Rapid genetic counseling and testing in newly diagnosed breast cancer

*Surgical and psychosocial implications*

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Rapid genetic counseling and testing in newly diagnosed breast cancer: surgical and psychosocial implications
Summary, general discussion and conclusions

Introduction to Rapid Genetic Counseling and Testing

Breast cancer is the most prevalent type of cancer among women. Currently, approximately 1 in 8 Dutch women develop breast cancer at some point in their lives. A minority of about 5% of breast cancer cases is caused by a germline mutation in one of several known breast cancer genes. Quantitatively, the most important known breast cancer genes are the BRCA1 and BRCA2 genes. There are several other genes that predispose to breast cancer (e.g., CHEK2, PALB2, PTEN, TP53, CDH1), but in this study we have focused on BRCA1 and BRCA2 as they are quantitatively the most important and have both been tested in a diagnostic setting for about 20 years.

Women who carry a germline mutation in one of the BRCA genes have a life time risk of 60-80% of developing breast cancer. Their risk of developing ovarian cancer is also significantly increased, ranging from 5-20% for BRCA2 gene mutation carriers and 35-55% for BRCA1 gene mutation carriers [1;2]. In addition to these risks, female breast cancer patients carrying a germline mutation in the BRCA1 or BRCA2 gene have an increased risk of developing a second primary, most often contralateral, breast cancer. The highest second breast cancer risk is for BRCA1 gene mutation carriers who have been diagnosed with a first breast cancer before the age of 40 years. In these patients, this risk is about 26% after 10 years of follow-up and 55% after 25 years of follow-up [3;4]. For BRCA2 gene mutation carriers who developed their first breast cancer after the age of 40 or 50 years, the risk of developing contralateral breast cancer is much lower. For those BRCA2 gene mutation carriers who developed their first breast cancer after the age of 40 years, the 10-year cumulative contralateral breast cancer risk is about 7% [4], and for those who developed their first breast cancer after the age of 50 years, the 25-year cumulative contralateral breast cancer risk is about 16% [3].

BRCA1 or BRCA2 gene mutation carriers who are diagnosed with a first breast cancer, and who are aware of their increased risk of a second primary breast cancer, will in general want to address this risk in some way. They may opt for frequent surveillance by mammography and MRI of the remaining breast tissue. In case of a favorable prognosis of their first breast tumor, risk-reducing surgery of the remaining breast tissue is another option, i.e. a risk-reducing contralateral mastectomy (RRCM). Risk-reducing surgery reduces the risk of a second breast tumor by about 95%, and there is accumulating evidence of a positive effect on survival, although this may not be the case for patients of all ages and with all tumor characteristics [5-8].
In the recent past, most women who had been diagnosed with breast cancer and who had an increased chance of having hereditary breast cancer, because of their young age at diagnosis or because of a significant family history of breast and/or ovarian or prostate cancer (i.e., high-risk breast cancer patients), were referred for genetic counseling and testing after their primary therapy. Those women who learned they were carrying a BRCA1 or BRCA2 gene mutation, and who considered risk-reducing surgery, had to undergo additional surgery. Furthermore, a breast reconstruction following a risk-reducing mastectomy can be more complicated in case of previous radiotherapy [9-10]. At that time, a BRCA1 and BRCA2 gene test result was only available after 4 or more months, and thus DNA test results could most often not be incorporated into primary treatment decisions. However, many non-commercial DNA laboratories have developed faster tests, making test results available within 4 weeks (at the time of this study), or now even after 2 weeks, if necessary. This has provided the opportunity for rapid genetic counseling and testing (RGCT) shortly after breast cancer diagnosis, in order to incorporate the results into treatment decisions. For example, if a woman would learn she is a BRCA1 or BRCA2 gene mutation carrier shortly after being diagnosed with breast cancer, she may opt for a bilateral mastectomy instead of unilateral breast surgery [11-13].

Although potentially beneficial, it was not clear whether undergoing RGCT would indeed lead to different treatment decisions. Also, concern was expressed that RGCT would be harmful; that it would cause too much stress at an already stressful time [14]. We performed the current study in order to evaluate the impact of RGCT on both decisions about primary surgical treatment and on psychosocial wellbeing.

Summary of the main findings
As described in chapter 2, we investigated female BRCA1 and BRCA2 gene mutation carriers diagnosed with breast cancer between 1995 and 2009 from the Erasmus Medical Center, Leiden University Medical Center, University Medical Center Utrecht and the Netherlands Cancer Institute. Most of these women, i.e. 219/287 (76%), were diagnosed with breast cancer before they had genetic testing and thus before they were aware of being a BRCA1 or BRCA2 gene mutation carrier. In other words, they had a diagnostic DNA test. Within this cohort of diagnostically tested women, when comparing those diagnosed in 2001-2009 with those diagnosed in 1995-2000, the median time between breast cancer diagnosis and genetic testing (as measured by the moment DNA test results became available) declined from 28 months to 14 months. Similarly, in this cohort, women underwent risk-reducing contralateral mastectomy sooner after diagnosis when diagnosed between 2001-2009 (median of 27 months) as compared to those diagnosed between 1995-2000 (median of 77 months). The remaining women described in this chapter (68/287, 24%) had a genetic test and learned that they were a BRCA1 or BRCA2 gene mutation carrier before they

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were diagnosed with breast cancer, i.e. they had a predictive test. When considering the complete time period of 1995 to 2009, the women who had a predictive test opted for an immediate risk-reducing contralateral mastectomy significantly more often than the women who had a diagnostic test (34% versus 8%, p < 0.001). We concluded from these data that there likely is a need for RGCT to guide surgical treatment decisions.

We also collected retrospective data on the impact of RGCT from 26 breast cancer patients who had undergone RGCT at the Family Cancer Clinic of the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital in Amsterdam between 2004 and 2008, as described in chapter 3. In this pilot study, 56% of the women who had unilateral breast cancer and learned that they were carrying a BRCA mutation opted for a bilateral mastectomy (as primary surgery), as compared to 20% of the women without a mutation (p = 0.07). A fifth of patients (5/26, 19%) reported having frequent worries about cancer recurrence, but none indicated that these worries impaired their daily functioning.

Second, we found that RGCT had an impact on primary surgical treatment decisions, but only when DNA test results were available in a timely manner. Twenty-two percent of the women who were offered RGCT and who received DNA test results before primary surgery opted for a bilateral mastectomy, as compared to 9% of those women who were offered usual care (OR 3.09, CI 1.15-8.31, p = 0.03). This finding is supported by self-reported patient data: women who received DNA test results before primary surgery reported significantly more often that RGCT influenced their treatment decisions than those women who received DNA test results after primary surgery (p < 0.01). Also, more women who were offered RGCT felt they had been actively involved in treatment decision-making than women who had been offered usual care (67% versus 48%, p = 0.06).
Third, we did not find any significant psychosocial differences at 6 or 12-month follow-up between women who were offered RGCT and women who were offered usual care. Although not reported in chapter 6, we have also compared the levels of health-related quality of life (HRQL) and anxiety and depression of the trial participants at 12-month follow-up with an age- and education matched group of women from the general Dutch population (data derived from the Profiles Registry [15]). The trial participants had statistically significantly lower health-related quality of life (HRQL) scores for most domains assessed, except for physical functioning, nausea/vomiting, pain, and sexual functioning, as well as higher anxiety scores. These high levels of distress are a normal reaction to being diagnosed with cancer and have been described in breast cancer patients not at high risk of having hereditary breast cancer as well [16-19].

As part of our randomized clinical trial, we also investigated patients’ and medical professionals’ attitudes towards and experiences with RGCT. The majority of surgeons and specialized breast cancer nurses who participated in the trial (n = 29) considered RGCT to be important when asked before the patient recruitment period (89%), and even a bit more so when asked after the patient recruitment period (96%). Although a substantial minority (39%) of professionals considered RGCT to be burdensome for patients, most believed that the advantages outweigh the disadvantages for both patients and professionals (70% and 75%, respectively). Similarly, 72% of professionals agreed that RGCT should be offered routinely to newly diagnosed, high-risk breast cancer patients. Most patients (74%) and medical professionals (85%) considered surgeons the most appropriate source for referral.

Last, we compared the distress level of newly diagnosed high-risk breast cancer patients in our trial with that of Norwegian breast cancer patients without (knowledge of) such increased risk. The patients in our trial knew of their high-risk, but had not yet had any genetic counseling. The Norwegian patients had not been assessed for their risk of having hereditary breast cancer. In both groups, distress levels were measured shortly after diagnosis, prior to primary surgery. On average, the high-risk breast cancer patients reported higher levels of depression than the non-high-risk breast cancer patients. Anxiety levels were similar between the two groups. Furthermore, in the high-risk breast cancer sample, both having children and having a recent prior history of psychological problems were associated significantly with both depression and anxiety following the diagnosis of breast cancer.

Methodological considerations

There are a number of methodological issues in our work that deserve discussion. First, some women (10/87) who were randomized to the usual care group received RGCT, which
was available but was not routinely recommended or offered. In all cases, these women initiated RGCT themselves or were referred by a physician other than their surgeon. Also, as clarified above, only 40% of the women who were randomized to the RGCT group opted for a rapid DNA test, and only 33% of women in the RGCT group received their DNA test result before primary surgery. This probably explains why, in our intention to treat analysis, we did not observe a significant difference between groups in choice of primary surgery, while we did in our per protocol analysis. At the time of the trial, national treatment guidelines and audit called for the start of primary treatment within three weeks of breast cancer diagnosis [20]. When designing the trial, we argued that waiting for genetic test results would be a valid reason for deviating from this guideline, i.e., delaying the start of treatment. One might even argue that a genetic test result should be part of the diagnostic work-up. However, in our trial, not all patients and surgeons were, understandably, willing to postpone surgery, afraid of being penalized through the NABON Breast Cancer Audit (NBCA) for intervals between diagnosis and start of treatment of more than three weeks [21]. During our trial, the time required to generate rapid genetic test results was approximately four weeks. Since conducting our trial, the turnaround time for genetic tests has been further reduced to between two and three weeks. This facilitates incorporating genetic test results more often into treatment decision making, without negative consequences as regard to clinical audits. We would note that, in the case of neo-adjuvant chemotherapy, which is increasingly part of primary breast cancer treatment, the need for very rapid return of genetic test results is less relevant, as there is ample time between diagnosis and date of surgery, or adjustment of chemotherapy. Nevertheless, in order for have test results available in a timely manner, eligible patients still need to be referred for genetic counseling shortly after their diagnosis.

Second, it is important to note that many patients were, to a greater or lesser degree, influenced by their surgeon in making treatment decisions, despite the fact that most patients wished to be actively involved in the decision-making process. At baseline, 73% of patients indicated that they preferred to be actively involved in making treatment decisions. At 6-month follow-up, 68% of the RGCT group versus 48% of the UC group reported that they had actually played an active role in making treatment decisions. Although this difference was not statistically significant (p = 0.06), it suggests that RGCT facilitates shared decision-making. However, this result may have been confounded to some degree by the fact that surgeons differ intrinsically in the extent to which they encourage shared decision making. In our trial, we stratified patients by hospital prior to randomization. However, we were not able to stratify by participating surgeon, and thus we could not control for potential differences between groups in surgeons’ communication skills, counseling style or personal preferences. Additionally, most patients also had consultations with specialized nurses who may have exerted some degree of influence on the decisional process as

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declined participation mentioned undergoing RGCT and/or participating in a trial as being too much at that time. Future studies are needed to identify specific subgroups of eligible women who are reluctant to undergo RGCT and/or who are more likely to experience RGCT as a highly stressful part of the diagnostic process.

Our study also has a number of strengths. First, it is, to the best of our knowledge, the first randomized clinical trial to investigate the impact of RGCT on both treatment choice and on psychological well-being. Second, the high rate of retention of patients throughout the trial, and the fact that patients were recruited from both academic and regional hospitals increased both the internal and the external validity/generalizability of our results. Finally, we assessed not only the patients’ attitudes towards and experiences with RGCT, but also those of the health care professionals involved in their treatment.

Clinical implications
RGCT is increasingly being offered to newly diagnosed breast cancer patients who are eligible for genetic counseling and testing in the Netherlands. The results presented in this thesis indicate that RGCT can indeed be safely offered on a routine basis to all newly diagnosed, eligible breast cancer patients, providing them with the opportunity of incorporating genetic test results into their decision making regarding primary treatment. We have no evidence that, as some have suggested, RGCT is “too much, too soon” for the average patient. With regard to its impact on surgical choice, RGCT can support those women with a BRCA1 or BRCA2 gene mutation who opt for an immediate bilateral mastectomy, if this is the type of surgery they prefer, as well as those women without a genetic predisposition who prefer and choose to undergo breast-conserving therapy. The fact that the time to return rapid test results has decreased to about two weeks, and will probably decrease even further in the (near) future, increases the likelihood that RGCT will play an important and relevant role in shared decision making and in empowering women to make well informed treatment decisions.

It is also anticipated that women with breast cancer associated with germline BRCA1/2 mutations may benefit from specific chemotherapeutic agents such as PARP-inhibitors, which are currently being investigated in several clinical trials [25;26]. Thus, knowledge of a breast cancer patient’s genetic status may also be increasingly important for deciding on the most appropriate adjuvant systemic treatment [27;28]. We would emphasize that (R)GCT will be particularly valuable for breast cancer patients who are eligible for genetic counseling and testing, and not necessarily for all women requiring chemotherapy.

However, in order to ensure that RGCT does not cause undue psychological distress and/or compromise quality of life, it is essential that women continue to have the choice as declined participation mentioned undergoing RGCT and/or participating in a trial as being too much at that time. Future studies are needed to identify specific subgroups of eligible women who are reluctant to undergo RGCT and/or who are more likely to experience RGCT as a highly stressful part of the diagnostic process.

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However, in order to ensure that RGCT does not cause undue psychological distress and/or compromise quality of life, it is essential that women continue to have the choice as
to whether they wish to undergo the procedure, and that they receive sufficient information regarding both the potential benefits and the potential burden associated with it. A potential risk in introducing RGCT as a routine part of breast cancer care is that patients who are offered RGCT may feel that they cannot refuse the offer. Although evidence is accumulating [8], there is not yet convincing data that additional risk-reducing surgery yields significant benefit in terms of overall survival [29]. Therefore, it is important that surgeons and clinical geneticists provide patients with balanced information about the procedure, and that they attempt to identify those women who may be vulnerable for adverse psychosocial effects. It is also important to keep in mind that a synchronous RRCM is not necessarily the best choice of surgery for all mutation carriers. Because the risk of contralateral breast cancer is inversely associated with age at first breast cancer diagnosis [2-4], it will be younger breast cancer patients with a BRCA1/2 mutation and a favorable prognosis, in particular, who will benefit most from a synchronous RRCM [8;30]. Therefore, age at breast cancer diagnosis and tumor grade (i.e., breast cancer prognosis) should be taken into account in making plans for additional risk-reducing surgery, which should preferably be provided within a multidisciplinary setting. Finally, we would stress the need to offer appropriate professional psychosocial support to all patients (considering) undergoing RGCT.

At the time the research underlying this thesis was designed and performed, most women suspected of having hereditary breast cancer were tested for mutations in the BRCA1 and BRCA2 genes only. From 2014 onwards, all genetic centers in the Netherlands also perform testing for the 1100delC mutation in the CHEK2-gene, and in 2017 many have started to implement the use of small next generation sequencing (NGS) gene panels. It is expected that, in the near future, gene panels for many more (breast) cancer genes will be widely available, and probably commonly used for genetic testing in breast cancer [31;32]. How this will influence genetic counseling practices is not yet clear. As it is likely that genes will also be included that are associated with lower cancer penetrance, it is essential in counseling newly diagnosed breast cancer patients who will have such a gene panel test to take into account the actual risk of a second primary tumor in case a pathogenic mutation in a gene other than BRCA1 or BRCA2 is found. It should be discussed with these patients whether there is any evidence for a significant increased risk of (another) primary tumor(s), and whether there is evidence for a significant impact of additional risk-reducing surgery on cancer-related and overall survival. Breast surgeons, medical oncologists, and clinical geneticists should be careful not to automatically consider all positive gene panel test results as an indication for risk-reducing surgery, especially since, with the use of larger gene panels, it is expected that the number of variants of unclassified significance will increase [32].
Directions for future research
It would be of interest to perform a similar randomized clinical trial to investigate the impact of using NGS panels in newly diagnosed breast cancer patients, since the impact of BRCA1/2 testing in the RGCT setting may not automatically apply to testing genes associated with lower or higher cancer risks and subsequently fewer or more implications for treatment and prevention. Ideally, such a trial should only be performed if time to return test results is no longer than two weeks, and preferably one week. However, since RGCT is increasingly being incorporated into routine breast cancer care in the Netherlands, performing such a randomized clinical trial would be considered unethical. Likewise, it is unclear whether a randomized clinical trial on the impact of RGCT on choice of chemotherapy could be performed. It would be feasible, though, to perform observational studies of the clinical and psychosocial impact of finding a (pathogenic or unclassified) variant in a gene associated with a lower second (breast) cancer risk shortly after diagnosis.

Another important issue to investigate would be the role of RGCT when it comes to mainstreaming genetics [33,34]. In the Netherlands and elsewhere, initiatives are being explored to have breast cancer surgeons order genetic testing for their patients. Potential benefits are fewer appointments for patients, shorter time to receive test results, and increased efficiency since, in line with current eligibility criteria, about 90% of patients will have negative test results. However, patients with negative test results may still need counseling about their own and their relatives’ risk of developing (another) breast cancer, and diagnoses of a rare tumor syndrome may be missed when using smaller gene panels. Also, making sure surgeons have sufficient knowledge to provide pre-test counseling and to interpret test results will be challenging. Experiences from the United States, where rates of synchronous RRCM are not only very high in patients carrying a pathogenic mutation but also in those carrying a variant of unknown significance [35], indicate that it is essential that both patients with a pathogenic mutation and those with a variant of unknown significance be referred for genetic counseling. Especially when it comes to larger gene panels, involvement of clinical geneticists will be essential in the correct interpretation of test results and their translation into treatment plans. Experiences with mainstreaming genetics of both patients and surgeons should be monitored closely to explore potential problems. Randomized controlled trials investigating different ways of providing pre- and/or post-test counseling, e.g. leaflets, videos, or consultations with surgeons only and/or clinical geneticists, may shed more light on this issue.

I would also propose to assess psychological distress in a series of consecutive, newly diagnosed breast cancer patients; both those at high-risk of having hereditary breast cancer and those who are at non-high-risk, from the same hospital(s). After the surgeon or specialized nurse has discussed with patients whether they are at increased risk of
having hereditary breast cancer, i.e. if they are eligible for genetic counseling and testing, but before the genetic counseling and surgical treatment takes place, both groups could be asked to complete a questionnaire assessing their psychological distress levels. Such a prospective study would help to clarify whether high-risk breast cancer patients indeed experience more psychological distress when they are informed of their high-risk status shortly following diagnosis. It would also be of interest to identify what their main areas of concern are (personal health, health risk of children and other relatives, etc.), and if they have unmet care needs.

Main conclusions and recommendations
RGCT has increasingly been integrated into routine breast cancer care. Our study results support the feasibility, potential benefit, and limited psychosocial risks associated with RGCT. We would recommend that medical professionals routinely offer RGCT to all newly diagnosed, eligible breast cancer patients. However, ultimately, the decision as to whether or not to undergo RGCT rests with the individual patient. The decision-making process, typically shared with the involved health care professionals, should be based on a well-informed understanding of the potential impact not only of RGCT, but also of the resultant surgical and adjuvant treatment choices on the woman's physical and psychosocial well-being. RGCT should be provided by a multidisciplinary team, including surgeons, clinical geneticists, specialized nurses, and psychosocial workers.

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References


