BRCA mutation carrier detection. A model-based cost-effectiveness analysis comparing the traditional family history approach and the testing of all patients with breast cancer

Jan Norum,1 Eli Marie Grindedal,2 Cecilie Heramb,3 Inga Karsrud,4 Sarah Louise Ariansen,3 Dag Erik Undlien,1 Ellen Schlichting,4 Lovise Mæhle3

ABSTRACT
Background Identification of BRCA mutation carriers among patients with breast cancer (BC) involves costs and gains. Testing has been performed according to international guidelines, focusing on family history (FH) of breast and/or ovarian cancer. An alternative is testing all patients with BC employing sequencing of the BRCA genes and Multiplex Ligation Probe Amplification (MLPA).

Patients and methods A model-based cost-effectiveness analysis, employing data from Oslo University Hospital, Ulleval (OUH-U) and a decision tree, was done. The societal and the healthcare perspectives were focused and a lifetime perspective employed. The comparators were the traditional FH approach used as standard of care at OUH-U in 2013 and the intervention (testing all patients with BC) performed in 2014 and 2015 at the same hospital. During the latter period, 535 patients with BC were offered BRCA testing with sequencing and MLPA. National 2014 data on mortality rates and costs were implemented, a 3% discount rate used and the costing year was 2015. The incremental cost-effectiveness ratio was calculated in euros (€) per life-year gained (LYG).

Results The net healthcare cost (healthcare perspective) was €40 503/LYG. Including all resource use (societal perspective), the cost was €5669/LYG. The univariate sensitivity analysis documented the unit cost of the BRCA test and the number of LYGs the prominent parameters affecting the result. Diagnostic BRCA testing of all patients with BC was superior to the FH approach and cost-effective within the frequently used thresholds (healthcare perspective) in Norway (€60 000–€80 000/LYG).

INTRODUCTION
Breast cancer (BC) is the most common cancer among women in most Western countries and may cluster in families.1–4 It has been estimated that 1/500 to 1/300 of US women have a deleterious mutation in BRCA1 or BRCA2.5 Around 10% of BC cases exhibit a higher familial incidence and functional mutations in BRCA1 or BRCA2. The mutations are responsible for the development of malignant tumours in approximately half of the cases.1 In Norway, genetic testing has been offered increasingly to patients with BC and/or ovarian cancer (OC) fulfilling traditional guidelines. This testing is here called the family history (FH) approach.2–6

What is already known about this subject?
► Around 10% of breast cancer (BC) cases exhibit a higher familial incidence and functional mutations in BRCA1 or BRCA2.
► Despite the use of the family history approach, several BRCA mutation-carrying patients with BC are not detected.
► An alternative is the testing of all patients with BC for BRCA mutation with sequencing and Multiplex Ligation Probe Amplification.

What does this study add?
► Employing data from the Oslo University Hospital into the model, we calculated the testing of all patients with BC being cost-effective (net healthcare cost of €40 503 per life-year gained), when compared with the family history approach.

How might this impact on clinical practice?
► Time has come for general diagnostic BRCA testing of all patients with BC.

Key questions

1Department of Surgery, Finnmark Hospital, Hammerfest, Norway
2Department of Medical Genetics, Oslo University Hospital, Oslo, Norway
3Department of Medical Genetics, Oslo University Hospital and University of Oslo, Oslo, Norway
4Section for Breast and Endocrine Surgery, Department of Cancer, Oslo University Hospital, Oslo, Norway

Correspondence to Professor Jan Norum; jan.norum@uit.no

To cite: Norum J, Grindedal EM, Heramb C, et al. ESMO Open 2018;3:e000328. doi:10.1136/esmoopen-2018-000328

Accepted 21 February 2018
Revised 20 February 2018
Received 19 January 2018

Original research

BMJ

ESMO Open. first published as 10.1136/esmoopen-2018-000328 on 13 April 2018. Downloaded from http://esmoopen.bmj.com/ on January 9, 2021 by guest. Protected by copyright.
health economic concerns. Today, new gene sequencing technologies and lowered cost of genetic testing may make it more feasible to test large populations. Several alternatives may detect the women at risk of BC and/or OC. Therefore, it is time for reviewing whether testing should be offered according to less strict criteria or not.

MATERIALS AND METHODS
In this non-randomised model-based study, we compared the results from a time of the traditional FH approach with the period of testing all patients with BC (both men and women) for BRCA mutations.

Treatment and comparator
We used a model-based cost-effectiveness analysis and employed both a healthcare and a societal perspective. The decision tree model (figure 1) compared an intervention (alternative 1) with the traditional FH approach (alternative 2). The perspective was lifetime. Data were taken from the daily practice at Oslo University Hospital, Ullevål (OUH-U) during two periods, 2013 and 2014/2015, respectively (figure 1).

Intervention arm (alternative 1)
Between 1 January 2014 and 31 August 2015, all patients diagnosed with BC, where the treating physician concluded that genetic testing could influence treatment decisions, were offered BRCA testing with sequencing...
and Multiplex Ligation Probe Amplification (MLPA) (first intervention). Up to 625 patients were treated for primary BC. Ninety-five patients (11.5%) refused the offer of testing due to unknown reasons. Seventy-two patients were not offered testing and 18 patients had undergone prior BRCA testing. Consequently, 535 patients were included into the model and 440 of them were tested in the intervention arm. We detected 13 (3%) BRCA mutation carriers (BRCA1: 10 patients, BRCA2: 3 patients). Family members of the detected mutation carriers were offered genetic counselling and testing (second intervention).

Traditional approach (alternative 2)
In 2013, all women were selected for testing and screening for BRCA mutation based on the national guidelines, here for simplicity named the ‘traditional-approach’. The national indicators of risk were:

- women with BC <50 years;
- women with BC and two close relatives (first-degree relative or second-degree relative through a man with BC) mean age <55 years or three close relatives with BC, at any age;
- men with BC;
- women with bilateral BC <60 years;
- women with BC and close relative with OC;
- woman with BC and close relative with prostate cancer <55 years;
- woman with OC, independent of age.

There were 388 patients treated for primary BC in 2013. Twenty-four were tested with complete sequencing of the BRCA genes and one mutation carrier detected. In total, 140 patients were tested for BRCA1/2 mutations (with sequencing and MLPA) and 116 using a more limited genetic test designed to detect Norwegian founder mutations. Two patients were mutation positive, one identified by sequencing, the other by the founder mutation test.

In the model-based economic analysis, the same number of patients had to be implemented into the two alternatives to make the costs and gains comparable. Due to a lower volume of patients in the output data from OUH-U in 2013 a balancing was done (FH=([116+24]*535/388]=193 patients, no FH=(535–193)=342 patients, detected mutation carriers=(1+1)*535/388=3 patients). As the total group contained 16 mutation carriers (figure 1, P1 and P11), consequently the undetected number in alternative 2 was 13 (figure 1, P14). When identifying a BRCA mutation carrier, family members were invited to testing. Figure 1 shows the decision tree and its pathway probabilities.

Effectiveness
We calculated the same outcome for healthy women with BRCA mutation detected through a systematic testing for BRCA mutations in both alternatives. Possible life-years gained (LYG) by prophylactic interventions among the patients with BC was not included as we had no solid data clarifying this variable.

Costs (C)
All costs were calculated in Norwegian unit costs (Norwegian krone) and converted into euros (€) at the rate of €1=9.2005 Kr as of 16 October 2015 (www.norges-bank.no). We calculated treatment costs according to the Norwegian diagnosis-related group (DRG) system and the 100% DRG value was used.17 The costing year was 2015.

Healthcare costs (C1)
The cost (DRG 930A) of a visit to a breast surgeon or a gynaecologist, the DRGs of breast conserving surgery (BCS) (DRG 260O) and mastectomy (DRG 258) (calculated according to the ‘no hospitalization tariff’) is shown in table 1. Thirty-five per cent of those undergoing mastectomy at the OUH-U did also undergo later reconstructions of their breasts. The cost of testing each patient with BC for mutations (sequencing and running MLPA) was calculated €5163 employing the refunding figure of the Norwegian Health Economics Administration (HELFO).18 The cost of the limited BRCA test was €948. The cost of testing family members for the known BRCA mutation, the cost of genetic counselling and the cost of PBM and PBSO are given in table 1. In case of bilateral surgery, the cost of surgery was raised by 25%.

During study period postoperative radiotherapy (RT) was recommended to the majority of women undergoing BCs and some of those undergoing mastectomy. We calculated the cost of RT using the DRG 851K (€216/fraction) and the 2014 data from the Northern Norway Regional Health Authority trust. Sixty-five per cent received two-field irradiation of the breast and 40 Gy in 15 fractions and 16% of them received another eight fractions as boost therapy. The remaining 35% got 50 Gy in 25 fractions. Furthermore, the DRG 850A (€275), planning of RT, was added. The mean savings per avoided patient undergoing RT was consequently calculated €4457. We calculated 75% of patients undergoing RT. Furthermore, we calculated half of them undergoing 5-year adjuvant hormonal therapy (AHT) and 50% zoledronic acid 4 mg intravenous twice a year for 5 years. This is according to the national recommendations.6 The cost of adjuvant chemotherapy (ACT) was given by DRG 856K (€1000). We calculated six cycles of chemotherapy6 and three-fourths of patients with BC were concluded candidates.2

Family members underwent testing for the specific BRCA mutation detected. The cost of such a test was €67. Based on the OUH-U data, the mean number of family members tested per mutation carrier was four persons. Furthermore, the detected mutation carriers underwent several procedures causing healthcare costs (table 1). Hormonal replacement therapy for those undergoing PBSO consisted of sequential treatment with estradiol and norethisterone acetate (cost Trisekvens) (€87.4×9 years – ages 46–55 years = €787).19
Table 1  Costs (undiscounted and discounted (3%)) and savings per patient with BC screened by the BRCA mutation approach (alternative 1) or the traditional FH approach (alternative 2)

| Costs (C)                                      | Unit cost | Alternative 1 Screening (€) | Alternative 1 Screening (€) 3 % dr | Alternative 2 FH approach (€) | Alternative 2 FH approach (€) 3% dr |
|------------------------------------------------|-----------|-----------------------------|-----------------------------------|-----------------------------|-----------------------------------|
| **Patients with BC**                           |           |                             |                                   |                             |                                   |
| Healthcare costs (C1)                          |           |                             |                                   |                             |                                   |
| Visit to breast surgeon                       | 311       | 311                         | 311                               | 311                         | 311                               |
| BCS (DRG 260O) (70%)                          | 1758      | 1231                        | 1231                              | 1231                        | 1231                              |
| Visit to a geneticist                         | 70        | 1                           | 1                                 | 3                           | 3                                 |
| Mastectomy (DRG 258) (30%)                    | 2312      | 694                         | 694                               | 694                         | 694                               |
| Radiotherapy (75%)                            | 4457      | 3343                        | 3343                              | 3343                        | 3343                              |
| Adjuvant hormonal therapy (50%)               | 1819      | 910                         | 858                               | 910                         | 858                               |
| Adjuvant chemotherapy (75%)                   | 6000      | 4500                        | 4500                              | 4500                        | 4500                              |
| Zoledronic acid (50%)                         | 138       | 690                         | 617                               | 690                         | 617                               |
| Reconstruction (12%)                          | 8089      | 971                         | 971                               | 971                         | 971                               |
| Screening for mutation                        | 5163      | 4246                        | 4246                              | 319                         | 319                               |
| BRCA INDEL screening                          | 948       | 0                           | 0                                 | 283                         | 283                               |
| PBM (DRG 502)                                 | 15694     | 381                         | 381                               | 88                          | 88                                |
| PBSO (DRG 359O)                               | 2315      | 56                          | 56                                | 13                          | 13                                |
| Hormonal replacement therapy                  | 787       | 19                          | 17                                | 4                           | 4                                 |
| Sum C1                                        | 17353     | 17226                       | 13360                             | 13235                       |                                   |
| **Patient-related costs (C2)**                |           |                             |                                   |                             |                                   |
| Visit surgeon                                 | 35        | 35                          | 35                                | 35                          | 35                                |
| Visit geneticist                              | 35        | 1                           | 1                                 | 1                           | 1                                 |
| Visit oncologist/radiotherapist               | 35        | 261                         | 261                               | 261                         | 261                               |
| Travelling                                    | 29        | 536                         | 536                               | 537                         | 537                               |
| Sum C2                                        | 833       | 833                         | 835                               | 835                         | 835                               |
| **Cost in other sectors (C3)**                |           |                             |                                   |                             |                                   |
| Production loss                               | 19123     | 19123                       | 19123                             | 19123                       | 19123                             |
| Sum C3                                        | 19123     | 19123                       | 19123                             | 19123                       | 19123                             |
| **Family members**                            |           |                             |                                   |                             |                                   |
| Healthcare costs (C1²)                        |           |                             |                                   |                             |                                   |
| Genetic counselling                           | 70        | 7                           | 7                                 | 2                           | 2                                 |
| Genetic testing, mutation known               | 67        | 6                           | 6                                 | 1                           | 1                                 |
| Visit to surgeon (DRG 930O)                   | 135       | 7                           | 7                                 | 2                           | 2                                 |
| PBM (DRG 502)                                 | 15694     | 763                         | 763                               | 176                         | 176                               |
| Visit to gynaecologist (DRG 913O)             | 140       | 7                           | 7                                 | 2                           | 2                                 |
| PBSO DRG 359O                                 | 2315      | 113                         | 100                               | 26                          | 23                                |
| Hormonal replacement therapy                  | 787       | 38                          | 34                                | 9                           | 7                                 |
| Sum C1²                                       | 941       | 920                         | 218                               | 213                         |                                   |
| **Patient-related costs (C2²)**               |           |                             |                                   |                             |                                   |
| Visit to surgeon (patient share)              | 35        | 2                           | 2                                 | 1                           | 1                                 |
| Visit to geneticist (patient share)           | 35        | 2                           | 2                                 | 1                           | 1                                 |
| Travelling                                    | 59        | 3                           | 3                                 | 1                           | 1                                 |
| Sum C2²                                       | 7         | 7                           | 7                                 | 3                           | 3                                 |
| **Cost in other sectors (C3²)**               |           |                             |                                   |                             |                                   |
| Production loss                               | 3187      | 77                          | 77                                | 30                          | 30                                |

Continued
Patient/family-related costs (C2)

Patients and family members have to cover a minor amount of €35 when visiting the gynaecologist, breast surgeon and geneticist, respectively.20 In Norway, the Regional Health Authorities (NRH) (there are four RHAs in Norway: northern, central, western and southeastern) covers the costs of transportation.21 Internationally, studies include this item as patient/family-related costs. To make our study comparable, we included costs of travelling here. We used the one-way patient contribution cost on patient’s share and the qualified guess by clinicians at OUH-U (€15).21

Costs in other sectors (C3)

Indirect costs in this setting were production losses. The mean income of Norwegians in 2014 was €57 127/year (www.ssb.no). We added employers’ costs due to pension and social costs (30%) and increased the costs by 3% from 2014 to 2015 based on the price index of Statistics Norway (€76 493). According to Statistics Norway, 76.9% of women, aged 25–74 years, were in the workforce and 64% of them were full-time workers.22 Based on these figures, we calculated the direct cost into a careful estimate of half of the mutation carriers being full-time workers. Based on the clinicians’ experience, the period out of workforce due to surgery, chemotherapy and RT was set to 6 months.23

Savings (S)

The main economic savings was due to avoided BC and OC among index patients’ healthy family members.

Healthcare savings (S1)

Based on the OUH-U data, two healthy female BRCA mutation carriers were detected per family (of identified patients with BC with BRCA mutation (2.1%)). The following risk reductions were used.2 We calculated that the absolute lifetime risk of BC (BRCA mutation carriers) was reduced from 58% to 8% (the level of the Norwegian population) by the PBM+PBSO intervention.2 Similarly,
the reduction in the FH approach was calculated 23% (3/13) of the intervention arm figure. The savings, when avoiding BC, was implemented in the model. Most BRCA1-associated cancers were supposed to be infiltrative, high grade and oestrogen receptor negative.\textsuperscript{24–26} We therefore calculated that 75% underwent ACT. One-fourth was concluded candidates for 5 years of AHT (either tamoxifen or anastrozole). Furthermore, based on national recommendations,\textsuperscript{6} we calculated a 50-50 share between the two drugs and used the HELFO refund (tamoxifen €378 plus anastrozole €1441).\textsuperscript{1,2,19}

The healthcare savings related to avoided OC due to PBM and PBSO was calculated as the value of reducing the absolute lifetime (at age 70) risk of OC by 52.2%, from 58% to 5.8%.\textsuperscript{2}

Patient/family-related savings (S2)

These savings were due to avoided travelling for diagnosis, surgery, RT and chemotherapy. Similarly, patients saved copayment for these examinations and treatments.

Savings in other sectors (S3)

These were production gains. We considered half of the female family members being in the workforce.\textsuperscript{2} Furthermore, we calculated women reported ill and out of workforce for 6 months during ACT. Based on family members’ median age (46 years) and clinicians’ experience, we chose a conservative estimate and calculated that female workers avoiding BC and/or OC stayed in the workforce for another 5 years.

Life-years gained

LYGs are mainly due to avoided cancer deaths. In the OUH-U data, healthy female family members of BRCA mutation carriers were aged 20–83 years (median 46 years, mean 46 years). In such a setting (detected at an ‘older age’), a more conservative approach had to be taken. The risk of BC and OC among BRCA mutation carriers at the age of 70 years in Norway was 58% in both cancers and at the 5-year survival was 88% and 44.5%, respectively.\textsuperscript{2} The general lifetime risk of BC and OC in the Norwegian population was 8% and 1.2%. Due to late intervention (mean 46 years) we calculated the achievable level in OC to 5.8%.\textsuperscript{2} Furthermore, we employed the life expectancy of Norwegian women aged 46 years in 2014 as the expected survival curve of mutation-carrying female family members undergoing PSCO and PBM. The time perspective was from the age of 46 to 90 years. Employing these figures, 5.9 undiscounted LYGs (3.0 LYGs, 3% discount rate (dr)) per women detected and undergoing PBSO and PBM was concluded.

Statistics and ethics

In this study, only descriptive statistics was employed. The calculation of costs, savings and life-years gained or lost was calculated employing the Microsoft Excel for Mac 2011.

In the OUH-U study, genetic testing was performed diagnostically, all activities were part of daily routines and all clinical information was registered in the electronic patient record (EPR) system at OUH-U. The study was carried out as a model-based quality of care analysis and consequently no approval from the Regional Committees for Medical and Health Research Ethics (REK) or from the Norwegian Social Science Data Services (NSD) was necessary.

**RESULTS**

In the intervention arm the number of undiscounted LYGs was 0.29 (5.9 LY*13*2/535) per patient with BC offered BRCA mutation testing. The corresponding figure of the traditional FH approach was 0.07 LYGs (5.9 LY*3*2/535). Discounting the LYGs (3%), the LYG was 0.14 LYGs (3.0 LY*13*2/535) and 0.03 LYGs (3.0 LY*3*2/535), respectively. Consequently, the net LYGs was 0.11 LYG (0.22 undiscounted LYG) per patient with BC enrolled.

The net healthcare cost (healthcare perspective) was increased by €4508 ( undiscounted, €4510) and the total costs ( savings exclusive) by €1184 ( undiscounted, €631) per patient with BC enrolled. The total discounted cost per LYG employing the healthcare perspective was €40503 ( undiscounted, €20 472). Focusing on the societal perspective, the corresponding figure was €5669 ( undiscounted, €5374). Details are shown in table 2.

In Norway, the healthcare perspective is used when decisions with regard to the implementation of any new therapy/ intervention in the healthcare service are made. Employing the frequently employed cut-off between €60 000 and €80 000/LY or quality-adjusted life year (QALY), this intervention was clearly cost-effective in Norway.

To clarify the solidity of our findings, we performed a univariate sensitivity analysis. We employed the healthcare perspective figure and the 3% dr as the baseline for comparison (€40 503). This perspective is employed when national decisions in Norway are taken.\textsuperscript{25} Due to uncertainties concerning our estimates, we varied the factors by ±50%. Results are given in figure 2. The unit cost of the test (total sequencing) and the number of patients testing positive for BRCA was calculated €11 113 and €12 445, respectively.

| Table 2 Cost-effectiveness (C/E) ratios depending on key costing assumptions |
|---------------------------------------------------------------|
| **Alternative 1**          | **Alternative 2**          | **C/E**          |
|---------------------------------------------------------------|
| **Screening** | **FH approach** | **Difference** |
|---------------------------------------------------------------|
| 0% dr | 3% dr | 0% dr | 3% dr | 0% dr | 3% dr |
| Health care perspective, net healthcare costs (C1-S1) | 17 964 | 17 837 | 13 454 | 13 329 | 20 472 | 40 503 |
| Societal perspective, all resource use (C1+C2+C3-S1-S2-S3) | 32 150 | 31 710 | 30 966 | 31 079 | 53 743 | 56 699 |

Effectiveness was calculated life-years gained (LYG), 0% and 3% discount rates (dr) were used. E=0.1113LYG/included woman, 3% dr. E=0.2203LYG/included woman, 0% dr. For the explanation of C1, C2, C3, S1, S2, S3, see table 1.

FH, family history.
LYGs per prevented cancer were the prominent factors affecting the result. None of the variations (maximum €60,755) in the sensitivity test made the cost-effectiveness figure passing reasonable cut-off level of cost per LYG.

**DISCUSSION**

We have documented that an intervention where all patients with BC are offered BRCA testing with sequencing and MLPA is costly, but cost-effective. The greatest benefit was achieved by the broad approach testing most patients with BC and no selection through the traditional FH approach. The sensitivity analysis revealed the major factors, influencing on the result, were the unit cost of the test itself and the LYGs per prevented cancer.

Looking at the test itself, it is costly (unit cost €5163). Employed as an offer to all Norwegian patients with BC and assuming our participation rate (82%), the national annual cost (budget impact) will be €14.1 million.28 However, during the last decade, the technology has improved and the cost of performing the test itself has dropped.29 We therefore estimated the hospital cost of running the test. This cost was one-third of the amount refunded by the HELFO. Based on this information, we believe the tariff will be reduced in the near future.

It is difficult to estimate the total LYGs due to the intervention.30 In our study, we did not focus on possible gains achieved by the patients with BC themselves. Following the diagnosis of BC, they underwent PBM and PBSO. Whereas this may obviously have saved life years due to prevented future new BC and/or OC, we experienced significant difficulties in defining this gain. In the study of Manchanda et al,29 they concluded a population screening for BRCA mutations in Ashkenazi Jewish women saving 0.090 more life years and 0.101 more QALYs resulting in 33days’ gain in life expectancy. Their baseline discounted (3.5% dr) incremental cost-effectiveness ratio was −£2079 per QALY. Translating these figures into a Norwegian BRCA mutation carrier setting (5-year survival of OC 44.5%, 5-year survival of BC 88%, lifetime risk of OC among BRCA mutation carriers increased by 52.2%, life expectancy of Norwegian women 83.5 years), the possible LYG by avoided OC among mutation-carrying patients with BC may be indicated 0.11 undiscounted LYG (0.05 discounted LYG) per woman screened [(83.5−(54.9+5) LY)*(1−0.445)*(0.525*(13−3)*0.88/535)]. Whereas there are several uncertainties related to this estimate, it is obvious that there are some improvements.

We believe the main benefit being connected to the prevented cancers among family members. Due to a delayed intervention in several family members, a maximum effect was not achieved. This is underlined by the fact that we now are aware of three relatives who already had contracted a cancer (BC (ages 52 and 57 years) and OC (age 46 years))
before the intervention was initiated. We therefore believe our estimate was reasonable.

The effect of the comparator (traditional FH approach) was low. To clarify the potential of this approach, we retrospectively considered all the additional cases detected by the screening intervention. Following the Norwegian guidelines, in an optimal setting 12 out of the 13 (92%) detected mutation-carrying patients with BC could have been revealed. The LYG per patient with BC receiving the screening test would then be only 0.01 LYG and the cost per LYG would raise far above the suggested cut-off limit. However, running this estimate correctly, the cost of such a careful and optimal approach should have been identified and added. However, investigators have documented that the FH approach detects only about half of the mutation carriers. Consequently, such a suggested successful detection is not achievable in daily life in the clinics.

The cost of travelling was a minor factor. Whereas we have focused on the most populated areas of Norway, this cost will obviously increase when employing a national perspective. However, when looking at the factor’s minimal influence on the total result, we still argue that it will be insignificant when introducing the screening intervention on a national level.

This study was performed at one single institution. Despite this is the largest institution in Norway, it could be questioned whether our findings are fully representative for the general Norwegian, Scandinavian or European population with respect to prevalence of BRCA mutations. According to Statistics Norway (www.ssb.no), the south-eastern region of Norway does have a higher percentage of immigration compared with the other Norwegian health regions. Whereas immigrants/people with immigrant background constituted 16.3% of the Norwegian population, they constituted one-third of the population of the Norwegian capital’s population (Oslo). More than half of the immigrants/born by immigrants were from other European countries. The top countries in terms of immigration were Poland, Lithuania, Sweden, Somalia, Germany, Iraq and Denmark (www.ssb.no). Consequently, we believe the Norwegian population is becoming more and more similar to the population of the other Scandinavian and European countries and the increasing number of immigrants will be in favour of the systematic testing, as the FH approach will be more difficult to handle among immigrants.

Norwegian patients may claim compensation for malpractice experienced in the specialised healthcare. The Norwegian System of Patient Injury Compensation handles the requests. Recently, we have seen the very first examples of complaints of malpractice due to limitations in examining FH or act (refer to BRCA testing and consequently prophylactic intervention) on known information. In such a situation, the genetic testing of all patients with BC looks beneficial, as patient injury compensations may be avoided. There are advocates for the use of QALYs in economic analysis. In the setting of inherited risk of BC and/or OC and suggested prophylactic interventions, there is psychiatric distress that may influence the quality of life. We have no quality of life data for the general population in Norway. Consequently, proper Norwegian quality of life data could not be implemented into the model. However, there are available data for the general population from our neighbouring country, Sweden. Employing these data and focusing on the quality of life of women in the general population aged 50–90 years, the undiscounted QALYs gained may be indicated 0.17 per women screened (0.086, 3% dr) and the cost/QALY from a healthcare perspective would be €52 419 and still below accepted cut-off levels. However, in such an assumption we have calculated patients undergoing PBM/PBSO having a similar quality of life as the general population. This is in accordance with a Dutch study that did not reveal any measurable impact on generic quality of life in high-risk women undergoing PBSO. Whereas this study may insufficiently describe patient preferences during the various health states potentially experienced in our model, it at least indicated a minor difference in quality of life.

We employed in 140 patients in the FH approach group a limited genetic test designed to detect Norwegian founder mutations. This method has a lower sensitivity than the more costly sequencing and MLPA. To assess the sensitivity of this test, we employed the limited genetic test on the 13 BRCA mutation carriers detected by sequencing and MLPA (alternative 1). A total of 8 out of 13 cases were detected, indicating a detection rate of 62%. This test was specifically designed based on knowledge on frequently observed mutations in Norway, and therefore will not be relevant in other populations. Other countries have however developed similar founder mutation tests based on the prevalence and spectrum of such mutations within their populations. Studies have shown that a significant number of mutation carriers will be missed when testing only for known founder mutations in a population. We therefore hypothesise that our results may be generalised to other populations even though the exact frequency and spectrum of BRCA mutations may vary between populations.

In the future, we will experience a ‘dam fishing effect’. As more and more of the BRCA mutation-carrying families detectable by the FH approach are revealed, the remaining ones have to be detected by other means. In this setting, a population-based screening has been recommended by several investigators. We suggest that BRCA testing should be offered to all patients with BC. The share of participants is crucial for the success of a screening tool. We therefore recommend efforts spent on convincing patients with BC to participate in testing.

In Norway, our new strategy (testing all patients with BC) was cost-effective based on the frequently used cut-off limits. In countries with lower cut-offs, the figure could be improved by just screening patients with BC below a certain age (<60 years).
CONCLUSIONS
In this study, we have shown that an intervention where all patients with BC were offered BRCA testing with sequencing and MLPA was cost-effective. The major factor influencing on the result was the unit cost of the test itself. We believe the time has come for general diagnostic BRCA testing of all patients with BC. Today, too many life years are lost employing the FH approach. We believe this strategy is better than a population-based screening.

Acknowledgements
We appreciate the comments of several colleagues during this work and the service offered by the library at the UIT–The Arctic University of North Norway in Tromsø.

Contributors
All authors have participated in the development of the project and the making of the final model-based analyses. They have also taken part in the writing process and they have all approved the final version.

Funding
The publication charges for this article have been funded by a grant from the publication fund of UiT–The Arctic University of Norway.

Competing interests
None declared.

Patient consent
Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval
No approval from the Regional Committees for Medical and Health Research Ethics (REK) or from the Norwegian Social Science Data Services (NSD) was necessary.

Provenance and peer review
Not commissioned; externally peer reviewed.

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© European Society for Medical Oncology (unless otherwise stated in the text of the article). All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES
1. Singer CF, Tea MK, Pristauz G, et al. Clinical practice guidelines for the prevention and early detection of breast and ovarian cancer in women from HBOC (hereditary breast and ovarian cancer) families. Wien Klin Wochenschr 2015;127:981–6.
2. Norum J, Hagen AI, Maehle L, et al. Prophylactic bilateral salpingo-oophorectomy (PBSO) with or without prophylactic bilateral mastectomy (PBM) or no intervention in BRCA1 mutation carriers: a cost-effectiveness analysis. Eur J Cancer 2008;44:963–71.
3. Hall JM, Lee MK, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. Science 1990;250:1684–9.
4. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:67–71.
5. King MC, Levy-Lahad E, Lahad A. Population-based screening for BRCA1 and BRCA2. 2014 Lasker Award. JAMA 2014;312:1091–2.
6. Naumé B, Aas T, Lundgren S, et al. National guidelines for the diagnosis, treatment and follow up of patients with breast cancer, IS-2240. Oslo: Norwegian Directorate of Health, 2016.
7. Levy-Lahad E, Gabai-Kapara E, Kaufman B, et al. Identification of BRCA1/BRCA2 carriers by screening in the healthy population and its implications. In: American Society of Clinical Oncology, Annual meeting. J Clin Oncol 2011;29:A1513.
8. Hartge P, Struwing JP, Wacholder S, et al. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. Am J Hum Genet 1998;64:963–70.
9. Metcalfe KA, Poll A, Royer R, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. J Clin Oncol 2010;28:387–91.
10. King MC, Marks JH, Mandell JB. New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643–6.
11. Hopper JL, Southey MC, Dite GS, et al. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2. Australian Breast Cancer Family Study. Cancer Epidemiol Biomarkers Prev 1999;8:741–7.
12. Petö J, Collins N, Barfoot R, et al. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 1999;91:943–8.
13. Hirsh-Yechezkel G, Chetrit A, Lubin F, et al. Population attributes affecting the prevalence of BRCA1 mutation carriers in epithelial ovarian cancer cases in Israel. Gynecol Oncol 2003;89:494–8.
14. de Sanjosé S, Leon-Mur L, Bércia V, et al. Prevalence of BRCA1 and BRCA2 germline mutations in young breast cancer patients: a population-based study. Int J Cancer 2003;106:588–93.
15. Shendure J, Ji H. Next-generation DNA sequencing. Nat Biotechnol 2008;26:1135–45.
16. Levine B, Steinberg K. Proposed shift in screening for breast cancer. JAMA 2015;313:525.
17. Norwegian Directorate of Health. Activity based funding 2015, IS-2230. Oslo: Norwegian Directorate of Health, 2014.
18. Lovdata. Regulations for remuneration of expenses in an out-patient setting. Oslo: Lovdata, 2016.
19. Felleskatalogen, Felleskatalogen. Oslo: Felleskatalogen AS, 2015.
20. Norwegian Directorate of Health. Patient copayment in hospitals and out-patient clinics. Oslo: Norwegian Directorate of Health, 2015.
21. Patient travel. Patient travel and reimbursement of necessary expenses. Skien: Patient travel, 2015.
22. Statistics Norway. Studies of labor, third quarter 2015. Oslo: Statistics Norway, 2015.
23. Norum J, Holfman M. Adjuvant fluorouracil, epirubicin and cyclophosphamide in early breast cancer: is it cost-effective? Acta Oncol 2005;44:735–41.
24. Moller P, Evans DG, Reis MM, et al. Surveillance for familial breast cancer: Differences in outcome according to BRCA mutation status. Int J Cancer 2007;121:1017–20.
25. Cancer Registry of Norway. Cancer in Norway 2013. Institute of population based cancer research. Oslo: Cancer Registry of Norway, 2015.
26. Cancer Registry of Norway. Cancer in Norway 2014. Institute of population based cancer research. Oslo: Cancer Registry of Norway, 2015.
27. The Norwegian Medicines Agency. Guidelines for the documentation for fast track health technology assessment (HTA) of drugs. Oslo: The Norwegian Medicines Agency, 2017.
28. Evans DG, Lalooi F, Howell S, et al. Low prevalence of HER2 positivity amongst BRCA1 and BRCA2 mutation carriers and in primary BRCA screens. Breast Cancer Res Treat 2016;155:597–601.
29. Manchanda R, Legood R, Burnell M, et al. Cost-effectiveness of population screening for BRCA2 mutations in Ashkenazi Jewish women compared with family history-based testing. J Natl Cancer Inst 2015;107:380.
30. Kadouri L, Hubert A, Rotenberg Y, et al. Cancer risks in carriers of the BRCA1/2 Ashkenazi founder mutations. J Med Genet 2007;44:467–71.
31. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253–8.
32. Madalinski JB, Hollenstein J, Bieker E, et al. Quality-of-life effects of prophylactic salpingo-oophorectomy versus gynecologic screening among women at increased risk of hereditary ovarian cancer. J Clin Oncol 2005;23:6890–8.
33. Burström K, Rehnberg C. Health related quality of life in Stockholm county 2002-2006. Report 2006:1. Unit of Social Medicine and Health Economy, Stockholm: Stockholm County Council, 2006.
34. Rosenthal E, Rogers K, Arnell C, et al. Erratum to: Incidence of BRCA1 and BRCA2 non-founder mutations in patients of Ashkenazi Jewish ancestry. Breast Cancer Res Treat 2015;151:233.
35. Kluska A, Balabas A, Paziewska A, et al. New recurrent BRCA1/2 mutations in Polish patients with familial breast/ovarian cancer detected by next generation sequencing. BMC Med Genomics 2015;8:19.
36. Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci U S A 2014;111:4205–10.
37. Hembregt-Vetić H, Björvall C, Flanèe BE, et al. BRCA1/2 testing in newly diagnosed breast and ovarian cancer patients without prior genetic counselling: the DNA-BONus study. Eur J Hum Genet 2016;24:881–8.