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A reproductive dilemma?

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A reproductive dilemma?

Optimizing counselling for couples with hereditary breast and ovarian cancer who consider using preimplantation genetic diagnosis

Joyce Gietel-Habets

A reproductive dilemma?

Optimizing counselling for couples with hereditary breast and ovarian cancer who consider using preimplantation genetic diagnosis

The studies presented in this thesis were performed at the School for Oncology and Developmental Biology (GROW) of Maastricht University in collaboration with the department of Clinical Genetics of the Maastricht University Medical Center (Maastricht UMC+).

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Stichting Jules Coenegracht Sr

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Science gathers knowledge faster than society gathers wisdom.

- Isaac Asimov -

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Chapter 1

General introduction and outline of the thesis

General introduction

At the clinical genetics department of the Maastricht University Medical Center (Maastricht UMC+), couples with hereditary breast and ovarian cancer (HBOC) frequently inquire about preimplantation genetic diagnosis (PGD). PGD is a method to prevent transmission of HBOC to a future child by selecting an embryo without HBOC before transferring it to the woman's uterus. This reproductive technique is facilitated by making use of in vitro fertilization (IVF). Due to technical developments, PGD is lately being referred to as preimplantation genetic testing (PGT) though for reasons of consistency, this dissertation adheres to the name PGD.

PGD for HBOC is reimbursed by the Dutch health insurance system. About two thirds of these counselees decide to initiate a PGD treatment.[1] Given the late onset character of the condition and the preventive possibilities, combined with its serious nature and the related burden, many struggle with the decision to opt for or refrain from PGD. The research project described in this dissertation was designed to investigate PGD awareness and knowledge, and the reproductive decision-making process of couples with HBOC. With this information we ultimately strive to customize educational and support practices to their characteristics, needs and wishes.

Hereditary breast and ovarian cancer (HBOC)

HBOC is a genetic cancer syndrome caused by mutations in the *BRCA1* and *BRCA2* genes. Generally 5-10% of all breast cancer cases are caused by genetic predispositions. Of these, 25% can be ascribed to mutations in the *BRCA1/2* genes.[2-3] The estimated prevalence of *BRCA1/2* mutations in the general population is 0.25-0.50% (i.e. 1 in 400 to 1 in 200 people has a *BRCA1/2* mutation).[4-5]

Female carriers of *BRCA1* and *BRCA2* mutations face a risk of respectively 72% and 69% of developing breast cancer, and respectively 44% and 17% of developing ovarian cancer before the age of eighty.[6] The estimated cumulative risks of breast cancer for male *BRCA1/2* carriers are 1.2% to 6.9%.[7-8] In addition, female carriers of a *BRCA 1/2* mutation face elevated risks of fallopian tube cancer, pancreatic cancer and possibly endometrial cancer and melanoma, whereas male mutation carriers additionally face elevated risks of prostate cancer, pancreatic cancer and possibly melanoma.[9-12] A *BRCA1* mutation is additionally associated with an increased risk of colorectal cancer for both males and females.[13]

Five and ten year survival rates for breast cancer among European women are 87% and 78% respectively. For ovarian cancer these rates are 46% and 34% respectively.[14-15] The literature suggests that survival rates for *BRCA* linked breast cancer are lower compared to sporadic breast cancer, especially for *BRCA1* mutations. On the contrary, survival rates for *BRCA* linked ovarian cancer appear to be higher in comparison to sporadic ovarian cancers.[3]

In order to reduce morbidity and mortality, female *BRCA1/2* carriers are advised to undergo surveillance of the breasts and/or risk-reducing surgery. In the Netherlands, intensified screening of the breasts is offered from 25 to 60 years of age. From then on, the regular population based screening program applies to female *BRCA1/2* carriers.[16] Moreover, prophylactic bilateral risk-reducing mastectomy (RRM) is discussed with women with a *BRCA1/2* mutation. RRM has been shown to reduce the occurrence of breast cancer to <1% after 4.5-8.4 years of follow up.[17-19] Screening of the ovaries has been proven to be ineffective for early detection of *BRCA1/2* associated ovarian cancer.[20-21] Therefore, female *BRCA1/2* mutation carriers are advised to undergo a bilateral risk reducing salpingo-oophorectomy from the age of 35-40 in case of a *BRCA1* mutation and from the age of 40-45 in case of a *BRCA2* mutation.[16]

Preimplantation genetic diagnosis (PGD) and other reproductive options

As HBOC is an autosomal dominant predisposition, there is a 50% risk for *BRCA1/2* mutation carriers to transmit the mutation to their offspring. Two reproductive options are available for couples with HBOC who want to prevent transmission of the *BRCA* mutation to their genetically related child: prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD). PND is performed during pregnancy. Usually, at 9 weeks of pregnancy, non-invasive fetal sex determination is conducted. For a male fetus, no additional testing is currently considered necessary as the slightly increased risk for breast cancer (1.2-6.9%)[7] is considerably lower than the general population risk of breast cancer for females in Western countries (14%).[14-15] In case of a female fetus, invasive testing of the *BRCA* mutation by means of chorionic villus sampling follows, with the intention to terminate the pregnancy if the *BRCA* mutation is detected. Most *BRCA* carriers and their partners consider PND as a too drastic option to prevent HBOC.[22-24] For those couples, PGD can be a more attractive alternative. PGD is performed before pregnancy by conducting in vitro fertilization (IVF), followed by analysis of one or a few embryonic cells. Embryos without the *BRCA* mutation are selected for transfer to the woman's uterus. For PGD for monogenic conditions such as HBOC, a genetic protocol needs to be developed which will take one to several months. The generally used haplotyping technique is based on comparison of haplotypes of family members with and without the mutation. Therefore, several first-degree family members have to contribute their DNA to enable the setup of the genetic protocol.[25] Once the genetic protocol is finalized, the IVF treatment can be initiated. Hormonal stimulation of the ovaries is necessary in order to produce multiple oocytes. Subsequently the oocytes are retrieved and fertilized using intracytoplasmic sperm injection (ICSI).[26-27] The embryos are biopsied, taking one or a few cells at day 3-6 post fertilization. The biopsied cells are analyzed, differentiating the embryos with the *BRCA* mutation from the embryos without the *BRCA* mutation. The morphologically best embryo without the *BRCA*

mutation is transferred to the woman's uterus. Other embryos without the *BRCA* mutation are cryopreserved for a possible future transfer. The chance of pregnancy after PGD is approximately 25% per cycle.[28] Most Dutch health insurers reimburse three IVF/PGD cycles. After three cycles approximately 50% of the couples establishes an ongoing pregnancy.

Other reproductive options for couples with HBOC are:

1. A natural pregnancy without genetic testing, which implies acceptance of the 50% risk of passing on the *BRCA* mutation to the child. The *BRCA* status of the child remains unknown until he or she decides to undergo DNA testing at adult age. This is still the most frequently used reproductive option by couples with HBOC.[23-24]
2. Using donor-gamete or -sperm, meaning that transmission of the mutation is prevented but the parent with the *BRCA* mutation is not genetically related to the child.
3. Adoption, meaning that transmission of the mutation is prevented but both parents are not genetically related to the child.
4. Ultimately, there is the option to refrain from having children.

Options 2-4 are rarely opted for by couples with HBOC.[23-24]

The dynamics of reproductive decision-making

Couples with HBOC are an exceptional group with unique reproductive concerns. In addition to the general (dis)advantages of PGD and PND, several considerations that are not applicable to other PGD indications further complicate decision-making. First, HBOC is a late onset predisposition with incomplete penetrance for which preventive and therapeutic options are available. This has raised ethical reservations towards the application of PND and PGD for this condition among critics and among potential users.[29-33] Second, the implications of this predisposition significantly differ between males and females. General regulations for good clinical practice in PGD disallow transferring an affected embryo, causing male carrier embryos with an only slightly increased cancer risk to be discarded in an already strict process of elimination. While this is a disadvantage of PGD for some couples, it is an advantage for others who want to wipe out the mutation in their family line or protect a potential son from having a similar reproductive dilemma in the future.[24] Third, for female carriers and their partners, family planning is further complicated by a relatively narrow time window while PGD is a time consuming trajectory. This narrow time window is caused by the advised risk reducing surgeries (i.e. removing breasts and ovaries before a certain age) which affect the woman's fertility and ability to breastfeed. Finally, an additional worry for female carriers and their partners is a hypothesized increasing effect of IVF hormones on the woman's breast and ovarian cancer risk, although a recent study indicates this concern might be unnecesary.[34] This illustrates the complexity of reproductive decision-making

for couples with HBOC. Adverse psychological effects like feelings of doubt and guilt are not uncommon among parents with a genetic susceptibility.[35-36]

The context of PGD and reproductive counseling in the Netherlands

PGD the Netherlands is a collaboration of the University Medical Centers Maastricht (Maastricht UMC+), Utrecht, Groningen and Amsterdam, founded in 2008. The Maastricht UMC+ is the only licensed PGD center in the Netherlands, which means that the PGD analysis is always performed there, though the IVF treatment can be conducted in one of the collaborating University Medical Centers. In this case, biopsied specimens of the embryos are transported to the Maastricht UMC+.

Since the start in 1995, PGD was only allowed for severe, fully penetrant diseases with an early age of onset. After a nation-wide debate in 2008, involving patients, politics and media, PGD for hereditary cancer syndromes including HBOC was approved.[37] Given the late age of onset, the incomplete penetrance and preventive and therapeutic options, a slippery slope was feared by critics if PGD indications were extended with hereditary cancer syndromes. On the other hand, also considering the tolerant policy regarding PND, supporters argued that the concerning couples should have the right for a free reproductive choice, especially regarding the potentially serious nature of hereditary cancer syndromes. Following this episode, several terms and conditions for PGD were recorded in the national PGD regulation.[37] First, a national committee for the assessment of new PGD indications was established. Second, in order to secure transparency in PGD practice, a yearly report of PGD applications and treatments was to be published by *PGD the Netherlands*. Today, a total of 4.024 PGD treatments (379 for HBOC) have been performed among 1.854 couples (172 for HBOC) which has resulted in the birth of 800 children (unknown for HBOC) in the Netherlands.[1]

PGD counseling in the Netherlands is organized as follows: couples who are referred or who personally request information about PGD are invited for an intake consultation at the Department of Clinical Genetics at the Maastricht UMC+. In the invitational letter, couples are asked to prepare themselves by studying the website of *PGD the Netherlands* where detailed information about PGD is provided. Some couples have already received information about PGD at one of the PGD transport IVF clinics. During the intake consultation at the Maastricht UMC+, a clinical geneticist with expertise on PGD provides verbal and written information about the PGD procedure, including embryo biopsy, chance of pregnancy, risk of misdiagnosis and health of children born after PGD. In addition, the physical and practical aspects and the possible burden of an IVF/ICSI procedure are discussed. Finally, the procedure and implications of PND as an alternative reproductive option and as an option to confirm the PGD diagnosis are discussed. A consultation with a psychologist is offered but is not obligatory. Such a psychological consultation focuses on an evaluation of the couple's emotional capacity

to cope with a PGD treatment and on providing guidance and support with reproductive decision-making. Subsequently, couples decide whether they want to opt for PGD. There is no time constraint for making a decision. Those who definitely opt for PGD are referred to a gynecologist at one of the participating IVF centers to determine their IVF suitability. Women with a *BRCA* mutation are advised to undergo additional breast screening within 3 months before the start of their IVF/PGD treatment.

Since HBOC was added to the list of approved conditions for PGD in the Netherlands it has been one of the most frequently requested indications for PGD. However, at the start of the research project described in this dissertation, it was unclear how many couples with HBOC were aware of PGD as a reproductive option or what their attitude was toward PGD. A meta-analysis that reviewed 13 studies of which two conducted in the Netherlands, focusing on hereditary cancer syndromes in general, showed that PGD awareness was rather low (30-35%), whereas acceptability was high (71%).[38] From the perspective of informed decision-making, awareness about one's options and gaining knowledge about these options are the first and necessary steps towards deliberation and weighing of pros and cons of the options, enabling someone to make an informed and personally best suitable choice. Informed reproductive decision-making has been shown to have a beneficial effect on psychological management by means of lowering decisional conflict and increasing personal wellbeing and decisional satisfaction.[39-40] Therefore, information provision about PGD for HBOC and consequently the awareness about this option should be enhanced. Health professionals who function as possible referrers for PGD (e.g. clinical geneticists, oncologists, gynecologists), may play an important role in raising awareness, and can be regarded as gatekeepers for couples who may benefit from PGD. Their referral behavior however, will partially depend on their own awareness and attitude regarding PGD for HBOC and it is therefore important to investigate their views and to develop recommendations for PGD referral. Moreover, it would be valuable to better understand couples' decision-making regarding PGD for HBOC. By identifying the principal (domains of) motives and considerations to opt for or refrain from PGD and investigate associations with personal characteristics, counseling can be improved and tailored to personal needs. With these goals in mind the present research project was initiated.

The research project

Research question

How well are couples with HBOC informed about PGD and how do they make a reproductive decision?

Aims

1. Assess awareness, knowledge and attitude regarding PGD among persons with HBOC and their partners as well as among their potential referring physicians.
2. Unravel the reproductive decision-making process of couples with HBOC.
3. Define educational and support needs in order to facilitate informed reproductive decision-making for couples with HBOC.
4. Provide suggestions to improve and customize reproductive counseling for couples with HBOC.

Study design

In order to asses awareness, knowledge and attitude regarding PGD among individuals with HBOC and their partners and among their potential referring physicians, two online cross sectional surveys were conducted. Carriers and partners of carriers were eligible for participation if they (or their partner) had a proven *BRCA1/2* mutation and participants were recruited through the websites and digital newsletters of several patient organizations. Healthcare professionals were eligible for participation if they were involved in the field of hereditary breast and ovarian cancer, reproduction or both and were recruited in collaboration with several Dutch professional associations (the associations for Clinical Geneticists, Genetic Counsellors, Obstetrics & Gynecology and Oncology). A mixed methods design was used to investigate the reproductive decision-making process of couples with HBOC and to define their educational and support needs. These topics were explored by conducting focus groups and interviews with couples with HBOC who had received PGD counseling and had made a reproductive choice in the past three years. The acquired qualitative data was used to develop a questionnaire about experiences with and support needs concerning reproductive decision-making and its main underlying motives and considerations, which was distributed among a larger group with similar inclusion criteria. For both the qualitative and the quantitative study, couples were recruited through the patient databases of the Maastricht UMC+ and the University Medical Centre Nijmegen (Radboud UMC).

Outline of this thesis

Chapter 2 presents an overview of PGD/PND awareness, knowledge and attitude among Dutch *BRCA1/2* carriers and their partners.
Chapter 3 presents an overview of PGD awareness, knowledge and attitude among potential referring physicians for couples with HBOC.

Chapter 4 describes the reproductive decision-making process of couples with HBOC, investigated in in-depth focus groups. In addition, couples' motives and considerations to opt for or refrain from PGD and PND are identified.

Chapter 5 concerns a quantitative study that builds on the results of chapter 4 and outlines the main thought processes in PGD decision-making. Moreover, the impact of several motivational domains on reproductive choice is described.

Chapter 6 elaborates on the patients' perspective regarding current PGD counseling and the (additional) need for guidance and support during and after the decision-making process.

Ultimately, the aim was to make suggestions to improve and customize education and support practices for couples with HBOC regarding reproductive decision-making. In addition, these findings may serve as a blueprint for optimizing counselling on PGD decision-making for other indications.

This thesis was sponsored by the Dutch Breast Cancer Foundation: Stichting Pink Ribbon (grant number: 2010.PS11.C74), the Netherlands organization for health research and development (ZonMw; grant number: 70-71300-98-106) and the Dutch Cancer Society (Alpe d'HuZes Foundation; grant number UM2013-6374).

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Part I

Awareness, knowledge and acceptability of PGD among couples with hereditary breast and ovarian cancer and involved professionals

Chapter 2

Awareness and attitude regarding reproductive options of persons carrying a *BRCA* mutation and their partners

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Abstract

Study question

To what extent are *BRCA* mutation carriers and their partners in the Netherlands aware about preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PND) as reproductive options and what is their attitude towards these options?

Summary answer

Awareness of PGD (66%) and PND (61%) among *BRCA* mutation carriers and their partners is relatively high and 80% and 26%, respectively, of *BRCA* carriers and their partners find offering PGD and PND for hereditary breast and ovarian cancer (HBOC) acceptable.

What is known already

Internationally, awareness of PGD among persons with a genetic cancer predisposition appears to be relatively low (35%) and although acceptability is generally high (71%), only a small proportion of mutation carriers would consider using PGD (36%). However, for HBOC, there are no studies available that investigated the perspective of individuals with a confirmed *BRCA1/2* mutation and their partners about PGD and PND including demographic and medical correlates of awareness and acceptability.

Study design, size, duration

A cross-sectional survey was completed by 191 participants between July 2012 and June 2013. Participants were recruited through patient organizations (88%) and the databases of two Clinical Genetics departments in the Netherlands (12%).

Participants/materials, setting, methods

Male and female *BRCA* carriers and their partners completed an online survey, which assessed demographic and medical characteristics, and awareness, knowledge, acceptability and consideration of PGD and PND as main outcomes. Correlations between demographic and medical characteristics and the main outcomes were investigated.

Main results and role of chance

The majority of respondents were female (87%), of reproductive age (86%) and about half reported a desire for a child in the future. About two-thirds (66%) were aware of PGD and 61% of PND for HBOC. PGD knowledge was moderate (5.5 on a 9-point scale) and acceptability of PGD and PND for HBOC was 80% and 26%, respectively. A minority would personally consider using PGD (39%) or PND (20%). Individuals with a higher educational level were more likely to be aware of PGD ($P<0.001$) and PND ($P<0.001$) and persons with a more immediate child wish were more often aware of PGD ($P=0.044$) and had more knowledge about PGD ($P=0.001$). PGD acceptability was positively associated with knowledge about PGD ($P=0.047$), and PND acceptability was higher among partners in comparison to carriers ($P=0.001$). Participants with a history of cancer and with

a higher perceived seriousness of breast and ovarian cancer were more likely to consider using PGD (P=0.003 and P<0.001 respectively) or PND (P=0.021 and P=0.017 respectively).

Limitations, reasons for caution

The response rate (23%) of participants invited by the clinical genetics departments was low, probably related to a simultaneous study that used a similar recruitment strategy within the same target group, which may have resulted in selection bias. Moreover, PGD knowledge was measured with an instrument that is not yet validated since to date such an instrument is not available in the literature. Finally, the cross-sectional design of this study limits us from drawing any causal conclusions.

Wider implications of the findings

Improvement of information provision remains needed, in order to timely inform all couples with HBOC about the available reproductive options and enable them to make a balanced reproductive decision. This may limit the risk of negative psychological impact due to decisional conflict and possible regret.

Study funding/competing interest(s)

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Introduction

Women who have a mutation in one of the breast cancer genes *BRCA1* or *BRCA2* face elevated risks of 27–57% of developing breast cancer and 6–40% of developing ovarian cancer by the age of 70.[1,2] In the Netherlands, ~13 000 women are diagnosed with breast cancer and ~1400 are diagnosed with ovarian cancer every year. Of the note, 5-10% of the cases are caused by a genetic mutation.[3] Preventive options are limited to chemoprevention and prophylactic surgery and although therapeutic options are available, average age prospects are reduced due to a relatively early age of onset.[4] Since hereditary breast and ovarian cancer (HBOC) is an autosomal dominant predisposition, carriers have a 50% risk of passing on the mutation to their offspring. Couples who want to have a child biologically related to both partners have three reproductive options: (i) Conception without *BRCA* diagnosis, and accept the risk of passing on the *BRCA* mutation, (ii) Prenatal Diagnosis (PND), i.e. *BRCA* diagnosis during pregnancy and possible termination of pregnancy (TOP) in case of a female carrier and (iii) Preimplantation Genetic Diagnosis (PGD), i.e. selection of IVF/ICSI embryo's free of the familial *BRCA* mutation before implantation in the uterus. The decision-making process considering these reproductive options has proven to be demanding for couples with HBOC. The emotional impact of the decision can be long lasting and significant, as particularly non-users of PGD and PND may be confronted with feelings of doubt and guilt up to years after the decision has been made.[5] In the Netherlands, PGD was introduced in 1995 and after nationwide political and ethical discussions, approved for late onset inherited cancer predisposition syndromes in 2008. Nowadays, HBOC is one of the most frequent indications for PGD in the Maastricht University Medical Centre+ (Maastricht UMC+), the only licensed PGD centre in the Netherlands. Of the couples with *BRCA* that seek reproductive counselling about PGD, ~60% opt for PGD.[6] PND for HBOC is available on a case-by-case basis in some University Medical Centres and both PGD and PND treatments are covered by the Dutch health insurance system. The available literature suggests that the rapid development of PGD may have outpaced the awareness of this reproductive option among couples with HBOC. In 2012, a meta-analysis was published reviewing 13 studies (conducted in the USA, several European countries and Israel) about PGD awareness and acceptability among persons with hereditary cancer, showing that awareness of PGD was low (30–35%), whereas acceptability was relatively high (71%).[7] Knowledge about PGD has not been properly measured in the studies to date, since its assessment generally pertains to mere awareness (i.e. having heard of…) instead of measuring actual PGD understanding. Moreover, among the studies that focussed on HBOC there was substantial variation in study populations: several included respondents for whom a genetic mutation had not been confirmed[8,9], many included only men or women[9-13], few specifically included participants of reproductive age[14,15] and/or investigated small samples sizes (<80).[8,10] Furthermore, the studies differed considerably in information provision about PGD, which was often scarce, before assessing PGD acceptability. These issues may have

caused bias, as they are likely to influence PGD awareness, knowledge and attitude. Moreover, most of these studies exclusively considered the views of mutation carriers and missed out on the valuable and influential perspective of the noncarrier partners. An overview of awareness, knowledge, acceptability and experiences regarding PND for HBOC is currently lacking in the literature. In many European countries, there are no clear regulations concerning PND for HBOC and despite its technical feasibility, it is generally not often performed.[16,17] This may be related to (un)awareness and/or (un)acceptability of this reproductive option and should be investigated. When viewing (reproductive) decision-making from a social-cognitive perspective, the decision-making process parallels behaviour change. Several well-known theories and models in this field propose various phases in which change takes place, for example the Precaution Adoption Process Model (PAPM)[18] and the Transtheoretical Model of Behaviour Change (TTM).[19] These theories describe several stages to change a health behaviour and show that the initial step towards well informed decision-making is becoming aware of the available options, and subsequently gaining knowledge about these options. A couple that is not aware of PGD or PND simply cannot consider using it. Only when being completely informed about the procedures, risks and benefits of the options, a couple can weigh the pros and cons of each option and make their personally best suitable reproductive choice. Therefore, information provision about PGD and PND for HBOC should be optimized. This can be realized by attuning this information provision to different socio-demographic subgroups. We investigated PGD and PND awareness, knowledge and acceptability as well as personal intention to use either of these options and their demographic and medical correlates, among *BRCA* carriers and their partners in the Netherlands, who were well informed about the implications of these options (i.e. given written information about PGD and PND). By gaining insight into this, guidance and support during the reproductive decision-making process for couples with HBOC can be optimized and adequately tailored to subgroups.

Materials and methods

Participants and procedures

Carriers of a *BRCA1* or *BRCA2* mutation and partners of carriers were invited to complete an online questionnaire anonymously between July 2012 and June 2013. Inclusion criteria were (i) having a confirmed *BRCA1/ 2* mutation or a partner with a confirmed *BRCA1/2* mutation and (ii) sufficient knowledge of the Dutch language. Recruitment strategies were aimed at persons in their reproductive age but this was not an inclusion criterion. Two different recruitment strategies were used. For the first strategy, announcements of the study were placed on several informative websites regarding breast and ovarian cancer, digital communities of patient organizations for HBOC and in the digital newsletter of the Dutch patient organization for HBOC. Persons interested in

participating could follow a link in the announcement, which led them to an introduction to the questionnaire providing detailed information about the study and contact details of the researcher in case of any additional questions. It was clearly stated that informed consent was given by initiating the questionnaire. For the second recruitment strategy, eligible couples were identified from the databases of two Dutch Clinical Genetics departments (Maastricht University Medical Centre+ (MUMC+) and Radboud University Medical Centre (Radboudumc). Individuals with a *BRCA1/2* mutation, diagnosed between 2008 (when PGD became available for HBOC in the Netherlands) and 2013 were selected from the databases and received an invitational letter accompanied by information about the study, including a link to the online questionnaire. The two strategies were aimed at both *BRCA* carriers and partners of carriers without the necessity to participate as a couple. Procedures were approved by the local medical ethics committee of the MUMC+.

Questionnaire

The questionnaire was based on a literature search and the results of a focus group study about decision-making on PGD and PND among couples with HBOC.[5] Before finalization, the questionnaire was pre-tested by two *BRCA* carriers (one male, one female) and their partners, which resulted in minor adaptations. The four main outcome variables concerned: (i) whether the participant was aware of the possibility of PGD or PND for HBOC before filling in the questionnaire (yes/no; two questions), (ii) the level of knowledge of PGD for HBOC among participants who were previously aware of PGD (nine questions), (iii) whether the participant regarded PGD or PND for HBOC acceptable (1=totally disagree, 5=totally agree; two questions) and (iv) whether the participant would personally consider using PGD or PND for HBOC or for another serious genetic condition (1=no, definitely not, 5=yes, definitely; two questions). PGD knowledge was measured with seven closed-ended questions (true/false/not sure) and two open ended questions (recoded into correct answer = 1, all other answers = 0). These nine items were transformed into a scale with a Cronbach's α of 0.72. In addition, current child wish (1=no (not anymore) /2=maybe, not sure /3=yes, in the future but not at this moment /4=yes, trying to get pregnant /5=yes, currently pregnant), perceived seriousness of breast and ovarian cancer (5-item scale) and the preferred reproductive option at present time (conception without *BRCA* diagnosis/PGD/PND/donor/adoption/refrain from children) were assessed. Demographic factors of interest were age, gender, educational level (1=no education completed, 8=university level), partner status (partner/no partner), religiosity (yes/no) and ethnicity (Dutch/non-Dutch). Medical factors included carrier status (carrier/partner of carrier), mutation type (*BRCA1/BRCA2*), personal history of breast/ovarian cancer (yes/no), history of breast/ovarian cancer among first degree family members (categorized into: <3/≥3), medical indication for IVF (yes/no), previous pregnancy (yes/no) and child(ren) (yes (how many)/no). After measuring awareness and knowledge and before assessing acceptability, detailed

information about PGD and PND procedures and risks was provided, based on the information given during a reproductive consultation by a clinical geneticist. An overview of the main questionnaire items is provided in Table 2.1.

Table 2.1: Main questionnaire items.

Questionnaire items	Answer options
Awareness	
Did you ever hear about PGD/PND before filling in this questionnaire?*	Yes(1)-no(0)
Did you know about the possibility of PGD/PND for HBOC in the Netherlands before filling in this questionnaire?*	Yes(1)-no(0)
Knowledge	
For PGD, an IVF treatment is always necessary	True(1)-false(0)-not sure(0)
PGD is possible in every hospital in the Netherlands	True(1)-false(0)-not sure(0)
With PGD for HBOC in the Netherlands couples can also choose the gender of the embryo	True(1)-false(0)-not sure(0)
With PGD for HBOC in the Netherlands the embryo is also screened for other predispositions than HBOC	True(1)-false(0)-not sure(0)
Hormone-use by the woman is not always necessary for a PGD treatment	True(1)-false(0)-not sure(0)
PGD takes place before the woman is pregnant	True(1)-false(0)-not sure(0)
When a couple is normally fertile, the chance of a pregnancy after a PGD treatment is nearly 100%	True(1)-false(0)-not sure(0)
What is a woman's maximum age for PGD in the Netherlands?	Open ended (40=1/all other values=0)
What is the chance (in%) of a pregnancy after a PGD treatment?	Open ended (20-25=1/all other values=0)
Acceptability	
I think PGD for HBOC is acceptable	Totally disagree(1)-totally agree(5)
I think PND for HBOC, including a possible pregnancy termination, is acceptable	Totally disagree(1)-totally agree(5)
Perceived seriousness HBOC	
I think breast and ovarian cancer are very serious conditions	Totally disagree(1)-totally agree(5)
The consequences of breast and ovarian cancer are very serious in comparison to other conditions	Totally disagree(1)-totally agree(5)
Consideration to use PGD and PND	
Would you personally consider to use PGD/PND for HBOC?*	No, definitely not (1)-yes, definitely (5)
Can you imagine that you would consider using PGD/PND for another serious hereditary disease than HBOC?*	No, definitely not (1)-yes, definitely (5)
Preferred reproductive option	
Which option to fulfil your child wish would you prefer? *(also if you won't or can't have any (more) children we would like to know what would have been the best option for you)*	NC/PGD/PND/donor oocyte or sperm cell/adoption/refrain from child wish/other…

* Question was separately stated for PGD and for PND. PGD = Preimplantation Genetic Diagnosis; PND = Prenatal Diagnosis; NC = Natural Conception; HBOC = Hereditary Breast and Ovarian Cancer; IVF = In Vitro Fertilization.

Data analysis

Collected data were automatically stored in SPSS 19.0 and then analysed. Descriptive statistics were used for an overview of PGD and PND awareness, knowledge, acceptability and personal intention to use these options among the general group and

within socio-demographic subgroups. Due to insufficient variation within the predictor ethnicity (Table 2.2), this variable was not included in further analyses. Pearson correlations, independent sample t-tests and Pearson chi-square tests were used to assess correlates of demographic and medical factors with the four outcomes of interest. The non-parametric Mann Whitney U-tests or Spearman correlations were used for analyses with ordinal variables. For multivariate analyses, a linear or logistic regression model (enter method) was built by including only the independent variables that showed significant associations with the outcome variables in the bivariate analyses. A significant outcome was defined when $P<0.05$. To determine which proportion of the sample was of reproductive age (18–40 years) we combined the age of all female respondents with the age of the female partners of the male respondents and calculated the proportion that was between 18 and 40 years old. Post hoc analyses were conducted in order to check whether the recruitment strategy (online versus clinical genetics centre) significantly influenced the main variables.

Results

Participants' characteristics

The survey was completed by 191 eligible participants of which the majority (88%) was recruited through the online recruitment strategy. The remainder (12%) was invited by the Clinical Genetics departments. Recruitment strategy (online versus clinical genetics centre) did not significantly influence the main variables. Table 2.2 provides an overview of participants' characteristics.

Awareness of PGD and PND for HBOC

Of the total sample 66% of respondents were aware of PGD for *BRCA,* with a higher awareness rate (84%) among respondents with a child wish. Descriptive statistics are shown in Table 2.3. Bivariate analyses (Table 2.4) showed that younger persons, those with a higher educational level, with a more immediate child wish and those without children were more often aware of PGD for HBOC. Multivariate analyses by means of logistic regression (Table 2.5) confirmed that respondents with a higher educational level and those with a more immediate child wish were more likely to be aware of PGD for HBOC. Awareness of PND for HBOC correlated with younger age, higher educational level, a more immediate child wish, being childless, having more family members with cancer and with a *BRCA1* mutation. Multivariate analyses confirmed that the higher educated were more likely to be aware of PND for HBOC.

Table 2.2: Participants' characteristics.

Demographic factors	Sample % (n=191)
Gender	
Male	12.6(24)
Female	87.4(167)
Age males (years)	
Mean	35.7(SD=7.4)
Range	26-53
Age females (years)	
Mean	34.1(SD=7.2)
Range	21-69
Females in reproductive age	
(18-40 years)	86.4(165)
Partner status	
Partner	88.0(168)
No partner	12.0(23)
Education	
Low	3.7(7)
Middle	40.8(78)
High	55.5(106)
Religious	
Yes	23.6(45)
No	76.4(146)
Ethnicity	
Dutch	92.7(177)
Other	7.3(14)
Medical history	
Carrier status	
Carrier	87.4(167)
Partner (50% male/50% female)	12.6(24)
Mutation type	
BRCA1	55.0(105)
BRCA2	45.0(86)
Have (had) cancer	
Yes	20.9(40)
No	79.1(151)
N of family members with cancer	
<3	40.4(72)
≥3	59.6(106)
Reproductive history	
IVF indication	
Yes	17.8(34)
No	82.2(157)
Previous pregnancy	
Yes	51.3(98)
No	48.7(93)
Children (whether or not biological)	
Yes	56.5(108)
No	43.5(83)
Child wish	
Yes	43.5(83)
Maybe	8.9(17)
No	47.6(91)

IVF = In Vitro Fertilization.

Table 2.3: Participants' background regarding PGD and PND for HBOC.

Awareness	% (n)
PGD for HBOC	
Aware	66.0 (126)
Unaware	34.0 (65)
Child wish: 43.5% (n=83)	
Aware	84.3 (70)
Unaware	15.7 (13)
PND for HBOC	
Aware	61.3 (117)
Unaware	38.7 (74)
Child wish: 43.5% (n=83)	
Aware	78.3 (65)
Unaware	13.3 (11)
Knowledge	
PGD for HBOC	
Low	22.8 (32)
Middle	39.7 (56)
High	37.5 (53)
Acceptability	
PGD for HBOC	
Yes	79.5 (132)
Not sure	13.3 (22)
No	7.2 (12)
PND for HBOC	
Yes	25.9 (43)
Not sure	31.3 (52)
No	42.8 (71)
Personal consideration	
PGD for HBOC	
Yes	39.2 (65)
Not sure	22.9 (38)
No	38.0 (63)
PGD for other serious genetic disease	
Yes	58.4 (59)
Not sure	31.7 (32)
No	9.9 (10)
PND for HBOC	
Yes	20.5 (34)
Not sure	20.5 (34)
No	59.0 (98)
PND for other serious genetic disease	
Yes	51.5 (68)
Not sure	30.3 (40)
No	18.2 (24)
Current reproductive preference	
Natural conception	50.6 (84)
PGD	38.0 (63)
PND	6.6 (11)
Donor oocyte/spermatozoa	0.6 (1)
Adoption	0.6 (1)
Refrain from children	3.6 (6)

Table 2.4: Correlates of demographic and medical characteristics with the main outcome variables (bivariate analyses).

	Awareness PGD	Awareness PND	Knowledge PGD	Acceptability PGD	Acceptability PND	Consideration PGD	Consideration PND
	P (Pearson's *r* / X^2 / t / Mann Whitney U / Spearman's r_s)						
Demographic factors							
Gender	0.399 (X^2=0.71)	0.804 (X^2=0.06)	0.952 (t=0.06)	0.356 (U=1785)	0.276 (U=1736)	0.826 (U=1949)	0.453 (U=1820)
Age	**0.000 (t=3.83)**	**0.011 (t=2.57)**	0.075 (*r*=-0.15)	0.493 (r_s=-0.05)	**0.011 (r_s=0.18)**	0.861 (r_s=0.13)	**0.039 (r_s=0.15)**
Partner status	0.050 (X^2=3.83)	0.356 (X^2=0.85)	0.085 (t=-1.73)	0.062 (U=1497)	0.587 (U=1801)	0.214 (U=1630)	0.924 (U=1909)
Education	**0.000 (t=6.54)**	**0.000 (t=6.09)**	**0.021 (*r*=0.20)**	**0.027 (r_s=0.160)**	0.869 (r_s=0.01)	0.316 (r_s=-0.07)	**0.003 (r_s=-0.21)**
Religious	0.544 (X^2=0.37)	0.124 (X^2=2.37)	0.999 (t=-0.00)	0.086 (U=2764)	0.402 (U=3021)	**0.035 (U=2616)**	0.233 (U=2910)
Medical history							
Carrier status	0.399 (X^2=0.71)	0.917 (X^2=0.01)	0.672 (t=0.43)	0.667 (U=1902)	**0.015 (U=1407)**	0.222 (U=1702)	0.434 (U=1812)
Mutation type	0.316 (X^2=1.01)	**0.013 (X^2=6.22)**	0.277 (t=1.09)	0.987 (U=4505)	0.801 (U=4422)	0.605 (U=4323)	**0.037 (U=3747)**
Personal history of cancer	0.545 (X^2=0.37)	0.391 (X^2=0.74)	0.822 (t=0.23)	**0.043 (U=2432)**	0.084 (U=2498)	**0.001 (U=2020)**	**0.016 (U=2293)**
Number of family members with cancer	0.290 (t=1.06)	**0.011 (t=2.57)**	0.987 (*r*=-0.00)	0.155 (r_s=-0.11)	0.251 (r_s=0.09)	0.085 (r_s=-0.13)	0.987 (r_s=0.001)
Reproductive history							
IVF indication	0.068 (X^2=3.33)	0.948 (X^2=0.01)	0.602 (t=0.52)	0.262 (U=2362)	0.802 (U=2598)	0.902 (U=3634)	0.838 (U=2611)
Previous pregnancy	0.084 (X^2=2.98)	0.429 (X^2=0.62)	0.093 (t=1.69)	0.345 (U=4220)	0.369 (U=4224)	0.090 (U=3924)	0.848 (U=4486)
Children	**0.000 (X^2=14.23)**	**0.005 (X^2=8.03)**	**0.024 (t=2.28)**	**0.019 (U=3650)**	0.892 (U=4432)	**0.023 (U=3638)**	0.991 (U=4478)
Child wish	**0.000 (t=5.78)**	**0.000 (t=4.34)**	**0.000 (r_s=0.27)**	0.157 (r_s=0.10)	0.082 (r_s=-0.13)	0.416 (r_s=-0.06)	**0.003 (r_s=-0.22)**
Personal background							
PGD/PND awareness	n.a.	n.a.	**0.008 (t=-2.70)**	**0.000 (U=2867)**	0.877 (U=2824)	0.901 (U=4051)	0.218 (U=2530)
PGD knowledge	n.a.	n.a.	n.a.	**0.007 (r_s=0.23)**	n.a.	0.514 (r_s=-0.06)	n.a.
Perceived seriousness of breast- and ovarian cancer	0.982 (U=3071)	0.596 (U=2065)	0.082 (r_s=-0.16)	0.109 (r_s=0.12)	0.088 (r_s=0.13)	**0.000 (r_s=0.27)**	**0.003 (r_s=0.23)**

PGD, preimplantation genetic diagnosis; PND, prenatal genetic diagnosis; r=Pearson's Correlation, X^2=Pearson Chi Square Value, t=Independent samples t-test, U=Mann Whitney U-test (non-parametric alternative for t-test when ordinal variables are involved), rs=Spearman's rho (non-parametric alternative for Pearson's correlation when ordinal variables are involved).

Knowledge about PGD for HBOC

The mean level of knowledge about PGD for HBOC, among those who were aware of PGD for HBOC, on a 9-point scale was 5.5 (SD=2.4). Bivariate analyses showed that knowledge about PGD positively correlated with educational level, a more immediate child wish and with being childless (Table 2.4). Multivariate analyses by means of linear regression confirmed that a more immediate child wish was associated with a higher level of knowledge about PGD for HBOC (Table 2.6).

Acceptability of PGD and PND for HBOC

The mean acceptability score of PGD for HBOC was 4.1 (SD=0.9) on a 5-point scale. Bivariate analyses showed that acceptability of PGD for HBOC positively correlated with educational level, being childless, having a personal history of cancer, previous awareness of PGD for HBOC and with knowledge about PGD for HBOC (Table 2.4). Multivariate analyses confirmed that respondents with a higher level of knowledge about PGD for HBOC were more likely to consider PGD for HBOC acceptable (Table 2.6). Regarding PND for HBOC, the mean acceptability score was 2.7 (SD=1.2) on a 5-point scale. Older age and being a partner (as opposed to being a carrier) positively correlated with a higher acceptability of PND for HBOC (Table 2.4). Multivariate analyses confirmed that partners were more likely to consider PND for HBOC acceptable than carriers (Table 2.6).

Personal consideration to use PGD and PND for HBOC

Mean scores for consideration to use PGD for HBOC or to use PGD for another serious genetic disease were 3.1 (SD=1.4) and 3.6 (SD=1.0) on a 5-point scale, respectively. A significantly higher proportion of participants would consider using PGD for another serious genetic condition than HBOC (t=−13.19, P<0.000). Consideration to use PGD for HBOC positively correlated with personal history of cancer and perceived seriousness of breast- and ovarian cancer, whereas it negatively correlated with being religious and having children (Table 2.4). Multivariate analyses by means of linear regression confirmed that respondents with a personal history of cancer and with a higher perceived seriousness of breast- and ovarian cancer were more likely to consider using PGD for HBOC (Table 2.6). Mean scores for consideration to use PND for HBOC or to use PND for another serious genetic disease were 2.4 (SD=1.3) and 3.4 (SD=1.1) on a 5-point scale, respectively. Again, a significantly higher proportion of participants would consider using PND for another serious genetic condition than HBOC (t=−16.67, P<0.000). Consideration to use PND for HBOC positively correlated with age, a *BRCA1* mutation, personal history of cancer, having a more immediate child wish and perceived seriousness of breast- and ovarian cancer, whereas it negatively correlated with educational level (Table 2.4). Multivariate analysis showed that participants with a personal history of cancer and those with a higher perceived seriousness of breast- and ovarian cancer were more likely to consider using PND for HBOC (Table 2.6).

Table 2.5: Associations between demographic and medical characteristics and awareness of Preimplantation genetic diagnosis and/or prenatal diagnosis (logistic regressions).

	Awareness PGD			Awareness PND		
	OR	95% CI	p	OR	95% CI	p
Age	0.970	0.916-1.026	0.289	0.992	0.931-1.057	0.802
Education	**1.897**	**1.438-2.503**	**0.000**	**1.954**	**1.405-2.719**	**0.000**
Partner status	0.344	0.116-1.019	0.054	*	*	*
Child wish	**1.408**	**1.009-1.965**	**0.044**	1.287	0.903-1.834	0.163
Children	1.447	0.567-3.694	0.440	1.438	0.475-4.353	0.520
Mutation type	*	*	*	0.511	0.215-1.216	0.129
Number of family members with cancer	*	*	*	0.802	0.561-1.148	0.228
Nagelkerke R^2		36.6%			35.4%	

OR=Odds Ratio (Exp(B)). 95% CI=95% Confidence Interval. P=value of significance (significant when <0.05). * not included in analysis, since only bivariate significant predictors were included.

Table 2.6: Associations between demographic and medical characteristics and knowledge, acceptability and consideration PGD/PND (linear regressions).

	Knowledge PGD		Acceptability PGD		Acceptability PND		Consideration PGD		Consideration PND	
	β	p	β	p	β	p	β	p	β	p
Age	*	*	*	*	0.105	0.209	0.035	0.651	0.023	0.779
Education	0.113	0.180	0.012	0.869	*	*	*	*	-0.125	0.101
Partner status	*	*	0.131	0.125	*	*	*	*	*	*
Religious	*	*	*	*	*	*	-0.063	0.392	*	*
Carrier status	*	*	*	*	**-0.268**	**0.001**	*	*	-0.125	0.054
Personal history of cancer	*	*	0.130	0.126	0.129	0.091	**0.218**	**0.003**	**0.176**	**0.021**
Child wish	**0.305**	**0.001**	-0.054	0.608	-0.060	0.487	*	*	-1.283	0.202
Previous pregnancy	*	*	*	*	*	*	-0.027	0.819	*	*
Children	0.037	0.699	-0.129	0.215	*	*	-0.190	0.127	*	*
PGD awareness	0.138	0.104	0.065	0.461	*	*	*	*	*	*
PGD knowledge	*	*	**0.179**	**0.047**	*	*	*	*	*	*
Perceived seriousness breast- and ovarian cancer	*	*	*	*	0.117	0.129	**0.314**	**0.000**	**0.184**	**0.017**
Model R^2	16.5%		14.3%		12.2%		20.8%		13.4%	

β=regression coefficient. P=value of significance (significant when <0.05). * not included in analysis, since only bivariate significant predictors were included.

Discussion

Reproductive decision-making can be challenging for couples with HBOC to such an extent that some couples experience a negative psychological impact for many years after making their reproductive choice.[5] To limit this negative psychological impact in the future, it is of great importance that couples are enabled to make a well informed and balanced decision. When conceptualizing reproductive decision-making in the context of stage models of behaviour change (e.g. PAPM, TTM), couples first need to be made aware of the available options. Next, they need to gain knowledge about these options and to start contemplating.[18,19] As stated before, a couple can only make their personally best suitable reproductive choice when being completely informed. This study shows that awareness of PGD (66%) and PND (61%) for HBOC in the Netherlands (84% and 78% for those with a child wish) is relatively high compared to the 35% awareness of PGD in other Western countries[7], although this still leaves one in five of the potential users unaware. A possible explanation for this raise in awareness is that PGD techniques and regulations have been rapidly evolving the last few years, which may have caused an overall increase in PGD awareness. Moreover, persons who responded to the study may be more aware of PGD than those who did not. It is possible that those motivated enough to respond were more likely to be motivated to seek information about their reproductive options. Both educational level and having a more immediate child wish increased the likelihood of being aware of PGD and PND. The positive relationship between awareness and a child wish, however, might run both ways: (i) couples with a more immediate child wish may more often be aware of PGD and PND due to a higher motivation to seek information about their reproductive options or (ii) couples who are unaware of PGD and PND may be more likely to refrain from their child wish, unwilling to take the risk of passing on the *BRCA* mutation since they are unaware of options that can prevent this. Although this last scenario is unlikely from a clinical experience point of view, given that a limited number of couples with a confirmed *BRCA* mutation choose to use PGD or PND when made aware of these possibilities, scientific data about this are still lacking and it would be a relevant topic for further study. Due to the cross-sectional design of this study we can merely detect the association and not its causality. Nevertheless, acceptability of PGD for HBOC is high (80%) and this corresponds with results from previous studies.[9,10,20] We found that both acceptability and personal consideration are significantly higher for PGD (80% and 39%) than for PND (26% and 20%) and noticed a large gap between acceptability and personal consideration to use PGD, whereas this gap was considerably smaller for PND. This may be explained by the fact that most couples with HBOC consider PGD as their best option from a moral point of view, but in comparison with their perceived seriousness of HBOC they often consider it a highly burdensome, time-consuming treatment with a relatively low chance of success as was shown by a qualitative study by Derks-Smeets et al..[5] In that study, all couples with HBOC who considered PND an acceptable option indeed chose this option, whereas PGD was used by less than half of the couples who considered this acceptable.

Moreover, 14% of women in the present study were not of reproductive age and 48% did not have a current child wish. This may have caused a lack of personal relevance concerning consideration to use PGD or PND for these participants and may partially explain the gap between PGD acceptability and consideration to use PGD, although this does not explain the difference between PGD and PND. In addition, we noticed that couples' consideration to use PGD or PND was significantly higher for other serious genetic conditions than for HBOC (PGD: 58% versus 39%, PND: 52% versus 20%). This indicates that moral and ethical reservations about using these reproductive techniques for late onset cancer predispositions such as HBOC are not limited to the general public but also play a role within the group of potential users. However, we did not specify any further characteristics of 'another serious genetic condition', which suggests that the comparison condition may have differed among respondents. This study also showed that respondents with more knowledge about PGD are more likely to consider PGD for HBOC acceptable, which is in concordance with the results of Meister et al..[21] This could be an indication of the general misconceptions about PGD among persons with little knowledge, concerning the impression of creating a 'designer baby' previously described by Roberts and Franklin.[22] Due to the commonly displayed stereotype of runaway technology, persons with little knowledge about PGD may believe that the selection of embryos is not solely focused on a serious genetic mutation but can additionally be used to select gender or even traits such as eye- and hair-colour which may negatively influence PGD acceptability. Hence, more knowledge about the actual possibilities and limitations of PGD often leads to more acceptability. When investigating the acceptability of PND for HBOC, we found that partners more often consider this acceptable than *BRCA* carriers. This is also described in previous qualitative studies as the quandary of carriers who wish to prevent further transmission of their genetic mutation but at the same time, when considering TOP, feeling guilty about denying themselves and family members with the mutation the right to live.[17,23] It should be mentioned though, that 93% of the carriers in the current study were women, and women are known to consider TOP for HBOC less acceptable than men.[14] In this light, it should also be considered that the technical procedure concerning TOP is performed on the woman's body, which might be an extra disadvantage of PND for women as opposed to men. Furthermore, we identified several associations of participants' demographic and medical characteristics with awareness, knowledge, acceptability and personal intention to use PGD or PND. Respondents with a higher educational level were more often aware of PGD and PND, and PGD awareness and knowledge were higher among those with a more immediate child wish. Persons with a higher educational level and a more immediate child wish might be more prone to search for information about their reproductive options. Health information seeking behaviour is generally related to socio economic status, and health problems (in this case, the genetic predisposition combined with an urgent child wish) are identified as the primary motivations for health information seeking.[24,25] An association between socio-economic status and PGD awareness has also been reported by Rich et al..[26] Finally, respondents were more

inclined to consider PGD as well as PND for HBOC when having a personal history of cancer and when having a higher perceived seriousness of breast- and ovarian cancer. This is in line with the findings from prior research that couples with HBOC base their decision whether to interfere in the reproductive process on their perceived seriousness of breast- and ovarian cancer[5,8] and that negative genetic and reproductive experiences positively influence attitude, acceptability and willingness to use PGD.[27]

Limitations

When interpreting the results of this study, several limitations need to be taken into account. The response rate (23%) of participants invited by the clinical genetics departments was low. This was probably related to a simultaneous study using a similar recruitment strategy within the same target group, which may have resulted in selection bias. Second, PGD knowledge was measured with an instrument that had not yet been validated. However, to our understanding there is no validated instrument to measure PGD knowledge available at this moment. In comparison to other studies that claim to have measured PGD knowledge by merely assessing PGD awareness, the measure used in this study may be a solid starting point to get insight into what eligible couples actually know about PGD. A third limitation may be that although we consider the likelihood of both members of a couple taking part in the study as small, we have not explicitly assessed this and we can, therefore, not exclude the possibility of dependence of observations in the sample. In the hypothesis testing no correction was made for multiple comparisons. Moreover, a minority (16%) was just passed reproductive age (defined as >40 years female age), which may have caused bias due to the lack of personal relevance of some questions. However, since PGD was introduced in the Netherlands in 1995, these participants may have been informed about PGD (whether or not during their reproductive years), which is relevant information for this study. Finally, the cross-sectional design of this study limits us from drawing any causal conclusions.

Implications for practice

Although awareness of both PGD and PND is relatively high among Dutch persons with HBOC who have a child wish, still one in five is unaware and may, therefore, not be able to make a well informed reproductive choice. To some extent, awareness and knowledge concerning PGD and PND are related to social-cognitive and even demographic factors, which should not be desirable. This study showed that persons with a higher educational level are more likely to be aware of PGD and PND, and that awareness and knowledge of PGD and PND can influence the acceptability of these reproductive options. This makes optimization of information provision about these options, attuned to different socio-demographic subgroups indispensable. Main information channels about HBOC should be identified and updated with comprehensible information about PGD and PND for all educational levels. Moreover, PGD and PND awareness, knowledge and acceptability of health professionals involved

in the field of HBOC should be investigated and they should be educated in identifying patients who are eligible for these reproductive options and in providing initial information about these options. However, providing detailed information about PGD and PND should remain the responsibility of the clinical geneticist.

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Chapter 3

Professionals' knowledge, attitude and referral behaviour regarding preimplantation genetic diagnosis for hereditary breast and ovarian cancer

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Abstract

Hereditary breast and ovarian cancer caused by a *BRCA1/2* mutation is the most frequent indication for preimplantation genetic diagnosis (PGD) in the Netherlands. The extent to which involved professionals are informed about this option, however, is unclear. The few available international studies mostly represent a limited range of professionals, and suggest that their knowledge about PGD for hereditary cancer syndromes is sparse and referral for PGD is based on limited understanding. A cross-sectional survey assessing awareness, knowledge, acceptability and PGD-referral for *BRCA* was completed by 188 professionals involved in the field of breast and ovarian cancer or reproduction. One-half of professionals were aware of PGD for *BRCA*, and most had a low to moderate level of knowledge. A total of 86% considered PGD for *BRCA* acceptable and 48% had referred patients with *BRCA* for PGD. Awareness and knowledge was higher among professionals who worked at a university hospital (compared with a general hospital). Knowledge of PGD was positively associated with discussing and referring for PGD, and PGD acceptability was associated with previous awareness. Although PGD counselling is the primary responsibility of the geneticist, other involved professionals may be gatekeepers as patients rely on them for raising awareness and referral.

Introduction

About 5-10% of all cancers are caused by a hereditary predisposition.[1] Women with a *BRCA1/2* mutation face an elevated risk of 27–57% of developing breast cancer and 6-40% of developing ovarian cancer by the age of 70 years.[2,3] Preventive possibilities are limited to chemoprevention and prophylactic surgery, which can be both physically and psychologically demanding. Although therapeutic options are available, hereditary breast and ovarian cancer (HBOC) caused by a *BRCA1/2* mutation accounts for a disproportionally large amount of life years lost as it occurs at a relatively young age.[4] As this is an autosomal dominant predisposition, there is a 50% risk of passing it on to the next generation. In the Netherlands, couples with a *BRCA1/2* mutation and a wish for a biological child have three reproductive options: a natural pregnancy, implying acceptance of the risk of passing on the *BRCA* mutation; prenatal diagnosis (diagnosis during pregnancy and possible termination of pregnancy in case of a female carrier); and preimplantation genetic diagnosis (PGD) (selection of IVF and intracytoplasmic sperm injection [ICSI] embryos, free of the *BRCA* mutation before implantation in the uterus).

As use of PGD was permitted for late-onset genetic cancer syndromes in the Netherlands in 2008, HBOC caused by a *BRCA1/2* mutation has been the most frequent indication for PGD, with 25 couples that started a PGD treatment for *BRCA* in 2013, 36 couples in 2014 and 45 couples in 2015.[5] Ethical concerns about PGD for late-onset cancer syndromes such as *BRCA* have risen internationally among patients and professionals owing to the condition's adult onset character, incomplete penetrance and availability of (albeit physically and emotionally traumatic) preventive and therapeutic options.[6-8]

Although PGD is nowadays available as a reproductive option for couples with *BRCA* in many countries, published data show that knowledge among involved health professionals is sparse and most would refer for PGD based on limited understanding of the procedure and its applications.[7,9,10] Moreover, professionals' intentions to refer eligible patients for PGD counselling often exceed their actual referral behaviour.[7,11] The few available studies focusing specifically on hereditary cancer syndromes[6,11,12] show that professionals' acceptability of PGD is often influenced by the nature of the predisposition and the patient's personal history of cancer. The previously mentioned studies focused on various outcomes, such as assessing PGD knowledge by awareness or measuring acceptability of PGD depending on patients' family history of cancer and reproductive history among gynaecologists, gynaecological oncologists, obstetricians or oncology nurses; only one study included clinical geneticists, the specialists who are primarily involved in PGD.[6] Therefore, we assessed awareness, knowledge and acceptability of PGD for *BRCA* among health professionals, and their referral behaviour (including clinical geneticists and genetic counsellors), and investigated possible associations of these outcomes with clinical and demographic factors. This study was carried out as part of an overarching project aimed at enhancing guidance and psychological support for couples with *BRCA* and a child wish in the Netherlands.

Materials and methods

Participants and procedures

Participants were recruited in collaboration with the following Dutch associations of health professionals that are involved in the field of hereditary breast and ovarian cancer, reproduction, or both: The Association of Clinical Genetics Netherlands (VKGN), The Dutch Association of Genetic Counsellors (NVGC), The Dutch Association for Obstetrics and Gynaecology (NVOG), and The Dutch Association for Oncology (NvVO). The associations sent one mass mail inviting their members to participate in the study. No reminders were sent. The approached professionals were gynaecologists, clinical geneticists, genetic counsellors, medical oncologists and fertility physicians. The single inclusion criterion was being a medical specialist involved in the field of reproduction, oncology, or both, whereas the single exclusion criterion was insufficient understanding of the Dutch language as the survey was in Dutch. The email invitation contained brief information about the study, contact details of the researcher and a link to the online questionnaire. It was clearly stated that participants gave their informed consent by initiating the questionnaire. Procedures were approved by the Medical Ethics Committee of the Maastricht UMC+, reference number: METC 12-4-075, dd 18-06-2012.

Questionnaire

To explore an appropriate basis for the questionnaire content and to ensure relevance of the questions for the approached professional groups, seven in-depth telephone interviews were conducted with several medical professionals (two clinical geneticists, two genetic counsellors, one gynaecologist, one gynaecologic oncologist and one medical oncologist) before the start of the study. The duration of these interviews was about 30 mins, and they addressed awareness, knowledge, attitude, referral behaviour and informational needs of PGD for *BRCA.* The interviews were audio taped, transcribed verbatim and analysed. On the basis of these interview data and available published data, a cross-sectional survey was developed. The survey was pilot tested by a clinical geneticist, a gynaecologist and a medical oncologist, and revised accordingly before circulation.

The four main outcome variables were as follows: awareness of the possibility of PGD for *BRCA*; the level of knowledge about PGD (in general and specifically for *BRCA*); acceptability of PGD for *BRCA*; and referral behaviour in relation to PGD for *BRCA*. Knowledge was assessed by two scales: the first scale consisted of 16 (categories of) medical indications, and measured knowledge of the conditions for which PGD is legally permitted in the Netherlands (of which 14 are permitted and two are not permitted), with a minimum score of 0 and a maximum score of 16. In this context, 'legally permitted' does not merely mean that it is reimbursed by government insurance; PGD for other conditions can be considered illegal in the Netherlands at the time of data-collection, even when paid for privately. On this scale, adjusted for the probability of

guessing a correct answer (50% per question), we defined a score of 0-8 as low, 9-12 as moderate and 13-16 as a high level of knowledge. The second knowledge scale consisted of 15 closed-ended questions (true/false/not sure) about the procedure of, and eligibility for, a PGD treatment in general (including three items specifically for *BRCA*), with a minimum score of 0 and a maximum score of 15. On this scale, similarly adjusted for the probability of guessing a correct answer (50% per question), we defined a score of 0-8 as low, 9-12 as moderate and 13-15 as a high level of knowledge. Acceptability of PGD for *BRCA* was measured with an ordinal scale (1=totally disagree to 5=totally agree), as were referral behaviour and the intention to refer for PGD for *BRCA* (1=no definitely not to 5=yes, definitely). We additionally asked participants whether they thought acceptability of PGD for *BRCA* should depend on the couple's personal or family history of cancer and if it should be the couple's autonomous decision whether PGD is acceptable (and therefore allowed) for them (both items: 1=totally disagree to 5=totally agree). The main questionnaire items are presented in Table 3.1. Demographic factors recorded were age, gender, partner status (partner/no partner), religiosity (yes/no), ethnicity (native Dutch/non-native) and children (yes/no). Partner status and having children were assessed as these factors may influence the participants' ability to relate to the patients' child wish and it consequently might influence their acceptability of PGD and their responsiveness in referring patients for PGD. Professional variables concerned medical specialty, currently in training (yes/no), years of clinical experience (<10/≥10), average number of patients with *BRCA* a month (0/1-5/6-10/>10), patients who are eligible for PGD (yes/no) and type of medical centre (general hospital or teaching/university hospital).

Data analysis

Questionnaire data were automatically stored in SPSS version 19.0 (IBM Corp., USA) and consequently analysed. Descriptive statistics were conducted to provide an overview of the four primary outcome measures. Owing to insufficient variation within 'ethnicity' this variable was excluded from further analyses. Moreover, because of insufficient variation within the variable 'medical specialty', it was impossible to compare the different medical specialties with additional analyses. We did however, conduct descriptive statistics for the subgroup' specialists in genetics', i.e. clinical geneticists and genetic counsellors: (26%, n=49), as these are the professionals who are specifically involved in PGD counselling.

To assess associations of demographic or clinical factors with the four outcomes of interest, Pearson correlations, independent sample t-tests and Pearson chi-squared tests were conducted. Mann–Whitney U tests or Spearman correlations were used as non-parametric alternatives when categorical variables were involved. Ultimately, a multiple linear or logistic regression model (enter method) was built for multivariate analyses. A significant outcome was defined as $P<0.05$.

Table 3.1: Main questionnaire items.

Questionnaire items	Answer options
Awareness	
Did you ever hear about PGD before filling in this questionnaire?	Yes(1)-no(0)
Did you know that PGD is an option for couples with *BRCA* in the Netherlands before filling in this questionnaire?	Yes(1)-no(0)
Knowledge PGD indications	
(Please select the conditions for which you think PGD is allowed in the Netherlands)	
Duchenne and Becker muscular Dystrophy	Yes(1)-no(0)
Haemophilia A/B	Yes(1)-no(0)
Adrenoleukodystrophy	Yes(1)-no(0)
Hereditary Motor and Sensory Neuropathy	Yes(1)-no(0)
Chromosomal anomalies (translocations)	Yes(1)-no(0)
Fragile X syndrome	Yes(1)-no(0)
Hereditary cardiac conditions	Yes(0)-no(1) [1]
Cystic fibrosis	Yes(1)-no(0)
Spinal Muscular Atrophy	Yes(1)-no(0)
Hereditary Breast and Ovarian Cancer	Yes(1)-no(0)
Huntington's Disease	Yes(1)-no(0)
Gender selection for non-medical reasons	Yes(0)-no(1)
Marfan Syndrome	Yes(1)-no(0)
Myotonic Dystrophy	Yes(1)-no(0)
Hereditary Ataxia	Yes(1)-no(0)
Familial Adenomatous Polyposis	Yes(1)-no(0)
All conditions mentioned above	Yes(0)-no(1)
None of the conditions mentioned above	Yes(0)-no(1)
I do not know	Yes(0)-no(1)
Acceptability	
I think PGD for *BRCA* is acceptable	Totally disagree(1)-totally agree(5)
I think that the acceptability of PGD for *BRCA* depends on the personal and/or family history of the patient concerning *BRCA*.	Totally disagree(1)-totally agree(5)
I think that the couple should decide whether their genetic predisposition is serious enough to justify PGD	Totally disagree(1)-totally agree(5)
Referral behaviour	
Do you ever discuss PGD with patients with *BRCA* who are eligible for PGD?	Yes(1)-no(0)
Do you intend to discuss PGD with patients with *BRCA* who are eligible for PGD in the future?	No, definitely not (1)-yes, definitely (5)
Do you ever refer patients with *BRCA* for PGD?	Yes(1)-no(0)
Do you intend to refer patients with *BRCA* for PGD in the future?	No, definitely not (1)-yes, definitely (5)

Table 3.1: continued

Questionnaire items	Answer options
Knowledge PGD procedures	
(Please select for each statement if it is true, false or if you are not sure)	
Questionnaire items: True (T) / False (F) / not sure	**Correct answer when statement is false**
For PGD, an IVF treatment is always necessary (T)	
PGD is possible in every academic hospital in the Netherlands (F)	There is only one licensed PGD centre in the Netherlands, but the IVF-treatment for PGD can take place at three other geographically dispersed hospitals.
Hormone-use by the woman is not always necessary for a PGD treatment (F)	Since IVF is necessary for PGD, the hormones needed for IVF should always be used by the woman.
PGD takes place before the woman is pregnant (T)	
When a couple is normally fertile, the chance of a pregnancy after a PGD treatment is nearly 100% (F)	The chance of a pregnancy after a PGD treatment is 20-25%
With a PGD treatment, the affected embryos are preserved (F)	With a PGD treatment, the affected embryos are discarded
In the Netherlands, PGD is only allowed for conditions with a 100% penetrance (F)	In the Netherlands, PGD is also allowed for conditions with an incomplete penetrance such as hereditary cancer predispositions
With PGD, the embryo is also screened for other conditions than the condition of interest (F)	With PGD, the embryo is only diagnosed for the condition or predisposition PGD is aimed at[2]
To date, there are no additional risks identified for PGD compared with regular IVF (T)	
The genetic preparation of a PGD treatment takes several months to one year (T)	
Currently, a maximum of three PGD treatments is reimbursed by the health insurance system in the Netherlands (T)	
In the Netherlands, less than 100 PGD treatments are performed on a yearly basis (F)	In 2013, 241 couples started a PGD treatment in the Netherlands (293 in 2014 and 329 in 2015)
In the Netherlands, couples can also choose the gender of the embryo when undergoing PGD for HBOC (F)	Gender selection for PGD is only allowed in specific cases when the condition of interest is sex-linked
With PGD for HBOC, male embryos with a *BRCA* mutation are also selected for implantation in the uterus (F)	PGD for *BRCA* is exclusively aimed at diagnosis of the *BRCA* mutation irrespective of the gender of the embryo
PGD for *BRCA* is also allowed for women with a *BRCA* mutation who have had breast cancer (T)	

PGD=preimplantation genetic diagnosis; PND=prenatal diagnosis; HBOC=hereditary breast and ovarian cancer. [1] At the time of data collection PGD for hereditary cardiac conditions was not allowed in the Netherlands. At present time this is assessed on a case by case basis by the Dutch National PGD Indications Committee; [2] This was correct at the time of data-collection. However, nowadays in some centres aneuploidy screening is added.

Results

In total, 231 professionals participated in this study, of which 188 (81%) completed the questionnaire and were included in the analyses. The remaining 43 participants (19%) dropped out before completing 90% of the questionnaire. From here on, 'total sample'

refers to the 188 participants that completed the questionnaire. Participants' characteristics are presented in Table 3.2. Response rates were 14.9% (28/187) for the association of clinical geneticists, 33.8% (22/65) for the association of genetic counsellors, 13.5% (122/902) for the association of gynaecology and obstetrics, and 47.1% (16/34) for the association of oncology.

Table 3.2: Participants' characteristics.

	% (n)
Demographic variables	
Gender	
Male	22.8 (42)
Female	77.2 (142)
Age (years)	
Mean (SD)	45.2 (9.6)
Minimum	30
Maximum	65
Partner status	
Partner	90 (162)
No partner	10 (18)
Children	
Yes	73.4 (135)
No	26.6 (49)
Religious	
Yes	18.5 (34)
No	81.5 (150)
Ethnicity	
Dutch	92.4 (170)
non-Dutch	7.6 (14)
Professional variables	
Specialty	
Gynaecologist	63.3 (119)
Clinical geneticist	14.9 (28)
Genetic counsellor	11.7 (22)
Medical oncologist	8.5 (16)
Fertility physician	1.6 (3)
In training	
Yes	24.5 (45)
No	75.5 (139)
Years of clinical experience (of those not in training: n=141)	
0-10	51.4 (71)
≥11	48.6 (67)
Average number *BRCA* patients/month	
<1	37.2 (68)
≥1	62.8 (115)
Contact with eligible PGD patients	
Yes	87.2 (164)
No	10.6 (20)
Not sure	2.1 (4)
Type of medical centre	
Teaching/university hospital	47.0 (86)
General hospital	53.0 (97)

Awareness of PGD for *BRCA*

Of the total sample, 51% of the professionals were aware of the possibility of PGD for *BRCA* in the Netherlands, whereas 88% of the specialists in genetics were aware (Supplementary Table S3.1). Bivariate analysis showed that awareness of PGD for *BRCA* was positively associated with being female (P=0.038, chi-squared=4.30), and with being employed at a teaching or university hospital (P<0.001, chi squared=30.67) (Supplementary Table S3.2). Multivariate analysis confirmed that participants working at a teaching or university hospital were more likely to be aware of PGD for *BRCA* (P<0.001, OR=0.092, CI 95% 0.037 to 0.229) (Supplementary Table S3.3).

Knowledge of PGD for *BRCA*

Knowledge of PGD was measured by two scales as described in the Materials and Methods section (Table 3.1). The 51% of participants who were aware of PGD for *BRCA* scored a mean of 9.2 (SD 4.6) out of 16.0 on the first scale (allowed PGD indications), with 43% scoring low, 26% scoring moderate and 31% scoring high. The same group scored a mean of 9.8 (SD 3.0) out of 15.0 on the second scale (PGD procedures), with 34% scoring low, 46% scoring moderate and 20% scoring high. The 49% of participants who were not aware of PGD for *BRCA* scored a mean of 8.6 (SD 2.8) out of 15 on the PGD 'procedures scale', with 52% scoring low, 37% scoring moderate and 11% scoring high. The specialists in genetics scored a mean of 12.3 (SD 3.8) on the 'allowed indications scale' (with 16% scoring low, 20% scoring moderate and 64% scoring high), and 11.5 (SD 2.1) on the 'procedures scale' (with 2% scoring low, 66% scoring moderate and 32% scoring high) (Supplementary Table S3.1). The specialists in genetics scored significantly higher than the other participants on both knowledge scales (P<0.001, t=6.04; P≤0.001, t=6.94, respectively). Bivariate analysis showed that both types of knowledge were positively associated with occasionally seeing patients who are eligible for PGD (P<0.001, t=−3.67; P=0.003, t=−2.99) and with being employed at a teaching or university hospital (P<0.001, t=5.06; P<0.001, t=4.85) (Supplementary Table S3.2). Multivariate analyses confirmed that professionals who occasionally see patients who are eligible for PGD (P=0.005, β=0.225; P=0.018, β=0.191) and professionals who work at a teaching or university hospital (P<0.001, β=−0.392;P<0.001, β=−0.421) are likely to have more knowledge about PGD indications and PGD procedures. Multivariate analyses additionally showed that professionals with a partner had more knowledge about PGD procedures (P=0.021, β=0.197) (Supplementary Table S3.4).

Acceptability of PGD for *BRCA*

The mean acceptability score of PGD for *BRCA* was 4.2 (SD 0.8) on a five-item scale for the total sample, which was similar for the specialists in genetics as a subgroup. Eighty-six per cent of the total sample and 92% of the specialists in genetics considered PGD for *BRCA* acceptable, which did not differ significantly. Nearly one third (31%) of the total

sample believed that PGD acceptability (and therefore approval) should be the patients' autonomous decision (16% of the specialists in genetics) and 29% of the total sample agreed that this should depend on the patients' personal and family history of cancer (40% of the specialists in genetics) (Supplementary Table S3.1).
Bivariate analyses showed that male participants and those with more knowledge about PGD procedures more often considered PGD for *BRCA* acceptable (respectively P=0.005, U=2277; P=0.006, rs=0.020) (Supplementary Table S3.2). Multivariate analyses showed that men and those who were previously aware of PGD for *BRCA* were more likely to consider PGD for *BRCA* acceptable (P=0.015, β=−0.234; P=0.019, β=0.277), whereas religious participants were less likely to consider PGD for *BRCA* acceptable (P=0.048, β=−0.173) (Supplementary Table S3.4).

Discussing and referring for PGD for *BRCA*

Of the total sample, 13% indicated that they never saw patients who were eligible for PGD. Of this 13%, more than one-half (64%) was not aware that *BRCA* is a legal indication for PGD. The analyses described in this paragraph were conducted among the subgroup of professionals who indicated that they occasionally saw patients who are eligible for PGD (87% of the total sample). Of this subgroup, 60% indicated that they currently discussed PGD with patients with *BRCA* (84% of the specialists in genetics), and 93% had the intention to do so in the future (94% of the specialists in genetics). Less than one-half (48%) ever referred a patient with *BRCA* for PGD (62% of the specialists in genetics), whereas 92% indicated the intention to do so in the future (90% of the specialists in genetics) (Supplementary Table S3.1).
Bivariate analyses showed that the likeliness of discussing PGD with patients and to refer them for PGD was higher among older participants (P=0.006, t=−2.79; P=0.046, chi-squared=−2.01, respectively), participants who were employed at a teaching or university hospital (P<0.001, chi-squared=17.81; P=0.001, X^2=11.72) and those who had more knowledge about both PGD indications (P<0.001, t=−4.26; P=0.003, t=−3.02) and procedures (P<0.001, t=−4.77; P<0.001, t=−4.18). Referring for PGD was additionally associated with PGD acceptability (P=0.037, U=2956) and discussing PGD (P<0.001, chi-squared=77.44). Participants who were still in training were less inclined to discuss PGD (P=0.005, chi-squared=8.03) and to refer for PGD (P=0.040, chi squared=4.23) (Supplementary Table S3.2). Multivariate analyses confirmed that professionals who were employed at a teaching or university hospital (P=0.002, OR=0.126, CI 95% 0.035 to 0.455), who had more knowledge about PGD procedures (P=0.015, OR1.291, CI 95% 1.051 to 1.585) and those who considered PGD for *BRCA* acceptable (trend: P=0.053, OR=1.779, CI 95% 0.992 to 3.194), were more likely to discuss PGD for *BRCA* with their patients. Additionally, they showed that participants who saw one or more patients with *BRCA* a month more often discussed PGD (P<0.001,OR=1.113, CI 95% 0.035 to 0.369) and referred for PGD (P=0.011, OR=5.195, CI 95% 1.450 to 18.605). A strong trend towards significance additionally suggested that participants who had more knowledge

about PGD procedures were also more likely to refer for PGD (P=0.050, OR=1.209, CI 95% 1.000 to 1.461) (Supplementary Table S3.3).

Discussion

This study suggests that overall, one-half of professionals of different specialties (including geneticists) involved in the care of persons with HBOC in the Netherlands are aware of PGD as a reproductive option, whereas this holds for 90% of the specialists in genetics. A minority of the study sample (13%) indicated that they never saw patients who are eligible for PGD or were not sure about this. More than one-half (64%) of this subgroup was not aware that PGD is a reproductive option for *BRCA*, and was, therefore, not aware of the fact that some of their patients may have been eligible for PGD. The only previous quantitative study that reported awareness of PGD for hereditary cancer syndromes among involved professionals (oncology nurses, USA) found that 22% of professionals were aware of PGD.[12] In comparison, awareness of PGD for *BRCA* among involved professionals in the Netherlands may be considered as relatively high. Although professionals with a specialty different than genetics should not necessarily have detailed knowledge about PGD for *BRCA*, it is important that they are aware of this reproductive option and its criteria for eligibility to refer eligible patients. Awareness was higher among professionals who worked at a teaching or university hospital, where education about relatively novel treatment options such as PGD is considered to be more accessible compared with general hospitals. Moreover, clinical genetics departments are exclusively located in university hospitals in the Netherlands as in many other European countries, which will enhance the possibility to consult and collaborate with clinical geneticists in these settings compared with general hospitals.

The mean level of knowledge about both PGD indications and PGD procedures was moderate among the subgroup that was aware of PGD for *BRCA*. To put this into perspective, we should point out that some of the PGD indications were not relevant to certain specialties, e.g., an oncologist does not need to be aware of the possibility of PGD for non-oncological genetic conditions. The subgroup 'specialists in genetics' had a high level of knowledge about the approved PGD indications; however, their level of knowledge of PGD procedures was moderate. Prior studies also reported a limited level of knowledge among health professionals (gynecological oncologists, obstetrics and gynecologists[11] and oncology nurses[12]) concerning PGD for hereditary cancer syndromes. Participants who at least occasionally saw patients who are eligible for PGD, and those who worked at a teaching or university hospital, had more knowledge about approved PGD indications and procedures, which is in line with expectations, as these subgroups are expected to be the most knowledgeable about PGD. Knowledge about PGD procedures was also higher among respondents with a partner. As 90% of participants had a partner, however, these unequal samples do not allow firm conclusions to be drawn from this result.

Acceptability of offering PGD for *BRCA* was equally high (>85%) among the general sample and the subgroup 'specialists in genetics'. Previous studies conducted in the USA and Spain reported an acceptability rate of 61–66% regarding PGD for hereditary cancer susceptibility among health professionals[12,13], whereas Julian-Reynier et al.[6] reported a 26% acceptability rate of PGD for *BRCA* among cancer geneticists in France. The relatively high acceptability rate of offering PGD for *BRCA* found in the present study might be related to the rapid development of PGD during the past few years, which may have increased PGD acceptability overall. Previous studies have shown that, given the moral and ethical dimensions of PGD, acceptability of this reproductive technique for hereditary cancer syndromes is not easy to capture in clear guidelines. Several of these studies found that most health professionals associate PGD acceptability with the nature of the predisposition or the patients' family history of cancer, reproductive history, or both[6,7,14], whereas other studies showed that most consider the patients' autonomy of highest value.[15,16] In the present study, nearly one third believed that it should be the patients' autonomous decision whether PGD is acceptable (and therefore should be approved for them), and a slightly smaller group believed this should depend on the patients' personal and family history of cancer. In the Netherlands, PGD for *BRCA* has been legally approved by the national PGD indications committee since 2008. When the committee is uncertain about a request for a new indication, the request is evaluated on a case by case basis in which several aspects are considered, such as the disease burden on the patient and his or her family. It is never the patient's autonomous decision whether PGD is an option.

Acceptability of PGD for *BRCA* was significantly higher among male health professionals, non-religious participants, those who were previously aware of PGD for *BRCA* and those with more knowledge about PGD procedures. Concerning the higher acceptability among male health professionals, this group was relatively small (23% male compared with 77% female), and additional research is required to confirm this finding and identify any underlying motives. Concerns (mostly moral and ethical) among religious persons about PGD have also been reported; these are based on the belief that PGD selects new life and that it should not be the privilege of human beings to do so.[8,17,18] Furthermore, previous awareness and knowledge of PGD have been associated with PGD acceptability[19,20], which may indicate that a better understanding of PGD, including its restrictions and limitations, may lead to less moral and ethical reservations and a higher acceptability.

A total of 85% of the specialists in genetics discussed PGD with their *BRCA*-patients, whereas Julian-Reynier et al.[6] showed that 59% of the participating French cancer geneticists discussed PGD for hereditary cancer with their patients. Although this may seem like a substantial difference between the Netherlands and France, at the time of the study by Julian-Reynier et al.[6], PGD for *BRCA* was not permitted in France, whereas in the Netherlands it had been permitted for several years at the time of data collection.

Less than one-half of participants in the present study who regularly saw patients who are eligible for PGD had ever referred a patient with HBOC for PGD, and 65% of the

specialists in genetics had, whereas intention to do so was over 90% in both groups. This referral gap has been previously reported by Klitzman et al.[7] and Brandt et al.[11] who indicated that this may be due to professionals' limited knowledge about PGD, not always enabling them to identify patients for whom PGD is an appropriate option. The present study showed that professionals with more knowledge about PGD were indeed more likely to refer a patient for PGD. Also, professionals who saw patients with *BRCA* on a monthly basis, and who worked at a teaching or university hospital, more often referred patients with *BRCA* for PGD. As only university hospitals have clinical genetics departments in the Netherlands, their channels for PGD referral may be more straightforward compared with general hospitals.

In both the Netherlands and other countries in which PGD for *BRCA* is available, it is important to increase awareness and knowledge about this reproductive option among the involved professionals. In a way, these healthcare providers are the gatekeepers of reproductive techniques such as PGD, and patients depend on them to know their options in order to make an informed choice.

Limitations

When interpreting the results of this study, several limitations need to be considered. To achieve conciseness of the survey and to prevent dropout, some concepts were assessed by a limited number of items, which may have reduced content validity. In addition, the response rates of some groups of medical specialists were relatively low, and medical oncologists are underrepresented in this study. This is, however, the largest sample to date exploring this topic among specialists in genetics who are primarily involved in PGD. It is known that overall response rates have been decreasing over the past few years, especially among medical specialists.[21,22] Moreover, low response rates do not necessarily result in selection bias[21], which is even less probable among medical specialists who are considered relatively homogenous as a group (in terms of education, knowledge, attitudes and behaviour) compared with the general population.[23,24] Ultimately, 43 participants dropped out at variable stages in the questionnaire, possibly owing to the length of the questionnaire. This may have skewed outcomes as drop out might have been higher among professionals who are least involved in, or in favour of, PGD.

Implications for practice

In the Netherlands, as in many other countries, no official guidelines are available for professionals on discussing and referring for PGD. The ongoing controversy about its approval for hereditary cancer syndromes, and the variable knowledge and attitudes of professionals about PGD, emphasize the need for clear standard of care guidelines within onco-genetics. Couples with HBOC should be made aware of their reproductive options, including PGD, so they can make an informed decision and negative psychological effect (such as doubt or decisional regret) can be minimized. To achieve

this, we should start by optimizing awareness and knowledge among healthcare providers who are trusted to be one of the main sources of information by their patients. The motives of professionals in deciding whether or not to refer for PGD should be further investigated, and awareness about PGD should be enhanced by means of additional education, especially in non-university hospitals. Extensive education about this topic for these professionals with limited time and pressure to stay up to date on new developments in their field may not be required as counselling about PGD should primarily be the responsibility of the clinical geneticist; however, the involved professionals should be aware of patients' options and have sufficient knowledge to identify patients who are eligible for PGD and refer them if desired. Furthermore, referral for PGD should become more embedded in our healthcare system; for example, by inserting a standard sentence about the possibility of PGD in the patient or family letter concerning the DNA-result in case of *BRCA1/2* mutation.

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Supplementary material

Table S3.1: Awareness, knowledge, acceptability and referral behaviour regarding PGD for *BRCA*.

	Total sample % (n)		Specialists in genetics % (n)	Non - genetics specialists % (n)
Awareness				
PGD for *BRCA*				
Aware	50.5 (95)		88 (44)	37 (51)
Unaware	49.5 (93)		12 (6)	63 (87)
Knowledge				
PGD indications				
Mean (SD)	9.2 (4.6)		12.3 (3.8)	8.1 (4.3)
Low	43.1 (81)		16 (8)	52.9 (73)
Moderate	25.5 (48)		20 (10)	27.5 (38)
High	31.4 (59)		64 (32)	19.6 (27)
		Unaware of PGD for *BRCA*		
PGD procedures				
Mean (SD)	9.8 (3)	8.6 (2.8)	11.5 (2.1)	9.2 (3)
Low	33.7 (63)	52.2 (48)	2 (1)	44.9 (62)
Moderate	46 (86)	37 (34)	66 (33)	39.1 (54)
High	20.3 (38)	10.9 (10)	32 (16)	16 (22)
Acceptability				
PGD for *BRCA* in general				
Mean (SD)	4.2 (0.8)		4.2 (0.7)	4.2 (0.9)
Yes	85.6 (161)		90 (45)	84 (116)
Not sure	10.1 (19)		8 (4)	10.9 (15)
No	4.3 (8)		2 (1)	5 (7)
Depends on personal/family cancer history				
Mean (SD)	2.7 (1.2)		2.8 (1.4)	2.6 (1.1)
Yes	28.7 (54)		40 (20)	24.6 (34)
Not sure	18.6 (35)		6 (3)	23.2 (32)
No	52.7 (99)		54 (27)	52.1 (72)
Patient's autonomy				
Mean (SD)	1.8 (1.2)		2.6 (1)	2.9 (1.2)
Yes	31.4 (59)		16 (8)	37 (51)
Not sure	18.1 (34)		24 (12)	15.9 (22)
No	50.5 (95)		60 (30)	47.1 (65)
Referral behaviour (among subgroup that sees eligible PGD patients: 87.2% / n=164)				
Ever discuss PGD for *BRCA*				
Yes	59.8 (98)		84 (42)	47.5 (56)
No	40.2 (66)		16 (8)	52.5 (62)
Intention to discuss PGD for *BRCA*				
Yes	92.7 (152)		94 (47)	91.5 (108)
Maybe	4.9 (8)		4 (2)	5.1(6)
No	2.4 (4)		2 (1)	3.3 (4)
Ever refer for PGD for *BRCA*				
Yes	48.2 (79)		62 (31)	40.7 (48)
No	51.8 (85)		38 (19)	59.3 (70)
Intention to refer for PGD for *BRCA*				
Yes	91.5 (150)		90 (45)	91.5 (108)
Maybe	5.5 (9)		6 (3)	5.1 (6)
No	3 (5)		4 (2)	3.3 (4)

Table S3.2: Correlates of demographic and medical characteristics with the main outcome variables (bivariate analyses).

	Awareness PGD	Knowledge PGD indications	Knowledge PGD procedures	Acceptability PGD	Discuss PGD	Referral behaviour PGD
	P (Pearson's ***r*** / X^2 / **t** / Mann Whitney **U** / Spearman's r_s)					
Demographic variables						
Gender (male/female)	**0.038 (X^2=4.30)**	*0.095 (t=-1.68)*	NS	**0.005 (U=2277)**	NS	NS
Age	NS	NS	NS	*0.081 (r_s=0.13)*	**0.006 (t=-2.79)**	**0.046 (X^2=-2.01)**
Partner status	NS	NS	NS	NS	NS	NS
Children	*0.098 (X^2=2.74)*	NS	NS	NS	NS	*0.062 (X^2=3.48)*
Religious	NS	NS	NS	NS	NS	NS
Professional variables						
In training	NS	*0.096 (t=1.67)*	NS	NS	**0.005 (X^2=8.03)**	**0.040 (X^2=4.23)**
Clinical experience (<10/>10 yrs.)	NS	NS	NS	NS	NS	NS
BRCA patients (<1/≥1 a month)	NS	NS	NS	NS	NS	**0.110(X^2=2.56)**
Contact with PGD patients	NS	**<0.001 (t=-3.67)**	**0.003 (t=-2.99)**	NS	**0.016 (X^2=5.79)**	*0.055 (X^2=3.68)*
Type of medical centre (general/teaching hospital)	**<0.001(X^2=30.67)**	**<0.001 (t=5.06)**	**<0.001 (t=4.85)**	NS	**<0.001(X^2=17.81)**	**0.001(X^2=11.72)**
Personal background						
Awareness of PGD	NA	NA	NA	*0.085 (U=3916)*	NA	NA
Knowledge of PGD indications	NA	NA	NA	NS	**<0.001 (t=-4.26)**	**0.003 (t=-3.02)**
Knowledge of PGD procedures	NA	NA	NA	**0.006 (r_s=0.20)**	**<0.001 (t=-4.77)**	**<0.001 (t=-4.18)**
Acceptability of PGD	NA	NA	NA	NA	*0.054 (U=2915)*	**0.037 (U=2956)**
Discuss PGD with patients	NA	NA	NA	NA	NA	**<0.001 (X^2=77.44)**

r=Pearson's Correlation; X^2=Pearson chi-squared value; t=t-value (independent samples t-test); U=Mann Whitney U-test (non-parametric alternative for t-test when ordinal variables are involved); r_s=Spearman's rho (non-parametric alternative for Pearson's correlation when ordinal variables are involved).
Bold=significant (P<0.05). *Italic=trend towards significance (P=0.05-0.10)*

Table S3.3: Associations between demographic / medical characteristics and awareness and referral behaviour PGD (logistic regressions).

	Awareness PGD			Discuss PGD			Referral behaviour PGD		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Gender	NS	NS	NS	NS	NS	NS	NS	NS	NS
Age	NS	NS	NS	NS	NS	NS	NS	NS	NS
Civil status (partner/no partner)	NS	NS	NS	NS	NS	NS	NS	NS	NS
Children	*0.362*	*0.139-1.276*	*0.062*	NS	NS	NS	NS	NS	NS
Religious	NS	NS	NS	*0.337*	*0.098-1.154*	*0.083*	NS	NS	NS
Clinical experience (<10/>10 yrs.)	NS	NS	NS	*0.237*	*0.046-1.215*	*0.084*	NS	NS	NS
BRCA patients (<1/≥1 a month)	NS	NS	NS	**0.113**	**0.035-0.369**	**<0.001**	**5.195**	**1.450-18.605**	**0.011**
Contact with PGD patients	NS	NS	NS	NA	NA	NA	NA	NA	NA
Type of medical centre (general/teaching hospital)	**0.092**	**0.037-0.229**	**<0.001**	**0.126**	**0.035-0.455**	**0.002**	*0.259*	*0.066-1.016*	*0.053*
Knowledge PGD (scale 1)	NA	NA	NA	NS	NS	NS	NS	NS	NS
Knowledge PGD (scale 2)	NA	NA	NA	**1.291**	**1.051-1.585**	**0.015**	*1.209*	*1.000-1.461*	*0.050*
Acceptability PGD	NA	NA	NA	*1.779*	*0.992-3.194*	*0.053*	NS	NS	NS
Discuss PGD	NA	NA	NA	NA	NA	NA	**25.463**	**6.168-105.126**	**<0.001**
Nagelkerke R^2		35.2%			46.6%			63.2%	

OR=Odds Ratio (Exp(B)); 95% CI=95% Confidence Interval; P=value of significance. **Bold=significant (P<0.05).** *Italic trend towards significance (P=0.05-0.10).*
NS=not significant. NA=not applicable.

Table S3.4: Associations between demographic / medical characteristics and knowledge and acceptability PGD (linear regressions).

Knowledge PGD indications			**Knowledge PGD procedures**		**Acceptability PGD**	
	β	**P**	**β**	**P**	**β**	**P**
Gender	NS	NS	NS	NS	**-0.234**	**0.015**
Age	NS	NS	NS	NS	NS	NS
Civil status (partner/no partner)	NS	NS	**0.197**	**0.021**	NS	NS
Children	NS	NS	NS	NS	NS	NS
Religious	NS	NS	*0.135*	*0.089*	**-0.173**	**0.048**
Clinical experience (<10/>10 yrs.)	NS	NS	NS	NS	NS	NS
BRCA patients (<1/≥1 a month)	NS	NS	NS	NS	NS	NS
Contact with PGD patients	**0.225**	**0.005**	**0.191**	**0.018**	NS	NS
Type of medical centre (general/teaching hospital)	**-0.392**	**<0.001**	**-0.421**	**<0.001**	NS	NS
PGD awareness	NA	NA	NA	NA	**0.277**	**0.019**
Knowledge of PGD indications	NA	NA	NA	NA	NS	NS
Knowledge of PGD procedures	NA	NA	NA	NA	*0.178*	*0.079*
Model R^2	22.3%		23%		16.6%	

β=regression coefficient; P=value of significance. **Bold=significant (P<0.05).** *Italic=trend towards significance (P=0.05-0.10).* NS=not significant. NA=not applicable.

Part II

The main thought processes and psychosocial consequences of PGD decision-making

Chapter 4

Decision-making on preimplantation genetic diagnosis and prenatal diagnosis: a challenge for couples with hereditary breast and ovarian cancer

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Abstract

Study question

How do couples with a *BRCA1/2* mutation decide on preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PD) for hereditary breast and ovarian cancer (HBOC) syndrome?

Summary answer

BRCA couples primarily classify PGD and/or PD as reproductive options based on the perceived severity of HBOC and moral considerations, and consequently weigh the few important advantages of PGD against numerous smaller disadvantages.

What is known already

Awareness of PGD is generally low among persons at high risk for hereditary cancers. Most persons with HBOC are in favor of offering PGD for *BRCA1/2* mutations, although only a minority would consider this option for themselves. Studies exploring the motivations for using or refraining from PGD among well-informed *BRCA* mutation carriers of reproductive age are lacking. We studied the reproductive decision-making process by interviewing a group of well-informed, reproductive aged couples carrying a *BRCA1/2* mutation, regarding their decisional motives and considerations.

Study design, size, duration

This exploratory, qualitative study investigated the motives and considerations taken into account by couples with a *BRCA1/2* mutation and who have received extensive counseling on PGD and PD and have made a well-informed decision regarding these options. Eighteen couples took part in focus group and dyadic interviews between January and September 2012.

Participants/materials, setting, methods

Semi-structured focus groups were conducted containing two to four couples, assembled based on the reproductive method the couple had chosen: PGD (n=6 couples) or conception without testing (n=8 couples). Couples who had chosen PD for *BRCA* (n=4) were interviewed dyadically. Two of the women, of whom one had chosen PGD and the other had chosen no testing, had a history of breast cancer.

Main results and the role of chance

None of the couples who opted for PGD or conception without testing found the use of PD, with possible pregnancy termination, acceptable. PD users chose this method because of decisive, mainly practical reasons (natural conception, high chance of favorable outcome). Motives and considerations regarding PGD largely overlapped between PGD users, PD users, and non-users, all mentioning some significant advantages (e.g., protecting the child and family from the mutation) and many smaller

disadvantages (e.g., the necessity of *in vitro* fertilization (IVF), low chance of pregnancy by IVF/PGD). For female mutation carriers, the safety of hormonal stimulation and the time required for PGD before undergoing prophylactic surgeries were important factors in the decision. Non-users expressed doubts about the moral justness of their decision afterwards and emphasized the impact the decision still had on their lives.

Limitations, reason for caution

The interviewed couples were at different stages in their chosen trajectory, up to three years after completion. This may have led to recall bias of original motives and considerations. Couples who did not actively seek information about PGD were excluded. Therefore the results may not be readily generalizable to all *BRCA* couples.

Wider implications of the findings

The perceived severity of HBOC and, for female mutation carriers, the safety of hormonal stimulation and the time frames for PGD planning before prophylactic surgeries are essential items *BRCA* couples consider in reproductive decision-making. The emotional impact of this decision should not be underestimated; especially non-users may experience feelings of doubt or guilt up to several years afterwards. PGD counseling with tailored information addressing these items and decisional support in order to guarantee well-informed decision-making is needed.

Introduction

Hereditary breast and ovarian cancer (HBOC) syndrome is an autosomal dominant predisposition caused by a mutation in breast cancer genes, *BRCA1* and *BRCA2*. Female mutation carriers face risks of 57% (*BRCA1*) and 49% (*BRCA2*) for breast cancer and 40% (*BRCA1*) and 18% (*BRCA2*) for ovarian cancer by the age of 70.[1] In contrast, Dutch women without a *BRCA* mutation have a lifetime risk of 12.7% and 1.3% for breast and ovarian cancer, respectively.[2] Among women worldwide, breast cancer is the most common malignancy and primary cause of cancer mortality. Around 5-10% of all breast cancer cases and over 30% of breast cancer diagnoses under the age of 30 are attributable to a *BRCA1/2* mutation.[3,4] Breast and ovarian cancer related to *BRCA* mutations is associated with a relatively early age of onset. Female mutation carriers are given the option of periodic screening and/or prophylactic surgery of breasts and/or ovaries to decrease morbidity and mortality.[5]

Persons with a *BRCA* mutation have a 50% prospect of passing on the susceptibility for HBOC to their offspring. Preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PD) are available reproductive options to prevent this. With PD, non-invasive fetal sex determination is performed at nine weeks of pregnancy and, in case of a female, this is followed by chorionic villus sampling with the intention to terminate the pregnancy if the fetus is affected. With the relatively new technique of PGD, *in vitro* fertilized (IVF) embryos are genetically diagnosed before implantation and only unaffected embryos are transferred to the uterus. However, the use of the aforementioned techniques, especially PD, for HBOC raises ethical concerns given the reduced penetrance of HBOC, its onset at adult age, and the availability of preventive and therapeutic options.[6,7] These characteristics may explain the generally low acceptability of PD for *BRCA* among persons affected with HBOC.[7,8] To date, studies exploring the motivations regarding PD uptake among well-informed *BRCA* mutation carriers of reproductive age are lacking.

For PGD, a physically demanding *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment is necessary regardless of the couple's fertility. Moreover, the chance of conception with IVF/ICSI is limited even among normally fertile couples given the pregnancy rate of 28.7% per aspiration in Europe.[9] This rate decreases even further when PGD is added due to the reduction of eligible embryos for transfer when excluding those with the genetic condition.

In the Netherlands, PGD was introduced in 1995 and, after nationwide political and ethical discussions, approved for late onset inherited cancer predisposition syndromes in 2008. Nowadays, HBOC is one of the most frequent indications for PGD in Maastricht University Medical Center (Maastricht UMC+), the only licensed PGD center in the Netherlands. PD for HBOC is available on a case-by-case base in several University Medical Centers. In the Netherlands, PGD and PD treatments are covered by the health insurance system. The female exclusion criteria for a PGD treatment are specified as following: age >40, BMI >30 and FSH level >15mIU/ml. Both PGD and PD are available for *BRCA* in many European countries as well as in the USA.[6,10-13]

In 2003, the European Society of Human Reproduction and Embryology (ESHRE) ethics taskforce argued that PGD was acceptable for adult onset and multifactorial diseases such as HBOC and other cancer predispositions, despite uncertainties about prospective improvements in preventive and therapeutic options.[14]

Opinion surveys among persons affected by HBOC show that the majority, after being informed about PGD, is in favor of offering PGD for *BRCA1/2* mutations, although only a minority would consider this option for themselves.[8,10,12,13,15-20] However, the aforementioned studies were not designed to explore the process from hypothetical acceptability or PGD intention to actual PGD use, since they frequently lacked a focus on *BRCA* mutation carriers of reproductive age and included persons with diverse levels of knowledge regarding PGD. The few studies available on attitudes and motives regarding PGD among couples who were well-informed (i.e., who had had an informative PGD consultation) or who had experience with PGD have been carried out in the general PGD population.[21,22,23] Nevertheless, motives may be dependent on the genetic condition PGD is considered for. In-depth studies regarding the motives and considerations taken into account by couples carrying a *BRCA* mutation are needed, in order to gain insight into the aspects influencing reproductive decision-making in this population. This knowledge can be valuable for the optimization of patient decision support for a growing group of couples facing this quandary.

This study therefore aims to provide an integral qualitative account of the decision-making process among couples carrying a *BRCA1/2* mutation, who seriously considered PGD as a reproductive option. Motives and considerations for opting for or against PGD as well as the reproductive alternatives (PD and conception without testing) were addressed. Furthermore, PGD users, PD users, and non-users were asked to reflect on the reproductive option chosen.

Materials and methods

Recruitment of couples

Couples carrying a *BRCA1/2* mutation were eligible for participation if they had received standardized counseling on their reproductive options by an expert in reproductive genetics between 2008 and 2012 at the PGD center of Maastricht UMC+, and had made a final decision whether or not to use PGD or PD. During counseling, verbal and written information was provided about the PGD procedure (including IVF/ICSI, embryo biopsy, chance of pregnancy, risk of misdiagnosis and health of children born after PGD). In addition, PD was discussed, consisting of non-invasive fetal sex determination, followed by chorionic villus sampling in case of a female fetus and termination of pregnancy (TOP) in case of an affected female fetus. Inclusion criteria for the study were at least eighteen years of age and a full understanding of the Dutch language. Exclusion criteria were presence of one or more medical reasons to reject the couple from PGD, severe physical

or psychological illness, presence of more than one indication for PGD, divorce, and foreign place of residency.

Out of a total of 69 potential couples, 47 couples were selected and invited to participate by letter. Purposive sampling[24] was conducted in order to include at least four couples from each reproductive choice (PGD, PD, and conception without testing) with variable demographic factors (i.e., sex of the mutation carrier, *BRCA1* and *BRCA2* mutations, asymptomatic mutation carriers, and breast cancer survivors). Based on an expected participation rate of 25%, 47 out of 69 eligible couples were selected. After informed consent, couples were contacted by telephone to schedule the interviews. Reasons for non-participation were collected (Table 4.1).

Table 4.1: Reasons for non-participation

Reason	n (couples)
Not interested	7
No response to the invitation	5
Unwillingness to participate in an interview	5
Unwillingness to look back at the decision made to conceive without testing (with or without unsuccessful PGD attempt in the past)	5
Divorce	2
Lack of time	1

n, number of couples; PGD, preimplantation genetic diagnosis

Procedure

A semi-structured topic guide was developed to direct both the focus group and the dyadic interviews, focussing on perception of the (dis)advantages of PGD and PD and the most decisive reasons for making the final reproductive decision. The topic guide was pretested in a personal interview, which was included in the analyses since no adjustments were made following. Focus groups were conducted containing two to four couples (n=four to eight persons), assembled based on the reproductive method the couple had chosen and subsequently used after counseling (PGD or conception without testing) in order to avoid disconcerting discussions within groups. All participants who were assembled in a focus group were offered a dyadic interview if they preferred this but none made use of this alternative. Focus group interviews are an effective qualitative research method to explore and clarify individuals' experiences, perceptions, and beliefs concerning a certain topic.[25] Couples who had chosen PD for HBOC were scheduled in dyadic interviews (i.e., an interview including both partners). This was done because of the delicate character of the subject and to avoid participants being confronted with couples who had experienced different pregnancy outcomes after PD. Focus groups were held at geographically convenient and neutral locations throughout the Netherlands, whereas dyadic interviews were held at the couples' homes. During the focus groups, the moderator, trained by an expert on (group) interviewing techniques, was accompanied by an assistant who took observational notes. Interviews were conducted between January and September 2012 and lasted between 80 and 100 min.

Before initiation of the interviews, participants completed a questionnaire on demographic parameters, personal reproductive and oncologic history, and family history.

Data preparation and analysis

All interviews were audio-taped and transcribed verbatim. Data analysis was performed using the software program Nvivo 9.0. Grounded theory approach was used allowing codes, concepts and categories to emerge from the data.[26] Open coding of the data was followed by axial coding, organizing the data into segments based on keywords and concepts to form categories and identify major themes. For reliability reasons, data were coded by two independent researchers with consultation of a third independent researcher in case of discordance. Since no new major themes emerged in the final interviews, saturation of themes was suggested.

Ethical approval

The procedures were approved by the local medical ethics committee of Maastricht UMC+.

Results

Couples' characteristics

Of the 47 invited couples, 22 were willing to participate. The overall response rate was 46.8%: 39.1% for PGD, 66.7% for PD, and 50.0% for non-users. Four willing couples were not interviewed because saturation of themes had been achieved. Thus, eighteen couples participated in the interviews (17 males and 18 females). One female partner of a male mutation carrier participated alone since her partner found the topic too difficult to discuss. This personal interview acted as a pre-test, but did not substantially deviate from the dyadic interviews. Other reasons for non-participation are summarized in Table 2.1.

Four focus groups were conducted, two among couples who decided to use PGD (three and two couples, respectively) and two among couples who decided not to use PGD or PD (three and four couples, respectively). Furthermore, five dyadic and one personal interviews were conducted; four dyadic interviews were among couples who opted for PD for HBOC (of whom one couple had initially chosen PGD but converted to PD after an unexpected natural conception, and one couple who converted their choice to PGD after a TOP), one was with a PGD couple (dyadic interview because of logistic reasons) and there was the aforementioned pre-test (personal interview) with the female partner of a couple who chose no testing (Figure 4.1). Counseling took place between six months and four years prior to the interviews and although all couples had made a reproductive

decision, participants were in different stages of enactment of their reproductive decision at the time of the interview (Figure 4.1). The couples' characteristics are summarized in Tables 4.2 and 4.3.

Table 4.2: Couples' characteristics.

	Reproductive choice (initial use)		
	PGD (n=6)	PD (n=4)	No testing (n=8[a])
Partner at risk (M/F)	3/3	1/3	2/6
History of breast cancer[b] (M/F)	0/1	0/0	0/1
Gene mutation			
BRCA1 (M/F)	1/1	0/3	2/4
BRCA2 (M/F)	2/2	1/0	0/2
Mean age (years) at time of the interview (SD)			
Male	33.5 (3.3)	33.5 (4.5)	32.9 (5.6)
Female	31.8 (2.2)	32.3 (1.9)	31.6 (2.3)
Education			
Education middle (M/F)	2/0	1/1	3/1
Education high (M/F)	4/6	3/3	4/7
Religious (Christianity) (M/F)	1/3	0/0	1/2
Not religious (M/F)	5/3	4/4	6/6
Time interval (months) between counseling and interview (SD)	22 (18.6)	33 (18.4)	31 (9.8)

PGD=preimplantation genetic diagnosis; PD=prenatal diagnosis; n=number of couples; M=male; F-female; *BRCA1*=breast cancer gene 1; *BRCA2*=breast cancer gene 2; SD=standard deviation [a] For one of these couples, only the female partner participated in the interview; [b] Both women were treated for breast cancer before PGD counseling.

General results

All participants but one indicated that they wanted a child biologically related to both partners. Reproductive decisions such as remaining childless, adoption, or use of donor gametes were only considered briefly, if at all. Most couples saw PGD and conception without testing as the only reproductive options. A minority of couples considered PD as a third option; all these couples ultimately decided to use PD. Before PGD counseling, the majority of couples, including those refraining from PGD, indicated that they intended to opt for PGD.

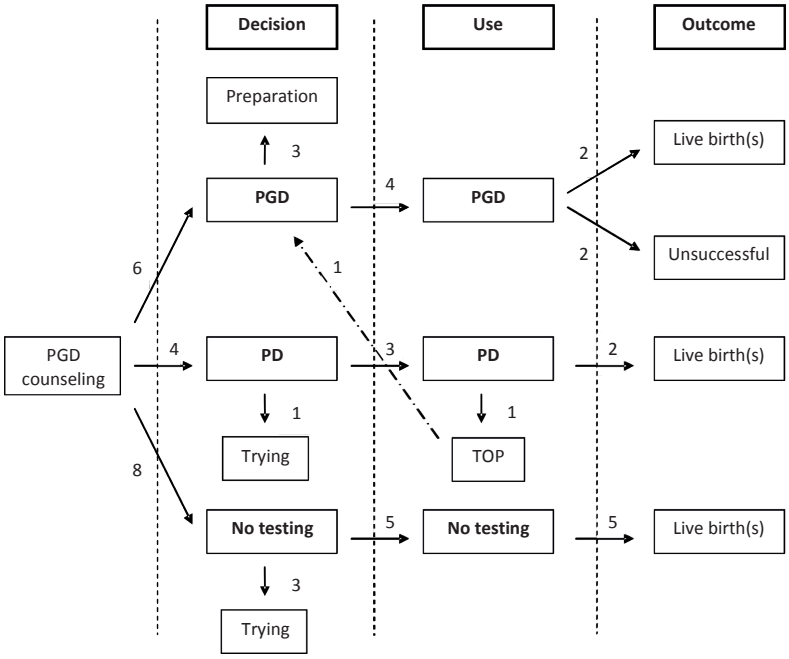

Figure 4.1: Couples' decisional process from PGD counseling until the interview. Dotted arrow = change of reproductive choice. n=number of couples; PGD=preimplantation genetic diagnosis; PD=prenatal diagnosis; TOP=termination of pregnancy.

There was a large overlap in motives and considerations to opt for or refrain from PGD mentioned by the participants who decided in favor of PGD and those who opted for PD or conception without testing. All three categories of couples mentioned a small number of important advantages and a larger number of less important disadvantages of PGD. Motives and considerations in the reproductive choices could be classified as physical, psychological, social, ethical/moral, and practical (Table 4.4). In the results, we distinguish moral from ethical considerations, by defining moral considerations as individual internal principles regarding a person's ideals and right or wrong conduct, and by defining ethical considerations as social or external rules of conduct in respect to human actions.[27]

Table 4.3: Couples' reproductive history at the time of interview.

Reproductive history	Couples (n=18)	Couple codes	Time interval (months) counseling - interview
Before reproductive counseling			
Infertility (IVF/ICSI indication)	3	3-7-14	3-38-38
≥1 child(ren) without testing	3	1-5-8	8-41-30
≥1 miscarriage(s)	1	1	8
After reproductive counselling			
Preparation phase PGD	3	1-2-3	8-6-3
Experience PGD			
1 PGD attempt, 0 live births	1	17[a]	26
2 PGD attempts, 1 live birth	1	12	42
2 PGD attempts, 1 live birth, 1 ongoing pregnancy	1	16	44
3 PGD attempts, 0 live births	1	11	27
Preparation phase PD (trying to conceive)	1	13	20
Experience PD			
1 PD attempt, 1 live birth of unaffected female	1	14	38
1 PD attempt, 1 TOP of affected female	1	17[a]	26
2 PD attempts, 2 live births of males	1	15	39
Preparation phase no testing (trying to conceive)	3	4-7-10	16-38-18
Experience no testing			
≥1 child(ren) without testing	5	5-6-8-9-18	41-36-30-28-41

n=number of couples; IVF=*in vitro* fertilization; ICSI=intracytoplasmic sperm injection; PGD=preimplantation genetic diagnosis; PD=prenatal diagnosis; TOP=termination of pregnancy. [a] Couple converted their choice from PD to PGD (after TOP).

Motives and considerations to opt for PGD

The most frequently mentioned motive in considering PGD was, in all categories of couples, protecting the future child from the *BRCA* mutation. In this context, the majority of couples primarily indicated they wanted to protect their child from the physical and psychological impact of the *BRCA* mutation, i.e., the risk of cancer and the quandary of whether or not to opt for genetic testing, prophylactic surgeries, and/ or reproductive options. One father said: "For me that was the most important thing. I don't want to burden my child with a little time-delayed bomb." (C6, conception without testing). Often, female participants illustrated their comments with personal experiences: "My mother died because of cancer, I am a mutation carrier myself. My breasts are removed... Therefore, I don't want my child to experience the same things that I did." (C17, PD). Some women specifically pointed out that radical surgery should not be classified as a good preventive measure for breast and/or ovarian cancer and that they felt a strong need to protect a potential daughter from this choice between two evils: "They say that nowadays there are good preventive measures. Well, if you classify this as a good preventive measure... when you, as a 27 or 28 year old woman, have to let them amputate your breasts... This I think, you cannot classify as a good measure, that's just nonsense." (C12, PGD).

Table 4.4: Motives considered regarding PGD, PD, and no testing for HBOC.

Preimplantation genetic diagnosis – Prenatal diagnosis – No testing		
	Motives to choose (n)	Motives to refrain (n)
Physical	***Protecting the child from mutation (13)***	*Potential influence of ovarian stimulation on cancer risks (10)*
	Protecting potential daughter from radical prophylactic surgeries (7)	*Potential effects on child's health due to biopsy in embryonic stage (9)*
	Additional medical check-ups woman (3)	*Physical strain of IVF treatment (5)*
Psychological	***Avoidance of feelings of guilt towards child (15)***	*Loss of romance and control regarding pregnancy (14)*
	Avoidance of TOP (7)	*Psychological strain emerging from success-related uncertainties during trajectory (11)*
	Reassurance from beginning of pregnancy (6)	*Dilemma in case of unsuccessfulness (8)*
	Preventing mutation in both males and females (3)	*Tired of medical procedures regarding BRCA (6)*
	Avoidance of stress and tension associated with PD (1)	*Inevitability of involving direct environment (6)*
	Participation in a remarkable process (1)	*Despite complex procedure, no guarantee for a healthy child (5)*
	Reassuring feeling of simulating nature by selecting the highest quality embryo (1)	*Emotional influence of hormone injections (4)*
	Preservation of romance and control regarding pregnancy (14)	*Necessity of IVF when normally fertile (4)*
	Faith in future medical developments regarding HBOC (10)	***Fear of disappointment (3)***
		Potential impact on relationship (3)
		Male mutation carrier's feelings of guilt towards partner undergoing procedure (3)
		Daily reminder of the seriousness of the predisposition during treatment (1)
Social	*Wiping out mutation in family line (12)*	***Fear of negative reactions from environment (5)***
	Protecting child from reproductive dilemma (8)	
	Pioneering for (younger) family members (1)	
	Confidence in capability to guide/support child with mutation through personal experiences (4)	
Moral/ethical	***Moral duty to protect the child (9)***	***Nature of condition (i.e. late onset, incomplete penetrance, preventive possibilities) (9)***
	Nature of condition (i.e. late onset, incomplete penetrance, preventive possibilities) (9)	*Disposal of affected (male) embryos (7)*
		Interference in a natural process/playing for God (4)
		Treatment was or could not be considered for previous child(ren) (2)
Practical	*PGD only minor addition in case of IVF or ICSI indication (4)*	*Relatively low chance of successful pregnancy (14)*
	Good accessibility and reimbursement of treatment (3)	*Frequent hospital appointments (13)*
	Relatively high chance of success (8)	*Relatively long duration of trajectory (8)*
		Difficult integration in timely planning of prophylactic surgeries (5)
		Desire for (large) family less achievable (3)
		Necessity to collect blood from near family members (2)

PGD=preimplantation genetic diagnosis; PD=prenatal diagnosis; HBOC=hereditary breast and ovarian cancer; n=number of couples that considered this motive (non-correlated to decisiveness); IVF=*in vitro* fertilization; TOP=termination of pregnancy; *BRCA*=breast cancer gene; ICSI=intracytoplasmis sperm injection.

The two female breast cancer survivors emphasized the physical and emotional severity of their disease, e.g.: "What I have been through, that's just really horrible, yes horrible, you know. I mean my surgeries and all... and the moment you have to undergo the chemotherapy, well, that is something you wish no one ever has to go through." (C8, conception without testing). A majority of couples expressed the desire to not only protect their own children, but to completely wipe out the *BRCA* mutation in the family line. For instance: "I strongly feel that I want to stop it with me." (C17, PD).
Half of the couples believed it was their moral duty to protect their future child(ren) from suffering, given the fact that they are aware of the risk and the reproductive options to avoid it: "I couldn't feel at ease with consciously burdening my child with this." (C13, PD). Avoidance of feelings of guilt towards future child(ren), accompanied by a fear of immense future regret when choosing the 'easier way', was frequently mentioned by couples of all three categories as a motive in favor of PGD or PD: "What I was afraid of myself, or still am actually, are those feelings of guilt. They might not be so relevant now, but in about twenty or thirty years when my child would go for a DNA test... Imagine it will be positive, then I would have to relive this all over again. And then, I would tell myself: it's your own fault and you could have prevented this…" (C6, conception without testing). Another woman expressed her concern that her son might go through the same reproductive dilemma as she did in case he turns out to be a *BRCA* mutation carrier: "Sometimes I look at my son and think: 'Will you end up in the same sticky situation with your partner as we did, just because we may have chosen the easy way out?'" (C18, conception without testing).

Motives and considerations to refrain from PGD

Couples in all three categories mentioned many motives to refrain from PGD, which could be subdivided into general motives, *BRCA*-related motives, and motives that are only of relevance to female mutation carriers.
General motives concerned the physical and psychological burden of an IVF treatment, especially for fertile couples: "To me it felt very serious, needing an IVF treatment while we are normally fertile." (C14, PD). The necessity to convert conception into a medical process and losing the sense of romance and control as a couple were a major drawback. Male mutation carriers expressed feelings of guilt towards their partner: "I would especially regret that I am the source of the evil in this case and you (i.e., the female partner) would have to go through all this hormone misery…" (C5, conception without testing). Couples who already had children before PGD for HBOC became available felt a moral drawback when considering PGD for a next child. Additionally, many couples feared the dilemma of what to do in case PGD would turn out to be unsuccessful. For some couples, especially those who had a desire for a large(r) family, this was a decisive reason to refrain from PGD: "Preferably, we would like to have two children. But what are the chances that we eventually would get two children through PGD?" (C15, PD). Moreover, almost half of the couples said that ethical motives

regarding selection in general had influenced their decision-making process, as well as the disposal of (male) affected embryos. As one participant expressed: “We talked about it a lot, and then I slowly began to realize that there would also be embryos which will be, well, discarded. And although they are affected, they are still embryos and therefore children, if you look at it that way. I’ve never been able to shake that off…” (C18, conception without testing). Additionally, practical issues like the relatively low chance of pregnancy, the frequent hospital appointments, the need to involve family members for the genetic preparation, and the long duration of the PGD trajectory played a role.

Whereas half of the couples indicated that the (very) high perceived severity of HBOC was an important reason to opt for PGD or PD, the other half stated that they had taken the nature of the condition into consideration and decided not to interfere in the reproductive process. One female non-carrier said: “We went thinking… What if? It’s fifty-fifty... Maybe it’s a boy, that would be positive. If it’s a girl, she only has a 50% chance of being a mutation carrier. Well, in case she inherits the mutation, there is a chance she won’t fall ill at all. And if she does, there may be good therapeutic options. That was our consideration, and we keep reminding ourselves of that.” (C18, conception without testing). While half of the couples felt moral drawbacks from selection in general, a substantial portion of the remaining couples had difficulties with accepting methods such as PGD and PD for HBOC because of the reduced penetrance and late onset character of the condition and the preventive and therapeutic options available. Not all female mutation carriers experienced their genetic predisposition as a burden to the extent that they wanted to prevent transmission of their mutation by means of PGD or PD: “It’s not like it makes you unhappy or something like that.” (C6, conception without testing), and “The amputation of my breasts you know, it all sounds very intense but I am not really that upset about it.” (C10, conception without testing). Other mentioned *BRCA*-related motives to refrain from PGD were the fact that using PGD would not guarantee a child free of breast and ovarian cancer due to the non-genetic background risk, confidence in being able to guide and support a child in case he/she inherits the mutation, and faith in future medical developments. As one father said: “It makes you start thinking… Imagine you would have a girl, yet another thirty years along the road medical science will look completely different. Who knows if they don’t have a vaccine for breast cancer by then?” (C7, conception without testing).

For female mutation carriers uncertainty regarding a potential influence of ovarian stimulation on the cancer risk was a very important aspect: “That’s actually your biggest concern, right? That you bring a child into this world and then you fall ill yourself, due to the hormones...” (C2, female breast cancer survivor, PGD). In addition to this, most female mutation carriers were very aware of the fact that their time window was limited due to the need for prophylactic surgeries: “If afterwards you still need preventive breast surgery and subsequently your ovaries have to be removed... and you don’t want to do all that on the same day... So then you start to calculate and eventually we became aware of the fact that maybe we should already be initiating the PGD trajectory while we were not even that occupied with the matter of having children yet.” (C12, PGD).

Moreover, the necessity of medical interference once more, next to all procedures female mutation carriers had gone through already, was mentioned as a disadvantage of PGD.

PGD versus PD

A minority of seven couples stated they would not opt for PD because of religious and/or ethical objections against TOP in general. Eleven couples, however, had made a personal reflection on the acceptability of TOP for HBOC. All six couples who opted for PGD clearly indicated perceiving a moral difference between embryo selection and TOP specifying that termination is a too drastic measure to avoid HBOC: "It depends on the consideration of selection which I think is still okay. But when taking my own life as an example, terminating a pregnancy is simply not justified." (C12, PGD).

The four couples who found PD for HBOC acceptable in fact chose this method. All four couples indicated that for them PGD was the most ideal option from a moral point of view as well. However, the relatively low chance of pregnancy by PGD, mostly in combination with the duration of the trajectory, directed their choice to PD. Furthermore, they appreciated the possibility of conceiving naturally without medical intervention: "Getting pregnant this way is a natural process like it is for other couples. You know, I have had my breast surgery and one day I will have to remove my ovaries... Sometimes you just want to be normal." (C17, PD, TOP affected girl). The PD couples all judged the 75% chance of a good outcome as fairly high. When explicitly discussing the possibility of conceiving an affected girl and the necessity of TOP, the couples said they felt prepared and had confidence in standing by their choice. One couple said: "Termination of pregnancy in case of an affected girl would obviously be a massive burden for us. However, I would prefer that instead of having to tell my daughter she might be a mutation carrier." (C13, planning to use PD after conception). However, the only PD couple who experienced TOP because of HBOC converted to PGD for their second attempt to fulfil their child wish, indicating that in spite of having no regrets about this first endeavour, they could not emotionally cope with another TOP. They additionally specified that after this experience, the disadvantages of PGD had diminished in their perception.

Other advantages of PD compared with PGD mentioned by the PD couples were the absence of the need to inform others about their attempts to conceive, which for PGD is necessary given the genetic preparations involving family members, and the possibility to control their own planning. The couples who already experienced PD perceived the two consecutive diagnostic steps as beneficial, like they had two chances to receive a good result: "The possibility of the sex determination in blood was a kind of a trigger for us... That could prevent us from the necessity of chorionic villus sampling, at only eight or nine weeks of pregnancy. At that point we would already know what sex we would be dealing with." (C15, PD, two sons). Another couple said: "It just became really burdensome when we found out it was a girl. We did not expect that at all. (...) That

tough decision suddenly became much more imminent and I was really concerned by that. But well, we still had a 50% chance..." (C14, PD, one unaffected girl).
All four PD couples took the fact that PD did not prevent HBOC in males into consideration in their decision-making. One couple initially had difficulties with the impossibility to avoid male mutation carriers by PD: "At first we struggled with the fact that in case of a boy no additional diagnostics would be carried out. We preferred a child without *BRCA* mutation, to put an end to this... But since termination of pregnancy is such a drastic measure we felt at ease to do it this way." (C17, PD, TOP affected girl). Besides the risk of TOP, the weeks of uncertainty when waiting for the PD results were mentioned as a major disadvantage of PD. One male said: "You only know after several weeks, it takes so long... For me that is the most prominent disadvantage." (C13, PD, trying to conceive). The same couple regretted the fact that their chance of having a girl was no longer 50/50 but dropped to 1/3, since both boys and girls have a 50% risk of carrying the *BRCA* mutation but only a girl with the mutation will be medically aborted in the Netherlands.

Emotional impact of reproductive decision-making

None of the couples regretted the choice they made. However, several couples said that becoming parents had changed their perspectives on pregnancy and parenthood. One woman who underwent PD said: "Only since I was pregnant myself I can really estimate the value of a pregnancy. Before that time I could not have imagined. I simply thought 'if it's not okay we'll terminate and try again.'" (C14, unaffected girl after PD). At the time of the interview, this couple had the intention to re-use PD for a second child. However, a few months later the couple was pregnant and informed the researcher that they had decided to continue this pregnancy of a second daughter without invasive diagnostics for HBOC. They did not feel capable of terminating the pregnancy in case of an unfavorable result and were confident in being able to guide and support a daughter with HBOC.
The couples who chose for PGD did not regret that choice, but indicated that although they had prepared themselves for the physical burden and the practical impact of the treatment, they had been unable to anticipate on the psychological strains: "The waiting during the actual treatment... during those two weeks of hormonal stimulation, if you are even able to manage that, until the moment of embryo transfer and the pregnancy test two weeks later. The tension... I never could have prepared myself for that." (C12). In addition, in some cases, the IVF/PGD treatment had had more impact on their spousal relationship than previously imagined. A male said: "There were many moments when you (i.e., the partner) were troubled and you couldn't really express yourself or I didn't really understand and then I could clearly feel the tension between us." (C11). During the treatment, the dilemma of how to proceed in case PGD would not succeed eventually arose. Since many couples perceived PGD as the most ideal option, they feared that the choice between remaining childless and choosing another option which

might not (completely) protect the child from HBOC would cause an emotional load: "It's a real drawback that once you have completed the trajectory it might not have been successful. What are you going to do then? Are you still going for the natural way? Well, that will obviously cause an emotional burden." (C11). Couples agreed that using PGD to conceive a first child made it ethically difficult to make a different choice for a second child. However, when PGD was not successful for any child, the conversion to conception without testing seemed to be much easier to make: "Our desire to become parents has only increased since our PGD experience. In case PGD remains unsuccessful, we will try to conceive the natural way. Ultimately, we have done whatever was possible. That was very important for us." (C11).

The PD couples felt at ease with the decisions made. Two out of three couples experiencing PD said they had been unsure about the extent to which they should involve their social network in the procedure; they needed support, but feared disturbing advice and social judgements: "At that point, you don't want to hear any arguments in favor of a different decision. You only want to hear that your decision is the only right one to make." (C17). Some couples experienced difficulties in explaining their choice to their social surrounding: "It is much easier to explain your choice for PGD to your social network than your choice to terminate the pregnancy in case of an unfavorable outcome. (...) It felt like we were among the very few who make a decision like this." (C15).

Half of the couples who had chosen for conception without testing expressed their doubts about the moral justness of their decision, even when the decision was made a few years ago and the couple had completed their family in the meantime: "And now you do hope that she doesn't have it. That is something you start to think about... We did make the right choice, didn't we?" (C9) and "But still, if it turns out that my second daughter would have it, while I did have this choice for her... I think I would go to pieces at that moment. I would always keep thinking; what if I had..., I wish I had, maybe…" (C8). Several couples emphasized that the reproductive decision-making process they went through still had a major impact on their lives: "It is só hard not to know whether we have made the right choice, I really can't say... But I still dwell on that on a daily basis." (C18). Many of these couples said they felt uncomfortable when confronted with the decision made. This is confirmed by the fact that unwillingness to look back at the decision made was one of the main reasons not to participate in the study among non-users.

Discussion

This study provides a qualitative assessment of the motives and considerations that well-informed couples carrying a *BRCA1/2* mutation take into account when deciding on PGD and PD. Perceived (dis)advantages and reasons to opt for or refrain from these

reproductive methods were explored and satisfaction with the choice made was assessed during semi-structured (focus group) interviews.

The most important factor taken into account was the perceived severity of HBOC, which was generally based on personal and familial experience with cancer and sacrifices to be made for preventive measures. Half of the couples perceived that living with HBOC was serious enough to outweigh disadvantages of PGD and/or PD; the others did not. All couples who opted for PGD clearly indicated perceiving a moral difference between embryo selection and the termination of a pregnancy, specifying that they considered PD as a too drastic measure to avoid HBOC. In contrast, all couples who found PD for HBOC acceptable actually chose this option, despite the fact that all these couples had a preference for PGD from a moral point of view. Some significant practical and psychological aspects directed their final choice towards PD, showing that the possibility of avoiding the risk of TOP by choosing PGD could not outweigh the negative aspects. This corresponds with findings from previous studies.[28,29] Several previous studies indicated that experience with TOP for a genetic disorder influences the acceptance of PGD, in particular for women.[29,30] This was also the case for the interviewed couple that experienced TOP after PD and subsequently opted for PGD, indicating that they did not want to terminate another pregnancy.

The same motives and considerations played a role for couples opting for PGD and couples refraining from PGD. The PGD couples mentioned numerous negative aspects of PGD, but indicated that the main advantage, 'preventing transmission of the *BRCA* mutation, both for their own child as well as future generations', outweighed the accumulated disadvantages. In the previous literature this advantage is usually separated from the benefit of protecting the child from possible physical and mental suffering.[13,20,22,31,32] The majority of motives to refrain from PGD, such as limited success rates, duration of the trajectory, procedural and human risks and safety, correspond to those reflected in previous studies.[13,31] Moreover, in the specific context of HBOC, we found in concurrence with Dekeuwer and Bateman[20] that female *BRCA* mutation carriers worry about the unknown influence of hormonal stimulation needed for IVF on their breast cancer risk. Several studies suggest an association, although inconsistent, between IVF medication and an increased breast cancer risk in both the general female population[33-35] and in women with HBOC.[36-39]

Women carrying a *BRCA* mutation have to cope with many decisions and life events in a short period of time (i.e., DNA testing, coping with an unfavorable test result, decision-making on possible medical interventions as well as reproductive decision-making). Since female *BRCA* mutation carriers are generally advised to undergo a risk-reducing salpingo-oophorectomy from their mid-thirties, the timeframe in which they can have offspring is tight. As a result, female carriers may feel forced to cope with complex reproductive issues at a (much) younger age than they might have wanted to.[16,17,20,40]

Several couples who eventually decided in favor of conception without testing for *BRCA* expressed feelings of doubt or even guilt afterwards, and feared the moment if it turns out that their child(ren) have inherited the *BRCA* mutation. These feelings are not

uncommon among parents with a genetic susceptibility.[41,42] The mere possibility of PGD and PD can cause an emotional burden once people become aware and choose to refrain from it, known as the technological imperative. This aspect should not be neglected in reproductive counseling. Couples choosing for a natural pregnancy without testing might be as much in need for emotional support during and even after this trajectory, as PGD or PD users may be. This group must not be forgotten.

Study strengths and limitations

This is the first study on motives and considerations regarding PGD and PD use in well-informed *BRCA1/2* mutation carrying couples of reproductive age. A substantial diversity of responses was attained by including PGD users, PD users, and non-users, male and female asymptomatic mutation carriers, as well as female breast cancer survivors, and their partners. Interviews were assembled according to the reproductive option chosen, in order to guarantee a safe environment in which one could express and discuss feelings and opinions openly and without judgement. We believe it therefore gives a rich and in-depth overview of reproductive motives.

All couples had made a reproductive decision, but the fact that the couples were at different stages in their chosen reproductive trajectory may have led to a coloured perception of experiences and outcomes, as well as recall-bias of motives and considerations. Our design excluded couples who did not actively seek information about PGD, or *a priori* decided to refrain from having their own, genetically related, children.

Conclusions and recommendations

Reproductive decision-making regarding PGD and PD has proven to be a very complex and stressful process for couples with HBOC. We found that the process was mainly guided by the couples' perceived seriousness of the predisposition as well as their moral views regarding selection. The safety of IVF and the compatibility of the PGD planning process with prophylactic surgeries were essential factors for female mutation carriers. For some couples, the emotional impact of the decision was substantial and long-lasting. Non-users could be confronted with feelings of doubt or guilt up to years after the decision has been made.

Reproductive counseling requires highly skilled professionals who are able to guide couples in a challenging process of reconciliation with a wide variety of moral considerations and emotions regarding their reproductive wishes. Knowledge of the condition-specific reproductive motives may motivate the adaptation of current best practice guidelines by means of further tailoring of counseling practices, e.g., by providing additional decision support in the form of a patient decision aid.[43] Such a decision aid should be offered complementary to counseling.

In addition, the emotional burden which is experienced by non-users after they have made their decision to refrain requires more attention. Emotional support, during the decision-making process as well as afterwards, should be actively offered to all couples, including those refraining from PGD and PD. Further research regarding the longterm consequences of the reproductive decision on emotional well-being is required.

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Chapter 5

Preimplantation genetic diagnosis for hereditary breast and ovarian cancer: motivational domains influencing couples' reproductive decision-making

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Submitted

Abstract

Study question

Which domains of motives and considerations primarily influence decision-making concerning preimplantation genetic diagnosis (PGD) for couples with hereditary breast and ovarian cancer (HBOC)?

Summary answer

Moral, psychological and physical motives and considerations are mainly associated with PGD-choice, while practical and social motives appear to be less substantial in PGD decision-making for couples with HBOC.

What is known already

The limited available data, exclusively from qualitative studies identified three main dimensions in general PGD decision-making: a cognitive, emotional and moral dimension. Specifically for couples with HBOC, the following five more detailed domains were identified: physical, psychological, moral, practical and social.

Study design, size, duration

Mixed methods were used; the cross sectional survey study (N=80) was based on the results of a previously conducted focus group study. Data were collected from June until January 2014.

Participants/materials, setting, methods

From the hospital database of the Maastricht UMC+, 129 persons with a *BRCA1/2*-mutation and their partners, who had made a reproductive decision were selected and invited to participate in an online survey. The survey assessed personal characteristics (demographic, clinical, reproductive and psychological) and perceived motives and considerations during PGD decision-making. The main outcome was PGD-choice (PGD vs. a natural pregnancy without genetic testing (NP)). Associations between personal characteristics and PGD-choice and associations between motivational domains and PGD-choice were investigated.

Main results and role of chance

The study sample comprised 80 participants including 25 couples (n=50). More than half were women (62%) and 98% of those women was of reproductive age. Younger participants (p=0.034) and those with a higher perceived susceptibility of HBOC for their future child (p=<0.002) were more likely to opt for PGD. The assessed motives and considerations were classified into six domains (physical, psychological pro-PGD, psychological con-PGD, practical, moral and social). Moral motives (p=<0.001; OR=11.173), psychological motives con-PGD (p=0.012; OR=3.642) and physical motives (p=0.025; OR=2.064) were negatively associated with choosing PGD. Psychological motives pro-PGD were positively associated with choosing PGD (p=0.001; OR=0.295).

Limitations, reasons for caution

The retrospective design of the study may have caused recall-bias. The relatively small sample size of this study calls for caution when interpreting the results and further research among larger sample sizes may be required.

Wider implications of the findings

While considerations in the moral domain show the strongest association with the decision to opt for or refrain from PGD, psychological and physical considerations significantly add to the determination of PGD-choice. The implications of PGD concerning these domains should be well addressed in PGD counselling for couples with HBOC.

Study funding/competing interest(s)

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Introduction

Hereditary breast and ovarian cancer syndrome (HBOC) is an autosomal dominant predisposition caused by a mutation in the breast cancer genes *BRCA1* or *BRCA2,* with a 50% risk of passing it on to the next generation. Female carriers of a *BRCA1* or *BRCA2* mutation face strongly increased risks of developing breast- or ovarian-cancer at a relatively young age[1,2] and are offered the options of intensive screening or prophylactic surgeries of breasts and ovaries. These prophylactic surgeries can be physically and emotionally traumatic and negatively affect fertility.[3,4] Moreover, breast cancer in *BRCA1/2* mutation carriers is often diagnosed at an early age, occasionally as an aggressive bilateral disease.[5-9] Therapeutic options pertain to surgery and chemotherapy.

Couples with HBOC have several reproductive options, some of which can prevent transmission of the *BRCA*-mutation to their offspring. These options are marked by numerous advantages and disadvantages which complicates reproductive decision-making. The two options that can prevent transmission of the *BRCA*-mutation for couples who desire a child genetically related to both partners are prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD). PND involves gender determination followed by invasive prenatal testing for the *BRCA*-mutation if the foetus is female and intended termination of pregnancy (TOP) in case of a female carrier. This option is rarely used by couples with HBOC[10,11], due to psychological, moral and ethical reservations regarding a (possible) TOP. The more innovative option of PGD is preferred by many couples.[10-15] PGD comprises selection before pregnancy, by means of in vitro fertilization (IVF) and subsequent *BRCA*-testing of the embryos before transfer to the woman's uterus.[16] Since PGD was allowed and reimbursed for late onset genetic cancer syndromes in the Netherlands in 2008, HBOC caused by a *BRCA1/2* mutation has been the most frequent indication for PGD.[17]

Most couples with HBOC still opt for a natural pregnancy without genetic testing.[11] Other options are using donor gametes (egg or sperm donation), adoption, or refrain from having children.

Couples with HBOC are an exceptional group when it comes to reproductive decision-making. In addition to the general advantages and disadvantages of PGD, several considerations that are not applicable to other PGD-indications further complicate decision-making. First, HBOC is a late onset predisposition with incomplete penetrance for which preventive and therapeutic options are available, which has raised ethical reservations towards embryo-selection for this condition.[10,11] Second, the implications of this predisposition significantly differ between males and females, with the slightly increased cancer risk for male carriers being lower than the general population risk for females.[18] General regulations for good clinical practice in PGD disallow transferring an affected embryo to the uterus, causing male carrier embryos to be discarded in an already strict process of elimination.[19] While this is a disadvantage of PGD for some couples, it is an advantage for others who want to wipe out the mutation in the family

line or protect a potential son from having the same reproductive dilemma in the future.[13] Third, for female *BRCA*-carriers and their partners family-planning regarding PGD is further complicated by a relatively narrow time-window due to the advised prophylactic surgeries in combination with the time consuming trajectory of PGD.[20] And finally, an additional worry for female *BRCA*-carriers and their partners is the unknown effect of the IVF hormones on the woman's breast cancer risk, although a recent study by Derks-Smeets et al.[21] indicates this concern may be unnecessary.

It is important to support these couples in making an informed decision, in order to prevent adverse psychological effects such as feelings of guilt and regret.[13] In-depth studies regarding the motives and considerations taken into account by couples with HBOC, are essential to gain insight into the dynamics of PGD decision-making in this unique group that currently constitutes one of the largest subgroups in the uptake of PGD in the Netherlands. This knowledge will be valuable for the optimization of counselling for a growing group of couples facing this decision, since possibilities for genetic diagnosis will continue to develop.

Most of the available studies on attitudes and motives regarding PGD have been carried out in the general PGD population.[22-26] However, as described above, motives are likely to depend on the condition PGD is requested for considering the wide variation in conditions and their implications. A previously conducted focus group study by our research group[13] identified the following five domains of motives and considerations in the reproductive decision-making process of couples with HBOC: physical, psychological, social, moral and practical. In the current study, with the aim to improve reproductive guidance and counselling for couples with HBOC, we questioned which motivational domains are most important in their reproductive decision-making process. We have set out to confirm the previously identified domains with quantitative data and investigated their influential strength. In addition, this study pioneered in investigating associations between demographic/clinical factors and reproductive choice.

Materials and methods

Participants and procedures

The current survey study is a follow-up study concerning motives and considerations identified by our previously conducted focus group study. In order to warrant topicality of the focus group data these have been published separately.[13]

For the current survey study, 129 couples with a proven *BRCA*-mutation who received reproductive counselling (focusing on the options PGD, PND and a natural pregnancy) within the last three years and had made a reproductive decision, were selected from the hospital database of the Maastricht University Medical Centre+ (Maastricht UMC+) and invited to participate by mail. Partners were asked to fill in the survey

independently, although participation of both partners was not required. Digital informed consent was given before starting the online questionnaire.

Data collection instrument

A questionnaire was developed based on the results of the focus group study of Derks-Smeets et al.[13] and the existing literature. While completing the questionnaire, participants were repeatedly asked to keep their reproductive decision-making process in mind and to base their answers on their thoughts and feelings at that time.

Demographic characteristics included gender, age, educational level, religiosity and ethnicity. Clinical factors that were collected included carrier status (carrier/partner), mutation type of respondent or carrier partner (*BRCA1/BRCA2*), mastectomy (applying to the respondent in case this was a female *BRCA*-carrier, or applying to the partner in case the partner was a female *BRCA*-carrier: yes/no), personal history of breast/ovarian cancer (applying to the respondent in case this was the *BRCA*-carrier, or applying to the partner in case the partner was the *BRCA*-carrier: yes/no), and number of carrier's first degree family members with breast/ovarian cancer (<3/≥3). Reproductive factors concerned medical indication for IVF (yes/no) and reproductive choice (PGD/PND/natural pregnancy without genetic testing). Finally, psychological factors recorded were the perceived susceptibility of the child regarding HBOC (six items: e.g. 'If we would do nothing to prevent that our child inherits the *BRCA*-mutation, I feel that the chance that our child will get breast cancer is:' 1=very low - 5=very high), the perceived seriousness of HBOC (four items: e.g. 'How serious would it be to you if your child would inherit the *BRCA*-mutation?' 1=not serious at all - 5=very serious) and the perceived controllability of HBOC (four items: e.g. 'Good options are available to protect someone with a *BRCA*-mutation from getting breast cancer' 1=strongly disagree - 5=strongly agree). These psychological concepts were retrieved from the revised Illness Perception Questionnaire (IPQ-R).[27]

In addition, 48 statements regarding motives and considerations of PGD decision-making that emerged from the focus group study were assessed with a five item scale (1=totally disagree - 5=totally agree) (Table 5.1). The statements were divided into the following six domains previously identified by Derks-Smeets et al.[13]: 1) Physical aspects (e.g. I am concerned about the physical burden that is associated with IVF/PGD), 2) Psychological aspects pro-PGD (e.g. It is important to me to prevent feelings of guilt towards my child for passing on the *BRCA*-mutation), 3) Psychological aspects con-PGD (e.g. I am concerned about the lack of romance regarding conception with PGD), 4) Practical aspects (e.g. I am concerned about the influence of the necessary hospital visits for PGD on my daily life), 5) Moral aspects (e.g. If we want to prevent HBOC, it is important to me that selection takes place before pregnancy) and 6) Social aspects (e.g. I am concerned about negative responses from my social environment if we would choose PGD). Before creating the domains, all statements were coded con-PGD (i.e. a higher score was associated with refraining from PGD) except for the statements in the domain

'psychological considerations pro-PGD' (i.e. a higher score was associated with opting for PGD). Of these 48 statements, several were not applicable to a small subgroup of respondents. For example: 'I dread the necessity of an IVF treatment for PGD' did not apply to respondents who already had an IVF indication regardless of PGD (n=12). We excluded these 12 respondents from this item and repeated this procedure for other items where applicable before creating the scales (see Table 5.1).
The main outcome variable was reproductive choice (PGD versus NP). Time investment for filling in the questionnaire was approximately 30 minutes.
The study was approved by the medical ethics committee of the Maastricht UMC+, reference number: METC 12-4-075.

Statistical analyses

Questionnaire data was analysed using IBM SPSS version 23.0. Descriptive statistics provided an overview of demographic, clinical, reproductive and psychological factors and PGD choice (PGD vs. NP). Reliability testing was conducted for each of the six defined domains by computing Cronbach's α. Binary logistic regression models were used to assess the association between demographic and clinical factors with PGD-choice. To determine the association of each domain and the distinct motives with PGD-choice, binary logistic mixed-effects models were conducted in which clustering within couples was corrected for. Additionally, the area under the receiver operating characteristic (ROC) curves, or AUC, were computed for each domain, in order to determine the domain's potential to discriminate between choosing PGD and NP. An AUC of 0.5 indicates no discriminative ability, an AUC of 1.0 indicates perfect discriminative ability. P-values of <0.05 were considered to indicate statistical significance.

Table 5.1: Domains, individual motives and their association with Reproductive Choice (binary logistic regressions).

Motives *(1=totally disagree-5=totally agree)*	Mean (SD)	Reproductive choice (NP vs. PGD) OR	95% CI	P
Domain Physical (7)				
Only applicable to female carriers or partners of female carriers (n=50): I am concerned about the possible effect of the IVF/PGD hormones on the woman's cancer-risk	3.48 (1.16)	0.704	0.424-1.169	0.175
I am concerned about the physical burden that is associated with IVF/PGD	3.31 (1.09)	0.564	0.347-0.918	**0.021**
I am concerned about the possible mood swings the IVF hormones can cause in a woman	3.29 (1.16)	1.248	0.819-1.900	0.302
I am concerned about the risk of complications associated with IVF/PGD (e.g. overstimulation, bleeding/infection after oocyte retrieval)	*3.25 (1.16)*	*0.687*	*0.443-1.065*	*0.093*
I am concerned about the possible risks of PGD for the child	3.10 (1.15)	0.518	0.325-0.825	**0.006**
Only applicable to participants without IVF-indication (n=64): I am concerned about the necessity of an IVF treatment for PGD	2.93 (1.16)	0.426	0.242-0.749	**0.003**
I am concerned that me or my partner would have to undergo another medical intervention due to the *BRCA*-mutation if we would choose PGD	*2.70 (1.24)*	*0.696*	*0.468-1.034*	*0.073*
Domain Psychological Pro-PGD (13)				
It is important to me to prevent a termination of pregnancy	4.40 (0.85)	1.553	0.895-2.695	0.118
It is important to me to protect my child from an increased cancer-risk	4.28 (1.01)	1.986	1.192-3.309	**0.008**
It is important to me to protect a possible daughter from needing prophylactic surgeries	4.20 (1.03)	2.173	1.299-3.637	**0.003**
It is comforting to me that once you are pregnant through PGD, you can be certain that the child does not carry the *BRCA*-mutation	4.18 (1.06)	1.874	1.171-3.000	**0.009**
It is important to me to protect my child from inheriting the *BRCA*-mutation	4.11 (1.02)	3.423	1.832-6.380	**0.000**
I want to wipe out the *BRCA*-mutation in our family	4.10 (1.11)	2.767	1.620-4.726	**0.000**
It is important to me that my child is biologically related to me and my partner	4.06 (1.07)	1.026	0.657-1.603	0.909
It is important to me to protect my child from having this reproductive dilemma in the future	3.99 (1.04)	2.354	1.389-3.989	**0.001**
I want to feel like we did everything within our power to protect our child from inheriting the *BRCA*-mutation	3.89 (1.14)	2.322	1.430-3.770	**0.001**
It is important to me to protect a boy as well from inheriting the *BRCA*-mutation	3.83 (1.11)	2.760	1.607-4.741	**0.000**
The anxiety during prenatal diagnosis until we get the test-result seems unbearable to me	3.68 (1.06)	1.313	0.838-2.057	0.235
It is important to me to prevent feelings of guilt towards my child for passing on the *BRCA*-mutation	3.63 (1.23)	1.775	1.166-2.701	**0.007**
I think it is my moral duty to protect my child from inheriting the *BRCA*-mutation	3.60 (1.21)	2.412	1.493-3.895	**0.000**

Table 5.1: continued.

Motives *(1=totally disagree-5=totally agree)*	Mean (SD)	Reproductive choice (NP vs. PGD) OR	95% CI	P
Domain Psychological Con-PGD (12)				
I am concerned about the psychological burden (anxiety, uncertainty, and possible disappointment) that is associated with PGD	3.79 (0.98)	0.473	0.259-0.863	**0.015**
Only applicable to male carriers (n=17): I fear having feelings of guilt towards my partner if she would have to undergo a PGD treatment while I am carrier of the *BRCA*-mutation	3.57 (1.14)	NA (excluded from analysis: insufficient observations)		
I am concerned about the dilemma of what to do if PGD is not successful and we still want to have children	3.55 (1.07)	1.184	0.755-1.856	0.463
Only applicable to males (n=30): I fear feeling powerless, if I have to watch my partner undergo a PGD treatment	3.33 (0.97)	NA (excluded from analysis: insufficient observations)		
A disadvantage of PGD is that the chance to have a big family through PGD is small	3.08 (1.16)	1.191	0.778-1.823	0.421
Only applicable to participants without IVF-indication (n=64): An advantage of prenatal diagnosis is that it enables us to conceive spontaneously	3.06 (1.14)	1.006	0.638-1.587	0.978
I am concerned about the lack of romance regarding conception with PGD	2.53 (1.24)	0.985	0.669-1.449	0.937
A reason to refrain from PGD would be that all this hassle is still no guarantee for having a healthy child	2.48 (1.19)	0.281	0.159-0.497	**0.000**
I am concerned about the possible negative influence of a PGD treatment on the relationship with my partner	2.34 (1.17)	0.707	0.467-1.071	0.102
A reason to refrain from PGD would be that one can still get breast or ovarian cancer without having a *BRCA*-mutation	2.24 (1.02)	0.242	0.125-0.468	**0.000**
I am concerned that undergoing a PGD treatment would constantly remind me of the *BRCA*-mutation	2.16 (1.00)	0.742	0.462-1.190	0.216
I dread the artificial way of conception with PGD	2.08 (1.08)	0.451	0.262-0.776	**0.004**
Domain Practical (4)				
I think the total duration of a PGD treatment (several months up to a year) is long	3.74 (1.08)	0.746	0.461-1.206	0.231
I think the chance of a successful pregnancy after a PGD treatment (20-25%) is low	3.69 (1.06)	1.083	0.690-1.698	0.729
I am concerned about the influence of the necessary hospital visits for PGD on my daily life	3.23 (1.12)	0.619	0.391-0.979	**0.040**
Only applicable to female carriers or partners of female carriers (n=50): I am concerned about the influence of a PGD treatment on our planning regarding the advised preventive surgeries	2.86 (1.11)	0.696	0.421-1.150	0.157
Domain Moral (8)				
If we want to prevent HBOC, it is important to me that selection takes place before pregnancy	4.05 (1.03)	1.761	1.092-2.841	**0.020**
I trust that we can adequately guide and support a child with the *BRCA*-mutation based on our personal experiences	3.54 (1.29)	0.276	0.136-0.561	**0.000**
I think a *BRCA*-carrier can live a good life	3.41 (1.24)	0.366	0.206-0.651	**0.001**
I trust that when our child reaches the age at which breast or ovarian cancer can develop, medical science has significantly improved	3.38 (1.32)	0.354	0.202-0.621	**0.000**
I think that if I would refrain from PGD, I would be well able to explain this choice to my child	3.19 (1.26)	0.210	0.100-0.445	**0.000**

Table 5.1: continued.

Motives *(1=totally disagree-5=totally agree)*	Mean (SD)	Reproductive choice (NP vs. PGD) OR	95% CI	P
I think we can take the gamble to pursue a natural pregnancy without genetic testing	3.00 (1.33)	0.430	0.270-0.685	**0.000**
It is not up to me to determine whether my child will have a *BRCA*-mutation or not	2.23 (1.06)	0.373	0.213-0.653	**0.001**
I have ethical reservations towards PGD (i.e. the selection of embryos)	1.61 (0.75)	0.717	0.386-1.332	0.292
Domain Social (4)				
Hardly being able to keep a PGD treatment private due to the many necessary hospital visits feels uncomfortable to me	2.88 (1.23)	1.084	0.731-1.608	0.689
I am concerned about having to involve family members for blood withdrawal if we would choose PGD	2.69 (1.28)	0.879	0.604-1.281	0.503
I am concerned about negative responses from my social environment if we would choose PND	2.60 (1.14)	1.173	0.763-1.802	0.466
I am concerned about negative responses from my social environment if we would choose PGD	1.88 (0.88)	0.926	0.538-1.592	0.780

Dependent variable: PGD-=1 - no PGD= 0. NP=Natural Pregnancy without testing; PGD=Preimplantation Genetic Diagnosis; NA=Not Applicable; OR=Odds Ratio; 95% CI=95% Confidence Interval. P=value of significance. **Bold=significant (P<0.05);** *Italic=trend towards significance (P=0.05-0.10).*

Results

Participant characteristics

The questionnaire was completed by 86 participants (response rate: 33%). Of those, six participants opted for PND. Since the size of this subgroup was deemed insufficient to include PND as a main outcome option from the perspective of statistical power, these six participants were excluded from the analyses and we confined the main outcome options to PGD and NP. The final study sample therefore consisted of 80 participants, among whom 25 couples (n=50). Participants' characteristics are summarized in Table 5.2.

Classification of motives into domains

After reliability analysis, the six defined domains were transformed into the following scales: 1) Physical (7 items relating to the physical burden of PGD/IVF: Cronbach's α=0.827); 2) Psychological pro-PGD (13 items capturing the desire to protect a child from HBOC without risking a TOP: Cronbach's α=0.941); 3) Psychological con-PGD (12 items assessing the psychological burden of PGD in terms of anxiety and possible disappointment: Cronbach's α=0.817); 4) Practical (4 items concerning the procedures, success rates and time investment of PGD: Cronbach's α=0.723); 5) Moral (8 items regarding the moral implications of PGD such as selection of embryo's and the technological imperative: Cronbach's α=0.838) and 6) Social (4 items relating to the

perspectives and possible interference of the social environment concerning PGD: Cronbach's α=0.741), see Table 5.1.

Table 5.2: Participants' characteristics.

Demographic factors	% (n)
Gender	
Male	37.5 (30)
Female	62.5 (50)
Age males (years)	
Mean	35.8 (SD=5.9)
Range	27-55
Age females (years)	
Mean	31.9 (SD=3.8)
Range	24-41
Females in reproductive age (18-40 years)	98 (49)
Education	
Low	3.8 (3)
Middle	28.8 (23)
High	67.5 (54)
Religious	
Yes	27.5 (22)
No	72.5 (58)
Ethnicity	
Dutch	98.8 (79)
Other	1.3 (1)
Medical history	
Carrier status	
Carrier	67.5 (54)
Partner	32.5 (26)
Mutation type	
*BRCA*1	52.5 (42)
*BRCA*2	47.5 (38)
Mastectomy (including female carrier partners of non-carrier respondents)	
Yes	20 (16)
No	80 (64)
Personal history of breast/ovarian cancer (including carrier partners of non-carrier respondents)	
Yes	6.3 (5)
No	93.8 (75)
N of family members with breast/ovarian cancer	
<3	55 (44)
≥3	45 (36)
Reproductive history	
IVF indication	
Yes	15 (12)
No	80 (64)
Don't know	5 (4)
Reproductive choice	
NP	30 (24)
PGD	70 (56)

IVF=In vitro fertilization; NP=Natural pregnancy without genetic testing; PGD=Preimplantation genetic diagnosis; PND=Prenatal diagnosis; HBOC=Hereditary breast and ovarian cancer caused by a *BRCA1* or *BRCA2* mutation.

Associations between participants' characteristics and PGD-choice

Younger participants and those who perceived their future child's susceptibility for HBOC as high(er) were more likely to choose PGD versus NP (Table 5.3). No significant associations were found for other demographic, clinical, reproductive or psychological factors.

Table 5.3: Associations between Demographic/Clinical Characteristics and Reproductive Choice (binary logistic regression).

	Reproductive choice (NP vs PGD)		
	OR	95% CI	p
Demographic factors			
Gender		NA	
Age	0.813	0.671-0.984	0.034
Education		NS	
Religious (yes/no)		NS	
Clinical factors			
Carrier status (carrier/partner)		NS	
Mutation type (*BRCA1/2)*		NS	
Mastectomy (yes/no)		NS	
Breast/ovarian cancer (yes/no)		NS	
N of family members with breast/ovarian cancer (<3/≥3)		NS	
Reproductive factors			
IVF indication (yes/no)		NS	
Psychological factors			
Perceived susceptibility HBOC	17.989	2.969-108.985	0.002
Perceived seriousness HBOC		NS	
Perceived controllability HBOC		NS	

NA=Not applicable; NS=Not significant; OR=Odds Ratio; 95% CI=95% Confidence interval. P=value of significance; Significant when P=<0.05.

Associations between motivational domains and PGD-choice

Univariate analyses showed that participants who refrained from PGD reported high agreement with moral motives (OR=11.2, P=<0.001), psychological burden of PGD (OR=3.7, P=0.012) and worries about the physical aspects of PGD (OR=2.1, P=0.025). Those who opted for PGD agreed more with psychological motives pro-PGD (OR=0.3, P=0.001).

The domains with practical and social motives and considerations did not show a significant association with the choice for PGD or NP (Table 5.4).

Multivariate analysis showed that when corrected for the other domains, only the moral domain was associated with PGD choice, i.e. participants who refrained from PGD were more likely to agree with considerations that relate to decreased moral acceptability of PGD (OR=5.1, P=0.020; Table 5.4).

Table 5.4: Associations between Domains and Reproductive Choice (binary logistic mixed-effects models).

	Reproductive choice (NP vs. PGD)		
	OR	95% CI	p
Domains (univariate analyses)			
Domain 1 Physical considerations	**2.064**	**1.097-3.882**	**0.025**
Domain 2 Psychological considerations pro-PGD	**0.295**	**0.143-0.611**	**0.001**
Domain 3 Psychological considerations con-PGD	**3.672**	**1.350-9.993**	**0.012**
Domain 4 Practical considerations			NS
Domain 5 Ethical considerations	**11.173**	**3.323-37.566**	**0.000**
Domain 6 Social considerations			NS
Domains (multivariate analysis)			
Domain 1 Physical considerations			NS
Domain 2 Psychological considerations pro-PGD	*0.366*	*0.124-1.082*	*0.069*
Domain 3 Psychological considerations con-PGD	*5.700*	*0.773-42.044*	*0.087*
Domain 4 Practical considerations			NS
Domain 5 Ethical considerations	**5.121**	**1.304-20.116**	**0.020**
Domain 6 Social considerations			NS

NP=natural pregnancy without testing; PGD=Preimplantation genetic diagnosis; OR=Odds Ratio; 95% CI=95% Confidence interval; P=value of significance; NS=Not significant; **Bold=significant (P<0.05);** *Italic=trend towards significance (P=0.05-0.10).*

ROC curves showed that participants who refrained from PGD were likely to have higher scores on the domains moral considerations (AUC=0.909, P=<0.001), psychological considerations con-PGD (AUC=0.761, P=<0.001), physical considerations (AUC=0.696, P=0.006), and practical considerations (AUC=0.666, p=0.019). Participants who opted for PGD were likely to have higher scores on the domains psychological considerations pro-PGD (AUC=0.854, P=<0.001) and social considerations (AUC=0.832, P=<0.001). The sum of all domains shows an AUC of 0.920 (P=<0.001), indicating a high discriminative ability between PGD and NP (Table 5.5).

Table 5.5: Association strength of individual Domains with Reproductive Choice (ROC curves).

	Reproductive choice (NP vs. PGD)		
	AUC	95% CI	p
Domain			
Domain 1 Physical considerations	**0.696**	**0.562-0.831**	**0.006**
Domain 2 Psychological considerations pro-PGD	**0.854**	**0.771-0.937**	**0.000**
Domain 3 Psychological considerations con-PGD	**0.761**	**0.651-0.872**	**0.000**
Domain 4 Practical considerations	**0.666**	**0.513-0.819**	**0.019**
Domain 5 Ethical considerations	**0.909**	**0.829-0.989**	**0.000**
Domain 6 Social considerations	**0.832**	**0.741-0.922**	**0.000**
Sum of domains	**0.920**	**0.854-0.986**	**0.000**

NP=Natural pregnancy without testing; PGD=Preimplantation genetic diagnosis; AUC=Area under the curve; 95% CI=95% Confidence interval; P=value of significance (significant if P<0.05); **Bold=significant (P<0.05).**

Individual motives within domains: association with PGD-choice

Univariate analyses were conducted for each motive within the domains in order to identify the individual motives and considerations that were significantly associated with PGD-choice.

Within the domain 'Physical' (seven motives), three motives were associated with refraining from PGD: 1) I am concerned about the physical burden that is associated with PGD, 2) I am concerned about the possible risks of PGD for the child, and 3) I am concerned about the necessity of an IVF treatment for PGD. Within the domain 'Psychological pro-PGD' (13 motives), ten motives were associated with opting for PGD: 1) It is important to me to protect my child from an increased cancer-risk, 2) It is important to me to protect a possible daughter from needing prophylactic surgeries, 3) It is comforting to me that once you are pregnant through PGD, you can be certain that the child does not carry the *BRCA*-mutation, 4) It is important to me to protect my child from inheriting the *BRCA*-mutation, 5) I want to wipe out the *BRCA*-mutation in our family, 6) It is important to me to protect my child from having this reproductive dilemma in the future, 7) I want to feel like we did everything within our power to protect our child from inheriting the *BRCA*-mutation, 8) It is important to me to protect a boy as well from inheriting the *BRCA*-mutation, 9) It is important to me to prevent feelings of guilt towards my child for passing on the *BRCA*-mutation, 10) I think it is my moral duty to protect my child from inheriting the *BRCA*-mutation. Within the domain 'Psychological con-PGD' (12 motives) four motives were associated with refraining from PGD: 1) I am concerned about the psychological burden (anxiety, uncertainty, and possible disappointment) that is associated with PGD, 2) A reason to refrain from PGD would be that all this hassle is still no guarantee for having a healthy child, 3) A reason to refrain from PGD would be that one can still get breast or ovarian cancer without having a *BRCA*-mutation, and 4) I dread the artificial way of conception with PGD. Within the 'Practical' domain (four motives) one motive was significantly associated with refraining from PGD: I am concerned about the influence of the necessary hospital visits for PGD on my daily life. Within the 'moral' domain (eight motives) seven motives were associated with refraining from PGD: 1) If we want to prevent HBOC, it is important to me that selection takes place before pregnancy, 2) I trust that we can adequately guide and support a child with the *BRCA*-mutation based on our personal experiences, 3) I think a *BRCA*-carrier can have a good life, 4) I trust that when our child reaches the age at which breast or ovarian cancer can develop, medical science has significantly improved, 5) I think that if I would refrain from PGD, I would be well able to explain this choice to my child, 6) I think we can take the gamble to pursue a natural pregnancy without genetic testing, and 7) It is not up to me to determine whether my child will have a *BRCA*-mutation or not. None of the individual motives in the 'social' domain were associated with reproductive choice (Table 5.1).

Discussion

In the current study we investigated motives for reproductive decision-making among couples with HBOC. Gaining insight into the decision-making process regarding PGD can help optimize counselling for this increasingly applied reproductive technique. Currently, most of the research in this area concerns PGD decision-making in general. Indication-specific investigation of the decision-making process will allow for tailoring of reproductive counselling to the individual patient. The present findings indicate that opting for PGD was associated with some personal characteristics, specifically: being of younger age and having a higher perceived susceptibility of HBOC for the future child. Considering that PGD is a time-consuming process and the fact that chances of pregnancy decrease as the female's age increases, it is comprehensible that PGD is a more attractive option for younger couples. The finding that participants with a higher perceived susceptibility of HBOC are more likely to opt for PGD was previously shown in a study by our research group.[11] These persons may be more motived to prevent transmission of the *BRCA*-mutation to their offspring. Possibly, more demographic, psychological or clinical characteristics are associated with PGD-choice. A recent study by Mor, Brennenstuhl and Metcalfe[28] for example identified previous infertility as a significant predictor for PGD uptake among women with a *BRCA1/2* mutation. However, the subsamples of participants in the current study that had an IVF indication for fertility reasons (n=12) or had a history of breast cancer (n=5) may have been too small to show significant associations. This should be kept in mind when interpreting these results.

The domains of PGD decision-making applied in the current study partially overlap with domains identified by previous studies about PGD decision-making in general.[22,23] The current study adds detail by focussing specifically on HBOC and by evaluating the association strength of each domain with PGD choice, allowing for more specific recommendations regarding counselling. The six domains in the present study showed high internal consistencies. The high area under the curve (AUC) of the sum of domains showed that with these detailed domains we are well able to discriminate between opting for and refraining from PGD.

The current study identified moral, physical and psychological motives and considerations that are significantly associated with either opting for or refraining from PGD. Apart from the primary motive to protect the future child from inheriting the *BRCA*-mutation, several other considerations such as the physical and the psychological burden of a PGD treatment influenced PGD choice. However, moral considerations show by far the strongest association with PGD choice. Participants who refrained from PGD reported higher agreement with moral considerations such as believing it is not up to the couple to intervene in the transmission of the *BRCA*-mutation, or thinking a *BRCA*-carrier can live a good life trusting that preventive and treatment options will significantly improve before the child reaches the age at which hereditary breast or ovarian cancer can develop, and feeling able to adequately guide and support a child with the *BRCA*-mutation based on personal experiences. It is notable that the single

moral consideration that was not significantly associated with PGD choice concerned reservations towards selecting and discarding embryo's. It appears that moral hesitations towards PGD are mainly related to the perceived seriousness of HBOC. One moral motive was individually associated with opting for PGD, specifically: If we want to prevent HBOC, it is important to me that selection takes place before pregnancy. However this is under the presumption that the couple desires to prevent transmission of the *BRCA*-mutation which refers to the core of the dilemma. A majority of couples with HBOC that have a child wish, pursue a natural pregnancy without genetic testing[11] and the group that is seen for counselling at the PGD outpatient clinic (i.e. the study sample in the present study) constitutes only a small percentage of this group. Of this subgroup one third still refrains from PGD after counselling (PGD annual report, 2017). It appears that a majority of couples with HBOC refrains from PGD based on moral grounds which are related to the perceived seriousness of the condition.

The finding that practical and social domains are not significantly associated with PGD-choice is in line with results from the focus group study of Derks-Smeets et al.[13] However, this does not mean that practical and social considerations should not be integrated in counselling. Another study by our research group investigating support needs of couples with HBOC considering PGD, showed that couples that tend towards PGD have several practical and social worries about the trajectory and are in need of guidance with these issues in order to be able to cope with their chosen reproductive trajectory and prevent negative psychological impact during and after the treatment.[29]

Limitations

Since PGD is generally applied to prevent relatively rare genetic conditions it is challenging to conduct research in this field among large sample sizes. The limited sample size of this survey study calls for caution with interpreting the results. In addition, the retrospective design of the study may have caused recall-bias; motives and considerations may have been different during PGD decision-making compared to the moment of completing the survey when most couples had already experienced PGD or NP. In an attempt to forestall this, the survey explicitly requested to reflect on the thoughts and feelings experienced during PGD decision-making. Regarding generalisation of the results it is import to keep in mind that this study was conducted in the Netherlands where three PGD treatments are reimbursed by the Dutch health care system, whereas the costs and logistical hurdles of PGD can be major drawbacks for couples in other countries where the costs of PGD are not covered by the health care system.[30]

Implications for practice

Based on these findings, deliberation of physical, psychological and especially moral aspects should be incorporated in PGD counselling in order to foster informed decision-making among these couples and prevent adverse psychological effects. The type and

form of counselling on these aspects merits further reflection. Investigation of possible benefits of an (additional) consult with a psychologist, or provision of decisional support such as a patient decision aid[31] is therefore recommended.

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Part III

Support needs of couples with hereditary breast and ovarian cancer during reproductive decision-making

Chapter 6

Support needs of couples with hereditary breast and ovarian cancer during reproductive decision-making

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Abstract

Objective

Reproductive decision-making for couples with hereditary breast and ovarian cancer (HBOC) is complex and can result in decisional conflict or regret. This study investigated couples' support needs and aimed to identify vulnerable couples. Ultimately, we should strive to develop a clear standard of care guideline regarding reproductive decision support.

Methods

Mixed methods were used for data collection. A focus group study was conducted among 18 couples (N=35) with HBOC who had made a reproductive decision after reproductive counselling. Subsequently, 129 similar couples (N=258) were invited to complete a cross-sectional survey based on the focus group study.

Results

Clinical and practical aspects of reproductive counselling were positively evaluated in the focus group study, although couples indicated a need for additional support with emotional and social concerns in which their relationship, social environment, and the way they picture their desired family were key elements. The survey was completed by 86 participants. Making a reproductive choice was experienced as (very) difficult by 43%, and 69% showed a need for additional support during decision making. Younger participants and those who opted for a natural pregnancy experienced more difficulty with reproductive decision-making, and partners showed a higher need for psychological support than carriers.

Conclusions

Couples with HBOC who need to make a reproductive decision have specific needs for guidance and support, of which the desired content and methods can vary. It is therefore important to identify vulnerable couples and to attune counselling to couples' needs.

Background

Women with hereditary breast and ovarian cancer (HBOC) caused by a *BRCA1/2* mutation have a severely increased risk of developing breast or ovarian cancer at a relatively young age.[1,2] The available preventive measures such as prophylactic surgeries are physically and emotionally traumatic.[3] Couples who want a biological child face a 50% risk of transmitting this predisposition to their offspring, although there are two reproductive techniques available that can prevent transmission. The first option is prenatal diagnosis (PND). Prenatal diagnosis involves foetal *BRCA* diagnosis during pregnancy and intended termination of pregnancy in case of a female carrier. Due to moral and ethical reservations regarding a (possible) termination of pregnancy for this late-onset predisposition,[4-8] the more novel technique of preimplantation genetic diagnosis (PGD) is preferred by many couples.[5,7,9] Preimplantation genetic diagnosis involves in vitro fertilization and subsequent *BRCA* testing of the embryos before transfer to the woman's uterus.[10] Since PGD was allowed for late onset genetic cancer syndromes in the Netherlands in 2008, HBOC has been the most frequent indication for PGD.[11] Other options are natural conception without genetic testing, adoption, using donor gamete or sperm, or refrain from having children. Reproductive decision making is highly preference sensitive and often demanding and can result in a negative psychological impact due to decisional conflict or regret.[5,12] A previous study showed a strong desire for assistance with reproductive decision-making among female *BRCA* carriers.[13] Several studies identified motives and considerations that play a role in this decision-making process.[5,14,15] To mitigate decisional conflict and regret, it is important that couples make an informed choice. Adequate decision support should help couples to gain relevant information, clarify their values, and deliberate about the decision they are trying to make.[16-18] Several studies regarding decision-making about prenatal testing confirmed that decisional conflict was lower when an informed decision was made.[16,19-21] To investigate specific needs regarding the content and methods for support during reproductive decision-making and to identify vulnerable couples, which to our knowledge has not been investigated before, we conducted an explorative focus group study and a confirmatory survey study.

Methods

Focus group study

Participants and procedures

Based on an expected participation rate of 25%, 47 couples with a proven *BRCA* mutation who received reproductive counselling within the last three years and had made a reproductive choice were selected from the hospital database of the Maastricht

UMC+ and invited by mail to participate. The method of "purposive sampling" was used to obtain a representative sample of the PGD population.[22] After couples returned a signed informed consent, they were contacted by telephone to schedule an interview. The study was approved by the medical ethics committee of the Maastricht UMC+, reference number: METC 12-4-075.

Data collection instrument

A semi structured topic guide regarding the perceived difficulty of reproductive decision-making and support needs was developed and pretested to direct the focus groups (see Data S1). Focus groups included two to four couples, assembled on reproductive choice to avoid disconcerting discussions within groups. Focus groups were held at geographically convenient and neutral locations throughout the Netherlands, were conducted between January and September 2012, and lasted between 80 and 100 minutes. Before initiation of the focus groups, participants completed a questionnaire on demographic parameters and reproductive and genetic history.

Analyses

All focus groups were audiotaped and transcribed verbatim. Data analysis was performed using NVivo 9.0. Grounded theory approach was used allowing codes, concepts, and categories to emerge from the data.[23] Open coding of the data was followed by axial coding, organizing the data into segments based on keywords and concepts to form categories and identify major themes. Data were coded by two independent researchers with consultation of a third independent researcher in case of discordance. Since no new major themes emerged in the final focus groups, saturation of themes was suggested.

Survey study

Participants and procedures

From the hospital database of the Maastricht UMC+, 129 couples with a proven *BRCA* mutation who received reproductive counselling within the last three years and had made a reproductive decision were randomly selected and invited to participate by mail. This sample possibly overlapped with the 47 couples invited for the focus group study. Partners were asked to fill in the questionnaire independently, although participation of both partners was not required. Digital informed consent was given before starting the online questionnaire. The study was approved by the medical ethics committee of the Maastricht UMC+, reference number: METC 12-4-075.

Data collection instrument

A questionnaire was developed based on the focus group study and the existing literature (see Data S2). Topics from the focus group study that were used to inform the survey design were "difficulty with reproductive decision-making" (mainly based on perceived seriousness, risk, and controllability of HBOC), "need for professional and social decision support," and "need for decision support tools." Demographic characteristics included gender, age, educational level (1=none or lower education to 8=university level), partner status, religiosity, and ethnicity. Clinical factors included carrier status, mutation type, mastectomy, carrier's history of breast/ovarian cancer, and number of carrier's first degree family members with breast/ovarian cancer. Reproductive factors concerned medical indication for in vitro fertilization, children, child wish, and reproductive choice. Finally, psychological factors recorded were the perceived risk of HBOC, the perceived seriousness of HBOC, and the perceived controllability of HBOC. The psychological concepts were retrieved from the revised Illness Perception Questionnaire,[24] based on Leventhal's Self-Regulatory Model.[25,26] Main outcomes were (1) perceived difficulty of reproductive decision-making, (2) need of psychological support during reproductive decision-making, and (3) need of practical decision support tools (identified in the focus group study). Time investment for filling in the questionnaire was approximately 10 minutes.

Statistical analyses

Questionnaire data were analysed using SPSS 23.0. Descriptive statistics provided an overview of demographic and clinical factors and the primary outcomes. Multivariate linear and logistic (enter method) regression models were built to assess associations of demographic and clinical factors with the three outcomes of interest. A significant outcome was defined as $P<0.5$.

Results

Focus group study

Participants' characteristics

Eighteen couples participated in the focus groups (response rate:46.8%). One female partner of a male carrier participated alone since her partner considered the topic too sensitive to discuss. For couples' characteristics, see Table 6.1.

Table 1: Couples' characteristics (focus groups)

	Reproductive choice			Total	
	PGD (n=6)	PND (n=4)	Natural pregnancy (n=8[a])	Male	Female
Partner at risk (M/F)	2/4	1/3	2/6		
History of breast cancer[b] (M/F)	0/1	0/0	0/1	0	2
Mutation type					
BRCA1(M/F)	1/1	0/3	2/4	3	8
BRCA2(M/F)	2/2	1/0	0/2	3	4
Mean age: years (SD)					
Male	33.5 (3.3)	33.5 (4.5)	32.9 (5.6)	33.3 (4.5)	
Female	31.8 (2.2)	32.3 (1.9)	31.6 (2.3)		31.9 (2.1)
Education					
Education middle (M/F)	2/0	1/1	3/1	6	2
Education high (M/F)	4/6	3/3	4/7	11	16
Religious (Christianity) (M/F)	1/3	0/0	1/2	2	5
Not religious (M/F)	5/3	4/4	6/6	15	13
Mean time interval (months) between counselling and interview (SD)	22 (18.6)	33 (18.4)	31 (9.8)	29 (15.6)	

PGD=Preimplantation genetic diagnosis; PND = Prenatal diagnosis; n=Number of couples. [a] Of one of these couples only the female partner participated in the interview; [b] Both women were treated for breast cancer before PGD counselling.

Difficulty with reproductive decision-making and support needs

All 18 couples experienced reproductive decision-making as complex and difficult to a certain extent, and two couples altered their initial choice. Couples were generally positive about reproductive counselling regarding the clinical and practical aspects that were discussed. In addition, they all expressed a need for support during decision-making and had received some - whether professional or social - support. Two couples (11%) indicated that they had not received the appropriate professional support during and after decision-making and still experienced adverse effects of this (e.g., feelings of doubt and/or guilt). Couples raised various aspects regarding their unmet needs for professional support during reproductive decision-making. One frequently discussed aspect was how to evaluate the available options regarding the desired family size one has in mind related to the time investment and chances of success. Another recurring topic was the lack of guidance on how to deal with the narrow time window for completing a family regarding the advised prophylactic surgeries for carrier women:

> *"I wanted to have my breasts and ovaries removed before I am 36. And then you start thinking: when do we want to have a child than? Because you don't want to do all that on the same day. So we started to calculate and realised that we should already initiate PGD or whatever we would choose, while we were actually not that into having babies yet …."*

Another repeatedly raised concern was the lack of support with the potential pressure on the partner relationship, as one woman who experienced PGD explained:

"Men and women can look so different at things emotionally. You go into that process together and you talk about it, but if your partner clings to a certain attitude and won't meet you half way or consider your feelings, you need help from outside."

An additional unmet support need was guidance on how to deal with the social environment after making a certain reproductive choice. This primarily concerned PND and subsequently PGD but also applied to deliberately pursuing a natural pregnancy for some couples. One woman who chose PGD said:

"But how do you explain this to other people who often know so little about it? I almost got into a fight with someone who kept saying I wanted an "überchild." It was hard to explain that it wasn't like this at all."

One woman who specifically indicated that she and her partner did not receive the appropriate psychological support during the decision-making process said:

"I missed the emotional and psychological support while trying to make a decision, also because the subject is so unknown. I eventually resorted to some online communities where similar subjects were discussed."

Although in general the guidance and support provided by the PGD physician (i.e., a clinical geneticist) were positively evaluated, couples repeatedly indicated a perceived lack of support from physicians who were indirectly involved in the reproductive trajectory:

"I noticed that if you talk to doctors who are not directly involved in PGD, they know very little about it, but despite that they often have personal ideas about it they want to project on you. During my last check-up after giving birth (PGD), I was asked by my gynaecologist if we chose to have a girl. I felt irritated by that and it would be nice if they knew a little more about it."

Ultimately, a majority suggested that the following decision support tools should be offered, in order of appreciation: (1) personal narratives of couples' experiences with reproductive decision-making and their chosen trajectory, (2) the opportunity to contact couples who are making a reproductive decision or have experienced one of the reproductive trajectories, (3) a consultation with a psychologist or social worker, and (4) a step-by-step decision-making tool such as a decision aid. The need to know about other couples' personal experiences was emphasized by a large majority. Most couples preferred these experiences to be provided in the form of written narratives, available to use in their private environment. However, many autonomously realized that these experiences are subjective and that caution should be taken particularly when reading very positive or negative stories.

Survey study

Participants' characteristics

The cross-sectional survey was completed by 86 participants (response rate: 33%). Among the 86 participants were 26 couples (n=52). For participants' characteristics, see Table 6.2. Only (borderline) significant results are described in this section. For a complete overview of the descriptive analyses, see Table S6.1. For a complete overview of the multivariate analyses, see Tables S6.2 and S6.3.

Table 6.2: Participants' characteristics (survey study).

	% (n)
Demographic factors	
Gender	
Male	38.4 (33)
Female	61.6 (53)
Age (years)	
Mean (SD)	33.5 (4.9)
Minimum	24
Maximum	55
Education	
Low (none or lower education)	3.5 (3)
Middle (middle education completed)	29.1 (25)
High (higher education completed)	67.4 (58)
Same partner as at PGD intake?	
No	9.3 (8)
Yes	90.7 (78)
Religious	
No	73.3 (63)
Yes	26.7 (23)
Ethnicity	
Dutch	98.8 (85)
Other	1.2 (1)
Clinical factors (carrier)	
Carrier status	
Carrier	68.6 (59)
Partner (50% male/50% female)	31.4 (27)
Mutation type	
*BRCA*1	53.5 (46)
*BRCA*2	46.5 (40)
Mastectomy	
No	77.9 (67)
Yes	22.1 (19)
Breast/ovarian cancer	
No	93 (80)
Yes	7 (6)
N of family members with cancer	
<3	45.7 (47)
≥3	45.3 (39)

Table 6.2: continued.

	% (n)
Reproductive factors	
IVF indication	
No	81.4 (70)
Yes	14 (12)
Children	
No	81.4 (70)
Yes	16.3 (14)
Child wish	
No	14 (12)
Yes	86 (74)
Reproductive choice	
Natural pregnancy	28.9 (24)
PGD	65.1 (54)
PND	6 (5)
Psychological factors (scale 1-5)	
Perceived risk HBOC	
Mean (SD)	3.7 (0.7)
Minimum	1.7
Maximum	5.0
Perceived seriousness HBOC	
Mean (SD)	4.0 (0.7)
Minimum	2.3
Maximum	5.0
Perceived controllability HBOC	
Mean (SD)	3.1 (0.7)
Minimum	1.5
Maximum	5.0

SD=Standard deviation; IVF=In vitro fertilization; HBOC=Hereditary breast and ovarian cancer caused by a *BRCA*1 or *BRCA*2 mutation; PGD=Preimplantation genetic diagnosis; PND=Prenatal diagnosis.

Difficulty decision-making

Forty-three percent experienced reproductive decision-making as (very) difficult, and 41% needed more than one month (up to more than one year) to make a final decision. Multivariate analyses showed that younger participants (P=0.042, β=−0.047, 95% CI, −0.091 to −0.002) and those who opted for a natural pregnancy (P=0.025, β=−0.560, 95% CI, −1.048 to −0.073) perceived decision-making as more difficult. A strong trend towards significance (P=0.059, β=0.263, 95% CI, −0.023 to 1.134) suggested that women who had undergone a mastectomy (68% prophylactic and 32% after breast cancer) and their partners had more difficulty with reproductive decision making.

Need for psychological support

Sixteen percent had needed psychological support during reproductive decision-making, and of those, 57% recalled that this support was offered. Of the total sample, 45% indicated that psychological support was offered, and of those, 33% was satisfied with what was offered. A majority (61%) believed that psychological support should be

routinely offered during the decision-making process, and 17% thought that a consultation with a psychologist or social worker should be obligatory. After making a reproductive choice, 13% was in need of (additional) psychological support and one participant (1%) experienced feelings of regret. Multivariate analyses showed that the need for psychological support was stronger among partners of carriers (P=0.038, odds ratio=0.168, 95% CI, 0.031-0.907), and a trend towards significance suggested that religious participants (P=0.089,odds ratio =4.171, 95% CI, 0.805-21.614) had a stronger need for psychological support.

Need for support tools

Of the practical support tools that were mentioned in the focus group study, personal narratives of couples' experiences were considered helpful by 51%, contact with couples in the same situation by 43%, a decision aid by 27%, and a consultation with a psychologist or social worker by 24%. A majority of 69% indicated that at least one of these support tools would have made their reproductive decision easier. Trends towards significance suggested that participants who perceived HBOC as more serious (P=0.074, β=0.341, 95% CI, −0.034 to 0.715) and those who opted for PGD or PND instead of a natural pregnancy (P=0.096, β =0.511, 95% CI, −0.093 to 1.116) were more in need of decision support tools.

Need for social support

Participants felt most supported by their family (69%), the Internet or other media (56%), and friends (47%). Almost half (45%) indicated that their reproductive choice was not influenced by anyone, closely followed by a group of 43% that indicated family had influenced their choice, while the Internet or other media had influenced the choice of 24%. One third (33%) indicated that their choice had been guided by a health professional.

Conclusions

Since reproductive decision-making is complex and highly preference sensitive for couples with HBOC, guidance and support should be attuned to their needs. The first (qualitative) part of this study showed that a majority of couples were positive about the current clinical and practical aspects that are discussed during reproductive counselling in the Netherlands, although their needs for support extend further. Nearly all couples indicated a need for additional support with emotional and social concerns in which their relationship, social environment, and the way they picture their desired family are key elements. In addition to professional support, couples showed a need for social support with their reproductive dilemma. This need appeared to be largely met by family

and friends. Previous literature shows that emotional support from family and friends is associated with lower psychological distress.[27] This could indicate that couples with an unsupportive or unreliable social network are more at risk for decisional conflict and might benefit from being offered additional support. Regarding decision support tools, access to personal narratives of other couples' experiences was most appreciated by couples. Although at present there is insufficient evidence about the effectiveness of personal narratives on informed decision-making and scientific guidance for a balanced presentation of these narratives is lacking, we should not ignore this need that has been raised before and further research on this topic is required.[28,29] Among couples who opted for PGD, a lack of support from involved professionals (other than the PGD physician) was experienced. Involved professionals should become better educated about PGD, especially since a previous study in the Netherlands showed that merely half of the professionals involved in reproduction and oncology is aware of PGD as a reproductive option for HBOC and their knowledge is limited,[30] while 66% of *BRCA* carriers and their partners are aware of PGD.[9]

The second (quantitative) part of this study showed that the need for professional guidance and support during reproductive decision-making can highly vary between couples with HBOC. Of those who needed psychological support, a little more than half recalled that this support was offered and one third was satisfied with what was offered. At the time these participants received reproductive counselling, policy was to routinely offer psychological support. Although the offered psychological support may have factually been higher because of recall bias, we should strive to adequately offer guidance and support in a way that all couples will positively evaluate this afterwards.

Younger couples experienced more difficulty with reproductive decision-making. This may be related to the fact that some couples are confronted with reproductive decision-making sooner than anticipated, due to the negative consequences of advised surgeries (prophylactic oophorectomy) on the reproductive life span of women with *BRCA*. The prematurity of their reproductive plans and/or possibly the early stage of their relationship may further complicate the decision-making process. The current study also suggests that women who had a mastectomy and their partners experience more difficulty with reproductive decision-making. Experience with (prophylactic) surgery is likely to increase the perceived severity of HBOC, which could increase the desire to prevent transmission and steer a couple towards PGD or PND. On the contrary, it has been shown that couples who have already undergone a severe medical trajectory are tired of medical interventions and have a desire to be “normal,” steering them more towards a natural pregnancy.[5] This paradox could result in decisional conflict or decisional regret and may be an indicator to be more alert when it comes to offering support to couples who have experienced medical intervention(s) due to HBOC. Moreover, partners of carriers were more often in need of psychological support during reproductive decision-making. This might be explained by the anticipation that partners are less familiar with HBOC and its possible consequences compared with their carrier partner. In addition, previous studies show that partners consider PGD and PND more

acceptable than *BRCA* carriers,[5,12,31] and the current study suggests that persons who opt for PGD or PND are more in need of decision support tools.
The borderline significant finding that religious couples are more in need of decision support probably reflects their ethical reservations towards selective reproductive techniques such as PGD and PND, which has been reported by prior studies.[3,32,33] Nevertheless, a higher need for psychological support implies that these couples may still want to consider these options and underlines the importance of providing them with adequate support to prevent feelings of guilt or regret due to either choice they make.
Furthermore, this study shows that couples who chose a natural pregnancy had more difficulty with reproductive decision-making than couples who opted for PGD or PND. A previous study by our research group showed that feelings of doubt or guilt that sometimes led to decisional regret were more common among couples who refrained from preventive reproductive options such as PGD and PND. [5] These couples must not be forgotten in terms of psychological support, both during and after the decision-making process. Since previous literature showed that negative feelings such as guilt, doubt, and regret reduce the likelihood of help-seeking from any professional source,[34-36] effective methods to reach these vulnerable subgroups should be further investigated.

Study limitations

The relatively small sample size of the survey study calls for caution with interpreting the (borderline) significant results, and further research among bigger sample sizes is required. Non responders could have different support needs from the sample presented here, and the retrospective design of the study may have caused recall bias. To our knowledge however, this is the first study to focus on reproductive decision support needs of couples with HBOC, and the use of mixed methods strengthens this study.

Clinical implications

Couples with HBOC who are facing a reproductive dilemma and are at risk for decisional conflict and its adverse psychological effects should be timely identified and provided with adequate guidance and support. This study suggests that persons at risk may be those of younger age, partners of carriers, religious persons, and couples who experienced a mastectomy. Moreover, couples who refrain from PGD or PND after having seriously considered one of these options should not be forgotten in the follow-up for psychological support. Since a clear standard care guideline for reproductive decision support is lacking, we should strive to develop one for couples with HBOC, which may also serve as a blueprint for other genetic indications. Although the results of this study would be a proper lead for such a guideline, further research is required to confirm and possibly add to these results considering the narrow focus of this topic in the existing literature.

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Supplementary material

Topic guide

Focus groups: support needs reproductive decision making

Welcome (15 min.)	Reception with coffee/tea etc. Complete questionnaire; recording: Demographics: age, gender, educational level, employment, marital status, religion Reproductive and genetic history Status reproductive trajectory
Background information about the study (5-10 min.)	Introduction moderator Purpose and setup of the focus group How will the data be used? What is expected of the participants? Explanation and permission audio-taping Questions?
Opening question: introduction round (10 min.)	*Please tell us who you are, where you are from and in which phase of the reproductive trajectory you are* (i.e. on waiting list, preparation phase, treatment phase (completed), and if completed was treatment successful?).
Introducing question (5 min.)	*How did you become aware of PGD and/or other reproductive options?*
Break (10 min.)	
Main questions information and support needs (30 min.)	*How difficult was it for you to make a reproductive choice?* *Did you need (psychological) support during the reproductive decision-making process and was this need fulfilled?* *By whom did you feel supported during the decision-making process?* *Can you think of any decision support tools that could have made it easier to make a reproductive decision? (e.g. a decision aid)* Expectations regarding reproductive information provision and counselling: *which topics should be discussed according to you?* *To what extend have these topics been discussed?* [evaluation of received counselling] *Which topics were not discussed, but should have been discussed according to you?* *When would you have preferred to receive information about these topics?* [potentially make scheme/flowchart to indicate phases] *If it was up to you to decide on the content of reproductive counselling, what should remain the same and what should be changed* (suggestions for improvement)?

	If it was up to you to determine what professional (psychological) support during reproductive decision-making should look like, what should remain the same and what should be changed (suggestions for improvement)?
Conclusion of focus group (5-10 min.)	Moderator summarizes *Do you have remarks or additions to this summary?* *We are going to conclude now. I would like to know what you think about/how you experienced this focus group session.* *Are there any topics we have not discussed, which you think are important to mention?*

Main questionnaire items (survey study)

Questionnaire items	Answer options
Perceived difficulty of the reproductive decision-making process	
How difficult did or do you think it is to make a reproductive choice?	Very easy (1) – Very difficult (5)
How much time did you need to make a reproductive choice?	Less than one week (1) – More than one year (5) / Not applicable, we did not yet decide (6)
Need for psychological support **Note added to each of the following questions: *with psychological support we mean a consultation with a psychologist or a social worker.***	
Did you need psychological support during your reproductive decision-making process?	No (0) / Yes (1) / I don't remember (2)
Was psychological support offered to you after reproductive counselling?	No (0) / Yes (1) / I don't remember (2)
Were you satisfied with the psychological support that was offered?	No (0) / Yes (1) / Not applicable, I did not make use of this (3)
Do you think that psychological support should be routinely offered after reproductive counselling?	No (0) / Yes, should be offered (1) / Yes, should be obligatory (2) / I don't know (4)
Did you need psychological support after you made your reproductive choice?	No (0) / Yes (1) / Not applicable, I did not make a choice yet (2)
Did you ever experience feelings of regret after making your reproductive choice?	No (0) / Yes (1) / Not applicable, I did not make a choice yet (2)
Need for reproductive decision support tools **Last 3 items recoded into a scale (Cronbach's α: 0.784). First item excluded from scale since this is one of the main outcomes (need for psychological support).**	
Please indicate which of the following tools could have made your decision regarding PGD easier.	
A consultation with a psychologist or a social worker	Definitely not (1) – Definitely (5)
Written personal narratives about PGD	Definitely not (1) – Definitely (5)
Personal contact with couples who are facing the same dilemma	Definitely not (1) – Definitely (5)
A decision aid	Definitely not (1) – Definitely (5)
Social support	
By whom or what source did you feel supported during reproductive decision-making? (more than one answer possible)	Nobody / family / friends / colleagues / the internet or other media / psychologist / other health practitioner / social worker / other patients / other…
Who or what source influenced your reproductive choice?(more than one answer possible)	Nobody / family / friends / colleagues / the internet or other media / psychologist / other health practitioner / social worker / other patients / other…

Perceived risk of HBOC **6 items recoded into a scale (Cronbach's α: 0.909)**	
The risk that someone with a *BRCA*-mutation transmits this mutation to his/her child is 50%. I think this risk is…	Very low (1) – very high (5)
The risk that someone with a *BRCA*-mutation has a daughter with this mutation is 25%. I think this risk is…	Very low (1) – very high (5)
If we would do nothing to prevent that our child inherits the *BRCA*-mutation, I feel that the chance that our child gets breast cancer is…	Very low (1) – very high (5)
If we would do nothing to prevent that our child inherits the *BRCA*-mutation, I feel that the chance that our child gets ovarian cancer is…	Very low (1) – very high (5)
How likely do you think it is that your child will have breast cancer if you would do nothing to prevent that your child inherits the *BRCA*-mutation?	Very unlikely (1) – very likely (5)
How likely do you think it is that your child will have ovarian cancer if you would do nothing to prevent that your child inherits the *BRCA*-mutation?	Very unlikely (1) – very likely (5)
Perceived seriousness of HBOC **4 items recoded into a scale (Cronbach's α: 0.813)**	
How serious would it be to you if your child would inherit the *BRCA*-mutation?	Not serious at all (1) – very serious (5)
If my child would inherit the *BRCA*-mutation, this would change his/her entire life…	Strongly disagree (1) – strongly agree (5)
If my child would get breast cancer, this would change his/her entire life…	Strongly disagree (1) – strongly agree (5)
If my child would get ovarian cancer, this would change his/her entire life…	Strongly disagree (1) – strongly agree (5)
Perceived controllability of HBOC **4 items recoded into a scale (Cronbach's α: 0.610)**	
There are good preventive possibilities to protect someone with a *BRCA*-mutation from getting breast cancer…	Strongly disagree (1) – strongly agree (5)
There are good preventive possibilities to protect someone with a *BRCA*-mutation from getting ovarian cancer…	Strongly disagree (1) – strongly agree (5)
There are good possibilities to cure breast cancer…	Strongly disagree (1) – strongly agree (5)
There are good possibilities to cure ovarian cancer…	Strongly disagree (1) – strongly agree (5)

HBOC=hereditary breast and ovarian cancer; PGD=preimplantation genetic diagnosis.

Table S6.1: Support needs during reproductive decision-making (survey study)

	Unless indicated otherwise: % (n)		
Perceived difficulty of the reproductive decision-making process			
Difficulty making choice (scale 1-5)			
Mean (SD)		3.2 (1.3)	
(very) easy		30.3 (26)	
Not easy, nor difficult		26.7 (23)	
(very) difficult		43.0 (37)	
Time needed for making choice (scale 1-5)			
Mean (SD)		2.5 (1.3)	
<1 week		29.1 (25)	
>1 week – 1 month		26.7 (23)	
>1 month – 6 months		24.4 (21)	
>6 months – 12 months		12.8 (11)	
>12 months		3.5 (3)	
N.a. (not yet decided)		3.5 (3)	
Need for psychological support (consultation with psychologist or social worker)			
During reproductive decision-making			
Need psychological support?		Psychological support offered? / Only those in need of psychological support	
No	81.4 (70)	No	24.4 (21) / 21.4 (3)
Yes	16.3 (14)	Yes	45.3 (39) / 57.1 (8)
Don't remember	2.3 (2)	Don't remember	30.2 (26) / 21.4 (3)
Satisfied with psychological support? (for those who was offered psychological support: 45.3% n=39)		Should psychological support be routinely offered?	
No	2.6 (1)	No	17.4 (15)
Yes	33.3 (13)	Yes, offered	60.5 (52)
N.a. (not used)	64.1 (25)	Yes, obligatory	17.4 (15)
		I don't know	4.7 (4)
After reproductive choice			
Need for psychological support?		Experience(d) feelings of regret?	
No	73.3 (63)	No	83.7 (72)
Yes	12.7 (11)	Yes	1.2 (1)
N.a. (no choice yet)	4.0 (12)	N.a. (no choice yet)	15.1 (13)
Need for reproductive decision support tools (scale 1-5)			
Access to written experiences of other couples		Personal contact with comparable couples	
Mean (SD)	3.3 (1.2)	Mean (SD)	3.0 (1.2)
(definitely) no	25.6 (22)	(definitely) no	40.7 (35)
(definitely) yes	51.1 (44)	(definitely) yes	43.0 (37)
Unsure	23.3 (20)	Unsure	16.3 (14)
Conversation with psychologist/social worker		Decision aid	
Mean (SD)	2.7 (0.9)	Mean (SD)	2.7 (1.1)
(definitely) no	46.5 (40)	(definitely) no	46.5 (40)
(definitely) yes	24.4 (21)	(definitely) yes	26.8 (23)
Unsure	29.1 (25)	Unsure	26.7 (23)
Need for at least one of four tools mentioned above		68.6 (59)	
Social support		Supported by	Choice influenced by
Nobody		7.0 (6)	45.3 (39)
Family		68.6 (59)	43.0 (37)
Friends		46.5 (40)	18.6 (16)
Colleagues		17.4 (15)	5.8 (5)
Internet/other media		55.8 (48)	24.4 (21)
Health professional		79.1 (68)	32.6 (28)
Psychologist/social worker		11.6 (10)	4.7 (4)
Geneticist		29.1 (25)	10.5 (9)
Other health practitioner		38.4 (33)	17.4 (15)
Fellow sufferers		9.3 (8)	4.7 (4)

SD=Standard deviation.

Table S6.2: Multivariate analyses for difficulty decision-making and need for decision-making tools (linear regressions)

	Difficulty reproductive decision-making			Support need (decision-making tools)		
	β	95% CI	P	β	95% CI	P
Demographic factors						
Gender			n.s.			n.s.
Age	**-0.047**	**-0.091- -0.002**	**0.042**			n.s.
Education			n.s.			n.s.
Same partner as at counselling (yes/no)			n.s.			n.s.
Religious (yes/no)			n.s.			n.s.
Clinical factors						
Carrier status (carrier/partner)			n.s.			n.s.
Mutation type (*BRCA*1/2)			n.s.			n.s.
Mastectomy (yes/no)	*0.263*	*-0.023-1.134*	*0.059*			n.s.
Number of family members with breast/ovarian cancer (<3/≥3)			n.s.			n.s.
Reproductive factors						
IVF indication (yes/no)			n.s.			n.s.
Children before reproductive counselling (yes/no)			n.s.			n.s.
Reproductive choice (NP vs. no NP)	**-0.560**	**-1.048- -0.073**	**0.025**	*0.511*	*-0.093-1.116*	*0.096*
Psychological factors						
Need for psychological support	**0.700**	**0.173-1.228**	**0.010**			
Risk perception HBOC			n.s.			
Perceived seriousness HBOC			n.s.	*0.341*	*-0.034-0.715*	*0.074*
Perceived controllability HBOC			n.s.			
Model R^2		**34.4%**			**20.4%**	

β=regression coefficient; 95% CI=95% Confidence Interval; P=value of significance. **Bold=significant (P<0.05);** *Italic=trend towards significance (P=0.05-0.10);* IVF=In vitro fertilization; HBOC=Hereditary breast and ovarian cancer caused by a *BRCA*1 or *BRCA*2 mutation; NP=Natural pregnancy without genetic testing.

Table S6.3: Multivariate analyses for psychological support need (logistic regression).

	Need for psychological support		
	OR	95% CI	p
Demographic factors			
Gender			n.s.
Age			n.s.
Education			n.s.
Same partner as at counselling (yes/no)			n.s.
Religious (yes/no)	*4.171*	*0.805-21.614*	*0.089*
Clinical factors			
Carrier status (carrier/partner)	**0.168**	**0.031-0.907**	**0.038**
Mutation type (*BRCA*1/2)			n.s.
Mastectomy (yes/no)			n.s.
Number of family members with breast/ovarian cancer (<3/≥3)			n.s.
Reproductive factors			
IVF indication (yes/no)			n.s.
Children before reproductive counselling (yes/no)			n.s.
Reproductive choice (NP vs. no NP)			n.s.
Psychological factors			
Risk perception HBOC			n.s.
Perceived seriousness HBOC			n.s.
Perceived controllability HBOC			n.s.
Model R^2		**57.7%**	

OR=Odds ratio; 95% CI=95% Confidence interval; P=value of significance; **Bold=significant (P<0.05);** *Italic=trend towards significance (P=0.05-0.10);* n.s.=not significant; IVF=In vitro fertilization; HBOC=Hereditary breast and ovarian cancer caused by a *BRCA*1 or *BRCA*2 mutation; NP=Natural pregnancy without genetic testing.

Part IV

Addenda

Chapter 7

General discussion

General discussion

In the past decade, preimplantation genetic diagnosis (PGD) became available for couples with hereditary cancer in several countries around the globe. In particular, PGD for hereditary breast and ovarian cancer (HBOC) is regularly asked, presumably related to its high population frequency. HBOC is caused by a mutation in the *BRCA1* or *BRCA2* gene. Since HBOC was added to the list of approved indications for PGD, it has been one of the most frequently requested indications in the Netherlands,[1] where it has been evaluated as a suitable strategy for couples wanting to avoid transmission of HBOC.[2] In addition to the new possibilities PGD created, it may have complicated reproductive decision-making for couples with HBOC. Given the late onset, incomplete penetrance and preventive possibilities of HBOC in relation to the possibly high burden of the disease, the decision whether or not to interfere in the natural reproductive process in order to prevent transmission is often described as complex.[3-7] Even though PGD may seem like an ideal option from a moral point of view, this strategy entails many physical, practical, psychological, moral and social aspects that require couples' careful deliberation. The aim of this dissertation was to provide more insight into couples' and professionals' awareness and knowledge, and couples' decision-making process regarding PGD. We have strived to improve our understanding of this unique patient group's perspective in an effort to enable adaptation of educational and support practices to characteristics, needs and wishes of these couples. This final chapter places results of the studies into perspective and provides implications for practice and future research.

This chapter broadly outlines: 1) the process of **informed reproductive decision-making**, from the counselee's perspective and the professional's perspective 2) couples' main **thought processes and the psychosocial consequences of PGD decision-making**, 3) couples' **support needs** and 4) **future perspectives and opportunities for research.**

Informed decision-making in the context of unique reproductive concerns

A unique patient group

Reproductive decision-making is a process not to be taken lightly since it may extensively impact current and future wellbeing of individuals and families. After PGD became available for HBOC in 2008, an increasing number of couples with HBOC started to find their way to the PGD outpatient clinic of the Maastricht UMC+. It was noticed that many of these couples struggled with deciding whether or not to opt for PGD and several altered their initial reproductive choice. This gave rise to a study investigating their motives and considerations in reproductive decision-making. The results taught us that couples with HBOC are an exceptional group with unique reproductive concerns (**chapter**

4). First of all, the characteristics of HBOC (i.e. late onset condition with incomplete penetrance for which preventive and therapeutic options are available) have raised ethical reservations towards the application of prenatal diagnosis (PND) and PGD among critics but also among potential users. Moreover, implications of HBOC significantly differ between males and females since male carriers only have a slightly increased risk of developing cancer compared to female carriers.[8,9] However, during PGD for HBOC, also male carrier embryos are discarded in an already strict process of elimination, as general regulations for good clinical practice disallow transferring an affected embryo. While this is a disadvantage of PGD for some couples, it is an advantage for others who want to wipe out the mutation in their family line or protect a potential son from having a similar reproductive dilemma in the future. In addition, for female carriers the advised risk reducing surgeries (i.e. removing breasts and ovaries before a certain age) can result in a narrow time window for family planning. For PGD, a genetic work up that takes several months and possibly more than one IVF treatments are needed, causing it to be a time consuming trajectory. Finally, the literature suggests that a *BRCA1/2* mutation may have a negative influence on a female's ovarian reserve which would reduce the chance of a successful PGD treatment for female carriers.[10-13] This illustrates the complexity of reproductive decision-making for couples with HBOC, and adverse psychological effects like feelings of doubt and guilt are not uncommon among parents with a genetic susceptibility.[14,15] Currently, the three most popular reproductive options for couples with HBOC respectively are: a natural pregnancy without genetic testing, PGD and PND. Alternative options such as using donor gametes, adoption or refrain from having children are rarely opted for (chapter 2). It is important that couples with HBOC make an informed reproductive decision. Informed decision-making has a beneficial effect on psychological management by means of lowering decisional conflict and increasing personal wellbeing and decisional satisfaction.[16-18] In order to facilitate this, information about reproductive options aimed at reaching all eligible couples and appropriate decision support should be provided. Becoming aware of one's options and gaining knowledge about these options are the first steps towards contemplating about their advantages and disadvantages, which is imperative for making an informed and personally best suitable choice.

The counselee's perspective

Awareness of PGD for HBOC

We found that awareness and acceptability of PGD are high in the Netherlands compared to other countries (chapter 2). Internationally, awareness and personal consideration to use PGD for HBOC have increased over the years,[7,19-21] while the acceptability of offering PGD for HBOC has been relatively high from the beginning.[4,5,7,19] Awareness of PGD was higher among couples with an actual or urgent child wish, and

among higher educated carriers and partners (chapter 2). The latter finding is in line with previous research,[19] that additionally reported that lower educated persons are less likely to be referred for cancer genetic counseling.[22] This may be partly explained by the patient's behavior since health information seeking behavior appears to be positively related to socioeconomic status.[23,24] Lower educated individuals may therefore be less knowledgeable about their medical options which decreases the likelihood that they will initiate their own referral. It has been shown that patients' initiative is important in the referral process and asking questions about genetic testing increases the likelihood of being referred for genetic counseling.[25,26] On the other hand, the importance of oncologists' behavior in the genetic testing process has been emphasized, since a lack of physicians' recommendation is the primary reason for not testing reported by high risk patients.[27] This also adversely affects the awareness of available reproductive techniques such as PGD and may explain why lower educated individuals are less likely to be aware of and referred for PGD. This suggests disparities in cancer genetic counseling resulting in suboptimal care for vulnerable subgroups. In general, it is undesirable that socioeconomic factors may determine the access to medical treatments such as PGD. Potential referrers play a significant role in this process and should therefore be educated about reproductive options that can prevent transmission of a serious genetic condition. In order to reach eligible individuals and couples, clinical geneticists should share their knowledge about PGD with possible referring specialists. In addition, it might be effective to incorporate a standard text about reproductive options in the patient/family letter when a *BRCA1/2* mutation is found.

PGD acceptability and general misconceptions

Persons with more knowledge of PGD were found to be more likely to consider PGD for HBOC acceptable (chapter 2). In the public debate PGD is sometimes associated with creating designer babies, generating misconceptions about this reproductive technique.[28-31] Due to the commonly displayed stereotype of runaway technology with a slippery slope, persons with little knowledge about PGD may believe that the selection of embryos is not solely focused on a serious genetic condition but may additionally be used to select gender or esthetical traits. Hence, more knowledge about the actual possibilities and limitations of PGD generally leads to more acceptability.

Nevertheless, these general misconceptions about PGD are not completely unfounded since gender selection under the premise of family balancing is currently being offered by private PGD clinics in Cyprus, the USA, Mexico and India. These countries have no PGD regulations and access to PGD depends on couples' financial resources. In most European countries however, PGD is regulated by law while it is prohibited in some. In the Netherlands, PGD is allowed for a number of serious genetic disorders and requests for new indications have to be approved by a multidisciplinary national indication committee. For couples who received information about PGD during a consultation at

our outpatient clinic, the debate regarding creating designer babies did not seem to play a significant role in their decision (chapter 3). When those who refrained from PGD were asked about their reasons, ethical concerns regarding a slippery slope were mentioned in passing, if at all. Similar findings have been reported previously.[32]

From acceptability to personal consideration to use PGD

The acceptability of offering PGD for HBOC vastly exceeded couples' personal consideration to use PGD (chapter 2). This finding has been reported internationally.[4,7,20,21,33,34] In addition, the hypothetical intention to pursue PGD is also higher among those not planning a future pregnancy.[20,34] At the PGD outpatient clinic of the Maastricht UMC+, about half of the couples with HBOC proceeds with PGD after their intake consultation.[1] Many couples come in with a simplified impression of PGD as the ideal reproductive option and are thrown by its actual implications. In chapter 2 couples who refrained from PGD clarified that PGD initially seemed like the ideal reproductive option, especially from a moral point of view, considering that transmission of HBOC can be prevented for their child without having to risk a termination of pregnancy (TOP). However, after receiving complete information about all its implications they encountered unexpected disadvantages that also made them view PGD as a physically and psychologically burdensome, time consuming treatment with a relatively low chance of success compared to a natural pregnancy (chapter 4). Furthermore, the hypothetical intention to use PGD for another serious genetic condition than HBOC was significantly higher for these couples (chapter 2) illustrating their ethical reservations towards PGD for HBOC. For the couples who opted for PGD, it was the only suitable reproductive option, since they were not ready to gamble with pursuing a natural pregnancy nor willing to terminate a pregnancy because of HBOC (chapter 4).

Incorporating male carriers and partners views in reproductive counseling

Until recently, males' views regarding PGD for HBOC have been underrepresented in the literature. Male carriers and partners may have a different perception of reproductive possibilities to prevent transmission of the mutation, since they do not personally have to undergo the treatment. A cross sectional study conducted in 2012 observed a higher acceptability of TOP among male *BRCA* carriers compared to female carriers.[20] Moreover, female carriers indicate that their partners have a substantial voice in deciding which reproductive path to follow.[20] Therefore, it is important to incorporate the male perspective in reproductive counseling. Chapter 2, 4 and 5 are three of the few

studies that investigated the views of male carriers and partners of female carriers.[20,35] Previous literature suggests that male *BRCA* carriers would tend to have a more passive approach towards information seeking and genetic risk reduction compared to females.[36] Nevertheless, feelings of guilt for possibly passing on the mutation to their child(ren) have also been reported among male *BRCA* carriers.[37,38]
Aside from the notion that male carriers experience feelings of guilt and helplessness as their partners would have to undergo a burdensome treatment like IVF/PGD to prevent transmission of the mutation to their child (**chapter 2**), we did not detect any gender differences in our studies. Levels of awareness, knowledge and acceptability of PGD did not differ between male and female participants, nor did their motives and considerations to opt or refrain from PGD (**chapter 2, 4 and 5**).

The professional's perspective

Health professionals play an important role in stimulating awareness about PGD, as a majority of couples with HBOC prefers to receive their primary information from a physician, preferably a genetic counselor (**chapter 6**).[39]

Awareness, attitude and referral behavior

In the Netherlands, half of the professionals involved in the care of persons with HBOC (clinical geneticists, genetic counselors, oncologists, gynecologists and fertility physicians) is aware of PGD as a reproductive option and a majority indicates a need for additional education about PGD (**chapter 3**). Compared to other countries, the awareness and acceptability of PGD for HBOC is high among professionals (**chapter 3**).[43,41] Acceptability strongly varies between countries. Professionals' acceptability of PGD for hereditary cancer syndromes has been low in France,[42] variable in the USA[26,41,43] and dependent on family and reproductive history in several European countries.[44] **Chapter 3** shows that PGD for HBOC is more often accepted by male professionals and those who are more knowledgeable about PGD. Religious professionals are less likely to consider PGD for HBOC acceptable. Professionals with more knowledge about PGD were more likely to refer for PGD (**chapter 3**). A large majority of health professionals indicated that they would refer an eligible couple with HBOC for PGD, while only a minority acted on this intention. This referral gap has previously been reported[40] and may partially be caused by a limited encounter of eligible patients who are willing to consider PGD leaving little opportunity to refer for PGD. However, this can only partially explain the observed referral gap and existing literature suggests that it is additionally related to the fact that possible PGD indications and referral routes are not always clear

to professionals (chapter 3) and to their lack of confidence in answering patients' basic questions about PGD.[26] As mentioned before, referral for genetic testing is often initiated by the patient. Therefore it is important to increase awareness about PGD among both *BRCA* carriers and their physicians in order to simulate patient-doctor communication about this topic.

The current and prospective situation

Internationally, health professionals' knowledge about PGD for genetic cancer syndromes has shown to be limited.[26,40-42] It would not be practical nor realistic to expect all health professionals to have detailed knowledge about something as specialistic as PGD. It is important however, that professionals involved in the care of persons with HBOC can identify and refer those who may benefit from PGD. In this respect, substantial gains can be made (chapter 3). In the Netherlands and other countries where PGD for HBOC is available, continuing medical education is needed to support providers in facilitating informed decisions regarding PGD. This is also stressed by other studies conducted in the USA.[45,46] Health professionals are an important gateway to awareness and knowledge about PGD. This does not merely apply to PGD but also to genetics in general. Houwink (2013) suggests that improvements in genetics education are needed to prepare primary care providers for the impact of ongoing rapid advances in genomics. Especially general practitioners acknowledged the importance of genetics education and emphasized their perceived knowledge deficiencies.[47] Based on Houwink's research, continuing professional development (CPD) modules were developed and offered on a specific website that provides information about genetics for general practitioners (www.huisartsengenetica.nl). This website also provides basic information about PGD. It is important to keep the provided information on PGD indications up to date and optimizing triage to genetic counsellors should have priority. Another possibility to increase knowledge on PGD is to address PGD already at time of HBOC diagnosis, and to include the relevant information in the letter for their involved family members.

Thought processes and psychosocial consequences of PGD decision-making

Motives and considerations to opt for or refrain from PGD

Reproductive decision-making is complex for couples with HBOC; and almost half of these couples experienced this process as (very) difficult (chapter 4). Feelings of internal conflict and guilt may arise, particularly among couples who opt for a natural pregnancy without genetic testing. Chapter 2 provides insight into the transition of PGD consideration to actual PGD use. Couples who opted for and who refrained from PGD

generally considered this as a treatment with a few important advantages and several less significant disadvantages. Overall, couples mentioned the same motivational domains, regardless of their decision. The decision-making process generally started with weighing the perceived seriousness of HBOC. In this stage, the couples' personal and family history of cancer and their reproductive history played an important role. This is in concordance with the existing literature stating that personal and family history of cancer have a significant impact on reproductive decisions, contributing to perceptions of risk, controllability and severity.[48] Based on the perceived seriousness of HBOC, couples decided if intervening in the natural reproductive process in order to prevent transmission to their future child is justified. Subsequently, they started weighing the identified pros and cons of PGD resulting in a decision in favor of or against using PGD.
The most frequently mentioned negative aspects of a PGD treatment were the physical and psychological burden, the long duration of the trajectory in combination with the relatively low success rate, the artificial way of conception in which the traditional sense of romance is lost, and the moral aspect of discarding embryos that can potentially develop into children who may lead a happy, healthy life in the context of HBOC (**chapter 4**). Considering the possible reluctance to use PGD due to the artificial way of conception it is worth noting that families with children born from PGD are found to have a higher affection toward each other than families with natural born babies.[49,50] This may be contributed to these couples' increased effort and awareness regarding conceiving a healthy child. Alternatively, this observation could origin from the communicative and emotional skills PGD parents pass on to their children, implying that couples who opt for PGD are more likely to possess certain characteristics. More insight in the latter suggestion requires further research.

Motivational domains

Motives and considerations in PGD decision-making could be classified into a physical, psychological, moral, practical and social domain **(chapter 4)**. The most frequently reported motive to opt for PGD was the desire to prevent HBOC and its related cancer risk in a future child, without having to risk a TOP **(chapter 2)**. Moral motives were the most influential in refraining from PGD and were mainly focused on the perceived seriousness of HBOC. Examples are the belief that a *BRCA* carrier can live a good life, ethical objections towards discarding embryos, and being confident that preventive and treatment options will significantly improve before the child reaches the age at which hereditary breast or ovarian cancer can develop. Meanwhile, the main underlying reason to opt for PGD was the perceived seriousness of HBOC as well.
Hopes and beliefs for future medical advancements played an important role for couples who refrained from PGD **(chapter 4 and 5)** as is underlined by previous literature.[48,51,52] These beliefs are not unjustified as in the last decade significant advances have been achieved in the cure and care for *BRCA* mutation carriers.[53-55] Although practical and

social aspects regarding PGD, such as time investment, numerous hospital visits, informing employers, potential negative impact on relationship with partner, and possible judgmental opinions from the social environment, were generally not decisive couples emphasized the need for support in coping with these aspects **(chapter 4 and 5)**. Therefore, some couples will probably benefit from psychological support with these practical and social issues, during reproductive decision-making and while undergoing the chosen reproductive trajectory.

The technological imperative

Chapter 4 shows that a significant number of couples opts for PGD due to a certain perceived moral obligation to do everything in their power to protect their future child from an increased cancer risk. If PGD would not be successful they had already decided to pursue a natural pregnancy expecting to be reassured by the fact that they had at least tried PGD. This may be the technological imperative at work, meaning that new technologies are inevitable and essential and that they must be developed and accepted for the good of society. In this case it refers to the perceived (moral) responsibility to use, or at least consider using PGD because it would seem morally unjustified to reject. It encourages the individual to contemplate potentially conflicting ethical views of 'what is the right thing to do' between themselves and significant others. *BRCA* carriers and couples have repeatedly reported this pervasive moral sense of responsibility towards others.[36,48] A previous study among *BRCA* carriers showed that the most frequently reported psychological concern was a perceived responsibility to utilize PGD and other technologies to reduce proliferation of their mutation. The majority of women agreed that even if PGD was not pursued, there was an implied responsibility to at least consider the options.[48] Another study showed that 38% of female *BRCA* carriers felt that not testing embryos would be irresponsible.[6] In this respect, counselors need to be aware of the fact that couples' autonomy in reproductive decision-making may be compromised due to a possibly experienced societal pressure.

Support needs

Current counseling

Counseling of *BRCA* mutation carriers is typically focused on risk-reducing strategies and cancer prevention. However, for men and women of reproductive age, counseling should extend to a possible child wish and reproductive issues. In this respect, timing of pregnancy, use of artificial reproductive techniques and if applicable, fertility preservation should be discussed.[33] We evaluated current reproductive counseling at the Maastricht UMC+ PGD outpatient clinic and outcomes were positive regarding its

clinical and practical aspects. Nevertheless, a majority indicated a need for additional support. Couples mentioned several emotional and social concerns in which their relationship, social environment, and the way they envisage their desired family were key elements (**chapter 6**). For example, couples who would like to have more children expressed difficulty to commit to PGD, given its limited chance of success compared to a natural pregnancy. If the treatment would only succeed for part of their desired children, it would be extremely difficult to make a morally less reassuring choice for the next child. Regarding the social environment, couples generally sought guidance with how to explain their reproductive choice to their friends and relatives and in addition to their future children. Moreover, couples repeatedly emphasized a need for support to deal with the potentially negative impact of the decision-making process and the PGD trajectory on their relationship. Carriers and partners of carriers can have different views regarding HBOC and the prevention of its transmission which complicates reproductive decision-making. Partners of carriers are more likely to consider PGD and PND as acceptable reproductive options (**chapter 2**)[20] and report a higher need for psychological support during reproductive decision-making (**chapter 6**). Previous qualitative studies have described the quandary of carriers who wish to prevent further transmission of their genetic mutation but at the same time, when considering prenatal testing or embryo selection, feeling guilty about denying themselves and family members with the mutation the right to live.[56,57] This suggests that certain subgroups of couples may benefit from additional decision support by a psychologist or social worker, aimed at reducing or preventing personal and intra-relational decisional conflict and consequent negative psychological impact.

Timing of information provision

A large majority of couples with HBOC believes that information about PGD should be provided to *BRCA* carriers, primarily by their genetic counselor (**chapter 6**; unpublished data). This is in concordance with existing literature.[36,39] With such a large percentage of *BRCA* carriers noting the importance of receiving information regarding PGD, we need to determine when and how the information about PGD can be optimally provided during the trajectory of HBOC diagnosis and counselling. Although some literature indicates that a majority of *BRCA* carriers expects information regarding reproductive options along with a positive genetic test result,[20,48] it must be taken into account that young female *BRCA* carriers are often overwhelmed when their carrier status is disclosed. The provision of PGD information during genetic counselling is generally viewed as valuable, but also potentially demanding of patients' cognitive and psychological resources. It requires a comprehension of medical technicalities and presents a set of ethically and emotionally charged decisions to be made on top of those patients were already making regarding testing and risk management. In addition, it has been reported that counselees are better able to process *BRCA*-related information after having had time

for reflection, which corresponds with studies indicating that for most people, distress levels after testing decrease over time.[58,59] Although risk management does not apply to male carriers, they have an equal risk of passing on the mutation to their offspring and are therefore in equal need of reproductive counselling. This complexity, plus the highly technical nature of PGD, makes it difficult to integrate PGD information into genetic counselling sessions that already cover probabilistic, emotionally charged risk information. This calls for phased information provision when it comes to reproductive options. During a positive *BRCA* test disclosure the counselee should at least be made aware of reproductive options that can prevent HBOC. The appropriate timing of more detailed information provision mainly depends on the existence and urgency of a child wish. The existing literature articulates a tension between cancer risk management (i.e. preventive surgeries) and life goals (e.g. having children.[48,60,61] As female *BRCA* carriers may experience an urgency to have children, they sometimes consider delaying their preventive surgeries in order to have children even at the expense of their own cancer risk.[51] This shows that the decisions regarding risk management and family planning often go hand in hand. As patients' characteristics and personal preferences differ, there may be a role for the counsellor to generate a customized plan for phased information provision featuring the counselee (Woodson et al., 2014; Hurley et al., 2012).[34,45]

Form of information provision

Another significant aspect to consider is the shape or form in which the information and decision support about PGD should be provided. Making a reproductive choice 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. A decision aid can be offered which should include information about alternative options and ideally incorporates questions and possible answers to clarify personal values. Compared to usual care interventions, decision aids have been found to improve persons' knowledge regarding their options, reduce decisional conflict, and decrease the amount of persons remaining undecided.[62,63,64] Incorporating a patient decision aid in reproductive counselling can therefore be helpful in reducing adverse psychological effects of reproductive decision-making. Moreover, as the ideal timing and setting for reproductive counselling is likely to be subjective, it may be an advantage that a decision aid can be used at the time and place of the counselee's preference. The first decision aid concerning reproductive decision-making for couples with hereditary cancer has recently been developed by our research team.[65] The decision aid was developed according to the International Patient Decision Aids Standards (IPDAS) in collaboration with relevant health care providers and couples at risk for hereditary cancer planning to have children. In addition to information about reproductive options, it incorporates probabilities of different outcomes and value clarification exercises (VCE) which can be linked to the partner's outcome to be compared and subsequently discussed in order to

facilitate joint decision-making. A pretest-posttest evaluation of the decision aid showed a reduction in decisional conflict, increased levels of knowledge and improved realistic expectations. Moreover, level of deliberation and decision self-efficacy improved for those with low baseline levels.[66] These findings support the use and continued optimization of decision support tools in reproductive counselling of couples with hereditary cancer. It is advised to provide this form of decision support in addition to general counselling. To attain its most effective and efficient use, the decision aid should be offered before the doctor-patient consultation, ideally resulting in a prepared couple with basic knowledge and defined remaining questions and personal concerns.

Personal narratives

The most frequently reported need for reproductive decision support by couples with HBOC was the need to learn about other couples' experiences with reproductive decision-making and their chosen reproductive path (**Chapter 6**). Couples preferred these experiences to be provided in the form of narratives, available to use in their private environment. However, as these narratives are based on personal experiences, they are subjective and caution should be taken particularly when incorporating very positive or negative stories in decision-making. Although at present there is insufficient evidence about the effectiveness of personal narratives on informed decision-making and scientific guidance for a balanced presentation of these narratives is lacking, we should not ignore this need that has been raised before.[67,68] Further research on this topic is required.

Limitations

The results, suggestions and recommendations presented in this dissertation should be regarded in the light of potential limitations. Particularly the relatively small sample sizes of the conducted studies call for caution with the interpretation and generalization of results. Since PGD is generally applied to prevent relatively rare genetic conditions, it is challenging to conduct research in this field among large sample sizes. Although the current study samples may be limited in size, we do not have any indications that they are not representative of the overall Dutch target group. We found that our target group of carriers and partners were overall very responsive and willing to participate in our studies, though it is possible that those who did not respond or declined to participate were individuals who had less interest in PGD. Moreover, the current results should be viewed in light of the retrospective design that was used in most studies and the possible resulting recall bias. More reliable results would be generated using a longitudinal study design with the follow up of couples during their reproductive

decision-making process. However, this process can be lengthy and may take several months to years. This would require a large scale and longitudinal study setup. The studies presented here can be viewed as an exploration of this topic in the Netherlands and further longitudinal research is indicated. Regarding generalisation of the results it is also important to keep in mind that these studies were conducted in the Netherlands where PGD is reimbursed by the Dutch health care system. In other countries, where these costs are not covered by the health care system, the costs and logistical hurdles of PGD can be major drawbacks for couples to opt for PGD and this can lead to different prioritization of motives and considerations.

Future perspectives and opportunities for future research

Subgroups at risk of decisional conflict

With regards to optimizing decision support it is important to bear in mind that some subgroups may be more vulnerable to decisional conflict and its possible adverse psychological effects. First, our data suggests that younger couples are more at risk of decisional conflict (chapter 6). Younger couples are sometimes confronted with reproductive decision-making sooner than anticipated due to the advised preventive surgeries for female carriers that compromise their reproductive life span. The possible prematurity of their relationship and reproductive plans may further complicate decision-making. Second, women who had a mastectomy and their partners were likely to have a higher perceived severity of HBOC (chapter 6) and may therefore be more inclined to opt for PGD. On the contrary, it has been shown that couples who have already undergone a serious medical trajectory such as a mastectomy are tired of medical interventions and have a desire to be “normal,” steering them more towards a natural pregnancy. This paradox could result in decisional conflict. Third, religious couples often report ethical reservations towards selective reproductive techniques such as PGD and PND.[5,19,35] Nevertheless, they express a higher need for psychological support with reproductive decision-making (chapter 6) implying that despite their reservations, some of these couples still need to consider these options. Ultimately, couples who refrained from PGD were more at risk of feelings of doubt and guilt which occasionally led to decisional regret (chapter 4). Each of these described subgroups reported increased difficulty with reproductive decision-making or a higher need for psychological support during decision-making, which underlines the importance of providing them with adequate support to prevent adverse psychological effects due to either choice they make. Additional research is required to confirm and possibly elaborate on these identified at-risk subgroups.

Need for guidelines concerning reproductive counseling for couples with HBOC

The availability of PGD for HBOC differs across countries and due to ethical objections, is still not fully accepted by the general public, *BRCA* carriers and their partners and professionals. A need for a standard of care guideline for referral and counseling of these couples regarding their reproductive options has been reported internationally (chapter 3).[45,46] Although the currently available data is too preliminary to draw firm conclusions, the results of this dissertation and the existing body of literature give rise to the following guideline suggestions.

During a positive *BRCA* test disclosure concerning a person of reproductive age, reproductive options should be (briefly) mentioned and a standard text about this may best be incorporated in the patient/family letter. The option of a follow up consultation to elaborate on reproductive options when relevant should be offered and if desired, scheduled at the time of the counselee's preference. Ideally, a digital decision aid should be provided before the follow up consultation by means of preparation and to generate questions to be discussed with the counselor. This may contribute to the efficiency and effectiveness of the doctor-patient consultation. Couples will be generally informed, enabling the counselor to focus on remaining questions and main considerations. During reproductive counseling, the counselor ought to be aware of possible subgroups that are at increased risk for decisional conflict and customize counseling if applicable. Additional support by a psychologist or social worker during and after the reproductive decision-making process should be offered. Suggested topics to focus on with additional support are provided in Box 7.1.

Box 7.1: Suggested topics for decision-making support regarding PGD for HBOC

To facilitate decision-making:

Primary focus: The perceived seriousness of HBOC and the actual personal and future child's cancer risk. Attention should be paid to the possible impact of personal and family experiences with cancer and preventive measures.

Potentially significant motives and considerations:
Physical:
The physical burden of an IVF/PGD treatment.
Psychological:
The psychological burden of an IVF/PGD treatment (i.e. the prolonged trajectory, anticipation of hormonal mood swings and other possible side effects, the possible anxiety of a perceived drop-out race PGD is often compared with, feelings of disappointment if the treatment is not successful).
Moral:
The couples' motivation to protect the future child from an increased cancer risk and possibly from preventive surgeries and a future reproductive dilemma.
The potentially perceived societal pressure to prevent transmission of the *BRCA* mutation.
The couples' desired number of children, the importance of achieving this goal and Its achievability by using PGD.
Potential feelings of guilt when the couple considers using PGD for a future child while already having one or more children for whom PGD was not used. In addition, the counsellor may focus on an effective coping strategy and build the couples' confidence to discuss their reproductive choices with their children in the future.
Hopes and beliefs for future medical developments in the prevention and care of breast and ovarian cancer.

To facilitate effective coping strategies with potential social and practical concerns during or after the PGD trajectory:

Social:
The possible impact on a couple's relationship (i.e. lengthy and potentially stressful trajectory, lack of romance regarding conception).
How to communicate the couple's chosen reproductive trajectory with their social environment and cope with potential judgemental opinions.
Practical:
The planning of a PGD trajectory, possibly in combination with preventive surgeries for a female carrier.
The achievability of frequent hospital visits and how to discuss this with the employer(s).

Developing international guidelines will be challenging due to significant legislative differences between countries. In several countries PGD for HBOC is not approved. Countries that allow PGD for HBOC differ in financial facilitation of this treatment. In the Netherlands, the costs of three PGD treatments are reimbursed by national health care insurance, whereas in some other countries accessibility of PGD depends on the couples' financial resources.

This dissertation has generated insight in the reproductive decision-making process and support needs of couples with HBOC. As mentioned, suggestions made are based on the

results of the current dissertation and the existing literature and can be used as an entry point for future research. Extensive research is needed to determine the appropriate timing and form of information provision and counseling, to confirm or elaborate on the identified vulnerable subgroups, and to map the needs and preferences of the professionals who have to provide this framework of standard care. Moreover, once a standard of care guideline is in place, regular evaluation and adaptation will be required due to the rapid evolvement of genetics and artificial reproductive techniques.

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Valorization

Valorization

Introduction

Breast cancer is the most frequently diagnosed type of cancer in women in the Netherlands and the number of diagnoses continues to rise to an estimated 20.000 in 2020. One in seven women will develop breast cancer during lifetime.[1] Aside from the individual burden, the societal and economic burden are high.[2]
Five to ten percent of breast cancer cases are caused by a hereditary predisposition.[3,4] Various gene mutations can increase the risk of breast cancer, of which a mutation in the *BRCA1* or *BRCA2* gene is most common. A mutation in one of these two genes increases the risk of developing several types of cancer, most significantly breast and ovarian cancer in female carriers. A *BRCA1/2* mutation increases the risk of breast cancer from 14% to 72% in women[5] and from less than 1% to 6.9% in men.[6-8] The risk of developing ovarian cancer is increased from less than 1% to 44% for women with a *BRCA1/2* mutation.[5,9] With regards to risk management, women with hereditary breast and ovarian cancer (HBOC) can opt for preventive surgeries (i.e. removal of breast and tuba or ovaries before a certain age) or intensive screening. Preventive measures are however rigorous and have a substantial impact on physical, emotional and psychological wellbeing, while intensive screening is associated with high levels of stress and cannot prevent cancer.

Since HBOC is an autosomal dominant predisposition, both male and female carriers have a 50% risk of passing the *BRCA1/2* mutation on to their children. Until 2008, prenatal diagnosis (PND) was the only reproductive option in the Netherlands to prevent transmission of a *BRCA1/2* mutation to a genetically related child. PND is a technique used to detect the *BRCA* mutation in the foetus at around 11 weeks of pregnancy with the intention to terminate the pregnancy in case the foetus is a female *BRCA* carrier. Terminating a pregnancy because of a late onset condition with incomplete penetrance such as HBOC is often regarded as emotionally demanding and morally (too) drastic. The low uptake of PND for HBOC suggested a need for an alternative method to prevent hereditary transmission of the *BRCA1/2* mutation. In 2008, preimplantation genetic diagnosis (PGD) became available for couples with HBOC in the Netherlands. This enabled selection of embryo's without the *BRCA* mutation before pregnancy through IVF, thereby establishing a pregnancy of a child without the *BRCA* mutation. PGD has been practiced in the Netherlands since 1995 for serious genetic conditions with an early age of onset. In its early years, PGD was not made available for late onset conditions such as HBOC because a slippery slope was feared. After an intense political and public debate, PGD for late onset hereditary cancer syndromes was approved trusting the responsibility of patients and professionals.

Relevance of scientific results for clinical practice and society

Although HBOC is nowadays the most frequently requested indication for PGD, a majority of couples with HBOC still opt for a natural pregnancy. The availability of PGD has in a way complicated reproductive decision-making for these couples. On the one hand, a less invasive method than PND to prevent transmission of the *BRCA* mutation is now being offered. On the other hand PGD can be a burdensome treatment with many physical, psychological, moral, social and practical aspects to consider. A female *BRCA* carrier additionally has to consider the integration of a lengthy PGD treatment into the timeline of possible preventive surgeries and may worry about the effect of the IVF hormones on her cancer risk. A common moral concern is that HBOC differs from most PGD indications in terms of its gender specific cancer risk. Currently all embryos with a *BRCA* mutation are discarded even though male embryo's with a mutation only have a slightly increased cancer risk.
At the Maastricht UMC+ PGD outpatient clinic it was noticed that many couples with hereditary breast and ovarian cancer struggle with making a reproductive choice and it is not uncommon that they alter their decision even while they are already in the process of fulfilling their child wish. Our qualitative assessment of the perceived (dis)advantages of PGD for HBOC shows that couples with HBOC who consider PGD are at risk for decisional conflict, possibly resulting in feelings of guilt and regret which may have a long-lasting impact on their lives (chapter 4).

Understanding the reproductive decision-making process and the support needs and wishes of these couples is imperative to provide proper support and prevent decisional conflict and its potential subsequent psychological burden. Besides their relevance for couples with HBOC and health care providers, the results of this dissertation show relevance at a political and economic level. The findings provide insight into the motives and considerations of couples who consider PGD for a late onset condition with an incomplete penetrance for which a slippery slope was feared by policy makers. Results show that couples extensively consider their reproductive options and thoroughly take into account the perceived seriousness of the condition. This indicates that the public shows responsibility in utilizing this reproductive option and that the legalization of PGD for late onset cancer syndromes was justified. Hence, the fear of a slippery slope which was the most profound argument against legalizing PGD for HBOC appears to be unfounded.
Economically, these studies can stimulate awareness of preventive measures regarding cancer among both end-users and professionals, possibly increasing their uptake and therefore decreasing the costs involved in the care and cure of one of the most expensive diseases in our society; cancer. The cost effectiveness of PGD has been investigated in the USA for Cystic Fibrosis (CF) and in Australia using retinoblastoma as an example.[10,11] Both studies concluded that PGD was cost-effective. The USA study demonstrated that the cost savings to the health care system of providing free IVF/PGD to all CF carrier couples compared to the lifetime costs of medical treatment for patients

affected by this disease, run to dozens of billions of dollars.[10,13] The results also provide tools to prevent and decrease the societal costs of long lasting adverse psychological effects that can be caused by undeliberate or uninformed reproductive decision-making. In addition, they provide a starting point for (inter)national guidelines for referral, counselling and decision support regarding PGD for HBOC. Possibly this may serve as a blueprint for other PGD indications. With these insights, counsellors can focus on subgroups that are more vulnerable for decisional conflict (couples who are young, religious, who experienced a severe medical intervention due to HBOC and those who are inclined to refrain from PGD) and we can start building a framework to introduce personalized decision support in reproductive counselling in order to enable the genetic counsellor to efficiently use her time and resources.

A direct effect of the findings generated by our qualitative assessment of the perceived (dis)advantages of PGD (**chapter 4**) and couples' support needs in reproductive decision-making (**chapter 6**) pertains to the development of the digital decision aid concerning reproductive decision-making for couples with hereditary cancer, developed by Reumkens et al., 2018.[13] This decision aid has proven to reduce decisional conflict, increase levels of knowledge and improve realistic expectations. Moreover, it improved levels of deliberation and decision self-efficacy for individuals with low baseline levels.

Outcomes of this dissertation have been and will be published in scientific medical journals and presented at national and international congresses and expert meetings. Where appropriate, outcomes will also be presented at patient organization meetings. Conclusions will be incorporated in an updated and extended version of the current digital decision aid regarding reproductive decision-making.

Remaining questions and future plans

Based on these results, counselling at our local PGD outpatient clinic has been improved. However a need for (inter)national standard of care guidelines remains. Current results are an important step but not sufficient to facilitate the development of such a guideline and additional research is needed. More specifically, investigation of appropriate decision support in reproductive decision-making that incorporates various PGD indications and international contextual differences such as the reimbursement of PGD, is required. Our results can serve as a starting point for more in depth and larger studies. When focussing on a specific genetic predisposition such as HBOC, achieving large sample sizes is challenging as the population of interest is limited. Therefore, we aim to expand our research to the entire PGD population while appreciating the conditions' variety in characteristics. Ultimately, we strive to develop a standard of care guideline for PGD referral, counselling and decision support in general.

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Summary

Summary

Hereditary breast and ovarian cancer syndrome (HBOC) is a genetic condition caused by a mutation in the *BRCA1* or *BRCA2* gene. This mutation results in a highly increased risk of developing several types of cancer, most significantly breast and ovarian cancer in female carriers. Breast cancer is the most frequently diagnosed type of cancer in women in the Netherlands and an estimated five to ten percent is genetically predisposed. The elevated cancer risks for female *BRCA1/2* carriers can be annihilated with preventive surgery by means of removing breasts and ovaries. However, preventive surgery is physically and emotionally demanding whereas the alternative option, intensive screening for early detection does not prevent cancer. In addition to these concerns regarding personal risk management, both male and female *BRCA* carriers of reproductive age commonly have concerns for their future child(ren). As HBOC is an autosomal dominant condition, there is a 50% risk of passing on the mutation to the next generation. Couples who desire a genetically related child have two reproductive options to prevent transmission of the mutation. Prenatal diagnosis (PND) is conducted during pregnancy to provide a *BRCA* diagnosis of the foetus around 11 weeks, with the intention to terminate the pregnancy if it turns out to be a female carrier. The uptake of PND for HBOC is generally low due to moral and emotional reservations. Preimplantation genetic diagnosis (PGD) was introduced as an alternative to PND and uses in vitro fertilization (IVF) to select embryo's without the *BRCA* mutation in order to establish a pregnancy of a child without HBOC. Since PGD for HBOC became allowed in the Netherlands in 2008 it has been one of the most frequently requested indications, although a majority of *BRCA* carriers still prefers a natural pregnancy without genetic testing (chapter 2). At the PGD outpatient clinic of the Maastricht UMC+, we observed couples struggling with their choice regarding PGD while they appeared to have unique reproductive concerns. With this in mind we decided to set up a number of studies in order to gain insight into the decision-making process and support needs of these couples. In addition, we were interested in mapping the levels of PGD awareness, knowledge and acceptability of couples and involved professionals. By gathering this information we aimed to increase insight in this unique patient group's perception and intended to provide recommendations to adapt education and support practices to these couples' characteristics, needs and wishes.

Chapter 2 provides an overview of PGD awareness, knowledge and acceptability of *BRCA* carriers and their partners in the Netherlands. Awareness is high compared to other countries, especially among those planning a future pregnancy, although one in five of them is still unaware of PGD as a reproductive option. Knowledge about PGD for HBOC is positively related to PGD acceptability. Accurate knowledge about the implications and limitations of PGD seems to enhance its acceptability. General acceptability of offering PGD for HBOC is high and vastly exceeds personal consideration to use PGD. Couples with HBOC would also be more likely to consider using PGD for a hypothetical other serious condition than for HBOC. This illustrates the moral reservations, not only

expressed by the general public and professionals but also by the possible end-users. Some couples with HBOC expressed adverse thoughts and feelings of denying themselves and family members the right to live by personally considering PGD or PND (chapter 4).

Chapter 3 depicts the perspective of professionals involved in the care of persons with HBOC, regarding PGD. Professionals' awareness of PGD as a reproductive option to prevent HBOC is high in the Netherlands compared to other countries. Professionals' knowledge about PGD for HBOC is however limited. When exclusively focussing on clinical geneticists and genetic counsellors, both PGD awareness and knowledge are significantly higher. Acceptability of PGD for HBOC is higher among male professionals and those who are more knowledgeable about PGD. Religious professionals are less likely to consider PGD an acceptable reproductive option to prevent HBOC. Ethical reservations of religious persons towards PGD in general and specifically for late-onset conditions are commonly reflected on in the literature. Intention rates to refer couples with HBOC for PGD are considerably high but they significantly exceed the actual referral rates. This referral gap has been shown internationally over the last decade, with professionals reporting a lack of confidence in answering basic questions about PGD. Continued education about PGD is advised among potential referring physicians like oncologists and gynaecologists. In order to reach all eligible couples we should additionally aim to customize doctor-patient communication to the patient's educational level, since lower educated individuals are currently underrepresented in specialised genetic care.

Couples' motives and considerations to opt for or refrain from PGD were qualitatively investigated by means of a focus group study in chapter 4 and quantitatively assessed by means of a cross sectional survey in chapter 5. Included couples had attended a PGD intake consultation and had made a decision regarding PGD less than three years ago. Couples with HBOC reported unique concerns regarding reproductive decision-making. The late onset character of the condition, in combination with its incomplete penetrance and preventive and therapeutic options, made it challenging to consider against a prolonged physically and psychologically demanding treatment with a relatively low chance of success like PGD. Moreover, female carriers often expressed additional concerns regarding the integration of the treatment into their planned timeline of preventive surgeries and the unknown effect of IVF hormones on their cancer risk. A commonly mentioned moral concern was that also male embryos with the *BRCA* mutation are discarded in the already strict process of elimination of PGD, even though male carriers only have a slightly increased cancer risk compared to female carriers. Overall, several important advantages were outnumbered by numerous smaller disadvantages. The perceived seriousness of the condition was the most important weight on the scale to establish whether using PGD was justified. Personal and family history of cancer mainly determined the perceived seriousness of HBOC. The couples' reproductive history (e.g. having one or more children through PGD or a natural

pregnancy, and requiring IVF regardless of PGD) was another important factor in PGD decision-making. Similar (dis)advantages were noted by a majority of couples regardless of their eventual decision to opt for PGD or not. These (dis)advantages could be categorized into a physical, psychological, moral, social and practical domain. The most influential motives and considerations during PGD decision-making were of moral and psychological nature. For example "*I think a BRCA carrier can live a good life*" (moral) and "*It's important to me to prevent feelings of guilt towards my child for passing on the BRCA-mutation*" (psychological). Although physical, social and practical considerations did not alter the ultimate decision, couples indicated a need for professional support to cope with foreseen related issues.

In **chapter 6** we both qualitatively and quantitatively assessed the support needs of couples with HBOC who made a decision regarding PGD in the last two years after their PGD intake consultation. Almost half considered this decision-making process (very) difficult and some experienced long-lasting adverse effects, such as feelings of guilt and regret (**chapter 4**). A majority indicated a need for additional support during decision-making. Several subgroups who may be at increased risk of decisional conflict were identified. Younger couples and those who opted for a natural pregnancy experienced more difficulty with decision-making and partners of carriers and religious persons were more likely to be in need of additional decision support. Younger couples were sometimes confronted with reproductive decision-making sooner than anticipated, due to the limited timeframe in which female *BRCA* carriers can have children when anticipating their (future) scheduled preventive surgeries. Couples who opted for a natural pregnancy were more likely to cope with feelings of guilt or regret. They sometimes retrospectively evaluated their choice - even though deliberately made at the time - as having chosen the easiest path and expressed concern about the price their child might have to pay. Proper psychological support, during and after reproductive decision-making is therefore advised and couples who refrained from PGD should not be forgotten in this respect. Partners of carriers are prone to be less knowledgeable about the condition's implications and have been reported to consider PGD and PND for HBOC more acceptable than carriers. This could result in their higher reported need for psychological support during reproductive decision-making. Although more extensive research is required to confirm these 'vulnerable subgroups', it is advised to keep them and potential others in mind during reproductive counselling.

Chapter 7 reflects on the results presented in this dissertation in the context of the existing body of literature. The current and prospective situation regarding reproductive counselling for couples with HBOC are discussed from different perspectives (i.e. the counselee's perspective, the professional's perspective and the male versus female perspective). Furthermore, the main thought processes and psychosocial consequences of PGD decision-making and couples' support needs are discussed. In response to the reported need for guidelines concerning reproductive counselling for couples with HBOC, suggestions for a standard of care guideline are given. Finally, suggestions for clinical practice and future research are deliberated on.

Nederlandse samenvatting

Samenvatting

Borstkanker is de meest voorkomende vorm van kanker onder vrouwen in Nederland. Geschat wordt dat 5 tot 10% een genetische oorzaak heeft. Erfelijke borst- en eiderstokkanker wordt in de meerderheid van de gevallen veroorzaakt door een mutatie in het *BRCA1* of *BRCA2* gen. Deze mutatie resulteert in een sterk verhoogd risico op het ontwikkelen van verschillende soorten kanker, voornamelijk borst- en eierstokkanker bij vrouwelijke draagsters. Het verhoogde risico op kanker bij vrouwelijke *BRCA*-draagsters kan worden geminimaliseerd door preventieve operaties, zoals het verwijderen van borsten, tuba en ovaria. Deze preventieve operaties zijn echter fysiek en emotioneel belastend terwijl het alternatief - intensieve screening ten behoeve van vroege detectie van kanker - is geassocieerd met stress bij de drager van de mutatie en het ontstaan van kanker niet kan voorkomen.
Naast deze zorgen met betrekking tot het beheersen van het persoonlijk risico op kanker maken zowel mannelijke als vrouwelijke *BRCA*-dragers in de reproductieve leeftijd zich dikwijls zorgen om eventuele toekomstige kinderen. Aangezien erfelijke borst- en eierstokkanker een autosomaal dominante aandoening is, bestaat er een risico van 50% dat de aanleg wordt overgedragen van ouder op kind. Paren met kinderwens hebben twee reproductieve opties waarmee het doorgeven van de mutatie aan een kind kan worden voorkomen: prenatale diagnostiek (PND) en preïmplantatie genetische diagnostiek (PGD). PND vindt plaats tijdens de zwangerschap. Hierbij wordt rond de 9^{e} week het geslacht van de foetus bepaald. Vervolgens wordt alleen bij een vrouwelijke foetus diagnostiek naar de *BRCA*-mutatie ingezet met de intentie de zwangerschap te beëindigen als het een *BRCA*-draagster betreft. Als alternatief kwam PGD beschikbaar in 2008, waarbij selectie al voor de zwangerschap plaatsvindt. PGD heeft als doel door middel van in vitro fertilisatie (IVF), een embryo zonder de *BRCA*-mutatie te selecteren en in de baarmoeder te plaatsen.

Erfelijke borst- en eierstokkanker is een van de meest voorkomende PGD indicaties sinds PGD hiervoor werd toegestaan in 2008. Bij navraag geeft de meerderheid van de paren echter nog steeds de voorkeur aan een natuurlijke zwangerschap zonder genetische diagnostiek (**hoofdstuk 2**). Op de PGD polikliniek van het Maastricht UMC+ viel op dat paren met erfelijke borst- en eierstokkanker regelmatig moeite hadden met het maken van een reproductieve keuze en dat zij unieke zorgen hieromtrent hadden. Naar aanleiding van deze observatie werd besloten een aantal studies op te zetten met als doel ons inzicht te vergroten in het reproductieve besluitvormingsproces en de behoeften aan ondersteuning van deze paren. Tevens wilden we de mate van bekendheid van PGD voor erfelijke borst- en eierstokkanker onder zowel paren als mogelijke verwijzers in kaart brengen, evenals hun kennis en attitude ten opzichte van PGD. Met het vergaren van deze informatie streefden wij ernaar om ons inzicht in de perceptie van het reproductieve besluitvormingsproces van deze unieke patiëntengroep te vergroten. Daarnaast hoopten we tot aanbevelingen te komen om de informatie-

voorziening en beslissingsondersteuning beter af te stemmen op de eigenschappen, behoeften en wensen van deze paren.

Hoofdstuk 2 geeft een overzicht van de bekendheid, kennis en aanvaardbaarheid van PGD onder *BRCA*-dragers en hun partners. De bekendheid van PGD in Nederland is hoog in vergelijking met andere landen, met name onder paren met erfelijke borst- en eierstokkanker die een actieve kinderwens hebben. Desondanks is nog steeds één op de vijf van deze paren niet bekend met de optie PGD. Meer kennis van PGD voor erfelijke borst- en eierstokkanker is geassocieerd met een hogere aanvaardbaarheid hiervan. Accurate kennis van de mogelijkheden en beperkingen van PGD lijkt bij te dragen aan de acceptatie van deze reproductieve optie. Hoewel een grote meerderheid van de *BRCA*-dragers in de reproductieve leeftijd het aanbieden van PGD voor BRCA aanvaardbaar vindt, overweegt een veel kleiner deel om zelf gebruik te maken van PGD. Paren met erfelijke borst- en eierstokkanker geven tevens aan meer geneigd te zijn gebruik te maken van PGD voor een hypothetische andere ernstige erfelijke aandoening dan voor erfelijke borst- en eierstokkanker. Dit illustreert de morele terughoudendheid onder zowel het algemene publiek als de mogelijke eindgebruikers van PGD voor *BRCA*. Een regelmatig voorkomend dilemma onder *BRCA*-dragers is het idee dat ze henzelf en familieleden met de *BRCA*-mutatie het recht om te leven zouden ontzeggen door PGD of PND te overwegen, terwijl ze zelf een goed leven leiden (hoofdstuk 4).

Hoofdstuk 3 geeft het perspectief op PGD weer van professionals die betrokken zijn bij de zorg voor *BRCA*-dragers. De bekendheid van PGD als reproductieve optie voor *BRCA*-dragers is hoog onder professionals in vergelijking met andere landen. Hun kennis over PGD voor erfelijke borst- en eierstokkanker is echter beperkt. De klinisch genetici en genetisch consulenten hebben significant meer kennis van PGD dan de overige professionals die betrokken zijn bij de zorg voor *BRCA*-dragers.
De aanvaardbaarheid van PGD voor *BRCA* is hoger onder mannelijke en niet religieuze professionals en bij degenen die meer kennis van PGD hebben. In de literatuur wordt de ethische terughoudendheid van religieuze personen met betrekking tot PGD, met name voor aandoeningen die op latere leeftijd tot uiting komen, regelmatig beschreven. De intentie van professionals om paren met erfelijke borst- en eierstokkanker te verwijzen voor PGD is erg hoog, hoewel maar een klein deel van de professionals ooit een paar heeft verwezen voor PGD. Deze kloof tussen intentie en daadwerkelijk verwijzen voor PGD is in het afgelopen decennium internationaal beschreven. Voortdurende bijscholing om basiskennis van PGD onder mogelijke verwijzers, zoals gynaecologen en oncologen, te bevorderen wordt daarom geadviseerd. Daarnaast is het aan te raden om zo veel mogelijk naar gepersonaliseerde informatievoorziening en communicatie te streven zodat patiënten in alle lagen van de samenleving kunnen worden bereikt. Tot op heden vormen de lager opgeleide patiënten een minderheid binnen de genetische gezondheidszorg, waaronder PGD.

In hoofdstuk 4 werden de motieven en overwegingen van *BRCA*-paren om wel of niet voor PGD te kiezen kwalitatief onderzocht, waarna werd beoogd deze resultaten te kwantificeren in hoofdstuk 5. In beide studies hadden de geïncludeerde paren een PGD intake gesprek gehad in het Maastricht UMC+ en minder dan drie jaar geleden een besluit genomen om wel of geen gebruik te maken van PGD. Deze paren gaven blijk van unieke, *BRCA*-gerelateerde zorgen met betrekking tot het maken van een reproductieve keuze. In moreel opzicht zouden de meeste *BRCA*-dragers voor PGD kiezen. Daarmee kan het doorgeven van de aanleg voor kanker immers voorkomen worden zonder dat er een mogelijke zwangerschapsafbreking aan te pas komt. Echter, het feit dat de aandoening pas op latere leeftijd tot uiting komt in combinatie met een onvolledige penetrantie (niet iedereen wordt ziek) en de voorhanden zijnde preventieve en behandelmogelijkheden, maken de afweging moeilijk. PGD is namelijk een langdurige, fysiek en psychologisch belastende behandeling met een relatief lage slagingskans ten opzichte van een natuurlijke zwangerschap. Bovendien hadden *BRCA*-draagsters vaak aanvullende zorgen omtrent het plannen van een PGD behandeling binnen het geadviseerde tijdschema van preventieve ingrepen en de mogelijke invloed van IVF hormonen op hun risico op kanker. Een morele zorg die regelmatig werd aangehaald was dat er bij PGD niet wordt gekeken naar het geslacht van de embryo's waardoor ook mannelijke embryo's met de mutatie niet worden teruggeplaatst in een al zo strikt proces van eliminatie, terwijl ze slechts een licht verhoogd risico op kanker hebben. Globaal genomen werden enkele belangrijke voordelen van PGD genoemd versus veel meer, maar minder zwaarwegende, nadelen. De ervaren ernst van de aandoening was de belangrijkste factor om te bepalen of het gebruik van PGD gerechtvaardigd was. De ervaren ernst werd voornamelijk bepaald door de persoonlijke- en de familiegeschiedenis met betrekking tot borst- en eierstokkanker. Daarnaast had de reproductieve geschiedenis van het paar (het wel of niet hebben van kinderen middels een natuurlijke zwangerschap en de noodzaak van IVF onafhankelijk van PGD) een significante invloed op de besluitvorming. Ongeacht hun keuze om wel of geen gebruik te maken van PGD, noemden paren vergelijkbare voor- en nadelen van PGD. Deze voor- en nadelen konden worden onderverdeeld in een fysiek, psychologisch, moreel, sociaal en praktisch domein. De belangrijkste motieven en overwegingen in het besluitvormingsproces waren van morele en psychologische aard. Enkele voorbeelden zijn: *"Ik vind dat een BRCA-drager een goed leven kan leiden"* (moreel) en *"het is belangrijk voor me om schuldgevoelens voor het doorgeven van de BRCA-mutatie naar mijn kind toe te voorkomen"* (psychologisch). Ondanks dat fysieke, sociale en praktische overwegingen geen significante invloed op de besluitvorming leken te hebben, gaven paren aan dat ze professionele ondersteuning wensten bij het omgaan met hieraan gerelateerde problematiek.

In hoofdstuk 6 werden de ondersteuningsbehoeften van paren met erfelijke borst- en eierstokkanker die in de afgelopen drie jaar een keuze omtrent PGD hadden gemaakt, zowel kwalitatief als kwantitatief onderzocht. Bijna de helft van de paren bestempelde

het besluitvormingsproces als (erg) moeilijk en sommigen ervoeren een langdurige negatieve uitwerking daarvan, waaronder schuldgevoelens en spijt (hoofdstuk 4). Een meerderheid gaf een behoefte aan aanvullende ondersteuning tijdens het besluitvormingsproces aan. Daarnaast werden verschillende subgroepen geïdentificeerd die mogelijk meer vatbaar zijn voor beslissingsambivalentie. Jongere paren en degenen die uiteindelijk voor een natuurlijke zwangerschap zonder PGD of PND kozen hadden retrospectief meer moeite met het maken van een reproductieve keuze. Daarnaast hadden partners van *BRCA*-dragers en religieuze personen vaker behoefte aan aanvullende ondersteuning tijdens het besluitvormingsproces. Een deel van de jongere paren werd mogelijk eerder dan verwacht geconfronteerd met het maken van een reproductieve keuze. Door de geadviseerde preventieve operaties voor vrouwelijke *BRCA*-draagsters is de tijd waarin deze vrouwen biologisch eigen kinderen kunnen krijgen namelijk beperkt, waardoor een eventuele PGD behandeling op tijd moet worden gestart. Met name paren die voor een natuurlijke zwangerschap zonder verder onderzoek hadden gekozen gaven aan achteraf schuldgevoelens en spijt te ervaren. Een deel van deze paren illustreerde dit door te benoemen dat ze wellicht voor de makkelijkste weg hadden gekozen en dat hun kind daar in de toekomst mogelijk de prijs voor zou moeten betalen. Adequate psychologische ondersteuning, tijdens en na de reproductieve besluitvorming wordt daarom geadviseerd. Juist paren die afzien van PGD mogen daarin niet worden vergeten. Partners van *BRCA*-dragers hebben vaak minder kennis van de implicaties van de aandoening en vinden reproductieve opties als PGD en PND vaker aanvaardbaar dan de *BRCA*-dragers zelf. Mogelijk resulteert dit in een grotere behoefte aan aanvullende ondersteuning tijdens het maken van een reproductieve keuze. Het is aan te raden hier rekening mee te houden tijdens de reproductieve counseling. Meer onderzoek is nodig om deze en mogelijk andere kwetsbare subgroepen aan te tonen.

Hoofdstuk 7 is een reflectie van de resultaten van deze thesis in het licht van de bestaande literatuur. De huidige en verbeterde situatie rondom reproductieve counseling van paren met erfelijke borst- en eierstokkanker wordt beschreven vanuit verschillende invalshoeken: het perspectief van de patiënt (met inachtneming van de verschillen tussen mannen en vrouwen en tussen dragers en partners) en het perspectief van de professional. Tevens worden de belangrijkste denkprocessen en de psychosociale gevolgen van besluitvorming rondom PGD beschreven. Naar aanleiding van de gerapporteerde behoefte aan richtlijnen aangaande reproductieve counseling voor paren met erfelijke kanker, worden hier inhoudelijke suggesties voor gedaan. Ter afsluiting worden suggesties voor de klinische praktijk en toekomstig onderzoek genoemd.

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Dankwoord

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Wilko, Jolie en Sofia, mijn alles. Wilko, bovenstaande zin zegt genoeg. Bedankt dat je bestaat. Jolie en Sofia zijn de kersen op onze taart. Telkens als je denkt dat het niet mooier kan worden, wordt het dat toch…

Curriculum Vitae

Curriculum Vitae

Joyce Habets werd geboren op 12 februari 1986 te Ubachsberg, gemeente Voerendaal. In 2009 behaalde ze haar bachelor Algemene Gezondheidswetenschappen aan de Universiteit Maastricht. Aan dezelfde universiteit rondde ze in 2011 de Master of Public Health in de richting Health Education and Promotion af. Haar wetenschappelijke masterthesis voltooide zij op de Islamitische Lamu Argipel voor de kust van Kenia, Afrika. Onder het vaandel van de Kenya Red Cross Society, evalueerde ze een 'Faith based' HIV/Aids interventie. Daarna werd zij aangenomen als onderzoeksassistente bij de vakgroep Health Ethics and Society van de Universiteit Maastricht waar ze bijdroeg aan een onderzoeksvoorstel gericht op het bevorderen van de pre- en postnatale gezondheidszorg in Kenia. In 2012 werd Joyce aangenomen als onderzoeker bij de afdeling Klinische Genetica van het Maastricht Universitair Medisch Centrum, op een onderzoeksproject naar de besluitvorming omtrent preïmplantatie genetische diagnostiek (PGD). In 2013 werd ze op dezelfde afdeling tevens aangenomen als casemanager PGD waardoor in haar functie de link tussen onderzoek en de praktijk werd gelegd. Het onderzoek groeide uit tot haar promotietraject. Hiermee vergrootte zij ons inzicht in het reproductieve besluitvormingsproces en de psychosociale gevolgen daarvan bij paren met erfelijke borst- en eierstokkanker. Daarnaast werden de behoeften aan begeleiding en ondersteuning van deze paren onderzocht. De subsidie voor het onderzoek van Stichting Pink Ribbon, ZonMw en KWF kankerbestrijding werd aangevuld met een persoonlijke onderzoeksbeurs die zij verkreeg van Stichting Jules Coenegracht Sr.

Joyce is getrouwd met Wilko Gietel en samen met hun kinderen Jolie (2016) en Sofia (2018) wonen zij in Voerendaal.

List of publications

Reumkens K, Tummers MHE, Severijns Y, **Gietel-Habets JJG**, van Kuijk SMJ, Aalfs CM, van Asperen CJ, Ausems MGEM, Collée M, Dommering CJ, Kets CM, van der Kolk LE, Oosterwijk JC, Tjan-Heijnen VCG, van der Weijden T, de Die-Smulders CEM, van Osch LADM. Reproductive decision-making in the context of hereditary cancer: the effects of an online decision aid on informed decision-making. J Community Genet 2020. https://doi.org/10.1007/s12687-020-00484-2.

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