Changes in the NHD model

1. Additional parameter - undiagnosed mortality to BC stage 4 (i.e. mortality at the time of death) -is added to the model. This parameter needs to be calibrated
2. Probability to be diagnosed changed from linear function based on time from onset to an annual probability in each stage (+2 more parameters).
3. The assumptions on disease progression changed. Originally the mean was equalised to the median reported in Broder (2021) study. In the new version the median was converted by simulating the 1 mln values assuming the beta distribution and that the reported range actually is a 90% CI. The remaining outliers were considered to be distributed within the 5 following years. The new calculated means were: Stage I to Stage II: 4 years (4.2724); Stage II to Stage III: 3 years (3.1811); Stage III to Stage IV: 2 years (1.9537). The second scenario will rely on the similar assumptions as in the Grail model on the exponential progression of cancer with the Stage I to II progression be replaced with the double time from stage II to Stage III: 6.3622.
4. The shape should be the same on smaller for more advanced cancer

The Delphi study by Broder et al (2021) reports the time to progression to the next stage for undiagnosed cancer.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Median time of BC progression: |  | | Median and range reported | Mean used in the base-case | Mean used in the scenario |
| Stage I to Stage II | |  | 3 (1-7) | 4.2724 | 6.3622 |
| Stage II to Stage III | |  | 2 (1-5) | 3.1811 | 3.1811 |
| Stage III to Stage IV | |  | <1(<1-4) | 1.9537 | 1.9537 |

Grail study by Hubbell et al (2021) used the following assumptions [based on the researchers’ opinion] about 4 possible options for cancer progression, - the time the person stays in the health state before either (a) progress to the next stage or (b) get diagnosed. They used the assumption on the shape in Weibull distribution of 1.

Table 1. Mean time in a health state before a person either (a) progress to the next stage or (b) get diagnosed Grail study by Hubbell et al (2021)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Vslow | Slow | Fast | AggFast |
| Time in stage |  |  |  |  |
| 1 | 10 | 7 | 4 | 2 |
| 2 | 4 | 3 | 2 | 1 |
| 3 | 2 | 1.5 | 1 | 0.5 |
| 4 | 1 | 1 | 1 | 0.5 |

The Delphi study by Broder et al (2021) reports the time to progression to the next stage for undiagnosed cancer.

|  |  |  |  |
| --- | --- | --- | --- |
| **Median time of BC progression:** | **Median and range** | |  |
| Stage I to Stage II | | 3 | 3 (1-7) |
| Stage II to Stage III | | 2 | 2 (1-5) |
| Stage III to Stage IV | | 1 | <1(<1-4) |

Using this two tables the probability to get diagnosed during one year for a person in each particular cancer state may be estimated (very roughly) as: = 1/(mean time in the health state + mean time to progression) (Table 3).

Table 3.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Probability of diagnosis | |  |  |  |  |
|  | Vslow | Slow | Fast | AggFast | Mean across the scenarios |
| Stage 1 | 0.076923 | 0.1 | 0.142857 | 0.2 | 0.129945 |
| Stage 2 | 0.166667 | 0.2 | 0.25 | 0.333333 | 0.2375 |
| Stage 3 | 0.333333 | 0.4 | 0.5 | 0.666667 | 0.475 |
| Stage 4 | 1 | 1 | 1 | 1 | 1 |

There are multiple options how to use these data in the new model:

Option 1. Similar to the first model, use the mean time from Broder et al (2021), and set the distributions around the mean symptomatic presentation rate as the mean across the scenarios (Table 3 last column) (use beta, calculate from the set mean and the calibration).

Option 2. Similar to the first model, use the mean time from Broder et al (2021), and set the priors on diagnostic rate to be within the range from slow to fast in the Table 3.

Option 3. To do a few models: one based on Broder et al (2021) and another one on a slower progressing cancer assumption (7,3,2 years, slow scenario).

Option 4. Incorporating all the uncertainty (almost). Sampling the mean time from a distribution (uniform or truncated normal within the range in the table 1) and fixing the shape to 1. (a) fixing the sympt presentation rate to one in Table 3 or (b) calibrating sympt presentation with the priors in table 3.

Option 5. Incorporating all the uncertainty. Sampling the mean time from a distribution (uniform or truncated normal within the range in the table 1) and the shape. (a) fixing the sympt presentation rate to one in Table 3 or (b) calibrating sympt presentation with the priors in table 3.