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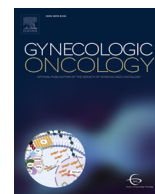
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Evaluation of a patient decision aid for *BRCA1/2* pathogenic variant carriers choosing an ovarian cancer prevention strategy

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HIGHLIGHTS

- Novel salpingectomy was chosen more often than salpingo-oophorectomy and more often in women with than without decision aid.
- The decision aid for *BRCA1/2* pathogenic variant carriers choosing an ovarian cancer preventive strategy was found feasible.
- The decision aid is highly appreciated among both *BRCA1/2* pathogenic variant carriers and their healthcare professionals.
- Knowledge on cancer risk, decisional conflict and regret and cancer worry were equal in women with or without decision aid.
- The decision aid was reported to increase knowledge about the preventive options and increase insight in personal values.

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ABSTRACT

Objective. Risk-reducing surgery is advised to *BRCA1/2* pathogenic variant (PV) carriers around the age of 40 years to reduce ovarian cancer risk. In the TUBA-study, a multicenter preference study (NCT02321228), *BRCA1/2*-PV carriers are offered a choice: the standard strategy of risk-reducing salpingo-oophorectomy or the novel strategy of risk-reducing salpingectomy with delayed oophorectomy. We evaluated feasibility and effectiveness of a patient decision aid for this choice.

Methods. Premenopausal *BRCA1/2*-PV carriers were counselled for risk-reducing surgical options in the TUBA-study; the first cohort was counselled without and the second cohort with decision aid. Evaluation was performed using digital questionnaires for participating women and their healthcare professionals. Outcome measures included actual choice, feasibility (usage and experiences) and effectiveness (knowledge, cancer worry, decisional conflict, decisional regret and self-estimated influence on decision).

Results. 283 women were counselled without and 282 women with decision aid. The novel strategy was

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chosen less frequently in women without compared with women with decision aid (67% vs 78%, $p = 0.004$). The decision aid was graded with an 8 out of 10 by both women and professionals, and 78% of the women would recommend this decision aid to others. Users of the decision aid reported increased knowledge about the options and increased insight in personal values. Knowledge on cancer risk, decisional conflict, decisional regret and cancer worry were similar in both cohorts.

Conclusions. The use of the patient decision aid for risk-reducing surgery is feasible, effective and highly appreciated among *BRCA1/2*-PV carriers facing the decision between salpingo-oophorectomy or salpingectomy with delayed oophorectomy.

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1. Introduction

Currently, ovarian cancer is the most lethal type of gynecological cancer, with a five-year-survival rate of only around 40% [1]. Unfortunately, screening is not effective [2,3]. In the general population, the lifetime risk of ovarian cancer is 1.3%, while women carrying a *BRCA1* or *BRCA2* pathogenic variant (PV) have a risk of developing ovarian cancer of around 44% and 17%, respectively, by the age of 80 years [4]. Therefore, women with a *BRCA1/2*-PV are advised to undergo risk reducing salpingo-oophorectomy (RRSO) at the age of 35–40 or 40–45 years, respectively [5]. RRSO is proven to be highly effective in reducing ovarian-cancer-risk by approximately 96% [6]. Although effective, RRSO induces premature and direct menopause, leading to physical complaints and sexual dysfunction in the short-term and a potential increased risk of cardiovascular disease, osteoporosis, cognitive impairment and mortality in the long-term, especially if hormone replacement therapy cannot be used [7]. Alternatives for the current risk-reducing strategy that delays premature menopause are urgently needed, but these evoke complex decision-making.

Epithelial ovarian cancer includes malignancies of the fallopian tubes, ovaries and peritoneum. The most common subtype is high-grade serous carcinoma [8]. Especially for this subtype, the fallopian tube plays a central role in cancer pathogenesis [9–11]. Based on this hypothesis, together with the detrimental sequelae of premature menopause caused by RRSO, a novel strategy has been proposed: risk-reducing salpingectomy (RRS) after completion of childbearing with delayed risk-reducing oophorectomy (RRO).

The Dutch TUBA study (NCT02321228), a prospective multicenter preference study, compares quality of life between the currently standard RRSO and the novel strategy of RRS with delayed RRO [12]. In the TUBA study, women with a *BRCA1/2*-PV chose between both strategies, since this preferential design appeared to be most appropriate according to both *BRCA1/2*-PV carriers and their healthcare professionals [13]. Due to this preferential design, women are confronted with a complex and highly personal decision. They have to determine how to weigh their elevated risk of cancer on one hand against the (unpredictable) consequences of premature menopause on the other hand.

Patient Decision Aids (ptDAs) are developed to help patients make complex decisions, by increasing knowledge and risk perception and giving insight into personal values [14,15]. Also, use of a ptDA encourages active patient participation and can improve shared decision-making [16]. Previous studies found that ptDAs have the ability to reduce decisional conflict and distress and improve decisional quality [14,17–20]. The latter is defined as the extent to which patients choose and/or receive healthcare interventions that are congruent with their informed and considered values. Previously developed ptDAs do not include the three options of no surgery, RRSO and RRS-RRO or are not specifically targeted to women with a *BRCA1/2*-PV [21–24].

To enhance the decision-making-process of each individual patient, a ptDA was developed as part of the TUBA study, including the three options of no surgery, RRSO and RRS-RRO [25]. We aimed to evaluate actual choice, feasibility and effectiveness of the ptDA in *BRCA1/2*-PV carriers who participate in the TUBA study and to investigate whether

decision quality improves, from both a women's and healthcare professionals' perspective.

2. Methods

2.1. Study design

This study is part of the TUBA study which has a prospective preferential design. Women with a *BRCA1/2*-PV choose their preferred risk-reducing strategy: either RRSO between 35 and 40 years (*BRCA1*) or between 40 and 45 years (*BRCA2*), in accordance with current standard recommendations in (inter)national guidelines [5,26], or RRS upon completion of childbearing with RRO at the age of 35–45 (*BRCA1*) or 40–50 (*BRCA2*) years. In 2017, the ptDA was implemented in counselling on risk-reducing surgical options among women with a *BRCA1/2*-PV. Initially, counselling included one or more consultation(s) with a doctor and/or (specialized) nurse and a study-specific patient information sheet. After implementation of the ptDA, counselling was extended with the ptDA, which was distributed during or after the first consultation. Because the oncological safety of RRS with delayed RRO is not proven, this strategy is offered only within the context of a clinical trial [12].

2.2. Decision aid

During the first period (2015–2017) of the TUBA study, the ptDA was developed and alpha-tested [25]. Two versions were developed: for *BRCA1* and *BRCA2* separately. The developmental process has been explained in detail previously [25]. The ptDA discusses three options of ovarian cancer risk management. The first option of no surgery, although highly exceptional in Dutch *BRCA1/2*-PV carriers [27], is included to put the effects of the other two options in perspective. The second option is RRSO, as currently recommended in (inter)national guidelines [5,26]. The third option is RRS with delayed RRO, the novel strategy that is currently being investigated in the TUBA study. The ptDA consists of two sections, of which the first section provides factual information and the second section provides insight into personal values by a step-by-step plan and a personal value clarification worksheet. Section one starts with information regarding ovarian cancer prognosis and the three options in ovarian cancer risk management with the main risks, benefits and (estimated) risk reduction. Then, more specific information on (estimated) ovarian and breast cancer probabilities is presented in pie charts and icon arrays for each option separately (Fig. 1). Thereafter, information on menopause, its potential consequences and hormone replacement therapy is given. Both versions of the ptDA can be found in the Supplementary Materials.

The ptDA was developed in accordance with the International Patient Decision Aids Standards (IPDAS) criteria and meets 37 of 43 criteria for development and content [25,28]. In this study, the ptDA was evaluated on seven effectiveness items: (1) recognize a decision needs to be made; (2) know options and their features; (3) understand that values affect decision; (4) be clear about option features that matter most; (5) discuss values with their practitioner; (6) become involved in preferred ways; and (7) improves the match between the

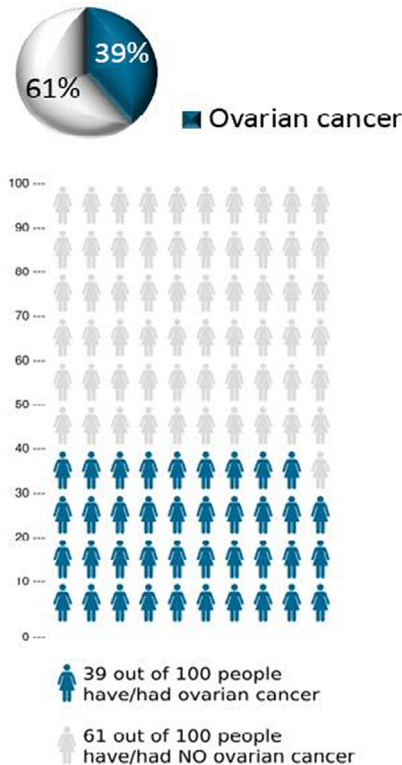
BRCA1 mutation carriers at age70

Fig. 1. Example of presentation of risks in the ptDA.

chosen option and the features that matter most to the informed patient. At least five out of the seven IPDAS criteria on effectiveness were fulfilled, as items 4 and 6 were unknown (Supplementary Table 1).

2.3. Study population

2.3.1. BRCA1/2 pathogenic variant carriers

All premenopausal women aged between 25 and 45 years carrying a BRCA1/2-PV who were counselled for risk-reducing surgery in one of the 13 hospitals participating in the TUBA study were included in this evaluation. All participants signed informed consent before inclusion according to the TUBA-study protocol that was approved by the Medical Ethics Committee of Arnhem-Nijmegen (registration number 2014–1269). The first half of the consecutively included women were counselled without and the second cohort with the ptDA. All participants, regardless of usage of the ptDA, completed questionnaires that they received during follow-up of the TUBA study. This follow-up is described in detail in the protocol of the TUBA study [12].

2.3.2. Healthcare professionals

Healthcare professionals, including doctors and (specialized) nurses, of the 13 hospitals participating in the TUBA study were also involved in this study. Some were involved in the developmental process of the ptDA and all were instructed on counselling and usage of the ptDA to optimize uniform counselling. All healthcare professionals received a questionnaire for evaluation of the ptDA.

2.4. Data collection and outcome measures

2.4.1. BRCA1/2 pathogenic variant carriers

All data on baseline characteristics of the study population, actual choice, feasibility and effectiveness of the ptDA were collected using digital questionnaires that were sent at the follow-up timepoints of

the TUBA study. The first questionnaire was sent pre-surgery (either RRSO or RRS) and consisted of questions about baseline characteristics, actual treatment choice and effectiveness. The latter derived from validated questionnaires including self-estimated ovarian cancer risk, a Cancer Worry Scale [29–31] and a Decisional Conflict Scale [32]. The Cancer Worry Scale ranges from 8 to 32 and scores of 14 or higher are defined as a severe cancer worry level; scores below 14 represent a low level of cancer worry. The Decisional Conflict Scale ranges from 0 to 100, and a higher sum represents higher conflict: scores below 25 are considered as low decisional conflict, scores between 25 and 37.5 as intermediate and scores above 37.5 are considered as high decisional conflict. Women counselled with the ptDA received additional questions on feasibility (actual usage of the ptDA and user experiences) and on effectiveness (self-estimated influence of the ptDA). Three months post-surgery, the questionnaire included the Cancer Worry Scale, and 12 months post-surgery effectiveness was measured by cancer worry and a Decisional Regret Scale [33]. The Decisional Regret Scale ranges from 0 to 100 in which a higher sum represents more regret. Also, the IPDAS criteria for effectiveness were evaluated.

2.4.2. Healthcare professionals

Data collection of the healthcare professionals started 1 year after implementation of the ptDA. All healthcare professionals were invited to complete a questionnaire on their professional characteristics, feasibility (actual usage of the ptDA, whether implementation was executed as planned and user experiences) and effectiveness (their estimate of the influence of the ptDA on participants' decision-making process).

2.5. Statistical analysis

Baseline data and data on feasibility of the ptDA were reported with descriptive statistics. Categorical variables were analyzed using the chi-square test and continuous variables with the Mann-Whitney *U* test. Linear models were used to compare period 1 (women without the ptDA) to period 2 (women with the ptDA) on decisional conflict and decisional regret, adjusted for BRCA-PV-type, age, hospital and time since hospital participation (to correct for potential learning curves). For the evaluation of cancer worry, a similar model was made but extended with a random effect for subject. Subgroup analyses for women within the recommended age range for RRSO (BRCA1 35–40 years and BRCA2 40–45 years of age) were performed since only this subgroup actually has a choice between RRS and RRSO. Women aged below the recommended age range have the choice between RRS or waiting until they reach the age at which RRSO can be performed. Two-sided *p*-values <0.05 were considered statistically significant. Analyses were performed using SPSS version 25.0.

3. Results

3.1. Study population

A total of 577 women participated in the TUBA study. Twelve women were excluded from this evaluation for not completing the baseline questionnaire. Of the remaining 565 women, 283 were counselled without the ptDA and 282 with the ptDA (Fig. 2). Participants had a median age of 37.7 years (range 25.8–45.9) and 51.7% carried a BRCA1-PV and 48.3% a BRCA2-PV. A total of 214 of the 292 BRCA1-PV carriers (73.3%) and 121 of the 273 BRCA2-PV carriers (44.3%) were within the recommended age range for RRSO (35–40 or 40–45 years of age, respectively). Baseline characteristics of all women are presented in Table 1. No differences were found in demographics and (familial) medical history between women counselled without or with the ptDA.

A total of 26 healthcare professionals from 13 participating centers were invited to participate, of whom 21 professionals from 11 centers

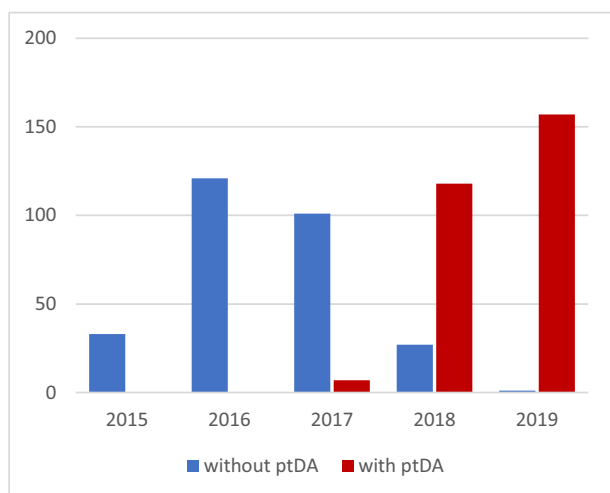


Fig. 2. Number of inclusions per year, separated for women without and with the ptDA.

Table 1
Baseline characteristics of women carrying a *BRCA1/2*-PV (N = 565).

Characteristic	Without ptDA (N = 283)	With ptDA (N = 282)	p-value
Demographics			
Age, years, median (range)	38.1 (28–45)	37.3 (25–45)	NS
Within advice age, ^a n (%)			NS
<i>BRCA1</i>	110 (38.9)	104 (36.9)	
<i>BRCA2</i>	63 (22.3)	58 (20.6)	
Level of education, n (%)			NS
Low	37 (13.1)	27 (9.6)	
Intermediate	112 (39.6)	93 (33.0)	
High	134 (47.3)	162 (57.4)	
Marital status, n (%)			NS
Married/relationship	256 (90.5)	255 (90.4)	
Single/divorced/widowed	27 (9.5)	27 (9.6)	
Working status, n (%)			NS
Employed	233 (82.3)	235 (83.3)	
Unemployed	50 (17.7)	42 (14.9)	
Unknown		5 (1.8)	
Medical history			
Pathogenic variant, n (%)			NS
<i>BRCA1</i>	146 (51.6)	146 (51.8)	
<i>BRCA2</i>	137 (48.4)	136 (48.2)	
Time since diagnosis, n (%)			NS
≤5 years	145 (51.2)	134 (47.5)	
>5 years	138 (48.8)	147 (52.1)	
Unknown	0	1 (0.4)	
History of cancer, n (%)			NS
Breast cancer	42 (14.8)	39 (13.8)	
Other	3 (1.1)	2 (0.7)	
First degree family history, n (%)			NS
Breast cancer	140 (49.5)	126 (45.0)	
Ovarian cancer	32 (11.3)	45 (16.1)	
Risk-reducing mastectomy, n (%)	121 (42.8)	102 (36.2)	NS
Psychological instability, ^b n (%)	50 (17.7)	47 (16.7)	NS
Offspring, n (%)			NS
Yes	252 (89.0)	245 (86.9)	
No	31 (11.0)	34 (12.1)	
Unknown	0	3 (1.1)	

N, number; ptDA, patient decision aid; NS, not significant.

^a Advice age: within the range of age in which is advised to perform standard RRSO: *BRCA1*: 35–40 years, *BRCA2*: 40–45 years.

^b Psychological instability includes current or previous severe anxiety, burn-out or depression.

responded (total response rate 81%). The healthcare professionals consisted of 17 gynecologists, one general physician and three nurses. Fifteen of the 21 professionals were employed in one of the eight university hospitals.

3.2. Actual choice

In total, the novel RRS with delayed RRO was chosen by 72% of all participants, less frequently by women counselled without the ptDA than by women with the ptDA (67% vs 78%, $p = 0.004$) (Supplementary Fig. 1). In the subgroup of women in the recommended age range of RRSO (*BRCA1* 35–40 years and *BRCA2* 40–45 years of age), RRS was chosen by 54% of the women without the ptDA and by 64% of women with the ptDA ($p = 0.055$). The main reasons for choosing RRSO were the feeling of having the lowest risk of developing cancer and the advantage of one single surgery. The main reasons for choosing RRS were the delay of menopause and its consequences, and the feeling of an opportunity to lower their cancer risk at younger age. Five women (3%) changed their choice after reading the ptDA; two changed from RRS to RRSO and three from RRSO to RRS. Of all women who underwent RRS, three of the 394 women (0.7%) requested and underwent RRO within 2 years after RRS (of which two women without the ptDA and one with the ptDA).

3.3. Feasibility

Eighty-five percent of women who were counselled after the introduction of the ptDA reported to have received the ptDA (234 of the eligible 282). Of them, 79% read the ptDA completely and an additional 14% read it partially. The main reasons for not reading as reported by the remaining 7% were either that it contained too much information or a lack of need for this information. The step-by-step plan to identify personal values was used by 47.5%. The main reason for non-use of the personal clarification worksheet was that women already had made their choice. The ptDA was planned to be distributed during or after the first consultation, which was the case in 88% of the women who reported to have received the ptDA. The other 12% received the ptDA prior to the first consultation. The moment that the ptDA was received was experienced as the correct timing by 96% of the women. The ptDA was graded with a median 8 out of 10 (interquartile [IQ] range 7–8). Especially clarity (reported by 66 women) and structuredness (reported by 44 women) were mentioned as strengths of the ptDA. The main suggested points of improvement were linguistic simplification (reported by eight women) and making the ptDA more concise (reported by seven women). Willingness to use a similar ptDA in the future for other medical decision-making was reported by 72%, and 78% would recommend this ptDA to others. Two women counselled without the ptDA reported that their decision did not reflect their considered values and four women reported the feeling of not being informed well enough, compared with none of women with the ptDA (both $p < 0.001$). The healthcare professionals graded the ptDA with a median 8 out of 10 (IQ range 7–8). Data on feasibility are presented in Fig. 3.

3.4. Effectiveness

Ovarian cancer risk perception did not differ between women without and with the ptDA, as visualized in Fig. 4. In Supplementary Fig. 2, cancer worry, decisional conflict and decisional regret are visualized. Mean cancer worry level was severe pre-surgery (14.8 and 14.4 in women without and with the ptDA, respectively) and lower after surgery (3 months post-surgery: 13.1 and 12.9, respectively; 12 months post-surgery: 13.2 and 12.5, respectively) and was not different between women without or with the ptDA. Decisional conflict was low overall and comparable in women without and with the ptDA as well, in all women and in the subgroup of women within the recommended age range. No significant differences were found in decisional regret scores 12 months post-surgery between women without or with the ptDA (13.9 vs 11.2, respectively). However, 34% of the women without the ptDA had a decisional regret score of zero, compared with 48% of the women with the ptDA. The self-estimated influence of the ptDA on several statements as reported by *BRCA1/2*-PV carriers and professionals is

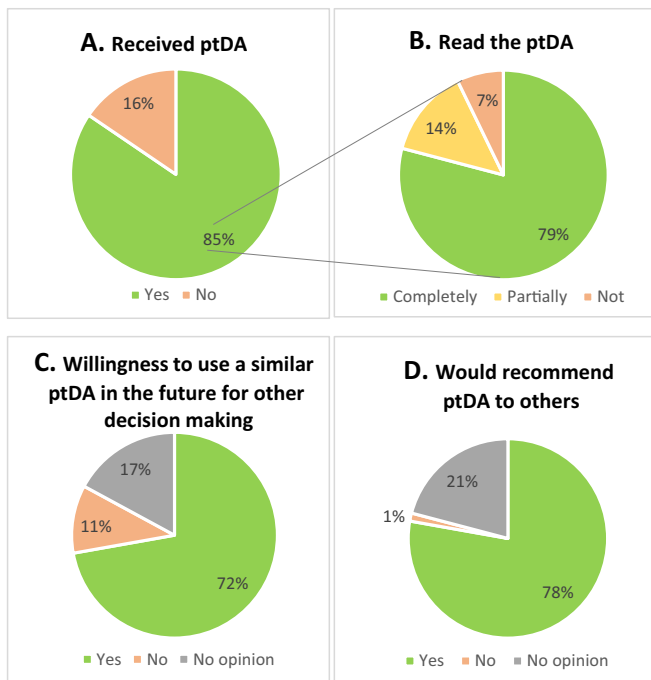


Fig. 3. Feasibility of the ptDA, divided in actual usage (A and B) and experiences (C and D).

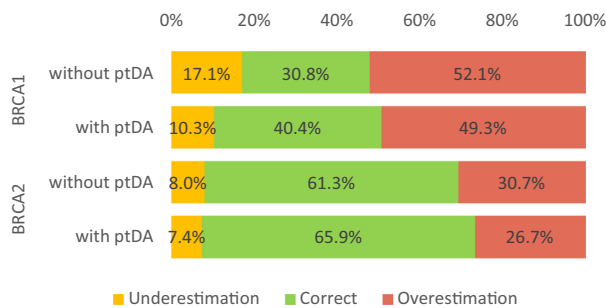


Fig. 4. Ovarian cancer risk perception. Correct is defined as perceived risk within a range of 20% of the actual risk: BRCA1 29–49% and BRCA2 6–26%.

presented in Fig. 5. Both women and healthcare professionals agreed with statements of increased knowledge about the options and increased insight in personal values. The step-by-step plan was reported as particularly helpful in decision-making and giving insight in personal values. The statement of having an increased influence in decision-making was reported by professionals, while women's opinions were divergent.

4. Discussion

In the present study, we evaluated a ptDA on actual choice, feasibility and effectiveness for BRCA1/2-PV carriers choosing their risk-reducing strategy in ovarian cancer risk management. We found that the novel strategy was chosen significantly more often in women with the ptDA, and that the ptDA was considered feasible, improved decisional quality and was positively evaluated by both BRCA1/2-PV carriers and their healthcare professionals. Women with the ptDA seemed to have more frequently a decisional regret score of zero, and an increased fear for cancer was not observed. The ptDA fulfills 37 out of 43 IPDAS criteria on development and content and at least five of seven IPDAS criteria on effectiveness, resulting in a total score of at least 43 out of 50, reflecting a feasible and effective decision aid.

This is the first study reporting on the evaluation of a decision aid including a novel strategy of risk-reducing surgery in ovarian cancer risk management. Up until now, the advice to reduce the increased risk of ovarian cancer in BRCA1/2-PV carriers has been to perform RRSO multiple years prior to natural menopause. The novel strategy of RRS with delayed RRO gives rise to a new opportunity, but consequently introduces a difficult decision. As demonstrated by the previously performed feasibility study, women with a BRCA1/2-PV noted the complexity of the decision and the difficulty of deciding based on risks [13].

The novel strategy was chosen most frequently, and this proportion was even higher in women using the ptDA compared to women without the ptDA. This might be due to a better-informed choice, supported by the finding that women with the ptDA significantly agreed more frequently with the statement of being satisfied with the amount of information. Patients who missed certain information may be more willing to choose standard care. Another explanation may be a steering character of the ptDA into the direction of RRS with delayed RRO; however, only a few patients changed their mind after reading the ptDA, and the decisions were changed in both ways. Thus, it is not likely that the ptDA is steering in one direction or the other. Another explanation may be that RRSO can be performed in every hospital in the Netherlands, whereas RRS is currently strongly discouraged outside the context of a clinical trial. Therefore, it is very likely that not all women undergoing RRSO are participating in this study, whereas probably almost all women undergoing RRS are represented. However, we have no reason to assume that the women undergoing RRSO in our study are different from the non-participating women undergoing RRSO in non-participating hospitals.

With regard to the effectiveness of the ptDA, decisional conflict was found to be equal in both groups. Previous evaluation studies of decision aids mainly described lowered decisional conflict after using a ptDA [34–36]. However, in our study, women already experienced a low level of decisional conflict. This finding can be explained by the elaborate patient information sheet that everyone received prior to entering the study. Also, many BRCA1/2-PV carriers have prior knowledge about carriership in their families, even before they underwent genetic testing themselves. Therefore, they may have decided about risk-reducing surgery prior to study participation, which can reduce decisional conflict as well. Moreover, informative counselling with attention for personal values can also result in low decisional conflict. We find it unlikely that counselling was very steering, since patients reported high satisfaction with their decision and that their decision reflects their personal values. Only one woman in the study reported to be unsatisfied with her decision and she was counselled without the ptDA. Moreover, she switched her choice prior to surgery. In contrast with previous research, we found no improvement in risk perception [14]. However, the perceived cancer risks were more or less similar to previous reported perceived risks among BRCA1/2-PV carriers [37]. Potentially, risk perception did not improve because of the high quality of the patient information sheet provided to all women in which attention is paid to educational information including cancer risks. Thus, due to the extensive patient information sheet, the influence of the ptDA may be underestimated and, potentially, the ptDA is even more effective in women who did not participate in this clinical trial.

The strengths of this study were the inclusion of both BRCA1/2-PV carriers and healthcare professionals and the execution of implementation, since 85% reported to have received the ptDA. Another strength is the inclusion of all three possible options in ovarian cancer risk management for BRCA1/2-PV carriers. In the Netherlands, the uptake of risk-reducing surgery is extremely high, and the option of no surgery was particularly included to provide a complete overview and to place the effects of the other two options in perspective [27]. However, the percentage of BRCA1/2-PV carriers considering any prophylactic surgery varies across cultures from 17% to 89% [27,38]. Therefore, this ptDA can serve as an addition to standard counselling of patients confronted with the options for ovarian cancer risk management to enhance

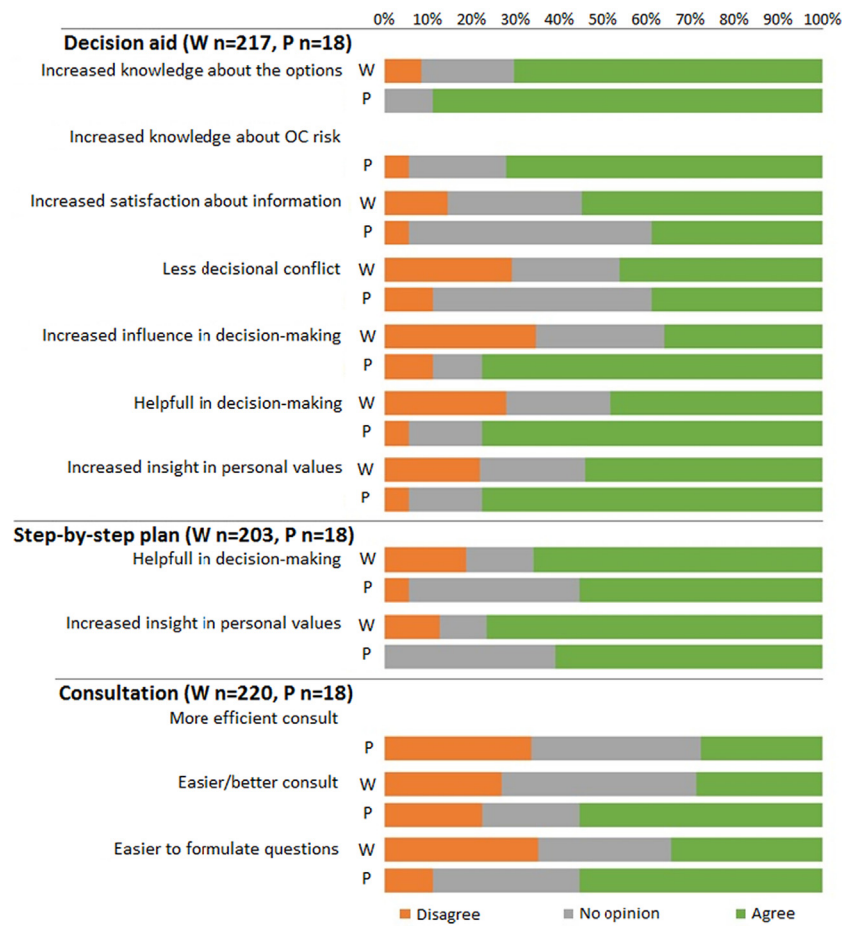


Fig. 5. Self-estimated influence of the ptDA on statements according to *BRCA1/2* carriers and healthcare professionals. OC, ovarian cancer; W, women carrying a *BRCA1/2-PV*; P, professionals.

informed and valued decision-making, potentially also in other countries. However, we should keep in mind that RRS should be performed only within the safe context of a clinical trial.

A limitation of this study is the allocation per group based on time period: the first 283 of all participants were counselled without the ptDA and the following 282 with the ptDA. In this study, we did comparisons between the two time periods, which might have affected the results since not all women actually received the ptDA during period 2. During the first years of the TUBA study, the ptDA was developed and alpha-tested. Then, accumulating centers were participating in the study and the impression for the need of a decision aid was rising. Therefore, we decided to offer the ptDA to all women in all centers after the ptDA was finalized. A stepped-wedge design was considered; however, we found it unethical to withhold the ptDA from women if the decision-making process could potentially be improved. All healthcare professionals were instructed on usage of the ptDA and counselling prior to implementation. Counselling quality might improve in time based on experience, and therefore women with ptDA, who were counselled at the moment that healthcare professionals were counselling for multiple months or years, may have had higher-quality counselling. Therefore, we corrected for this time variable in our analysis.

In conclusion, the patient decision aid for *BRCA1/2-PV* carriers who are facing the decision between salpingo-oophorectomy or salpingectomy with delayed oophorectomy is feasible, effective and highly appreciated. We recommend usage of this ptDA for women at high risk for ovarian cancer and therefore, and we have implemented this ptDA in standard counselling of women in the recently started international TUBA-WISP II study. This study is a sequential study of the

current TUBA study, initiated in collaboration with the WISP study group. The focus of the TUBA-WISP II study is on safety of RRS with delayed RRO, as this novel strategy option can be offered as standard care only as soon as safety is proven. The ptDA helps *BRCA1/2-PV* carriers to make an individual informed decision between premature menopause and ovarian cancer risk.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2021.08.019>.

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