PC-DNA		NfC-PC-heredity	
			High scores (%)*	(R)	High scores (%)*	(R)	High scores (%)*	(R)
Acceptance	*-Copingstyle*	Acceptance	28	ns	29	ns	29	ns
	-'Uncertainty is bearable'		4	.30	4	.21	6	.31
Misinter-pretation	*-Perception*	Level of inaccuracy of counselees' interpretation of their own cancer-risks	76	.40	78	.36	69	.55
Active coping	*-Copingstyle*	Active	15	.27	17	.15	24	.26
	-Changes in life	Psychological	15	.31	14	.20	13	.26
		Medical-physical	8	.26	8	.12	7	.18
	-Intention to undergo surveillance and/or surgery	Surveillance or surgery of ovaries (PBSO)	42	.15	46	.10	46	.19
		Mastectomy (PBM)	41	.20	54	.16	46	.20
		Breast surveillance	65	.13	66	.10	67	.10
Passive coping	*-Copingstyle*	Avoidance	19	.37	18	.27	16	.28
		Denial	35	.22	3	.20	3	.18
		Renaming	14	.20	14	.18	15	.22
Distress	*-'Uncertainty is unbearable'*	Cancer	19	.60	20	.42	25	.47
		DNA-test result	37	.34	32	.42	41	.34
		Heredity	10	.31	12	.35	17	.52
		Self	26	.45	26	.39	33	.40
	-Distress	Negativity	60	.66	60	.51	56	.60
		Worries	60	.67	60	.46	62	.52
		BRCA-stigma	5	.56	5	.50	4	.51
		BRCA-mastery	24	.46	20	.46	23	.47
		BRCA-vulnerability	18	.61	18	.47	16	.49

*Ns=not significant; *Cells show percentages of counselees with NfC-PC<0 who has 'high' mean scores, i.e. acceptance copingstyle>5, sum of 'uncertainty is unbearable'<16, inaccuracy>0, psychological change>15, medical-physical change>9, denial/renaming>6, avoidance>20, uncertainty is unbearable>4, negativity>0, worries>0, stigma>34, mastery<13, vulnerability>24*

3.2.5. Question 4: correlations with cognitive understanding

The counselees' unfulfilled NfC (NfC-PC) was not correlated with the counselees' level of understanding according to themselves and the genetic-counselor, and not with the actually communicated DNA-test result and cognitive-need for structure (R's<.20, p(R)'s>.05).

4. Discussion

4.1. Conclusions

Before and after receiving DNA-test results, the majority of counselees experienced an unfulfilled need for certainty about the DNA-test result, heredity and cancer. The communication of PM decreased uncertainty about the DNA-test result, but increased uncertainty about cancer and heredity (i.e. meaning for relatives); this is understandable because one's genetic status may have consequences for medical treatment as well as for one's relatives. The communication of UV's did not fulfill any of the counselees' needs for certainty, and on all domains of uncertainty, UV-counselees experienced a more unfulfilled need for certainty than PM/UR-counselees. UR-counselees experienced more fulfillment of their NfC compared with PM/UV-counselees and with the intake-measurement.

Counselees differentiated the unfulfilled NfC between the domains of cancer, DNA-test result and heredity. The unfulfilled NfC did not correlate with the counselees' cognitive-understanding of the DNA-test result.

This study is limited by its relatively large and specific number of decliners (which is comparable to other studies in the Netherlands) and by lack of baseline-measurement. We only described the short-term impact of DNA-testing and included cancer-patients only; however, similar results were found when we performed (unpublished) analyses in retrospective studies in unaffected counselees and their untested, unaffected relatives (277,321). NfC-scores and PC-scores may have influenced each other and/or may both reflect other variables such as personality; however, such influence would lead to a small difference between NfC and PC, but we did find large differences between both (d's>.6).

The extent to which the counselees' need for certainty remained unfulfilled after genetic-counseling, correlated strongly with distress, misinterpretation of genetic-information, and passive coping. It correlated moderately with active-coping and only weakly with acceptance. Thus, only few counselees accept unfulfilled NfC, and the majority transformed their perception, reacted passively and/or experienced distress.

If we regard acceptance of the dual reality of genetic-uncertainty and the counselee's wish for certainty as psychologically beneficial (138,395,401), psychological care may help them living meaningfully while accepting uncertainties. It may help them in the acceptance of dual realities, by finding/creating some extent of subjective certainty,

without denying the reality of being a cancer-patient (e.g.378). In other terms, they may learn to neither try to deny PC nor give-up their NfC, and accepting the situation and experiencing the uncertainty as bearable.

On the basis of the results, we suggest six shifts in the implicit/explicit hypotheses that psychological researchers may have about DNA-testing.

4.2. Unspecific-trait-hypothesis

Previous studies on genetic-counseling focused on general, trait-like variables, but did not clarify how these general concepts were related to specific experiences of uncertainty. We examined state-items about DNA-testing, heredity and cancer, which showed differences, changed after DNA-test result disclosure, and were strongly related with copingstyles. Additionally, we also measured trait-items about the self, but non-presented analyses showed that these trait-items did not appear to be sensitive enough to track the impact of DNA-testing. Because these trait-items did not change after DNA-test result disclosure and were not correlated with copingstyles and distress. This suggests that the counselees' experience of uncertainty is understood in most detail when measured with sensitive items about the current experience of NfC/PC in specific domains. Future studies should examine how specific-NfC/PC relates to the cancer-patients' general experience/needs of certainty, vulnerability and assumptions about life (131,137,410,411).

4.3. Uncertainty-causes-distress-hypothesis

It has been suggested that the communication of uncertain genetic-information directly evokes distress (86,203). However, this study suggests that neither the actually communicated DNA-test result nor the counselees' PC or NfC strongly predicted distress as sole predictor. It is the balance between NfC and PC, i.e. the level to which the NfC remains unfulfilled after genetic-counseling, that strongly predicted distress.

4.4. Accuracy-matters-hypothesis

From the perspective of genetic-counselors, DNA-testing is offered as a means to inform counselees about their cancer-risks and medical options, and to help them to make well-informed medical decisions (cf.412,413). From this perspective, several studies have focused on the accuracy of the counselees' perception, and on how counselors may improve this (66,70,78). In contrast, counselees describe health care professionals 'to rely on numbers to fulfill certain obligations to inform patients, to steer decision making, and to prevent unrealistic expectations', and thought professionals 'are insensitive toward the more general impact that numerical information could have within their illness experience' (149, p.327-8). This description is understandable because counselees do not ask for DNA-testing in order to become 'accurate' and 'well-informed' (1,5,6), and frequently value their own opinion as more important than that of the genetic-counselor (203,285). They want to

receive certainty about their own and their relatives' cancer-risks and to know which medical decisions to make (1,5,6). That is, they want to find meaningful ways to live with the uncertainties about cancer, and to find a basis for hope (149).

Before DNA-testing, genetic-counselors assess counselees' needs and motivations to have a test, and inform them about the potential uncertainty that may result from DNA-testing. We suggest developing genetic-counseling as a personal, two-directional and reciprocal process (283) with explicit focus on these needs and interpretations.

One may argue that for some counselees, accuracy of perception is less important than knowing what to think, what to do, and what to hope for (i.e. NfC-PC). As long as the necessary medical care is provided, some counselees may benefit more from psychosocial help to learn to live meaningfully with the uncertainty of cancer and heredity than from undergoing expensive genetic-counseling, which has a large likelihood of detecting uncertain UR/UV-results, followed by uncertainty, distress and poorly-informed medical-decisions (277,340). The counselees' needs may also be taken into account when considering communicating UV's, low-penetrance-genes and unexpected findings in whole-genome-sequencing. Such information may not fulfill the counselees' motivation to undergo DNA-testing, cause misinterpretation and distress.

4.5. Cognitions-cause-uncertainty-and-distress-hypothesis

Many studies focused on the counselees' perception of the communicated cancer-risks, and tried to predict uncertainty and distress by their cognitive-understanding of the DNA-test result (70,66,277). These authors seemed to assume that cognitions cause uncertainty and distress. However, the counselees' cognitions were often poor predictors of the counselees' reactions (66,68,76). The best predictors of distress were not the counselees' (mainly cognitive) recollections but their interpretations (277,340). The current study underlines these criticisms. PC, NfC and NfC-PC were not related with cognitive understanding, but to social and inner resources, such as purpose-in-life, self-acceptance and open family communication (see method). Thus, information-focused variables, i.e. the actually communicated DNA-test result and cognitive risk-perception, did not strongly predict distress but counselee-centered variables did (i.e. NfC-PC) (cf.400).

4.6. Paternalism-hypothesis

The intention of genetic-counseling is to counsel in a non-directive way, give counselees a free choice, and respond to the counselees' needs (40-42). In practice, genetic-counseling sometimes represents more a teaching-model than a counseling-model (99,311,414,415), meaning that counselors may verbally dominate the dialogue and advise directively (416). From such a paternalistic perspective, authors assumed a direct relationship between the genetic-counselor's role and false cognitions (78) which seemed to lead them to the conclusion that counselors should improve risk communication skills (54,56,311,264).

However, these paternalistic assumptions seem oversimplified. Genetic-counselors may actually have little influence on the counselees' lives. For instance, the counselees' perception is not only connected with the communicated genetic-information, but also with their experiences with their own and their relatives' cancer (35,68,71,73,164,166-169). Therefore, the accuracy of the counselees' perception does not strongly depend on the communicated message (400), but on individual processes, such as coping and (mis)interpretation of the DNA-test result. This is confirmed by studies suggesting that patient-centered aspects of interventions change the counselees' perception more than information-centered aspects (327,400).

4.7. Non-tautology-hypothesis

Many studies have searched for possible predictors of distress, such as social-support, stigma and vulnerability (417), uncertainty (418), and risk-perceptions (70,66,277). However, these predictors may not be other phenomena than distress, only differently measured by different instruments. Distress may underlie all these predictors. Therefore, examining how variables such as uncertainty relate to distress, may be similar to stating a tautology: e.g. NfC-PC strongly correlated with negativity and worries. That is, one aspect of distress was related to another aspect, but we do not know their causal directions. Such tautologies should be studied with correlations to show consistencies, as we did, and not with regression analyses to show predictions.

When we assume that variables such as stigma, vulnerability and uncertainty are different expressions of the same distress, the criterion that defines a variable as 'bad' or 'good' transforms. Previous studies have searched for predictors with the largest effect sizes, but it may be more important to search for variables that express the counselees' lived experience of distress most fully and fundamentally. Qualitative studies suggest that feelings of uncertainty are the essence of the counselees' lived experience of being at risk for cancer (6,62,389,390). More studies are needed to understand the counselees' experience of uncertainty in genetic-counseling and other diseases.

Chapter 11

Summary and discussion

1. The main thread of this thesis

'Emery claimed that by 1984 there had been an evolution from what Kessler described as content-oriented to person-oriented genetic counseling. He based his claim on the acknowledgement in the literature that genetic information often has profound psychological effects, which may have long-term consequences that can extend to relatives. He asserted that a qualified genetic counselor had to be aware of the client's fears, hopes, defenses, and rationalizations in order to help him/her deal with his/her problems in a realistic manner. Many of the providers promoting psychological goals were trained in psychiatry or psychology and were well aware that clients do not necessarily make logical or rational choices (although they may be logical to the client). They recognized that scientific explanations are only one way to understand risk, allowing for personal interpretation and meaning. Genetic science does not necessarily alleviate guilt or anxiety in the client. In some cases, the information itself may actually raise anxiety or reinforce feelings of guilt or responsibility. A psychological goal of genetic counseling aims to help clients cope with such feelings and adapt to their circumstances. (37)

Since many years, the practice of genetic-counselors in the Netherlands seems to have been dominated by a counselee-oriented approach. The development of genetic-counseling towards a counselee-oriented approach has been acknowledged and described by many authors, such as Kessler. He used the term 'person-orientation' which was in contrast with 'content-orientation', which means according to him 'that the focus of the session was overwhelmingly focused on the provision of medical information and genetic facts rather than on an attempt to explore personal meanings, attitudes, feelings, and dynamic issues' (419).

Thus, Kessler used his terms to describe how genetic-counselors communicate with counselees. To distinguish our focus from Kessler's, we have chosen to use different terms: information-oriented and counselee-oriented. Kessler has focused on the practice of genetic-counseling, but we have focused on the psychological processes that follows the genetic-counseling sessions and that may be described in psychological studies. The 'information orientation' and 'counselee orientation' describe how the communicated information and the communication process influence the counselees' lives in general in aftermath of the sessions.

On the basis of the current counselee-oriented practice of genetic-counseling in for instance the Netherlands, we had expected to find many counselee-oriented studies. In contrary, the literature seems to be dominated by studies that are mainly information-orientated (see chapter 1). For instance, many studies described the impact of DNA-test

result disclosure on risk-perception, medical decisions and distress. But it is not clear what a DNA-test result really *means* for a counselee, and how she embeds the result in her life.

In this chapter, I draw the main thread of this thesis by summarizing and discussing the results from previous chapters. I will do that by discussing five counselee-oriented themes. DNA-testing has a far-reaching impact on the lives of counselees (paragraph 2). The subjective interpretation of counselees is a complex but important phenomenon (3). This interpretation explains and mediates the impact of DNA-testing (4). The whole family is involved in the counseling process (5). Genetic-counseling is a complex procedure in which different pieces of information are communicated, and differences may exist between subgroups of counselees (6). Theoretical and clinical implications are not discussed in this chapter, but are presented in the addendum.

2. Conclusion 1: The far-reaching impact of DNA-test results

Many authors have described which factual consequences DNA-testing may have on the lives of counselees. For instance, the disclosure of BRCA1/2-test results – especially PMs (Pathogenic Mutations) - has shown to lead to a more frequent uptake of surveillance and prophylactic surgery of breasts and/or ovaries (e.g.221,247,397,420-423,255). In the period of waiting for the DNA-test result and shortly after that, many counselees seem to feel somewhat distressed, but these feelings seem to normalize over time (183). We also found that up to 50% of all counselees with a PM or UV-result (Unclassified-Variant) had undergone PBM (Prophylactic Bilateral Mastectomy) or PBSO (Prophylactic Bilateral Salpingo Oophorectomy) within 5 years after the DNA-test result (chapter 5), and that the majority of all counselees (PM, UV and UR/Uninformative-Results) underwent frequent surveillance of breasts and/or ovaries (chapters 5 and 6). Most counselees did not report significant distress or psychopathology in our study, but between 5% and 25% of them reported clinical levels of distress (chapters 5 and 6), especially counselees who had received a UV-result (chapters 3 and 6).

Thus, like previous studies, we have reported that DNA-testing is often followed by medical decisions and symptoms of distress and psychopathology. But this conclusion may not completely explain what counselees experience as really important after DNA-testing. The range of medical and psychopathological outcomes is relatively narrow, as a recent review concluded that 'new research is necessary to develop the array of outcome measures' by means of more sensitive and specific instruments (424). The reported medical facts and psychopathological symptoms do not seem to create a lively image of what is precisely going on in the experience of counselees, because they do not answer the questions: what do these medical facts and psychological symptoms really *mean* for the counselee, and how does she embed these in her life? To answer these questions, we

have developed new instruments, and studied new counselee-oriented aspects of the counselees' lives that were influenced by the DNA-test result. We call these aspects counselee-oriented because they focus on the personal meaning that a DNA-test result has on the counselees' lives.

We found that not only medical and psychopathological domains of the counselees' lives had been influenced by the disclosure of the DNA-test result. The Life Changes Questionnaire in chapters 3 and 6 showed that the counselees had experienced significant changes in their existential view on life, their experiences of their body, personality and emotional well-being, coping with uncertainty and relationships. There was a large variation in the extent that the DNA-test result influenced the lives of individual counselees; some reported small or no changes at all, and others reported very large changes. The counselees attributed most changes to the DNA-test result, but some counselees mentioned that the cancer had also contributed to these changes.

Despite the fact that psychopathology was absent in more than three-quarters of all participants, the majority of all counselees felt vulnerable, stigmatized, and felt low mastery over their cancer (chapters 5 and 6). Moreover, more than two-third of all counselees experienced an unfulfilled need for certainty regarding the DNA-test result, the heredity of cancer in the family, and their own cancer (chapter 10).

Thus, when we focused on information-oriented impact-measures, we did not find a very large impact of DNA-testing on the lives of counselees. But when we used counselee-oriented instruments, significant changes in life were found, especially regarding the experience of vulnerability, uncertainty, existential view on life, and the counselees' experience of themselves. These changes were described as the essence of being-at-risk and were associated with many other important psychological processes, such as distress (chapters 3 and 10). In summary, the disclosure of DNA-test results significantly influences the counselees' lives, ranging from practical and visible changes to deep and not primarily visible changes. Moreover, these deep changes seem to be an essential part of the counselees' experience of DNA-testing. This has also been suggested by previous qualitative and theoretical studies (59-61,425,426).

3. Conclusion 2: The subjective interpretations of DNA-test results

> *The genetic-counselor has provided me with all the certainties that she had regarding the possibility that I could carry a genetic mutation. But an uncertain factor always remains. I recall that she laughed when I said: 'You say that this pedigree is suspicious? Really? OK. I hear you. I know what you're really saying.' The genetic-counselor laughed, because we could not avoid the truth. You know, genetic-counselors are not saying that aloud –that is how science is- but they are actually telling this story, that I have the mutation.* (Based on interview RL-006)

One of the aims of genetic-counseling is to help counselees understand the genetic contributions to their disease (52). For that reason, researchers have asked counselees how they understand their DNA-test results. As we discussed in chapter 4, many studies used ambiguous questions, such as 'what are your risks to develop cancer?' It was unclear whether the answer to such a question reflected the counselees' recollections or interpretations of their cancer-risks or an unidentifiable mixture of both. Other authors have asked counselees about their understanding and their cognitions of the communicated risks. But few have studied what it *means* to be at risk to develop cancer or to carry a PM. Moreover, many studies have only discussed the counselees' perception of their own cancer-risks and not of other pieces of information communicated by the genetic-counselor.

For these reasons, we asked counselees to recall the communicated DNA-test result category, and to recall and interpret their own cancer-risks, their relatives' risks, and the likelihood that cancer is heritable in the family. All these aspects differed significantly from each other, suggesting that these different questions measure different aspects of the counselees' perception. This suggests that the counselees' perception indeed consists of multiple elements. Many aspects were also intercorrelated, which is understandable because they were about the same DNA-test result and about the same counselee in the same family (see chapter 1, 1.3.2.3.).

How accurate was the counselees' perception, that is: how much did their perception deviate from the actually communicated information? When we asked counselees, the large majority of them answered that they had understood the communicated information. When we asked them to identify which DNA-test result category (i.e. PM, UR or UV) had been communicated, the large majority answered accurately, except for women with UVs, who inaccurately regarded these as being either a PM or a UR in 25% (chapters 3-6). When we asked counselees about their recollections and interpretations of the *meaning* of the DNA-test result for cancer-risks and heredity-likelihood, their answers were most frequently inaccurate, i.e. they differed significantly from what actually had been communicated (chapters 4-6, 9). These results suggest that counselees accurately perceive the general meaning of the DNA-test result –such as the DNA-test result category-, but they do not accurately recall and interpret the precise meaning of the result for their life, that is for their own cancer-risks, their relatives' risks and the likelihood that cancer is heritable in the family.

After the DNA-test result disclosure session, the counselees' recollections and interpretations changed slightly 'in the right direction', that is they deviated less from the actually communicated genetic information, compared to the first measurement after the intake session (chapter 4-6). However, as described above, the recollections and interpretations differed significantly from the actually communicated information at all measurement moments. This seems to suggest that before genetic-counseling, counselees

already had developed strong ideas about their cancer-risks and heredity-likelihood which were only slightly adapted, as if they had a pre-set bandwidth within they subtly adjusted their perceptions.

In summary, we have confirmed previous studies that have suggested that genetic information is not simply 'taken up as value-neutral objective truth, but rather risk information is deeply subjective, interiorized against a pre-existing sense of self' (63). The counselees' perception of the communicated genetic information has also shown to be a broad complex process which cannot be examined by using a single, ambiguous question. The counselees' perception can be compared with a children's whisper game: the genetic-counselor communicates 'A', but the counselees recalls 'B' and interprets 'C' (chapter 7). Thus, the counselees' interpretation of facts are not similar to the communicated facts; some may say: the world of genetic-counseling does not consist of facts, but this world is constructed by the counselees (cf.427).

4. Conclusion 3: Models explaining the impact of genetic-counseling

As reported, we have found that the communication of a BRCA1/2-result had influenced a broad range of outcomes in the counselees' lives (1.2.1.), and that many counselees perceived the DNA-test result differently than their genetic-counselor (1.2.2.). This raises the question: how did the actually communicated genetic-information influence the outcomes, and how is this related to the counselees' own perception?

Few previous studies have answered the question *how* the disclosure of DNA-test results has influenced the counselees' lives. Most studies described the impact of testing on the counselees' lives, and they simply showed differences between the outcomes of PM, UR and UV-results (e.g.183). Other studies assumed that the communication of genetic-information directly predicts the outcomes.

This simple model of genetic-counseling has only been confirmed in our retrospective study: the communication of a PM or a UR directly correlated with the counselees' decision to (not) undergo PBSO and/or PBM (chapter 5). This finding need not tell that the communication of a DNA-test result directly causes counselees to opt for prophylactic surgery and undergo surveillance, but it may simply reflect the general guidelines. Because surgery options are more strongly suggested in case of PM and not strongly in case of UR, and for surgeons it is not common policy to perform PBSO and/or PBM in case of UR. Thus, this result seems to show that the guidelines are being followed. It does not mean that in general, the communication of a DNA-test result directly causes other outcomes such as psychological well-being and changes in life. This finding should also be nuanced by the fact that in our prospective study, none of the pieces of

communicated genetic-information (including the PM and UR-categories) was directly related with any outcomes (chapter 6); this result may be explained by the fact that the measurement-moment was shortly after the disclosure of the DNA-test result.

In contrast to this simple model, we have found that the counselees' perception of the communicated cancer-risks and heredity-likelihood correlated with and/or mediated their medical decisions and distress. All reported effects sizes were moderate to large (chapters 5 and 6). The outcome-measures correlated especially strongly with the counselees' interpretations of their own cancer-risks. Thus, how counselees subjectively think and feel about their DNA-test result had strongly influenced their lives, regardless of their recollections and the actually communicated DNA-test result.

Moreover, the accuracy of the counselees' perception of cancer-risks correlated as strongly with information-oriented as with counselee-oriented variables, but the latter also explained/mediated the influence of the information-oriented variables (chapter 9). This means that the information-oriented variables did *not directly* correlate with the accuracy but it did correlate with the accuracy only *via* the complete mediation of the counselee-oriented variables. Thus, information-oriented variables, such as the communication of a pathogenic DNA-test result, influenced the counselees' perception *because* they seemed to evoke a personal and existential process in the counselee. The counselees' risk-perception was not determined by merely rationally knowing 'I am at risk' (i.e. information-oriented), but by the personal and existential meaning of knowing this (i.e. counselee-oriented).

These findings confirm qualitative studies indicating that when counselees are confronted with risk-information, they 'translate the probabilistic statements into terms with personal meaning' (62), and try to 'embed this information in the general story of their lives' (59). By subjectively translating and embedding this information, the counselees seemed to have distorted the originally communicated cancer-risks, creating their own perception of the DNA-test result that deviates from what the genetic-counselor had actually communicated. Subsequently, counselees made medical decisions and experienced distress on the basis of this inaccurate interpretation, and not on the basis of the actually communicated information or on the basis of their recollections. Moreover, the medical, psychological and existential impact of genetic-counseling was explained by these personal and existential processes, such as the counselees' unfulfilled need for certainty about the DNA-test result, heredity-likelihood and cancer (chapter 10).

In summary, we have shown that counselee-oriented variables correlated equally strong or stronger with the impact of DNA-testing compared to information-oriented variables, and they also mediated the influence of information-oriented variables. This is in line with other qualitative or theoretical studies that have suggested that the counselees' perception should be used as a main predictor or mediator of the impact of genetic-counseling (e.g.77,79,90). These results may be exemplified by Emma's following remark:

'The genetic-counselor has communicated many 'facts'. But when I reflect on what this result really means for my life, and when I have to make medical decisions, I do not use figures and facts. I simply follow my own feelings. And they tell me something completely different than the genetic-counselor.'

5. Conclusion 4: DNA-testing involves untested relatives

Previous studies have shown that counselees often inform their untested relatives about the DNA-test result, and they have described the impact of DNA-testing on the relatives' lives from the perspective of the counselee and/or from a merely qualitative point of view.

Previous studies suggested that the counselees' experiences with cancer in their family influence their perception of the communicated information (e.g.164,166-168). Like many studies, we have examined whether the counselees' perception was influenced by the number and percentage of relatives with cancer and/or who has deceased due to cancer (chapters 3, 5, 6, 9, 10). These pedigree-variables did not influence the results, and neither did the openness to discuss hereditary cancer in the family (chapters 8, 9). Why did these 'familial facts' not influence the counselees' perception and outcomes?

Firstly, unpublished analyses on the prospective study suggested that not the numbers of affected relatives and the factual openness influenced the counselees' perception, but the meaning of these family characteristics did. For instance, not the communication openness per se mattered, but the experienced social support and equality and trust in the familial relationships did. The moral support that the counselees had received and their experiences of their relationships with relatives, nuclear family and friends influenced the counselees' interpretations of the DNA-test result. Other studies also suggest that the most important predictor is not the mere sum of affected and deceased relatives, but it is the personal meaning that a counselee attaches to her experience of being a member of a family with many cancer patients, such as the extent to which she identifies with a deceased relative (355,328).

Secondly, the familial facts may influence the counselees' perception and outcomes not directly but only *indirectly*. Because a counselee who grows up in a family with many cancer-patients may develop a feeling of vulnerability to develop cancer, and may even start to expect the occurrence of cancer. Counselees from high risk families may feel fundamentally insecure (428), and feelings of being-at-risk may become a part of their identity (61) (see also 2.1.5.). Subsequently, this vulnerability or identity may have determined their interpretation of cancer-risks and heredity before genetic-counseling, which has shown to be difficult to change during counseling (1.2.2.) and which influences the outcomes (1.2.3.). Thus, family-experiences may have formed the counselees' identity,

which may subsequently have influenced their risk-perception and the outcomes of genetic-counseling.

We found that the untested relatives in our family study felt 'much involved' during the genetic-counseling process (chapter 7). Ten percent would even have preferred being involved more in the genetic-counseling process, 25% would have liked receiving direct information from the genetic-counselor – e.g. a letter -, and 15% would have preferred to have had a face-to-face conversation with the genetic-counselor (unpresented data; no differences between PM/UV/UR). These low percentages may reflect the fact that the untested relatives participating in our study were already well informed by the tested counselee, and that they were much involved during the genetic-counseling process; thisfinding that relatives were well informed and strongly involved may also be due to sample biases (chapters 7-8).

The relatives' perception of their own risk to develop cancer had been influenced by the actual DNA-test result like in a children's whisper game: noise had occurred in the recollection, interpretation, and communication by the probands before the relatives created their own recollections and interpretations of the DNA-test result. The lives of relatives had somewhat changed after DNA-test result disclosure, both regarding medical and psychological aspects. These changes were only directly correlated with the relatives' recollections and interpretations of the DNA-test result.

Probably, the untested relatives' interpretations and consequences also deviated from what the proband/counselee had communicated because these relatives had used their own experiences with cancer as well as their own experiences with the specific messenger of 'the genetic news'. For instance, one relative said about the counselee who had told the genetic news: 'She always exaggerates information; therefore, I do not think that the genetic problem is as big as she says that it is'.

In summary: Relatives felt much involved in genetic-counseling, but some would have preferred more involvement. DNA-test result disclosure had an indirect, significant impact on the lives of untested relatives. We have shown that the family history may have indirectly influenced the counselees' perception, like in a children's whisper game. The counselee had communicated message 'C', this information was subsequently filtered by the indirect, non-reassuring and closed communication process, and the relative recalled having received 'D', interpreted this as 'D' and the impact on his/her life was only related with 'D'. Thus, DNA-testing seems to be a social event, in which relatives are involved. Giving a personal meaning to a DNA-test result may inherently be a social process (cf.90,375,376).

6. Conclusion 5: De-simplifying the models of genetic-counseling

> *'I have to admit,'* Emma said, *'that I did not know beforehand what it really meant to request for genetic-counseling. I had expected that they would just ask a few questions about my family and about my own cancer history. Immediately after that, they would prick me with a needle to get a blood sample. I would just have to wait for a month or so, and then I would hear that I either have the gene, or that I do not. The first result would imply that I had to have my unaffected breast and ovaries removed. The second result would imply that I could open a bottle of champagne. But the real DNA-test result was neither black nor white, it was gray. There are no rules for what I have to think and to do.'*

Like Emma, many counselees seemed to simplify the genetic-information, and think in terms of black-or-white, i.e.: 'either I get cancer or I do not get cancer' (216,217). Not only counselees seem to simplify genetic-counseling. Despite the complexity of genetic-counseling (e.g. tables 1 and 3 in chapter 6), many psychological researchers have only included a relatively small number of predictors, outcomes and moderators. For instance, few studies have used mediation, moderation, or structural equation models. This tendency towards simplification may reflect the researchers' own need for certainty and non-ambiguity (345-386). Or they followed the scientific rule of parsimony, that is: using the simplest or most frugal route of explanation available.

Recently, the literature seems to show a trend of de-simplifying the models of genetic-counseling. More recently published psychological studies on genetic-counseling use more extended models, and include many predictors and covariates. A reason for this trend may be that previous studies only reported small or moderate effect sizes, and showed different results for different groups of counselees. For instance, reviews suggested that simple models of DNA-test results rarely directly predict the psychological impact of DNA-testing (66,68,76,70,71), and that counselees with different DNA-test results experience different levels of distress (183).

To render justice to the complexity of genetic-counseling, and to avoid too hastily excluding hypotheses, we have included many variables in our studies. In this paragraph, we discuss how the results of our studies were influenced by the variation in the actually communicated genetic information, and by the variation between the counselees.

6.1. The variation of communicated genetic information

This paragraph summarizes how the study results have (not) been influenced by variation in the information actually communicated by the genetic-counselor. We describe the variation in the DNA-test result nomenclature, in the communicated genetic-information,

between the individual genetic-counselors and the participating departments of genetic-counseling.

Firstly, the whisper game of genetic-counseling may have started among the genetic-counselors, who use many different terms to refer to non-pathogenic DNA-test results. Our literature study showed that different authors may use the same term to express a different meaning; thus, many terms seemed to have been used unreliably. Many terms also showed to be non-valid, because the term did not express what it was intended to do. Some words seemed to disclose a particular value –intended or unintended-, such as the word 'non-informative' seemed to imply the non-usefulness of this result (cf.429). Therefore, we suggested developing a new nomenclature. We did not systematically study whether this Babylonian speech confusion about the BRCA1/2-terminology had also influenced the counselees. However, the following quote suggests that the choice of words may have influenced the counselees' perception of an unclassified variant:

> *'The genetic-counselor told me that something… unqualified was found. It is called that way, isn't it? This means that… It was not qualified, so that must not be right then. Yes, that is it. They found a deviation in my genes. That's why my relatives and I have developed cancer.'*

Secondly, we found that the communicated information was very diverse (chapters 6 and 9). Previous studies only examined a small range of information, but we included a larger one. In chapter 4, we summarized six pieces of information that we regarded as being the most important: the DNA-test result category (PM, UR, UR), the heredity-likelihood, the counselees' cancer-risks, her untested relatives' risks, medical options for risk management, and options for relatives to undergo DNA-testing. In chapters 6 and 9, we reported that many genetic-counselors frequently add explanations to these six main pieces of information, which may be due to the tailoring of information to the counselee (430).

We found that different DNA-test results had led to somewhat different perceptions. Counselees perceived a PM-result more accurately than UR/UV-results, possibly because of its relatively clear meaning and unequivocal medical consequences. PM-counselees seemed to benefit from mirroring the cancer-risks (e.g. 80% at risk also implies 20% not at risk), possibly because this communication format counteracted the counselees' inclination to misinterpret a PM-result as implying 100% risk (216,217).

Counselees perceived a UR or UV as less accurate, possibly because they mixed the meaning of the DNA-test result and the pedigree (chapter 4), or because the result was not like they had expected. This counselees' confusion over the meaning of the DNA-test result became even larger when other genetic-counselors added extra explanations, such as

using multiple formats or mirroring risks, when counseling was by phone and/or letter instead of face-to-face, and hwen a flyer explaining genetic-counseling was provided.

Different DNA-test results had also led to somewhat different outcomes. Long after having received the DNA-test result, PM-counselees had more often undergone surgery than UR-counselees, and UV-counselees experienced more symptoms of depression (chapter 4). Shortly after DNA-testing, the communication of the counselees' cancer-risks, the PM- and UV-results indirectly correlated with medical intentions and feeling vulnerable (chapters 5 and 6).

However, all these differential effects of the actually communicated genetic-information on the impact on the counselees' lives were completely mediated by the counselee-oriented variables, such as the counselees' interpretations. The mediation effects were somewhat different for the different DNA-test results (i.e. moderated mediation), but the general results were similar for all DNA-test results.

Third, we found differences between individual genetic-counselors. For instance, some genetic-counselors always mirrored the communicated risks but others did not, and some communicated during the intake session that a UV-result may be found and others did not. Some genetic-counselors evaluated most of their counseling sessions as to-the-point, and others evaluated their sessions as emotional. Unfortunately, we could not study the effects of individual counselors on the results of our study, because our sample was too small to perform multilevel analysis.

Fourth, there were also slight differences between the five participating medical centers. These results have not been reported in the previous chapters because these are only trends (all p-values>.05, p<.10). These effects were mediated by a consistent use of counseling-related factors in the centers, such as communicating risks in words, communicating the a priori detection rate of a PM during the intake session, and having face to face counseling. The extent to which the summary letter was clear also differed per center, which may also have contributed to different study outcomes for different centers. We also found differences in the personality variables of counselees between the different centers, which seem to confirm stereotypes in the Netherlands. Counselees in Groningen showed relatively few emotions and reported not thinking frequently about existential issues. Counselees in the Randstad (Leiden, Rotterdam, Amsterdam) had a more independent personality, and less frequently asked friends and relatives to support them in their genetic-counseling process. Counselees in Maastricht were more emotional and social in coping with their DNA-test result.

In summary, many different pieces of communicated genetic-information have shown to influence the counselees' perception and the impact on their lives. But all these aspects

were mediated/explained by counselee-oriented variables. In the end, a relatively simple model remained: the communicated information influenced the counselees' interpretations which subsequently influenced the counselees' medical decisions and well-being (i.e. mediation).

Many variables showed to be not significant in our studies. This does not imply that these variables may not be clinically relevant. For instance, some of these variables may have become non-significant because they have not frequently been communicated; we did not report their effects because we only described effects with $p<.01$ and $R>.20$. Another possibility is that these variables overlapped and/or interacted with other variables, which we have not studied. These infrequently communicated pieces of information may also reflect our small sample sizes and the possibility that the genetic-counselors have adjusted the information to the counselees' skills and situation (i.e. tailoring). We have not examined such effects of tailoring. See more methodic comments in paragraph 4 of the addendum.

6.2. The variation of counselees

Several studies have suggested that counselees with and those without cancer differ in their experience of the DNA-test result (249,5,71). Because a DNA-test result may tell an unaffected counselee whether she will develop cancer, and the DNA-test result mainly tells an affected counselee what the risks of her relatives are. In the retrospective study (chapters 3-5, 7-8), we have included both affected and unaffected counselees, but we did not find any differences between both groups. We have also included the counselees' medical history in all our studies, but these did not significantly influence the results.

This does not necessarily mean that different counselees with different cancer histories do not experience genetic-counseling differently, but this only means that our core measures were *not directly* influenced by these cancer history variables, i.e. the recollections and interpretations of risks, the accuracy of these recollections and interpretations, distress and medical decisions. The cancer history may have influenced the result *indirectly* or in interaction with other variables, but we have not studied this.

In summary, having had cancer has shown to be less important than the counselees' own interpretations and uncertainty regarding the DNA-test result. Thus, not the facts, but the counselees' interpretation of these facts had influenced their decisions and distress.

We have also added questions about sociodemographics, personality and family variables (chapters 3-10), but these did not directly correlate with the core variables in our study, with two exceptions. The more autonomous a counselee was, the more her perception deviated from the originally communicated genetic-information (chapters 4-6). This is understandable, because the more autonomous an individual is, the more likely it is that she creates her own opinion because she relies relatively more on her own opinion.

Family characteristics, such as the openness to discuss cancer in the family, influenced the way in which the counselee had communicated the DNA-test result to her untested relatives (chapter 8). For instance, counselees communicated DNA-test results more indirectly and more reassuring in families with a closed communication style.

6.3. Summary of the variation

Together with other authors, we have criticized previous studies for their simple underlying model of genetic-counseling which seems to have caused small effect sizes (68,66,76). Therefore, we have added a larger number of variables in our studies. Many pieces of communicated information and many personal characteristics of the counselee did not strongly influence the results. We have presented these non significant results in our studies, to show that our hypothesized counselee-oriented model was not influenced by these. Despite the inclusion of many variables, our model remained relatively simple, because all studies confirmed the mediating role of counselee-oriented variables. In paragraph 4 of the addendum, we describe how our model has over-simplified the situation of genetic-counseling, and we do suggestions for elaborations of our model in future research.

7. Limitations and implications for future research

7.1. Limitations

In 1.2.5., we argued that genetic-counseling is a complex process which involves many variables and many interactions. Compared with previous studies, we have extended the theoretical model of genetic-counseling with many new elements. Unfortunately, our model was also limited. These limitations were mostly due to practical reasons. For instance, our decisions for the type of statistical tests and the number of included variables were bound by our relatively small sample –which was the largest possible sample that we could collect in the Netherlands in this time period. Below, we summarize the most important limitations.

Firstly, the number of included variables was limited. We have included a small range of instruments to measure personality, coping styles, illness representations and other instruments based on cognitive theory. We have not examined the role of relatives, friends and other sources of information such as the Internet (cf.1.2.4.). All information was subjective, because we did not videotape the counseling sessions, and only used the counselees' questionnaire, summary letters, medical files and checklists. A real baseline-measurement was not possible in our studies due to practical reasons; thus, we do not know how the counselees' perception was before the genetic-counseling: we only know their perceptions after the intake and after the DNA-test result disclosure. We have not

examined whether the counselees' perception three months after the DNA-test result was predictive of their perception and outcomes later in time (i.e. longitudinal). We have not asked counselees whether they had read the summary letter sent by the counselor, and whether they had understood this letter; it can be expected that having read the letter (or not) has influenced the counselees' perception.

Secondly, we have not presented all results because of the limited length of the articles/chapters. For instance, we have only presented the influence of the counselees' perception of breast cancer risks, because 96% of all counselees reported that their breast cancer risk influenced their lives more than their ovarian cancer risk (chapters 3-10). We have separately analyzed the 4% of counselees who had reported that their ovarian cancer risks were most influential; these analyses did not lead to different conclusions, but this was probably due to the small sample.

Third, we have assumed that mediation was present in our studies, but we have not *proven* its presence (see chapter 1, 1.3.3.4.), because the results may also be explained by confounding. However, mediation was strongly indicated by the study design and our theoretical framework (188). By assuming that mediation was present, we also assumed that the DNA-test result caused the perception. It seems more likely that counselees already had certain perceptions before DNA-testing, which influenced their decision to request for genetic-counseling. We have categorized all data into three groups in our mediation models: predictors, mediators and outcomes. Interactions between variables have not been studied, such as the interactions between recollections and interpretations.

Moreover, we have assumed that causal directions were present in our studies, that is: the risk-information changed the risk-perception which changed the psychological and medical outcomes. These assumptions were suggested by the qualitative data in our pilot interview study (chapter 3), and by the Life Changes Questionnaire in which we explicitly asked counselees about changes in life *caused by* genetic-counseling. However, we could not determine the presence of causality due to the design of the studies. For instance in the retrospective studies (chapters 4-5, 7), there was only one measurement-moment after the DNA-test result disclosure, but the statistical model that we tested in these chapters/articles assumed causality over time (i.e. risk-information had changed the perception). In the prospective study (chapters 6, 9-10) we have only presented results for measurement-moment 2 (T2); inclusion of T1 did not significantly change the results/effect sizes. Hence, causality has to be confirmed in intervention studies.

Fourth, we have translated risks that were communicated in percentages into categorical risks on a 1-7 scale, and we have used these translations in our subsequent calculations (chapters 4-7, 9). Genetic-counselors usually communicated genetic-risks in percentages and in words. However, which risk was verbally communicated, was not always reported in the retrospective medical files (chapters 4-5, 7) and was also not always reported in the checklist filled-in by the genetic-counselor (chapters 6, 9). Therefore, we

had to use the communicated risks in percentage. However, we could not ask the counselees which percentage they recalled to have been communicated, because the majority had forgotten which percentage was mentioned by the counselor (chapter 4, 6); this finding has not been reported in previous studies in which the counselees were simply asked 'what is your risk to develop cancer?' (cf. chapter 4). Thus, we had to combine the communicated risks in percentages with the recalled risks in categories. For that reason, we translated the percentage-risks into the 1-7 scale. As reported in the chapters, the results did not change when we checked the translation with the verbal information that we could find in some summary letters and checklists, and when we did subgroup analyses with percentage-risks only or categorical-risks only.

Fifth, we had decided to present only statistical relationships with small, moderate or large effect sizes with a p-value smaller than .20 (see chapter 1, 1.3.3.4.). On the one hand, this may have excluded clinically relevant results (i.e. type II statistical error). On the other hand, the large number of tests in combination with not performing a Bonferroni correction increased the likelihood of finding relationships that are not actually true (i.e. type I statistical error). We do not expect that these statistical errors have caused us to overlook relevant results, because we have confirmed our findings in multiple samples.

Sixth, we have only examined the general relationships of the communicated genetic-information with the counselees' perception and outcomes. We did not study the specific effects of tailoring of information to the counselees' needs, as genetic-counselors frequently do (430) (see discussion of chapter 6).

Seventh, our studies were limited by the samples. Only female BRCA1/2-counselees – most of whom had already had cancer - were included, because these counselees belong to the most frequently tested group of counselees in genetic-counseling in the Netherlands. The counselees' sociodemographic characteristics were comparable with other studies in BRCA1/2-counselees, which for instance shows that they were relatively highly educated (e.g.169,482). The sample sizes were relatively small compared to the large number of subgroups and variables that we studied. Due to this small sample size we were not able to use more complex statistical models such as multilevel modeling in which the different genetic-counselors and the different departments of clinical genetics are analyzed as separate levels.

Seventh, our studies have only been performed in the Netherlands, which may have influence the results. For instance in other countries, both the counseling procedure and distress of counselees may differ (183,477). In the Netherlands, it is common practice that the genetic-counselor draws an extensive pedigree and communicates cancer-risks for both the counselee and her relatives on the basis of this pedigree, which may not always be done in for instance the United States. It is likely that this common practice in the Netherlands has influenced the counselees' perception of the DNA-test result, for instance

because they mixed the meaning of the DNA-test result and the meaning of the pedigree (chapter 4).

7.2. Implications for future research

We have kept our models relatively simple, to avoid deduction bias –i.e. applying large theories/models to the empirical reality-, and to start with the counselees' experience as a consequence of a counselee-oriented approach. We have extended the simple input-output-model that has been used frequently in genetic-counseling, and have added the mediation model (chapters 5, 6). On the basis of the detected importance of the counselees' interpretation we have suggested a shift from an information-oriented approach towards a counselee-oriented approach in the fields of genetic-counseling and risk-perception. These themes are relatively new – especially in the field of clinical genetics - but more studies are required to create and test more complex models. Knowledge from other fields such as risk-perception may be included in future models (90).

Of course, we suggest that future research should replicate our findings, while overcoming the limitations of our studies. We advise building new instruments to measure more elements of the counselee-oriented perception and outcomes. The hypothetical explanations in paragraph 2 should be examined in depth, such as the relationships between information-oriented and counselee-oriented variables (2.1.), the importance of the counselees' need for certainty (2.2.), and the counselees' skills to live with dual realities such as the unfulfilled need for certainty (2.3.).

It has been suggested that the best way to examine such counselee-oriented topics is by means of qualitative or phenomenological studies (e.g.6,483). We recommend performing studies with a mixed qualitative and quantitative design, so that the significance level of the results can be determined.

Our studies had an observational, non-interfering nature. Intervention studies are required to determine whether the counselee-oriented phenomena can be changed. For instance, a specific counselee-oriented skills training for genetic-counselors may be developed, or standardized interview questions may be created for use during the counseling sessions (cf. paragraph 5). Psychologists may study the effects of using improved flyers explaining genetic-counseling (cf.5.3.), medical and psychological follow-up sessions for instance by means of an Internet intervention (cf.5.5.), and individual or group psychotherapy (cf.6.4.). *Finally*, the role of the genetic-counselor may be examined. In our studies, we have only focused on the information-oriented and counselee-oriented processes, but not at counselor-oriented processes and how these may be related to the other processes. It may be relevant to study which characteristics of individual counselors predict the outcomes of genetic-counseling, and for what reasons.

8. Summary by means of Emma's example

Emma's quest for explanations of the genetic contributions to the occurrence of cancer in her family did neither start with the communication of information. Nor did it start when she visited the department of genetic-counseling. It started when she grew up in a family in which many relatives had cancer, which alerted her about the possibility that she could also develop cancer. Feeling vulnerable to develop cancer has always been a fundamental part of her identity. For many years already, her perception of her future had been marked by uncertainties regarding the development of her cancer, the possibility of developing a secondary tumor and her relatives' risks. Her uncertainties grew over time, and she felt especially uncertain about her daughter who may develop cancer one day. Like many other counselees, she finally asked for genetic-counseling, not to develop 'an accurate perception of her and of her relatives' cancer risks', but to fulfill her need for certainty.

Unfortunately, Emma's need for certainty would not actually be fulfilled. Emma had expected to receive clear-cut genetic-information: 'either I have the gene or I do not have the gene'. But the genetic-counselor had communicated nuanced information both during the intake session and the session in which the DNA-test result was disclosed. Emma was explained that a UV-result was found, and intermediate cancer-risks had been communicated on the basis of the pedigree. Additionally, the genetic-counselor provided her with many extra explanations and information, which eventually did not directly influence her perception, but may have added to her experience of the communicated information as being complex, and to feeling confused.

The actually communicated information is important to understand Emma's inner processes. Without first orienting ourselves, as researchers and clinicians, on the actually communicated genetic-information, we cannot understand the processes that occurred at the same time inside this counselee and that will significantly influence her life. Both information-oriented and counselee-oriented processes are needed to understand how a counselee experiences a DNA-test result, interprets it, and embeds it in her life.

In her perception, Emma mixed the meaning of the DNA-test result with the meaning of the pedigree. Because she recalled and interpreted that the UV-result *meant* that she and her relatives had high cancer-risks. Her recollection differed from what had actually been communicated. She was not convinced of what the genetic-counselor had communicated, and she believed more in her own interpretation of the UV-test result as being a PM. Emma told her interpretation to her relatives, and possibly due to the indirect and non-reassuring way in which she had communicated this result, her relatives also created their own recollections and interpretations that were dissimilar to hers.

Emma's perception of the UV-result was influenced by both the actually communicated information and by her ideas about her cancer, such as its duration and

severity. These information-oriented processes could be explained by the personal and existential meaning that this DNA-test result had for her. The actually communicated cancer-risks triggered her need for certainty; she experienced this unfulfilled need for certainty as unbearable and in reaction to that, she created her own interpretation that deviated from what the genetic-counselor had actually communicated. Emma had many ideas about her illness, for instance, she expected that she would be ill for many years; these cognitions were mediated/explained by her feelings of vulnerability and having an uncertain future which she had developed many years ago, and that had been triggered/increased by the UV-result; these fundamental feelings of vulnerability made her feel that this UV-result meant that she carries a PM. Of course, these are Emma's examples of mediation processes, and each counselee may experience her own individual mediation processes.

Emma experienced the impact of the UV-result as far-reaching. For instance, she decided to undergo PBM because of her (mis)interpretation of the UV-result as implying that she has a large risk to develop cancer again. The DNA-test result had also triggered and increased her awareness of her feelings of vulnerability and uncertainty. Her body started to feel 'even more differently than before DNA-testing, like a time bomb'. She worried much, and she experienced her uncertainties as the essence of these worries.

In summary, both the information-oriented and counselee-oriented approaches are needed to explain the experiences of a counselee like Emma. Of course, the difference between the information-oriented and the counselee-oriented approaches is not always clear-cut, and elements of both may overlap. For instance, we have categorized the counselee's cognitions and coping styles such as denial and avoidance as information-oriented, because the instruments that we used to measure cognitions and coping styles were applied to one specific situation, i.e. the DNA-test result, and the questions were mostly formulated in terms of cognitions. For instance, denial and avoidance may also be described from an existential, counselee-oriented level as a fundamental mechanism of a counselee.

It is obvious that an absolute, purely Counselee-Oriented Approach does not exist. In practice, all genetic-counselors use both information-oriented and counselee-oriented elements in their sessions. We hope that our study provides further support for the development of such an integrated approach, with a better understanding of the counselee-oriented processes.

Chapter 12

Addendum:
Theoretical and practical implications

1. Introduction

'Tout est bien dit, mais il faut cultiver notre jardin.' (Voltaire in 431)

The eleven previous chapters of this thesis have described how the disclosure of DNA-test results may influence the counselees' perception, their medical decisions and psychological well-being. Moreover, we have demonstrated that the counselee-oriented processes may explain the impact of DNA-testing better than information-oriented processes.

What do these outcomes precisely mean? In this chapter, we discuss several theoretical and clinical implications of our studies. They create an answer to questions that several researchers, genetic-counselors, psychologists and social workers have asked us about our study results.

We describe these implications in this addendum and not in the discussion chapter, because they could not directly be derived from our results. This chapter has a more theoretical and clinical nature than the discussion, and will not be restricted to the published results from our studies but will also include other theoretical and empirical articles and will also present some additional results of our studies. These implications should be regarded as hypotheses to be confirmed in future studies.

Several researchers have asked us what the results of our studies precisely mean. For instance: how are the information-oriented and counselee-oriented processes related? Why did we find that the counselees' need for certainty is so important, and that their perceived uncertainty is so frightening? Are counselees able to live with their unfulfilled need for certainty? These questions will be discussed in paragraph 2. Paragraph 3 will discuss ethical implications of the counselee-oriented approach in the practice of genetic counseling. After this, suggestions for future studies are sketched on the basis of a discussion of the limitations of our studies (paragraph 4). In paragraphs 5 and 6, we will propose a number of concrete psychosocial interventions, because several genetic-counselors, psychologists and social workers have asked us for practical suggestions how to apply a counselee-oriented approach in clinical practice.

2. Theoretical implications

This paragraph 2 describes how the information-oriented and counselee-oriented processes may be related to each other: are they different or do they interact, etc.? Before going into these explanations, I clarify the terminology that I will explicitly use in the following paragraphs: 'approach', 'process', 'practice' and 'ethics'. These are nouns to which the adjectives 'counselee-oriented' and 'information-oriented' may be applied.

In chapter 1, I have described that many researchers have a dominantly information-oriented approach. In response to that, I tried to develop a counselee-oriented approach in this thesis. My counselee-oriented 'approach' means that I focused on different phenomena, i.e. on counselee-oriented processes instead of on information-oriented processes. These 'processes' are the counselee-oriented processes inside a counselee ('her experience'), such as the way how she provides a subjective meaning to the DNA-test result and how she embeds it in her life; these are not merely cognitive information-incorporating processes but these are also about the subjective interpretation, meaning-making and embedding of the DNA-test result in the counselee's life (cf. chapters 9 and 10). Genetic-counselors and psychologists may also focus on these counselee-oriented processes in their clinical sessions which may be called 'counselee-oriented practice'.

Why did I focus on counselee-oriented processes in this thesis? In the first place because the current goals, policy and practice of genetic-counseling imply a counselee-oriented approach but in contrast, the psychological literature seems to dominantly focus on information-oriented processes (see chapter 1). In the second place, I did not neutrally describe the counselee-oriented processes, but – like many genetic-counselors – I assumed that it is *good* to focus on these processes in my research. That is, my counselee-oriented approach was not merely descriptive but also normative, i.e. the norms and values of me as a researcher and psychologist were counselee-oriented. This may be called a 'counselee-oriented ethics', which I will describe in paragraph 3.

Thus, both my approach and ethics have been oriented on counselee-oriented processes. This paragraph 2 starts with discussing on counselee-oriented *processes*.

2.1. How are the information-oriented and counselee-oriented processes related?

> *How my life has changed after the DNA-test result? I started to think differently about heredity. I started to realize that other relatives could also undergo the same cancer-experience as I have. I'm not thinking that simply and rationally about the heredity anymore. I've learnt that these are not mere facts, but it contains a real story about the heredity, and its consequences. (…) This information has changed my life. It is as if you cannot trust your own body any more after the DNA-test result. It leaves you alone. It makes you uncertain, because it increased my risk of developing cancer again. It took me a long time before I regained some trust. (…) Due to the confrontation with your death and deepest vulnerabilities, you start appreciating life more. Such as living in the here and now, and taking priorities in relationships. I'm not saving money anymore to go on holiday over 20 years; I'm going on holiday now. I became much more aware of everything that happens in my life. (...) Uncertainty had never existed in my vocabulary before genetic-*counseling*, I was always self-confident. Now, I cope completely*

differently with uncertainties in life. (…) How? I feel uncertain about my self. Frankly, I cannot deal with it. I find it unbearable. (Based on interview RL-027)

The communication of a DNA-test result starts many information-oriented and counselee-oriented processes inside the counselee. Previous chapters showed that the DNA-test result is not only taken up as 'mere facts', but it has a personal, existential meaning of 'a real story' for the counselee, as this counselee said. But how are these 'mere facts' and this 'real story' related to each other? Generally speaking: how are the information-oriented and counselee-oriented processes related to each other?

We have found that the counselee-oriented processes mediated the effects of the information-oriented processes on outcomes such as the counselees' risk-perception (chapters 5-9). Thus, all information-oriented processes influenced the perception indirectly via the counselee-oriented variables. It was unthinkable that the information-oriented processes would directly have influenced the counselees' perception (chapter 1, 1.3.3.4.). It was only the counselees' interpretation that directly influenced their lives. But what does this mediation precisely mean? What are the precise differences between the information-oriented and counselee-oriented processes, and how do they interact?

The answer to these questions are relevant to understand the impact of DNA-testing on the counselees' lives, it may offer clues for the psychological care of counselees who experience distress in aftermath of DNA-testing, and it may generate hypotheses for future studies (see paragraphs 4 and 6). I will roughly sketch five possible answers that are given by other authors in psycho-oncology, and I will conclude with the remark that there is yet not enough evidence to decide which answer is most likely to be true.

2.1.1. Background and foreground

The information-oriented and counselee-oriented approaches differ in focus. The information-oriented approach has a relatively specific, narrow focus, because it examines processes in a specific small part of the counselees' life that is only related to the genetic-counseling, such as cancer-risks or the counselees' cognition about her illness. The counselee-oriented approach has a broad focus on larger processes; it examines for instance how counselees embed the DNA-test result in their lives, and how their personal and existential context of their lives influences the perception of the genetic-information, and vice versa. The counselees' need for certainty and vulnerability has already existed before the counselee visited the department of clinical genetics, and are probably triggered or intensified by genetic-counseling.

Thus, counselee-oriented factors –the counselees' life in general- seem to be the background or context which gives the specific DNA-test result at the foreground its ultimate meaning for the counselee (cf.432). The specific experiences of genetic-counseling may be at the foreground of the counselees' experience at one specific

moment; the counselee for instance pays attention to the communicated risks and uses a specific style to cope with these risks. But this specific experience and this coping style can only be understood against the background of the counselees' whole life.

Many different names are used in the literature for this background that defines the meaning of the foreground, such as 'field' (432), 'foundations', 'meaning' or 'horizon' (e.g.433). It has been suggested that the background, and its relationship with the foreground, is most effectively uncovered when qualitative, phenomenological research methods are used (e.g.6).

In summary, the counselee-oriented processes may be described as the background against which the foreground of the information-oriented processes can be understood.

2.1.2. Different perspectives or modes

It has been said that psychology started when Wundt, Freud and others discovered that psychological phenomena could be described from multiple perspectives (i.e. point-of-view, cf. 'approach'; cf. 'Zweideutigkeit', 434). Genetic-counseling may also be described from different perspectives. For instance, researchers may describe that a DNA-test result changes the counselees' well-being (that is how it 'functions'), but that does not tell how the DNA-test result feels for the counselee and what consequences she has in mind (that is what it 'means' to her). Thus, we use a different perspective when we describe the function ('syntax') of the DNA-test result, than when we describe the meaning ('semantics') of that result. We find totally different answers when we ask counselees from a functionalist perspective or from a meaning-oriented perspective. The same DNA-test result ('function') may have totally different meanings for different counselees. This could be compared with a linguistic sentence: its grammar and spelling may not have the same meaning for the speaker and the receiver of the sentence.

What different perspectives may a counselee have regarding her own processes? Counselees do not seem to merely have a cognitive 'perspective' on themselves, they also *experience* themselves. To express this self-experience, one may use the term 'modus' instead of 'perspective' (433,435). For instance, one third of all counselees in our studies had reported that their 'self-experience of their body' and their 'self-experience of their personality' had significantly changed due to the DNA-test result (chapters 3, 5 and 6). The interviews suggested three different ways in which the counselees experienced themselves: living-mode, reflection-mode and physics-mode.

The interviews with the counselees revealed that they did not experience their body – especially their breasts – in the same perspective or mode as they did in the past. In everyday life, healthy people may not be aware of their body functions: they do not feel the beating of their heart and the streaming of their blood, and their breasts just feel as a

normal part of themselves, thus: they are simply living their lives. They are in the everyday life mode of 'living' (living-mode) (433,435).

People may take a moment to stop, think and talk about how their body functions: at that moment, they are not simply living but talking, and they are in a different mode (reflection-mode). For instance, counselees told in the interviews that after DNA-testing, they had started reflecting about their body instead of merely experiencing and living their lives: 'I started thinking, thinking and thinking. My body became a continuous stream of thoughts and worries.' (Based on interview RL-009)

When we are confronted with an illness, we may experience our body in even another mode, that is: we regard our body as a mere physical, biological thing that is not functioning and that may not feel 'us' (physics-mode) (389,390). Counselees spoke about their body as a mere physical thing: 'my breasts are time bombs', 'I cannot trust my body anymore', 'my body feels distant' and 'I cannot get connected with my body anymore'. The majority of all counselees felt a fundamental physical vulnerability regarding their body, which may suggest that they are in the physics-mode and not in the living-mode (chapter 6; 75). To return to their daily life mode, counselees said that they had to 'regain trust in the body' and to 'do activities that make my life feel meaningful, so that I can start living a normal daily life again, to get in a flow, and to forget about my uncertainties'. (Based on interview RL-012)

The information-oriented approach speaks about medical facts and risks, that is: the reflection-mode or the physics-mode. In contrast, the counselee-oriented approach seems to discuss how the counselees' experience of their living-mode has changed due to the communication of the genetic-information.

In summary, the information-oriented and the counselee-oriented approaches may be regarded as different perspectives or modes to describe the counselees' experiences of the communicated genetic-information and their selves. The disclosure of the DNA-test result seems to have changed the counselees' mode or perspective, but counselees said that they were able to return 'to a higher mode' (cf.436).

2.1.3. Meaning-based coping

In the previous chapters, I used the term 'interpretation of a DNA-test result'. Another expression for this is 'the meaning of a DNA-test result for the counselee'. Generally, psychologists differentiate between situational/specific meaning and global meaning (131,137). Global meaning, or the sense that one's life has meaning, involves one's subjective general conviction that one is actively fulfilling a unique role or purpose in life, in which one is able to live to one's potential as a human being (130). This should not be mixed with faith or religion, which involves one's belief in a higher transcendent power, and one's connectedness with this power (132). The information-oriented approach may

regard the specific meaning of genetic-counseling, and the counselee-oriented approach the global meaning in the counselees' life.

Situational meaning, or appraised meaning, is the meaning that an individual attaches to a specific situation such as DNA-testing, and is regarded as an essential element in coping with stressful life events (131,137,437). When confronted with such a situation, people may first appraise the situation as relevant or irrelevant to them (primary appraisal), and evaluate their personal sources to deal with it (secondary appraisal).These appraisal processes strongly interact with the counselees' global meaning (3^{ary} appraisal). E.g. a counselee may try to create a clear-cut, certain answer in reaction to the actually communicated, uncertain DNA-test results (2^{ary}), because she fundamentally assumes that life is certain and predictable (3^{ary}) (cf. chapter 10).

When people experience a situation as incongruent with their global meaning, distress may arise. E.g. when a counselee highly values having certainty, she may experience distress when she receives an uncertain DNA-test result. The level of distress has shown in our studies to be unrelated to the information-oriented facts, but is strongly related to the meaningful (re)appraisal of the information, i.e. the counselees' interpretations (cf.438). Well-being is assumed to depend on the extent to which a patient is able to integrate a stressful life event, like the DNA-test result, in her life/global meaning via 3^{ary} appraisal (439,440). This was confirmed in our study that showed that counselees who experienced an unfulfilled need for certainty, experienced distress (chapter 10).

Incongruence between situational and global meaning can be solved by reappraisal of global meaning. E.g. a counselee may reorder her fundamental values in life: how I look in the mirror is not as important as my risk to develop cancer, therefore I may undergo PBM; despite being a mutation-carrier, I still experience meaning by being a mother and friend. Thus, after a period of perceived anxiety or meaninglessness (126), a counselee may undergo a personal transition by developing new meaning, and by doing so, she learns to live adequately with the fact that she may be at risk to develop cancer, and/or that she carries a PM which she may have transmitted to her children (441).

In summary, the information-oriented approach seems to primarily focus on the specific meaning of the DNA-test result, and the counselee-oriented approach on the global meaning in the counselees' life. Differences between this specific and global meaning may be experienced as stressful, and may be solved by either changing the specific meaning (e.g. changing the interpretation), or by changing the global meaning (e.g. actively creating certainties and meaning in life).

2.1.4. Confrontation with the ultimate concerns of life

We have found large existential changes in life since DNA-testing (chapters 3, 5-6), which confirms other studies about familial cancer (153,442,443). There is a large literature on the

positive existential impact or so-called 'post traumatic growth' after cancer diagnosis (e.g.127,130,137,141,444), which may be applied to genetic-counseling.

Many post-traumatic growth studies seem to assume that when a person is confronted with a certain theme in a specific situation, this teaches her about life in general, e.g. it may shake her fundamental ideas about the world. For instance, when a counselee is confronted with the uncertainty over the DNA-test result, she may subsequently generalize this result to her general experience of her body and her self-experience (cf.445,446). Thus, the genetic-counseling situation may be a teacher or 'boundary situation' to the counselees, which may teach them that not only the DNA-test result is uncertain, but also life itself (cf.447). Existential lessons may be an inherent part of genetic-counseling. For instance, the communication of genetic-risks tells a counselee about the physical limitations of life (she cannot change her DNA), the cancer-risks may indirectly refer her to the possibility of death, she may not feel free regarding her 'genetic fate', and may feel fundamentally stigmatized and 'different than other people, as being a mutation-carrier' (60,126). The fundamental ideas that a counselee has about life may also be shattered. A counselee may say: 'I have always assumed that the world is a predictable, just and benevolent place to live, in which good things happen to good people. But these have proved to be false assumptions, because it is not just that I and/or my relatives have received this unexpected DNA-test result' (448).

In summary, the communicated information (i.e. information-oriented) may teach the counselee general lessons about life or may shake her fundamental ideas about the world (i.e. counselee-oriented).

2.1.5. Am I my genes?

It has been suggested that individuals in our western society have a strong focus on the body and may develop and define their identity according to their physical characteristics (449,450). If this is true, we can expect that especially counselees from families with many cancer patients have developed their self-identity in relationship with their cancer-experiences in their family. From a young age onwards, they may implicitly or explicitly have been defining themselves as 'a person from a cancer family' and/or as 'a person who is at risk to develop cancer'. This identification with their genetic background seems to be strengthened by the communication of DNA-test results (cf. 2.1.2.) (61). That is, their genetic status may become a small or even large part of who they are. We also found in our studies that the counselees' self was related to the communicated genetic information (chapter 10).

What does it mean when the communicated information is pessimistic in an individual who identifies strongly with her physical and genetic characteristics? Her self-image may become negative, and an existential identity crisis may be evoked: who am I? Am I my genes? Am I a cancer patient? (61) Her self-image may become completely

focused on the past (i.e. genetic background of her family) and her future (i.e. possible development of recurrence of cancer), and she may not experience the present in its totality (449, p. 29). Like a cancer diagnosis, the genetic diagnosis may cause a one-sided focus on being-a-patient and forgetting that one also is a mother, an employee, etc. (138)

In summary, a counselee may identify with her genetic status. Thus, she uses the information-oriented facts to create her counselee-oriented sense of self.

2.1.6. Summary

I have presented five ways to describe how the information-oriented and counselee-oriented processes may be related to each other, such as background and foreground, different perspectives or modes, meaning-based coping, genetic counseling as a teacher about life, and identification of one's self with the genetic information. Which answer is true? Or are all true? I have provided some evidence and arguments for each possibility. But the precise relationship between information-oriented and counselee-oriented processes has not been a main research question of our studies, and has to be examined in more detail in future studies. It may be useful to analyze these five hypothetical relationships in conversation with a counselee, e.g. when she reports psychopathology in aftermath of DNA-testing. This analysis may yield clues for a better understanding of the counselee and for possible psychological treatment (see also paragraphs 2.3. and 6).

2.2. Why is Need for Certainty so important and is Perceived Uncertainty so frightening?

> *I asked for genetic counseling, because I wanted to have certainty about the reason why I had developed cancer, and to know my daughters' risks. (…) I was certain that they would find a pathogenic mutation that would explain everything. (…) I had expected to hear the genetic-counselor communicating either 'yes' or 'no'. After the result, I felt that they had only communicated a little 'yes'. The result was not certain. I had not expected that it would bring so much uncertainty! (…) But I did not let the uncertainties control my life. I wanted to be in control: I had to be. Therefore I started thinking: 'it is true, I have the mutation'. But I know that this idea is not true.* (Based on interview RL-013)

Why do counselees have such a strong need for certainty, like the counselee in this example? Why do they seem so anxious for uncertainty? Why do they seem to react to an unfulfilled need for certainty by avoidance, denial and renaming coping strategies, and not by acceptance (chapter 10)? I will hypothesize sociological and psychological answers to these questions.

Individuals in modern western countries live in a society that is full of risks, risk communication and choices based on risk calculations (451-453). For instance, population-

wide health education consists of the communication of health risks, such as that of smoking. Despite the fact that western people are confronted with many risks and their associated uncertainties, we find it often difficult to make decisions (454). Possibly as a reaction to these difficulties in decision-making, we may cling to techniques, and wait until instruments – such as DNA-tests – tell us what to do. If these instruments do not give a clear-cut answer we may become frustrated (449,452,455). For these reasons, we may also have high expectations of medical care and of medical techniques, and may feel frustrated when these do not provide clear-cut answers to the question 'what do I have to decide?' (449,450,455). These sociological trends seem to be reflected in the high demands that many counselees have regarding DNA-testing (1,5,6,148,216,359-361). Thus, counselees may demand certainty and control over DNA-testing, as they always cope with risk information, and like everybody in the population does.

However, genetic risks seem to differ from of other types of risks, which is psychologically processed in a different way. For instance, despite the fact that everyone has to deal with risks, counselees who undergo genetic-testing for hereditary breast and/or ovarian cancer experience more distress and show more active health-improving behavior than the general population (325). Possibly more than other risks in life, genetic risks seem to be inherently related to existential and identity questions (61,62,389,390). A logic reason for distress and active behavior may be that genetic risks may confront counselees with the possibility of illness, reduced quality-of-life and eventually death; other health risks may not directly confront counselees with such existential threats (e.g.101,363,456). In contrast with other risk information, counselees may also experience an existential plight to undergo DNA-testing and disclose the result to their relatives (425). Genetics may also be more personal than other risks, because this risk is already part of them, and other health risks are less 'embodied' (cf. 2.1.5.1.; 62).

Moreover, genetic risks are not changeable or avoidable, in contrast with health risks, such as smoking. The fact that one's own genetic risks are not controllable, and that the genetic status may be felt as being 'unjust', 'not right' or 'not what they deserve', may interfere with the counselees' fundamental assumption in life that 'bad things only happen to bad people'; the possible undermining of this fundamental psychological assumption by genetic information may add to the difficulties for counselees to accept the genetic risk information (448). Thus, genetic-risks seem to be more fundamental, personal, and unavoidable than other health risks. This may give the high emotional and existential value to genetic-risks for counselees.

Counselees may not able to live their daily lives when they are continuously aware of their genetic risks (cf. 2.1.2.). Like all people, they may need certain fundamental 'assumptions', 'schemas' or 'illusions' to fulfill their daily lives, such as a basic feeling of certainty (448,448,457). For instance, we have to believe that we are to some extent invulnerable when we cross the street. We have to believe in the meaningfulness of the

world, in which events 'make sense'. The world is benevolent and just: good things happen to good people, and bad things to bad people. We have to believe that we are valuable persons (self-worth). Finally, we have to believe that we are in control of our own lives, even if this is an obvious illusion to other people (454).

These fundamental assumptions are very resistant to change, because they are the invisible fundament and guarantee of our daily lives. We do not want to transform such fundamental assumptions, not even when we are confronted with genetic-risk information (458). When a counselee is confronted with such threatening risk-information, she may realize that she is *not* invulnerable, and that the world is not always predictable, just and benevolent, and that she cannot trust herself anymore (cf.390,448). Staring into this existential uncertainty may be emotionally overwhelming (e.g.101,363,456). For that reason, when she is confronted with such feelings, -instead of acknowledging this existential uncertainty- she may start avoiding and denying this information, distorting her perception of reality (e.g. inaccurate risk-perception), and start actively coping by making radical medical decisions such as PBM and PBSO (cf.chapter 10; 126,459).

Thus, people are said to have an important, inborn –possibly even evolutionary- tendency of being cognitively conservative regarding fundamental psychological assumptions in life. This may also be shown in the counselees' reactions to the DNA-test result, because they may experience the DNA-test result as dangerous to their fundamental assumptions. In reaction to that potential danger, they may react in a conservative manner.

How are the counselees' conservative tendencies shown in the context of genetic-counseling? Counselees may use information-oriented cognitive mechanisms to assimilate the information in their pre-existing schemas. For instance, they may underestimate the likelihood of negative events and overestimate the likelihood of positive events, and appear to operate on the basis of an illusion of invulnerability, like many people do (216,302,358,448,460). Our results also suggested that counselees do not adjust their interpretations to the actually communicated risks, but they seemed to assimilate the risks in their possibly pre-existing fundamental assumptions (cf. chapters 3-6; 461). Whether counselees accommodate their schema to the communicated risk, depends on the personal and existential situation of the counselee (cf.448,462), such as social resources and attachment style (cf.448), personality weaknesses and strengths/resilience (cf.463) and the amount of physical limitations (cf.464). We have found that the more previous experiences of uncertainties a counselee had in life, the more did she adjust her interpretations adequately to the actually communicated risk-information (chapter 10). Possibly, previous experiences with uncertainty may have made her schemas more flexible, and/or enabled her to experience the new uncertain situation as not-being a threat for herself.

In summary, counselees who undergo DNA-testing seem to have a strong fundamental need for certainty, like all people have, but possibly even stronger because genetic risk information is more personal, fundamental and unavoidable than other health risks.

2.3. How can counselees live with their unfulfilled need for certainty?

> *I had received the result, but I still knew nothing. The result was uncertain, and consequently I felt uncertain as a person. Usually, I am a person who wants to have certainty, and to know what to do. But now, I was uncertain what to do. Is it a mutation, or isn't it? Shall I wait for the genetic-counselor or not? Am I able to wait? That is the question. Can you leave it and wait until you develop cancer, until they give you an advice what to do? I started to think. (…) I made the decision to have my ovaries removed. Because I shall not live with uncertainty! Even if surgery meant that I would only have two children in life. No breasts, no more children. (…) It just stops all the bothering. I knew that it would help, because this decision fitted my personality. (…) I still do not regret the decision. Because I have prevented the worst case scenario: living with uncertainty, which would have made me restless, knowing the recurrence risks. (…) Eventually, the DNA-test result has turned out to be the best scenario: the DNA-test result was OK, I would not have developed cancer. Despite that, it was a good decision, because it provided me with inner peace.* (Based on interview RL-034)

'Thou shalt not live with uncertainty.' This seems to be one of the commandments of this counselee, which created an awkward predicament for her because she had actually received a UV-result which could not provide her with certainty. Her situation was similar to that of many other counselees: her need for certainty stumbled upon the actual uncertainty of the DNA-test result (chapter 10). This raises the question: are counselees able to live satisfactorily with the paradoxes of DNA-testing, such as this contradiction of the counselees' need for certainty versus their actual uncertainty? Are counselees able to accept both realities in such a discrepancy? I will try to answer this question by means of psycho-oncologic literature.

Having cancer, or being at risk to develop cancer (again), has been associated with many contradictions/discrepancies, as our study confirms (401). Examples in our study were: certainty versus uncertainty, positive versus negative emotions, objective risk-information versus subjective perception, recollections versus interpretations, physical/medical facts versus the own body experiences, and so on.

Patients are assumed to cope optimally with their illness experience, when they are able to acknowledge and/or integrate the co-existence of these 'dual realities', without collapsing one or both of these realities (401). However, we found that the majority of counselees did not seem to accept such dualities. For instance, only 6% of all counselees

who experienced the paradox of the need for certainty and the perceived uncertainty used an accepting coping style, and most counselees used avoiding coping (chapter 10). Moreover, the discrepancy of objective risk-information versus subjective risk-perception was 'solved' by the dominance of the counselees' subjective perceptions.

What would acceptance of a contradiction/discrepancy look like? It would mean that people have more than one evaluation about the same subject, e.g. they respect their need for certainty and at the same time they acknowledge that they have actually received much less certainty. In the ideal situation, both sides –need for certainty and perceived uncertainty- would be fully acknowledged; neither one of these sides would be dominated by the other side. This could be called a 'dual attitude' (465,466).

Are counselees able to accept two opposite feelings or thoughts about the DNA-test result at the same time? Wilson et al describe that all of us have dual attitudes regarding many topics (466). Usually, one aspect is more salient or explicit on the foreground, but that does not deny that another implicit aspect may exist at the background (cf.2.1.1.). For instance, in their daily lives, counselees may act as if everything is normal, but in the back of their mind there may be a feeling of vulnerability and uncertainty. They may act as if they have certainty, but still acknowledge the actual uncertainty when we ask them about that. Counselees may put their experiences of certainty in front to avoid being overwhelmed by anxiety in their daily lives (cf. 2.2.). This dual attitude may explain that counselees do not report severe distress or limitations to their daily lives, but at the same time do experience significant changes in their feelings of vulnerability and uncertainty. One counselee explained to me:

> *'Everyday I feel, up to my bones, that I will die eventually… soon… but while acknowledging this, I know that I want to use the time that I still have. I have to! In the beginning, I could only experience the meaninglessness of it all, the loss of expectations. I have learnt that meaninglessness is not the only and the last possible that I could experience during the remaining time of my life. I appreciate life more, social relationships, the birds in the tree… Now, I feel the meaninglessness of it all… but I also feel deeply connected to it all, and I feel the value and meaning of every day that is given to me.'*

Accepting the discrepancy of the unfulfilled need for certainty means that a counselee learns to create certainty and meaning in every day life, e.g. stay focused at her job, friendships, moments of happiness, etc. At the same time, she acknowledges that she stands in a larger landscape of genetic uncertainty and possible physical limitations. Counselees may learn to switch between this certainty and uncertainty; for instance, they may try to stay with one of both sides while not being afraid that the other side will return

(cf.432). Counselees may learn to trust themselves in their ability of switching and returning to the other side.

Several psychotherapeutic intervention studies have provided evidence that counselees may benefit from a dual attitude. For instance, existential group therapy helps BRCA1/2-counselees to integrate the communicated risks in their lives, and as a side-effect they may also improve the accuracy of their risk-perception (467,426). The aim of such existential interventions is to help counselees to find ways to live a meaningful life, despite the limitations and uncertainties of their illness (145,378,384,468,469). They are stimulated to explore their feelings of ambivalence and uncertainty, but with a positive focus on finding meaning. As two parallel processes, deepening of existential feelings goes hand-in-hand with active positive meaning-making. Counselees are stimulated to explore a broad range of possible meanings, priorities and identities in life, which helps them to acknowledge explicitly that they are not only a patient or person-at-risk (like many patients; 138), but that they are also a mother, a friend, an admirer of classical music, and so on (cf. 2.1.2.).

Not all individuals may be able to develop a dual attitude to the same extent, because some may not adequately have learnt as a child to have a dual attitude (e.g. Piaget, Kohut and Kernberg in: 470, cf.428). More research is required to understand which counselees are able to develop a dual attitude. For instance, new instruments may be developed to predict which counselees are able to develop a dual attitude and who may not. Such instruments may help geneticists and other physicians in tailoring their communication to their patients. For instance, they may use a more directive, reassuring communication style when they speak with patients who do not have sufficient skills to accept ambiguous, uncertain medical information. In the consultations of other patients, they may have a more nuanced, non-directive style and may focus more on the existentence of dual realities. Such new instruments may be aimed at helping genetic-counselors to attune to the counselees' needs, and may not be used 'as a trick'.

3. Implications for a counselee-oriented ethics applied to practice

3.1. Counselor-oriented ethics

In this dissertation, I have described the (further) development of a counselee-oriented, integrative approach in genetic-counseling. In the discussions of the chapters, I have advocated several counselee-oriented suggestions for clinical practice and further research. Underlying these suggestions was often a counselee-oriented ethics that may be experienced as new by some readers. Therefore, I will provide some ethical reflections in this paragraph.

In general, a counselee-oriented ethics means that the counselor, psychologist, social worker or researcher is not primarily focused on how genetic information is

transfered, but they primarily focus on the counselees' needs (see 3.3.). Their attitude/approach can be described as being attuned to counselee-oriented processes. Thus, counselee-oriented ethics is not merely 'a theory' or a 'dogmatic set of norms and values', but it is manifested in the approach and the practice of genetic-counselors. Therefore, it would be inconsistent to focus in this paragraph on the theory instead of on the practice of counselee-oriented ethics. For that reason, I discuss the counselee-oriented ethics in relationship to the counselee-oriented results from our studies, and I examine whether genetic-counselors are actually able to develop a counselee-oriented approach in clinical practice.

To explain the meaning of counselee-oriented ethics, I will start describing how it differs from two different ethics that seem to dominate the current literature and clinical practice, i.e. counselor-oriented and information-oriented ethics. The information-ethics overlaps with Kessler's 'content-orientation' and also elements from his 'person-orientation' (419). The counselee-oriented ethics includes elements from Kessler's 'person-orientation', and is an extrapolation of our study results in combination with recent trends in the literature. See De Wert for a discussion of the limitations of the counselor-oriented and information-oriented ethics, especially regarding the many different forms of directivity and non-directivity (429).

Before the start of genetic-counseling as a formal medical discipline in the 40s of the 20th century, counselor-oriented ethics dominated the practice of eugenic programs (36,43,429). People who followed such ethics were paternalistic and coercive in their communication style, made decisions for the counselees or forced them to make decisions.

From its origin as a formal discipline, genetic-counseling explicitly followed non-paternalistic and non-coercive ethical ideals, possibly to avoid these abusive practices in the past (see chapter 1; 43,44,471). Despite these ethic ideals, some counselors –especially in the beginning years- have been described as following their own aims in counseling instead of using a non-paternalistic approach (43,44).

3.2. Information-oriented ethics

Information-oriented ethics follows a 'consumer model of autonomy' (472), 'in which the genetic-counselor has to provide the counselee with all the information that she needs to make an autonomous decision' (471). This ethics forms the basis of the non-directive counseling style that has been adapted by the Dutch departments of genetic-counseling from the beginning (471).

Is an information-oriented ideal actually attainable in clinical practice? This ethics assumes that the provision of information causes autonomous decisions by counselees. We found indeed that genetic-counselors communicate a wide range of information (e.g. chapter 6) and that counselees indeed make their own decisions. However, most of these decisions were not directly caused by the communicated information, but seemed to

depend on the interpretations and personal context of the counselee (chapters 5 and 6). Thus, the disclosure of genetic information did not seem to 'cause' autonomous decisions, but counselees seemed to be already autonomous before genetic-counseling: they seemed to already have their own 'autonomous' perception of cancer and genetics before they underwent genetic-counseling, and they processed the communicated information in an autonomous way (359). One may argue that genetic-counseling did respect the counselees' autonomy by providing them with information and letting them have their own interpretations and make their own decisions (cf.429).

Thus, it is unclear whether genetic-counseling can stimulate the counselees in their autonomy to make their own decisions. One may also argue, that counselees should not only be autonomous in the final decisions that they make, but also in the decision making process (429). This means for instance that the counselor adjusts the information to the counselee and provides the counselee – as the definition says – with 'the information *she needs*'. Thus, not only the provision of information may be ethically relevant, but the tailoring of information to her needs may be. I identify tailoring information to the counselees' needs as an essential practical consequence of counselee-oriented ethics, because that ethics focuses on the counselee, and information-oriented ethics focuses on the information transfer.

The 'consumer model of autonomy' also assumes that 'communicating all information' is by definition good; this ethical ideal of open communication has also been integrated in national and international guidelines that warrants the counselees' 'right to know' (e.g. World Health Organization). However, not all counselees may want to receive 'all information'. Information-oriented ethics may not provide a satisfying answer to the question whether tested counselees and their untested relatives have the 'right not to know' the DNA-test result (154,473,474). Should the counselees' and relatives' wishes of not-wanting-to-be-informed be respected, or should information be disclosed, even if the information does not have large medical consequences and many counselees seem to experience difficulties in coping with this result (e.g. UV-result)? The information-oriented ethics cannot answer this question, because it is a *contradictio in terminis*; that is, information-oriented ethics seems to consist of two possibly conflicting elements: the open communication of all information and respecting the counselees' autonomy (including their desire not-to-know) at the same time.

The information-oriented, nondirective ethics has been criticized for assuming that counselors communicate information in a value-neutral way. This is not actually possible, because genetic-counseling involves a human-to-human encounter which is inherently value-laden; for instance, counselors decide what kind of info should be given and in what kind of format, and this involves a value judgment (475,476).

Moreover, like in other medical disciplines (477), several studies have suggested that it may be difficult for genetic-counselors to always adhere to the ideal of non-

directiveness, which may be due to the fact that some counselees need or ask for a more directive approach (e.g.475,471).

In summary, information-oriented ethics tells that genetic-counseling should provide counselees with much relevant information to make autonomous decisions. But despite the fact that all information is communicated, this does not seem to *cause* counselees to make more autonomous decisions. It may be paternalistic to communicate all information and not listen to the counselees' 'right not to know', and it may be difficult for counselors to adhere to an information-oriented ethics.

3.3. Counselee-oriented ethics

Counselee-oriented ethics is attuned to the counselees' needs, and assumes that the genetic-counselor takes care for the totality of a counselee and not only for informing them. This ethics also seems to be applied by many genetic-counselors in the Netherlands, and also by many other physicians (45,46).

The counselee-oriented ethics implies that not each patient may need autonomy and non-directiveness of communication, i.e. the main information-oriented ideals. Counselee-oriented ethics may also imply that not all counselees may need DNA-testing as a means to fulfill their need for certainty; alternatives for DNA-testing may be explored, such as waiting or referral to a psychologist or social worker.

To which needs of the counselee may researchers focus on? Previous studies mainly described the counselees' wishes for information provision and assistance with decision-making (53-56). However, this kind of research has been criticized for being too information-oriented by mainly asking about knowledge, plans and behaviors (37). Also more personal and existential needs may be explored, such as the counselees' need for certainty, feeling of closure about the family history of cancer, developing mastery over cancer, undermining anxieties, etc.

How can a genetic-counselor practically explore these needs in the counseling sessions? A genetic-counselor may pay explicit attention to the needs, context and perception of the counselee, by asking questions about this (see paragraph 4). A counselor may use this conversation to 'tailor the communication of information'. That is, the genetic-counselor may tailor the communication of genetic-information to the counselee's needs, situation and perception (cf.430). In previous studies, genetic information was often tailored to information-oriented processes, such as the counselees' understanding skills and questions about their medical decisions. It has been suggested to broaden the assessment of the counselees' needs to a broader range of personal and existential issues, such as the personal meaning of genetic-testing in the context of the counselees' lives (38,476).

How can a genetic-counselor adjust the session to the counselees' needs? It has been suggested that the genetic-counselor and counselee 'share and struggle together'

with opinions, thoughts and feelings to determine the aims and procedure of counseling for this individual counselee (471). This assumes that the genetic-counselor creates an open atmosphere in which reflection can occur and in which the counselee feels free to express her ideas and feelings (471). It has been suggested that an open communication may be fostered when the counselor shows her own vulnerability and humility, that is: when the counselee experiences that her needs and interpretations are equally valued by the genetic-counselor as the counselor's own ideas (471). The counselor and counselee may try to be personally engaged in the counseling process 'as a team', that is: a personal responsiveness to the other, a relationship between individuals that is grounded in ambiguity, uncertainty, openness, trust and respect (471). In such an atmosphere, the genetic-counselor may also communicate her own uncertainties about the situation; openness of the counselor may foster openness of the counselee. Additionally, instead of being a unidirectional process, counselee-oriented genetic counseling may be a reciprocal dialogue (283), which includes listening, hearing and sharing information (471).

How can a genetic-counselor introduce the counselee-oriented approach to a counselee? Counselees may not expect a counselee-oriented ethics, may feel unequal to the counselor, and may even be afraid to express their true feelings. Genetic-counselors may try to overcome this problem by not only explaining the procedure of genetic-counseling, but also by discussing the relationship between the counselor and counselee, and asking the counselee's wishes regarding their relationship.

Can a counselee-oriented ethics be attained in clinical practice? In contrast with information-oriented ethics, counselee-oriented ethic goals seem better attainable in practice. Several interventions have been developed on the basis of a counselee-oriented ethics, and these seem to yield better results than studies following information-oriented ethics. For instance, tailoring has shown to be effective in enhancing the counselees' knowledge, the accuracy of the counselee's perception and well-informed decision-making (430). The process of 'sharing and struggling together to find the appropriate decision has shown to facilitate the decision making process, enhance self-determination, promote autonomy, and advance beneficence' (471). Explicitly addressing the counselees' perception lowers distress and raises satisfaction (cf.312,313) and enhances the accuracy of the counselees' risk-perception (282). The positive regard and empathic confrontations during the dialogues may also improve recollections (cf.309-311,478). It has also been suggested, that all types of interventions are effective in improving genetic-counseling because of the counselee-oriented elements of these interventions (284).

3.4. Examples of the counselee-oriented approach

A first example of counselee-oriented ethics has been discussed in chapter 10. The question was raised whether genetic-counselors are ethically justified to try to give counselees an accurate perception of the communicated information. It was argued that counselees may

have their own justified reasons to have a perception that deviates from their genetic-counselor (I do not use the paternalistic term 'inaccurate perception' here). Genetic-counselors may invite counselees to discuss and to test their interpretations for their accuracy. But genetic-counselors may not provide corrections in reaction to the counselees' expressed perceptions, when counselees have not fully provided them with informed consent to do so. To get this informed consent, genetic-counselors may discuss in the beginning of the first genetic-counseling session what their expectations are about the counselor-counselee relationship (e.g. providing 'corrections' in the counselee's perception?), and ask whether the counselee agrees with this.

A second example is the question whether UVs should be communicated or not to counselees. A counselee-oriented ethics would use the counselees' needs as criterium. Counselees seem to request for genetic counseling to fulfill their need for certainty about the heredity and the cancer-risks of themselves and their relatives, to be able to make well-informed medical decisions (i.e. 'knowing what to do'), reduction of distress –and uncertainty in particular-, and facilitate communication with relatives (e.g. chapters 9 and 10).

However, the counselees' need for certainty was not fulfilled by the UV-result (chapter 10). Well-informed decision-making was not shown, because UV-counselees misinterpreted the communicated genetic-information as 'false alarm'. On the basis of this inaccurate perception, they made poorly-informed medical decisions (chapters 3-6). Many experienced distress; on the long-term, the communicated UV-result directly predicted symptoms of depression (chapter 4). UV-counselees communicated more indirect and less reassuring information to relatives compared to PM/UR's; consequently, these relatives felt more at-risk to develop cancer (chapters 7- 8). In contrast, PM/UR-counselees, reported more fulfillment of their needs for certainty after DNA-testing, experienced less distress, had a fairly accurate perception of the PM/UR-result and cancer-risks, and had communicated the DNA-test result more neutrally to relatives.

In summary, the UV-result did not fulfill the needs of the counselees, and at the same time, this result did not have other medical implications than UR. For that reason, we proposed in chapters 3, 5, 6 and 10 that it is justified according to the counselee-oriented ethics to communicate unclassified-variants as uninformatives, i.e. 'we did not detect any mutations explaining the occurrence of cancer' instead of 'we detected a mutation/genetic-change with unknown clinical consequences'. An exception to this ethical decision of non-communication would for instance be a situation in which additional genetic investigation in the family is needed, such as cosegration-analysis and functional testing.

We may extrapolate these findings about UVs to low penetrance genes or whole genome sequencing. A mutation in a low penetrance gene is associated with a relatively small cancer-risk, e.g. 2% to 15%, in contrast with the high penetrance of the two major

susceptibility alleles, BRCA1/2. Whole genome sequencing means that not only BRCA1/2-mutations may be detected but also mutations which may be associated with diseases other than breast and ovarian cancer. One may hypothesize that counselees may also experience an unfulfilled need for certainty and/or may experience distress when these ambiguous and/or unexpected test results are communicated, because - like UVs - this communicated information may be perceived as ambiguous, uncertain or unexpected. On these grounds, it may be argued that these results should not be communicated, as long as these genetic results do not imply a difference in the medical care of the counselees. More studies are required to examine the ethical foundation of communicating low-penetrance genes and unexpected results from whole genome sequencing.

A third example is the so-called 'duty to recontact' (e.g.479). Genetic-counselors are assumed to have the duty to recontact counselees when new genetic information becomes available. Does a counselee really need to be recontacted, if there is new information without medical consequences? What does recontacting do psychologically with a counselee? How may they benefit from it? It could also be argued that recontacting may re-evoke uncertainty and distress which the counselees may perceive as unwanted at that moment. Recontacting may also go against their need for being in control and setting the agenda, when the initiative for recontacting is in the hands of the genetic-counselor.

It may also be argued that counselees create a better perception, experience decision-making as easier and may consequently experience less distress, when the genetic-counselors help them during a follow-up session in interpreting the DNA-test result and reflecting on its medical consequences. For instance, many counselees in our study said that they liked being contacted by us –the researchers- at a long-time after DNA-test result disclosure; they said that talking and reflecting about their DNA-test result helped them 'to put things straight in their minds'. Thus, recontacting a counselee may not only be a 'medical duty' (e.g.479) but also a 'psychological duty' for the genetic-counselors. More research is needed to examine the ethical basis and the balance between medical and psychological benefits and costs - i.e. cost effectiveness - of organizing a follow-up session.

3.5. Limitations of the counselee-oriented approach

The application of a counselee-oriented ethics in clinical practice may also raise many questions. Are counselees able to reflect on themselves, and express what they need? Do they know what they need? Do they know enough about genetic-counseling to express what they precisely need from the genetic-counselor? When counselees say that they need something, is that also what they really need: is a genetic-counselor able to make a distinction between the real needs of a counselee and her psychological resistance to discuss certain needs? Does a genetic-counselor have to follow a counselee when she is avoiding important feelings and needs? Does the genetic-counselor have enough skills to

explore these counselee-oriented needs? Is she able to assess which counselees are able to have a non-paternalistic, equal relationship with the genetic-counselor and who are not? Is the genetic-counselor herself able to fulfill a non-paternalistic role? And to what extent does the genetic-counselor passively have to follow the counselees' needs?

The most extremist variant of a counselee-oriented ethics would imply that the counselee is left alone in her process, and the genetic-counselor only follows the counselee and does not explicitly discuss the meaning and the medical consequences of the DNA-test result if the counselee does not start speaking about this. A softer variant claims that the aim of this physician-patient interaction is 'to elucidate the patient's values and what he or she actually wants, and to help the patient select the available interventions that realize these values' (480). This means that the genetic-counselor has a more active role in helping the counselee to explore her interpretations. The counselor may fulfill her most active role when she 'helps the patient determine and choose the best health-related values that can be realized in the clinical situation' (480). The latter means that the genetic-counselor shows alternatives to the counselees' interpretations, and helps the counselee to weigh multiple possibilities. Thus, there are many different gradations in which the counselor can be directive or non-directive in counseling, while focusing on the counselees' needs (429). Which model should be followed? A counselee-oriented ethics would suggest that the genetic-counselor and counselee discuss and determine the relationship during the intake session (see 5.2.). At least, the counselor should ask for permission to discuss alternatives to the counselees' perception, and make clear when she is speaking about her opinion instead of merely speaking about the medical facts (429).

One of the biggest practical limitations to the counselee-oriented ethics may be the relatively limited time and funds available for genetic-counseling. This may hinder genetic-counselors to perform an extensive assessment of the counselee's situation and to thoroughly discuss the possible meanings and consequences of the DNA-test result for the counselee. Moreover, for financial reasons, it may be useful when genetic-counselors help counselees to have 'an accurate perception' and to follow the suggested medical risk-reducing options; however, this paternalistic and directive approach is contradictory to a counselee-oriented ethics.

Time and fund restrictions may not limit genetic-counselors in developing a counselee-oriented attitude. Counselors may not be able to perform a large number of extensive counselee-oriented interventions, but their counselee-oriented attitude may help them in attuning better to the counselee and to perform a small number of counselee-oriented interventions, within the time limits. For instance, one Dutch study suggest that genetic-counselors are able to discuss some psychosocial issues, without making the counseling sessions longer, when they had followed a short skills training (56). As examples, we suggest in paragraph 4 several questions that genetic-counselors may

use to start such a dialogue. More research is needed to help genetic-counselors to optimally develop a counselee-oriented approach within the given time limitations.

These limitations seem to suggest that in practice, genetic-counselors have to find a balance between the needs of the counselees on the one hand, and the practical possibilities of genetic-counseling on the other hand. They may for instance include their own ideas about what is needed most in the counselees' situation (481; cf. discussion in chapter 5). For these reasons, the implications that we discuss in paragraphs 5 and 6 do not merely follow a counselee-oriented ethics, but also information-oriented ethics such as improvement of the counselees' perception. But in the end, the counselee-oriented ethics assumes that it is the counselee who defines when the balance feels 'right'.

4. Implications for genetic-counselors

4.1. Genetic-counselors 'do a good job', and may do it even better

> *'The genetic-counselor has done a good job. She has explained everything very well, and I know all the facts now. But I am just not convinced that this is the only truth.'*
> (Based on interview RL-02)

The results of our study may be disappointing for genetic-counselors. Because we have shown that the actually communicated information only has a small, indirect effect on the counselees' perception, medical decisions and psychological outcomes. The counselees' own interpretations seem to be more important in explaining the impact of genetic-counseling than the genetic-counseling process itself. Do these results imply that genetic-counselors do not 'do a good job', and that they should reduce their activities to taking a blood sample, testing the DNA, and communicating that either a mutation has been found or has not been found? No. Beside ethical reasons (3.3.), our study provides several reasons why genetic-counselors 'do a good job'.

Despite the fact that many counselees felt that their fundamental needs were not fulfilled after genetic-counseling, they were very satisfied with genetic-counseling as such. For instance, unpresented results from the prospective study showed that 96% of all counselees evaluated genetic-counseling as useful, 91% evaluated the counseling as 'good' and 79% as 'pleasant', 95% evaluated the explanations as good, 57% reported that they had received new information that they did not have before genetic-counseling, and 93% would request for DNA-testing again. Thus, there is some evidence that genetic-counselors 'did a good job' from a counselee-oriented perspective.

Our studies also provided several information-oriented arguments why genetic-counselors were successful in their counseling sessions. Counselees were enabled by

genetic-counseling to make medical decisions with more medical information than they probably had before genetic-counseling, regardless of the fact that they may 'misinterpret' this information. Our family study has suggested that the genetic-counselor is the most reliable factor in the 'whisper game of genetic-counseling', because the communicated information correlated about .40 with the counselees' recollections, and the relationships between all other steps in the whisper game were much lower (chapter 7). The counselees' recollections and interpretations of their cancer-risks and heredity-likelihood also changed after the DNA-test result 'in the right direction' of the actually communicated DNA-test result (but these changes remained small and differed from the actual result) (chapter 6). When counselees were counseled by phone instead of face-to-face, their perception was slightly more inaccurate, which may suggest that the interaction between the genetic-counselor and the counselee actually influence the counselees' perception (chapter 9).

In summary, from an information-oriented perspective, genetic-counselors had a positive influential role in helping counselees with their need for information. But their influence seemed to be restricted to a certain bandwidth in which the counselee changed her perception. The counselees' personal and existential background seems to have determined this bandwidth even before they had met the genetic-counselor for the first time. Can genetic-counselors change this bandwidth? A recent review suggested that many interventions can indeed significantly improve the counselees' perception, especially thanks to the counselee-oriented elements of these interventions (284). Moreover, several studies showed that counseling based on counselee-oriented ethics may improve the counselees' perception (see paragraph 3). But the extent to which the counselees' perception can be influenced has still to be determined, and the size of the bandwidth may vary among counselees.

In this paragraph, I will describe several possible implications of our studies for genetic-counseling. The aim of these implications is not to change the counselees' bandwidth – which seems ethically unjustified (3.3.) –, but its aim is to make genetic-counseling even more counselee-oriented than it often already is. Thus, these suggestions should not be followed as 'a trick', but as a way to start a dialogue with the counselee. Table 1 provides an overview of these implications, which should not be regarded as a complete overview or guideline for genetic-counseling, but as examples in addition to existing counseling guidelines. All of our suggestions are loosely based on our study results in combination with previous studies, and their efficacy still has to be confirmed in empirical studies.

4.2. Implications for the counseling of counselees

4.2.1. Interventions before counseling

Many counselees had high expectations of genetic-counseling after the intake session. This raises the question whether the possible outcomes of genetic-counseling had been discussed sufficiently with the counselees. Before they have the first genetic-counseling session, counselees may be prepared by provision of information, e.g. via a flyer, letter, group-wise instruction or the internet. Pre-counseling explanation may help counselees to develop more realistic expectations about genetic-counseling, which may prevent disappointment and misinterpretation at a later stage of genetic-counseling. Provision of a flyer (e.g.484) has indeed shown to improve the accuracy of the counselees' risk-perception (chapter 9).

We suggest focusing this pre-counseling information on the discussion of certainties and uncertainties that genetic-counseling may yield. Additionally, the possible psychological consequences of the outcomes may be discussed, such as feeling uncertain and distressed. Examples are the likelihood to find a PM, and uncertainties that may arise after a result, for instance regarding medical decisions, telling relatives, the sensitivity of DNA-testing, and the inherent uncertain meaning of risks, i.e. the uncertainty whether and when the counselee may develop cancer (chapter 10). When the policy is to communicate UV's, the counselees' perception and distress may be lowered when the possibility of finding a UV is mentioned during the intake (chapters 3 and 9).

4.2.2. Interventions during the start of the first session

We suggest that the main focus of genetic-counselors during the intake session is to create a positive counselor-counselee working alliance that satisfies the counselees' needs. Several studies have shown that a positive working alliance is associated with patient adherence and satisfaction (485,486,487). It has been suggested that it is the depth of the relationship that helps counselees to actively explore their own ideas and feelings (e.g.488). All interventions that we provide below should be regarded as a means to foster the working alliance.

Previous studies have shown that counselees do not know what to expect from the counselor-counselee relationship, and some counselees may expect a traditional hierarchy between patient and doctor. The genetic-counselor may break this expectation by discussing several possibilities how to work together (cf. 3.3.). For instance, the genetic-counselor may ask what the counselee wishes, and may explain that genetic-counseling may differ from other medical disciplines because the intention is to have a discussion/dialogue and not to give a lecture/monologue, and the geneticist is the counselee's companion and is not the person who makes the decisions. Additionally, the counselor may tell that genetic-information is 'not a standard story' and does not have

standard consequences for each counselee; it has always a personal, subjective meaning and consequences. Which medical options is the best for a counselee, depends on her counselee's medical situation but also on her own thoughts and feelings. The counselor may explain about the counselor-counselee relationship, that the counselor may ask questions about the counselee's thoughts and feelings, and explores the possible meaning of the communicated information in the counselees' life. An explicit agreement should be made how the counselor-counselee relationship will be (see: 'informed consent to correct inaccuracies', 3.4.). Which psychosocial interventions may follow, depends on this agreement.

The counselor may be better able to follow the counselee's needs, when she explicitly explores the counselee's personal and existential context during the beginning of the first session. This exploration may also be important from an information-oriented perspective. For instance, our studies have shown that the counselee's personal context predicts her interpretations, distress and her medical decisions (chapter 9). Tailoring of information to the counselee's context is predictive of a more accurate perception and better attention/focus by the counselee; to be able to do this, the genetic-counselor has to know some basic information about the counselee's situation (430,476).

A broad range of questions may be asked. We mention a few in table 2 that have been derived from our studies, and that may be used as a means to start a conversation, to strengthen the working alliance and to attune to the counselee's needs. For instance, the counselee may reveal her experience of her context when she is asked about their motivation to undergo genetic-counseling, and why she wants to do it at this moment in her life. Her expectations may be explored by means of the question how much certainty she wants and expects to receive from genetic-counseling, and what this certainty may be about. We also suggest asking questions about the way how a counselee copes with her cancer, and with the cancer in the family.

4.2.3. Interventions later in the first and second sessions

Counselors may be better able to follow the counselees' needs, and to help them in expressing their wishes, when they ask counselees about their perception at three moments during genetic-counseling: at the beginning and at the end of the first session, and at the end of the DNA-test result disclosure session. The perception at the beginning of the first session may be used to tailor the genetic information that is discussed in the session, and that may immediately give the feeling to the counselee that she can discuss her feelings and interpretations with the genetic-counselor. Exploring perceptions at the end of sessions may inform the genetic-counselor how well the counselee has understood the information, and to start a discussion about the meaning of the DNA-test result.

Table 2 provides examples of risk-perception questions that may be effective. Our studies have shown that general questions, such as 'how well have you understand this?'

and 'which DNA-test result category have you received?' may not be useful, because the answers to these questions were unrelated to the actual understanding, perception and outcomes of genetic-counseling. Questions should be specific and cover the personal meaning of the DNA-test result. It is important to make an explicit difference between the counselees' recollections –i.e. their understanding of the information- and their interpretations –i.e. giving the result a personal meaning and embedding it in their lives. These questions about the counselees' interpretations have shown to be strongly related with the outcomes of genetic-counseling (chapters 3-8). Counselees may be stimulated to express their interpretations, by explaining that the communicated risks may feel differently compared to what has been communicated; the genetic-counselor is interested in these feelings and personal ideas, because she would like to explore what consequences may be most suitable for the counselee.

Some counselees may experience questions about their own perception as a 'school examination' which will be 'judged' by the genetic-counselor. Moreover, 'discussion on the part of the counselor has the potential to function as coercion in the life of the client' (489). The counselor should therefore be very explicit about the intention behind these questions, and emphasize that all feelings and thoughts may be expressed, and that there are neither good nor bad answers. When the counselor asks additional questions or offers additional explanations in reaction to the counselees' perception, she may explicitly ask for permission to avoid giving the counselee the feeling of 'being wrong'. For the same reason, asking questions may be preferred over giving an additional 'lecture'; questions may help the counselee exploring her own interpretations, and test the accuracy and applicability of these interpretations (this is called a 'Socratic dialogue' (490).

At the end of each session, the genetic-counselor may explore the possible medical and psychological consequences and the involvement of the family after DNA-testing. This may help the counselee to embed the DNA-test result in her life, and the genetic-counselor may provide her with additional explanations and suggestions if needed. If there is a follow-up session (e.g. via the Internet,cf. 98) these questions may also be asked to explore changes in the counselees' ideas and feeling about the meaning of the DNA-test result and possible consequences.

The counselor may use the information about the counselees' personal context and perception when she tailors the genetic-information. Both the content and the presentation of information can be tailored (430). Usually, tailoring will be an automatic subconscious process when there is a reciprocal dialogue between the genetic-counselor and counselee. Tailoring may also include the format of communicating risks, e.g. in words and/or in percentages. We suggest to be careful in communicating UR/UV-results in multiple formats and mirroring the risks (i.e. 80% at risk also implies 20% not at risk), because this has shown to make the counselees' perception less accurate. It may be helpful when the risks for PM-carriers are mirrored (chapter 9).

4.2.4. Limitations

As we discussed in 2.5., the genetic-counselor's possibilities to perform a 'perfect counselee-oriented session' may be limited by for instance time restrictions. However, the literature is optimistic: many interventions by genetic-counselors have shown to be effective, even when the intervention was relatively small (56,284). This may suggest that the general attention for counselee-oriented ethics, or the awareness of possibilities to start a dialogue, may already improve the genetic-counseling sessions.

4.3. Implications of the counseling for relatives

Our family study has shown that relatives often feel strongly involved in the genetic-counseling process, and may experience significant changes in their perceptions, medical decisions, and psychological well-being. Their perception was often inaccurate, which seemed to be caused by the 'noise' that had occurred within the counselee/proband during the 'whisper game of genetic information'. Most of all, some relatives wished to be more involved in genetic-counseling (chapters 7 and 8). This suggests that it may be relevant – i.e. it may fulfill the needs of untested relatives –, when genetic-counselors pay explicit attention to the meaning of DNA-test results for untested relatives.

Genetic-counselors may explore together with the counselee for which relatives the genetic-information may be relevant, and to whom and how the information may be communicated by the counselee. In this exploration, the counselor may provide suggestions on how to communicate the results, or provide a flyer with suggestions for family communication of DNA-test results.

Currently, genetic-counselors often suggest the counselee that she may copy her own summary letter that the counselor sends her. We suggest that genetic-counselors write or copy a letter specifically created for relatives, and provide this to the counselee for further distribution in the family (this can be a standard letter for relatives). The counselee's own summary letter often includes personal information which she may not want to share with her relatives; this may prevent her from distributing the letter. Many summary letters include little or only ambiguous information for the untested relatives (unpresented data in studies 3-10). We expect that having to copy the letter for their relatives may create an additional threshold for counselees to share the letter. For these reasons, it seems more likely that summary letters will be distributed when the counselor provides the counselee with specific letters for specific relatives. This letter may include an invitation for relatives to ask the genetic-counselor for additional explanation if they need.

Providing counselees with specific letters for relatives is common practice when a PM is detected. We also suggest doing this in UR/UV-families, because the communication of DNA-test results within families may be even more indirect and inadequate than PM-results due to the ambiguous nature of these results (cf. chapters 7 and 8).

Table 1. *Recommendations for genetic-counseling*

Discussions for national and international policy

- development of a sound and reliable BRCA1/2-terminology (chapter 2)
- ethical foundations of genetic-counseling (3.1.-3.3.)
- ethical and psychological acceptance of communicating UV's (3.4.)
- ethical and psychological acceptance of communicating results for low penetrance genes and whole genome sequencing (3.4.)
- ethical issues regarding the duty to re-contact counselees (3.4.)
- direct communication with untested relatives (chapters 7 and 8)
- re-define criteria for referral to a psychologist or social worker (6.1.)

General counselee-oriented ethics / attitude (3.4.)

- following the counselees' needs
- exploration of alternatives to DNA-testing
- flexible adjustment of directiveness/non-directiveness to the counselee's needs
- tailored communication
- exploration of the counselees' context, needs and perception
- exploration of the meaning and consequences of the DNA-test result
- open, responsive atmosphere
- equal counselor-counselee relationship
- reciprocal dialogue
- empathic confrontations
- balance between counselees' needs and medical possibilities
- ask informed consent to correct inaccuracies in the counselees' perception
- discuss possibility of recontacting

Pre-counseling preparation of counselees for uncertainty

The preparation of counselees may include an explanation of genetic and psychological aspects of counseling*, including uncertain DNA-test results and their psychological consequences*:

- preparation by flyer, letter, group meetings, internet
- mentioning of the possibility of detecting UV-results (if communicated)

Intake session

- preparation by explanation of counseling: general procedure, relationship, uncertain outcomes
- global exploration of the personal and existential context of the counselee, e.g.: motivation to undergo DNA-testing, motivation to request testing at this moment in life, coping with cancer
- at the beginning of the session: exploration of the counselees' perception (cf. table 2)
- tailor genetic information to the context and perception of the counselee
- at the end of the session: exploration of the counselees' perception
- exploration of consequences: whether DNA-testing suits the counselees' context best (discuss alternatives); involvement/consequences of relatives; intended medical consequences; current or expected psychological impact

DNA-test result disclosure session

- tailor genetic information to the context and perception of the counselee
- if the counselee is emotional, explore these emotions by means of questions
- at the end of the session: exploration of the counselees' perception
- exploration of consequences: involvement/consequences of relatives; intended medical consequences; current or expected psychological impact

follow-up

- exploration of the counselees' perception
- exploration of consequences for medical decisions and psychology
- exploration of the involvement/consequences/contacting of relatives
- additional explanation, tailored to the counselees' context and perception
- psychological individual or group meetings (6.1.-6.5.)

Table 2. *Examples of questions for counselee-oriented counseling, derived from interviews and instruments in our studies; questions may be used to start a dialogue and attune to the counselee*

Counselee's motivation

- What made you request for genetic-counseling at this specific moment in your life?
- What is the possible meaning of genetic-counseling for you?
- Who else has influenced your decision to undergo genetic-counseling? (partner/kids/relatives; degree of coercion)
- When did you become aware that the cancer in your family is hereditary? (when, how, by whom)
- Given the occurrence of cancer in your family, how do you feel about your personal risk of cancer?
- Are there others in your life that you getting this genetic counseling for? (self versus others)
- What information do you think is important for me to know about you and about your life?

Counselees' expectations and wishes

- What are your expectations and hopes about me/the counseling? (counselor-counselee relationship and information)
- How do you think that the result may help you and/or your relatives to cope with your/their cancer or your/their risk to develop cancer?

Counselee's perception

- Recollection: How would you tell your partner, relatives or friends what I have told you about the information/DNA-test result/pedigree?
- Interpretation: Regardless of what I have communicated, what do you think and feel yourself about your own risk/your relatives' risk to develop cancer/for the likelihood that cancer is heritable in the family?
- Interpretation: How is it to receive this (un)expected information/result/pedigree?

Consequences of DNA-test result (subsequent to exploration of emotional reaction)

- How do you think this information may be of any help to you?
- What do you intend to do with this information/result/pedigree? (e.g. medical decisions, informing relatives)
- How certain do you feel now about the heredity of your cancer/your cancer-risks/relatives' cancer-risks? (e.g. understanding, preventive management options, future expectations, communication with others)
- How are you going to deal with the uncertainty of the information/result/pedigree?

Familial context

- Which of your relatives have you informed about you undergoing genetic-counseling? And how did they respond? (at intake/pretest)
- Who in your family will you inform about this DNA-test result? What (content) and how (process) are you going to tell them?

At the end of a session

- How do you feel about this session?
- What has felt most important to you from our conversations that you take home with you?
- What do you need to support you as you process this result?

5. Implications for the psychological care of counselees

5.1. Who needs psychological care?

> *In the past, I was a perfectionist who wanted to be in top of everything and who always wanted to have certainty in life. For that reason, I became very depressed after the DNA-test result, which confronted me with lots of uncertainty. I was not in control. I started to question the meaning of life and the justice of carrying this mutation* (i.e. UV result-JV). *But I have changed since then. I've learnt to accept things as they are. All things have to go their own way and all people have to live their own lives. Of course, I still want to be in control of my life –and I usually am!- but it is not an inflexible urge anymore. I'm not afraid of uncertainty anymore, I just let it be and live my own live. I know the meaning in life and there is inner peace. I feel complete again as a human being. (…) Yes, I was severely distressed after the DNA-test result. But no, I did not need professional help for that.* (Based on: RL-06)

Which counselees may need referral by the genetic-counselor to a social worker or psychologist? It is common practice in the Netherlands, that genetic-counselors automatically refer counselees who have decision problems, problems with coming to terms with the test result, problems in the partner-relationship, problems with informing children or relatives, etc. (e.g.491).

This common practice seems to assume a simple, information-oriented model, similar to the underlying model in previous studies in which distress was correlated with information-oriented variables (cf. chapter 4). In the discussion-sections of chapters 5 and 10, we suggested on the basis of non-presented results that the personal and existential meaning of the DNA-test result may be a better explanation of who needs professional psychological care. Table 3 shows these results (cf.507). The counselees' self-reported wish for psychological help was *not* correlated with the actually communicated DNA-test result category, cancer-risks and heredity, but it was correlated with their intentions to undergo surgery, their symptoms of psychopathology, and being a young mother. Independently from these psychopathological problems, the need for psychological care was also equally strongly predicted and completely mediated by several counselee-oriented variables, such as having an inaccurate perception, using passive coping styles, existential concerns, high need for certainty and low perceived certainty, feeling and thinking that they and/or their relatives have a high risk to develop cancer, and problems in family relationships (see table 3).

What does this mean? Neither the actually communicated information nor the counselees' medical intentions and psychopathology was directly correlated with counselees needed psychological care, but the counselees' interpretations and the

personal meaning of these facts did (cf. chapters 5 and 6). For instance, some counselees seemed to experience strong distress after DNA-testing but they did not wish to receive psychological care. Others did not show severe distress, but they strongly wished psychological care. The main difference between counselees who want and who do not want to receive psychological care can be defined by their way of embedding the DNA-test and the distress in their lives, for instance by the creation of an inaccurate perception, or having a strong need for certainty.

In the past, several authors and probably also policy makers seemed to assume that the absence of pathological levels of distress in the large majority of counselees implied that 'these counselees do not require psychological help' (492; cf. chapters 5-6). However, the absence of psychopathology may only say that the distress/psychopathology instruments were too insensitive or a-specific to describe the specific and personal concerns of counselees (cf.74,323,492). Psychological care may not only be restricted for counselees with psychopathology. Our studies have shown that, despite the absence of severe psychopathology, many counselees feel uncertain, vulnerable, and stigmatized and may experience difficulties interpreting the DNA-test result 'correctly'.

Of all counselees, one in 6 actively reported to need psychological care (both in the retrospective and prospective studies). But only one in 25 had actually received that help. This may be due to the fact that counselees may not have expressed their psychological needs to the genetic-counselor (cf.493), or to the inadequacy of current referral criteria. We recommend developing and using other referral criteria which may be further operationalized in future studies (e.g. table 3). Psychological screening instruments may be used, but we suggest that these should also include items other than psychopathology and which are oncology-specific and genetics-specific. (cf.507)

Table 3. *Criteria for referral to a social worker or psychologist, defined by the correlations between the counselees' wish for help and these criteria.*

1. **surgery intentions**
   intention to undergo surgery of breasts and/or ovaries (.57, .66) *

2. **large 'inaccurate' perception**
   large difference between the counselees' interpretation and the actually communicated DNA-test result (.56) **

3. **passive coping styles**
   distraction, renaming, avoidance and denial (.50, .25, .25, .25) *; **

4. **psychopathology**
   negativity and worries (.48, .43) *

5. **existential concerns**
   vulnerability, uncertainty, lack of purpose in life, lack of self-acceptance (.30, .26, .30, .28) **

6. **high need for certainty and low perceived certainty**
   need for certainty and perceived certainty (.21, .34, .31, .27; ,22, .34, .27, 30)**

7. **interpretations of high risks and heredity**
   feeling and thinking of being at high risks to develop cancer (again), and high heredity; feelings of large vulnerability (.28, .21, .27)

8. **young woman with children**
   number of children living at home (.29) *

9. **familial problems**
   lack of trust and justice in the relationships within the family (.25)

*Unpresented results from the prospective study (chapters 6, 9 and 10), confirming the criteria discussed in and based on data the retrospective study (chapter 5). Figures are correlations and partial correlations. Only R>.20, p<.01 are presented. All items are measured three months after the DNA-test result (i.e. T2). All criteria are linear scales (see chapter 6, 9 and 10). Wish for psychological help was measured on a 1-7 semantic differential, ranging from 1, no wish, to 7, strong wish; 16% of all counselees mainly reported wishing to receive psychological help >4, 68% mainly reported not wanting to receive psychological help. All criteria have been corrected for psychopathological symptoms (i.e. partial correlations). All results were comparable with non-parametric tests. * When these information-oriented variables (criteria 1, 3, 4 and 8) are included in mediation regression analyses together with counselee-oriented variables, they do not directlycorrelate with the need for psychological help anymore, and the counselee-oriented variables remain as the only significant correlations, (i.e. complete mediation; see chapter 6 for explanation). ** When the results are not corrected for the psychopathological symptoms, the correlations are significantly higher, with larger effect sizes.*

5.2. Counselee-oriented interventions

Several psychologists and social workers have asked me to provide suggestions how counselees may 'optimally cope' with an unfulfilled need for certainty. The counselee-oriented ethics would suggest that each counselee may need an individual approach, and that the counselee's needs are followed in psychological care. It has been suggested that counselees may benefit from a psychologist or social worker who does not provide answers but mainly asks questions to help the counselee to discover her own truth, i.e. a Socratic dialogue (490). However, I will describe some general therapeutic interventions that may assist in individual cases. Similar to the suggested interventions for genetic-counselors, all interventions should be regarded as a means to foster the working alliance and to help the counselee fulfilling her needs.

For instance, it may help to explore the counselee's interpretations and embedding of the DNA-test result in her life, by means of questions such as suggested in tables 1 and 2. A counselee may also be stimulated to explore what she really needs at this moment in life. For instance, DNA-testing may not be the most suitable option, for instance because the counselee may not be ready yet to undergo DNA-testing due to her personal and existential life situation. To assess this, psychologists may develop a model regarding 'existential stages of readiness for genetic-counseling' (cf.377). This may be operationalized by means of a 'needs questionnaire' for the counselee, or a checklist for the genetic-counselor.

In 2.3., we described that many counselees experience difficulties with living in dual realities, such as needing certainty on the one hand and not having received certainty about the DNA-test on the other hand. I suggested that counselees can learn to accept the existence of both realities without denying one of both, and can learn to trust themselves in switching their focus from one reality to the other, and back. Many psychotherapeutic interventions may be used to help them to develop a dual attitude, such as existential-therapeutic interventions (467,426). On the basis of literature, I suggest several therapeutic interventions to explore the dual attitude (e.g.494,378,468,145,495,440).

Firstly, existential experiences may be explored with the counselee, for instance about existential anxiety, death, being at-risk, being a cancer-patient, being 'guilty' or 'responsible' for transmitting a PM to her children, identity questions, etc. Counselees may be assisted to stay focused and to deepen/intensify these existential themes, and not automatically avoiding them. Research has shown that deeper explorations in therapy may help counselees in detoxifying existential feelings and cause better therapy outcomes (496,497,126).

Secondly, counselees may be stimulated to not solely focus on the negative, existential, limited side of life, but to broaden their focus. Counselees may be inclined to identify their identity with their risk-status, and 'forget' that they are not only a person-at-risk, but also a mother and a friend, and so on (see 2.1.5. and: 61). They may be stuck in this

mode of being at-risk or being a patient (see 2.1.2). Therefore, therapists have suggested to stop reflecting and concentrating on their existential issues: they may take time for 'dereflexion' (cf.498) and 'decentration' (499).

Concretely speaking, a counselee may be stimulated to pay attention to the certainties, meanings and meaningful goals that she currently experiences, has experienced or may experience in life. She is asked for a broad exploration of meanings, and to subsequently revalue, reorder and reorganize these, and to finally make steps to realize these meaningful goals. These certainties and meanings may range from a practical level – e.g. listening to music, being together with her partner– to an abstract level – e.g. defining the ultimate meaning in life. Research shows that cancer-patients who are able to reengage in meaningful goals despite their uncertainties and physical limitations, experience more positive affect (143). Otherwise formulated, they are helped in meaning-based coping as described in 2.1.3. (131). Thus, the psychologist or social worker may explore both the uncertainties and existential questions on the hand, and the certainties and meaningful experiences in the counselees' daily life on the other hand.

Third, the psychologist or social worker may pay explicit attention to the switching between these two realities, such as the switch that counselees may experience when they are meaningfully living their daily lives and suddenly feel vulnerable and uncertain about their genetic status. Counselees could explore previous 'switching experiences' in previous periods of uncertainty in life, and explore how they may actively switch between both realities. For instance, the psychologist or social worker could explore which situations automatically trigger a switch between two realities, and what reason is behind this (cf.458).

Fourth, several studies have shown that counselees may benefit from psycho-education, that is from explanation of their situation (e.g.500). Didactics may lower distress and may facilitate a normalization process, i.e. they may help a counselee to experience her situation as a normal reaction to an abnormal situation. Information from this thesis may be included in this psycho-education, e.g. the fact that many counselees may feel uncertain and vulnerable. It may be explained that dual realities may exist next to each other and that for instance being at-risk does not necessarily mean that one's identity has to change. Didactics may not only be provided during a session, but also by means of flyers with explicit psycho-educational information (e.g.484).

Fifth, psychologists and social workers may explicitly recognize the counselees' needs, situation and perception, for many counselees in our pilot study said that they felt 'seen' and 'recognized' thanks to our interview, and they experienced this recognition as valuable (see quote in 1.1.). The psychotherapist Boszormenyi-Nagy writes that it is important to give explicit recognition to an individual who is struck by an unchangeable fate, such as one's genetic background (501). He would say that an individual will not be able to develop a 'dual attitude' and to cope actively with her situation, when her

victimhood is not first recognized. Thus, the creation of a dual attitude may assume the explicit recognition of the counselees' worries and needs.

Sixth, explicit attention may be given to the untested relatives of the counselee. We found that relatives are involved in the genetic-counseling process. But this involvement may not be without emotional and relational consequences for the counselee. For instance, counselees wished to receive psychological help when they had the feeling that they could not trust their relatives, and that they did not receive the care from relatives that they actually felt they deserved (see table 3). Additionally, unresolved family myths may be revived, loyalty conflicts may occur, and family-conflicts may start (112-114). Other studies have also shown that the counselees' family-experiences with cancer may predict their level of distress (491). Creation of a dual attitude may also be helpful in such family situations. More specifically, counselees may be helped to combine their loyalty towards and identification with their family with being autonomous, such as asking relatives for their opinion and at the same time making their own medical decisions (114,501).

Finally, our studies suggested that counselees did not make their medical decisions on the basis of the actually communicated facts or of their recollections, but on the basis of their own interpretations (chapters 5, 6 and 10). Therefore, we suggest that a psychologist or social worker explores the subjective, emotional ways of reasoning when a counselee wishes to receive psychological care about her decision to undergo surgery of her breasts or ovaries. We recommend to not only use cognitive techniques during this exploration - as is often suggested (502-503) -, but also to use techniques that may help counselees to deepen and to stay focused on their feelings, such as mindfulness (504-506).

> *'My life has changed due to genetic-counseling. It was a difficult process. But it was worth it. I have learned much, I know what to expect from my cancer, what medical decisions to make and what to tell my children. And above all, I have learned to be myself, and not to be distracted by uncertainty.'* (Loosely based on interview RL-006)

6. Main conclusions

1. BRCA1/2-counseling can be compared with a children's whisper game. The genetic-counselor has actually communicated 'A', the counselee recalls 'B', interprets this as 'C', and experiences distress and makes medical decisions on the basis of 'C'. The counselee communicates this information to her relatives, who recall 'D', interpret 'E' and experience distress and make medical decisions on the basis of 'C'.
2. The disclosure of BRCA1/2-results has a far-reaching impact, which includes medical, psychological and existential changes in life (1.2.1.).

3. The counselees' perception of the BRCA1/2-result deviates significantly from the actually communicated information, and consists of multiple elements such as recollections and interpretations of cancer-risks and heredity-likelihood (1.2.2.).
4. The communication of BRCA1/2-results do not directly correlate with the far-reaching impact of genetic-counseling, but the counselees' perception does correlate with and mediate this impact (1.2.3.).
5. Relatives feel strongly involved in the genetic-counseling process. They experienced a significant impact of the DNA-test result on their lives. This was only correlated with their own subjective perception that deviated from the actually communicated information (1.2.4.).
6. The unfulfilled need for certainty may be frightening for counselees, possibly because of the personal and fundamental meaning of DNA-test results for counselees (2.2.).
7. Few counselees seemed to accept the unfulfilled need for certainty, which may cause denial and distress; acceptance may be increased by helping counselees to acknowledge both the uncertainties and the certainties in their life (i.e. form a dual attitude) (2.3.).
8. We suggest genetic-counselors to follow a counselee-oriented ethics in their clinical practice, which focuses on the counselees' needs, and assumes that the counselor takes care for the totality of the counselee and not only for the disclosure of information; examples to start a dialogue have been provided (3.3.; 5.1.).
9. The communication of UV's may not be in line with this counselee-oriented ethics because it does not fulfill the counselees' needs and it seems to evoke significant distress in many counselees, but at the same time it does not have important medical implications 3.4.).
10. Genetic-counselors seem to be the most reliable factor in the communication process of genetic-counseling, and the counselees' and their relatives' interpretations seem to predict the noise in the 'whisper game' (5.1.).
11. We suggest revisiting national and international policies, for instance regarding DNA-terminology, ethical foundations of genetic-counseling, and recontacting counselees (5.1.).
12. Genetic-counselors are advised to provide counselees with letters for their relatives which explain the DNA-test result (5.2.).
13. Most counselees do not develop psychopathology after DNA-testing, but the majority do feel vulnerable, and about one-sixth would like to receive psychological help, especially those intending to undergo surgery, having an inaccurate perception, asking existential questions and feeling uncertain (6.1.).
14. Psychologists and social workers may help counselees by developing a dual attitude, for instance by acknowledging that they need certainty and that they may not actually experience certainty at the same time. (6.2.).

Samenvatting

Summary in Dutch

Deel I: de fundamenten

Emma komt uit een familie waarin veel mensen kanker hebben gehad. Er is bij haar zelf een aantal jaren geleden borstkanker geconstateerd. De tumor is verwijderd, maar ze blijft zich onzeker voelen over een recidief. Ze overweegt daarom om haar niet-aangedane borst ook uit voorzorg te laten amputeren. Daarnaast voelt ze zich erg onzeker over de vraag of haar gezonde familieleden –en vooral haar dochter van 10 jaar- ook een verhoogd risico hebben op het krijgen van kanker. Om die reden is ze naar de afdeling Klinische Genetica gegaan. Een geneticus heeft een stamboom met haar aangedane en niet-aangedane familieleden getekend. Op grond daarvan is vastgesteld dat de kans dat een persoon in haar familie kanker krijgt groter is dan gemiddeld bij vrouwen in de bevolking. Vervolgens is er bij haar een DNA-test gedaan om te onderzoeken of zij een genetische aanleg heeft die verklaart waarom zij –en haar aangedane familieleden- borstkanker hebben ontwikkeld. In dit onderzoek werd een afwijking in het DNA gevonden, een zogenaamde Unclassified-Variant. Van deze afwijking is nog niet wetenschappelijk bekend of het gaat om een onschuldige afwijking –zoals die wel vaker voorkomt- of dat het inderdaad gaat om een afwijking die verklaart waarom meerdere individuen in haar familie kanker hebben gekregen. Dit proefschrift gaat om de vraag: hoe kijkt Emma tegen deze uitslag aan, welke invloed heeft het op haar leven, en welke informatie vertelt ze door aan haar familieleden? (Geanonimiseerd interview voorbeeld uit de pilot studie)

Eén op de acht à negen vrouwen in de bevolking ontwikkelt borstkanker gedurende haar leven. Ongeveer vijf tot tien procent van al deze patiënten heeft de borstkanker vermoedelijk ontwikkeld als gevolg van een genetische aanleg. Er kan bij een individu een DNA-test worden gedaan om te kijken of deze persoon inderdaad deze genetische aanleg heeft waardoor ze borst- en/of eierstokkanker heeft gekregen ('symptomatisch testen'), of wat haar kans is om borst- en/of eierstokkanker voor de eerste keer te krijgen ('presymptomatisch testen'). Meestal wordt er dan gezocht naar een DNA-afwijking in het BRCA1 of BRCA2-gen (BRCA = BReast CAncer). Er zijn ook andere genen betrokken bij erfelijke borst- en/of eierstokkanker, maar die genen zijn nog niet wetenschappelijk ontdekt of die worden meestal niet onderzocht bij een individu. Een dergelijk DNA-onderzoek dat bij een individu wordt gedaan, noemen we een 'erfelijkheidsadvies' (in het Engels: 'genetic counseling') bij een 'adviesvraagster' ('counselee'), en dit advies wordt gegeven door een klinisch geneticus of een genetisch consulent.

Er zijn drie soorten uitslagen bij een BRCA1/2-test mogelijk: een niet-informatieve uitslag, een pathogene mutatie en een unclassified-variant. In het eerste geval kan er geen verandering in een BRCA1/2-gen worden gevonden. Dat wil niet zeggen dat dit individu 'zeker' geen genetische aanleg tot het ontwikkelen van borstkanker heeft, want het kan

ook zijn dat deze persoon – en haar familieleden – borstkanker hebben ontwikkeld als gevolg van een ander gen dan BRCA1 of BRCA2. Deze uitslag noemen we een 'Niet-Informatieve Uitslag' (NIU), hoewel deze term eigenlijk niet klopt want een NIU geeft wel degelijk informatie, namelijk dat er geen afwijking in één van de BRCA1/2-genen is gevonden. In een dergelijk geval geeft een geneticus een statistische inschatting van de risico's die deze persoon en haar niet-aangedane familieleden hebben om kanker te krijgen; deze inschatting wordt gemaakt met behulp van tabellen en op grond van de familiestamboom. In het tweede geval kan er een BRCA1/2-afwijking of 'pathogene mutatie' (PM) worden gevonden. In dat geval heeft een adviesvraagster zonder kanker een kans van 45-85% om een eerste tumor te ontwikkelen, en tevens een kans van 11-69% om ovariumcarcinoom te krijgen. De kans dat een adviesvraagster met kanker opnieuw kanker krijgt is bij een PM-uitslag 60%. In het derde geval kan er een verandering in een BRCA1/2 gen worden gevonden waarvan het nog onduidelijk is of dat een onschuldige afwijking is, of dat dit inderdaad een pathogene (dat is: ziekteveroorzakende) afwijking is. Dit heet een unclassified-variant (UV). In dat geval communiceert de geneticus risico's op grond van de stamboom.

Wie op grond van de DNA-uitslag en/of stamboom een groot risico heeft om (opnieuw) kanker te krijgen, komt in aanmerking om geregeld de borsten en/of eierstokken te laten controleren, of om die chirurgisch te laten verwijderen. Tevens komen familieleden bij een PM-uitslag in aanmerking om een DNA-test te laten doen om te laten bepalen of zij ook deze pathogene DNA-afwijking hebben .

In **hoofdstuk 1** wordt aan de hand van de literatuur beschreven hoe genetici vroeger overwegend een informatie-georiënteerde benadering hadden wanneer ze spraken met adviesvraagsters. Tegenwoordig lijken ze steeds vaker een adviesvraagster-georiënteerde benadering te hebben. Wanneer een geneticus overwegend georiënteerd is op informatie wil dat zeggen dat hij vooral aandacht besteed aan de overdracht van de genetische informatie, zoals de kankerrisico's, DNA-uitslag categorie (NIU, PM, UV) en de medische consequenties voor de patiënt. Wanneer een geneticus overwegend georiënteerd is op de adviesvraagster wil dat zeggen dat hij niet alleen aandacht besteedt aan de overdracht van genetische informatie maar ook aan de psychologische en persoonlijke behoeftes van de patiënten, hoe zij aankijken tegen de uitslag en hoe ze de uitslag in hun leven kunnen inbedden. Sinds tientallen jaren lijken zowel de officiële doelstelling als de praktijk van erfelijkheidsadvisering zich sterk te oriënteren op de adviesvraagster.

Wat opvalt, is dat er relatief weinig adviesvraagster-georiënteerd psychologisch onderzoek is gedaan naar erfelijkheidsadvisering. In voorgaande onderzoeken is er bijvoorbeeld gekeken of een DNA-uitslag een rechtstreekse invloed heeft op allerlei uitkomsten zoals de medische keuzes of het ontstaan van psychopathologie bij een adviesvraagster, zoals depressie en angst. De resultaten van deze onderzoeken spreken

elkaar echter geregeld tegen en laten zelden rechtstreekse verbanden zien tussen de DNA-uitslag en de impact op het leven van de adviesvraagsters. Andere wetenschappers onderzochten bijvoorbeeld de specifieke gedachtegangen (cognities) die adviesvraagsters hebben over de DNA-uitslag. Deze studies naar de cognitieve waarneming gingen echter uit van specifieke en rationele modellen, die onvoldoende recht leken te doen aan de persoonlijke betekenis van een DNA-uitslag voor de adviesvraagster, en de manier waarop zij de uitslag op een subjectieve manier in haar leven inbedt.

Het doel van de studies die in dit proefschrift zijn beschreven is het onderzoeken van de psychologische impact die DNA-uitslagen op het leven van adviesvraagsters kunnen hebben. Om dit doel te bereiken hebben we zes verschillende deelstudies uitgevoerd: een literatuurstudie naar de termen die genetici gebruiken (hfst. 2), een verkennend onderzoek met interviews bij 24 adviesvraagsters die in het verleden een UV-uitslag hebben gehad ('retrospectieve pilot study': hfst. 3), een retrospectieve studie met vragenlijsten bij 204 adviesvraagsters die in het verleden een NIU/PM/UV-uitslag hebben gehad (hfst. 4-5), een prospectieve studie waarin we 248 adviesvraagsters een vragenlijst hebben laten invullen op korte termijn na het eerste gesprek met de geneticus en na de DNA-uitslag (hfst. 6, 9-10), en een vragenlijstonderzoek bij 70 ongeteste familieleden van adviesvraagsters die in het verleden een NIU/UV-uitslag hebben gehad (hfst. 7-8).

Hoofdstuk 2 gaat over de terminologie die genetici gebruiken om te spreken over niet-pathogene uitslagen, zoals NIU en UV. Taal is een belangrijk instrument van de geneticus, wiens doel het is om adviesvraagsters te adviseren bij een mogelijke familiaire aanleg voor kanker. Toch is er niet eerder onderzocht of de termen die worden gebruikt wel de meest geschikte termen zijn. Om die reden hebben hebben we gekeken of de termen op een valide en betrouwbare manier worden gebruikt.

Met validiteit bedoelen we dat een term uitdrukt wat deze bedoelt uit te drukken. De term 'unclassified variant' (UV) is bijvoorbeeld niet valide, omdat veel van deze DNA-afwijkingen weldegelijk geclassificeerd worden door genetici; het is alleen op dit moment nog onbekend wat iedere klasse precies betekent. Bovendien keken we ook of de term helder was, of alle relevante informatie door de term wordt omvat en of de term kan leiden tot verwarring. Al deze validiteitsaspecten hebben we onderzocht door middel van een theoretisch/analytisch onderzoek van de meest gebruikte termen.

Met betrouwbaarheid bedoelen we dat verschillende mensen dezelfde term gebruiken om hetzelfde fenomeen aan te duiden. Om dat laatste te onderzoeken, hebben we onderzocht of auteurs termen op een consistente manier gebruiken in 202 recente Engelstalige artikelen.

De conclusie van ons onderzoek was dat er veel verschillende termen worden gebruikt in de literatuur, maar dat weinig daarvan valide en betrouwbaar zijn. De meest betrouwbare Engelse termen zijn 'variant of uncertain clinical significance' (wat gelijk staat

aan een UV-uitslag) en 'true negative' (er wordt geen afwijking in één individueel familielid gevonden terwijl andere familieleden wel één bepaalde afwijking hebben). De meest valide termen zijn 'variant of uncertain clinical significance' en 'niet pathogene uitslag'. Wij adviseerden om een nieuwe terminologie te ontwikkelen die voldoende betrouwbaar en valide is. In dit proefschrift gebruikten wij de termen 'UV' en 'NIU' omdat die termen in Nederland het meeste worden gebruikt.

Hoofdstuk 3 gaat over 24 adviesvraagsters die in het verleden een UV-uitslag hebben gehad. In deze deelstudie hebben we in interviews een aantal nieuwe thema's onderzocht, die als basis dienden voor de volgende hoofdstukken.

Voorgaande onderzoekers bestudeerden vaak hoe adviesvraagsters een DNA-uitslag waarnemen aan de hand van één algemene vraag, zoals 'wat is uw kans om kanker te krijgen?' Het is onduidelijk of het antwoord op deze vraag weergeeft wat de adviesvraagster zich herinnert over de DNA-uitslag die de geneticus heeft meegedeeld, of dat het weergeeft wat de adviesvraagster zelf denkt en voelt over de DNA-uitslag. Om die reden vroegen wij zowel naar de herinneringen van de adviesvraagsters als naar hun interpretaties, door middel van de vragen: 'wat herinnert u zich dat de geneticus heeft meegedeeld' ('herinnering') en 'wat denkt en voelt u zelf, los van wat de geneticus heeft verteld' ('interpretatie'). Het blijkt dat de adviesvraagsters twee verschillende antwoorden geven op deze twee vragen.

Van alle 24 adviesvraagster herinneren 16 zich correct dat er een UV-uitslag is meegedeeld, maar 7 herinnert een PM en 1 een NIU. Negentien interpreteren dit als een PM, en 5 als een NIU.

Deze misinterpretatie bleek gevolgen te hebben voor hun medische keuzes: adviesvraagsters die de uitslag als een PM interpreteerden hadden vaker hun borsten en/of eierstokken laten verwijderen dan adviesvraagsters die het als een NIU interpreteerden (53% tegen 0%).

Daarnaast noemde 25% van alle adviesvraagsters dat de UV-uitslag hun leven enigszins had veranderd; ze merkten vooral op dat ze anders tegen het leven zijn gaan aankijken, andere medische keuzes hebben gemaakt, hun lichaam anders ervaren en veranderingen merken in hun persoonlijkheid en emoties. Deze veranderingen konden niet worden toegeschreven aan bijvoorbeeld de stamboom.

Samenvattend: we ontdekten dat UV-adviesvraagsters de meegedeelde genetische informatie anders interpreteerden en herinnerden, en dat de UV-uitslag hun leven op meerdere terreinen had veranderd.

Deel II: de ontwikkeling van een adviesvraagster-georiënteerd integratief perspectief op genetische counseling

In **hoofdstuk 4** bouwden we voort op de bevinding dat adviesvraagsters hun herinneringen en interpretaties van elkaar onderscheidden. In deze retrospectieve deelstudie ontwikkelden wij een nieuw model van de perceptie/waarneming van adviesvraagsters, zodat we dit model in de volgende deelstudies konden gebruiken om te verklaren hoe een DNA-uitslag via de perceptie van de adviesvraagsters kan leiden tot allerlei veranderingen in hun leven.

De reden dat wij een nieuw model van de perceptie van adviesvraagsters hebben ontwikkeld, moet gezocht worden in de wetenschappelijke context. Studies van voorgaande onderzoekers kunnen grofweg ingedeeld worden in twee groepen: de ene groep vooronderstelde dat een DNA-uitslag een rechtstreeks invloed heeft op de medische keuzes en het psychologische welzijn van adviesvraagsters (dus zonder rekening te houden met de eigen perceptie van de adviesvraagsters), en de andere groep vooronderstelde dat deze invloed indirect verloopt via de perceptie van de adviesvraagsters. Deze 'perceptiestudies' maakten echter geen expliciet onderscheid tussen herinneringen en interpretaties. Bovendien vroegen verschillende onderzoekers hoe de adviesvraagster aankijkt tegen haar eigen kans om kanker te krijgen, terwijl de meeste adviesvraagsters zelf al kanker hadden gehad en zij zich op dit moment vooral zorgen maakten om de risico's die hun familieleden hadden om kanker te krijgen. De resultaten van deze eigen-risico-perceptie-studies spreken elkaar geregeld tegen, en verklaren nog steeds maar een klein deel van de veranderingen in het leven van de adviesvraagsters. Ons nieuwe model bestaat uit meerdere onderdelen: we vroegen de adviesvraagsters zowel naar hun herinneringen als naar hun interpretaties van zowel hun eigen kankerrisico's als van de erfelijkheid van kanker in de familie.

Zoals wij ook al hadden gevonden in de deelstudie in hoofdstuk 2, vonden wij opnieuw dat de herinneringen en interpretaties van elkaar verschilden. Daarnaast zagen de advievraagsters hun eigen kankerrisico's en de erfelijkheid als twee verschillende fenomenen. Dit suggereert dat de perceptie van de adviesvraagsters bestaat uit vier verschillende elementen: herinnerd eigen kankerrisico, geïnterpreteerd eigen kankerrisico, herinnerde erfelijkheid en geïnterpreteerde erfelijkheid. We vonden niet alleen dat deze vier elementen significant van elkaar verschilden, maar ook dat ze met elkaar samenhangen (verschil en samenhang zijn statistisch gezien twee andere dingen); dat is logisch, omdat het gaat over hetzelfde onderwerp, namelijk de DNA-uitslag.

We hebben meer onderwerpen onderzocht. We vonden bijvoorbeeld dat veel adviesvraagsters niet in staat waren om het precieze percentage van hun kankerrisico te herinneren dat hen door de geneticus was meegedeeld. Dat kan verklaren waarom risico-

perceptie-studies vonden dat de adviesvraagsters geen juiste perceptie hadden. Dit suggereert dat het nuttiger is om adviesvraagsters niet te vragen om hun herinnering uit te drukken in percentages maar in woorden, bijvoorbeeld in categorieën van 1, zeer kleine kans, tot 7, zeer grote kans. Verder leken ze de betekenis van de DNA-uitslag en van de stamboom door elkaar te halen. We ontdekten dat adviesvraagsters met een UV-uitslag het grootste verschil maakten tussen hun herinneringen en interpretaties, en dat adviesvraagsters met een NIU het kleinste verschil hadden. De vraag 'heeft u deze uitslag begrepen' en de vraag welke uitslagcategorie (NIU, PM, UV) een adviesvraagster heeft gekregen bleken tevens niet toereikend te zijn om te bekijken hoe een uitslag bij een adviesvraagster aankomt en hoe ze die in haar leven inbedt; de antwoorden op deze vragen hangen niet samen met de antwoorden op de vragen naar de specifieke herinneringen en interpretaties van risico's en erfelijkheid. Al deze resultaten werden niet beïnvloed door andere variabelen, zoals de stamboom en sociodemografische gegevens.

Samenvattend: we ontdekten dat de waarneming van de adviesvraagsters in twee maal twee elementen uitgesplitst kan worden, te weten: herinneringen versus interpretaties, eigen kankerrisico's versus erfelijkheid. In hoofdstuk 6 hebben we nog meer elementen toegevoegd aan deze vier elementen in de perceptie van adviesvraagsters. We adviseerden genetici om expliciet te vragen naar deze verschillende elementen in de perceptie van de adviesvraagsters, om een dialoog op gang te brengen over de mogelijke betekenis die de DNA-uitslag op het leven van een adviesvraagster kan hebben.

In **hoofdstuk 5** gebruikten we de vier perceptievariabelen uit het voorgaande hoofdstuk om in een retrospectieve studie te voorspellen welke invloed DNA-uitslagen op de lange termijn hebben op het leven van adviesvraagsters. Zoals gezegd gingen sommige voorgaande onderzoekers ervan uit dat een DNA-uitslag een rechtstreekse invloed heeft op allerlei uitkomstmaten, dus zonder rekening te houden met de perceptie. Weer andere onderzoekers gingen ervan uit dat de invloed van de uitslag op deze uitkomstmaten werd 'gemedieerd' door de perceptie van de adviesvraagsters. Dat de uitslag 'medieert' wil zeggen dat de uitslag zorgde voor een bepaalde perceptie die vervolgens weer zorgde voor een bepaalde uitkomst. Als er dus sprake is van mediatie, dan verloopt de invloed van de DNA-uitslag op het leven van de adviesvraagster dus via de perceptie; de perceptie 'verklaart' dan de invloed van de DNA-uitslag. Wij hebben met behulp van statistische mediatie-toetsen onderzocht of er sprake was van mediatie.

In voorgaande studies werden vaak grove, niet-specifieke uitkomstmaten gebruikt, zoals het aantal symptomen van depressiviteit en angst. Verschillende reviews hebben inmiddels getoond dat de meeste adviesvraagsters geen psychopathologische niveaus van bijvoorbeeld depressiviteit en angst ervaren. Op grond hiervan is er wel eens beweerd dat een DNA-uitslag geen verstrekkende impact heeft. Mede op basis van de retrospectieve interviews die wij hebben gehouden menen wij dat deze conclusie

voorbarig is, en dat er veeleer andere uitkomstinstrumenten moeten worden gebruikt die specifiek gaan over genetica en die tegelijkertijd breder zijn omdat ze gaan over de brede impact van DNA-uitslagen op het leven van adviesvraagsters. Daarom hebben we een breed scala aan uitkomstenmaten gebruikt in deze en in de andere deelstudies, namelijk: veranderingen in verschillende terreinen in het leven als gevolg van de DNA-uitslag (zie hfst. 3), kwetsbaarheid, gestigmatiseerd voelen door de DNA-uitslag, en controle over de kanker. Daarnaast onderzochten we ook uitkomsten die al in eerdere studies zijn bestudeerd: medische keuzes zoals medische controle en/of preventieve chirurgische verwijdering van borsten/eierstokken, het huidige psychologische welzijn (angst, depressiviteit, etc.) en de huidige kwaliteit-van-leven.

De mededeling van een PM-uitslag in plaats van een NIU bleek een rechtstreekse voorspeller te zijn van de operatieve verwijdering van borsten en/of eierstokken bij de adviesvraagsters (dus zonder mediatie van de perceptie). Een kleine helft van zowel de adviesvraagsters met een PM hadden hun borsten en/of eierstokken namelijk laten verwijderen, en de meerderheid onderging frequente medische controle; dit was vaker dan bij NIU's. Dit resultaat is begrijpelijk, want het is niet gebruikelijk dat een geneticus expliciet met een adviesvraagster de mogelijkheid bespreekt om een operatie te ondergaan na een NIU, terwijl deze optie wel wordt besproken na een PM.

Ondanks dat de meerderheid van de adviesvraagsters geen psychopathologisch hoge niveaus van stress rapporteerden, noemde de meerderheid gevoelens van kwetsbaarheid en gebrek aan controle over de kanker. De mededeling van een UV-uitslag voorspelde in deze deelstudie – dus vijf jaar na de uitslag – dat de adviesvraagster meer depressieve klachten had dan adviesvraagsters met PM of NIU; adviesvraagsters met een UV-uitslag hadden bovendien even vaak preventieve chirurgie ondergaan als PM-dragers. Alle andere psychologische uitkomsten werden alleen voorspeld en/of volledig gemedieerd door de perceptie van de patiënten.

Samenvattend: we vonden dat de mededeling van een PM er rechtstreeks voor zorgde dat patiënten vaker een chirurgische ingreep ondergingen, terwijl de mededeling van een NIU voorspelde dat ze dat minder vaak ondergingen. Bijna alle andere medische en psychologische uitkomsten werden alleen voorspeld en/of volledig verklaard door de perceptie van de patiënten. Tevens vonden we dat UV-uitslagen gepaard gingen met meer depressiviteit en met vergelijkbaar medisch gedrag zoals bij PM-uitslagen; dit impliceert dat deze adviesvraagsters hun medische keuzes niet op grond van de DNA-uitslag maar op grond van hun eigen inaccurate perceptie maken. Op grond van deze bevindingen adviseerden we om UV's voortaan niet mee te delen aan adviesvraagsters, wanneer daar geen duidelijke medische of wetenschappelijke noodzaak voor is. In plaats daarvan kan er worden meegedeeld – zoals bij een UR – dat er 'nu geen verklaring is gevonden voor de kanker' en 'dat toekomstig onderzoek mogelijk meer kan uitwijzen'.

In **hoofdstuk 6** probeerden we opnieuw om de uitkomsten te voorspellen aan de hand van zowel de daadwerkelijk meegedeelde DNA-uitslag en de perceptie van de adviesvraagsters, maar dan op korte termijn na de mededeling van een DNA-uitslag (dit is dus een 'prospectieve studie'). In dit hoofdstuk namen we meer variabelen in onze analyses op. Als voorspeller gebruikten we alle mogelijke stukken informatie die een geneticus kan meedelen. Als mediator gebruikten we ook de perceptie die adviesvraagsters hebben over het kankerrisico van hun familieleden. Als uitkomsten vroegen we niet alleen naar de medische keuzes die de adviesvraagsters al gemaakt hebben, maar ook naar intenties voor medische controle en/of operatie. Tevens onderzochten we de levenscontext van de adviesvraagsters. Onder dat laatste vallen ondermeer hun medische geschiedenis, sociodemografische variabelen, familierelaties, de invloed van andere ingrijpende levensgebeurtenissen, hoe adviesvraagsters omgaan met de uitslag ('copingstijlen'), de beelden die ze hebben van hun kanker ('ziekte representaties') en hun persoonlijkheid.

Het blijkt dat de meegedeelde genetische informatie op korte termijn geen enkele uitkomst rechtstreeks voorspelt zonder dat de perceptie erbij betrokken is. Alle medische en psychologische uitkomsten werden namelijk alleen voorspeld en/of volledig gemedieerd door de perceptie van de adviesvraagsters, en dan vooral door hun interpretatie van hun eigen risico om kanker te krijgen. De contextuele factoren beïnvloeden weliswaar de perceptie van de adviesvraagsters, maar hadden geen sterke invloed op de uitkomsten.

Samenvattend: op korte termijn bepaalt vooral de eigen perceptie van adviesvraagsters welke medische en psychologische impact een DNA-uitslag heeft op hun leven, en niet de daadwerkelijk meegedeelde genetische informatie. De belangrijke rol die de eigen interpretaties van de adviesvraagsters hadden, bevestigt wat Lee et al schrijven (63): 'Genetische informatie wordt niet simpelweg opgepikt door adviesvraagsters alsof het gaat om een waardevrije, objectieve waarheid. Risico-informatie is diep subjectief van aard; een adviesvraagster verinnerlijkt deze informatie vanuit haar achtergrond en geschiedenis als persoon.' Adviesvraagsters moeten genetische informatie op een flexibele manier integreren in hun levensverhaal (59).

Deel III: de ontwikkeling van een familieleden-georiënteerd, integratief perspectief op genetische counseling

> *De geneticus had een UV-uitslag meegedeeld aan Emma, en vertelde haar dat haar haar familieleden een matig verhoogd risico hebben om kanker te krijgen. Zij herinnerde zich echter dat er een UV-uitslag en een sterk verhoogd risico was meegedeeld. Zij interpreteerde dit als een PM-uitslag die een zeer sterk verhoogd risico*

impliceerde, en zij vertelde deze uitslag op een indirecte, niet-geruststellende en moeilijk te begrijpen manier aan haar familieleden. Haar familieleden herinnerden zich op hun beurt niet dat Emma een PM en een zeer sterk risico had meegedeeld, maar zij herinnerden zich een PM-uitslag en een matig verhoogd risico. Los van wat Emma had verteld, dachten deze familieleden dat ze zelf maar een klein risico hadden om kanker te krijgen. Op grond van deze interpretatie kozen ze ervoor om niet frequent hun borsten en/of eierstokken te laten controleren, en voelden zich niet gestrest.

In **hoofdstuk 7** onderzochten we of de communicatie van genetische informatie in een familie vergeleken kan worden met een fluisterspelletje zoals kinderen dat doen. Een duidelijk voorbeeld hiervan is Emma. Abstract geformuleerd heeft de geneticus 'A' aan haar gecommuniceerd, maar zij herinnerde zich 'B', interpreteerde dit als 'C' en communiceerde dit aan haar familieleden die zich vervolgens 'D' herinnerden en 'E' interpreteerden.

In deze retrospectieve studie vonden we inderdaad dat er sprake lijkt te zijn van een fluisterspelletje. Elke stap in dit model verschilde significant van alle andere stappen, en de verschillende stappen hingen slecht met elkaar samen. De informatie die aan het begin van het fluisterspel was meegedeeld door de geneticus, voorspelde nauwelijks de informatie die op het eind aankwam in de interpretatie van de familieleden. Daarnaast vonden we dat de sterkste samenhang bestond tussen wat de geneticus had meegedeeld en de herinnering van de adviesvraagsters; dit lijkt er op te wijzen dat de meeste miscommunicatie in dit fluisterspelletje niet ontstaat in de communicatie tussen de geneticus en de adviesvraagsters, maar in het interpretatieproces van de adviesvraagster en in de communicatie naar familieleden.

Samenvattend: wij vonden dat informatie slecht wordt doorgegeven in families, mede als gevolg van de eigen interpretaties die de adviesvraagsters en de familieleden hadden ten aanzien van de uitslag. Wij adviseerden dat genetici expliciet met de adviesvraagsters bespreken hoe zij de uitslag aan hun familieleden willen meedelen. Tevens suggereerden we dat genetici duidelijke brieven of folders meegeven aan alle adviesvraagsters met NIU's en UV's (nu wordt het vaak alleen aan PM-families gegeven). Hierin kan er dan heldere genetische informatie worden gegeven voor specifieke familieleden, met de mogelijkheid dat de familieleden een gesprek hebben met de geneticus; deze brieven of folders kunnen dan door de adviesvraagsters overhandigd worden aan de familieleden.

In h**oofdstuk 8** breidden wij het fluisterspel uit met twee stappen, namelijk met het communicatieproces tussen de adviesvraagster en de familieleden, en met de impact die de DNA-uitslag op het leven van de familieleden heeft. We onderzochten namelijk of niet alleen de inhoud maar ook de manier waarop de adviesvraagster genetische informatie

meedeelt (het communicatieproces) van invloed is op de perceptie en de impact bij familieleden. Dit communicatieproces bestond uit drie elementen: de begrijpelijkheid, de directheid en de geruststellendheid waarmee de uitslag is meegedeeld.

We vonden in deze retrospectieve studie dat de herinneringen en interpretaties van de familieleden inderdaad sterk werden voorspeld door het communicatieproces, terwijl die helemaal niet werden voorspeld door de inhoud van de meegedeelde informatie. Dus hoe de familieleden dachten over de NIU/UV-uitslag werd wel bepaald door de manier waarop de adviesvraagster de uitslag had meegedeeld maar niet door de feitelijke inhoud van de uitslag.

De NIU/UV-uitslagen hadden een relatief grote impact op familieleden: zij meldden dat hun leven zowel op psychologisch als op medisch gebied enigszins was veranderd, velen ondergingen frequente medische controle van de borsten/eierstokken en 20% had hun borsten laten verwijderen, maar de meesten voelden zich niet gestrest over hun risico om kanker te krijgen. Al deze uitkomsten werden alleen voorspeld door de eigen herinneringen en interpretaties van de familieleden, en niet door de informatie die het familielid of de geneticus daadwerkelijk hadden meegedeeld.

De perceptie en de uitkomsten van de adviesvraagsters werden niet voorspeld door familiefactoren, zoals de openheid waarin families spraken over kanker. Deze familiefactoren bepaalden wel het communicatieproces. UV-uitslagen werden minder geruststellend en indirecter meegedeeld dan NIU's, en leidden bij familieleden tot radicalere medische keuzes die vergelijkbaar waren met PM-uitslagen.

Samenvattend: de communicatie van NIU/UV-uitslagen had een relatief grote impact op het leven van de ongeteste familieleden (PM-uitslagen konden we niet meenemen in deze studie). Deze impact werd alleen voorspeld door de herinneringen en interpretaties van de familieleden, die op hun beurt voorspeld werden door de manier waarop de adviesvraagster de informatie had meegedeeld.

Deel IV: onderzoeken van de adviesvraagster-georiënteerde betekenis die adviesvraagsters geven aan de DNA-uitslag

In **hoofdstuk 9** onderzochten we waarom de interpretatie van adviesvraagsters afweek van wat de geneticus daadwerkelijk heeft meegedeeld op korte termijn na de DNA-uitslag. We onderzochten hierbij zowel informatie-georiënteerde als adviesvraagster-georiënteerde verklaringen, die gebaseerd waren op suggesties en bevindingen van eerdere studies.

We vonden dat zowel informatie-georiënteerde als adviesvraagster-georiënteerde verklaringen de mate voorspelden waarin de interpretatie van adviesvraagsters afweek van de daadwerkelijk meegedeelde informatie. De informatie-georiënteerde verklaringen

betroffen: de manier waarop de kankerrisico's waren gepresenteerd (in woorden, percentages of beide), een PM-uitslag of een NIU/UV-uitslag, en verschillende cognitieve variabelen zoals de verwachting dat er in de toekomst alsnog een PM wordt meegedeeld, ideeën over de eigen kanker, en specifieke manieren van omgaan met de DNA-uitslag ('copingstijlen'). De adviesvraagster-georiënteerde verklaringen betroffen het leven van de adviesvraagster in de algemeenheid, en hoe zij de DNA-uitslag daarin inbedden, zoals: persoonlijkheidsvariabelen (autonomie, gevoel van controle in het leven, etc.), existentiële vragen (het leven ervaren als zinvol, nadenken over de eindigheid van het bestaan, etc.), en de behoefte aan zekerheid ten aanzien van de DNA-uitslag, de erfelijkheid en de kanker.

Het bleek dat de invloed van de informatie-georiënteerde verklaringen op de interpretatie volledig werd gemedieerd/verklaard door de adviesvraagster-georiënteerde verklaringen. Dit wil zeggen, dat de informatie-georiënteerde processen zorgden voor een inaccurate perceptie omdat zij een persoonlijk, existentieel proces in de adviesvraagster opriepen. Alleen dankzij deze adviesvraagster-georiënteerde verklaringen beïnvloeden de informatie-georiënteerde variabelen de perceptie. Dit bevestigt de eerder geciteerde uitspraak van Lee e.a. (63) dat adviesvraagsters genetische informatie niet louter cognitief in zich opnemen alsof het gaat om een waardevrije, objectieve waarheid. Zij verinnerlijken deze informatie vanuit hun fundamentele behoefte naar zekerheid, en vanuit hun achtergrond en geschiedenis als persoon. (dit proefschrift, en naar: 63)

In **hoofdstuk 10** onderzochten we in welke mate de behoefte aan zekerheid van de adviesvraagsters werd vervuld door de DNA-uitslag. Studies van andere onderzoekers hebben namelijk gesuggereerd dat adviesvraagsters een DNA-test ondergaan om hun behoefte aan zekerheid te vervullen (het gaat hen dus niet louter om het krijgen van 'een accurate perceptie' van de DNA-uitslag, hun kankerrisico's en erfelijkheid).

Wij vonden dat 58% tot 94% van alle adviesvraagsters het gevoel hadden dat hun behoefte aan zekerheid grotendeels niet vervuld werd door de DNA-uitslag. Dit betekent dat hun behoefte aan zekerheid groter was dan de zekerheid die ze ervoeren ten aanzien van de DNA-uitslag, de erfelijkheid en de kanker. Na een PM-uitslag voelden de adviesvraagsters zich zekerder over de PM-uitslag dan voorafgaand aan de uitslag, maar vervolgens ontstonden er nieuwe onzekerheden over de betekenis van de uitslag voor de erfelijkheid en de kanker, zoals onzekerheid over de medische keuzes die zijzelf en/of hun familieleden zouden kunnen ondergaan. Adviesvraagsters aan wie een UV was meegedeeld ervoeren geen verandering na de UV-uitslag in de mate waarin hun behoefte aan zekerheid over de DNA-uitslag, de erfelijkheid en hun kanker werd vervuld. Net als PMs en UVs ervoeren adviesvraagsters aan wie een NIU was meegedeeld ervoeren een onvervulde behoefte aan zekerheid; toch meldden zij vergeleken met de andere uitslagen relatief veel zekerheid over de DNA-uitslag, de erfelijkheid en hun kanker vergeleken met de PM- en de UV-uitslagen en met de periode voorafgaand aan de DNA-uitslag.

De onvervulde behoefte aan zekerheid over de DNA-uitslag, de erfelijkheid en hun kanker correleerde zeer sterk met de mate van stress die de adviesvraagsters ervoeren, met het hebben van een inaccurate perceptie en met passieve copingstijlen zoals ontkenning en vermijding. De onvervulde behoefte aan zekerheid hingen bij minder dan 6% van alle adviesvraagsters samen met acceptatie. Dit lijkt erop te wijzen dat adviesvraagsters hun onvervulde behoefte aan zekerheid niet accepteerden, maar de meegedeelde genetische informatie in hun interpretatie verdraaiden en ontkenden (waarschijnlijk om een 'schijn-zekerheid' te creëren). Als gevolg van hun onvervulde behoefte ervoeren zij mogelijk grote stress.

Samenvattend: de meerderheid van de adviesvraagsters had het gevoel dat de DNA-uitslag hun behoefte aan zekerheid over de DNA-uitslag, de erfelijkheid en hun kanker niet vervulde. De meesten accepteerden de onvervulde behoefte aan zekerheid niet, maar gingen de informatie herinterpreteren of ervoeren stress.

Deel V: Conclusies en implicaties

In **hoofdstuk 11**, de samenvatting en discussie, vatten we de voorgaande hoofdstukken samen en plaatsten we de resultaten in het bredere perspectief van eerdere onderzoeken en de klinische praktijk. De rode draad werd samengevat met vijf punten. Ten eerste beschreven wij onze bevinding dat een DNA-uitslag een verstrekkende impact heeft op het leven van veel adviesvraagsters, omdat zij zich kwetsbaar en onzeker voelden, ook al was er geen sprake van duidelijke psychopathologie bij de meeste adviesvraagsters. Ten tweede vonden we dat adviesvraagsters een DNA-uitslag anders interpreteren dan wat de geneticus daadwerkelijk had meegedeeld. Ten derde toonden we aan dat de informatie die een geneticus meedeelt geen rechtstreeekse impact heeft op het leven van adviesvraagster, maar deze invloed loopt altijd via de subjectieve perceptie van de adviesvraagster. Ten vierde zagen we dat familieleden zich betrokken voelden bij de genetische-counseling van hun geteste familielid/adviesvraagster, en de DNA-uitslag beïnvloedde de perceptie en de impact op het leven van de familieleden, zoals een fluisterspelletje bij kinderen. Ten vijfde lieten we zien dat er een grote variatie bestond in de informatie die verschillende genetici aan verschillende adviesvraagsters hadden gecommuniceerd, en er bestond ook een grote variaties tussen de adviesvraagsters onderling. Daarom hebben wij in onze deelstudies nieuwe modellen ontwikkeld die complexer waren in vergelijking tot voorgaande studies.

In **hoofdstuk 12**, het addendum, beschreven we verschillende theoretische en klinische implicaties van onze studies. We bespraken dit in een apart hoofdstuk, omdat deze implicaties niet alleen gebaseerd zijn op de gepresenteerde onderzoeksresultaten maar ook op andere studies. Dit hoofdstuk was bedoeld als een antwoord op het verzoek van

verschillende genetici en psychologen om hen handvaten te bieden voor zowel nieuwe theorievorming als voor de praktijk, op grond van onze studies.

Ten eerste beantwoordden we meerdere theoretische vragen die zich impliciet in onze onderzoeksresultaten bevonden.

We beschreven verschillende hypotheses om het verschil tussen de informatie-georiënteerde en de adviesvraagster-georiënteerde benaderingen te beschrijven. Voor iedere hypotheses waren valide argumenten of empirische aanwijzingen aan te voeren geen daarvan waren doorslaggevend en daarom trokken we geen conclusies.

We beschreven mogelijke redenen waarom veel adviesvraagsters een grote behoefte hebben aan zekerheid, en onzekerheid als beangstigend kunnen ervaren. We lieten zien dat een DNA-uitslag meer dan andere gezondheidsrisico's lijkt te gaan over fundamentele, existentiële thema's in het leven van adviesvraagsters. Een DNA-uitslag kan fundamentele vooronderstellingen die mensen impliciet hebben over het leven bedreigen of ondermijnen, zoals 'goede dingen overkomen goede mensen' en 'ik ben onkwetsbaar'.

We lieten, ondermeer op grond van psychotherapeutische studies bij kankerpatiënten zien hoe adviesvraagsters kunnen omgaan met een onvervulde behoefte aan zekerheid, namelijk door een duale houding te hebben. Enerzijds accepteert een adviesvraagster dan dat zij een grote behoefte heeft aan zekerheid. Anderzijds accepteert ze dat ze op dit moment die zekerheid niet heeft. Ze kan leren wisselen ('switchen') tussen het leggen van de aandacht op de behoefte aan zekerheid of op het gebrek aan zekerheid. We adviseerden om hier verder wetenschappelijk onderzoek naar te doen, vooral om erachter te komen welke adviesvraagsters in staat zijn om een dergelijke duale houding te ontwikkelen en wie niet. Dit kan grote implicaties en handvaten voor de praktijk opleveren: een arts kan dan genuanceerd en non-directief communiceren en een duale houding stimuleren bij iemand die dat aankan, terwijl een arts op een eenzijdigere, directievere manier kan communiceren bij iemand voor wie het lastig of onmogelijk is om een duale houding te ontwikkelen.

Ten tweede onderzochten we de ethische implicaties van onze onderzoeksresultaten. We beschreven het verschil tussen een geneticus-georiënteerde, een informatie-georiënteerde en een adviesvraagster-georiënteerde ethiek. Een counselor-georiënteerde ethiek wordt tegenwoordig weinig toegepast in de praktijk, en impliceert dat de geneticus een paternalistische, alles-bepalende houding heeft ten opzichte van de adviesvraagster. Een informatie-georiënteerde ethiek gaat uit van een 'consumptiemodel van autonomie', waarbij de geneticus een adviesvraagster voorziet van informatie waarmee ze autonome beslissingen kan nemen. In deze benadering legt de geneticus dus het zwaartepunt bij het meedelen van informatie aan de adviesvraagster; de geneticus is niet directief om te

vermijden dat de adviesvraagster in haar autonomie wordt beknot. Het wordt gesuggereerd dat deze ethiek soms moeilijk uitvoerbaar is in de praktijk.

Een adviesvraagster-georiënteerde ethiek volgt de behoeftes van de adviesvraagster, en vooronderstelt dat de geneticus zorg draagt voor de totaliteit van de adviesvraagster en niet alleen voor het meedelen van de informatie. Dit betekent dat een geneticus ook op een directieve wijze kan communiceren indien dat nodig is voor de adviesvraagster, en dat het meedelen van genetische informatie niet perse de beste manier hoeft te zijn voor een adviesvraagster om bijvoorbeeld haar behoefte aan zekerheid te vervullen. Deze ethiek impliceert voor de praktijk dat de geneticus expliciet aandacht besteedt aan de behoeftes van de adviesvraagster. Er komt dan een dialoog tot stand tussen de geneticus en de adviesvraagster waarbinnen zij samen bepalen wat de doelstelling van de erfelijkheidsadvisering is, hoe de relatie tussen hen beiden vorm kan krijgen, en welke betekenis de DNA-uitslag voor de adviesvraagster kan hebben.

De adviesvraagster-georiënteerde ethiek impliceerde bovendien een op maat gesneden ('tailored') communicatie van de DNA-uitslag. De geneticus onderzoekt dan eerst wat de behoeftes en mogelijkheden van de adviesvraagster zijn en hoe zij de kanker en de mogelijke erfelijkheid interpreteert; op grond hiervan past de geneticus de inhoud en de manier van communiceren aan aan de adviesvraagster. Eén van de mogelijke implicaties van een adviesvraagster-georiënteerde ethiek is dat DNA-uitslagen, zoals UVs, niet worden meegedeeld omdat die de behoefte van adviesvraagsters slecht bevredigen, geen medische implicaties hebben, en toch een grote medische en psychologische impact hebben voor veel adviesvraagsters.

In de praktijk zullen genetici echter een balans moeten zien te vinden tussen de medische en financiële mogelijkheden enerzijds, en een ethische oriëntatie op de adviesvraagster anderzijds. Bijvoorbeeld de ene adviesvraagster heeft behoefte en mogelijkheden om een dialogische relatie met de geneticus aan te gaan en te reflecteren op zichzelf zodat de geneticus in het gesprek ook diep kan ingaan op de persoonlijke betekenis van de DNA-uitslag voor de adviesvraagster. Een andere adviesvraagster heeft die behoeftes en mogelijkheden misschien niet, waardoor de geneticus bij die persoon een meer directieve houding kan aannemen.

Ten derde beschreven we meerdere beperkingen bij onze studies, en gaven we aanbevelingen voor verder wetenschappelijk onderzoek.

Ten vierde bespraken we dat genetici in de praktijk vaak al aan adviesvraagster-georiënteerde en informatie-georiënteerde ethische normen lijken te voldoen, zoals dat de erfelijkheidsadvisering lijkt aan te sluiten op de behoeftes aan veel adviesvraagsters gezien hun positieve evaluaties. We gaven meerdere praktische handvaten aan genetici met als doel om hen te helpen zich in de praktijk nog meer te oriënteren op de

adviesvraagsters, zoals expliciet met adviesvraagsters een dialoog aangaan over hun perceptie, zowel voorafgaand aan als na de mededeling van een DNA-uitslag. In tabellen 1 en 2 beschrijven wij meerdere aanbevelingen en suggereren wij verschillende vragen die gebruikt kunnen worden om een dialoog met een adviesvraagster te starten. Deze suggesties zijn los gebaseerd op onze studies en op voorgaande onderzoeken, maar de effectiviteit daarvan moet nog in toekomstig empirisch onderzoek worden bewezen.

Ten vijfde beschreven we vanuit een adviesvraagster-georiënteerde ethiek dat adviesvraagsters niet alleen behoefte hebben aan psychologische begeleiding wanneer er sprake is van psychopathologie of wanneer zij voor moeilijke keuzes staan. Het zijn veeleer adviesvraagsters die moeite hebben met het inbedden van de DNA-uitslag in hun leven die behoefte hebben aan psychologische zorg, bijvoorbeeld wanneer hun perceptie erg afwijkt van wat de geneticus heeft meegedeeld, en wanneer ze zich kwetsbaar en onzeker voelen. Zoals dat al meestal gebeurt, bevelen we het adviesvraagsters-georiënteerde uitgangspunt aan dat psychologen en maatschappelijk werkers aansluiten bij de behoeftes en de perceptie van de adviesvraagsters. In dialoog met de adviesvraagster en in aansluiting op diens capaciteiten kunnen ze mogelijkheden onderzoeken hoe de adviesvraagsters een eventuele duale houding kunnen ontwikkelen ten aanzien van de DNA-uitslag. Tevens adviseren we dat de verwijzing naar psychologen wordt verbeterd, omdat 16% van de adviesvraagsters heeft gezegd dat ze behoefte hebben aan extra psychologische begeleiding terwijl maar 4% die daadwerkelijk heeft gekregen.

Belangrijkste conclusies

1. Het meedelen van BRCA1/2-uitslagen kan worden vergeleken met een fluisterspelletje. De geneticus deelt 'A' mee, de adviesvraagster herinnert zich 'B', interpreteert 'C', ervaart stress en maakt medische keuzes op grond van 'C'. Vervolgens communiceert ze deze informatie aan haar familieleden, die zich herinneren dat er 'D' is gecommuniceerd, maar die 'E' interpreteren en die op grond daarvan stress ervaren en medische keuzes maken.
2. Het meedelen van BRCA1/2-uitslagen heeft een verstrekkende impact op het leven van de adviesvraagsters, zoals medische, psychologische en existentiële veranderingen.
3. De perceptie die adviesvraagsters hebben van een BRCA1/2-uitslag wijkt significant af van wat er daadwerkelijk is meegedeeld door de geneticus. Deze perceptie bestaat uit verschillende elementen zoals de herinneringen en interpretaties die adviesvraagsters hebben van hun kankerrisico en erfelijkheid.
4. De verstrekkende impact van erfelijkheidsadvisering op het leven van adviesvraagsters wordt niet rechtstreeks voorspeld door de communicatie van

BRCA1/2-uitslagen , maar deze wordt wel voorspeld en gemedieerd door de perceptie van de adviesvraagsters .

5. Familieleden voelen zich erg betrokken bij erfelijkheidsadvisering, en ervaren een aanzienlijke impact van de DNA-uitslag op hun leven. Deze impact wordt voorspeld door hun eigen interpretatie, die afwijkt van wat er daadwerkelijk aan hen is meegedeeld.
6. De onvervulde behoefte aan zekerheid kan beangstigend zijn voor adviesvraagsters, mogelijk omdat DNA-uitslagen gaan over persoonlijke en fundamentele thema's in hun leven.
7. De onvervulde behoefte aan zekerheid lijkt bij bijna geen enkele adviesvraagsters samen te gaan met acceptatie; dit lijkt te leiden tot ontkenning en stress.
8. We bevelen aan dat genetici een adviesvraagster-georiënteerde ethiek volgen (zoals dat nu al vaak gebeurt), die zich richt op de behoeftes van de adviesvraagster en die zorg draagt voor de totaliteit van de adviesvraagster en niet alleen bij het meedelen van informatie; dit houdt in dat er een gelijkwaardige dialoog tussen de geneticus en de adviesvraagster tot stand wordt gebracht.
9. De communicatie van UV's lijkt niet in lijn te zijn met een adviesvraagster-georiënteerde ethiek, omdat een UV-uitslag de behoeftes van de adviesvraagsters niet vervult en een grote psychologische impact lijkt te hebben, terwijl het geen belangrijke medische consequenties heeft.
10. Genetici lijken de meest betrouwbare factor te zijn in het fluisterspel dat erfelijkheidsadvisering vaak is. De grootste verwarring in het fluisterspel lijkt te worden veroorzaakt doordat de adviesvraagster en haar familieleden de informatie op hun eigen manier interpreteren.
11. We adviseren om de discussie aan te gaan over een aantal thema's ten aanzien van het nationale en internationale beleid, zoals de DNA-terminologie, de ethische fundering van erfelijkheidsadvisering, en de lange termijn contacten van de geneticus met de adviesvraagsters ('follow-up' of 'duty to recontact').
12. Genetici worden geadviseerd om alle adviesvraagsters te voorzien van brieven voor hun familieleden waarin de DNA-uitslag wordt uitgelegd.
13. De meeste adviesvraagsters ontwikkelen geen psychopathologie na een DNA-uitslag, maar de meerderheid voelt zich wel kwetsbaar, en een zesde van alle adviesvraagsters zou graag psychologische hulp ontvangen, vooral degenen die overwegen om een operatie te ondergaan, een inaccurate perceptie hebben, existentiële vragen stellen en zich onzeker voelen.
14. Psychologen en maatschappelijk werkers kunnen adviesvraagsters helpen om een duale houding te ontwikkelen, bijvoorbeeld door hen te helpen erkennen dat ze behoefte hebben aan zekerheid, terwijl die zekerheid er op dat moment niet daadwerkelijk is.

Tabel 1. *Aanbevelingen voor de praktijk van genetici*

Algemene adviesvraagster-georiënteerde houding

- Volg de behoeftes van de adviesvraagster
- Onderzoek alternatieven voor het ondergaan van een DNA-test
- Pas de mate van (non-)directiviteit aan op de behoeftes van de adviesvraagster
- Pas de communicatie aan de adviesvraagster aan
- Verken de context, behoeftes en perceptie van de adviesvraagster
- Verken de betekenis en gevolgen van de DNA-uitslag
- Een open, toegankelijke sfeer
- Een gelijkwaardige geneticus-adviesvraagster relatie
- Een wederzijdse dialoog
- Empathische confrontaties
- Balanceer tussen de behoeftes van de adviesvraagster en de medische mogelijkheden
- Vraag om toestemming om de adviesvraagster te wijzen op onjuistheden in haar perceptie
- Bespreek de mogelijkheid om opnieuw contact op te nemen

Voorbereiding van de adviesvraagsters op de onzekerheid voorafgaand aan het eerste gesprek
De voorbereiding kan een uitleg bevatten van de genetische en psychologische aspecten van erfelijkheidsadvisering, inclusief de mogelijkheid dat er onzekere DNA-uitslagen worden gevonden en hun mogelijke psychische consequenties.

- Voorbereiding via folder, brief, groepsbijeenkomst, internet
- Noem de mogelijkheid dat een UV kan worden gevonden (indien het beleid is om UV's te communiceren)

Intake sessie

- Voorbereiding door middel van uitleg: algemene procedure, geneticus-adviesvraagster relatie, onzekere uitkomsten
- Algemene verkenning van de persoonlijke en existentiële context van de adviesvraagster
  Bijv. motivatie om (nu) een DNA-onderzoek te ondergaan, omgaan met kanker
- Aan het begin van de sessie: verken de perceptie van kankerrisico en erfelijkheid
- Pas de communicatie van de genetische informatie aan op de context en perceptie van de adviesvraagster
- Op het eind van de sessie: verken de perceptie van de adviesvraagster
- Verken de mogelijke gevolgen: verken of het ondergaan van een DNA-test wel het beste past bij de context en behoeftes van de adviesvraagster (bespreek alternatieven); bespreek hoe familieleden erbij betrokken kunnen worden en/of hoe de uitslag relevant voor hen kan zijn; mogelijke medische gevolgen; huidig of verwacht toekomstig psychisch welbevinden

DNA-uitslag sessie

- Pas de genetische informatie aan op de context en perceptie van de adviesvraagster
- Als de adviesvraagster emotioneel is, verken deze emoties aan de hand van vragen.
- Op het eind van de sessie: verken de perceptie van de adviesvraagster
- Verken de mogelijke gevolgen: bespreek hoe familieleden erbij betrokken kunnen worden en/of hoe de uitslag relevant voor hen kan zijn; mogelijke medische gevolgen; huidig of verwacht toekomstig psychisch welbevinden

Follow-up sessie

- Verken de perceptie van de adviesvraagster
- Verken de mogelijke medische en psychologische gevolgen van de uitslag
- Verken de betrokkenheid/gevolgen/communicatie naar familieleden
- Aanvullende uitleg, aangepast aan de context en perceptie van de adviesvraagster
- Psychologische individuele of groepsbijeenkomsten

Tabel 2. *Voorbeelden van adviesvraagster-georiënteerde vragen, afgeleid van de interviews en de vragenlijsten in onze studies; deze vragen kunnen gebruikt worden om een dialoog te starten en af te stemmen op de adviesvraagster*

De motivatie van de adviesvraagster

- Hoe bent u er toe gekomen om op dit moment in uw leven te vragen om erfelijkheidsadvisering?
- Wat hoopt u dat deze erfelijkheidsadvisering u zal opleveren?
- Wie hebben invloed gehad op uw verzoek om erfelijkheidsadvisering en hoe? (partner, kinderen, familieleden; mate van dwang)
- Wanneer bent u zich bewust geworden dat kanker misschien erfelijk is in uw familie? (hoe, door wie)
- Gegeven het feit dat meerdere familieleden kanker hebben gehad, hoe denkt u over uw eigen kans om kanker te krijgen?
- Voor wie vraagt u om dit erfelijkheidsadvies? (voor uzelf, voor anderen)
- Welke informatie denkt u dat voor mij belangrijk is om te weten over u en uw leven?

De verwachtingen en wensen van de adviesvraagster

- Wat zijn uw verwachtingen van mij/erfelijkheidsadvisering? (relatie geneticus-adviesvraagster, en informatie)
- Hoe denkt u dat deze genetische informatie u en/of uw familieleden zou kunnen helpen om beter om te gaan met de kanker of de kans om kanker te krijgen?

De perceptie van de adviesvraagster

- Herinnering: Hoe zou u aan uw partner, familieleden of vrienden vertellen wat ik u heb verteld over de genetische informatie/DNA-uitslag/stamboom?
- Interpretatie: Los van wat ik u heb verteld, hoe denkt en voelt uzelf over uw kans om kanker te krijgen/over de kans van uw familieleden om kanker te krijgen/over de erfelijkheid van kanker in de familie?
- Interpretatie: Hoe is het voor u om deze (on)verwachte informatie/uitslag/stamboom te horen?

Gevolgen van de DNA-uitslag (volgend op een eerste verkenning van de emotionele reactie van de adviesvraagster)

- Hoe denkt u dat deze informatie u zou kunnen helpen?
- Wat bent u van plan om met deze informatie/uitslag/stamboom te gaan doen? (bijv. medische keuzes, vertellen aan familieleden)
- Hoe (on)zeker voelt u zich nu over de erfelijkheid van kanker in uw familie/uw kans om kanker te ontwikkelen/de kans van familieleden om kanker te ontwikkelen? (bijv. feitelijk begrip, preventieve medische opties, verwachtingen voor de toekomst, aan anderen vertellen)
- Hoe gaat u om met de onzekerheid van deze informatie/uitslag/stamboom?

Familiaire context

- Welke familieleden heeft u verteld dat u erfelijkheidsadvisering zou krijgen? Hoe reageerden zij? (bij de intake/bij de uitslag)
- Welke familieleden wilt u over deze uitslag gaan vertellen? Wat (inhoud) en hoe (process) gaat u dit aan hen vertellen?

Op het eind van een sessie

- Hoe voelt u zich over dit gesprek?
- Wat is het belangrijkste dat u van deze gesprekken meeneemt naar huis?
- Wat heeft u nodig om zo goed mogelijk met deze uitslag om te kunnen gaan?

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Curriculum vitae

Joël Vos was born on the 2nd of April 1980 in Rotterdam. Already as a young child, he was interested in the different ways how people live their lives and how they cope with stressful life events. He especially liked reflecting on it, and writing about it; the story goes that even before he was formally able to write, he 'wrote' his first book, be it with his own invented letters. After having finished the secondary school 'De Lage Waard' in Papendrecht in 1998 (VWO), he discovered that his interests were optimally realized by studying psychology and philosophy.

From 1998 onwards, Joël followed all courses of 'Clinical and Health Psychology', 'Philosophy of Social Sciences' and 'Cognitive-Neuro Psychology (previously: Theoretical Psychology)' at the Leiden University. In 2004, he graduated cum laude in his psychology master, and in 2005 cum laude in his philosophy master. His interests were reflected in his selection of courses on existentialism, which focused on the way how people design and live their lives. Both his master theses were about the existential impact of immigration on the lives of immigrants, because he felt that most previous scientific studies focused too much on external aspects of immigration; i.e. the psychological black-box of immigrants had still to be opened. His philosophy thesis was rewarded with the Leo Polak Prize 2006 for the best thesis in the Netherlands about the humanization of society. Joël writes frequently about societal themes, and several of his essays were published in national newspapers. His essays have been awarded, for instance by the Serge Heederik Award for the best philosophy essay, which was about the psychological impact of 9-11 on society.

Joël continued realizing his interests by performing the studies described in this thesis at the department of Clinical Genetics in the Leiden University Medical Center (2005-2010). The Dutch Cancer Society financially enabled him and his team of fellow-researchers to do this research. In this period, he was also a part-time teacher at the Centre for Child and Family Studies of the Leiden University, followed several courses in statistics, and was (co)researcher in scientific studies, e.g. on religion/meaning-making in students and on the effects of contextual psychotherapy.

He is not only interested in theoretically studying how people live their lives, but he also wants to actually counsel people. For that reason, he has been trained in existential, contextual, cognitive-behavioral and group psychotherapy. In the past, he treated patients at the Psychomedical Center Parnassia in The Hague, performed psychological assessments with clients at the NOA Foundation Amsterdam, wrote personality reports and gave existential counseling for his clients in his private psychology practice. For instance, he has developed a meaning-centered group psychotherapy for students 'to learn how to make decisions, to live life more fully'. His international interests were reflected in his involvement in several developmental projects abroad; among other things he worked with Birmese political refugees in Thailand, and initiated/coordinated a school project in Ghana. He is board member of COME, Communications in the Middle East, which organizes dialogue seminars between young Israelian and Palestinian people.

One of the findings of his studies, described in this thesis, is that existential processes may play an important role in the lives of cancer patients. In addition, other studies have indicated that many cancer patients would like to receive professional help to find ways to live their lives meaningfully, despite their physical limitations and uncertainties of having cancer. However, there are few effective psychotherapies that explicitly help cancer patients with their existential questions. For that reason, Joël is now coordinating a study on the development, implementation and testing of meaning-centered group psychotherapy for cancer-patients, based on the works of Frankl and Breitbart. He has received a grant from the Dutch Cancer Society / Alpe d'Huzes for doing this research together with fellow-researchers at the Vrije Universiteit Amsterdam. Joël also supervises other studies on existential psychotherapy, also in cooperation with universities abroad.

Scientific publications & recent submissions

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