Opening the psychological black box in genetic counseling

Vos, J.

Chapter 5

Opening the psychological black box in genetic-counseling:

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

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Abstract

Background

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

Methods

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

Results

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

Discussion

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

1. Introduction

1.1. Background

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

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

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

1.2. The current study

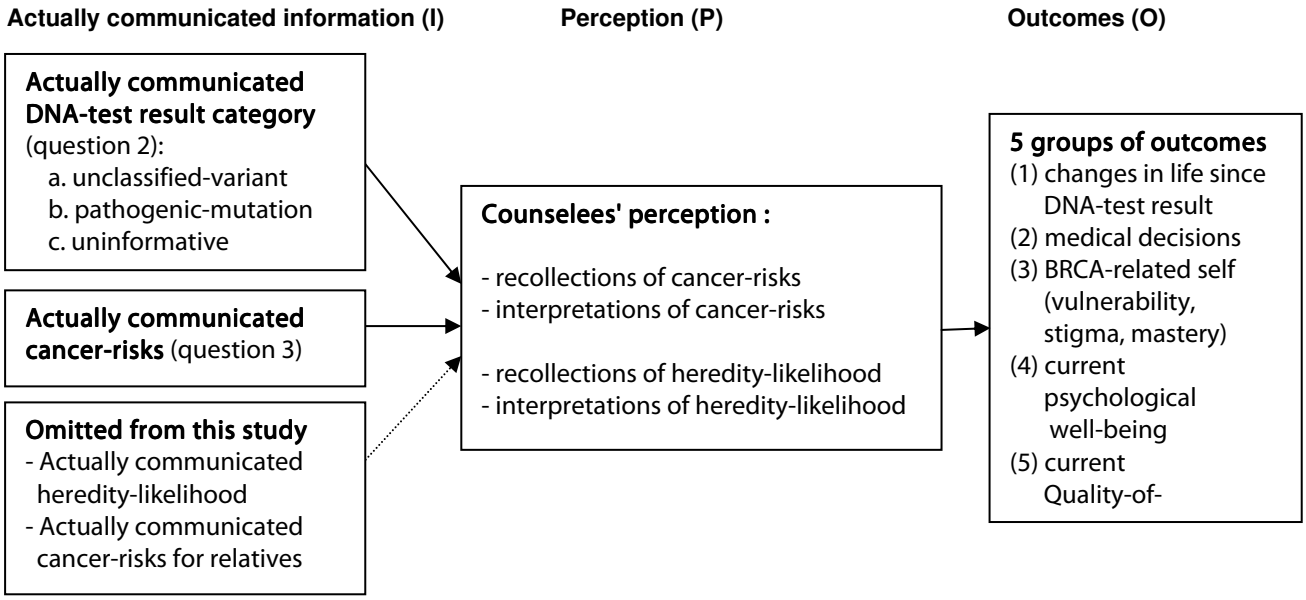
Our previous studies in chapters 3 and 4 only covered the counselees' perception. In current study, we tested all three parts of the model, by means of three research questions. *The first question* was: do counselees recall and interpret cancer-risks and heredity-likelihood differently from what the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

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

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

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

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



2. Method

2.1. Participants and procedure

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

2.2. Instruments

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

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

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

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

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

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

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

Table 1. *Overview of instruments and items*

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

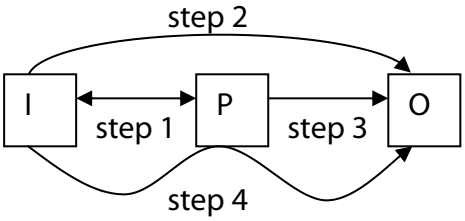
2.3. Statistical analyses

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

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

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

Figure 2. *Figure showing mediation steps*



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

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

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

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

3. Results

3.1. Participants

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

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

Table 3. *Description of outcomes*

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

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

3.2. Question 1

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

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

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

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

3.3. Question 2

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

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

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

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

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

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

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

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

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

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

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

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

3.4. Question 3

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

3.4.1. Unclassified-variants

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

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

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

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

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

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

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

See footnote in table 5.

3.4.2. Pathogenic-mutations

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

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

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

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

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

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

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

See footnote in table 5.

3.4.3. Uninformative DNA-test results

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

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

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

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

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

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

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

See footnote in table 5.

4. Discussion

4.1. Conclusions

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

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

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

4.2. Direct prediction

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

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

4.3. Perception

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

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

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

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

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

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

4.4. Inaccuracy of perception

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

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

4.5. Possible explanations

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

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

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

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

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

4.6. Unclassified-variants

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

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

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

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

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

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

4.7. Methodological issues

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

4.8. Implications

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

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

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

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

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