Opening the psychological black box in genetic counseling

Vos, J.

Chapter 8

Family communication matters:

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

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Abstract

Background

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

Methods

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

Results

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

Discussion

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

1. Introduction

1.1. Background

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

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

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

1.2. General family communication timeline

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

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

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

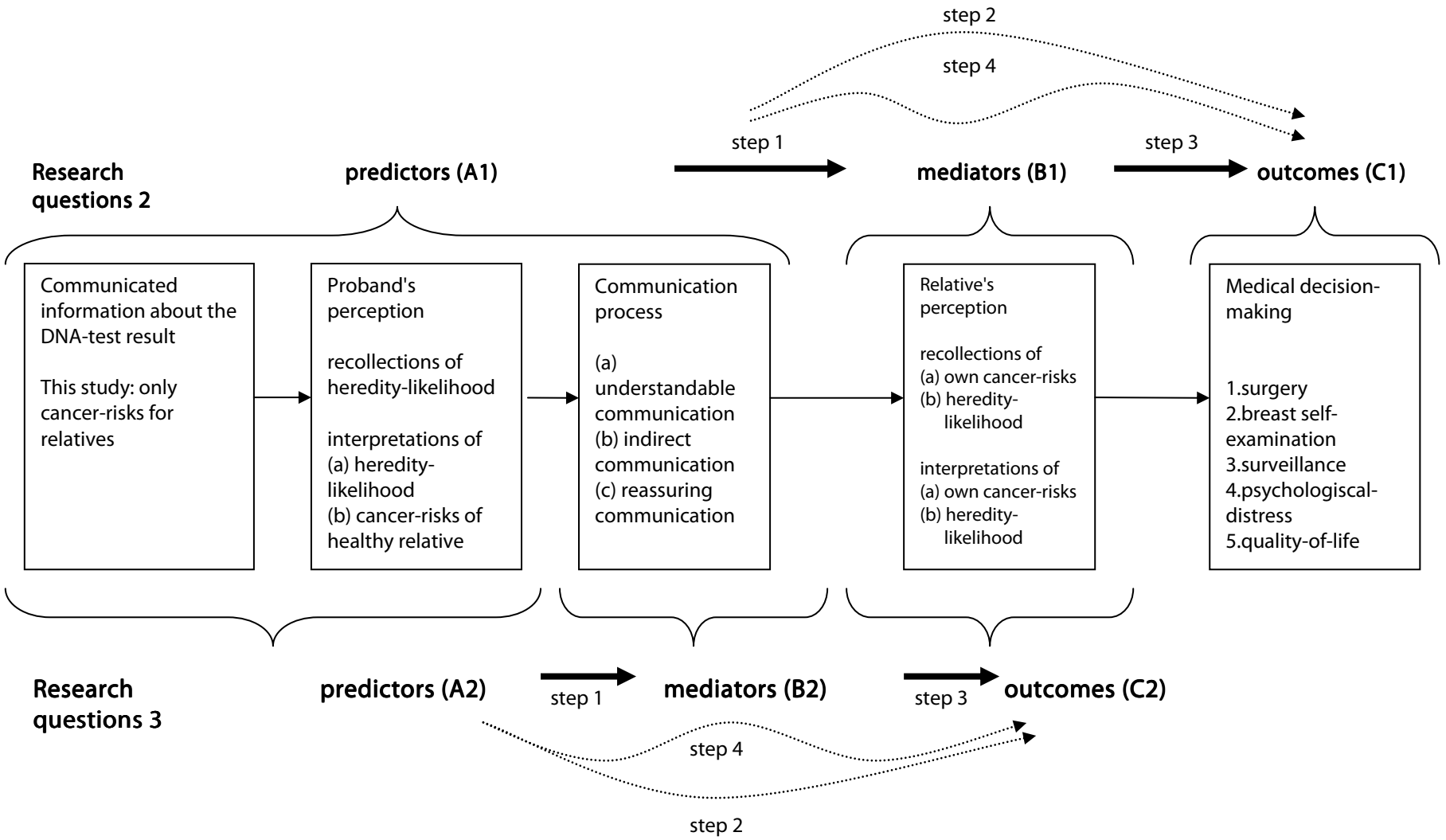
Second, the proband perceives the communicated information. We operationalize 'perception' as a person's recollections and interpretations of DNA-test result category, cancer-risks and heredity-likelihood (277,285). This perception has shown to be inaccurate in many probands, and significant differences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

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

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

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

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



1.3. Research questions

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

2. Method

2.1. Procedure

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

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

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

2.2. Instruments and analyses

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

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

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

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

Table 1. *Overview of instruments*

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

Table 1. *Continued*

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

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

3. Results

3.1. Population

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

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

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

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

3.2. Preparatory analyses

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

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

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

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

3.3. Question 1: outcomes

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

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

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

See table 1 for description of the scales

3.4. Question 2: prediction of medical decisions

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

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

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

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

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

Table 5. *Results for research question 2*

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

3.5. Question 3: prediction of relatives' perceptions

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

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

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

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

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

Table 6. *Results for research question 3*

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

See footnote table 5 for explanation

3.7. Question 4: family characteristics

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

Table 7. *Results for research question 4*

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

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

4. Discussion

4.1. Conclusion

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

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

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

4.2. Communication matters

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

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

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

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

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

4.3. Limitations

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

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

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

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

4.4. Implications

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

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

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