Opening the psychological black box in genetic counseling

Vos, J.

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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Patient Education & Counseling 2011: in press

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).

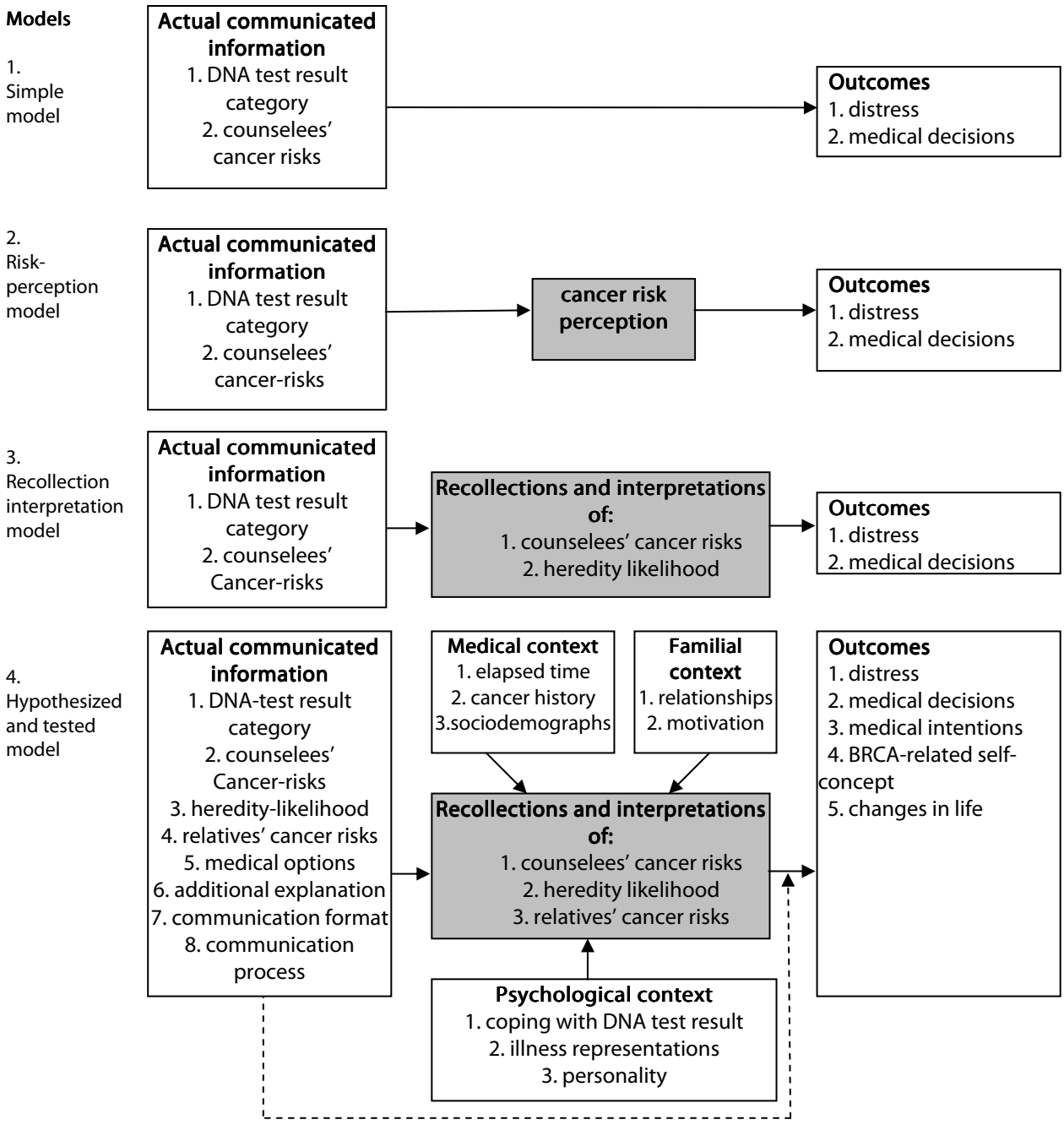
The majority of follow-up studies have addressed the impact of genetic counseling and test results, whereas only a few have explained how genetic counseling leads to the observed changes. Explanatory studies are important to help understand why genetic counseling sometimes has a negative impact on counselees (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).

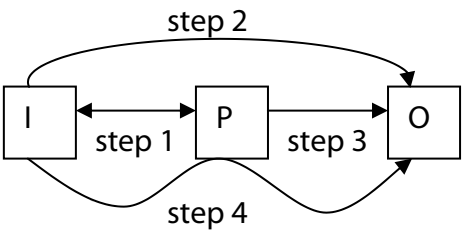
2.3. Statistics

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).