### Appendix 1

Table A1 Complete list of model input parameter values

| Parameter                                                                 | Type          | Category              | N     | Mean       | Standard error | Distribution | Distribution parameters | Source |
|---------------------------------------------------------------------------|---------------|-----------------------|-------|------------|----------------|--------------|-------------------------|--------|
| **Recurrence breast cancer post breast conserving therapy**              | Probability   | Age < 40              | 189   | 0.0437     | 0.0150         | Beta         | α = 8.46, β = 180.54    | [39]   |
|                                                                           |               | Age 40-49             | 576   | 0.0230     | 0.0063         | Beta         | α = 13.43, β = 562.57   |        |
|                                                                           |               | Age 50-59             | 1093  | 0.0160     | 0.0038         | Beta         | α = 17.76, β = 1075.24  |        |
|                                                                           |               | Age 60-69             | 1138  | 0.0151     | 0.0036         | Beta         | α = 17.43, β = 1120.57  |        |
|                                                                           |               | Age ≥ 70              | 679   | 0.00916    | 0.0037         | Beta         | α = 6.25, β = 672.75    |        |
| **Background risk of breast cancer in Norwegian female population 2015**  | Probability   | Age 20-24             | Calculated from rates per 100 000 | 0.0000 | 0.0001 | Assumed fixed | [14]   |
|                                                                           |               | Age 25-29             | 0.0002 |            |                |              |                         |        |
|                                                                           |               | Age 30-34             | 0.0000 |            |                |              |                         |        |
|                                                                           |               | Age 35-39             | 0.0014 |            |                |              |                         |        |
|                                                                           |               | Age 40-44             | 0.0011 |            |                |              |                         |        |
|                                                                           |               | Age 45-49             | 0.0017 |            |                |              |                         |        |
|                                                                           |               | Age 50-54             | 0.0021 |            |                |              |                         |        |
|                                                                           |               | Age 55-59             | 0.0025 |            |                |              |                         |        |
|                                                                           |               | Age 60-64             | 0.0032 |            |                |              |                         |        |
|                                                                           |               | Age 65-69             | 0.0031 |            |                |              |                         |        |
|                                                                           |               | Age 70-74             | 0.0026 |            |                |              |                         |        |
|                                                                           |               | Age 75-79             | 0.0029 |            |                |              |                         |        |
|                                                                           |               | Age 80-84             | 0.0029 |            |                |              |                         |        |
|                                                                           |               | Age ≥ 85              | 0.0029 |            |                |              |                         |        |
| **Background risk of ovarian cancer in Norwegian female population 2015** | Probability   | Age 40-44             | Calculated from rates per 100 000 | 0.0001 | 0.0001 | Assumed fixed | [14]   |
|                                                                           |               | Age 45-49             | 0.0003 |            |                |              |                         |        |
|                                                                           |               | Age 50-54             | 0.0004 |            |                |              |                         |        |
|                                                                           |               | Age 55-59             | 0.0005 |            |                |              |                         |        |
|                                                                           |               | Age 60-64             | 0.0006 |            |                |              |                         |        |
|                                                                           |               | Age 65-69             | 0.0006 |            |                |              |                         |        |
|                                                                           |               | Age 70-74             | 0.0006 |            |                |              |                         |        |
|                                                                           |               | Age 75-79             | 0.0006 |            |                |              |                         |        |
|                                                                           |               | Age 80-84             | 0.0006 |            |                |              |                         |        |
|                                                                           |               | Age ≥ 85              | 0.0006 |            |                |              |                         |        |
| **Uptake of genetic testing among Norwegian relatives of carriers**       | Probability   | Age 18-29             | 0.3000 | 0.0837     | Beta           | α = 9, β = 21 | [40]   |
|                                                                           |               | Age 30-49             | 0.8235 | 0.0654     | Beta           | α = 28, β = 6  |        |
|                                                                           |               | Age 50+               | 0.8090 | 0.0894     | Beta           | α = 16, β = 4  |        |
| **Uptake of mastectomy for identified carriers**                         | Probability   | Index patient          | 0.3960 | 0.0263     | Beta           | α = 137, β = 209 | [41]  |
|                                                                           |               | FDR 25-35             | 0.1214 | 0.0168     | Beta           | α = 46, β = 333 |        |
|                                                                           |               | FDR 35-60             | 0.1186 | 0.0107     | Beta           | α = 108, β = 803 |        |
| **Uptake of bilateral salpingo oophorectomy for identified carriers**   | Probability   | Index patient          | 0.3689 | 0.0163     | Beta           | α = 321, β = 554 | [42]  |
|                                                                           |               | FDR 25-35             | 0.1029 | 0.0156     | Beta           | α = 39, β = 340 |        |
|                                                                           |               | FDR 35-60             | 0.2764 | 0.0270     | Beta           | α = 76, β = 199 |        |
|                                                                           |               | FD 41-60              | 0.3469 | 0.0189     | Beta           | α = 221, β = 416 |        |
| **Relative risk of breast cancer post prophylactic bilateral mastectomy**| Relative risk | Relative risk         | 0.0900 | 0.0038     | Log-normal     | ln(RR): -2.4079, se(ln(RR)): 0.3406 | [17]  |

95% CI: [0.010, 0.038]
| Topic                                                                 | Parameter                                      | Value                          | CI                         | Log-normal ln(RR): | se[ln(RR)]: |
|----------------------------------------------------------------------|-----------------------------------------------|--------------------------------|---------------------------|---------------------|------------|
| Relative risk of ovarian cancer post prophylactic bilateral salpingo-oophorectomy (BSO) | Relative risk                                | 0.1500                         | [0.030, 0.410]            | -1.8971             | 0.6671     |
| Relative risk of breast cancer post both prophylactic surgeries     | Relative risk                                | 0.0500                         | [0.010, 0.220]            | -2.9957             | 0.7885     |
| Relative risk of breast cancer post prophylactic BSO for premenopausal patients | Relative risk                                | 0.4500                         | [0.150, 0.320]            | -0.7985             | 0.1933     |
| Background mortality risk in the 2015 Norwegian female population    | Probability Age 20-110 Calculated from age-dependent life-expectancy | Assumed fixed                  |                           |                     |            |
| Relative survival breast cancer                                     | Probability Stage I                           | 0.9990                         |                           |                     |            |
|                                                                      | Probability Stage II                          | 0.9230                         |                           |                     |            |
|                                                                      | Probability Stage III                         | 0.7600                         |                           |                     |            |
|                                                                      | Probability Stage IV                          | 0.2550                         |                           |                     |            |
| Relative survival ovarian cancer                                     | Probability Local                             | 0.9320                         |                           |                     |            |
|                                                                      | Probability Regional                          | 0.6160                         |                           |                     |            |
|                                                                      | Probability Distant                           | 0.3420                         |                           |                     |            |
| Stage at diagnosis of breast cancer patients aged <50                | Probability Stage I                           | 0.3450                         | V(p) = 0.113              | Dirichlet           | a_0 = 0.3450 a_0 = 1 [19] |
|                                                                      | Probability Stage II                          | 0.5760                         | V(p) = 0.122              | Dirichlet           | a_2 = 0.5760 a_2 = 0.0350 |
|                                                                      | Probability Stage III                         | 0.0350                         | V(p) = 0.016              | Dirichlet           | a_3 = 0.0440 a_3 = 0.0440 |
|                                                                      | Probability Stage IV                          | 0.0440                         | V(p) = 0.02               | Dirichlet           | a_4 = 0.0440 a_4 = 0.0440 |
| Stage at diagnosis of breast cancer patients aged 50-69              | Probability Stage I                           | 0.5710                         | V(p) = 0.122              | Dirichlet           | a_0 = 0.5710 a_0 = 1 [19] |
|                                                                      | Probability Stage II                          | 0.3630                         | V(p) = 0.115              | Dirichlet           | a_2 = 0.0310 a_2 = 0.0450 |
|                                                                      | Probability Stage III                         | 0.0210                         | V(p) = 0.010              | Dirichlet           | a_3 = 0.0440 a_3 = 0.0440 |
|                                                                      | Probability Stage IV                          | 0.0450                         | V(p) = 0.021              | Dirichlet           | a_4 = 0.0440 a_4 = 0.0440 |
| Stage at diagnosis of breast cancer patients aged ≥ 70               | Probability Stage I                           | 0.3390                         | V(p) = 0.112              | Dirichlet           | a_0 = 0.3390 a_0 = 1 [19] |
|                                                                      | Probability Stage II                          | 0.4920                         | V(p) = 0.125              | Dirichlet           | a_2 = 0.4920 a_2 = 0.0650 |
|                                                                      | Probability Stage III                         | 0.0650                         | V(p) = 0.030              | Dirichlet           | a_3 = 0.0650 a_3 = 0.0650 |
|                                                                      | Probability Stage IV                          | 0.1040                         | V(p) = 0.046              | Dirichlet           | a_4 = 0.1040 a_4 = 0.1040 |
| Stage at diagnosis of ovarian cancer Norwegian patients diagnosed 2004 through 2007 | Probability Local                             | 0.1210                         | 0.0154                    | Dirichlet           | a_0 = 0.1210 a_0 = 1 [20] |
|                                                                      | Probability Regional                          | 0.1820                         | 0.0149                    | Dirichlet           | a_2 = 0.1820 a_2 = 0.0697 |
|                                                                      | Probability Distant                           | 0.6970                         | 0.0091                    | Dirichlet           | a_3 = 0.0697 a_3 = 0.0697 |
| Relative risk of breast cancer with ATM mutation                     | Relative risk                                | 2.800                          | 90% CI: [2.200, 3.700]    | Log-normal ln(RR): | 1.0296    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 0.1580    |
| Relative risk of ovarian cancer with ATM mutation                    | Relative risk                                | 2.7842                         | 95% CI: [1.333, 5.267]    | Log-normal ln(RR): | 1.0239    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 0.3504    |
| Relative risk of breast cancer with BARD1 mutation                  | Relative risk                                | 1.3760                         | 95% CI: [0.604, 2.930]    | Log-normal ln(RR): | 0.3191    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 0.4028    |
| Relative risk of ovarian cancer with BARD1 mutation                 | Relative risk                                | 2.1194                         | 95% CI: [0.303, 2.349]    | Log-normal ln(RR): | 0.7511    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 1.1079    |
| Relative risk of breast cancer with BRCA1 mutation Age 20-29         | Relative risk                                | 18.000                         | 95% CI: [4.4, 75.0]       | Log-normal ln(RR): | 2.8903    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 0.7234    |
| Relative risk of breast cancer with BRCA1 mutation Age 30-39         | Relative risk                                | 36.000                         | 95% CI: [25.0, 52.0]      | Log-normal ln(RR): | 3.5835    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 0.1868    |
| Relative risk of breast cancer with BRCA1 mutation Age 40-49         | Relative risk                                | 31.000                         | 95% CI: [25.0, 52.0]      | Log-normal ln(RR): | 3.4340    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 0.1868    |
| Relative risk of breast cancer with BRCA1 mutation Age 50-59         | Relative risk                                | 16.000                         | 95% CI: [9.6, 27.0]       | Log-normal ln(RR): | 2.7726    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 0.2638    |
| Relative risk of breast cancer with BRCA1 mutation Age ≥ 60          | Relative risk                                | 11.000                         | 95% CI: [5.0, 25.0]       | Log-normal ln(RR): | 2.3979    |
|                                                                      | Relative risk                                |                                |                           | se[ln(RR)]:        | 0.4106    |
| Mutant         | Relative Risk | Age Group | 95% CI       | Log-normal ln(RR) | se[ln(RR)] |
|---------------|---------------|-----------|--------------|-------------------|------------|
| BRCA1         | 1.000         | 20-29     | [1, 1]       |                   | 0          |
| BRCA1         | 38.000        | 30-39     | [17.0, 88.0] |                   | 3.6376     | 0.4194     |
| BRCA1         | 61.000        | 40-49     | [38.0, 99.0] |                   | 4.1109     | 0.2443     |
| BRCA1         | 30.000        | 50-59     | [14.0, 65.0] |                   | 3.4012     | 0.3917     |
| BRCA1         | 48.000        | ≥ 60      | [17.0, 88.0] |                   | 3.8712     | 0.4082     |
| BRCA2         | 19.000        | 20-29     | [4.4, 82.0]  |                   | 2.9444     | 0.7462     |
| BRCA2         | 16.000        | 30-39     | [9.3, 29.0]  |                   | 2.7726     | 0.2901     |
| BRCA2         | 9.500         | 40-49     | [5.9, 15.0]  |                   | 2.2513     | 0.2380     |
| BRCA2         | 11.000        | 50-59     | [6.6, 17.0]  |                   | 2.3979     | 0.2414     |
| BRCA2         | 9.200         | ≥ 60      | [5.1, 17.0]  |                   | 2.2192     | 0.3071     |
| BRCA2         | 1.000         | 20-29     | [1, 1]       |                   | 1.8405     | 0.7642     |
| BRCA2         | 1.000         | 30-39     | [1, 1]       |                   | 0          | 0          |
| BRCA2         | 6.300         | 40-49     | [1.4, 28.0]  |                   | 1.6402     | 0.8471     |
| BRCA2         | 19.000        | 50-59     | [9.1, 41.0]  |                   | 2.9444     | 0.3840     |
| BRCA2         | 7.300         | ≥ 60      | [1.8, 30.0]  |                   | 1.9879     | 0.7177     |
| BRIP1         | 1.6212        | Relative | [0.899, 3.008]|                   | 0.4830     | 0.3882     |
| BRIP1         | 7.1480        | Relative | [4.527, 10.550]|                  | 1.9668     | 0.2158     |
| CDH1          | 6.6000        | Relative | [2.2, 19.9]  |                   | 1.8871     | 0.6694     |
| CDH1          | 1.9879        | Relative | [0.462, 6.090]|                  | 0.6866     | 0.6901     |
| CHEK2         | 3.0000        | Relative | [2.600, 3.500]|                  | 1.0968     | 0.0904     |
| CHEK2         | 0.6999        | Relative | [0.345, 1.273]|                  | -0.3569    | 0.3331     |
| NBN           | 2.7000        | Relative | [0.909, 3.700]|                  | 0.9933     | 0.2026     |
| NBN           | 1.1910        | Relative | [0.459, 3.091]|                  | 0.1748     | 0.4865     |
| PALB2         | 5.3000        | Relative | [3.000, 9.400]|                  | 1.6677     | 0.2914     |
| PALB2         | 3.1879        | Relative | [9.5]        | Log-normal ln(RR):| 0          | 0          |
| CDH1          | 1.9879        | Relative | [0.462, 6.090]|                  | 0.6866     | 0.6901     |
| CDH1          | 3.0000        | Relative | [2.600, 3.500]|                  | 1.0968     | 0.0904     |
| CHEK2         | 0.6999        | Relative | [0.345, 1.273]|                  | -0.3569    | 0.3331     |
| NBN           | 2.7000        | Relative | [0.909, 3.700]|                  | 0.9933     | 0.2026     |
| NBN           | 1.1910        | Relative | [0.459, 3.091]|                  | 0.1748     | 0.4865     |
| PALB2         | 5.3000        | Relative | [3.000, 9.400]|                  | 1.6677     | 0.2914     |
| PALB2         | 3.1879        | Relative | [9.5]        | Log-normal ln(RR):| 0          | 0          |
| Relative risk of breast cancer with PTEN mutation | Relative risk | 41.440 | 0.8379 |
| Relative risk of breast cancer with RAD51C mutation | Relative risk | 0.9377 | 0.5544 |
| Relative risk of ovarian cancer with RAD51C mutation | Relative risk | 5.3714 | 0.3122 |
| Relative risk of breast cancer with RAD51D mutation | Relative risk | 1.0630 | 0.3707 |
| Relative risk of ovarian cancer with RAD51D mutation | Relative risk | 14.550 | 0.3234 |
| Relative risk of breast cancer with STK11 mutation | Relative risk | 15.200 | 0.4306 |
| Relative risk of ovarian cancer with STK11 mutation | Relative risk | 27.000 | 0.4924 |
| Relative risk of breast cancer with TP53 mutation | Relative risk | 19.8590 | 0.0023 |
| Relative risk of ovarian cancer with TP53 mutation | Relative risk | 2.9227 | 0.0033 |

| Prevalence of ATM mutation breast cancer patients | Probability | 0.0185 | Dirichlet Parameter sets were created by assuming probability of not having, or having one of the mutations at birth is multinomial. See own section (“Evidence synthesis for prevalence of rare mutations”): |
| Prevalence of BARD1 mutation breast cancer patients | Probability | 0.0057 | |
| Prevalence of BRCA1 mutation breast cancer patients | Probability | 0.0277 | |
| Prevalence of BRCA2 mutation breast cancer patients | Probability | 0.0223 | |
| Prevalence of BRIP1 mutation breast cancer patients | Probability | 0.0038 | |
| Prevalence of CDH1 mutation breast cancer patients | Probability | 0.0043 | |
| Prevalence of CHEK2 mutation breast cancer patients | Probability | 0.0158 | |
| Prevalence of NBN mutation breast cancer patients | Probability | 0.0028 | |
| Prevalence of PALB2 mutation breast cancer patients | Probability | 0.0102 | |
| Prevalence of PTEN mutation breast cancer patients | Probability | 0.0025 | |
| Prevalence of RAD51C mutation breast cancer patients | Probability | 0.0025 | |
| Prevalence of RAD51D mutation breast cancer patients | Probability | 0.0020 | |
| Prevalence of STK mutation breast cancer patients | Probability | 0.0060 | |
| Prevalence of TP53 mutation breast cancer patients | Probability | 0.0040 | |

| Probability of VUS as result with ATM mutation | Probability | 0.081 | Beta \( \alpha = 40 \) \( \beta = 448 \) [25] |
| Probability of VUS as result with BARD1 mutation | Probability | 0.024 | Beta \( \alpha = 12 \) \( \beta = 476 \) |
| Probability of VUS as result with BRCA1 mutation | Probability | 0.004 | Beta \( \alpha = 2 \) \( \beta = 486 \) |
| Probability of VUS as result with BRCA2 mutation | Probability | 0.008 | Beta \( \alpha = 4 \) \( \beta = 464 \) |
| Probability of VUS as result with BRIP1 mutation | Probability | 0.038 | Beta \( \alpha = 19 \) \( \beta = 469 \) |
| Probability of VUS as result with CDH1 mutation | Probability | 0.010 | Beta \( \alpha = 5 \) \( \beta = 483 \) |
| Probability of VUS as result with CHEK2 mutation | Probability | 0.034 | Beta \( \alpha = 17 \) \( \beta = 471 \) |
| Mutation                        | Probability of VUS as result | Probability | Beta | $\alpha$ | $\beta$ |
|--------------------------------|-----------------------------|-------------|------|----------|--------|
| NBN                            | 0.018                       | 0.0061      | Beta | $\alpha = 9$ | $\beta = 479$ |
| PALB2                          | 0.024                       | 0.0070      | Beta | $\alpha = 12$ | $\beta = 476$ |
| PTEN                           | 0.002                       | 0.0020      | Beta | $\alpha = 1$ | $\beta = 487$ |
| RAD51C                         | 0.014                       | 0.0054      | Beta | $\alpha = 7$ | $\beta = 481$ |
| RAD51D                         | 0.006                       | 0.0035      | Beta | $\alpha = 3$ | $\beta = 485$ |
| STK11                          | 0.004                       | 0.0029      | Beta | $\alpha = 2$ | $\beta = 486$ |
| TP53                           | 0.001                       | 0.0050      | Beta | $\alpha = 6$ | $\beta = 482$ |

Pre-test probability that first-degree relative carriers same mutation as index patient

Probability 0.5000 Assumption based on dominant inheritance

Number of daughters for index patients born between 1956-1961

Outcome per patient

Range [0 – 3], target average no. female births

0.8400 Assumed fixed Binomial $n = 3$ $p = 0.28$ [49]

Cost of genetic testing of index patient when test includes genes BRCA1 and BRCA2

Cost per patient

Sanger sequencing and MPLA

$2,195$ $439$ Gamma $\alpha = 25$ $\beta = 87.8$ See own section (“Cost estimation of genetic testing”)

Cost of targeted genetic testing of first-degree relative

Cost per patient

Sanger sequencing

$138$ $28$ Gamma $\alpha = 25$ $\beta = 5.52$

Cost of breast cancer examination

Cost per patient

$1,414$ $283$ Gamma $\alpha = 25$ $\beta = 56.56$ See own section (“Cost estimation of the breast cancer patient pathway”)

Cost of axillary lymph node excision with metastasis, primary cancer in index patient

Cost per patient

High-throughput sequencing and MPLA

$4,796$ $959$ Gamma $\alpha = 25$ $\beta = 191.84$

Cost of systemic adjuvant therapy in HER2 negative patient

Cost per patient

$2,763$ $557$ Gamma $\alpha = 25$ $\beta = 110.52$

Cost of adjuvant hormonal therapy in pre-menopausal patient

Cost per patient

$151$ $30$ Gamma $\alpha = 25$ $\beta = 6.04$
| Cost of adjuvant hormonal therapy in post-menopausal patient | Cost per patient | $ 2 466 $ 493 | Gamma | $\alpha = 25$ | $\beta = 98.64$ |
| Cost of adjuvant radiotherapy regimen | Cost per patient | $ 3 131 $ 626 | Gamma | $\alpha = 25$ | $\beta = 125.24$ |
| Cost of follow-up, mammogram | Cost per patient | $ 26 $ 5 | Gamma | $\alpha = 25$ | $\beta = 1.04$ |
| Cost of follow-up, breast surgeon check-up | Cost per patient | $ 33 $ 6 | Gamma | $\alpha = 25$ | $\beta = 1.32$ |
| Cost of follow-up, general practitioner check-up | Cost per patient | $ 36 $ 7 | Gamma | $\alpha = 25$ | $\beta = 1.44$ |
| Cost of ovarian cancer year 1 | Cost per patient | $ 6 408 $ 1 282 | Gamma | $\alpha = 25$ | $\beta = 256.32$ |
| Cost of ovarian cancer year 2 | Cost per patient | $ 327 $ 65 | Gamma | $\alpha = 25$ | $\beta = 13.08$ |
| Cost of ovarian cancer year 3 through 5 | Cost per patient | $ 218 $ 44 | Gamma | $\alpha = 25$ | $\beta = 8.72$ |
| Cost of ovarian cancer year 6 through 10 | Cost per patient | $ 36 $ 7 | Gamma | $\alpha = 25$ | $\beta = 1.44$ |
| Cost of prophylactic mastectomy with reconstructive surgery | Cost per patient | $ 15 607 $ 3 121 | Gamma | $\alpha = 25$ | $\beta = 624.28$ |
| Cost of prophylactic bilateral salpingo-oophorectomy | Cost per patient | $ 3 869 $ 774 | Gamma | $\alpha = 25$ | $\beta = 154.76$ |
| Share of patients expected to opt for breast conserving therapy over mastectomy | Cost shifter | 0.82 | SE N/A, assumed N= 3 415 [14] Beta | $\alpha = 2800$ | $\beta = 615$ |
| Share of patients having axillary lymph node metastasis | Cost shifter | 0.15 | Beta | $\alpha = 512$ | $\beta = 2903$ |
| Share of breast cancer patients with HER2 positive tumor | Cost shifter | 0.15 | Beta | $\alpha = 512$ | $\beta = 2903$ |
| Share of pre-menopausal breast cancer patients needing hormonal therapy for 10 years | Cost shifter | 0.20 | Beta | $\alpha = 683$ | $\beta = 2732$ |
| Quality of life general population age 0 - 20 | Baseline utility weight | 0.89 | Assumed fixed by Norwegian Medicines Agency | [43] |
| Quality of life general population age 21 - 34 | Baseline utility weight | 0.87 | Assumed fixed by Norwegian Medicines Agency | [30, 43] |
| Quality of life general population age 35 - 44 | Baseline utility weight | 0.85 | Assumed fixed by Norwegian Medicines Agency | [30, 43] |
| Quality of life general population age 45 - 54 | Baseline utility weight | 0.82 | Assumed fixed by Norwegian Medicines Agency | [30, 43] |
| Quality of life general population age 55 - 74 | Baseline utility weight | 0.80 | Assumed fixed by Norwegian Medicines Agency | [30, 43] |
| Quality of life general population age 75 - 88 | Baseline utility weight | 0.76 | Assumed fixed by Norwegian Medicines Agency | [31, 43] |
| Quality of life general population age ≥ 89 | Baseline utility weight | 0.72 | Assumed fixed by Norwegian Medicines Agency | [43] |
| Utility weight decrement from anxiety with positive test result of genetic testing | Utility multiplier | 0.005 | Beta | $\alpha = 215$ | $\beta = 4459$ |
| Utility weight stage I and stage II breast cancer breast conserving therapy | Utility multiplier | 0.7270 | Beta | $\alpha = 171$ | $\beta = 64$ |
| Event Description                                                                 | Utility Multiplier | Beta Parameters | Reference |
|----------------------------------------------------------------------------------|--------------------|-----------------|-----------|
| Utility weight stage I and stage II breast cancer breast conserving therapy w/ hormonal therapy | 0.6530 0.0310 Beta α = 153 β = 81 | [46]             |
| Utility weight stage I & II breast cancer w/ mastectomy with reconstruction      | 0.7270 0.0290 Beta α = 171 β = 64 | [46]             |
| Utility weight stage III and IV breast cancer w/ chemotherapy and radiotherapy  | 0.5520 0.0460 Beta α = 64 β = 52 | [46]             |
| Utility weight stage III and IV breast cancer w/ chemo-, radio – and hormonal therapy | 0.6860 0.0430 Beta α = 79 β = 36 | [46]             |
| Utility weight prophylactic mastectomy                                           | 0.9710 0.0110 Beta α = 225 β = 7 | [45, 46]        |
| Utility weight prophylactic BSO                                                  | 0.9200 0.0400 Beta α = 41 β = 4 | [45]             |
| Utility weight both prophylactic surgeries in one year                           | 0.8900 0.0550 Beta α = 28 β = 3 | [45]             |
| Utility weight localized (early) ovarian cancer                                  | 0.8100 0.0980 Beta α = 12 β = 3 | [47]             |
| Utility weight regional (advanced) ovarian cancer                                | 0.5500 0.1330 Beta α = 7 β = 6 | [47]             |
| Utility weight distant (end-stage) ovarian cancer                                | 0.1600 0.0950 Beta α = 2 β = 12 | [47]             |
Appendix 2 Evidence synthesis for relative risks
Table A2.1. Searches and results

| Parameter to estimate | Literature search                                                                 | Articles for evaluation |
|-----------------------|-----------------------------------------------------------------------------------|-------------------------|
| Relative risk with ATM mutation | 03-24-2017: Medline: ('Ataxia Telangiectasia Mutated Proteins/genetics [Mesh] AND 'breast neoplasms' [MeSH Terms]”) 34 results | 6 articles |
| Relative risk with BARD1 mutation | 04-04-2017: Medline: ('bard1') AND 'risk’ 72 results | 10 articles |
| Relative risk with BRCA1 mutation | 04-03-2017: Other sources: 1 result (ovarian specifically) 1 article | 2 articles |
| Relative risk with BRCA2 mutation | 04-03-2017: Other sources: 1 result 1 article | 1 article |
| Relative risk with BRIP1 mutation | 04-05-2017: Medline: (“brip1”) AND “risk” 102 results | 5 articles |
| Relative risk with CDH1 mutation | 04-06-2017: Medline: (((‘cdh1’) AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘cdh1’) AND ‘risk’) AND ovarian neoplasms[MeSH Terms]) 61 results |
04-05-2017:
Other sources:
2 results (breast specifically)
3 results (ovarian specifically)
2 articles

Relative risk with **CHEK2** mutation 04-07-2017:
Medline: `(((‘chek2’) AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘chek2’) AND ‘risk’) AND ovarian neoplasms[MeSH Terms])`
208 results

04-05-2017:
Other sources:
3 results (breast specifically)
1 result (ovarian specifically)
8 articles

Relative risk with **NBN (NSB1)** mutation 04-07-2017:
Medline: `(((‘nbn’) AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘nbn’) AND ‘risk’) AND ovarian neoplasms[MeSH Terms])`
55 results

04-05-2017:
Other sources:
3 results
1 result (ovarian specifically)
4 articles

Relative risk with **PALB2** mutation 04-10-2017:
Medline: `(((‘palb2’) AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘palb2’) AND ‘risk’) AND ovarian neoplasms[MeSH Terms])`
123 results

04-05-2017:
Other sources:
1 result (breast specifically)
1 result (ovarian specifically)
1 article
Relative risk with PTEN mutation
04-11-2017:
Medline: (((‘pten’) AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘pten’) AND ‘risk’) AND ovarian neoplasms[MeSH Terms])
203 results

04-11-2017:
UpToDate: “pten”
1 result

04-11-2017:
Other sources:
1 result (breast specifically)

Relative risk with RAD51C mutation
04-11-2017:
Medline: (((‘rad51c’) AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘rad51c’) AND ‘risk’) AND ovarian neoplasms[MeSH Terms])
47 results

04-05-2017:
Other sources:
1 result (ovarian specifically)

Relative risk with RAD51D mutation
04-12-2017:
Medline: (((‘rad51d’) AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘rad51d’) AND ‘risk’) AND ovarian neoplasms[MeSH Terms])
23 results

04-05-2017:
Other sources:
1 result (ovarian specifically)

Relative risk with STK11 mutation
04-17-2017:
Medline: (((‘stk11’) AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘stk11’) AND ‘risk’) AND ovarian neoplasms[MeSH Terms])
1 article
Relative risk with TP53 mutation

04-17-2017:

Medline: (((‘tp53’ AND ‘risk’) AND breast neoplasms[MeSH Terms]) OR (((‘tp53’ AND ‘risk’) AND ovarian neoplasms[MeSH Terms])))

376 results*

12 results

04-05-2017:

Other sources:

1 result (breast specifically)

1 result (ovarian specifically)

1 article

1 article

*Search narrowed by truncating to existing meta-analyses
Table A2.2. Included studies for re-estimation with random effects meta-analysis, or direct inclusion in the model

| Gene (Organ) | Study | Year | Study type | Country   | Outcome measure | Value    | Variance | Requires pooling |
|-------------|-------|------|------------|-----------|-----------------|----------|----------|------------------|
| ATM (BC)    | [10]  | 2015 | MA         | Several   | RR              | 2.8000   | 0.0249   | No               |
| ATM (OC)    | [50]  | 2016 | CC         | US        | OR              | 2.7842   | 0.1227   | No               |
| BARD1 (BC)  | [51]  | 2006 | CC         | Iceland   | OR              | 1.7601   | 0.130    | Yes              |
|             | [52]  | 2006 | CC         | Several   | OR              | 1.7108   | 0.023    | Yes              |
|             | [53]  | 2008 | CC         | Poland    | OR              | 1.2318   | 0.032    | Yes              |
|             | [54]  | 2009 | CC         | Australia | OR              | 0.8430   | 0.054    | Yes              |
| BARD1 (OC)  | [55]  | 2015 | MA         | Several   | OR              | 2.1194   | 0.750    | No               |
|             | [22]  |      |            |           |                 |          |          |                  |
| BRCA1 (BC)  | [22]  | 2003 | MA         | Several   | RR, by age      | 11-36    |          | No               |
|             | [22]  |      |            |           |                 |          |          |                  |
| BRCA1 (OC)  | [22]  | 2003 | MA         | Several   | RR, by age      | 1-61     |          | No               |
|             | [22]  |      |            |           |                 |          |          |                  |
| BRCA2 (BC)  | [22]  | 2003 | MA         | Several   | RR, by age      | 9.2-19   |          | No               |
|             | [22]  |      |            |           |                 |          |          |                  |
| BRCA2 (OC)  | [22]  | 2003 | MA         | Several   | RR, by age      | 1-19     |          | No               |
|             | [22]  |      |            |           |                 |          |          |                  |
| BRIP1 (BC)  | [56]  | 2016 | CC         | Several   | OR              | 1.6213   | 0.0821   | No               |
| Gene      | Year1 | Country1 | Year2 | Country2 |Transform | Effect | SE | p-value | Significance |
|-----------|-------|----------|-------|----------|----------|--------|----|---------|--------------|
| BRIP1 (OC)| 2016  | CC       | 2015  | OR       | 8.3078   | 0.0557 | Yes|
|           | 2015  | CC       | Several | OR       | 3.9963   | 0.1589 | Yes|
| CDH1 (BC) | 2015  | MA       | Several | RR       | 6.6000   | 1.6187 | No |
| CDH1 (OC) | 2005  | CC       | US    | OR       | 1.6765   | 0.5281 | Yes|
|           | 2012  | CC       | US    | OR       | 1.1148   | 0.1086 | Yes|
| CHEK2 (BC)| 2015  | MA       | Several | RR       | 3.0000   | 0.0081 | No |
| CHEK2 (OC)| 2016  | CC       | US    | OR       | 0.6998   | 0.0948 | No |
| NBN (BC)  | 2015  | MA       | Several | RR       | 2.7000   | 0.0410 | No |
| NBN (OC)  | 2015  | CC       | Several | OR       | 1.1910   | 0.2366 | No |
| PALB2 (BC)| 2015  | MA       | Several | RR       | 5.3000   | 0.0849 | No |
| PALB2 (OC)| 2015  | CC       | Several | OR       | 3.1879   | 0.7020 | No |
| PTEN (BC) | 2012  | CC       | US    | OR       | 25.8266  | 0.3470 | Yes|
|           | 2013  | CC       | France | OR       | 46.0909  | 1.0345 | Yes|
| PTEN (OC) |        |         | No evidence |         |
| Gene/Region  | Summary/Year | Study Design | Location(s) | Effect Measure | OR/RR | 95% CI Low | 95% CI High | Convention |
|-------------|--------------|--------------|-------------|----------------|-------|------------|------------|------------|
| RAD51C (BC) | 2012         | CC           | US, Australia | OR             | 0.9377 | 0.2128     | No         |
| RAD51C (OC) | 2016         | CC           | US          | OR             | 5.3680 | 0.1171     | No         |
| RAD51D (BC) | 2007         | CC           | Australia   | OR             | 1.0440 | 0.0981     | Yes        |
|             | 2016         | CC           | UK          | OR             | 0.4791 | 2.6690     | Yes        |
| RAD51D (OC) | 2015         | CC           | Several     | OR             | 14.9641 | 0.1629     | Yes        |
|             | 2016         | CC           | US          | OR             | 8.9178  | 1.0916     | Yes        |
|             | 2016         | CC           | UK          | OR             | 9.3821  | 1.1271     | Yes        |
| STK11 (BC)  | 2000         | MA           | Several     | RR             | 15.200  | 1.1102     | No         |
| STK11 (OC)  | 2000         | MA           | Several     | RR             | 27.000  | 1.3827     | No         |
| TP53 (BC)   | 2003         | CC           | US          | OR             | 19.8590 | 0.1213     | No         |
| TP53 (OC)   | 2016         | CC           | US          | OR             | 2.9203  | 0.1928     | No         |

Abbreviations: MA = Meta-analysis, CC = Case-control, OR = Odds-ratio, RR = Relative risk

We assumed that because the incidence of breast and ovarian cancer is in themselves < 1% in the non-exposed population [14] the odds-ratios would approximate the relative risk, as explained in Zhang and Yu [66]. We also tested with their method of adjusting an odds-ratio to a relative risk using the population risk and only observed a difference in the OR and RR starting at the third decimal and therefore concluded the assumption was reasonable.

We then calculated the 95% confidence intervals and parametrised log-normal distributions for the input parameters in the probabilistic sensitivity analysis as in Briggs et al. p.89-90 [36].
### Table A2.3. Pairwise MA results and model comparisons

| Gene  | Organ | Model  | Model fit | Unconstrained parameters | Residual deviance | DIC | Heterogeneity $\tau$ | Mean OR | Median OR | 2.5% | 97.5% |
|-------|-------|--------|-----------|--------------------------|-------------------|-----|----------------------|--------|-----------|------|-------|
| BARD1 | Breast | FE     | 5         | 12.1                     | 62.3              |     |                      | 1.376  | 1.367     | 1.119| 1.367 |
|       |       | RE     | *         | 8                        | 8.2               | 60.9| 0.38                 | 1.513  | 1.334     | 0.604| 2.930 |
| BRIPI | Ovary | FE     | *         | 3                        | 5.2               | 28.4|                     | 7.148  | 6.992     | 4.527| 10.65 |
|       |       | RE     |           | 4                        | 4.12              | 28.2| 1.27                 | 95.58  | 6.249     | 0.190| 182.9 |
| CDH1  | Ovary | FE     | *         | 3                        | 3.17              | 18.8|                     | 1.987  | 1.566     | 0.462| 6.095 |
|       |       | RE     |           | 4                        | 3.75              | 20.0| 1.82                 | 43.32  | 1.642     | 0.038| 78.78 |
| PTEN  | Breast| FE     | *         | 3                        | 3.35              | 22.8|                     | 41.44  | 33.32     | 13.51| 118.7 |
|       |       | RE     |           | 4                        | 3.83              | 23.9| 1.49                 | 103.8  | 40.26     | 1.184| 2257  |
| RAD51D| Breast| FE     | *         | 3                        | 4.25              | 18.9|                     | 1.063  | 1.011     | 0.554| 1.884 |
|       |       | RE     |           | 4                        | 3.83              | 18.7| 2.41                 | 15.06  | 0.541     | 0.005| 27.21 |
| RAD51D| Ovary | FE     | *         | 4                        | 4.34              | 29.3|                     | 14.55  | 13.56     | 6.600| 28.22 |
|       |       | RE     |           | 7                        | 5.10              | 30.7| 0.78                 | 43.54  | 13.16     | 1.579| 134.3 |

* Chosen model

#### A2.1 Inclusion and exclusion criteria

We included studies that had an appropriate design (i.e. case-control, or meta-analysis), as far as possible patients in the carrier groups unselected for family history. For the case control studies we checked that the outcome was rare and approximate to what was observed from the Cancer Registry’s 2015 report [14].

Studies that did not summarise extractable data, used inappropriate outcome measures, or otherwise gave an impression of low quality were excluded.

#### A2.2 Choice of model for pooling data

We pooled the estimates from the studies using Bayesian fixed effects (FE) and random effects (RE) models with vague priors in WinBUGS version 14.3, using a binomial likelihood function, and logit link function.

We checked which of the FE or RE model had the best fit by comparing the resulting mean total residual deviance to the number of unconstrained parameters. We also compared the DIC values for both models. We employed a burn-in period of 50 000 iterations, and sampled 50 000 iterations from the posteriors. The models were run with two separate chains with drastically different initial values to assess convergence in their separate posterior estimates and investigated the Brooks Gelman-Rubin plots. We also checked the samples’ serial dependency by assessing the auto-correlation plots.

The best fitting model in each case was chosen, given that the estimate seemed appropriate. As visible in the table, there was for most a high degree of between-study heterogeneity in the ‘treatment effect’, which was expected given the very limited number of studies, and cancer penetrance of different variants within genes.
# Fixed Effect Model
# Binomial likelihood, logit link

```stan
model{
    for (i in 1:ns) {
        delta[i,1] <- 0
        mu[i] ~ dnorm(0,.0001)
        for (k in 1:2) {
            r[i,k] ~ dbin(p[i,k],n[i,k])
            logit(p[i,k]) <- mu[i] + delta[i,k]
            rhat[i,k] <- p[i,k] * n[i,k]
            dev[i,k] <- 2 * (r[i,k] * (log(r[i,k]) - log(rhat[i,k])))
            + (n[i,k] - r[i,k]) * (log(n[i,k]) - r[i,k]) -
            log(n[i,k]) -
            rhat[i,k])
        }
        resdev[i] <- sum(dev[i,])
        delta[i,2] <- d[2]     # trial-specific LOR distributions
    }
    totresdev <- sum(resdev[])           #Total Residual Deviance
    d[1]<- 0              # treatment effect is zero for reference treatment
    d[2] ~ dnorm(0,.0001) # vague prior for treatment effect
    or <- exp(d[2])
    }

Data
# ns= number of studies
list(ns=3)
  r[,1]  n[,1]  r[,2]  n[,2]
  14    36276   11   1915
  1    1060     8    911
  1   2772     11   3429
END

Initial Values
```
Appendix 4 Cost estimation of genetic testing

Because the tariffs for laboratory services is currently being updated in Norway due to discrepancies of reimbursement and actual costs we decided to use a departmental micro costing analysis by the department of medical genetics at Oslo University Hospital for estimating the costs of testing. We valued the costs in Norwegian Kroner (NOK) and then adjusted to US dollars (USD) with the 2016 year average exchange rate of 8.3987NOK/USD [29].

Table A4.1. Bottom-up cost estimation for modelled testing strategies

| Alternative | Intervention | Component | Cost | Notes/source |
|-------------|--------------|-----------|------|--------------|
| All         | Genetic counselling pre test | Examination hereditary cancer | $172 | Tariff M05a*2[75] |
|             |              | Counselling before carrier diagnostic | $172 | Tariff M05a*2[75] |
| DNA extraction from blood |              | If negative | $344 |          |
|             |              | Counselling after carrier diagnostic | $172 | Tariff M05a*2[75] |
|             |              | If positive | $516 |          |
|             |              | Materials and equipment | $9 |          |
|             |              | Direct labour | $46 |          |
|             |              | Indirect labour | $13 |          |
|             |              | Overhead | $26 |          |
|             |              | Capital | $0 |          |
|             |              | Maintenance service | $0 |          |
|             |              | Capital | $94 |          |
| MPLA       |              | Materials and equipment | $34 | Per gene |
| Current practice | MPLA | See above | $228 | 2 genes |
| 7-gene panel | MPLA | See above | $798 | 7 genes |
| 14-gene panel | MPLA | See above | $1,469 | 13 genes |
| Current practice | Sanger sequencing (inc. interpretation) | Materials and equipment | $722 |          |
|             |              | Direct labour | $615 |          |
|             |              | Indirect labour | $176 |          |
|             |              | Overhead | $342 |          |
|             |              | Capital | $59 |          |
|             |              | Maintenance service | $54 |          |
|             |              | Maintenance service | $1,967 |          |
| 7/14 gene panel | High throughput sequencing per analysis | Materials and equipment | $432 |          |
|             |              | Direct labour | $395 |          |
|             |              | Indirect labour | $120 |          |
| SNP genotyping per analysis | Overhead | $241 |          |
|             |              | Capital | $371 |          |
|             |              | Maintenance service | $334 |          |
|             |              | Capital | $1,893 |          |
| Interpretation per gene | Materials and equipment | $82 |          |
|             |              | Direct labour | $226 |          |
|             |              | Indirect labour | $68 |          |
|             |              | Overhead | $138 |          |
|             |              | Capital | $12 |          |
|             |              | Maintenance service | $11 |          |
|             |              | Maintenance service | $537 |          |
| 7-gene panel | $483 | 7 HBOC genes |
| 14-gene panel | $897 | 14 HBOC genes |
| Targeted analysis of relative | MPLA | See above | $114 | 1 gene |
| Sanger sequencing | See above | $24 | 1 exon |
Table A4.2. Testing costs (excluding counselling)

| Alternative               | Generation | Total cost |
|---------------------------|------------|------------|
| Targeted testing of relative | Relative   | $ 138      |
| Current practice          | Index      | $ 2 195    |
| 7-gene panel              | Index      | $ 3 711    |
| 14-gene panel             | Index      | $ 4 796    |
Appendix 4 Cost estimation of genetic testing

Because the tariffs for laboratory services is currently being updated in Norway due to discrepancies of reimbursement and actual costs we decided to use a departmental micro costing analysis by the department of medical genetics at Oslo University Hospital for estimating the costs of testing. We valued the costs in Norwegian Kroner (NOK) and then adjusted to US dollars (USD) with the 2016 year average exchange rate of 8.3987NOK/USD [29].

Table A4.1. Bottom-up cost estimation for modelled testing strategies

| Alternative | Intervention | Component | Cost | Notes/source |
|-------------|-------------|-----------|------|--------------|
| All         | Genetic counselling pre test | Examination hereditary cancer | $172 | Tariff M05a*2[75] |
|             |             | Counselling before carrier diagnostic | $172 | Tariff M05a*2[75] |
|             |             | If negative | $344 |
|             |             | Counselling after carrier diagnostic | $172 | Tariff M05a*2[75] |
|             |             | If positive | $516 |
| DNA extraction from blood |             | Materials and equipment | $9 |
|             |             | Direct labour | $46 |
|             |             | Indirect labour | $13 |
|             |             | Overhead | $26 |
|             |             | Capital | $0 |
|             |             | Maintenance service | $0 |
|             |             | $94 |
| MPLA | Materials and equipment | $34 | Per gene |
| Current practice | MPLA | Direct labour | $40 |
| 7-gene panel | MPLA | Indirect labour | $11 |
| 14-gene panel | Sanger sequencing (inc. interpretation) | Materials and equipment | $722 |
| Current practice | Sanger sequencing (inc. interpretation) | Direct labour | $615 |
| 7/14 gene panel | High throughput sequencing per analysis | Materials and equipment | $432 |
| 7/14 gene panel | High throughput sequencing per analysis | Direct labour | $395 |
| 7-gene panel | SNP genotyping per analysis | Materials and equipment | $82 |
| 14-gene panel | SNP genotyping per analysis | Direct labour | $226 |
| Targeted analysis of relative | Interpretation per gene | Materials and equipment | $16 |
| 7-gene panel | Interpretation per gene | Direct labour | $18 |
| 14-gene panel | Interpretation per gene | Indirect labour | $35 |
| Sanger sequencing | Interpretation per gene | Indirect labour | $69 |

*Cost per exon for 82 amplicons

7 HBOC genes

14 HBOC genes

1 gene

1 exon
Table A4.2. Testing costs (excluding counselling)

| Alternative               | Generation | Total cost |
|---------------------------|------------|------------|
| Targeted testing of relative | Relative  | $ 138      |
| Current practice           | Index      | $ 2 195    |
| 7-gene panel               | Index      | $ 3 711    |
| 14-gene panel              | Index      | $ 4 796    |
Appendix 5 Cost estimation of the breast cancer patient pathway

A5.1. Breast cancer follow-up pathway

The Norwegian treatment of breast cancer currently follows a set patient pathway.[12] This process has four main parts:

- Examination
- Surgery
- Adjuvant therapy
- Follow-up

In the estimation we identified the main resource drivers of the pathway for a patient fitting to our modelled index – and relative individuals. For hospital services we used the diagnosis related groups for a given procedure. For outpatient services we used the respective tariffs. Tariffs were doubled in parity with Norwegian guidelines [32]. For pharmaceuticals we used the publicly available prices in Norway. These are undoubtedly higher than the actual cost, since the government negotiates bulk-order rebates. These rebates are not publicly disclosed and cannot be estimated. We valued the costs in Norwegian Kroner (NOK) and transformed to US dollars (USD) with the 2016 year average exchange rate of 8.3987NOK/USD [29].
# Table A5.1.1 Bottom-up cost estimation for breast cancer treatment

| Category | Procedure | Subcat. 1 | Subcat. 2 | Subcat. 3 | Cost | Notes/source |
|----------|-----------|-----------|-----------|-----------|------|--------------|
| Examination | Consultation breast surgeon | | | | $ 33 | (Tariff H01) [75] |
| | Mammogram | | | | $ 26 | (Weighted unit cost outpatient radiology) [75] |
| | Biopsy | | | | $ 1227 | (DRG260O) [76] |
| | Consensus conference | | | | $ 128 | (Tariff for surgeon, radiologist, pathologist, and oncologist, A01, B01, H01) [77] |
| Surgery | Breast conserving therapy | 82% of patients | 12% benign | 88% malign W/ comp. | $ 5 396 | (DRG 261)[76] |
| | | | | W/o comp. | $ 4 994 | (DRG 259)[76] |
| | Total mastectomy w/reconstructive surgery | 18% of patients | | | $ 15 607 | (DRG 502)[76] |
| | Axillary lymph node excision | 85% of patients | | | $ 2 774 | (DRG 234O)[76] |
| | Axillary lymph node with metastasis | 15% pf patients | | | $ 2.77 | (DRG269)[76] |
| | EC regimen x 4 | Epirubicin | 85% HER2- | | $ 11 051 | (DRG 270)[76] |
| | | Cyclofosfamid | Administration | | | $ 4 424 | (90mg x 4)[79]* |
| | | Paclitaxcel | Administration | | | $ 105 | (2000mg x 4)[79]* |
| | Taxan regimen | | | | $ 777 | (Tariff H05 x4)[75] |
| | | | | | $ 429 | (80mg/m² x 12)[80] |
| | | | | | $ 1 286 | (Tariff H05 x12)[75] |
| | EC regimen x 4 | Epirubicin | 15% HER2+ | | $ 1 652 | (7300mg/year)[82]* |
| | | Cyclofosfamid | Administration | | | $ 214 | (712.5mg/year)[83]* |
| | | Paclitaxcel | Administration | | | $ 218 | (6mg/kg x16)[81]* |
| | Taxan regimen (12 weeks) | | | | $ 1 562 | (Tariff H05 x17)[75] |
| | Herceptin† | Start dose | | | $ 26 | (8mg/kg x1)[91]‡ |
| | (Every third week, one year) | Maintenance Administration | | | $ 1 234 | (6mg/kg x 16)[81]* |
| | Radiotherapy (x 15 over three weeks) | Outpatient radiotherapy | | | $ 1 967 | (DRG 851K x 15)[76] |
| | Adjuvant hormone therapy | Tamoxiphen (5-10 years) | 20mg daily dose | 80% 5 years | | $ 151 | (8mg/kg x 1)[81]‡ |
| | | | 20% 10 years | Pre-menopausal || |
| | | Aromatase inhibitor (5 years) | 2.5mg daily dose | | $ 382 | (84)/[78]* |
| | | | Post-menopausal | | | |
| | | Calcium supplement (5 years) | 1000mg daily dose | | $ 1 652 | [83]* |
| | Follow-up § | Zoledronic acid (5 years) | 8mg/year | | | $ 214 | (Tariff H05 x 2) [75] |
| | | Administration | | | $ 218 | (Weighted unit cost outpatient radiology) [75] |
| | | Mammmogram (Yearly, 10 years) | | | $ 33 | (Tariff H01) [73] |
| | | Consultation breast surgeon (Year 1,2,5, 10) | | | $ 36 | (Tariff 2AD)[84] |
According to official prices, likely differs from actual costs due to (confidential) bulk-order rebates, assumes no waste of leftovers.

†Assumed average height 1.67 m (5ft6in). ‡Assumed average weight 60 kg (132 lbs). §According to standards at Oslo University Hospital. || Assume average 50 years at menopause [85]

Figure A5.1. Illustration of the model’s implementation of time - and patient specific costs of breast cancer treatment

A5.2. Prophylactic surgery

No follow-up or diagnosing costs. Assume DRGs cover average hospital costs of the surgery.

Table A5.2. Costs assumed to be applicable for prophylactic surgery

| Category | Procedure                                      | Cost      | Notes/source |
|----------|------------------------------------------------|-----------|--------------|
| Surgery  | Total mastectomy w/ reconstructive surgery     | $15 607   | (DRG 502)[76]|
| Surgery  | Bilateral salpingo-oophorectomy                 | $ 3 869   | (DRG 3550)[76]|
| Both     |                                                | $ 19 476  |              |
Appendix 6 Cost estimation ovarian cancer patient pathway

These estimates were calculated from the Norwegian Directorate of Health’s Action Program for gynaecologic cancer [86]. Outpatient tariffs were doubled in parity with Norwegian guidelines [32]. We valued the costs in Norwegian Kroner (NOK) and transformed to US dollars (USD) with the 2016 year average exchange rate of 8.3987NOK/USD [29].

Table A6 Bottom-up cost estimation of ovarian cancer treatment

| Category                  | Procedure                         | Cost   | Notes/source |
|---------------------------|-----------------------------------|--------|--------------|
| Examination               | Consultation gynecologist         | $ 66   | (Tariff B20)[75] |
| Surgery                   | Bilateral salpingo-oophorectomy    | $ 3,869| (DRG 355) [76] |
| Adjuvant systemic therapy | Carboptin*                        | $ 120  | [87] †       |
|                           | Paclitaxel                        | $ 122  | [87] †       |
|                           | Administration                    | $ 1,904| [87] †       |
| Follow-up                 | Oncologist consultation (2 years) | $ 327  | (Tariff H02) [77] |
|                           | Oncologist consultation (3 years) | $ 218  | (Tariff H02) [77] |
|                           | GP consultation (5 years)         | $ 36   | (Tariff 2AD)[84] |

* Appropriate dose highly individualized and established with AUC = 5 as the target in Calverts formula [88]. † Adjusted for inflation from 2013 to 2016, (8%) [34]

Figure A1 Illustration of model’s implementation of time-dependent ovarian cancer treatment costs
## Appendix 7 Impact inventory
### Table A7 Impact inventory

| Sector                  | Type of impact                        | Included in this analysis from … perspective | Notes on sources of evidence                          |
|-------------------------|---------------------------------------|---------------------------------------------|-----------------------------------------------------|
| Health                  | Health outcomes (effects)             |                                             |                                                     |
|                         | Health related quality of life, QALYs| ✓                                            | Literature review and national guidelines           |
|                         | Breast cancer cases                   | ✓                                            | Literature review, official statistics              |
|                         | Breast cancer specific mortality      | ✓                                            | Literature review, official statistics              |
|                         | Ovarian cancer cases                  | ✓                                            | Literature review, official statistics              |
|                         | Ovarian cancer specific mortality     | ✓                                            | Literature review, official statistics              |
|                         | Effect of initial testing on female first-degree relatives | ✓ | Literature review |
|                         | Effect of initial testing on male first-degree relatives | ✓ | Literature review |
|                         | Non-informative test results          | ✓                                            | Literature review                                   |
|                         | Medical costs                         |                                             |                                                     |
|                         | Paid for by third-party payer, $      | ✓                                            | Hospital resource use with unit costs and tariffs   |
|                         | Paid for by patients out-of-pocket    | *                                           |                                                     |
|                         | Future related medical costs          | ✓                                            | Hospital resource use with unit costs and tariffs   |
| Productivity            | Labour market earnings                |                                             |                                                     |
|                         | Cost of lost productivity             |                                             |                                                     |
| Consumption             | Cost of non-medical expenses for patient |                                           |                                                     |
| Social services         | Not identified                        |                                             |                                                     |
| Legal/criminal system   | None                                  |                                             |                                                     |
| Education               | None                                  |                                             |                                                     |
| Housing                 | None                                  |                                             |                                                     |
| Environment             | None                                  |                                             |                                                     |
Appendix 8 Model validation
To provide external validation we sought to find good additional evidence – not used in model parametrisation – to which we could compare key model output. Where such evidence could not be obtained we report the verification (internal validation) of model outputs. This shows that the model performs as intended and is able to recreate observed events used for the input parameters.

Our approach for external validation was to compare model outcomes in key strata with newer external data than the data informing the model parameters. We focused on validating the output primary – and recurrent breast cancer incidence, ovarian cancer incidence, and mortality.

A8.1. Incidence rate calculations from model simulation
For incidence rates we stratified on the age-group categories in the external (updated) data material to allow a transparent comparison. We calculated the number of person-years at risk in each age-category, and

We calculated the sum of time under observation for each simulated individual to obtain the person-years in the time (age)-intervals, $T$, and the number of events in the intervals, $f$. This gives the incidence rates $h = \frac{f}{T}$. We calculated the 95% confidence intervals as, lower: $h \times \exp\left(- \frac{1.96}{\sqrt{f}}\right)$, upper: $h \times \exp\left(\frac{1.96}{\sqrt{f}}\right)$ [89].

A8.2. Cumulative survival
For model mortality we show Kaplan-Meier plots of survival from background mortality, and total mortality which includes the disease specific excess mortality, compared to a newer Norwegian mortality data.

A8.3. Validation target sources
The incidence data informing the model parameters were extracted from the Norwegian Cancer Registry’s 2016 report ‘Cancer in Norway 2015’ [14]. Since then, a new report was published, ‘Cancer in Norway 2016’ [37] which is used to compare model incidence output. These report are published with the entire Norwegian population as the sample and does not as such present uncertainty intervals around the rates.

We were unable to find additional evidence that fit our target population to which we could compare model incidence of recurrent breast cancers. For this reason we can only demonstrate internal validity. We reviewed the original source’s [39] online appendix for events per person-years at risk (‘Web table 2’), and calculated the incidence rate and the 95% confidence interval around this.

For mortality, we used the newest available life-table from Statistics Norway and calculated the cumulative survival using conventional life-table analysis [38].
A8.4. Results

A8.4.1. Primary breast cancer incidence

Figure A8.1. (Primary) breast cancer incidence rates (95% confidence intervals) by age from model compared to validation target.

The model was set up to run a life-time analysis with relatives from age 20 simulating 100,000 individuals. From the calculated incidence rates and confidence intervals, the output was interpreted as corresponding to the validation targets.
A8.4.2. Ovarian cancer incidence

Figure A8.2. Ovarian cancer incidence rates (95% confidence intervals) relatives by age from model compared to validation target.

The model was set up to run a life-time analysis with relatives from age 20 simulating 100,000 individuals. From the calculated incidence rates and confidence intervals, the output was interpreted as corresponding to the validation targets.
A8.4.3. Breast cancer recurrence

The model was set to no genetic testing and age of the index patients was set at 50, to match the setting and age in the study [39], which reported the 10-year risk of recurrence for patients age 50-59, with an incidence rate of 1.9% (95% C.I. 1.62 - 2.22%). We calculated the person-years at risk and events during this time interval from the model output. There was 8896 breast cancer recurrences in 455,171 person-years, giving a 10-year incidence rate of 1.95% (95% C.I. 1.91 – 2.0%). This could be interpreted as the model agreeing with the input data, verifying the internal validity. Unfortunately, we did not find another external source that could be used for external validation.

A8.4.4. Survival index patients

Figure A8.3. Cumulative survival of index patients from model output compared to validation target. Total mortality includes disease-specific and background mortality.
A8.4.5. Survival relatives

Figure A8.4. Cumulative survival of relatives from model output compared to validation target. Total mortality includes disease-specific and background mortality.

For survival of both index and relatives, the model produces very background mortality-survival as the external validation target. Total mortality-survival deviates, particularly for index patients. This is likely due to the excess mortality from the patient population experiencing breast cancer recurrence, and the selection of mutation carriers in the model population not as prevalent in the general population.