MANC-RISK-SCREEN Version 1: Parameters, Sources, and Assumptions

Table 1: Clinical parameters in deterministic model

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| **Parameter** | **Value** | **Sources and Assumptions** |
| Uptake for screening | 69.1% | NHS Digital Screening and Immunisations Team, 2021 [1]  Women have an equal chance of missing any screen regardless of order in the screening programme |
| Uptake for prediction of risk of breast cancer | 100% in base case  60% in sensitivity analysis | Expert opinion |
| Uptake for receipt of risk information | 100% in base case  95% in sensitivity analysis | Expert opinion |
| Proportion of women who change screening intervals based on risk information | 100% in base case  80% in base case | Expert opinion |
| Proportion of cancers detected by screening | 43.1% | Cancer Research UK, 2022 [2] |
| Age of death due to all-cause mortality | ~weibull(8.97,86.74) | Office for National Statistics 2021 [3]  Using the probability of dying at a given age, a small Markov model was created for a hypothetical starting at the age of birth. This Markov model contained the states alive and dead and recorded the number of individuals expected to die at each age. From this, a simulated data set was created containing the age of death for each individual in the cohort. Using the fitdistrplus package in R, a Weibull distribution was fit to this data. |
| Survival for stage 1 breast cancer | exp(-5.462) | Office for National Statistics 2019 [4]  Exponential survival curve fitted for median survival for women with stage 1 cancer at 5 years post-diagnosis. A previous version of this model had used Nottingham Prognostic Indicator grade rather than stage but found an exponential curve to be the best fit of multiple models selected. As such the same model was applied to data related to cancer stage |
| Survival for stage 2 breast cancer | exp(-4.023) | Office for National Statistics 2019 [4]  Exponential survival curve fitted for median survival for women with stage 2 cancer at 5 years post-diagnosis. A previous version of this model had used Nottingham Prognostic Indicator grade rather than stage but found an exponential curve to be the best fit of multiple models selected. As such the same model was applied to data related to cancer stage |
| Survival for stage 3 breast cancer | exp(-2.465) | Office for National Statistics 2019 [4]  Exponential survival curve fitted for median survival for women with stage 3 cancer at 5 years post-diagnosis. A previous version of this model had used Nottingham Prognostic Indicator grade rather than stage but found an exponential curve to be the best fit of multiple models selected. As such the same model was applied to data related to cancer stage |
| Survival for stage 4 breast cancer for women aged up to 54 | exp(-1.787) | Office for National Statistics 2019 [4]  Exponential survival curve fitted for median survival for women aged under 54 with stage 4 cancer at 5 years post-diagnosis. A previous version of this model had used Nottingham Prognostic Indicator grade rather than stage but found an exponential curve to be the best fit of multiple models selected. As such the same model was applied to data related to cancer stage |
| Survival for stage 4 breast cancer for women aged 55 to 74 | exp(-1.388) | Office for National Statistics 2019 [4]  Exponential survival curve fitted for median survival for women aged 55 to 74 with stage 4 cancer at 5 years post-diagnosis. As this age group covered two age bands in the underlying data, a weighted average of the median 5-year survival was calculated. A previous version of this model had used Nottingham Prognostic Indicator grade rather than stage but found an exponential curve to be the best fit of multiple models selected. As such the same model was applied to data related to cancer stage |
| Survival for stage 4 breast cancer for women aged over 75 | exp(-1.011) | Office for National Statistics 2019 [4]  Exponential survival curve fitted for median survival for women aged over 75 with stage 4 cancer at 5 years post-diagnosis. A previous version of this model had used Nottingham Prognostic Indicator grade rather than stage but found an exponential curve to be the best fit of multiple models selected. As such the same model was applied to data related to cancer stage |
| Breast cancer incidence by age | See “Incidence\_mortality\_ONS2” input csv | Cancer Research UK 2022 [5] |
| 10 year risk of breast cancer estimated using the Tyrer-Cuzick version 8 and Volpara breast density group | See “synthetic\_risk\_data.csv” input | Observations of breast density (using Volpara TruDensity), 10 year breast cancer risk (using Tyrer-Cuzick version 8 and Volpara TruDensity), and lifetime risk (using Tyrer-Cuzick version 8 and Volpara TruDensity) for 15,613 women were shared securely by the BC-PREDICT research team. In order to allow this input data to be shared outside the research team, a synthetic data set was created using the synthpop package in R. This approach resulted in a data set with 15,613 synthetically generated observations of breast density, 10 year risk, and lifetime risk. The approach also preserves the structure of the underlying data including correlations. |
| Lifetime risk of breast cancer estimated using the Tyrer-Cuzick version 8 and Volpara breast density group | See “synthetic\_risk\_data.csv” input | Observations of breast density (using Volpara TruDensity), 10 year breast cancer risk (using Tyrer-Cuzick version 8 and Volpara TruDensity), and lifetime risk (using Tyrer-Cuzick version 8 and Volpara TruDensity) for 15,613 women were shared securely by the BC-PREDICT research team. In order to allow this input data to be shared outside the research team, a synthetic data set was created using the synthpop package in R. This approach resulted in a data set with 15,613 synthetically generated observations of breast density, 10 year risk, and lifetime risk. The approach also preserves the structure of the underlying data including correlations. |
| Volpara breast density estimate | See “synthetic\_risk\_data.csv” input | Observations of breast density (using Volpara TruDensity), 10 year breast cancer risk (using Tyrer-Cuzick version 8 and Volpara TruDensity), and lifetime risk (using Tyrer-Cuzick version 8 and Volpara TruDensity) for 15,613 women were shared securely by the BC-PREDICT research team. In order to allow this input data to be shared outside the research team, a synthetic data set was created using the synthpop package in R. This approach resulted in a data set with 15,613 synthetically generated observations of breast density, 10 year risk, and lifetime risk. The approach also preserves the structure of the underlying data including correlations. |
| Probability that a cancer is metastatic given the age of the woman | 25=4.62%  35=8.67%  45=10.98%  55=12.71%  65=14.25%  75=15.98%  85=17.30% | Age nearest to woman’s current age at diagnosis of cancer used |
| Fraction of cancers that are ductal carcinoma in situ | 21.1% | NHS Digital Screening and Immunisations Team 2021 [1] |
| Probability of cancer being diagnosed as stage I, II, or III given size of tumour | See supplementary appendix X | Kollias et al. (1998), Wen et al. (2015) [6,7]  The supplementary data provided in Wen et al. provided observations of cancer size, number of lymph node involvements, and other variables for 1,661 women. Given that none of the patients had metastatic cancer, it was possible to determine the stage of cancer for each woman using the size of the tumour and number of lymph nodes involved. This data was used to determine the probability that cancers of different sizes would be of different stages. However, the data set contained few observation for women with very small tumours. As such, data from Kollias et al. was combined with that included in Wen et al. to provide a better representation of the distribution of stages in very small cancers. As Kollias et al. only included whether lymph nodes were involved or not and did not state the number of nodes, it was assumed that half of patients with node involvement had one node and half had more than one node. The distributions of stages across cancer size was compared between the studies and aside from the smallest cancers the studies showed close agreement. |
| Mammographic sensitivity by Volpara Density Group (VDG) | VDG1=85.0%  VDG2=77.6%  VDG3=69.5%  VDG4=61.0%  Average=75.7% | Wanders et al. (2017) [8] |
| Detection rate of mammography in high density screens | 4.2 per 1,000 screens | Tice et al. (2013) [9] |
| Incremental detection rate of magnetic resonance imaging mammography in high density screens after negative mammography | 5 per 1,000 screens | Vreeman et al. (personal communication, 2015) see Gray et al. (2017) [10] |
| Incremental detection rate of ultrasound mammography in high density screens after negative mammography | 3 per 1,000 screens | Tice et al (2013) [9] |
| Recall rate for screening | 4.56% | Burnside et al. (2018) [11] |
| Biopsy rate for screening | 2.40% | NHS Digital Screening and Immunisations Team (2021) [1] |
| Growth Model Parameters | | |
| Mean doubling rate for tumours | 4.12 | Weedon-Fekjær et al. (2008) [12] |
| Standard deviation of doubling rate for tumour | 3.93 | Weedon-Fekjær et al. (2008) [12] |
| Mean tumour doublings at clinical detection | 6.5 | Weedon-Fekjær et al. (2008) [12] |
| Standard deviation of tumour doublings at clinical detection | 0.535 | Weedon-Fekjær et al. (2008) [12] |
| Mean tumour doublings at screen detection | 6.12 | Weedon-Fekjær et al. (2008) [12] |
| Standard deviation of tumour doublings at screen detection | 0.96 | Weedon-Fekjær et al. (2008) [12] |
| Log normal mean of tumour growth rate | 1.07 | Weedon-Fekjær et al. (2008) [12] |
| Log normal standard deviation of tumour growth rate | 1.31 | Weedon-Fekjær et al. (2008) [12] |
| Maximum tumour size (mm) | 128 | Weedon-Fekjær et al. (2008) [12] |
| Starting tumour size (mm) | 0.25 | Weedon-Fekjær et al. (2008) [12] |

Table 2: Costs use din deterministic model

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| --- | --- | --- |
| **Parameter** | **Value** | **Sources and Assumptions** |
| Cost of risk stratification | £8.17 | Ongoing microcosting study |
| Cost of mammography screen | £60.93 | Pragmatic microcosting  See supplementary appendix X |
| Cost of follow up | £106.16 | Inflated from value in Gray et al. (2017) [10] |
| Cost of biopsy | £290 | NHS England [13] |
| Cost of ultrasound screening | £52 | NHS England [13] |
| Cost of MRI screening | £114 | NHS England [13] |
| Cost of treating breast cancer by stage, age, and time lived with cancer | See supplementary appendix X | Laudicella et al. (2015) [14]  Laudicella provide estimates of the costs of treating breast cancer in the UK from the two years preceding to eight years following diagnosis. Costs are broken down by stage of cancer (early versus late) and age (under or over 65). These costs were included as an input table in the model. They were then inflated to 2022 levels. An exponential regression was then fit to the data to predict the total cost of treating an individual’s cancer given the length of time they had the cancer, their age of diagnosis, and the stage of their cancer. If a patient was alive for over 8 years following diagnosis the cost of treating their cancer was assumed to be £0 in any subsequent years. |
| Cost of treating a ductal carcinoma in-situ | £9,480.15 | Inflated from value in Gray et al. (2017) [10] |

Table 3: Utility values used in the deterministic model

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Value** | **Sources and Assumptions** |
| Age-related utility values for healthy individuals | 30=0.938  35=0.915  40=0.907  45=0.882  50=0.864  55=0.834  60=0.822  65=0.807  70=0.804  75=0.779  80=0.753  85=0.699  90=0.650  95=0.650  100=0.650 | Ara and Brazier (2011) [15] |
| Utility early breast cancer in the first year | 0.82 | Naik et al. (2017) [16]  Potential utility values were identified from two systematic reviews of utility values in breast cancer [17,18]. From the studies included in these reviews, three studies which estimated utility values covering local and metastatic cancer, conducted in high income countries, and using either EQ-5D and relevant value sets or the time-trade off approach were identified. A focus group was then held with three women who had recovered from breast cancer to decide which of the three sets of utility values they felt best represented the experience of women in the UK.  The values in the chosen study did not change between the first and subsequent years and it was for this reason that the women in the focus group chose the set. However, the ability to choose different values for subsequent years was retained in the model in case future research suggests this is useful for inclusion. |
| Utility early breast cancer in subsequent years | 0.82 | Naik et al. (2017) [16]  Potential utility values were identified from two systematic reviews of utility values in breast cancer [17,18]. From the studies included in these reviews, three studies which estimated utility values covering local and metastatic cancer, conducted in high income countries, and using either EQ-5D and relevant value sets or the time-trade off approach were identified. A focus group was then held with three women who had recovered from breast cancer to decide which of the three sets of utility values they felt best represented the experience of women in the UK.  The values in the chosen study did not change between the first and subsequent years and it was for this reason that the women in the focus group chose the set. However, the ability to choose different values for subsequent years was retained in the model in case future research suggests this is useful for inclusion. |
| Advanced breast cancer in the first year | 0.75 | Naik et al. (2017) [16]  Potential utility values were identified from two systematic reviews of utility values in breast cancer [17,18]. From the studies included in these reviews, three studies which estimated utility values covering local and metastatic cancer, conducted in high income countries, and using either EQ-5D and relevant value sets or the time-trade off approach were identified. A focus group was then held with three women who had recovered from breast cancer to decide which of the three sets of utility values they felt best represented the experience of women in the UK.  The values in the chosen study did not change between the first and subsequent years and it was for this reason that the women in the focus group chose the set. However, the ability to choose different values for subsequent years was retained in the model in case future research suggests this is useful for inclusion. |
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Table 4: Input parameters with sampling distributions and hyperparameters used in PSA

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| --- | --- | --- | --- |
| Parameter | Distribution | Hyperparameter 1 | Hyperparameter 2 |
| Mammographic Sensitvity | | Mean | Standard deviation |
| Beta 1 | Normal | 1.47 | 0.1 |
| Beta 2 | Normal | 6.51 | 0.5 |
| VDG modifiers | |  |  |
| VDG 1 | Beta | 96 | 16 |
| VDG 2 | Beta | 298 | 86 |
| VDG 3 | Beta | 212 | 93 |
| VDG 4 | Beta | 61 | 39 |
| Supplemental imaging | |  |  |
| US | Beta | 35.89 | 11927 |
| MRI | Beta | 99.495 | 19799.5 |
|  |  |  |  |
| Growth rate distribution | | Mean | Standard deviation |
|  | Normal | 1.07 | 0.09 |
|  | Normal | 1.31 | 0.11 |
|  |  |  |  |
|  |  |  |  |
| Survival post-BC | | Mean | Correlated draws |
| stage 1 | Multivariate normal (MVN) | -5.46 | See Table 5 |
| stage 2 | MVN | -3.82 | See Table 5 |
| stage 3 | MVN | -2.72 | See Table 5 |
| Survival metastatic BC |  | Mean | Correlated draws |
| stage 4, age <55 | MVN | -1.79 | See Table 6 |
| stage 4, age 55-74 | MVN | -1.39 | See Table 6 |
| stage 4, age >74 | MVN | -1.01 | See Table 6 |
| Utility weights | | | |
| Early | 1-exp(MVN) | -1.71 | See Table 7 |
| Advanced cancer | 1-exp(MVN) | -1.39 | See Table 7 |
| Costs |  | Mean | Standard Deviation |
| Risk stratification | Log normal | 2.09 | 0.06 |
| Cost multiplier | Normal | 0 | 0.10 |

Table 6: Covariance matrix for survival post-BC

|  |  |  |
| --- | --- | --- |
| 0.08878 |  |  |
| 0.01819 | 0.00373 |  |
| 0.01866 | 0.00384 | 0.00395 |

Table 7: Covariance matrix for metastatic survival

|  |  |  |
| --- | --- | --- |
| 0.01157 |  |  |
| 0.00884 | 0.00705 |  |
| 0.00804 | 0.00613 | 0.00560 |

Table 8: Covariance matrix for utility values

|  |  |
| --- | --- |
| 0.00309 |  |
| 0.00446 | 0.00643 |

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