Integrating germline genetic testing into routine care of patients with breast or ovarian cancer

Acceptability and feasibility of implementing mainstream genetic testing pathways

Kyra Bokkers

Integrating germline genetic testing into routine care of patients with breast or ovarian cancer

Acceptability and feasibility of implementing mainstream genetic testing pathways

Kyra Bokkers

ISBN: 978-94-6469-327-0

Cover & Lay-out: Stefanie van den Herik || HerikMedia || herikmedia.nl
Printing: ProefschriftMaken || proefschriftmaken.nl

Integrating germline genetic testing into routine care of patients with breast or ovarian cancer

Acceptability and feasibility of implementing mainstream genetic testing pathways

Integreren van genetisch onderzoek in de routinezorg voor patiënten met borst- of eierstokkanker

Aanvaardbaarheid en haalbaarheid van een nieuwe werkwijze

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 8 juni 2023 des ochtends te 10.15 uur

door

Kyra Bokkers

geboren op 3 november 1988
te Hoogezand-Sappemeer

Promotoren:

Prof. dr. M.G.E.M. Ausems
Prof. dr. R.P. Zweemer

Beoordelingscommissie:

Prof. dr. L. Hooft
Prof. dr. M.J.E. Mourits
Prof. dr. R.H. Sijmons
Dr. A.J. Witkamp
Prof. dr. P.O. Witteveen

Content

Chapter 1

General introduction

Genetic testing to identify germline pathogenic variants plays an important role in the care of patients with cancer. The results of such a genetic test can guide treatment options and can inform patients of potentially increased risks of developing a second cancer. Furthermore, in case a germline pathogenic variant in a cancer susceptibility gene is identified, family members are also eligible for germline genetic testing to determine if they too are at increased risk of developing cancer for which surveillance and other preventive options may be available. In addition, the identification of a pathogenic variant in a cancer susceptibility gene may affect choices and planning regarding reproduction.

Germline genetic testing in breast and ovarian cancer

Several genes have been identified as predisposing to breast and/or ovarian cancer, including both moderate and high-risk genes (1, 2). Germline pathogenic variants in the *BRCA1* and *BRCA2* genes are the most common hereditary causes of both breast and ovarian cancer and are considered high-risk genes. Pathogenic variants in the genes *RAD51C, RAD51D* and *PALB2* are also associated with both breast and ovarian cancer (2). These genes are considered moderate-risk genes for both cancer types, while *PALB2* has a high risk of breast cancer (2, 3). Pathogenic variants in the genes *ATM, BARD1* and *CHEK2* are only associated with an increased risk of breast cancer and are all considered moderate-risk genes (2). All of these genes are included in gene panels in the Netherlands and are tested when patients are eligible for genetic testing. In addition, there are other genes that are also associated with breast or ovarian cancer but are not tested regularly because pathogenic variants in these genes are more rare, such as *TP53*, *CDH1* and the Mismatch Repair (MMR) – genes (3, 4). This thesis focuses on the genes that are included in standard gene panels and specifically addresses the implications of identifying a pathogenic variant in a *BRCA1* or *BRCA2* gene. Pathogenic variants in these genes are associated with the highest risks of breast and ovarian cancer.

Depending on the size of the gene panel, a pathogenic variant in one of the breast cancer susceptibility genes can be found in 5 – 14% of unselected patients with breast cancer (1, 5-7). Overall, approximately in 2% of unselected breast cancer patients a pathogenic variant in a *BRCA1* or *BRCA2* gene can be found (1, 5, 6, 8). The probability of identifying a pathogenic variant in one of the breast cancer susceptibility genes depends mainly on age at diagnosis, tumor characteristics and family history. Therefore, eligibility criteria for germline genetic testing have been developed for patients with breast cancer based on these factors (9, 10), which increases the probability of finding a pathogenic variant to approximately 9% (5, 7), and specifically for the *BRCA1* and *BRCA2* genes to approximately 3 – 6% (5, 7, 11).

It is known that 10 – 15% of patients with epithelial ovarian cancer, including patients with primary fallopian tube cancer, are carriers of a germline pathogenic variant in the *BRCA1* or *BRCA2* gene, regardless of age at diagnosis or family history (11-13). Therefore, all women with epithelial ovarian cancer, which accounts for 90% of all women with ovarian cancer (14), are eligible for germline genetic testing (9, 15, 16).

Women who are carriers of a pathogenic variant in the *BRCA1* or *BRCA2* gene have an increased lifetime risk of developing breast cancer which can be as high as 72% at age 70, and an increased risk of ovarian cancer, which can be as high as 44% at age 80 (17). Men who are carriers of a pathogenic variant in the *BRCA2* gene are particularly at increased cancer risk, with an estimated cumulative risk of 7% at age 70 for breast cancer and 27% at age 75 for prostate cancer (18). In addition, both men and women may have an increased risk of developing pancreatic cancer, especially when they carry a pathogenic variant in the *BRCA2* gene and have a positive family history for pancreatic cancer (19).

Clinical implications of genetic testing of the *BRCA1* and *BRCA2* genes

The identification of a pathogenic variant in a *BRCA1* or *BRCA2* gene has clinical impact on: (1) treatment, (2) primary and secondary prevention of cancer, (3) family members, and (4) choices and planning regarding reproduction.

(1) Impact on treatment

Female breast cancer patients with a germline pathogenic variant in a *BRCA1* or *BRCA2* gene may opt for mastectomy rather than breast-conserving surgery (20). Several previous studies have shown that, when test results are available before surgery, significantly more patients with breast cancer who are carriers of a pathogenic *BRCA1* or *BRCA2* gene variant choose (double) mastectomy compared to patients with breast cancer without such a pathogenic gene variant (21-24). Moreover, treatment with Poly Adenosine Diphosphate-Ribose Polymerase (PARP) inhibitors has proven particularly effective for patients with Her2-negative breast cancer who are carriers of a pathogenic variant in a *BRCA1* or *BRCA2* gene (25, 26).

From all ovarian cancer patients who are eligible for treatment with PARP inhibitors, those who are carriers of a germline or somatic variant in the *BRCA1* or *BRCA2* gene show the best response (27).

(2) Impact on primary or secondary prevention of cancer

Female breast cancer patients have an increased risk of developing a second breast cancer in the contralateral breast when they carry a germline pathogenic variant in the *BRCA1* or *BRCA2* gene. Because of this increased risk, these patients may opt for regular surveillance to detect a possible second cancer at an early stage or contralateral mastectomy to minimize their risk of developing a second cancer (17). In addition, breast cancer patients have an increased risk of developing ovarian cancer. Because of this increased risk, preventive removal of the ovaries and fallopian tubes is advised between the ages of 35 and 45 years and after completion of childbearing (9, 16). This procedure minimizes the risk of developing ovarian cancer and is advised as current screening methods have not proven effective in reducing mortality (28, 29).

Ovarian cancer patients who are carriers of a germline pathogenic variant in a *BRCA1* or *BRCA2* gene have an increased risk of developing breast cancer. Because of this increased risk, patients with ovarian cancer and such a pathogenic variant may consider regular breast checkups or preventive risk-reducing mastectomy of both breasts. However, studies have shown that the risk of metachronous breast cancer among ovarian cancer patients with a pathogenic variant in the *BRCA1* or *BRCA2* gene is lower than for unaffected women who also carry such a pathogenic variant (30-32). Together with the high mortality rate of ovarian cancer, the use of preventive measures, especially risk-reducing surgery, is therefore often not justified (30-33). These choices are influenced by both the morbidity and mortality of the cancer and the residual risks of developing cancer, mainly depending on the patient's age (34). Hence, during shared decision-making these factors should be taken into account.

Male breast cancer patients with a pathogenic variant in the *BRCA2* gene are eligible for regular surveillance for prostate cancer, i.e., by periodic PSA testing (35).

(3) Impact on family members

When a pathogenic variant in a *BRCA1* or *BRCA2* gene is identified in a breast or ovarian cancer patient, unaffected family members are eligible for predictive genetic testing. If they carry the same pathogenic variant, they too may have an increased risk of developing breast, ovarian, prostate cancer and sometimes other cancers like pancreatic cancer (36). Depending on the age and gene involved, these family members are eligible for preventive measures, such as regular surveillance or risk-reducing surgeries.

(4) Impact on choices and planning regarding reproduction

Identifying a pathogenic variant in a *BRCA1* or *BRCA2* gene affects multiple decisions regarding reproduction for both male and female carriers. First of all, couples are faced with the choice whether or not they want to have children (37, 38). For female carriers, this also affects their planning if they want to have biological children, because of the timing to preventively remove the ovaries and fallopian tubes. Other options may be choosing surrogacy or adoption (38).

A carrier of a pathogenic variant in a *BRCA1* or *BRCA2* gene has a 50% chance of passing this variant on to their offspring. For some couples this might not be acceptable (37, 38). Nowadays, couples can consider preimplantation genetic testing (PGT) before pregnancy and prenatal diagnosis (PND) during pregnancy (37, 38).

Pre-test genetic counseling and testing provided by a genetic healthcare professional

Pre- and post-test counseling for germline genetic testing is usually provided by genetic healthcare professionals only (i.e., clinical geneticists and genetic counselors). In this pathway, patients are referred to a genetics department by their treating doctor or nurse. Pre-test counseling includes reviewing and confirming family history, determining whether the patient is eligible for genetic testing, obtaining informed consent and ordering the genetic test if the patient is eligible and accepts the genetic test. Typically, this takes about 40 to 50 minutes per patient (39-41). Test results are disclosed by the genetic counselor by telephone, in-person or via video conference (42).

Barriers to access to genetic testing

Despite the important implications of genetic testing for patients and family members, currently not all eligible patients with breast or ovarian cancer are referred for genetic testing (43-47). Even after the proven benefit of PARP inhibitors as a treatment for ovarian cancer patients who are carrier of a *BRCA1* or *BRCA2* pathogenic variant, there remains a gap between patients eligible for testing and actual testing rates. Although all patients with epithelial ovarian cancer are eligible for genetic testing, large-scale studies show that testing rates in these patients is between 10% and 35% (43, 45). Testing rates among eligible breast cancer patients are more difficult to determine because not all breast cancer patients are eligible for genetic testing and this depends on multiple eligibility criteria. Studies that evaluated testing rates among eligible patients found that between 25% and 45% of eligible patients are not tested (44, 47, 48).

Several factors play a role in this underutilization of genetic testing. In many countries, financial constraints are major limiting factors, such as poverty and the lack of proper health insurance (11, 49, 50). In the Netherlands, however, the healthcare system includes mandatory basic health insurance, which covers the costs of genetic counseling and testing (51). Thus, we expect that financial constrains do not play a major role in the Netherlands for patients with cancer who fulfill genetic testing criteria. However, financial constrains are not the only limiting factors in the underutilization of genetic testing. Testing rates are also low in state-funded healthcare systems (29). Patients may also decline genetic testing because they do not want to know genetic testing results (47). These patient-related barriers partially explain the underutilization of genetic testing especially in patient groups with low socio-economic status and ethnic minorities (11, 29, 52-56). However, the main problem is that still a large proportion of patients is never referred by their treating healthcare professional for genetic testing (11, 29, 44, 46, 47, 53, 56, 57). This may be due to lack of knowledge among healthcare professionals about genetic testing, but this is mainly due to the difficulty in identifying and referring those at-risk patients (29, 50, 53, 58). Research among untested patients has shown that in the absence of these barriers (i.e., no financial constraints and clear recommendation by their treating healthcare professional), the majority of them would have wanted to undergo genetic testing, especially when the test result would affect treatment or benefit family members (29, 57, 59).

Another barrier in the access to genetic testing is long waiting lists at genetics departments. Due to the increasing number of patients eligible for genetic testing, there is currently a shortage of sufficient genetic counselors and clinical geneticists to provide this care in a timely manner (42, 46, 60). Therefore, germline genetic testing in patients with breast cancer cannot always be performed before surgery (49, 61), and thus preventing patients from incorporating the genetic test result into their surgical and preventive choices. Altogether, the suboptimal identification of patients with breast and ovarian cancer who are carriers of a pathogenic variant in a *BRCA1* or *BRCA2* gene leads to missed opportunities to effectively treat patients, prevent cancers and identify at-risk unaffected family members (29, 62).

These barriers in access to germline genetic testing have led to several new initiatives to improve testing in patients with cancer (63). The review by Hoskins et al. showed large differences in testing rates between hospital sites due to different approaches to increase genetic testing rates for ovarian cancer, such as an opt-out system for genetic testing. Another alternative method that was developed and implemented was mainstream genetic testing, which led to 100% testing rates for patients with ovarian cancer in the Royal Marsden hospital in the United Kingdom (64).

Pre-test genetic counseling and testing provided by a non-genetic healthcare professional

In recent years, there has been a shift in the opinion that pre-test genetic counseling in patients with cancer should be provided exclusively by genetic healthcare professionals to the notion that pre-test genetic counseling can also be provided by non-genetic healthcare professionals (65, 66). This is due to the increasing number of eligible patients, to the fact that most patients do not carry a pathogenic variant in any of the cancer susceptibility genes, and that genetic testing is now considered an integral part of the care pathway of patients with breast or ovarian cancer. In a mainstream genetic testing pathway, pre-test genetic counseling is offered by the doctor or nurse (specialist) already treating the patient. George et al. were the first to report the results of such a mainstream genetic testing pathway for patients with ovarian cancer in the Mainstreaming Cancer Genetics (MCG) program (64).

Although it has been described that genetic testing was also requested by other healthcare professionals prior to the MCG initiative (67-69), an actual protocol for mainstream genetic testing had not been reported until this program. These initiatives without such a protocol have shown important limitations, such as healthcare professionals ordering genetic testing without any form of pre-test counseling (56, 67) or a lack of knowledge about genetics amongst healthcare professionals, requiring more training (69).

Many other mainstream genetic testing initiatives have followed since the MCG initiative, primarily for ovarian cancer (70-86), increasingly for breast cancer (71, 77, 81, 86-92), and to a lesser extent for prostate cancer (75, 93, 94), endometrial cancer (95), and pancreatic cancer (75, 96).

Aim and research questions

For this thesis, we integrated germline genetic testing into routine care for patients with ovarian or breast cancer. To achieve this, we first developed and later implemented a mainstream genetic testing pathway for these patients in which the treating doctor or nurse (specialist) provided pre-test counseling and ordered the genetic test. This pathway has been implemented in all hospitals involved in breast or ovarian cancer care in the service area of the UMC Utrecht genetics department, including the University Medical Center Utrecht and three other hospitals for ovarian cancer. For breast cancer, this pathway was implemented in the same hospitals and five additional hospitals. At a later stage, this pathway was also introduced in four hospitals in the service area of the UMC Groningen genetics department and successfully implemented in two of them.

The overall aim of the projects described in this thesis was to develop and implement mainstream genetic testing pathways to ensure that all eligible patients are offered germline genetic testing early after diagnosis. Early results of genetic testing facilitate personalized treatment options and ensures that family members can be informed in a timely manner when a hereditary cause is found.

Our research questions were:

1) What are the attitudes of non-genetic healthcare professionals in ovarian and breast cancer care towards offering pre-test genetic counseling and ordering a germline genetic test?
2) Is it feasible for non-genetic healthcare professionals in ovarian and breast cancer care to incorporate genetic testing into routine care?
3) How do patients experience genetic care when a genetic test is offered by their treating healthcare professional compared with patients who are offered a genetic test by a genetic healthcare professional?
4) Does implementation of a mainstream genetic testing pathway result in more eligible patients being offered genetic testing?
5) What effect will a mainstream genetic testing pathway have on the genetics-related healthcare costs?

Outline of this thesis

This thesis consists of three parts. The first part reviews the literature in a systematic way on mainstream genetic testing pathways in cancer care and evaluates the feasibility of incorporating a mainstream genetic testing workflow into daily practice (**Chapter 2**).

The second part focuses on mainstream genetic testing in patients with ovarian cancer. The development and implementation of this new workflow is described in **Chapter 3**. This chapter also evaluates the experiences of gynecologic oncologists, gynecologists with a subspecialty training in oncology and nurse specialists with mainstream genetic testing. **Chapter 4** compares the experiences of patients who received mainstream genetic care with patients who received standard genetic care (pre-test counseling at a genetics department). **Chapter 5** evaluates the proportion of patients who were offered germline genetic testing and the healthcare costs from a healthcare payer perspective both before and after implementing the new workflow.

The third part of this thesis focuses on mainstream genetic testing in patients with breast cancer. **Chapter 6** describes the development and implementation of the new workflow and evaluates the experiences of surgeons, medical oncologists, nurse specialists and

nurses with this new workflow. The experiences of patients receiving mainstream genetic care compared with patients receiving standard genetic care are described in **Chapter 7**. **Chapter 8** summarizes the findings of this thesis and finally, **Chapter 9** comprises the general discussion of these findings and discusses future perspectives.

References

1. Hu C, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. N Engl J Med. 2021;384(5):440-451.
2. Breast Cancer Association C, Dorling L, Carvalho S, Allen J, Gonzalez-Neira A, Luccarini C, et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021;384(5):428-439.
3. Pavanello M, Chan IH, Ariff A, Pharoah PD, Gayther SA, Ramus SJ. Rare Germline Genetic Variants and the Risks of Epithelial Ovarian Cancer. Cancers (Basel). 2020;12(10).
4. Huber-Keener KJ. Cancer genetics and breast cancer. Best Pract Res Clin Obstet Gynaecol. 2022;82:3-11.
5. Beitsch PD, Whitworth PW, Hughes K, Patel R, Rosen B, Compagnoni G, et al. Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? J Clin Oncol. 2019;37(6):453-460.
6. Samadder NJ, Riegert-Johnson D, Boardman L, Rhodes D, Wick M, Okuno S, et al. Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome. JAMA Oncol. 2021;7(2):230-237.
7. Buys SS, Sandbach JF, Gammon A, Patel G, Kidd J, Brown KL, et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. Cancer. 2017;123(10):1721-1730.
8. Li J, Wen WX, Eklund M, Kvist A, Eriksson M, Christensen HN, et al. Prevalence of BRCA1 and BRCA2 pathogenic variants in a large, unselected breast cancer cohort. Int J Cancer. 2019;144(5):1195-1204.
9. Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102.
10. Dutch Federation of Medical Specialist. Breast Cancer Guideline 2020 [Available from: https://richtlijnendatabase.nl/richtlijn/borstkanker/algemeen.html].
11. Kurian AW, Ward KC, Howlader N, Deapen D, Hamilton AS, Mariotto A, et al. Genetic Testing and Results in a Population-Based Cohort of Breast Cancer Patients and Ovarian Cancer Patients. J Clin Oncol. 2019;37(15):1305-1315.
12. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654-2663.
13. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011;121(2):353-357.
14. Gaona-Luviano P, Medina-Gaona LA, Magana-Perez K. Epidemiology of ovarian cancer. Chin Clin Oncol. 2020;9(4):47.

15. Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245.
16. Commissie Richtlijnen Gynaecologische Oncologie (CRGO). Guideline hereditary and familial ovarian cancer 2015 [updated June 1. Available from: https://www.oncoline.nl/erfelijk-en-familiair-ovariumcarcinoom].
17. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402-2416.
18. Nyberg T, Frost D, Barrowdale D, Evans DG, Bancroft E, Adlard J, et al. Prostate Cancer Risks for Male BRCA1 and BRCA2 Mutation Carriers: A Prospective Cohort Study. Eur Urol. 2020;77(1):24-35.
19. Li S, Silvestri V, Leslie G, Rebbeck TR, Neuhausen SL, Hopper JL, et al. Cancer Risks Associated With BRCA1 and BRCA2 Pathogenic Variants. J Clin Oncol. 2022;40(14):1529-1541.
20. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol. 2020;38(18):2080-2106.
21. Wevers MR, Aaronson NK, Verhoef S, Bleiker EM, Hahn DE, Kuenen MA, et al. Impact of rapid genetic counselling and testing on the decision to undergo immediate or delayed prophylactic mastectomy in newly diagnosed breast cancer patients: findings from a randomised controlled trial. Br J Cancer. 2014;110(4):1081-1087.
22. Metcalfe KA, Eisen A, Poll A, Candib A, McCready D, Cil T, et al. Rapid Genetic Testing for BRCA1 and BRCA2 Mutations at the Time of Breast Cancer Diagnosis: An Observational Study. Ann Surg Oncol. 2021;28(4):2219-2226.
23. Yadav S, Jinna S, Pereira-Rodrigues O, Reeves A, Campian S, Sufka A, et al. Impact of preoperative BRCA1/2 testing on surgical decision-making in patients with newly diagnosed breast cancer. Breast J. 2018;24(4):541-548.
24. Culver JO, Freiberg Y, Ricker C, Comeaux JG, Chang EY, Banerjee V, et al. Integration of Universal Germline Genetic Testing for All New Breast Cancer Patients. Ann Surg Oncol. 2023;30(2):1017-1025.
25. Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021;16(3):255-282.
26. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405.
27. Tew WP, Lacchetti C, Ellis A, Maxian K, Banerjee S, Bookman M, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-3493.
28. Menon U, Gentry-Maharaj A, Burnell M, Singh N, Ryan A, Karpinskyj C, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2021;397(10290):2182-2193.

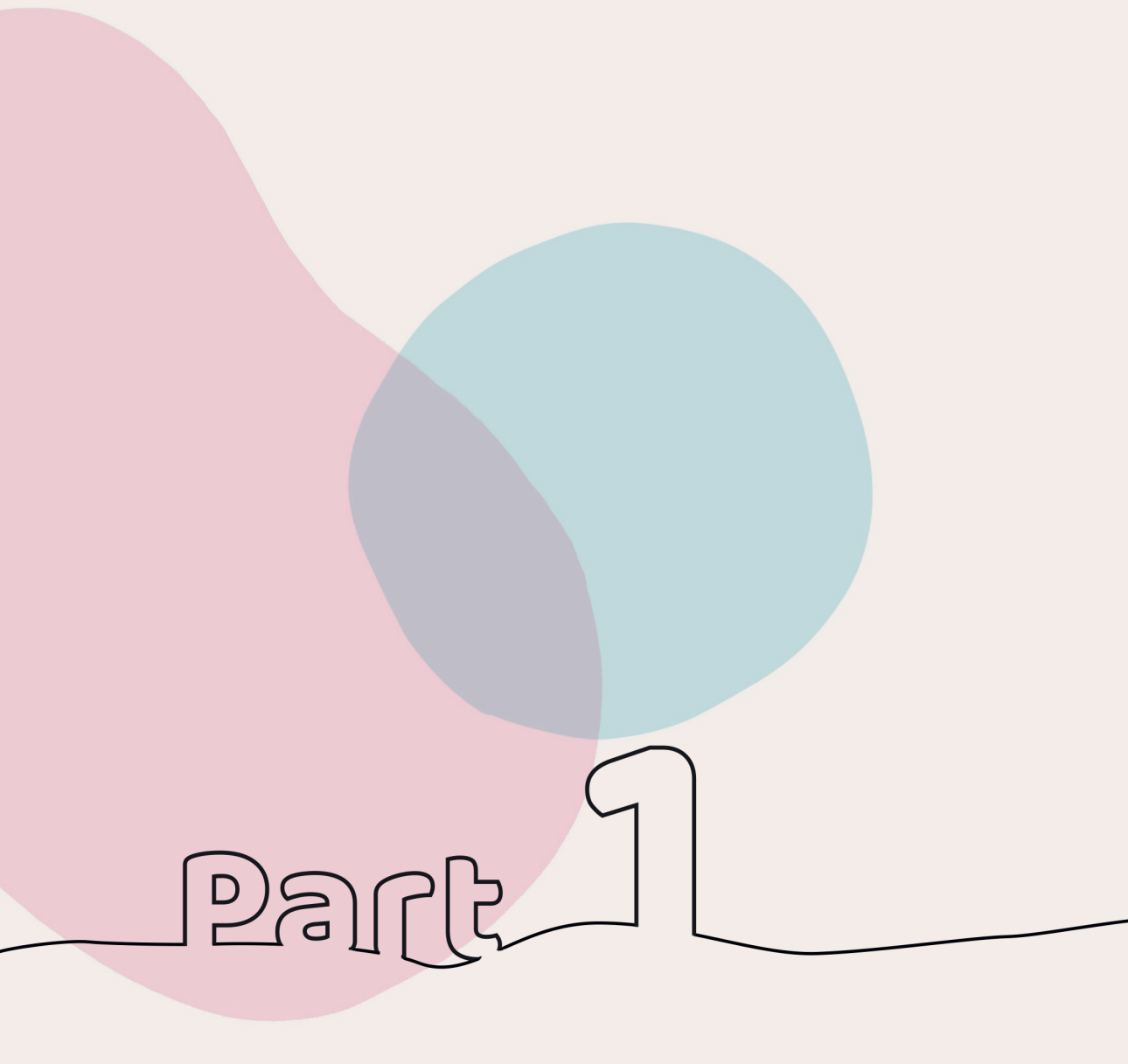
29. Hoskins PJ, Gotlieb WH. Missed therapeutic and prevention opportunities in women with BRCA-mutated epithelial ovarian cancer and their families due to low referral rates for genetic counseling and BRCA testing: A review of the literature. CA Cancer J Clin. 2017;67(6):493-506.
30. Domchek SM, Jhaveri K, Patil S, Stopfer JE, Hudis C, Powers J, et al. Risk of metachronous breast cancer after BRCA mutation-associated ovarian cancer. Cancer. 2013;119(7):1344-1348.
31. Gangi A, Cass I, Paik D, Barmparas G, Karlan B, Dang C, et al. Breast cancer following ovarian cancer in BRCA mutation carriers. JAMA Surg. 2014;149(12):1306-1313.
32. Vencken PM, Kriege M, Hooning M, Menke-Pluymers MB, Heemskerk-Gerritsen BA, van Doorn LC, et al. The risk of primary and contralateral breast cancer after ovarian cancer in BRCA1/BRCA2 mutation carriers: Implications for counseling. Cancer. 2013;119(5):955-962.
33. McGee J, Giannakeas V, Karlan B, Lubinski J, Gronwald J, Rosen B, et al. Risk of breast cancer after a diagnosis of ovarian cancer in BRCA mutation carriers: Is preventive mastectomy warranted? Gynecol Oncol. 2017;145(2):346-351.
34. Evans DG, Lalloo F, Ashcroft L, Shenton A, Clancy T, Baildam AD, et al. Uptake of risk-reducing surgery in unaffected women at high risk of breast and ovarian cancer is risk, age, and time dependent. Cancer Epidemiol Biomarkers Prev. 2009;18(8):2318-2324.
35. Page EC, Bancroft EK, Brook MN, Assel M, Hassan Al Battat M, Thomas S, et al. Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers. Eur Urol. 2019;76(6):831-842.
36. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 2.2023 - [updated January 10, 2023. Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf].
37. Lombardi L, Trumello C, Stuppia L, Antonucci I, Brandao T, Babore A. BRCA1/2 pathogenetic variant carriers and reproductive decisions: Gender differences and factors associated with the choice of preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PND). J Assist Reprod Genet. 2022;39(7):1433-1443.
38. Skrovanek E, Dunbar-Jacob J, Dunwoody C, Wesmiller S. Integrative Review of Reproductive Decision-making of Women Who Are BRCA Positive. J Obstet Gynecol Neonatal Nurs. 2020;49(6):525-536.
39. Albada A, Ausems MG, van Dulmen S. Counselee participation in follow-up breast cancer genetic counselling visits and associations with achievement of the preferred role, cognitive outcomes, risk perception alignment and perceived personal control. Soc Sci Med. 2014;116:178-186.
40. Eijzenga W, Aaronson NK, Hahn DE, Sidharta GN, van der Kolk LE, Velthuizen ME, et al. Effect of routine assessment of specific psychosocial problems on personalized communication, counselors' awareness, and distress levels in cancer genetic counseling practice: a randomized controlled trial. J Clin Oncol. 2014;32(27):2998-3004.
41. Cohen SA, Nixon DM. A collaborative approach to cancer risk assessment services using genetic counselor extenders in a multi-system community hospital. Breast Cancer Res Treat. 2016;159(3):527-534.

42. Stoll K, Kubendran S, Cohen SA. The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. Am J Med Genet C Semin Med Genet. 2018;178(1):24-37.
43. Kurian AW, Ward KC, Abrahamse P, Bondarenko I, Hamilton AS, Deapen D, et al. Time Trends in Receipt of Germline Genetic Testing and Results for Women Diagnosed With Breast Cancer or Ovarian Cancer, 2012-2019. J Clin Oncol. 2021;39(15):1631-1640.
44. Alberty-Oller JJ, Weltz S, Santos A, Pisapati K, Ru M, Weltz C, et al. Adherence to NCCN Guidelines for Genetic Testing in Breast Cancer Patients: Who Are We Missing? Ann Surg Oncol. 2021;28(1):281-286.
45. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National Estimates of Genetic Testing in Women With a History of Breast or Ovarian Cancer. J Clin Oncol. 2017;35(34):3800-3806.
46. Hoskins PJ. Inadequate Rates of BRCA Testing with its Negative Consequences for Women with Epithelial Ovarian Cancer and their Families: an Overview of the Literature. Clin Oncol (R Coll Radiol). 2018;30(8):472-483.
47. Hafertepen L, Pastorino A, Morman N, Snow J, Halaharvi D, Byrne L, et al. Barriers to genetic testing in newly diagnosed breast cancer patients: Do surgeons limit testing? Am J Surg. 2017;214(1):105-110.
48. Stuckey A, Febbraro T, Laprise J, Wilbur JS, Lopes V, Robison K. Adherence Patterns to National Comprehensive Cancer Network Guidelines for Referral of Women With Breast Cancer to Genetics Professionals. Am J Clin Oncol. 2016;39(4):363-367.
49. Kurian AW, Li Y, Hamilton AS, Ward KC, Hawley ST, Morrow M, et al. Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer. J Clin Oncol. 2017;35(20):2232-2239.
50. Hinchcliff EM, Bednar EM, Lu KH, Rauh-Hain JA. Disparities in gynecologic cancer genetics evaluation. Gynecol Oncol. 2019;153(1):184-191.
51. Kroneman M, Boerma W, van den Berg M, Groenewegen P, de Jong J, van Ginneken E. Netherlands: Health System Review. Health Syst Transit. 2016;18(2):1-240.
52. Baars JE, van Dulmen AM, Velthuizen ME, Theunissen EB, Vrouenraets BC, Kimmings AN, et al. Migrant breast cancer patients and their participation in genetic counseling: results from a registry-based study. Fam Cancer. 2016;15(2):163-171.
53. McCarthy AM, Bristol M, Domchek SM, Groeneveld PW, Kim Y, Motanya UN, et al. Health Care Segregation, Physician Recommendation, and Racial Disparities in BRCA1/2 Testing Among Women With Breast Cancer. J Clin Oncol. 2016;34(22):2610-2618.
54. van der Giessen JAM, van Riel E, Velthuizen ME, van Dulmen AM, Ausems M. Referral to cancer genetic counseling: do migrant status and patients' educational background matter? J Community Genet. 2017;8(4):303-310.
55. White S, Jacobs C, Phillips J. Mainstreaming genetics and genomics: a systematic review of the barriers and facilitators for nurses and physicians in secondary and tertiary care. Genet Med. 2020;22(7):1149-1155.

56. Armstrong J, Toscano M, Kotchko N, Friedman S, Schwartz MD, Virgo KS, et al. Utilization and Outcomes of BRCA Genetic Testing and Counseling in a National Commercially Insured Population: The ABOUT Study. JAMA Oncol. 2015;1(9):1251-1260.
57. Kurian AW, Griffith KA, Hamilton AS, Ward KC, Morrow M, Katz SJ, et al. Genetic Testing and Counseling Among Patients With Newly Diagnosed Breast Cancer. JAMA. 2017;317(5):531-534.
58. Morrow A, Chan P, Tucker KM, Taylor N. The design, implementation, and effectiveness of intervention strategies aimed at improving genetic referral practices: a systematic review of the literature. Genet Med. 2021;23(12):2239-2249.
59. Vargason AB, Turner CE, Shriver CD, Ellsworth RE. Genetic testing in Non-Hispanic Black women with breast cancer treated within an equal-access healthcare system. Genetics in Medicine. 2022;24(1):232-237.
60. Hoskovec JM, Bennett RL, Carey ME, DaVanzo JE, Dougherty M, Hahn SE, et al. Projecting the Supply and Demand for Certified Genetic Counselors: a Workforce Study. J Genet Couns. 2018;27(1):16-20.
61. Katz SJ, Kurian AW, Morrow M. Treatment Decision-making and Genetic Testing for Breast Cancer: Mainstreaming Mutations. JAMA. 2015;314(10):997-998.
62. LeVasseur N, Chia S. Cancer screening and prevention in BRCA mutation carriers: a missed opportunity? Br J Cancer. 2019;121(1):1-2.
63. McCuaig JM, Armel SR, Care M, Volenik A, Kim RH, Metcalfe KA. Next-Generation Service Delivery: A Scoping Review of Patient Outcomes Associated with Alternative Models of Genetic Counseling and Genetic Testing for Hereditary Cancer. Cancers (Basel). 2018;10(11).
64. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.
65. Rajagopal PS, Catenacci DVT, Olopade OI. The Time for Mainstreaming Germline Testing for Patients With Breast Cancer Is Now. J Clin Oncol. 2019;37(24):2177-2178.
66. Aalfs CM, Westermann AM, van El CG. [Making better use of the clinical geneticist's expertise; treating physician could request a DNA test for most cancer patients]. Ned Tijdschr Geneeskd. 2017;161:D1525.
67. Cragun D, Camperlengo L, Robinson E, Caldwell M, Kim J, Phelan C, et al. Differences in BRCA counseling and testing practices based on ordering provider type. Genet Med. 2015;17(1):51-57.
68. Keating NL, Stoeckert KA, Regan MM, DiGianni L, Garber JE. Physicians' experiences with BRCA1/2 testing in community settings. J Clin Oncol. 2008;26(35):5789-5796.
69. Prochniak CF, Martin LJ, Miller EM, Knapke SC. Barriers to and motivations for physician referral of patients to cancer genetics clinics. J Genet Couns. 2012;21(2):305-325.
70. Bednar EM, Oakley HD, Sun CC, Burke CC, Munsell MF, Westin SN, et al. A universal genetic testing initiative for patients with high-grade, non-mucinous epithelial ovarian cancer and the implications for cancer treatment. Gynecol Oncol. 2017;146(2):399-404.

71. Benusiglio PR, Korenbaum C, Vibert R, Ezenfis J, Geoffron S, Paul C, et al. Utility of a mainstreamed genetic testing pathway in breast and ovarian cancer patients during the COVID-19 pandemic. Eur J Med Genet. 2020;63(12):104098.
72. Colombo N, Huang G, Scambia G, Chalas E, Pignata S, Fiorica J, et al. Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer. J Clin Oncol. 2018;36(13):1300-1307.
73. Flaum N, Morgan RD, Burghel GJ, Bulman M, Clamp AR, Hasan J, et al. Mainstreaming germline BRCA1/2 testing in non-mucinous epithelial ovarian cancer in the North West of England. Eur J Hum Genet. 2020;28(11):1541-1547.
74. Gleeson M, Kentwell M, Meiser B, Do J, Nevin S, Taylor N, et al. The development and evaluation of a nationwide training program for oncology health professionals in the provision of genetic testing for ovarian cancer patients. Gynecol Oncol. 2020;158(2):431-439.
75. Hamilton JG, Symecko H, Spielman K, Breen K, Mueller R, Catchings A, et al. Uptake and acceptability of a mainstreaming model of hereditary cancer multigene panel testing among patients with ovarian, pancreatic, and prostate cancer. Genet Med. 2021;23(11):2105-2113.
76. Ip E, Young AL, Scheinberg T, Harrison M, Beale P, Goodwin A. Evaluation of a mainstream genetic testing program for women with ovarian or breast cancer. Asia Pac J Clin Oncol. 2022;18(5):e414-e419.
77. McCuaig JM, Thain E, Malcolmson J, Keshavarzi S, Armel SR, Kim RH. A Comparison of Patient-Reported Outcomes Following Consent for Genetic Testing Using an Oncologist- or Genetic Counselor-Mediated Model of Care. Curr Oncol. 2021;28(2):1459-1471.
78. McLeavy L, Rahman B, Kristeleit R, Ledermann J, Lockley M, McCormack M, et al. Mainstreamed genetic testing in ovarian cancer: patient experience of the testing process. Int J Gynecol Cancer. 2020;30(2):221-226.
79. Powell CB, Laurent C, Ciaravino G, Garcia C, Han L, Hoodfar E, et al. Streamlining genetic testing for women with ovarian cancer in a Northern California health care system. Gynecol Oncol. 2020;159(1):221-228.
80. Rahman B, Lanceley A, Kristeleit RS, Ledermann JA, Lockley M, McCormack M, et al. Mainstreamed genetic testing for women with ovarian cancer: first-year experience. J Med Genet. 2019;56(3):195-198.
81. Richardson M, Min HJ, Hong Q, Compton K, Mung SW, Lohn Z, et al. Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System. Cancers (Basel). 2020;12(2).
82. Rumford M, Lythgoe M, McNeish I, Gabra H, Tookman L, Rahman N, et al. Oncologist-led BRCA 'mainstreaming' in the ovarian cancer clinic: A study of 255 patients and its impact on their management. Sci Rep. 2020;10(1):3390.
83. Sadinsky MB, Power J, Ambrosio E, Palma L, Zeng X, Foulkes WD, et al. Patient Experience with a Gynecologic Oncology-Initiated Genetic Testing Model for Women with Tubo-Ovarian Cancer. Curr Oncol. 2022;29(5):3565-3575.

84. Yoon SY, Wong SW, Lim J, Ahmad S, Mariapun S, Padmanabhan H, et al. Oncologist-led BRCA counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes. J Med Genet. 2022;59(3):220-229.
85. Czekalski MA, Huziak RC, Durst AL, Taylor S, Mai PL. Mainstreaming Genetic Testing for Epithelial Ovarian Cancer by Oncology Providers: A Survey of Current Practice. JCO Precis Oncol. 2022;6:e2100409.
86. McVeigh TP, Sweeney KJ, Brennan DJ, McVeigh UM, Ward S, Strydom A, et al. A pilot study investigating feasibility of mainstreaming germline BRCA1 and BRCA2 testing in high-risk patients with breast and/or ovarian cancer in three tertiary Cancer Centres in Ireland. Fam Cancer. 2022. Online ahead of print.
87. Grindedal EM, Jorgensen K, Olsson P, Gravdehaug B, Luras H, Schlichting E, et al. Mainstreamed genetic testing of breast cancer patients in two hospitals in South Eastern Norway. Fam Cancer. 2020;19(2):133-142.
88. Kemp Z, Turnbull A, Yost S, Seal S, Mahamdallie S, Poyastro-Pearson E, et al. Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer. JAMA Netw Open. 2019;2(5):e194428.
89. Lee YQ, Yoon SY, Hassan T, Padmanabhan H, Yip CH, Keng WT, et al. Attitudes and training needs of oncologists and surgeons in mainstreaming breast cancer genetic counseling in a low-to-middle income Asian country. J Genet Couns. 2022 Oct;31(5):1080-1089.
90. Scott N, O'Sullivan J, Asgeirsson K, Macmillan D, Wilson E. Changing practice: moving to a specialist nurse-led service for BRCA gene testing. Br J Nurs. 2020;29(10):S6-S13.
91. Beard C, Monohan K, Cicciarelli L, James PA. Mainstream genetic testing for breast cancer patients: early experiences from the Parkville Familial Cancer Centre. Eur J Hum Genet. 2021;29(5):872-880.
92. Stromsvik N, Olsson P, Gravdehaug B, Luras H, Schlichting E, Jorgensen K, et al. "It was an important part of my treatment": a qualitative study of Norwegian breast Cancer patients' experiences with mainstreamed genetic testing. Hered Cancer Clin Pract. 2022;20(1):6.
93. Scheinberg T, Goodwin A, Ip E, Linton A, Mak B, Smith DP, et al. Evaluation of a Mainstream Model of Genetic Testing for Men With Prostate Cancer. JCO Oncol Pract. 2021;17(2):e204-e16.
94. Abusamra SM, Solorzano MA, Luke M, Quarles J, Jacobs MF, Das S, et al. Satisfaction With Clinician-Led Germline Genetic Counseling in Patients With Prostate Cancer. J Urol. 2022;208(5):1007-1017.
95. Ryan NA, Donnelly L, Stocking K, Evans DG, Crosbie EJ. Feasibility of Gynaecologist Led Lynch Syndrome Testing in Women with Endometrial Cancer. J Clin Med. 2020;9(6).
96. Ramsey ML, Tomlinson J, Pearlman R, Abushahin L, Aeilts A, Chen HZ, et al. Mainstreaming germline genetic testing for patients with pancreatic cancer increases uptake. Fam Cancer. 2023 Jan;22(1):91-97.


Part 1

Part 1

General overview of mainstream genetic testing

Chapter 2

The feasibility of implementing mainstream germline genetic testing in routine cancer care – a systematic review

Kyra Bokkers [1,†], Michiel Vlaming [1,†], Ellen G. Engelhardt [2], Ronald P. Zweemer [3], Inge M. van Oort [4], Lambertus A.L.M. Kiemeney [4,5], Eveline M.A. Bleiker [2,6,7] and Margreet G.E.M. Ausems [1]

† These authors contributed equally to this work

1. Division Laboratories, Pharmacy and Biomedical Genetics, Department of Genetics, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
2. Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
3. Department of Gynecological Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
4. Department of Urology, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands
5. Department for Health Evidence, Radboud University Medical Center, Geert Grooteplein Zuid 21, 6525 EZ Nijmegen, The Netherlands
6. Department of Clinical Genetics, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
7. Family Cancer Clinic, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

Cancers (Basel). 2022 Feb 19;14(4):1059.

Simple summary

Germline genetic testing for patients with cancer can have important implications for treatment, preventive options, and for family members. In a mainstream genetic testing pathway, pre-test counseling is performed by non-genetic healthcare professionals, thereby making genetic testing more accessible to all patients who might benefit from it. These mainstream genetic testing pathways are being implemented in different hospitals around the world, and for different cancer types. It is important to evaluate how a mainstream genetic testing pathway can be made sustainable and if quality of genetic care is maintained. We show in this systematic review that it is feasible to incorporate a mainstream genetic testing pathway into routine cancer care while maintaining quality of care. A training procedure for non-genetic healthcare professionals and a close collaboration between genetics and other clinical departments are highly recommended to ensure sustainability.

Abstract

Background: Non-genetic healthcare professionals can provide pre-test counseling and order germline genetic tests themselves, which is called mainstream genetic testing. In this systematic review, we determined whether mainstream genetic testing was feasible in daily practice while maintaining quality of genetic care.

Methods: PubMed, Embase, CINAHL, and PsychINFO were searched for articles describing mainstream genetic testing initiatives in cancer care.

Results: Seventeen articles, reporting on 15 studies, met the inclusion criteria. Non-genetic healthcare professionals concluded that mainstream genetic testing was possible within the timeframe of a routine consultation. In 14 studies, non-genetic healthcare professionals completed some form of training about genetics. When referral was coordinated by a genetics team, the majority of patients carrying a pathogenic variant were seen for post-test counseling by genetic healthcare professionals. The number of days between cancer diagnosis and test result disclosure was always lower in the mainstream genetic testing pathway than in the standard genetic testing pathway (e.g., pre-test counseling at genetics department).

Conclusions: Mainstream genetic testing seems feasible in daily practice with no insurmountable barriers. A structured pathway with a training procedure is desirable, as well as a close collaboration between genetics and other clinical departments.

Keywords: Genetic counseling; Mainstream genetic testing; Cancer; Feasibility; Quality of care; Systematic review

Introduction

The use of germline genetic tests in cancer care is changing rapidly. Gene panel testing is increasingly being used instead of single gene testing, and the criteria for genetic testing have been broadened in several types of cancer (1-3). In addition, new treatment options are now available that depend on the results of genetic testing. For example, poly (ADP-ribose) polymerase (PARP) inhibitors can be used in the treatment of patients with ovarian, breast, or prostate cancer, and they are especially beneficial for patients carrying a germline or somatic pathogenic variant in a *BRCA* gene (4-6). These changes in genetic testing and care, together with the growing numbers of eligible patients who can benefit from genetic testing and the limited capacity of the genetics departments to meet the needs of the increasing numbers of patients, have paved the way for mainstream genetic testing. In a mainstream genetic testing pathway, non-genetic healthcare professionals (NGHCPs) provide pre-test counseling (e.g., review cancer family history, discuss possible implications of a genetic test) and order the genetic test after obtaining informed consent. These NGHCPs are not formally trained as genetic counselors or clinical geneticists. In the standard genetic testing pathway, these steps are taken by genetic counselors or clinical geneticists.

The development and implementation of a mainstream genetic testing pathway was first described by George et al. in 2016 in ovarian cancer patients, within the Mainstreaming Cancer Genetics program (7). Subsequently, several other mainstream genetic testing initiatives arose around the globe in a research setting, mainly in ovarian cancer, but also in other cancers (8-11).

The systematic review of Scheinberg et al. studied the acceptability of mainstream genetic testing (12). They showed that mainstream genetic testing in cancer care was acceptable for patients and NGHCPs to manage the growing demand for genetic tests. They also concluded that mainstream genetic testing was feasible. To make recommendations for implementing a mainstream genetic testing pathway in daily practice, it is important to determine clear end points for feasibility and to guarantee that quality of care is maintained. To maintain quality of care, NGHCPs should be well equipped to perform pre-test counseling. The systematic review of Scheinberg et al. included studies on ovarian, breast and colorectal cancer (12). Since then, multiple new mainstream initiatives in different types of cancers have been published.

We performed a systematic review to assess the available literature on mainstream genetic testing in cancer care. The following research questions will be answered: (1) Is mainstream genetic testing in cancer patients feasible for NGHCPs in daily practice? and

(2) Is the quality of genetic care maintained when patients undergo mainstream genetic testing?

Materials and methods

This review was conducted according to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) report (13).

Eligibility criteria

Studies were eligible for inclusion if a mainstream genetic testing pathway in patients with cancer was evaluated. This pathway had to meet the following three criteria: (1) counseling and ordering of genetic testing was performed by a medical specialist, nurse specialist or nurse, not formally trained as a clinical geneticist or genetic counselor, (2) pre-test counseling was performed, and (3) genetic testing was performed with the primary aim of identifying pathogenic germline variants in patients with cancer.

We considered the study of George et al. (7), published in 2016, to be the first key paper on mainstream genetic testing, and we searched for studies that were published from 2013 onwards, because it is unlikely that earlier mainstream genetic testing initiatives exist. Studies were excluded when predictive genetic testing was performed in healthy individuals. Other exclusion criteria were only a conference abstract being published, being published in another language than English, and lack of availability of a full-text article. Furthermore, we excluded reviews and articles not containing any data (e.g., opinion papers).

Search strategy and databases

Our search consisted of three main criteria: (1) cancer, (2) germline genetic testing, and (3) mainstream genetic testing. The full search was performed in collaboration with a library information specialist, and is shown in Table S1. We searched the following databases: PubMed, Embase, CINAHL and PsychINFO on 4 November 2020. Additional studies were identified through backward and forward reference searching for all included papers.

Data collection

All identified studies were imported into Rayyan (14), a web tool for independent screening of abstracts. All abstracts were screened by two authors (KB and MA or KB and MV) for eligibility.

Outcomes

We assessed the feasibility and quality of care of mainstream genetic testing. Whether the mainstream genetic testing initiatives were feasible for NGHCPs to implement in daily practice was assessed based on two outcomes: (1) the time investment for NGHCPs to discuss and order genetic testing and whether this was acceptable for them, and (2) barriers and facilitators for NGHCPs regarding mainstream genetic testing.

We assessed quality of genetic care based on the following outcomes: (1) whether some form of training in genetics and genetic counseling was offered; (2) whether an informed consent procedure was described and how informed consent was documented; (3) whether patients carrying a pathogenic variant were invited for post-test counseling at a genetics department; (4) turnaround times for genetic testing (i.e., days between cancer diagnosis, discussing the DNA test, obtaining the blood sample, availability of test result, and disclosure of the test result to the patient); and (5) whether genetic testing was performed according to national guidelines (i.e., whether eligible patients were missed and whether ineligible patients were offered testing unnecessarily).

Critical appraisal

Two authors (KB and MV) independently evaluated all selected articles using the Quality Improvement Minimum Quality Criteria Set (QI-MQCS), because mainstream genetic testing is considered to improve quality of care (15). The QI-MQCS covers 16 domains (see Supplementary Methods) for evaluating articles with a quality improvement intervention. These domains mainly focus on the rationale and motivation behind the intervention, how well the intervention can be implemented, whether the intervention is sustainable and has the potential for larger rollouts, and whether the study methods are sufficiently well described. The number of met criteria is noted in Table S2. The QI-MQCS does not supply cut-off values indicating high versus low quality of an article.

Results

We identified 537 articles through database searching. Five more articles were identified through reference and citation searching. After removing duplicates, another 439 articles were excluded based on title and abstract. The remaining 43 articles were assessed based on their full text, which led to the elimination of 26 more articles, resulting in 17 articles eligible for our analysis. See Figure 1 for the entire selection process.

Characteristics

We included 17 papers that reported on 15 studies. These 15 studies included nine mainstream genetic testing pathways for patients with ovarian cancer, three for breast

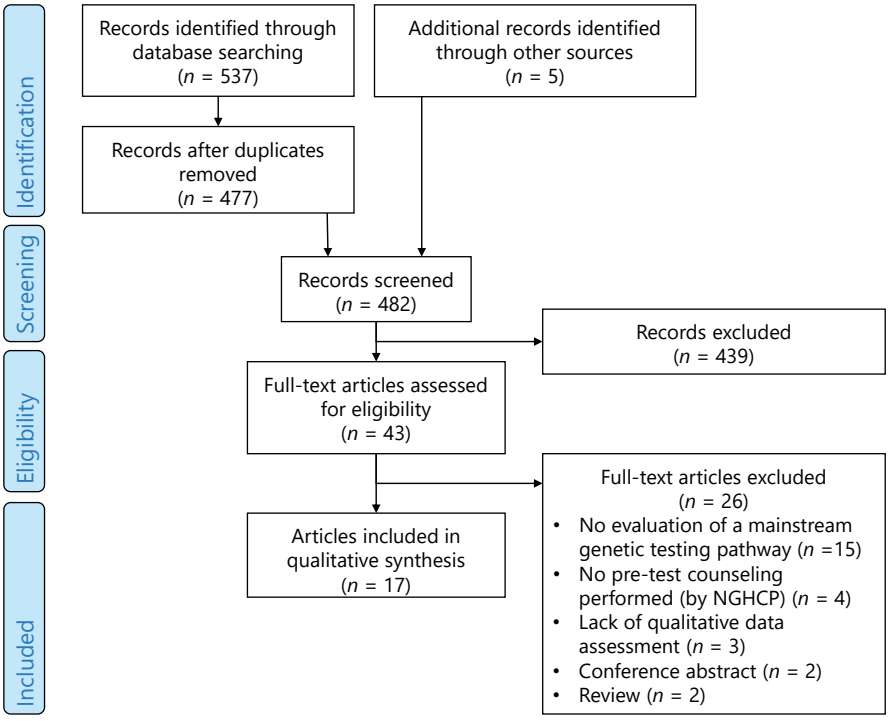


Figure 1. Prisma flow chart

cancer, one for breast and ovarian cancer, one for endometrial cancer and one for prostate cancer. Of these 15 studies, 2 were performed in multiple countries and 13 in one country, mainly in the United Kingdom (8 out of 15 studies). All studies, except one (16), were conducted in a research setting. The outcomes on feasibility and quality of care for each study are described in Table S2.

Feasibility

Time investment for NGHCPs

The time investment for NGHCPs to discuss genetic testing with patients is shown in Table 1. Four out of seven studies described mainstream genetic testing initiatives for patients with ovarian cancer (7, 17 – 20). The duration in minutes to discuss genetic testing varied from an average of 8 to 20 minutes and discussing genetic testing was possible within the available timeframe.

Barriers and facilitators for NGHCPs

Barriers and facilitators of mainstream genetic testing for NGHCPs (7,8,11,17-21) are shown in Table 2.

Table 1. Time investment for NGHCPs to perform pre-test counseling and disclose genetic test results

	References
Extra time to discuss genetic test	
- No significant added time	(19)
- 6–10 min (21/64 NGHCPs) and 11–20 min (17/64 NGHCPs)	(18)
- 8 min	(9,20)
- 10 min	(11)
- 20 min	(17)
Extra time to disclose genetic test result	
- 6–10 min (21/54 NGHCPs) and 4–5 min (8/54 NGHCPs)	(18)
- 9 min	(11)
NGHCPs (strongly) agreed that discussing genetic testing was possible within the timeframe of a consultation	(7,8,11,17,20)
Workload increased slightly (24/46 NGHCPs) or did not increase (19/46 NGHCPs)	(18)

Table 2. Barriers and facilitators of mainstream genetic testing for NGHCPs

	References
Barriers	
- Concerns about added time pressure	(11,19)
- Inadequate knowledge about genetics	(11)
- Lack of knowledge of VUSs	(11,21)
- Lack of local infrastructure	(18)
- Lack of human resources	(18)
- Lack of funding/unwillingness to allocate funds	(18)
Facilitators	
- Supporting materials (training and Frequently Asked Questions)	(7,8,17,20)
- Approved clinical protocol	(7,8,17,20)
- Information sheets to provide to patients	(7,8,17)
- Assistance of a nurse consultant	(11)
- Required written test packages	(11)
- Education program	(11)

Quality of care

Training of NGHCPs

In 14 out of 15 studies, a training program was offered to NGHCPs (7-9,11,17-27). One study reported that NGHCPs could attend informational meetings, but they did not receive any specific training in medical genetics (16). Five studies (8,21,22,26,27) used a training program that was identical to or based on the Mainstreaming Cancer Genetics

(MCG) program (7). This MCG training consisted of online videos. All articles that described the content of the training stated that it covered the informed consent procedure (7,11,17-19,22,23,25,27). Additionally, basic information about the tested genes was provided in multiple training programs. In addition, some training programs provided a detailed explanation of the mainstream genetic testing pathway, health insurance information, and/or billing policies (7,11,22). In most studies (four out of six) that explicitly described time investment to complete the training, a time investment of approximately one hour was stated (9,11,18,20). George et al. described a training of less than 30 minutes (7). Only Scott et al. described a more extensive training with, among other things, half a day of training by the genetics department about interpreting results and about referral of patients with other cancer syndromes (27). In four studies, time investment was not explicitly described, but it was stated that the training was based on the training of George et al. (8,21,24,26). The effect that the training had on, for example, knowledge or skills was only described by Gleeson et al. (18). Gleeson et al. showed a significant improvement of skills 12 months after the training, but there was no significant difference in knowledge. Skills were self-reported based on the Influences on Patient Safety Behaviors Questionnaire (IPSBQ) (28). In this questionnaire, NGHCPs assessed whether the training was adequate and offered regularly enough to ensure that all eligible patients were offered genetic testing.

Informed consent

All included studies described that patients provided informed consent before NGHCPs ordered a genetic test. In 10 out of the 15 studies, written informed consent was obtained (7-9,11,16,18-20,24-26), and one study described that verbal and/or written informed consent was obtained before testing (23). Two studies described using the MCG training program, but did not clearly mention if they also used the predefined consent forms developed in this program (21,27).

Six studies specified in their article or supplementary material what they considered key topics that should be discussed during pre-test counseling for genetic testing (7,8,17,18,20,26). All necessary elements for pre-test counseling are shown in Table 3.

Genetic counseling for pathogenic variants

In three studies, all patients with a pathogenic variant were invited by the genetics department for post-test counseling by genetic healthcare professionals (7,8,19,20). In these studies, attendance for post-test counseling was nearly 100%. In the MCG-breast study, two patients out of 117 did not attend post-test counseling at a genetics department (8). One of these patients contacted the genetics department later.

In 11 studies, NGHCPs needed to refer patients themselves if the results showed a pathogenic variant (9,11,16,17,21-27). In three studies, all or nearly all patients were

Table 3. Necessary elements for pre-test genetic counseling in mainstream genetic testing

	References
Topics for pre-test genetic counseling	
- Discussing the genes that are tested and their role in the development of cancer	(7,8,17,18,20,26)
- The possible implications of a genetic test for patients (mainly on treatment) and family members	(7,8,17,18,20,26)
- Possible outcomes of a genetic test (i.e., normal result, pathogenic or uncertain variant)	(17,20,26)
- Costs	(17,18,20)
- The possibility of additional pre-test counseling at a genetics department	(17,18)
Informed consent	
- Written informed consent	(7-9,11,18-20,24-26)
- Oral and/or written informed consent	(23)
- Informed consent obtained (not specified as verbal or written)	(17,21,22,27)
Patient information material [a]	
- A summary of the information discussed and/or additional information was provided to the patient in an information sheet after discussing the genetic test	(7-9,11,16-20,26,27)

[a] McLeavy et al. and Rahman et al. used the training developed in the MCG program, but they did not state whether they also used the predefined information sheets developed for patients (21,24).

referred for post-test counseling at a genetics department (9,23,26), although in one of these studies reminder letters for oncologists to refer a patient were necessary (23). One study reported that 14 out of 18 patients with a pathogenic variant were referred for post-test counseling, and two patients were referred outside of the study period (21). Attendance for post-test counseling after referral was between 91% and 100% (9,26). In the ENGAGE study, 76% of patients with a pathogenic variant attended post-test counseling in the European countries, whereas in the US 34% of patients attended post-test counseling (17).

Turnaround times

The turnaround times are summarized in Figure 2. For most studies, a test result was obtained within 3 to 6 weeks after discussing the genetic test with the patient and ordering the test. The longest mean turnaround time was reported by Richardson et al., with 191 days (27 weeks) from discussing the genetic test to disclosing the test result to the patient (25). An average time was not measured in the study of McLeavy et al., but they reported that 45% of patients in their study received their test results more than 12 months after diagnosis (24). For all studies that compared turnaround times of the mainstream genetic testing pathway with the standard pathway, there was a reduction in turnaround times during the mainstream pathway (7,8,22,25-27).

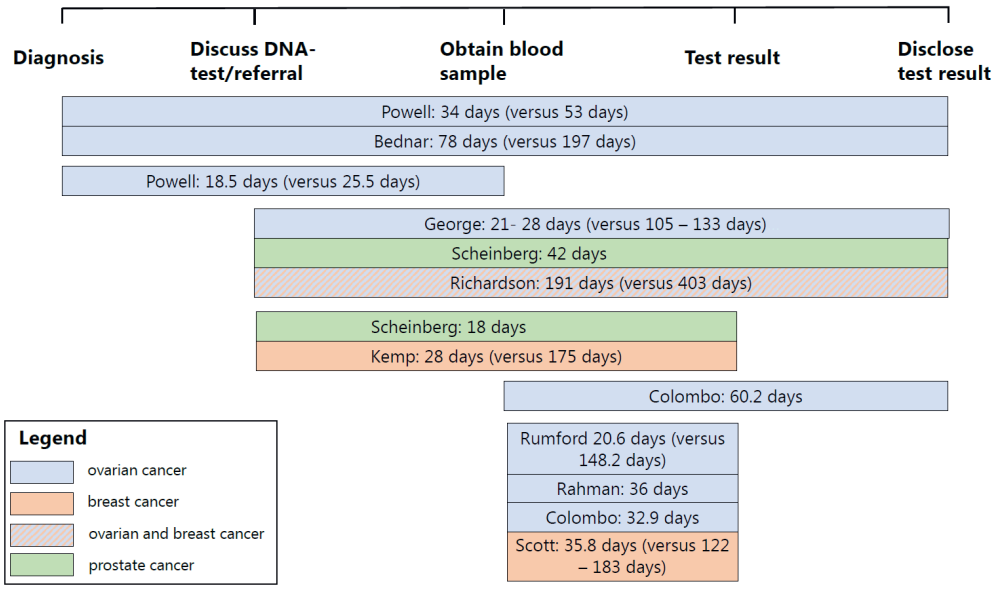


Figure 2. Turnaround times from diagnosis to disclosure of the test result in the patient
Note: if multiple turnaround times were mentioned in one study, these turnaround times are all shown separately. In the articles, turnaround times were reported as calendar days, working days or weeks and these are all shown here as calendar days. Turnaround times of the standard genetic testing pathway are shown between brackets if they were mentioned in the articles.

Three studies reported on the time between obtaining the test result with a pathogenic variant and referral to or attendance at a genetics department for post-test counseling (17,21,23). For most patients, this time varied between 12 working days and 6 weeks (21,23). In the study of Rahman et al., 2 out of 16 referred patients had a longer time to referral of up to 127 working days. Flaum et al. (23) reported that referred patients received an appointment within 10 weeks at the genetics department. The majority of patients with a pathogenic variant in the ENGAGE study received post-test counseling at the genetics department the same day the test result was available (median 0.0 weeks, range 0.0 to 30.9 weeks) (17).

Adherence to guidelines

Only two studies reported whether genetic tests were offered and/or performed according to current guidelines. In the study performed in Norway, it was assessed for all patients with breast cancer how many patients were eligible for genetic testing according to the Norwegian Breast Cancer Group (NBCG) criteria (16). Of all patients with breast cancer who did not meet the NBCG criteria, 23% were offered genetic testing by their surgeon or oncologist. Genetic testing was performed in 96% of these patients. Genetic testing was offered to 75% of the patients who did fulfill NBCG criteria, and 96% of these patients got

tested. In the study by Gleeson et al., 93.1% of tested patients with ovarian cancer met national guidelines (18).

Critical appraisal

The number of QI-MQCS criteria met per article varied between 6 and 13 out of 16, with an average of 8.9. Domains that were described sufficiently in nearly all articles were 'Organizational motivation' (16/16 met criteria), 'Intervention description' (16/16), 'Implementation' (15/16) and 'Timing' (15/16). The most insufficiently described domains were 'Organizational characteristics' (2/16 met criteria), 'Penetration/Reach' (3/16), 'Adherence' (4/16) and 'Health outcomes' (4/16).

Discussion

Based on the results of this systematic review, we conclude that it is feasible to incorporate mainstream genetic testing into daily practice because (1) the required time investment was acceptable for NGHCPs, despite the slightly increased workload, and (2) several facilitators and no insurmountable barriers were reported. We conclude that the quality of genetic care was maintained during mainstream genetic testing because (1) these mainstream genetic testing initiatives included genetics training for NGHCPs, (2) a comprehensive informed consent procedure was incorporated to ensure informed decision-making, (3) most eligible patients received additional genetic counseling in case of a pathogenic variant, and (4) the turnaround times for genetic testing were comparable or shorter than in the standard genetic testing pathway. The fifth outcome measurement for quality of care, i.e., the proportion of patients receiving mainstream genetic testing that meet the eligibility criteria for testing, is understudied. Based on a combination of the results of our systematic review and those of the systematic review of Scheinberg et al. (12), we postulate that mainstream genetic testing can be successfully implemented in daily practice.

Feasibility

Duration and key elements of pre-test counseling

It is important that the time investment is reported in articles, because an acceptable time investment is a prerequisite for the implementation of a mainstream genetic testing pathway in daily practice. Compared to standard genetic counseling with an average time investment of 40 to 50 minutes (29,30), the duration of genetic counseling by NGHCPs, with an average of 8 to 20 minutes, is shortened substantially. On the other hand, the consultation time with the NGHCP is significantly increased. When mainstream genetic testing becomes part of the standard care, this additional time should be anticipated in the planning.

We identified two key discussion points for pre-test counseling that were described in six studies in this review, i.e., explanation of genes tested and cancer risks, and possible implications of a genetic test for the patients and their relatives (7,8,17,18,20,26). There was a wide range in number of discussion points that these studies identified as key topics for informed consent, with up to 11 discussion points in the ENGAGE study that they deemed as basic topics of informed consent (17). The ASCO policy statement describes that it is important to explain the purpose and possible outcomes of genetic tests (31). Moreover, potential consequences and cancer risks for patients and family members, caused by pathogenic variants in high-, moderate-, and low-penetrant genes, should be discussed, as well as the possibility of finding variants of unknown significance. For example, patients with ovarian cancer need to be informed about the potential impact on their treatment, but also the increased risk of breast cancer for themselves when a pathogenic variant in a *BRCA* gene is identified. Patients should also be informed about the potential increased risk of breast, ovarian or prostate cancer for their family members (32,33).

Shared decision-making is essential in genetic pre-test counseling and a lack of time has shown to be an important barrier for shared decision-making (34-36). In contrast, research has also shown that reducing the amount of information provided during pre-test counseling is preferred by some patients (37,38). However, reducing the amount of information could result in less knowledge and more anxiety or distress in patients. Studies measuring anxiety and distress in patients who underwent genetic testing in a mainstream genetic testing pathway have shown low anxiety and distress scores (9,11,20,24,25,39). To put this into perspective, we need larger studies that compare anxiety and distress scores between the mainstream and the standard genetic testing pathway with pre-test counseling and testing at the genetics department. Ultimately, it is important that the patient can make an informed decision regarding genetic testing, without experiencing an overload of information or unacceptable distress. Whether any important information that is needed to make an informed decision is left out by NGHCPs in mainstream genetic testing is not known and should be studied. It is also not known which topics are considered the most important by patients.

Barriers and facilitators for implementation of mainstream genetic testing

The two most important barriers to mainstream genetic testing were inadequate knowledge by NGHCPs and the lack of time during appointments. The latter, however, was only described in one study, by the NGHCPs who had the least experience with mainstream genetic testing (19). When asked, the extra time investment was acceptable for NGHCPs (7,8,11,17,20). Lack of knowledge or self-confidence could be solved with a training procedure before NGHCPs discuss genetic testing.

All these barriers were experienced in a research setting. Gleeson et al. determined which barriers were experienced by NGHCPs that would prevent them from continuing with mainstream genetic testing (18). These were the lack of local infrastructure or systems to support the mainstream genetic testing pathway, lack of human resources, and lack of funding. It is important that these barriers are considered when implementing mainstream genetic testing in daily practice. Factors that might be insurmountable are lack of human resources and lack of funding, but these differ between hospitals and countries, and the workflow can be adjusted to overcome these factors.

Facilitators for mainstream genetic testing are the offer of a training program, FAQ forms, information sheets, and an approved clinical protocol. In this protocol, it should be stated clearly when NGHCPs can discuss and order genetic tests themselves and which actions are needed to obtain consent, order the genetic test, and when post-test counseling is needed by a genetic healthcare professional.

Quality of care

Training

For NGHCPs, it is important to learn about specific key topics that are needed to inform a patient before deciding whether or not to perform the genetic test. Training is therefore an important part of mainstream genetic testing initiatives, as all articles except one described that a training was used for NGHCPs prior to consulting patients (7-9,11,17-27). It was not reported how many of the available NGHCPs actually participated in the studies, and whether some of them declined to participate. Therefore, the results of these studies might be biased, if only the highly motivated NGHCPs participated. It was not described whether these training initiatives were accredited or certified. If the training is accredited, this might motivate more skeptical NGHCPs to participate in and complete the training.

Several modules have been developed to train healthcare professionals in how to provide counseling regarding hereditary diseases (40,41). Many of these have been developed for NGHCPs and they mainly focus on attitudes about counseling, communication skills and knowledge. Unfortunately, there is a lot of variability among these training modules, and the evidence on their effectiveness is disputable (40). In most of the studies in our systematic review, the time investment for NGHCPs was 30 minutes to one hour.

Post-test counseling

Although all studies reported that patients should receive post-test counseling by a genetic counselor in the case of a pathogenic variant, the actual referral and attendance rates varied between these studies. The most important difference between these studies seems to be whether or not these appointments for post-test counseling were directly coordinated by the genetics team. In the studies where patients were directly invited by

the genetics team, almost all patients attended these appointments (7,8,19,20). In the other studies, there was a larger variation in the number of referrals and/or attendance of patients for an appointment with a genetic counselor, ranging from 34% to 100% of patients with a pathogenic variant attending post-test counseling (17). It is striking in the ENGAGE study that the proportion of patients who attended post-test counseling in European countries is substantially higher than in the US. A clear explanation for this difference was not reported, but we can speculate that differences in healthcare costs for patients might play a role.

It is essential that all patients are offered post-test counseling by a member of the genetics team when a pathogenic variant is identified. Therefore, we recommend that appointments for post-test counseling be directly coordinated by the genetics team. Post-test counseling should be tailored to every patient, and attention should be paid to the practical implications and psychosocial impact of this test result. In addition, there is an important task in guiding patients to inform at-risk family members about cascade testing. Research has shown that even within the genetics departments the uptake of cascade testing is low, ranging from 21 to 44% (42). Given the time constraints at oncology departments, it is conceivable that this uptake will be even lower without guidance on cascade testing at a genetics department. Post-test counseling is not only important for patients carrying a pathogenic variant, but also for all uncertain variants that are communicated to patients. The clinical implications of an uncertain variant are often limited, but it is important that patients understand these implications. As research has shown that patients as well as NGHCPs often misinterpret the consequences of these variants (17,43-45), post-test counseling at a genetics department might be preferable for these uncertain variants as well.

Turnaround time

When the genetic test result has consequences for the treatment of cancer, it is important that turnaround times for genetic testing are minimized. For patients with ovarian cancer and prostate cancer for example, there is clear evidence that patients carrying a pathogenic variant in a *BRCA* gene have the highest response rates to PARP inhibitors (5,46). The longest delay in the turnaround time for the standard genetic testing pathway is probably the time between referral and first appointment with a genetic counselor due to long waiting lists (47). A prior study showed that the mainstream genetic testing pathway resulted in higher numbers of genetic tests and a lower number of referrals to the genetics departments (48). Therefore, mainstream genetic testing could be an important facilitator for improving access to genetic healthcare, without increasing the workload for genetic HCPs. This is an additional benefit because the burden on the clinical genetics service is rising (49).

Although most of the included studies reported on turnaround times, it is difficult to compare these results because different time points were used. The most frequently used turnaround time was the time between discussing a genetic test and disclosing the result to the patient, which ranged between 3 and 27 weeks. This illustrates that there are large differences between countries and laboratories. All studies that compared their mainstream genetic testing pathway with the standard pathway showed a reduction in turnaround time during the mainstream genetic testing period. However, it should be noted that most studies compared their turnaround times with periods before the implementation of their mainstream genetic testing pathway, and testing techniques might have been slower in those periods.

Adherence to guidelines

Whether patients who received genetic testing fulfilled the criteria as stated in the national guidelines was only reported in two of the included studies (16,18). As most studies reported on mainstream genetic testing pathways for patients with ovarian cancer, adherence to guidelines is not an important issue because in most countries, all patients with (non-mucinous) epithelial ovarian cancer are eligible for genetic testing (50). Only one study reported whether genetic testing was performed according to guidelines in patients with breast cancer (16). In this study, almost 25% of patients who were tested did not meet the eligibility criteria, while 25% of eligible patients did not receive testing. This high proportion of tested patients not fulfilling eligibility criteria is comparable with the 35% of tested patients not meeting the eligibility criteria in the DNA-direct study (51). In this study, NGHCPs ordered genetic testing for patients with breast cancer without pre-test counseling. The high percentage of ineligible patients in the DNA-direct study illustrates that it is not always clear to NGHCPs which patients are eligible for genetic testing. This should be considered when implementing a mainstream genetic testing pathway for other types of cancer than ovarian cancer. Testing criteria should be simple and clear for NGHCPs to prevent testing of (significant numbers of) patients who do not meet the eligibility criteria. Testing more patients than necessary not only increases healthcare costs, but it can also induce unnecessary stress in patients and produce results that might be challenging to interpret (52). On the other hand, not testing eligible patients can have serious treatment implications, and it can also result in family members not taking precautions to prevent or detect cancer at an early stage.

Limitations

This review has some limitations. The results of our review may not easily be generalized to mainstream genetic testing in cancer settings other than ovarian cancer, as the majority (9 out of 15) of these initiatives available in the literature describe a mainstream genetic testing pathway for patients with ovarian cancer. The eligibility criteria for genetic testing

in ovarian cancer are much more concise than they are for other types of cancer. Therefore, mainstream genetic testing in other types of cancer is more challenging.

Another limitation is that there are no predefined and general definitions for feasibility and quality of care for genetic testing. Therefore, other articles might use other definitions to determine these outcomes.

Lastly, the number of criteria met on the QI-MQCS critical appraisal tool per article was on average 8.9 out of 16. This means that, on average, only 56% of the domains were described sufficiently. The QI-MQCS manual did not always have strict guidance on whether a domain should be scored as 'met' or 'not met'. Therefore, we might have been stricter than necessary, which could have resulted in lower scores.

Suggestions for the implementation of mainstream genetic testing

This review shows that there are multiple mainstream genetic testing initiatives which vary in their set-up. There are several elements that should be incorporated into mainstream genetic testing initiatives to increase the likelihood of successful implementation. These recommendations are summarized in Table 4.

Table 4. Recommendations for implementing a mainstream genetic testing pathway

Include a training module with
- key topics for pre-test counseling
- an informed consent procedure
Provide clear instructions indicating when patients are eligible for genetic testing
Include FAQ forms and a clear protocol
Invite patients directly for post-test counseling in case a pathogenic variant is found (without the necessity of a referral by the NGHCP)
Close collaboration between genetic and non-genetic departments

Future research

Barriers regarding the local infrastructure were mentioned. It is important to explore in detail what these barriers are and to investigate this in different countries, due to differences in healthcare systems. In addition, the proportion of NGHCPs not willing to participate in mainstream genetic testing initiatives and their arguments for this should be studied further, as mainstream genetic testing initiatives can only be successful when a significant proportion of NGHCPs are participating. Mainstream genetic testing may become the new standard of care for specific patient populations, and therefore all NGHCP should be participating in the future.

Currently, somatic genetic testing is increasingly used simultaneously with or as a prescreen for germline genetic testing (53). We think that matched germline and somatic testing in a mainstreaming pathway can supplement each other, but further research is needed to evaluate if this is also feasible.

So far, mainstream genetic testing pathways have foremost been evaluated for patients with breast and ovarian cancer. For other types of cancers, there may be different barriers and facilitators that should be evaluated further.

To determine whether mainstream genetic testing is an acceptable alternative for standard genetic testing, these outcomes should be evaluated more often in comparison to a control group receiving standard genetic testing.

Conclusions

The available studies show that mainstream genetic testing for germline variants is feasible in the daily practice of NGHCPs treating patients with cancer. Mainstream genetic testing pathways present an acceptable increase in workload for NGHCPs, and the introduction almost always includes a training procedure. With the introduction of mainstream genetic testing pathways that include training for the NGHCP, the quality of care seems to be maintained. For feasibility as well as for quality of care, it is important that the genetics department has a pivotal role in the mainstream genetic testing pathways, especially in the coordination of post-test counseling of patients with a pathogenic germline variant.

Supplementary materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers14041059/s1, Table S1: Search strategy; Table S2. Outcomes on quality of care and feasibility for each study.

Author contributions: K.B.: Conceptualization, Investigation, Methodology, Visualization, Writing—original draft; M.V.: Conceptualization, Investigation, Methodology, Visualization, Writing—original draft; E.G.E.: Investigation, Methodology, Writing—review & editing; R.P.Z.: Conceptualization, Methodology, Writing—review & editing; I.M.v.O.: Writing—review & editing; L.A.L.M.K.: Writing—Review & editing; E.M.A.B.: Conceptualization, Methodology, Writing—review & editing; M.G.E.M.A.: Conceptualization, Investigation, Methodology, Writing—review & editing. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Dutch Cancer Society (KWF, grant 12601).

Conflicts of interest: The authors declare no conflict of interest.

References

1. Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102.
2. Swisher EM. Usefulness of Multigene Testing: Catching the Train That's Left the Station. JAMA Oncol. 2015;1(7):951-952.
3. Yadav S, Hu C, Hart SN, Boddicker N, Polley EC, Na J, et al. Evaluation of Germline Genetic Testing Criteria in a Hospital-Based Series of Women With Breast Cancer. J Clin Oncol. 2020;38(13):1409-1418.
4. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;382(22):2091-2102.
5. Tew WP, Lacchetti C, Ellis A, Maxian K, Banerjee S, Bookman M, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-3493.
6. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405.
7. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.
8. Kemp Z, Turnbull A, Yost S, Seal S, Mahamdallie S, Poyastro-Pearson E, et al. Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer. JAMA Netw Open. 2019;2(5):e194428.
9. Ryan NA, Donnelly L, Stocking K, Evans DG, Crosbie EJ. Feasibility of Gynaecologist Led Lynch Syndrome Testing in Women with Endometrial Cancer. J Clin Med. 2020;9(6):1842.
10. Ryan NAJ, McMahon R, Tobi S, Snowsill T, Esquibel S, Wallace AJ, et al. The proportion of endometrial tumours associated with Lynch syndrome (PETALS): A prospective cross-sectional study. PLoS Med. 2020;17(9):e1003263.
11. Scheinberg T, Goodwin A, Ip E, Linton A, Mak B, Smith DP, et al. Evaluation of a Mainstream Model of Genetic Testing for Men With Prostate Cancer. JCO Oncol Pract. 2021;17(2):e204-e216.
12. Scheinberg T, Young A, Woo H, Goodwin A, Mahon KL, Horvath LG. Mainstream consent programs for genetic counseling in cancer patients: A systematic review. Asia Pac J Clin Oncol. 2021;17(3):163-177.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-1012.
14. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
15. Hempel S, Shekelle PG, Liu JL, Sherwood Danz M, Foy R, Lim YW, et al. Development of the Quality Improvement Minimum Quality Criteria Set (QI-MQCS): a tool for critical appraisal of quality improvement intervention publications. BMJ Qual Saf. 2015;24(12):796-804.

16. Grindedal EM, Jorgensen K, Olsson P, Gravdehaug B, Luras H, Schlichting E, et al. Mainstreamed genetic testing of breast cancer patients in two hospitals in South Eastern Norway. Fam Cancer. 2020;19(2):133-142.
17. Colombo N, Huang G, Scambia G, Chalas E, Pignata S, Fiorica J, et al. Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer. J Clin Oncol. 2018;36(13):1300-1307.
18. Gleeson M, Kentwell M, Meiser B, Do J, Nevin S, Taylor N, et al. The development and evaluation of a nationwide training program for oncology health professionals in the provision of genetic testing for ovarian cancer patients. Gynecol Oncol. 2020;158(2):431-439.
19. Percival N, George A, Gyertson J, Hamill M, Fernandes A, Davies E, et al. The integration of BRCA testing into oncology clinics. Br J Nurs. 2016;25(12):690-694.
20. Powell CB, Laurent C, Ciaravino G, Garcia C, Han L, Hoodfar E, et al. Streamlining genetic testing for women with ovarian cancer in a Northern California health care system. Gynecol Oncol. 2020;159(1):221-228.
21. Rahman B, Lanceley A, Kristeleit RS, Ledermann JA, Lockley M, McCormack M, et al. Mainstreamed genetic testing for women with ovarian cancer: first-year experience. J Med Genet. 2019;56(3):195-198.
22. Bednar EM, Oakley HD, Sun CC, Burke CC, Munsell MF, Westin SN, et al. A universal genetic testing initiative for patients with high-grade, non-mucinous epithelial ovarian cancer and the implications for cancer treatment. Gynecol Oncol. 2017;146(2):399-404.
23. Flaum N, Morgan RD, Burghel GJ, Bulman M, Clamp AR, Hasan J, et al. Mainstreaming germline BRCA1/2 testing in non-mucinous epithelial ovarian cancer in the North West of England. Eur J Hum Genet. 2020;28(11):1541-1547.
24. McLeavy L, Rahman B, Kristeleit R, Ledermann J, Lockley M, McCormack M, et al. Mainstreamed genetic testing in ovarian cancer: patient experience of the testing process. Int J Gynecol Cancer. 2020;30(2):221-226.
25. Richardson M, Min HJ, Hong Q, Compton K, Mung SW, Lohn Z, et al. Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System. Cancers (Basel). 2020;12(2):338.
26. Rumford M, Lythgoe M, McNeish I, Gabra H, Tookman L, Rahman N, et al. Oncologist-led BRCA 'mainstreaming' in the ovarian cancer clinic: A study of 255 patients and its impact on their management. Sci Rep. 2020;10(1):3390.
27. Scott N, O'Sullivan J, Asgeirsson K, Macmillan D, Wilson E. Changing practice: moving to a specialist nurse-led service for BRCA gene testing. Br J Nurs. 2020;29(10):S6-S13.
28. Taylor N, Parveen S, Robins V, Slater B, Lawton R. Development and initial validation of the Influences on Patient Safety Behaviours Questionnaire. Implement Sci. 2013;8:81.
29. Albada A, Ausems MG, van Dulmen S. Counselee participation in follow-up breast cancer genetic counselling visits and associations with achievement of the preferred role, cognitive outcomes, risk perception alignment and perceived personal control. Soc Sci Med. 2014;116:178-186.

30. Eijzenga W, Aaronson NK, Hahn DE, Sidharta GN, van der Kolk LE, Velthuizen ME, et al. Effect of routine assessment of specific psychosocial problems on personalized communication, counselors' awareness, and distress levels in cancer genetic counseling practice: a randomized controlled trial. J Clin Oncol. 2014;32(27):2998-3004.
31. Robson ME, Bradbury AR, Arun B, Domchek SM, Ford JM, Hampel HL, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol. 2015;33(31):3660-3667.
32. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402-2416.
33. Page EC, Bancroft EK, Brook MN, Assel M, Hassan Al Battat M, Thomas S, et al. Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers. Eur Urol. 2019;76(6):831-842.
34. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision-making. Patient education and counseling. 2014;94(3):291-309.
35. Legare F, Ratte S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Educ Couns. 2008;73(3):526-535.
36. Pieterse AH, Stiggelbout AM, Montori VM. Shared Decision-making and the Importance of Time. JAMA. 2019;322(1):25-26.
37. Bradbury AR, Patrick-Miller LJ, Egleston BL, DiGiovanni L, Brower J, Harris D, et al. Patient feedback and early outcome data with a novel tiered-binned model for multiplex breast cancer susceptibility testing. Genet Med. 2016;18(1):25-33.
38. Underhill-Blazey M, Blonquist T, Chittenden A, Pozzar R, Nayak M, Lansang K, et al. Informing models of cancer genetics care in the era of multigene panel testing with patient-led recommendations. J Genet Couns. 2021;30(1):268-282.
39. Yoon SY, Wong SW, Lim J, Ahmad S, Mariapun S, Padmanabhan H, et al. Oncologist-led BRCA counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes. J Med Genet. 2022;59(3):220-229.
40. Medendorp NM, van den Heuvel LM, Han PKJ, Hillen MA, Smets EMA. Communication skills training for healthcare professionals in providing genetic counseling: A scoping literature review. Patient Educ Couns. 2021;104(1):20-32.
41. Starkings R, Shilling V, Jenkins V, Fallowfield L. A systematic review of communication interventions to help healthcare professionals discuss genetic testing for breast cancer. Breast Cancer Res Treat. 2020;183(1):9-21.
42. Menko FH, Ter Stege JA, van der Kolk LE, Jeanson KN, Schats W, Moha DA, et al. The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: a systematic review of the literature and implications for clinical practice. Fam Cancer. 2019;18(1):127-135.

43. Clift K, Macklin S, Halverson C, McCormick JB, Abu Dabrh AM, Hines S. Patients' views on variants of uncertain significance across indications. J Community Genet. 2020;11(2):139-145.
44. Kurian AW, Li Y, Hamilton AS, Ward KC, Hawley ST, Morrow M, et al. Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer. J Clin Oncol. 2017;35(20):2232-2239.
45. Macklin SK, Jackson JL, Atwal PS, Hines SL. Physician interpretation of variants of uncertain significance. Fam Cancer. 2019;18(1):121-126.
46. Ghose A, Moschetta M, Pappas-Gogos G, Sheriff M, Boussios S. Genetic Aberrations of DNA Repair Pathways in Prostate Cancer: Translation to the Clinic. Int J Mol Sci. 2021;22(18):9783.
47. Hoskovec JM, Bennett RL, Carey ME, DaVanzo JE, Dougherty M, Hahn SE, et al. Projecting the Supply and Demand for Certified Genetic Counselors: a Workforce Study. J Genet Couns. 2018;27(1):16-20.
48. Cohen SA, Nixon DM. A collaborative approach to cancer risk assessment services using genetic counselor extenders in a multi-system community hospital. Breast Cancer Res Treat. 2016;159(3):527-534.
49. Stoll K, Kubendran S, Cohen SA. The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. Am J Med Genet C Semin Med Genet. 2018;178(1):24-37.
50. Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245.
51. Sie AS, van Zelst-Stams WA, Spruijt L, Mensenkamp AR, Ligtenberg MJ, Brunner HG, et al. More breast cancer patients prefer BRCA-mutation testing without prior face-to-face genetic counseling. Fam Cancer. 2014;13(2):143-151.
52. Hogarth S, Javitt G, Melzer D. The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. Annu Rev Genomics Hum Genet. 2008;9:161-182.
53. Frugtniet B, Morgan S, Murray A, Palmer-Smith S, White R, Jones R, et al. The detection of germline and somatic BRCA1/2 genetic variants through parallel testing of patients with high-grade serous ovarian cancer: a national retrospective audit. BJOG. 2022;129(3):433-442.

Supplementary Methods

Quality Improvement Minimum Quality Criteria Set (QI-MQCS) – Version 1.0

ID: Author, year: Reviewer:

Intervention: Outcome:

Domain	Minimum standard	Score
1. Organizational Motivation: Organizational problem, reason, or motivation for the intervention Consider quality of care problems; organizational problems; regulations, legal constraints, and externalfinancial incentives at the target organization; or organizational motivation.	Names or describes at least one motivationfor the organization's participation in the intervention	Not metMet
2. Intervention Rationale: Rationale linking the intervention to its expected effects Consider citations of theories, logic models, or existing empirical evidence that links the intervention toits expected effects.	Names or describes a rationale linking at least one central intervention component tointended effects	Not metMet
3. Intervention Description: Change in organizational or provider behavior Consider the presented details that describe the change in the delivery of care, provider behavior, or structure of the organization needed to replicate the evaluated intervention including the involved keypersonnel.	Describes at least one specific change in detail including the personnel executing the intervention	Not metMet
4. Organizational Characteristics: Demographics or basic characteristics of the organization Consider environment (e.g., urban/rural, academic/non-academic), type of care (e.g., primary care),size of the organization, patient mix, staff mix, or reimbursement type.	Reports at least two organizational characteristics	Not metMet
5. Implementation: Temporary activities used to introduce potentially enduring changes Consider types of staff involved, activities or methods used such as pilot testing or Plan-Do-Study-Act(PDSA) cycles, staff education, and involvement of stakeholders in introducing the intervention.	Names at least one approach used to introduce the intervention	Not metMet
6. Study Design: Study design and comparator Consider the type of evaluation (e.g., post-only, pre-post, time series, parallel control group, randomized groups; same participants assessed multiple times or different samples) / how the authorsevaluated whether the intervention worked	Names the study design	Not metMet

7. Comparator: Information about comparator care processes Consider details about the control group or the status quo without the intervention (even if there was noformal control group / data), e.g., the existing standard of care / routine care / before the intervention was introduced, or care processes used in the control group.	Describes at least one key care process	Not metMet
8. Data Source: Data source and outcome definition Consider the data sources (e.g., routine hospital data, data collected by the study investigator), the datacollection method (e.g., survey, interview, objective/subjective measurement) and the outcome of interest is defined (e.g., definition of a reportable patient fall).	Describes the data source and defines theoutcome of interest	Not metMet
9. Timing: Timing of intervention and evaluation Consider the clarity of the timeline of the intervention, e.g., when introduced, when fully implemented, when evaluated relative to the intervention implementation status, and a clear indicationof whether baseline data (defined as before the intervention was introduced) was present.	Describes the timing of the intervention and evaluation to determine the presenceof baseline data and the followup period after all intervention components were fully implemented	Not metMet
10. Adherence / Fidelity: Adherence to the intervention Consider reporting of compliance with the intervention for the duration of the study, fidelity data on intervention use, or described mechanisms that ensures compliance (e.g., provider reminder integratedin electronic health record that cannot be skipped).	Reports fidelity information for at least one intervention component, or describesevidence of adherence or a mechanism ensuring compliance to the intervention	Not metMet
11. Health Outcomes: Patient health-related outcomes Consider patient and non-professional care-giver health-related outcomes (including e.g., quality of life), but exclude satisfaction, provider-behavior (e.g., number of diagnostic tests ordered, knowledge)and process improvements.	Reports data on at least one health-relatedoutcome	Not metMet
12. Organizational Readiness: Barriers and facilitators to readiness Consider reported QI resources and culture (e.g., existing QI committee, leadership commitment, priorQI experience, staff attitudes, and education and decision support resources) and results of barriers and facilitator assessments.	Reports at least one organizational-level barrier or facilitator	Not metMet
13. Penetration / Reach: Penetration / reach of the intervention Consider the number of units or sites participating in the intervention compared to the available / eligible units (e.g., the number of participating sites without knowing how many sites were initiallyapproached / were eligible is not sufficient).	Describes the proportion of all eligible units who actually participated	Not metMet

14. Sustainability: Sustainability of the intervention Consider discussions of sustainability, reference to organizational resources (e.g., costs and necessary commitments) and policy changes needed to sustain the intervention after withdrawal of study personnel and research resources, evidence of enduring changes (e.g. automated electronic reminders),or an extended duration of the intervention period as evidence of sustainability.	Describes the sustainability or the potentialfor sustainability	Not metMet
15. Spread: Ability to be spread or replicated Consider evidence of spread or failure to spread and large rollouts; available resources such as atoolkits, how-to manuals, protocols, or booklets that describe the intervention in detail and couldfacilitate spread and replication; or discussions of spread potential.	Describes the potential for spread, existingtools for spread, or spread attempts / large-scale rollout	Not metMet
16. Limitations: Interpretation of the evaluation Consider whether the interpretation of the reported findings takes the study design (e.g., the lack ofcomparator) or other evaluation limitations into account; refers to the presented data (not future research / developments or intervention limitations)	Reports at least one limitation of the design / evaluation	Not metMet

Supplementary Table 1. Search strategy

Source	Search strategy
PubMed	(“neoplasms”[mh] OR “neoplas*”[tiab] OR “paraneoplas*”[tiab] OR “cancer*”[tiab] OR “tumor”[tiab] OR “tumors”[tiab] OR “tumour*”[tiab] OR “malignan*”[tiab] OR “carcinoma*”[tiab] OR “metast*”[tiab] OR “adenocarcin*”[tiab] OR “carcin*”[tiab] OR “HBOC”[tiab] OR “HNPCC”[tiab] OR “lynch*”[tiab] OR “Colorectal Neoplasms, Hereditary Nonpolyposis”[mh]) **AND** (“genetic testing”[mh] OR “genetic test*”[tiab] OR “genetic screen*”[tiab] OR “gene test*”[tiab] OR “DNA test*”[tiab] OR “genetic counseling”[mh] OR “genetic counsel*”[tiab] OR “Genetic Services”[mh] OR “Genes, Neoplasm”[mh] OR “Germ-line Mutation”[mh] OR “germ-line mutation*”[tiab] OR “germline mutation*”[tiab] OR “Genetic Service*”[tiab] OR “germline screen*”[tiab] OR “germline test*”[tiab]) **AND** (“patient centered care”[mh] OR “mainstream*”[tiab] OR “streamline*”[tiab] OR “patient centered care”[tiab] OR “patient focused care”[tiab] OR “focused testing”[tiab] OR “service delivery model*”[tiab] OR “genetic counselor extender*”[tiab] OR “patient navigation*”[tiab] OR “health services accessibility”[mh] OR “health services accessibility”[tiab] OR “oncologist-led*”[tiab] OR “oncologist led*”[tiab] OR “oncologist coordinate*”[tiab] OR “non-clinical geneticist*”[tiab] OR “gynaecologist-led*”[tiab] OR “gynecologist-led*”[tiab] OR “gynaecologist led*”[tiab] OR “gynecologist led*”[tiab] OR “gynaecologist coordinate*”[tiab] OR “gynecologist coordinate*”[tiab] OR “Physician coordinate*”[tiab] OR “Physician led*”[tiab] OR “Physician-led*”[tiab])
Embase	(“neoplasm”/exp OR “neoplas*”:ti,ab,kw OR “paraneoplas*”:ti,ab,kw OR “cancer*”:ti,ab,kw OR “tumor”:ti,ab,kw OR “tumors”:ti,ab,kw OR “tumour*”:ti,ab,kw OR “malignan*”:ti,ab,kw OR “carcinoma*”:ti,ab,kw OR “metast*”:ti,ab,kw OR “adenocarcin*”:ti,ab,kw OR “carcin*”:ti,ab,kw OR “HBOC”:ti,ab,kw OR “HNPCC”:ti,ab,kw OR “lynch*”:ti,ab,kw OR “hereditary nonpolyposis colorectal cancer”/exp) **AND** (“genetic screening”/exp OR “genetic test*”:ti,ab,kw OR “genetic screen*”:ti,ab,kw OR “gene test*”:ti,ab,kw OR “DNA test*”:ti,ab,kw OR “genetic counseling”/exp OR “genetic counsel*”:ti,ab,kw OR “genetic service”/exp OR “germline mutation”/exp OR “germline mutation*”:ti,ab,kw OR “germ-line mutation*”:ti,ab,kw OR “genetic service*”:ti,ab,kw OR “germline screen*”:ti,ab,kw OR “germline test*”:ti,ab,kw) **AND** (“patient care”/de OR “mainstream*”:ti,ab,kw OR “streamline*”:ti,ab,kw OR “patient centered care”:ti,ab,kw OR “patient focused care”:ti,ab,kw OR “focused testing”:ti,ab,kw OR “service delivery model*”:ti,ab,kw OR “genetic counselor extender*”:ti,ab,kw OR “patient navigation*”:ti,ab,kw OR “health care access”/de OR “health services accessibility”:ti,ab,kw OR “oncologist-led*”:ti,ab,kw OR “oncologist led*”:ti,ab,kw OR “oncologist coordinate*”:ti,ab,kw OR “non-clinical geneticist*”:ti,ab,kw OR “gynaecologist-led*”:ti,ab,kw OR “gynecologist-led*”:ti,ab,kw OR “gynaecologist led*”:ti,ab,kw OR “gynecologist led*”:ti,ab,kw OR “gynaecologist coordinate*”:ti,ab,kw OR “gynecologist coordinate*”:ti,ab,kw OR “physician coordinate*”:ti,ab,kw OR “physician led*”:ti,ab,kw OR “physician-led*”:ti,ab,kw) Filter – Sources: Embase, Embase and MEDLINE Filter – Publication types: Article, Article in Press

CINAHL	((MH “Neoplasms”) OR (TI neoplas* OR AB neoplas*) OR (TI paraneoplas* OR AB paraneoplas*) OR (TI cancer* OR AB cancer*) OR (TI tumor or AB tumor) OR (TI tumors or AB tumors) OR (TI tumour* or AB tumour*) OR (TI malignan* OR AB malignan*) OR (TI carcinoma* or AB carcinoma*) OR (TI metast* OR AB metast*) OR (TI adenocarcin* or AB adenocarcin*) OR (TI carcin* or AB carcin*) OR (TI HBOC or AB HBOC) OR (TI HNPCC OR AB HNPCC) OR (TI lynch* or AB lynch*) OR (MH “Colorectal Neoplasms, Hereditary Nonpolyposis”)) **AND** ((MH “Genetic Screening” OR MH “Cancer Screening”) OR (TI genetic test* OR AB genetic test*) OR (TI genetic screen* OR AB genetic screen*) OR (TI gene test* OR AB gene test*) OR (TI DNA test* OR AB DNA test*) OR (MH “Genetic Counseling”) OR (TI genetic counsel* OR AB genetic counsel*) OR (MH “Genes, Neoplasm”) OR (TI germ-line mutation* OR AB germ-line mutation) OR (TI germline mutation* OR AB germline mutation*) OR (TI Genetic Service* OR AB Genetic Service*) OR (TI germline screen* OR AB germline screen*) OR (TI germline test* OR AB germline test*)) **AND** ((MH “Patient Care”) OR (TI mainstream* OR AB mainstream*) OR (TI streamline* OR AB streamline*) OR (TI patient centered care OR AB patient centered care) OR (TI patient focused care OR AB patient focused care) OR (TI focused testing OR AB focused testing) OR (TI service delivery model* OR AB service delivery model*) OR (TI genetic counselor extender* OR AB genetic counselor extender*) OR (TI patient navigation* OR AB patient navigation*) OR (MH “Health Services Accessibility”) OR (TI health services accessibility OR AB health services accessibility) OR (TI oncologist-led* OR AB oncologist-led*) OR (TI oncologist led* OR AB oncologist led*) OR (TI oncologist coordinate* OR AB oncologist coordinate*) OR (TI non-clinical geneticist* OR AB non-clinical geneticist*) OR (TI gynaecologist-led* OR AB gynaecologist-led*) OR (TI gynaecologist led* OR AB gynaecologist led*) OR (TI gynecologist-led* OR AB gynecologist-led*) OR (TI gynecologist led* OR AB gynecologist led) OR (TI gynaecologist coordinate* OR AB gynaecologist coordinate*) OR (TI gynecologist coordinate* OR AB gynecologist coordinate*) OR (TI physician coordinate* OR AB physician coordinate*) OR (TI physician led* OR AB physician led*) OR (TI physician-led OR AB physician-led*)) Filter – Limit to: Linked Full Text, Abstract Available Filter – Publication type: Journal Article Filter – Source Types: Academic Journals Filter – Language: English
Psycinfo	(exp “neoplasms”/ OR “neoplas*”.ab,ti. OR “paraneoplas*”.ab,ti. OR “cancer*”.ab,ti. OR “tumor”.ab,ti. OR “tumors”.ab,ti. OR “tumour*”.ab,ti. OR “malignan*”.ab,ti. OR “carcinoma*”.ab,ti. OR “metast*”.ab,ti. OR “adenocarcin*”.ab,ti. OR “carcin*”.ab,ti. OR “HBOC”.ab,ti. OR “HNPCC”.ab,ti. OR “lynch*”.ab,ti. OR “hereditary nonpolyposis”.ab,ti.) **AND** (exp “genetic testing”/ OR “genetic test*”.ab,ti. OR “genetic screen*”.ab,ti. OR “gene test*”.ab,ti. OR “DNA test*”.ab,ti. OR exp “genetic counseling”/ OR “genetic counsel*”.ab,ti. OR “germ-line mutation*”.ab,ti. OR “germline mutation*”.ab,ti. OR “Genetic Service*”.ab,ti. OR “germline screen*”.ab,ti. OR “germline test*”.ab,ti.) **AND** (“mainstream*”.ab,ti. OR “streamline*”.ab,ti. OR “patient centered care”.ab,ti. OR “patient focused care”.ab,ti. OR “focused testing”.ab,ti. OR “service delivery model*”.ab,ti. OR “genetic counselor extender*”.ab,ti. OR “patient navigation*”.ab,ti. OR “health services accessibility”.ab,ti. OR “oncologist-led*”.ab,ti. OR “oncologist led*”.ab,ti. OR “oncologist coordinate*”.ab,ti. OR “non-clinical geneticist*”.ab,ti. OR “gynaecologist-led*”.ab,ti. OR “gynecologist-led*”.ab,ti. OR “gynaecologist led*”.ab,ti. OR “gynecologist led*”.ab,ti. OR “gynaecologist coordinate*”.ab,ti. OR “gynecologist coordinate*”.ab,ti. OR “Physician coordinate*”.ab,ti. OR “Physician led*”.ab,ti. OR “Physician-led*”.ab,ti.)

Supplementary Table 2. Outcomes on quality of care and feasibility for each study

Study, year, country	Study population	Mainstream genetic testing pathway	Training	Feasibility	Quality of care	QI-MQCS[c] met (n)
George et al., Percival et al., 2016, UK (7, 19) MCG study	Patients 207 patients with non-mucinous epithelial ovarian cancer. NGHCPs 13 doctors and 2 clinical nurse specialists.	Pre-test counseling and requesting genetic testing by NGHCP from cancer team. Pathway 'v1' (July '13 – May '14): disclosing test result to patient by NGHCP. Pathway 'v2' (May '14 – Nov '14): disclosing test result to patient by genetics team (in writing). Post-test counseling by genetic counselor for patients carrying a pathogenic variant.	Content: Background of mainstream genetic testing, information about *BRCA* genes, information about the protocol and how to fill in the informed consent form. Format: Online videos, freely accessible. Nurses could attend face-to-face training. Time investment: Less than 30 minutes.	Time investment: - NGHCPs agreed (on average 4.2/5[a]) that discussing genetic testing was possible within the timeframe of a consultation, but no specific information about the amount of time was provided. - Nurses that performed pre-test counseling in majority of patients reported that no significant extra time was added to a consult. Facilitators: - NGHCPs strongly agreed (on average 4.8/5[a]) that supporting materials (training and FAQ) were helpful. - NGHCPs strongly agreed (on average 4.7/5[a]) that it is useful to have an approved clinical protocol. - NGHCPs strongly agreed (on average 4.6/5[a]) that the information sheets to provide to patients were useful. Barriers: - 1/5 nurse reported concerns about added time pressures.	Turnaround times: - Average time between discussing genetic testing and disclosing result is 3 – 4 weeks in mainstream genetic testing pathway (12 – 15 weeks in standard genetic testing pathway). Post-test counseling: - 33/33 patients with a pathogenic variant in a *BRCA* gene attended their appointment at the genetics department. Informed consent procedure: - Written informed consent. - Key counseling points described in FAQ form: role of *BRCA* genes in causing cancer, relevance of genetic testing for patients and family members. - Additional information sheets for patients were provided.	George: 10/16 Percival: 6/16
Bednar et al., 2017, US (22)	Patients 1636 patients with high-grade ovarian cancer. - NGHCPs discussed and ordered genetic testing for 84 patients. NGHCPs Gynecologic oncologists or medical oncologists.	Physician-coordinated genetic testing as one of three methods to increase uptake of genetic testing: pre-test counseling, informed consent, requesting genetic testing and disclosing test result by NGHCPs. Referral for post-test counseling by genetic counselor for patients with a pathogenic variant.	Content: Informed consent, testing options, billing policies and health insurance coverage, instructions about specimen collection and several examples of possible test results. Format: National meetings and conferences and further education by genetic counselors if needed. Time investment: Not reported.	Not reported.	Turnaround times: - Time between initial gynecology consultation and completion of genetic counseling: 78 days during mainstream genetic testing period (197 days before mainstream genetic testing pathway was introduced). Informed consent procedure: - Informed consent obtained (not specified as verbal or written). - Key counseling points not described. - No additional information sheets for patients were described.	11/16

Colombo et al., 2018, US, Italy and Spain (17)
 	
ENGAGE study
	Patients
	710 patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.
	- 690 patients received genetic testing.
	
	NGHCPs
	52 oncologists and oncology nurses.
		Pre-test counseling, requesting genetic testing and disclosing test result by NGHCPs.
		
		Post-test counseling by genetic counselor was recommended for patients with a pathogenic variant in a *BRCA* gene.
			Content: Background information about *BRCA* genes, genetic testing guidelines and the informed consent procedure.
			
			Format: Online presentation.
			
			Time investment: Not reported.
				Time investment:
				- A median of 20 minutes for pre-test counseling was invested by the NGHCP (range 2 – 115 minutes), reported by patients.
				- 24/32 (strongly) agreed that discussing genetic testing was possible within the timeframe of a consultation.
				
				Facilitators:
				Determined by NGHCPs (after counseling 10 patients):
				- 27/32 (strongly) agreed that supporting materials were very helpful.
				- 27/32 (strongly) agreed that it is useful to have an approved clinical protocol.
				- 27/32 (strongly) agreed that patient information sheets were very useful.
					Turnaround times:
					- Median time between collecting blood sample and reporting
					  - test result to NGHCP was 4.7 weeks (range: 0.0 – 32.1 weeks).
					  - test result to patient was 8.6 weeks (range: 0.7 – 35.6 weeks).
					- Median time between disclosing pathogenic variant and appointment at genetics department was 0.0 weeks (0 – 30.9 weeks).
					
					Post-test counseling:
					- Counseling at a genetics department for pathogenic variant: 75.8% of patients in Europe and 35.7% in US.
					
					Informed consent procedure:
					- Informed consent obtained (not specified as verbal or written).
					- Key counseling points described in PowerPoint presentation: purpose of test and eligibility criteria, general information about genes, possible test results, technical aspects and accuracy of test, economic considerations, possibility of genetic information discrimination, psychosocial aspects, confidentiality, utilization of test result, alternatives to genetic testing, disclosure.
					- Additional information sheets for patients were provided.
						8/16

Rahman et al., 2018, UK (21)	Patients 122 patients with high-grade non-mucinous epithelial ovarian cancer. NGHCPs Medical and clinical oncologists.	Pre-test counseling, requesting genetic testing and disclosing test result by NCHCPs. Referral for post-test counseling by genetic counselor for patients with a pathogenic variant.	Training is based on training of George et al. (7).	Barriers: - Lack of knowledge of VUS for NGHCPs.	Turnaround times: - Median time between obtaining blood and result was 26 working days (14 – 48 days). - Most patients with a pathogenic variant were referred between 12 – 43 working days. Post-test counseling: - 4/18 of patients carrying a *BRCA* pathogenic variant had not yet been referred to a genetics department at the end of the study. Subsequently 2/4 patients were referred after the end of the study (98 and 127 working days after test results). Informed consent procedure: - Informed consent obtained (not specified as verbal or written). - Key counseling points not described. - No additional information sheets for patients were described.	8/16
Kemp et al., 2019, UK (8) MCG Breast study	Patients 1184 patients with breast cancer. NGHCPs 12 oncologists, 8 surgeons and 3 nurse specialists.	Pre-test counseling and requesting genetic testing by NGHCPs. Disclosing test result to patient by genetics team (in writing). Post-test counseling by genetic counselor for patients with a pathogenic variant.	Training is based on training of George et al. (7).	Time investment: - NGHCPs agreed (on average 4.0/5[a]) that discussing genetic testing was possible within the timeframe of a consultation. Facilitators: - NGHCPs strongly agreed (on average 4.7/5[a]) that supporting materials (training and FAQ) were helpful. - NGHCPs agreed (on average 4.0/5[a]) that it is useful to have an approved clinical protocol. - NGHCPs strongly agreed (on average 4.8/5[a]) that information sheets to provide to patients were useful.	Turnaround times: - Time between consultation and test result was on average 4 weeks (in standard genetic testing pathway 25 weeks). Post-test counseling: - 117/117 patients with a pathogenic variant were offered post-test counseling at a genetics department (115 attended). Informed consent procedure: - Written informed consent. - Key counseling points analogous to MCG program. - Additional information sheets for patients were provided.	8/16

McLeavy et al., 2019, UK (24)	Patients 170 patients with high grade non mucinous ovarian cancer. NGHCPs Oncologists.	Pre-test counseling, written informed consent, requesting genetic testing and disclosing test result by NGHCPs. Referral for post-test counseling by genetic counselor for patients with a pathogenic variant.	Training is based on training of George et al. (7).	Not reported.	Turnaround times: - 13/29 patients who returned questionnaire received test result >12 months after diagnosis. Informed consent procedure: - Written informed consent. - Key counseling points not described. - No additional information sheets for patients were described.	7/16
Flaum et al., 2020, UK (23)	Patients 480 patients with non-mucinous epithelial cancer of the ovary, fallopian tube or peritoneum (including carcinosarcoma). NGHCPs Oncologists and surgeons.	Pre-test counseling, requesting genetic testing and disclosing test result by oncologists or surgeons. Referral for post-test counseling by a genetic counselor for patients with a pathogenic variant.	Content: Informed consent procedure. Format: Not reported. Time investment: Not reported.	Not reported.	Turnaround times: - 35/38 patients with a pathogenic variant in a *BRCA* gene were referred for post-test counseling at a genetics department within 6 weeks after test result. 3/38 patients were referred between 3 and 5 months after test result. - Referred patients received appointment <10 weeks. Post-test counseling: - 38/39 patients with a pathogenic variant in *BRCA* gene were referred for post-test counseling at a genetics department. - Reminder letters to oncologists necessary for 5 patients with *BRCA* pathogenic variant. Informed consent procedure: - Verbal and/or written informed consent. - Key counseling points not described. - No additional information sheet for patients were described.	6/16

Gleeson et al., 2020, Australia (18)	Patients 273 patients with high-grade non-mucinous epithelial ovarian cancer. NGHCPs 157 medical and gynecological oncologists, advanced medical trainees and oncology nurses. - 47 completed questionnaires.	Pre-test counseling, requesting genetic testing and disclosing test result by NGHCPs. Post-test counseling by a genetic counselor for patients with a pathogenic variant.	Content: Information about mainstream genetic testing (rationale and suggested approach), informed consent procedure and delivering results. Format: Piloted face-to-face training with a PowerPoint presentation. Time investment: One hour. - NGHCPs scored significantly better ($p<0.05$) at 'Skills' and 'Environmental context and resources' 12 months after training than pre-training. No difference in knowledge was detected.	Time investment: - 21/64 NGHCPs spend on average 6 – 10 minutes obtaining consent for genetic testing and 17/64 spend 11 – 20 minutes.[b] - Disclosing test results by NGHCPs took 6 – 10 minutes for 21/54 and 4 – 5 minutes for 8/54. - Workload increased slightly for 24/46 of healthcare providers or had no impact for 19/46. Barriers: Barriers that would prevent mainstream genetic testing from continuing by NGHCPs: 61% identified barriers - Lack of local infrastructure: 31.9%. - Lack of human resources: 27.8%. - Lack of funding / unwillingness to allocate funds: 22.2%. - Lack of influential individuals to lobby for continuation: 15.3%. - Inability to incorporate the service into local health policy and planning: 13.7%.	Adherence to guidelines: - 241/273 of patients met national guidelines. Informed consent procedure: - Written informed consent. - Script provided for initiating a conversation about genetic testing including: relevance of genetic test for treatment options, *BRCA* genes and cancer risks, costs, duration of genetic testing, post-test counseling at genetics department if pathogenic variant was found, possibility of additional pre-test counseling at genetics department, genetic test is optional. - Additional information sheets for patients were provided.	13/16
Grindedal et al., 2020, Norway (16)	Patients 131/356 patients with invasive breast cancer were offered genetic testing. - 125/131 received genetic testing. NGHCPs Surgeons and oncologists.	Pre-test counseling, requesting genetic testing and disclosing test result by NGHCPs. Referral for post-test counseling by a genetic counselor for patients with a pathogenic variant.	There was no specific training, but only informational meetings were organized in collaboration with the genetics department.	Not reported.	Adherence to guidelines: - 47/202 of patients who did not meet NBCG criteria were offered testing. - 69/92 patients who did meet NBCG criteria were offered genetic testing. Informed consent procedure: - Written informed consent. - Key counseling points not described. - Additional information sheets for patients were provided.	9/16

Powell et al., 2020, USA (20)	Patients 43 patients with epithelial ovarian, fallopian tube and peritoneal cancer. Control group 101 patients with epithelial ovarian, fallopian tube and peritoneal cancer from other sites. NGHCPs 6 gynecologic oncologists.	Pre-test counseling, informed consent, and requesting genetic testing by NGHCPs. NGHCPs placed online consult for genetics department to follow-up. Test results by letter when no pathogenic variant was found and no positive family history. Post-test counseling by a genetic counselor for patient with a pathogenic variant.	Content: Not reported. Format: Training with principal investigator and genetic counselor. Time investment: one hour.	Time investment: - Consenting for genetic testing added on average 8 minutes to the consultation, reported by NGHCPs. - 4/6 NGHCPs (strongly) agreed that discussing genetic testing was possible within the timeframe of a consultation. Facilitators: - 6/6 of NGHCPs strongly agreed that supporting materials (training, information sheet and FAQ) were helpful. - 6/6 of NGHCPs considered that it is useful to have an approved clinical protocol.	Turnaround times: - Median time between diagnosis and obtaining blood sample was 18.5 days (25.5 days at other sites with standard genetic testing pathway). - Median time between diagnosis and notification of gene test result was 34 days (53 days at other sites). Post-test counseling: - Referral to genetics department was 100% (genetics department was notified at time of consent). Informed consent procedure: - Written informed consent. - Key counseling points described in checklist: possible results, implications for patients' treatment options, risk of other cancers, possible implications for family members, costs. - Additional information sheets for patients were provided.	12/16
Richardson et al., 2020, Canada (25)	Patients 165 patients with non-mucinous ovarian cancer, breast cancer <35 years of age, or triple negative breast cancer <65 years. - 49 participated in study. Control group 537 patients meeting HBOC testing criteria tested through standard genetic testing pathway. - 99 participated in study. NGHCPs 19 oncologists - 8 completed survey.	Pre-test counseling, requesting genetic testing and disclosing test result by NGHCPs. Referral for post-test counseling by a genetic counselor for all patients (regardless of test result).	Content: Information about testing and consenting patients. Format: Not reported. Time investment: Not reported.	Not reported.	Turnaround times: - Time between referral and return of genetic result was 191 days (sd 174) in mainstream genetic testing pathway compared to 403 days (sd 312) in standard genetic testing pathway. Informed consent procedure: - Written informed consent. - Script provided for pre-test counseling (not included in article). - No additional information sheets for patients were described.	11/16

Rumford et al., 2020, UK (26)	Patients 268 patients with non-mucinous ovarian cancer. - 255 received genetic testing. NGHCPs Oncologists.	Pre-test counseling, requesting genetic testing and disclosing test result by NGHCPs. Referral for post-test counseling by a genetic counselor for patients with a pathogenic variant.	Training is based on training of George et al. (7).	Not reported.	Turnaround times: - Mean time between obtaining blood sample and returning test result was 20.6 calendar days (range 11 – 42 calendar days). Before implementing mainstream genetic testing pathway, the mean time was 148.2 calendar days. Post-test counseling: - Post-test counseling at a genetics department was offered to all patients with a pathogenic variant (31/34 patients attended). Informed consent procedure: - Written informed consent. - Key counseling points described in article: discussion of *BRCA* gene, possible implications of the different test results for patient and family members. - Additional information sheet for patients were provided.	10/16

Ryan et al., 2020, UK (9,10)	Patients 305 patients with endometrial cancer - 300 received genetic testing. NGHCPs Gynecological oncology consultants or senior trainees.	IHC and MSI testing on tumor first and targeted *MLH1* methylation if indicated. Germline testing only if tumor triage was positive and/or women <50 years or strong personal/family history of Lynch syndrome-associated tumors. Pre-test counseling, requesting tumor and if necessary germline genetic testing and disclosing test result by NGHCPs. Referral for post-test counseling by a genetic counselor for patients with a pathogenic variant.	Content: Not reported. Format: Individualized training with a clinical geneticist and a genetic counselor. NGHCPs had the opportunity to observe clinical practice in two cancer genetic clinics. Time investment: One hour.	Time investment: - Recordings showed that consenting for genetic testing took on average 8 minutes, but this depended on whether a patient was consented before surgery (6 minutes, 29 seconds), on the day of surgery (3 minutes, 58 seconds) or during follow-up (10 minutes, 18 seconds).	Post-test counseling: - 13/13 patients who tested positive for Lynch syndrome were offered and received formal genetic counselling at a genetics department. Informed consent procedure: - Written informed consent. - Key counseling points not described. - Additional information sheets for patients were provided.	8/16

Scheinberg et al., 2020, Australia (11)	Patients 66 patients with metastatic prostate cancer. - 63 received genetic testing. NGHCPs 12 oncologists.	Pre-test counseling, requesting genetic testing and disclosing test result by NGHCPs. Referral for post-test counseling by a genetic counselor for patients with pathogenic variant.	Content: Information about genetic testing, counseling and study procedures. Format: Individual, face-to-face training. Time investment: One hour.	Time investment: - NGHCPs spend on average 10 minutes on pre-test counseling (self-reported). - Returning results by NGHCPs took on average 9 minutes (self-reported). - 6/8 agreed or strongly agreed that discussing genetic testing was possible within the timeframe of a consultation. Barriers: - 7/9: time investment for genetic counseling during an appointment was a barrier. - 3/9: inadequate knowledge about genetics was a barrier. - 2/8 did not feel confident they understood VUSs. Facilitators: - 8/9: nurse consultant could assist. - 8/9: required written testing packages. - 7/9: education program for oncologist.	Turnaround times: - Median time between pre-test counseling and test results was 18 days (SD 5 days). - Median time between pre-test counseling and disclosing test results to patients was 42 days (SD 30 days). Informed consent procedure: - Written informed consent. - Key counseling points not described. - Additional information sheets for patients were provided.	8/16

Scott et al., 2020, UK (27)	Patients 290 patients with breast cancer who fulfilled MCG received genetic testing. NGHCPs Two nurses participated.	Pre-test counseling, requesting genetic testing and disclosing test result by NGHCPs. Referral for post-test counseling by a genetic counselor for patients with pathogenic variant.	Content: Based on training of George et al. (7), but was complemented with patient observations, a formal consent training and practical training about genetics. Format: The practical training included making three generations family history tree. Half a day of training was provided by the clinical genetics service about interpreting test results and referring patients with other cancer syndromes. Time investment: A minimum of half a day of training.	Not reported.	Turnaround times: - Average waiting time between genetic testing and test results was 35.8 days. Before implementing the mainstream genetic testing pathway there was a wait time of 12 – 14 weeks from referral to appointment and 4 – 6 months to get test results from time of testing. Informed consent procedure: - Informed consent obtained (not specified as verbal or written). - Key counseling points not described. - Additional information sheets for patients were provided.	8/16

[a] scores: 1 = Strongly disagree, 2 = Disagree, 3 = Unsure, 4 = Agree, 5 = Strongly agree
[b] adjusted from original article after contacting first author, because of an error in the publication
[c] Quality Improvement Minimum Quality Criteria Set
FAQ frequently asked questions

Part 2

Part 2

Mainstream genetic testing of patients with ovarian cancer

Chapter 3

Positive experiences of healthcare professionals with a mainstreaming approach of germline genetic testing for women with ovarian cancer

Kyra Bokkers [1], Ronald P. Zweemer [2], Marco J. Koudijs [1], Sanne Stehouwer [1], Mary E. Velthuizen [1], Eveline M.A. Bleiker [3,4], and Margreet G.E.M. Ausems [1]

1. Division Laboratories, Pharmacy and Biomedical Genetics, Department of Genetics, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
2. Department of Gynecological Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
3. Division of Psychosocial Research and Epidemiology, The Netherlands Cancer institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
4. Department of Clinical Genetics, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

Fam Cancer. 2022 Jul;21(3):295-304.

Abstract

According to current guidelines, all women with epithelial ovarian cancer are eligible for genetic testing for *BRCA* germline pathogenic variants. Unfortunately, not all affected women are tested. We evaluated the acceptability and feasibility for non-genetic healthcare professionals to incorporate germline genetic testing into their daily practice. We developed and implemented a mainstreaming pathway, including a training module, in collaboration with various healthcare professionals and patient organizations. Healthcare professionals from 4 different hospitals were invited to participate. After completing the training module, gynecologic oncologists, gynecologists with a subspecialty training in oncology, and nurse specialists discussed and ordered genetic testing themselves. They received a questionnaire before completing the training module and 6 months after working according to the new pathway. We assessed healthcare professionals' attitudes, perceived knowledge, and self-efficacy, along with the feasibility of this new mainstream workflow in clinical practice, and evaluated the use and content of the training module. The participation rate for completing the training module was 90% (n = 19/21). At baseline and after 6 months, healthcare professionals had a positive attitude, high perceived knowledge and high self-efficacy toward discussing and ordering genetic testing. Knowledge had increased significantly after 6 months. The training module was rated with an average of 8.1 out of 10 and was considered useful. The majority of healthcare professionals (9/15) was able to discuss a genetic test in five to 10 minutes. After completion of a training module, non-genetic healthcare professionals feel motivated and competent to discuss and order genetic testing themselves.

Keywords: Epithelial ovarian cancer; Genetic counseling; *BRCA*; Mainstream genetic testing; Online training

Introduction

Epithelial ovarian cancer (EOC) is the most lethal type of gynecological cancer; around 185,000 women die of the disease every year (1). Genetic testing is currently recommended for all women with EOC (2-4) because of the high prevalence of pathogenic *BRCA* germline variants, irrespective of age of diagnosis or family history (5,6). Furthermore, the testing indications have been expanded, since the results allow for individualized treatment options with PARP inhibitors in women with platinum-sensitive EOC who carry a pathogenic germline or somatic variant in a *BRCA* gene (3,7). If a genetic test reveals a germline pathogenic variant in a cancer predisposition gene such as *BRCA1* or *BRCA2*, family members also become eligible for a genetic test. Family members who carry the same pathogenic variant can take measures to prevent cancer, or diagnose it at an early stage (2,4,8).

Despite the importance of genetic testing for affected women and their family members, studies have shown that substantial numbers of eligible cancer patients are currently not tested (9,10). This has led to many initiatives to improve the uptake of genetic testing (11). One of these initiatives is mainstreaming of genetic testing. With mainstreaming, germline genetic testing is incorporated into routine cancer care and is offered to patients by non-genetic healthcare professionals (HCP) treating them (12,13).

Mainstream genetic testing initiatives for women with EOC have been successfully implemented in several countries, with positive experiences among patients and HCPs (12-19). Although several of these initiatives included some form of education in genetic counseling, they did not evaluate HCPs' experiences with these training modules (12-17,19-23). We consider it important to ensure that HCPs who are not formally trained in genetics and genetic counseling have sufficient knowledge and self-efficacy to discuss genetic testing before mainstream genetic testing is implemented into the routine care of women with EOC.

In the current study, we aimed to develop and implement a mainstreaming pathway for germline genetic testing in women with EOC, including an online training module for gynecologic oncologists, gynecologists with a subspecialty training in oncology, and nurse specialists. Our specific research objectives were: (1) to assess HCPs' attitudes toward and knowledge of mainstream genetic testing, and their self-efficacy to discuss genetic testing before and 6 months after completion of a training module, (2) to have our training module evaluated by the users, and (3) to gain insight into the feasibility for HCPs to incorporate mainstream genetic testing into the routine care of women with EOC.

Materials and methods

Development of the training module

We developed a concise online training module for all participating HCPs. The content of this training module was determined by our project team, which consisted of HCPs from the departments of genetics, gynecology, medical oncology and pathology involved in the care of women with EOC, and patient advocates. This resulted in four short (7 minutes each) educational films (see Supplementary File 1).

Development and implementation of the care pathway for mainstream genetic testing

Our pathway for mainstream genetic testing was adapted from the workflow developed in the Mainstreaming Cancer Genetics Programme (13). Flowchart shown in Figure 1.

We organized a kick-off meeting in four hospitals in the Utrecht region to introduce the new workflow. These four hospitals are involved in the care of patients with ovarian cancer in this region. Gynecologic oncologists, gynecologists with a subspecialty training in oncology, and nurse specialists working in these hospitals were subsequently invited to complete the online training module in a personal electronic learning environment. After completion, HCPs received a manual with instructions and all necessary forms, including a patient information letter.

In our pathway, trained HCPs discussed the possibility of germline genetic testing (*BRCA1/2, RAD51C/D* and *BRIP1*) and the implications for family members with all newly diagnosed women with EOC (including fallopian tube and extra ovarian carcinomas) and women who had a personal history of EOC and had not been tested previously. In addition, HCPs completed a checklist (see Supplementary File 2) for every woman indicating whether she required additional counseling at the department of genetics after receiving their test result (e.g., indication for Lynch syndrome testing based on patient and/or family history or multiple family members with ovarian cancer implying preventive measures for female family members). If indicated by this checklist based on our national guidelines (2,24), the HCP referred the patient to the department of genetics for further counseling.

After discussing the possibility of testing, written information about genetic testing was handed out to patients. If patients agreed to undergo genetic testing, they completed a written consent form and the test was ordered.

Patients received their test result in a letter from the department of genetics, along with general information about this result. A copy of this letter was sent to both the HCP who ordered the genetic test and the general practitioner. In the event of a positive test

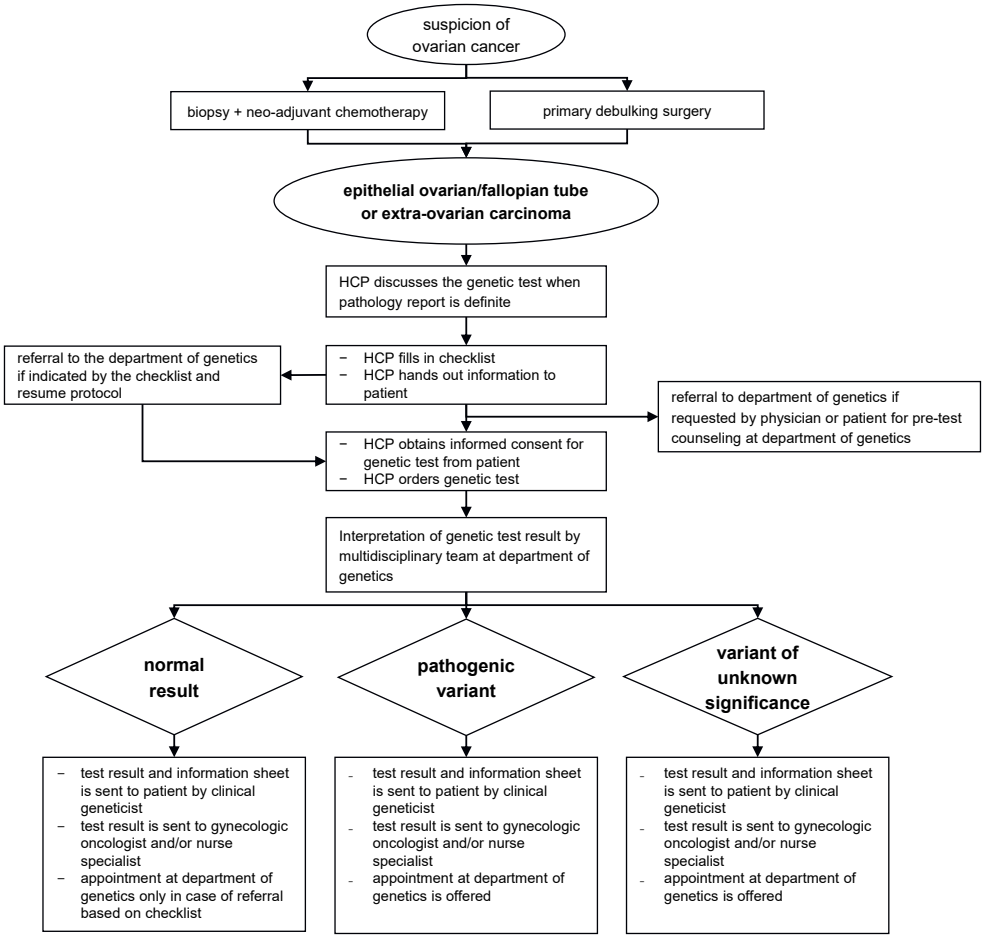


Figure 1. Flow-chart for mainstreaming pathway for healthcare professionals offering germline genetic testing to women with ovarian cancer

result, i.e., a pathogenic variant or variant of unknown significance, an appointment at the department of genetics was added to the letter. Patients with a negative test result received an invitation for an appointment only if indicated by the checklist.

This pathway was implemented in all four hospitals: implementation started in the first hospital in April 2018 and in the last one in June 2019 (one academic hospital and three non-academic teaching hospitals).

Study procedure

We used a prospective follow-up design. The participating HCPs received two questionnaires. A first questionnaire (T0) had to be completed before starting the online training module and a second questionnaire (T1) was sent 6 months after implementing

the new mainstreaming pathway for genetic testing. These questionnaires consisted of self-developed questions based on previous research by George et al. (13).

Attitude, perceived knowledge, self-efficacy, and knowledge

The T0 and T1 questionnaires consisted of 13 statements to assess HCPs' attitudes (five statements), perceived knowledge (three statements), and self-efficacy (five statements) toward mainstream genetic testing (13). The HCPs rated these statements using a 5-point Likert rating scale (from strongly disagree to strongly agree). In addition, this second questionnaire contained one extra question about attitudes toward mainstream genetic testing. Both questionnaires contained the same five knowledge questions, including two statements, and three multiple choice questions. Every statement had three response-categories: true, false and 'I do not know'.

Evaluation of the training module

After each film, HCPs completed a self-developed questionnaire about the relevance of the discussed topics (5-point Likert scale from not useful at all to very useful) and their opinions regarding the duration of the films (5-point scale from far too long to far too short). Appreciation for each film was evaluated on a scale of one to 10.

At the end of the training module, we asked participants to assess the module as a whole, with appreciation on a scale of one to 10, and the usefulness, level of difficulty, duration, and their appreciation of the online format, using a 5-point Likert scale. In addition, they were asked whether they thought that important content was missing or whether they had ideas or advice on improving the training module.

After working according to this new workflow for 6 months, we asked the HCPs whether, in retrospect, they felt any information was missing from the training module.

Feasibility

We measured the feasibility of HCPs incorporating genetic testing into their routine work in relation to three outcomes: time investment, reasons for not discussing genetic testing, and how often additional appointments were needed to discuss and order genetic testing.

After 6 months, the HCPs estimated how much time they needed to discuss and order genetic testing (less than five minutes, 5–10 minutes, 10–20 minutes, more than 20 minutes). In addition, they were asked to rate whether this time investment was 'as expected' on a 5-point Likert rating scale (much worse than expected to much better than expected).

Both at baseline and after 6 months, the HCPs were asked to provide the two most important reasons for not discussing the possibility of genetic testing with all eligible patients.

After 6 months they estimated how often their patients needed an additional appointment to discuss genetic testing, and reported the most important reasons for such an appointment.

Statistical Analyses

We used descriptive statistics to detail the characteristics of the HCPs, time investment, reasons for not discussing the possibility of genetic testing, and whether additional appointments were needed. We compared the characteristics of the HCPs in the T0 and T1 groups using the independent t-test for continuous variables and the chi-square test for categorical variables to determine whether the HCPs who filled in both questionnaires were representative of the entire group.

With paired analysis using the Wilcoxon signed-rank test we compared the total number of correct answers to the knowledge questions between T0 and T1, and all statements regarding attitude, perceived knowledge and self-efficacy between T0 and T1. A p-value < 0.05 was considered as statistically significant. Statistical analyses were performed using IBM SPSS statistics 25.0.0.2.

Results

Participation

Twenty-one HCPs received login codes to the online training module. Nineteen (90%) HCPs completed the entire training module. One HCP completed part of the online training module.

The first questionnaire was completed by 20 out of 21 HCPs (95%) from four hospitals. The second questionnaire was completed by 15 out of 17 HCPs. Two HCPs were not sent a second questionnaire because they had completed the online training module less than 6 months before the end of our study period.

The total group consisted of 20 HCPs. Their characteristics are presented in Table 1. There were no statistically significant differences in the characteristics of the 15 HCPs who filled in both questionnaires compared to the five HCPs who only completed the first questionnaire.

Table 1. Characteristics of participating HCPs

Characteristics of HCPs	Total group n = 20
Mean age (range)	47 (31-64)
Sex, n (%)	
- Female	12 (60)
- Male	8 (40)
Disciplines, n (%)	
- Gynecologic oncologist	5 (25)
- Gynecologist with a subspecialty training in oncology	7 (35)
- Gynecologist in training	2 (10)
- Nurse or nurse specialist (in training)	6 (30)
Hospital, n (%)	
- Academic hospital	7[a] (33.3)
- Non-academic teaching hospital	14[a] (66.7)

[a] One healthcare professional worked in both an academic and nonacademic teaching hospital.

Attitude, perceived knowledge, self-efficacy, and knowledge

Table 2 shows the number of HCPs that 'agreed' or 'strongly agreed' with the statements regarding attitude, perceived knowledge, and self-efficacy toward mainstream genetic testing. Both at baseline and after 6 months, a majority of HCPs agreed (strongly) to most of these statements. Only for the statements about attitude and self-efficacy related to offering genetic testing directly after diagnosing ovarian cancer, the majority of HCPs neither agreed nor disagreed at both time points. With paired analysis, there were no significant differences between T0 and T1 for any of these statements. However, there seems to be a positive trend in the perceived knowledge of HCPs regarding the advantages and disadvantages of genetic testing ($p = 0.058$).

One HCP had a neutral attitude toward discussing and ordering genetic testing at baseline and thought that discussing and ordering genetic testing would be too time-consuming. The same HCP did have a positive attitude after 6 months. Another HCP had a positive attitude at baseline but a neutral attitude after 6 months; the new workflow was too time-consuming, this HCP felt insecure about their knowledge regarding genetic testing, and felt that clinical geneticists and genetic counselors had more experience and tools to discuss genetic testing.

Table 3 shows the knowledge questions and how many HCPs answered these questions correctly at baseline (before the online training module) and 6 months after implementing the new mainstreaming pathway. Paired analysis (between T0 and T1) for the total number of correct answers for all five questions were available for 14 HCPs. The total

Table 2. Attitude, perceived knowledge, and self-efficacy of HCPs (n = 15) before (T0) and 6 months after completing the training module (T1)

Questions	T0 (strongly) agree n (%)	T1 (strongly) agree n (%)	p-value
Attitude			
- It is important for patients to have a choice whether or not to have a genetic test performed	14 (93.3)	13 (86.7)	ns
- It is important to offer genetic testing immediately after diagnosing ovarian cancer	6 (40)	5 (33.3)	ns
- It is important that all patients with ovarian cancer have access to genetic testing	15 (100)	15 (100)	ns
- I am positive toward offering a genetic test myself	14 (93.3)	14 (93.3)	ns
- It is important when discussing genetic testing to pay attention to the psychosocial consequences of genetic testing	14 (93.3)	14[a] (100)	ns
- Gynecologic oncologists, oncologists with a subspecialty training in oncology, and nurse specialists are capable of discussing and ordering genetic testing themselves after completing an online training module	N/A	13 (86.6)	ns
Perceived knowledge			
- I understand the advantages and disadvantages of a genetic test	12 (80)	15 (100)	0.058
- I understand the importance of genetic testing for patients with ovarian cancer	14 (93.3)	15 (100)	ns
- I understand the importance of genetic testing for family members of patients with ovarian cancer	15 (100)	15 (100)	ns
Self-efficacy			
- I am confident that I can discuss the advantages and disadvantages of a genetic test	15 (100)	13 (86.7)	ns
- I am confident that I am able to discuss a genetic test with all patients with ovarian cancer directly after diagnosing ovarian cancer	8 (53.3)	7 (46.7)	ns
- I am confident that I am able to order a genetic test myself	15 (100)	15 (100)	ns
- I am confident that I am able to recognize psychosocial problems in patients and subsequently refer patients to a specialist social worker	15 (100)	14 (93.3)	ns
- I am confident that I am able to explain what genetic testing in tumor tissue entails and what the differences are with genetic testing in blood samples	12 (80)	15 (100)	ns

The remaining HCPs either answered: 'neither agree, nor disagree', 'disagree', or 'strongly disagree'. *N/A* not applicable, *ns* not significant. [a] One missing value.

number of correct answers remained constant for seven HCPs after working for 6 months according to the new mainstreaming pathway, and improved for the other seven HCPs. The measured difference with paired analysis is statistically significant (p = 0.016).

Table 3. Knowledge of HCPs (n=14) before (T0) and 6 months after completing the training module (T1)

Questions	T0 Correct answer n (%)	T1 Correct answer n (%)
- What is the prevalence of *BRCA* mutations in patients with ovarian cancer?	3 (21.4)	9 (64.3)
- Patients with ovarian cancer are eligible for genetic testing only when other family members have breast and/or ovarian cancer	14 (100)	14 (100)
- A hereditary cause for ovarian cancer can be excluded if no mutation is found in one of the *BRCA* genes	13 (92.9)	13 (92.9)
- What is the meaning of a *BRCA* mutation that is found with a tumor test only?	11 (78.6)	13 (92.9)
- What is the meaning of a *BRCA* mutation that is found with a blood test only?	11 (78.6)	14 (100)

Evaluation of the training module

The four individual films were ranked, with an average rating of between 7.9 and 8.1 out of 10. The majority (> 75%) of HCPs considered the duration of each individual film to be 'exactly right' and all discussed topics to be relevant.

The evaluation of the overall online training module is shown in Table 4. Immediately after completing the training module, two out of 19 HCPs mentioned that they missed information regarding the impact of genetic testing on insurance. After 6 months, two out of 15 HCPs mentioned that, in retrospect, they missed practical tips on how to order genetic testing. In addition, one HCP would have wanted to know the estimated time investment for discussing and ordering genetic testing.

Feasibility

HCPs were able to discuss a genetic test in five to 10 minutes (9/15) or 10 to 20 minutes (6/15). For 14 out of 15 HCPs this time investment was as expected or better than expected. Most HCPs were able to order the genetic test in less than 5 minutes (8/14), the remainder needed 5 to 10 minutes (n = 5) or 10 to 20 minutes (n = 1). For 13 out of 14 HCPs this time investment was as expected or better than expected.
The main reasons for not discussing genetic testing differed between 'forgotten' (T0) and 'no appropriate moment' (T1) and are illustrated in Figure 2.

Table 4. Evaluation of the overall online training module (n = 19 HCPs)

Average rating out of 10 (range)	8.1 (7 – 10)
Usefulness of online training module, n (%)	
- (Reasonably/very) useful	18 (94.7)
- Not useful (at all)	1 (5.3)
Level of difficulty, n (%)	
- **(**Much) too high	0 (0)
- Exactly right	16 (84.2)
- (Much) too low	3 (15.8)
Appreciation of online format, n (%)	
- (Very) pleasant	16 (84.2)
- Fairly pleasant	3 (15.8)
- Not pleasant (at all)	0 (0)
Duration of online training module, n (%)	
- (Much) too long	2 (10.5)
- Exactly right	17 (89.5)
- (Much) too short	0 (0)

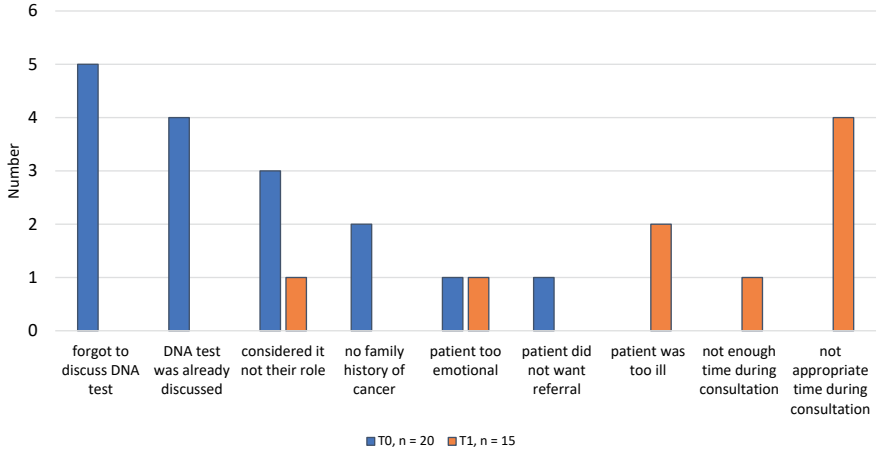


Figure 2. The main reasons for not discussing genetic testing before (T0) and 6 months after completing the training module (T1)

Less than half (7/15) of the HCPs reported that they had scheduled an additional appointment to discuss genetic testing for at least one patient. Reasons for this were that patients needed reflection time to consider genetic testing (n = 6), that there was not enough time during the consultation (n = 4), and that discussing genetic testing would be too much information for the patient in one consultation (n = 4).

Discussion

This study shows that gynecologic oncologists, gynecologists with a subspecialty training in oncology and nurse specialists feel motivated and competent to discuss and order germline genetic testing in women with EOC themselves. HCPs had a positive attitude, high self-efficacy, and high perceived knowledge both before and 6 months after working according to the new workflow. This high acceptability among HCPs is comparable to the results of other mainstreaming studies (12-14,16,17,19). Furthermore, 90% of the invited HCPs from four hospitals completed the training module and participated in our study.

We considered training an essential part of the implementation of our mainstream genetic testing pathway. Pre-test genetic counseling and informed consent are important, because the results of a genetic test can have serious implications for patients and family members (2,4). Training on genetic counseling should therefore also focus on the practical and emotional implications of a genetic test (25,26). We incorporated these aspects into our training module (see Supplementary File 1). Earlier research has shown that a majority of HCPs consider their knowledge about genetic testing to be inadequate (27). A training intervention can be successful in increasing the perceived knowledge, self-efficacy and positive attitude of HCPs toward discussing and ordering genetic testing (14). In our study, HCPs already had a positive attitude, high perceived knowledge, and high self-efficacy at baseline. This might be due to the close collaboration between the gynecology and genetics departments in our region. These outcomes persisted 6 months after completing our training module, which may be due to a ceiling effect. Importantly, after completing our online training module and with 6 months hands-on experience in discussing and ordering genetic testing themselves, the attitude remained positive, and perceived knowledge and self-efficacy remained high. We did see a significant increase in knowledge about genetic testing after 6 months. However, it should be noted that we asked a limited number of questions that do not cover all necessary aspects for pre-test counseling. The experiences of patients are the best indicator whether non-genetic HCPs are well equipped to perform pre-test counseling themselves.

The majority of HCPs took around 10 minutes to discuss and order genetic testing, which was ‘as expected’ or ‘better than expected’ for almost all of them. This time investment is comparable to the results from previous studies (14,17) and seems to be acceptable to HCPs. Furthermore, 86% of HCPs agreed that, after completion of the training module, mainstream genetic testing should be incorporated into their routine work. This time investment is substantially shorter than the average time investment for traditional genetic counseling (on average 40 to 45 minutes) (28,29). For patients with EOC, an extended family history is not necessary to determine if the patient is eligible for genetic testing. We developed a short standardized checklist to evaluate family history in our mainstream

model. In addition, we expect that non-genetic HCPs explain possible implications of a genetic test in a more general way.

After 6 months, the participants reported they no longer forgot to discuss genetic testing and their main reason for not discussing genetic testing was because they thought there was no appropriate moment during the consultation. In addition, about half of the HCPs felt confident discussing genetic testing with patients directly after diagnosing ovarian cancer. A standard moment to discuss and order genetic testing can further reduce the risk of HCPs forgetting to discuss it. However, it is important to take into consideration the timing of the different consultations and the amount of information that patients already receive after diagnosis. There are differences between hospitals, and adaptation of pathways or division of tasks in accordance with local workflows is often necessary. Our findings show that it is feasible for HCPs to incorporate germline genetic testing, including asking for patients' written informed consent, into their daily work. Gleeson et al. showed that the most important barrier for non-genetic HCPs to continue with mainstream genetic testing was that they did not feel confident that there was a structured workflow, including collaboration with a department of genetics (14). During our study period, this new workflow was already incorporated into standard care, and HCPs could discuss and order genetic testing for all women with EOC.

An advantage of the workflow that we implemented is that it can easily be adapted if gene panels change. In the course of our study, the ovarian cancer gene panel consisted of the five core genes (*BRCA1, BRCA2, BRIP1, RAD51C* and *RAD51D)*, and it is likely that the gene panel will be expanded with other cancer genes, such as *PALB2,* in the near future. Tumor testing can also be incorporated into our workflow. Tumor testing has the advantage that it can be used as a pre-test for germline genetic testing (30). When a pathogenic variant is found in the tumor there is a 50% chance of the existence of a germline pathogenic variant, and patients and their family members should be prepared for this outcome. Therefore, adequate pre-test counseling and informed consent are equally important when discussing and ordering a tumor test first. Our training module covers the difference between germline and somatic variants. Therefore, after completing our training module, HCPs will be well equipped to first discuss and order a tumor test, and, if necessary, subsequently a germline test. An additional advantage of incorporating our workflow into a tumor first workflow is that germline testing can be offered directly to patients when a tumor test fails or cannot be performed.

Although our new workflow seemed feasible in this study setting, the financial consequences need to be taken into account. There should be adequate reimbursement for the extra time investment that HCPs need when discussing and ordering genetic

testing. Future research should focus on the shift of responsibilities between the involved departments and the changes in financial sources.

A major strength of our study is that we developed our training module and workflow in collaboration with our project team consisting of multiple HCPs and two patient organizations. We could therefore identify barriers and facilitators for all involved parties. Other strengths are the before-and-after design to test the knowledge, attitude, and self-efficacy of HCPs, the inclusion of both academic and non-academic teaching hospitals, and the subsequent high participation rate of HCPs which improves the generalizability of our outcomes.

There are limitations for this study. Our study population was small, which makes it more difficult to observe significant effects, and we did not use standardized questionnaires to assess knowledge, attitude, and self-efficacy. To our knowledge, there are no suitable and validated questionnaires available to generate results that would answer our specific research questions. In addition, we only measured self-reported outcomes, and did not objectively measure skills. Therefore, the results of our study cannot easily be extrapolated to other non-genetic HCPs. Last, we did not compare our results to a control group of HCPs that did not receive any training in pre-test genetic counseling.

Future research

For mainstream models to be successful and effective it is important that patients can make a well informed decision regarding genetic testing after pre-test counseling. So far, the experiences of patients with mainstream genetic testing have been investigated in multiple studies, but as far as we know there are no randomized trials. In addition, there is a lack of studies that focus on more quality of care outcomes (12,13,15,17,19). In the future, patient experiences should be evaluated in more detail and should include not only satisfaction, but also outcomes that evaluate quality of care, such as patients' understanding of received information, decisional conflict, and decision regret. In addition, it is important to consider alternative models that address the increasing demand for genetic testing, and to compare these alternative models, such as direct genetic testing models (31,32), embedding genetic counsellors into oncology clinics (33,34), and tumor-first genetic testing models (30).

Conclusion

Preceded by an online training module, the implementation of a mainstreaming pathway for germline genetic testing in women with EOC seems feasible and acceptable for non-genetic HCPs.

Supplementary Information: The online version contains supplementary material available at https:// doi. org/ 10. 1007/ s10689- 021- 00277-7.

Acknowledgements: We thank the members of our project team involved in the development of the training program and the set-up of the mainstreaming pathway: Els Butter, Jeanne van Echtelt, Geert Frederix, Kees Gerestein, Jeske van Harssel, Trudy Jonges, Wendy de Leng and the patient organizations 'Olijf' foundation, Dutch Breast Cancer Society (BVN), and Oncogen. We also thank all participating gynecologic oncologists, gynecologists with a subspecialty training in oncology, and nurse specialists from the University Medical Center Utrecht, Diakonessenhuis Utrecht, Meander Medical Center Amersfoort, and St. Antonius Hospital Nieuwegein/Utrecht, The Netherlands.

Author contribution: KB: conceptualization, methodology, formal analysis, investigation, writing—original draft, writing—review & editing, project administration. RPZ: conceptualization, investigation, methodology, writing—review & editing, supervision. MJK: methodology, investigation, writing—review & editing. SS: conceptualization, writing—review & editing. MEV: formal analysis, investigation, data curation, writing—review & editing. EMAB: methodology, writing—review & editing, supervision. MGEMA: conceptualization, methodology, writing—review & editing, supervision, funding acquisition.

Funding: M.G.E.M. Ausems received a grant from AstraZeneca for development and filming of the training module. AstraZeneca was not involved in the development of its content.

Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Declarations

Conflict of interest: K. Bokkers, R.P. Zweemer, M.J. Koudijs, S. Stehouwer, M.E. Velthuizen, and E.M.A. Bleiker have nothing to disclose. M.G.E.M. Ausems received a grant from AstraZeneca for development and filming of the training module. AstraZeneca was not involved in the development of its content.

Ethical approval: This study was reviewed by the Medical Review Ethics Committee (MREC) of the UMC Utrecht in March 2018 and the Medical Research Involving Human Subjects Act (WMO) did not apply to our study and therefore official approval by the MREC was not necessary.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. CRGO. Guideline hereditary and familial ovarian cancer 2015 [updated June 1. Available from: https://www.oncoline.nl/erfelijk-en-familiair-ovariumcarcinoom].
3. Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245.
4. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 2.2019 2018 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf].
5. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654-2663.
6. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011;121(2):353-357.
7. Tew WP, Lacchetti C, Ellis A, Maxian K, Banerjee S, Bookman M, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-3493.
8. US Preventive Services Task Force, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;322(7):652-665.
9. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National Estimates of Genetic Testing in Women With a History of Breast or Ovarian Cancer. J Clin Oncol. 2017;35(34):3800-3806.
10. Hoskins PJ. Inadequate Rates of BRCA Testing with its Negative Consequences for Women with Epithelial Ovarian Cancer and their Families: an Overview of the Literature. Clin Oncol (R Coll Radiol). 2018;30(8):472-483.
11. McCuaig JM, Armel SR, Care M, Volenik A, Kim RH, Metcalfe KA. Next-Generation Service Delivery: A Scoping Review of Patient Outcomes Associated with Alternative Models of Genetic Counseling and Genetic Testing for Hereditary Cancer. Cancers (Basel). 2018;10(11).
12. Colombo N, Huang G, Scambia G, Chalas E, Pignata S, Fiorica J, et al. Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer. J Clin Oncol. 2018;36(13):1300-1307.
13. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.

14. Gleeson M, Kentwell M, Meiser B, Do J, Nevin S, Taylor N, et al. The development and evaluation of a nationwide training program for oncology health professionals in the provision of genetic testing for ovarian cancer patients. Gynecol Oncol. 2020;158(2):431-439.
15. McLeavy L, Rahman B, Kristeleit R, Ledermann J, Lockley M, McCormack M, et al. Mainstreamed genetic testing in ovarian cancer: patient experience of the testing process. Int J Gynecol Cancer. 2020;30(2):221-226.
16. Percival N, George A, Gyertson J, Hamill M, Fernandes A, Davies E, et al. The integration of BRCA testing into oncology clinics. Br J Nurs. 2016;25(12):690-694.
17. Powell CB, Laurent C, Ciaravino G, Garcia C, Han L, Hoodfar E, et al. Streamlining genetic testing for women with ovarian cancer in a Northern California health care system. Gynecol Oncol. 2020;159(1):221-228.
18. Wright S, Porteous M, Stirling D, Lawton J, Young O, Gourley C, et al. Patients' Views of Treatment-Focused Genetic Testing (TFGT): Some Lessons for the Mainstreaming of BRCA1 and BRCA2 Testing. J Genet Couns. 2018;27(6):1459-1472.
19. Yoon SY, Wong SW, Lim J, Ahmad S, Mariapun S, Padmanabhan H, et al. Oncologist-led BRCA counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes. J Med Genet. 2022;59(3):220-229.
20. Bednar EM, Oakley HD, Sun CC, Burke CC, Munsell MF, Westin SN, et al. A universal genetic testing initiative for patients with high-grade, non-mucinous epithelial ovarian cancer and the implications for cancer treatment. Gynecol Oncol. 2017;146(2):399-404.
21. Flaum N, Morgan RD, Burghel GJ, Bulman M, Clamp AR, Hasan J, et al. Mainstreaming germline BRCA1/2 testing in non-mucinous epithelial ovarian cancer in the North West of England. Eur J Hum Genet. 2020;28(11):1541-1547.
22. Rahman B, Lanceley A, Kristeleit RS, Ledermann JA, Lockley M, McCormack M, et al. Mainstreamed genetic testing for women with ovarian cancer: first-year experience. J Med Genet. 2019;56(3):195-198.
23. Rumford M, Lythgoe M, McNeish I, Gabra H, Tookman L, Rahman N, et al. Oncologist-led BRCA 'mainstreaming' in the ovarian cancer clinic: A study of 255 patients and its impact on their management. Sci Rep. 2020;10(1):3390.
24. Dutch Association of Medical Specialists. Guideline Breast Cancer 2020 [updated February 7 Available from: https://richtlijnendatabase.nl/richtlijn/borstkanker/algemeen.html].
25. Korngiebel DM, Zech JM, Chappelle A, Burke W, Carline JD, Gallagher TH, et al. Practice Implications of Expanded Genetic Testing in Oncology. Cancer Invest. 2019;37(1):39-45.
26. Shipman H, Flynn S, MacDonald-Smith CF, Brenton J, Crawford R, Tischkowitz M, et al. Universal BRCA1/BRCA2 Testing for Ovarian Cancer Patients is Welcomed, but with Care: How Women and Staff Contextualize Experiences of Expanded Access. J Genet Couns. 2017;26(6):1280-1291.
27. Hamilton JG, Abdiwahab E, Edwards HM, Fang ML, Jdayani A, Breslau ES. Primary care providers' cancer genetic testing-related knowledge, attitudes, and communication behaviors: A systematic review and research agenda. J Gen Intern Med. 2017;32(3):315-324.

28. Eijzenga W, Aaronson NK, Hahn DE, Sidharta GN, van der Kolk LE, Velthuizen ME, et al. Effect of routine assessment of specific psychosocial problems on personalized communication, counselors' awareness, and distress levels in cancer genetic counseling practice: a randomized controlled trial. J Clin Oncol. 2014;32(27):2998-3004.
29. Legare F, Ratte S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Educ Couns. 2008;73(3):526-535.
30. Vos JR, Fakkert IE, de Hullu JA, van Altena AM, Sie AS, Ouchene H, et al. Universal Tumor DNA BRCA1/2 Testing of Ovarian Cancer: Prescreening PARPi Treatment and Genetic Predisposition. J Natl Cancer Inst. 2020;112(2):161-169.
31. Hoberg-Vetti H, Bjorvatn C, Fiane BE, Aas T, Woie K, Espelid H, et al. BRCA1/2 testing in newly diagnosed breast and ovarian cancer patients without prior genetic counselling: the DNA-BONus study. Eur J Hum Genet. 2016;24(6):881-888.
32. Plaskocinska I, Shipman H, Drummond J, Thompson E, Buchanan V, Newcombe B, et al. New paradigms for BRCA1/BRCA2 testing in women with ovarian cancer: results of the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) study. J Med Genet. 2016;53(10):655-661.
33. Kentwell M, Dow E, Antill Y, Wrede CD, McNally O, Higgs E, et al. Mainstreaming cancer genetics: A model integrating germline BRCA testing into routine ovarian cancer clinics. Gynecol Oncol. 2017;145(1):130-136.
34. Rana HQ, Kipnis L, Hehir K, Cronin A, Jaung T, Stokes SM, et al. Embedding a genetic counselor into oncology clinics improves testing rates and timeliness for women with ovarian cancer. Gynecol Oncol. 2021;160(2):457-463.

Supplementary File 1. Supporting information regarding online training module

The training module was evaluated and accredited by national accreditation bureaus of the scientific organizations for gynecologists and nurse specialists as part of the national CME accreditation.

Film 1: Mainstreaming of genetic testing in patients with cancer (duration: 7.5 minutes).

This film contains the following elements:

- Short introduction film with a clinical geneticist giving an explanation of the term mainstreaming of genetic testing and why this new workflow is important for patients with cancer.
- Slides with a voice over explaining:
    - How cancer develops and how hereditary and environmental factors play a role.
    - The difference between germline and somatic mutations.
    - The difference between genetic testing in blood and genetic testing in tumor tissue.
    - The importance of genetic testing in patients with cancer.
    - The difference between diagnostic and predictive genetic testing.
    - A summary of the above.

Film 2: *BRCA1* and *BRCA2*, genetic testing in ovarian cancer patients (duration: 5.5 minutes).

This film contains the following elements:

- Short introduction film with a clinical geneticist giving an overview of the content of the film.
- Slides with a voice over explaining:
    - The eligibility criteria for genetic testing in patients with ovarian cancer.
    - The prevalence of pathogenic variants in the *BRCA* genes and the difference in prevalence between the histologic subtypes.
    - Cancer risks associated with pathogenic variants in the *BRCA* genes.
    - Pattern of inheritance for pathogenic variants in the *BRCA* genes.
    - Screening recommendations for family members.
    - Possible changes in the future, for example the expected expansion of the gene panel and the role of tumor testing.
    - A summary of the above.

Film 3: The new workflow for genetic testing (duration: 7 minutes)

This film contains the following elements:

- Short introduction film with a clinical geneticist giving an overview of the content of the film.
- Sides with a voice over explaining:
    - The entire workflow (step-by-step).
    - How to fill out the checklist to determine if the patient is eligible for referral to the department of genetics.
    - How to fill out the informed consent form.

Film 4: Practical advice on how to discuss genetic testing (duration: 10 minutes)

This film contains the following elements:

- Short introduction film with a clinical geneticist giving an overview of the content of the film.
- Slides with a voice over explaining:
    - Communication about and timing of genetic testing.
    - Elements to discuss with a patient.
    - Possible outcomes of a genetic test and the implications of these outcomes.
- Film with:
    - A gynecologic oncologist and a patient. This shows a simulation consultation on how to discuss a genetic test, including:
        - Importance of genetic testing (possible implications for treatment options and risk of breast cancer).
        - Possible consequences for family members.
        - Procedure (blood test, time to result, and result send via letter).
    - A patient who is carrier of a pathogenic variant in the BRCA1 gene and currently using PARP inhibitors. She explains the impact that genetic testing had on her and her family and why genetic testing is important for every woman with ovarian cancer.
    - A specialized social worker. She explains what impact a pathogenic variant in a *BRCA* gene can have on patient and her family members, elaborates on the emotional consequences and explains the supportive role of a social worker in the process of genetic testing.

Supplementary File 2. checklist indicative for referral to genetics department

Checklist 'referral to genetics department'

	yes	no
Does your patient have:		
- a first or second degree relative with ovarian cancer?	☐	☐
- a synchronous or metachronous Lynch syndrome associated carcinoma*?	☐	☐
- a first degree relative with endometrial or colon cancer, and diagnosed under the age of 50 years or the ovarian cancer diagnosed under the age of 50 years.	☐	☐
- 2 or more first or second degree relatives with a Lynch syndrome associated carcinoma*?	☐	☐
- (current or previous) breast cancer or ductal carcinoma in situ?	☐	☐

*Lynch syndrome associated carcinomas: colorectal carcinoma, endometrial carcinoma, stomach cancer, carcinoma of the small intestine, urinary tract carcinomas, ovarian cancer, pancreatic carcinoma, brain tumor, bile duct carcinoma and sebaceous gland carcinoma.

Can 1 or more questions be answered with "yes"? → patient is eligible for referral to the genetics department

This checklist should be included in the patient file.

Contact the genetics department easily when you have questions regarding this checklist or when you think the patient is eligible for referral and this is not reflected in the checklist. (original checklist includes telephone numbers)


4

Chapter 4

Mainstream genetic testing for women with ovarian cancer provides a solid basis for patients to make a well-informed decision about genetic testing

Kyra Bokkers [1], Eveline M.A. Bleiker [2,3,4], Jacob P. Hoogendam [5], Mary E. Velthuizen [1], Henk W.R. Schreuder [5], Cornelis G. Gerestein [5,6], Joost G. Lange [7], Jacqueline A. Louwers [8], Marco J. Koudijs [1], Margreet G.E.M. Ausems [1], and Ronald P. Zweemer [5]

1. Department of Genetics, Division Laboratories, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
2. Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
3. Family Cancer Clinic, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
4. Department of Clinical Genetics, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
5. Department of Gynecological Oncology, University Medical Center Utrecht, Heidelberglaan 100, PO Box 85500, 3584 CX Utrecht, The Netherlands
6. Department of Gynecology, Meander Medical Center, Maatweg 3, 3813 TZ Amersfoort, The Netherlands
7. Department of Gynecology, St. Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands
8. Department of Gynecology, Diakonessenhuis, Bosboomstraat 1, 3582 KE Utrecht, The Netherlands

Hered Cancer Clin Pract. 2022 Sep 8;20(1):33.

Abstract

Background: There is a growing need for genetic testing of women with epithelial ovarian cancer. Mainstream genetic testing provides an alternative care pathway in which non-genetic healthcare professionals offer pre-test counseling themselves. We aimed to explore the impact of mainstream genetic testing on patients' experiences, turnaround times and adherence of non-genetic healthcare professionals to the mainstream genetic testing protocol.

Methods: Patients receiving pre-test counseling at the gynecology departments between April 2018 and April 2020 were eligible to participate in our intervention group. Patients receiving pre-test counseling at the genetics department between January 2017 and April 2020 were eligible to participate in our control group. We evaluated patients' experiences with questionnaires, consisting of questions regarding knowledge, satisfaction and psychosocial outcomes. Patients in the intervention group were sent two questionnaires: one after pre-test counseling and one after receiving their DNA test result. Patients in our control group were sent one questionnaire after receiving their test result. In addition, we collected data regarding turnaround times and adherence of non-genetic healthcare professionals to the mainstream genetic testing protocol.

Results: Participation was 79% in our intervention group (105 out of 133 patients) and 60% in our control group (91 out of 152 patients). Knowledge regarding genetics, decisional conflict, depression, anxiety, and distress were comparable in the two groups. In the intervention group, the risk of breast cancer in patients carrying a pathogenic germline variant was discussed less often (49% versus 74% in control group, $p \leq 0.05$), and the mean score of regret about the decision to have genetic testing was higher than in the control group (mean 12.9 in the intervention group versus 9.7 in the control group, $p \leq 0.05$), although below the clinically relevant threshold of 25. A consent form for the DNA test and a checklist to assess family history were present for ≥ 95% of patients in the intervention group.

Conclusions: Mainstream genetic testing is an acceptable approach to meet the increase in genetic testing among women with epithelial ovarian cancer.

Keywords: Epithelial ovarian cancer; Mainstream genetic testing; Patients' perspectives; Genetic counseling; Turnaround times; Psychosocial outcomes; Knowledge; Satisfaction

Introduction

Genetic testing for patients with ovarian cancer has increased over the years, due to expanding eligibility criteria and individualized treatment options that are dependent on DNA test results. All patients with epithelial ovarian cancer (EOC) are eligible for genetic testing (1-3). Patients with platinum-sensitive EOC are sensitive to treatment with PARP inhibitors, with an increased response when a pathogenic variant in a *BRCA* gene is present (2,4).

With mainstream genetic testing, non-genetic healthcare professionals (HCPs) perform pre-test counseling and order germline genetic testing for their patients (5,6). Additional counseling by a genetic counselor or clinical geneticist is only required in case of a pathogenic variant or variant of unknown significance in a cancer predisposition gene. The importance of genetic testing for patients with EOC and low referral rates to genetics departments in the past have led to the rise of mainstream genetic testing initiatives around the world (7,8).

We have previously implemented a mainstream genetic testing pathway in four hospitals in the Netherlands, and we have shown that gynecologic oncologists, gynecologists with a subspecialty training in oncology, and nurse specialists feel capable of performing pre-test counseling and ordering genetic testing themselves and are motivated to do so (9). Earlier research has shown that patients with EOC appreciate being offered a DNA test shortly after diagnosis (10-13), and their distress and cancer worry do not increase following genetic counseling (11,14).

However, with mainstream genetic testing, non-genetic HCPs need to incorporate genetic testing into their routine practice. The time spent on pre-test counseling may be considerably shorter compared to the duration of the pre-test counseling performed by clinical geneticists or genetic counselors. In addition, with mainstream genetic testing there is no wait time for patients to receive pre-test counseling. This is beneficial for possible treatment options, but also eliminates a time period for patients to consider genetic testing before their first pre-test counseling. This may result in more distress or decisional conflict or regret in patients.

Because of these differences in the clinical setting, it is impossible for non-genetic HCPs to provide the same pre-test counseling as provided by a clinical geneticist or genetic counselor. These differences are acceptable as long as patients are able to make a well-informed decision regarding genetic testing without experiencing excessive distress or regret. In addition, non-genetic HCPs need to incorporate an informed consent procedure

and identify patients who might benefit from additional counseling at a genetics department, for example for genetic testing for Lynch syndrome.

Many studies have shown high acceptability of mainstream genetic testing approaches among EOC patients (5,6,15-21). So far, these outcomes have only been evaluated sporadically with a control group receiving pre-test genetic counseling at a genetics department (16,18-20). Two of these studies included both patients with breast and ovarian cancer, and post-test counseling was always performed by a genetic counselor or clinical geneticist (16,19). Another study predominantly considered patient satisfaction (18).

In this study, we will assess the impact of mainstream genetic testing on patient care in comparison to genetic counseling and testing performed by a clinical geneticist or genetic counselor. The impact on patient care is evaluated based on psychosocial outcomes, knowledge and satisfaction of patients, turnaround times, and the adherence of non-genetic HCPs to the mainstream genetic testing protocol.

Material and methods

Mainstream genetic testing pathway

We previously described the development and workflow of our mainstream genetic testing pathway (9). We implemented this pathway in the four hospitals in our region where patients are diagnosed and treated for EOC. In April and August 2018, we started in the two hospitals with the highest numbers of newly diagnosed patients with EOC. In March and July 2019, we implemented our pathway in the other two hospitals. After completion of a training module, non-genetic HCPs could perform pre-test genetic counseling and order genetic testing for all patients eligible for genetic testing according to national guidelines (i.e., EOC, including fallopian tube and extra ovarian carcinomas), including patients who were diagnosed in the past and had not yet received genetic testing (1). These non-genetic HCPs included gynecologic oncologists, gynecologists with a subspecialty training in oncology, and nurse specialists. If indicated by the patient or non-genetic HCP, patients could still be referred for pre-test counseling by a genetic HCP (e.g., when the patient had questions that the non-genetic HCP could not answer). Our gene panel first consisted of the genes: *BRCA1* and *BRCA2* (1). During our study, this panel was complemented by the genes *BRIP1, RAD51C,* and *RAD51D*.

During pre-test counseling, non-genetic HCPs informed patients of the implications of genetic testing and handed out an information sheet with general information about genetic testing. For patients who accepted genetic testing, written informed consent was

obtained and the DNA test ordered. In addition, non-genetic HCPs filled out a checklist to identify patients with a relevant personal or family history indicative for referral to a genetics department (e.g., meeting eligibility criteria for Lynch syndrome testing and/or preventive measures for family members).

The genetics department sent the test results to patients in a letter, which also included a general information sheet explaining this result. This letter was also sent to the HCP who had ordered the DNA test and to the general practitioner. An invitation for post-test counseling at the genetics department was added to this letter for all patients carrying a pathogenic variant or variant of unknown significance within five working days, or patients with a relevant personal or family history within 6–8 weeks.

Standard genetic testing pathway

For patients referred to the genetics department, a clinical geneticist or genetic counselor performed pre-test counseling and acquired information regarding the family history, obtained written informed consent and ordered the DNA test. During our study period, patients could either be referred to the genetics department by non-genetic HCPs who were not trained in the mainstream genetic testing pathway (e.g., general practitioners or medical oncologists) or by trained non-genetic HCPs when there was an indication for such a referral. Test results were discussed with the patient in person, via telephone or videoconference. Subsequently, the test result and possible implications of this result for patient and family members were summarized in a letter to the patient. This letter was also sent to the general practitioner and the non-genetic HCP who referred the patient.

Study design and participants

All patients who received pre-test genetic counseling and testing in the mainstream genetic testing pathway were invited prospectively to participate in our questionnaire study between April 2018 and April 2020 (see Figure 1). All patients who received pre-test counseling were eligible to participate in our intervention group, even if they declined genetic testing. They received information about the study, including a response sheet, directly after discussing the DNA test with their HCP (T0). We sent a reminder letter after two weeks to all patients for whom a DNA test was requested by a non-genetic HCP. The first questionnaire was sent to patients who accepted the invitation to participate in our study. Patients only received a second questionnaire if a DNA test was performed. This second questionnaire was sent to patients approximately four weeks after receiving their test result (T1).

For our control group, we retrospectively invited patients who had received pre-test genetic counseling and testing in the standard genetic testing pathway to participate in our questionnaire study at least four weeks after receiving the test result. We identified

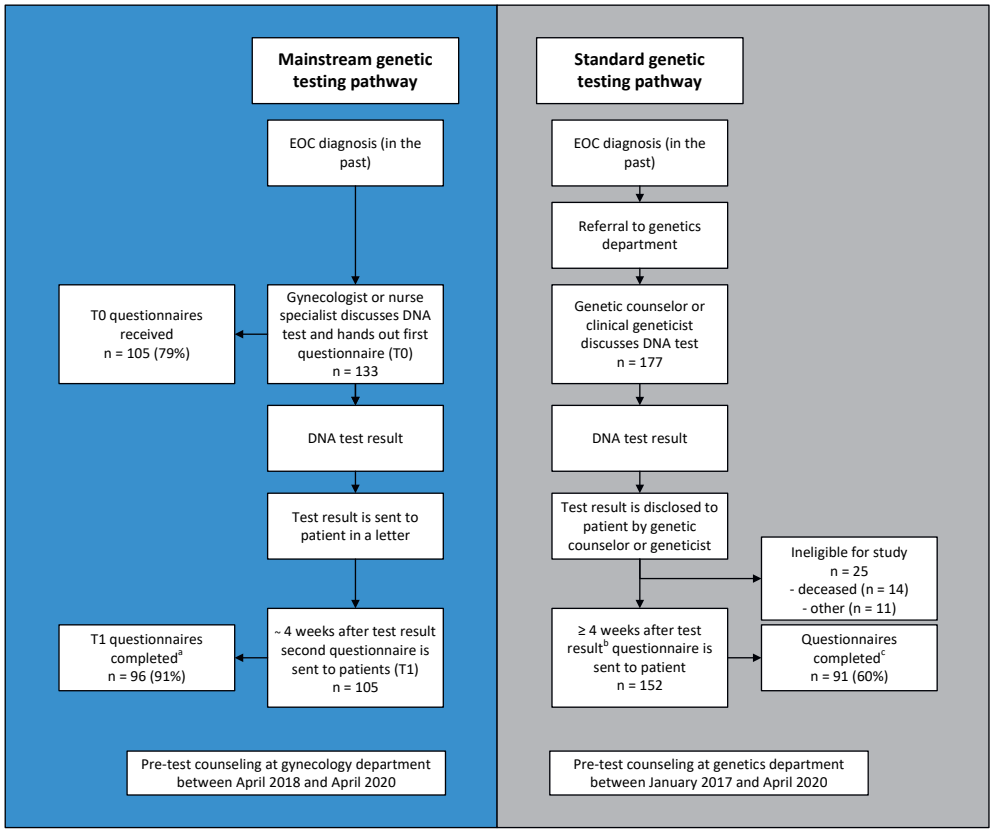


Figure 1. Study design and participation in questionnaire study.
[a] Two questionnaires were returned without being completed and with a comment that the patient had died. [b] Patients in the control group received pre-test genetic counseling both before and during our study period (from January 2017 until April 2020). Patients who received genetic counseling during our study period received the questionnaire approximately four weeks after the test result was made available. Patients who received genetic counseling before our study period received the questionnaire between four weeks and one year after receiving the test result. [c] Two patients were excluded after receiving the questionnaire, one because of a language barrier and one because the patient received counseling for breast cancer and the EOC was diagnosed after preventive surgery.

all patients with EOC who had received pre-test counseling at the genetics department between January 2017 and April 2020. We only invited patients to participate in our study when we could confirm vital status and current address. In addition, we excluded patients who previously declined to participate in research, had not completed their genetic counseling, or when a pathogenic variant in one of the ovarian cancer genes was already identified in a family member. We sent out a reminder letter after two weeks to non-responders.

We obtained data from medical records of patients who participated in our questionnaire study regarding: diagnosis, age at diagnosis, interval between receiving test result and completing the questionnaire, turnaround times, genes tested, and test results. The consent forms for diagnostic germline genetic testing and checklists evaluating patients' personal and family history were only evaluated for patients in the intervention group. For the evaluation of these consent forms, checklists and, in addition, turnaround times, our intervention group consisted of all patients who received mainstream genetic testing and not only the patients who participated in our questionnaire study.

Questionnaires

The questionnaires consisted of nine elements: (1) sociodemographics, (2) treatment history, (3) distress, (4) anxiety and depression, (5) knowledge, (6) discussed topics during pre-test counseling, (7) satisfaction with pre-test counseling, (8) satisfaction with receiving the test result, and (9) satisfaction with the decision to accept or decline genetic testing. Table 1 shows which elements were present in the different questionnaires for the intervention and control group.

Outcome measures

Psychosocial outcomes

Psychosocial outcomes consisted of (1) anxiety and depression, (2) distress, (3) decisional conflict, and (4) decision regret.

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) (22,23). The HADS is a validated questionnaire consisting of 14 items with a four-point Likert scale: seven questions for anxiety (HADS-A) and seven questions for depression (HADS-D). Scores for both subscales range between zero and 21. Scores on a subscale ≥ 11 indicate clinically significant levels of anxiety or depression (24).

Distress was measured using the one-item Distress Thermometer (DT) (25). The DT has a scale from 0 to 10, with 0 indicating 'no distress' and 10 indicating 'extreme distress'. A score of ≥ 4 indicates moderate to severe distress (25).

Decisional conflict was measured with the decisional conflict scale (26,27). This questionnaire consists of 16 items with a five-point Likert scale for each question. A total score and five subscores can be determined, all ranging from 0 to 100, with 0 indicating no decisional conflict and 100 indicating maximal decisional conflict. The question: '*I expect to stick with my decision*' was left out of the T1 questionnaire for the intervention group and questionnaire for the control group because these questionnaires were sent after the DNA test had already been performed and therefore this question did not apply at that time.

Table 1. Overview of topics in questionnaires

			Intervention group		Control group
			T0 questionnaire	*T1 questionnaire*	
Elements	**Tool**				
Sociodemographics			x		x
Treatment history			x		x
Distress	-	DT	x	x	x
Anxiety and depression	-	HADS	x	x	x
Knowledge			x	x	x
Discussed topics during pre-test counseling			x		x
Satisfaction with pre-test counseling			x		x
Satisfaction with receiving the test result				x	x
Satisfaction with the decision to accept or decline DNA testing	-	DCS	x	x	x
	-	DRS		x	x

DT Distress Thermometer, *HADS* Hospital Anxiety Depression Score, *DCS* Decisional Conflict Scale, *DRS* Decision Regret Scale.

The level of decision regret was measured with the decision regret scale (28). This questionnaire consists of five items with a 5-point Likert scale. Scores range between 0 and 100, with 0 indicating no regret and 100 indicating maximal regret.

Knowledge and discussed topics

Knowledge was measured with five statements adapted from Claes et al. that can be answered with 'true', 'false' or 'don't know' (29).

Discussed topics consisted of (1) consequences for patients' treatment, (2) possible implications for family members, and (3) the associated higher risk of developing breast cancer if a pathogenic variant in a *BRCA* gene is found. Patients were able to select one or more of these three options and were asked to select the topic that was most important to them.

Satisfaction

The patients' satisfaction with pre-test counseling and how they received the test result were measured using self-developed questions, derived from the questionnaires used in the Mainstreaming Cancer Genetics (MCG) program and developed for the TIME trial,

which evaluated breast cancer patients' experiences with rapid genetic testing and counseling (6,30).

Turnaround times

For both groups, we evaluated the time between diagnosis, pre-test counseling, and communicating the test result to the patient. For patients in the control group, we also included the time of referral. For patients in the intervention group, we also included the time of additional post-test counseling at the genetics department, if applicable.

We used the date of the histology report as the time of diagnosis. If a histology report was lacking, the date of the cytology report was used. For patients in the intervention group, we used the date that the letter with the test result was sent to the patient as the time that the test result was communicated to the patient. For patients in the control group, we used the date that the test result was first communicated to the patient, which was foremost the date of a telephone consultation.
If the month and/or day of the date were missing, June and/or the 15th were added in order to be able to calculate the turnaround times.

Adherence to the mainstream genetic testing protocol

We assessed whether written informed consent was obtained for diagnostic germline genetic testing based on the presence of a consent form in the patient file. In addition, we assessed whether non-genetic HCPs evaluated whether the patient required additional post-test counseling at the genetics department based on patient or family history. We determined this based on the presence of the checklist in the patient file. We also assessed whether or not patients were actually referred to the genetics department if indicated by this checklist.

Statistical analyses

We calculated mean and standard deviation or median and range for continuous variables and frequencies and percentages for categorical variables. Groups were compared using univariate analysis with logistic regression or a chi-square test for categorical variables and linear regression for continuous variables. We performed multivariate analyses on the decisional conflict scale, the decision regret scale, the HADS and DT. We adjusted for the possible confounders, based on literature and expert opinion: having a pathogenic variant or variant of unknown significance, having one or more children, educational level, having a personal history of another type of cancer in addition to the EOC diagnosis, the interval between receiving the DNA test result and completing the questionnaire, and being offered genetic testing ≤ 6 months after diagnosis. We imputed (five times) the missing data (< 6%) of these outcomes and possible confounders. For the calculation of the turnaround times, we excluded the extreme outliers. We defined extreme outliers as

values that were either 3 times the interquartile range above the 3rd quartile value or 3 times below the 1st quartile. IBM SPSS statistics 26.0.0.1 was used to perform the statistical analyses.

Results

Participation and patient characteristics

During our study period, non-genetic HCPs requested a DNA test for 133 patients, of whom 105 (79%) participated in our study (intervention group). We received 105 T0 questionnaires and 96 T1 questionnaires. We identified 177 patients with EOC who had received pre-test counseling at the genetics department between January 2017 and April 2020. In total, 152 patients were eligible to participate in our questionnaire study, and 91 of these patients (60%) completed the questionnaire (control group). See also Figure 1.

For both groups, we did not receive any questionnaires from patients who declined genetic testing. Because the control group was invited retrospectively, there was a longer period of time (p = 0.000) between receiving the test result and completing the questionnaire (mean 232 days, sd 14.6) compared to the intervention group (mean 57 days, sd 3.1).

The patient characteristics are shown in Table 2. The study group consisted mainly of patients with high-grade serous EOC. Most patients had one or more children, an intermediate educational level and a Dutch native background. In our intervention group, the mean age was higher and there were significantly more patients who had one or more children. There were no statistically significant differences between the responders and non-responders in the intervention group with regard to age at diagnosis, whether patients were newly diagnosed at time of pre-test counseling or not, histology, types of genes tested and test result (data not shown).

Psychosocial outcomes

Table 3 shows the decisional conflict, decision regret, anxiety, depression and distress for both groups. The univariate analyses did not show any significant differences in decisional conflict or decision regret between the two groups. When corrected for our confounders with multivariate analyses, decision regret was significantly higher in our intervention group. There were no significant differences for anxiety, depression, or distress between the two groups with univariate and multivariate analyses.

Knowledge and discussed topics

The average number of correct answers for the five knowledge statements was 3.0 (sd 1.6) in the intervention group, and 3.3 (sd 1.4) in the control group (p = 0.155). Considering

Table 2. Patient characteristics

	Intervention group, n = 105	Control group, n = 91	P-value
Age at diagnosis, mean (sd)	67.4 (9.6)	63.0 (11.1)	0.003*
Newly diagnosed at time of being offered genetic testing[a], n (%)	91 (86.7)	62 (68.1)	0.002*
Histology, n (%)			
- Serous,	78 (74.3)	64 (70.3)	0.183
- high grade	- 72	- 51	
- low grade	- 5	- 6	
- grade unknown	- 1	- 7	
- Endometrioid	5 (4.8)	6 (6.6)	
- clear cell	5 (4.8)	4 (4.4)	
- Mucinous	8 (7.6)	7 (7.7)	
- Other/unknown	9 (8.6)	10 (11)	
DNA test results, n (%)			
- Normal	95 (90.5)	74 (81.3)	0.068
- Pathogenic variant or variant of unknown significance	10 (9.5)	17 (18.7)	
Children, n (%)			
- No	12 (11.4)	20 (22.0)	0.038*
- Yes	92 (87.6)	67 (73.6)	
- Unknown	1 (1.0)	4 (4.4)	
Educational level[b], n (%)			
- Low	9 (8.6)	9 (9.9)	0.851
- Intermediate	71 (67.6)	58 (63.7)	
- High	24 (22.9)	23 (25.3)	
- Unknown	1 (1.0)	1 (1.1)	
Migrant status[c], n (%)			
- Dutch Native	92 (87.6)	82 (90.1)	0.946
- Migrant	10 (9.5)	8 (8.8)	
- Western	- 8	- 6	
- Non-Western	- 2	- 2	
- Unknown	3 (2.9)	1 (1.1)	
Personal history of another type of cancer, n (%)	16 (15.7)	15 (17.2)	0.774

[a] Newly diagnosed at time of being offered genetic testing was defined as receiving pre-test counseling ≤ 6 months after diagnosis for the intervention group and being referred to the genetics department ≤ 6 months after diagnosis for the control group. [b] Educational level is subdivided into low, intermediate or high level as categorized by the Dutch Standard Classification of Education 2021 (31). Low level education is no education, primary education or lower secondary education,

intermediate level education is upper secondary education and high-level education is tertiary education. [c] Migrant status is defined by Statistics Netherlands (CBS) as having at least one parent who was born abroad (32). A distinction can be made between a Western migration background (country of origin in Europe (excluding Turkey), North America, and Oceania, or from Indonesia or Japan) and a non-Western migration background (country of origin in Africa, South America or Asia (excluding Indonesia and Japan) or from Turkey). If a person is born in the Netherlands, the migration background is determined by the mother's country of birth. When the mother is born in the Netherlands as well, then the migration background is determined by the father's country of birth. * $p \leq 0.05$.

the individual statements, patients in the intervention group scored significantly worse on the statement 'A woman who has a sister with a pathogenic variant (gene alteration) in an ovarian cancer gene has a 50% chance (1 in 2) of having this gene alteration as well' compared to the control group. Comparisons between the two groups for every individual statement are shown in Supplementary Table 1.

The discussed topics during pre-test counseling are shown in Figure 2. The possible impact of the DNA test result on the treatment were discussed with only a third of both groups, according to the patients. Patients in both groups reported that the possible implications for family members were most important to them: 72% of patients in the intervention group and 65% of patients in the control group.

Patient satisfaction

Questions regarding satisfaction of patients with pre-test counseling and receiving their test result are shown in Tables 4 and 5. In the intervention group a significantly higher proportion of patients indicated that it did not matter to them how they received their test result. In addition, a significantly higher proportion of patients in this group answered that they were unsure whether or not they had enough time to weigh the advantages and disadvantages of a DNA test.

Turnaround times

The turnaround times in the intervention group were significantly shorter than those in the control group, see Table 6.

Adherence to the protocol

The checklist to assess whether the patient had a relevant personal or family history for referral to a genetics department was present in the patient file for 126 out of 133 patients (94.7%). For 14 patients, there was a reason to refer the patient to the genetics department based on their checklist. Three of these patients (21.4%) had not been referred to the genetics department. The checklist of one of these patients was already assessed by the genetics department at time of the test result and they agreed that a referral was not necessary. For the other two patients, it was not clear why they were not referred. A signed

Table 3. Decisional conflict, decision regret, anxiety, depression and distress

			univariate		*multivariate*	
	Intervention group, n = 96	**Control group, n = 91**	**mean diff or OR (95% CI)**	**p-value**	**mean diff or OR (95% CI)**	**p-value**
Decisional conflict scale, mean (sd)						
- total score	19.7 (12.0)	19.3 (14.4)	0.4 (-3.5 – 4.3)	0.844	2.7 (-2.4 – 7.8)	0.294
- uncertainty subscore	17.5 (19.8)	20.0 (21.3)	-2.5 (-8.6 – 3.5)	0.408	3.5 (-4.7 – 11.8)	0.402
- informed subscore	20.2 (19.8)	19.1 (18.0)	1.1 (-3.7 – 5.9)	0.655	2.4 (-4.1 – 8.8)	0.472
- support subscore	19.5 (13.9)	19.4 (16.9)	0.1 (-4.4 – 4.7)	0.947	0.4 (-5.8 – 6.7)	0.889
- values clarity subscore	25.0 (16.2)	24.0 (17.4)	1.0 (-4.0 – 5.9)	0.702	2.9 (-3.8 – 9.6)	0.400
- effective decision subscore	16.8 (15.7)	15.1 (14.8)	1.8 (-2.7 – 6.2)	0.433	3.8 (-2.3 – 10.0)	0.215
Decision regret scale, mean (sd)						
- total score	12.9 (13.2)	9.7 (11.0)	3.2 (-0.4 – 6.7)	0.079	4.9 (-0.7 – 9.7)	0.047*
HADS-Anxiety, mean (sd)	5.7 (4.1)	5.3 (3.7)				
Subgroups, n (%)						
- ≤ 10	84 (87.5)	75 (82.4)	1.3 (0.6 – 3.1)	0.523	2.7 (0.8 – 9.2)	0.101
- ≥ 11	11 (11.5)	13 (14.3)				
- missing	1 (1.0)	3 (3.3)				
HADS-Depression, mean (sd)	4.6 (4.1)	3.6 (3.7)				
Subgroups, n (%)						
- ≤ 10	84 (87.5)	86 (94.5)	0.5 (0.2 – 1.7)	0.291	0.7 (0.1 – 3.7)	0.715
- ≥ 11	9 (9.4)	5 (5.5)				
- missing	3 (3.1)	0				
Distress Thermometer, mean (sd)	3.9 (2.5)	3.7 (2.5)				
Subgroups, n (%)						
- ≤ 3	46 (47.9)	49 (53.8)	0.8 (0.4 – 1.4)	0.418	0.6 (0.3 – 1.4)	0.270
- ≥ 4	50 (52.1)	42 (46.2)				
- missing	0	0				

Decisional conflict and decision regret are measured on a scale of 0 to 100, with a higher score indicating more decisional conflict or regret. For the continuous variables, i.e., decisional conflict scale and decision regret scale, the difference between the mean score for the control group and the intervention is shown (mean diff). For the dichotomous variables, i.e., HADS-Anxiety, HADS-Depression and Distress Thermometer, the odds ratio between the two groups is shown. *OR* Odds Ratio, *CI* Confidence interval. * $p \leq 0.05$.

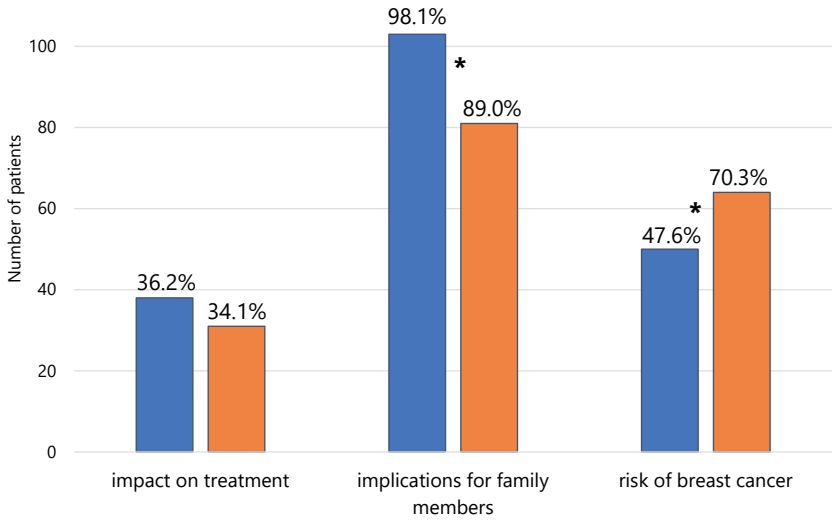


Figure 2. Discussed topics during pre-test counseling
The figure shows the percentage of patients who reported whether the following topics were discussed: (1) women with ovarian cancer and a pathogenic variant in an ovarian cancer gene can sometimes receive additional treatment if the ovarian cancer comes back later, (2) for family members it may be important to know if a woman with ovarian cancer has a pathogenic variant in an ovarian cancer gene, and (3) when a woman with ovarian cancer has a pathogenic variant in a *BRCA1* or *BRCA2* gene, she also has a higher chance of developing breast cancer. *$p \leq 0.05$.

Table 4. Questions indicating satisfaction with pre-test counseling

	Options	Intervention group, n = 105	Control group, n = 91	P-value
Clarity of discussed information regarding the DNA test, n (%)	- (very) clear - unsure/not clear	98 (93.3) 7 (6.7)	89 (97.8) 2 (2.2)	0.156
Received written information after discussing DNA test, n (%)	- yes - no - missing	81 (77.1) 22 (21.0) 2 (1.9)	not asked[a]	N/A
Clarity of received written information after discussing the DNA test, n (%)	- (very) clear - Unsure/not clear	75 (92.6) 6 (7.4)	88 (96.7) 3 (3.3)	0.239
There was enough time to weigh the advantages and disadvantages of a DNA test, n (%)	- yes - no - don't know	80 (76.2) 4 (3.8) 21 (20)	86 (94.5) 1 (1.1) 4 (4.4)	0.002*
Feeling of having a choice whether or not to perform a DNA test, n (%)	- yes - no - don't know - missing	97 (92.4) 3 (2.9) 5 (4.8) 0	79 (86.8) 9 (9.9) 2 (2.2) 1 (1.1)	0.082
Satisfaction with being offered a DNA test, n (%)	- (very) satisfied - unsure/not satisfied - missing	95 (90.5) 9 (8.6) 1 (1)	88 (96.7) 3 (3.3) 0	0.134
Preferred moment to be offered a DNA test, n (%)	- directly after diagnosis - during treatment - after completion of treatment - in case of recurrence - other - missing	57 (54.3) 3 (2.9) 30 (28.6) 4 (3.8) 8 (7.6) 3 (2.9)	45 (49.5) 2 (2.2) 38 (41.8) 4 (4.4) 2 (2.2) 0	0.236

N/A Not applicable. * $p \leq 0.05$. [a] For the control group it was assumed that all patients did receive written information after discussing the DNA test and therefore this was not asked in the questionnaire.

consent form for diagnostic genetic testing was present in the electronic patient file of 130 patients (97.7%).

Table 5. Questions indicating satisfaction with receiving test result

	Options		Intervention group, n = 96	Control group, n = 91	P-value
It was clear how the test result would be communicated, n (%)	-	yes	85 (88.5)	86 (94.5)	0.057
	-	no	9 (9.4)	2 (2.2)	
	-	missing	2 (2.1)	3 (3.3)	
Clarity of written information about the test result, n (%)	-	(very) clear	88 (91.7)	83 (91.2)	0.161
	-	unsure/not clear	5 (5.2)	1 (1.1)	
	-	missing	3 (3.1)	7 (7.7)	
Looking back, information was missed to consider the DNA test, n (%)	-	yes	4 (4.2)	4 (4.4)	0.949
	-	no	88 (91.7)	84 (92.3)	
	-	missing	4 (4.2)	3 (3.3)	
Number of days between pre-test counseling and communicating test result to patient, median (range)			36 (11 – 366)	55 (15 – 112)	0.055
Satisfied with number of days between pre- test counseling and receiving test result, n (%)	-	(very) satisfied	78 (81.3)	71 (78.0)	0.467
	-	Unsure/not satisfied	14 (14.6)	17 (18.7)	
	-	missing	4 (4.2)	3 (3.3)	
Ways of receiving test result, n (%)	-	letter	N/A (all via a letter)	14 (15.4)	N/A
	-	telephone		39 (42.9)	
	-	consultation at genetics department		33 (36.3)	
	-	other		1 (1.1)	
	-	missing		4 (4.4)	
Satisfied with how test result was received, n (%)	-	yes	59 (61.5)	75 (82.4)	0.002*
	-	no	1 (1.0)	0	
	-	no preference	34 (35.4)	13 (14.3)	
	-	missing	2 (2.1)	3 (3.3)	

N/A Not applicable. * $p \leq 0.05$.

Table 6. Turnaround times for the genetic testing pathways

Days between:	**Intervention group n = 133**	**Control group n = 91**	**p-value**
Diagnosis and pre-test counseling, median (range)	45[a] (-29[b] – 260)	194[c] (6 – 592)	0.000*
- diagnosis and referral	N/A	72[c] (-3 – 575)	N/A
- referral and pre-test counseling	N/A	70 (-3 – 240)	N/A
pre-test counseling and communicating test result to patient, median (range)	35[d] (11 – 72)	55 (15 – 112)	0.000*
sending letter with test result to patient and additional appointment at genetics department, median (range), n = 21	6 (0 – 58)	N/A	N/A
- normal result, n = 7	20 (6 – 42)		
- pathogenic or uncertain variant, n = 14	5.5 (0[e] – 58[f])		

N/A Not applicable. All turnaround times are presented in calendar days. * $p \leq 0.05$. [a] Based on 121 cases, 12 extreme outliers were excluded. [b] One patient was invited for pre-test counseling because a relative of hers had received genetic counseling. Her referral followed after she already had pre-test counseling. [c] Based on 78 cases, 13 extreme outliers were excluded. [d] Based on 128 cases, 5 extreme outliers were excluded. [e] For one patient the number of days between test result and additional appointment was 0 days, because the result was not sent in a letter, but the clinical geneticist visited the patient while she was admitted in the hospital. [f] One patient postponed post-test counseling until she had completed her treatment.

Discussion

In this study, we evaluated the impact of mainstream genetic testing on genetic care of patients with EOC, based on patients' experiences, turnaround times and adherence of non-genetic HCPs to the mainstream genetic testing protocol. We compared these outcomes to those of a control group receiving standard genetic care (pre-test counseling performed by a genetic counselor or clinical geneticist). So far, only four previous studies have evaluated genetic care of patients receiving mainstreamed genetic care in direct comparison to a valid control group, and for the majority with a limited number of patients in these groups (16,18-20).

We showed that decisional conflict, anxiety, depression and distress were comparable for the patients in our intervention and control group. We did find differences in regret, discussed topics, and knowledge between the two groups. It is not surprising to find these differences between the two groups, as non-genetic HCPs did not have the same training as clinical geneticists. In addition, they have limited time during consultations to include pre-test genetic counseling. We think these differences are acceptable as long as patients do not experience high levels of decision regret or distress, and feel that they can make an informed choice whether or not to perform genetic testing.

The level of decision regret was significantly higher in our intervention group compared to our control group. Although no definite cut-off scores have been determined for decision regret so far, other studies have used a cut-off score of 25 to indicate strong levels of regret (33,34). In our study, the level of regret in both groups are far below this threshold (12.9 in the intervention group, 9.7 in the control group) and in line with the previous study of McLeavy et al. (17). In addition, decision regret is measured on a scale of 0 to 100 and this three-point difference in level of regret seems clinically irrelevant.

The other psychosocial outcomes (decisional conflict, anxiety, depression and distress) were comparable between the two groups. Decisional conflict in both groups was far below the previously determined cut-off level of concern of 37.5 (35). This is in line with the research of Richardson et al. (19). In contrast, Yoon et al. did see a significantly higher decisional conflict in patients receiving pre-test counseling by a non-genetic HCP compared to patients receiving pre-test counseling by a genetic counselor or clinical geneticist (20). However, in this study decisional conflict scores for both groups were also below the level of concern of 37.5, and therefore they concluded that this difference was clinically irrelevant. Anxiety and depression have not previously been evaluated in patients receiving mainstreamed genetic care. The levels of anxiety and depression we found in our study are comparable with the outcomes of Beek et al. (11). They showed that patients who received pre-test counseling by a genetic counselor or clinical geneticist

had a median anxiety level of 5.0 and a median depression level of 3.0 six months after diagnosis. Distress levels have been evaluated in a few studies and, as in our study, have been comparable between patients receiving mainstreamed genetic care and patients receiving pre-test counseling by a clinical geneticist or genetic counselor (16,18-20).

For patients to make an informed decision, it is important that they are aware of the possible implications of a DNA test for themselves, but also for family members. Overall, knowledge about genetics was similar between the two groups, which is in line with previous studies (16,19). However, the statement that a sister with a pathogenic variant in an ovarian cancer gene has a 50% chance of having the same pathogenic variant was answered incorrectly by significantly more patients in our intervention group. However, for patients to make a well-informed decision whether or not to perform a DNA test, we believe it is sufficient to have general knowledge of possible implications for family members. Detailed information about inheritance patterns only becomes relevant when a pathogenic variant is identified, and for these patients post-test counseling is always performed by a genetics counselor or clinical geneticist.

Significantly fewer patients in the intervention group mentioned that the possible higher risk of breast cancer for patients with EOC carrying a pathogenic *BRCA1/2* variant was discussed during pre-test counseling. So far, only Colombo et al. also have assessed which topics were discussed during pre-test counseling, although they did not specifically ask about the possible higher risk of breast cancer (5). We asked specifically about the risk of breast cancer for patients with ovarian cancer. Especially in patients suffering from advanced disease stage, potential breast cancer risk might not always be clinically relevant, and therefore not discussed during pre-test counseling. It is important for family members to be informed about the possible risk of breast cancer, but this is only relevant when a pathogenic variant is identified, for which all patients receive post-test counseling by a genetic counselor or clinical geneticist. When implementing a mainstream genetic testing pathway, we recommend educating non-genetic HCPs to include in their pre-test counseling the possible higher risk of breast cancer for patients with EOC carrying a pathogenic variant in a *BRCA* gene.

Overall, satisfaction with the genetic care pre- and post-test was high in both groups. We considered it foremost important to analyze patients who were unhappy with the care they received. Only four (4%) of the 105 patients felt that they had not had enough time to consider the advantages and disadvantages of a DNA test, which indicates that the majority (96%) of patients in our intervention group had enough time to consider the DNA test. Regarding the satisfaction with the way the test result was received, the majority of patients in the mainstream group (99%) considered it acceptable to receive this result in a letter. It is possible that patients in our intervention group would have chosen another

way of receiving their test result if they had been offered a choice. However, providing post-test counseling to all patients via telephone or face-to-face consultation would be more time-consuming. Therefore, we foremost wanted to evaluate if receiving the test result in a letter was acceptable to patients.

The timing of genetic testing is important to consider, as patients might be eligible for primary treatment with PARP inhibitors if a pathogenic *BRCA* variant is identified (4,36). In this study, the mainstream genetic testing pathway resulted in a significant reduction in wait time to pre-test counseling, similar to other studies (6,15,19,37). This is beneficial for making early treatment decisions. However, only about 50% of patients in both groups in our study preferred to be offered genetic testing directly after being diagnosed with EOC. On the other hand, even though about 35% of patients might have preferred to be offered genetic testing in a later stage (e.g., after completion of treatment), they were still satisfied that they had been offered germline genetic testing. Timing of genetic testing should also be considered when implementing workflows that use tumor testing as a pre-test for germline genetic testing (38). Given these differences in preferences regarding timing between our groups, it is important that non-genetic HCPs are aware of these differences and explore patients' preferences during pre-test counseling. Any patient who expresses doubts about genetic testing during pre-test counseling should be referred to a genetics department for more extensive counseling in making a decision about whether or not to perform genetic testing.

It is important to identify those patients who might benefit from additional genetic testing or should be given advice about preventive measures. We have shown that it is feasible for non-genetic HCPs to identify these patients by completing checklists, as these checklists were present in more than 95% of patient files. However, this system only works if patients are referred when indicated by the checklist, which was omitted for two patients in our study. For the implementation of future mainstream genetic testing initiatives, it is important to incorporate a procedure that ensures that all patients who require additional counseling are offered post-test counseling at a genetics department.

For the sustainability of a mainstream genetic testing pathway, it is important that it can be easily adapted to changes in gene panels. Indeed, our gene panel was expanded to include *BRIP1, RAD51C* and *RAD51D* and this could be easily adapted in the workflow (9). Our training provided the basic tools to provide pre-test counseling that are also applicable to other genes.

The strengths of our study are the comparison of a mainstream genetic testing pathway with the standard genetic testing pathway from the patients' perspective and the high participation rate in both groups (intervention group (79%) and control group (60%)). So

far, most studies evaluating both mainstreamed and standard genetic care have evaluated only a small group of less than 50 patients receiving mainstreamed genetic care (16,18,19).

A limitation of our study is the design. Part of our control group was invited to participate retrospectively, which could be up to a year after pre-test counseling. Therefore, it is possible that there is some recall bias in our results. In addition, in the intervention group the mean age of diagnosis was higher, more patients were newly diagnosed at time of pre-test counseling and more patients had children. We expected the mean age and the number of newly diagnosed patients to be higher in this group because of an increased awareness of genetic testing amongst non-genetic HCPs. We cannot explain why more patients in the intervention group had children. We accounted for being newly diagnosed and having children as possible confounders by including these in our multivariate analyses. We did not ask patients about their family history, therefore we could not evaluate if this had any impact on our study outcomes. Another limitation is that we only evaluated patient experiences in our control group after receiving the test result. Therefore, we could not compare experiences between our intervention and control group after pre-test counseling.

Overall, this study demonstrates that the pre-test counseling provided in our mainstream genetic testing pathway enables patients to make a well-informed decision about genetic testing. Although we did find differences in genetic care between the two groups, patients receiving mainstreamed genetic care did not experience unacceptably high levels of distress or decision regret. In addition, all patients carrying a pathogenic variant or variant of unknown significance in our study were invited for post-test counseling at a genetics department. This ensured that all these patients received detailed information about the implications of their test result for themselves and their family members. We previously showed that, after completion of an online training module, non-genetic HCPs, such as gynecologic oncologists, feel motivated and competent to discuss and order germline genetic testing themselves (9). This, in combination with the positive experiences of patients shown in this study, indicates that mainstream genetic testing provides a feasible and sustainable new care pathway for all patients with EOC. In training non-genetic HCPs, it is important to especially consider the possible higher risk of breast cancer for patients carrying a pathogenic variant in a *BRCA* gene. In addition, we recommend incorporating a procedure to ensure that all patients who require additional counseling are offered post-test counseling at a genetics department.

Abbreviations: *EOC* Epithelial ovarian cancer; *HCP* Healthcare professional; *HADS* Hospital Anxiety and Depression Scale; *DT* Distress Thermometer; *MCG* Mainstreaming Cancer Genetics.

Supplementary Information

The online version contains supplementary material available at https:// doi. org/ 10. 1186/ s13053- 022- 00238-w. Additional file 1: Supplementary Table 1. Knowledge of patients in the intervention and control group. For all statements patients could choose between 'true', 'false', and 'don't know'. *$p \leq 0.05$.

Acknowledgements: First, we thank all patients who participated in this study. We also thank all participating gynecologic oncologists, gynecologists with a subspecialty training in oncology, and nurse specialists from the University Medical Center Utrecht, Diakonessenhuis Utrecht, Meander Medical Center Amersfoort, and St. Antonius Hospital Nieuwegein/Utrecht, The Netherlands.

Authors' contributions: The study was designed by KB, EMAB, MGEMA, and RPZ. KB, JPH and MEV performed the statistical analyses. HWRS, CGG, JGL, RZ, and JAL contributed to the data acquisition. KB, EMAB, MGEMA, and RPZ wrote the main manuscript text. All authors read and approved the final manuscript.

Funding: AstraZeneca sponsored the training module that was developed as part of this project, and was not involved in the development of its content.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate: This study was reviewed by the Medical Review Ethics Committee (MREC) of the UMC Utrecht in March 2018 and the Medical Research Involving Human Subjects Act (WMO) did not apply to our study. Written informed consent to participate in the questionnaire study was obtained for all patients.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

References

1. CRGO. Guideline hereditary and familial ovarian cancer 2015 [updated June 1. Available from: https://www.oncoline.nl/erfelijk-en-familiair-ovariumcarcinoom].
2. Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021 2021 [Available from: https://www.nccn.org/guidelines.]
4. Tew WP, Lacchetti C, Ellis A, Maxian K, Banerjee S, Bookman M, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-3493.
5. Colombo N, Huang G, Scambia G, Chalas E, Pignata S, Fiorica J, et al. Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer. J Clin Oncol. 2018;36(13):1300-1307.
6. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.
7. McCuaig JM, Armel SR, Care M, Volenik A, Kim RH, Metcalfe KA. Next-Generation Service Delivery: A Scoping Review of Patient Outcomes Associated with Alternative Models of Genetic Counseling and Genetic Testing for Hereditary Cancer. Cancers (Basel). 2018;10(11).
8. Scheinberg T, Young A, Woo H, Goodwin A, Mahon KL, Horvath LG. Mainstream consent programs for genetic counseling in cancer patients: A systematic review. Asia Pac J Clin Oncol. 2021;17(3):163-177.
9. Bokkers K, Zweemer RP, Koudijs MJ, Stehouwer S, Velthuizen ME, Bleiker EMA, et al. Positive experiences of healthcare professionals with a mainstreaming approach of germline genetic testing for women with ovarian cancer. Fam Cancer. 2022;21(3):295-304.
10. Bjornslett M, Dahl AA, Sorebo O, Dorum A. Psychological distress related to BRCA testing in ovarian cancer patients. Fam Cancer. 2015;14(4):495-504.
11. Van de Beek I, Smets EMA, Legdeur MA, de Hullu JA, Lok CAR, Buist MR, et al. Genetic counseling of patients with ovarian carcinoma: acceptance, timing, and psychological wellbeing. J Community Genet. 2020;11(2):183-191.
12. Fox E, McCuaig J, Demsky R, Shuman C, Chitayat D, Maganti M, et al. The sooner the better: Genetic testing following ovarian cancer diagnosis. Gynecol Oncol. 2015;137(3):423-429.
13. Gleeson M, Meiser B, Barlow-Stewart K, Trainer AH, Tucker K, Watts KJ, et al. Communication and information needs of women diagnosed with ovarian cancer regarding treatment-focused genetic testing. Oncol Nurs Forum. 2013;40(3):275-283.

14. Bish A, Sutton S, Jacobs C, Levene S, Ramirez A, Hodgson S. Changes in psychological distress after cancer genetic counselling: a comparison of affected and unaffected women. Br J Cancer. 2002;86(1):43-50.
15. Bednar EM, Oakley HD, Sun CC, Burke CC, Munsell MF, Westin SN, et al. A universal genetic testing initiative for patients with high-grade, non-mucinous epithelial ovarian cancer and the implications for cancer treatment. Gynecol Oncol. 2017;146(2):399-404.
16. McCuaig JM, Thain E, Malcolmson J, Keshavarzi S, Armel SR, Kim RH. A Comparison of Patient-Reported Outcomes Following Consent for Genetic Testing Using an Oncologist- or Genetic Counselor-Mediated Model of Care. Curr Oncol. 2021;28(2):1459-1471.
17. McLeavy L, Rahman B, Kristeleit R, Ledermann J, Lockley M, McCormack M, et al. Mainstreamed genetic testing in ovarian cancer: patient experience of the testing process. Int J Gynecol Cancer. 2020;30(2):221-226.
18. Powell CB, Laurent C, Ciaravino G, Garcia C, Han L, Hoodfar E, et al. Streamlining genetic testing for women with ovarian cancer in a Northern California health care system. Gynecol Oncol. 2020;159(1):221-228.
19. Richardson M, Min HJ, Hong Q, Compton K, Mung SW, Lohn Z, et al. Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System. Cancers (Basel). 2020;12(2):338.
20. Yoon SY, Wong SW, Lim J, Ahmad S, Mariapun S, Padmanabhan H, et al. Oncologist-led BRCA counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes. J Med Genet. 2022;59(3):220-229.
21. Hamilton JG, Symecko H, Spielman K, Breen K, Mueller R, Catchings A, et al. Uptake and acceptability of a mainstreaming model of hereditary cancer multigene panel testing among patients with ovarian, pancreatic, and prostate cancer. Genet Med. 2021;23(11):2105-2113.
22. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-370.
23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370.
24. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
25. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Distress Management. Version 2.2021 2021. [Available from: https://www.nccn.org/guidelines].
26. Koedoot N, Molenaar S, Oosterveld P, Bakker P, de Graeff A, Nooy M, et al. The decisional conflict scale: further validation in two samples of Dutch oncology patients. Patient Educ Couns. 2001;45(3):187-193.
27. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30.
28. Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E, et al. Validation of a decision regret scale. Med Decis Making. 2003;23(4):281-292.

29. Claes E, Evers-Kiebooms G, Boogaerts A, Decruyenaere M, Denayer L, Legius E. Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. Am J Med Genet A. 2003;116A(1):11-19.
30. Wevers MR, Ausems MG, Verhoef S, Bleiker EM, Hahn DE, Hogervorst FB, et al. Behavioral and psychosocial effects of rapid genetic counseling and testing in newly diagnosed breast cancer patients: design of a multicenter randomized clinical trial. BMC Cancer. 2011;11:6.
31. Statistics Netherlands. The Dutch Standard Classification of Education, SOI 2021. [Available from: https://www.cbs.nl/nl-nl/onze-diensten/methoden/classificaties/onderwijs-en-beroepen/standaard-onderwijsindeling--soi--/standaard-onderwijsindeling-2021].
32. Statistics Netherlands. Migration Background 2021 [Available from: https://www.cbs.nl/en-gb/onze-diensten/methods/definitions/migration-background].
33. Sheehan J, Sherman KA, Lam T, Boyages J. Association of information satisfaction, psychological distress and monitoring coping style with post-decision regret following breast reconstruction. Psychooncology. 2007;16(4):342-351.
34. Zhong T, Bagher S, Jindal K, Zeng D, O'Neill AC, MacAdam S, et al. The influence of dispositional optimism on decision regret to undergo major breast reconstructive surgery. J Surg Oncol. 2013;108(8):526-530.
35. O'Connor AM. User Manual - Decisional Conflict Scale 2010 [Available from: https://decisionaid.ohri.ca/docs/develop/User_Manuals/UM_decisional_conflict.pdf].
36. Mirza MR, Coleman RL, Gonzalez-Martin A, Moore KN, Colombo N, Ray-Coquard I, et al. The forefront of ovarian cancer therapy: update on PARP inhibitors. Ann Oncol. 2020;31(9):1148-1159.
37. Rumford M, Lythgoe M, McNeish I, Gabra H, Tookman L, Rahman N, et al. Oncologist-led BRCA 'mainstreaming' in the ovarian cancer clinic: A study of 255 patients and its impact on their management. Sci Rep. 2020;10(1):3390.
38. Vos JR, Fakkert IE, de Hullu JA, van Altena AM, Sie AS, Ouchene H, et al. Universal Tumor DNA BRCA1/2 Testing of Ovarian Cancer: Prescreening PARPi Treatment and Genetic Predisposition. J Natl Cancer Inst. 2020;112(2):161-169.

Supplementary Table 1. Knowledge of patients in the intervention and control group

Questions	Options	Intervention group, T1 n = 96	Control group n = 91	p-value
All women with a pathogenic variant (gene alteration) in an ovarian cancer gene will someday develop ovarian cancer, n (%)	- correct	49 (51.0)	41 (45.1)	0.374
	- incorrect	46 (47.9)	50 (54.9)	
	- missing	1 (1.0)	0	
A woman without a pathogenic variant (gene alteration) in an ovarian cancer gene can still develop ovarian cancer, n (%)	- correct	75 (78.1)	72 (79.1)	0.977
	- incorrect	20 (20.8)	19 (20.9)	
	- missing	1 (1.0)	0	
A woman with a pathogenic variant (gene alteration) in an ovarian cancer gene can pass this alteration on to her children, n (%)	- correct	79 (82.3)	80 (87.9)	0.284
	- incorrect	17 (17.7)	11 (12.1)	
	- missing	0	0	
A woman may have inherited a pathogenic variant (gene alteration) in an ovarian cancer gene from her father, n (%)	- correct	45 (46.9)	45 (49.5)	0.725
	- incorrect	51 (53.1)	46 (50.5)	
	- missing	0	0	
A woman who has a sister with a pathogenic variant (gene alteration) in an ovarian cancer gene has a 50% chance (1 in 2) of having this gene alteration as well, n (%)	- correct	36 (37.5)	54 (59.3)	0.002*
	- incorrect	58 (60.4)	33 (36.3)	
	- missing	2 (2.1)	4 (4.4)	

For all statements patients could choose between 'true', 'false', and 'don't know'.
T1: questionnaire sent to patients approximately four weeks after receiving their DNA test result.
*$p \leq 0.05$


5

Chapter 5

Mainstream germline genetic testing for patients with epithelial ovarian cancer leads to higher testing rates and a reduction in genetics-related healthcare costs from a healthcare payer perspective

Kyra Bokkers [1], Geert W.J. Frederix [1,2], Mary. E. Velthuizen [1], Maaike A. van der Aa [3], Cornelis G. Gerestein [4,5], Eleonora B.L. van Dorst [4], Joost G. Lange [6], Jacqueline A. Louwers [7], Wouter Koole [1], Ronald P. Zweemer [4], and Margreet G.E.M. Ausems [1]

1. Division Laboratories, Pharmacy and Biomedical Genetics, Dept. of Genetics, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands
2. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Universiteitsweg 100, 3584 CX Utrecht, the Netherlands
3. Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Godebaldkwartier 419, 3511 DT Utrecht, the Netherlands
4. Department of Gynecological Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands
5. Department of Gynecology, Meander Medical Center, Maatweg 3, 3813 TZ Amersfoort, the Netherlands
6. Department of Gynecology, St. Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, the Netherlands
7. Department of Gynecology, Diakonessenhuis, Bosboomstraat 1, 3582 KE Utrecht, the Netherlands

Gynecol Oncol. 2022 Oct;167(1):115-122.

Abstract

Objective: Germline genetic testing is increasingly offered to patients with epithelial ovarian cancer by non-genetic healthcare professionals, so called mainstream genetic testing. The aim of this study was to evaluate the effect of implementing a mainstream genetic testing pathway on the percentage of newly diagnosed patients with epithelial ovarian cancer to whom genetic testing was offered and the genetics-related healthcare costs.

Methods: The possible care pathways for genetic counseling and testing and their associated costs were mapped. Patient files from all newly diagnosed patients with epithelial ovarian cancer before (March 2016 – September 2017) and after (April 2018 – December 2019) implementing our mainstream genetic testing pathway were analyzed. Based on this analysis, the percentage of newly diagnosed patients to whom genetic testing was offered was assessed and genetics-related healthcare costs were calculated using a healthcare payer perspective based on a Diagnosis-Related Group financing approach.

Results: Within six months after diagnosis, genetic testing was offered to 56% of patients before and to 70% of patients after implementation of our mainstream genetic testing pathway ($p = 0.005$). Genetics-related healthcare costs decreased from €3.511,29 per patient before implementation to €2.418,41 per patient after implementation of our mainstream genetic testing pathway (31% reduction, $p = 0.000$).

Conclusion: This study shows that mainstream genetic testing leads to a significantly higher proportion of newly diagnosed patients with epithelial ovarian cancer being offered germline genetic testing. In addition, it significantly reduces genetics-related healthcare costs per patient.

Highlights

- With mainstream genetic testing, genetic testing is offered more often after diagnosis to patients with ovarian cancer.
- Genetics-related healthcare costs per patient can be significantly reduced with a mainstream genetic testing pathway.
- High morbidity and mortality might be a barrier for offering germline genetic testing to patients with ovarian cancer.
- Around 10% of patients with epithelial ovarian cancer decline germline genetic testing.

Keywords: Mainstream genetic testing; Testing rates; Healthcare costs; Epithelial ovarian cancer

Introduction

All patients with epithelial ovarian cancer (EOC) are eligible for genetic testing (1-3). Over the last few years, more genes have been identified as cancer predisposition genes for EOC (4), and treatment with Poly Adenosine Diphosphate-Ribose Polymerase (PARP) inhibitors for patients carrying a pathogenic variant in a BRCA1 or BRCA2 gene has proven to be effective for both first line treatment and in recurrent disease (5).

Despite the importance of genetic testing, referral rates for patients with EOC have remained low (6). Therefore, different initiatives have been taken to increase the number of patients who are offered genetic testing (7). Mainstream genetic testing is one of these initiatives. With mainstream genetic testing, non-genetic healthcare professionals (HCPs) incorporate germline genetic testing into their routine care, offering pre-test counseling and requesting the genetic test themselves (8). Mainstream genetic testing pathways, predominantly for EOC, have been implemented around the world and have shown positive experiences amongst HCPs and patients (9, 10).

Although low referral rates were the main drivers to implement mainstream genetic testing, there is limited research on the impact of such a care pathway on the proportion of eligible patients who are offered genetic testing before and after implementation. Only one study has evaluated how many of the patients presenting at the gynecology department were actually offered genetic testing before and after implementing a physician-coordinated genetic testing pathway (11).

For mainstream genetic testing pathways to become sustainable as standard care, healthcare costs of these pathways should be considered as well. So far, the costs of a mainstream genetic testing pathway have only been evaluated by George et al. in the UK (8), who showed a significant cost reduction. The healthcare costs and care pathways differ between countries. Therefore, it is important to evaluate the impact of mainstream genetic testing on healthcare costs in other countries and healthcare systems. In the Netherlands, the healthcare system is a variation on a Diagnosis-Related Group (DRG) system, in which there are predefined rates for healthcare costs (12-14).

We have recently implemented a mainstream genetic testing pathway for patients with EOC in which gynecologic oncologists and nurse specialists perform pre-test counseling and request germline genetic testing themselves (15). We have shown that this new care pathway is acceptable to these non-genetic HCPs and that it is feasible for them to incorporate these tasks into their daily practice. The aim of this study was to evaluate the impact of our mainstream genetic testing pathway on the proportion of newly diagnosed

patients with EOC to whom germline genetic testing was offered and genetics-related healthcare costs using a healthcare payer perspective by comparing a period before and after implementation of this new care pathway.

Materials and methods

Study design and data collection

This study was part of a multi-center, prospective, observational study on the acceptability and feasibility of the implementation of a mainstream genetic testing pathway for patients with EOC. We have previously developed and implemented sequentially a mainstream genetic testing pathway in the four hospitals in the central region of the Netherlands, consisting of one academic and three non-academic teaching hospitals. Details of the development and protocol of this pathway are available elsewhere (15).

Non-genetic HCPs (i.e., gynecologic oncologists, gynecologists with a subspecialty training in oncology and nurse specialists) were first required to complete a concise accredited online training module consisting of four short films with a duration of approximately 30 minutes in total. Only trained non-genetic HCPs received the necessary forms to perform pre-test counseling and order the germline genetic test themselves. Genetic testing for the entire region was coordinated and performed at the University Medical Center Utrecht. Post-test counseling with a genetic HCP (i.e., clinical geneticist or genetic counselor) was offered to those patients carrying a (likely) pathogenic variant or variant of unknown significance in a cancer predisposition gene or with a relevant personal or family history requiring further evaluation by a genetics team. If required by the patient or the non-genetic HCP, patients could also be referred to the genetics department for pre-test genetic counseling performed by a genetic HCP.

The Netherlands Comprehensive Cancer Organisation (IKNL) provided data on all newly diagnosed patients with EOC who were diagnosed or treated in the participating hospitals between March 2016 and December 2019. Subsequently, we consulted the electronic patient files of the gynecology departments of the local hospitals of these patients to evaluate the time of diagnosis. The time of diagnosis was based on the date of the histology report, and if absent, the date of the cytology report. We also evaluated if a genetic test had been offered and at what time. The time of offering the genetic test was based on the date of referral to the genetics department or the date that pre-test counseling was offered by the non-genetic HCP. When no genetic test had been offered and/or performed, we reviewed these files to identify any reasons for this. In addition, we evaluated the electronic patient files of the genetics department of the University Medical Center Utrecht, which were available for all patients who accepted genetic testing or

were referred to the genetics department but did not opt for genetic testing. From these patient files, we ascertained whether patients received pre-test counseling and genetic testing, and if not, any reasons for this. In addition, for deceased patients, we reviewed if a genetic test had been offered through a family member. We evaluated the gynecology and genetics files between January 2021 and March 2021. In addition, in March 2022 we evaluated if a genetics file was present for all patients who had not been offered genetic testing previously. If present, we only checked if a genetic test had been performed since we first evaluated these patient files. All data were stored in the Electronic Data Capturing tool 'Castor EDC' (16).

For both assessing the number of newly diagnosed patients to whom genetic testing was offered and calculating the genetics-related healthcare costs, we only selected patients to whom genetic testing had been offered within six months after diagnosis. We excluded patients who had been offered genetic testing before their EOC diagnosis (e.g., genetic testing because of a family or personal history of breast cancer or predictive testing because of a known pathogenic variant in a cancer predisposition gene in the family). We considered six months a reasonable time period to be offered genetic testing, as most treatments are completed within six months after diagnosis. We evaluated a time period before (March 2016 – September 2017) and after implementing our new mainstream genetic testing pathway (April 2018 – December 2019). Depending on the start date for each hospital, the period after implementing our mainstreaming pathway varied between hospitals (for the Academic hospital from April 2018 to December 2019, and for the three non-academic teaching hospitals from August 2018, March 2019, and July 2019 respectively to December 2019). We selected a period of at least six months before implementing our mainstream genetic testing pathway to ensure there was no overlap of patients between the two time periods.

Percentage of patients to whom genetic testing was offered

For each patient, we evaluated whether a germline genetic test had been offered (i.e., referral to the genetics department or pre-test counseling by a non-genetic HCP) within six months after diagnosis, and whether a genetic test had been performed. If no genetic test had been offered and/or performed, we checked the files for possible reasons.

Cost analysis

In the Netherlands, a basic health insurance package is mandatory for all citizens. Citizens pay a premium for this basic package to insurers which is dependent on their income. All genetic care is covered by this basic health package. Insurers reimburse hospitals based on predefined rates for healthcare costs in so called Diagnosis Treatment Combinations (DBCs), which is a variation on the Diagnosis-Related Group (DRG) system (12-14). A DBC covers a full package of costs for a diagnosis treatment combination, including diagnostics,

consultation costs, HCPs' salary, and other possible costs for services provided during the hospital stay. A DBC reflects the average costs for the care provided. More than one DBC may apply to a patient. These costs are partly based on fixed national rates, determined by the Dutch ministry of Health and partly on agreements made between healthcare providers and health insurers (13).

The genetic care can be divided into different DBC packages. For patients with cancer who are eligible for diagnostic genetic counseling and testing, these packages can be divided into a simple and complex trajectory. Patients who refrain from diagnostic genetic testing after pre-test counseling fall into the simple trajectory unless there is a need for psychosocial support at the genetics department. Patients who, after pre-test counseling, opt for a genetic test fall into the complex trajectory. The DBCs do not include the costs of a genetic test.

First, we mapped the possible care pathways for genetic counseling and testing and their associated costs (Figure 1). Before the implementation of our mainstream genetic testing pathway, pre-test counseling was only offered at the genetics department. After implementing our mainstream genetic testing pathway, non-genetic HCPs could perform pre-test counseling themselves at the gynecology department, but the option to refer for pre-test counseling at the genetics department remained. Based on electronic health records, we determined the number of patients in each care pathway in the two time periods and calculated the genetics-related healthcare costs per patient (i.e., costs for simple or complex trajectory and, if applicable, costs for germline panel genetic testing). We calculated the average costs per patient based on the total claimed costs for all patients who received at least pre-test counseling at the genetics department or completed genetic testing at the gynecology department. We used the most recent national prices to best determine the impact on the current healthcare costs. National prices for 2021 were set at €543,02 for a simple trajectory, €1713,27 for a complex trajectory and €1831,00 for germline panel genetic testing (17).

Ethics approval and consent to participate

This study was reviewed by the Medical Review Ethics Committee (MREC) of the UMC Utrecht in March 2018 and the Medical Research Involving Human Subjects Act (WMO) did not apply to our study.

Statistical analyses

Descriptive statistics were used to describe the number and percentages of patients in all care pathways. The proportion of patients to whom genetic testing was offered before and after implementation of our mainstream genetic testing pathway was compared using the Pearson Chi-square test. Genetics-related healthcare costs between the two time

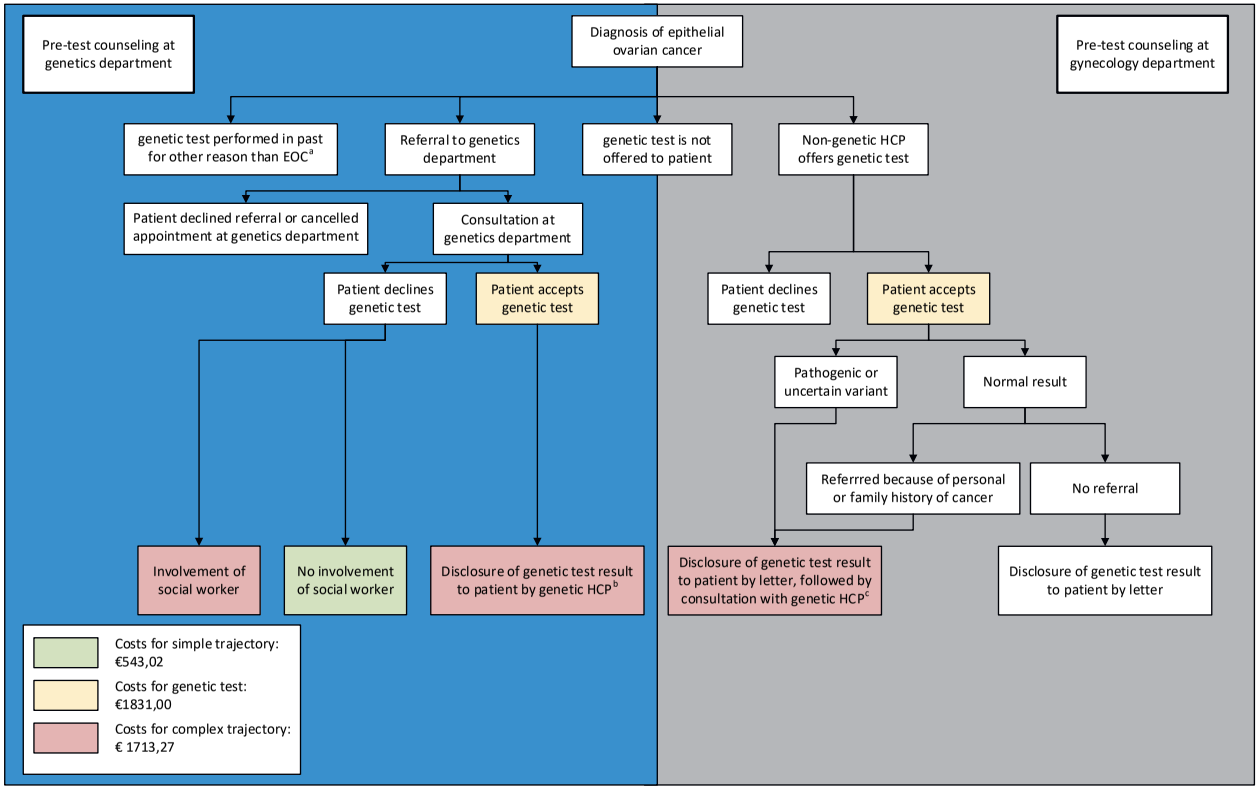


Figure 1. Pathways for genetic testing with pre-test counseling by a genetic HCP and non-genetic HCP

Note: These pathways are not in chronological order. Before April 2018 all patients with epithelial ovarian cancer had to be referred for pre-test counseling and testing at a genetics department (left side of this figure). After implementing our mainstream genetic testing pathway, there was still an option to refer patients to the genetics department, but trained non-genetic HCPs also had the option to offer pre-test counseling themselves at the gynecology department (right side of this figure). [a] Genetic testing could have been offered before the ovarian cancer diagnosis because of a family or personal history of breast cancer or predictive testing because of a known pathogenic variant in a cancer predisposition gene in the family. [b] At the University Medical Center Utrecht, the majority of genetic test results were disclosed during a telephone consultation. Patients who carried a pathogenic variant or variant of unknown significance were subsequently invited for in-person post-test counseling at the genetics department. [c] Patients were invited for in-person post-test counseling at the genetics department.

periods were compared using the Mann-Whitney U test. A p-value <0.05 was considered as statistically significant. Statistical analyses were performed using IBM SPSS statistics 26.0.0.1.

Results

Percentage of newly diagnosed patients to whom genetic testing was offered and reasons for not offering genetic testing

Before the implementation of our mainstream genetic testing pathway

We identified 183 patients who were newly diagnosed with EOC between March 2016 and September 2017 and to whom no genetic testing was offered before this diagnosis (Figure 2). At time of checking the patient files, 102/183 patients (56%) were offered genetic testing within six months after diagnosis, of whom 91/102 patients (89%) received pre-test counseling by a genetic HCP, and 90/91 patients (99%) completed genetic testing. The other 11/102 patients (11%) declined referral or cancelled their appointment after referral to the genetics department.

The remaining 81/183 patients (44%) were not offered genetic testing within six months after diagnosis, In total, 24/81 patients (29%) were offered a genetic test at least six months after diagnosis and for 3/81 patients (4%) family members were referred to a genetics department, because the patient was too sick to attend the genetics department or had died. The remaining 54/81 patients (67%) were not offered genetic testing. For the majority of these patients, we could not find a possible reason for this. However, we did notice that 40/54 patients (74%) had died and 19/40 patients (48%) had died within six months after diagnosis.

After the implementation of our mainstream genetic testing pathway

We identified 162 patients who were newly diagnosed with EOC between April 2018 and December 2019 and who had not been offered genetic testing prior to their EOC diagnosis (Figure 3). Genetic testing was offered to 114/162 patients (70%) within six months after diagnosis ($p = 0.005$ in comparison to 56% before implementation), of whom 19/114 patients (17%) were referred to the genetics department and 95/114 patients (83%) were offered genetic testing by a non-genetic HCP of the gynecology department. In total, 17/19 patients (89%) referred to the genetics department received pre-test counseling and 17/17 patients (100%) completed genetic testing. The other 2/19 patients (11%) declined referral or cancelled their appointment after referral. In the mainstreaming pathway, 90/95 patients (95%) who were offered genetic testing accepted the genetic test, and

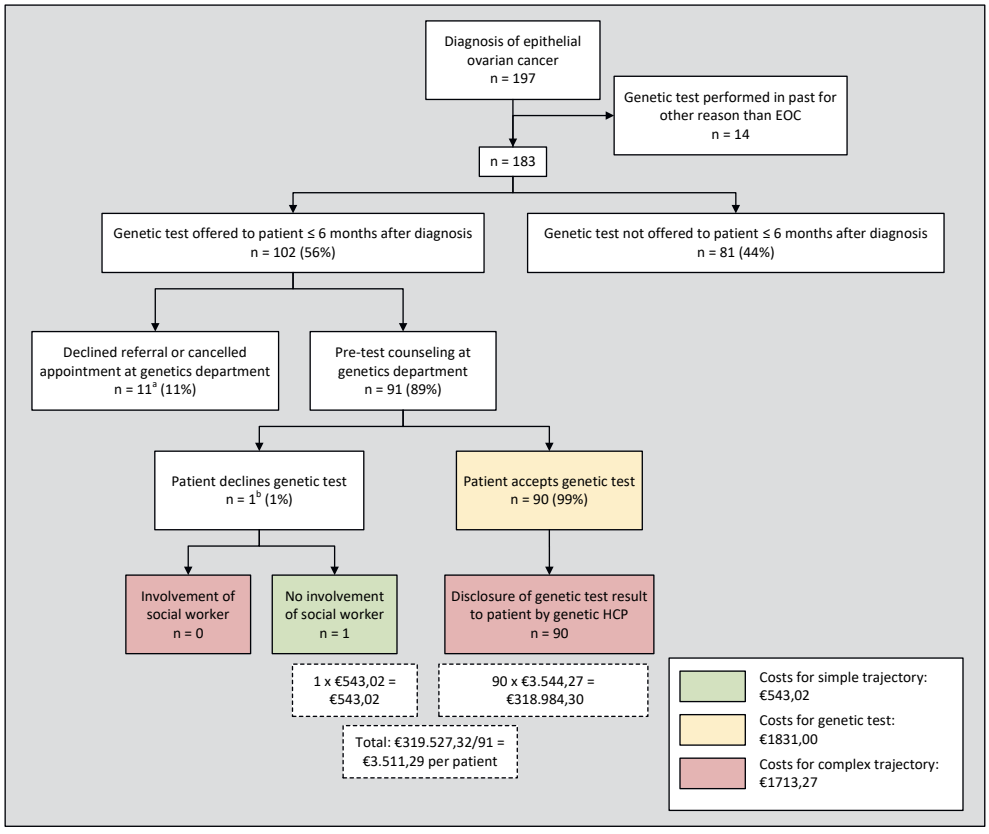


Figure 2. Percentage of newly diagnosed patients to whom genetic testing was offered and genetics-related healthcare costs before the implementation of our mainstream genetic testing pathway

EOC epithelial ovarian cancer, *HCP* healthcare professional. [a] Three of these patients initially declined referral for genetic testing but accepted genetic testing at a later stage via our mainstream genetic testing pathway. One patient died shortly after referral. [b] Patient declined genetic testing because she 'had too much on her mind' at time of pre-test counseling.

88/90 patients (98%) completed genetic testing. The other 5/95 patients (5%) declined genetic testing.

The remaining 48/162 patients (30%) were not offered genetic testing within six months after diagnosis at time of checking the patient files. In total, 11/48 patients (23%) were offered a genetic test at least six months after diagnosis, and for 5/48 patients (10%) family members were referred to a genetics department. The remaining 32/48 patients (67%) had not been offered genetic testing. Again, for the majority of these patients, we could not find a possible reason for this, but 20/32 of these patients (63%) had died, 11/20 (55%) had died within six months after diagnosis.

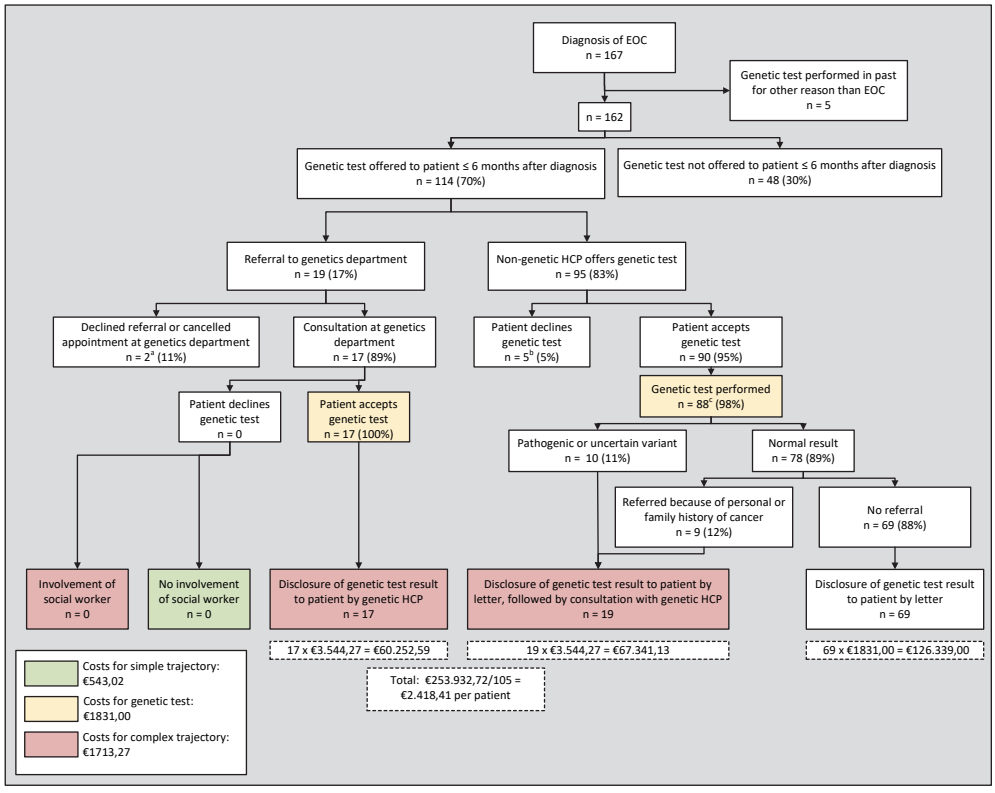


Figure 3. Percentage of newly diagnosed patients to whom genetic testing was offered and genetics-related healthcare costs after implementation of our mainstream genetic testing pathway.

EOC epithelial ovarian cancer, *HCP* healthcare professional. [a] For both patients it was not the right time to discuss genetic testing. Both patients indicated that they would contact the genetics department in a later stage, but omitted to do so. [b] Three patients needed time to think before making a decision about genetic testing, and genetic testing was not addressed a second time, for one patient her children considered genetic testing unnecessary, for one patient it is unclear if this patient declined genetic testing or if testing was not performed for another reason [c] Two patients accepted genetic testing, but for unclear reasons these tests were never performed.

Genetics-related healthcare costs

Period before the implementation of our mainstream genetic testing pathway

In total, 90 patients received pre-test counseling, genetic testing and post-test counseling by a genetic HCP (Figure 2). The genetics-related costs for these patients included the costs for both the complex trajectory and the genetic test. One patient received pre-test counseling only, because the patient elected not to proceed with genetic testing. The genetics-related costs for this patient only included the costs of the simple trajectory. Based on these costs, the genetics-related healthcare costs before implementing our mainstream genetic testing pathway were €3.511,29 per patient.

Period after the implementation of our mainstream genetic testing pathway
In total, 69 patients received pre-test counseling and testing by a non-genetic HCP and did not require additional counseling at the genetics department (Figure 3). For these patients, the healthcare costs only included the costs of the genetic test. In addition, 19 patients received pre-test counseling and testing by a non-genetic HCP bud did require additional counseling at the genetics department. Therefore, the costs for these patients included both the costs of the complex trajectory and the costs of the genetic test. For 17 patients, pre-test counseling, genetics testing and post-test counseling were performed by a genetic HCP. For these patients, the costs for both the complex trajectory and the genetic test were included. Based on these costs, the genetics-related healthcare costs after implementing our mainstream genetic testing pathway were €2.418,41 per patient, which is a 31% reduction (p = 0.000) compared to healthcare costs per patient before implementation of our mainstream genetic testing pathway.

Discussion

This study evaluated both the proportion of patients with newly diagnosed EOC to whom germline genetic testing was offered and genetics-related healthcare costs in a period before and after implementing a mainstream genetic testing pathway. After implementing our mainstream genetic testing pathway, the proportion of newly diagnosed patients who were offered genetic testing increased from 56% to 70% and genetics-related healthcare costs per patient decreased by 31%.

Low referral rates for germline genetic testing is one of the main reasons to start with mainstream genetic testing. Previous studies have focused mainly on the number of patients who accepted genetic testing after being offered genetic testing. In our study, these rates were between 95% and 100%. This is comparable to previous studies showing testing rates between 80% and 100% after pre-test counseling (8, 18, 19). In addition, Yoon et al. showed that these testing rates were comparable between a mainstream and standard genetic testing pathway (18). Powell et al. showed that a significantly higher number of patients completed genetic testing in a mainstream genetic testing pathway (100%) in comparison to patients in a standard genetic testing pathway (85.2%) (20). Flaum et al. showed that the number of genetic tests increased after implementing their mainstream genetic testing pathway (21). However, eligibility criteria for genetic testing were stricter before implementing their mainstream genetic testing pathway, which makes it difficult to assess the actual impact of this pathway. To evaluate the effect of mainstream genetic testing, testing rates should be compared with the number of patients eligible for genetic testing. Only one other study evaluated how many patients, who presented at their gynecology clinic, were offered genetic testing in the same clinic

before and after implementing a mainstream genetic testing pathway (11). In this study, a physician-coordinated genetic testing pathway was implemented, in which the number of patients recommended to have genetic counseling and testing had increased to 87% after implementing this pathway. It is difficult to attribute this increase to the effect of mainstream genetic testing, as multiple interventions were used in this study to increase the rates of recommendation and acceptance of genetic testing (i.e., integrating genetic counselors within the gynecologic oncology department and assisted genetic counseling referral).

After implementation of our mainstream genetic testing pathway, still 30% of newly diagnosed patients had not been offered genetic testing within six months after diagnosis. A large proportion of these patients (63%) had died, 55% of whom died within six months of the diagnosis. A reason for not offering genetic testing to all patients might be the high morbidity and mortality amongst patients with EOC (4). For newly diagnosed patients there is much to discuss during a consultation and genetic testing is usually not a first priority. It is possible that non-genetic HCPs simply do not get around to perform pre-test counseling. This is in line with our previous findings, where non-genetic HCPs reported that their main reasons for not discussing genetic testing was that the patient was too ill or there was no appropriate moment during the consultation to discuss genetic testing (15). Moreover, it is notable that after implementation of our mainstreaming pathway a substantial proportion of patients (23%) who had not been offered genetic testing within six months after diagnosis were offered genetic testing at a later stage. However, by postponing to discuss the genetic test there is a greater chance that this will be forgotten or that the patient will have died. Because genetic testing is beneficial not only to patients but also to family members, it is important that family members be informed about genetic testing when the patient has died. Family members should then be referred to a genetics department for pre-test counseling and testing.

Incorporating a tumor-first approach into our workflow might increase the testing rates even further (22). Tumor material is almost always obtained, at least for diagnostic purposes, and tumor material can be evaluated for genetic alterations at the same time as establishing the diagnosis. However, it remains important to incorporate an informed consent procedure for all of these patients, as patients may not opt for genetic testing. In this study, approximately 11% of patients declined an appointment at the genetics department for pre-test counseling after referral. This is comparable with the data in the studies of Bednar et al. (11) and McGee et al. (23). For daily practice, it is important to realize that between 5% and 11% of patients with EOC decline germline genetic testing. Therefore, we plea to implement a pre-test counseling procedure when considering tumor and germline genetic testing.

For a new care pathway to be sustainable, it is important to consider the impact on healthcare costs as well. We showed a reduction in genetics-related healthcare costs per patient of 31% in a DRG system. George et al. reported that their mainstream pathway led to an approximate 13-fold reduction in resource requirement, resulting in a cost reduction of approximately £2.6 M per year (8). However, these costs are based on the estimated number of genetics appointments and associated costs, instead of the actual number of genetics appointments. For this estimation, they only considered patients with a pathogenic variant who would need an additional appointment at the genetics department after mainstream genetic testing. They did not take into account patients that might need additional counseling at the genetics department because of a personal or family history of cancer.

In both our study and the study performed by George et al., costs were based on the costs of counseling at the genetics departments. However, implementing a mainstream genetic testing pathway causes a shift in range of duties between non-genetic and genetic HCPs. Performing pre-test counseling and requesting the genetic test themselves increases the workload of non-genetic HCPs. So far, the costs for pre-test counseling have only been incorporated into the DBCs for genetic care performed by genetic counselors. The DBCs used by non-genetic HCPs for the care they provide do not include their additional time investment to perform pre-test counseling, which is around 10 minutes for the majority of non-genetic HCPs based on our previous research (15). Non-genetic HCPs cannot use the DBCs for genetic care because these are based on the time investment and salary of genetic HCPs. It is important in the future that DBCs be adjusted to account for the time and resources that non-genetic HCPs spend on pre-test counseling and requesting genetic testing. Incorporating this additional time investment into these DBCs would increase the billable rates for the care provided by these non-genetic HCPs, and therefore also cause a shift in costs between the DBCs used by the genetics and gynecology department. That said, previous research has shown that the increase in workload is limited and not comparable to the pre-test counseling offered at a genetics department (9). Therefore, we expect the reduction in healthcare costs to remain significant even if the slight increase in workload is incorporated into the billable care for EOC patients. The overall impact on healthcare costs also depends on the effects, e.g., the cancers that could have been prevented in patients and family members due to the timely identification of a pathogenic variant in a cancer predisposition gene. Previous studies have shown that it is cost-effective to offer genetic testing to all patients with EOC (24, 25).

A major strength of this study is that all data are based on the actual number of newly diagnosed patients with EOC provided by the comprehensive cancer registration, and that we were able to review the medical files of all these patients.

This study also has limitations. We evaluated two different time periods to assess the impact of our mainstream genetic testing pathway on testing rates. With the increasing utility of PARP inhibitors, the rise in our testing rates may be biased. In addition, the percentage of patients that was offered a genetic test and declined was based on the information from the patient records. We do not know if non-genetic HCPs always documented in their patient files when a patient declined referral to a genetics department or did not opt for a germline genetic test after pre-test counseling. Therefore, the number of patients that was offered a genetic test and also the number of patients that declined referral might be an underestimation. However, given the high mortality in our study group, we consider it more plausible that an appropriate time to discuss a genetic test could not be found and that indeed no genetic test was offered to these patients. More details about the diagnoses might help support this assumption. Therefore, it is a limitation that we did not include more information about the diagnoses, e.g., histology or stage. Another limitation of our study is that the healthcare costs were based on a healthcare payer perspective, and therefore do not reflect the actual costs.

In conclusion, mainstream genetic testing increases testing rates amongst newly diagnosed patients with EOC, and significantly reduces genetics-related healthcare costs using a healthcare payer perspective. This study shows that mainstream genetic testing may be sustainable for the routine care of patients with EOC.

CRediT authorship contribution statement: K. Bokkers: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. G.W.J. Frederix: Conceptualization, Methodology, Formal analysis, Writing – review & editing. M.E. Velthuizen: Formal analysis, Investigation, Data curation, Writing – review & editing. M. van der Aa: Resources, Writing – review & editing. C.G. Gerestein: Resources, Writing – review & editing. E.B.L. van Dorst: Resources, Writing – review & editing. J.G. Lange: Resources, Writing – review & editing. J.A. Louwers: Resources, Writing – review & editing. W. Koole: Writing – review & editing. R.P. Zweemer: Conceptualization, Methodology, Writing – review& editing, Supervision. M.G.E.M. Ausems: Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Funding: Grant ID: AZNL201700234

Declaration of Competing Interest: AstraZeneca sponsored the training module that was developed as part of this project, and was not involved in the development of its content.

Acknowledgements: We thank all participating gynecologic oncologists, gynecologists with a subspecialty training in oncology, and nurse specialists from the University Medical

Center Utrecht, Diakonessenhuis Utrecht, Meander Medical Center Amersfoort, and St. Antonius Hospital Nieuwegein/Utrecht, The Netherlands, Grant ID: AZNL201700234.

References

1. Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19(1):77-102.
2. Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245.
3. CRGO. Guideline hereditary and familial ovarian cancer 2015 [updated June 1. Available from: https://www.oncoline.nl/erfelijk-en-familiair-ovariumcarcinoom].
4. Lheureux S, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. Lancet. 2019;393(10177):1240-1253.
5. Tew WP, Lacchetti C, Ellis A, Maxian K, Banerjee S, Bookman M, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-3493.
6. Hoskins PJ. Inadequate Rates of BRCA Testing with its Negative Consequences for Women with Epithelial Ovarian Cancer and their Families: an Overview of the Literature. Clin Oncol (R Coll Radiol). 2018;30(8):472-483.
7. McCuaig JM, Armel SR, Care M, Volenik A, Kim RH, Metcalfe KA. Next-Generation Service Delivery: A Scoping Review of Patient Outcomes Associated with Alternative Models of Genetic Counseling and Genetic Testing for Hereditary Cancer. Cancers (Basel). 2018;10(11).
8. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.
9. Bokkers K, Vlaming M, Engelhardt EG, Zweemer RP, van Oort IM, Kiemeney L, et al. The Feasibility of Implementing Mainstream Germline Genetic Testing in Routine Cancer Care-A Systematic Review. Cancers (Basel). 2022;14(4):1059.
10. Scheinberg T, Young A, Woo H, Goodwin A, Mahon KL, Horvath LG. Mainstream consent programs for genetic counseling in cancer patients: A systematic review. Asia Pac J Clin Oncol. 2021;17(3):163-177.
11. Bednar EM, Oakley HD, Sun CC, Burke CC, Munsell MF, Westin SN, et al. A universal genetic testing initiative for patients with high-grade, non-mucinous epithelial ovarian cancer and the implications for cancer treatment. Gynecol Oncol. 2017;146(2):399-404.
12. Busse R, Geissler A, Aaviksoo A, Cots F, Hakkinen U, Kobel C, et al. Diagnosis related groups in Europe: moving towards transparency, efficiency, and quality in hospitals? BMJ. 2013;346:f3197.
13. Kroneman M, Boerma W, van den Berg M, Groenewegen P, de Jong J, van Ginneken E. Netherlands: Health System Review. Health Syst Transit. 2016;18(2):1-240.
14. Scheller-Kreinsen D, Quentin W, Busse R. DRG-based hospital payment systems and technological innovation in 12 European countries. Value Health. 2011;14(8):1166-1172.

15. Bokkers K, Zweemer RP, Koudijs MJ, Stehouwer S, Velthuizen ME, Bleiker EMA, et al. Positive experiences of healthcare professionals with a mainstreaming approach of germline genetic testing for women with ovarian cancer. Fam Cancer. 2022;21(3):295-304.
16. Castor. Electronic Data Capture (EDC) Software for Clinical Trials 2022 [Available from: https://www.castoredc.com/].
17. Prestatie- en tariefbeschikking medisch-specialisitsche zorg 2021. In: Table with rates for DRG care products and other care products from January 1, editor.: Dutch Healthcare Association; 2021 [Available from: https://puc.overheid.nl/nza/doc/PUC_319970_22/1/].
18. Yoon SY, Wong SW, Lim J, Ahmad S, Mariapun S, Padmanabhan H, et al. Oncologist-led BRCA counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes. J Med Genet. 2022;59(3):220-229.
19. Rumford M, Lythgoe M, McNeish I, Gabra H, Tookman L, Rahman N, et al. Oncologist-led BRCA 'mainstreaming' in the ovarian cancer clinic: A study of 255 patients and its impact on their management. Sci Rep. 2020;10(1):3390.
20. Powell CB, Laurent C, Ciaravino G, Garcia C, Han L, Hoodfar E, et al. Streamlining genetic testing for women with ovarian cancer in a Northern California health care system. Gynecol Oncol. 2020;159(1):221-228.
21. Flaum N, Morgan RD, Burghel GJ, Bulman M, Clamp AR, Hasan J, et al. Mainstreaming germline BRCA1/2 testing in non-mucinous epithelial ovarian cancer in the North West of England. Eur J Hum Genet. 2020;28(11):1541-1547.
22. Vos JR, Fakkert IE, de Hullu JA, van Altena AM, Sie AS, Ouchene H, et al. Universal Tumor DNA BRCA1/2 Testing of Ovarian Cancer: Prescreening PARPi Treatment and Genetic Predisposition. J Natl Cancer Inst. 2020;112(2):161-169.
23. McGee J, Peart TM, Foley N, Bertrand M, Prefontaine M, Sugimoto A, et al. Direct Genetics Referral Pathway for High-Grade Serous Ovarian Cancer Patients: The "Opt-Out" Process. J Oncol. 2019;2019:6029097.
24. Eccleston A, Bentley A, Dyer M, Strydom A, Vereecken W, George A, et al. A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. Value Health. 2017;20(4):567-576.
25. Hurry M, Eccleston A, Dyer M, Hoskins P. Canadian cost-effectiveness model of BRCA-driven surgical prevention of breast/ovarian cancers compared to treatment if cancer develops. Int J Technol Assess Health Care. 2020;36(2):104-112.

Part 3

Part 3

Mainstream genetic testing of patients with breast cancer


6

Chapter 6

Surgical oncologists and nurses in breast cancer care are ready to provide pre-test genetic counseling

Kyra Bokkers [1], Eveline M.A. Bleiker [2,3,4], Cora M. Aalfs [1], Thijs van Dalen [5], Mary E. Velthuizen [1], Petra Duijveman [1,6], Rolf H. Sijmons [7], Wouter Koole [1], Ernst J.P. Schoenmaeckers [8], and Margreet G.E.M. Ausems [1]

1. Division Laboratories, Pharmacy and Biomedical Genetics, dept. of Genetics, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands
2. Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
3. Family Cancer Clinic, The Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands
4. Department of Clinical Genetics, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
5. Department of surgery, Diakonessenhuis, Bosboomstraat 1, 3582 KE Utrecht, The Netherlands
6. Department of surgery, St. Antonius Hospital, Soestwetering 1, 3543 AZ Utrecht, The Netherlands
7. Department of Genetics, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
8. Department of surgery, Meander Medical Center, Maatweg 3, 3813 TZ Amersfoort, The Netherlands

Ann Surg Oncol. 2023 Online ahead of print.

Abstract

Background: Pre-test genetic counseling for patients with breast cancer is increasingly being provided by non-genetic healthcare professionals. We evaluated the attitudes, knowledge and self-efficacy of surgeons, oncologists and nurses regarding mainstream genetic testing and the feasibility to incorporate pre-test genetic counseling into routine care.

Methods: We offered an online training to healthcare professionals from 13 hospitals and implemented a mainstream genetic testing pathway in 11/13 (85%) hospitals. Questionnaires were sent before (T0) and 6 months after (T1) completing the training. Those who did not complete the training received a questionnaire to assess their motivations.

Results: In 11 hospitals, 80 (65%) healthcare professionals completed the training, of whom 70 (88%) completed both questionnaires. The attitudes, (perceived) knowledge and self-efficacy of healthcare professionals were high both at baseline and 6 months after completing the training. After 6 months, their perceived knowledge about the advantages and disadvantages of a genetic test and implications for family members had significantly improved ($p = 0.012$ and $p = 0.021$, respectively). For the majority (89%), the time investment for pre-test genetic counseling was less than 15 minutes per patient and as expected or better. Healthcare professionals considered the total time investment feasible to incorporate mainstream genetic testing into their daily practice. The main barrier to complete the training was lack of time. The online training was considered useful, with a rating of 8/10.

Conclusion: Surgical oncologists and nurses in breast cancer care feel well-equipped and motivated to provide pre-test genetic counseling after completion of an online training module.

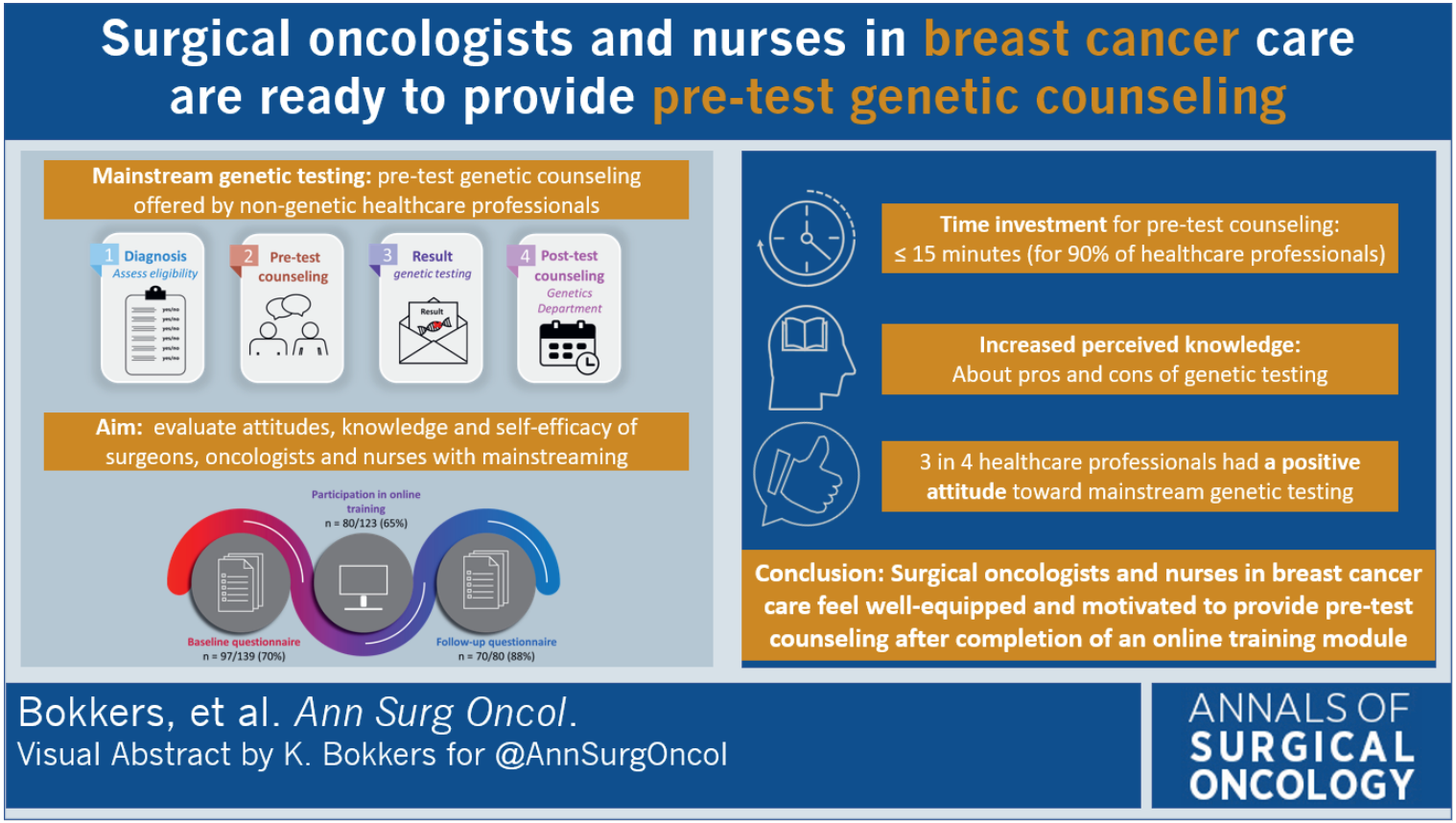
Brief Summary:

Breast surgeons and nurse specialists are increasingly offering pre-test genetic counseling to patients with breast cancer, so called mainstream genetic testing. This study shows that these non-genetic healthcare professionals have a positive attitude, sufficient knowledge and feel confident to provide this care themselves. Moreover, it is feasible for them to incorporate mainstream genetic testing into their routine care.

Keywords: Breast cancer; Mainstream genetic testing; Genetic counseling; Feasibility; Attitude; Online training

Visual Abstract

Ann Surg Oncol. 2023 Online ahead of print.



Introduction

In 5 – 10% of breast cancer cases, a germline pathogenic variant in one of the breast cancer genes can be found (1-3). The identification of a hereditary cause may affect both surgical and chemotherapeutic treatment and may help decision-making for risk reducing options for both patients and family members (4-6).

Traditionally, pre-test genetic counseling (GC) is provided by genetic healthcare professionals (HCPs) at genetics departments (7). However, not all eligible patients are being referred (8-11), and in those tested, results are not always available before surgery (12, 13). In addition, the burden on genetics departments is rising as waiting lists increase (7, 14).

One strategy to offer genetic testing (GT) to a larger proportion of patients and to decrease time to test results, is to implement mainstream GT. In this approach, pre-test GC is being provided by non-genetic HCPs instead of genetic HCPs (15-17). Ideally, these initiatives include training, because many HCPs lack knowledge or confidence to offer pre-test GC (13, 18-21). Mainstream GT has been shown to be feasible and acceptable for both patients and HCPs (22, 23). However, research has focused primarily on ovarian cancer patients. There is limited information on the experiences of HCPs with mainstream GT in breast cancer patients (17, 24). To our knowledge, no studies have evaluated attitudes of HCPs before and after the implementation of mainstream GT. In addition, there is limited information on the feasibility to incorporate such a pathway into routine care. Regarding feasibility, previous studies have focused primarily on time investment.

In this study, we invited HCPs in breast cancer care to complete an online training about GT and we implemented a mainstream GT pathway for patients with breast cancer. Nurse specialists, nurses and doctors work closely together in the care pathway of patients with breast cancer; therefore, we included all these disciplines. We evaluated (1) HCPs' attitudes toward incorporating mainstream GT into their daily practice, their knowledge of GT, and self-efficacy to offer pre-test GC both before and after implementing mainstream GT, (2) the feasibility for HCPs to incorporate mainstream GT into their daily practice, (3) HCPs' experiences with our online training module and their reasons for not completing the training.

Methods

Implementation of mainstream genetic testing

Needs and preferences of HCPs

To map the needs and preferences of HCPs involved in breast cancer care, we organized two multidisciplinary focus group meetings. These included surgical oncologists, nurse specialists, a medical oncologist, a radiation oncologist, a clinical geneticist, a genetic counselor, a social worker from the genetics department, a psychologist, and a patient advocate. Based on the discussion points from the first focus group meeting, we performed an online questionnaire among all HCPs in breast cancer care in the service area of the UMC Utrecht genetics department (Supplementary materials). The results of this survey were discussed during the second focus group meeting.

Online training module

The online training module consisted of four short films (duration between 7.5 and 15.5 minutes, Supplementary materials). Our training module was adapted from the module we developed earlier for HCPs involved in ovarian cancer care (25).

Mainstream genetic testing pathway

Based on the outcomes of the focus group meetings and survey, we developed a mainstream GT pathway for breast cancer care (Figure 1). This pathway was adapted from the one developed in the Mainstreaming Cancer Genetics program (16), and the pathway we previously developed for ovarian cancer (25).

Any HCP involved in the treatment of patients with breast cancer could provide pre-test GC themselves when they had completed the training, and patients (1) were eligible for GT based on patient characteristics and independent of family cancer history, and (2) did not require further genetic evaluation and/or counseling at the genetics department prior to testing. These criteria were assessed by the HCP by completing two checklists (Supplementary materials). If eligible for mainstream GT, HCPs provided pre-test GC and handed out an information sheet to the patient. Patients who consented to GT completed a written consent form and the HCP ordered the genetic test. The gene panel consisted of the genes *BRCA1, BRCA2, CHEK2, PALB2* and *ATM.* The genetics department sent the test result in a letter to the patient, the HCP who ordered the test, and the patients' general practitioner. An appointment at the genetics department was only added in case a (likely) pathogenic variant or variant of uncertain clinical significance (VUS) was found or if there was a reason for additional post-test GC based on the second checklist.

Implementation of mainstream genetic testing

We implemented our mainstream pathway in nine hospitals in our region: one academic hospital and eight non-academic teaching hospitals in a stepwise manner (between September 2019 and February 2021).

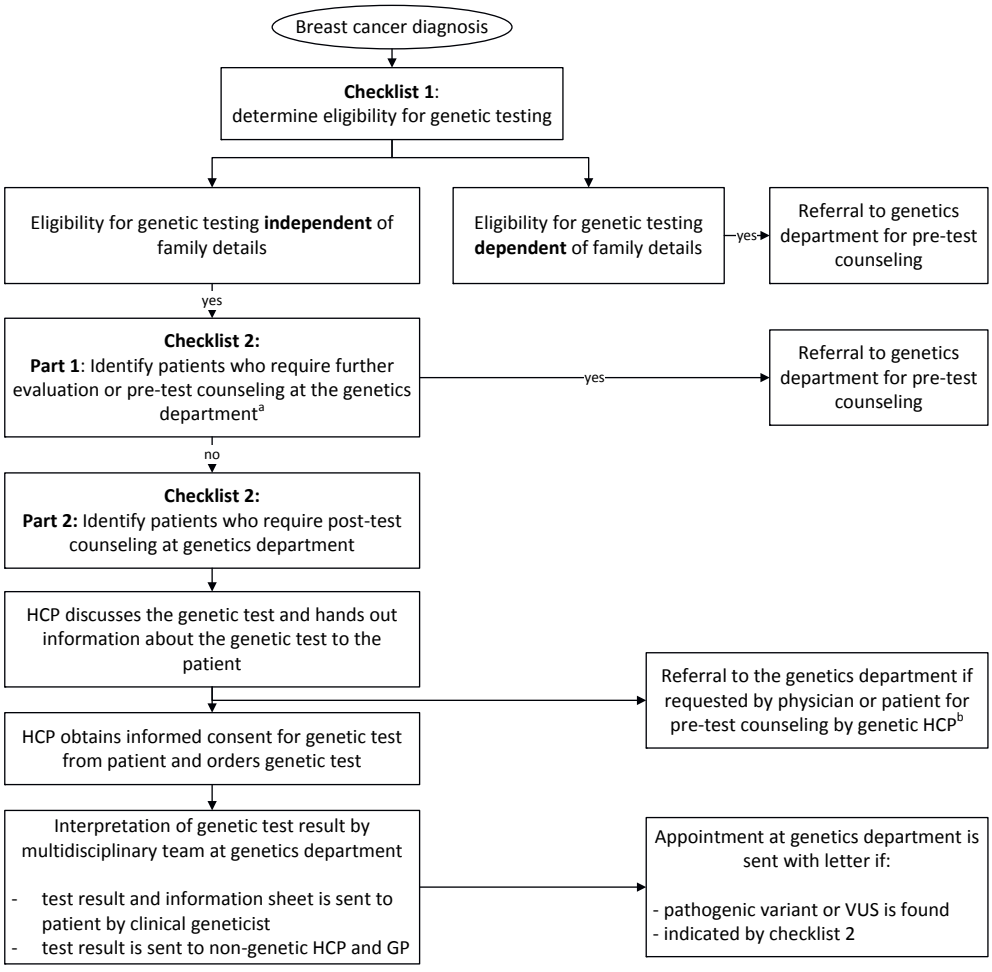


Figure 1. Flow-chart for mainstream genetic testing in patients with breast cancer
HCP healthcare professional, *GP* general practitioner, *VUS* variant of uncertain clinical significance. [a] Further genetic evaluation and/or counseling at the genetics department prior to testing, e.g., for additional genetic testing of the *TP53* gene or targeted genetic testing of a known familial pathogenic variant. [b] Referral to the genetics department for pre-test genetic counseling was optional if requested by the patient or non-genetic healthcare professional (e.g., if the patient had questions that the non-genetic healthcare professional could not answer).

From May 2021 to September 2021, the pathway was also introduced in four non-academic teaching hospitals in the Northern region of the Netherlands and implemented in two of them during our study period. Due to logistical reasons, the pathway was implemented in the other two hospitals at a later stage, after our study had ended (March 2022). We organized a kick-off meeting in each hospital to introduce our new workflow. Subsequently, HCPs received personal login codes for the training. All HCPs who completed the training received a manual with information and forms to provide pre-test GC and GT. Before the implementation of our pathway, all patients with breast cancer needed to be referred to a genetic HCP for pre-test genetic counseling.

Study procedure

A prospective follow-up design was used. Two questionnaires were sent to participating HCPs to assess their attitudes and experiences. The first questionnaire was completed before accessing the online training (T0). After 6 months, the second questionnaire (T1) was sent to HCPs who completed the training. Items of the questionnaires are shown in the Supplementary materials.

Attitudes, perceived knowledge, self-efficacy, and knowledge

Both the T0 and T1 questionnaire contained 13 self-developed statements to evaluate HCPs' attitudes regarding mainstream genetic testing (four statements), perceived knowledge (three statements), and self-efficacy (i.e., confidence in providing pre-test genetic counseling, five statements) (25). The second questionnaire contained two extra statements regarding HCPs' attitudes. All statements were rated using a five-point Likert rating scale, ranging from strongly disagree to strongly agree.

Knowledge was assessed with four self-developed multiple-choice questions, comparable to the questions in our previous study (25). In addition, knowledge was assessed with five statements adapted from Claes et al. (26), which could be answered with 'true', 'false' or 'I do not know'.

Feasibility of mainstream genetic testing

Feasibility was assessed based on HCPs' (1) estimated time investment to discuss and order GT, (2) need for additional appointments for pre-test GC, (3) experiences with the supporting resources to provide pre-test GC, and (4) reasons for not discussing GT with all eligible patients.

Evaluation of online training module and reasons for not completing the module

A short questionnaire was completed after viewing each film and at the end to evaluate the training module. These included questions on duration, usefulness of the content and online format, and level of difficulty, using five-point Likert scales. In addition, HCPs

rated each film and the entire training on a scale of 1 – 10. After 6 months, we asked HCPs whether, in retrospect, they had missed information in the online training.

HCPs who did not complete the online training received a questionnaire to assess their motivations for not starting or completing the training, consisting of three to ten multiple choice questions.

Statistics

All analyses were performed using IBM SPSS statistics 26.0.0.1. Descriptive statistics were used to describe HCPs' characteristics, reasons for not discussing the option of GT, time investment, and need for additional appointments to provide pre-test GC. We compared the characteristics between HCPs using the independent *t*-test or Mann-Whitney *U*-test for continuous variables and the chi-square test or Fisher's Exact Test for categorical variables. Attitude, perceived knowledge, and self-efficacy were recoded into positive (agree or strongly agree) and negative (neutral, disagree or strongly disagree). We compared these statements between T0 and T1 using the Wilcoxon signed-rank test for paired analysis to assess whether their answers had changed (i.e., no change, from negative to positive or vice versa). The knowledge questions were also compared between T0 and T1 using the Wilcoxon signed-rank test for paired analysis, both for the individual questions and the total score of all combined questions (possible scores between 0 and 9). We included the answers of the T0 questionnaire only if HCPs also completed the T1 questionnaire. A p-value < 0.05 was considered statistically significant.

Ethical approval

This study was reviewed by the Medical Review Ethics Committee (MREC) of the UMC Utrecht in August 2019 and the Medical Research Involving Human Acts (WMO) did not apply to our study and therefore official approval by the MREC was not necessary.

Results

Participants

Figure 2 shows the number of HCPs who completed the training and participated in the questionnaire study. In total, 83% of the invited nurses (n = 50/60) completed the training versus 46% of invited doctors (n = 36/79, p = 0.000). In addition, 71% of HCPs working in a surgical department (n = 67/94) completed the training versus 42% of HCPs working in an oncology or radiotherapy department (n = 19/45, p = 0.001).

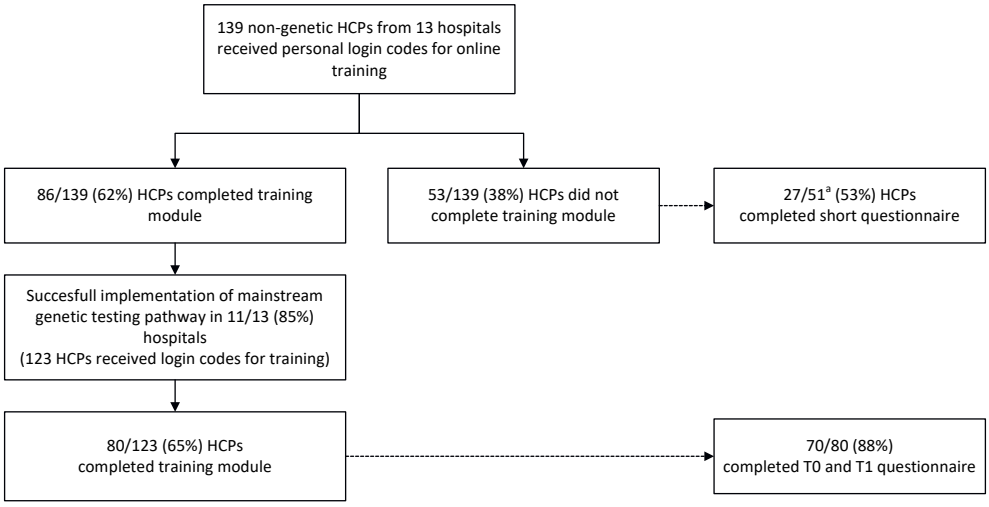


Figure 2. Participation of non-genetic healthcare professionals in online training and questionnaire study.
HCP healthcare professional. [a] Two healthcare professionals were not sent the short questionnaire.

Table 1 shows the basic characteristics of all HCPs who completed both questionnaires. The majority of participants were female (84%) with an average age of 48 years, working as a nurse in a surgical department (51%), and with varying experience in breast cancer care. Of all HCPs who received the T1 questionnaire (n = 80), 94% of nurses (n = 43/46) versus 77% of doctors (n = 26/34) competed this questionnaire (p = 0.047).

Attitudes, perceived knowledge, self-efficacy, and knowledge

Table 2 shows HCPs' attitude toward mainstream GT, perceived knowledge of GT, and self-efficacy to discuss and order GT, both at baseline (T0) and after 6 months (T1). The majority of HCPs 'agreed' or 'strongly agreed' with all statements. Only a narrow majority felt confident to explain the differences between germline and tumor testing (53% at T0 and 55% at T1). There were no significant differences in attitude and self-efficacy before and 6 months after completing the training. Reasons for not having a positive attitude toward mainstream GT are shown in the Supplementary materials. Perceived knowledge of the advantages and disadvantages of GT and the importance of GT to family members had improved significantly 6 months after completing the training (p = 0.012 and p = 0.021, respectively).

Table 3 shows the number of HCPs that answered the knowledge questions correctly and their average total score both at baseline and 6 months after completing the training.

Table 1. Characteristics of participating non-genetic healthcare professionals

Characteristics	Total group n = 70
Age in years, mean (sd)	48.0 (9.9)
Sex, n (%)	
- Female	59 (84.3)
- Male	11 (15.7)
Disciplines, n (%)	
Surgical department	53 (75.7)
- Surgical oncologist	- 16 (30.2)
- Nurse specialist/physician assistant/nurse (in training)	- 36 (67.9)
- Other	- 1 (1.9)
Oncology department	17 (24.3)
- Medical oncologist	- 10 (58.8)
- Nurse specialist/physician assistant/nurse (in training)	- 7 (41.2)
Years working in breast cancer care, n (%)	
- < 5	14 (20.0)
- 5 – 10	17 (24.3)
- 10 – 15	15 (21.4)
- > 15	24 (34.3)

With paired analyses, there were no significant differences in knowledge for any of the individual knowledge questions and the total scores of all questions combined.

Feasibility of mainstream genetic testing

In total, 76% of HCPs (n = 53/70) had provided pre-test GC and/or ordered a genetic test (on average five HCPs per hospital). These HCPs included 30 nurses (57%) working in a surgical department, 15 surgical oncologists (28%), six nurses working in an oncology department (11%), and two medical oncologists (4%).

The majority of HCPs (72%) both performed pre-test GC and ordered genetic tests. The time investment for pre-test counseling was less than 15 minutes per patient for 89% of HCPs (n = 40/45). This was as or better than expected for 91% of HCPs (n = 41/45). The time investment to order a genetic test was less than 15 minutes for 86% of HCPs (n = 37/43). This was as or better than expected for 70% of HCPs (n = 30/43). The total time investment for all tasks was feasible for 83% of HCPs (n = 44/53). In total, 34% of HCPs (n = 18/53) needed to schedule additional appointments to provide pre-test GC, 17% of HCPs (n = 9/53) received questions they could not answer, and more than 88% considered the supporting material as useful (Supplementary Materials).

Table 2. Statements evaluating HCPs' attitude, perceived knowledge, and self-efficacy at baseline (T0) and six months (T1) after completing the training module, n = 70

Statements	T0 (strongly) agree n (%)	T1 (strongly) agree n (%)	Paired comparison between T0 and T1 + n (%)	- n (%)	= n (%)	p-value
Attitude						
- I am positive toward offering a genetic test myself	48 (68.6)	52 (74.3)	7 (10.0)	3 (4.3)[a]	60 (85.7)	ns
- It is important for patients to have a choice whether or not to have a genetic test performed	65 (97.0)[b]	65 (97.0)[b]	1 (1.5)	1 (1.5)	65 (97.0)	ns
- It is important to offer genetic testing immediately after diagnosing breast cancer	41 (62.1)[c]	39 (59.1)[c]	8 (12.1)	10 (15.2)	48 (72.7)	ns
- It is important that all patients with breast cancer who are eligible for genetic testing have access to genetic testing	65 (98.5)[c]	65 (98.5)[c]	1 (1.5)	1 (1.5)	64 (97.0)	ns
- It is important to pay attention to the psychosocial consequences of genetic testing when discussing genetic testing	66 (100)[c]	65 (98.5)[c]	0	1 (1.5)	65 (98.5)	ns
- Surgical oncologists, radiation oncologists, medical oncologists and nurse specialists are capable of offering pre-test genetic counseling and request genetic testing themselves after completing an online training module	Not asked	43 (65)[c]	N/A	N/A	N/A	N/A
- Surgical oncologists, radiation oncologists, medical oncologists and nurse specialists are capable of offering pre-test genetic counseling and request genetic testing themselves *without* completing an online training module	Not asked	1 (2)[c]	N/A	N/A	N/A	N/A
Perceived knowledge						
- I understand the advantages and disadvantages of a genetic test	47 (70.1)[b]	58 (86.6)[b]	15 (22.4)	4 (6.0)	48 (71.6)	0.012*
- I understand the importance of genetic testing for patients with breast cancer	63 (95.5)[c]	66 (100)[c]	3 (4.6)	0	63 (95.4)	ns
- I understand the importance of genetic testing for family members of patients with breast cancer	55 (83.3)[c]	63 (95.5)[c]	10 (15.2)	2 (3.0)	54 (81.8)	0.021*

Self-efficacy						
- I am confident that I can discuss the advantages and disadvantages of a genetic test	46 (69.7)[c]	53 (80.3)[c]	13 (19.7)	6 (9.1)	47 (71.2)	ns
- I am confident that I am able to discuss a genetic test with all patients with breast cancer directly after diagnosing breast cancer	49 (74.2)[c]	45 (68.2)[c]	6 (9.1)	10 (15.1)	50 (75.8)	ns
- I am confident that I am able to order a genetic test myself	54 (81.8)[c]	54 (81.8)[c]	7 (10.6)	7 (10.6)	52 (78.8)	ns
- I am confident that I am able to recognize psychosocial problems in patients and subsequently refer patients to a specialist social worker	55 (83.3)[c]	53 (80.3)[c]	5 (7.6)	7 (10.6)	54 (81.8)	ns
- I am confident that I am able to explain what genetic testing in tumor tissue entails and what the differences are with genetic testing in blood samples	35 (53.0)[c]	36 (54.5)[c]	7 (10.6)	6 (9.1)	53 (80.3)	ns

N/A not applicable, *ns* not significant, *p < 0.05. Scores consisted of five options: (1) strongly disagree, (2) disagree, (3) agree, nor disagree, (4) agree, (5) strongly agree. *Paired* analyses with Wilcoxon signed rank test comparing whether patients were positive (agree/strongly agree) or negative (agree, nor disagree/disagree/strongly disagree).

+ negative at T0 and positive at T1, – positive at T0 and negative at T1, = positive or negative in both questionnaires. [a] The reasons for three HCPs to have a more negative attitude were pre-test genetic counseling was too time consuming, limited experience with mainstream genetic testing, and there was no appropriate time during a consultation to offer pre-test genetic counseling. [b] Total number of paired measurements was n = 67, [c] Total number of paired measurements was n = 66.

Table 3. Number of correct answers of healthcare professionals to knowledge questions before (T0) and 6 months after completing the training module (T1), n = 68

Questions	T0	T1	Comparison (paired) between T0 and T1			
	correct answer n (%)	correct answer n (%)	+ n (%)	- n (%)	= n (%)	p-value
- What is the prevalence of a pathogenic variant in one of the breast cancer genes?	36 (52.9)	32 (47.1)	12 (17.7)	16 (23.5)	40 (58.8)	ns
- What is the meaning of a pathogenic variant in one of the breast cancer genes found only with a tumor test?	45 (66.2)	46 (67.6)	13 (19.1)	12 (17.7)	43 (63.2)	ns
- What is the meaning of a pathogenic variant in one of the breast cancer genes found only with a blood test?	55 (80.9)	59 (86.8)	10 (14.7)	6 (8.8)	52 (76.5)	ns
- What are the implications of a pathogenic variant in one of the breast cancer genes for obtaining disability or life insurance?	55 (80.9)	60 (88.2)	8 (11.8)	3 (4.4)	57 (83.8)	ns
- All women with a pathogenic variant (gene alteration) in a breast cancer gene will someday develop breast cancer	68 (100)	68 (100)	0 (0)	0 (0)	68 (100)	ns
- A woman without a pathogenic variant (gene alteration) in a breast cancer gene can still develop breast cancer	68 (100)	66 (97.1)	0 (0)	2 (2.9)	66 (97.1)	ns
- A woman with a pathogenic variant (gene alteration) in breast cancer gene can pass this alteration on to her children	67 (98.5)	68 (100)	1 (1.5)	0 (0)	67 (98.5)	ns
- A woman may have inherited a pathogenic variant (gene alteration) in a breast cancer gene from her father	68 (100)	68 (100)	0 (0)	0 (0)	68 (100)	ns
- A woman who has a sister with a pathogenic variant (gene alteration) in a breast cancer gene has a 50% chance (1 in 2) of having this gene alteration as well	50 (74.6)[a]	53 (79.1)[a]	11 (16.4)[a]	8 (11.9)[a]	48 (71.7)[a]	ns
Total score, median (min – max)	8.0 (5 – 9)[a]	8.0 (5 - 9)[a]	21 (31.3)[a,b]	18 (26.9)[a,b]	28 (41.8)[a,b]	ns

ns not significant, + number of healthcare professionals who answered the individual questions incorrect at T0 and correct at T1 or had a higher total score at T1 than at T0, − number of healthcare professionals who answered the individual questions correct at T0 and incorrect at T1 or had a lower total score at T1 than at T0, = number of HCPs who had the same answer (correct or incorrect) at T0 and T1 for the individual questions or had the same total score at T1 as at T0. [a] n = 67, [b] Compared with those HCPs whose scores remained the same or improved, a significant higher proportion of HCPs working in a surgical department (n = 17/50, 34%) had a lower overall score after 6 months than oncological HCPs (n = 1/17, 6%, p = 0.028).

The main reason for not discussing GT with patients before the online training (T0) was that HCPs forgot to discuss it, whereas after 6 months (T1) the main reason was that patients were too emotional (Figure 3).

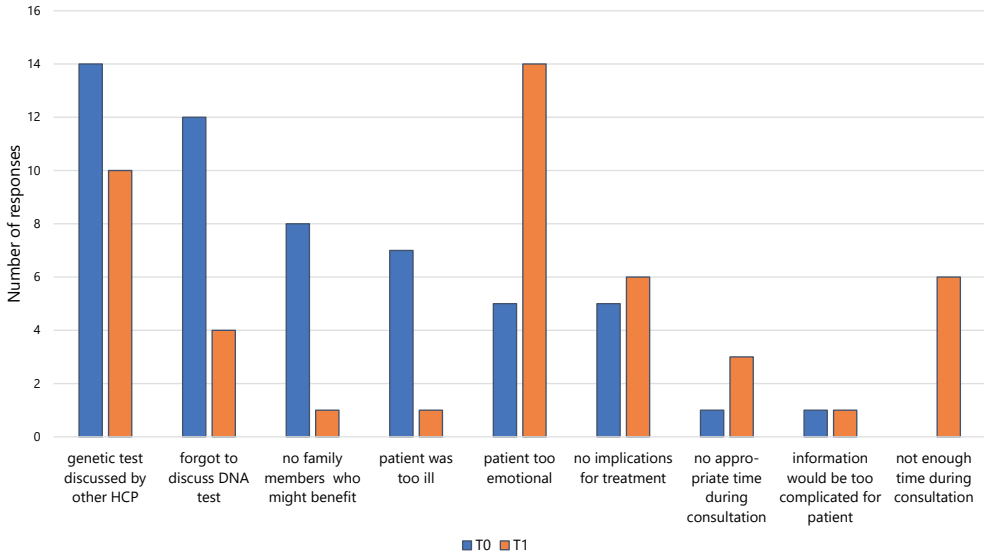


Figure 3. Reasons of non-genetic healthcare professionals for not discussing genetic testing before (T0) and 6 months after completing the online training module (T1), n = 69
Multiple reasons could be given.

In total, 25% of HCPs (n = 17/67) had not provided pre-test GC and/or requested GT during the 6 months after completing the training. They consisted of eight medical oncologists (47%), six nurses (35%) working in a surgical department, two surgical oncologists (12%), and one nurse (6%) working in an oncology department. The main reasons were that HCP did not encounter patients eligible for GT (n = 11), colleagues discussed and/or ordered GT (n = 5), there was not enough time (n = 1), or no appropriate moment (n = 1) during consultations.

Evaluation of online training module and reasons for not completing the module

The median rating for the training was eight out of ten. The majority of HCPs considered the training to be useful (95%), appreciated the online format (99%) and considered the level of difficulty and duration to be exactly right (80% and 78%, respectively) (Supplementary materials). Six months after completing the training, 11% of HCPs (n = 6/53) indicated that, in retrospect, they had missed information in the training.

We received 27/51 (53%) questionnaires from HCPs who did not complete the online training. Their main reasons were having no time or being too busy (n = 17/27, 63%).

Discussion

In this study, we implemented mainstream GT for patients with breast cancer and show that surgical oncologists, nurse specialists and nurses in breast cancer care are ready to provide pre-test GC.

Attitudes, perceived knowledge, self-efficacy and knowledge

HCPs had a positive attitude, high self-efficacy and high perceived knowledge both before and after implementing our mainstream pathway. Previous research has shown conflicting results, with both HCPs having a positive attitude toward mainstream GT (17, 18, 24), but also expressing concern about their ability to provide adequate pre-test GC (13, 19, 21). A possible explanation for the positive attitude and high participation rate in our training is the close involvement of HCPs in shaping our new pathway. This allowed them to raise concerns and consider the new pathway.

After 6 months, the self-perceived knowledge of HCPs had improved regarding the advantages and disadvantages of GT and the consequences for family members. Therefore, we believe that our training had a positive influence on HCPs' confidence to provide pre-test GC as described in previous research (27, 28). Other studies evaluating the experiences of HCPs with mainstream GT have also shown that these HCPs are confident to consent patients for GT (17, 24). In addition, we found an improvement in self-perceived knowledge regarding the advantages and disadvantages of GT amongst gynecologic HCPs participating in mainstream GT for ovarian cancer, although due to the relatively small sample size, this was not a significant difference (25). Our training probably contributed to this effect, although we did not evaluate these outcomes in HCPs who did not complete a training module.

We did not measure an objective increase in knowledge after completing the training. However, overall knowledge scores were already high at baseline, suggesting a ceiling effect. Interestingly, one in four HCPs had worse overall knowledge scores 6 months after completing the training than at baseline. However, this decrease in knowledge was not significant. Especially, questions about the prevalence of detecting a pathogenic variant and the difference between blood and tumor GT seemed to have contributed to this. The question about the prevalence of a pathogenic variant might have been too specific, whereas the question about tumor GT might still be too difficult for HCPs in breast cancer care. Tumor testing is currently not used as a pre-screen for germline genetic testing, as

it is in ovarian cancer care (29). This is consistent with HCPs' self-efficacy; only a small majority felt confident to discuss the difference between blood and tumor testing. This suggests a specific training need when tumor testing becomes more prominent in the future. To our knowledge, no other studies have evaluated knowledge after implementing mainstream GT.

Feasibility of mainstream genetic testing

Timing of pre-test GC can be challenging, because at time of diagnosis emotions are high and patients already receive a lot of information (30, 31). This is also shown in the relatively high proportion of HCPs (33%) who did not feel confident to discuss GT directly after diagnosis. However, surgical decisions may require a timely test result (12). In our study, the majority of HCPs managed to discuss GT within 15 minutes, which they considered as or better than expected. This timeframe is comparable with previous research in which HCPs needed between 8 and 20 minutes for pre-test GC (22). The time to order a genetic test in our study was also less than 15 minutes for most HCPs. Although they still considered this time investment as or better than expected, the time to order a genetic test was one of the main reasons for a negative attitude. Therefore, this time investment should be reduced, for example, by delegating these tasks to outpatient staff. Most importantly, however, the total time investment required by HCPs to discuss and/or order GT was feasible for more than 80% of HCPs. This is in line with previous research in which HCPs agreed that it was possible to discuss GT within the timeframe of a consultation (22).

Notably, especially nurse specialists and nurses were closely involved in our mainstream genetic testing pathway. Before the implementation of this pathway, these HCPs were already actively involved in the referral of eligible patients to the genetics department under the supervision of surgical oncologists. This study shows that nurse specialists and nurses are well-equipped to perform these tasks and may play an important role in the implementation of a mainstream genetic testing pathway.

Evaluation of online training module and reasons for not completing the module

The majority of HCPs appreciated our training module, which is consistent with previous research (22). However, we did see a wide variation in overall appreciation, and some HCPs considered our training too easy. We included a wide variety of HCPs (nurses, nurse specialists, doctors) from different departments, that might explain differences in training needs (32, 33). Therefore, it might be useful to develop a more tailored training for each discipline. Only one HCP agreed that HCPs were capable of providing mainstream GT without training. This indicates that the HCPs in this study considered training a prerequisite for providing mainstream GT.

The main barrier for HCPs to refrain from participating was lack of time. These HCPs consisted mainly of doctors (e.g., surgical oncologists and medical oncologists). This implies that the success of mainstream GT mainly depends on the involvement of dedicated nurses and nurse specialists.

Strengths and limitations

A strength of this multicenter study is the large sample size, high participation rate and the before-and-after design. Also, prior to the development of our training module and mainstream GT pathway, we performed a needs assessment among all HCPs involved. We believe that the high participation of HCPs can partly be explained by the close collaboration both during the development and implementation phases.

A limitation is that we did not use validated questionnaires since these were non-existent. In addition, the majority of participating HCPs worked in a surgical department. Therefore, our conclusions cannot be generalized for all HCPs in breast cancer care. Although we invited medical oncologists to participate in our mainstream GT pathway, in our study, these HCPs rarely discussed and ordered GT themselves. This is notable, because previous research into mainstream GT in breast cancer care has shown significant involvement of oncologists between 30% and 100%, probably due to differences in care pathways (19, 34-37). In our study, patients eligible for GT were initially seen by the surgical team. However, the importance of GT by medical oncologists is expected to increase due to the rise of PARP-inhibiting therapies in carriers of germline *BRCA1/2* pathogenic variants (38). Future research should focus on experiences of medical oncologists and also on the impact of mainstream genetic testing on genetic testing rates.

Conclusion

This study shows that HCPs working in a surgical department (i.e., surgical oncologists, nurse specialists and nurses) have a positive attitude, feel confident, and capable to provide pre-test GC to patients with breast cancer. In addition, it is feasible for them to incorporate these tasks into their routine work.

Funding: AstraZeneca [grant number: AZNL201900216] and Pfizer [grant number: 54265341] partly funded the appointment of KB and thereby facilitated the implementation of the mainstream genetic testing pathway. They had no involvement in the study design, collection of data, analyses or writing the manuscript.

Acknowledgements: We thank all healthcare professionals and patient advocates for their contribution to the development of our mainstream genetic testing pathway and training module, including Sanne Stehouwer, Els van Riel, Bernou Huizenga, Sissi Grosfeld, Tineke Kempees, Desirée van den Bongard, Desirée Hairwassers, Nathalie Wittebolle, and Rhodé Bijlsma and volunteers from the Dutch Breast Cancer Society (BVN) and Oncogen. We also

thank all participating surgical oncologists, nurse specialists, nurses, medical oncologists and radiation oncologists from the University Medical Center Utrecht, Diakonessenhuis Utrecht, Meander Medical Center Amersfoort, St. Antonius Hospital Nieuwegein/Utrecht, Alexander Monro Hospital Bilthoven, Riverienland Hospital Tiel, St. Jansdal Hospital Harderwijk, Gelre Hospitals Apeldoorn, Beatrix Hospital Gorinchem, Wilhelmina Hospital Assen, Medical Center Leeuwarden, Martini Hospital Groningen, and Isala Clinics Zwolle. We thank Richard Brohet for his advisory role with respect to the statistical analyses.

References

1. Hu C, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. N Engl J Med. 2021;384(5):440-451.
2. Kurian AW, Hughes E, Handorf EA, Gutin A, Allen B, Hartman AR, et al. Breast and Ovarian Cancer Penetrance Estimates Derived From Germline Multiple-Gene Sequencing Results in Women. JCO Precis Oncol. 2017;1:1-12.
3. Tung N, Battelli C, Allen B, Kaldate R, Bhatnagar S, Bowles K, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. Cancer. 2015;121(1):25-33.
4. Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021;16(3):255-282.
5. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol. 2016;27(suppl 5):v103-v10.
6. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol. 2020;38(18):2080-2106.
7. Stoll K, Kubendran S, Cohen SA. The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. Am J Med Genet C Semin Med Genet. 2018;178(1):24-37.
8. Alberty-Oller JJ, Weltz S, Santos A, Pisapati K, Ru M, Weltz C, et al. Adherence to NCCN Guidelines for Genetic Testing in Breast Cancer Patients: Who Are We Missing? Ann Surg Oncol. 2021;28(1):281-286.
9. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National Estimates of Genetic Testing in Women With a History of Breast or Ovarian Cancer. J Clin Oncol. 2017;35(34):3800-6.
10. Hafertepen L, Pastorino A, Morman N, Snow J, Halaharvi D, Byrne L, et al. Barriers to genetic testing in newly diagnosed breast cancer patients: Do surgeons limit testing? Am J Surg. 2017;214(1):105-110.
11. Baars JE, van Dulmen AM, Velthuizen ME, Theunissen EB, Vrouenraets BC, Kimmings AN, et al. Migrant breast cancer patients and their participation in genetic counseling: results from a registry-based study. Fam Cancer. 2016;15(2):163-171.
12. Armstrong J, Lynch K, Virgo KS, Schwartz MD, Friedman S, Dean M, et al. Utilization, Timing, and Outcomes of BRCA Genetic Testing Among Women With Newly Diagnosed Breast Cancer From a National Commercially Insured Population: The ABOARD Study. JCO Oncol Pract. 2021;17(2):e226-e35.
13. Kurian AW, Li Y, Hamilton AS, Ward KC, Hawley ST, Morrow M, et al. Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer. J Clin Oncol. 2017;35(20):2232-2239.

14. Hoskovec JM, Bennett RL, Carey ME, DaVanzo JE, Dougherty M, Hahn SE, et al. Projecting the Supply and Demand for Certified Genetic Counselors: a Workforce Study. J Genet Couns. 2018;27(1):16-20.
15. Colombo N, Huang G, Scambia G, Chalas E, Pignata S, Fiorica J, et al. Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer. J Clin Oncol. 2018;36(13):1300-1307.
16. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.
17. Kemp Z, Turnbull A, Yost S, Seal S, Mahamdallie S, Poyastro-Pearson E, et al. Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer. JAMA Netw Open. 2019;2(5):e194428.
18. Douma KF, Smets EM, Allain DC. Non-genetic health professionals' attitude towards, knowledge of and skills in discussing and ordering genetic testing for hereditary cancer. Fam Cancer. 2016;15(2):341-350.
19. Lee YQ, Yoon SY, Hassan T, Padmanabhan H, Yip CH, Keng WT, et al. Attitudes and training needs of oncologists and surgeons in mainstreaming breast cancer genetic counseling in a low-to-middle income Asian country. J Genet Couns. 2022;31(5):1080-1089.
20. Eccles BK, Copson E, Maishman T, Abraham JE, Eccles DM. Understanding of BRCA VUS genetic results by breast cancer specialists. BMC Cancer. 2015;15:936.
21. Hallowell N, Wright S, Stirling D, Gourley C, Young O, Porteous M. Moving into the mainstream: healthcare professionals' views of implementing treatment focussed genetic testing in breast cancer care. Fam Cancer. 2019;18(3):293-301.
22. Bokkers K, Vlaming M, Engelhardt EG, Zweemer RP, van Oort IM, Kiemeney L, et al. The Feasibility of Implementing Mainstream Germline Genetic Testing in Routine Cancer Care-A Systematic Review. Cancers (Basel). 2022;14(4):1059.
23. Scheinberg T, Young A, Woo H, Goodwin A, Mahon KL, Horvath LG. Mainstream consent programs for genetic counseling in cancer patients: A systematic review. Asia Pac J Clin Oncol. 2021;17(3):163-177.
24. Richardson M, Min HJ, Hong Q, Compton K, Mung SW, Lohn Z, et al. Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System. Cancers (Basel). 2020;12(2).
25. Bokkers K, Zweemer RP, Koudijs MJ, Stehouwer S, Velthuizen ME, Bleiker EMA, et al. Positive experiences of healthcare professionals with a mainstreaming approach of germline genetic testing for women with ovarian cancer. Fam Cancer. 2022;21(3):295-304.
26. Claes E, Evers-Kiebooms G, Boogaerts A, Decruyenaere M, Denayer L, Legius E. Communication with close and distant relatives in the context of genetic testing for hereditary breast and ovarian cancer in cancer patients. Am J Med Genet A. 2003;116A(1):11-9.

27. Medendorp NM, van den Heuvel LM, Han PKJ, Hillen MA, Smets EMA. Communication skills training for healthcare professionals in providing genetic counseling: A scoping literature review. Patient Educ Couns. 2021;104(1):20-32.
28. Meiser B, Woodward P, Gleeson M, Kentwell M, Fan HM, Antill Y, et al. Pilot study of an online training program to increase genetic literacy and communication skills in oncology healthcare professionals discussing BRCA1/2 genetic testing with breast and ovarian cancer patients. Fam Cancer. 2022;21(2):157-166.
29. Vos JR, Fakkert IE, de Hullu JA, van Altena AM, Sie AS, Ouchene H, et al. Universal Tumor DNA BRCA1/2 Testing of Ovarian Cancer: Prescreening PARPi Treatment and Genetic Predisposition. J Natl Cancer Inst. 2020;112(2):161-169.
30. Ardern-Jones A, Kenen R, Eeles R. Too much, too soon? Patients and health professionals' views concerning the impact of genetic testing at the time of breast cancer diagnosis in women under the age of 40. Eur J Cancer Care (Engl). 2005;14(3):272-281.
31. Ormel I, Magalhaes M, Josephson D, Tracey L, Law S. How to know what to know: Information challenges for women in the diagnostic phase of breast cancer. Patient Educ Couns. 2021;104(1):179-185.
32. Crellin E, McClaren B, Nisselle A, Best S, Gaff C, Metcalfe S. Preparing Medical Specialists to Practice Genomic Medicine: Education an Essential Part of a Broader Strategy. Front Genet. 2019;10:789.
33. McClaren BJ, Crellin E, Janinski M, Nisselle AE, Ng L, Metcalfe SA, et al. Preparing Medical Specialists for Genomic Medicine: Continuing Education Should Include Opportunities for Experiential Learning. Front Genet. 2020;11:151.
34. Beard C, Monohan K, Cicciarelli L, James PA. Mainstream genetic testing for breast cancer patients: early experiences from the Parkville Familial Cancer Centre. Eur J Hum Genet. 2021;29(5):872-880.
35. Stromsvik N, Olsson P, Gravdehaug B, Luras H, Schlichting E, Jorgensen K, et al. "It was an important part of my treatment": a qualitative study of Norwegian breast Cancer patients' experiences with mainstreamed genetic testing. Hered Cancer Clin Pract. 2022;20(1):6.
36. McCuaig JM, Thain E, Malcolmson J, Keshavarzi S, Armel SR, Kim RH. A Comparison of Patient-Reported Outcomes Following Consent for Genetic Testing Using an Oncologist- or Genetic Counselor-Mediated Model of Care. Curr Oncol. 2021;28(2):1459-1471.
37. Grindedal EM, Jorgensen K, Olsson P, Gravdehaug B, Luras H, Schlichting E, et al. Mainstreamed genetic testing of breast cancer patients in two hospitals in South Eastern Norway. Fam Cancer. 2020;19(2):133-142.
38. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405.

Supplementary File

Content

Survey regarding needs assessment of non-genetic healthcare professionals involved in breast cancer care

Response: 51/89 (57%)

Supplementary Table 1. Characteristics of participating non-genetic healthcare professionals from nine hospitals

Characteristics	Total group, n = 51 n (%)
Disciplines,	
- Nurse specialist/physician assistant (in training)	17 (33.3)
- Surgical oncologist	14 (27.5)
- Medical oncologist	11 (21.6)
- Nurse	7 (13.7)
- Radiation oncologist	2 (3.9)
Hospital, n (%)	
- Non-academic teaching hospital	42 (82.4)
- Academic hospital	9 (17.6)
Years working in breast cancer care, n (%)	
- < 5	13 (25.5)
- 5 – 10	19 (37.2)
- 10 – 15	8 (15.7)
- > 15	11 (21.6)

Supplementary Table 2. Results of Survey, n = 51

Questions	Response categories	Responses n (%)
For which genetic testing eligibility criteria do you want to offer pre-test counseling and order genetic testing yourself?	- Offer mainstream genetic testing to all patients eligible for genetic testing	13 (26)
	- Offer mainstream genetic testing only to a selected group: patients with breast cancer < 40 years and triple negative breast cancer < 60	16 (31)
	- Initially start with mainstream genetic testing in a selected group (bullet 2) and at a later stage expand to all eligibility criteria for genetic testing	21 (41)
	- I do not know	1 (2)
	- No preference	0
If mainstreaming is not applied (immediately) to all eligibility criteria, what is your preference for patients who are eligible for genetic testing but not for mainstream genetic testing?	- Referral of these patients to the genetics department	36 (71)
	- The medical specialist/nurse specialist provides general information about genetic testing, arranges for blood storage and conducts a telephone consultation with a genetic healthcare professional	13 (25)
	- I do not know	1 (2)
	- No preference	1 (2)
Do you think the medical specialist/nurse specialist should also ask about other cancers/other symptoms related to rarer hereditary causes of breast cancer?	- Yes	28 (55)
	- No	10 (20)
	- I do not know	10 (20)
	- No preference	3 (6)
Are you willing to ask for more comprehensive family information and not just ask about breast, ovarian and prostate cancer in the family?	- Yes	35 (68)
	- No	8 (16)
	- I do not know	5 (10)
	- No preference	3 (6)
Are you willing to measure a skull circumference?	- Yes	14 (27)
	- No	31 (61)
	- I do not know	6 (12)
	- No preference	0

When a pathogenic variant or variant of uncertain clinical significance is found, patients receive post-test counseling at the genetics department to discuss the result and its implications. Which patients do you think should also receive post-test counseling from a genetics counselor when no pathogenic variant or variant of unknown clinical significance is found in a breast cancer gene?	-	All patients, regardless of family history	7 (14)
	-	Only patients with a family history of breast cancer	2 (4)
	-	Only patients with a family history of breast cancer and/or indicators of a rare tumor syndrome	41 (80)
	-	No preference	0
	-	I do not know	1 (2)
In your opinion, how should duties be divided between medical specialists and nurse specialists with respect to mainstream genetic testing?	-	The medical specialist provides pre-test counseling and assesses the family history	2 (4)
	-	The nurse (specialist) provides pre-test counseling and assesses the family history	21 (41)
	-	The medical specialists provides pre-test counseling and the nurse (specialists) assesses the family history	5 (10)
	-	The nurse (specialist) provides pre-test counseling and the medical specialist assesses the family history	1 (2)
	-	Both medical specialist and nurse (specialist) perform pre-test counseling and assess the family history	9 (17)
	-	Referral of patient to genetics department	3 (6)
	-	No preference	8 (16)
	-	I do not know	2 (4)

Supporting information regarding online training module

Content of online training module

The training module was evaluated and accredited by the national accreditation bureaus of the scientific organizations for surgical oncologists, medical oncologists, nurses, and nurse specialists as part of the national CME accreditation.

Film 1: Mainstream genetic testing in cancer patients (duration: 7.5 minutes).

This film contains the following elements:

- Short introductory film with a clinical geneticist explaining the term mainstream genetic testing and why this new workflow is important for cancer patients.
- Slides with a voice-over explaining:
  - Short overview of the content of all four films.
  - How cancer develops and how hereditary and environmental factors play a role.
  - The difference between germline and somatic pathogenic variants.
  - The difference between germline genetic testing in blood and genetic testing in tumor tissue.
  - The importance of genetic testing in cancer patients.
  - The difference between diagnostic and predictive genetic testing.
  - A summary of the above.

Film 2: genetic testing in breast cancer patients (duration: 12.5 minutes).

This film contains the following elements:

- Short introductory film with a clinical geneticist giving an overview of the film's content.
- Slides with a voice-over explaining:
  - Prevalence of hereditary causes in breast cancer patients.
  - The eligibility criteria for genetic testing in breast cancer patients, including the relevance of genetic testing in patients with Ashkenazi Jewish ancestry.
  - The prevalence of pathogenic variants in the genes *BRCA1, BRCA2, CHEK2, ATM,* and *PALB2.*
  - Cancer risks associated with pathogenic variants in the genes *BRCA1, BRCA2, CHEK2, PALB2,* and *ATM*.
  - Explanation of life time risks.
  - Possible implications of genetic testing for family members (including screening recommendations and the possibility of risk reducing surgery).

- Possible implications on treatment for women carrying a pathogenic variant in one of the breast cancer genes.
- Male breast cancer; chance of carrying a pathogenic variant in one of the breast cancer genes, cancer risks and possible implications of finding a pathogenic variant.
- Pattern of inheritance for pathogenic variants in the genes *BRCA1, BRCA2, CHEK2, PALB2,* and *ATM*.
- Involvement of higher risk of breast cancer in rare syndromes.
- A summary of the above.

Film 3: The new workflow for genetic testing (duration: 8.5 minutes)

This film contains the following elements:

- Short introductory film with a clinical geneticist giving an overview of the film's content.
- Sides with a voice-over explaining:
  - The entire workflow (step-by-step).
  - How to complete the checklist to determine eligibility for genetic testing.
  - How to complete the checklist to determine if the patient is eligible for referral to the genetics department.
  - How to complete the informed consent form.

Film 4: Practical advice on how to discuss genetic testing (duration: 15.5 minutes)

This film contains the following elements:

- Short introductory film with a clinical geneticist giving an overview of the film's content.
- Slides with a voice-over explaining:
  - Communication about and timing of genetic testing.
  - Elements to discuss with a patient, including the duration of a genetic test.
  - Possible outcomes of a genetic test and the implications of these outcomes.
  - Possible implications for insurance.
- Film with:
  - A surgical oncologist and a patient. This shows a simulation consultation on how to offer pre-test counseling for genetic testing.
  - A patient who has a pathogenic variant in the BRCA2 gene. She explains the impact that genetic testing has had on her and her family and why genetic testing is important for any woman with breast cancer.
  - A specialist social worker. She explains the impact a pathogenic variant in a *BRCA*

gene can have on a patient and her family members, addresses the emotional impact and explains the supportive role of a social worker in the process of genetic testing.

Supplementary Table 3. Evaluation of overall online training module, n = 85

Rating out of 10, median (range)	8 (5 – 10)
Usefulness of online training module, n (%)	
- (Reasonably/very) useful	81 (95.3)
- Not useful (at all)	4 (4.7)
Level of difficulty, n (%)	
- (Much) too high	0 (0)
- Exactly right	68 (80.0)
- (Much) too low	17 (20.0)
Appreciation of online format, n (%)	
- (Fairly/very) pleasant	84 (98.8)
- Not pleasant (at all)	1 (1.2)
Duration of online training module, n (%)	
- (Much) too long	14 (16.5)
- Exactly right	66 (77.6)
- (Much) too short	5 (5.9)

Supplementary Table 4. Reasons for not completing the training module, n = 27/51 (52.9%)

	N (%)
Respondents	
- Surgical oncologists	12 (44.4)
- Medical oncologists	9 (33.3)
- Nurses/nurse specialists working in an oncology department	4 (14.8)
- Nurses/nurse specialists working in a surgical department	1 (3.7)
- Radiation oncologists	1 (3.7)
Reasons for not completing the training module (multiple answers could be provided)	
- No time/too busy	17 (63.0)
- Forgotten	8 (29.6)
- Mainstream genetic testing should not be part of my work[a]	7 (25.9)
- Technical problems with training module	3 (11.1)
- Genetic testing is requested by colleagues	2 (7.4)
- Encounter not enough patients eligible for genetic testing to build expertise	1 (3.7)

There were no significant differences between the respondents and non-respondents regarding disciplines or department they worked in. [a] HCPs who did not consider mainstream genetic testing as part of their work, mainly considered this as part of the work of a surgical nurse/nurse specialist (n = 6) or genetic HCP (n = 4).

Checklists to identify eligible patients for genetic testing and post-test counseling

1

Checklist 1: Eligibility criteria for genetic testing in breast cancer

UMC Utrecht

Patient details	Date of diagnosis: ..... Hospital: ..... Surgical oncologist:..... Nurse (specialist):..... Email address: ..... Telephone number:.....

CHECKLIST risk factors for hereditary cause breast cancer /DCIS	**Yes**	**No**
Male	☐	☐
< 40 years of age	☐	☐
< 50 years of age and:		
* bilateral breast cancer (whether or not diagnosed at the same time)	☐	☐
* a first-degree family member with breast cancer < 50 years of age	☐	☐
* a family member with prostate cancer < 60 years of age	☐	☐
* two or more first or second degree family members with breast cancer in the same branch of the family?	☐	☐
< 60 years of age and:		
* triple negative breast cancer	☐	☐
Does patient have:		
* a family member with a known *BRCA1/2* pathogenic variant	☐	☐
* a history of contralateral breast cancer < 50 years of age	☐	☐
* multiple tumors in one breast with first tumor < 50 years of age	☐	☐
* a first-degree male family member with breast cancer	☐	☐
* two or more first and/or second degree family members with breast cancer of whom at least one < 50 years of age, in the same branch of the family	☐	☐
* a history of ovarian or fallopian tube carcinoma	☐	☐
* a family member with ovarian or fallopian tube carcinoma	☐	☐
* a Jewish ancestry	☐	☐

'yes' for at least 1 grey shaded criterion?	➔ continue with **checklist 2** to determine if you can offer pre-test genetic counseling and order genetic testing
'yes' for only white shaded criteria?	➔ refer patient to genetics department and skip **checklist 2.** Pre-test genetic counseling is offered by a genetic healthcare professional
'no' for all eligibility criteria?	➔ patient is not eligible for genetic testing

Have you ordered genetic testing? ☐ Yes ☐ No

In case of a referral, is it urgent? ☐ Yes ☐ No

Please fax this list including all relevant correspondence and pathology report to the genetics department of the University Medical Center Utrecht.

Was a treatment plan discussed with patient? ☐ No ☐ Yes

If yes, which plan? ☐ mastectomy ☐ breast conserving surgery ☐ Neoadjuvant chemotherapy

Is the operation date known? ☐ No ☐ Yes, on .....

Does patient want to postpone the surgery date if the result of the genetic test is not yet known ☐ No ☐ Yes ☐ Not discussed

At which phone number(s) can the patient be reached? ..... / .....

Additional information .....

.....

.....

2 **Only complete this checklist if you answered 'yes' for at least one of the grey shaded criteria on checklist 1!**

UMC Utrecht

Checklist 2: referral to genetics department

Patient details	Date: ..... Hospital: ..... Surgical oncologist:..... Nurse (specialist):..... Email address: ..... Telephone number:.....

	Yes	No
Does your patient have:		
1. breast cancer/DCIS ≤25 years of age?	☐	☐
2. breast cancer ≤35 years of age and Her2neu positive?	☐	☐
3. bilateral *lobular* breast cancer (whether or not diagnosed at the same time) with first diagnosis <50 years?	☐	☐
4. a family member with a known pathogenic variant in one of the breast cancer genes?	☐	☐
5. (a history of) sarcoma, brain tumor or adrenal cortex		
a) in your patient, with first diagnosis <46 years of age for one of these tumors or the breast cancer?	☐	☐
b) in ≥1 first or second degree family member, with diagnosis <46 year for family member or for your patient with breast cancer?	☐	☐

If 'yes for one or more of these questions → refer patient to genetics department for pre-test genetic counseling. You do not have to complete the rest of this checklist.

	Yes	No
Does your patient have:		
6. a first or second degree family member with breast cancer and is your patient male?	☐	☐
7. a second primary breast cancer/DCIS with first diagnosis <50 years of age?*	☐	☐
8. a first or second degree family member with breast cancer/DCIS and is the average age of diagnosis for patient and family member <50 years of age?	☐	☐
9. ≥2 first and/or second degree family members with breast cancer/DCIS?	☐	☐
10. ≥2 first and/or second degree family members with ovarian cancer? (of whom at least one first degree family member)	☐	☐

You can now offer pre-test genetic counseling and request the DNA test **(note: this applies only if the first five questions on this checklist can be answered with 'no' and at least one grey shaded criterion on checklist 1 is 'yes').**
If you have checked one or more boxes with "yes," the patient will receive an additional appointment at the genetics department after the results of the DNA test are known. You do not have to do anything for this yourself. This checklist is faxed to the genetics department and can be used as a formal referral document.

** This includes a second primary tumor diagnosed at the same or different times, multiple tumors in the same breast or in both breasts and multicentric breast cancer.*

Please add this checklist to the electronic patient file

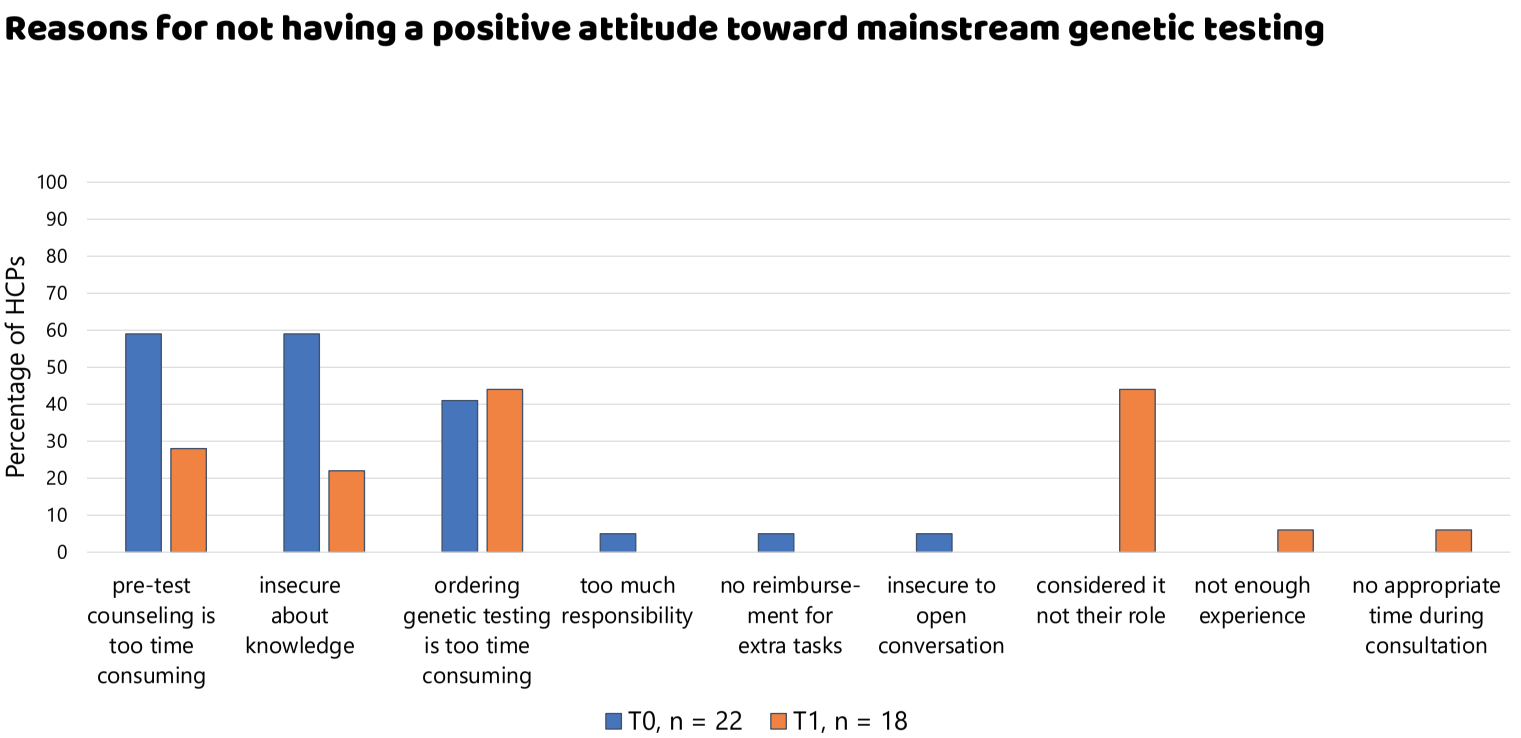
Please contact the genetics department if you have any questions about this checklist or if you think there might be a reason to refer your patient and this is not indicated by this checklist. (original checklist included telephone numbers)

Content of questionnaires

Supplementary Table 5. Overview of questions in the T0 and T1 questionnaire

Topics	T0	T1
Background information	X	
Statements to assess		
- Attitude towards mainstream genetic testing	X	X
- Perceived knowledge of genetic testing	X	X
- Self-efficacy to offer mainstream genetic testing	X	X
Questions assessing knowledge of genetic testing	X	X
Feasibility of mainstream genetic testing		
- Performance of tasks, time investment and necessity of additional appointments		X
- Experiences with supporting resources (e.g., usefulness of training or manual, unanswerable questions from patients, missed information)		X
- Reasons for not discussing genetic testing	X	X

T0 Questionnaire before starting the online training module. *T1* Questionnaire six months after completing the online training module.



Supplementary Figure 1. Reasons of non-genetic healthcare professionals in breast cancer care for not having a positive attitude toward mainstream genetic testing before (T0) and six months after completing the training module (T1)
Multiple reasons could be given. Since the T0 questionnaire was completed before experiencing mainstream genetic testing, the answers about time investment for pre-test genetic counseling and ordering genetic testing were based on HCPs' expectations, starting with 'I think…'

Additional information regarding feasibility for non-genetic HCPs to incorporate germline genetic testing into routine care of breast cancer patients

Supplementary Table 6. Additional appointments for pre-test genetic counseling, receiving unanswerable questions from patients, usefulness of supporting resources

	T1, n = 53 n (%)	Reasons/explanations:
Additional appointments for pre-test genetic counseling		- Patient needed time to consider the genetic test (n = 15) - There was not enough time during one consultation (n = 7) - Patient needed to get clarity regarding family history (n = 1)
- Yes	18 (34.0)	
- No	35 (66.0)	
Unanswerable questions		- Detailed consequences of a pathogenic variant for patient or family members (n = 3) - The chance of having an hereditary cause (n = 1) - Eligibility criteria (n = 1) - How to proceed if there is a more complex family history (n = 2) - How to proceed if there is a family history of cancer but no hereditary cause (n = 1)
- Yes	9 (17.0) [a]	
- No	44 (83.0)	
I considered it useful to receive information about genetic testing (e.g., the online training module and manual) before providing pre-test genetic counseling myself		N/A
- (Strongly) agree	49 (92.4)	
- Neutral/ (strongly) disagree	2 (3.8)	
- Missing	2 (3.8)	
I considered it useful to give written information about genetic testing to the patient after pre-test counseling		N/A
- (Strongly) agree	47 (88.7)	
- Neutral/ (strongly) disagree	4 (7.5)	
- Missing	2 (3.8)	

N/A not applicable. [a] One HCP could not specify which questions were unanswerable.

Supplementary Table 7. Performance of tasks and time investment for providing pre-test genetic counseling and ordering a genetic test

	n (%)
Performance of tasks, n = 53	
- Pre-test genetic counseling and ordering genetic test	38 (71.7)
- Pre-test genetic counseling only	7 (13.2)
- Ordering genetic test only	5 (9.4)
- Other	3 (5.7)
Time investment to offer pre-test genetic counseling, n = 45	
- < 5 minutes	2 (4.5)
- 5 – 10 minutes	23 (51.1)
- 10 – 15 minutes	15 (33.3)
- 15 – 20 minutes	5 (11.1)
- > 20 minutes	0 (0)
Time investment to order genetic test, n = 43	
- < 5 minutes	2 (4.7)
- 5 – 10 minutes	18 (41.9)
- 10 – 15 minutes	17 (39.5)
- 15 – 20 minutes	5 (11.6)
- > 20 minutes	1 (2.3)

Chapter 7

Patients' experiences with pre-test genetic counseling provided by breast cancer healthcare professionals: results from a large prospective multicenter study

Kyra Bokkers [1], Eveline M.A. Bleiker [2,3,4], Mary E. Velthuizen [1], Ron Koelemij [5], Josephina P.J. Burgmans [6], Jean H. Klinkenbijl [7], Arjan P. Schouten van der Velden [8], Nieke Vermulst [5,9], Bernou F. Huizinga [10], Arjen J. Witkamp [11], Tanja Frakking [12], Richard M. Brohet [13], Cora M. Aalfs [1], Wouter Koole [1], Ernst J.P. Schoenmaeckers [14], and Margreet G.E.M. Ausems [1]

Breast. 2023 Mar 29;69:349-357. Online ahead of print after minor revisions.

1. Division Laboratories, Pharmacy and Biomedical Genetics, Dept. of Genetics,
University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
2. Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute,
Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
3. Family Cancer Clinic, The Netherlands Cancer Institute,
Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
4. Department of Clinical Genetics, Leiden University Medical Center,
Albinusdreef 2, 2333 ZA Leiden, The Netherlands
5. Department of Surgery, St. Antonius Hospital, Soestwetering 1, 3543 AZ Utrecht, The Netherlands
6. Department of Surgery, Diakonessenhuis, Bosboomstraat 1, 3582 KE Utrecht, The Netherlands
7. Department of Surgery, Gelre Hospitals, Albert Schweitzerlaan 31,
7334 DZ Apeldoorn, The Netherlands
8. Department of Surgery, St. Jansdal Hospital,
Wethouder Jansenlaan 90, 3844 DG Harderwijk, The Netherlands
9. Department of Surgery, Rivierenland Hospital,
President Kennedylaan 1, 4002 WP Tiel, The Netherlands
10. Department of Surgery, Alexander Monro Hospital,
Professor Bronkhorstlaan 10, 3727 MB Bilthoven, The Netherlands
11. Department of Surgery, University Medical Center Utrecht,
Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
12. Department of Surgery, Beatrix Hospital,
Banneweg 57, 4204 AA Gorinchem, The Netherlands
13. Department of Epidemiology and Statistics, Isala Hospital,
Dokter van Heesweg 2, 8025 AB Zwolle, The Netherlands
14. Department of Surgery, Meander Medical Center, Maatweg 3, 3813 TZ Amersfoort, The Netherlands

Abstract

Background*:* Pre-test genetic counseling of patients with breast cancer is increasingly being offered by non-genetic healthcare professionals.

Methods*:* We evaluated experiences of patients with breast cancer who received pre-test counseling from their surgeon or nurse (mainstream group) in comparison to experiences of patients who received pre-test counseling from a clinical geneticist (usual care group). Between September 2019 and December 2021, patients received a questionnaire after pre-test counseling (T0) and four weeks after receiving their test results (T1) to evaluate psychosocial outcomes, knowledge, discussed topics and satisfaction.

Results*:* We included 191 patients in our mainstream and 183 patients in our usual care group and received, respectively 159 and 145 follow-up questionnaires. Levels of distress and decisional regret were comparable in both groups. Decisional conflict was higher in our mainstream group ($p = 0.01$), but only 7% had clinically relevant decisional conflict (vs 2% in usual care group). The possible implications of a genetic test on (secondary) breast or ovarian cancer risks were less frequently discussed in our mainstream group ($p = 0.03$ and $p = 0.000$, respectively). In both groups knowledge about genetics was comparable, satisfaction was high and the majority of patients in both groups preferred to give both verbal and written consent for genetic testing.

Conclusion*:* Mainstreamed genetic care provides sufficient information for the majority of breast cancer patients to decide about genetic testing with minimal distress.

Keywords: Breast cancer; Patients' perspectives; mainstream genetic testing; Genetic counseling; Psychosocial outcomes; Satisfaction

Introduction

Genetic test results in patients with breast cancer can impact both patients' treatment and preventive options. Especially pathogenic variants in a *BRCA1/2* gene can influence these choices (1, 2). Previously, only surgical treatment was impacted by genetic test results, such as risk-reducing mastectomy of the contralateral breast (3). Nowadays, systematic treatment options are also influenced by these test results. Patients with a pathogenic variant in a *BRCA1/2* gene have shown to respond well to treatment with platinum-based chemotherapy in triple-negative breast cancer and to Poly Adenosine Diphosphate-Ribose Polymerase (PARP) inhibitors in Her2-negative breast cancer (4-6). With these increasing implications of genetic testing on treatment, there is also an increase in the number of eligible patients (7). However, the workforce of genetics departments is insufficient to meet this growing demand (8, 9).

This imbalance between supply and demand has led to innovative ways of offering genetic testing. This includes the mainstreaming of genetic testing, with non-genetic healthcare professionals (HCPs) such as surgeons, oncologists and nurses providing pre-test genetic counseling and ordering genetic tests, instead of usual genetic care provided by genetic HCPs (i.e., clinical geneticists and genetic counselors) (10, 11). Mainstream genetic testing pathways have been successfully introduced for ovarian cancer (12, 13). Given the high acceptability and feasibility for both patients and HCPs, these pathways are increasingly being implemented for breast cancer (14-24).

Pre-test counseling by a non-genetic HCP is different from pre-test counseling by a genetic HCP because of differences in expertise and available time. This raises concerns that with mainstream genetic testing informed consent may not be obtained, it may lead to increased psychosocial problems (e.g., more distress or regret), or patients may receive insufficient information to make an informed decision about genetic testing. So far, studies have shown positive experiences in breast cancer patients (16-18, 21, 23, 24). However, these studies were either qualitative in nature (18, 23), focused only on acceptability (16), did not compare experiences with a group of patients receiving usual genetic care (16, 18, 23), or involved only a limited number of breast cancer patients (16, 17, 24). To our knowledge, no studies have evaluated outcomes such as distress and anxiety at different time points between patients who received pre-test counseling from different HCPs (non-genetic versus genetic).

We have developed and implemented a mainstream genetic testing pathway for patients with breast cancer. We recently reported that surgical oncologists and nurse specialists feel motivated and competent to provide pre-test counseling to patients with breast cancer (25). In the current paper, we report on the experiences of patients with mainstream

genetic testing. We aimed to assess patients' psychosocial outcomes, knowledge about genetics and satisfaction both after pre-test genetic counseling and after receiving the genetic test result and to compare these outcomes with patients who received usual genetic care.

Patients and methods

Study design and participants

First, our mainstream genetic testing pathway for breast cancer was implemented as standard care in nine hospitals (25). In the current multicenter, prospective, observational study, we evaluated patients' experiences with mainstream genetic testing and compared these with experiences of patients who received usual genetic care. Between September 2019 and December 2021, patients who received pre-test genetic counseling from a non-genetic HCP were invited to participate in our mainstream group and patients who received pre-test genetic counseling from a genetic HCP were invited to participate in our usual care group (Figure 1). Both newly diagnosed patients and patients with breast cancer in their history could participate. After pre-test counseling, patients could opt for genetic testing (*BRCA1, BRCA2, CHEK2, PALB2*, and *ATM).* Patients were excluded if they did not speak Dutch, if a pathogenic variant in one of the breast cancer susceptibility genes had been previously identified in a family member, or if the patient had had testing of some of these genes previously.

Mainstream genetic care pathway

The development and implementation of our mainstream pathway is described previously (25). After completing an online training module, non-genetic HCPs could provide pre-test counseling and order genetic tests themselves (Figure 1). In our study, this was predominantly performed by HCPs working at a surgical department. Two checklists were completed to determine eligibility for mainstream genetic testing (25). In addition, these checklists identified patients who required post-test genetic counseling. Patients were eligible for mainstream genetic testing if (1) eligibility for genetic testing could be determined independent of family data, and (2) further evaluation at a genetics department prior to testing was unnecessary (e.g., for counseling and testing of the *TP53* gene). After pre-test counseling, HCPs handed out an information sheet about genetic testing to patients and obtained written informed consent before ordering the genetic test. The two checklists and the consent form were sent to the genetics department of the UMC Utrecht.

Test results were sent in a letter by the genetics department to the patient, the HCP who ordered the genetic test and the general practitioner. Patients received an invitation for

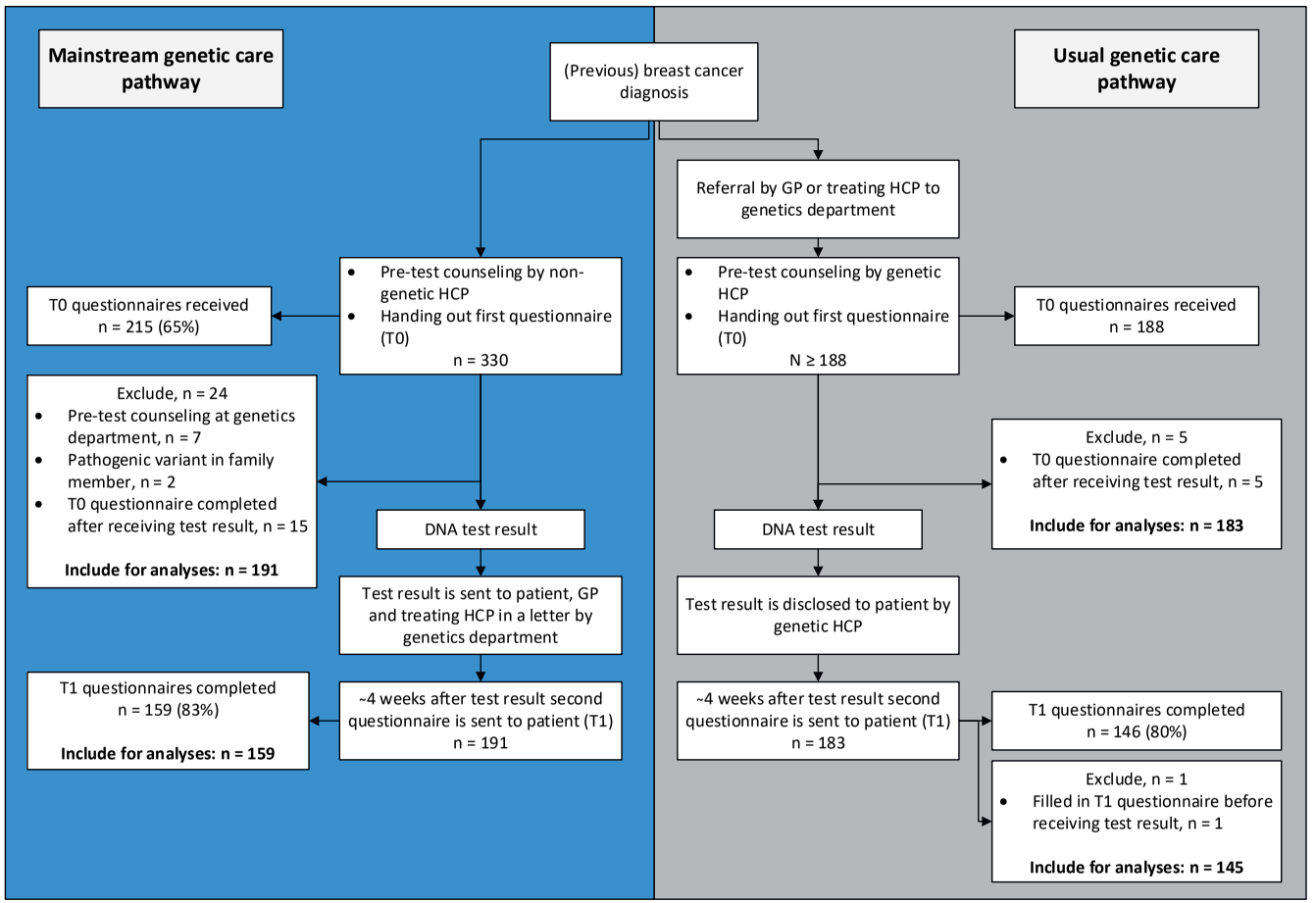


Figure 1. Mainstream and usual genetic care for breast cancer patients including response rates
GP general practitioner, *HCP* healthcare professional.

post-test counseling by a genetic HCP if a (likely) pathogenic variant or variant of uncertain clinical significance was identified. Patients also received this invitation if they had a relevant personal or family history, as identified by the checklist, to receive appropriate screening recommendations for their family members.

Usual genetic care pathway

Patients were referred by their treating physician or nurse to the genetics department if this HCP had not (yet) completed the training or if patients' eligibility for genetic testing depended on family data (i.e., relatives affected with breast, ovarian or prostate cancer). Referred patients received pre-test counseling from a genetic HCP, who collected more details about the family to confirm eligibility for testing. Written informed consent was obtained for all patients who consented to genetic testing. Genetic test results were communicated to the patient by telephone, in person or in a videoconference. In addition, a letter was sent to the patient, the HCP who referred the patient and the general practitioner, summarizing the family history, test results, and any advice for patient and family members.

Procedures

Participants were asked to complete two questionnaires (overview of topics in Online Supplements). The first questionnaire (T0) was handed out after pre-test counseling if counseling was provided face-to-face. For the usual care group, this questionnaire could also be sent with the letter summarizing the pre-test counseling. Information about the study and a form to accept or decline participation were sent with this questionnaire. After two weeks, written reminders were sent to non-responders of our mainstream group only. The second questionnaire (T1) was sent approximately four weeks after receiving the genetic test result. Written reminders were sent to non-responders of both groups after four weeks and telephone reminders after eight weeks.

Our primary outcomes were the impact of mainstream genetic testing on psychosocial outcomes (i.e., distress, anxiety, depression, decisional conflict and decision regret). Secondary outcomes were patients' knowledge, the topics discussed during pre-test counseling, and patients' satisfaction with the genetic testing process, including the informed consent procedure.

Clinical data

At the genetics department of the UMC Utrecht, we reviewed the medical records of all participants to obtain their age at diagnosis, number of days between diagnosis and pre-test counseling, test result and eligibility criteria for genetic testing. The date of pre-test counseling for the mainstream group was determined by proxy based on the date the checklist was completed; if that was unavailable, we used the date the consent form

was completed. We assessed whether patients were eligible for genetic testing according to national guideline criteria and, if they were eligible, which criteria they fulfilled (26). Eligibility for genetic testing was assessed based on the family pedigree for all patients in the usual care group and for the patients in the mainstream group who had received post-test counseling at the genetics department. For the other patients in the mainstream group, eligibility for genetic testing was assessed based on the completed checklist.

Statistical analyses

Between-group analyses were performed using the Chi-square test or Fishers Exact test for categorical outcomes and the independent T-test or Mann-Whitney U test for continuous outcomes. Within-group analyses comparing outcomes between T0 and T1 were assessed with the McNemar test for binary outcomes or the Wilcoxon-signed Rank test for continuous outcomes. General Linear Models for repeated measures were used to compare if the difference in anxiety, depression, distress and knowledge were comparable in the mainstream and usual care group over time. We used multivariate analysis to assess the differences in anxiety, distress and decisional conflict, stratified for the differences in characteristics between the two groups and adjusting for correlating variables. IBM SPSS statistics 26.0.0.1 was used to perform the statistical analyses. A (two-sided) p-value <0.05 was considered as significant.

Results

Participants

After exclusion of ineligible patients, 191 patients were included in our mainstream group and 183 patients in our usual care group, of whom respectively 159 (83%) and 146 (80%) patients completed both questionnaires (Figure 1). The usual care group included significantly more patients with children. The mainstream group included significantly more patients who received pre-test counseling within two weeks after diagnosis, more male patients, and their eligibility was more often based on patient criteria (Table 1).

Psychosocial outcomes

After pre-test counseling, levels of anxiety, distress and decisional conflict were significantly higher for patients in the mainstream group compared with patients in the usual care group (Table 2). After adjusting for the number of days between diagnosis and pre-test counseling with multivariate analysis, this difference between the two groups regarding anxiety and distress disappeared (respectively, $p = 0.53$ and $p = 0.62$). The higher decisional conflict in our mainstream group remained significant after adjustment for time between diagnosis and pre-test counseling, having children and the differences in eligibility criteria between the two groups ($p = 0.02$).

Table 1. Characteristics of respondents

	Mainstream group n = 191	Usual care group n = 183	p-value
Age at diagnosis, mean (sd)	48.7 (11.8)	50.3 (11.0)	0.184
Gender, n (%)			
- Male	10 (5.2)	1 (0.5)	0.01*
- Female	181 (94.8)	182 (99.5)	
Days between diagnosis and pre-test genetic counseling, n (%)			
- 0 – 14	160 (83.8)	49 (26.8)	0.000*
- > 14	31 (16.2)	134 (73.2)	
Previously diagnosed with BC, n (%)			
- Yes	35 (18.3)	26 (14.2)	0.28
- No	156 (81.7)	157 (85.8)	
Genetic test results, n (%)			
- Normal	170 (89.0)	165 (90.2)	0.71
- Pathogenic variant or VUS	21 (11.0)	18 (9.8)	
Children, n (%)			
- Yes	146 (76.4)	155 (84.7)	0.04*
- No	45 (23.6)	28 (15.3)	
Education, n (%)			
- Low	4 (2.1)	6 (3.3)	0.31
- Intermediate	91 (47.6)	100 (54.6)	
- High	93 (48.7)	77 (42.1)	
- Missing	3 (1.6)	0	
Migrant status, n (%)			
- Dutch background	168 (88)	159 (86.9)	0.94
- Migrant, Western	12 (6.3)	12 (6.6)	
- Migrant, non-Western	10 (5.2)	11 (6.0)	
- Missing	1 (0.5)	1 (0.5)	
Personal history of another type of cancer, n (%)			
- Yes	26 (13.6)	29 (15.8)	0.54
- No	165 (86.4)	154 (84.2)	

Eligibility criteria for genetic testing, n (%)			
- BC <40 years			
- Yes	58 (30.4)	35 (19.1)	0.01*
- No	133 (69.6)	148 (80.9)	
- Triple-negative BC <60 years			
- Yes	61 (31.9)	23 (12.6)	0.000*
- No	130 (68.1)	160 (87.4)	
- Multiple tumors with 1st diagnosis <50 years			
- Yes	42 (22.0)	29 (15.8)	0.13
- No	149 (78.0)	154 (84.2)	
- Personal history of OC			
- Yes	1 (0.5)	0	1.00
- No	190 (99.5)	183 (100)	
- Jewish background			
- Yes	6 (3.1)	3 (1.6)	0.50
- No	185 (96.9)	180 (98.4)	
- Eligible based on family history			
- Yes	33 (17.3)	53 (29.0)	0.007*
- No	158 (82.7)	130 (71.0)	
- Eligible according to guidelines			
- Yes	172 (90.1)	130 (71.0)	0.000*
- No	19[a] (9.9)	53 (29.0)	

BC breast cancer, *VUS* variant of uncertain clinical significance, *OC* ovarian cancer. [a] 8/19 (42%) DNA tests were conducted in the mainstream group with consent of a genetic healthcare professional. * $p < 0.05$.

After receiving test results, there were no significant differences for most psychosocial outcomes except for the 'support and effective decision' score of the decisional conflict scale. Within the mainstream and usual care group, there was a significant decrease in anxiety (respectively, $p = 0.000$ and $p = 0.000$) and decisional conflict (respectively, $p = 0.000$ and $p = 0.03$) after receiving the test result (Online Supplements). Within the mainstream group, distress levels significantly decreased after receiving the test results ($p = 0.001$, Online Supplements).

Table 2. Comparison of psychosocial outcomes between groups at T0 and T1

	T0			T1		
Variable	**Mainstream group n = 191**	**Usual care group n = 183**	**p-value**	**Mainstream group n = 159**	**Usual care group n = 145**	**p-value**
HADS-Anxiety, median (IQR)						
- Total score	7.0 (7.0)	5.0 (7.0)	0.002*	5.0 (6)	4.0 (5)	0.17
Subgroups, n (%)						
- 0 – 7	101 (52.9)	122 (66.7)	0.022*	115 (72.3)	113 (77.9)	0.48
- 8 - 10	38 (19.9)	21 (11.5)		28 (17.6)	23 (15.9)	
- 11 – 21	50 (26.2)	39 (21.3)		15 (9.4)	9 (6.2)	
- Missing	2 (1.0)	1 (0.5)		1 (0.6)	0	
HADS-Depression, median (IQR)						
- Total score	3.0 (5.0)	3.0 (5.0)	0.58	4.0 (4.0)	4.0 (4.0)	0.47
Subgroups, n (%)						
- 0 – 7	155 (81.2)	148 (80.9)	0.96	135 (84.9	118 (81.4)	0.62
- 8 - 10	19 (9.9)	20 (10.9)		14 (8.8)	16 (11.0)	
- 11 – 21	15 (7.9)	14 (7.7)		9 (5.7)	11 (7.6)	
- Missing	2 (1.0)	1 (0.5)		1 (0.6)	0	
Distress Thermometer, median (IQR)						
- Total score	6.0 (4.0)	4.0 (5.0)	0.01*	4.0 (4.0)	4.0 (4.0)	0.46
Subgroups, n (%)						
- ≤ 3	55 (28.8)	73 (39.9)	0.01*	66 (41.5)	69 (47.6)	0.26
- ≥ 4	135 (70.7)	104 (56.8)		93 (58.5)	75 (51.7)	
- Missing	1 (0.5)	6 (3.3)		0	1 (0.7)	
Influence of genetic testing on tension or distress, n (%)						
- Yes, less tension or distress	2 (1.0)	4 (2.2)	0.63	9 (5.7)	10 (6.9)	0.82
- No	134 (70.2)	122 (66.7)		89 (56.0)	77 (53.1)	
- Yes, more tension or distress	54 (28.3)	54 (29.5)		60 (37.7)	57 (39.3)	
- Missing	1 (0.5)	3 (1.6)		1 (0.6)	1 (0.7)	

Decisional conflict, median (IQR)						
Total score	20.3 (18.8)	15.6 (18.8)	0.01*	15.0 (20.0)	13.3 (20.0)	0.14
Subgroups, n (%)						
- 0 – 37.5	169 (88.5)	176 (96.2)	0.04*	152 (95.6)	141 (97.2)	0.45
- > 37.5	13 (6.8)	4 (2.2)		5 (3.1)	2 (1.4)	
- Missing, n (%)	9 (4.7)	3 (1.6)		2 (1.3)	2 (1.4)	
Uncertainty score	4.2 (25.0)	0 (25.0)	0.65	0.0 (16.7)	0 (25.0)	0.08
- Missing, n (%)	1 (0.5)	1 (0.5)		1 (0.6)	2 (1.4)	
Informed score	25.0 (25.0)	16.7 (33.3)	0.02*	16.7 (25.0)	16.7 (25.0)	0.61
- Missing, n (%)	2 (1.0)	0		1 (0.6)	2 (1.4)	
Support score	25.0 (25.0)	16.7 (25.0)	0.004*	16.7 (16.7)	8.3 (25.0)	0.003*
- Missing, n (%)	5 (2.6)	0		1 (0.6)	2 (1.4)	
Values clarity score	25.0 (25.0)	25.0 (25.0)	0.02*	25.0 (33.3)	16.7 (33.3)	0.07
- Missing, n (%)	7 (3.7)	2 (1.1)		1 (0.6)	2 (1.4)	
Effective decision score	18.8 (25.0)	12.5 (25.0)	0.002*	16.7 (25.0)	0 (25.0)	0.02*
- Missing, n (%)	2 (1.0)	0		2 (1.3)	2 (1.4)	
Decision regret, median (IQR)						
Total score				0 (10.0)	0 (10.0)	0.93
Subgroups, n (%)	N/A	N/A	N/A			
- 0 – 25				153 (96.2)	138 (95.2)	0.49
- > 25				3 (1.9)	5 (3.4)	
- Missing, n (%)				3 (1.9)	2 (1.4)	

HADS Hospital Anxiety and Depression Scale, *IQR* Interquartile range, *N/A* Not applicable. Outcomes are not corrected for 'time since diagnosis'. * $p < 0.05$.

Knowledge and discussed topics

There were no significant differences in knowledge between the mainstream and usual care group at both time points (Online Supplements). Within the mainstream group, there was a significant increase in total knowledge scores after receiving the test result (p = 0.003).

In the mainstream group, 'the consequences of genetic testing for chemotherapeutic treatment' were discussed significantly more often than in the usual care group, whereas in the usual care group 'the increased risk of a second breast cancer and ovarian cancer for carriers of a pathogenic variant in a *BRCA1/2* gene' was discussed more often (Figure 2a). In both groups, patients considered 'the consequences of genetic testing on family members' most important (Figure 2b).

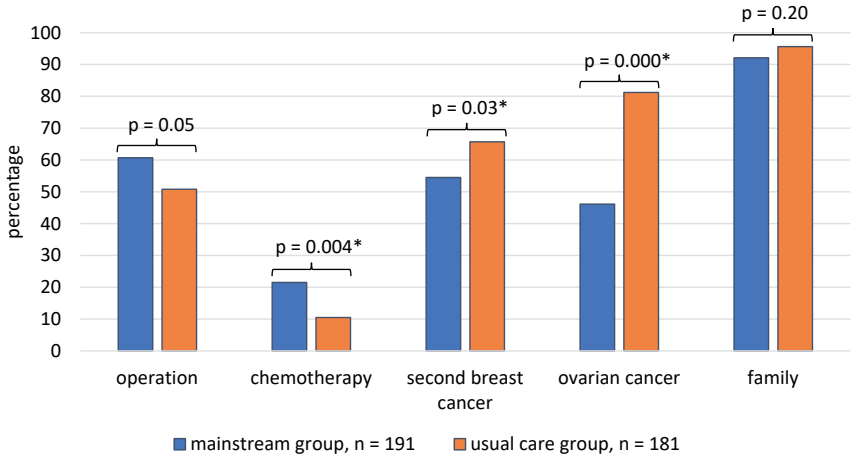


Figure 2a. Discussed topics during pre -test counseling for the mainstream and usual care group

Patients were asked whether one or more of these topics were discussed. For every topic, the percentage of patients who said that it was discussed is displayed in this bar chart. * p < 0.05.

Satisfaction

In both groups, the majority of patients were satisfied with pre-test counseling regarding the information received, the amount of time to consider the genetic test and the preferred moment to be offered a genetic test (Table 3). In the mainstream group, significantly more patients were unsure whether they had received sufficient information and amount of time to consider the genetic test and whether they thought the information discussed was clear. In both groups, the majority of patients felt that 'immediately after diagnosis' was the best moment to offer genetic testing.

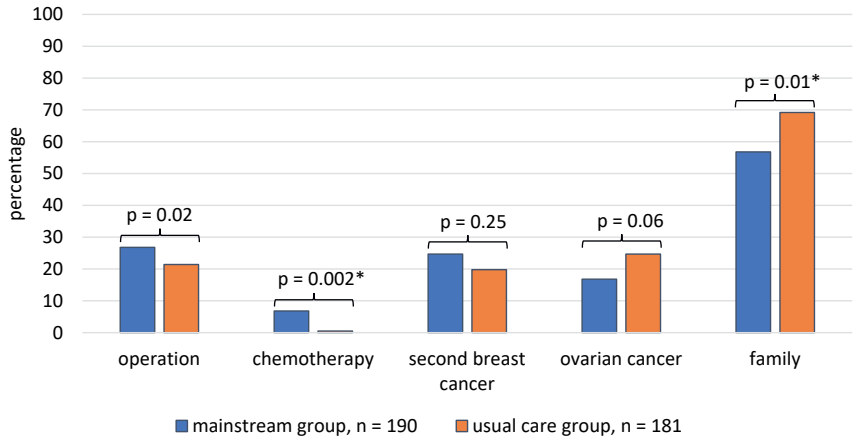


Figure 2b. Topics that patients in the mainstream and usual care group considered most important

Patients were asked to select the topic they considered most important. For every topic, the percentage of patients who said it was most important is displayed. If patients selected more than one topic, both were included in the bar chart. * $p < 0.05$.

The majority of patients in both groups were satisfied with how and what information they received about the test result (Table 4). In the mainstream group, for more patients it was unclear how they would receive the test result. In addition, the majority of patients in this group preferred a letter to receive the test result, whereas in the usual care group the majority preferred a telephone consultation.

In both the mainstream and usual care group, the majority of patients gave both verbal and written informed consent and also preferred this (Online Supplements).

Table 3. Questions indicating satisfaction with pre-test genetic counseling

	Response categories	Mainstream group n = 191	Usual care group n = 183	p-value
Clarity of discussed information regarding the genetic test, n (%)	- (Very) clear	168 (88.0)	179 (97.8)	0.001*
	- Unsure	18 (9.4)	4 (2.2)	
	- Not clear (at all)	3 (1.6)	0	
	- Missing	2 (1.0)	0	
Received written information after discussing genetic test, n (%)	- Yes	140 (73.3)	144 (78.8)	0.22
	- No	50 (26.2)	38 (20.8)	
	- Missing	1 (0.5)	1 (0.5)	
Clarity of received written information after discussing the genetic test, n (%)	- (Very) clear	128 (91.4)	136 (94.4)	0.10
	- Unsure	9 (6.4)	4 (2.8)	
	- Not clear (at all)	2 (1.4)	4 (2.8)	
	- Missing	1 (0.7)	0	
There was enough information to decide whether or not to perform the genetic test, n (%)	- Yes	171 (89.5)	177 (96.7)	0.04*
	- No	1 (0.5)	0	
	- Don't know	16 (8.4)	6 (3.3)	
	- Missing	3 (1.6)	0	
There was enough time to decide whether or not to perform the genetic test, n (%)	- Yes	167 (87.4)	177 (96.7)	0.002*
	- No	7 (3.7)	0	
	- Don't know	15 (7.9)	6 (3.3)	
	- Missing	2 (1.0)	0	
I felt I had a choice whether or not to perform a genetic test, n (%)	- Yes	168 (88.0)	165 (90.2)	0.54
	- No	13 (6.8)	13 (7.1)	
	- Don't know	8 (4.2)	4 (2.2)	
	- Missing	2 (1.0)	1 (0.5)	

Satisfaction with being offered a genetic test, n (%)	-	(Very) satisfied	183 (95.8)	175 (95.6)	0.77
	-	Unsure	7 (3.7)	5 (2.7)	
	-	Not satisfied (at all)	0	0	
	-	Missing	1 (0.5)	3 (1.6)	
Preferred moment to be offered a genetic test, n (%)	-	Directly after (first) diagnosis	160 (83.3)	126 (68.9)	0.000*
	-	After the (first) operation	8 (4.2)	6 (3.3)	
	-	After completion of treatment	5 (2.6)	26 (14.2)	
	-	In case of recurrence	7 (3.7)	4 (2.2)	
	-	No preference	2 (1.0)	3 (1.6)	
	-	Other[a]	4 (2.1)	8 (4.4)	
	-	Missing/unclear	5 (2.6)	10 (5.5)	
It was clear that after talking to the doctor or nurse specialist about the genetic test, I could choose to have an additional conversation with a genetics healthcare professional about it	-	Yes	107 (56.0)	N/A	N/A
	-	No	79 (41.4)		
	-	Missing	5 (2.6)		

N/A Not applicable. [a] In the mainstream group, two patients preferred genetic counseling in the second consultation after diagnosis, and two preferred counseling after breast cancer was diagnosed in a family member. In the usual care group, four patients preferred genetic counseling in a second or later consultation after diagnosis, two patients preferred to have genetic counseling before diagnosis, one patient considered the best moment to be determined by the doctor or nurse, and one patient preferred genetic counseling after breast cancer was diagnosed in a family member.

Table 4. Questions indicating satisfaction with receiving test result

	Response categories	Mainstream group n = 159	Usual care group n = 145	p-value
It was clear how the test result would be communicated, n (%)	- Yes	120 (75.5)	135 (93.1)	0.000*
	- No	38 (23.9)	7 (4.8)	
	- Missing	1 (0.6)	3 (2.1)	
Clarity of written information about the test result, n (%)	- (Very) clear	148 (93.1)	136 (93.8)	0.18
	- Unsure	10 (6.3)	4 (2.8)	
	- Not clear (at all)	0	0	
	- Missing	1 (0.6)	5 (3.4)	
Clarity of discussed information about the test result	- (Very) clear	N/A	138 (95.2)	N/A
	- Unsure		1 (0.7)	
	- Not clear (at all)		1 (0.7)	
	- Missing		5 (3.4)	
The doctor or nurse specialist discussed the result of the DNA test	- Yes	101 (63.5)	N/A	N/A
	- No, I have not had a new appointment after receiving the result	40 (25.2)		
	- No, I did have an appointment after receiving the result, but the result was not discussed	16 (10.1)		
	- Missing	2 (1.3)		
Looking back, there was insufficient information to decide on the DNA test, n (%)	- Yes	8 (5.0)	5 (3.4)	0.58
	- No	149 (93.7)	137 (94.5)	
	- Missing	2 (1.3)	3 (2.1)	
Ways of receiving test result, n (%)	- Letter	N/A	6 (4.1)	N/A
	- Telephone		122 (84.1)	
	- Video consultation		14 (9.7)	
	- Missing		3 (2.1)	

Satisfied with how test result was received, n (%)	-	Yes	117 (73.6)	120 (82.8)	0.09
	-	No	12 (7.5)	5 (3.4)	
	-	No preference	29 (18.2)	18 (12.4)	
	-	Missing	1 (0.6)	2 (1.4)	
Preferred way of receiving the test result	-	Letter	127 (79.9)	11 (7.6)	0.000*
	-	Telephone	16 (10.1)	96 (66.2)	
	-	Consultation at genetics department	6 (3.8)	18 (12.4)	
	-	Video consultation	1 (0.6)	9 (6.2)	
	-	Both telephone or personal consultation and letter	4 (2.5)	1 (0.7)	
	-	No preference	0	3 (2.1)	
	-	Other	4 (2.5)	5 (3.4)	
	-	Missing	1 (0.6)	2 (1.4)	
In case of a preferred personal conversation: preferred specialist to receive the result of the DNA test from	-	Treating doctor	13 (41.9)	16 (12.1)	0.000*
	-	Nurse specialist	7 (22.6)	3 (2.3)	
	-	Clinical geneticist/genetic counselor	10 (32.3)	107 (81.1)	
	-	No preference	1 (3.2)	3 (2.3)	
	-	Other	0	3 (2.3)	
It was clear that the result of the genetic test could also have consequences for family members	-	Yes	158 (99.4)	142 (97.9)	0.48
	-	No	0	1 (0.7)	
	-	Missing	1 (0.6)	2 (1.4)	
It was clear when the result of the genetic test would be discussed by a clinical geneticist/genetic counselor	-	Yes	87 (54.7)	N/A	N/A
	-	No	70 (44.0)		
	-	Missing	2 (1.3)		

N/A Not applicable.

Discussion

To our knowledge, this is the largest study to evaluate the experiences of breast cancer patients with mainstreamed genetic testing compared with the experiences of patients who received usual genetic care including pre-test counseling by a genetic HCP. This study shows that mainstreamed genetic care allows the majority of patients to make an informed decision about genetic testing, and it results in acceptable levels of distress, decisional conflict and regret.

Psychosocial outcomes

Adjusting for the time between diagnosis and pre-test counseling, we did not observe statistically significant differences, either after pre-test counseling or after receiving the test result, in distress, anxiety or depression between the patients who received pre-test counseling from a non-genetic HCP and those who received it from a genetic HCP. Only two previous studies compared psychosocial outcomes between breast cancer patients receiving mainstreamed versus usual genetic care. However, these studies included both patients with breast and ovarian cancer, their mainstream groups were limited in size (<50 patients), and these groups only included 11 patients with breast cancer (17, 21). As in our study, no difference in distress levels between the two groups was found in either of the other studies. Only one study compared anxiety and depression levels between two groups (21). In this study, patients who received mainstreamed genetic care were more likely to screen positive on the 'general emotions' domain of the 'psychosocial aspects of hereditary cancer (PAHC)' questionnaire relating to anxiety and depression amongst others. However, it is unclear whether the number of days between diagnosis and pre-test counseling affected these outcomes.

In our study, decisional conflict after pre-test counseling was higher in patients who had received mainstreamed genetic care. However, only a small proportion of these patients (7%) had clinically relevant decisional conflict, versus 2% of patients in our usual care group. The only study that evaluated this outcome did not find a significant difference in decisional conflict between patients who had received mainstreamed and usual genetic care (17).

As far as we know, decisional regret after performing a genetic test has not been evaluated previously for patients with breast cancer. We showed that regret was comparable and low in both groups, which is in line with previous research for patients with ovarian cancer (27, 28). This suggests that even if some patients experience more decisional conflict after pre-test counseling by a surgeon or nurse (instead of a genetic HCP), the majority will not regret their choice to undergo genetic testing.

Knowledge and discussed topics

Knowledge about genetic testing was comparable in the two groups in our study. This is in line with the study of Richardson et al. (17), but in contrast to the study of McCuaig et al. where knowledge was higher in their usual care group (21). However, their study included more extensive knowledge questions than our study. We believe that it is important for patients to have a basic understanding of genetic testing to make a well-informed decision about genetic testing. Detailed information about risks and implications for family members is needed especially when a pathogenic variant in a breast cancer gene is identified.

A notable finding is that the possible higher risk of a second breast cancer or ovarian cancer after identifying a pathogenic variant in a *BRCA1/2* gene was discussed less often in our mainstream group.

Satisfaction

Satisfaction of patients with mainstreamed genetic care was high, as also reported in previous studies (16, 17, 21, 24). However, only two studies included a limited number of patients in their usual care group as comparison (17, 21). Interestingly, in our mainstream group significantly more patients considered the provided information or time insufficient to consider genetic testing or were unsure about this. Although the majority of patients receiving mainstreamed genetic care were satisfied with the information and amount of time they received, this highlights the importance of recognizing those patients who require more extensive pre-test counseling. In addition, more patients in our mainstream group considered the information discussed during pre-test counseling unclear. This is in line with the study by McCuaig et al., who showed that in the mainstream group fewer patients considered the information helpful or given in a way that they understood (21).

The preferred moment for pre-test counseling in both groups was directly after diagnosing breast cancer, which is in line with previous research (23, 29). The preferred way to receive the test result differed between patients in both group. However, this is probably biased by the way most patients actually received their test result (i.e., in a letter in the mainstream group and by telephone in the usual care group). It also indicates that most patients do not object to receiving their test result in a letter.

One of the concerns about mainstream genetic testing, as identified by previous research, is the inability to obtain proper informed consent for genetic testing, possibly due to HCPs not providing pre-test counseling (30). With written consent, there is a higher chance that pre-test counseling is provided. Our study is unique in that we evaluated patients' experiences with our informed consent procedure. Although many mainstream genetic testing pathways do include written informed consent for genetic testing (12), this is not

standard practice. This study shows that patients do prefer to give both written and verbal informed consent for genetic testing.

Limitations

This study has several limitations. Because of the differences in eligibility criteria for pre-test counseling by a non-genetic HCP (i.e., surgeon or nurse) or by a genetic HCP, the two groups were not comparable. We adjusted for the known differences with multivariate analyses, but there may have been other differences that we did not account for (e.g., current age or stage of treatment). In addition, geneticists and genetic counselors were expected to hand out information about the study to eligible patients themselves or send this information to the patient. Due to logistical reasons, we do not know how many eligible patients received pre-test counseling by a genetic HCP and how many of these patients received the study material. Although it cannot be excluded that this information was provided to a selection of patients, most sociodemographic characteristics, e.g., migrant status and educational level, were comparable for the patients in the two groups.

Conclusion

This study shows that mainstream genetic testing for the majority of breast cancer patients provides sufficient support and information for decision-making without unacceptable distress, decisional conflict or regret.

However, this study also shows that for some patients more personalized attention is necessary. It is important to further investigate for which patients mainstream genetic testing is insufficient and who therefore should be referred for pre-test counseling by a genetic HCP.

Acknowledgements of research support for the study: We thank all patients who participated in our study and all surgical oncologists, medical oncologists, nurse specialists and nurses from the Meander Medical Center Amersfoort, St. Antonius Hospital Utrecht, Diakonessenhuis Utrecht, Gelre Hospitals Apeldoorn, St. Jansdal Hospital Harderwijk, Rivierenland Hospital Tiel, Alexander Monro Hospital Bilthoven, University Medical Center Utrecht and Beatrix Hospital Gorinchem who participated in our mainstream genetic testing pathway. We also thank the genetic healthcare professionals from the University Medical Center Utrecht for supporting this study and enabling timely post-test counseling if needed.

Authors' Contributions: Conceptualization: KB, MGEMA; Methodology: KB, EMAB, BFH, CMA, EJPS, MGEMA; Formal analysis: KB, RMB; Investigation: KB, RK, JPJB, JHK, APSV, NV,

BFH, AJW, TF, WK, EJPS; Resources: KB, MEV; Data curation, KB; Writing – original draft: KB; Writing – review & editing: KB, EMAB, MEV, RK, JPJB, JHK, APSV, NV, BFH, AJW, TF, RMB, CMA, WK, EJPS, MGEMA; Visualization: KB; Supervision: MGEMA; Project Administration: KB, MEV; Funding acquisition: MGEMA

Ethics Approval and consent to participate: This study is registered at the International Clinical Trials Registry Platform (NL9712) and was reviewed by the Medical Reviews Ethics Committee (MREC) of the UMC Utrecht in August 2019. The Medical Research Involving Human Subjects Act (WMO) did not apply to this study. We obtained written informed consent for all participants. This study was performed in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable.

Data availability: The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations of interest: The authors have no conflicts of interest to declare.

Funding information: AstraZeneca and Pfizer partly funded the appointment of KB and thereby facilitated the implementation of the mainstream genetic testing pathway. They had no involvement in the development of the content of the program.

References

1. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol. 2016;27(suppl 5):v103-v10.
2. Tung NM, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, et al. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol. 2020;38(18):2080-2106.
3. Tung NM, Garber JE. BRCA1/2 testing: therapeutic implications for breast cancer management. Br J Cancer. 2018;119(2):141-152.
4. Poggio F, Bruzzone M, Ceppi M, Ponde NF, La Valle G, Del Mastro L, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol. 2018;29(7):1497-1508.
5. Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021;16(3):255-282.
6. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405.
7. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National Estimates of Genetic Testing in Women With a History of Breast or Ovarian Cancer. J Clin Oncol. 2017;35(34):3800-6.
8. Hoskovec JM, Bennett RL, Carey ME, DaVanzo JE, Dougherty M, Hahn SE, et al. Projecting the Supply and Demand for Certified Genetic Counselors: a Workforce Study. J Genet Couns. 2018;27(1):16-20.
9. Stoll K, Kubendran S, Cohen SA. The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. Am J Med Genet C Semin Med Genet. 2018;178(1):24-37.
10. Colombo N, Huang G, Scambia G, Chalas E, Pignata S, Fiorica J, et al. Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer. J Clin Oncol. 2018;36(13):1300-1307
11. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.
12. Bokkers K, Vlaming M, Engelhardt EG, Zweemer RP, van Oort IM, Kiemeney L, et al. The Feasibility of Implementing Mainstream Germline Genetic Testing in Routine Cancer Care-A Systematic Review. Cancers (Basel). 2022;14(4):1059.
13. Scheinberg T, Young A, Woo H, Goodwin A, Mahon KL, Horvath LG. Mainstream consent programs for genetic counseling in cancer patients: A systematic review. Asia Pac J Clin Oncol. 2020;17(3):163-177.

14. Beard C, Monohan K, Cicciarelli L, James PA. Mainstream genetic testing for breast cancer patients: early experiences from the Parkville Familial Cancer Centre. Eur J Hum Genet. 2021;29(5):872-880.
15. Grindedal EM, Jorgensen K, Olsson P, Gravdehaug B, Luras H, Schlichting E, et al. Mainstreamed genetic testing of breast cancer patients in two hospitals in South Eastern Norway. Fam Cancer. 2020;19(2):133-142.
16. Kemp Z, Turnbull A, Yost S, Seal S, Mahamdallie S, Poyastro-Pearson E, et al. Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer. JAMA Netw Open. 2019;2(5):e194428.
17. Richardson M, Min HJ, Hong Q, Compton K, Mung SW, Lohn Z, et al. Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System. Cancers (Basel). 2020;12(2):338.
18. Stromsvik N, Olsson P, Gravdehaug B, Luras H, Schlichting E, Jorgensen K, et al. "It was an important part of my treatment": a qualitative study of Norwegian breast Cancer patients' experiences with mainstreamed genetic testing. Hered Cancer Clin Pract. 2022;20(1):6.
19. Benusiglio PR, Korenbaum C, Vibert R, Ezenfis J, Geoffron S, Paul C, et al. Utility of a mainstreamed genetic testing pathway in breast and ovarian cancer patients during the COVID-19 pandemic. Eur J Med Genet. 2020;63(12):104098.
20. Lee YQ, Yoon SY, Hassan T, Padmanabhan H, Yip CH, Keng WT, et al. Attitudes and training needs of oncologists and surgeons in mainstreaming breast cancer genetic counseling in a low-to-middle income Asian country. J Genet Couns. 2022;25(12):1873-1884.
21. McCuaig JM, Thain E, Malcolmson J, Keshavarzi S, Armel SR, Kim RH. A Comparison of Patient-Reported Outcomes Following Consent for Genetic Testing Using an Oncologist- or Genetic Counselor-Mediated Model of Care. Curr Oncol. 2021;28(2):1459-1471.
22. Scott N, O'Sullivan J, Asgeirsson K, Macmillan D, Wilson E. Changing practice: moving to a specialist nurse-led service for BRCA gene testing. Br J Nurs. 2020;29(10):S6-S13.
23. Wright S, Porteous M, Stirling D, Lawton J, Young O, Gourley C, et al. Patients' Views of Treatment-Focused Genetic Testing (TFGT): Some Lessons for the Mainstreaming of BRCA1 and BRCA2 Testing. J Genet Couns. 2018;27(6):1459-1472.
24. McVeigh TP, Sweeney KJ, Brennan DJ, McVeigh UM, Ward S, Strydom A, et al. A pilot study investigating feasibility of mainstreaming germline BRCA1 and BRCA2 testing in high-risk patients with breast and/or ovarian cancer in three tertiary Cancer Centres in Ireland. Fam Cancer. 2022. Online ahead of print.
25. Bokkers K, Bleiker EMA, Aalfs CM, van Dalen T, Velthuizen ME, Duijveman P, et al. Surgical oncologists and nurses in breast cancer care are ready to provide pre-test genetic counseling. Ann Oncol. In press.
26. Dutch Federation of Medical Specialists. Breast Cancer Guideline 2020 [Available from: https://richtlijnendatabase.nl/richtlijn/borstkanker/algemeen.html].

27. Bokkers K, Bleiker EMA, Hoogendam JP, Velthuizen ME, Schreuder HWR, Gerestein CG, et al. Mainstream genetic testing for women with ovarian cancer provides a solid basis for patients to make a well-informed decision about genetic testing. Hered Cancer Clin Pract. 2022;20(1):33.
28. McLeavy L, Rahman B, Kristeleit R, Ledermann J, Lockley M, McCormack M, et al. Mainstreamed genetic testing in ovarian cancer: patient experience of the testing process. Int J Gynecol Cancer. 2020;30(2):221-226.
29. Wevers MR, Aaronson NK, Bleiker EMA, Hahn DEE, Brouwer T, van Dalen T, et al. Rapid genetic counseling and testing in newly diagnosed breast cancer: Patients' and health professionals' attitudes, experiences, and evaluation of effects on treatment decision-making. J Surg Oncol. 2017;116(8):1029-1039.
30. Charron M, Kaiser B, Dauge A, Gallois H, Lapointe J, Dorval M, et al. Integrating hereditary breast and ovarian cancer genetic counselling and testing into mainstream clinical practice: Legal and ethical challenges. Crit Rev Oncol Hematol. 2022;178:103797.

Supplementary Materials and Data

Content

Supplementary File 1. Topics in questionnaires

Table 1. Summary of topics in the T0 and T1 questionnaire

Topics	Description	T0 questionnaire	T1 questionnaire

Sociodemographic data	- Having children (yes/no)
	- Educational level based on the Dutch Standard Classification of Education 2021[1]:
	  - Low level: no, primary or lower secondary education
	  - Intermediate level: upper secondary education
	  - High-level: tertiary education
	Country of birth of patient and parents. Migrant status was recorded based on the definition of Statistics Netherlands (CBS)[2]: when at least one of the parents comes from a foreign country. When born in the Netherlands, migration background is determined by the mothers country of origin. If the mother was born in the Netherlands as well, migration background is determined by the fathers' country of origin.
	  - A Western migration background: country of origin in Europe (excluding Turkey), North America, Oceania, Indonesia or Japan.
	  - A non-Western migration background: country of origin in Turkey, Africa, South America, or Asia (excluding Indonesia and Japan)
	- Personal history of other cancers
		X	

Outcome Measures			
Distress	One-item distress thermometer:		
- *One-item Distress Thermometer*[3]	- Range between 0 (no distress) and 10 (maximal distress). - Levels ≥ 4 indicate a clinically relevant elevated level of distress[3]	X	X
- *One self-developed question*	The self-developed question: 'did pre-test genetic counseling affect your feelings of tension or distress?' could be answered with 'no', 'yes, more tension or distress' or 'yes, less tension or distress'	X	X

Anxiety and depression - *Hospital Anxiety and Depression Scale*[4,5]	The Hospital Anxiety and Depression Scale: - Seven items evaluating anxiety (HADS-A) - Seven items evaluating depression (HADS-D) - Score between 0 and 21 for each subscale - Score ≥ 11 for each subscale indicates clinically relevant anxiety or depression[6]	X	X
Knowledge[7]	Five statements, as used in our mainstreaming-study for ovarian cancer patients (responses: true, false or don't know)	X	X
Satisfaction with informed consent	Self-developed questions to assess in what form consent was obtained and patients' preferences.		X
Discussed topics during pre-test genetic counseling	Five options to evaluate whether the HCP had discussed potential impact of genetic testing on (1) the operation choice, (2) chemotherapeutic choice, (3) increased risk of developing a second breast cancer, (4) increased of developing ovarian cancer, and (5) family members. Patients could select the topics discussed and which they considered most important.	X	
Satisfaction with pre-test genetic counseling[7-9]	Self-developed questions, and based on those used in the Mainstreaming Cancer Genetics program, the TIME trial, and our previous research on mainstream genetic testing for ovarian cancer patients	X	
Satisfaction with receiving genetic test result[7-9]	Self-developed questions, and based on those used in the Mainstreaming Cancer Genetics program, the TIME trial, and our previous research on mainstream genetic testing for ovarian cancer patients		X
Satisfaction with the decision to accept or decline genetic testing			
- *Decisional Conflict Scale*[10,11]	Decisional Conflict Scale: - Sixteen items - Total score and five subscores ranging from 0 (no decisional conflict) to 100 (maximal decisional conflict). - Score of ≥ 37.5 indicates clinically relevant [13] decisional conflict	X	X [a]
- *Decision Regret Scale*[12]	Decision Regret Scale: - Five items, with total score between 0 (no decision regret) and 100 (maximal decision regret). - Score of ≥ 25 indicates clinically relevant decision regret [14,15]		X

[1] Statistics Netherlands: The Dutch Standard Classification of Education, SOI 2021. https://www.cbs.nl/nl-nl/onze-diensten/methoden/classificaties/onderwijs-en-beroepen/standaard-onderwijsindeling--soi--/standaard-onderwijsindeling-2021
[2] Statistics Netherlands: Migration Background, 2021. https://www.cbs.nl/en-gb/onze-diensten/methods/definitions/migration-background
[3] National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Distress Management. Version 2.2021 2021
[4] Spinhoven P, Ormel J, Sloekers PP, et al: A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 27:363-70, 1997
[5] Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361-70, 1983
[6] Bjelland I, Dahl AA, Haug TT, et al: The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 52:69-77, 2002
[7] Bokkers K, Bleiker EMA, Hoogendam JP, et al: Mainstream genetic testing for women with ovarian cancer provides a solid basis for patients to make a well-informed decision about genetic testing. Hered Cancer Clin Pract 20:33, 2022
[8] George A, Riddell D, Seal S, et al: Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep 6:29506, 2016
[9] Wevers MR, Ausems MG, Verhoef S, et al: Behavioral and psychosocial effects of rapid genetic counseling and testing in newly diagnosed breast cancer patients: design of a multicenter randomized clinical trial. BMC Cancer 11:6, 2011
[10] Koedoot N, Molenaar S, Oosterveld P, et al: The decisional conflict scale: further validation in two samples of Dutch oncology patients. Patient Educ Couns 45:187-93, 2001
[11] O'Connor AM: Validation of a decisional conflict scale. Med Decis Making 15:25-30, 1995
[12] Brehaut JC, O'Connor AM, Wood TJ, et al: Validation of a decision regret scale. Med Decis Making 23:281-92, 2003
[13] O'Connor AM: User Manual - Decisional Conflict Scale, 2010
[14] Sheehan J, Sherman KA, Lam T, et al: Association of information satisfaction, psychological distress and monitoring coping style with post-decision regret following breast reconstruction. Psychooncology 16:342-51, 2007
[15] Zhong T, Bagher S, Jindal K, et al: The influence of dispositional optimism on decision regret to undergo major breast reconstructive surgery. J Surg Oncol 108:526-30, 2013
[a] In the T1 questionnaire we omitted the question: 'I expect to stick with my decision' of the decisional conflict scale because it was not applicable after the genetic test had already been performed.

Supplementary File 2. General Linear Model analyses

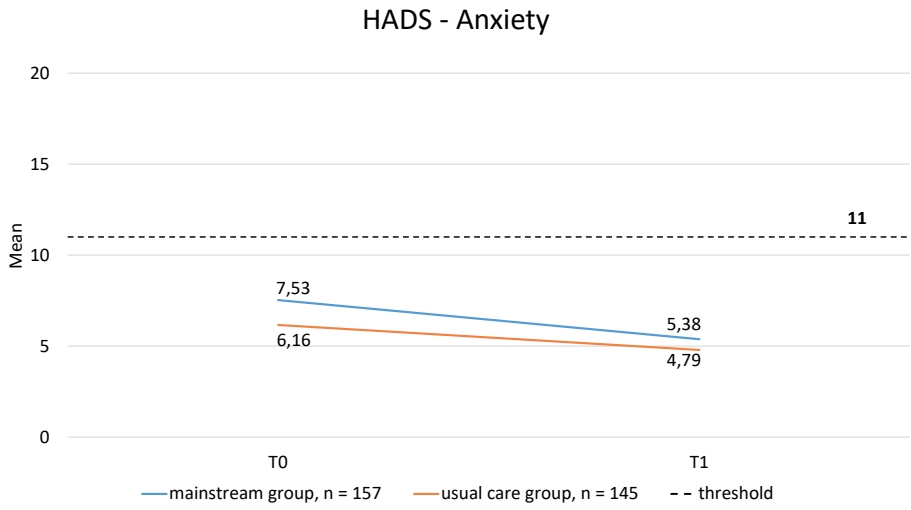


Figure 1. Change in mean levels of anxiety between T0 (after pre-test counseling) and T1 (after receiving the test result) for both the mainstream and usual care group
Total scores could range between 0 and 21. Threshold for concern is 11. With paired analysis, there is a significant decrease in anxiety at T1 in comparison to T0 for both the mainstream group (p = 0.000) and the usual care group (p = 0.000). There is no significant difference in decrease of anxiety in time between the two groups (p = 0.06).

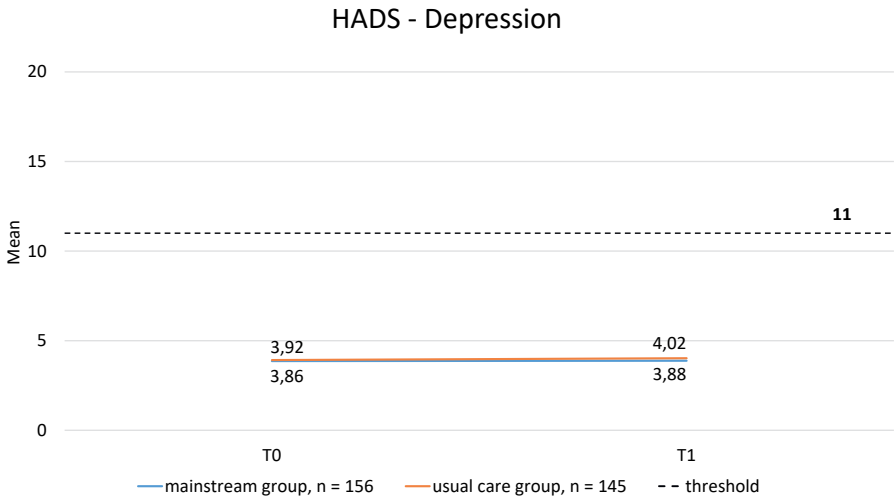


Figure 2. Change in mean levels of depression between T0 (after pre-test counseling) and T1 (after receiving the test result) for both the mainstream and usual care group
Total scores could range between 0 and 21. Threshold for concern is 11. With paired analysis, there is no significant difference in anxiety at T1 in comparison to T0 for both the mainstream group (p = 0.93) and the usual care group (p = 0.55). There is no significant difference in the change in depression levels in time between the two groups (p = 0.82).

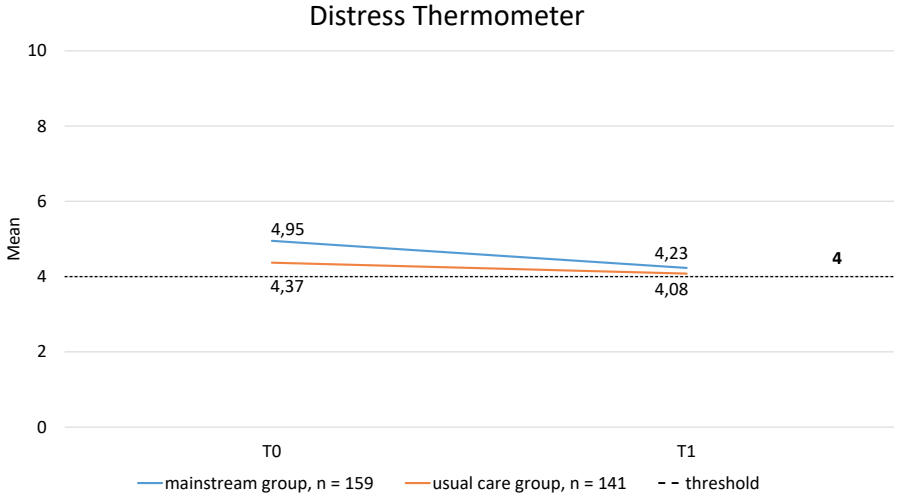


Figure 3. Change in mean levels of distress between T0 (after pre-test counseling) and T1 (after receiving the test result) for both the mainstream and usual care group
Total scores could range between 0 and 10. Threshold for concern is 4. With paired analysis, there is a significant decrease in distress at T1 in comparison to T0 for the mainstream group (p = 0.001), but not for the usual care group (p = 0.11). There is no significant difference in decrease in distress in time between the two groups (p = 0.14).

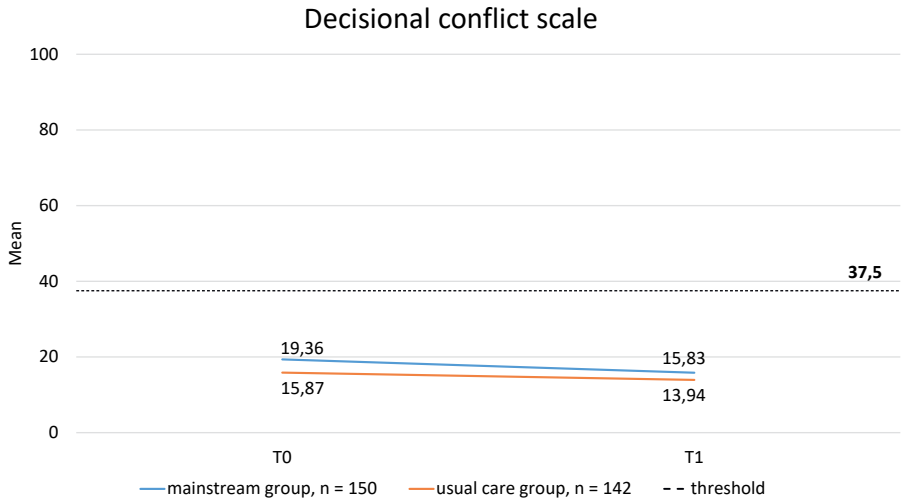


Figure 4. Change in mean levels of decisional conflict between T0 (after pre-test counseling) and T1 (after receiving the test result) for both the mainstream and usual care group

Total scores could range between 0 and 100. Threshold for concern is 37.5. With paired analysis, there is a significant decrease in decisional conflict at T1 in comparison to T0 for both the mainstream group (p = 0.000) and the usual care group (p = 0.03). There is no significant difference in decrease in time between the two groups (p = 0.23).

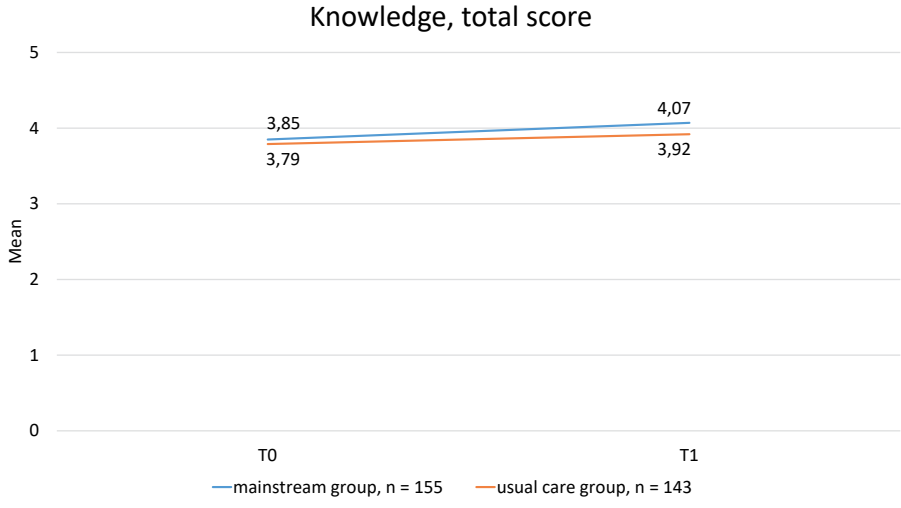


Figure 5. Change in mean total knowledge scores between T0 (after pre-test counseling) and T1 (after receiving the test result) for both the mainstream and usual care group

Total knowledge scores could range between 0 and 5. With paired analysis, there is a significant increase in knowledge for the mainstream group (p = 0.003), but not for the usual care group (n = 0.18). There is no significant difference in increase in time between the two groups (p = 0.48).

Supplementary File 3. Knowledge about genetic testing

Table 1. Comparison of knowledge about genetic testing between the mainstream and usual care group, both at T0 and T1.

	T0			T1		
Statement	**Mainstream group n = 190 n (%)**	**Usual care group n = 182 n (%)**	**p-value**	**Mainstream group n = 157 n (%)**	**Usual care group n = 144 n (%)**	**p-value**
All women who carry a mutation (gene alteration) in a gene for breast cancer will develop breast cancer (false)						
- Correct answer	115 (60.5)	106 (58.2)	0.65	109 (69.4)	95 (66.0)	0.52
- Incorrect answer	75 (39.5)	76 (41.8)		48 (30.6)	49 (34.0)	
A woman who does not carry a mutation (gene alteration) in a gene for breast cancer, can still develop breast cancer (true)						
- Correct answer	172 (90.5)	166 (91.2)	0.82	149 (94.9)	135 (93.8)	0.80
- Incorrect answer	18 (9.5)	16 (8.8)		8 (5.1)	9 (6.3)	
A woman who carries a mutation (gene alteration) in a gene for breast cancer, can pass this on to her children (true)						
- Correct answer	181 (95.3)	166 (91.2)	0.09	150 (95.5)	137 (95.1)	1.00
- Incorrect answer	8 (4.2)	16 (8.8)		7 (4.5)	7 (4.9)	
- Missing	1 (0.5)	0				
A woman who carries a mutation (gene alteration) in a gene for breast cancer, can have inherited this by her father (true)						
- Correct answer	135 (71.1)	134 (73.6)	0.58	131 (83.4)	111 (77.1)	0.17
- Incorrect answer	55 (28.9)	48 (26.4)		26 (16.6)	33 (22.9)	

A woman who has a sister with a pathogenic variant in a gene for breast cancer has a 50% change (1 in 2) of also carrying the mutation (true)							
-	Correct answer	103 (54.2)	107 (58.8)	0.37	97 (61.8)	86 (59.7)	0.71
-	Incorrect answer	87 (45.8)	75 (41.2)		60 (38.2)	58 (40.3)	
Total score							
-	≤ 2	30 (15.8)	26 (14.3)	0.55	10 (6.4)	15 (10.4)	0.56
-	3	37 (19.5)	39 (21.4)		24 (15.3)	25 (17.4)	
-	4	68 (35.8)	55 (30.2)		63 (40.1)	54 (37.5)	
-	5	54 (28.4)	62 (34.1)		60 (38.2)	50 (34.7)	
-	Missing	1 (0.5)	0				

Supplementary File 4. Preferences regarding consent for genetic testing

Table 1. Consent for genetic testing for the mainstream and usual care group

	Response categories		Mainstream group n = 158	Usual care group n = 145	p-value
Was consent provided?, n (%)	-	Only verbally	9 (5.7)	9 (6.2)	0.32
	-	Only in writing	31 (19.6)	19 (13.1)	
	-	Both verbally and in writing	117 (74.1)	117 (80.7)	
	-	No	0	0	
	-	Missing	1 (0.6)	0	
Preference for consent for genetic test, n (%)	-	Verbal consent is sufficient	29 (18.4)	28 (19.3)	0.81
	-	Consent must also be given in writing	129 (81.6)	116 (80.0)	
	-	Missing	0	1 (0.7)	
Preference for consent about sharing result of genetic test with family members, n (%)	-	Only verbally is sufficient	20 (12.7)	34 (23.4)	0.01*
	-	Verbally and in writing	138 (87.3)	110 (75.9)	
	-	Missing	0	1 (0.7)	
Healthcare professionals should (even without permission of the patient) be able to share genetic test results with family members if it may be relevant to the health of family members, n (%)	-	(Strongly) agree	92 (58.2)	87 (60.0)	0.93
	-	Neutral	27 (17.1)	23 (15.9)	
	-	(Strongly) disagree	39 (24.7)	34 (23.4)	
	-	Missing	0	1 (0.7)	

* $p < 0.05$.

Chapter 8

General discussion and future recommendations

Despite the evident clinical implications of germline genetic testing for patients and family members, still not all eligible patients with breast or ovarian cancer receive such testing. With the growing number of patients eligible for genetic testing and the insufficient capacity at genetics departments, there is a need to restructure the genetic care for these patients. Mainstream genetic testing contains all elements to address these problems.

The aim of this thesis was to improve access to genetic testing with a mainstream genetic testing pathway for patients with breast or ovarian cancer who are eligible for germline genetic testing according to current care guidelines. We developed and implemented a mainstream genetic testing pathway for patients with breast cancer and for patients with ovarian cancer and evaluated if this approach was both feasible and acceptable to patients and non-genetic healthcare professionals, and provided good quality of care.

Based on the results of our studies, we conclude that:

1. Non-genetic healthcare professionals in both breast and ovarian cancer care have predominantly positive attitudes toward mainstream genetic testing (**Chapter 3 and 6**).
2. It is feasible for these non-genetic healthcare professionals to incorporate mainstream genetic testing into their routine care (**Chapter 2, 3, and 6**).
3. Mainstream genetic testing provides a good quality of care for patients and allows them to make well-informed decisions about genetic testing (**Chapter 4 and 7**).
4. Mainstream genetic testing leads to higher testing rates in patients with ovarian cancer (**Chapter 5**).
5. Mainstream genetic testing for ovarian cancer patients leads to a reduction in genetics-related healthcare costs (**Chapter 5**).

This chapter reflects on the main findings of our studies following patients' perspectives, healthcare professionals' perspectives and quality of care, and discusses clinical implications and future perspectives.

Patients' perspectives

Can patients make a well-informed decision about genetic testing?

It is important that patients can make a well-informed decision about genetic testing. Our studies show that this is feasible in a mainstream genetic testing pathway for the majority of patients with breast or ovarian cancer, without increasing distress and without unacceptable decisional conflict or regret (**Chapter 4 and 7**). However, making a well-informed decision is complex, and relies primarily on the patients' understanding of the core message rather than the exact endpoints, such as cancer risks (1, 2). In our review

(**Chapter 2**) we identified two key elements to incorporate in the informed consent procedure: 1) the explanation of the genes tested and the associated cancers for which patients may be at increased risk, and 2) the possible implications of the result of the genetic test for both patients and their family members. These elements were incorporated in our online training for both the ovarian cancer and breast cancer team (**Chapter 3 and 6**). Pre-test genetic counseling also includes a fine balance between giving all necessary information and not giving too much information. Many patients prefer less information to make a decision than is provided by genetic counselors, and especially information provided in a less complex way (3, 4). Providing too much and too complicated information can even have a reverse effect, resulting in a lack of understanding amongst patients regarding genetic testing (4), and therefore preventing patients from making a well-informed decision. On the other hand, pre-test genetic counseling is not always provided in mainstreaming pathways, especially in those pathways without a clear protocol, thus eliminating informed consent altogether (5). Obtaining written informed consent helps healthcare professionals to provide some form of pre-test genetic counseling before ordering a genetic test. Although written consent is not a prerequisite for genetic testing, we found that it is included in most mainstream genetic testing pathways (**Chapter 2**). In addition, our research shows that the majority of patients with breast cancer actually prefer to give both verbal and written consent for the genetic test and for sharing the result with family members (**Chapter 7**).

Although mainstream genetic testing provided good quality of care for the majority, for some patients this new pathway led to increased decision regret in ovarian cancer patients (**Chapter 4**) and higher decisional conflict in breast cancer patients after pre-test counseling (**Chapter 7**) regarding their choice to perform genetic testing. Although the proportion of patients with clinically relevant decisional conflict or regret was low, it is important to investigate why some patients have higher regret or decisional conflict and to identify these patients. Moreover, in our ovarian cancer study, we were only able to measure decisional conflict after receiving the test result and therefore do not know whether there were differences between the two groups directly after pre-test counseling, as in our breast cancer study. These differences in regret and decisional conflict between patients may be due to differences in information needs between different groups of patients. For example, patients with low health literacy are known to have different information needs than patients with high health literacy (4, 6-8). Education of non-genetic healthcare professionals should therefore also address these differences in counseling, such as providing plain-language or visual aids (9-11). In addition, pre-test counseling by a non-genetic healthcare professional is less extensive than pre-test counseling by a genetic counselor. For some patients, the information provided may be too limited. Providing tailored information using online tools may be a solution for this (12, 13). Lastly, patients in a mainstream pathway may have less time to consider genetic testing. Whereas patients

referred to the genetics department have several days between discussing the referral and actual pre-test genetic counseling, patients in a mainstream genetic testing pathway may be offered genetic testing without this time to consider genetic testing. Pre-test counseling may even be provided during the same consultation in which the diagnosis is discussed, but this should be studied in more detail. Ultimately, mainstream genetic testing may not be sufficient for a small proportion of patients with breast or ovarian cancer. Therefore, it is important to identify those patients who need more information or psychosocial support during their decision-making process about genetic testing. These patients should be referred for more extensive pre-test genetic counseling by a genetic healthcare professional.

What is the best time to offer a genetic test?

Timing of pre-test genetic counseling is one of the challenges of mainstream genetic testing. Because of the treatment implications, genetic testing in mainstream initiatives is mainly offered directly after diagnosis. In our ovarian cancer study (**Chapter 4**) only half of patients in both the mainstream and usual care group preferred genetic testing directly after diagnosis, and about 1/3rd preferred genetic testing after completion of treatment. In our breast cancer study (**Chapter 7**) the majority of patients preferred genetic testing shortly after diagnosis and before surgery (>80% in our mainstream group and around 70% in our usual care group group). Previous research has shown that the best timing to offer genetic testing to patients diagnosed with both breast cancer and patients with ovarian cancer was directly after diagnosis, and with acceptable levels of distress (14-19). However, our studies also suggest that some patients need time to process their diagnosis and prepare for possible genetic testing. This is supported by our observations that (1) one of the main reasons for not providing pre-test genetic counseling was that patients were too emotional during the consultation and (2) around half of non-genetic healthcare professionals needed an additional appointment for at least one patient to provide pre-test genetic counseling (**Chapter 3 and 6**). In a mainstream genetic testing pathway, creating more time between diagnosis and pre-test genetic counseling may require scheduling additional appointments. It may not always be feasible to create time for these additional appointments and non-genetic healthcare professionals may be inclined to refer patients to the genetics department for pre-test genetic counseling and testing instead of discussing and ordering the genetic test themselves. In addition, because of treatment implications, there may not always be time to schedule additional appointments to discuss genetic testing.

Healthcare professionals' perspectives

Do healthcare professionals welcome mainstream genetic testing pathways?

Non-genetic healthcare professionals, such as surgeons, gynecologists and nurses/nurse specialists play a vital role in the implementation of mainstream genetic testing pathways. For these non-genetic healthcare professionals to participate in such a new care pathway and keep participating after the implementation phase, it is important they support the new pathway, see the relevance of changing their work and feel capable to work according to the new pathway (20, 21). Only increasing knowledge is insufficient to bring about behavioral change in offering more genetic testing (22). Training therefore should not only focus on factual genetic knowledge, but should also help healthcare professionals understand the importance of genetic testing for patients and family members and should provide the tools necessary to provide pre-test genetic counseling (e.g., how to discuss or when to discuss genetic testing). We did include these different aspects into our online training modules (**Chapter 3 and 6**). However, there is still insufficient data on the best training to both promote a positive attitude, increase self-efficacy, and increase the knowledge about genetic testing. The optimal format in which to offer training is not clear and preferences and education needs might differ between the different non-genetic healthcare professionals involved (23-25), and between different healthcare systems and countries. More research into these differences in needs is required to prepare all non-genetic healthcare professionals to provide pre-test genetic counseling themselves. Healthcare professionals in our study appreciated the training and, in fact, considered training an essential part of implementing a mainstream genetic testing pathway (**Chapter 6**). Our review shows that healthcare professionals in previous studies have also expressed a positive attitude towards the training and complementary resources, such as FAQ sheets (**Chapter 2**). Gleeson et al. have shown that training oncology healthcare professionals leads to increased perceived skills, knowledge and attitudes (26). Our review shows that mainstream programs worldwide do include some form of training (**Chapter 2**). This is especially driven by previous research in which a lack of knowledge and confidence was reported by non-genetic healthcare professionals (27-31). Our research has shown that training can increase self-perceived knowledge of healthcare professionals on the advantages and disadvantages of genetic testing (**Chapter 3 and 6**). Having more confidence in explaining genetic testing to patients, will increase self-confidence and may contribute to better adherence to guidelines.

Overall, the majority of healthcare professionals that participated in our study, did welcome mainstream genetic testing. However, we did see some differences between the healthcare professionals involved in our ovarian cancer and breast cancer mainstreaming pathway. For ovarian cancer, the majority of participating healthcare professionals

consisted of doctors and almost all invited gynecologic oncologists and gynecologists with a subspecialty training in oncology were actively involved in the pathway (**Chapter 3**). In previous mainstreaming studies for ovarian cancer, participating healthcare professionals also consisted for the majority or only of doctors (26, 32-46). On the other hand, in our breast cancer mainstreaming pathway, the majority of participating healthcare professionals consisted of nurses and nurse specialists (**Chapter 6**). This is in contrast to the majority of previous studies about mainstreaming for breast cancer, in which healthcare professionals involved consisted predominantly of doctors (29, 33, 39, 41, 44, 47-50). These previous studies also showed a large role for medical oncologists (29, 39, 47, 48, 50). This is striking because in our study several medical oncologists completed our online training and participated in our questionnaire study, but rarely offered pre-test genetic counseling and ordered genetic testing themselves. This suggests that the majority of eligible patients were already offered genetic testing by their surgical oncologists. Future studies are needed to confirm if indeed the majority of eligible patients were tested before the appointment with their medical oncologist. This variety of disciplines involved in mainstream pathways also highlights the differences in healthcare pathways around the world. For other healthcare professionals who consider to implement a mainstream genetic testing pathway, it is important to take into account the healthcare structures that exist locally and adapt a mainstream genetic testing pathway accordingly. We also observed differences between the participating hospitals. Especially in our breast cancer project, our pathway was best incorporated into those hospitals where dedicated nurses and nurse specialists provided pre-test genetic counseling and requested genetic testing. Having dedicated healthcare professionals who support and promote the mainstream genetic testing pathway, previously described as mainstream champions by Hallowell et al., are beneficial to the sustainability and involvement of other non-genetic healthcare professionals in a mainstream genetic testing pathway (28).

Is it feasible for non-genetic healthcare professionals to incorporate mainstream genetic testing into daily practice?

Not only internal barriers might prevent healthcare professionals to participate in a mainstream genetic testing pathway. External barriers can also prevent them from changing their behavior (20, 22, 51). One major barrier as identified in previous studies was a lack of time during consultations to provide pre-test genetic counseling. However, this seems primarily to be the case for healthcare professionals with minimal or no experience with mainstream genetic testing (**Chapter 2**). This is related to the previously mentioned healthcare professionals' attitude. The expectation that pre-test genetic counseling takes up a lot of time can prevent healthcare professionals from participating in a mainstream genetic testing pathway. Training can help in managing these expectations, because the added time investment of pre-test genetic counseling to the consultations was not a limiting factor for healthcare professionals who had experience with mainstream

genetic testing (**Chapter 2**). The total time investment in our studies to provide pre-test genetic counseling was less than 15 minutes for the majority of participating healthcare professionals (**Chapter 3 and 6**). Previous studies have also shown that pre-test genetic counseling can be performed within 8 to 20 minutes (**Chapter 2**).

Who is paid for genetic counseling and genetic testing?

A shift in tasks and responsibilities also needs to be accompanied by adequate resources to comply to these new workflows, such as dedicated personnel and enough financial support. With the current mainstream genetic testing pathways there is a reduction in total healthcare costs and costs per patient from a healthcare payer perspective (**Chapter 5**). However, the extra responsibilities taken on by non-genetic healthcare professionals are not included in the current billable costs. In the Netherlands, hospitals receive predetermined fees for Treatment Diagnosis Combinations (DBCs) from insurers. A DBC reflects the average costs from diagnosis to treatment to follow-up (52-54). Genetic care can be divided into two trajectories: a simple trajectory and a complex trajectory. When only pre-test genetic counseling is provided, the counseling falls into the simple trajectory. When additional tasks are performed, such as confirming cancer diagnosis of affected relatives, genetic testing or psychosocial care, the counseling falls into the complex trajectory. The costs of the genetic test are not included in the DBCs (55). So far, genetic care is only included in the DBCs of genetic healthcare professionals. Therefore, non-genetic healthcare professionals are currently not reimbursed for providing pre-test genetic counseling and testing their patients. In the future, the DBCs should be restructured to reflect the extra amount of work provided by non-genetic healthcare professionals. In addition, there should be adequate reimbursement for the work that genetic healthcare professionals currently provide without reimbursement. In our mainstream genetic testing pathways, all genetic test results are sent to patients by the genetic department in a letter. In addition, especially for the breast cancer pathway, quality control was more extensive. Because the eligibility criteria for breast cancer genetic testing are more complex, it was necessary to verify early on whether ordered genetic tests were justified according to the national guidelines. Overall, testing more eligible patients, will lead to reduction in healthcare costs, because of the optimization of treatment choices and opportunities for preventive measures for both patients and family members (56, 57).

Quality of care

What is needed to uphold good quality of genetic care?

The main purpose of mainstream genetic testing is to improve access to genetic testing in eligible patients. However, an additional advantage in a time of a limited workforce from the genetics departments, is that pre-test genetic counseling provided by non-genetic

healthcare professionals is less time consuming. And especially for ovarian cancer, most patients do not require post-test genetic counseling by a genetic healthcare professional, because only a relatively small proportion of patients carry a pathogenic variant in an ovarian cancer gene or require further evaluation into Lynch syndrome. In contrast, the mainstream genetic testing pathway for breast cancer still requires significant involvement from the genetics department. Although not presented in this thesis, approximately half of all breast cancer patients required post-test genetic counseling because of their family history to make a risk assessment for family members and provide appropriate screening recommendations. Moreover, as already mentioned, the mainstream genetic testing pathway for breast cancer was more complex and therefore required more quality control by the genetics department. The genetics department of the UMC Utrecht recently decided to partially appoint dedicated nurses/nurse specialists from the hospitals that participate the most in our mainstream genetic testing pathway for breast cancer. This means that in addition to their current tasks, they will receive training from the genetics department and a limited amount of time per week to perform these post-test consultations for the genetics department. This will reduce the number of consultations that need to be provided by genetic healthcare professionals even further. The additional expectation with a dedicated nurse/nurse specialist as such a central figure per hospital is that this will increase the quality of the mainstream genetic care at these hospitals. Because of the extensive eligibility criteria for breast cancer, it is a challenge for non-genetic healthcare professionals to identify all eligible patients for testing and in previous studies this led to testing rates among ineligible patients of 16 – 35% (48, 58, 59). Previous research of Cohen et al. has shown that such a collaborative approach with dedicated nurses/nurse specialists is effective in increasing the number of patients who correctly receive genetic testing and ensuring good quality of care (59).

Methodological considerations

What are the strengths of our research and which elements can be improved in future research?

An important strength of this study is that we were able to include large groups of patients who received mainstream genetic testing or pre-test genetic counseling by a genetic healthcare professional, for both the breast and ovarian cancer study. And especially in our breast cancer study, this allowed us to make a valid comparison with patients who received pre-test genetic counseling from a genetic healthcare professional. A limitation of our ovarian cancer study is that patients who received pre-test genetic counseling in the genetics department did not receive a questionnaire until after the test result, which made it impossible to compare this care pathway immediately after pre-test genetic counseling.

For future research, it is important to evaluate medical oncologists' attitudes and experiences with mainstream genetic testing. Although we invited medical oncologists to participate in our breast cancer mainstreaming project, they were unable to put this into practice because of the lack of patients in their practice who were eligible for genetic testing and met our criteria for mainstream genetic testing (i.e., eligibility for genetic testing independent of family data). However, this is likely to change in the future as therapeutic options increasingly depend on the results of genetic testing (60-62).

It is also important to evaluate training more thoroughly. So far, a comparison between trained and untrained healthcare professionals participating in mainstream genetic testing is lacking. Finally, there has been insufficient research on the impact of mainstream genetic testing on the proportion of eligible patients with breast cancer who receive genetic testing. Because of the extensive eligibility criteria, this requires more detailed evaluation of the medical and family data of newly diagnosed patients with breast cancer. This should be investigated more thoroughly to determine whether certain patient groups are underrepresented in the mainstream genetic testing pathways. Subsequently, training and pathways can be adapted to improve on this. In addition, optimal timing to offer pre-test genetic counseling should be investigated in more detail: at what stage of the treatment process can genetic testing best be offered to patients, and how to identify those patients who need more time to consider genetic testing or more extensive pre-test counseling at a genetics department.

Future perspectives

How to offer genetic testing to every eligible patient?

Although mainstream genetic testing has increased testing rates among eligible patients, still not all eligible patients receive genetic testing. In our ovarian cancer study 30% of newly diagnosed patients were not offered genetic testing within six months of their diagnosis (**Chapter 5**). In previous research by Bednar et al., about 15% of patients did not receive genetic testing after implementation of mainstream genetic testing, among other strategies to improve testing rates (32). It is important to further elucidate the reasons behind this. It is noteworthy that in our breast cancer cohort in particular, a high percentage of patients had a high level of education (>40% in both groups). This raises the question whether patients with a lower education were underrepresented and this should be studied in more detail in the future.

Because patients can choose not to opt for a genetic test, focusing on the number of patients who were offered genetic testing provides more insight than merely focusing on the number of patients tested. The proportion of patients that declined testing in our

ovarian cancer study was between 6% and 11% (**Chapter 5**), which is still a substantial proportion and in line with previous research (32, 63). However, whether or not a genetic test was performed is a clear endpoint, whereas offering a genetic test is not, as this is not always clearly documented in the patient file. But even with patients declining a genetic test, still not all patients are offered genetic testing. Therefore, it is important to assess specific barriers that prevent and facilitators that enable the provision of genetic testing to all eligible patients. For ovarian cancer, especially the high morbidity and mortality seems to play an important role. Incorporating tumor testing might be a solution for this. For breast cancer, the extensive eligibility criteria may be preventing healthcare professionals from identifying all eligible patients. There is an increasing debate whether or not to implement universal genetic testing for all patients with breast cancer.

What is the role of tumor testing as a prescreen for germline genetic testing in ovarian cancer?

Treatment with PARP inhibitors is especially effective for ovarian cancer patients with a pathogenic variant in a *BRCA1* or *BRCA2* gene. This does not only include germline but also somatic variants. In the Netherlands, a tumor-first approach has been developed and implemented previously to identify all patients eligible for this treatment (64). Based on the results of this study and the validation of the tumor test (65, 66), the tumor first approach is now nationally being implemented as a prescreen to identify patients who are eligible for germline genetic testing. With such a pathway, both patients with germline and somatic variants can be identified. These somatic variants would be missed with germline genetic testing only. An additional advantage is that only patients in whom a pathogenic variant is identified need additional germline analysis to establish if the pathogenic variant is a germline or somatic variant.

The relevance of tumor testing in these patients has been underlined by many studies and guidelines (67-71). However, the sensitivity of detecting mutations and differences between assays through somatic testing compared to germline genetic testing is still a matter of debate and consequently recommended strategies on how to incorporate tumor testing into the care pathway of ovarian cancer patients differ. The British Gynaecological Cancer Society advocates parallel tumor and germline testing (68), mainly based on the SIGNPOST study which showed that 20% of germline pathogenic variant were missed when the tumor test was used as a prescreen for germline genetic testing (72). Frugtniet et al. also prefers such an approach with parallel testing, but showed a much lower germline pathogenic variant rate of 2% that would be missed with tumor testing first (73). It is striking that Bekos et al. also missed 2% of germline pathogenic variants with such an approach, but considered this acceptable and encouraged tumor testing first (74). The ASCO guideline on the other hand prefers germline genetic testing first and to only offer tumor testing to patients who do not harbor a germline pathogenic variant (70). Kwon et

al. argued that this strategy of germline genetic testing first and subsequent tumor testing may identify most carriers of a pathogenic variant in one of the ovarian cancer genes, but that it is not a cost-effective strategy (75). The problem with this germline testing-first strategy is also that it depends on a high proportion of patients that is offered genetic testing, which is still not optimal in many hospitals (75). There are also studies in which all pathogenic variants identified with germline testing were also identified with tumor testing (76, 77). These studies and guidelines illustrate the difficulties in tumor testing and the different opinions of healthcare professionals about what they consider acceptable.

Despite tumor testing being a prescreen test, it is still important to offer proper pre-test genetic counseling and prepare patients for the possibility of identifying a germline pathogenic variant (69, 78). As already mentioned, it is known that patients may choose not to opt for a germline genetic test (32, 63). Patients therefore should be aware that after identifying a pathogenic variant in their tumor, their risk of harboring a germline pathogenic variant is then 50%. Genetic counseling should be offered before biopsy or surgery in order to perform the tumor genetic test on the tissue obtained. Counseling at this timing might be challenging, as patients may not yet have a final diagnosis.

Another challenge of this tumor first approach is how to deal with a tumor test that fails. It is important not to forget genetic evaluation in these patients. In previous studies, between 20% and 57% of patients who did not complete tumor testing, received germline genetic testing (64, 79). A second tumor test may be considered if additional surgery follows. If this is not applicable, a germline genetic test should be offered to these patients. However, it should be kept in mind that this process can be time consuming and that patients may die in the meantime. Genetic evaluation should then be advised to first-degree family members. In addition, performing multiple tumor tests and sometimes additional germline tests is expensive and not cost-effective.

Lastly, it is important to ensure that all patients with a pathogenic variant in the tumor are offered germline genetic testing. In previous research referral rates were between 88% and 94%(64, 79).

So far, studies have advocated the use of tumor-first testing or mainstream genetic testing for patients with ovarian cancer. None of these studies have described a combined pathway for tumor-first and mainstream genetic testing, where mainstream genetic testing is used for those patients in whom a pathogenic variant is identified with a tumor test. There are advantages and disadvantages for both pathways. Because of the high morbidity and mortality among ovarian cancer patients, there is not always sufficient time to offer and perform germline genetic testing. Material for tumor testing is almost always obtained via biopsy or surgery. Therefore, testing this tumor tissue will be possible for the majority of

patients. However, during pre-test genetic counseling for a tumor test, patients should also be aware that if a pathogenic variant is identified in the tumor tissue, they automatically have a 50% chance of carrying a germline pathogenic variant. Therefore, it is necessary that healthcare professionals also have sufficient knowledge of germline genetic testing to adequately inform the patient. When a pathogenic variant is identified in the tumor, the patient will be prepared for this outcome and the necessary follow-up steps. It is then easy for the non-genetic healthcare professional who provided pre-test genetic counseling for the tumor test to also discuss the germline genetic test instead of referring the patient for pre-test germline genetic counseling by a genetic healthcare professional. This makes the genetic testing pathway more efficient than referring every patient with a pathogenic variant in the tumor to a genetics department. In addition, these non-genetic healthcare professionals can easily order a germline genetic test if the tumor test fails.

To summarize, tumor testing first appears to be the most cost-effective strategy (75). However, there is still debate about the sensitivity to identify all patients carrying a pathogenic germline variant in a cancer susceptibility gene with a tumor test. In addition, the pathway is more complex when a tumor test fails and may create a delay in testing or even prevent testing at all. Last, it is a challenge to ensure proper pre-test genetic counseling.

Is it time to implement universal genetic testing for patients with breast cancer?

In recent years, more debate has started regarding the eligibility criteria for genetic testing in patients with breast cancer. Although NCCN guidelines have been updated to include more patients with breast cancer eligible for testing, there are increasing studies that advocate genetic testing in all patients with breast cancer. The rationale to switch from guideline-based testing to universal genetic testing is to identify more patients who might carry a germline pathogenic variant in one of the breast cancer susceptibility genes. It is well-known that there are disparities in access to genetic testing between different patient groups (27, 80-86). With the different eligibility criteria, it is more difficult to identify patients who are eligible for genetic testing, especially when eligibility is dependent on family data. Sun et al. found universal genetic testing in breast cancer to be cost-effective and to be able to prevent around 2000 breast cancer and ovarian cancer diagnosis per year in the United Kingdom (57). In addition, studies have shown that the prevalence of identified pathogenic variants is equal between patients who complied to NCCN testing criteria as patients who did not comply to these criteria, missing up to 48% of patients who carry such a pathogenic variant with guideline based testing (87-90). It should be noted though, that the pathogenic variants in high-risk genes were mainly identified in patients who comply to testing criteria (87, 89, 91). This difference can easily be explained, because testing criteria were developed to identify patients with a *BRCA1/2* pathogenic variant and

are less suited to identify patients at risk of carrying a pathogenic variant in moderate risk genes (90). This also is an argument in favor of universal screening, because testing criteria are not adjusted to identify these other pathogenic variants. And although these pathogenic variants in other breast cancer susceptibility genes are not always clinically actionable for the patients, they may be significant for family members, who might be eligible for preventive measures if they also carry the same pathogenic variant.

However, universal genetic testing also has its limitations and therefore its opponents. Increased testing rates will likely increase the number of variants of unknown clinical significance (VUS) identified. Studies have shown that VUS rates are especially higher in the racial minority groups (27, 80, 88). When universal testing leads to more testing of minorities, it will most likely increase the VUS rate (92). In addition, as already mentioned, expanding eligibility criteria will increase the number of pathogenic variants identified in the moderate-risk genes. Copur stated that current guidelines are not yet well established and therefore, identifying more pathogenic variants in moderate risk genes will only lead to more questions and distress (93). Previous research has shown discrepancies in treatment as advised in guidelines and actually provided to patients who carry a VUS or pathogenic variant in a moderate-risk gene (94, 95). However, as most mainstream genetic testing pathways ensure that all patients with a pathogenic variant or variant of unknown significance receive post-test genetic counseling from a genetic healthcare professional, this seems to be less of an issue. In addition, with increasing testing rates, the VUS rates are expected to decrease, especially when gaining more insight into the variants identified in minority groups. Another important barrier to universal testing are the limited resources to provide pre-test genetic counseling to all these patients. Because of these concerns, some studies have proposed to implement universal testing only in patients diagnosed below the age of 60 or 65, and to still incorporate the family criteria when patients are diagnosed above this age (96, 97). Although these studies do not yet agree if universal testing should be age dependent, they all advocate that the current guidelines should be adapted to identify more patients who carry a pathogenic variant in one of the breast cancer genes and especially the moderate-risk breast cancer genes.

In summary, although universal genetic testing will lead to the identification of more pathogenic variants, especially in the moderate risk genes, there are still significant barriers to implement this in daily practice. There need to be more established guidelines for managing the identification of pathogenic variants in these moderate-risk genes and adequate resources to cope with the increasing number of patients requiring pre- and posttest genetic counseling. Especially for these increasing rates of counseling, mainstream genetic testing may be part of the solution, but this still requires more resources.

What are prerequisites to disseminate the mainstreaming of genetic testing in cancer care?

The increasing use of genetic testing for patients with cancer is not only applicable to breast and ovarian cancer, but for many other cancer types as well, such as prostate and pancreatic cancer. The existing mainstream genetic testing pathways for breast and ovarian cancer provide us with important success factors for a sustainable implementation:

1. Mainstream genetic testing requires devoted healthcare professionals to effectively incorporate genetic testing into their daily work.
2. A concise online training for non-genetic healthcare professionals about genetic counseling and testing is important to increase their motivation, self-efficacy and knowledge about genetic testing. Training should be recurrent as guidelines and knowledge change over time. Ideally, training about genetic testing should be integrated into the education of non-genetic healthcare professionals, with lectures but also practical experience, such as internships.
3. Successful mainstream genetic testing initiatives require a close collaboration between non-genetic and genetic departments (including clinical laboratory geneticists), to ensure that non-genetic healthcare professionals feel supported in this new workflow and to uphold quality of care.
4. It is important to ensure that all patients who need post-test genetic counseling will be offered such counseling by a genetic healthcare professional. This includes patients with a (likely) pathogenic variant in one of the breast cancer genes, patients with a VUS and patients with a relevant personal or family history. An effective way to ensure this is to invite these patients directly to the genetics department at time the test result is disclosed. A checklist is well suited to identify patients with a relevant personal or family history.

Conclusion

The results of this thesis show that mainstream genetic testing can be successfully incorporated into standard care of all patients with breast or ovarian cancer who are eligible for genetic testing. Non-genetic healthcare professionals feel motivated and confident to provide pre-test genetic counseling and can incorporate this into routine practice. Patients feel well-informed to make a decision regarding genetic testing, and mainstream genetic testing leads to higher testing rates and a reduction in genetics-related healthcare costs. There are, however, conditions to ensure that quality of care is maintained. These include adequate training of non-genetic healthcare professionals, logistics to ensure post-test genetic counseling with a genetic healthcare professional if needed, and most of all, sufficient resources. Although mainstream genetic testing increases the testing rates, still not all patients with breast and ovarian cancer eligible

for genetic testing receive genetic testing. Therefore, additional measures are needed to optimize these testing rates and to reduce disparities. Incorporating tumor testing into mainstream initiative for ovarian cancer and simplifying the eligibility criteria for genetic testing for breast cancer seem promising.

Referenties

1. Reyna VF, Edelson S, Hayes B, Garavito D. Supporting Health and Medical Decision-making: Findings and Insights from Fuzzy-Trace Theory. Med Decis Making. 2022;42(6):741-754.
2. Reyna VF, Nelson WL, Han PK, Pignone MP. Decision-making and cancer. Am Psychol. 2015;70(2):105-118.
3. Ardern-Jones A, Kenen R, Eeles R. Too much, too soon? Patients and health professionals' views concerning the impact of genetic testing at the time of breast cancer diagnosis in women under the age of 40. Eur J Cancer Care (Engl). 2005;14(3):272-281.
4. Joseph G, Pasick RJ, Schillinger D, Luce J, Guerra C, Cheng JKY. Information Mismatch: Cancer Risk Counseling with Diverse Underserved Patients. J Genet Couns. 2017;26(5):1090-1104.
5. Charron M, Kaiser B, Dauge A, Gallois H, Lapointe J, Dorval M, et al. Integrating hereditary breast and ovarian cancer genetic counselling and testing into mainstream clinical practice: Legal and ethical challenges. Crit Rev Oncol Hematol. 2022;178:103797.
6. Kaphingst KA, Blanchard M, Milam L, Pokharel M, Elrick A, Goodman MS. Relationships Between Health Literacy and Genomics-Related Knowledge, Self-Efficacy, Perceived Importance, and Communication in a Medically Underserved Population. J Health Commun. 2016;21 Suppl 1:58-68.
7. Lea DH, Kaphingst KA, Bowen D, Lipkus I, Hadley DW. Communicating genetic and genomic information: health literacy and numeracy considerations. Public Health Genomics. 2011;14(4-5):279-289.
8. Peterson EB, Chou WS, Gaysynsky A, Krakow M, Elrick A, Khoury MJ, et al. Communication of cancer-related genetic and genomic information: A landscape analysis of reviews. Transl Behav Med. 2018;8(1):59-70.
9. Langford A, Studts JL, Byrne MM. Improving knowledge and decision readiness to participate in cancer clinical trials: Effects of a plain language decision aid for minority cancer survivors. Patient Educ Couns. 2021;104(2):422-426.
10. van der Giessen JAM, Ausems M, van Riel E, de Jong A, Fransen MP, van Dulmen S. Development of a plain-language guide for discussing breast cancer genetic counseling and testing with patients with limited health literacy. Support Care Cancer. 2021;29(6):2895-2905.
11. Tea MM, Tan YY, Staudigl C, Eibl B, Renz R, Asseryanis E, et al. Improving comprehension of genetic counseling for hereditary breast and ovarian cancer clients with a visual tool. PLoS One. 2018;13(7):e0200559.
12. Albada A, van Dulmen S, Spreeuwenberg P, Ausems MG. Follow-up effects of a tailored pre-counseling website with question prompt in breast cancer genetic counseling. Patient Educ Couns. 2015;98(1):69-76.
13. Nguyen MH, Smets EM, Bol N, Loos EF, van Laarhoven HW, Geijsen D, et al. Tailored Web-Based Information for Younger and Older Patients with Cancer: Randomized Controlled Trial of a Preparatory Educational Intervention on Patient Outcomes. J Med Internet Res. 2019;21(10):e14407.

14. Wevers MR, Aaronson NK, Bleiker EMA, Hahn DEE, Brouwer T, van Dalen T, et al. Rapid genetic counseling and testing in newly diagnosed breast cancer: Patients' and health professionals' attitudes, experiences, and evaluation of effects on treatment decision-making. J Surg Oncol. 2017;116(8):1029-1039.
15. Wevers MR, Ausems MG, Verhoef S, Bleiker EM, Hahn DE, Brouwer T, et al. Does rapid genetic counseling and testing in newly diagnosed breast cancer patients cause additional psychosocial distress? results from a randomized clinical trial. Genet Med. 2016;18(2):137-144.
16. Wright S, Porteous M, Stirling D, Lawton J, Young O, Gourley C, et al. Patients' Views of Treatment-Focused Genetic Testing (TFGT): Some Lessons for the Mainstreaming of BRCA1 and BRCA2 Testing. J Genet Couns. 2018;27(6):1459-1472.
17. Bjornslett M, Dahl AA, Sorebo O, Dorum A. Psychological distress related to BRCA testing in ovarian cancer patients. Fam Cancer. 2015;14(4):495-504.
18. Fox E, McCuaig J, Demsky R, Shuman C, Chitayat D, Maganti M, et al. The sooner the better: Genetic testing following ovarian cancer diagnosis. Gynecol Oncol. 2015;137(3):423-429.
19. Van de Beek I, Smets EMA, Legdeur MA, de Hullu JA, Lok CAR, Buist MR, et al. Genetic counseling of patients with ovarian carcinoma: acceptance, timing, and psychological wellbeing. J Community Genet. 2020;11(2):183-191.
20. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA. 1999;282(15):1458-1465.
21. Sheeran P, Maki A, Montanaro E, Avishai-Yitshak A, Bryan A, Klein WM, et al. The impact of changing attitudes, norms, and self-efficacy on health-related intentions and behavior: A meta-analysis. Health Psychol. 2016;35(11):1178-1188.
22. Paul JL, Leslie H, Trainer AH, Gaff C. A theory-informed systematic review of clinicians' genetic testing practices. Eur J Hum Genet. 2018;26(10):1401-1416.
23. Crellin E, McClaren B, Nisselle A, Best S, Gaff C, Metcalfe S. Preparing Medical Specialists to Practice Genomic Medicine: Education an Essential Part of a Broader Strategy. Front Genet. 2019;10:789.
24. Houwink EJ, van Luijk SJ, Henneman L, van der Vleuten C, Jan Dinant G, Cornel MC. Genetic educational needs and the role of genetics in primary care: a focus group study with multiple perspectives. BMC Fam Pract. 2011;12:5.
25. McClaren BJ, Crellin E, Janinski M, Nisselle AE, Ng L, Metcalfe SA, et al. Preparing Medical Specialists for Genomic Medicine: Continuing Education Should Include Opportunities for Experiential Learning. Front Genet. 2020;11:151.
26. Gleeson M, Kentwell M, Meiser B, Do J, Nevin S, Taylor N, et al. The development and evaluation of a nationwide training program for oncology health professionals in the provision of genetic testing for ovarian cancer patients. Gynecol Oncol. 2020;158(2):431-439.
27. Kurian AW, Li Y, Hamilton AS, Ward KC, Hawley ST, Morrow M, et al. Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer. J Clin Oncol. 2017;35(20):2232-2239.

28. Hallowell N, Wright S, Stirling D, Gourley C, Young O, Porteous M. Moving into the mainstream: healthcare professionals' views of implementing treatment focussed genetic testing in breast cancer care. Fam Cancer. 2019;18(3):293-301.
29. Lee YQ, Yoon SY, Hassan T, Padmanabhan H, Yip CH, Keng WT, et al. Attitudes and training needs of oncologists and surgeons in mainstreaming breast cancer genetic counseling in a low-to-middle income Asian country. J Genet Couns. 2022;31(5):1080-1089.
30. Douma KF, Smets EM, Allain DC. Non-genetic health professionals' attitude towards, knowledge of and skills in discussing and ordering genetic testing for hereditary cancer. Fam Cancer. 2016;15(2):341-50.
31. Eccles BK, Copson E, Maishman T, Abraham JE, Eccles DM. Understanding of BRCA VUS genetic results by breast cancer specialists. BMC Cancer. 2015;15:936.
32. Bednar EM, Oakley HD, Sun CC, Burke CC, Munsell MF, Westin SN, et al. A universal genetic testing initiative for patients with high-grade, non-mucinous epithelial ovarian cancer and the implications for cancer treatment. Gynecol Oncol. 2017;146(2):399-404.
33. Benusiglio PR, Korenbaum C, Vibert R, Ezenfis J, Geoffron S, Paul C, et al. Utility of a mainstreamed genetic testing pathway in breast and ovarian cancer patients during the COVID-19 pandemic. Eur J Med Genet. 2020;63(12):104098.
34. Colombo N, Huang G, Scambia G, Chalas E, Pignata S, Fiorica J, et al. Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer. J Clin Oncol. 2018;36(13):1300-1307.
35. Czekalski MA, Huziak RC, Durst AL, Taylor S, Mai PL. Mainstreaming Genetic Testing for Epithelial Ovarian Cancer by Oncology Providers: A Survey of Current Practice. JCO Precis Oncol. 2022;6:e2100409.
36. Flaum N, Morgan RD, Burghel GJ, Bulman M, Clamp AR, Hasan J, et al. Mainstreaming germline BRCA1/2 testing in non-mucinous epithelial ovarian cancer in the North West of England. Eur J Hum Genet. 2020;28(11):1541-1547.
37. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Sci Rep. 2016;6:29506.
38. Ip E, Young AL, Scheinberg T, Harrison M, Beale P, Goodwin A. Evaluation of a mainstream genetic testing program for women with ovarian or breast cancer. Asia Pac J Clin Oncol. 2022;18(5):e414-e419.
39. McCuaig JM, Thain E, Malcolmson J, Keshavarzi S, Armel SR, Kim RH. A Comparison of Patient-Reported Outcomes Following Consent for Genetic Testing Using an Oncologist- or Genetic Counselor-Mediated Model of Care. Curr Oncol. 2021;28(2):1459-71.
40. McLeavy L, Rahman B, Kristeleit R, Ledermann J, Lockley M, McCormack M, et al. Mainstreamed genetic testing in ovarian cancer: patient experience of the testing process. Int J Gynecol Cancer. 2020;30(2):221-6.
41. McVeigh TP, Sweeney KJ, Brennan DJ, McVeigh UM, Ward S, Strydom A, et al. A pilot study investigating feasibility of mainstreaming germline BRCA1 and BRCA2 testing in high-risk

patients with breast and/or ovarian cancer in three tertiary Cancer Centres in Ireland. Fam Cancer. 2022. Online ahead of print.

42. Powell CB, Laurent C, Ciaravino G, Garcia C, Han L, Hoodfar E, et al. Streamlining genetic testing for women with ovarian cancer in a Northern California health care system. Gynecol Oncol. 2020;159(1):221-228.
43. Rahman B, Lanceley A, Kristeleit RS, Ledermann JA, Lockley M, McCormack M, et al. Mainstreamed genetic testing for women with ovarian cancer: first-year experience. J Med Genet. 2019;56(3):195-198.
44. Richardson M, Min HJ, Hong Q, Compton K, Mung SW, Lohn Z, et al. Oncology Clinic-Based Hereditary Cancer Genetic Testing in a Population-Based Health Care System. Cancers (Basel). 2020;12(2).
45. Sadinsky MB, Power J, Ambrosio E, Palma L, Zeng X, Foulkes WD, et al. Patient Experience with a Gynecologic Oncology-Initiated Genetic Testing Model for Women with Tubo-Ovarian Cancer. Curr Oncol. 2022;29(5):3565-3575.
46. Yoon SY, Wong SW, Lim J, Ahmad S, Mariapun S, Padmanabhan H, et al. Oncologist-led BRCA counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes. J Med Genet. 2022;59(3):220-229.
47. Beard C, Monohan K, Cicciarelli L, James PA. Mainstream genetic testing for breast cancer patients: early experiences from the Parkville Familial Cancer Centre. Eur J Hum Genet. 2021;29(5):872-880.
48. Grindedal EM, Jorgensen K, Olsson P, Gravdehaug B, Luras H, Schlichting E, et al. Mainstreamed genetic testing of breast cancer patients in two hospitals in South Eastern Norway. Fam Cancer. 2020;19(2):133-142.
49. Kemp Z, Turnbull A, Yost S, Seal S, Mahamdallie S, Poyastro-Pearson E, et al. Evaluation of Cancer-Based Criteria for Use in Mainstream BRCA1 and BRCA2 Genetic Testing in Patients With Breast Cancer. JAMA Netw Open. 2019;2(5):e194428.
50. Stromsvik N, Olsson P, Gravdehaug B, Luras H, Schlichting E, Jorgensen K, et al. "It was an important part of my treatment": a qualitative study of Norwegian breast Cancer patients' experiences with mainstreamed genetic testing. Hered Cancer Clin Pract. 2022;20(1):6.
51. Wright S, Porteous M, Stirling D, Young O, Gourley C, Hallowell N. Negotiating jurisdictional boundaries in response to new genetic possibilities in breast cancer care: The creation of an 'oncogenetic taskscape'. Soc Sci Med. 2019;225:26-33.
52. Busse R, Geissler A, Aaviksoo A, Cots F, Hakkinen U, Kobel C, et al. Diagnosis related groups in Europe: moving towards transparency, efficiency, and quality in hospitals? BMJ. 2013;346:f3197.
53. Kroneman M, Boerma W, van den Berg M, Groenewegen P, de Jong J, van Ginneken E. Netherlands: Health System Review. Health Syst Transit. 2016;18(2):1-240.
54. Scheller-Kreinsen D, Quentin W, Busse R. DRG-based hospital payment systems and technological innovation in 12 European countries. Value Health. 2011;14(8):1166-1172.

55. Prestatie- en tariefbeschikking medisch-specialisitsche zorg 2021. In: Table with rates for DRG care products and other care products from January 1, editor.: Dutch Healthcare Association; 2021.
56. Hoskins PJ, Gotlieb WH. Missed therapeutic and prevention opportunities in women with BRCA-mutated epithelial ovarian cancer and their families due to low referral rates for genetic counseling and BRCA testing: A review of the literature. CA Cancer J Clin. 2017;67(6):493-506.
57. Sun L, Brentnall A, Patel S, Buist DSM, Bowles EJA, Evans DGR, et al. A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer. JAMA Oncol. 2019;5(12):1718-1730.
58. Sie AS, van Zelst-Stams WA, Spruijt L, Mensenkamp AR, Ligtenberg MJ, Brunner HG, et al. More breast cancer patients prefer BRCA-mutation testing without prior face-to-face genetic counseling. Fam Cancer. 2014;13(2):143-151.
59. Cohen SA, Nixon DM. A collaborative approach to cancer risk assessment services using genetic counselor extenders in a multi-system community hospital. Breast Cancer Res Treat. 2016;159(3):527-534.
60. Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021;16(3):255-282.
61. Tew WP, Lacchetti C, Ellis A, Maxian K, Banerjee S, Bookman M, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-3493.
62. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405.
63. McGee J, Peart TM, Foley N, Bertrand M, Prefontaine M, Sugimoto A, et al. Direct Genetics Referral Pathway for High-Grade Serous Ovarian Cancer Patients: The “Opt-Out” Process. J Oncol. 2019;2019:6029097.
64. Vos JR, Fakkert IE, de Hullu JA, van Altena AM, Sie AS, Ouchene H, et al. Universal Tumor DNA BRCA1/2 Testing of Ovarian Cancer: Prescreening PARPi Treatment and Genetic Predisposition. J Natl Cancer Inst. 2020;112(2):161-169.
65. de Jonge MM, Ruano D, van Eijk R, van der Stoep N, Nielsen M, Wijnen JT, et al. Validation and Implementation of BRCA1/2 Variant Screening in Ovarian Tumor Tissue. J Mol Diagn. 2018;20(5):600-611.
66. Weren RD, Mensenkamp AR, Simons M, Eijkelenboom A, Sie AS, Ouchene H, et al. Novel BRCA1 and BRCA2 Tumor Test as Basis for Treatment Decisions and Referral for Genetic Counselling of Patients with Ovarian Carcinomas. Hum Mutat. 2017;38(2):226-235.
67. Capoluongo E, Ellison G, Lopez-Guerrero JA, Penault-Llorca F, Ligtenberg MJL, Banerjee S, et al. Guidance Statement On BRCA1/2 Tumor Testing in Ovarian Cancer Patients. Semin Oncol. 2017;44(3):187-197.
68. Sundar S, Manchanda R, Gourley C, George A, Wallace A, Balega J, et al. British Gynaecological Cancer Society/British Association of Gynaecological Pathology consensus for germline and tumor testing for BRCA1/2 variants in ovarian cancer in the United Kingdom. Int J Gynecol Cancer. 2021;31(2):272-278.

69. Vergote I, Gonzalez-Martin A, Ray-Coquard I, Harter P, Colombo N, Pujol P, et al. European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer. Ann Oncol. 2022;33(3):276-287.
70. Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245.
71. Miller RE, Leary A, Scott CL, Serra V, Lord CJ, Bowtell D, et al. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. Ann Oncol. 2020;31(12):1606-1622.
72. Chandrasekaran D, Sobocan M, Blyuss O, Miller RE, Evans O, Crusz SM, et al. Implementation of Multigene Germline and Parallel Somatic Genetic Testing in Epithelial Ovarian Cancer: SIGNPOST Study. Cancers (Basel). 2021;13(17):4344.
73. Frugtniet B, Morgan S, Murray A, Palmer-Smith S, White R, Jones R, et al. The detection of germline and somatic BRCA1/2 genetic variants through parallel testing of patients with high-grade serous ovarian cancer: a national retrospective audit. BJOG. 2022;129(3):433-442.
74. Bekos C, Grimm C, Kranawetter M, Polterauer S, Oberndorfer F, Tan Y, et al. Reliability of Tumor Testing Compared to Germline Testing for Detecting BRCA1 and BRCA2 Mutations in Patients with Epithelial Ovarian Cancer. J Pers Med. 2021;11(7):593.
75. Kwon JS, Tinker AV, Santos J, Compton K, Sun S, Schrader KA, et al. Germline Testing and Somatic Tumor Testing for BRCA1/2 Pathogenic Variants in Ovarian Cancer: What Is the Optimal Sequence of Testing? JCO Precis Oncol. 2022;6:e2200033.
76. Fumagalli C, Tomao F, Betella I, Rappa A, Calvello M, Bonanni B, et al. Tumor BRCA Test for Patients with Epithelial Ovarian Cancer: The Role of Molecular Pathology in the Era of PARP Inhibitor Therapy. Cancers (Basel). 2019;11(11):1641.
77. Rivera D, Paudice M, Gismondi V, Anselmi G, Vellone VG, Varesco L, et al. Implementing NGS-based BRCA tumour tissue testing in FFPE ovarian carcinoma specimens: hints from a real-life experience within the framework of expert recommendations. J Clin Pathol. 2021;74(9):596-603.
78. Li MM, Chao E, Esplin ED, Miller DT, Nathanson KL, Plon SE, et al. Points to consider for reporting of germline variation in patients undergoing tumor testing: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(7):1142-1148.
79. McCuaig JM, Care M, Ferguson SE, Kim RH, Stockley TL, Metcalfe KA. Year 1: Experiences of a tertiary cancer centre following implementation of reflex BRCA1 and BRCA2 tumor testing for all high-grade serous ovarian cancers in a universal healthcare system. Gynecol Oncol. 2020;158(3):747-753.
80. Kurian AW, Ward KC, Howlader N, Deapen D, Hamilton AS, Mariotto A, et al. Genetic Testing and Results in a Population-Based Cohort of Breast Cancer Patients and Ovarian Cancer Patients. J Clin Oncol. 2019;37(15):1305-1315.
81. Hinchcliff EM, Bednar EM, Lu KH, Rauh-Hain JA. Disparities in gynecologic cancer genetics evaluation. Gynecol Oncol. 2019;153(1):184-191.

82. Baars JE, van Dulmen AM, Velthuizen ME, Theunissen EB, Vrouenraets BC, Kimmings AN, et al. Migrant breast cancer patients and their participation in genetic counseling: results from a registry-based study. Fam Cancer. 2016;15(2):163-171.
83. McCarthy AM, Bristol M, Domchek SM, Groeneveld PW, Kim Y, Motanya UN, et al. Health Care Segregation, Physician Recommendation, and Racial Disparities in BRCA1/2 Testing Among Women With Breast Cancer. J Clin Oncol. 2016;34(22):2610-2618.
84. van der Giessen JAM, van Riel E, Velthuizen ME, van Dulmen AM, Ausems M. Referral to cancer genetic counseling: do migrant status and patients' educational background matter? J Community Genet. 2017;8(4):303-310.
85. Armstrong J, Toscano M, Kotchko N, Friedman S, Schwartz MD, Virgo KS, et al. Utilization and Outcomes of BRCA Genetic Testing and Counseling in a National Commercially Insured Population: The ABOUT Study. JAMA Oncol. 2015;1(9):1251-1260.
86. White S, Jacobs C, Phillips J. Mainstreaming genetics and genomics: a systematic review of the barriers and facilitators for nurses and physicians in secondary and tertiary care. Genet Med. 2020;22(7):1149-1155.
87. Beitsch PD, Whitworth PW, Hughes K, Patel R, Rosen B, Compagnoni G, et al. Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? J Clin Oncol. 2019;37(6):453-460.
88. Samadder NJ, Riegert-Johnson D, Boardman L, Rhodes D, Wick M, Okuno S, et al. Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome. JAMA Oncol. 2021;7(2):230-237.
89. Whitworth PW, Beitsch PD, Patel R, Rosen B, Compagnoni G, Baron PL, et al. Clinical Utility of Universal Germline Genetic Testing for Patients With Breast Cancer. JAMA Netw Open. 2022;5(9):e2232787.
90. Yang S, Axilbund JE, O'Leary E, Michalski ST, Evans R, Lincoln SE, et al. Underdiagnosis of Hereditary Breast and Ovarian Cancer in Medicare Patients: Genetic Testing Criteria Miss the Mark. Ann Surg Oncol. 2018;25(10):2925-2931.
91. Culver JO, Freiberg Y, Ricker C, Comeaux JG, Chang EY, Banerjee V, et al. Integration of Universal Germline Genetic Testing for All New Breast Cancer Patients. Ann Surg Oncol. 2022.
92. Kurian AW, Ward KC, Abrahamse P, Bondarenko I, Hamilton AS, Deapen D, et al. Time Trends in Receipt of Germline Genetic Testing and Results for Women Diagnosed With Breast Cancer or Ovarian Cancer, 2012-2019. J Clin Oncol. 2021;39(15):1631-1640.
93. Copur MS. Universal Genetic Testing for All Breast Cancer Patients. Oncology (Williston Park). 2019;33(8):683731.
94. Kurian AW, Ward KC, Abrahamse P, Hamilton AS, Deapen D, Morrow M, et al. Association of Germline Genetic Testing Results With Locoregional and Systematic Therapy in Patients With Breast Cancer. JAMA Oncol. 2020;6(4):e196400.
95. Murphy BL, Yi M, Arun BK, Gutierrez Barrera AM, Bedrosian I. Contralateral Risk-Reducing Mastectomy in Breast Cancer Patients Who Undergo Multigene Panel Testing. Ann Surg Oncol. 2020;27(12):4613-4621.

96. Desai NV, Yadav S, Batalini F, Couch FJ, Tung NM. Germline genetic testing in breast cancer: Rationale for the testing of all women diagnosed by the age of 60 years and for risk-based testing of those older than 60 years. Cancer. 2021;127(6):828-833.
97. Tung N, Desai N. Germline Genetic Testing for Women With Breast Cancer: Shifting the Paradigm From Whom to Test to Whom NOT to Test. J Clin Oncol. 2021;39(31):3415-3418.

Chapter 9

Summary

It is important to identify patients with breast or ovarian cancer who are carriers of a pathogenic variant in one of the cancer susceptibility genes, because this may impact treatment and surveillance options for both patients and family members. However, in the standard genetic testing pathway in which pre-test counseling is provided by clinical geneticists and genetic counselors, not all patients are adequately referred for genetic counseling and testing for a variety of reasons. To make genetic testing more accessible to all eligible patients and to increase awareness amongst healthcare professionals, mainstream genetic testing pathways are being implemented in many hospitals around the world. In a mainstream genetic testing pathway, non-genetic healthcare professionals (i.e., doctors and nurses already treating the patient) provide pre-test genetic counseling and order a genetic test themselves.

The first part of this thesis provided an overview of existing mainstreaming pathways worldwide. We performed a systematic review on existing initiatives to assess the feasibility of implementing such a pathway into routine genetic cancer care and the impact on quality of care (**Chapter 2**). This review included the assessment of 15 studies, predominantly describing mainstream genetic testing pathways for ovarian cancer (n = 9) and performed in the United Kingdom (n = 8). The main barriers to integrate mainstream genetic testing into standard care were insufficient knowledge amongst non-genetic healthcare professionals and lack of time during consultations. The 8 to 20 minutes required to provide pre-test genetic counseling was considered acceptable to most healthcare professionals, and almost all mainstream initiatives included some form of training for healthcare professionals. The main facilitators for integrating mainstream genetic testing were the use of supporting materials, such as a certified protocol and information sheets to hand out to patients. Mainstream initiatives resulted in shorter turnaround times between diagnosis and test result. An important prerequisite for maintaining good quality of care was that all patients who carry a pathogenic variant in one of the cancer susceptibility genes should receive post-test genetic counseling by a genetic healthcare professional, and a system must be in place to ensure this. More research needs to be done on the proportion of patients who incorrectly receive genetic testing with mainstream genetic testing (i.e., patient who do not fulfill eligibility criteria for genetic testing).

The second part of this thesis focused on mainstream genetic testing for patients with ovarian cancer. We developed and implemented a mainstream genetic testing pathway in all hospitals involved in ovarian cancer care in the service area of the UMC Utrecht genetics department, including the University Medical Center Utrecht and three other hospitals between April 2018 and June 2019 (**Chapter 3**). In addition, we reported on the experiences of 19/21 (90%) gynecologic oncologists, gynecologists with a subspecialty training in oncology and nurse specialists. Pre-test genetic counseling took between

five to ten minutes for 9/15 healthcare professionals (60%) and 10 to 20 minutes for 6/15 healthcare professionals (40%). Healthcare professionals already had a positive attitude, high perceived knowledge and high self-efficacy toward this mainstream genetic testing approach before completing the training module, which did not significantly change six months after working according to the new mainstreaming workflow. Knowledge about genetic testing had increased significantly after six months.

The experiences of 105/133 patients (79%) with mainstream genetic testing were described in **Chapter 4** and were compared to the experiences of 91/152 patients (60%) who received pre-test genetic counseling at a genetics department. In both groups, knowledge regarding genetics, decisional conflict, depression, anxiety, and distress after receiving the test result were comparable. The risk of breast cancer for patients carrying a pathogenic germline variant in a *BRCA1* or *BRCA2* gene was discussed with only 49% of patients in the mainstream group versus 74% of patients in the usual care group. In the mainstream group, regret about the decision to accept genetic testing was higher than in the usual care group, but still far below the threshold for clinically relevant regret.

In **Chapter 5** the effect of mainstream genetic testing on testing rates and genetics-related healthcare costs was evaluated by comparing a period before (March 2016 – September 2017) and after (April 2018 – December 2019) implementing our mainstream genetic testing pathway. After implementation, a significantly higher proportion of patients (70%) were offered genetic testing within six months after diagnosis compared to the period before implementation (56%). Genetics-related healthcare costs had decreased from approximately 3500 euros per patient before implementation to 2400 euros per patient after implementation, which is a 31% reduction.

The last part of this thesis focused on mainstream genetic testing for patients with breast cancer. This pathway was developed and implemented between September 2019 and February 2021 in all hospitals in the service area of the UMC Utrecht genetics department, including the University Medical Center Utrecht and eight other hospitals. In May 2021 until September 2021, this pathway was also implemented in two hospitals in the service area of the UMC Groningen genetics department (**Chapter 6**)**.** In addition, the experiences of 70 healthcare professionals from the breast cancer team with this new pathway were described. The attitude, (perceived) knowledge and self-efficacy toward this new care pathway were already high at baseline and did not significantly change after six months. There was a significant improvement in the perceived knowledge about the advantages and disadvantages of a genetic test and the implications of a test result for family members. The total time investment for pre-test genetic counseling was less than 15 minutes for 40/45 healthcare professionals (89%). The majority of healthcare professionals (44/53,

83%) considered the total time investment feasible to implement into their daily work. The main barrier for not completing the training was a lack of time.

In **Chapter 7** we compared the experiences of 191 patients who received mainstream genetic care with 183 patients who received pre-test genetic counseling from a genetic healthcare professional. Most psychosocial outcomes, both after pre-test genetic counseling and after receiving the test result, were comparable after adjusting for the time between diagnosis and pre-test genetic counseling. Decisional conflict was significantly higher in the mainstream group after pre-test genetic counseling, but only 7% had clinically relevant decisional conflict. The possible implications of a genetic test on a second cancer were discussed less often in the mainstream group during pre-test genetic counseling and in the mainstream group more patients were unsure or disagreed that they had enough information or time to consider genetic testing.

Finally, **Chapter 8** contains a general discussion of our main findings, adressing the opportunities and challenges of mainstream genetic testing from a patient and healthcare profesional perspective and with respect to quality of care. Furthermore, future perspectives such as tumor testing in ovarian cancer and universal testing for breast cancer are discussed, together with the main prerequisites to disseminate the mainstreaming of genetic testing. This chapter concludes that mainstream genetic testing can be succesfully incorporated into standard care of all patients with breast or ovarian cancer who are eligible for genetic testing as long as conditions are met to ensure quality of care.

Chapter 9

Appendices

Nederlandse samenvatting

Acknowledgements/Dankwoord

About the author

Nederlandse samenvatting

Bij patiënten met borst- of eierstokkanker kan er sprake zijn van een erfelijke aanleg die verantwoordelijk is voor het ontstaan van de kanker of hieraan heeft bijgedragen. Een erfelijke aanleg ontstaat door een afwijking of variant in één van de genen die een relatie hebben met het ontstaan van borst- of eierstokkanker. Genetische afwijkingen kunnen alleen in de tumor of in alle cellen van het lichaam voorkomen. Alleen als de genafwijking in alle cellen van het lichaam voorkomt, is er sprake van een erfelijke aanleg. Onderzoek naar een erfelijke aanleg wordt ook wel kiembaan genetisch onderzoek genoemd. Een persoon die drager is van een erfelijke aanleg heeft een hoger risico om kanker te ontwikkelen.

Het is belangrijk om een genetische test aan te bieden aan alle patiënten met eierstokkanker en aan die patiënten met borstkanker die voor dit onderzoek in aanmerking komen (afhankelijk van onder andere leeftijd van diagnose, tumorkarakteristieken zoals hormoonstatus en/of borst-, prostaat- of eierstokkanker in de familie). Het identificeren van een erfelijke aanleg voor kanker kan in de eerste plaats belangrijk zijn voor de behandeling van patiënten. Bij een erfelijke aanleg ten gevolge van een pathogene variant in het *BRCA1*- of *BRCA2*-gen, kunnen patiënten met borstkanker er bijvoorbeeld voor kiezen om de gehele borst te laten verwijderen in plaats van alleen de tumor. Bij eenzelfde erfelijke aanleg bij patiënten met eierstokkanker weten we dat zij goed reageren op behandeling met zogenaamde PARP-remmers. Dit zijn medicijnen die ervoor zorgen dat in de tumor afwijkingen in de genen niet hersteld kunnen worden, waardoor de tumorcellen dood gaan. Ook kunnen patiënten met borstkanker en een erfelijke aanleg een hoger risico hebben om nog een keer borstkanker te krijgen. Daarnaast kunnen zij een hoger risico hebben om eierstokkanker te krijgen. Patiënten met eierstokkanker daarentegen, kunnen bij een erfelijke aanleg ook een verhoogd risico hebben om borstkanker te krijgen. Hiervoor kunnen preventieve maatregelen genomen worden, zoals extra controleadviezen of preventieve operaties. Als bij een patiënt een erfelijke aanleg wordt gevonden, dan kunnen familieleden ook drager zijn van die erfelijke aanleg. Zij kunnen zich hierop laten testen en als zij ook drager zijn, hebben ook zij een verhoogd risico op het ontwikkelen van één of meerdere vormen van kanker. Ook familieleden komen dan in aanmerking voor preventieve maatregelen om kanker vroegtijdig te ontdekken of te voorkómen.

Van oudsher worden alle patiënten met borst- of eierstokkanker verwezen naar een afdeling genetica als zij in aanmerking komen voor genetisch onderzoek. Hier wordt de familie verder in kaart gebracht en krijgen patiënten uitleg over het genetisch onderzoek door een genetische zorgprofessional (klinisch geneticus, arts-assistent, physician assistant of genetisch consulent). Als er op basis van alle gegevens een reden is voor genetisch onderzoek en patiënten kiezen hiervoor, dan kan het genetisch onderzoek worden

aangevraagd. Om uiteenlopende redenen worden echter niet alle patiënten met borst- of eierstokkanker die voor genetisch onderzoek in aanmerking komen verwezen naar een afdeling genetica. Daarnaast zijn er momenteel lange wachtlijsten voor patiënten voordat zij terecht kunnen op een afdeling genetica. Om genetisch onderzoek toegankelijker te maken voor *alle* patiënten die daarvoor in aanmerking komen en om bewustwording onder zorgprofessionals te vergroten, wordt wereldwijd in veel ziekenhuizen het zogenaamde mainstreamen van genetisch onderzoek ingevoerd. Dit houdt in dat niet-genetische zorgprofessionals (zorgprofessionals die niet werkzaam zijn op een afdeling genetica, zoals behandelend artsen, verpleegkundig specialisten of verpleegkundigen) het genetisch onderzoek bespreken met hun patiënten en dit onderzoek ook zelf aanvragen.

Om kiembaan genetisch onderzoek te integreren in de routinezorg van patiënten met borst- of eierstokkanker, hebben we een zorgpad ontwikkeld waarbij niet-genetische zorgprofessionals werkzaam in de borst- of eierstokkankerzorg zelf het genetisch onderzoek bespreken en aanvragen bij hun patiënten. Dit zorgpad hebben we vervolgens geïmplementeerd in alle ziekenhuizen die betrokken zijn bij de zorg van patiënten met borst- en/of eierstokkanker in het verzorgingsgebied van de afdeling genetica van het UMC Utrecht. In een later stadium werd dit zorgpad ook geïmplementeerd in twee ziekenhuizen die betrokken zijn bij de zorg van patiënten met borstkanker in het verzorgingsgebied van de afdeling genetica van het UMC Groningen. Het doel van dit onderzoek was om ervoor te zorgen dat alle patiënten met borst- of eierstokkanker die in aanmerking komen voor genetisch onderzoek, dit onderzoek ook aangeboden krijgen kort nadat de diagnose is gesteld. Het is belangrijk om vroegtijdig te weten of een patiënt drager is van een erfelijk aanleg vanwege de behandelopties en ten behoeve van het informeren van familieleden.

Onze onderzoeksvragen waren:

1. Wat is de houding van niet-genetische zorgprofessionals die werkzaam zijn in de borst- of eierstokkankerzorg tegenover het zelf bespreken en aanvragen van kiembaan genetisch onderzoek?
2. Is het haalbaar voor deze zorgprofessionals om genetisch onderzoek te integreren in de routinezorg?
3. Hoe ervaren patiënten de genetische zorg als genetisch onderzoek is besproken en aangevraagd door een niet-genetische zorgprofessional? En zijn er verschillen met patiënten bij wie genetisch onderzoek is besproken en aangevraagd door een genetische zorgprofessional?
4. Zorgt een zorgpad, waarbij gebruikt wordt gemaakt van het mainstreamen van genetisch onderzoek, ervoor dat meer patiënten die ervoor in aanmerking komen genetisch onderzoek aangeboden krijgen?
5. Wat is het effect van het mainstreamen van genetisch onderzoek op de genetica-gerelateerde zorgkosten?

Het eerste deel van dit proefschrift geeft een overzicht van de gepubliceerde studies over het mainsteamen van genetisch onderzoek bij patiënten met kanker. We voerden een systematische review uit naar deze bestaande initiatieven om te bepalen hoe haalbaar het is om het mainstreamen van genetisch onderzoek te implementeren in de routinezorg van patiënten met kanker en om te evalueren in hoeverre deze aangepaste werkwijze de kwaliteit van zorg beïnvloedt (**Hoofdstuk 2**). In deze review werden in totaal 15 studies beoordeeld, die met name zorgpaden beschreven voor patiënten met eierstokkanker (n = 9) en die uitgevoerd waren in het Verenigd Koninkrijk (n = 8). De belangrijkste barrières om het mainstreamen van genetisch onderzoek te integreren in de routinezorg van patiënten met kanker waren een gebrek aan kennis en tijd onder niet-genetische zorgprofessionals om zelf genetisch onderzoek te bespreken en aan te vragen. Gemiddeld kostte het deze zorgprofessionals 8 tot 20 minuten om het genetisch onderzoek met hun patiënten te bespreken, wat voor de meerderheid van hen acceptabel was. Daarnaast ontvingen de meeste zorgprofessionals een training voordat ze zelf startten met het bespreken en aanvragen van genetisch onderzoek. Voor het mainstreamen van genetisch onderzoek waren het aanbieden van ondersteunend materiaal, zoals een protocol en aanvullende informatie om aan de patiënt mee te geven na het bespreken van genetisch onderzoek, behulpzaam. Het mainstreamen van genetisch onderzoek zorgde tevens voor een kortere tijd tussen het stellen van de diagnose en het ontvangen van de uitslag van genetisch onderzoek. Een belangrijke voorwaarde voor het behouden van een goede kwaliteit van zorg is om er voor te zorgen dat alle patiënten die drager blijken te zijn van een erfelijke aanleg een gesprek aangeboden krijgen met een genetische zorgprofessional. Het is daarbij belangrijk om een goed systeem in te bouwen waarbij al deze patiënten worden geïdentificeerd en dit aanbod daadwerkelijk krijgen. Meer onderzoek is nodig om te bepalen hoeveel patiënten ten onrechte genetisch onderzoek krijgen aangeboden bij het mainstreamen van genetisch onderzoek, dat wil zeggen het aantal patiënten dat niet voldoet aan de criteria om formeel in aanmerking te komen voor genetisch onderzoek maar bij wie dit wel is verricht.

Het tweede deel van dit proefschrift richt zich op het mainstreamen van genetisch onderzoek bij patiënten met eierstokkanker. Voor deze groep patiënten ontwikkelden we een zorgpad waarbij genetisch onderzoek werd besproken en aangevraagd door gynaecologisch oncologen, oncologen met oncologie als aandachtsgebied en verpleegkundig specialisten. Dit zorgpad werd geïmplementeerd tussen april 2018 en juni 2019 in alle ziekenhuizen die betrokken zijn bij de zorg van patiënten met eierstokkanker in het verzorgingsgebied van de afdeling genetica van het Universitair Medisch Centrum Utrecht, waaronder het UMC Utrecht en drie andere ziekenhuizen (**Hoofdstuk 3**). Daarnaast rapporteren we over de ervaringen van 19 van de 21 niet-genetische zorgprofessionals (90%). Het bespreken van genetisch onderzoek kostte 5 tot 10 minuten voor 9 van de 15 zorgprofessionals (60%) en 10 tot 20 minuten voor 6 van de

15 zorgprofessionals (40%). Deze niet-genetische zorgprofessionals hadden voorafgaand aan het volgen van de kennismodule een positieve houding tegenover het zelf bespreken en aanvragen van genetisch onderzoek en een hoge mate van zelfvertrouwen ten aanzien van hun kennis en kunde om dit zelf te doen. Nadat zij zes maanden ervaring hadden opgedaan met deze nieuwe werkwijze, hadden zij nog steeds een positieve houding en hoge mate van zelfvertrouwen. Kennis over eierstokkanker en erfelijkheid was bij deze zorgprofessionals na zes maanden significant toegenomen.

In **Hoofdstuk 4** staan de ervaringen van 105 patiënten beschreven bij wie het genetisch onderzoek was besproken en aangevraagd door een niet-genetische zorgprofessional. Deze ervaringen werden vergeleken met de ervaringen van 91 patiënten bij wie het genetisch onderzoek was besproken en aangevraagd door een genetische zorgprofessional. Na het ontvangen van de uitslag van het genetisch onderzoek waren kennis over eierstokkanker en erfelijkheid, twijfel over de beslissing om wel of geen genetisch onderzoek te verrichten, depressie, angst en stress in beide groepen vergelijkbaar. Het verhoogde risico op borstkanker voor dragers van een erfelijke aanleg in het *BRCA1*- of *BRCA2*-gen werd slechts met 49% van de patiënten besproken bij wie het genetisch onderzoek was besproken door een niet-genetische zorgprofessional ten opzichte van 74% van de patiënten bij wie het genetisch onderzoek was besproken door een genetische zorgprofessional. Daarnaast hadden patiënten, na het ontvangen van de uitslag van het genetisch onderzoek, een hogere mate van spijt over de beslissing om genetisch onderzoek te laten uitvoeren als dit was besproken door een niet-genetische zorgprofessional. Echter, de gemiddelde mate van spijt in deze groep lag onder de grenswaarde waarboven er sprake is van klinisch relevante spijt.

Hoofdstuk 5 beschrijft het effect van het mainstreamen van genetisch onderzoek bij eierstokkanker op het aantal genetische testen onder nieuw gediagnosticeerde patiënten en op de genetica-gerelateerde zorgkosten. Hierbij werd een periode vóór (maart 2016 - september 2017) en na (april 2018 - december 2019) de implementatie van dit nieuwe zorgpad vergeleken. Na implementatie van het mainstreamen kreeg een significant hoger deel van de patiënten (70%) binnen zes maanden na diagnose een genetische test aangeboden in vergelijking met de periode vóór implementatie (56%). De genetica-gerelateerde zorgkosten waren gedaald van ongeveer 3500 euro per patiënt vóór de implementatie naar 2400 euro per patiënt na de implementatie van het mainstreamen, wat een vermindering is van 31% in genetica-gerelateerde zorgkosten.

Het derde deel van dit proefschrift richt zich op het mainstreamen van genetisch onderzoek bij borstkanker. Voor deze groep patiënten ontwikkelden we een zorgpad waarbij genetisch onderzoek werd besproken en aangevraagd door oncologisch chirurgen, verpleegkundig specialisten en mammacare verpleegkundigen. Dit zorgpad werd geïmplementeerd

tussen september 2019 en februari 2021 in alle ziekenhuizen in het verzorgingsgebied van de afdeling genetica van het Universitair Medisch Centrum Utrecht, waaronder het UMC Utrecht en acht andere ziekenhuizen. In mei 2021 tot september 2021 werd dit zorgpad ook geïmplementeerd in twee ziekenhuizen in het verzorgingsgebied van de afdeling genetica van het Universitair Medisch Centrum Groningen (**Hoofdstuk 6**). Daarnaast werden de ervaringen van 70 zorgprofessionals uit het borstkankerteam geëvalueerd, bestaande uit voornamelijk oncologisch chirurgen en verpleegkundigen en verpleegkundig specialisten van de afdeling chirurgie. Deze niet-genetische zorgprofessionals hadden een positieve houding en hoge mate van zelfvertrouwen ten aanzien van hun kennis en kunde en een hoge mate van kennis over borstkanker en erfelijkheid voorafgaand aan de implementatie van dit zorgpad. Na zes maanden waren hun houding, zelfvertrouwen en kennis niet significant veranderd. Deze niet-genetische zorgprofessionals hadden na zes maanden meer vertrouwen in hun kennis over de voor- en nadelen van genetisch onderzoek en de implicaties van genetisch onderzoek voor familieleden. De tijdsinvestering voor het bespreken van genetisch onderzoek was minder dan 15 minuten voor 40 van de 45 zorgprofessionals (89%). De meerderheid van de zorgprofessionals (44 van de 53, 83%) vond de totale tijdsinvestering om genetisch onderzoek te bespreken en aan te vragen haalbaar om in hun dagelijkse werk te implementeren. Tijdgebrek was de belangrijkste belemmering om de training niet af te ronden.

Hoofdstuk 7 toont de ervaringen van 191 patiënten waarbij het genetisch onderzoek was besproken door een niet-genetische zorgprofessional. Hun ervaringen werden vergeleken met de ervaringen van 183 patiënten waarbij het genetisch onderzoek was besproken door een genetische zorgprofessional. De meeste psychosociale uitkomsten, zowel na het bespreken van het genetisch onderzoek als na ontvangen van de testuitslag, waren vergelijkbaar tussen de twee groepen na gecorrigeerd te hebben voor de tijd tussen diagnose en het bespreken van het genetisch onderzoek. Patiënten met wie het genetisch onderzoek was besproken door hun behandelend arts of verpleegkundig specialist hadden significant meer twijfel over de keuze om wel of geen genetisch onderzoek te verrichten, maar slechts 7% van hen had klinisch relevante twijfel. In deze groep werden de mogelijke gevolgen van een genetische test voor het risico op een nieuwe vorm van kanker minder vaak besproken. Daarnaast bestond deze groep uit meer patiënten die twijfelden of het niet eens waren dat zij voldoende informatie of tijd hadden gehad om over het genetisch onderzoek na te denken.

Ten slotte bevat **Hoofdstuk 8** een algemene bespreking van onze belangrijkste bevindingen, waarbij de kansen en uitdagingen van het mainstreamen van genetisch onderzoek aan bod komen vanuit het perspectief van de patiënt en van de zorgprofessional. Ook wordt ingegaan op de kwaliteit van de zorg. Voorts worden toekomstperspectieven besproken zoals genetisch onderzoek van tumormateriaal bij eierstokkanker en het aanbieden van

genetisch onderzoek aan alle patiënten met borstkanker (universeel testen), samen met de belangrijkste voorwaarden om het mainstreamen van genetisch onderzoek verder te implementeren in andere ziekenhuizen en bij andere vormen van kanker. De conclusie van dit hoofdstuk is dat een zorgpad waarbij genetisch onderzoek wordt besproken en aangevraagd door een niet-genetische zorgprofessional met succes kan worden geïntegreerd in de routinezorg voor alle patiënten met borst- of eierstokkanker die voor dit onderzoek in aanmerking komen. Het is daarbij belangrijk om de kwaliteit van zorg te waarborgen door het aanbieden van een training aan niet-genetische zorgprofessionals en door ervoor te zorgen dat alle patiënten die dat nodig hebben een aanvullend gesprek krijgen met een genetische zorgprofessional.

Acknowledgements/Dankwoord

De afgelopen jaren heb ik hard gewerkt om tot een eindresultaat te komen waar ik enorm trots op ben. Tijdens dit promotietraject zijn er veel mensen die mij geïnspireerd, gemotiveerd en gesteund hebben. Daarvoor wil ik hen oprecht bedanken.

Allereerst wil ik mijn promotor en begeleider bedanken, prof. dr. M.G.E.M. Ausems. Beste Margreet, vanaf het begin van mijn promotietraject ben jij nauw betrokken geweest bij mijn projecten. Je bent enorm gedreven en gepassioneerd om de zorg voor patiënten met kanker beter te maken, wat ertoe heeft geleid dat we samen het mainstreamen van genetisch onderzoek in Utrecht echt op de kaart hebben gezet. Ik heb er veel respect voor hoe jij patiëntenzorg en onderzoek combineert. Ondanks je drukke schema gaf je me altijd het gevoel dat ik bij je kon aankloppen als ik daar behoefte aan had. Daarnaast waardeer ik de steun en het vertrouwen dat je me gaf.

Dan mijn tweede promotor, prof. dr. R.P. Zweemer. Beste Ronald, jij was een perfecte aanvulling op mijn promotieteam. Waar ik zelf nog wel eens kon verzanden in details, was jij heel goed in het teruggaan naar de hoofdlijnen en het niet ingewikkelder maken dan nodig is. Daarnaast waardeer ik het vertrouwen dat je me gaf. Een mooi compliment vond ik toen je bij één van onze laatste besprekingen de groei benoemde die je vond dat ik tijdens mijn promotietraject heb doorgemaakt. Je gaf aan dat je een andere PhD student had gesproken die moeite had met het schrijven van artikelen en tegen haar had gezegd: ‘dan moet je eens met Kyra gaan praten, die had dat in eerste instantie ook en nu gaat dat haar heel goed af.’

Prof. dr. E. Bleiker, prof. dr. M.H. Emanuel, dr. A.M. van Eerde, beste Eveline, Mark Hans en Albertien. Als begeleidingscommissie van mijn promotieonderzoek konden jullie vanaf een afstandje meekijken met mijn onderzoek en ook gerichte feedback geven. Ik waardeer hoe jullie kritisch hebben meegedacht en geadviseerd over de planning en met name de haalbaarheid hiervan soms ook ter discussie stelden. Eveline, daarnaast wil ik jou bedanken voor je inhoudelijke hulp bij mijn onderzoek. Jouw meedenken bij de opzet van het onderzoek en je kritische blik bij mijn artikelen heeft mij enorm geholpen.

Prof. dr. L. Hooft, prof. dr. P.O. Witteveen, dr. A.J. Witkamp, prof. dr. M.J.E. Mourits en prof. dr. R.H. Sijmons, bedankt voor het lezen en beoordelen van mijn proefschrift.

Een belangrijk onderdeel van dit promotietraject was het implementeren van een nieuw zorgpad voor genetisch onderzoek bij patiënten met borst- of eierstokkanker. Mijn dank gaat uit naar alle patiënten die mee hebben gedaan aan ons onderzoek. Ik waardeer het dat zij de tijd hebben genomen om onze vragenlijsten in te vullen over hun ervaringen

rondom genetisch onderzoek. Mede dankzij hun feedback hebben we de werkwijze rondom deze zorgpaden kunnen verbeteren. Ook wil ik de patiëntverenigingen -Olijf- en -Stichting Erfelijke Kanker Nederland- bedanken voor hun betrokkenheid bij de opzet van deze nieuwe zorgpaden en het meelezen met de teksten die we hadden opgesteld om patiënten te informeren.

Daarnaast heb ik veel hulp gehad van artsen, verpleegkundig specialisten en verpleegkundigen bij de opzet en uitvoering van deze projecten. Ik wil alle zorgprofessionals bedanken uit het UMC Utrecht, Diakonessenhuis Utrecht, St. Antonius Nieuwegein/ Leidsche Rijn, Meander Medisch Centrum Amersfoort, Alexander Monro Ziekenhuis Bilthoven, Gelre Ziekenhuis Apeldoorn, St. Jansdal Ziekenhuis Harderwijk, Rivierenland Ziekenhuis Tiel en Beatrix Ziekenhuis Gorinchem, die op één of andere wijze bij deze projecten betrokken waren.

Daarbij wil ik het oncoteam van de afdeling genetica apart bedanken voor hun kritische blik en feedback, zowel bij de opzet als na de implementatie van het mainstreamen voor borst- en eierstokkanker. Marjolein, in het bijzonder wil ik jou bedanken, voor het overnemen van zorgtaken tijdens mijn vakanties en je actieve bijdrage aan het verbeteren van de zorgpaden. Wat super dat jij, samen met Dietje, de coördinerende rol bij het mainstreamen van me hebt overgenomen. Ook wil ik Wouter, Marco en Esmée bedanken voor hun betrokkenheid bij mijn onderzoek vanuit het lab. Zonder jullie hulp was het niet gelukt om de kwaliteit van zorg zo nauwkeurig in de gaten te houden.

Binnen de afdeling genetica wil ik ook de arts-assistenten bedanken. Ondanks mijn dubbele rol als onderzoeker en arts hebben jullie me warm verwelkomt binnen de groep. Marieke, wij konden het gelijk met elkaar vinden toen jij op de afdeling kwam werken. Daarbij hebben we de complete Downton Abbey serie gekeken, vaak met pizza en wijn. Ook kon ik een paar keer met jou meekijken toen ik na lange tijd weer wat patiëntenzorg ging doen. Bedankt voor je hulp daarbij en bovenal de gezelligheid. Marijn, inmiddels al klinisch geneticus, jij was mijn "buddy" tijdens dit promotietraject. Dit was met name vanwege de patiëntenzorg die ik deed, maar daarbij heb ik vooral ook veel steun van je gehad binnen mijn onderzoek. Bedankt dat ik twijfels, zorgen, maar ook successen en toekomstplannen met je kon delen.

Ook zijn er mensen die niet inhoudelijk bij dit onderzoek betrokken waren, maar van wie ik veel steun heb gehad. Lieve Sanne en Yara, jullie hebben er echt voor gezorgd dat ik me thuis voelde in Utrecht. Natuurlijk kenden we elkaar al van de studie biologie, wat mijn plan B was toen ik werd uitgeloot voor geneeskunde. Maar ondanks dat we elkaar al een tijd niet hadden gezien nadat ik alsnog geneeskunde ben gaan studeren en jullie naar het midden van het land verhuisden, kon ik in Utrecht gelijk aanschuiven bij de maandelijkse

bier-en-pizza. Daarnaast hebben we veel leuke uitjes ondernomen met zijn drieën, van disco rolschaatsen, tot glas snijden, tot het knutselen van twerkende volgels. En toen jij, Sanne, op 50 meter afstand kwam wonen, zagen we elkaar nog vaker. Jij bent niet voor niets mijn paranimf. Bedankt voor het samen sporten, op anderhalve meter afstand wandelen tijdens corona, het brengen van boodschappen tijdens zelfisolatie, het wijn drinken, maar vooral ook je humor en luisterend oor.

Het afgelopen jaar is de flexruimte van de afdeling genetica een plek geweest waar ik veel steun had aan de andere PhD studenten die daar aan het werk waren. Michiel, of zoals Albertien zou zeggen Robin (van Batman), met jou heb ik nauw samengewerkt aan de review. Daarnaast kon ik inhoudelijk met je sparren over mails, presentaties en noem maar op. Maar bovenal heb ik enorm veel lol met jou gehad. Je hebt een enorme dosis humor, waardoor ik regelmatig in een deuk lag. Bedankt voor je steun en gezelligheid. Marlies, Laura, Esmée en Margriet, bedankt voor de vele koffiemomentjes en wandelingetjes. Met jullie heb ik nooit een saaie dag gehad, van ochtendgymnastiekoefeningen tot 's avonds karaoke. Lieke, wat een verrassing om jou weer tegen te komen in Utrecht. Samen met Juliette waren we al eerder collega's in Groningen. Jij wist me altijd goede raad te geven en ook gerust te stellen als ik dacht dat het niet zou lukken.

Jeanine, Mary en Gina, team Ausems was niet compleet zonder jullie. Jeanine, jij was al even bezig met je promotieonderzoek toen ik op de afdeling kwam. Het was fijn dat je me wegwijs kon maken in het doen van onderzoek. Daarnaast wil ik je bedanken voor de gezellige etentjes en wandelingen buiten het werk om. Mary, zonder jou had ik jaren langer over dit onderzoek gedaan. De logistiek die nodig was om alles in goede banen te leiden, heb jij grotendeels op je genomen, met name voor het borstkankerproject. Ik waardeer je hulp hierbij enorm. Gina, jij was met name betrokken bij het project van Michiel, maar ook mij heb je geholpen met het verzamelen van data in verschillende ziekenhuizen.

Anna en Ilse, samen de tripple B's (heeft Ronald stiekem een voorkeur voor promovendi van wie de acchternaam met een B begint?), het was heel prettig om af en toe bij jullie op de kamer te werken. Bij jullie was er altijd een werkplek voor mij en de lekkere koffie was een bonus. Op jullie kamer kon ik hard werken afwisselen met veel gezelligheid tijdens of na het werk. Jullie hebben me ook echt geleerd om alle successen te vieren, of ze nou groot zijn of klein.

Daarnaast zijn er vele vrienden die me altijd gesteund hebben tijdens mijn onderzoek. De meesten van jullie ken ik al heel lang, van mijn studie geneeskunde (Marian, Elsemarie, Hilde, Renée en Liselotte), mijn ene jaar studie biologie (Martha) of zelfs nog van de middelbare school (Paula, Taylan, Bianca en later ook Thaïra). Ik wil jullie allen bedanken voor jullie steun tijdens mijn promotietraject. Ondanks de geografische afstand, drukke

banen en gezinnen, ben ik erg dankbaar dat we nog steeds contact hebben. Ook al zien we elkaar niet zo vaak, het voelt altijd weer vertrouwd.

Alle meiden van Vocal Venture, wat was het heerlijk om elke dinsdagavond met jullie te zingen. Dit was echt een uitlaatklep voor mij en wat heb ik een leuke mensen ontmoet. Rosanne, in eerste instantie waren wij alt-maatjes. Bij mijn allereerste repetitie zat ik naast je en wat heb ik veel lol met je gehad. En ondanks dat je al een tijd gestopt bent bij het koor, hebben we nog steeds contact en ben je inmiddels een goede vriendin.

Lieve Ivy, lieve pief (hoe die bijnaam is ontstaan weten we volgens mij allebei niet meer), de keuze om jou als paranimf te vragen had ik denk ik al gemaakt voordat ik aan dit promotietraject begon. Ik maak dankbaar gebruik van je kledingkast als ik een bruiloft heb of etentje en ook is de slaapplaats soms heel fijn als ik afspraken heb in Groningen. Maar bovenal heb je mij als grote zus altijd gesteund bij alles wat ik doe. Ik kan altijd bij je terecht en jij voelt ook feilloos aan wanneer ik juist behoefte heb aan meer contact. Zo belde je me tijdens de coronatijd en lockdowns elke dag. En op de momenten dat ik me wat minder goed voelde stuurde jij me bloemen of een kaartje. Lieve Jesper, jij hebt mij er gratis als schoonzus bij gekregen. Bedankt dat ik altijd welkom ben bij jullie en de fijne gesprekken tijdens wandelingen waarbij we onze ervaringen over werk konden delen. Lieve Stijn en sinds kort ook Felien, wat ben ik trots om jullie tante te zijn en hoewel jullie je dat waarschijnlijk nog niet beseffen, heb ik de regelmatige face-time sessies met jullie erg gewaardeerd.

Lieve papa en mama, zonder jullie steun had ik dit promotietraject nooit kunnen doen. Jullie staan echt altijd voor mij klaar en hebben altijd in mij geloofd. Dat heeft me door vele moeilijke momenten heen geholpen. Bedankt voor alles.

Curriculum vitae

Kyra Bokkers was born on November 3rd 1988 in Hoogezand-Sappemeer. She lived in a small town called Borgercompagnie for most of her childhood. In 2007 she graduated from high school (Winkler Prins, Veendam) and started studying at the University of Groningen. After obtaining her propaedeutic degree in biology, Kyra started studying medicine, also at the University of Groningen. She graduated as a medical doctor in 2014, after which she worked as a clinical resident in cardiology and pulmonary diseases at the Martini Hospital in Groningen. In 2016, she started working at the department of genetics of the University Medical Center Groningen as a resident in clinical genetics, primarily in oncogenetics. This work experience sparked her interest in research. In September 2017, she started a research project under the supervision of prof. dr. Margreet Ausems and prof. dr. Ronald Zweemer at the University Medical Center Utrecht. During this project, she developed and implemented a mainstream genetic testing pathway for patients with ovarian cancer. In 2019, Kyra started her PhD trajectory and developed and implemented a mainstream genetic testing pathway for patients with breast cancer. For both projects, the experiences of patients and healthcare professionals were carefully evaluated. For a large part of her PhD trajectory, she combined her research work with patient care in oncogenetics. Since February 2023, she has been working as a resident in clinical genetics at the University Medical Center Utrecht.