Opening the psychological black box in genetic counseling

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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)

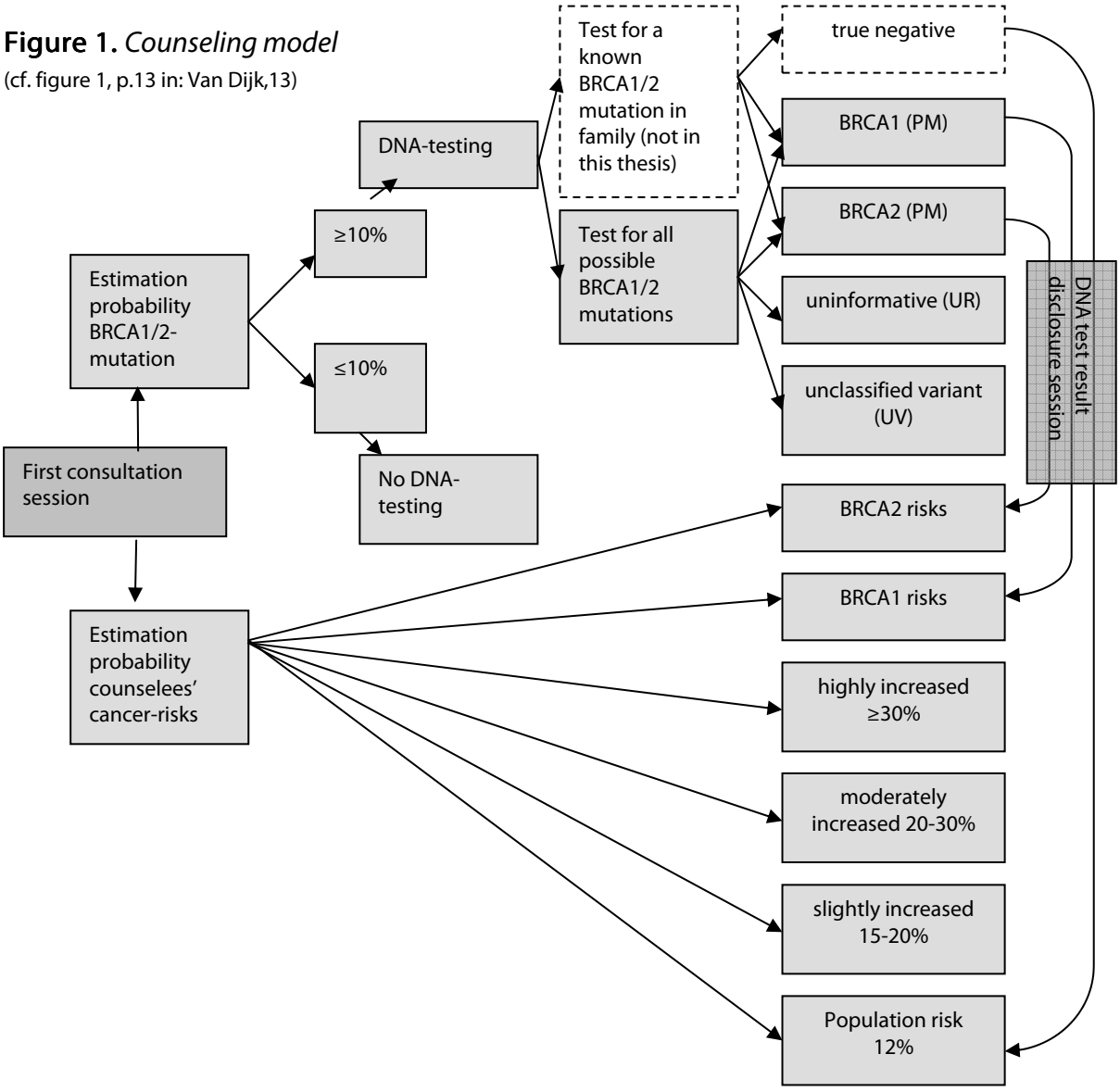
Individuals from families with many cases of breast and/or ovarian cancer may be referred to a department of Clinical Genetics or Familial Cancer Clinic in the Netherlands. The genetic-counselor or clinical-geneticist (in the following: 'genetic-counselor') follows a standard counseling protocol (9,10),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

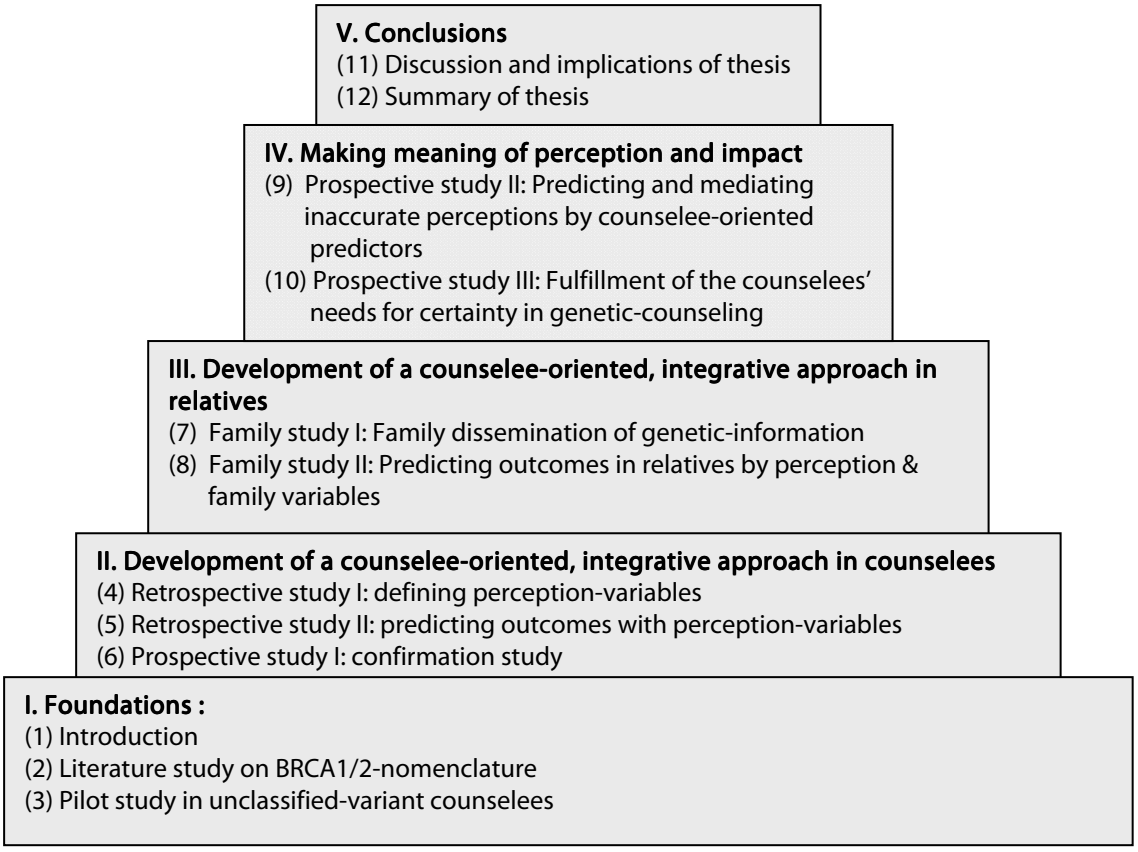
In the third part, we performed a study on the family communication of DNA-test results and its impact on the counselees' untested relatives. We used the counselee-oriented, integrative perspective that we had developed in part two of this thesis in this study. More specifically, the application of this 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’