New procedures for genetic testing and counselling of patients with breast or ovarian cancer

Hildegunn Høberg Vetti

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The present work has been carried out during 2012-2019 at the Western Norway Familial Cancer Center, Department of Medical Genetics, at Haukeland University Hospital.

Since March 2016 I have been a part time PhD student affiliated to the Department of Clinical Science, genetics group, at the University of Bergen. Associate professor Cathrine Bjorvatn has been main supervisor, and Professor Geir Egil Eide at the Department of Global Public Health and Primary Care has been co-supervisor.

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Contents

Abstract

The aim of this PhD project was to evaluate alternative procedures for genetic testing and counselling of patients newly diagnosed with breast or ovarian cancer, in order to meet the expected increasing need of this health service.

We performed a prospective study, the DNA-BONus study, in which we consecutively offered *BRCA* testing and familial risk assessment to unselected patients with newly diagnosed breast (N=893) or ovarian (N=122) cancer between September 2012 and February 2015, without formal pre-test genetic counselling. Out of the 488 patients who underwent genetic testing 7 of 405 patients (2%) with breast cancer and 19 of 83 patients (22%) with ovarian cancer carried a germline pathogenic *BRCA* variant (**Paper I**). All carriers fulfilled at least one of the Norwegian *BRCA* test criteria (**Paper I**). There was a significant decline in the mean levels of anxiety symptoms (**Paper I**) and cancer related psychological distress (**Paper II**) from inclusion to six months after dissemination of the *BRCA* test result. Predictors of increased distress were young age, short time since diagnosis, low level of perceived social support, high level of decisional conflict, diagnosis of ovarian cancer, and living with a partner (**Paper II**). By investigating RNA splicing, we showed that the intronic *BRCA1* c.5407-25T>A variant leads to partial skipping of exon 22, resulting in the truncated protein p.Gly1803GlnfsTer11. Combined with allele frequency data and clinical information from 20 families, this indicated that *BRCA1* c.5407-25T>A is a likely pathogenic variant with reduced penetrance (**Paper III**).

In conclusion, the current thesis showed that a simplified procedure for *BRCA* testing was accepted and overall well tolerated by women newly diagnosed with breast or ovarian cancer. However, we also identified more vulnerable subgroups that may need more counselling and support to benefit from diagnostic *BRCA* testing. Testing of large groups of individuals with low a priori risk of carrying a germline *BRCA* pathogenic variant, like unselected patients with breast cancer in our study, may lead to detection of more DNA variants with reduced penetrance.

List of Publications

Paper I

Høberg-Vetti H, Bjorvatn C, Fiane BE, Aas T, Woie K, Espelid H, Rusken T, Listøl W, Haavind MT, Knappskog PM, Haukanes BI, Steen VM, Hoogerbrugge N. *BRCA1/2* testing in newly diagnosed breast and ovarian cancer patients: the DNA-BONus study. *Eur J Hum Genet.* 2016;24:881-888.

Paper II

Høberg-Vetti H, Eide GE, Siglen E, Listøl W, Haavind MT, Hoogerbrugge N, Bjorvatn C. Cancer related distress in unselected women with newly diagnosed breast or ovarian cancer undergoing *BRCA1/2* testing without pre-test genetic counselling. *Acta Oncol.* 2019;58:175-181.

Paper III

Høberg-Vetti H, Ognedal E, Buisson A, Vamre TBA, Ariansen S, Hoover JM, Eide GE, Houge G, Fiskerstrand T, Haukanes BI, Eide GE, Bjorvatn C and Knappskog PM. The intronic *BRCA1* c.5407-25T>A variant causing partly skipping of exon 22 – a likely pathogenic variant with reduced penetrance?
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[1]A revised version of this paper has been published in *Eur J Hum Genet*. 2020 Mar 20 [Epub ahead of print]

Abbreviations

ACMG:	American College of Medical Genetics
ATM:	Ataxia-telangiectasia mutated gene
BRCA1:	Breast cancer 1 gene
BRCA2:	Breast cancer 2 gene
BRIP1:	BRCA1-interacting protein 1
CDH1:	Cadherin 1
CHEK2:	Checkpoint kinase 2
BIC:	Breast Cancer Information Core
BRCT:	BRCA1 C-terminus
DCS:	Decisional conflict scale
DNA:	Deoxyribonucleic acid
ENIGMA:	Evidence-based Network for the Interpretation of Germline Mutant Alleles
FDA:	US Food and Drug Administration
HADS:	Hospital anxiety and depression scale
HADS-A:	Hospital anxiety and depression scale – anxiety
HADS-D:	Hospital anxiety and depression scale – depression
IES:	Impact of event scale
IES-A:	Impact of events – avoidance
IES-I:	Impact of events – intrusion
ISEL:	Interpersonal support evaluation list
MGM:	Department of medical genetics
MLH1:	Mutator L homologue gene 1
MLPA:	Multiplex ligation-dependent probe amplification
MMR:	Mismatch repair
MRI:	Magnetic resonance imaging
MSS:	Manchester scoring system
MSH2:	Mutator S homologue gene 2
MSH6:	Mutator S homologue gene 6

NCCN:	National Comprehensive Cancer Network
NGS:	Next generation sequencing
PALB2:	Partner and localiser of BRCA2
PARP:	Poly (ADP-ribose) polymerase
PCR:	Polymerase chain reaction
PTEN:	Phosphatase and tensin homolog
RAD51C:	RAD51 paralog C
RAD51D:	RAD51 paralog D
REK:	Regional committee for medical and health research ethics
RKAK:	Western Norway Familial Cancer Center
RNA:	Ribonucleic acid
SD:	Standard deviation
SEM:	Standard error of means
STK11:	Serine/threonine protein kinase 11
TP53:	Tumour protein p53
VUS:	Variant of uncertain significance

1. Introduction

Cancer constitutes a major health problem and is the second leading cause of death globally [1]. While ageing can be considered the main risk factor for cancer development, identification of environmental risk factors like radiation, tobacco use, and infections has been important to develop strategies for prevention and early diagnosis of cancer. However, hereditary factors also play a significant role, and in a subset of cancer cases the underlying main cause is a germline pathogenic variant in a high-penetrant cancer gene. It is important to identify patients with a hereditary cause of cancer because this gives a unique opportunity to prevent cancer, i.e. a second primary cancer in the patient, and cancer in relatives who have inherited the same predisposition. In addition, genetic information can guide treatment decisions in patients already affected by cancer.

This thesis concerns different aspects connected to *BRCA* genetic testing of patients with breast and/or ovarian cancer. The work presented was carried out between 2012 and 2019, a period of time in which the demand of genetic testing escalated – both inside and outside the healthcare system. In this introduction, the background for the study will be presented.

1.1 Short overview of important developments in medical genetics

Medical genetics is a relatively young discipline within medicine. It builds on a longer research tradition of human genetics [2], where some important milestones were Gregor Mendel's first description of the laws of inheritance in 1865, the determination of the DNA double-helix structure in 1953 [3, 4], and the identification of the correct human chromosome number in 1956 [5]. After cracking of the genetic code in the 1960's it became possible to study genetic variation and its association with disease, leading to the development of the field of medical genetics from the 1970'es [2].

Already in 1972, clinical genetics was acknowledged as a separate speciality field in medicine in Norway, as one of the first countries in the world [6].

Victor McKusick (1921-2008), widely considered the founding father of medical genetics, started to catalogue human genetic phenotypes in the annual compendium "Mendelian Inheritance in Man" ("MIM) in 1966. Due to great advances in molecular techniques thousands of genetic conditions have been mapped and characterised and are now easily accessible in the online version "Online Mendelian Inheritance in Man" OMIM [7]. Sanger sequencing of DNA was introduced in 1975 [8], but it took an extensive collaborative effort to sequence the complete human genome – through the Human Genome Project initiated in 1990 and completed in 2003 [9, 10]. The development of massive parallel sequencing techniques in the following decade, also known as next generation sequencing (NGS), increased the capacity and reduced the turn-around time of sequencing dramatically [11-13]. While it took 13 years and $2.7 billion to sequence the first complete human genome, an individual's genome can now be sequenced in a few days for less than $1.500 [14].

The combination of rapid development in technologies and plummeting costs has made clinical genetic testing increasingly affordable and accessible. Today NGS allows for analysis of multiple genes simultaneously at the same cost as single gene tests, and diagnostic genetic testing is entering everyday practice in most medical disciplines.

1.2 Breast cancer and ovarian cancer in the population

Breast cancer is the most common cancer among women, with globally more than 2 million new cases diagnosed each year [15]. In Norway 3,596 new cases of breast cancer were registered in 2018 and the estimated risk of developing breast cancer by the age of 75 years is 8.9% [16]. The 5-year relative survival rate is 90.7%, and the 15-year relative survival rate is 78.3% [16]. Ovarian cancer is less common; around 300,000 new cases are diagnosed yearly worldwide (444 new cases in Norway in 2018), but the survival is poor: 48.9% and 33.0% 5- and 15-year relative survival rate,

respectively [15, 16]. The cumulative risk of ovarian cancer by the age of 75 years in the population is 1.3% [16].

1.3 Cancer and genetics

At the cellular level, cancer is a genetic disease. The disorder is characterised by uncontrolled cell growth caused by genomic instability [17]. The transformation of normal cells into cancer cells, i.e. tumourigenesis, is a multistep process in which alterations in multiple cancer genes accumulate over time. In most cases, the first of these genetic events occurs in a somatic single cell, i.e. it is a somatic mutation, and the subsequent genetic alterations occur in daughter cells from this single cell. The process often takes several years, and increasing age is the most important risk factor for developing cancer. However, in the case of hereditary cancer, the first genetic alteration is already present at conception, i.e. it is a germline mutation and will therefore be present in all cells of the body. People carrying germline pathogenic variants in cancer genes are more prone to develop cancer at a young age and to develop multiple primary tumours.

1.4 Hereditary breast and ovarian cancer

Although most breast and ovarian cancers occur in patients with no familial risk of the disease, there is an important minority of cases that are caused by a germline pathogenic variant (Figure 1). The first report of a family with suspected hereditary breast and ovarian cancer was published in 1971 [18]. In 1994 the BReast CAncer 1 gene (*BRCA1)* was identified [19], followed by the BReast CAncer 2 gene (*BRCA2)* in 1995 [20]. After 25 years of search for "*BRCA3*" it has become evident for most researchers that additional single genes contributing to a substantial share of hereditary breast and ovarian cancer do not exist [21]. This leaves *BRCA1* and *BRCA2* – hereafter collectively denoted *BRCA* - the main causative genes for autosomal dominant hereditary breast and ovarian cancer. Individuals with a pathogenic variant in one of these genes will be referred to as "*BRCA* carriers" in this thesis. In addition, there are other genes associated with high risk of breast cancer, like *TP53, PTEN, STK11,*

PALB2 and *CDH1* [22-26], but pathogenic variants in these genes are far less prevalent than pathogenic variants in the *BRCA* genes. In addition, there are genes associated with moderate risk of breast cancer, mainly *ATM* and *CHEK2* [27, 28]. More than 15% of patients with breast cancer have one or more first degree relatives with breast cancer [29]. However, in a substantial share of these familial breast cancer cases an underlying genetic alteration in known risk genes cannot be identified. There is increasing evidence that a fraction of these cases can be explained by a polygenic risk, where multiple common genetic variants together give an elevated risk, while each variant alone is only associated with a minor risk [30]. Ovarian cancer can also be seen in Lynch syndrome (hereditary colorectal cancer) caused by genetic alterations in the mismatch repair (MMR) genes (mainly *MLH1*, *MSH2* and *MSH6*) [31-33] and in rare cases familial ovarian cancer can be caused by alterations in *RAD51C*, *RAD51D* or *BRIP1* [33-38].

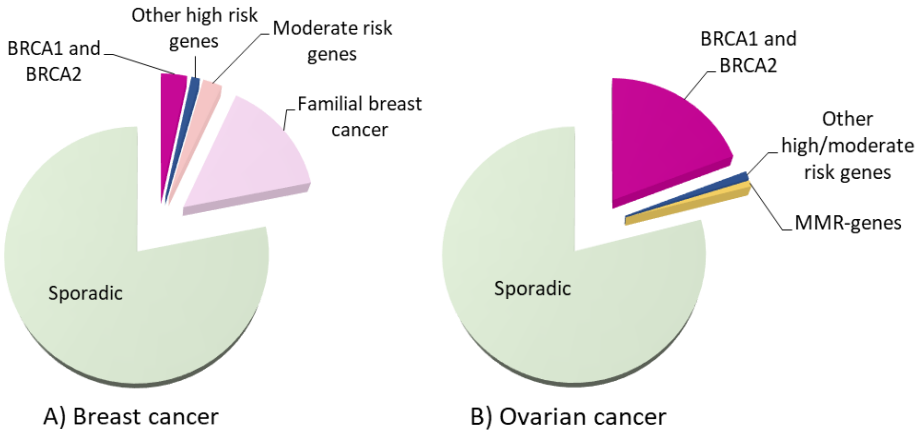

Figure 1
Relative distribution of different hereditary factors contributing to A) breast cancer [28, 29], and B) ovarian cancer [31, 33, 35]

1.4.1 *BRCA1* and *BRCA2*

BRCA1 is located on chromosome 17q21.3 and consists of 23 coding exons. The main transcript (NM_007294.3) encodes a large protein of approximately 220 kDa consisting of 1863 amino acids [39]. The BRCA1 protein has been implicated in numerous important cellular processes including cell cycle regulation, maintenance of

genome integrity, and repair of double stranded DNA breaks through homologous recombination [40]. Through the two BRCA1 C-terminal (BRCT) domains, BRCA1 interacts with proteins involved in transcription and DNA damage response [41]**.** *BRCA2* is located on chromosome 13q13.1 and consists of 27 coding exons. The main transcript (NM_000059.3) encodes a protein of 384 kDa consisting of 3418 amino acids [42]. Like BRCA1, the BRCA2 protein also has a central role in homologous DNA repair [41].

1.4.2 Prevalence

The prevalence and relative contribution of germline pathogenic variants in *BRCA1* and *BRCA2* varies between different populations. Together these two genes account for 1.8-6.1% of patients with breast cancer [43-47] and 8.0-28.5% of patients with ovarian cancer [31, 33, 48-51].

1.4.3 Cancer risk

For a woman with a *BRCA1* pathogenic variant, the cumulative risk by age 70 years is 45-66% for developing breast cancer and 31-59% for developing ovarian, fallopian tube, or primary peritoneal cancer [52-55]. The corresponding risk for a woman with a *BRCA2* pathogenic variant is 27-61% for breast cancer and 6-16.5% for ovarian, fallopian tube, or primary peritoneal cancer [52-55]. For women already affected by breast cancer, the risk of contralateral breast cancer within 20 years is around 40% for *BRCA1* carriers and 26% for *BRCA2* carriers [53]. In addition, pathogenic variants in *BRCA2* are associated with increased risk of pancreatic cancer in both men and women and an aggressive form of prostate cancer in men [56-59]. Men with *BRCA2* pathogenic variants are also at increased risk for breast cancer [60].

There are some striking features concerning pathology of cancers occurring in *BRCA* carriers. Breast cancer among *BRCA1* carriers are more often high grade and triple negative, i.e. negative for oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2), compared to sporadic breast cancer [61]. *BRCA2* carriers, however, show distribution of breast cancer subtypes more similar to

the general population of breast cancer patients [61]. Ovarian cancer is mainly high grade serous in both *BRCA1* and *BRCA2* carriers [31, 33].

1.4.4 Surveillance and risk-reduction

Women carrying a *BRCA* pathogenic variant are offered surveillance and risk-reducing surgery, to reduce the risk of cancer and/or cancer related mortality [62, 63]. The Norwegian guidelines recommend annual breast MRI and mammography from age 25, bilateral salpingo-oophorectomy at age 35-40 years (*BRCA1*) or 40-45 years (*BRCA2*), and optional risk reducing mastectomy from age 25 years [64]. While the intention with regular surveillance is early detection and better prognosis of cancer, risk reducing surgery aims at reducing the incidence of cancer. Breast screening with MRI and mammography has been shown to downstage breast cancer and improve survival in *BRCA* carriers [65, 66]; in contrast, screening for ovarian cancer has been documented non-effective [67, 68]. Risk reducing bilateral salpingo-oophorectomy reduces the incidence of ovarian cancer and improves survival [69] and risk reducing mastectomy has been shown effective to reduce the incidence of breast cancer [70, 71].

Chemoprophylaxis with anti-oestrogens is used in some countries [62, 63], but has not been part of the recommendations for *BRCA* carriers in Norway.

1.4.5 Cancer treatment

Previously, cancer treatment did not differ depending on *BRCA* carrier status. Even if most surgeons would hesitate to do breast conserving surgery, until recently the Norwegian guidelines did not specify breast cancer treatment for *BRCA* carriers. With increasing evidence of the effect of platinum based chemotherapy in *BRCA* carriers [72, 73], however, carboplatin was added to standard neoadjuvant therapy for *BRCA* carriers with local advanced breast cancer in the national treatment guidelines in November 2015 [74]. A specific recommendation for primary breast cancer surgery in *BRCA* carriers, i.e. bilateral mastectomy, was included in the 2018 guidelines [75]. Targeted treatment with Poly (ADP-ribose) polymerase (PARP)-inhibitors was approved by the US Food and Drug Administration (FDA) in 2014 [76] and was

subsequently approved in Norway for treatment of ovarian cancer with an identified *BRCA* pathogenic variant (germline or somatic) in 2015 [77]. In addition to having documented effect on breast and ovarian cancer, PARP-inhibitors may also be effective in other cancer types with BRCA deficiency [78-82].

Accordingly, the identification of a *BRCA* pathogenic variant has impact on both the treatment of patients affected with BRCA-related cancer as well as upon their healthy relatives – who can benefit from increased surveillance and risk-reducing surgery.

1.5 *BRCA* genetic testing

More than ten thousand different germline variants have been found in the *BRCA* genes [83-85]. When interpreting *BRCA* variants with respect to pathogenicity, a 5-tier system is often used [86], in which class 1 variants are benign, class 2 likely benign (also called non-disease causing), class 3 variants of uncertain clinical significance (VUS), class 4 likely pathogenic and class 5 pathogenic (collectively called disease causing). The variant interpretation is based on a number of variables such as allele frequencies in the general population, segregation data from the affected families, reputable sources like PubMed and ClinVar, and functional assays, building evidence of pathogenicity or benign impact, as presented by the ACMG (American College of Medical Genetics) guidelines [87] and ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) criteria [88].
BRCA variants classified as likely pathogenic (class 4) and pathogenic (class 5) increase the risk of cancer by impairing the protein structure or function. Other variants classified as likely benign or benign are not associated with increased risk of cancer. However, for a large number of *BRCA* variants the knowledge is very limited or conflicting, and these are therefore classified as VUS (class 3).

Soon after the identification of the *BRCA* genes it became evident that in some populations, e.g. the Ashkenazi Jewish and the Polish, a limited number of founder mutations were causing a majority of the hereditary breast and ovarian cancer cases [89]. This was also the case for Norway, where four founder mutations were reported

to be responsible for 68% of families with hereditary breast and ovarian cancer [90]. Customised founder mutations tests were developed, which made it possible to offer genetic testing to a large number of individuals at a relatively low cost.

The Norwegian *BRCA* founder mutation test included initially two prevalent pathogenic *BRCA1* variants, c.1556del (BIC: 1675delA) and c.1016dup (BIC: 1135insA). It was soon expanded with c.697_698del (BIC: 816delGT) and c.3228_3229del (BIC: 3347delAG). Later, other pathogenic variants were added to the test, as more frequent pathogenic variants were discovered by Sanger sequencing of families with high suspicion of hereditary breast and ovarian cancer. A two-step model was commonly used in familial cancer clinics in Norway until 2015: a founder mutation test was offered at low threshold to affected and unaffected individuals seeking genetic counselling for hereditary breast and ovarian cancer. If the founder mutation test was negative, or if the family was not of Norwegian ancestry, more comprehensive analyses like Sanger sequencing and Multiplex Ligation Probe Amplification (MLPA) of *BRCA1* and *BRCA2* were performed in affected members of families fulfilling the criteria for high suspicion of a pathogenic *BRCA* variant. These criteria have been continuously revised, see Table 1.

Because genetic tests were expensive, criteria were developed to select patients with high likelihood of having a pathogenic *BRCA* variant. Similar criteria have been used in other countries [91]. With falling costs, the criteria were broadened at each revision, both for the founder mutation test and for comprehensive analysis with sequencing of the total coding region of *BRCA1* and *BRCA2* (Table 1) [64, 74, 92]. The 2010 criteria were the result of a long-standing national debate between leading health professionals in several speciality fields (surgeons, gynaecologists, oncologists and clinical geneticists), Norwegian health authorities, and other stakeholders [92-94].

Table 1 Development in the Norwegian diagnostic *BRCA* genetic test criteria over the years

Year:	2003		2010		2015*	2019*
Diagnosis	**Founder mutation test**	**Sequencing**	**Founder mutation test and MLPA**	**Sequencing**	**Diagnostic *BRCA* test, including sequencing and MLPA**	**Diagnostic *BRCA* test, including sequencing and MLPA**
Unilateral FBC			< 50 years	< 35 years	< 50 years	< 60 years
OC	< 45 years		< 70 years	< 50 years	Any age	Any age
Bilateral FBC	< 60 years	< 35 years	Any age	< 50 years	< 60 years	
FBC and OC	BC < 60 years, OC any age	BC < 50 years, OC < 60 years	Any age	BC < 50 years, OC any age	Any age	Any age
Male BC			Any age	Any age	Any age	Any age
FBC and a FDR with BC	Both BC < 50 years	Both BC < 35 years	One of the BC < 50 years	Mean age 50 years	Mean age 55 years	Mean age 55 years
FBC and a FDR with OC	BC < 60 years, OC any age	BC < 50 years, OC < 60 years	Any age	BC < 50 years, OC any age	Any age	Any age
FBC and ≥ 2 FDR with BC	≥ 4 BC, any age	≥ 3 BC <50 years	Any age	BC mean age 60 years	Any age	Any age
OC and FDR with OC	Any age	Both OC < 60 years	Any age	Any age		
				BC < 50 years and FDR with prostate cancer < 55 years	BC any age and FDR with prostate cancer < 55 years	BC any age and FDR with prostate cancer < 55 years

Abbreviations: FBC: female breast cancer, BC: breast cancer OC: ovarian cancer; FDR: first degree relative (or second degree relative through male); MLPA: multiplex ligation probe amplification.
*In addition to these criteria, surgeons, oncologists and gynaecologists may order diagnostic *BRCA* testing if the test result will have major impact on treatment decisions.

The advantage of a test that only detects well-known pathogenic variants that have previously been identified in multiple families with hereditary breast and ovarian cancer ("founder mutation test") is that the interpretation of the result is quite straightforward. With more comprehensive testing, like sequencing of the total coding regions of one or more genes, there is an inherent risk of detecting sequence variants of uncertain clinical significance (VUS). The risk of detecting a VUS is higher in patients with low a priori risk of carrying a pathogenic variant, and increases with the number of genes investigated [95]. According to international guidelines, a VUS is not clinically actionable [86], but may nevertheless cause considerable uncertainty and difficulty among carriers of such variants and their physicians [96-98]. Missense variants and variants in non-coding parts of the genes are especially difficult to interpret and will often fall into the VUS category [83, 99].

Another argument used in favour of founder mutation tests is that the cost usually has been low, compared to Sanger sequencing. With falling prices of sequencing after the introduction of NGS, the technical cost is hardly an argument anymore. However, the biological and clinical interpretation of rare variants still represents a considerable workload in genetic diagnostic laboratories, and requires highly competent personnel of which there is scarcity in the public health care system.

If there is high suspicion of hereditary breast and ovarian cancer, sequencing of the total coding region and analysis for large rearrangements should always be performed for both genes. A negative result of a founder mutation test does not exclude hereditary breast and ovarian cancer.

1.6 Genetic counselling

The most common practice of *BRCA* testing has been referral of selected patients to departments of clinical genetics for specialised face-to-face genetic counselling. The genetic counselling procedure traditionally includes collection and confirmation of family history, risk assessment and eventually *BRCA* testing followed by a post-test counselling session with dissemination of test results and advice concerning

surveillance programs and follow-up [100]. Most definitions of genetic counselling are based on the work of Fraser from 1974 [101], including the newer definition from the National Society of Genetic Counselors in USA [102]:

"Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence. Education about inheritance, testing, management, prevention, resources and research. Counseling to promote informed choices and adaptation to the risk or condition."

The definition reflects that the genetic counselling process is closely linked to the genetic investigation of the patient and family seeking attention from genetic professionals. Most cancer genetic clinics have a team-based approach, in which clinical geneticists, genetic counsellors and clinical laboratory geneticists work in close collaboration to meet the need of families with hereditary cancer.

This traditional genetic counselling is usually appreciated by the patients [100], and has been shown to reduce the levels of anxiety, depression, psychological distress and decisional conflict regarding genetic testing [85, 103, 104].

1.7 Legal Framework

In Norway, genetic testing is regulated by formal legislation through "the Biotechnology Act" [105]. This Act distinguishes between predictive and diagnostic genetic testing: predictive testing requires genetic counselling before, during and after testing, while no formal genetic counselling is required for a diagnostic test. However, diagnostic *BRCA* genetic testing will usually have a predictive component as well, e.g. in a woman affected with breast cancer the test will be predictive for the risk of ovarian cancer and contralateral breast cancer. With respect to this, and the patients' general right to information "…that is necessary to obtain an insight into his or her health condition and the content of the health care" as stated in "the Patients'

Rights Act" [106], genetic testing of patients affected by cancer needs to be organised in a way that ensures that the need of information and counselling is met.

1.8 Changing landscape of clinical cancer genetics

1.8.1 Important events concerning hereditary breast and ovarian cancer

The work constituting this thesis coincided in time with several events that have contributed to the increasing demand of *BRCA* genetic testing and increasing awareness about hereditary breast and ovarian cancer among patients, health care personnel and the public. Since these events illustrate the rapid development and change of practice in the field, some of them will be presented briefly in the following.

In 2013 the American actress Angelina Jolie published an opinion editorial in the New York Times, informing that she was carrying a *BRCA1* pathogenic variant and had chosen prophylactic bilateral mastectomy to reduce her risk of dying from cancer [107]. This lead to a global increase in referrals for *BRCA* testing and prophylactic mastectomy, the so-called Angelina Jolie effect [108].

In 2013, the Myriad monopoly of *BRCA*-analyses in USA ended, after a patent termination by the US Supreme Court [109]. This was followed by a rapid growth in commercial laboratories offering genetic testing service [27], and contributed to falling costs and increasing access to *BRCA* testing, including direct-to-consumer testing [110].

In 2014, PARP-inhibitors were approved by US Food and Drug Administration (FDA) for treatment of patients with ovarian cancer in USA [76], followed by a governmental approval in Norway in October 2015 [77].

A more local event was organised by the patient organisation The Norwegian Breast Cancer Society in October 2016. In their yearly Pink Ribbon Campaign, they had hereditary breast cancer as main focus this year, and raised awareness through information activities all over the country [111].

1.8.2 Personalised medicine

The rapid technological development has facilitated extensive molecular characterisation of tumours. The valuable insight in tumour biology has permitted personalised treatment based on molecular changes in the individual tumour. Personalised medicine, or precision medicine, can be defined as adjusted treatment based on the individual's biology, and aims at increased effect and reduced side-effects of the treatment [112]. Genetic testing is a major component of personalised cancer medicine, focusing on molecular changes in the tumour, i.e. somatic genetic alterations. However, germline alterations will by nature be present in the tumour as well as in normal cells, and are reaching increasing attention as targets for treatment [113]. Risk reducing and preventive measures in healthy carriers of germline pathogenic *BRCA* variants are a well-established practice of personalised medicine. In addition, there is now an increasing use of diagnostic *BRCA* testing to tailor cancer treatment (see section 1.4.4 and 1.4.5). This is sometimes referred to as "treatment focused genetic testing". Of note, by the increasing use of molecular profiling of tumours, more carriers of pathogenic germline *BRCA* variants will also be identified through this new route.

1.8.3 New procedures for genetic testing and genetic counselling.

Traditional pre- and post-test genetic counselling in specialised cancer genetics clinics is relatively time consuming and the capacity is not dimensioned for the expected rise in diagnostic genetic testing of patients with newly diagnosed cancer. To meet the increasing demand of diagnostic genetic testing, new service delivery models are needed. These new procedures should be dimensioned for large patient groups and a short turnover-time from referral/testing to genetic test result.

The use of telephone counselling facilitates a more rapid process, and has been shown non-inferior to face-to-face genetic counselling for persons at increased risk for hereditary cancer, when it comes to psychosocial distress [114, 115]. However, telephone counselling will often lead to a lower uptake for genetic testing, compared to traditional genetic counselling sessions [115, 116]. Alternatively, patients can be

offered *BRCA* testing prior to genetic counselling and take advantage of different digital information tools [117]. Studies that have investigated genetic testing of unselected patients with breast or ovarian cancer without prior genetic counselling have used different ways of delivering information about the genetic test: written information only [118], a combination of telephone and written information [48], oral information given by non-genetic clinicians [44, 119], and video-based information [120].

BRCA mutated ovarian cancer may respond to PARP inhibitors regardless if the mutation (i.e. pathogenic variant) is germline or somatic. For this reason, some groups argue for universal *BRCA* testing of all ovarian cancers (without pre-test genetic counselling), and to proceed with genetic counselling and germline *BRCA*-testing if a pathogenic *BRCA* variant is detected in the tumour [121].

Regardless of which model has been used, in patients where a pathogenic *BRCA* variant has been found, or in case of a highly suggestive family history for hereditary cancer, face-to-face counselling at a cancer genetics clinic should be offered [122]. This allows for discussion of the consequences of the results for the patient and the family, and also discussion of additional genetic tests when relevant. Predictive genetic testing for a known *BRCA* pathogenic variant should always be performed in the context of formal genetic counselling [105].

While psychosocial aspects have been investigated thoroughly in patients undergoing traditional genetic counselling and testing for suspected hereditary cancer [85, 103, 123, 124], less is known about the psychosocial aspects of offering genetic testing without pre-test genetic counselling to unselected women newly affected with breast or ovarian cancer. In contrast to women seeking genetic counselling because of a suspicious family history of hereditary breast and ovarian cancer, the women who are tested as part of the routine diagnostic work-up in a cancer clinic may be less aware of the possibility that their cancer can have a hereditary cause, and thus be less prepared for a positive result [125, 126]. Receiving a potential life threatening cancer diagnosis is associated with significant distress [127-130], and women who are newly

diagnosed with breast or ovarian cancer are often overwhelmed with information and choices they have to make [131]. When introducing new service delivery models for genetic testing of this vulnerable patient group, the psychosocial aspects need to be addressed.

2. Aims of the project

The overall aim of this PhD project was to evaluate alternative procedures for diagnostic genetic testing and counselling of patients with newly diagnosed breast or ovarian cancer, in order to meet the expected increasing need of this health service.

Specific aims are presented according to the papers that constitute the present thesis:

Paper I

The objective of the first publication was to assess the feasibility of offering *BRCA* testing to unselected newly diagnosed patients with breast or ovarian cancer without prior face-to-face genetic counselling. We aimed to

1. Document the uptake of *BRCA* genetic testing at time of diagnosis
2. Determine the frequency of *BRCA* pathogenic variants in unselected patients with breast or ovarian cancer
3. Evaluate the usefulness of existing Norwegian criteria for *BRCA* genetic testing
4. Investigate the symptoms of anxiety and depression at inclusion and during follow-up

Paper II

In Paper II we further evaluated the psychosocial aspects in women who were offered *BRCA* testing shortly after a diagnosis of breast or ovarian cancer and aimed to

5. Document the level and course of cancer related psychological distress
6. Identify predictors of cancer related psychological distress

Paper III

In Paper III we examined in more detail a *BRCA1* sequence variant that was detected in two patients in the DNA-BONus study. The aim was to

7. Determine the pathogenicity of the intronic *BRCA1* splice variant c.5407-25T>A

3. Materials and methods

Paper I and Paper II are based on results from the same main study, the DNA-BONus study, and will be presented together in the materials and methods section. Methods and materials for Paper III will be presented separately.

3.1 Paper I and Paper II: the DNA-BONus study

3.1.1 Design, recruitment and participants

We performed a prospective multicentre study with consecutive inclusion from September 2012 to April 2015. All patients who were treated for newly diagnosed breast cancer (N=893) or ovarian cancer (N=122) were invited to participate in the DNA-BONus study, regardless of family history or age at diagnosis. The patients were recruited from four hospitals in Western Norway (Haukeland University Hospital, Stavanger University Hospital, Haugesund Hospital and Førde Central Hospital), including three surgical departments and two gynaecological departments. The patients received an information sheet (Appendix 1A) and also had the opportunity to call a genetic counsellor if further information was needed. The patients could choose to join the genetic testing study (DNA-BONus part 1) with or without participating in the associated study of psychosocial aspects (DNA-BONus part 2).

3.1.2 DNA analysis and clinical assessment

All participants in the DNA-BONus study were tested for 20 pathogenic variants in the *BRCA1* gene and 10 pathogenic variants in the *BRCA2* gene that previously had been identified in multiple families with hereditary breast and ovarian cancer in Norway (Paper I, Supplementary Table). In addition, the *BRCA1* and *BRCA2* genes were analysed by Multiplex Ligation-dependent Probe Amplification (MLPA) technology to detect copy number variation in both genes.

The genetic test result was given to the patient by a genetic counsellor around three weeks after blood sample collection (Figure 1):

- Negative *BRCA* test result and negative family history: information was given by letter.
- Negative *BRCA* test result and positive family history or personal history fulfilling criteria for *BRCA* sequencing: information by phone call and letter. The patient was offered genetic counselling in an outpatient clinic. Based on collection of traditional extended family history and confirmation of cancer diagnoses in relatives, selected patients were then offered extended genetic testing with Sanger sequencing of all exons and flanking intron sequences in both *BRCA1* and *BRCA2*, according to current clinical guidelines at that time.
- Positive *BRCA* test result: information by phone call. The patient was offered genetic counselling in an outpatient clinic within maximum 2 weeks, and a second blood sample was collected to verify the result of the test. Relatives at risk were subsequently informed by the index patient and were offered genetic counselling and testing.

In addition, the results were reported to the doctor who included the patient in the study.

All patients were categorised according to the current Norwegian genetic test criteria (Table 1, 2010 criteria) before *BRCA* testing was performed, based on clinical information retrieved from their medical record and self-reported structured family history given on the request form for DNA analysis (Appendix 1B). The participants were in addition rated by the Manchester scoring system for *BRCA* testing, version 1 [132]. The system takes into account age dependent occurrence of cancer in the breasts, ovaries, pancreas, and prostate in all family members under the condition of an autosomal dominant inheritance pattern. In general, a higher Manchester score indicates higher probability of a pathogenic *BRCA* variant being present, e.g. a score above 15 corresponds to 10% probability, a common used threshold for *BRCA* testing in many countries [91, 132].

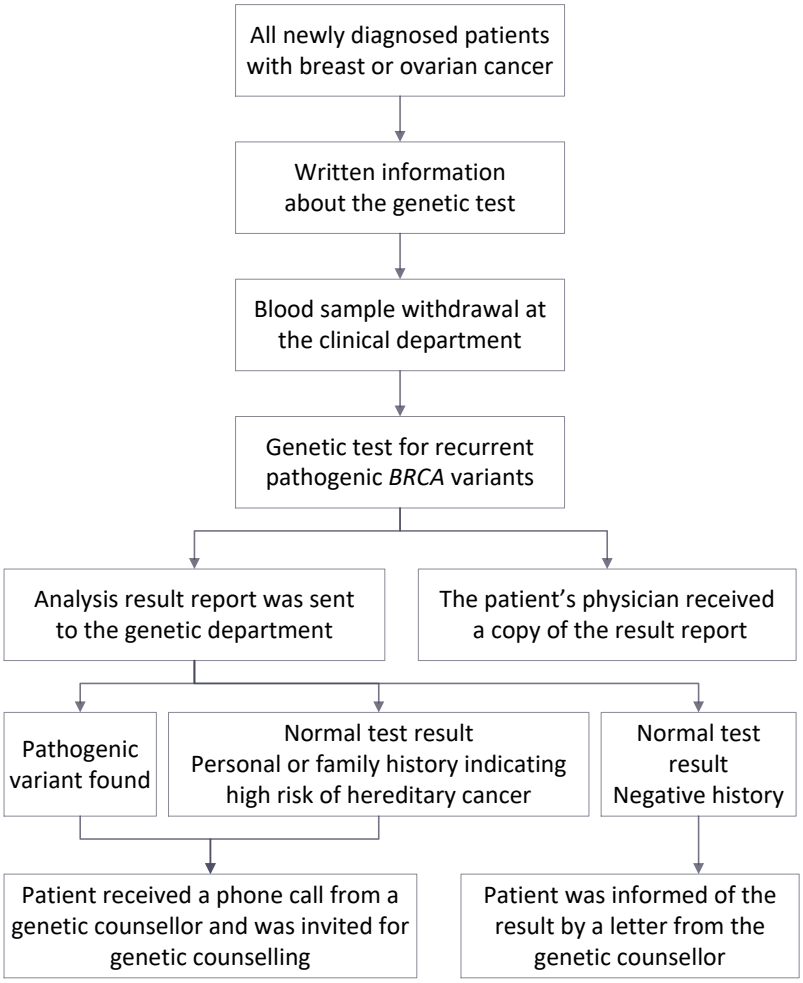

Figure 2
Flow chart showing the recruitment of patients and the reporting of genetic test results in the DNA-BONus study

3.1.3 Psychosocial measurements

Participants who consented to participate in part 2 of the prospective DNA-BONus study were asked to fill in questionnaires at three measurement points. The first questionnaire was given to the participants along with the invitation to the study (T1).

The second and third questionnaires were mailed to the participants one week (T2) and 6 months (T3) after disclosure of the *BRCA* test result, respectively (Figure 3).

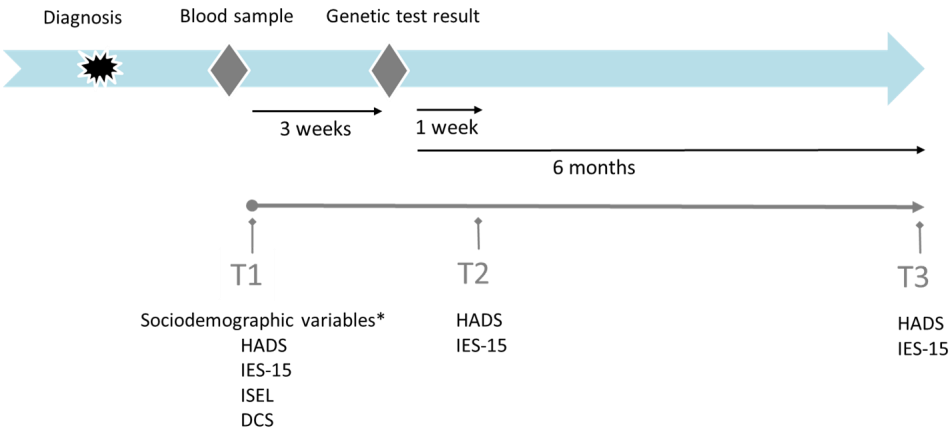

Figure 3
Timeline showing data collection and questionnaires used in the prospective DNA-BONus study, part 2
*Sociodemographic variables: education, biological children, cohabitating status, employment status

Outcome variables

Anxiety and depression

We used the Hospital Anxiety and Depression Scale (HADS) to measure symptoms of anxiety and depression as an outcome in Paper I. HADS was originally developed to screen for anxiety and depression among non-psychiatric patients [133]. It comprises two subscales for symptoms of anxiety and depression, respectively, each with 7 items to be scored on a four-point (0-3) scale, giving a range of sub scores from 0 to 21. Subscale scores equal to or above eight were used as cut-off for defining higher levels of anxiety and depression [134].

Subjective distress

We defined distress as intrusive thoughts and avoidance behaviour, and used the Impact of Event Scale – 15 (IES-15) to measure this outcome in Paper II [135]. IES-

15 is a 15 item questionnaire comprising two subscales [135]. The intrusion subscale (IES-I) includes seven items and is scored from 0-35, and the avoidance behaviour subscale (IES-A) consists of eight items and is scored from 0-40. The subscale scores are considered low in the range of 0-8, moderate at 9-19 and severe at 20 and above. Intrusion symptoms include unbidden thoughts and images both awake and during sleep, waves of overwhelming feelings of fear and repetitive behaviour. Avoidance responses include denial of the meaning and consequences of the threatening event, blunted sensation, emotional numbness and attempts to block out unpleasant feelings and memories. IES was originally developed to measure current stress reactions after any specific traumatic event; in our study 'cancer diagnosis' was defined as the specific event.

Socio-demographic characteristics

At T1 we included questions about sociodemographic variables; i.e. education level, biological children, cohabitation and employment status.

Social support

The concept of perceived social support was measured by the version of the Interpersonal Support Evaluation List (ISEL) used by King and colleagues [136], which consists of 30 items that are answered with a score from 1-4. This version measures five different and independent sources for experienced social support: appraisal support, self-esteem support, group belonging support, emotional closeness support, and tangible aid [85, 136, 137]. The average sum score for each participant was used.

Decisional conflict

We used the Decisional Conflict Scale (DCS) to measure the study participants' ambivalence toward making a choice of undergoing *BRCA* testing [138, 139]. This scale contains 16 items, which is scored from 0-4. Three dimensions of decisional conflict are measured: uncertainty about selection of alternatives (3 items), specific factors contributing to uncertainty (9 items) and perceived effectiveness of decision making (4 items). Higher scores indicate higher levels of decisional conflict. The sum

score of all items was converted to a 0-100 scale, where total scores below 25 are associated with low level of decisional conflict and scores above 37.5 are associated with problems in implementing decisions.

3.2 Paper III

3.2.1 Patient materials and clinical assessment

We recruited families from Haukeland University Hospital, and Oslo University Hospital in Norway, Hospices de Lyon in France, and Allegheny Health Network, Pittsburgh, PA in USA, in which the *BRCA1* c.5407-25T>A variant had been identified in at least one family member before June 1st 2019. We collected clinical information and family history from the patients' medical files. The family histories were rated by the Manchester Scoring System version 3 [140].

3.2.2 Control materials and variant allele frequency

Anonymous blood donors from Haukeland University Hospital were used as controls for DNA and RNA analyses. The variant allele frequencies were retrieved from an in-house database and from different populations using the gnomAD database [141].

3.2.3 DNA, RNA and protein analyses

cDNA synthesis was performed using RNA purified from patient-derived blood, breast and ovarian tissue. For RNA splicing analysis, cDNA was amplified by PCR, followed by Sanger sequencing and next generation sequencing (NGS). To assess for a potential leakage of normal full-length transcript from the variant allele leading to biallelic expression of full-length transcript, a PCR fragment including the SNP *BRCA1* c.4837A>G (rs1799966) was amplified from carriers heterozygote for this SNP. Full transcriptome sequencing of RNA from blood was performed using TruSeq and HiSeq 4000 Sequencing System (Illumina). For protein analysis, plasmid constructs were generated by cloning wild-type and p.(Gly1803GlnfsTer11) BRCA1 cDNA into a eukaryotic expression vector. After transfection into HeLa cells, lysates were analysed by qPCR and Western blot.

3.3 Statistical methods

Descriptive statistics were given as mean values, standard deviations (SD), standard error of means (SEM), range, and proportions.
McNemar's exact test was used for paired categorical variables.
The **independent samples *t*-test** was used to compare the means of two independent groups.
The **chi- square test** was used compare proportions in two independent groups.
The **paired samples *t*-test** was used to compare changes over time in mean scores of IES and HADS.
Mixed linear modelling was used to identify the characteristics related to the IES-I and IES-A and to test the changes of IES-I and IES-A over time. All predictors were entered into the mixed linear models to assess both main effects and possible interactions with time. The regression analyses were run backwards stepwise, both with and without interaction with time.
Nonresponse was analysed with **multiple logistic regression analysis**.

The significance level was set at 0.05 for all statistical tests. Missing values were replaced by the individual's own average score for each questionnaire if 60% or more of the items were filled in by the respondents. The statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) using versions 22.0 (Paper I) and 24.0 (Paper II and Paper III).

3.4 Ethical considerations

Research involving humans always requires a careful consideration of the procedures to be used to protect the rights and confidentiality of human beings. The studies in this PhD project have been carried out according to the Declaration of Helsinki [142]. All subjects in the prospective DNA-BONus study (Paper I and Paper II) gave their written consent based on an information sheet. They were also offered to call a

genetic counsellor, if they had questions regarding the study or the written information. The DNA-BONus study was preceded by a long-standing debate in Norway about whether and how an offer of diagnostic genetic testing for patients with breast/ovarian cancer should be introduced [94]. The Norwegian Directorate of Health concluded that more knowledge was needed before genetic testing of all patients with breast or ovarian cancer could be implemented in clinical practice. The present study was a response to this call for more knowledge and served as a preparation for the anticipated increasing demand for genetic testing of newly diagnosed patients with cancer.

The DNA-BONus study was approved by the Regional Committee for Medical and Health Research Ethics, REK-Vest 2012-60 and 2012-62, and was also evaluated positively by the Norwegian Directorate of Health (Paper I and II).

The study of *BRCA1* c.5407-25T>A was evaluated by the Regional Committee for Medical and Health Research Ethics, REK Nord 2018/996, and classified as a quality of care study (Paper III).

4. Results

The main results of the three papers constituting this thesis are presented below. The results of Paper I and Paper II (the DNA-BONus study) will be presented together, and the results of Paper III will be presented separately.

4.1 Paper I and Paper II: the DNA-BONus study

4.1.1 Study sample

A total of 1,015 patients with either breast cancer (N=893) or ovarian cancer (N=122) were offered *BRCA* testing at the time of cancer diagnosis. In total, 488 women completed genetic testing (Figure 4); 405 (45.4%) of the breast cancer patients and 83 (68.0%) of the ovarian cancer patients. More than half of the participants (55.7%) fulfilled at least one of the Norwegian 2010 *BRCA* test criteria (Table 1). After exclusion of 242 patients who got access to a website and an information video as an intervention (results not part of this thesis) and one patient who turned out to be diagnosed not recently, but nine years earlier, 772 invited women were eligible and 309 gave consent for the psychosocial substudy in Paper II (Figure 4). Since Paper I was published before all respondents had answered the questionnaires at T3, the HADS analyses in Paper I were based on a smaller subset of participants (N=215). Main characteristics of the study sample in Paper II are given in Table 2.

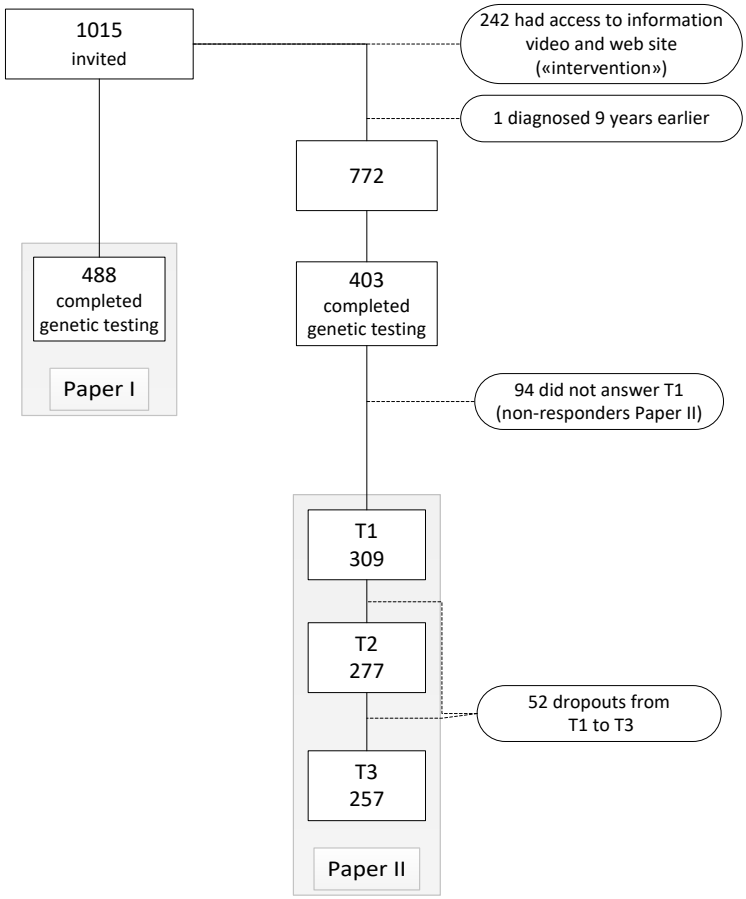

Figure 4
Flow chart showing inclusion of study samples for the different parts of the DNA-BONus study (Paper I and Paper II) on women having genetic testing shortly after a diagnosis of breast or ovarian cancer

4.1.2 Genetic test results

We found a pathogenic *BRCA* variant in seven (1.7%) of the 405 patients with breast cancer and 19 (22.3%) of the 83 patients with ovarian cancer. All carriers of a pathogenic *BRCA* variant met the Norwegian 2010 *BRCA* test criteria.

Table 2 Sociodemographic and main medical variables for participants in the DNA-BONus study: study sample of Paper I, Paper II, and dropouts

Variables	Eligible for Paper II N = 403		Non-responders Paper II N = 94		Responders Paper II N = 309		Dropouts from T1 to T3 Paper II N = 52	
Age, years, *mean (SD)*	57.3	(12.3)	61.1	(13.9)	56.1	(11.5)	56.8	(12.7)
Manchester score*, *mean (SD)*	8.8	(7.1)	8.2	(8.3)	9.0	(6.7)	8.8	(5.3)
Breast cancer, *n (%)*	335	(83.1)	76	(80.9)	259	(83.8)	43	(82.7)
Ovarian cancer, *n (%)*	68	(16.9)	18	(19.1)	50	(16.2)	9	(17.3)
Genetic test criteria fulfilled, *n (%)*	220	(54.6)	46	(48.9)	173	(56.0)	30	(57.7)
Pathogenic *BRCA* variant, *n (%)*	21	(5.2)	6	(6.4)	15	(4.9)	2	(3.8)
Education, *n (%)*								
Primary school					50	(16.5)	12	(23.5)
High school					115	(38.0)	14	(27.5)
University					138	(45.5)	25	(49.0)
Missing, *n*					6		1	
Employed, *n (%)*					189	(62.2)	24	(47.1)
Missing, *n*					5		1	
Having biological children, *n (%)*					272	(89.2)	44	(88.0)
Missing, *n*					4		2	
Cohabitant, *n (%)*					218	(71.2)	29	(56.9)
Missing, *n*					3		1	
ISEL at T1, *mean (SD)*					3.46	(0.47)	3.40	(0.4)
DCS at T1, *mean (SD)*					19.0	(15.2)	22.5	(17.1)
Missing, *n*					5		1	
IES-I T1, *mean (SD)*					14.6	(9.4)	17.6	(10.7)
Missing, *n*					1			
IES-A T1, *mean (SD)*					12.7	(9.2)	16.0	(10.0)
HADS-A T1, *mean (SD)*					6.6	(4.3)	7.9	(4.8)
Missing, *n*					15		1	
HADS-D T1, *mean (SD*)					3.3	(3.1)	4.3	(3.7)
Missing, *n*					3			

Abbreviations: T1/T3: first and last time points for questionnaires in the study; SD: standard deviation; ISEL: Interpersonal Support Evaluation List (range: 1-4); DCS: Decisional Conflict Scale (range:0-100); IES: Impact of Event Scale (Intrusion subscale range: 0-35; Avoidance subscale range: 0-40); HADS: Hospital Anxiety and Depression Scale (range: 0-21)
*range: 2-unlimited

4.1.3 Psychological outcomes

Table 3 shows the results from the HADS (Paper I) and IES-15 (Paper II) questionnaires. The mean HADS subscale score for anxiety symptoms decreased statistically significantly from 6.84 at time of inclusion to 4.88 six months after

disclosure of the *BRCA* test result ($p < 0.001$). During the observation period there was no significant change in the mean depression symptoms score, which was low at all measurement points.

We also found a significant decrease in cancer related psychological distress from T1 to T3, as measured with IES-15. The mean IES-Intrusion score decreased from 14.6 at T1 to 12.1 at T2 ($p < 0.001$) and with a further significant decrease to 9.7 at T3 ($p < 0.001$) (Table 3). The mean IES-Avoidance score was 12.7 at T1, decreased statistically significantly to 10.2 at T2 ($p<0.001$), but with no further statistical significant decrease from T2 to T3 (mean score 9.7).

Table 3 HADS and IES subscale scores at different time points in women undergoing genetic *BRCA* testing in the DNA-BONus study

Paper	Time point; subscale	At inclusion (T1)	One week after disclosure of genetic test result (T2)	Six months after disclosure of genetic test result (T3)
I	**HADS-Anxiety** (scale 0-21), *n*	213	191	167
	Subscale score, *mean (SD)*	6.84 (4.28)	5.29 (4.06)	4.88 (3.86)
	Score ≥ 8, *n (%)*	85 (39.9)	45 (23.6)	33 (19.8)
I	**HADS-Depression** (scale 0-21), *n*	215	190	169
	Subscale score, *mean (SD)*	3.32 (3.07)	2.90 (3.30)	2.65 (3.04)
	Score ≥ 8, *n (%)*	22 (10.2)	19 (10.0)	18 (10.7)
II	**IES-Intrusion** (scale 0-35), *n*	308	277	257
	Subscale score, *mean (SD)*	14.6 (9.4)	12.1 (9.3)	9.7 (8.3)
	Score ≥ 20, *n (%)*	99 (32.1)	68 (24.5)	36 (14.0)
II	**IES-Avoidance** (scale 0-40), *n*	309	277	256
	Subscale score, *mean (SD)*	12.7 (9.2)	10.2 (8.2)	9.7 (8.3)
	Score ≥ 20, *n (%)*	73 (23.6)	44 (15.9)	41 (16.0)

Abbreviations: T1/T2/T3: time points for questionnaires in the study; HADS: Hospital Anxiety and Depression Scale; SD: standard deviation; IES: Impact of Event Scale

The results of the mixed linear regression analyses showed that younger age, shorter time since diagnosis, lower level of perceived social support, and a diagnosis of ovarian cancer were predictors of higher IES-Intrusion and IES-Avoidance (Paper II, Table 3). In addition, two additional predictors of higher IES-Intrusion were found:

higher level of decisional conflict regarding the genetic test, and living with a partner (Paper II, Table 3).

4.2 Paper III: The intronic *BRCA1* c.5407-25T>A variant

We identified 20 different families with the intronic *BRCA1* c.5407-25T>A variant. Among carriers of the variant, the mean age at breast cancer diagnosis (N=12) was 49.9 years (SD 9.9) and the mean age at ovarian cancer diagnosis (N=11) was 60.4 years (SD 11.3). The mean Manchester score in the 20 rated families was 16.4 (SD 9.2).

The *BRCA1* c.5407-25T>A variant was identified in 1/400 anonymous blood donors, and 0/784 in-house (non-cancer) diagnostic exomes. In the gnomAD database (v2.1.1), the allele frequency of this variant is reported to be 1/141,398 in total and 1/64,566 in non-Finnish European population [141].

Sequencing of cDNA from blood, breast and ovarian tissue showed that *BRCA1* c.5407-25T>A leads to skipping of exon 22. The exon skipping results in a frameshift and predicts a truncated BRCA1 protein (Gly1803GlnfsTer11). *BRCA1* c.5407-25T>A carriers heterozygous for the SNP rs1799966 (c.4837A>G) were shown to express a small amount of correctly spliced transcript (including exon 22) originating from the *BRCA1* c.5407-25T>A allele (Paper III, Figure 2). An NGS-based semi-quantitative analyses of patient-derived RNA indicated that 10-13% of total full-length transcript was generated from the variant allele in blood (N=3) and 20% in healthy breast tissue (N=1) (Paper III, Supplementary Table S2).

5. Discussion

5.1 Methodological considerations

5.1.1 The DNA-BONUS study design (Paper I and II)

For the DNA-BONus study, a prospective longitudinal study design was chosen, since we were interested in the outcome of offering genetic testing shortly after a diagnosis of breast or ovarian cancer. Prospective design is considered a strength, compared to retrospective or cross-sectional design. Another strength was that we included all patients with newly diagnosed breast or ovarian cancer; the patients were not selected by age or family history. However, we systematically collected family history from all participants, which was also a strength of our study.

Our study was designed for integration in daily practice at clinical departments diagnosing and treating patients with breast or ovarian cancer. In this way, the study could serve as a preparation for the expected increased need for treatment focused genetic testing in the future. However, a limitation with studies in a "naturalistic setting" like this is that the study conditions are more challenging to standardise. Five different clinical departments recruited participants to the study, and some variation in logistics was inevitable, like e.g. timing of the invitation, wording by the local nurse or physician, blood sampling facilities etc. Because of ongoing inclusion of breast cancer patients to another research project, one of the departments invited to collaborate in the DNA-BONus study declined, resulting in patients with breast cancer were not recruited from the southern part of our region where founder mutations are most prevalent. Consequently, the breast cancer cohort and ovarian cancer cohort in our study were not drawn from the exact same geographical population.

5.1.2 DNA analysis (Paper I)

For the DNA-BONus study we developed a screening test using TaqMan Low Density Arrays to screen for 30 variants previously detected in multiple families in Norway. The selection of variants to include in the test was mainly based on a survey carried out by the Norwegian Directorate of Health in 2009 of all *BRCA* pathogenic variants detected in Norway. MLPA was added to the screening test, since several Norwegian families previously had been identified with large rearrangements in the *BRCA* genes.

The disadvantage of using a test with a limited number of predefined variants is of course that the test will not detect all pathogenic variants, some carriers will be lost if this was the only test performed. To ensure that those participating in our study had access to equal standard of genetic testing as they would have had through ordinary health care, participants fulfilling existing clinical criteria for sequencing (Table 1) were offered sequencing of the whole coding region of *BRCA1* and *BRCA2* after genetic counselling. Furthermore, sequencing of *BRCA1* and *BRCA2* cannot exclude pathogenic variants in other genes, and this was our rationale for having a low threshold for the genetic counsellor to contact patients if their personal or family history indicated that other genes should be analysed (e.g. *PTEN* or *TP53*).

There were several reasons for choosing a limited screening test instead of full *BRCA* sequencing or multigene panel test in this study. Firstly, genetic testing of an unselected group of patients with low a priori risk of having a pathogenic variant, would potentially lead to a high number of variants of uncertain clinical significance. We chose to be cautious, when expanding the target group for genetic testing through our new model, and therefore only included pathogenic *BRCA* variants that had already been identified in Norwegian patients. This was also in line with the conclusion from the Norwegian Health Authorities after the national debate preceding our study [94]. Secondly, we needed a test that could be easily integrated in the existing pipeline in our diagnostic laboratory, with a response time less than three weeks. Finally, the cost of full sequencing in all patients was too high for our limited research budget.

5.1.3 Family history assessment (Paper I and III)

For Paper I, information about family history was collected through a structured questionnaire on the request form for genetic testing (Appendix 1B). This information was used to categorise the study participants according to the Norwegian 2010 *BRCA* test criteria and to select patients for invitation to clinical genetic counselling and further genetic testing. In addition, the family histories were rated by the Manchester Scoring system (MSS), a tool that has been developed to identify families at high risk of having a pathogenic *BRCA* variant [132]. The system was first published in 2004 (MSS1) [132] and was revised in 2009 to include information about tumour pathology (MSS2) [143], with a second revision in 2017 (MSS3) [140]. Because of limited information about pathology we used the first version, MSS1, when rating all participants in Paper I. In addition, carriers of pathogenic variants were recalculated with MSS2 after collection of pathology information and confirmation of cancer diagnoses in the family.

In Paper III, the third version of the Manchester scoring system (MSS3) was used. Although the system was not developed with variant interpretation in mind, we found it useful in both Paper I and Paper III, to quantify the burden of relevant cancer in the families. Of note, it has also been used by the group developing the system, in interpretation of a *BRCA1* splice variant [144].

The families included in Paper III were mainly from our own department, but in addition we recruited families from collaborators who had access to families with the same variant. The *BRCA1* c.5407-25T>A variant is rare, and the selection of families was based on the availability of DNA test results and clinical and family information. Ideally, a segregation analysis would have been performed, but unfortunately the sizes of the individual families were too small.

5.1.4 Psychosocial measurements (Paper I and II)

For the psychosocial measurements we used pre-existing and validated questionnaires. By using well known questionnaires, the quality is often established, and the strength is that this gives the opportunity to compare the results with previous

studies. The reliability of the selected instruments has been satisfying in previous studies, and this was also the case in our study. The Cronbach's alpha value had a range of 0.83 to 0.88 for HADS-Anxiety, 0.80 to 0.86 for HADS-Depression, 0.93 to 0.95 for IES-Intrusion, and 0.86 to 0.87 for IES-Avoidance at the three assessments. For the predictor variables the Cronbach's alpha values were 0.92 (ISEL), and 0.96 (DCS).

Ideally, the results of the DNA-BONus study could be generalised to all patients offered genetic testing short time after a diagnosis of breast or ovarian cancer. However, we only had data on the 488 patients (48 % of invited patients) actually pursuing genetic testing. Due to ethical regulations, we could not collect information about the patients who did not consent to the study. However, by using data from the Cancer Registry of Norway we knew that participants in our study were younger (mean age 56.9 years at breast cancer diagnosis and 60.5 years at ovarian cancer diagnosis) than the average patients diagnosed with breast or ovarian cancer in Norway. According to the Norwegian Cancer Registry, the mean age at breast cancer diagnosis was 62.2 years and the mean age at ovarian cancer was 64.8 years in the years 2012-2015 [145]. For the psychosocial substudy, the data were collected in an even smaller subgroup, i.e. the results in Paper II were based on answers from 40% of those invited (309/772). The response rate for the psychosocial substudy among those undergoing genetic testing was 77% (309/403). In a multiple logistic regression of genetic test only versus genetic test and responding to questionnaire on age, Manchester score, diagnosis, genetic test criteria and mutation carrier status, only age was significant. The mean age was statistically significantly lower among participants also answering the questionnaires (56.1 years) compared to those who only participated in the genetic testing study (61.1 years) ($p = 0.001$). This indicates a selection bias toward younger patients for both the genetic testing study and even more so for the psychosocial substudy. On this background we could argue that our results may not be representative for the older patient population. We also did a multiple logistic regression analysis in all that responded at T1 ($n = 309$) of dropping out at T3 on age, Manchester score, diagnosis, genetic test criteria, mutation carrier

status, education, employment, having biological children, having a partner, and T1 mean values for ISEL, DCS, IES-I, IES-A, HADS-A and HADS-D. We found that participants who dropped out of the psychosocial study from the first (T1) to the last (T3) questionnaire were characterised by lower levels of education ($p = 0.048$), lower share of employment ($p = 0.032$), and lower share of cohabitation ($p = 0.034$). Due to a small number of patients identified with a pathogenic *BRCA* variant, no specific conclusion could be drawn for this particular subgroup.

5.1.5 Assessment of the splice variant *BRCA1* c.5407-25T>A (Paper III)

To assess the effect of the intronic *BRCA1* c.5407-25T>A variant on splicing, we analysed RNA extracted from carriers of the variant, and showed that the variant leads to skipping of exon 22. We had access to samples from blood as well as from breast and ovarian tissue, the latter being the most relevant tissue concerning the cancer risk for carriers of pathogenic *BRCA1* variants. Our RNA analyses showed similar results in all three tissue types, indicating that blood is a relevant source of RNA for analyses of *BRCA1*, with respect to breast and ovarian cancer. This is in accordance with previous studies [146, 147].

The access to patient derived RNA was a strength in our study, compared to e.g. a minigene assay, which is often used when appropriate patient material is not available. In a minigene assay a fragment including the variant sequence of interest and flanking intronic sequences is amplified by PCR from patient genomic DNA and cloned into a minigene vector. Following transfection into cultured cells, the transcripts generated from the variant construct are analysed and compared to wild-type. The minigene assay has the advantage that expression from the allele harbouring the variant can be analysed separately, without contribution from the wild-type allele. However, this is an artificial *in vitro* assay, which does not necessarily reflect the splicing process *in vivo*.

The presence of a coding SNP (c.4837A>G) in *BRCA1* exon 15 enabled us to document that some *BRCA1* full-length transcripts were also expressed from the c.5407-25T>A variant allele. Furthermore, we were able to perform a semi-

quantitative analysis of the amount of full-length *BRCA1* transcript including exon 22 that was expressed from the variant allele, through NGS-based sequencing of only the PCR products containing exon 22. When interpreting splice variants, the detection and quantification of "leakage" of full-length transcript from the variant allele is very important, since this can lead to maintenance of some tumour suppressor effect if the normal allele is disrupted by a somatic mutation. Our full transcriptome RNA sequencing was not very successful, as only a limited number of reads mapped to the *BRCA1* sequence. This could have been improved by increasing the number of reads, but high cost made this unjustifiable. A better approach would be targeted enrichment of the *BRCA1* gene before sequencing. We did an attempt on this, but unfortunately, we did not succeed. We will modify the protocol in future experiments. Furthermore, sequencing using "long read" platforms like Oxford Nanopore Technologies may solve some of the problems with quantification of different transcripts [148].

Multifactorial likelihood analyses are very helpful tools commonly used in evaluation of variants of uncertain significance in *BRCA1* [88, 149, 150]. These methods combine data from different independent sources like histopathology of tumours, family history, co-segregation with the disease in the family, and observed co-occurrence of the variant with a pathogenic *BRCA1* variant in trans. This is a powerful tool when enough data is available; however, for many rare variants the amount of data input will not be sufficient to reach a conclusion regarding pathogenicity [151, 152]. Furthermore, these methods have been designed to distinguish between benign sequence variants and pathogenic high-penetrance variants, and are not well suited for variants of potential reduced penetrance. An attempt was made to perform a multifactorial likelihood analysis on the *BRCA1* c.5407-25T>A variant, however the model failed for this variant just like it had done for other intermediate risk variants (Adrien Buisson, personal communication).

5.2 Discussion of specific findings

5.2.1 Genetic testing in newly diagnosed patients with breast or ovarian cancer

In our study, we found an uptake rate of genetic testing among newly diagnosed patients with breast cancer of 45%. For patients with ovarian cancer, the uptake rate was 68%. There are few comparable studies on uptake of *BRCA* testing in unselected patients newly diagnosed with breast or ovarian cancer. Nilsson et al. performed a study similar to ours and found that 67% of unselected patients with breast cancer accepted the offer of *BRCA* testing [118]. Kurian et al. performed a large retrospective survey among women two months after primary breast surgery, and found that 66% of the patients wanted genetic testing [153]. The uptake rate is generally higher among patients with ovarian cancer, with the highest rate reported (100%) in the mainstream cancer genetics programme in UK [119]. Several factors could affect the patients' decision to undergo genetic testing soon after diagnosis. Our study was performed before the approval of treatment with PARP-inhibitors for BRCA-deficient ovarian cancer, and the genetic test results would in most cases not have an effect upon the treatment of the patient. When genetic testing is performed mainly to inform cancer treatment, a higher uptake rate would be expected. Genetic counselling is by tradition non-directive with no right and wrong decisions concerning genetic testing. However, patients tend to follow their physician's advice when it comes to treatment decisions [154], and this could also impact their choice of having treatment focused genetic testing. Contrary, "my doctor didn't recommend it" was the most common reason high-risk patients reported for not having genetic testing in the survey of Kurian et al [153]. In our study, the main information was given in the written information letter, but we cannot rule out that a difference in wording or other local factors may have influenced the patients' final choice to undergo testing (see section 5.1.1). This could e.g. explain the higher uptake rate observed for patients of the smaller hospitals compared to Haukeland University Hospital (see Table 4).

Table 4. Uptake rate of genetic testing at the different participating clinical departments in the DNA-BONus study

Department	Breast surgery Haukeland	Breast surgery Førde	Breast surgery Haugesund	Gynaeco-logical Haukeland	Gynaeco-logical Stavanger
Patients invited, *n*	671	117	105	58	64
Blood samples returned, *n (%)*	283 (42.2)	65 (55.6)	57 (54.3)	35 (60.3)	48 (75.0)

At Haukeland University Hospital multiple research studies are ongoing at all times, and some patients may have chosen to participate in other studies instead of ours. The information about different studies comes on top of all other information related to the diagnosis, and for some patients the total information load can be overwhelming [131], resulting in the information about genetic testing is lost "in the crowd".

We found a lower mean age of participants in our study compared to average patients with breast or ovarian cancer diagnosed in Norway in the same period (se section 5.1.4). We also found that a majority of the participants were eligible for diagnostic *BRCA* testing according to the national guidelines. This indicates that patients with higher risk of carrying a *BRCA* pathogenic variant were more likely to undergo genetic testing in our study. Our findings are in line with other studies, reporting that younger age and higher presumed risk of carrying a *BRCA* pathogenic variant are predictors of *BRCA* testing uptake [153, 155].

Practical issues like easy access to blood sampling services can also affect the total share of patients pursuing genetic testing. For example, studies have shown that more patients go on with the genetic test if it is performed immediately after face-to-face genetic counselling as compared to telephone based genetic counselling [114].

In this study, we found a high frequency of pathogenic *BRCA* variants among patients with ovarian cancer (22.3%). Other studies have reported a frequency of 8.0-28.5% in unselected cohorts of ovarian cancer, with the highest numbers reported in populations with high prevalence of founder mutations [31, 48-51]. Among our breast cancer patients, the frequency was among the lowest reported, 1.7%, similar to what

was recently reported in a large study from Sweden (1.8%) [43]. A study from Oslo found a frequency of 3.1% [44] among unselected patients with breast cancer. In other populations, the carrier frequency varies, and the highest frequencies have been found in Asia (4.7-5.4%) [45, 47] and in cohorts including patients of Ashkenazi Jewish descent (6.1%) [46]. While more than half of the patients with ovarian cancer in our study were recruited from the southern part of our health region, this was the case for only 14% of the patients with breast cancer, resulting in a less prominent founder effect among the included breast cancer patients. Also, because of our two-step model of genetic testing, we cannot rule out that rare pathogenic variants may have been missed in patients not fulfilling criteria for sequencing of the complete coding regions of *BRCA1* and *BRCA2*.

Clinical criteria for genetic testing are constantly changing and subject of debate [156-158]. The overall trend is that testing criteria are expanding, as the cost of genetic testing continues to fall. Moreover, the genetic test result is becoming increasingly important for treatment decisions. Until recently, a commonly used threshold for *BRCA* testing eligibility has been a 10% chance of finding a pathogenic variant [91]. We investigated the usefulness of the Norwegian criteria for *BRCA* genetic testing (Table 1), and found that all patients with identified pathogenic *BRCA* variants in the DNA-BONus study fulfilled one or more of the 2010 *BRCA* test criteria. Thus, the criteria seemed sufficient to detect most of the carriers in the DNA-BONus study. However, because of the high frequency of pathogenic *BRCA* variants among patients with ovarian cancer we recommended that all patients with ovarian cancer should be offered *BRCA* genetic testing, regardless of family history and age (Paper I). The Norwegian Health Authorities has implemented this recommendation in national guidelines since 2015 [74], and several countries have similar guidelines [159, 160]. For any patient with ovarian cancer, the likelihood of having a germline pathogenic *BRCA* variant exceeds 10% in the Norwegian and in many other populations.

However, the likelihood of being a *BRCA* carrier is much lower for a patient with breast cancer, only 1.7% in our study. We identified a pathogenic *BRCA* variant in

3.0% of patients with breast cancer fulfilling the Norwegian *BRCA* test criteria. This indicates that the Norwegian criteria already have set a low threshold for testing of patients with breast cancer, and the findings in our study did not provide a basis for changing the current recommendations. Similar to our results, a study from US on 488 unselected patients with breast cancer found that all (N=30) identified *BRCA* carriers fulfilled the 2015 National Comprehensive Cancer Network (NCCN) criteria, which have many similarities to the Norwegian 2010 criteria [46, 161].

The Norwegian Health Authorities recently approved a change in the Norwegian criteria, stating that all women diagnosed with breast cancer before the age of 60 years should be offered *BRCA* genetic testing, regardless of family history or tumour pathology [64]. This change was mainly based on the result from the aforementioned study from Oslo, where they found similar sensitivity (around 90%) of this age criterion alone as for the more complex clinical test criteria [44]. The change results in more than a doubling of the number of women with breast cancer eligible for genetic testing. The hope is that simplifying of the criteria will lead to more genetic tests ordered by the breast surgeons and oncologists.

The discussion continues whether criteria are needed for patients with breast cancer, or if the time now has come to offer all patients with breast cancer genetic testing [44, 162, 163]. Despite falling costs and broadened criteria for genetic testing, there is still a substantial underuse of genetic testing of patients with breast and ovarian cancer. Several studies have shown that a significant share of patients fulfilling *BRCA* genetic test criteria do not undergo genetic testing [156, 164-167]. There is no help in refining criteria that in an ideal world would identify all carriers, if individuals meeting those criteria are not tested. Lack of physicians' referral to genetic counselling has been reported as a main barrier for genetic testing of patients with breast and ovarian cancer [153, 165, 168]. Even without formal pre-test genetic counselling as a requirement for diagnostic genetic testing, the recommendation (or not) from the patient's physician can influence the likelihood of going forward with genetic testing [153].

The Norwegian Biotechnology Act is currently under revision. One of the proposed changes specifies that the purpose of the genetic test determines whether it is predictive or not; e.g. *BRCA* testing of a woman already affected by breast cancer is considered a diagnostic test, even if a positive result will be predictive for her risk of ovarian cancer. Another proposed change is that genetic counselling should be differentiated and adjusted to the specific situation in which genetic testing is performed. These two changes could facilitate more diagnostic genetic testing performed by non-genetic health care professionals.

However, the rapid development in genetics has generated a knowledge gap among non-genetic physicians that needs to be filled [169]. Education of key providers like oncologists, surgeons and gynaecologists can potentially increase the rate of patients being tested [119]. Education may also be of great importance to avoid unnecessary "over-testing". It is a paradox that there are still thousands of unrecognised carriers of highly penetrant pathogenic variants in *BRCA1* or *BRCA2*, and at the same time there are thousands of people spending money, time and worries on genetic testing for variants with uncertain associations with cancer risk through less justified genetic testing. While health professionals, researchers, and health authorities develop evidence-based guidelines for genetic testing, counselling and follow-up, commercial interests are now playing an increasing role in this field. Companies offer direct-to-consumer tests for hereditary cancer risk, with highly variable content and quality, and usually with no associated genetic counselling service [110, 170]. Clinical genetic departments experience an increasing number of referrals of people who have ordered genetic self-tests, and who needs help to interpret the result. There are several reports of these results being uninformative, directly wrong or at the best inaccurate [171, 172].

Establishing good procedures and securing access for genetic testing in health care is therefore important to reduce "leakage" of patients to direct-to-consumer testing that causes more burden than benefit both for the patients and the community. A new approach for improving genetic testing for cancer predisposition is population based genetic screening. Although yet not implemented in form of national screening

programs, this approach is gaining increasing support among experts in the field [173-175].

5.2.2 Psychosocial aspects of genetic testing shortly after cancer diagnosis

Overall, the study participants who underwent genetic testing shortly after receiving a diagnosis of breast or ovarian cancer seemed to cope well with the new and simplified procedure for genetic testing. In accordance with this, a recent Swedish study reported high patient satisfaction with a similar procedure in patients newly diagnosed with breast cancer [176]. In our study the mean values of anxiety and depression symptoms as measured by HADS were low and the mean values of cancer related distress as measured by IES-15 were moderate both before and after genetic testing. We also documented a statistically significant decline in the mean levels of anxiety symptoms (HADS-A), intrusion (IES-I) and avoidance (IES-A) during the follow-up time which also included the dissemination of the *BRCA* test result. Still, around 40% of the patients scored above the cut-off level for anxiety (Paper I, Table 3), 32% had intrusion scores in the severe range and 24% had avoidance scores in the severe range at inclusion (Paper II, Table 2). The proportion of patients with high scores on anxiety, intrusion and avoidance symptoms dropped significantly during follow-up. Similar results have been shown in other studies on patients with breast or ovarian cancer and in individuals undergoing genetic testing for hereditary breast and ovarian cancer [85, 104, 126, 128, 177, 178].

The subgroup of patients with higher levels of anxiety and/or cancer related distress needs more attention. A high level of distress has been shown to have a negative impact on the patient's ability to receive and remember information and can lead to lower adherence and compliance to treatment and follow-up [179]. This could be of potential clinical significance when genetic testing at the time of diagnosis is becoming common practice [154, 158, 180]. Patients with higher levels of distress may have more difficulties in understanding the consequences of genetic testing. The principle of informed consent from the patient is important in all aspects of medical practice, including genetic testing. In our study, all patients signed a written consent

form for the genetic test, but even so one of the participants expressed in a later focus group interview that she could not remember that she had signed any consent [131]. This shows that signing a written informed consent not necessarily means that a patient is informed, but also raises an opposite concern: what about the patients (52% of invited patients in our study) that did not have a genetic test? For some of the patients the decision may have been a result of an active choice of not having the genetic test, but for others the situation may have been that they were not aware of declining a diagnostic genetic test. Those with higher levels of distress are more vulnerable for not comprehending the large amount of information received in the period immediately after diagnosis [179]. There is a potential that these patients miss the testing opportunity if healthcare professionals are not aware of the implication of distress and take the necessary time to discuss genetic testing in person with these patients [131]. In that aspect, the predictors of increased distress identified in our study can be useful to select patients that need more attention.

Younger patients are more distressed after receiving a cancer diagnosis than the elderly; this has been shown in multiple studies including ours (Paper II) [130, 177, 181]. Genetic testing is especially important in younger patients, because of a higher risk of germline pathogenic variants being present - with a potentially higher impact on their life expectancy. It would therefore be reasonable to make extra effort in assuring that these young patients receive sufficient information to take an active choice regarding genetic testing. On the other side, it is reassuring that young patients in general are more likely to undergo genetic testing. Both our as well as other studies have shown that the acceptance/referral rate for genetic testing is higher among younger patients [155, 165, 182].

Another important predictor of increased distress is shorter time since diagnosis (Paper II) [126, 128, 130, 178]. Since the levels of distress decreased quite quickly, one could argue that postponing the genetic test only a few weeks could be beneficial. However, when the genetic test result is important to guide immediate treatment of the patient, postponing is of course not an option, and the present study served as a preparation for this situation. For patients where the initial treatment will not differ

between carriers and non-carriers of pathogenic germline variants, introducing genetic testing at a later stage could be an alternative – especially if the patient has high levels of distress or anxiety.

Many guidelines now recommend genetic testing for all patients with ovarian cancer [159, 174, 180]. In our study, patients with ovarian cancer had higher levels of distress as compared to patients with breast cancer. These patients could benefit from in-person discussion of genetic testing, e.g. with their gynaecologist or oncologist.

We found that perceived social support, as measured by ISEL [136], was a strong predictor of lower levels of both intrusion and avoidance in women undergoing genetic testing shortly after a diagnosis of breast or ovarian cancer (Paper II). Some researchers equate having a partner and having social support [181], but our study indicates that these are two different factors that cannot be used interchangeably. While high levels of perceived social support predicted lower levels of intrusion and avoidance in our study, we found that women living with a partner had statistically significantly higher levels of intrusion symptoms at all three assessment points compared to women living alone. We do not have an explanation of this finding in our data, and previous research has shown diverging results when it comes to the effect of marriage or marriage-like relationship on psychosocial distress in patients with cancer [129, 181, 183, 184]. However, the quality of an intimate relationship seems to be important [185]. Furthermore, the gender issue must be kept in mind. One study found that men with cancer were less likely to develop symptoms of psychological distress if they were married, while female cancer patients had lower levels of psychological distress if they were not married [186]. The size of the effect in our study was modest, and therefore not necessarily clinically relevant. Nevertheless, it would be interesting if future studies could confirm whether having a cohabitating partner constitutes an extra burden for women newly diagnosed with breast or ovarian cancer. If so, the possible reasons should be explored.

5.2.3 *BRCA* variants with reduced penetrance

In Paper III, we showed that *BRCA1* c.5407-25T>A causes aberrant splicing and a premature stop codon leading to a truncated BRCA1 protein with loss of the important BRCT domain. Furthermore, our results indicated a leakage of normal transcript from the variant allele. The biological consequence of a small leakage of normal transcript from a spliceogenic DNA variant is not fully known, but this could lead to synthesis of functional protein and maintenance of some tumour suppressor effect. "Leaky" splice variants are therefore usually classified as VUS [151, 187, 188]. However, the decreased amount of normal transcript could lead to a reduced, although not completely absent, tumour suppressor effect of potential clinical significance. In line with this, it is possible that the *BRCA1* c.5407-25T>A variant is associated with an increased risk of breast and ovarian cancer, but the magnitude of risk may be lower than for truncating pathogenic *BRCA1* variants. "Leaky" splice variants have been described to be disease causing with reduced penetrance for other genes [189-191], and this could also be the case for *BRCA1* and *BRCA2* [151].

The clinical characteristics of the studied families with *BRCA1* c.5407-25T>A were consistent with hereditary breast and ovarian cancer of reduced penetrance. The mean age of onset of breast or ovarian cancer was 49.9 and 60.4 years, respectively, which is lower than reported for the general population (62.2 and 64.8 years, respectively in the years 2012-2015) [145], but higher than reported in a large international prospective study of clinically ascertained carriers of a *BRCA1* pathogenic variant (median age of 44 and 54 years, respectively) [53]. However, a population-based study found a mean age at diagnosis of 50.3 years in women with a pathogenic *BRCA1* variant [43]. The mean Manchester score was 16.4 in the 20 families with *BRCA1* c.5407-25T>A. In the DNA-BONus study (Paper I), the mean Manchester score was 8.3 in patients with a negative *BRCA* genetic test result and 23.3 in patients where a truncating pathogenic *BRCA* variant was found and not previously known in the family. Since the Manchester calculations in the *BRCA* negative patients in the DNA-BONus study were based solely on the self-reported structured family history collected at inclusion and did not adjust for pathology information, the groups are not directly comparable. However, taken together the Manchester scores could indicate

an intermediate cancer burden in families with *BRCA1* c.5407-25T>A; higher than for average patients with breast and ovarian cancer, but lower than for families with truncating *BRCA* variants.

In the DNA-BONus study, we found *BRCA1* c.5407-25T>A in two patients with breast cancer. One of the patients was diagnosed through the population mammography screening at age 64 years and had two close relatives with ovarian cancer after 70 years. The other patient was diagnosed at the age of 47, in a surveillance program for *BRCA* negative familial breast cancer. The breast cancer cases were on her mother's side of the family, while the *BRCA1* c.5407-25T>A variant was inherited from the father.

While we were not able to calculate the penetrance of the *BRCA1* c.5407-25T>A in our small cohort of carriers, this has been done for the *BRCA1* missense variant c.5096G>A, p.(Arg1699Gln), which we identified in a woman with breast cancer at the age of 76 in the DNA-BONus study [192]. The ENIGMA consortium has investigated 129 families with p.(Arg1699Gln) and estimated the risk of breast cancer by age 70 years to be 20% and the risk of ovarian cancer by age 70 years to be 6% [149].

It is worth noting that three out of the seven breast cancer patients identified with pathogenic *BRCA* variants in the DNA-BONus study had a variant associated with (possible) moderate penetrance. As the indications for genetic testing keeps broadening, it is likely that more variants with low/moderate penetrance will be identified. This is a familiar story in the field of medical genetics: the first patients and families that come to attention are those with the most severe phenotype. When the genetic cause has been identified, more patients are tested, and often it turns out that the phenotype is more variable than first assumed. For several cancer genes it has been documented that the penetrance is higher when there is a positive family history compared to when the family history is negative [26, 193]. Modifying genetic and non-genetic factors play an important role in this variability in penetrance [194, 195].

Panel tests where multiple cancer predisposing genes are tested simultaneously are now gradually replacing single gene testing in cancer genetics clinics [27, 196]. Several of these panels include genes associated with moderate cancer risk and even genes where the associated cancer risk has not been sufficiently documented [27, 197]. The clinical significance of variants in such genes is not as obvious as truncating variants in e.g. *BRCA1,* and the effect is more modifiable by other genetic and non-genetic factors. Over time genetic test results have become increasingly complex. The picture is no longer "black or white", which is important to be aware of both for doctors ordering genetic tests and for people undergoing testing. When moderate penetrant variants are identified in a family, this is in most cases not the only contributing factor to the cancer burden in the family and family members testing negative for the variant is not necessarily at low risk. Since many of the factors contributing to aggregation of cancer in a family are still unknown, and not possible to identify by a simple test, the family history retains its value as a picture of the total burden of risk in that specific family. Even with easier access to broader genetic tests the family history will be important for risk assessment of individuals.

Furthermore, the complexity of genetic testing and risk assessment understates the importance of securing access to genetic competence also in the era of personalised medicine and mainstreaming of genetic testing into cancer clinics. Genetics professionals should take active part in multidisciplinary teams, to discuss complex genetic test results before clinical action is taken on the basis of the result. Patients with complex results on diagnostic genetic tests should be referred to post-test face-to face genetic counselling.

6. Conclusions

- In our DNA-BONus study, 45% of patients with breast cancer and 68% of patients with ovarian cancer accepted *BRCA* genetic testing when offered shortly after diagnosis (**Paper I**).
- We identified a germline pathogenic *BRCA* variant in a high share (22%) of women with ovarian cancer but only in 2% of women with breast cancer (**Paper I**).
- All carriers of a germline pathogenic *BRCA* variant fulfilled at least one of the Norwegian *BRCA* test criteria as defined in 2010 (**Paper I**).
- Overall the study participants seemed to cope well with the new and simplified procedure for diagnostic genetic testing without pre-test genetic counselling. There was a statistically significant decline in the mean levels of anxiety symptoms (**Paper I**) and cancer related psychological distress (**Paper II**) from inclusion to six months after dissemination of the *BRCA* test result.
- Predictors of increased distress were young age, short time since diagnosis, low level of perceived social support, high level of decisional conflict, diagnosis of ovarian cancer, and living with a partner (**Paper II**).
- The intronic *BRCA1* c.5407-25T>A variant that was identified in two participants in the DNA-BONus study causes partial skipping of exon 22, and is a likely pathogenic variant with possible reduced penetrance (**Paper III**).

7. Future perspectives

This thesis illustrates the rapid development in the field of clinical cancer genetics. The DNA-BONus study served as a preparation for a near future when genetic testing would guide treatment decisions in patients newly diagnosed with cancer. This future has already entered clinical practice, and new routines for genetic testing and counselling of patients with newly diagnosed breast or ovarian cancer have been implemented in our health region based on the experiences from this study. At a national and international level, Paper I added to the body of knowledge that has led to recommendations of genetic *BRCA* testing for all patients with ovarian cancer.

Despite increasing access to genetic testing there is still a significant share of eligible patients who does not undergo genetic testing, e.g. around half of the patients invited in our study. Future studies that investigate why people accept or decline genetic testing would be helpful for the planning of new routines for diagnostic genetic testing of patients with cancer.

The criteria for genetic testing continue to broaden, and eventually this could lead to a practice where genetic testing is becoming available for all patients with specific forms of cancer. A further expansion of the access to genetic testing is not unlikely, e.g. to patients with all forms of cancer, and ultimately to everyone through direct-to-consumer genetic testing and population screening. Future studies should focus on evaluation of different levels of genetic information and counselling. New effective ways of delivering genetic information to large target groups are needed, at the same time as access to genetic counselling must be ensured for subgroups in need of extra intervention. Studies that explore the experiences of individuals identified with pathogenic *BRCA* variants through these new models of genetic testing would be of interest.

As elaborated in Paper III, the classification of *BRCA* sequence variants is challenging and extremely important for proper clinical management of patients carrying these variants. For “leaky” splice variants the ultimate goal would be to find

a correlation between the amount of normal transcript produced by the variant allele and the magnitude of cancer risk. National and international collaboration and sharing of sequence and functional data should be a priority for diagnostic genetic laboratories, researchers and authorities.

Several of these aspects will be addressed in ongoing and future research projects at the Western Norway Familial Cancer Center. We will study the use of chatbot technology as a communication tool to support individuals undergoing genetic testing for hereditary breast and ovarian cancer. In another study, we will determine the prospective cancer risk in families with suspected hereditary cancer, but where pathogenic variants in high risk cancer genes have not been identified. Finally, we have initiated a national collaborative study to reveal discrepancies in interpretation of *BRCA1* sequence variants in Norway.

8. References

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ARTICLE

BRCA1/2 testing in newly diagnosed breast and ovarian cancer patients without prior genetic counselling: the DNA-BONus study

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Germline *BRCA1/2* testing of breast and ovarian cancer patients is growing rapidly as the result affects both treatment and cancer prevention in patients and relatives. Through the DNA-BONus study we offered *BRCA1/2* testing and familial risk assessment to all new patients with breast ($N=893$) or ovarian ($N=122$) cancer diagnosed between September 2012 and April 2015, irrespective of family history or age, and without prior face-to-face genetic counselling. *BRCA1/2* testing was accepted by 405 (45.4%) and 83 (68.0%) of the patients with breast or ovarian cancer, respectively. A pathogenic *BRCA1/2* variant was found in 7 (1.7%) of the breast cancer patients and 19 (22.3%) of the ovarian cancer patients. In retrospect, all *BRCA1/2* mutation carriers appeared to fulfill current criteria for *BRCA1/2* testing. Hospital Anxiety and Depression Scale (HADS) scores showed that the mean levels of anxiety and depression were comparable to those reported for breast and gynecological cancer patients in general, with a significant drop in anxiety symptoms during a 6-month follow-up period, during which the test result was forwarded to the patients. These results show that *BRCA1/2* testing is well accepted in newly diagnosed breast and ovarian cancer patients. Current test criteria based on age and family history are sufficient to identify most *BRCA1/2* mutation carriers among breast cancer patients. We recommend germline *BRCA1/2* testing in all patients with epithelial ovarian cancer because of the high prevalence of pathogenic *BRCA1/2* variants.
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INTRODUCTION

Breast cancer is by far the most common cancer in women worldwide, with more than 1.6 million new cases diagnosed each year. Ovarian cancer is substantially less common, with ~240 000 new cases each year, but with higher mortality.[1] Most cases of breast and ovarian cancer are sporadic, but a minor fraction (2–8% and 8–15%, respectively) is caused by inheritance of pathogenic germline variants in *BRCA1* or *BRCA2*, with variation in prevalence and relative contribution of *BRCA1* and *BRCA2* in different populations.[2–8] It is important to identify these patients because the presence of such germline variants affects treatment, follow-up and further cancer prevention in patients with breast or ovarian cancer.[9,10] In addition, it may strongly influence upon their close relatives, as *BRCA1/2* testing can identify healthy *BRCA1/2* mutation carriers at high risk and thereby prevent cancer and cancer-related deaths through increased surveillance and prophylactic surgery.[10–16]

The most common current practice of *BRCA1/2* testing is based on referral of suspected high-risk patients to clinical genetics services for specialized face-to-face genetic counselling. This procedure traditionally includes collection and confirmation of family history, risk assessment and eventually *BRCA1/2* testing followed by a post-test counselling with dissemination of test results and advice concerning surveillance and follow-up.[17–19] Based on family history, *BRCA1/2*-negative families with increased risk of familial breast cancer can also be identified.[18,20]

However, this traditional approach is time consuming and resource demanding for both the patient and the health-care system, with an inherent risk of focusing too much on healthy relatives and not reaching all the cancer patients in question. Moreover, the discovery that *BRCA1/2* status can inform treatment decisions in breast and ovarian cancer patients has led to an increased demand for *BRCA1/2* testing at the time of cancer diagnosis.[9,21] New approaches to *BRCA1/2* testing and genetic counselling may be needed to meet this situation. The aim of this project was therefore to assess the feasibility and impact of offering *BRCA1/2* testing to all newly diagnosed patients with breast or ovarian cancer without prior face-to-face genetic counselling. We here report the uptake of *BRCA1/2* testing, the incidence of pathogenic *BRCA1/2* variants and the individual risk profiles among these unselected breast and ovarian cancer patients. As the psychosocial impact of such *BRCA1/2* testing in newly

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diagnosed cancer patients without prior genetic counselling is scarcely described,[22] we also examined the symptoms of anxiety and depression at inclusion and during the follow-up period of 6 months.

PATIENTS AND METHODS

Recruitment of patients

The patients were recruited from four hospitals in Western Norway (Haukeland University Hospital, Stavanger University Hospital, Haugesund Hospital and Førde Central Hospital), including three surgical departments and two gynecological departments, from September 2012 to April 2015. All patients with newly diagnosed breast or ovarian cancer were invited to participate in the study (for overview, see Figure 1). The patients received written information on the project and general information on hereditary breast and ovarian cancer, including the mode of inheritance and the potential consequences of a positive test results; such as the elevated cancer risk, recommended follow-up and risk-reducing strategies for the patient and healthy relatives. They were also informed that a positive test result could affect the surgical treatment of breast cancer patients, whereas specific information on novel therapies, like PARP-inhibitors, was not given. In addition, the patients had the opportunity to contact a genetic counselor on telephone for any further questions. All participants signed informed consent and filled in a structured questionnaire on personal and family medical history. The patients could choose *BRCA1/2* testing with or without participating in an associated study of psychosocial aspects (see below). A blood sample was then collected at the local hospital and sent to a central laboratory for *BRCA1/2* analysis. The study protocol was approved by the Regional Committee for Medical and Health Research Ethics (reference number REK Vest 2012-60).

DNA isolation, BRCA mutation analysis and clinical assessments

Genomic DNA was purified from EDTA-anticoagulated blood using the QiaSymphony instrument (Qiagen, Hilden, Germany). Genotyping of a panel of 20 pathogenic *BRCA1* and 10 pathogenic *BRCA2* variants that are recurrent in the Norwegian population was carried out using TaqMan Low-Density Arrays on the ABI 9700 instrument (Applied Biosystems, Foster City, CA, USA) as recommended by the manufacturer. An overview over the variants and sequences for the corresponding primers and probes is given in the Supplementary Table 1. In addition, the *BRCA1* and *BRCA2* genes were analyzed for deletions and insertions by Multiplex Ligation-dependent Probe Amplification (MLPA) technology (P002 BRCA1 and P045 BRCA2 MLPA probe mixes; MRC-Holland, Amsterdam, The Netherlands).

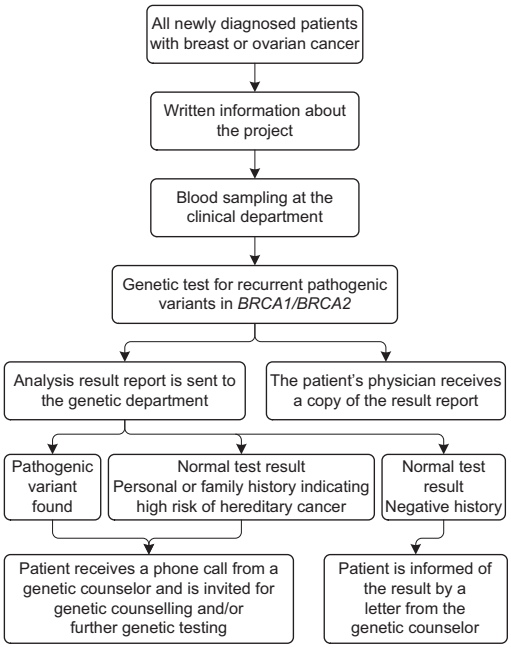

Figure 1 Flowchart showing the inclusion of patients and reporting of results in the DNA-BONus study.

The result of the *BRCA1/2* testing was given to the patient by a genetic counselor within 3 weeks after blood sample collection (Figure 1). In addition, the result was reported to the clinician who was responsible for treating the patient, to be filed in the patient's medical record at the hospital. If the test result was negative and there was no increased familial cancer risk, the patient received the result by letter. Patients with a positive test result or with a personal or family history indicative of a high risk of hereditary cancer were contacted over the phone by a genetic counselor and were offered traditional face-to-face genetic counselling and further investigations in one of our outpatient clinics.

Based on collection of family history and confirmation of cancer diagnoses in relatives, selected patients were then offered extended genetic testing, with Sanger sequencing of all exons and flanking intron sequence in both *BRCA1* and *BRCA2*. We used the following reference sequences: *BRCA1*: NG_005905.2 (gene), NM_007294.3 (mRNA), NP_009225.1 (protein); *BRCA2*: NG_012772.3 (gene), NM_000059.3 (mRNA) and NP_000050.2 (protein)).

To classify the sequence variants we followed the recommendations given by the International Agency for Research on Cancer (IARC).[23] Pathogenic (class 5) and likely pathogenic (class 4) variants were regarded as positive genetic test results and have been submitted to the Leiden Open Variation Database (LOVD 3.0 shared installation; www.databases.lovd.nl/shared/genes). In this article we use the term *BRCA1/2* mutation carrier for patients in whom a pathogenic or likely pathogenic variant was found.

All patients were categorized before *BRCA1/2* testing depending on the presence of increased familial cancer risk or not. Increased risk was defined as personal at risk cancer history (eg, patients with young age at diagnosis, bilateral breast cancer or both breast and ovarian cancer) or positive family history (eg, close relative with breast cancer before 50 years of age or ovarian cancer at any age, two or more relatives with breast cancer or both breast and ovarian cancer in relatives) or a combination of personal at risk cancer history and positive family history, according to the current national clinical criteria for *BRCA1/2* testing (see also legend to Table 1). The participants were in addition rated by the Manchester scoring system for *BRCA1/2* testing.[24,25]

Psychological measurements

Participants who gave informed consent for the psychosocial part of the project were asked to fill in questionnaires at baseline when they were offered genetic testing (T1), at 1 week after disclosure of the *BRCA1/2* test result (T2) and 6 months after disclosure of the *BRCA1/2* test result (T3). In the present study, we have used data from the Hospital Anxiety and Depression Scale (HADS).[26] HADS comprises two subscales for symptoms of anxiety and depression, respectively, each with 7 items to be scored on a 4-point (0–3) scale, giving a range of subscores from 0 to 21. The reliability of the HADS subscales in this study, as estimated with Cronbach's α, had a range of 0.83–0.88 for HADS anxiety and 0.80–0.86 for HADS depression at the three assessments. Subscale scores of ≥ 8 were used as cutoff for defining higher, caseness-relevant levels of anxiety and depression.[27]

Statistical methods

Descriptive statistics were used for psychological and clinical variables, reporting the mean values, SD and range. To analyze the changes over time in HADS anxiety and depression scores, we used a paired sample *t*-test and McNemar's exact test. Independent sample *t*-test was used to compare the means of two independent groups and χ^2 test was used to analyze dichotomous variables for independent groups.

Missing values were replaced by the individual's own average score for HADS if 60% or more of the items were filled in by the respondents. All statistical

Table 1 DNA-BONus study population

	Number of patients included	*Mean age (years)*	*Current national criteria for BRCA1/2 testing* [a]					*Manchester scores at inclusion*	
			At risk personal cancer history only (N)	*Positive family history only (N)*	*Fulfilled Both at risk personal history and family history (N)*	*Total number of patients fulfilling criteria, N (%)*	*Not fulfilled Number of patients outside current criteria for BRCA1/2 testing,*[a] *N (%)*	*Number of patients with combined Manchester score ≥ 15, N (%)*	*Number of patients with combined Manchester score < 15, N (%)*
Breast cancer									
Total	405	56.9 Range: 23–89	103	48	51	202 (49.9%)	203 (50.1%)	41 (10.1%)	364 (89.9%)
Pathogenic *BRCA1/2* variant identified, *N* (%)	7 (1.7%)	50.6 Range: 32–76	3	1	2	6 (85.7%)	1[b] (14.3%)	2 (28.6%)	5 (71.4%)
Ovarian cancer									
Total	83	60.5 Range: 24–88	49	4	17	70 (84.3%)	13 (15.7%)	26 (31.3%)	57 (68.7%)
Pathogenic *BRCA1/2* variant identified, *N* (%)	19 (22.3%)	56.5 Range: 44–72	10	0	8	18 (94.7%)	1[b] (5.3%)	11 (57.9%)	8 (42.1%)

Positive family history: first-degree relative with breast cancer before age 50 years or ovarian cancer at any age, two or more breast cancer cases or both breast and ovarian cancer on the same side of the family, male relative with breast cancer or known *BRCA1/2* mutation in the family.
[a]Criteria for clinical *BRCA1/2* founder mutation testing of patients with breast or ovarian cancer, as outlined by the Norwegian Health Authorities: at risk personal history; breast cancer before age 50 years, ovarian cancer before age 70 years, bilateral breast cancer, both breast and ovarian cancer or male breast cancer at any age.
[b]These numbers represent two patients who apparently did not fulfill current national test criteria upon inclusion. They were reclassified after genetic counselling, and in retrospect, both were eligible for diagnostic *BRCA1/2* testing according to the test criteria.

analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY, USA).

RESULTS

A total of 1015 patients with either breast cancer ($N=893$) or ovarian cancer ($N=122$) were offered *BRCA1/2* testing at the time of cancer diagnosis, of whom 405 (45.4%) of the breast cancer patients and 83 (68.0%) of the ovarian cancer patients completed the genetic testing. The mean age of the participants was 56.9 years (SD 12.4, range (min–max) 23–89) in the patients with breast cancer and 60.5 years (SD 11.9, range 24–88) in the patients with ovarian cancer (Table 1). Among the participants, 202 (49.9%) of the patients with breast cancer and 70 (84.3%) of the patients with ovarian cancer were eligible for *BRCA1/2* testing according to current national clinical guidelines (Table 1). The median time from diagnosis to blood sampling was 34 days (mean 68, range 0–1402) and the median time from diagnosis to the patient received initial test result was 52 days (mean 87, range 12–1423) (data not shown). For 13 patients, the interval between diagnosis and blood sampling exceeded 1 year.

A pathogenic *BRCA1/2* variant was identified in 7 (1.7%) of the 405 breast cancer patients (mean age of 50.6 (SD 15.8, range 32–76) years; Table 1), of whom 6 carried a *BRCA1* and 1 a *BRCA2* pathogenic variant (Table 2). Three *BRCA1* and one *BRCA2* mutation carriers had a breast cancer that was triple negative (Er-/Pr-/HER2-) and all seven breast cancers were HER2 negative (Table 2). Interestingly, as many as 19 (22.3%) of the 83 ovarian cancer patients (mean age 56.5 (SD 9.1, range 44–72) years) were *BRCA1/2* mutation carriers (Table 1), including 15 with a pathogenic *BRCA1* variant and 4 patients with a pathogenic *BRCA2* variant (Table 2). Most ovarian cancers were serous carcinomas, apart from one poorly differentiated carcinoma and one endometroid adenocarcinoma. The majority of the mutation carriers ($N=21$; 80.8%) were identified by the standard test panel of recurrent mutations (Table 2), where 3 of the most frequent Norwegian pathogenic founder variants in *BRCA1* (c.1556del, c.697_698del and c.3228_3229del) were detected in 15 (57.7%) of the mutation carriers. Four additional pathogenic variants were identified by Sanger sequencing of selected breast cancer ($N=94$) or ovarian cancer ($N=31$) patients with a particularly high risk of carrying a pathogenic *BRCA1/2* variant, based on the personal and family history (see Table 2). During the first (years 2012–2013) and second (years 2014–2015) half of the DNA-BONus study period, 26.1% (55 out of 211) and 25.3% (70 out of 277) of the participants were selected for Sanger sequencing, respectively. Out of the total population of 488 patients, no one had *BRCA1/2* alterations that could be detected by MLPA.

Among the 272 patients fulfilling the current national criteria for diagnostic *BRCA1/2* testing at inclusion, 6 out of 202 breast cancer patients (3.0%) and 18 out of 70 ovarian cancer patients (25.7%) were found to be mutation carriers (Table 1). Among 216 patients not meeting current clinical test criteria at inclusion, the corresponding numbers of *BRCA1/2* mutation carriers were 1 of the 203 breast cancer patients (0.5%) and 1 of the 13 ovarian cancer patients (7.7%). However, it should be noted that the breast cancer patient with a pathogenic *BRCA1* variant and the ovarian cancer patient with a pathogenic *BRCA2* variant, who apparently had negative family histories upon inclusion, were both subsequently reclassified as having familial risk, based on extended pedigrees obtained through the genetic counselling (see below, Discussion section).

The mean combined Manchester score at inclusion was 8.9 (range 2–71) (data not shown), with 67 out of 488 patients (13.7%) having a score of ≥ 15 (Table 1). A pathogenic *BRCA1/2* variant was found in 13 out of 67 patients (19.4%) with a score of ≥ 15 and in 13 out of 421 patients (3.1%) with a score <15 (Table 1; summarized numbers). Among the 26 *BRCA1/2* mutation carriers, the mean combined Manchester score at inclusion was 19.5 (range 4–71) (Table 2; summarized numbers). After genetic counselling and collection of additional clinical information, including pathology reports, the scores could be recalculated for 25 of the 26 mutation carriers (Table 2). The mean combined score increased to 27.7 (range 14–81) (data not shown), with 24 mutation carriers having a score of ≥ 15, whereas the remaining mutation carrier had a score of 14 (Table 2).

All 26 *BRCA1/2* mutation carriers accepted the offer of traditional face-to-face post-test genetic counselling. Among participants with a negative result on the initial *BRCA1/2* panel and MLPA analysis, genetic counselling was offered for 188 patients (40.3% of total) with a personal at risk cancer history indicating further genetic testing (eg, young age at diagnosis or more than one primary cancer) or with a positive family history indicative of either familial breast cancer (eg, two or more breast cancer cases in first-degree relatives) or another hereditary cancer syndrome. The acceptance rate for genetic counselling in this group was 93.6% ($N=176$).

Because of the potential risk of imposing additional psychosocial burden by offering and performing *BRCA1/2* testing in the newly diagnosed cancer patients, we measured the level of anxiety and depression scores before testing and at 1 week and 6 months after disclosure of the test result in a subset of participants (Table 3). Among these 215 patients, the median time from diagnosis to blood sampling was 32 days (mean 56, range 0–436) and median time from diagnosis to received result was 50 days (mean 75, range 12–456) (data not shown). The mean HADS subscale score for anxiety symptoms was 6.84 (SD 4.28) at baseline (ie, time of inclusion), with a significant decrease to 4.88 (SD 3.86) 6 months after disclosure of the *BRCA1/2* test result ($P<0.001$). The percentage of patients with higher levels of anxiety symptoms, defined as scores ≥ 8, decreased significantly from inclusion (39.9%) to 1 week (23.6%, $P<0.001$) and 6 months (19.8%, $P<0.001$) after disclosure of the test result, respectively. During the observation period there was no significant change in depression symptoms, with a mean HADS score of 3.32 (SD 3.07) at baseline and 2.65 (SD 3.04) at 6 months. Approximately 10% of the patients showed higher levels of depression symptoms with a score of ≥ 8, both at baseline and follow-up measurements (Table 3). There were no significant differences in HADS scores between patients with breast ($N=138$) and ovarian ($N=29$) cancer, or between mutation carriers ($N=8$) and noncarriers ($N=159$) (data not shown).

To explore the effect of time after diagnosis on the HADS scores, we divided the sample in two groups, with $N=171$ (83.0%) having less than and $N=35$ (17.0%) having more than 90 days from cancer diagnosis to blood sampling. There were no significant differences in HADS scores between the two groups (data not shown).

Compared with the participants who only agreed to genetic testing (mean age 61.6 years), the patients who also took part in the psychosocial study were significantly younger ($P<0.001$), with a mean age of 56.2 years (data not shown). There were no significant differences between the two groups regarding educational level or type of cancer diagnosis (breast or ovarian).

DISCUSSION

The main findings in this study are that: (1) most patients with newly diagnosed ovarian cancer accept germline *BRCA1/2* testing, with significantly lower uptake among breast cancer patients; (2) there is a high prevalence of *BRCA1/2* mutation carriers in the group of ovarian cancer patients; (3) all patients who were identified with a

Table 2 Clinical and genetic data on the *BRCA1/2* mutation carriers that were identified in the DNA-BONus study

			Clinical information						BRCA1/2 pathogenic variant				
LOVD ID	Cancer	Pathology	Age at diagnosis (5-year interval)	Previous cancer (age in 5-year interval)	Known BRCA1/2 family	Norwegian criteria[a]	Manchester score[b] At inclusion	Manchester score[b] After genetic counselling	Gene	DNA level	Protein level	Clinical classification	Included in panel or not[c]
34523	Breast	Low differentiated carcinoma, Er-/Pr-/HER2-	30–35		No	P	10	18	*BRCA1*	c.3228_3229del	p.(Gly1077AlafsTer8)	BIC: class 5 –- pathogenic	Panel
32380	Breast	Medullary carcinoma, Er-/Pr-/HER2-, grade 3	30–35		No	P	8	21	*BRCA1*	c.697_698del	p.(Val233AsnfsTer4)	BIC: class 5 – pathogenic	Panel
34522	Breast	Ductal carcinoma, Er+/Pr+/HER2-, grade 1	45–50		No	P+F	12	Pending	*BRCA1*	c.5407–25T>A	p.Gly1803GlnfsTer11	Our ranking: class 4[d]	Panel
32381	Breast	Ductal carcinoma, Er+/Pr+/HER2-, grade 1	60–65		No	F	22	19	*BRCA1*	c.5407–25T>A	p.Gly1803GlnfsTer11	Our ranking: class 4[d]	Panel
32382	Breast	Ductal carcinoma, Er+/Pr-/HER2-, grade 3	75–80		No	None[e]	4	19	*BRCA1*	c.5096G>A	p.(Arg1699Gln)	BIC: unknown IARC: class 5 – pathogenic Reduced penetrance[f]	Not in panel
34528	Contralateral breast	Medullary carcinoma, Er-/Pr-/HER2-, grade 3	40–45	Breast cancer age 35–40	No	P	14	26	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34538	Contralateral breast	Ductal carcinoma, Er-/Pr-/HER2-, grade 2	50–55	Breast cancer age 50–55	Yes	P+F	24	36	*BRCA2*	c.3847_3848del	p.(Val1283LysfsTer2)	BIC: class 5 – pathogenic	Panel
43839	Ovarian	Endometroid adenocarsinoma	40–45		No	P	13	26	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34529	Ovarian	Serous adenocarcinoma	45–50		Yes	P+F	71	59	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34530	Ovarian	Serous papillary adenocarcinoma	45–50		No	P	13	15	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34539	Ovarian	Poorly differentiated serous adenocarcinoma	45–50		No	P	14	24	*BRCA2*	c.7069_7070del	p.(Leu2357ValfsTer2)	BIC: class 5 – pathogenic	Not in panel
34531	Ovarian	Serous adenocarcinoma	50–55		No	P+F	23	31	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34524	Ovarian	Serous carcinoma	50–55		No	P	13	25	*BRCA1*	c.3228_3229del	p.(Gly1077AlafsTer8)	BIC: class 5 – pathogenic	Panel
43840	Ovarian	Serous adenocarcinoma	50–55		yes	P+F	23	30	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34532	Ovarian	Serous papillary adenocarcinoma	50–55		No	P+F	27	31	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34535	Ovarian	Serous carcinoma	50–55		No	P+F	28	26	*BRCA1*	c.4065_4068del	p.(Asn1355LysfsTer10)	BIC: class 5 – pathogenic	Panel
34540	Ovarian	Serous carcinoma	55–60	Colon cancer age 55–60	No	P+F	30	30	*BRCA2*	c.4936_4939del	p.(Glu1646GlnfsTer23)	BIC: class 5 – pathogenic	Not in panel
34526	Ovarian	Serous carcinoma	55–60		No	P+F	33	34	*BRCA1*	c.697_698del	p.(Val233AsnfsTer4)	BIC: class 5 – pathogenic	Panel
34536	Ovarian	Serous adenocarcinoma	55–60		No	P	13	14	*BRCA1*	c.1016dup	p.(Val340GlyfsTer6)	BIC: class 5 – pathogenic	Panel
34533	Ovarian	Serous adenocarcinoma	55–60		No	P	13	15	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34534	Ovarian	Serous adenocarcinoma	60–65		No	P+F	27	27	*BRCA1*	c.1556del	p.(Lys519ArgfsTer13)	BIC: class 5 – pathogenic	Panel
34537	Ovarian	Serous adenocarcinoma	65–70	Breast cancer age 45–50	No	P	15	17	*BRCA1*	c.1687C>T	p.(Gln563Ter)	BIC: class 5 – pathogenic	Not in panel

Table 2 (Continued)

			Clinical information						BRCA1/2 pathogenic variant			
LOVD ID	Cancer	Pathology	Age at diagnosis (5-year interval)	Previous cancer (age in 5-year interval)	Known BRCA1/2 family	Norwegian criteria[a]	Manchester score[b] At inclusion	Manchester score[b] After genetic counselling	Gene	DNA level	Protein level	Clinical classification	Included in panel or not[c]
34527	Ovarian	Poorly differentiated carcinoma	65–70		No	P	10	18	*BRCA1*	c.697_698del	p.(Val233AsnfsTer4)	BIC: class 5 – pathogenic	Panel
34541	Ovarian	Serous papillary adenocarcinoma	65–70		No	P+F	20	20	*BRCA2*	c.7069_7070del	p.(Leu2357ValfsTer2)	BIC: class 5 – pathogenic	Not in panel
34525	Ovarian	Serous adenocarcinoma	70–75		Yes	P+F	16	81	*BRCA2*	c.3228_3229del	p.(Gly1077AlafsTer8)	BIC: class 5 – pathogenic	Panel
43838	Ovarian	Serous carcinoma	70–75		No	None[e]	10	31	*BRCA2*	c.5217_5223del	p.(Tyr1739Ter)	BIC: class 5 – pathogenic	Panel

Abbreviations: BIC, Breast cancer Information Core database, http://research.nhgri.nih.gov/bic/; IARC, International Agency for Research on Cancer, http://www.iarc.fr.
[a]Patients fulfilled Norwegian *BRCA1/2* diagnostic testing criteria because of personal at risk cancer history (P) or positive family history (F) or both of these (P+F).
[b]Combined Manchester score based on (1) patient-reported information at inclusion and (2) pathology adjustments and detailed family history retrieved after genetic counselling.
[c]'Panel' = pathogenic variants included in the panel screening test (Supplementary table 1); 'Not in panel' = pathogenic variants found by Sanger sequencing of the total coding region of *BRCA1* and *BRCA2*.
[d]In our diagnostic lab the BRCA1 c.5407-25T>A variant has been found in six independent families with breast and/ovarian cancer, and mRNA analysis from one mutation carrier has previously indicated partial loss of exon 22, r.5407_5467del.
[e]These patients did not fulfill current test criteria upon inclusion, but additional information obtained at genetic counselling revealed that they had a positive family history and thus in retrospect were eligible for diagnostic *BRCA1/2* testing.
[f]According to Spurdle *et al*,[35] this variant is associated with intermediate risk of breast and ovarian cancer.

pathogenic *BRCA1/2* variant fulfill our current clinical criteria for diagnostic *BRCA1/2* testing; and (4) the level of anxiety and depression symptoms in the participants at inclusion was comparable to what can be found in cancer patients in general.[28,29]

Ovarian and breast cancer patients with pathogenic *BRCA1/2* variants are candidates for targeted drug therapy, such as PARP inhibitors.[21] Recently, the US Food and Drug Administration (FDA) approved a PARP inhibitor for use in ovarian cancer (http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm427554.htm). Our study shows that, even before such treatment options became available, *BRCA1/2* testing was well accepted among newly diagnosed patients, with 68% participation rate among the women with ovarian cancer, whereas 45% of patients with breast cancer chose to undergo *BRCA1/2* testing. There may be a selection bias among the participants because, on average, patients with breast cancer and ovarian cancer in our study were younger (mean age 56.9 and 60.5 years, respectively) as compared with patients with these cancers in the Norwegian population in general. According to national numbers, the mean age of all cases with breast cancer and ovarian cancer diagnosed between 2008 and –2012 was 61.5 and 65.4 years, respectively,[30] thereby indicating that older patients may have declined participation in our study. This could be particularly relevant for breast cancer patients with low *a priori* risk of carrying a pathogenic *BRCA1/2* variant. The assumption of a certain degree of risk-based selection in the uptake is further supported by the fact that among the participants, 50% of the patients with breast cancer and >80% of the patients with ovarian cancer were eligible for diagnostic *BRCA1/2* testing according to the current clinical guidelines. For obvious reasons the uptake will be higher when the result of *BRCA1/2* testing influences treatment options.[21]

In total, we identified 26 patients with a pathogenic *BRCA1/2* variant and by that identified 22 new *BRCA1/2* families. This finding supports a need for increased availability and use of such *BRCA1/2* testing, as a supplement to the existing referral systems and service in cancer genetics. Our study also reports a high prevalence (22.3%) of pathogenic *BRCA1/2* variants in ovarian cancer patients, substantially higher than reported by others.[3–5] This may be caused by a high prevalence of pathogenic founder variants in our population, but surprisingly the prevalence among patients with breast cancer is rather low (1.7%) compared with international data.[2,6] The highest prevalence of *BRCA1/2* mutation carriers has been reported in populations with very strong founder effects, and most studies on the frequency of pathogenic *BRCA1/2* variants in patients with sporadic breast cancer have had some form of selection criteria, for example, young age at onset or triple-negative histology.[2,7,8] In the DNA-BONus study, we offered genetic testing to all patients with newly diagnosed breast cancer that, in combination with a rather low prevalence of pathogenic *BRCA2* variants in the Norwegian population,[6] at least in part may explain the rather low frequency of pathogenic *BRCA1/2* variants among our patients with breast cancer.

At inclusion, all but two of the 26 *BRCA1/2* mutation carriers fulfilled the current clinical recommendations for diagnostic *BRCA1/2* testing in Norway. One patient with breast cancer after the age of 75 years apparently had a negative family history according to the information forwarded at inclusion. However, further examination revealed that her sister died from ovarian cancer before the age of 50 years. The other patient was a woman with ovarian cancer after the age of 70 years. We were informed at inclusion that she had two first-degree relatives with abdominal cancer and cervical cancer, respectively, both after the age of 70 years. During the genetic counselling these diagnoses were both confirmed to be ovarian cancer cases. Thus, all mutation carriers in this study fulfilled current national

Table 3 HADS anxiety and depression subscale scores at various time points for a subset of DNA-BONus participants

	At inclusion (T1)	*One week after disclosure of genetic test result (T2)*	*Six months after disclosure of genetic test result (T3)*
HADS anxiety			
No. of patients	213	191	167
Subscore mean (SD)	6.84 (4.28)	5.29[a] (4.06)	4.88[b] (3.86)
Score ≥8 (%)	39.9	23.6[c]	19.8[d]
HADS depression			
No. of patients	215	190	169
Subscore mean (SD)	3.32 (3.07)	2.90[e] (3.30)	2.65[f] (3.04)
Score ≥8 (%)	10.2	10.0 [g]	10.7[h]

Abbreviation: HADS, Hospital Anxiety and Depression Scale.
[a]T1 *vs* T2: $P<0.001$.
[b]T1 *vs* T3: $P<0.001$; paired sample *t*-test.
[c]T1 *vs* T2: $P<0.001$.
[d]T1 *vs* T3 $P<0.001$; McNemar's exact test.
[e]T1 *vs* T2: $P=0.32$.
[f]T1 *vs* T3: $P=0.11$; paired sample *t*-test.
[g]T1 *vs* T2: $P=1.00$.
[h]T1 *vs* T3: $P=0.42$; McNemar's exact test.

criteria for diagnostic *BRCA1/2* testing when a proper personal and family history had been taken.

The Manchester scoring system is a frequently used tool to identify individuals and families at high risk of having a pathogenic *BRCA1/2* variant.[24] In this study, we found that the Manchester scores obtained at inclusion were markedly lower than the real values (see below). In retrospect, all *BRCA1/2* mutation carriers had combined Manchester scores at ≥14 points, demonstrating that the hereditary breast and ovarian cancer families identified through testing of patients with incidental breast or ovarian cancer do not differ significantly from families identified through the traditional route. These findings indicate that most *BRCA1/2* mutation carriers can be identified through evidence-based clinical criteria, also within a group of incidental patients.

In order to identify patients at risk of non-*BRCA1/2* familial breast cancer and other causes of hereditary cancer, we systematically collected structured family history from the participants before *BRCA1/2* testing and employed a low threshold for our genetic counselors to contact the participants for additional information. Indeed, the importance of family history should not be neglected when the availability of *BRCA1/2* testing increases and more patients with breast cancer are tested in routine clinical practice. Most familial breast cancer risk is not caused by pathogenic *BRCA1/2* variants, and women belonging to *BRCA1/2*-negative breast cancer families are also at increased risk for breast cancer.[20] The importance of obtaining a structured family history was illustrated by the fact that *BRCA1/2* mutation carriers in our study scored significantly higher in the Manchester scoring system when taking into account the information collected during the genetic counselling procedure, as compared with the rating based on the initial self-reported information. In this regard, oncologists and surgeons may need additional support and training to extract a structured and relevant family history.[31,32]

The traditional genetic counselling procedure has obvious benefits with respect to high-quality family history collection, and it has been shown to increase cancer-related knowledge and decrease distress in newly diagnosed cancer patients with an elevated risk of hereditary cancer.[33] However, because this procedure is resource demanding, alternative approaches are needed when treatment-driven genetic testing is offered to larger patient groups with lower probability of carrying a pathogenic *BRCA1/2* variant. Written, telephone-based or digital information provided by a clinical geneticist or genetic counselor, together with adequate information from the oncologist or surgeon, could be considered as an alternative for some patients.[22] Patients at increased risk of psychosocial distress should have easy access to genetic counselling. An open telephone line to a genetic counselor might not be optimal for patients newly diagnosed with cancer, as we experienced that <20 patients actually contacted the genetic counselor for more information before testing throughout the whole DNA-BONus study period of two-and-a-half years. In order to discuss the consequences of the *BRCA1/2* test results for the patient and other family members, as well as to explain complex test results and other hereditary causes of cancer, we also advise genetic counselling in case of a positive *BRCA1/2* test result and in case of a personal or family history suggestive of hereditary cancer.

As the most common current practice of *BRCA1/2* testing is based on referral of selected high-risk subjects to extensive face-to-face procedures of genetic counselling before *BRCA1/2* testing,[17,18] we investigated whether our new simplified approach could lead to increased anxiety or depression in the newly diagnosed patients. Interestingly, the level of anxiety symptoms was comparable to those reported for patients with breast cancer and gynecological cancer in general,[28,29] but higher than normal population values.[34] Approximately 40% of the patients had a HADS subscale score above the defined threshold for symptoms of anxiety[27] at inclusion, and the level of anxiety decreased significantly during the 6-month follow-up period that also included the dissemination of the *BRCA1/2* test result. The drop in the level of anxiety symptoms during the observation period may simply reflect the adjustment to the cancer diagnosis and treatment, and genetic testing in our study did not appear to influence on this expected drop.

There are some limitations to our study. Because of ethical regulations, we had no information about the patients who declined participation in the study. Another limitation is that Sanger sequencing of the *BRCA1/2* genes was only performed on selected high-risk patients, implying that some of the lower-risk patients could be carriers of rare *BRCA1/2* variants that were not covered by the *BRCA1/2* panel test. In this respect, it should be noted that the methods and two-step procedure for *BRCA1/2* testing (ie, multiplex panel test for recurrent variants, plus optional *BRCA1* plus *BRCA2*

Sanger sequencing) remained unchanged during the whole inclusion period, and that the fraction of patients who were sequenced was almost the same in the first and second half of the DNA-BONus study. Another potential weakness is that patients with previously known pathogenic *BRCA1/2* variants, who were diagnosed with cancer during the DNA-BONus study period, might have declined participation because of low relevance, thereby reducing the total count of *BRCA1/2* mutation carriers among the participants. Finally, some of the psychosocial results are limited by a small number of participating *BRCA1/2* mutation carriers and should therefore be interpreted with caution.

In conclusion, we show that *BRCA1/2* mutation testing is well accepted among patients with newly diagnosed breast or ovarian cancer. We further conclude that current clinical guidelines are sufficient to identify the majority of the *BRCA1/2* mutation carriers among patients with breast cancer. Because of the high prevalence of pathogenic *BRCA1/2* variants, we recommend that all patients with epithelial ovarian cancer are offered germline *BRCA1/2* testing, irrespective of age or family history of cancer.

CONFLICT OF INTEREST

N Hoogerbrugge is scientific consultant to AstraZeneca since June 2014. HP Eikesdal has received PARP inhibitors free of charge from AbbVie and AstraZeneca for use in clinical trials in patients with breast cancer. The other authors declare no conflict of interest.

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Supplementary Information accompanies this paper on European Journal of Human Genetics website (http://www.nature.com/ejhg)

Supplementary Table.

Gene	Mutation	VIC probe sequence	FAM probe sequence	Forward Primer Sequence	Reverse Primer Sequence
BRCA1	c.1A>G	TGAGACGGATGTAACAAA	TGAGACGGATAACAAA	TTGTTATTTTTGTATATTTTCAGCTGCTTGTGA	GCTTCTCAGTGGTGTTCAAATCATT
BRCA1	c.697_698del	TGAGACGGATGTAACAAA	TGAGACGGATAACAAA	TTGTTATTTTTGTATATTTTCAGCTGCTTGTGA	GCTTCTCAGTGGTGTTCAAATCATT
BRCA1	c.1016dup	CAGATCTACCTTTTTTTCTGTG	AGATCTACCTTTTTTTTCTGTG	CCAACATAACAGATGGGCTGGAA	GGAACATCTTCAGTATCTCTAGGATTCTCT
BRCA1	c.1072del	CATGGCAGTTTCTG	CATGGCATTTCTG	CCCTGTGTGAGAGAAAAGAATGGAA	TTCATCACTTCTGGAAAACCACTCA
BRCA1	c.1450G>T	AACTGAAAATCTAATTATAGGAGC	ACTGAAAATCTAATTATATGAGC	GGCAAGCCTCCCCAACT	AACTGCCAAATCTGCTTTCTTGAT
BRCA1	c.1556del	CAAATCTGCTTTCTTGATAAA	CAAATCTGCTTTCTGATAAA	ACCTACATCAGGCCTTCATCCT	TCCGTTTGGTTAGTTCCCTGATTT
BRCA1	c.2351_2357del	CTCGTTACTGGAAGTTAG	CAGGAAAGTATCTGGAAGTT	GTTAAGTGGAGAAAGGGTTTTGCAA	GTTCTGTTTTTGCCTTCCCTAGAGT
BRCA1	c.3048_3052dup	TGGGAAATGAGAACATTC	ATGAGATGAGAACATTC	CTGCTAGAGGAAAACTTTGAGGAACA	GGCTAATTGTGCTCACTGTACTTG
BRCA1	c.3084_3094del	CACAATTAGCCGTAATAACA	ATTAGCCGGAGAAAAT	TCACCTGAAAGAGAAATGGGAAATGA	CCCACTTCATTAGTACTGGAACCT
BRCA1	c.3178G>T	CTCCAGTATTAATGAAATAG	CTCCAGTATTAATTAAATAG	GCTCAAGCAATATTAATGAAGTAGGTTCCA	CTCTGTTTCTACCTAGTTCTGCTTGAA
BRCA1	c.3228_3229del	TTTTGGCCCTCTGTTTC	AATTTTGGCCCTGTTTC	CCAGTGATGAAAACATTCAAGCAGAA	GTTGCAAAACCCCTAATCTAAGCAT
BRCA1	c.3331_3334del	CTTCATATTCTTGCTTTTTTATT	ACTTCTTCATATTCTTTTTTATT	TTCCTGGAAGTAATTGTAAGCATCCTG	TCTCAGAACAAACCTGAGATGCATG
BRCA1	c.3607C>T	CCCCTCTTCGGTAACCC	CCCCTCTTCAGTAACCC	GTCCAGAAAGGAGAGCTTAGCA	GGGAAGCTCTTCATCCTCACTAGAT
BRCA1	c.4065_4068del	TTGCTCTTCTTGATTATTT	TGCTTTGCTCTTCTTATTT	GAGGAACGGGCTTGGAAGA	TTGTAAAATGTGCTCCCCAAAAGC
BRCA1	c.4745del	CCTTCTGAAGACAGAGCC	CTTCTGAAGCAGAGCC	TCTTCTCTGATGACCCTGAATCTGA	GCCAACACGAGCTGACTCT
BRCA1	c.5047G>T	ACTAATCTAATTACTGAAGAGACT	ACTAATCTAATTACTGAATAGACT	TGCCAGAAAACACCACATCACTTTA	CTCATGTGGTTTTATGCAGCAGAT
BRCA1	c.5075-2A>C	CATTCTGCAGATGCTGA	CATTCTGCCGATGCTGA	GAGGCTCTTTAGCTTCTTAGGACAGCACT	CTAACTACCCATTTTCCTCCCGCA
BRCA1	c.5266dup	CAAGAGAATCCCAGGACAG	AAGAGAATCCCCAGGACAG	GAAACCACCAAGGTCCAAAGC	TGAGGGAGGGAGCTTTACCTTT
BRCA1	c.5407-25T>A	AAGGAAAGAGCATTCAAAG	AAGGAAAGAGCTTTCAAAG	CCTGGGTGACAGAGCAAGAC	GGCTGCACAACCACAATTGG
BRCA1	c.5511G>A	CGAGAGTGGGTGTTGGAC	CGAGAGTGAGTGTTGGAC	GTGAGGCACCTGTGGTGACC	CCTGTGGCTCTGTACCTGTG
BRCA2	c.1796_1800del	TGATGAAACATCTTATAAAGGA	CATGATGAAACATAAAGGA	TCTGTAGCTTTGAAGAATGCAGGTT	CTGGGCTGAACAGTTAATTAGTTCTGA
BRCA2	c.2047_2050del	AAGATCCTGAGAGATTACT	AATCAAGATCCTGATTACT	GCTCTTTTGGGACAATTCTGAGGAA	CAGGCATGACAGAGAATCAGCTT
BRCA2	c.2808_2811del	AGGTGATAAACAAGCAACC	CAGGTGATAAGCAACC	CGAACCCATTTTCAAGAACTCTACCA	TCTCCTCTGCAAGAACATAAACCAAA
BRCA2	c.3847_3848del	TTTTTCACTTACAGTTTTATC	ATTTTTTTCACTTAGTTTTATC	AAGTAAATGTCATGATTCTGTTGTTTCAATGT	TCTTCAACAAAAGTGCCAGTAGTCA
BRCA2	c.4821_4823delinsC	CCACAGTCTCAATAGAAA	CCACAGTCGATAGAAA	CCCCAAAGTGTAAAGAAATGCAGAA	ACTTTTTGATGTTTTGAGATTTTCAGTTTGTCT
BRCA2	c.5217_5223del	CATGCTACTGTTACTTAAAT	TAGACATGCTACTGTTTAAG	GACAAAAATCATCTCTCCGAAAAACAAGA	ACCTCATCAGAATGGTAGGAATAGCT
BRCA2	c.5290_5291del	AGTTTATTTTTTGAGAGATATC	AAGTTTATTTTTTGAGATATC	GCATGTCTAACAGCTATTCCTACCA	AACATTCTTCAATACTGGCTCAATACCA
BRCA2	c.8323dup	CCCCAGAATCTCTTATGTTAA	CCCAGAATCTCTTAATGTTAA	TGATGCCTGTACACCTCTTGAAG	CAATGACTGATTTTTACCAAGAGTGCAA
BRCA2	c.8331+2T>C	AGAGTGCAAATTAATTTACCTTT	AGTGCAAATTAATTTGCCTTT	TATTCTTCATGGAGCAGAACTGGTG	TAAATGTAAAACTTCTAGAATTTAACTGAATCAATGACTG
BRCA2	c.9118-2A>G	TTTGTTTTCTGTAGGTTTC	TGTTTTCTGTGGGTTTC	AAGTGCTTGTTAGTTTATGGAATCTCCAT	AACAAGATGGCTGAAAGTCTGGAT

Overview over the 20 *BRCA1* and 10 *BRCA2* recurrent mutations, with sequence information for the corresponding primers and probes that were used for the genotyping by TaqMan Low Density Arrays in the DNA-BONus study.

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ORIGINAL ARTICLE

Cancer-related distress in unselected women with newly diagnosed breast or ovarian cancer undergoing *BRCA1/2* testing without pretest genetic counseling

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ABSTRACT

Background: Genetic testing is increasing in patients newly diagnosed with cancer. This study investigated the levels, course and predictors of cancer-related distress, defined as intrusion and avoidance, in women undergoing *BRCA1/2* testing without pretest genetic counseling shortly after a diagnosis of breast or ovarian cancer.

Material and methods: Unselected for family history or age, 259 women with breast cancer and 50 women with ovarian cancer, underwent *BRCA1/2* testing shortly after diagnosis. Cancer-related distress was measured with the Impact of Event Scale before and after genetic testing. In order to identify predictors of distress, the subscale scores were regressed on baseline predictor variables including sociodemographic and medical variables, perceived social support, and decisional conflict regarding genetic testing.

Results: The mean levels of intrusion and avoidance were in the moderate range both before and after genetic testing with a statistically significant decline during follow-up. Younger age, shorter time since diagnosis, lower levels of social support, and a diagnosis of ovarian cancer predicted higher levels of both intrusion and avoidance. In addition, higher levels of decisional conflict and living with a partner predicted higher levels of intrusion.

Conclusions: Women having genetic testing shortly after a diagnosis of breast or ovarian cancer had a moderate mean level of cancer-related distress, which decreased with time. Health personnel offering genetic testing to newly diagnosed women with breast or ovarian cancer should be aware of the potential predictors for increased cancer-related distress identified in this study: younger age, less perceived social support, higher levels of decisional conflict regarding genetic testing, and living with a partner.

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Background

Genetic testing has become increasingly important in patients diagnosed with breast or ovarian cancer in recent years, as the presence of germline variants not only predicts a high risk of breast and ovarian cancer, but also gives an opportunity for personalized cancer treatment. After the introduction of poly-(ADP-ribose) polymerase (PARP) inhibitors for treatment of ovarian cancer in *BRCA1/2* mutation carriers, diagnostic genetic testing of patients with ovarian cancer has been implemented in routine clinical practice in several countries [1–3]. Although less established, similar procedures are gradually introduced in breast cancer clinics, since decisions regarding surgery and neoadjuvant chemotherapy might be directed by *BRCA1/2* carrier status [4–6]. This new approach often implies that the genetic test is performed a short time after diagnosis, without traditional pretest genetic counseling or risk assessment. While previously cancer-related distress has been thoroughly investigated in persons receiving traditional genetic counseling for hereditary cancer [7–10], less is known about the cancer-related distress in women newly affected with breast or ovarian cancer who are offered genetic testing regardless of age and family history, and who undergo genetic testing without pretest genetic counseling. In contrast to women seeking genetic counseling because of a suspicious family history of hereditary breast and ovarian cancer, the women who are tested as part of the routine diagnostic work-up in a cancer clinic may be less aware of the possibility that their cancer can have a hereditary cause, and thus be less prepared for a decision making process regarding genetic testing. Obviously, receiving a potential

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Supplemental data for this article can be accessed here.

life-threatening cancer diagnosis is associated with significant distress [11–14]. Concern has been raised that introducing genetic testing shortly after diagnosis would impose an additional psychological burden for women in this stressful situation [15], but so far, the evidence does not support this concern [16].

High levels of distress interfere with the patients' ability to perceive important information given by health personnel [17] and may constitute an obstacle for understanding the consequences of genetic testing [18]. More attention should therefore be drawn to the patients with higher levels of distress.

We define distress as intrusive thoughts and avoidance responses in this study. Intrusion and avoidance are often associated with post-traumatic stress disorder (PTSD), but are also studied as reactions to actual or possible threatening events without implicating the status of a PTSD-diagnosis [8,9], as in this article. Intrusion symptoms include unbidden thoughts and images both awake and during sleep, waves of overwhelming feelings of fear and repetitive behavior. Avoidance responses include denial of the meaning and consequences of the threatening event, blunted sensation, emotional numbness, and attempts to block out unpleasant feelings and memories [19].

The relatively low correlation between stressful life events on one hand, and adverse outcome on the other, has stimulated the search for moderating variables [20,21], and social support has a central position in this research. To seek social support seems to be one of the most successful coping strategies and is often associated with favorable health outcome [22,23]. One theory, 'the buffer theory', states that social support protects against the potential pathogenic effects of stressful life events, and that this protective property is activated when needed, e.g., when a person is diagnosed with cancer and/or is undergoing genetic testing [20,24].

While some people find it easy to make a choice about genetic testing, others have stronger ambivalence toward this. Women who are newly diagnosed with breast or ovarian cancer are often overwhelmed with information and choices they have to make [18]. Underlying decisional conflict regarding genetic testing may have an impact on the experienced distress for these women.

There are some well-described predictors of psychological distress among cancer patients, e.g., young age and short time since cancer diagnosis, while other predictors have shown more ambiguous effects in different studies, e.g., educational level, employment status, marital status, and cancer type [13,14,25–27].

The aim of this study was to document the level, course and predictors of cancer-related distress, in patients undergoing genetic testing a short time after the diagnosis of breast- or ovarian cancer.

Material and methods

Study design and participants

The patients participated in a prospective multi-site study in which genetic testing for pathogenic *BRCA1/2* variants and familial cancer risk assessment were offered to all women newly diagnosed with breast or ovarian cancer, the DNA-BONus study. The study protocol and the results of the genetic testing have been published in details elsewhere [28]. All patients with newly diagnosed breast or ovarian cancer, unselected for age and family history, were consecutively invited to participate, from September 2012 to April 2015. The participants could choose to participate only in the genetic testing study, in an associated psychosocial study, or both. This article presents data exclusively from patients participating in the psychosocial study. The participants did not receive genetic counseling prior to testing, but were given written information about hereditary breast and ovarian cancer in addition to brief information from their treating physician or nurse. The genetic test result was given to the patient in a letter from a genetic counselor if the test result was normal and there was no indication for further genetic testing. Patients who tested positive for a *BRCA1/2* mutation, or had a personal or family history suspicious of elevated familial cancer risk, received a phone call from a genetic counselor with information about the result and were invited to a post-test face-to-face genetic counseling session.

The first questionnaire in the psychosocial sub study was given to the participants along with the invitation to the study (T1). The second and third questionnaires were mailed to the participants 1 week (T2) and 6 months (T3) after disclosure of the *BRCA1/2* test result, respectively.

The study protocol was approved by the Regional Committee for Medical and Health research Ethics (REK Vest 2012-62).

Study measurements

Clinical and sociodemographic variables

Self-reported family history was retrieved from all participants in the DNA-BONus study through a structured written questionnaire linked to the blood sampling for genetic testing [28]. Clinical information was collected from the participants' medical files. Questions about education level, biological children, cohabitation, and employment status were included in the first questionnaire (T1).

Subjective distress

Subjective distress was measured with the Impact of Event Scale (IES-15) [19]. This is a 15-item questionnaire comprising two subscales: intrusion thoughts (IES-I), which includes seven items and is scored from 0 to 35, and avoidance behavior (IES-A), which consists of eight items, and is scored from 0 to 40. The scale was developed to measure current stress reactions after any specific traumatic event [19]. In the present study, 'cancer diagnosis' was defined as the specific event. The sub-scale scores are considered low in the range of 0–8, moderate at 9–19 and severe at 20 and above [19].

Social support

The concept of perceived social support was measured by the version of the Interpersonal Support Evaluation List (ISEL) used by King and colleagues, which consists of 30 items that

are answered with a score from 1 to 4 [7,29]. The average sum score for each participant was used.

Decisional conflict

To measure the participant's ambivalence toward making a choice of undergoing *BRCA1/2* genetic testing we used the Decisional Conflict Scale (DCS) [30,31]. In the DCS, 16 items are scored from 0 to 4, where three dimensions of decisional conflict are measured: uncertainty about selection of alternatives (three items), specific factors contributing to uncertainty (nine items), and perceived effectiveness of decision making (four items). Higher scores indicate higher levels of decisional conflict. The sum score of all items was converted to a 0–100 scale, where total scores below 25 are associated with low level of decisional conflict and scores above 37.5 are associated with problems in implementing decisions [31].

Statistical methods

Missing values were replaced by the respondent's own average score for each questionnaire if at least 60% of the items were filled in by the respondent. Descriptive statistics were used to describe the sociodemographic, clinical and psychological variables, reporting the mean values, median values, standard deviation (SD), standard error of means (SEM), range and proportions. Paired sample *t*-tests and paired Wilcoxon–Mann–Whitney tests were used to compare changes in IES scores between the different time points.

To identify the characteristics related to the levels of IES-I and IES-A and to test the changes of IES-I and IES-A over time, the subscale scores were regressed on the baseline predictor variables using mixed linear modeling. The mixed linear model uses all available data, and can account for correlations between repeated measurements on the same subjects and has sufficient flexibility to model time effects [32]. All predictors were entered into the mixed linear models to assess both main effects and possible interactions with time. The regression analyses were run backwards stepwise, both with and without interaction with time. The significance level was set at .05 for all statistical tests, and results were reported as estimates with 95% confidence intervals. All statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS, version 24.0) (SPSS Inc., Chicago, IL).

Results

Study sample

Of 772 eligible women in the DNA-BONus study, 403 (52.2%) underwent genetic testing and 309 (40.0%) gave consent for the psychosocial sub study: 259 women diagnosed with breast cancer and 50 women diagnosed with ovarian cancer. The mean age of the participants was 56.1 years (range: 24–89 years). The mean time from diagnosis to returning the first questionnaire (T1) was 45 (median: 26) days for patients with breast cancer and 156 (median: 76) days for patients with ovarian cancer. On average, participants returned T1 two days before blood sampling for the genetic test. Cancer treatment was initiated for 256 patients before T1, 31 participants had not started cancer treatment before T1, and treatment status was unknown for 22 participants at T1. The sociodemographic and clinical characteristics of the study sample are provided in detail in Table 1.

Level of intrusion (IES-I) and avoidance (IES-A) before and after genetic testing

Table 2 show the mean levels of IES-I and IES-A scores at the three measurement points. The mean IES-I score was 14.6 (median 14.0) at T1 and decreased statistically significantly to 12.1 (median 9.0) at T2 ($p < .001$) and with a further statistical significant decrease to 9.7 (median 7.0) at T3 ($p < .001$). The overall decrease from T1 to T3 was 5.2, which corresponds to 14.9% of the total IES-I scale (0–35). The mean IES-A score was 12.7 (median 11.0) at T1, decreased statistically significantly to 10.2 (median 8.0) at T2 ($p < .001$), but with no further statistical significant decrease from T2 to T3 (mean score 9.7, median 8.0). The overall decrease in IES-A score from T1 to T3 was 3.0, 7.5% of the total IES-A scale (0–40). At inclusion nearly one-third and one-fourth of the patients, respectively, had IES-I and IES-A scores indicating a severe stress response, Table 2. At T3 the proportions of patients with scores in the severe range were reduced to 14.0 and 16.0% for IES-I and IES-A, respectively, Table 2.

Mixed linear models for intrusion and avoidance

The results of the mixed linear regression analyses for IES-I and IES-A scores are given in Table 3. After backward stepwise selection, the final model showed that younger age was a predictor of higher IES-I, i.e., for each 10 years decrease in age the mean value of IES-I score increased with 1.80, Table 3. Additional predictors of higher levels of IES-I were shorter time since diagnosis, lower level of perceived social support, higher level of decisional conflict regarding the genetic test, diagnosis of ovarian cancer and living with a partner. Higher levels of IES-A was associated with younger age, shorter time since diagnosis, lower level of perceived social support and a diagnosis of ovarian cancer. For both IES-I and IES-A, none of the predictor variables retained in the final model showed significant interaction with time. For full overview over the mixed linear regression analyses for IES-I and IES-A, see online Supplemental Tables S1 and S2.

Discussion

We found that women who chose *BRCA1/2* genetic testing shortly after a diagnosis of breast- or ovarian cancer had mean levels of intrusion and avoidance in the moderate range both before and after genetic testing, with a statistical significant decrease during a mean time of 7.5 months follow-up. Younger age, shorter time since diagnosis, a diagnosis of ovarian cancer, lower levels of social support, higher levels of decisional conflict, and living with a partner, predicted higher levels of distress.

Table 1. Baseline variables for the study population.

Diagnostic group	Breast cancer, $N = 259$		Ovarian cancer, $N = 50$		All respondents, $N = 309$	
Continuous variables	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age, years	55.7	(11.5)	58.3	(11.4)	56.1	(11.5)
Time from diagnosis to T1[a], days	45	(72)	156	(259)	63	(129)
Time from T1 to T2[b], days	52	(48)	46	(21)	51	(46)
Time from T1 to T3[c], days	226	(39)	225	(30)	226	(38)
DCS[d], range: 0–100	19.7	(15.2)	15.3	(13.3)	19.0	(15.2)
ISEL, range: 1–4	3.46	(0.46)	3.46	(0.48)	3.46	(0.47)
Categorical variables						
Categories	*N*	(%)	*N*	(%)	*N*	(%)
Education						
Primary school	42	(16.2)	8	(16.0)	50	(16.2)
High school	91	(35.1)	24	(18.0)	115	(37.2)
University	121	(46.7)	17	(34.0)	138	(44.7)
Missing	5	(1.9)	1	(2.0)	6	(1.9)
Employed	161	(62.2)	28	(56.0)	189	(61.2)
Missing	4	(1.5)	1	(2.0)	5	(1.6)
Having biological children	228	(88.0)	44	(88.0)	272	(88.0)
Missing	4	(1.5)	0	(0.0)	4	(1.3)
Living with a partner	180	(69.5)	38	(76.0)	218	(70.6)
Missing	3	(1.2)	0	(0.0)	3	(1.0)
Detection method						
Screen-detected	106	(40.9)	0	(0.0)	106	(34.3)
Symptomatic	137	(52.9)	50	(100)	187	(60.5)
Other	16	(6.2)	0	(0.0)	16	(5.2)
Stage[e]						
I	123	(47.5)	4	(8.0)	127	(41.1)
II	108	(41.7)	9	(18.9)	117	(37.9)
III	21	(8.1)	23	(46.0)	44	(14.2)
IV	7	(2.7)	13	(26.0)	20	(6.5)
Unknown	0	(0.0)	1	(2.0)	1	(0.3)
DCS category						
Low (0–24)	150	(59.1)	35	(70.0)	185	(60.9)
Intermediate (25–37.5)	75	(29.5)	9	(18.0)	84	(27.6)
High (>37.5)	29	(11.4)	6	(12.0)	35	(11.5)
Post-test genetic counseling						
Not offered	156	(60.2)	18	(36.0)	174	(56.3)
Offered, not accepted/received	34	(13.2)	8	(16.0)	42	(13.6)
Offered and received	69	(26.6)	24	(48.0)	93	(30.1)
BRCA1/2 mutation found	6	(2.3)	9	(18.0)	15	(4.9)
FDR with breast or ovarian cancer	56	(21.6)	3	(6.0)	59	(19.1)
FDR with other cancer	86	(33.2)	20	(40.0)	106	(34.3)

Sociodemographic and clinical characteristics of the 309 participants in a study of psychosocial aspects of genetic testing in women newly diagnosed with breast or ovarian cancer in western Norway between September 2012 and April 2015 (the DNA-BONus study).

SD: standard deviation; T1/T2/T3: successive time points for questionnaires in the study; DCS: Decisional Conflict Scale; ISEL: Interpersonal Support Evaluation List; FDR: first degree relative.

[a]Five missing breast cancer, one missing ovarian cancer; [b]233 valid breast cancer, 39 valid ovarian cancer; [c]218 valid breast cancer, 41 valid ovarian cancer; [d]5 missing breast cancer; [e]breast cancer stage according to Union for International Cancer Control (UICC), ovarian cancer stage according to International Federation of Gynecology and Obstetrics (FIGO).

The majority of the participants had a high level of education, were working and living with a partner. In addition, they reported a high average level of perceived social support. This may indicate that the participants represent a self-selected group of resourceful women. We know from previous studies that patients seeking traditional genetic counseling for hereditary cancer are highly selected and resourceful [7,8]. The same tendency of self-selection might have occurred in our study. The finding of low levels of decisional conflict may, not surprisingly, reflect that those with higher levels of decisional conflict declined genetic testing and/or to answer the questionnaires.

The mean levels of intrusion and avoidance symptoms in the present study were in the moderate range (IES subscale scores 9–19) at all measurements, with mean IES scores ranging from 14.6 (IES-I) and 12.7 (IES-A) at T1 to 9.7 (IES-I and IES-A) at T3. The change in mean IES-I score from T1 to T3 is of a magnitude (14.9% of the total IES-I scale) which may indicate a clinical significant reduction in intrusion during a mean follow-up of 7.5 months. Our results are in line with previous reports on patients newly diagnosed with breast cancer [12,16]. Wevers et al. [16] found in their study of breast cancer patients at high risk of hereditary breast cancer mean levels of IES-I at 18.6–18.7 before surgery, and 11.8–12.4 at 6 months follow-up. The corresponding IES-A scores were 14.0–15.0 before surgery and 10.1–10.5 at 6 months follow-up [16]. In a large study of more than 3000 women with breast cancer unselected for hereditary cancer

Table 2. Levels of IES intrusion and IES avoidance.[a]

Time point: subscale	At inclusion (T1)	One week after disclosure of genetic test result (T2)	Six months after disclosure of genetic test result (T3)
IES-Intrusion (scale 0–35), *N*	308	277	257
Mean score (SEM)	14.6 (0.5)	12.1 (0.6)	9.7 (0.5)
Median (IQR)	14.0 (7.0–22.0)	9.0 (4.0–19.0)	7.0 (4.0–14.0)
Grouped, *N (%)*			
Minor, score 0–8	102 (33.1)	132 (47.7)	147 (57.2)
Moderate, score 9–19	107 (34.7)	77 (27.8)	74 (28.8)
Severe, score ≥20	99 (32.1)	68 (24.5)	36 (14.0)
IES-avoidance (scale 0–40), *N*	309	277	256
Mean score (SEM)	12.7 (0.5)	10.2 (0.5)	9.7 (0.5)
Median (IQR)	11.0 (6.0–19.0)	8.0 (4.0–15.0)	8.0 (3.0–15.0)
Grouped, *N (%)*			
Minor, score 0–8	117 (37.9)	142 (51.3)	138 (53.9)
Moderate, score 9–19	119 (38.5)	91 (32.9)	77 (30.1)
Severe, score ≥20	73 (23.6)	44 (15.9)	41 (16.0)

Distribution of IES subscales at different time points in 309 women undergoing genetic *BRCA1/2* testing when newly diagnosed with breast or ovarian cancer in western Norway between September 2012 and April 2015.
IES = Impact of Event Scale (Horowitz et al. 1979); SEM: standard error of the mean; IQR: interquartile range.
[a]All paired comparisons between the time points were statistically significant at the 0.001-level using the paired *t*-test or the paired Wilcoxon/Mann–Whitney test except for the comparison of T2 and T3 for IES-avoidance.

Table 3. Simplified linear regression models of IES intrusion and avoidance subscales.

Variables	IES-intrusion			IES-avoidance		
Categories	b	95% CI	*p* value	b	95% CI	*p* value
Intercept	34.35	(25.59, 43.10)	<.001	38.50	(30.48, 46.53)	<.001
Ovarian versus breast cancer	3.53	(1.10, 5.96)	.005	3.36	(1.03, 5.69)	.005
Age per 10 years	−1.80	(−2.58, −1.03)	<.001	−1.02	(−1.75, −0.30)	.006
Months from diagnosis to T1	−0.25	(−0.46, −0.05)	.017	−0.21	(−0.41, −0.01)	.039
DCS per 10 points score	0.67	(0.10, 1.24)	.022			
ISEL	−3.71	(−5.60, −1.83)	<.001	−5.86	(−7.62, −4.09)	<.001
Questionnaire time point			<.001			<.001
T1	0.00	Reference		0.00	Reference	
T2	−2.38	(−3.24, −1.52)		−2.19	(−2.96, −1.41)	
T3	−4.73	(−5.75, −3.70)		−2.67	(−3.57, −1.78)	
Living with a partner	2.56	(0.639, 4.48)	.010			

Final model of mixed linear regression analyses for IES subscales in 309 women undergoing genetic testing when newly diagnosed with breast or ovarian cancer in western Norway between September 2012 and April 2015.
b: estimated regression coefficient; CI: confidence interval; *p* value: from *F*-test; IES: Impact of Event Scale (0–35/40); DCS: Decisional Conflict Scale (0–100); ISEL: Interpersonal Support Evaluation List (1–4); T1: time of inclusion; T2: one week after disclosure of genetic test result; T3: six months after disclosure of genetic test result.

risk, O'Connor et al. [12] reported mean scores of IES-I to be 10.1 and 7.8, 3 months and 15 months after surgery, respectively. The mean scores of IES-A in the same study were 10.0 and 8.4, 3 months and 15 months after surgery, respectively [12]. Like in these previous reported studies, the IES-scores in our study showed a statistical significant decline with time. These findings are also in line with our previous study on persons undergoing genetic testing for hereditary breast or ovarian cancer, with the highest scores of both intrusion and avoidance before genetic testing (mean IES-I: 12.4, mean IES-A: 9.2), and statistical significant lower scores after disclosure of the genetic test result (mean IES-I: 9.6, mean IES-A: 7.7) [7]. Although the mean scores were in the moderate range it should be noted that in our study one-third of the patients had intrusion scores in the severe range and one-fourth had avoidance scores in the severe range, at inclusion. A diagnosis of breast or ovarian cancer is a potential life-threatening event, and receiving the diagnosis is associated with high levels of distress [12,13]. However, adjustment to the new situation takes place quite immediately, and the proportion of patients with higher levels of distress decreases with time [27], as demonstrated in our study.

A high level of distress has a negative impact on the patient's ability to receive and remember information and can lead to lower adherence and compliance to treatment and follow-up [17]. Identification of patients with higher levels of intrusion and avoidance is therefore of interest to ensure better health care for these patients. Our study confirms the significance of young age as a predictor of intrusion and avoidance symptoms after a diagnosis of cancer. Consistent with findings in previous studies in patients with breast or ovarian cancer [12,14,16], we also found that the level of cancer-related distress is inversely correlated to time since diagnosis.

Looking at the two different cancer types in our study group, patients with ovarian cancer had higher levels of both intrusion and avoidance symptoms as compared to patients with breast cancer. This may reflect the severity of the ovarian cancer disease, which was more often diagnosed at an advanced stage. There are few studies in the literature

comparing psychological distress in patients with breast cancer and ovarian cancer directly, but our results are consistent with a recent meta-analysis where PTSD was reported more prevalent among survivors of gynecological cancer compared to survivors of breast cancer [33].

The protective effect of perceived social support on distress following a cancer diagnosis was confirmed in our study, and the effect was evident at all time points. Our findings show that this general resource also plays an important role in how a person copes with specific life events such as receiving a cancer diagnosis and simultaneously undergoing genetic testing. One should be aware that the protective effect is associated with *perceived* social support—as it is experienced by the person herself. In the light of this, our finding of increased intrusion symptoms in women living with a partner is interesting.

Previous research has shown diverging results when it comes to the effect of marriage or marriage-like relationship on psychological distress in patients with cancer [13,25,26,34]. Studies that have looked thoroughly into the complexity of this matter have revealed that the *quality* of the intimate relationship is decisive for whether having a partner has a positive or negative impact on the psychological distress in patients with cancer [35]. Furthermore, there seems to be a gender effect: while men with cancer are less likely to develop symptoms of psychological distress if they are married, female cancer patients have lower levels of psychological distress if they are not married [36]. In addition, both breast and ovarian cancer affect organs inevitable connected to female body image and sexuality, a fact that may be of importance for the observed difference between women with and without a cohabitating partner in our study.

In this study, traditional pretest genetic counseling was not given. Since genetic counseling has been shown to reduce decisional conflict regarding genetic testing [10], the finding that higher levels of decisional conflict at baseline predicted more intrusive thoughts both at baseline and at follow-up measurements is worth noting. Patients with higher levels of decisional conflict could benefit from more counseling and support in the decision making process, with potential both to reduce the level of distress, and to increase the uptake of genetic testing. However, integration of genetic testing into busy cancer clinics requires alternative ways of providing such support. For this purpose, some education and information resources already exist, and new tools for decision-making support are under development [37]. More use of web-based technology and applications based on artificial intelligence, could contribute to more personalized information and counseling of patients undergoing genetic testing.

A limitation to our study is that it was not possible to collect information about the patients who declined genetic testing, due to ethical regulations. The participants in our study may therefore not be representative for all patients with newly diagnosed breast or ovarian cancer. Furthermore, the number of mutation carriers was too low to detect a potential effect of a positive gene test result on the levels of intrusion and avoidance.

In summary, our study documents a moderate level of cancer-related distress in women having genetic *BRCA1/2* testing without pretest genetic counseling shortly after a diagnosis of breast- or ovarian cancer, and that the level of distress decreases with time. Although this indicates that a simplified procedure for genetic testing of large patient groups with newly diagnosed cancer is feasible, we identified possible predictor factors for experiencing increased cancer-related distress: younger age, less perceived social support, higher levels of decisional conflict, and being a woman living with a partner. Clinicians should be aware of this when offering diagnostic genetic testing, to make sure that the more vulnerable patients do not miss the opportunity for personalized treatment.

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No potential conflict of interest was reported by the authors.

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Supplemental Table 1
Results from mixed linear regression analyses of IES subscale Intrusion in the DNA-BONus study on psychosocial aspects of genetic testing in 309 women newly diagnosed with breast or ovarian cancer in western Norway between September 2012 and April 2015

Variables	Unadjusted models			Fully adjusted model			Simplified model		
Categories	b	95% CI	*p*-value	b	95% CI	*p*-value	b	95% CI	*p*-value
Intercept				31.31	(21.01, 41.61)	< 0.001	34.35	(25.59, 43.10)	< 0.001
Ovarian vs. breast cancer	1.81	(-0.62, 4.24)	0.145	1.64	(-1.50, 4.679)	0.304	3.53	(1.10, 5.96)	0.005
Age per 10 years	-1.33	(-2.10, -0.57)	0.001	-1.42	(-2.47, -0.37)	0.008	-1.80	(-2.58, -1.03)	< 0.001
Months from diagnosis to T1	-0.11	(-0.32, 0.10)	0.289	-0.28	(-0.50, -0.07)	0.010	-0.25	(-0.46, -0.05)	0.017
DCS per 10 percent score	0.78	(0.19, 1.38)	0.010	0.71	(0.11, 1.31)	0.020	0.67	(0.10, 1.24)	0.022
ISEL	-3.06	(-4.96, -1.17)	0.002	-3.76	(-5.73, -1.78)	< 0.001	-3.71	(-5.60, -1.83)	<0.001
Questionnaire time point			< 0.001			< 0.001			< 0.001
T1	0.00	reference		0.00	reference		0.00	reference	
T2	-2.28	(-3.13, -1.42)		-2.35	(-3.22, -1.48)		-2.38	(-3.24, -1.52)	
T3	-4.63	(-5.65, -3.62)		-4.68	(-5.71, -3.65)		-4.73	(-5.75, -3.70)	
Genetic counselling post-test			0.146			0.733			
Not offered	0.00	reference		0.00	reference				
Offered, not accepted/received	2.81	(-0.00, -5.62)		0.87	(-2.09, 3.83)				
Offered and received	0.50	(-1.49. 2.48)		-0.32	(-2.60, 1.95)				
Education			0.407			0.832			
Primary School	0.00	reference		0.00	reference				
High School	-0.49	(-3.17, 2.19)		-0.83	(-3.58, 1.92)				
University	0.85	(-1.77, 3.47)		-0.54	(-3.43, 2.36)				
Employed	2.10	(0.25, 3.94)	0.026	1.32	(-1.03, 3.67)	0.269			
Having biological children	2.06	(-0.84, 4.95)	0.163	2.28	(-0.55, 5.11)	0.114			
Living with a partner	2.65	(0.67, 4.62)	0.009	2.01	(-0.25, 4.05)	0.053	2.56	(0.639, 4.48)	0.010
Detection method			0.026			0.216			
Symptomatic	0.00	reference		0.00	reference				
Screening	-2.59	(-4.48, -0.71)		-1.92	(-4.09, 0.26)				
Other	-1.59	(-5.62, 2.44)		-0.46	(-4.77, 3.86)				
Stage			0.499			0.565			
I	0.00	reference		0.00	reference				
II	0.44	(-1.57, 2.45)		-0.14	(-2.17, 1.90)				
III	1.18	(-1.57, 3.92)		1.02	(-2.18, 4.24)				
IV	2.73	(-1.06, 6.52)		2.97	(-1.54, 7.49)				
Mutation carrier	2.33	(-1.83, 6.48)	0.271	1.49	(-2.89, 5.88)	0.503			
FDR with cancer			0.298			0.762			
Not reported FDR with cancer	0.000	reference		0.00	reference				
FDR with other cancer	-1.57	(-3.67, 0.52)		-0.77	(-2.87, 1.33)				
FDR with BO cancer	0.03	(-2.36, 2.42)		-0.13	(-2.71, 2.46)				

Abbreviations: b: estimated regression coefficient; CI: confidence interval; p-value: from F-test; IES: Impact of Event Scale (0-35/40) (Horowitz et al 1979); T1: time of inclusion; T2: one week after disclosure of genetic test result; T3: six months after disclosure of genetic test result; DCS: Decisional Conflict Scale (0-100); ISEL: Interpersonal Support Evaluation List (1-4); FDR: first degree relative; BO: breast or ovarian

Supplemental Table 2
Results from mixed linear regression analyses of IES subscale Avoidance in the DNA-BONus study on psychosocial aspects of genetic testing in 309 women newly diagnosed with breast or ovarian cancer in western Norway between September 2012 and April 2015

Variables	Unadjusted models			Fully adjusted model			Simplified model		
Categories	b	95% CI	*p*-value	b	95% CI	*p*-value	b	95% CI	*p*-value
Intercept (Avoidance)				33.46	(23.48, 43.43)	< 0.0001	38.50	(30.48, 46.53)	< 0.001
Ovarian vs. breast cancer	2.11	(-0.26, 4.48)	0.081	2.67	(-0.39, 5.72)	0.087	3.36	(1.03, 5.69)	0.005
Age per 10 years	-0.32	(-1.08, 0.44)	0.411	-0.45	(-1.47, 0.56)	0.378	-1.02	(-1.75, -0.30)	0.006
Months from diagnosis to T1	-0.07	(-0.27, 0.14)	0.517	-0.20	(-0.41, 0.00)	0.055	-0.21	(-0.41, -0.01)	0.039
DCS per 10 percent score	0.57	(-0.01, 1.14)	0.055	0.28	(-0.30, 0.86)	0.337			
ISEL	-5.55	(-7.32, -3.77)	< 0.001	-5.95	(-7.86, -4.03)	< 0.001	-5.86	(-7.62, -4.09)	< 0.001
Questionnaire time point			< 0.001			< 0.001			< 0.001
T1	0.00	reference		0.00	reference		0.00	reference	
T2	-2.14	(-2.93, -1.36)		-2.21	(-3.01, -1.42)		-2.19	(-2.96, -1.41)	
T3	-2.68	(-3.57, -1.78)		-2.65	(-3.56, -1.73)		-2.67	(-3.57, -1.78)	
Genetic counselling post-test						0.391			
Not offered	0.00	reference		0.00	reference				
Offered, not accepted/received	2.08	(-0.61, 4.79)		0,63	(-2.22, 3.47)				
Offered and received	-0.90	(-2.83, 1.03)		-1.17	(-3.38, 1.04)				
Education			0.339			0.356			
Primary School	0.00	reference		0.00	reference				
High School	1.05	(-1.55, 3.65)		1.86	(-0.80, 4.53)				
University	1.85	(-0.69, 4.39)		1.87	(-0.94, 4.67)				
Employed	0.70	(-1.11, 2.51)	0.446	0.78	(-1.49, 3.05)	0.498			
Having biological children	0.89	(-1.94, 3.72)	0.535	1.41	(-1.33, 4.15)	0.311			
Living with a partner	-0.25	(-2.20, 1.70)	0.801	0.21	(-1.76, 2.18)	0.834			
Detection method			0.298			0.111			
Symptomatic	0.00	reference		0.00	reference				
Screening	-1.43	(-3.28, 0.43)		-2.19	(-4.30, -0.08)				
Other	-1.24	(-5.18, 2.70)		-2.13	(-6.28, 2.03)				
Stage			0.558			0.520			
I	0.00	Reference		0.00	reference				
II	-1.00	(-2.95, 0.95)		-1.18	(-3.15, 0.79)				
III	-0.22	(-2.87, 2.44)		-1.56	(-4.66, 1.53)				
IV	1.38	(-2.31, 5.08)		0.32	(-4.08, 4.72)				
Mutation carrier	1.20	(-2.86, 5.25)	0.562	1.24	(-3.02, 5.50)	0.567			
FDR with cancer			0.274			0.515			
Not reported FDR with cancer	0.00	Reference		0.00	reference				
FDR with other cancer	-1.34	(-3.37, 0.70)		-0.65	(-2.69, 1.38)				
FDR with BO cancer	0.63	(-1.70, 2.95)		0.88	(-1.61, 3.38)				

Abbreviations: b: estimated regression coefficient; CI: confidence interval; p-value: from F-test; IES: Impact of Event Scale (0-35/40) (Horowitz et al 1979); T1: time of inclusion; T2: one week after disclosure of genetic test result; T3: six months after disclosure of genetic test result; DCS: Decisional Conflict Scale (0-100); ISEL: Interpersonal Support Evaluation List (1-4); FDR: first degree relative; BO: breast or ovarian

Appendix

Appendix 1

A. Information sheet

B. Request form

HELSE BERGEN
Haukeland Universitetssykehus

Regionalt kompetansesenter for arvelig kreft

Forespørsel om deltakelse i forskningsprosjekt

DNA-testing av pasienter med brystkreft og/eller eggstokkreft i Norge undersøkelsen (*DNA BONus*)

Delstudie 1: Vurdering av risiko for arvelig bryst- og eggstokkreft basert på familiehistorie og DNA-testing av pasienter med bryst- og/eller eggstokkreft i Norge

Delstudie 2: Psykososiale aspekter ved genetisk testing av pasienter som behandles for brystkreft eller eggstokkreft

Bakgrunn og hensikt

Ca 2 % av alle tilfeller av brystkreft og ca 10% av alle tilfeller av eggstokkreft kan skyldes en nedarvet genfeil i BRCA1- eller BRCA2-genet. Denne studien er todelt. Delstudie 1 vil bidra til å kartlegge forekomsten av slike genfeil i Norge ved å tilby gentest til alle pasienter som er under behandling for bryst- eller eggstokkreft. Gjennom innhenting av opplysninger om krefttilfeller i deltakernes familier vil den også gi en oversikt over det totale behovet for genetisk utredning og veiledning av pasienter med bryst- eller eggstokkreft. Prøver samlet inn i denne studien vil også utgjøre et viktig grunnlag for søk etter andre genetiske forhold som kan tenkes å bidra til kreftutvikling. I delstudie 2 ønsker vi å undersøke hvordan personer som har kreft opplever å få tilbud om en gentest, og evt måtte forholde seg til en arvelig risiko for kreft for seg og familien. Dette for at vi skal kunne bedre planlegge fremtidig ivaretakelse av personer som gjennomfører gentester, for eksempel i forhold til hvilken informasjon de trenger og når denne informasjonen er mest gunstig å gi. Regionalt kompetansesenter for arvelig kreft, Helse Vest, er ansvarlig for begge disse delstudiene.

Hva innebærer studien?

Du kan velge å delta enten i begge delstudiene, bare i delstudie 1, eller bare delstudie 2. Pasienter med økt risiko for arvelig kreft, og som oppfyller kriterier fastsatt av Helsedirektoratet, har mulighet for å velge genetisk testing og utredning uten å delta i forskning.

Delstudie 1:

a) Dersom du velger å delta i studie 1, vil du bli testet for vanlige genfeil i *BRCA1*- og *BRCA2*-genene. Det blir tatt en blodprøve av deg, og du må fylle ut et skjema ("rekvisisjon") med opplysninger om egen sykdom og kreftsykdommer i familien. Du vil selv få informasjon om resultatet av gentesten etter 2-4 uker. Resultatet vil også bli formidlet til behandlende lege. Hvis du får påvist genfeil, eller andre forhold gir grunnlag for videre genetisk utredning (slik som flere tilfeller av kreft i familien), vil du få tilbud om genetisk veiledning.

b) Avidentifiserte prøver fra delstudie 1 vil etter at *BRCA*-gentesten er utført inngå i en forskningsbiobank og kan bli brukt til å kartlegge andre genetiske faktorer som kan være forbundet med kreftutvikling.

Besøksadresse: Haukeland Universitetssykehus, Jonas Liesvei 65,
Postadresse: Helse Bergen HF, Postboks 1, 5021 Bergen
Telefon 55 97 54 75 – Telefaks 55 97 54 79, E-post: rkak@helse-bergen.no
Besøk vår internettside http://www.helse-bergen.no/arveligkreft

DNA BONus

Delstudie 2:

Hvis du velger å delta i delstudie 2, må du fylle ut ett spørreskjema før gentesten, ett rett etter gentestsvaret er formidlet og ett ca 6 måneder etter gentest. Det vil ta ca 20 min å fylle ut spørreskjemaene.

Mulige fordeler og ulemper

Det å få påvist en genfeil, som medfører høy risiko for kreft, kan oppleves som en ekstra belastning i en fase hvor man er under behandling for en alvorlig kreftsykdom. Dette medfører nye valgsituasjoner med hensyn på risikoreduserende tiltak, og en visshet om at ens familiemedlemmer også kan ha høy risiko for å få kreft. Fordelen med å vite om at man har en genfeil kan på den annen side være at man dermed får en forklaring på hvorfor man ble syk, evt. også hvorfor mange i familien er rammet av kreft. For noen kan muligheten for å gjøre risikoreduserende tiltak (se kapittel B) med hensyn på ny kreftsykdom også være en stor fordel. Dersom en genfeil påvises kan nære familiemedlemmer, slik som døtre og søstre, i tillegg få tilbud om adekvat oppfølging. Vi ser også at noen av spørsmålene i delstudie 2 kanskje kan minne deg på ting du synes er vanskelig å tenke på. Dersom disse spørsmålene skulle bekymre deg eller det er andre forhold ved spørreskjemaene du vil diskutere er du hjertelig velkommen til å ta kontakt med oss, se kontaktinfo under.

Hva skjer med prøvene og informasjonen om deg?

Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Resultatet av gentesten blir lagret i prøvedatabasen og pasientjournalen ved Senter for medisinsk genetikk og molekylærmedisin og i din journal ved sykehuset der du blir behandlet for kreftsykdommen. I tillegg til informasjonen som du selv oppgir i spørreskjemaene, vil vi innhente supplerende informasjon fra din sykejournal ved sykehuset der du blir behandlet for kreftsykdommen. Det kan også bli innhentet informasjon om deg fra Kreftregisteret. Denne informasjonen, og informasjonen som du selv oppgir i rekvisisjonsskjemaet (delstudie 1) og evt spørreskjemaene (delstudie 2) vil bli oppbevart avidentifisert på forskningsserveren ved Haukeland Universitetssykehus.

Prøvene vil bli lagret avidentifisert i en forskningsbiobank ved Regionalt kompetansesenter for arvelig kreft, og vil kunne bli brukt til å identifisere andre genetiske faktorer av betydning for kreftuvikling (se kapittel B, personvern). Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dersom du ønsker å delta, undertegner du den/de aktuelle samtykkeerklæring(ene) på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg, kan du kontakte overlege Hildegunn Høberg Vetti eller genetisk veileder Cathrine Bjorvatn, tlf nr 55 97 54 75.

DNA BONus

Kontakttelefon

Hvis du ønsker å snakke med en genetisk veileder for å få mer informasjon om hva gentesten går ut på, eller du har andre spørsmål i forhold til arvelig kreft eller denne studien, kan du ringe vår kontakttelefon, **tlf nr 55 97 54 75**

Du er også velkommen til å ta kontakt på e-post: rkak@helse-bergen.no

Ytterligere informasjon om studien finnes i kapittel *A* – *utdypende forklaring av hva studien innebærer.*

Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – *Personvern, biobank, økonomi og forsikring.*

Samtykkeerklæring følger etter kapittel B.

Med vennlig hilsen

Hildegunn Høberg Vetti
Overlege

Cathrine Bjorvatn
Genetisk veileder, PhD

Kapittel A- utdypende forklaring av hva studien innebærer

Bakgrunn og hensikt

De fleste tilfeller av kreft er ikke arvelig betinget, men i ca 5-10 % av tilfellene er arv trolig en viktig årsaksfaktor. Ca 2 % av alle tilfeller av brystkreft og ca 10% av alle tilfeller av eggstokkreft kan skyldes en nedarvet genfeil i ett av de to genene som kalles *BRCA1* eller *BRCA2*, men dette tallet er usikkert og varierer mye fra populasjon til populasjon. I Norge har gentesting i mange år vært tilbudt familier med høy forekomst av brystkreft og/eller eggstokkreft. Men det viser seg at slik testing basert på familiehistorie ikke er egnet til å fange opp alle pasienter som har en arvelig form for brystkreft eller eggstokkreft. Denne studien er todelt.

Delstudie 1 vil bidra til å kartlegge forekomsten av slike genfeil i Norge, og vil trolig føre til at flere personer med genfeil i *BRCA1*- eller *BRCA2*-genet blir identifisert. I tillegg vil den identifisere pasienter med en familiær form for hhv brystkreft eller eggstokkreft, men hvor dette ikke skyldes genfeil i *BRCA1*- eller *BRCA2*-genet. Vi vil også se nærmere på pasientene som får påvist genfeil og deres familier, og sammenligne disse med familier som er identifisert gjennom tradisjonell medisinsk genetisk utredning. Det vil også være aktuelt å forsøke å identifisere andre genetiske forhold som påvirker kreftrisiko og kreftutvikling.

Delstudie 2: Hovedmålet i denne delstudien er å kartlegge de psykososiale aspekter ved genetisk testing av alle pasienter som er under behandling for bryst- eller eggstokkreft. Vi ønsker å undersøke hvordan genetisk informasjon kan gis best mulig innenfor en vanlig klinisk hverdag. Det foreligger per i dag ingen publiserte forskningsartikler som omhandler psykososiale aspekter ved gentesting av denne gruppen pasienter. Genetisk informasjon skiller seg fra annen informasjon i det at den også gir informasjon om nære familiemedlemmer sin risiko. Dette gjør håndteringen av informasjonen spesiell, og det kan være av betydning for familiemedlemmer å få del i kunnskap om bærerstatus. Vi ønsker å innhente kunnskap, slik at vi kan legge til rette for at kreftpasienter får et best mulig tilbud i forhold til gentesting og oppfølging i fremtiden.

Hvem blir invitert til å delta i studien?

Pasienter som er under behandling for brystkreft eller eggstokkreft ved sykehusene i Helse Vest vil bli invitert til å delta.

Hva innebærer studien?

Dersom du er villig til å delta i delstudie 1, vil det bli tatt en blodprøve av deg, og du vil bli bedt om å fylle ut et skjema med opplysninger om egen sykdom og forekomst av kreftsykdommer i familien din. Blodprøven og skjemaet med opplysninger vil bli sendt til Senter for medisinsk genetikk og molekylærmedisin, sammen med undertegnet samtykkeskjema. Der vil prøven bli analysert for de hyppigst forekommende genfeil i *BRCA1*- og *BRCA2*-genene i den norske befolkningen. Ca 90 % av alle som hadde påvist genfeil i *BRCA1*-genet eller *BRCA2*-genet per juli 2009 (i Norge) hadde en av disse genfeilene.

Svaret vil foreligge etter 2-4 uker. Dersom svaret er normalt (det er ikke påvist noen genfeil), vil du få informasjon om dette gjennom et brev fra en av prosjektmedarbeiderne. Dersom det blir påvist en genfeil, vil du bli oppringt fra en av prosjektmedarbeiderne og få tilbud om en genetisk veiledningssamtale innen 2 uker. Resultatet vil også bli formidlet til din behandlende lege uansett resultat. Hvis det fremkommer andre opplysninger som gir grunnlag for å mistenke at det foreligger arvelig kreft i din familie, vil du også få en telefon fra en av prosjektmedarbeiderne, selv om resultatet av gentesten er normalt, se nedenfor.

Dersom du sier ja til å delta i delstudie 2, "Psykososiale aspekter ved genetisk testing av kvinner med nyoppdaget bryst- eller eggstokkreft", innebærer det at du må fylle ut tre spørreskjema. Det første før tilbud om gentest, det andre rett etter tilbud om gentest og det siste vel 6 måneder etter tilbud gentest. Det vil ta ca 20 min å fylle ut spørreskjemaene.

Påvist genfeil - betydning for deg

Kvinner som har en genfeil i *BRCA1*- eller *BRCA2*-genet har økt risiko for å få brystkreft og eggstokkreft. For kvinner som allerede har gjennomgått brystkreft innebærer dette en økt risiko for å få kreft igjen, enten i samme bryst dersom det er gjort brystbevarende operasjon, eller i det andre brystet. Behandlingen av arvelig brystkreft kan således tenke seg å bli annerledes og mer omfattende enn ved en sporadisk form for brystkreft. Denne mer omfattende behandlingen vil ofte innebære fjerning av hele brystet hvor kreftsvulsten ble funnet. Det vil også diskuteres risikoreduserende tiltak med hensyn på det friske brystet, enten i form av regelmessige kontroller med MR/mammografi eller ved kirurgisk fjerning av kjertelvevet. Risikoreduserende fjerning av eggstokker vil vanligvis anbefales ved ca 40 års alder til de som har fått påvist genfeil.

For kvinner som har eggstokkreft vil behandlingen av kreftsykdommen ikke bli annerledes dersom det skulle påvises en genfeil. Men siden genfeilen medfører en høy risiko for også å få brystkreft, vil man ofte diskutere risikoreduserende tiltak med hensyn på brystkreft, vanligvis i form av regelmessige kontroller med MR/mammografi.

Påvist genfeil - betydning for din familie

Dersom det blir påvist en genfeil hos deg, kan dette ha betydning for andre personer i din familie. Dette vil bli drøftet med deg under den genetiske veiledningssamtalen. Barn og søsken av en person med genfeil i *BRCA1*- eller *BRCA2*-genet, har 50 % risiko for å være bærer av den samme genfeilen. Slektninger som ønsker det vil få tilbud om genetisk veiledning og gentest. Friske kvinner som får påvist genfeil i *BRCA1*- eller *BRCA2*-genet vil ha tilbud om risikoreduserende tiltak som skissert ovenfor. Menn som får påvist genfeil i *BRCA2*-genet kan bli anbefalt kontroller pga økt risiko for prostatakreft.

Normalt resultat av gentesten

De fleste kvinner vil få beskjed om at gentesten er normal, det vil si at vi ikke har funnet noen av de kjente norske genfeilene i *BRCA1* eller *BRCA2* genet. Men det finnes også andre årsaker til arvelig brystkreft og arvelig eggstokkreft. Det kan derfor i enkelte tilfeller være aktuelt med utvidet genetisk utredning/testing og genetisk veiledning. Dette kan være på bakgrunn av opplysninger om andre krefttilfeller i familien, du selv har hatt kreft flere ganger, du selv var svært ung da du fikk kreft, spesielle karakteristika ved kreftsykdommen hos deg eller opplysninger om brystkreft hos menn.

Mulige ulemper

For de som får påvist en genfeil kan dette oppleves som en ekstra belastning i en fase hvor man er under behandling for en alvorlig kreftsykdom. I tillegg vil det å få informasjon om at ens familiemedlemmer, spesielt søstre og døtre, vil være i risiko for å ha samme genfeil, være tøft å forholde seg til. Nye valgsituasjoner med hensyn på risikoreduserende tiltak, f.eks fjerning av eggstokker ved 40 års alder, vil også innebære en tilleggsbelastning, både for pasienten og for evt slektninger med samme genfeil. Tidsbruken ved å fylle ut spørreskjemaene kan representere en ulempe. Det vil ta ca. 20 min å fylle ut spørreskjema 1 og noe mindre tid på spørreskjema 2 og 3. Det kan også tenke seg at enkelte spørsmål i

spørreskjemaene kan trigge bekymring eller minne studiedeltakerne på ting de synes er vanskelig å tenke på.

Mulige fordeler

Fordelen med å få vite om man har en genfeil i *BRCA1*- eller *BRCA2*-genet kan være at man med det får en forklaring på hvorfor man ble syk, og evt. hvorfor mange i familien har vært rammet av kreftsykdom. For noen kan muligheten for å gjøre risikoreduserende tiltak med hensyn på ny kreftsykdom også være en stor fordel. Tilsvarende vil risikoreduksjon og mulighet for tidlig diagnostikk for slektninger også kunne oppfattes som en fordel, siden det er svært alvorlig sykdom det er snakk om, og risikoreduksjon vil kunne forhindre kreftutvikling og dermed sykelighet og død.

Fordelen med å delta i delstudie 2 er at du kan med din erfaringskunnskap være med å bidra til et bedret fremtidig helsetilbud for andre pasienter i din situasjon.

Hva skjer med prøvene og informasjonen om deg?

Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Resultatet av *BRCA*-gentesten blir lagret i prøvedatabasen og pasientjournalen ved Senter for medisinsk genetikk og molekylærmedisin og i din journal ved sykehuset der du blir behandlet for kreftsykdommen. Etter at prøvene er analysert for de vanlig forekommende genfeil i *BRCA*-genene vil de bli overført til en forskningsbiobank, se kapittel B. Opplysningene som er registrert om deg, inkl spørreskjemaene som utgjør delstudie 2 vil i avidentifisert form bli lagret på Haukeland Universitetssykehus sin forskningsserver inntil alle resultatene er bearbeidet og publisert.

Kapittel B - Personvern, biobank, økonomi og forsikring

Personvern

Opplysninger som registreres om deg er personalia og opplysninger du selv gir på spørreskjema. I tillegg til denne informasjonen vil vi innhente informasjon om aktuell diagnose (inkl nærmere klassifisering av denne) og tidligere sykdommer fra din sykejournal ved sykehuset der du blir behandlet for kreftsykdommen. Det kan også bli innhentet informasjon om deg fra Kreftregisteret.

Resultat av *BRCA*-gentesten vil bli oppbevart og meddelt deg og din behandlende lege som skissert ovenfor. For utvidete genetiske studier med tanke på å kartlegge andre genetiske faktorer som kan ha sammenheng med kreftutvikling, vil opplysningene og prøvene bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Resultater av disse undersøkelsene vil ikke bli knyttet direkte til deg, og du vil følgelig heller ikke få noen informasjon om disse resultatene.

En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg.

Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Haukeland Universitetssjukehus ved administrerende direktør er databehandlingsansvarlig.

Biobank

Blodprøvene som blir tatt og informasjonen utledet av dette materialet vil bli lagret i en forskningsbiobank ved Regionalt kompetansesenter for arvelig kreft. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Leder av Regionalt kompetansesenter for arvelig kreft, Helse Vest, p.t. Hildegunn Høberg Vetti, er ansvarshavende for forskningsbiobanken. Biobanken planlegges å vare til 2027. Etter dette vil materiale og opplysninger bli destruert og slettet etter interne retningslinjer.

Utlevering av materiale og opplysninger til andre

Hvis du sier ja til å delta i studiens del 1b), gir du også ditt samtykke til at prøver og avidentifiserte opplysninger utleveres til våre samarbeidspartnere ved Radboud University Nijmegen Medical Centre i Nederland.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi

Begge delstudiene og biobanken er finansiert av Regionalt kompetansesenter for arvelig kreft.

Forsikring

Ved deltagelse i studien gjelder pasientskadeerstatningsloven.

Informasjon om utfallet av studien

Resultater fra studien vil bli publisert i internasjonale vitenskapelige tidsskrift. Informasjon om resultatene vil også bli lagt ut på internettsidene til Regionalt kompetansesenter for arvelig kreft (www.helse-bergen.no/arveligkreft).

HELSE BERGEN
Haukeland universitetssjukehus

Regionalt Kompetansesenter for Arvelig Kreft
Senter for Medisinsk Genetikk og Molekylærmedisin
Haukeland Universitetssjukehus,
Jonas Lies vei 65, 5021 BERGEN
Tel: 55 97 54 75 E-mail: rkak@helse-bergen.no

Rekvirent: *Overlege Hildegunn Høberg Vetti, RKAK*
Behandlende lege (mottar kopi av svar):

Fødselsnr:
Navn:
Adresse:
Postnr/sted:

TIL PRØVETAKER

Til denne analysen trengs **6 ml EDTA-blod (lilla kork)**

Prøve tatt dato: kl.
Prøvetaker sign:

Rekvisisjon Arvelig bryst-/eggstokkreft DNA BONus

Denne rekvisisjon skal brukes til pasienter med diagnose brystkreft eller eggstokkreft for undersøkelse av kjente mutasjoner i *BRCA1*– og *BRCA2*-genet. For at blodprøven skal analyseres må pasienten ha mottatt informasjonsskriv, undertegne skriftlig informert samtykke (vedlegges) og fylle ut informasjon om egen sykdom og forekomst av kreft i familien nedenfor:

Fylles ut av pasienten

Mitt telefonnummer:

Egen sykdom:

☐ Brystkreft
☐ Høyre bryst Dato: _____ Alder: _____
☐ Venstre bryst Dato: _____ Alder: _____

☐ Eggstokkreft Dato: _____ Alder: _____

Evt annen sykdom:

Familieopplysninger:

Er det kjent genfeil forbundet med økt risiko for kreft i familien? ☐ Nei ☐ Ja Hvilken:_____

Krefttilfeller i familien:

Fyll ut så godt du kan. For personer med kreft, vennligst oppgi alder da diagnosen ble stilt. Ved behov for mer plass kan baksiden av skjemaet brukes.

	NB! En linje per person	Brystkreft			Eggstokkreft			Evt annen kreftsykdom	
		Ja	Alder ved diagnose	Nei	Ja	Alder ved diagnose	Nei	Krefttype	Alder ved diagnose
Nærmeste familie	Søster 1								
	Søster 2								
	Datter 1								
	Datter 2								
	Mor								
	Brors datter								
	Andre (hvem?)								
Mors slekt	Mormor								
	Mors søster 1								
	Mors søster 2								
	Andre:								
Fars slekt	Farmor								
	Fars søster 1								
	Fars søster 2								
	Andre:								

Appendix 2

Poster DNA-BONus

Lurer du på om kreftsjukdommen din er arveleg?

DNA BONus er eit forskingsprosjekt for å kartleggje arveleg brystkreft og eggstokkreft. Alle som får påvist brystkreft eller eggstokkreft kan ta del i prosjektet.

For å delta ønskjer vi at du tek ein blodprøve og svarar på nokre spørsmål.

Ønskjer du meir informasjon om prosjektet?

www.helse-bergen.no/arvelegkreft

Kontakt genetisk veiledar:

Telefon: 55 97 54 75

E-post: rkak@helse-bergen.no

DNA BONus

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Haukeland universitetssjukehus

Regionalt kompetansesenter for arveleg kreft

Appendix 3

Del 1: HADS

Del 2: ISEL

Del 3: IES-15

Del 4: DCS

Del 1

Her kommer noen spørsmål om hvordan du føler deg. For hvert spørsmål setter du kryss for et av de fire svarene som best beskriver dine følelser **den siste uken**. Ikke tenk for lenge på svaret – de spontane svarene er best.

1. **Jeg føler meg nervøs og urolig**

   3 ☐ Mesteparten av tiden
   2 ☐ Mye av tiden
   1 ☐ Fra tid til annen
   0 ☐ Ikke i det hele tatt

2. **Jeg gleder meg fortsatt over tingene slik jeg pleide før**

   0 ☐ Avgjort like mye
   1 ☐ Ikke fullt så mye
   2 ☐ Bare lite grann
   3 ☐ Ikke i det hele tatt

3. **Jeg har en urofølelse som om noe forferdelig vil skje**

   3 ☐ Ja, og noe svært ille
   2 ☐ Ja, ikke så veldig ille
   1 ☐ Litt, bekymrer meg lite
   0 ☐ Ikke i det hele tatt

4. **Jeg kan le og se det morsomme i situasjoner**

   0 ☐ Like mye som før
   1 ☐ Ikke like mye nå som før
   2 ☐ Avgjort ikke som før
   3 ☐ Ikke i det hele tatt

5. **Jeg har hodet fullt av bekymringer**

   3 ☐ Veldig ofte
   2 ☐ Ganske ofte
   1 ☐ Av og til
   0 ☐ En gang i blant

6. **Jeg er i godt humør**

   3 ☐ Aldri
   2 ☐ Noen ganger
   1 ☐ Ganske ofte
   0 ☐ For det meste

7. **Jeg kan sitte i fred og ro og kjenne meg avslappet**

   0 ☐ Ja, helt klart
   1 ☐ Vanligvis
   2 ☐ Ikke så ofte
   3 ☐ Ikke i det hele tatt

8. Jeg føler meg som om alt går langsommere

3 ☐ Nesten hele tiden
2 ☐ Svært ofte
1 ☐ Fra tid til annen
0 ☐ Ikke i det hele tatt

9. Jeg føler meg urolig som om jeg har sommerfugler i magen

0 ☐ Ikke i det hele tatt
1 ☐ Fra tid til annen
2 ☐ Ganske ofte
3 ☐ Svært ofte

10. Jeg bryr meg ikke lenger om hvordan jeg ser ut

3 ☐ Ja, jeg har sluttet å bry meg
2 ☐ Ikke som jeg burde
1 ☐ Kan hende ikke nok
0 ☐ Bryr meg som før

11. Jeg er rastløs, som om jeg stadig må være aktiv

3 ☐ Uten tvil svært mye
2 ☐ Ganske mye
1 ☐ Ikke så veldig mye
0 ☐ Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting

0 ☐ Like mye som før
1 ☐ Heller mindre enn før
2 ☐ Avgjort mindre enn før
3 ☐ Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk

3 ☐ Uten tvil svært ofte
2 ☐ Ganske ofte
1 ☐ Ikke så veldig ofte
0 ☐ Ikke i det hele tatt

14. Jeg kan glede meg over gode bøker, radio og TV

0 ☐ Ofte
1 ☐ Fra tid til annen
2 ☐ Ikke så ofte
3 ☐ Svært sjelden

Del 2

Dette spørreskjemaet består av en serie med spørsmål og påstander som beskriver mennesker på ulike måter. Hvert av disse spørsmålene kan passe på deg i større eller mindre grad. For hvert spørsmål skal du velge den ruten som passer best med din vurdering av deg selv og sette kryss. Det er ingen riktige eller gale svar – velg det alternativet som best beskriver hvordan du opplever deg selv på disse områdene i livet ditt.

1. Jeg kjenner noen jeg kan snakke med ofte og som jeg føler meg helt trygg på å ta opp ethvert problem jeg måtte ha

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

2. De fleste vennene mine synes jeg er dyktig

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

3. Jeg blir sjelden invitert til å gjøre noe sammen med andre

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

4. Jeg føler meg ikke sterkt involvert i noen andre personers liv

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

5. Hvis jeg bestemte meg for å gå på kino eller lignende, ville jeg lett finne noen å gå sammen med

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

6. Jeg kjenner noen som kunne hjelpe meg med gamle møbler, kjøkkenutstyr og lignende hvis jeg flyttet til en ny leilighet/hus og trengte det.

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

7. De fleste av vennene mine er mer tilfreds og lykkeligere med seg selv enn det jeg er

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

8. Jeg kjenner ingen der jeg bor som ville låne meg bilen sin hvis jeg trengte det

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

9. Jeg kjenner ingen der jeg bor som kunne hjelpe meg med å gjøre problemene mine mer oversiktlig og forståelig.

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

10. De bånd jeg har til mine nære venner er svært viktig for meg.

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

11. Jeg kan kontakte noen som jeg liker å være sammen med når jeg måtte ønske det

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

12. Jeg kjenner noen som jeg snakker med ofte og som jeg ville føle meg ekstra trygg på å ta opp ethvert seksuelt problem jeg måtte ha

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

13. Jeg kjenner ingen der jeg bor som ville bruke flere timer på å hjelpe meg med en viktig oppgave

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

14. Jeg har noen som jeg vil beskrive som en nær og fortrolig venn eller venninne

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

15. Jeg tilhører en gruppe der jeg bor som møtes regelmessig eller som regelmessig gjør ting sammen

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

16. De fleste av vennene mine mener jeg har fortjent de gode tingene som har skjedd i livet mitt

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

17. Det er ingen der jeg bor som jeg ville føle meg helt trygg på å ta opp følelser om ensomhet og depresjon

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

18. De fleste som kjenner meg godt setter stor pris på meg

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

19. Jeg har ikke et nært og kjærlig forhold til noen

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

20. Jeg kjenner noen som ville lånt meg 2000 kr hvis jeg trengte det for min egen del

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

21. Jeg er ikke medlem av noen sosiale grupper eller foreninger (slik som idrettslag, kirkeforeninger og lignende)

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

22. Jeg kjenner ingen der jeg bor som kunne lage mat eller handle inn hvis jeg var syk

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

23. Det finnes ingen der jeg bor som jeg føler meg helt trygg på å snakke med om helseproblemer

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

24. De fleste har flere nære venner enn jeg har

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

25. Jeg føler meg følelsesmessig nær andre

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

26. Hvis jeg trenger en venn/venninne til å hjelpe med å pusse opp, så har jeg noen der jeg bor som ville hjelpe meg

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

27. Jeg kjenner noen som jeg snakker med ofte og som jeg ville føle meg helt trygg på å snakke med om mitt sosiale liv

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

28. De fleste vennene/venninnene mine er mer interessante enn jeg

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

29. Jeg vet ikke om mange mennesker som virkelig bryr seg om meg

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

30. Jeg har ingen venner/venninner der jeg bor, utenom min ektefelle/samboer, som ville trøste meg ved å vise omsorg

1 ☐ Passer helt for meg
2 ☐ Passer delvis for meg
3 ☐ Passer delvis ikke for meg
4 ☐ Passer slett ikke for meg

Del 3

Nedenfor finner du en liste over utsagn fra mennesker som opplever vanskelige hendelser. Vennligst les hvert utsagn og indiker hvor ofte disse kommentarene har vært riktige for deg i løpet av de **siste syv dagene**. Hvis du ikke har opplevd noen av disse reaksjonene i denne perioden, vennligst marker det ved å sette kryss for "aldri".

1. Jeg har hatt perioder med sterke følelser omkring det å ha fått en kreftsykdom

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

2. Ting jeg har sett og hørt minnet meg plutselig om det å ha kreft

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

3. Tanker om det å ha kreft har trengt seg på også når jeg ikke har villet

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

4. Bilder av det å ha kreft har plutselig dukket opp i tankene mine

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

5. Enhver påminnelse har vekket følelser knyttet til det å ha kreft

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

6. Jeg har hatt vanskelig for å sove på grunn av tanker og bilder om det å ha fått en kreftsykdom

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

7. Jeg har vonde drømmer om det å ha kreft

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

8. Jeg vet mange uforløste følelser om kreft er der, men jeg har skjøvet dem bort

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

9. Jeg har ikke tillatt meg å bli følelsesmessig berørt når jeg tenker på det å ha en kreftsykdom eller blir minnet på det

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

10. Jeg har ønsket å bli kvitt minner om det å ha en kreftsykdom

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

11. Jeg har forsøkt å la være å snakke om det å ha kreft

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

12. Jeg har opplevd det uvirkelig, som om det å ha en kreftsykdom ikke var virkelig

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

13. Jeg har holdt meg unna ting eller situasjoner som kan minne meg om det å ha kreft

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

14. Mine følelser om det å ha kreft er nærmest lammende

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

15. Jeg har ikke tillatt meg selv å ha tanker om det å ha kreft

0 ☐ I høy grad
1 ☐ Ganske mye
2 ☐ Middels
3 ☐ Noe
4 ☐ Litt
5 ☐ Aldri

Del 4

Under kommer noen spørsmål knyttet til valget om å ta en gentest eller ikke og hvor godt forberedt du synes du er.

A. Hvilket valgalternativ foretrekker du? Vennligst kryss av.

☐ Gjennomføre gentest
☐ **Ikke** gjennomføre gentest

B. Tenk nå på det valget du er i ferd med å ta/nettopp har tatt, og les følgende kommentarer andre personer kan ha når de er i ferd med å ta valg om behandling etc. Marker hvor enig eller uenig du er ved å sette kryss i den ruten fra (meget enig) til (meget uenig), som passer best med det valget du er i ferd med å ta/nettopp har tatt.

1. Jeg vet hvilke valgalternativ som er tilgjengelig for meg.

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

2. Jeg kjenner til fordeler med de ulike valgalternativene

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

3. Jeg kjenner til hvilke risikoer og ulemper de ulike valgalternativene har

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

4. Jeg har klart for meg hvilke fordeler som er viktigst for meg

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

5. Jeg har klart for meg hvilke risikoer og ulemper som påvirker meg mest

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

6. Jeg har klart for meg hva som er viktigst for meg (fordeler eller risikoer/ulemper)

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

7. Jeg har tilstrekkelig støtte fra andre til å foreta valget

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

8. Jeg velger uten press fra andre

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

9. Jeg har nok innsikt til å foreta valget

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

10. Jeg har klart for meg hva som er det beste valgalternativet for meg

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

11. Jeg er sikker på hva jeg skal velge

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

12. Jeg føler det er et enkelt valg å ta

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

13. Jeg føler jeg har foretatt et informert valg

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

14. Mitt valg viser hva som er viktig for meg

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

15. Jeg forventer at jeg vil holde fast ved mitt valg

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

16. Jeg er tilfreds meg mitt valg

0 ☐ Meget enig
1 ☐ Enig
2 ☐ Verken enig eller uenig
3 ☐ Uenig
4 ☐ Meget uenig

Dersom du ønsker å gjennomføre gentest, vennligst gå til spørsmål C
Dersom du ikke ønsker å gjennomføre gentest, vennligst gå til spørsmål D

C.
Dersom du har krysset av for at **du ønsker å gjennomføre en gentest**, kan du angi hovedgrunnen (e) til dette:

_____
_____
_____

D.
Dersom du har krysset av for at **du ikke ønsker å gjennomføre en gentest**, kan du angi hovedgrunnen (e) til dette:

_____
_____
_____

Dersom du ikke ønsker gentest på det nåværende tidspunkt, tror du at du vil vurdere gentest ved en senere anledning?

☐ Ja
☐ Nei
☐ Usikker

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