Reproductive decision support in hereditary cancer

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The development and evaluation of an online decision aid

Kelly Reumkens

The research presented in this thesis was conducted within GROW School for Oncology and Developmental Biology, at the Department of Clinical Genetics of the Maastricht University Medical Center (Maastricht UMC+).

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Contents

Chapter 1

General introduction

General introduction

The studies reported on in this dissertation were conducted as part of a research line, investigating reproductive decision-making among persons having a genetic predisposition to cancer and their partners. Previous studies of this research line explored the reproductive decision-making process of couples[1,2] and indicated a need for support in addition to reproductive counselling.[1,3] In collaboration with all clinical genetic centres of the Netherlands, an online decision aid was developed to support couples during reproductive decision-making, with the aim of minimizing the negative psychological consequences among couples during and after this process. This dissertation describes the development process and evaluation of the decision aid, as well as opportunities for continued implementation.

Hereditary cancer

Of all cancers, approximately 5% are caused by a genetic predisposition. A predisposition for hereditary cancer usually has an autosomal dominant inheritance pattern, implying that there is a 50% risk in each pregnancy of transmitting the mutation in one of the cancer genes to offspring. Transmission implies passing on an increased lifetime risk of developing cancer. To illustrate this, carriers of a *BRCA1/2* mutation, the most frequent cause of hereditary breast and ovarian cancer (HBOC), have a lifetime risk of 69-72% of developing breast cancer and 17-44% of developing ovarian cancer before the age of eighty.[4] In comparison, the lifetime risk for women in the general population of developing breast cancer is 12.7% and 1.3% for ovarian cancer.[5] The relatively frequent mutations in the *BRCA1* or *BRCA2* breast cancer genes are the cause of 30% of the breast cancer diagnoses under the age of thirty.[6] Therefore, from the age of 25, surveillance programs are recommended for female *BRCA1/2* mutation carriers such as clinical breast examinations and annual mammography's. Female *BRCA1/2* mutation carriers can also opt for preventive (surgical) interventions (e.g. prophylactic mastectomy) to improve their chances of survival. Hereditary Non-Polyposis Colorectal Cancer (HNPCC; also known as Lynch syndrome) is the most common hereditary colorectal cancer predisposing syndrome. Without medical interventions, the lifetime risk for colorectal and endometrial cancers approaches 25-70% and 15-55% respectively.[7-10] The onset of disease of HNPCC is relatively young (average 45 years) and regular colonoscopy is recommended by the age of twenty-five.[11] Familial Adenomatous Polyposis coli (FAP) is the second most common hereditary colorectal cancer syndrome. Unless surgical interventions are performed (e.g. colectomy), the lifetime risk of developing cancer for patients with FAP is almost

100%. Also for FAP, the onset of disease is relatively young, as the mean age of developing cancer is 39 years for individuals who do not undergo colectomy (range: 34-43 years).[12] For patients with FAP, colorectal screening is recommended from the age of 10-12 years. HBOC, HNPCC, FAP and several syndromes resulting from mutations in rare genes are regarded as high penetrance cancer susceptibility syndromes (the risk of cancer increases approximately 5- to 50-fold compared to the population risk). However, there are many more prevalent moderate-risk genes (relative risk ≥1.5 and <5.0) and low-risk genes (relative risk <1.5).[13] In this thesis we will focus on high-risk cancer susceptibility syndromes.

Reproductive options

Persons who are aware that they have a predisposition for hereditary cancer are usually confronted with frequent and intense surveillance programs and face decisions on possible preventive therapies (e.g. prophylactic mastectomy and colectomy) at a relatively young age. Treatment for their cancer, preventive or otherwise, may also interfere with their desire to have children. For example, female carriers of a *BRCA1/2* mutation are generally advised to undergo a preventive oophorectomy from their mid-thirties[14] which shortens their fertile life span by several years. Moreover, they may face difficult decisions regarding their wish to have children.

Some couples may decide to refrain from having children, while others choose to have children who are not genetically related to the partner carrying the genetic mutation by using donor gametes. Yet others, may choose to adopt. Most couples, however, pursue their wish to have genetically related children.[15] If they accept the risk of passing on the mutation to their child, they can try to conceive naturally. When the child is born, it will be unknown if he or she has inherited the mutation or not. Usually the uncertainty about the carrier status of the child will last for a long time as for most cancers with adult age onset, international guidelines discourage testing the child at a young age.[16]

For couples who opt for a genetically related child and accept medical assistance to prevent transmission of the mutation to the next generation, there are two options available in the Netherlands: prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD). Both options are covered by the Dutch health insurance system. PND can be performed once a pregnancy is established. Information about the presence or absence of the mutation in the fetal DNA can be obtained by analyzing the familial mutation in chorionic villi or amniotic fluid. A chorionic villus biopsy can be performed between 11-14 weeks of pregnancy by taking a sample of chorionic villi from

the placenta for testing. Amniocentesis can be performed from 15 weeks of pregnancy by taking a sample of amniotic fluid. In both cases there is a small risk of a miscarriage; around 0.2% for a chorionic villus biopsy and around 0.1% for an amniocentesis.[17] Chorionic villus biopsy is applied more frequently for hereditary cancer syndromes compared to amniocentesis because the result will be known earlier in the pregnancy. Couples receive the results regarding the mutation status of the fetus 2-3 weeks after the chorionic villus biopsy or amniocentesis. If the fetus has inherited the mutation, couples have the choice to terminate the pregnancy or not. Usually, this dilemma has been discussed extensively with couples prior to the prenatal test and only couples who intend to terminate the pregnancy are expected to embark on prenatal testing. Counsellors will also elaborate on the fact that the decision to continue the pregnancy after prenatal testing may violate the autonomy of the future child, as the parents have the knowledge that he or she has an increased cancer risk.

For HBOC, an extra step can be added to the prenatal testing process, as the consequences of inheriting the mutation differ depending on the gender of the fetus. Non-invasive prenatal testing (NIPT) in the ninth week of pregnancy can reveal the gender of the fetus within 1-2 weeks. NIPT does not carry the risk of a miscarriage as only blood sampling of the pregnant mother and her partner is needed. In the case of a male fetus, most parents will decide to accept the small risk of cancer for their son. If the woman is pregnant with a female fetus, further invasive diagnostics is offered.

In 2008, PGD for inherited cancer predisposition syndromes was approved in the Netherlands after a nationwide political and ethical discussion. PGD implies that embryos obtained by in vitro fertilization (IVF) are examined for the familial mutation and only mutation-free embryos are transferred into the uterus. For IVF, ovarian hyperstimulation is necessary, through hormone supplements for the woman. Subsequently, oocytes will be harvested by a so-called pickup procedure. The oocytes are fertilized through intra cytoplasmatic sperm injection (ICSI). If fertilization is successful, the embryo will undergo cleavage divisions and the number of cells will rapidly increase. One cell or a few cells from each embryo of three respectively 5-6 days old is biopted to analyze the familial mutation. Depending on the day of biopsy, fresh transfer within 24-48 hours (on day 4 or 5 after fertilization) or transfer of cryopreserved and thawed embryos (several weeks after the biopsy) can take place. Only embryos without the mutation in the biopted specimen are transferred into the uterus.

In the Netherlands, all PGD analyses are centrally performed in the Maastricht University Medical Centre (MUMC+) which harbors the only clinical genetic centre authorized to perform PGD since 1995. A transport construction has been established with the University Medical Centers of Utrecht, Amsterdam and Groningen, where couples can undergo their IVF treatment. PGD is a physically and psychologically intensive and relatively lengthy trajectory, and the chance of an ongoing pregnancy is approximately 25% per treatment.[18] The benefit of PGD is that if an ongoing pregnancy is established, a child without the inherited mutation will be born. In this way, PGD circumvents the emotional and physical burden of a pregnancy termination after prenatal testing.[19]

Uptake and acceptability of PND and PGD for hereditary cancer

After couples receive the results of a genetic test indicating that one of the partners is a carrier of a predisposition to hereditary cancer, approximately half of the couples in the reproductive age consider PND or PGD.[20] Among Dutch couples who are aware that one of them carries the *BRCA1/2* mutation, the acceptability of PGD (80%) was found to be notably higher compared to PND (26%).[2] Of these couples, 39% would consider PGD and 20% would consider PND for themselves.[2] Thirty percent of Dutch couples who are aware that either partner has FAP would consider PGD, which was the same for PND (30%).[21] However, the actual uptake of PND for late onset hereditary cancer is remarkably lower. Until 2013, only six out of more than 3000 couples with HBOC in the Netherlands performed PND (<0.2%) and six out of 364 couples with FAP (1.6%).[22] Couples indicated several reasons for refraining from PND. Some couples indicated religious and/or ethical objections, others found a termination of a pregnancy in the case of an unfavorable result too drastic, and the weeks of uncertainty when waiting for the PND results were also mentioned as a major disadvantage.[1] PND for hereditary cancer is not standardly offered to couples in all University Medical Centers in the Netherlands. Usually, PND for high risk cancer genes (e.g. FAP) is only available on a case-by-case basis.

To date, around 2000 couples have been treated with PGD, around 3900 PGD treatments have been performed, and over 800 children have been born via IVF-PGD.[23] Since PGD was legalized for hereditary cancer predisposition syndromes, HBOC and FAP has become one of the most frequently applied indications for PGD. To date, 146 couples with *BRCA1/2* have started a PGD treatment, 31 couples with FAP and ten couples with HNPCC.[23]

Reproductive decision-making in the oncogenetic setting

Typically, counselees who are of reproductive age will receive basic information regarding the reproductive options before and/or after genetic testing for the familial mutation. Before genetic testing, the emphasis will be on the cancer risk for the person involved and on the advantages and disadvantages of molecular testing. The results of the DNA test are usually communicated via telephone or by letter as in the Netherlands most people who opt for predictive DNA testing for hereditary cancer will visit the clinical genetic center only once (prior to genetic testing). For persons with a mutation in one of the cancer predisposition genes, the reproductive risks and options are once again briefly mentioned in the letter they receive following the predictive DNA testing. Follow-up consultations are only planned for individuals or couples who indicate that they have specific questions concerning the reproductive risks or that they are in need of additional support. These individuals or couples will receive a consultation specifically addressing the possible reproductive options. As the decision regarding reproductive options is preference-sensitive, couples should be counselled and guided by healthcare providers during reproductive decision-making in a non-directive way.

In the last decade, mainly qualitative studies have been initiated to investigate the experiences of couples regarding their reproductive decision-making process in the oncogenetic setting. These studies found that, overall, couples experience the reproductive decision-making process as difficult and emotionally demanding.[1,24-29] Couples have to cope with their own increased risk of developing cancer and they are concerned about their chances of passing on the predisposition to cancer to offspring.[30] Especially couples opting for natural conception without genetic testing may experience more difficulties during reproductive decision-making compared to couples who opt for PND or PGD[3], with feelings of doubt or guilt lasting up to several years after the reproductive decision-making was indicated.[1] A recent study by our research group emphasized the variety of aspects deliberated on by couples when deciding on their most suitable reproductive option. These motives and considerations can be categorized into physical, psychological, practical, social, and ethical considerations.[1] For example, regarding PGD, couples consider the physical strains of the IVF treatment, psychological aspects such as perceptions of loss of romance and control regarding pregnancy, but also practical considerations regarding hospital appointments and the accessibility and reimbursement of treatments. Furthermore, social considerations (e.g. wiping out the mutation in the family line, and protecting a future child from the same reproductive dilemmas) and ethical considerations (e.g. interference in a natural process, and the moral duty to protect the future child) are indicated to be important

considerations during reproductive decision-making. A recent study among couples with HBOC showed that making a reproductive decision was experienced as difficult or very difficult by 43% of the participants, and 69% expressed a need for additional support during reproductive decision-making.[3] The development and application of decision support for persons having a genetic predisposition to cancer and their partners who wish to have children has been explicitly advocated.[1,31,32]
For preference-sensitive decisions, such as the decision regarding reproductive options, decision aids are useful for providing patients with information and additional support during decision-making.[33] To date, no decision support is systematically implemented in the reproductive counselling of persons having a genetic predisposition to cancer and their partners. This stimulated the development of an evidence-based decision aid to support our target group in making an informed reproductive decision.

Development of decision support

In recent decades, medical decision-making has experienced a paradigm shift, with a transition from paternalistic models towards more equitable or collaborative models of counsellor-patient interaction.[34-36] Autonomy for medical decisions has gradually shifted and patients are more actively involved in the decision-making regarding their own health rather than being a passive recipient of healthcare.[36-38]
This shift is also present in the oncogenetic setting. Especially regarding reproductive options, deliberated decisions need to be made as the consequences of these decisions do not only concern the person at risk, but also family members and (potential) offspring. The decision regarding which reproductive option to pursue should therefore ideally involve an informed decision-making process by an educated and empowered couple. Patient decision aids can be helpful in achieving the engagement of patients in their own health, resulting in a process in which patients make informed decisions. In a systematic review, it was found that compared to usual care interventions, decision aids: 1) improved knowledge; 2) created more realistic expectations; 3) decreased decisional conflict; 4) increased active decision-making; 5) reduced the number of patients remaining undecided; and 6) produced greater agreement between values and choice.[39]

The general aim of this thesis was to develop, evaluate, and implement an evidence-based online decision aid to support persons having a genetic predisposition to cancer and their partners in making an informed decision regarding reproductive options. With the decision aid, we aimed to provide adequate information during reproductive decision-making and to provide support in increasing participants' deliberation

regarding reproductive options, and facilitating concordance between the values that matter most to them and the reproductive option chosen. A collaboration was set up with a steering group including counsellors (e.g. clinical geneticists, genetic counsellors, and social workers), experts in health communication and medical decision-making, psychologists, and the intended end-users of the decision aid, i.e. persons having a genetic predisposition to cancer and their partners who are planning to have children. The decision aid was developed according to the International Patient Decision Aids Standards (IPDAS).[40] First, we investigated the preferences and needs of both end-users (couples) and intermediaries (counsellors) regarding the content and functionalities of the decision aid to guide the systematic development through the use of a qualitative approach. Subsequently, we established the effectiveness of the decision aid on the short term and the longer term by assessing the outcome measures of decisional conflict, informed decision-making, knowledge, realistic expectations, level of deliberation, and decision self-efficacy. A reproductive decision was considered to be informed if a participant had a sufficient knowledge level, a high level of deliberation and if the preferred reproductive option was value-consistent.[41] Last, as many (proven) effective decision aids are often infrequently used in daily practice following trial periods,[42] we conducted an explorative study on opportunities for continued implementation. By doing so, we hope to maximize the impact of the decision aid by increasing the awareness and reach of the decision aid, facilitating its implementation, and optimizing the sustained use of the decision aid after finalizing this project.

A multicenter collaboration was set-up to guide this project in which the clinical genetic centres of the following medical centers participated: Maastricht UMC+, University Medical Centre Utrecht, University Medical Centre Groningen, Amsterdam University Medical Centre, the Netherlands Cancer Institute; Antoni van Leeuwenhoek Hospital Amsterdam, Radboud University Medical Centre Nijmegen, Erasmus University Medical Centre Rotterdam, and University Medical Centre Leiden. The Dutch Cancer Society (Alpe d'HuZes Foundation; grant number UM2013-6374) funded the project.

Outline of the thesis

C*hapter 2* and *Chapter 3* describe the developmental process of the online decision aid using mainly qualitative approaches. First, we used the input of both couples and the involved counsellors during a needs assessment study to guide the development of the decision aid since the needs of both stakeholder groups are essential to ensure a successful development and uptake of the decision aid.[43-45] The prototype decision aid was developed and modified in an iterative process. The user-friendliness, strengths and limitations of the prototype decision aid were assessed several times during usability testing. Subsequently, the final decision aid was pilot-tested. *Chapter 4* describes the evaluation of the decision aid by means of a nationwide pretest-posttest study. This chapter focuses on the immediate and short-term effects of the decision aid on various outcomes related to informed decision-making (i.e. decisional conflict, knowledge, realistic expectations, level of deliberation and decision self-efficacy). C*hapter 5* outlines the prolonged effects of the decision aid and investigates the number of participants making an informed reproductive decision three months after reviewing the decision aid. C*hapter 6* focuses on opportunities and preferences of oncogenetic counsellors for continued implementation of the decision aid. Finally, in the General Discussion in C*hapter 7,* findings from these studies and their implications are reflected on and recommendations for future research and for the daily practice of reproductive counselling in hereditary cancer are given.

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Part I

Development

Chapter 2

Reproductive decision support: preferences and needs of couples at risk for hereditary cancer and clinical geneticists

Kelly Reumkens, Anne van Oudheusden, Joyce Gietel-Habets, Marly Tummers, Christine de Die-Smulders, Liesbeth van Osch

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Abstract

For couples at high risk of transmitting a cancer predisposition to offspring, reproductive decision-making can be challenging. As the choice between available reproductive options is preference-sensitive, the use of a decision aid can support these couples in their decisional process. The present study aims to investigate preferences and needs of involved stakeholders regarding the development and implementation of a patient decision aid. Semi-structured interviews assessing the needs and preferences regarding the content and functionalities of a decision support program were conducted among seven couples at risk for hereditary cancer and among eight clinical geneticists involved in oncogenetic counseling. Many similarities were found between the expressed preferences and needs of both stakeholder groups concerning the content, barriers and facilitating factors regarding the use of the decision aid, and its implementation. Emphasis was placed on the use of simple non-medical language, an extensive explanation of the procedures and techniques used in prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD), and the role of health care providers to refer couples to the decision aid. Both stakeholder groups were in favor of incorporating narrative stories in the decision aid. Integrating the present findings with knowledge on reproductive decisional motives and considerations is essential in guiding the development of a decision aid that corresponds to the preferences and needs of end-users.

Background

Individuals with a family history of cancer may face the decision on whether or not to undergo genetic testing. This decision may set in motion a cascade of decisions, including deciding on whether or not to inform family members and, if available, whether or not to take up periodic screening and preventive therapies in case of a confirmed mutation. Carriers of reproductive age additionally face challenging decisions regarding one's wishes to have children and the welfare of their future child(ren).[1,2] As most types of hereditary cancer are transmitted in an autosomal dominant pattern, there is a 50% risk of transmitting the mutation. This knowledge plays a substantial role in the reproductive decision-making process.[3] Carrier status impacts the decision of mutation carriers to have biological children.[4] Apart from deciding to not have children, couples may decide to pursue options to have non-biological children (e.g. adoption, foster parenting). Most couples, however, pursue their wish to have biological child(ren).[4]

Carrier couples who want a biological child can opt for natural conception without genetic testing and accept the risk of passing on the susceptibility to cancer to the child, prenatal diagnosis (PND) assuming the intention to terminate the pregnancy (TOP) in case the fetus is a carrier of the genetic mutation[5] or preimplantation genetic diagnosis (PGD). PGD involves a multi-stage diagnostic process in which embryos derived by in vitro fertilization (IVF) are screened for the presence of the familial mutation before pregnancy is established. Subsequently, only embryos without the mutation are transferred into the uterus.[5] Previous research showed that approximately half of couples consider PND or PGD after receiving a positive genetic test result for hereditary cancer[6] and the majority think PND and PGD should be offered to mutation carriers.[4]

In deliberating the options for fulfilling one's wish to have children, couples carefully consider various personal values and advantages and disadvantages of all reproductive options, previously categorized into physical, psychological, social, ethical and practical considerations.[1] Research has demonstrated that couples often experience the reproductive decision-making process as very difficult.[2,7,8] Feelings of uncertainty, regret and guilt are common.[1] In addition to reproductive counseling, decision support may be helpful to support couples during reproductive decision-making.[1,8-10] Although recent studies have provided more insight into the reproductive decision-making process of carrier couples,[1,2,7,8] and the application of decision support has been advocated,[1,9,11] currently, no structural decision support is available. High quality evidence shows positive effects of decision aids on various patient outcomes, such as increased knowledge regarding potential options, reduced decisional conflict, and facilitation of informed and value-based decision-making.[12-14]

The present study is part of a larger research project on the development and implementation of an online patient decision aid. The decision aid is developed according to the International Patient Decision Aids Standards (IPDAS). The first step in the development process is to provide insight into the preferences and needs of important stakeholders regarding the content and implementation of the decision aid. Both patients' and practitioners' decisional needs may influence the quality of the decision and a thorough understanding of the needs of both stakeholder groups is essential to ensure successful development and promotion of the use of the intended decision aid.[15-17] In this manuscript, we present the outcomes of a needs assessment among both groups as the first step towards the development of a patient decision aid for reproductive decision-making among couples at risk for hereditary cancer.

Methods

Semi-structured interviews were conducted among couples at risk for hereditary cancer (Study 1) and clinical geneticists (Study 2).

Participants

The Clinical Genetics Department of the Maastricht University Medical Centre (MUMC+) is the only department in the Netherlands authorized to perform PGD. The MUMC+ has set up a database of couples who have had reproductive counseling for hereditary cancer since 2008 when PGD was approved for late onset inherited cancer predisposition syndromes in the Netherlands. Seventeen couples from this database who have had reproductive counseling for hereditary cancer between January 2013 and January 2015 were randomly selected and contacted to participate in Study 1. Couples were eligible for participation if one partner was a mutation carrier for hereditary cancer for which PND and PGD are available in the Netherlands, if both partners were 18 years or older, and if both partners had sufficient knowledge of the Dutch language. Couples received an invitational letter for participation, an informative letter, and an informed consent form for each partner. For Study 2, clinical geneticists of the nine Clinical Genetics Departments in the Netherlands who were involved in oncogenetic counseling were invited by e-mail to participate with exclusion of the clinical geneticists of the MUMC+ who are all directly involved in the project.

Instrumentation and procedures

Separate semi-structured topic guides were developed for guidance of the dyadic and individual interviews. The content of both topic guides was focused on the content, layout, format, dissemination and implementation strategies of the patient decision aid (See Table 2.1). Clinical geneticists received additional questions concerning their professional perspectives regarding the development and implementation of the decision aid in order to facilitate structural decision support use and referral within consultations. The interviews were conducted by two researchers (K.R. and A.O.) and held in the home environment of couples with both partners participating and at convenient workplaces for clinical geneticists. All interviews were audiotaped. Participants were asked to fill out a brief questionnaire prior to the start of the interview. Apart from demographic factors (e.g. age and gender) couples were asked about their carrier status (e.g. type of hereditary cancer syndrome), current reproductive preferences (e.g. natural conception without genetic testing, PND, PGD, and refraining from fulfilling one's wish to have a child(ren)), internet experience (1= no experience, 4= a lot of experience) and expectations concerning the expected use of a decision aid (1= definitely not, 5= definitely). Clinical geneticists were also asked about work experience in the counseling of couples at risk for hereditary cancer (1= less than one year experience, 5= more than 10 years' experience), and experience with decision aids (1= no experience, 4= a lot of experience).

Table 2.1 Overview of Main Questions Asked During Dyadic (Study 1) and Individual (Study 2) Interviews

Study 1. Couples

Content
- What information do you consider important in order to make an appropriate reproductive decision?
- What kind of information assisted or could have assisted you in making a reproductive decision?
- Please specify your preferences with respect to functionalities and/or applications that can be included in the decision aid.

Lay-out
- What do you think a decision aid should look like (appearance)?
- What are your wishes regarding the layout of the decision aid?

Barriers and facilitating factors
- Please identify potential barriers for yourself regarding the use of the decision aid.
- Which suggestions do you have in order to prevent these barriers?
- Please identify facilitating factors for yourself regarding the use of the decision aid.

Dissemination and implementation
- How and when would you like to be informed about the decision aid?
- When and where would you have preferred to use the decision aid?

Study 2. Clinical geneticists

Content
- What information do you consider important for couples in order to make an informed decision?
- What are your ideas with regard to the inclusion of functionalities and/or applications in the decision aid?

Lay-out
- What do you think a decision aid should look like (appearance)?
- What are your wishes regarding the layout of the decision aid?

Barriers and facilitating factors
- What do you consider potential barriers for couples to use the decision aid?
- What do you consider potential facilitating factors for couples to use the decision aid?
- What would be barriers for yourself to refer to the decision aid as intended?
- What would be facilitating factors for yourself to refer to the decision aid as intended?

Dissemination and implementation
- What are your preferences with respect to the availability of the decision aid?
- What do you consider the best point in time to use the decision aid?
- How do you consider your role as clinical geneticist with regard to the implementation of the decision aid?

Data analysis

Qualitative data derived from the audiotaped interviews were transcribed verbatim and independently analyzed by two researchers (K.R. and A.O.). A phenomenological investigation method was used to explore preferences and needs of couples at risk for hereditary cancer and clinical geneticists.[18] Open and axial coding was performed to derive and categorize main themes. Coding of the data was done by two independent researchers and comparison of coding was conducted in order to reach consensus. Data from the brief questionnaires were analyzed by descriptive statistics using SPSS version 23.

Results

Fifteen semi-structured interviews with seven couples (n=14 individuals) and eight clinical geneticists were conducted between April and June 2015 with an average duration of 62 minutes (range 40-75). After five couples and six clinical geneticists, data saturation seemed to be achieved. Two additional interviews were conducted, in which no new or salient data were generated and data collection was concluded.

Study 1: Needs assessment among couples

Couples' characteristics

Seven couples gave informed consent for participation (response rate 41.2%) with a mean age of 33.4 years for males (SD=3.0), and 30.6 years (SD=2.8) for females. Table 2.2 shows an overview of couples' characteristics. Main reasons for non-participation were a lack of time and not wanting to relive the psychological burden associated with reproductive decision-making. The majority (79%) expressed a positive intention towards the use of a decision aid, if it had been available at the time of their reproductive decision (mean=4.29, SD=0.99). Most respondents had ample experience with internet and computers (93%; mean=3.71, SD=0.61).

Table 2.2 Couples' characteristics

Characteristic	*n*	Percentage (%)
Gender		
Male (M)	7	50.0
Female (F)	7	50.0
Mean age (in years)		
Male	30.6 (SD=2.8)	
Female	33.4 (SD=3.0)	
Education		
Low	1	7.1
Middle	5	35.8
High	8	57.1
Gender of Carriers		
Female	7	100.0
Mutation type		
BRCA 1/2	2	28.6
Lynch	1	14.3
Familial adenomatous polyposis	1	14.3
Retinoblastoma	1	14.3
Paraganglioma	1	14.3
Hereditary diffuse gastric cancer	1	14.3
Reproductive decision		
PGD	10	71.4
Natural conception	4	28.6

Seven couples (*n*=14 individuals) participated in the interviews

Preferences and needs regarding the content of the decision aid

In addition to the main reproductive options (natural conception without genetic testing, PND and PGD), the principles of decision support were explained prior to the interviews.

Informational content of the decision aid and presentation of information

Couples expressed a need for a complete explanation in the decision aid of the procedures and techniques used in PND and PGD, including procedures for IVF and pregnancy termination. Participants put particular emphasis on the duration, physical consequences, and the expected psychological burden of the PND and PGD trajectory.

For someone who is not specialized in genetics, a clear and comprehensive overview of the medical process provided in the decision aid gives you an understanding of the complexity, which enables you to understand the required time and therefore be more patient. [C7]

Also, information about success rates, such as the chance of pregnancy with PGD and risks, such as the likelihood of a miscarriage after PND, were mentioned by the majority as having a significant influence on reproductive decision-making. Some couples added that duration of the procedures and family planning are strongly related and should therefore also be emphasized in the decision aid.

Family planning might be different than expected. If you opt for PGD, a large family is less realistic. So, family planning should be part of the decision aid. [C6]

One couple pointed out that clear information should be provided about the time and effort required to prepare for PGD (e.g. visitations required with various health care providers). Another couple pointed out that it would be helpful to explain why family members need to be involved in case one opts for PGD and how the involvement of family members can be related to a longer duration of the trajectory. The majority emphasized the need for simple non-medical language and comprehensible content, as couples would like to share the information in the decision aid with relatives who are generally unfamiliar with the subject.

Functionalities and applications in the decision aid

Most couples were of the opinion that images may contribute to the creation of a realistic impression regarding the procedures of PND and PGD. However, some also expressed their concern regarding the complexity of images. Additionally, the majority

recognized the use of videos as helpful in demonstrating procedures and techniques. None of the couples thought that it would be helpful to present some type of a conclusion or advice regarding a "best fitting option" after completing the decision aid. Instead, most couples preferred some form of an evaluation, such as an overview of couples' preferences and values. The majority was of the opinion that it would be better to provide an overview and let couples interpret this overview by themselves. A few couples acknowledged that the inclusion of a chat application or discussion forum could be valuable. However, a regularly expressed concern was the risk of receiving incorrect information.

Reliable and tailored information is necessary. A forum may raise unnecessary concerns as certain issues may not be applicable to all couples. [C7]

A potential alternative indicated by almost all couples was the provision of narrative stories (i.e. personal stories of couples who have already made a reproductive decision). Reading stories of experienced couples would make the decision-making process more personal as couples do not only want to read about scientific facts. One couple added it would be helpful to know that there are more couples who are struggling with the same problems.

Barriers and facilitating factors regarding the use of the decision aid

Several couples indicated the use of difficult language (e.g. medical abbreviations) and an extensive amount of text as potential barriers to the use of the decision aid. Although a long duration was not considered as a barrier by most couples, a maximum duration of 60 minutes was recommended. In order to promote first use of the decision aid, the majority indicated that reliability of the information and expertise of the development team were important facilitating factors. Furthermore, all couples were of the opinion that referral to the decision aid by their health care provider would encourage use of the decision aid.

Implementation of the decision aid

All but one couple agreed that the best time for implementing the decision aid would be in-between the moment of receiving a positive genetic test result and the follow-up consultation at one of the clinical genetic departments. Providing the decision aid before follow-up consultations was desirable as the decision aid may raise important questions to discuss with health care providers. Several couples believed that this may lead to a more interactive consultation. However, some concerns were expressed

about providing the decision aid immediately after confirmation of a genetic mutation as this can be an emotionally challenging time. All couples agreed that it is the role of the health care provider to choose the best moment to refer couples to the decision aid. To foster implementation, most couples suggested including information about the decision aid in the standard report they receive after consultation.

Study 2: Needs assessment among clinical geneticists

Clinical geneticists' characteristics

All eight clinical geneticists who were invited participated in the dyadic interviews (two males and six females) with a mean age of 53.0 years (SD=2.8) for males and 45.8 years (SD=8.3) for females. The majority had more than 10 years of work experience in the area of oncogenetic counseling; however, half of the clinical geneticists had no experience with the use of patient decision aids (mean=1.50, SD=0.53).

Preferences and needs regarding the content of the decision aid

Informational content of the decision aid and presentation of information

Although clinical geneticists agreed upon natural conception without genetic testing, PND and PGD as main reproductive options in the decision aid, two clinical geneticists indicated that attention to other reproductive options (e.g. refraining from fulfilling one's wish to have a child, and use of donor gametes) would also be helpful to make couples aware of the availability of these options. Furthermore, the majority considered a complete explanation of the procedures and techniques used in PND and PGD (e.g. duration, physical and emotional burden, inclusion criteria, IVF and pregnancy termination) and information about success rates (e.g. pregnancy) as important issues to be included in the decision aid. According to the majority, the decision aid should clearly indicate the required time investment for PGD (e.g. visitations required with various health care providers) and the timing of PND procedures (i.e. required duration of pregnancy). Also, the waiting time related to the genetic test result and the possibility of a moral dilemma concerning a pregnancy termination with PND were mentioned as important issues to be included in the decision aid. Clinical geneticists agreed the decision aid should create realistic expectations and therefore also negative features (e.g. the risk of not having unaffected embryos to transfer with PGD) and risks (e.g. increased risk of miscarriage with PND) should be described.

Functionalities and applications in the decision aid

Six clinical geneticists mentioned that the use of visual materials, especially videos, in addition to text would be valuable to create a realistic impression of procedures and techniques used in PND and PGD. Three clinical geneticists suggested the importance of balancing the language used in the decision aid to relate to people of lower and higher education. To accomplish this, all clinical geneticists agreed on the use of different presentation formats (e.g. text, videos, images, graphics). Additionally, five clinical geneticists preferred some form of an evaluation, such as an overview of couples' preferences and values, after completing the decision aid over a conclusion or advice regarding a "best fitting option."

It is better to list all points discussed in the decision aid together with couples' answers, instead of providing a conclusion. Couples can interpret their answers by themselves together with a health care provider. [CG 3]

All but one of the clinical geneticists expressed concerns regarding a chat application, with the main concern that incorrect information could be presented.

Sometimes, the first part of a consultation consists of explaining inaccuracies and only after that you can start discussing facts. That is something that can also occur as a result of a chat application included in the decision aid. [CG 2]

Although objectivity and the provision of balanced information remained an essential point, most clinical geneticists indicated that the use of narrative stories could be beneficial.

A video in which couples tell their experiences with the reproductive option of their choice would be interesting. This could absolutely be of additional value to the decision aid. But make sure it shows the whole spectrum of positive and negative stories. [CG 2]

Barriers and facilitating factors regarding the use of the decision aid

Clinical geneticists agreed upon the importance of referral to the decision aid by involved health care providers to promote its initial use. The use of difficult language (e.g. medical terms) was considered to be a hindrance for couples regardless of educational level, and a maximum duration of 60 minutes to complete the decision aid was recommended. To facilitate the sustained use of the decision aid, the majority emphasized user-friendliness and the use of evidence-based and up-to-date information.

Preferences and needs concerning the implementation of the decision aid

When asked about their opinion regarding the availability of the decision aid, clinical geneticists were divided on whether the decision aid should be freely available (e.g. free access on the internet) or whether access should be restricted to eligible couples (e.g. by means of unique login data, distributed by health care providers). The preference for a freely available tool was mainly based on the idea that a larger group of potential couples could be reached, whereas those in favor of restricted access expressed concerns about reaching a wrong audience (e.g. carriers for which PND or PGD is not available).
Optimal timing for implementing the decision aid was considered to be in between the moment of receiving a positive genetic test result and follow-up consultations (e.g. aftercare and consultations regarding available reproductive options). All clinical geneticists agreed that it is the responsibility of counselors to refer to the decision aid. To promote implementation, clinical geneticists agreed that referral should not take too much effort or greatly deviate from their daily practice. Including a link to the online decision aid in the standard report counselees receive after consultation was therefore suggested by all clinical geneticists.

Discussion

This study provides insights into the preferences and needs of couples at risk for hereditary cancer and clinical geneticists involved in oncogenetic counseling with respect to the development and implementation of a patient decision aid regarding reproductive decision-making. Couples and clinical geneticists expressed similar ideas and opinions regarding the content, barriers and facilitating factors regarding the use of the decision aid, and its implementation. Both stakeholder groups agreed on the inclusion of information about success rates, risks, procedures, and techniques used in PND and PGD and the responsibility of health care providers to refer to the decision aid in order to optimize utilization. Furthermore, the use of visual materials, especially videos, was considered important in order to create a realistic impression of procedures and techniques used in PND and PGD. Emphasis was placed on the use of simple non-medical language. Overall, there appears to be a strong preference among both stakeholder groups for incorporating narrative stories that detail the experiences of couples with reproductive decision-making.

Research recommendations

Currently, insufficient evidence exists about the effectiveness of narrative stories on informed decision-making and how to incorporate these stories in decision aids.[19,20] Future research is therefore necessary to explore essential elements for the content of narrative stories and its effectiveness on decision-making.

Study limitations

A limitation of Study 1 relates to the fact that only couples who had already made a reproductive decision were included. These couples had to reflect in retrospect on their reproductive decision-making process, which may have led to recall bias. These couples, however, have extensive experience with the decision-making process and may therefore be better able to evaluate and describe their needs and wishes throughout the entire process. Furthermore, only clinical geneticists were included in Study 2. Although they are likely to be most involved in the implementation and use of the decision aid, other health care providers such as genetic counselors, social workers, PGD/IVF physicians, and gynecologists may add other valuable insights.

Practical implications

The findings from this study, combined with results from preliminary investigations regarding reproductive decisional motives and considerations among the target group,[1] will guide the development of a patient decision aid on reproductive options for couples at risk for hereditary cancer and child wish. Ultimately, it is expected that this decision support will enable end-users to make an informed decision, which may lessen the negative psychological impact of decision-making on couples' daily life and wellbeing.

Conclusion

Although the reproductive decision-making process of couples with hereditary cancer has increasingly been investigated and the provision of decision support is suggested, currently, no specific decision support tool is available for this target group. The present study provides an overview of the preferences and needs of couples and clinical geneticists regarding reproductive decision support. Integrating these findings with findings regarding reproductive decisional motives and considerations from previous studies is essential in guiding the development of a patient decision aid that optimally corresponds to the preferences and needs of end-users.

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Chapter 3

The development of an online decision aid to support persons having a genetic predisposition to cancer and their partners during reproductive decision-making: a usability and pilot study

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Abstract

An online decision aid to support persons having a genetic predisposition to cancer and their partners during reproductive decision-making was developed. A two-phase usability test was conducted among 12 couples (N=22; 2 persons participated without their partner) at risk for hereditary cancer and 15 health care providers. Couples and health care providers expressed similar suggestions for improvements, and evaluated the modified decision aid as acceptable, easy to use, and comprehensible. The final decision aid was pilot tested (N=16) with paired sample t tests comparing main outcomes (decisional conflict, knowledge, realistic expectations regarding the reproductive options and decision self-efficacy) before (T0), immediately (T1) and 2 weeks after (T2) use of the decision aid. Pilot testing indicated decreased decisional conflict scores, increased knowledge, and improved realistic expectations regarding the reproductive options, at T1 and T2. No effect was found for couples' decision self-efficacy. The positive findings during usability testing were thus reflected in the pilot study. The decision aid will be further evaluated in a nationwide pretest–posttest study to facilitate implementation in the onco-genetic counselling setting. Ultimately, it is expected that the decision aid will enable end-users to make an informed decision.

Introduction

A predisposition for hereditary cancer is usually autosomal dominant, implying that there is a 50% risk of transmitting the mutation to offspring. Transmission of a predisposition for hereditary cancer to offspring means passing on a generally highly increased risk of developing cancer. For the relatively frequent breast cancer gene mutations in *BRCA1*or *BRCA2* this implies risks of 27-57% and 6-40% of developing breast respectively ovarian cancer by the age of 70.[1,2] This knowledge may evoke challenging reproductive decision-making processes among persons having a genetic predisposition to cancer and their partners.[3-6] Couples with a predisposition for hereditary cancer who want a genetically related child can opt for natural conception without genetic testing, accepting the risk of passing on the predisposition for cancer to a child, or they could opt for prenatal diagnosis (PND) assuming the intention to terminate the pregnancy if the fetus has the mutation,[7] or for preimplantation genetic diagnosis (PGD), to prevent transmission of the mutation to their offspring. PGD involves a multi-stage diagnostic process in which embryos are examined for the presence of the familial mutation before pregnancy is established.[7] Annually approximately 60 couples with a predisposition for hereditary cancer start a PGD procedure in the Netherlands,[8] a number that has been steadily increasing since its introduction 10 years ago. In 2016, a total of 40 couples with a predisposition for hereditary breast and ovarian cancer *(HBOC)* started a PGD procedure and 7 couples with familial adenomatous polyposis *(FAP)*. The uptake of PND for hereditary cancer is relatively low (<2%) with up till 2013 only a total of six couples with *HBOC* performed PND (<0.2%) and a total of six couples with *FAP* (1.6%).[9] Although awareness of PGD (66%) and PND (61%) are similar, the acceptability of PGD (80%) is notably higher compared to PND (26%).[10]

The decision regarding which reproductive option to choose is highly preference-sensitive. Research has shown that persons having a genetic predisposition to cancer and their partners may experience the reproductive decision-making process as complex.[6,11-13] A recent study among couples with *HBOC*, showed that 43% experienced reproductive decision-making as (very) difficult.[13] Feelings of uncertainty and guilt may be experienced, particularly among couples who opt for natural conception without genetic testing.[5] In deliberating the reproductive options, couples consider personal values and (dis)advantages of all options, which can be categorized into physical (e.g. physical burden of IVF treatment necessary for PGD), psychological (e.g. loss of romance regarding pregnancy), social (e.g. eliminate mutation in family line), ethical (e.g. moral duty to protect the child) and practical considerations (e.g. frequent hospital appointments).[5]

The decision regarding which reproductive option to pursue should ideally involve an informed decision-making process by an educated and empowered couple. In order to promote informed decision-making, decisional support strategies can be effective. Compared to usual care interventions, decision aids have been found to improve people's knowledge regarding their options, reduce decisional conflict, and decrease the proportion of people remaining undecided.[13-16] Incorporating a patient decision aid in reproductive counselling can therefore be helpful in supporting persons having a genetic predisposition to cancer and their partners in making their reproductive decision.[5,17]

The present report is part of a project on the development and implementation of an online decision aid. Firstly, we conducted a needs assessment study regarding the preferences and needs of couples and health care providers regarding the decision aid.[18] We integrated the results of the needs assessment study with knowledge on reproductive decisional motives and considerations and designed a concept version of the decision aid.[18] Its user friendliness, strengths and limitations were assessed during usability testing and some modifications were made. Subsequently, the final decision aid was pilot tested. We report on the results of the usability testing and the preliminary results regarding the effectiveness of the decision aid, generates during beta testing (i.e. end-user testing) by means of a pilot study.[19]

Methods

Developmental process and content of the decision aid

The decision aid was developed according to the International Patient Decision Aids Standards[20] in collaboration with a steering group including health care providers (e.g. clinical geneticists, and social workers), experts in health communication and medical decision-making, psychologists and persons having a genetic predisposition to cancer and their partners who are planning to have children. Our needs assessment study showed many similarities between the expressed preferences and needs of both couples and health care providers concerning the content, barriers and facilitating factors regarding the use of the decision aid, and its implementation.[18] The prototype of the decision aid contained:

1. Information about the risk of transmitting the mutation to offspring.
2. Information about couples' options to have genetically related child(ren) (natural conception without genetic testing, PND and PGD) with the aim to increase

knowledge. In the needs assessment study, participants agreed upon natural conception without genetic testing, PND and PGD as main reproductive options to be included in the decision aid.[18] Adoption and use of donor gametes are mentioned in the decision aid to make couples aware of the existence of these options. However, as most couples pursue their wish to have genetically related child(ren),[21] these options were not included further.

3. Probabilities of different outcomes and the burden of the treatment of reproductive options (e.g. risk of miscarriage after PND, likelihood of pregnancy with PGD) to increase participants' accuracy of risk comprehension. Based on current recommendations[22] and the preferences of end-users, probabilities were presented in multiple suitable formats using text and videos (e.g. verbal, and population diagrams).
4. A summary table of important features of each reproductive option to facilitate comparison.
5. Values clarification exercises (VCE).[23] Participants were presented with 18 statements representing values and motives considered important for reproductive decision-making.[5] Participants were asked to rate personal agreement of each statement on a scale from 1 (disagree) to 6 (agree). By linking login codes, an automated combined overview of both partners' input could be generated to facilitate communication about agreements and possible discrepancies.
6. A question prompt sheet, providing examples of questions and requests for additional information and space for own questions, to facilitate discussion with health professionals and others.
7. Information regarding the scientific resources used to underpin the decision aid content, information on the development team (including 'conflicts of interest COI'), funding resources and contact information.

Usability testing

Minor textual revisions were made after review of the prototype decision aid by the steering group. Subsequently, a two-phase usability test with couples and health care providers was conducted. After the first phase the decision aid was adapted based on provided feedback. To make final modifications, a second usability phase was conducted.

Participants and recruitment

Dutch couples who consider PGD are referred to the Clinical Genetics Department of the Maastricht University Medical Centre (Maastricht UMC+) for an once only informative consultation. The couples are registered in a database. Eligible participants for the usability test were selected from this database. Couples were eligible for participation if one partner had a confirmed mutation for a hereditary cancer syndrome for which PND and PGD are available in the Netherlands, if they had made a reproductive decision (as indicated in medical records), if both partners were 18 years or older, had sufficient knowledge of the Dutch language, and if they had ample experience with the use of computers and the Internet. Although participation of both partners was encouraged, participation of one partner (regardless of being carrier) was allowed. Couples who provided written informed consent for participation were contacted by telephone to schedule an appointment at the hospital, or, if preferred, at the couple's home.
Furthermore, two representatives of each of the nine Clinical Genetics Departments in the Netherlands, who were directly involved in the counseling and care of end-users (e.g. clinical geneticists and gynecological oncologists) were invited to participate (N=18). Appointments were scheduled at convenient workplaces.

Procedures

Usability testing was conducted using a mixed methods design (i.e. qualitative and quantitative) in between March and June 2016. First, couples and health care providers were asked to fill in a brief questionnaire. Age, gender, educational level, carrier status, type of cancer, and experience with the use of computers and the Internet were assessed for couples. Health care providers completed questions concerning their professional perspectives regarding the feasibility of implementing the decision aid. Subsequently, participants were invited to an online 'cognitive walkthrough' of the decision aid in presence of the researcher. They were asked to think aloud and to express freely their opinion regarding its content, functionalities, format and layout.[24] The researchers occasionally asked predetermined questions. 'Thinking aloud' sessions were followed by interviews. The content of the semi-structured topic guides for the interviews focused on the perceived comprehensibility, usability, efficiency and acceptability of the decision aid and were largely similar for the couples and the health care providers. At the end of the interviews, couples were asked to evaluate the decision aid with regard to content, lay-out and usability on a scale of 1-10 and to complete the System Usability Scale (SUS) for the subjective assessment of usability.[25-27] Couples received 15 euros in vouchers and their travel expenses were

reimbursed. Health care providers were asked to evaluate the decision aid in terms of quality, completeness, lay-out and usability on a scale of 1-10 with higher scores indicating better usability.

Data analysis

Qualitative data derived from the audiotaped 'thinking aloud' sessions and the interviews were transcribed verbatim. Open coding (developing categories of information) and axial coding (exploring the relationship of categories) was performed independently by two researchers (K.R. and M.T.) to derive and categorize main issues. Data from the demographic questionnaire and SUS were analysed by means of descriptive statistics and quantified as mean and standard deviation or absolute number and percentage, using SPSS version 23.

Pilot study

Participants and recruitment

Health care providers of all Clinical Genetics Departments in the Netherlands recruited eligible couples during or after oncogenetic consultation. The same inclusion criteria were used as for usability testing, except that couples had not yet made a reproductive decision. Couples were eligible if they expressed the wish to have children within 5 years and have not yet made a definitive decision regarding their preferred reproductive option. Although participation of both partners was encouraged, participation of one partner was allowed.

Procedures and instrumentation

Adaptation of feedback provided during usability testing resulted in the final decision aid. It was pilot tested from November 2016 to January 2017. Eligible couples were provided with an information brochure, to introduce the study together with a link to an online registration page. After registration, participants received online information about the study and an online informed consent form. After providing consent, participants were directed to an online (baseline) questionnaire (T0) and received a personal login code for the decision aid. Duration of visits and page visits were monitored. Immediately after use of the decision aid, participants were directed to the second online questionnaire (T1). Two weeks after baseline, participants were asked by e-mail to complete the last questionnaire (T2). Participants who did not complete the questionnaire received a reminder by e-mail. Questionnaires were completed separately

by both partners. After completing all questionnaires, participants received 15 euros in vouchers.

A demographic questionnaire assessed gender, age, educational level, carrier status, type of cancer, and personal history of cancer at T0. Less than primary, primary and lower secondary education was considered as low education levels. Upper secondary and post-secondary non-tertiary education was considered as middle education levels. Tertiary education was considered as a high education level. In addition, participants' reproductive history was assessed. The primary outcome measure, i.e. participants' level of *decisional conflict*, was assessed by the Decisional Conflict Scale at T0, T1 and T2. The questionnaire contains 16 items, each scored on a 5-point Likert scale ranging from 0 (strongly agree) to 4 (strongly disagree). Total scores range from 0 (no decisional conflict) to 100 (extremely high decisional conflict).[28] Participants' current *knowledge of the three reproductive options* was assessed by 15 closed-ended questions (true/false/not sure) at T0, T1 and T2, see Table 3.1.[10] Three questions measured participants' knowledge of natural conception without genetic testing (e.g. 'When opting for natural conception, there is a 50% risk of transmitting the mutation to offspring'), five questions measured knowledge of PND (e.g. 'prenatal diagnosis takes place during pregnancy') and seven questions measured knowledge of PGD (e.g. 'In vitro fertilization (IVF) is necessary to perform PGD'). One point was provided for each correctly answered question, which could lead to a maximum score of 15. *Realistic expectations regarding the three reproductive options* were assessed by three questions at T0, T1 and T2 (i.e. "what is the extra risk of miscarriage due to PND?", "what is the chance of pregnancy after one IVF treatment with PGD?", "what is the risk of complications with PGD?"). These questions contained eight to eleven response options. One point was provided for each correctly answered question, which could lead to a maximum score of three.[29] Participants' *decision self-efficacy* was assessed by the Decision Self-Efficacy Scale at T0, T1 and T2. The questionnaire contains 11 items, each scored on a 5-point Likert scale ranging from 0 (not at all confident) to 4 (very confident). Total scores range from 0 (extremely low self-efficacy) to 100 (extremely high self-efficacy).[30]

Table 3.1 Knowledge of the three reproductive options (pilot study)

No.	Item
	Natural conception without genetic testing
1	When opting for natural conception, there is a 50% risk of transmitting the mutation to offspring (T)
2	When opting for natural conception, besides standard procedures, there will be no extra examinations performed during pregnancy (T)
3	When opting for natural conception, during delivery it is already clear whether your child has the mutation (F)
	Prenatal diagnosis
4	Prenatal diagnosis takes place during pregnancy (T)
5	When opting for prenatal diagnosis, you and your partner can naturally conceive (T)
6	Results of prenatal diagnosis will always follow within 1 week (F)
7	Prenatal diagnosis is possible from 6 weeks of pregnancy upon (F)
8	Prenatal diagnosis is possible in most of the medical centers in the Netherlands (T)
	PGD
9	In vitro fertilization (IVF) is necessary to perform PGD (T)
10	PGD is possible in every hospital in the Netherlands (F)
11	For PGD, cooperation of family members is a prerequisite (T)
12	Hormone-use by the woman is necessary for a PGD treatment (T)
13	PGD takes place before the woman is pregnant (T)
14	A PGD treatment takes at least 6 months (T)
15	In the Netherlands, a woman's maximum age for PGD is 45 (F)

Total score range 0 to 15

Data analysis

To test for intra-couple correlation, we compared two models for testing the difference in the main outcome (decisional conflict); one linear mixed-effects model in which clustering within couples was corrected for, and one model without correction. Both models yielded similar results, and a likelihood-ratio test showed that correction did not lead to a better fit (likelihood ratio=0.60, p=0.44). Therefore, all participants can be analyzed as separate individuals and we chose to report the simpler model without correction for clustering and used paired sample t tests to compute differences between the first and subsequent measurements. P-values of <0.05 were considered to indicate statistical significance.

Compliance with ethical standards

This study was approved by the medical ethics committee of Maastricht UMC+ (METC 14-5-089) and registered in the Dutch Trial Register (NTR5467). The authors declare that they have no conflict of interest. All procedures performed in this study were in accordance with the ethical standards of the medical ethics committee of Maastricht University Medical Centre and have been performed in accordance with the

ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all patients included in this study.

Results

Usability testing

Couples' characteristics

Thirty-nine couples who had reproductive counseling for hereditary cancer between 2013 and 2015, were invited for participation by mail. Twelve couples provided written informed consent (N=22; 2 persons participated without their partner), and participated in usability testing (response rate 30.8%). Main reasons for non-participation were a lack of time and not wanting to relive the psychological burden associated with reproductive decision-making. The mean age was 34.5 years for males (SD=4.5) and 29.9 years (SD=3.7) for females. Most participants were highly educated (64%), a minority had lower education levels (14%) and 23% had an average education level. The types of cancer concerned hereditary breast and ovarian cancer (N=6), familial adenomatous polyposis (N=2), Lynch syndrome (N=3) and multiple endocrine neoplasia (N=1).

Usability results couples

During the first phase of the usability test, three couples and one female participant without partner (N=7 persons) participated. A frequently expressed concern during the 'think aloud' sessions was the amount of scrolling needed to read all provided information. Other suggestions mainly pertained to textual improvements and adaptions to further improve lay-out (e.g. change the order of information and a change of colors). The average duration of the sessions was 71 minutes (range 60-80). Seven couples and one female participant without partner (N=15 persons) participated in the second phase of usability testing to make final modifications. In general, couples appreciated the lay-out and stated that information in the decision aid was clear and comprehensible. Most couples indicated that they would have used the decision aid, if it had been available at the time of reproductive decision-making, and stated that all functions included in the decision aid were well integrated (Table 3.2). Couples generally agreed that the decision aid was not unnecessarily complex (Table 3.2). With a mean SUS score (range 0 to 100) of 91.33 (SD=7.61), the decision aid's usability was considered high. Couples graded the decision aid on a scale of 1-10 with a mean of

8.5 (SD=0.5) for the content, a mean of 8.3 (SD=0.8) for lay-out and a mean of 8.0 (SD=0.9) for usability.

Table 3.2 System Usability Scale results (usability study)

No.	Item	N=15 Mean (SD)
1	I think that I would like to use the DA frequently	3.07 (1.16)
2	I found the DA unnecessarily complex	0.20 (0.78)
3	I thought the DA was easy to use	3.53 (0.74)
4	I think that I would need technical support to be able to use the DA	0.00 (0.00)
5	I found the various functions included in the DA well integrated	3.47 (0.64)
6	I thought there was too much inconsistency in the DA	0.40 (1.06)
7	I would imagine that people would learn to use the DA very quickly	3.53 (0.52)
8	I found the DA very cumbersome to use	0.07 (0.26)
9	I felt very confident using the DA	3.73 (0.46)
10	I needed to learn a lot before I could get going with the DA	0.13 (0.35)
	Total score	91.33 (7.61)

Total score range 0-100; higher scores indicate higher perceived usability. DA: decision aid

Health care providers' characteristics

Fifteen health care providers participated (response rate 83.3%) in the 'think aloud' sessions and individual interviews (1 male and 14 females). The mean age for males was 61 years and mean age for females was 43.5 years (SD= 6.7). These health care providers were clinical geneticists (N=6), gynecological oncologists (N=3), genetic counselors (N=2), social worker (N=1), medical oncologists (N=2) and an ophthalmologist (N=1; involved in the care and counseling of persons with a predisposition for retinoblastoma and their partners). The majority had more than five years of work experience in the area of oncogenetic counseling and 80% had no or limited experience with the use of decision aids.

Usability results health care providers

The average duration of the sessions was 59 minutes (range 15-80). Similar to couples, health care providers highly appreciated the lay-out of the decision aid, although during 'think aloud' sessions the use of more subtle colors was suggested. Several textual suggestions (e.g. avoidance of medical/technical terms) and suggestions to change the order of information were provided. The different forms of information provision (e.g. written and video-based) and the VCE were appreciated. To promote (continued) implementation, it was suggested to include a link to the decision aid in the standard report couples receive after consultation. The format of the final decision aid was considered as acceptable, easy to use and comprehensible. Health care providers

graded the decision aid on a scale of 1-10 with a mean score of 8.2 (SD=0.5) for quality, a mean of 8.5 (SD=0.5) for completeness, a mean of 7.9 (SD=0.4) for lay-out and a mean of 7.3 (SD=0.7) for usability. The moderate mean usability score of 7.3 was likely due to the order in which information was presented in the decision aid. Changes were made to the decision aid based on feedback provided.

Pilot study

Participants' characteristics

Eight couples (N=16) participated in the pilot study. A response rate could not be estimated because the exact number of patients invited by each Clinical Genetics Department is unknown due to the large number of counselors recruiting. Table 3.3 shows an overview of the sample characteristics. Participants' average age was 32.4 years for males (SD=4.6) and 29.1 years (SD=4.3) for females. None of the participants had a low education level. Of the participants, 68.8% already had a preferred option in mind at baseline, 31.2% did not. None of the participants changed their mind from T0-T1 and from T0-T2. The mean time spent using the decision aid was 27 minutes (range 2-104 minutes) and participants viewed on average 20 out of 36 pages. 69% viewed at least 25 pages with pages on contact information and disclaimer being the least viewed.

Preliminary effects of decision aid

All 16 participants completed T0 and T1 and 15 participants completed T2. As shown in Table 3.4, mean decisional conflict scores (range 0-100) decreased from a mean of 27.6 (SD=19.3) at baseline, to 11.8 (SD=15.3) at T1 (t=5.73; p<0.001; ES=1.73) and 8.3 (SD=6.4) at T2 (t=3.37; p=0.01; ES=1.12). The mean level of knowledge (range 0-15) increased from 8.2 (SD=3.5) at baseline, to 12.4 (SD=3.7) at T1 (t=-7.73; p<0.001; ES=-1.93) and 12.8 (SD=2.1) at T2 (t=-10.05; p<0.001; ES=-2.69). Further, realistic expectations regarding the three reproductive options (range 0-3) increased from 0.4 (SD=0.5) at baseline, to 1.9 (SD=1.0) at T1 (t=-6.45; p<0.001; ES=-0.75) and 1.3 (SD=1.0) at T2 (t=-4.33; p<0.001; ES=-0.25). Couples' decision self-efficacy (range 0-100) slightly increased but did not significantly change over time from 80.4 (SD=16.9) at baseline, to 81.3 (SD=16.0) at T1 (t=-0.28; p=0.782; ES=-0.07) and 83.9 (SD=19.6) at T2 (t=-0.38; p=0.708; ES=-0.10).

Table 3.3 Sample characteristics (pilot study)

Sample characteristics (n=16)	N	%
Gender		
Male (M)	8	50.0
Female (F)	8	50.0
Age (years)		
Male	32.4 (SD=4.6)	
Female	29.1 (SD=4.3)	
Education		
Middle	7	43.8
High	9	56.2
Carrier status		
Male	2	12.5
Female	6	87.5
Syndrome		
Hereditary Breast and Ovarian Cancer	7 (5F/2M)	87.5
Lynch syndrome	1 (F)	12.5
Have (had) cancer		
Yes	4	25.0
No	12	75.0
Reproductive history		
Children		
Yes	2	12.5
No	14	87.5
Planning to have children		
Currently pregnant	2	12.5
Planning to have children within five years	14	87.5
Preferred reproductive option in mind at T0		
Yes	11	68.8
No	5	31.2

Table 3.4 Overview of main outcome measures (pilot study)

Questionnaire (N=16)	Means (SD)			Paired samples t-test			
	T0	T1	T2	T0-T1		T0-T2	
				T	*p*	*T*	*p*
Decisional conflict							
Total score (0-100)	27.6 (19.3)	11.8 (15.3)	8.3 (6.4)	5.73	<0.001	3.37	0.010
Uncertainty	43.8 (28.5)	27.6 (30.4)	29.2 (27.7)	3.67	0.002	2.19	0.047
Informed	40.6 (22.5)	17.7 (18.5)	11.3 (13.7)	5.21	<0.001	5.97	<0.001
Values clarity	30.2 (26.2)	19.3 (21.9)	11.9 (15.6)	2.78	0.014	3.54	0.004
Support	24.0 (16.6)	17.7 (18.0)	13.7 (14.1)	1.60	0.131	2.65	0.020
Effective decision	17.6 (15.0)	8.0 (15.3)	5.6 (11.5)	4.54	<0.001	1.71	0.126
Knowledge							
Total score (0-15)	8.2 (3.5)	12.4 (3.7)	12.8 (2.1)	-7.73	<0.001	-10.05	<0.001
Natural conception (0-3)	2.0 (1.0)	2.3 (0.9)	2.5 (0.9)	-1.78	0.096	-2.45	0.028
PND (0-5)	1.8 (1.7)	3.9 (1.4)	4.5 (2.0)	-5.33	<0.001	-3.96	<0.001
PGD (0-7)	4.4 (1.8)	6.1 (1.9)	6.4 (0.9)	-5.65	<0.001	-3.67	0.003
Realistic expectations (0-3)	0.4 (0.5)	1.9 (1.0)	1.3 (1.0)	-6.45	<0.001	-4.33	<0.001
Decision self-efficacy (0-100)	80.4 (16.9)	81.3 (16.0)	83.9 (19.6)	-0.28	0.782	-0.38	0.708

Discussion

This study presents the development and preliminary evaluation of an online decision aid that aims to support persons having a genetic predisposition to cancer and their partners during their reproductive decision-making. Previous studies demonstrated that these couples may experience the decision-making process as complex.[6,11,12,31] The decision aid aims to decrease participants' level of decisional conflict, increase participants' knowledge, improve realistic expectations regarding the available reproductive options and increase participants' decision self-efficacy. The high mean score on the SUS indicates that the decision aid meets the needs of the target population. During usability testing, couples and health care providers expressed similar suggestions for improvements. Overall the decision aid was evaluated as acceptable, easy to use, and comprehensible. The positive findings during usability testing were reflected in the preliminary results regarding efficacy of the decision aid, indicated by reduction of couples' decisional conflict levels, increases in knowledge levels and improvement of realistic expectations regarding available reproductive options. This suggests that with use of the decision aid, informed decision-making among persons having a genetic predisposition to cancer and their partners during reproductive decision-making may be improved. Despite the complexity of the decision,

couples' confidence in their ability to make a decision was already high at baseline and did not increase as a result of decision aid use, possibly reflecting a ceiling effect. This may be explained by the finding that 11 out of 16 participants already had a preferred reproductive option in mind at baseline, indicating that couples had already considered the available reproductive options to a certain extent. However, although couples overall felt confident about making a reproductive decision, baseline knowledge levels were relatively low. As a solid knowledge base is regarded as a prerequisite for informed decision-making,[32] this finding further emphasizes the need for informational support among our sample.

In order to optimize the impact of the decision aid with regard to decision self-efficacy, the use of modeling techniques may be considered,[33] for instance by means of incorporating narrative stories in the decision aid. Previous research, including a needs assessment regarding the current decision aid, indicated that both couples and health care providers advocate the provision of narrative stories during reproductive decision-making.[5,18] These personal stories detail the experiences of couples with reproductive decision-making and are aimed at providing illustrative examples of others' experiences. Narratives can be useful in overcoming preconceived beliefs and cognitive biases and integrating narratives into healthcare communication is increasingly being recommended.[34,35] Currently insufficient evidence exists about the effectiveness of narrative stories on informed decision-making and how to incorporate these stories in decision support tools.[36,37] Future research should explore essential elements of the content of narrative stories and their effectiveness in facilitating decision-making.

A limitation of this study relates to the small sample size and selection bias towards higher educated and possibly higher health literate users which may limit generalizability of the results. Subsequently, the decision aid will be further evaluated in a nation-wide effect study to draw more robust conclusions. Ultimately, it is expected that the decision aid will enable end-users to make an informed decision, which may lessen the negative psychological impact of decision-making on couples' daily life and wellbeing.

Conclusions

The current findings indicate that the decision aid was well received by both couples and health care providers as reflected in high usability scores and promising preliminary efficacy during the pilot study. The decision aid will be further evaluated in a nationwide pretest-posttest study.

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Part II

Evaluation

Chapter 4

Online decision support for persons having a genetic predisposition to cancer and their partners during reproductive decision-making

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Abstract

A nationwide pretest-posttest study was conducted in all clinical genetic centres in the Netherlands, to evaluate the effects of an online decision aid to support persons who have a genetic predisposition to cancer and their partners in making an informed decision regarding reproductive options. Main outcomes (decisional conflict, knowledge, realistic expectations, level of deliberation and decision self-efficacy) were measured before use (T0), immediately after use (T1), and at two weeks (T2) after use of the decision aid. Paired sample *t* tests were used to compute differences between the first and subsequent measurements. T0-T1 and T0-T2 comparisons indicate a significant reduction in mean decisional conflict scores with stronger effects for participants with high baseline decisional conflict. Furthermore, use of the decision aid resulted in increased knowledge levels and improved realistic expectations. Level of deliberation only increased for participants with lower baseline levels of deliberation. Decision self-efficacy increased for those with low baseline scores, whereas those with high baseline scores showed a reduction at T2. It can be concluded that use of the decision aid resulted in several positive outcomes indicative of informed decision-making. The decision aid is an appropriate and highly appreciated tool to be used in addition to reproductive counseling.

Introduction

Most hereditary cancer syndromes follow an autosomal-dominant inheritance pattern, implying that there is a 50% risk of transmitting a pathogenic variant to offspring, with a high risk of a future malignancy as a consequence. For the relatively frequent breast cancer gene mutations in BRCA1 or BRCA2, this implies risks of 27-57% and 6-40% of developing breast respectively ovarian cancer by the age of 70.[1,2] Persons having a genetic predisposition to cancer and their partners have to make fundamental decisions about future reproduction and face difficult challenges.[3-6] Couples have three options to fulfill their wish for a child that is genetically related to both parents. The first option is natural conception without genetic testing, implying acceptance or taking the risk of passing on the pathogenic variant. Furthermore, there are two options for having a genetically related child to both parents without a pathogenic variant. The first option is natural conception with prenatal diagnosis (PND), offering the choice to terminate the pregnancy if the fetus has the pathogenic variant.[7] The second option is preimplantation genetic diagnosis (PGD). PGD offers the option to obtain embryos by in vitro fertilization (IVF) and screen them for the familial pathogenic variant. Only embryos without the pathogenic variant are transferred into the uterus.[7] Levels of awareness for PND (61%) and PGD (66%) are similar, and couples consider PGD (80%) to be more acceptable for hereditary cancer compared to PND (26%).[8]

Couples may experience difficulties with reproductive decision-making[3,9,10] and it was reported that for some, even years later, the impact of reproductive decision-making still had an influence on their lives at a daily basis.[4] In deliberating the options, couples consider personal values and (dis)advantages of the options, such as physical (e.g., burden of PGD treatment), psychological (e.g., loss of sense of romance), social (e.g., elimination of the pathogenic variant in family line), ethical (e.g., moral duty to protect the child), and practical considerations (e.g., reimbursement of treatment).[4] Which reproductive option suits them best, should ideally be decided in an informed decision-making process by an educated and empowered couple, supported by a dedicated health care provider. In order to promote informed reproductive decision-making, the use of decision aids can be effective.[4,11-14] The present study is part of a larger study on the development and implementation of an online decision aid, developed in accordance with the International Patient Decision Aids Standards.[15-17] In this study, we report on the effects of the decision aid evaluated in a nationwide pretest-posttest study in all clinical genetic centres in the Netherlands.

Methods

Participants and recruitment

Health care providers (e.g., clinical geneticists) of all Clinical Genetics Departments in the Netherlands recruited eligible couples during or after oncogenetic consultations from January 2017 to January 2018. Couples were eligible for participation if one partner had a pathogenic variant predisposing for autosomal dominant hereditary cancer, for which PND and PGD are available in the Netherlands. These hereditary cancers include, but are not limited to carriers and partners of carriers of the following types of hereditary cancer: hereditary breast and ovarian cancer (HBOC), hereditary colon cancer (e.g., familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC/Lynch Syndrome), Peutz-Jeghers syndrome, multiple endocrine neoplasia (MEN1/2), retinoblastoma, Von Hippel Lindau disease, Li-Fraumeni syndrome, familial atypical multiple mole/melanoma syndrome (FAMMM). Furthermore, couples needed to have the intention to have children within the next 5 years, and had not yet made a definitive decision regarding their preferred reproductive option. Both partners had to be 18 years or older and both partners needed to have sufficient knowledge of the Dutch language.

Procedures

Eligible couples were provided with an information brochure including a link to an online registration page. After registration, both partners received an informed consent form by e-mail. After providing online informed consent, both partners were individually directed to an online (baseline) questionnaire (T0). Questionnaires were completed separately by both partners. Subsequently, they received a personal login code for the decision aid. It was allowed to use the decision aid together. Duration of use and page visits were monitored. Immediately after use of the decision aid, participants were directed to the second questionnaire (T1). Two weeks after baseline, participants were asked by e-mail to complete a third questionnaire (T2). A reminder was sent to participants who did not complete the T1 questionnaire within 1 day, or the T2 questionnaire within 7 days. An incentive of 15 euros in vouchers was provided after completion of all questionnaires. This study was approved by the medical ethics committee of Maastricht UMC+ (METC 14-5-089).

Content of the decision aid

An extensive explanation of the developmental process and the specific content of the decision aid are provided elsewhere.[16] Overall the decision aid contained:

1. Information about the risk of transmitting the pathogenic variant to offspring and couples' options to have genetically related children.
2. Treatment burden of reproductive options and the chances of different outcomes (e.g., risk of miscarriage after PND) presented in multiple suitable formats using text and videos (e.g., verbal, and population diagrams).[15,18]
3. A comparative summary table of important features of each option.
4. Value clarification exercises (VCE).[19] A total of 18 statements represent values and motives considered important for reproductive decision-making.[4]
5. By linking login codes, a combined overview of both partners' responses on the VCE was provided.
6. A question prompt sheet, providing examples of questions and requests for additional information and space for own questions.
7. Information regarding the scientific resources used to underpin the decision aids content, the development team, funding resources and contact information.

Instrumentation

Gender, age, educational level, carrier status, disease type, number of children and couples' planning for having children were assessed at T0. Less than primary education, primary and lower secondary education were considered as low education levels. Upper secondary and post-secondary non-tertiary education was considered as middle education levels. Tertiary education was considered as a high education level. At T0 and T2, couples were also asked if they already had a consultation with a healthcare provider. The main subject of this consultation (1= solely focusing on the reproductive options, 2= focusing on the consequences of having the pathogenic variant, the reproductive options concerned only a small part) and the profession of the healthcare provider were assessed.

The primary outcome measure, that is, participants' level of ***decisional conflict*** (at T0, T1, T2), was assessed by the Decisional Conflict Scale.[20] The questionnaire contained 16 items (Cronbach's α=0.82). Three items (α=0.90) were used to assess values of uncertainty about the decision, three items (α=0.84) assessed feelings of being informed, three items (α=0.90) assessed personal beliefs regarding the reproductive options, three items (α=0.63) assessed feelings of being supported in making a reproductive decision and four items (α=0.82) assessed the feeling of having made an effective decision. Each item was scored on a 5-point Likert scale ranging from 0

(strongly agree) to 4 (strongly disagree). Total scores ranged from 0 (no decisional conflict) to 100 (extremely high decisional conflict).[20] As the items in the effective decision subscale could not be completed by couples who did not have a preferred reproductive option in mind, a combined score was also calculated for the four other subscales. These 12 items were summed, divided by 12, and multiplied by 25. Total scores ranged from 0 (no decisional conflict) to 100 (extremely high decisional conflict).

Participants' current ***knowledge of the three reproductive options*** (at T0, T1, T2) was assessed by 15 items.[8] Three questions measured participants' knowledge of natural conception without genetic testing (e.g., "When opting for natural conception, there is a 50% risk of transmitting the pathogenic variant to offspring"; 1= correct, 2= incorrect, 3= not sure), five questions measured knowledge of PND (e.g., "PND takes place during pregnancy") and seven questions measured knowledge of PGD (e.g., "IVF is necessary to perform PGD"). One point was provided to each correctly answered question, with a maximum score of 15.

Participants' ***decision self-efficacy*** (at T0, T1, T2) was assessed by the Decision Self-Efficacy Scale.[21] The questionnaire contained 11 items (Cronbach's α=0.84), each scored on a 5-point Likert scale ranging from 0 (not at all confident) to 4 (very confident). Total scores ranged from 0 (extremely) to 100 (extremely high).[21]

Realistic expectations regarding the reproductive options (T0, T1, T2) were assessed by three questions (i.e., "What is the extra risk of miscarriage due to PND?", "What is the chance of pregnancy after one IVF treatment with PGD?", "What is the risk of complications with PGD?"). These questions contained eight to 11 answer options. One point was provided to each correctly answered question, with a maximum score of three.[22]

Level of deliberation (T0, T1, T2) was measured by the Deliberation Scale.[23] The questionnaire contained six items (Cronbach's α=0.90), each scored on a 5-point Likert scale ranging from 1 (totally disagree) to 5 (totally agree). Total scores ranged from 6 (low level) to 30 (high level).

Evaluative items (T1). Participants were asked to give an overall appreciation score for the decision aid at a scale from 1-10 and to indicate in open-ended questions positive and negative features and possibilities for improvements. Furthermore, 10 items (e.g., perceived efficiency and active trust) were used to assess user perceptions[24] including two items of the system usability scale (SUS).[25] Each item was scored on a 5-point Likert scale ranging from 0 (totally disagree) to 4 (totally agree).

Lastly, participants' ***preparation for decision making*** (T1) was measured by the Preparation for Decision Making Scale.[26] The questionnaire contained 10 items (Cronbach's α=0.92), each scored on a 5-point Likert scale ranging from 1 (totally not) to 5 (a lot). Total scores ranged from 0 (low level) to 100 (high level).[26]

Data analysis

Data from the baseline characteristics were analyzed by means of descriptive statistics. Cohen's d was used to report effect sizes; Cronbach's alpha was computed to assess reliability. Furthermore, an intra-couple correlation test was performed before evaluating effects. We compared two models to test for intra-couple correlation regarding the main outcome (decisional conflict); one linear mixed-effects model in which clustering within participants over time and within couples was corrected for, and one model without correction for clustering within couples. Both models yielded similar results, and a likelihood-ratio test showed that correction for the clustering of observations within couples did not lead to a better model fit (likelihood ratio =0.00, p=1.000). Therefore, all participants were analyzed as independent from each other and therefore we chose to report the simpler model without correction for clustering and used the paired sample *t*-test to compute differences between the first and subsequent measurements. For in-depth analyses, a median split was performed for all main outcome measures. Analyses were performed using IBM SPSS version 23 and R version 3.3.3. P-values of <0.05 were considered to indicate statistical significance.

Results

Baseline characteristics

A total of 140 participants visited the registration page, of which 133 provided informed consent. T0 was completed by 115 participants (86.5%) and 110 participants actually visited the decision aid (82.7%). 102 participants completed T1 (76.7%) and 86 participants completed T2 (64.7%). 80.4% of the participants filled out the T1 questionnaire immediately after visiting the decision aid. T2 was on average filled out 17.7 days after T0 (SD=10.05). The mean time spent using the decision aid was 27 min (range 5-95 min) and participants viewed a mean of 15 out of 36 pages. Table 4.1 shows an overview of baseline characteristics. The average age of males (M=31.6, SD=3.6) was slightly higher compared to females (M=29.2, SD=2.9). Most participants were highly educated (57.4%). The most frequently reported hereditary cancer syndrome was HBOC (85.2%).The majority of the participants (89%) already had a consultation in which the reproductive options were discussed. The consultation, mostly with clinical geneticists, focused mainly on the consequences of having the pathogenic variant (58.9%). In 41.1% of the participants, the reproductive options had been the main topic. The majority of the participants had heard of PND (73.0%) and PGD (89.6%) before participation in this study and most of them had also received

information: on PND: 59.1%, on PGD: 69.6%. A little over half of the participants (51.4%) had a preferred reproductive option in mind at baseline.

Table 4.1 Baseline characteristics (N=115)

	N	Percentage
Gender		
Male	51	44.3
Female	64	55.7
Age (years)		
Male	31.6 (SD 3.6)	
Female	29.2 (SD 2.9)	
Education		
Low	11	9.6
Middle	38	33.0
High	66	57.4
Carrier status		
Male carrier	36	31.3
Female carrier	79	68.7
Syndrome		
HBOC	98	85.2
Lynch syndrome	8	7.0
FAP	2	1.7
Li-Fraumeni syndrome	2	1.7
Melanoma syndrome	1	0.9
Hereditary diffuse gastric cancer syndrome	2	1.7
Hereditary leiomyomatosis and renal cell cancer	2	1.7
Children		
Yes	20	17.4
No	95	82.6
Planning to have children		
Trying to conceive now	11	9.6
Within 2 years	70	60.9
Within 5 years	28	24.3
Not sure yet	4	3.5
Otherwise	2	1.7

FAP: Familial Adenomatous Polyposis; HBOC: Hereditary Breast and Ovarian Cancer

Effects of the decision aid

As shown in Table 4.2, total mean *decisional conflict* scores (range 0-100) for all five subscales significantly decreased from 25.30 at baseline, to 18.06 at T1 (Effect Size (ES)=0.73) and 17.22 at T2 (ES=0.51). Total mean decisional conflict scores (range

0-100) excluding the effective decision subscale, significantly decreased from 35.54 at baseline, to 25.33 at T1 (ES=0.78) and 26.31 at T2 (ES=0.44). In-depth analyses (Table 4.3) indicated that participants with high baseline decisional conflict scores (≥33), excluding the effective decision subscale, had a significant reduction in total scores from baseline (M=51.35) to T1 (M=34.46; ES=1.29) and T2 (M=34.72; ES=0.80) whereas participants with low baseline decisional conflict scores (<33) only showed a significant reduction in total scores at T1 (ES=0.43).

As shown in Table 4.2, the mean level of *knowledge* (range 0-15) significantly increased from 9.28 at baseline, to 13.16 at T1 (ES=-1.37) and 12.63 at T2 (ES=-1.11). In-depth analyses (Table 4.3) indicated that knowledge scores significantly increased for both participants with high (>10) and low (≤10) baseline knowledge levels.

As shown in Table 4.2, *Realistic expectations* (range 0-3) significantly increased from 0.72 at baseline, to 1.63 at T1 (ES=-0.85) and 1.08 at T2 (ES=-0.37). In-depth analyses (Table 4.3) showed that realistic expectations were significantly increased at T1 and T2 for participants with low (≤1) baseline levels.

As shown in Table 4.2, with a mean score of 23.23 (range 6-30), the level of *deliberation* was relatively high at baseline and did not show an overall increase over time. However, in-depth analyses (Table 4.3) indicated that participants with lower baseline levels of deliberation (≤24) showed a significant increase over time from 19.44 at baseline, to 22.19 at T1 (ES=-0.57) and 22.27 at T2 (ES=-0.53). No effect was found for participants with higher baseline levels of deliberation (>24).

As shown in Table 4.2, participants' *decision self-efficacy* (range 0-100) did not significantly increase from baseline (77.23) to T1 (79.43; ES=-0.16). From baseline to T2, decision self-efficacy significantly increased (m=79.81; ES=-0.23). In-depth analyses (Table 4.3) indicated that decision self-efficacy of participants with low baseline scores (≤75) significantly increased from 67.00 at baseline to 73.07 at T1 (ES=-0.47) and 75.78 at T2 (ES=-1.03), whereas those with high baseline scores (>75) showed a significant reduction in self-efficacy at T2 (ES=0.37).

Depth of use of the decision aid

As shown in Table 4.4, both users with low engagement (≤15 pages) and users with high engagement (>15 pages) showed decreased decisional conflict scores, increased knowledge levels and increased realistic expectations at T1 and T2 (all p's <0.05; decisional conflict in high engagement group: p=0.05). Only users with high engagement showed increased levels of deliberation and increased decisional self-efficacy at T1 and T2 (all p's <0.05).

Table 4.2 Effects of use of the decision aid on main outcome measures

	T0 (baseline)	T1 (immediately after use of the decision aid)	T2 (2 weeks after baseline)	T0-T1			T0-T2		
	Means	(SD)		*T*	*p*	*ES*	*T*	*p*	*ES*
Decisional conflict									
Total score (0-100) [a]	25.30 (11.61)	18.06 (11.60)	17.22 (13.46)	5.78	<0.001	0.73	3.65	0.001	0.51
Total score (excl. effective decision; 0-100)	35.54 (19.03)	25.33 (15.74)	26.31 (19.50)	7.88	<0.001	0.78	4.11	<0.001	0.44
Uncertainty	44.14 (28.00)	35.89 (25.81)	34.12 (24.15)	5.10	<0.001	0.51	4.58	<0.001	0.50
Informed	31.60 (20.25)	18.07 (13.28)	20.10 (16.48)	7.24	<0.001	0.72	4.51	<0.001	0.49
Values clarity	34.32 (22.40)	23.60 (17.99)	22.25 (18.56)	5.79	<0.001	0.58	5.21	<0.001	0.57
Support	32.10 (19.49)	23.76 (16.64)	22.16 (16.74)	6.07	<0.001	0.60	4.93	<0.001	0.53
Effective decision[a]	22.22 (16.72)	15.77 (15.10)	12.98 (14.21)	3.68	<0.001	0.46	3.48	0.001	0.48
Knowledge									
Total score (0-15)	9.28 (2.76)	13.16 (1.85)	12.63 (1.90)	-13.89	<0.001	-1.37	-10.28	<0.001	-1.11
Natural conception (0-3)	2.29 (0.64)	2.66 (0.57)	2.81 (0.65)	-5.58	<0.001	-0.55	-5.81	<0.001	-0.62
PND (0-5)	2.14 (1.29)	3.92 (1.10)	3.73 (1.47)	-12.64	<0.001	-1.25	-8.14	<0.001	-0.86
PGD (0-7)	4.85 (1.54)	6.58 (0.83)	6.42 (0.95)	-11.03	<0.001	-1.09	-8.69	<0.001	-0.92
Realistic expectations (0-3)	0.72 (0.71)	1.63 (1.12)	1.08 (0.96)	-9.08	<0.001	-0.85	-3.92	<0.001	-0.37
Level of deliberation (6-30)	23.23 (4.47)	23.90 (3.70)	24.07 (3.42)	-1.39	0.168	-0.16	-1.28	0.204	-0.16
Decision self-efficacy (0-100)	77.23 (12.20)	79.43 (15.39)	79.81 (14.21)	-1.57	0.119	-0.16	-2.11	0.037	-0.23

[a] N=63 for T0-T1; N=52 for T0-T2

Table 4.3 In-depth analyses for main outcome measures based on median split baseline scores

	T0 (baseline)	T1 (immediately after use of the decision aid)	T2 (2 weeks after baseline)	T0-T1			T0-T2		
	Means	(SD)		*T*	*p*	*ES*	*T*	*p*	*ES*
Decisional conflict (0-100)[a]									
Low baseline (<33)	21.23 (9.77)	17.06 (11.13)	18.79 (16.00)	3.16	0.003	0.43	0.82	0.419	0.12
High baseline (≥33)	51.35 (13.36)	34.46 (15.10)	34.72 (19.78)	8.92	<0.001	1.29	5.16	<0.001	0.80
Knowledge (0-15)									
Low baseline (≤10)	6.93 (2.12)	12.70 (2.04)	12.11 (1.94)	-14.04	<0.001	-2.07	-11.11	<0.001	-1.83
High baseline (>10)	11.21 (1.36)	13.54 (1.61)	13.02 (1.80)	-10.38	<0.001	-1.39	-6.57	<0.001	-0.94
Realistic expectations (0-3)									
Low baseline (≤1)	0.54 (0.50)	1.52 (1.11)	0.98 (0.89)	-9.32	<0.001	-0.92	-4.85	<0.001	-0.48
High baseline (≥2)	2.15 (0.38)	2.46 (0.88)	1.85 (1.14)	-1.17	0.264	-0.32	0.94	0.367	0.26
Level of deliberation (6-30)									
Low baseline (≤24)	19.44 (4.06)	22.19 (3.36)	22.27 (3.46)	-3.22	0.003	-0.57	-2.68	0.013	-0.53
High baseline (>24)	27.22 (2.03)	26.48 (2.99)	26.39 (3.14)	1.43	0.166	0.27	1.30	0.208	0.27
Decision self-efficacy (0-100)									
Low baseline (≤75)	67.00 (7.42)	73.07 (15.16)	75.78 (13.59)	-3.20	0.003	-0.47	-6.59	<0.001	-1.03
High baseline (>75)	88.18 (6.98)	86.11 (13.95)	82.45 (14.60)	0.92	0.361	0.14	2.22	0.033	0.37

[a] Decisional conflict scale excluding effective decision subscale

Table 4.4 Effects of the decision aid related to depth of use

	T0 (baseline)	T1 (immediately after use of the decision aid)	T2 (2 weeks after baseline)	T0-T1			T0-T2		
	Means	(SD)		*T*	*p*	*ES*	*T*	*p*	*ES*
Decisional conflict (0-100)[a]									
Low engagement[b]	35.75 (21.12)	27.08 (15.83)	25.57 (16.99)	4.48	<0.001	0.63	3.93	<0.001	0.59
High engagement[c]	35.55 (16.95)	23.58 (15.85)	27.79 (22.35)	6.58	<0.001	0.96	2.02	0.050	0.32
Knowledge (0-15)									
Low engagement	9.22 (2.97)	12.37 (2.03)	11.95 (1.93)	-7.59	<0.001	-1.06	-5.64	<0.001	-0.85
High engagement	9.34 (2.64)	14.00 (1.14)	13.39 (1.62)	-12.94	<0.001	-1.89	-8.96	<0.001	-1.45
Realistic expectations (0-3)									
Low engagement	0.64 (0.76)	1.45 (1.14)	1.08 (1.03)	-5.49	<0.001	-0.75	-3.25	0.002	-0.45
High engagement	0.84 (0.65)	2.08 (0.90)	1.24 (0.87)	-9.81	<0.001	-1.39	-2.92	0.005	-0.41
Level of deliberation (6-30)									
Low engagement	23.63 (4.72)	22.87 (4.33)	23.51 (3.99)	1.13	0.268	0.18	0.20	0.842	0.03
High engagement	22.58 (4.23)	24.78 (2.64)	24.67 (2.72)	-3.43	0.002	-0.57	-2.31	0.028	-0.42
Decision self-efficacy (0-100)									
Low engagement	77.68 (13.42)	77.64 (16.85)	77.38 (15.19)	0.02	0.985	0.00	0.04	0.968	0.01
High engagement	76.89 (11.44)	81.19 (14.21)	82.00 (12.96)	-2.67	0.010	-0.39	-3.65	0.001	-0.60

[a] Decisional conflict scale excluding effective decision subscale; [b] ≤15 pages. [c] >15 pages

Evaluation of the acceptability

The mean score on the Preparation for Decision Making Scale (range 0 to 100) was 62.3 (SD=19.6). A majority (82.2%) thought it was easy to find information in the decision aid (M=3.24, SD=0.81), found the various functions well integrated (84.2%, M=3.05, SD=0.73), the information offered consistent (90.1%, M=3.43, SD=0.70) and relevant (82.6%, M=3.41, SD=0.64). Furthermore, participants found the decision aid easy to use (90.1%, M=3.22, SD=0.74) and trusted the offered information (94.1%, M=3.40, SD=0.63). A majority (80.2%) indicated that their awareness regarding the available options increased (M=2.97, SD=0.88), 93.5% thought that it would be useful to develop the decision aid also for other hereditary diseases (M=3.51, SD=0.66), 94.1% would recommend the decision aid to others (M=3.51, SD=0.64) and 80.2% (M=3.05, SD=0.89) would use the decision aid again in the future.
Participants graded the decision aid on a scale of 1-10 with a mean of 8.2 (SD=0.94). The avoidance of medical or technical terms was appreciated and the provided information was clear, neutral (i.e. not guiding) and comprehensible. Particularly, the value clarification exercises and informational videos were appreciated, but the inclusion of narrative stories, translation into the English language and making it better compatible for use on mobile devices were frequently mentioned improvements.

Discussion

To our knowledge, this is the first study to report on the effects of a decision aid to support persons having a genetic predisposition to cancer and their partners in decision-making regarding their reproductive options. Overall immediate (T0-T1) and sustained (T0-T2) effects were found for decisional conflict, knowledge, and realistic expectations, only sustained effects were found for decisional self-efficacy. No main effects were demonstrated for the level of deliberation. However, analyses on depth of use of the decision aid showed that users with high engagement showed a significant effect on all outcome measures. This indicates that using the decision aid to its full extent positively influences all main outcome measures. Furthermore, in-depth analyses showed both immediate and sustained effects in increasing deliberation among those with lower baseline levels of deliberation. This indicates that the decision aid is capable of encouraging deliberation among couples who are in the early stages of decision-making.[27] Furthermore, in-depth analyses showed stronger effects for participants with lower baseline levels of realistic expectations, self-efficacy and high

levels of decisional conflict, further corroborating the conclusion that the decision aid particularly supports couples with higher needs for reproductive decision support.
A notable finding is the small but significant reduction in decisional self-efficacy scores at T2 for participants with high baseline scores, indicating that use of the decision aid introduced some uncertainty among those who felt confident in their decision-making ability at baseline. A solid knowledge base is regarded as a prerequisite for informed decision-making.[23] Post-hoc analyses indicated that baseline knowledge levels were identical for participants with low and high baseline scores of decision self-efficacy (M=9.21 respectively M=9.20), suggesting that the expressed confidence in decision-making was not based on adequate knowledge levels. As the decision aid had such strong effects on knowledge of reproductive options, the information provided in the decision aid may have resulted in the identification of possible misconceptions or knowledge gaps, and possibly a further realization of the complexity of the decision among those with high baseline decisional self-efficacy. This finding furthermore emphasizes the importance of embedding the decision aid in a counseling process with adequate follow-up counseling for couples who are still in need of professional support after viewing the decision aid.

Study limitations

The use of a pretest - posttest design restricts the internal validity, as maturation and history effects as well as effects due to repeated testing cannot be controlled for. Although the execution of measurements immediately before and after the use of the decision aid minimizes the likelihood of bias, possible interference of other factors, such as use of other information sources or different exposure to impactful counseling, cannot be excluded. Furthermore, the majority of the participants did not use the complete decision aid. This could be due to the length and amount of information in the decision aid. Further investigation of possible consequences of abbreviating the decision aid on the effectiveness of the decision aid is therefore recommended. Lastly, as urgency of child wish is not standardly registered in all clinical genetic centres and hospital regulations prohibited the distribution of non-participating individuals, we cannot provide an estimate of the number of eligible couples and we were unable to calculate a response rate.

Research recommendations

The majority of the participants in this study were highly educated (57%). Although this is in line with general characteristics of oncogenetic counselees,[28] this number is notably high compared to the numbers in the general Dutch population (30%).[29] This

further exposes the need for research on measures to improve referral of patients with a lower educational background. Furthermore, as the reproductive decision is often not implemented within several months after reproductive counseling or after reviewing the decision aid, a long-term follow-up to measure decision adherence (e.g., 18 months after reviewing the decision aid) would be useful.

Practice implications

Use of the decision aid resulted in several positive outcomes indicative of informed decision-making which may lessen the negative psychological impact of decision-making on couples' daily life and well-being. The decision aid is an appropriate and highly appreciated tool to be used in addition to reproductive counseling. In-depth analyses showed that the couples who are in highest need of reproductive decision support are those who are most supported by the decision aid which increases the overall impact of the decision aid. Currently, we are conducting an explorative implementation study to clarify optimal timing of providing the decision aid and how to incorporate the decision aid in daily practice. To further increase the impact of the decision aid, the content of the tool will be adapted to other hereditary conditions.

Conclusion

The current findings indicate that the decision aid can be effective in supporting persons having a genetic predisposition to cancer and their partners in making an informed decision regarding reproductive options. Further research is needed to indicate prolonged effects on informed decision-making and informed choice.

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Chapter 5

Reproductive decision-making in the context of hereditary cancer: prolonged effects of an online decision aid

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Submitted

Part III

Implementation

Chapter 6

Exploring the preferences of involved health professionals regarding the implementation of an online decision aid to support couples during reproductive decision-making in hereditary cancer: a mixed methods approach

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Abstract

To support persons having a genetic predisposition to cancer and their partners during reproductive decision-making, an online decision aid was developed and evaluated. To maximize the impact of the support tool, this mixed methods study aims at developing the optimal implementation strategy for the decision aid. A questionnaire to assess the critical determinants that may affect this implementation was completed by health professionals involved in oncogenetic counselling (N=46). Subsequently, semi-structured focus groups (N=19) and individual telephonic interviews (N=15) were performed with a subset of health professionals. All health professionals indicated to be willing to refer couples to the decision aid, preferably at the moment of receiving the genetic test result. They agreed that the primary requirement for implementation in daily practice was ease of referring couples and preferably free online accessibility. Referral to the tool was able to be included in the standard report couples receive after consultation, thereby making the use of additional paper-based materials redundant (e.g. flyers). Furthermore, incorporating the link to the decision aid on patient organization websites was suggested. Health professionals agreed that implementation would benefit more from promoting awareness regarding the decision aid rather than the inclusion of the tool in official clinical guidelines. To foster implementation of the decision aid, the distribution of online newsletters and the designation of a contact person charged with continued implementation in each Clinical Genetic Center were suggested. Based on these preferences and recommendations, the implementation of the online decision aid will be nationally executed to optimize impact.

Introduction

In recent decades, an increasing number of evidence-based patient decision aids have been developed to assist patients in the decision-making process of (complex) medical decisions. They have been proven effective in improving decision quality while enhancing, not replacing, the traditional process of patient counselling by practitioners.[1] However, decision aids usually do not automatically fit into routine care and are often not routinely used in daily practice.[2,3] To optimize the impact of patient decision aids, it is therefore of great importance to focus on the active implementation after proven effectiveness.[4,5] Significant gaps have been indicated between the number of patients eligible, the number of patients actually provided successfully with the decision support tool, and those who actually used the tool.[6-8] Although the implementation phase is considered to be a complex process, it is important to optimize this process of providing eligible patients with the tool to optimize the overall reach.

Research efforts with regard to decision support in the area of hereditary cancer are lagging behind compared to applications in non-hereditary cancer (e.g. treatment options), prenatal testing and in pregnancy care in general.[1] There have been some initiatives to support persons with a predisposition to hereditary cancer in their decision-making regarding genetic testing[9,10] and communicating genetic test results with family members and children.[11] However, no initiatives to support couples with a predisposition to hereditary cancer in the decision-making regarding their wish to have children have been reported in the literature. The present study is part of a larger study on the development, evaluation, and implementation of an online decision aid with the aim of supporting persons having a genetic predisposition to cancer and their partners in making an informed reproductive decision.[12-14] The decision aid is meant for couples who have a high genetic risk, mostly 50%, due to autosomal dominant inheritance, of transmitting a pathogenic variant to offspring with a high risk of a future malignancy (e.g. Hereditary Breast and Ovarian Cancer, Lynch syndrome, and Familial Adenomatous Polyposis coli). Consequently, these couples face complex reproductive decisions.[15-20] Some couples may decide to refrain from having children, while others choose for donor gametes or to adopt children. Most couples, however, pursue their wish to have genetically related children.[21] Therefore, the decision aid focuses on the options to fulfil the wish for a child that is genetically related to both partners, namely; (1) natural conception without genetic testing, implying acceptance of the risk of passing on the pathogenic variant; (2) natural conception with prenatal diagnosis (PND), offering the choice to terminate the pregnancy if the fetus has the pathogenic

variant[22]; (3) preimplantation genetic diagnosis (PGD), offering couples the option to obtain embryos by in vitro fertilization (IVF) and examine them for the familial pathogenic variant. Only embryos without the pathogenic variant will be transferred into the uterus.[22]

The decision aid was developed as a tool to be used in the home environment and has been proven to be effective in supporting couples during their reproductive decision-making process. A reduction in mean decisional conflict scores, an increase in decisional self-efficacy scores, knowledge levels, levels of deliberation and improved realistic expectations were found.[13,14,23] This study aims at developing the optimal implementation strategy for the decision aid by investigating the preferences of health professionals involved in oncogenetic consultations in the Netherlands. Engaging these health professionals, who will be the primary sources of referral during the implementation phase, is important to understand potential barriers and find solutions on how to overcome these barriers. We used a mixed methods approach with a questionnaire, focus groups, and individual interviews.

Methods

Participants and recruitment

Health professionals of all Clinical Genetics Centers in the Netherlands (N=9) were selected by a staff member of each center and were invited by email to participate in this study. All health professionals were involved in the oncogenetic counselling of couples. The email contained a short description of the goal of this study and the estimated time investment required. Inclusion criteria were experience with the counselling of persons having a genetic predisposition to cancer and their partners of reproductive age, understanding of the Dutch language, and knowledge about the existence of the decision aid and its main goals. It was allowed to forward the invitation to eligible colleagues who had not been invited yet. After permission for participation had been granted, they received a link to the online questionnaire and date proposals for a focus group or individual interview. It was allowed to complete the questionnaire without participating in an interview afterwards. The participants in a focus group or individual interview received a login code to the decision aid by email, and were asked to review the decision aid prior to the interviews.

Content of the decision aid

An extensive explanation of the developmental process and the specific content of the decision aid is provided elsewhere.[13] Overall, the decision aid contained:

1. Information about the risk of transmitting the pathogenic variant to offspring and couples' options to have children genetically related to both partners.
2. Treatment burden of reproductive options and the chances of different outcomes (e.g. risk of miscarriage after PND) presented in multiple suitable formats using text and videos (e.g. verbally, and through population diagrams).[12,24]
3. A comparative summary table of important features of each option.
4. Value clarification exercises (VCE).[25] A total of 18 statements represent values and motives considered important for reproductive decision-making.[17]
5. A combined overview of both partners' responses on the VCE, by linking login codes.
6. A question prompt sheet, providing examples of questions and requests for additional information and space for own questions.
7. Information regarding the scientific resources used to underpin the decision aids content, the development team, funding resources, and contact information.

Instrumentation

The online questionnaire collected basic data on gender, age, job title, and participant's work experience in counselling couples (1 = less than one year of experience, 5 = more than ten years of experience) and included a section regarding implementation of the decision aid. Firstly, an assessment was made of how detailed health professionals would like to discuss the decision aid during consultations 1= joint use of the decision aid (i.e. reviewing and filling out the decision aid together with the couples during consultation); 2= referral of couples to the decision aid and discussing the main results afterwards during a follow-up consultation; 3= referral of couples to the decision aid without discussing the main results afterwards; 4= otherwise). Secondly, nine items of the Measurement Instrument for Determinants of Innovations (MIDI) were used. The MIDI is an instrument for assessing the critical determinants that may affect implementation of innovations (e.g. decision aids). Two categories of determinants were addressed in the questionnaire: 1) determinants associated with the innovation (i.e. compatibility and relevance for client); and 2) determinants associated with the adopting person (i.e. descriptive norm, self-efficacy, awareness of content of innovation, patient satisfaction, outcome expectations, cooperation of patient, and professional obligation).[26]

A subset of the health professionals participated in a focus group or individual interview. A focus group was scheduled where three or more health professionals per Clinical Genetic Center were willing to participate. Focus groups were held at convenient workplaces for health professionals throughout the Netherlands. In the case of just one or two participating health professionals per center, individual interviews by phone were scheduled. The focus groups and interviews were conducted by one researcher (K.R.; female PhD student) who has extensive experience in conducting and analysing qualitative research and data. To direct the focus groups and individual interviews, a semi-structured topic guide was developed, based on the MIDI.[26] The content of the topic guide focused on the professional perspectives of health professionals regarding the implementation of the online decision aid within oncogenetic consultations in the Netherlands. The topic guide contained three main themes: 1) *the innovation* [i.e. perceived appropriateness of the decision aid for referral and preferences regarding availability of the decision aid (i.e. freely accessible or restricted access)]; 2) *the adopting person* (i.e. perceived personal advantages and/or disadvantages regarding the use of the decision aid by couples and best point in time for couples to review the decision aid); 3) *referral possibilities and preferences* (i.e. best point in time to refer couples to the decision aid, preferences with respect to discussing the results of the decision aid, e.g. only referral or discussing the main results, and facilitators and barriers for referring couples). The topic guide was similar for the focus groups and interviews and was pretested in an individual telephonic interview, which was included in the analyses since the interview did not result in significant changes to the topic guide. All interviews were audiotaped and the researcher took observational notes during the interviews.

Statistical analyses

Data from the questionnaire were analyzed by means of descriptive statistics, using SPSS version 23. Qualitative data derived from the audiotaped interviews were analyzed by one researcher (K.R.). The audiotaped interviews were replayed several times and summarized to derive main themes and to explore preferences of involved health professionals regarding the implementation of the decision aid. The coding structure was developed based on the first interview by two authors (K.R. and Dr. L.v.O.), however K.R. performed coding of the remaining interviews.

Results

Questionnaire

Participants' characteristics

A total of 46 health professionals completed the questionnaire (two males and 44 females). We were unable to calculate a response rate due to the large number of health professionals forwarding the invitation email to recruit eligible colleagues. One female participant was excluded from data analyses (dropout 2.2%) as she indicated not being aware of the existence of the decision aid. The mean age was 43.4 years (SD=10.69). The participants were clinical geneticists (N=23), genetic counsellors (N=9), medical students in residency (N=7), social workers (N=2), physician assistants in training (N=2), a nurse practitioner (N=1), and a physician specialized in reproductive counselling (N=1). Most health professionals (60.0%) had more than five years of work experience in the area of oncogenetic counselling.

The majority preferred to solely refer couples to the decision aid (68.9%), whereas some also wished to discuss the main results (24.5%). Only one counsellor was in favor of reviewing the decision aid in its full extent with couples (2.2%), and two health professionals were unsure (4.4%).

Determinants associated with the innovation and adopting person (MIDI)

The majority of the health professionals (38 out of 45) had reviewed the decision aid at least once (84.4%) before completing the questionnaire; the others had not done this or were yet to do this. Of these 38 health professionals, almost all thought that couples would be satisfied with the decision aid (92.1%), and found the decision aid appropriate to be used by couples (92.1%). Of the 45 health professionals who completed the questionnaire, 64.5% thought that couples would actually use the decision aid, 33.3% were unsure and 2.2% did not think so. The majority thought that it was part of their professional duties to refer couples to the decision aid (73.3%). More than half of the health professionals found the decision aid currently compatible within their daily routine clinical practice (57.8%). Almost all (91.1%) thought that they were able to refer couples to the decision aid, and 88.9% thought that at least half of their colleagues would actually refer couples to the decision aid. Almost all health professionals (93.3%) acknowledged the importance of improving informed decision-making among couples by offering them the decision aid, but just over half of the health professionals (55.5%)

expected this goal to be accomplished, in contrast to 44.5% who indicated being unsure.

Focus groups and individual interviews

A total of 34 health professionals (all females) agreed to participate in a focus group or individual interview. Three to seven health professionals (total N=19) joined in per focus group and 15 health professionals participated in the interviews. The interviews were performed in April and May 2018. The average duration was 38 minutes (range 31-44) for the focus groups and 34 minutes (range 25-52) for the individual interviews. After three focus groups and 12 interviews, data saturation seemed to have been achieved. One additional focus group and three additional interviews were subsequently conducted in which no new or salient data were generated and data collection was closed.

The innovation

Perceived appropriateness of the decision aid for referral

All health professionals agreed that the current version of the decision aid was appropriate to provide to eligible couples and no suggestions for improvements were provided. When referring couples to the decision aid, the majority of the health professionals noticed enthusiasm among couples for using the decision aid. After using the decision aid couples provided overall positive feedback with the decision aid being pleasant in its use and helpful in improving couples' knowledge levels.

Preferences regarding availability of the decision aid

All health professionals but one were in favor of a freely available tool on the Internet instead of restricted accessibility by means of unique login data distributed by health professionals. Unique login data were indicated to be a barrier for health professionals as this requirement made it complicated to refer couples to the decision aid. Furthermore, a freely available tool may make the decision aid more easily accessible for couples and other interested relatives.

The adopting person

Perceived personal advantages and/or disadvantages regarding use of the decision aid by couples

Health professionals who saw couples during follow-up consultations indicated that those couples who reviewed the decision aid were well-informed. This was indicated by almost all health professionals to be one of the key advantages of the decision aid for health professionals themselves, as it could contribute to saving time through not having to explain all elements of each reproductive option in detail during consultations. Health professionals indicated that instead of focusing merely on information provision, they have more time left to ask couples about psychological issues during reproductive decision-making and couples' motives, consideration and values, which might lead to more interactive consultations.

Best point in time for couples to review the decision aid

Almost all health professionals indicated that the best point in time for couples to review the decision aid should be left to couples' considerations. The reproductive decision-making process is complex and dynamic, and health professionals agreed that the best moment to review the decision aid differs for each couple. The emotional and psychological state of a couple plays an important role in deciding the best moment to use the decision aid.

Referral possibilities and preferences

Best point in time to refer couples to the decision aid

The way in which the genetic test result is communicated with a person differs per Clinical Genetic Center. In some centers results are explained in a consultation, whereas in other centers a letter is sent. In some centers a phone call is the usual way to communicate results. Most couples will not visit the Clinical Genetic Center for follow-up consultations after receiving the genetic test result. Follow-up consultations are only planned for persons who indicate that they are in need of additional support. Therefore, health professionals agreed that referral of eligible couples to the decision aid was best done at the time of receiving the genetic test result.

Preferences with respect to discussing the results of the decision aid

Although most health professionals were willing to discuss the main results of the decision aid with couples, almost all health professionals indicated that in practice no follow-up consultations are planned and thus the results of the decision aid will not be discussed with the person or couple. Furthermore, due to time restrictions within consultations, referring couples to the decision aid is most feasible. An option that seemed appropriate to all health professionals would be to refer couples to the decision aid and ask couples during follow-up consultations (only if applicable) if there are any remaining questions. For those couples who would like to discuss the results of the decision aid in more detail, facilitating a consultation with a social worker was recommended by most health professionals. Almost all health professionals mentioned that, except for referring couples to the decision aid, there should be no obligations as health professionals do not want to feel compelled to take specific actions.

Facilitators for and barriers to referring couples

To continue referral of couples to the decision aid, all health professionals expressed the need to keep referral of couples easy and practical within daily practice. The majority found paper-based materials (e.g. flyers and business cards) inconvenient and old-fashioned although some would appreciate having flyers available to hand out to couples. A freely accessible link to the decision aid in the standard report that counselees receive after consultation does not require too much time effort, is easy to incorporate in daily practice, and there is no need to change current work processes. Incorporating the decision aid in official clinical guidelines was not deemed necessary by virtually all health professionals. Focusing on increasing the awareness regarding the decision aid (e.g. by incorporating the decision aid on patient organization websites, on the national PGD website (http://www.PGDNederland.nl), and the national website of the information center for hereditary diseases (http://www.erfelijkheid.nl), as well as familiarising with the tool among health professionals, was indicated to be of greater importance. According to the majority, familiarising with the tool needs some time and referrals to the decision aid will occur more frequently when health professionals start to see the actual effects of the decision aid during daily counselling. In order to secure continued implementation of the decision aid, health professionals expressed the need for someone who keeps the tool up-to-date. The distribution of online newsletters was suggested. The designation of a contact person charged with continued implementation in each Clinical Genetic Center could be helpful to foster implementation of the decision aid. Some health professionals indicated that adapting the decision aid for other

hereditary conditions might also be helpful to make the decision aid more generally applicable.

Discussion

The main goal of the present study was to explore options for the optimal implementation strategy for an online decision aid within the oncogenetic setting. We found that all health professionals indicated to be willing to refer couples to the decision aid, preferably at the moment of receiving the genetic test result. Health professionals agreed that keeping referral of couples to the decision aid easy to apply within daily practice, was the primary requirement for implementation of the decision aid. Most health professionals preferred to refer couples to the decision aid without the use of paper-based materials (e.g. flyers). Free online accessibility of the tool was preferred, with referral to the tool included in the standard report couples receive after consultation. Although health professionals agreed that the current version of the decision aid is appropriate to provide to eligible couples, just over half of the health professionals indicated in the questionnaire that the decision aid fits within their routine clinical practice. The recruitment of couples for the effect study[14] occurred with flyers including unique login data for the decision aid. The experience of health professionals during this recruitment period may have contributed to the strong preference for the use of a freely accessible decision aid, as many participants indicated that they found the use of paper-based materials (e.g. flyers) inconvenient. Health professionals indicated login data and flyers to be important barriers for the implementation of the decision aid. We therefore expect that the planned adaptations for the implementation of the decision aid will increase health professionals' confidence that referral fits within their routine clinical practice. Furthermore, incorporating the link to the decision aid on patient organization websites was suggested. Health professionals agreed that implementation would benefit more from promoting awareness regarding the decision aid rather than the inclusion of the tool in official clinical guidelines. Suggestions for increasing awareness and foster implementation of the decision aid included the distribution of online newsletters, the designation of a contact person charged with continued implementation in each Clinical Genetic Center, as well as a party responsible for updating the tool.

To accomplish optimal implementation of the decision aid, the decision aid needs to be adapted into a freely accessible tool. The tool would then be provided to couples at the moment of receiving the genetic test result through the inclusion of information about

the decision aid in the standard report couples receive after consultation. In one of our previous studies, couples agreed with health professionals that the best time for implementing the decision aid would be between the moment of receiving a positive genetic test result and the follow-up consultation (if applicable).[12] Furthermore, inclusion of information about the decision aid in the standard report couples receive after the consultation was also suggested by couples themselves.[12] Further, patient organizations need to be approached to further explore their willingness to incorporate the decision aid on their websites to increase awareness of the tool. Lastly, frequent updating of decision aids is essential due to new evidence becoming available. In the oncogenetic setting, developments in genetic testing and reproductive technologies are expected to progress rapidly. Development and evaluation of the decision aid were performed with the help of a large research- and steering group that is also actively involved in the continued development and adaptation of the decision aid. In order to ensure the decision aid being up-to-date, negotiations with patient organizations and national organizations tasked with public information provision regarding hereditary diseases will be initiated. Based on the preferences and recommendations investigated in this study, the implementation of the online decision aid will be nationally executed to optimize impact. As one of the main outcomes of this study was to adapt the decision aid into a freely accessible tool, a broader range of possible intermediaries (e.g. general practitioners, oncologists, and gynaecologists) may be considered to add other valuable insights.

Some limitations should be mentioned. First, the number of participants within the focus groups was limited and this may have restricted interaction and discussion between participants. Secondly, although the coding structure was developed based on the first interview by two authors (K.R. and L.v.O.), the coding of the remaining interviews was performed by one author only (K.R.) which may decrease the validity of our study. Lastly, transcripts were not returned to participants. Returning transcripts to participants has both pros (e.g. strengthens the trustworthiness of the findings) and cons (e.g. alter the interpretation of the original data set), and we decided to not made use of member-checking of our data.

Conclusion

This study provides insights into preferences and recommendations of health professionals regarding the implementation of the online decision aid. These recommendations will guide the development of the optimal implementation strategy for the decision aid, which will be nationally executed to optimize impact of the decision aid.

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Part IV

Addenda

Chapter 7

General discussion

General discussion

The general aim of the studies presented in this thesis was to develop and evaluate an online patient decision aid for persons having a genetic predisposition to cancer and their partners who wish to have children (i.e. the end-users). Previous studies of our research group and others indicated that many couples experience reproductive decision-making as difficult[1-8] and acknowledge the need for reproductive decision support, in addition to existing reproductive counselling.[1,2] In the current project, a decision aid was developed with the help of input from end-users and involved healthcare providers in the oncogenetic setting (e.g. clinical geneticists, genetic counsellors, and social workers). After the decision aid was developed, its effects on various outcome measures, i.e. informed decision-making, decisional conflict, knowledge, realistic expectations, level of deliberation, and decision self-efficacy, were assessed. The results of the studies in this thesis show that the decision aid is an appropriate tool to support end-users in making an informed reproductive decision.
In this final chapter, the main findings of this thesis will be reflected upon. Recommendations for daily practice of reproductive counselling in hereditary cancer will be provided. Also, limitations to consider when interpreting the results of this thesis, as well as ideas for future research, will be discussed.

Overview of main findings

The decision aid was systematically developed according to the International Patient Decision Aids Standards (IPDAS)[9] in collaboration with a steering group including end-users, healthcare providers (e.g. clinical geneticists and social workers), experts in health communication and medical decision-making, and psychologists. We started with a constructive literature review and obtained extensive information regarding existing patient decision aids. Based on these results, we formulated provisional components to be incorporated in the decision aid. Subsequently, we conducted semi structured individual interviews with end-users and involved healthcare providers (**Chapter 2**). With this needs assessment, we obtained information about their viewpoints regarding the possible content of the decision aid. Both stakeholders had little or no experience with patient decision aids; their preferences were therefore mainly based on expectations. Nevertheless, they were able to clearly formulate their needs and wishes regarding the features they would like to see incorporated in the decision aid and to reflect on how to incorporate the decision aid in daily practice in the oncogenetic setting. Many similarities were found between the expressed preferences

and needs of both stakeholders. Emphasis was placed on the use of simple non-medical language, an extensive explanation of the procedures and techniques used in prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD), and the role of healthcare providers in referring couples to the decision aid. Almost all couples and most of the healthcare providers indicated that incorporating narrative stories in the decision aid (i.e., personal stories of couples who have already made a reproductive decision) could be beneficial. The provided recommendations during the needs assessment study formed the basis for the development of the prototype decision aid.

The next step in the iterative development approach was to discuss the prototype with end-users and healthcare providers involved in oncogenetic counselling (e.g. clinical geneticists, genetic counsellors, and gynaecological oncologists). We performed a two-phase usability test (**Chapter 3**) with a functional prototype of the decision aid. After the first phase, the decision aid was adapted based on the feedback provided. To make final modifications, a second usability phase was conducted. End-users and healthcare providers were generally satisfied with the decision aid and provided useful insights and suggestions for further improvements, in particular with regard to its attractiveness and ease of use. Based on the feedback provided during the usability study, we adapted the prototype decision aid with regard to the content (textual changes) and lay-out (e.g. we changed the order of information provided in the decision aid, as well as the colors). Couples and healthcare providers evaluated the final decision aid as acceptable, easy to use, and comprehensible.
Subsequently, the final decision aid was further tested in a pilot study (**Chapter 3**) by using a pretest-posttest design to evaluate preliminary results. The positive findings during usability testing were reflected in the preliminary results of the pilot test, indicated by a reduction of couples' decisional conflict, increased knowledge, and improvement of realistic expectations regarding available reproductive options. These study results suggest that using the decision aid will improve informed reproductive decision-making among end-users. After the pilot study, a full effect study was conducted to evaluate the effects of the decision aid on the short term (immediately, and two weeks after using the decision aid) and the long term (three months after using the decision aid) (**Chapter 4** and **Chapter 5**). All nine clinical genetic centers in the Netherlands participated in the effect study and virtually all couples who registered to participate in the effect study actually used the decision aid. Overall, the decision aid was positively evaluated by couples (mean=8.2; scale 1-10), a finding that may reflect the intensive involvement of stakeholders during the developmental process. Furthermore, the findings of the effect evaluation confirmed the preliminary results of the pilot study, indicating sustained effects on various outcome measures indicative for

informed reproductive decision-making both on the short term and the long term. We found an overall reduction in mean decisional conflict scores, an increase in informed decision-making, increased knowledge, realistic expectations, the level of deliberation, and couples' decision self-efficacy. Subgroup analyses indicated significant effects for all socio-demographic and clinical subgroups, with less generalized effects for participants who had not had a consultation with a healthcare provider at baseline or between baseline and three months after using the decision aid, and those who plan to have children in the more distant future (>2 years).

As not all couples had implemented their reproductive decision (i.e. trying to conceive or starting the PGD trajectory) three months after using the decision aid, a follow-up measurement after eighteen months is currently being conducted in which decision adherence of couples is assessed.

After careful development and establishing the efficacy of the decision aid, developing an optimal implementation strategy is indispensable to warrant continued use of the tool. For the routine use of decision aids, merely their (online) availability is insufficient.[10] As clinicians' referral to decision support tools in daily practice often ceases after closing research periods,[11] we conducted an explorative implementation study among involved healthcare providers in order to find methods to ensure continued use of the decision aid (**Chapter 6**). We aimed to clarify current procedures in daily oncogenetic counselling and investigated how the decision aid can fit into routine clinical care. All healthcare providers participating in the implementation study indicated that there were willing to structurally refer couples to the decision aid, preferably at the moment of informing couples of the genetic test results. They agreed that the primary requirement for structural implementation in daily practice was ease of referring couples and preferably free online accessibility of the tool. Furthermore, suggestions for fostering implementation of the decision aid included incorporating the link to the decision aid on patient organization websites, distributing online newsletters, and designating a contact person charged with continued implementation in each clinical genetic center. These recommendations from healthcare providers will be combined with preferences of end-users to guide the development of a best-fitting implementation strategy for the decision aid.

Reflection on project results and implications

Some important issues that emerged during this project related to the study design and study population, possibilities to optimize the content of the decision aid, and ways to facilitate its continued implementation, will now be reflected upon.

Design and study population

Non-experimental effect study

We initially intended to conduct a multicenter randomized control trial (RCT) for the effect evaluation of the decision aid. Couples were to be randomized by means of separate randomization schedules for each of the participating clinical genetic centers. However, during the pilot study it became evident that recruitment of eligible couples was occurring slower than anticipated. Recruitment estimations prior to the start of the project were based on the annual number of consultations performed in each clinical genetic center. However, as timing or the urgency of the wish to have children is not standardly registered in hospital files, the exact number of eligible couples (i.e. those who wish to have children within five years) could only be estimated. The lower than expected number of eligible couples resulted in the decision to use a one-group pretest-posttest design for the effect evaluation of the decision aid.

Due to its non-experimental nature, the results of the effect study should be interpreted with caution. The use of a pretest-posttest design restricts the internal validity, as maturation and history effects as well as effects due to repeated testing cannot be controlled for. Although the execution of measurements immediately before and after the use of the decision aid minimizes the likelihood of bias, possible interference due to other factors cannot be excluded. For example, it is possible that end-users made use of other information sources (e.g. patient organization websites) or other supportive interventions (e.g. leaflets or booklets) during, or more likely after, using the decision aid. Despite the overall relatively small sample sizes in reproductive genetics, future studies regarding the development of decision support tools in this setting should strive for the use of experimental designs to provide the strongest level of evidence with minimal bias.

Selectivity of the study population

Involving multiple stakeholders in the development and evaluation of interventions is an important step in the actual implementation of the intervention in daily practice.[12] We expected that involving these stakeholders in the entire developmental process would also increase their commitment to the tool, which may benefit its implementation later on. However, some limitations related to the study population of the needs assessment and the explorative implementation study need to be discussed.

Firstly, in our needs assessment study we included only clinical geneticists, while other healthcare providers (e.g. social workers, genetic counsellors, oncologists) involved in the reproductive counselling of couples might have provided additional valuable information from their own unique viewpoints. In the subsequent studies (i.e. usability study and the explorative implementation study), a broader range of healthcare providers was included to assure representation of their opinions regarding the decision aid and its incorporation in the daily oncogenetic counselling. Secondly, the needs assessment included only couples who had already made their reproductive decision and who had visited the clinical genetic center for a consultation regarding reproductive options at least once. These couples are able to reflect on their reproductive decision-making process and indicate the points of improvement and the features of a decision aid that could have supported them during this process. However, additionally including couples who were just starting the reproductive decision-making process may have resulted in more detailed information on current needs and preferences during decision-making. Lastly, the explorative implementation study was limited to healthcare providers in the field of oncogenetics. The inclusion of representatives of all clinical genetic centers in the Netherlands contributed to the generalizability of the results for these healthcare providers. However, the perspectives of actual users of the decision aid, i.e. the couples, can also provide valuable information regarding the sustained implementation of the tool. Their perspectives towards the continued development and implementation of the decision aid are therefore currently being investigated in a follow-up study.

Furthermore, during the effect evaluation of the decision aid it was not feasible to collect information about non-responders. Privacy regulations in several of the clinical genetic centers prohibited gathering data on non-participating couples. We were therefore not able to calculate a response rate for the effect study, nor do we have data on the characteristics of non-responders, or their reasons for not participating in our studies. It is for instance possible that mostly highly educated persons were willing to participate in our studies. This will be further discussed in the next paragraph. Registration of participation requests or invitations by healthcare providers and non-

response analysis should be considered for future studies as this will provide insight into the generalizability of study results.

Educational level of end-users

The majority of the end-users participating in our studies were highly educated. This is in line with general characteristics of counselees in cancer genetic counselling[13] with more middle- and highly educated patients visiting the clinical genetic centers in the Netherlands. Nevertheless, underrepresentation of individuals with a lower educational background during the development phase may have resulted in undervaluation of, and therefore suboptimal adaptation to, their needs and wishes. It is, for example, known that people with a lower education and/or health literacy are poorer at interpreting risk information[14] and have different preferences with regard to the content and presentation of information than participants with higher levels of education and health literacy. Previous studies for instance indicate that people with a lower educational background prefer the use of pictographs to communicate small numerators, commonly used in genetics.[15] Furthermore, they may particularly benefit from the use of narrative health communication materials,[16-18] as will be discussed later on in this chapter.

Several measures were taken to optimize the comprehensibility of the decision aid for individuals of different educational backgrounds. Based on current recommendations[19] and the preferences of end-users, probabilities (e.g. risk of miscarriage after PND, likelihood of pregnancy with PGD) are for instance presented in multiple suitable formats (i.e. verbal, numerical, and graphical) using both text and videos. However, although we found no difference in effect of the decision aid between low/middle- and high education groups, only 8.2% of the participants were low educated, therefore we cannot state with certainty that the decision aid is effective for couples of all educational levels (**Chapter 5**). Due to the complexity of genetic information and overall lower understanding and knowledge of genetic principles among lower educated subgroups,[20-22] future studies aiming to develop decision support tools for target groups within the genetic population would be advised to thoroughly map the education level of the target group and ensure adequate representation of all educational levels within the study samples during all research phases.

Optimization of the content of the decision aid

Reproductive options included in the decision aid

Most couples with a predisposition for hereditary cancer choose for options to have children that are genetically related to both partners.[23] A minority decides to refrain from having children or to choose for options to have children who are not genetically related to one or both partners (e.g. gamete donation, adoption, and foster parenting). We asked stakeholders about their preferences about which reproductive options should be included in the decision aid (**Chapter 2**). After careful deliberation, and based on literature findings, the preferences of stakeholders, and desired conciseness of the tool, we decided to focus on the options to have children that are genetically related to both partners, i.e. natural conception without genetic testing, PND, and PGD, while briefly mentioning the other reproductive options in the decision aid. This selectivity may however be considered incongruent to principles of informed decision-making and defined standards of decision support interventions.[24]

We unequivocally agree that it is important that couples are aware of all available options in order to make a fully informed decision, particularly in the case of preference-sensitive decisions such as decision-making regarding reproductive options. However, incorporation of all available options, with some options being debatable for certain target groups within reproductive genetics (e.g. adoption for couples with Huntington's disease), requires the provision of extensive information, not only from a medical point of view but also from a legal, psychological, and ethical viewpoint. This would have made the decision aid more complicated and it would be at the expense of the completeness of information regarding the three main reproductive options used by our target group (i.e. natural conception without genetic testing, PND, and PGD). As current findings indicate that the majority of users did not review all information in the decision aid (mean page visits: 15 out of 36), we propose a multi-layered approach for the continued development of the decision aid. In a stepwise manner, couples are first provided with information regarding the key elements of each available reproductive option, and subsequently in-depth information regarding the reproductive options is tailored based on the needs of couples. With this approach, we facilitate couples in making a fully informed reproductive decision while at the same time assuring the conciseness and user-friendliness of the decision aid.

It is striking to note that the number of couples who refrain from having children or who choose for offspring not genetically related to one or both partners, is higher among couples with other hereditary conditions[25,26] compared to genetic cancer

syndromes. Therefore, when adapting the tool for other hereditary conditions such as Huntington's disease and myotonic dystrophy, careful deliberation of the reproductive options to be included in the decision aid is certainly warranted.

Incorporation of narrative stories in the decision aid

Narrative stories provide illustrative examples of others people's experiences relevant to the decision to be made. To date, it is unclear whether including narratives stories in decision aids enhances the effectiveness of these tools or how useful patients judge these stories to be in supporting them in their decision-making process.[27,28] Some argue that by the use of narratives, people make (health) decisions based on the values and choices of someone else, whereas others propose that narratives provide essential emotional and social information to give meaning and perspective to the decision to be made.[17]

In our needs assessment and effect evaluation, many couples expressed a need for reading personal stories regarding the decision-making process and the experiences of couples who had already decided on one of the reproductive options. They indicated that reading about experiences of couples in similar situations would comply with their need for an emotional or experiential counterpart to the scientific facts provided by their healthcare provider and within the decision aid. They indicated that reading about how other couples coped with the decision process would be supportive in their own decision-making. Narratives detail the behavior and the expressed ways of thinking of persons who faced similar decisions, and incorporate aspects of role modelling. The decision-maker tries to learn from these proficient peer couples (i.e. models) having competencies to which they aspire themselves. The models can transmit experiential knowledge and can teach the decision-maker coping skills and strategies for managing the decision-making process, which may raise the self-efficacy of the couples.[29] Incorporating modelling techniques in the form of narrative stories, may therefore optimize the impact of the tool with regard to decision self-efficacy and thereby overall facilitate informed decision-making.

However, in line with the current debate on the effectiveness of the incorporation of narratives in decision aids,[30] during the needs assessment study clinical geneticists indicated that objectivity and the provision of balanced narrative information in the decision aid were key issues to be addressed before deciding on their use.

Our research team is currently developing a set of narrative stories, detailing the experiences of couples opting for or refraining from natural conception without genetic testing, PND, or PGD. However, before incorporating such stories in the decision aid, thorough investigation of their impact is warranted as, insufficient evidence exists regarding whether narrative stories facilitate or bias informed decision-making.[30]

Dyadic processes during reproductive decision-making

One of the most common social relationships in which decision-making takes place is that of couples. The partners have to make decisions together in several domains of life. Generally the decision regarding reproductive planning is a dyadic process. Therefore, the focus in this thesis was also on informed decision-making at the couple level as well as informed decision-making for individuals. We found that although the decision aid resulted in a higher likelihood of couple-based informed decision-making, still the majority of couples did not meet all conditions for informed decision-making (**Chapter 5**). In the continued development of the decision aid, we therefore aim to further optimize joint informed decision-making among our end-users.

Couples may benefit from the inclusion of additional methods to further facilitate intra-couple communication and joint decision-making. The value clarification exercises currently included may for instance be adapted to include a more explicit specification of differences in both partners' scores on, and perceived importance of, the individual values. Furthermore, we could stimulate couples more explicitly to communicate about these differences regarding important values during reproductive decision-making.
Another example is the incorporation of diaries, a method that is often used in cognitive behavioural therapy,[31] to facilitate the communication between partners. Couples are asked to detail their thoughts and feelings regarding any aspects of the decision in a diary that is shared between the partners. Reading about each other's thoughts and feelings and subsequently stimulating discussion among the partners may enhance intra-couple communication and deliberation and thereby facilitate joint decision-making.
In line with the above, we recommend the use of reliable measures of joint decision-making and/or aspects thereof during future evaluations of support tools involving joint decisions. This will yield more in-depth information on the interaction and communication processes during decision-making and the effect of the decision aid on these processes.

Furthermore, the content and format of our decision aid was implicitly targeted to reproductive decision-making in heterosexual relationships. The increasing demand for

medically assisted reproduction among singles, lesbian and gay couples, and transsexuals may however require the development of alternative and more inclusive content.[32]

Additional considerations to optimize the impact of the decision aid

A frequently mentioned improvement during the effect evaluation was related to the fact that the decision aid is currently not compatible for use on mobile devices. Given the increased use of mobile applications in our society and to make sure that couples can access the tool at any time and anywhere, compatibility with the screen characteristics of smaller mobile devices should be strived for.

Lastly, couples in the effect study indicated that they particularly appreciated the informational video materials (**Chapter 4**). This was also reflected in the user statistics; almost all participants watched the informational videos, whereas text pages were only partly visited by most participants. To optimize the use of the informational content, and thereby increase knowledge of the reproductive options, the development of additional informational videos should be considered.

Continued implementation of the decision aid

Free online accessibility of the tool

During the course of this project, a change in the preferences of healthcare providers regarding the availability of the decision aid was noted. In the needs assessment, healthcare providers disagreed as to whether the decision aid should be freely available (e.g. free access on the internet) or whether access should be restricted to eligible couples (e.g. by means of unique login data, distributed by healthcare providers) (**Chapter 2**). However, during the implementation study, healthcare providers agreed on a freely accessible tool on the internet. Free accessibility was generally thought to facilitate the dissemination of the tool; couples can access the tool at any time and anywhere. Furthermore, a freely accessible decision aid allows equal access to the information provided in the decision aid, including for those couples who wish to gather information regarding the reproductive options without, or prior to, visiting a clinical genetic center, as well as interested family members and friends.
However, it should be taken into account that free accessibility of the decision aid may lead to uncontrollability and therefore dispersion of the user group. By providing open access, individuals and couples outside of the target group may also use the tool (e.g.

persons with a predisposition for a hereditary condition for which PND and/or PGD are not offered in the Netherlands). This may increase the risk of misunderstanding and possibly an increased number of couples requesting a consultation with a healthcare provider based on incorrect information. Attention should therefore be paid to monitor such possible negative side effects of free accessibility of the tool. Nevertheless, we should advocate that all couples are provided with the assistance of a healthcare provider during reproductive decision-making if needed.

Timing of providing the decision aid to couples

The readiness for decision-making and the perceived urgency of reproductive planning among couples are important factors in the determination of the optimal timing of providing the decision aid. Based on the outcomes of the needs assessment and implementation study, we aim to propose structural referral by healthcare providers to the decision aid by briefly introducing the decision aid during the consultation in which the outcome of the genetic test is discussed, and including a link to the freely accessible tool in the standard report that couples receive after consultation. This strategy requires minimal time and effort from the healthcare providers as it does not substantially change current work processes and can therefore be considered relatively easy to incorporate in daily practice.
However, although a generic protocolled approach could result in an optimal reach of the decision aid, we should never lose sight of the specific needs and circumstances of couples when determining the offer of decision support. By asking about a couple's wish to have children, decision support can be better tailored to the needs of couples at a specific time. Healthcare providers can decide to refer the person or couple to the decision aid during or immediately after the consultation, or to postpone referral until the wish to have children becomes pressing.

Furthermore, we wish to emphasize the importance of investigating if and how to include other healthcare providers involved in reproductive counselling in the referral to the decision aid. With an expanding scope of preconception counselling,[33,34] it is useful to explore possibilities for referral by general practitioners, gynaecologists and/or midwives. Involvement of these healthcare providers may optimize the distribution of the tool, and consequently its impact.

Concluding remarks

The main question to be answered in this thesis was whether the systematically developed decision aid was effective in supporting end-users in making an informed reproductive decision. Our results suggest that the decision aid is capable of doing so, demonstrating both immediate and sustained effects on various indicators of informed decision-making (**Chapter 3**, **Chapter 4**, and **Chapter 5**). We recommend continued implementation of the decision aid in the clinical oncogenetic setting in addition to regular genetic counselling on the available reproductive options. We expect that couples with a predisposition to other hereditary conditions will also benefit from a similar decision aid. Recently we started a new project to extend and adapt the decision aid for other indications. By increasing its reach and effectiveness, we expect to optimize the overall impact of the decision aid in counselling the total genetic population. With these efforts, we aim to contribute to the further establishment of decision support within the field of clinical genetics, and particularly reproductive genetics, a field that is in constant evolution and is known for its rapid technological advances. These advances are expected to open up innumerable possibilities and options, often of increasing complexity, which patients, carriers, and people at risk of transmitting a predisposition to offspring will have to decide on. The importance of high-quality counselling and decision support in this field can therefore not be overstated.

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Valorization

Valorization

This paragraph describes the societal value of the results from this thesis. The importance of the results for the patient group and the broader setting of clinical oncogenetics will be discussed.

In this research project we aimed to develop (**Chapter 2** and **3**) and evaluate (**Chapter 4** and **5**) an evidence-based online patient decision aid to support couples with a predisposition to cancer during reproductive decision-making. A predisposition for hereditary cancer usually has an autosomal dominant inheritance pattern, implying that there is a 50% risk in each pregnancy of transmitting the mutation in one of the cancer genes to offspring. Transmission implies passing on an increased lifetime risk of developing cancer. In the last decade, mainly qualitative studies have been initiated to investigate the experiences of couples confronted with this increased risk for their offspring, regarding their reproductive decision-making process. These studies found that, overall, couples experience the reproductive decision-making process as difficult and emotionally demanding.[1-5] Couples have to cope with their own increased risk of developing cancer and they are concerned about the risk of passing on the predisposition to cancer to offspring.[6] A recent study among couples with Hereditary Breast and Ovarian Cancer (HBOC) who had made a reproductive decision after reproductive counselling, showed that 69% expressed a need for additional support during reproductive decision-making in addition to existing reproductive counselling.[5]

In the Netherlands, all couples of reproductive age who plan to have children have access to preconception counselling by general practitioners, gynecologists and/or midwives. In addition, persons of reproductive age who might have a predisposition for hereditary cancer may be referred to one of the nine Clinical Genetic Departments in the country to receive information about genetic testing and their reproductive options to prevent transmission of the mutation to offspring. Follow-up consultations with a specialized clinical geneticist, psychologist or social worker can be scheduled on request for persons with a cancer predisposition who indicate that they have specific questions concerning the reproductive risks or are in need of additional support.

The present research demonstrates the added value of our online decision aid to support couples during reproductive decision-making in addition to existing reproductive counselling. Decision aids are useful for providing patients with information and additional support during decision-making[7] and have been proven effective in improving decision quality while enhancing, not replacing, the traditional process of patient

counselling by healthcare providers.[8] Although research efforts with regard to decision support in the area of hereditary cancer are lagging behind compared to applications in non-hereditary cancer (e.g. treatment options), in prenatal testing and in pregnancy care in general,[8] the concept of decision support in itself is not new in the area of hereditary cancer. There have been initiatives to support persons with a predisposition to hereditary cancer in their decision-making regarding genetic testing,[9,10] communicating genetic test results with family members and children[11] and regarding risk-reducing surgeries.[12] However, a patient decision aid specifically tailored to couples involved in reproductive decision-making in hereditary cancer, has not been developed and reported on before.

A collaboration was set up with a steering group including counsellors (e.g. clinical geneticists, genetic counsellors, and social workers), experts in health communication and medical decision-making, psychologists, and the intended end-users of the decision aid, i.e. persons having a genetic predisposition to cancer and their partners who are planning to have children, to guide the development of the decision aid and to optimize its reach. After we developed and evaluated the online decision aid, we conducted an explorative study on opportunities for continued implementation (**Chapter 6**) because many (proven) effective decision aids are often infrequently used in daily practice following trial periods.[13] By conducting this study we intended to maximize the impact of the decision aid by increasing the awareness and reach of the decision aid, facilitating its implementation, and optimizing the sustained use of the decision aid after finalizing this project. To further increase the awareness of the tool, the outcomes of our studies have been, and will be, published in scientific medical journals and presented at national and international scientific conferences, meetings of involved professionals (e.g. presentations at department meetings) and at patient organization meetings.

Based on the results of the study described in **Chapter 6**, we strive to structurally implement the decision aid in the reproductive counselling of persons having a genetic predisposition to cancer and their partners who are planning to have children. The decision aid will be freely available on the Internet enabling all healthcare providers, patients and relatives of patients to use the decision aid without costs. This will facilitate the overall reach of the tool, also among couples who will never visit the Clinical Genetic Department. We will strive to incorporate the decision aid on commonly used websites such as patient organization websites and the national PGD website (http://www.PGDNederland.nl). Also, the link to the decision aid will be included in the standard report that counselees receive after consultation. In this way,

referral to the decision aid can be relatively easily incorporated in daily practice of healthcare providers. The possibility for referral to the decision aid by general practitioners, gynecologists and/or midwives, which will aid to further increase of the reach and thereby the impact of the decision aid, needs to be explored. Further development of the decision aid, technical maintenance, and keeping it continuously up-to-date, requires recourses. To cover these costs we could consider submitting an application for an implementation grant (e.g. Dutch Cancer Society).

The decision aid will serve both healthcare providers (e.g. clinical geneticists and social workers) and patients. Healthcare providers may benefit from the decision aid as it could contribute to an improvement of the reproductive decision quality among their patients.[14] If the decision aid is used by the couple before scheduled counseling, healthcare providers do not have to explain all elements of each reproductive option in detail. Patients will be better informed, which may lead to more interactive consultations and more time to discuss psychological issues and couples' motives and considerations. In this way, patients will benefit from the decision aid by enabling them to make a more informed reproductive decision. Supporting couples in making an informed reproductive decision will probably reduce feelings of doubt and uncertainty and may lessen the negative psychological impact of decision-making on couples' daily life and wellbeing. Furthermore, as a substantial part of carrier couples are not aware of their reproductive options,[15] timely introduction to the decision aid by healthcare providers during preconception care and reproductive counseling is expected to result in an overall higher awareness of reproductive options among carrier couples. More couples will be able to make a well though-out decision regarding their reproductive options, preventing regret or hard feelings afterwards.[1]

The content of the tool is currently being adapted to other hereditary conditions for which reproductive techniques are available in the Netherlands. With this continued development, we aim to facilitate informed reproductive decision-making among the entire patient group and therewith further increase the impact of the decision aid. Furthermore, we are exploring the possibilities for translation and adaptation of the content of the decision aid to facilitate international application of the tool.

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Summary

Summary

Of all cancers, approximately 5% are caused by a genetic predisposition. A predisposition for hereditary cancer usually has an autosomal dominant inheritance pattern, implying that there is a 50% risk in each pregnancy of transmitting the mutation in one of the cancer genes to offspring. Transmission implies passing on an increased lifetime risk of developing cancer. To illustrate this, female carriers of a *BRCA1/2* mutation, the most frequent cause of hereditary breast and ovarian cancer (HBOC), have a lifetime risk of 69-72% of developing breast cancer and 17-44% of developing ovarian cancer before the age of eighty. In comparison, the lifetime risk for women in the general population of developing breast cancer is 12% and approximately 1% for ovarian cancer. This knowledge may play a substantial role in the reproductive decision-making process of couples of whom one of both partners has a genetic predisposition to cancer. These couples may decide to refrain from children, while others opt to have children who are not genetically related to the partner who is carrying the genetic mutation by using donor gametes, or some may opt for adopting a child. Most couples, however, pursue their wish to have (a) genetically related child(ren). These couples can opt for (1) natural conception without genetic testing, (2) prenatal diagnosis (PND), or (3) preimplantation genetic diagnosis (PGD). If a couple opts for natural conception without genetic testing, they accept the risk of passing on the mutation to their child. When the child is born it will hence be unknown if he or she has inherited the mutation or not. Couples who opt for prenatal testing will try to conceive naturally. Once a pregnancy is achieved information about the presence or absence of the mutation in the fetal DNA can be obtained by analyzing the familial mutation in chorionic villi or amniotic fluid. If the fetus has inherited the mutation, couples have the choice to terminate the pregnancy or not. Finally, PGD implies that embryos obtained by *in vitro* fertilization (IVF) are examined for the familial mutation and only mutation free embryos are transferred into the uterus. PGD is a physically intensive and relatively lengthy trajectory with a chance of an ongoing pregnancy of approximately 25% per treatment. However, PGD circumvents the emotional and physical burden of a pregnancy termination after prenatal testing.

The decision regarding which reproductive option to opt for is highly preference-sensitive. Previous research has shown that couples who are aware that one of them has a genetic predisposition to cancer may experience the reproductive decision-making process as complex. The decision regarding which reproductive option to pursue should ideally involve an informed decision-making process by an educated and empowered couple. During this process, couples carefully consider various personal

values and deliberate advantages and disadvantages of all reproductive options. In order to promote informed decision-making, decisional support strategies such as patient decision aids can be effective. Decision aids have been found to improve people's knowledge regarding their options, reduce decisional conflict, and decrease the proportion of people remaining undecided. Incorporating a decision aid in reproductive counselling can therefore be helpful in supporting couples who are aware that one of them has a genetic predisposition to cancer in making their reproductive decision.

The aim of this thesis was to develop and evaluate an online patient decision aid to support such couples in making an informed reproductive decision. **Chapter 1** provides an introduction in hereditary cancer, the available reproductive options, the uptake and acceptability of these reproductive options, reproductive decision-making in the oncogenetic setting, and the development of decision support. Furthermore, it presents an outline of the thesis.

Part I of this thesis describes the developmental process of the decision aid. A qualitative needs assessment study was performed to investigate preferences and needs of stakeholders regarding the development and implementation of the decision aid (**Chapter 2**). Semi-structured interviews assessing the needs and preferences regarding the content and functionalities of a decision support program were conducted among couples at risk for hereditary cancer (N=7 couples) and among clinical geneticists involved in oncogenetic counseling (N=8). Investigating the needs of both stakeholder groups is considered pivotal to ensure successful development and uptake of the decision aid. Many similarities were found between the expressed preferences and needs of both stakeholder groups concerning the content, barriers and facilitating factors regarding the use of the decision aid, and its implementation. Emphasis was placed on the use of simple non-medical language, an extensive explanation of the procedures and techniques used in PND and PGD, and the role of healthcare providers to refer couples to the decision aid. Both stakeholder groups were in favor of incorporating narrative stories in the decision aid. The findings from this study were integrated with knowledge on reproductive decisional motives and considerations to guide the development of the decision aid.

In **Chapter 3** the development of the prototype decision aid and its modifications in an iterative process, are described. The decision aid was developed according to the International Patient Decision Aids Standards in collaboration with a steering group including healthcare providers (e.g. clinical geneticists, and social workers), experts in health communication and medical decision-making, psychologists and the primary target group, i.e. persons having a genetic predisposition to cancer and their partners

who are planning to have children. The user friendliness, strengths and limitations of the prototype decision aid were assessed several times during usability testing among couples and healthcare providers. Couples and healthcare providers expressed similar suggestions for improvements, and evaluated the modified decision aid as acceptable, easy to use, and comprehensible. The final decision aid was pilot tested among a subsample of the target group (N=16), assessing the main outcomes decisional conflict, knowledge, realistic expectations regarding the reproductive options and decision self-efficacy before (T0), immediately after (T1) and 2 weeks after (T2) use of the decision aid. The positive findings during usability testing were reflected in the pilot study indicating decreased decisional conflict scores, increased knowledge, and improved realistic expectations regarding the reproductive options, at T1 and T2. There were no indications that use of the decision aid was beneficial to increase couples' decision self-efficacy. No further modifications to the decision aid were needed after pilot testing and further evaluation of the decision aid is described in **Part II**.

In **Chapter 4** and **Chapter 5** of **Part II**, the decision aid was further evaluated in a nationwide pretest–posttest study in all clinical genetic centers in the Netherlands. **Chapter 4** provides insights into the immediate (T1) and short-term (T2) effects of the decision aid on various outcomes related to informed decision-making such as decisional conflict, knowledge, realistic expectations, level of deliberation and decision self-efficacy. Furthermore, couples were asked to give an overall appreciation score for the decision aid at a scale from 1-10. Couples were eligible for participation if one partner had a pathogenic variant predisposing for autosomal dominant hereditary cancer, for which PND and PGD are available in the Netherlands. Furthermore, couples needed to have the intention to have children within the next 5 years, and had not yet made a definitive decision regarding their preferred reproductive option. Both partners had to be 18 years or older and both partners needed to have sufficient knowledge of the Dutch language. Participants graded the decision aid with a mean of 8.2 (SD=0.94). T0-T1 and T0-T2 comparisons with paired sample t-tests (N=115) indicated a significant reduction in mean decisional conflict scores with stronger effects for participants with high baseline decisional conflict. Furthermore, use of the decision aid resulted in increased knowledge levels and improved realistic expectations. The level of deliberation only increased for participants with lower baseline levels of deliberation. Decision self-efficacy increased for those with low baseline scores, whereas those with high baseline scores showed a slight reduction at T2. The strong effects of the decision aid on knowledge of reproductive options may have resulted in the identification of possible misconceptions or knowledge gaps, and possibly a further realization of the complexity of the decision among those with high baseline decisional self-efficacy.

Overall, it can be concluded that use of the decision aid resulted in several positive outcomes on the short-term indicative of informed decision making, with stronger effects among individuals who are in highest need of reproductive decision support.

Chapter 5 outlines the prolonged effects of the decision aid three months after use of the decision aid (T3) among 93 participants. Furthermore it was investigated how many participants had made an informed reproductive decision. T0-T3 comparisons showed an overall positive effect for all outcome measures with 58.0% of the participants making an informed decision regarding their preferred reproductive option at T3 (T0=14%). Additionally, we analyzed the effects of the decision aid on the decrease of decisional conflict, and the increase in knowledge, realistic expectations, level of deliberation, and decision self-efficacy for various subgroups. Significant effects on all outcome measures were found for males as well as females, low/middle educated as well as high educated participants, carriers as well as partners of carriers, participants with as well as participants without a history of cancer, and for participants who had had a consultation with a healthcare provider at baseline or in-between T0 and T3. No effect for self-efficacy was found for participants who had not had a consultation with a healthcare provider at baseline or in-between T0 and T3. Furthermore, whereas significant effects were found for all outcome measures for participants who plan to have children in the near future (≤2 years), no effects were found for realistic expectations, level of deliberation and decisional self-efficacy for participants who plan to have children in the more distant future (>2 years). As the reproductive decision is often not implemented within several months after reproductive counseling or after reviewing the decision aid, a long-term follow-up to measure decision adherence (e.g. 18 or 24 months after reviewing the decision aid) will be conducted in the near future. In conclusion, our findings in **Chapter 4** and **Chapter 5** suggest that the decision aid is an appropriate tool to support our target group in making an informed reproductive decision. The decision aid was most supportive for those couples who plan to have children in the near future (≤2 years) and those who had had a consultation with a healthcare provider.

To maximize impact of this support tool, an additional study was performed to develop a best-fitting implementation strategy for the decision aid by the use of a mixed methods design, i.e. a questionnaire among 46 healthcare providers to assess the critical determinants that may affect implementation combined with semi-structured focus groups (N=19) and individual telephonic interviews (N=15) (**Chapter 6)**. Opportunities and preferences of oncogenetic counselors for continued implementation of the decision aid were assessed. Counselors agreed that the primary

requirement for structural implementation in daily practice was ease of referral to the decision aid and preferably free online accessibility of the tool. To foster implementation of the decision aid, the distribution of online newsletters, incorporating the link to the decision aid on patient organization websites, and the designation of a contact person charged with continued implementation in each clinical genetic centre were suggested. Based on these preferences and recommendations, the implementation of the online decision aid will be nationally executed to optimize impact. Furthermore, adaptation of the decision aid to fit the needs of couples with other hereditary conditions is recommended.

Finally, in the General Discussion in **Chapter 7**, findings from these studies and their implications are reflected up on. Study limitations (e.g. non-experimental effect study, selectivity of the study population, and not discussing all reproductive options in detail) and recommendations for future research and for the daily practice of reproductive counselling in hereditary cancer are discussed.

Nederlandse samenvatting

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Ongeveer vijf procent van alle personen met kanker heeft een erfelijke aanleg daarvoor. Bij een erfelijke aanleg voor kanker is er meestal sprake van een autosomaal dominant overervingspatroon. Dat wil zeggen dat er een risico bestaat van 50% in elke zwangerschap dat de erfelijke aanleg voor kanker wordt doorgegeven aan het nageslacht. Personen met de erfelijke aanleg voor kanker hebben een verhoogd risico op het ontwikkelen van kanker. Ter illustratie, vrouwen met een erfelijke aanleg voor borst- en eierstokkanker hebben een risico van 69-72% op borstkanker en 17-44% op eierstokkanker vóór hun tachtigste levensjaar. Bij vrouwen zonder de erfelijke aanleg is dit risico veel lager, 12% voor borstkanker en ongeveer 1% voor eierstokkanker.

De wetenschap dat er voor eventuele kinderen een verhoogd risico op kanker bestaat, kan de keuze voor het krijgen van kinderen sterk beïnvloeden. Sommige paren waarvan een van de partners een erfelijke aanleg voor kanker heeft, zullen afzien van het krijgen van kinderen. Anderen kiezen voor het gebruik van donoreicellen of donorzaadcellen. Als er op die manier een zwangerschap tot stand komt, zal het kind niet genetisch verwant zijn aan beide partners. Het adopteren van kind(eren) is ook een optie. De meeste paren willen echter kinderen die verwant zijn aan beide partners. Paren met deze wens kunnen kiezen voor (1) een natuurlijke zwangerschap zonder onderzoek naar de erfelijke aanleg bij het toekomstige kind, (2) prenatale diagnostiek, (3) of Preïmplantatie Genetische Diagnostiek (PGD). Wanneer een paar kiest voor een natuurlijke zwangerschap zonder onderzoek naar de erfelijke aanleg bij het toekomstige kind, accepteren zij het risico van 50% dat het kind de erfelijke aanleg voor kanker erft. Paren die kiezen voor prenatale diagnostiek proberen op een natuurlijke manier zwanger te raken. In de zwangerschap kan vervolgens door middel van een vlokkentest (11-14de week) of vruchtwaterpunctie (vanaf de 15de week) worden onderzocht of het ongeboren kind de erfelijke aanleg voor kanker heeft. Als blijkt dat het ongeboren kind de erfelijke aanleg heeft geërfd, kan het paar ervoor kiezen om de zwangerschap af te breken. Dit wordt door veel paren als emotioneel zwaar ervaren. PGD vindt plaats voordat de vrouw zwanger is en wordt daarom door veel paren als een meer aanvaardbare optie beschouwd. Bij PGD wordt de zwangerschap tot stand gebracht door middel van een in vitro fertilisatie (IVF) behandeling (reageerbuis-bevruchting). Daarbij worden eicellen buiten het lichaam van de vrouw bevrucht met zaadcellen van de partner. De embryo's die zo ontstaan worden onderzocht op de aanwezigheid van de erfelijke aanleg voor kanker. Vervolgens komen alleen embryo's zonder de erfelijke aanleg in aanmerking voor plaatsing in de baarmoeder. Zo kan een zwangerschap ontstaan van een kind zonder de erfelijke aanleg voor kanker. PGD is

(voor de vrouw) fysiek belastend en heeft een relatief lange doorlooptijd. Per behandeling is de kans op een doorgaande zwangerschap ongeveer 25%. In vergelijking met prenatale diagnostiek voorkomt PGD echter wel de emotionele en fysieke belasting van een mogelijke zwangerschapsafbreking.

Het maken van een keuze voor een van de reproductieve opties wordt door veel paren met een erfelijke aanleg voor kanker als moeilijk ervaren en is sterk afhankelijk van hun persoonlijke voorkeuren en wensen. Idealiter is het paar optimaal geïnformeerd en hebben beide partners voldoende kennis om deze belangrijke keuze te maken. In een geïnformeerd keuzeproces overwegen paren zorgvuldig de voor- en nadelen van de reproductieve opties gebaseerd op hun persoonlijke waarden en normen. Om paren te ondersteunen in het maken van een geïnformeerde reproductieve keuze kan een "keuzehulp" effectief zijn.
Keuzehulpen zijn informatiepakketten zoals brochures of interactieve websites bedoeld om mensen te helpen met het maken van keuzes tussen verschillende (medische) opties. De keuzehulp verhoogt kennis door duidelijk te maken welke opties beschikbaar zijn en wat de voor- en nadelen zijn van iedere optie. Daarnaast ondersteunt de keuzehulp de patiënt in het bepalen van de waarde die hij/zij hecht aan deze voor- en nadelen. Keuzehulpen kunnen bij de patiënt leiden tot meer realistische verwachtingen ten aanzien van (medische) opties, meer betrokkenheid bij de besluitvorming en grotere tevredenheid over de uiteindelijke keuze.

Het huidige project heeft als doel een digitale patiënten keuzehulp te ontwikkelen en te evalueren om paren met een erfelijke aanleg voor kanker te ondersteunen in het maken van een geïnformeerde reproductieve keuze. **Hoofdstuk 1** biedt een introductie in erfelijke kanker, de reproductieve opties, het reproductieve keuzeproces en de ontwikkeling van de keuzehulp. Vervolgens wordt de indeling van dit proefschrift uiteengezet.
Deel I van dit proefschrift beschrijft het systematische ontwikkelingsproces van de keuzehulp. Een kwalitatieve studie werd uitgevoerd waarbij onderzoek werd gedaan naar de voorkeuren en behoeftes van paren en betrokken zorgverleners ten aanzien van de ontwikkeling en implementatie van de keuzehulp (**hoofdstuk 2**). Zeven paren met een erfelijke aanleg voor kanker en acht klinisch genetici betrokken bij de begeleiding van paren met een kinderwens, werden door middel van interviews gevraagd naar hun behoeftes en voorkeuren ten aanzien van de keuzehulp. Dergelijk onderzoek is essentieel voor een succesvolle ontwikkeling en op termijn het daadwerkelijke gebruik van de keuzehulp. Er waren veel overeenkomsten tussen de behoeftes en voorkeuren van paren en klinisch genetici ten aanzien van (1) de inhoud

van de keuzehulp, (2) belemmeringen en faciliterende factoren ten aanzien van het gebruik van de keuzehulp en (3) de implementatie van de keuzehulp. De deelnemers benadrukten het belang van het gebruik van begrijpelijke taal zonder vakjargon, een uitgebreide uitleg van alle relevante procedures en technieken rondom prenatale diagnostiek en PGD, en de rol van zorgverleners om paren te verwijzen naar de keuzehulp. De bevindingen van deze studie werden gecombineerd met kennis over motieven en overwegingen die een rol spelen tijdens het reproductieve keuzeproces. Dit samen vormde de basis voor de ontwikkeling van het prototype van de keuzehulp.

In **hoofdstuk 3** wordt het ontwikkelingsproces van de keuzehulp verder beschreven. De keuzehulp werd ontwikkeld op basis van internationale richtlijnen voor patiënten keuzehulpen. De stuurgroep die betrokken werd bij de ontwikkeling van de keuzehulp bestond uit betrokken zorgverleners, experts in gezondheidscommunicatie en medische besluitvorming, psychologen en paren met een kinderwens en een erfelijke aanleg voor kanker. Aan de hand van een iteratief proces werden de gebruiksvriendelijkheid en de sterke en zwakke punten van het prototype van de keuzehulp meerdere malen geëvalueerd. De paren en zorgverleners hadden gelijksoortige suggesties ter verbetering van de keuzehulp en vonden de aangepaste keuzehulp gemakkelijk in het gebruik en goed te begrijpen. De definitieve keuzehulp werd vervolgens getest onder 16 deelnemers tijdens een pilotstudie. De effecten op de belangrijkste uitkomstmaten, namelijk onzekerheid ten aanzien van de reproductieve keuze, kennis en realistische verwachtingen met betrekking tot de reproductieve opties, en de mate waarin men zich in staat voelt om een reproductieve keuze te maken (effectiviteitsgevoel), werden onderzocht vóór (tijdstip T0), meteen na (T1) en twee weken (T2) na het gebruik van de keuzehulp. Tijdens de pilotstudie was bij de deelnemers een afname te zien in de ervaren onzekerheid ten aanzien van de reproductieve keuze. Bovendien nam hun kennis toe en hadden deelnemers zowel op T1 als op T2 meer realistische verwachtingen ten aanzien van de reproductieve opties. Er werd geen effect gevonden op het effectiviteitsgevoel van deelnemers. Er waren na de pilotstudie geen verdere aanpassingen aan de keuzehulp nodig. De evaluatie van de definitieve keuzehulp wordt beschreven in **deel II** van dit proefschrift.

In **hoofdstuk 4** en **hoofdstuk 5** van **deel II** worden de studies beschreven waarin de keuzehulp verder werd geëvalueerd. In alle klinische genetische centra in Nederland werden potentiële deelnemers geworven. Er werd gebruikgemaakt van een *one group pretest posttest* design waarbij deelnemers vóór (tijdstip T0), meteen na (T1) en twee weken (T2) na het gebruik van de keuzehulp een vragenlijst invulden. In **hoofdstuk 4** worden de directe (T1) en korte termijn effecten (T2) van de keuzehulp beschreven.

Men kon deelnemen aan de studie wanneer een van beide partners een erfelijke aanleg voor een autosomaal dominante vorm van kanker had waarvoor prenatale diagnostiek of PGD wordt aangeboden in Nederland. Verder moesten deelnemers de intentie hebben om binnen 5 jaar hun kinderwens te vervullen en mocht men nog geen definitieve reproductieve keuze hebben gemaakt. De deelnemers moesten 18 jaar of ouder zijn en de Nederlandse taal voldoende beheersen. Een aantal belangrijke uitkomstmaten gerelateerd aan het maken van een geïnformeerde reproductieve keuze, zoals onzekerheid ten aanzien van de reproductieve keuze, kennis en realistische verwachtingen met betrekking tot de reproductieve opties, de mate waarin men de verschillende reproductieve opties tegen elkaar heeft afgewogen (deliberatie) en de mate waarin men zich in staat voelt om een reproductieve keuze te maken (effectiviteitsgevoel), werden geëvalueerd. Daarnaast werd aan deelnemers gevraagd om de keuzehulp te beoordelen met een "rapportcijfer" op een schaal van 1-10.
Deelnemers beoordeelden de keuzehulp gemiddeld met een 8.2 (SD=0.94). Vergelijkingen tussen T0 en T1 en tussen T0 en T2 onder 115 deelnemers door middel van gepaarde t-toetsen lieten een significante afname zien in de ervaren onzekerheid, waarbij er een sterker effect was voor deelnemers met een hoge mate van onzekerheid op T0. Ook resulteerde het gebruik van de keuzehulp in een toename in kennis en meer realistische verwachtingen ten aanzien van de reproductieve opties op T1 en T2. De mate van deliberatie nam enkel toe bij deelnemers met een lage mate van deliberatie op T0. Het effectiviteitsgevoel van deelnemers nam enkel toe voor degenen met een laag effectiviteitsgevoel ten aanzien van het maken van een reproductieve keuze op T0. Bij degenen die zichzelf op T0 reeds goed in staat achtten om een reproductieve keuze te maken, was een lichte daling in het effectiviteitsgevoel zichtbaar. Een mogelijke verklaring daarvoor zou kunnen zijn dat de sterke toename in kennis over de reproductieve opties tot gevolg heeft gehad dat deze deelnemers mogelijke misvattingen en kennishiaten bij zichzelf ontdekten, waardoor zij zich realiseerden hoe moeilijk het reproductieve keuzeproces kan zijn. Er kan worden geconcludeerd dat het gebruik van de keuzehulp resulteerde in diverse positieve effecten op de korte termijn die bijdragen aan het maken van een geïnformeerde reproductieve keuze. Het effect was sterker voor personen die meer behoefte lijken te hebben aan ondersteuning tijdens het reproductieve keuzeproces.

Hoofdstuk 5 beschrijft de effecten drie maanden na het doorlopen van de keuzehulp (T3) onder 93 deelnemers. Er werd onderzocht hoeveel deelnemers in staat zijn om een geïnformeerde reproductieve keuze te maken. Vergelijkingen tussen T0 en T3 lieten positieve effecten zien voor alle belangrijke uitkomstmaten. Van de deelnemers maakte 58% een geïnformeerde keuze ten aanzien van hun reproductieve voorkeursoptie op

T3. Op T0 was dit 14%. Daarnaast toonden subgroep analyses aan dat de keuzehulp effectief is voor zowel mannen als vrouwen, voor hoger en laag/gemiddeld opgeleiden, voor zowel personen met de erfelijke aanleg voor kanker als hun partners, voor deelnemers die wel kanker hebben gehad en voor deelnemers zonder een voorgeschiedenis van kanker, en voor deelnemers die een consult hebben gehad met een zorgverlener vóór het doorlopen van de keuzehulp of tussen T0 en T3. Voor deelnemers die geen consult met een zorgverlener hadden gehad, werd een effect gevonden op alle belangrijke uitkomstmaten behalve voor het effectiviteitsgevoel. Verder werd een significant effect gevonden op alle uitkomstmaten voor deelnemers met een kinderwens in de nabije toekomst (≤2 jaar). Daarentegen werd geen effect gevonden voor deelnemers met een kinderwens in de verdere toekomst (>2 jaar) voor realistische verwachtingen ten aanzien van de reproductieve opties, mate van deliberatie en het effectiviteitsgevoel. Aangezien de keuze van paren een paar maanden na reproductieve begeleiding door een zorgverlener en/of het doorlopen van de keuzehulp meestal nog niet definitief of geïmplementeerd is, zal een vervolgstudie met een langere follow-up worden uitgevoerd die het effect van de keuzehulp na twee jaar onderzoekt. Het doel daarvan is vooral om na te gaan of paren blijven bij hun aanvankelijke reproductieve keuze. Op basis van de bevindingen in **hoofdstuk 4** en **hoofdstuk 5** kan worden geconcludeerd dat de keuzehulp geschikt is om paren te ondersteunen in het maken van een geïnformeerde keuze ten aanzien van de reproductieve opties. De meeste effecten werden gevonden voor paren met een actievere kinderwens en paren die naast het doorlopen van de keuzehulp een gesprek hadden gehad met een zorgverlener.

Om de impact van de keuzehulp te optimaliseren werd een aanvullende studie uitgevoerd om een geschikte implementatiestrategie te ontwikkelen. Een vragenlijst werd ingevuld door 46 zorgverleners gevolgd door focusgroepen (N=19) en individuele telefonische interviews (N=15). Het doel was het inventariseren van belemmerende en bevorderende factoren ten aanzien van de implementatie van de keuzehulp (**hoofdstuk 6**). Zorgverleners gaven unaniem aan dat het op een eenvoudige manier kunnen verwijzen van paren naar de keuzehulp en het publiek toegankelijk maken van de keuzehulp de belangrijkste voorwaarden zijn voor succesvolle implementatie in de dagelijkse praktijk. Om de implementatie van de keuzehulp te stimuleren adviseerden zorgverleners (1) het verspreiden van online nieuwsbrieven, (2) het vermelden van een link naar de keuzehulp op patiëntenorganisatiewebsites en (3) het aanwijzen van contactpersonen in ieder klinisch genetisch centrum die de leiding nemen in de implementatie van de keuzehulp in hun centrum. De digitale keuzehulp zal op nationaal niveau worden geïmplementeerd. Daarnaast zal de keuzehulp in vervolgonderzoek

zodanig worden aangepast dat deze ook geschikt is voor paren met andere erfelijke aandoeningen.

Tot slot wordt in **hoofdstuk 7** gereflecteerd op de studieresultaten en worden beperkingen van de studies besproken zoals het feit dat er geen experimenteel design voor het evalueren van de keuzehulp is gebruikt, selectiviteit ten aanzien van deelnemers binnen de verschillende studies en het feit dat niet alle reproductieve opties even gedetailleerd worden toegelicht in de keuzehulp. Verder worden aanbevelingen gedaan voor toekomstig wetenschappelijk onderzoek en voor de verdere begeleiding van paren bij het maken van een reproductieve keuze.

Dankwoord

Dankwoord

Het dankwoord, een mooie manier om iedereen te bedanken die op welke wijze dan ook een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift.

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Curriculum Vitae

Curriculum Vitae

Kelly Reumkens werd geboren op 27 december 1991 te Heerlen. Na in 2010 haar VWO-diploma te hebben behaald aan het Sophianum college te Gulpen, startte ze met de Bachelor opleiding Gezondheidswetenschappen aan de Universiteit Maastricht. Kelly koos ervoor de studierichting Preventie en Gezondheid te volgen. In 2013 behaalde zij haar Bachelor diploma en startte aansluitend met de Master Health Education and Promotion, tevens aan de Universiteit Maastricht. Onder begeleiding van dr. Liesbeth van Osch schreef zij haar wetenschappelijke masterthesis op de afdeling Klinische Genetica van het Maastricht Universitair Medisch Centrum. Deze masterthesis bracht de motieven, overwegingen en informatiebehoeften van koppels in kaart ten aanzien van het keuzeproces rondom erfelijke kanker en kinderwens. Het schrijven van deze masterthesis wekte haar interesse voor wetenschappelijk onderzoek en vormde de basis voor de start als promovendus op de afdeling Klinische Genetica, direct na het behalen van haar Master diploma. Gedurende haar promotieonderzoek ontwikkelde en evalueerde Kelly een digitale patiënten keuzehulp om koppels te ondersteunen tijdens het keuzeproces rondom erfelijke kanker en kinderwens. Deze keuzehulp en de belangrijkste resultaten van haar promotieonderzoek heeft zij op verschillende nationale en internationale congressen gepresenteerd en staan beschreven in dit proefschrift. In 2016 won zij de award voor beste posterpresentatie op het congres van de Nederlandse Vereniging voor Psychosociale Oncologie. Ditzelfde congres heeft zij het daaropvolgende jaar mede georganiseerd.