**Appendix 1**

**MODEL APPENDIX: THE DUTCH MISCAN-EAC MODEL STRUCTURE AND CALIBRATION**

**MODEL OVERVIEW**

The Dutch MISCAN-EAC model is a semi-Markov microsimulation model for esophageal adenocarcinoma (EAC). The population is simulated individual by individual, and each person can evolve through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the Dutch MISCAN-EAC model generates durations in states. With the assumption of exponential distribution of the duration in each state, this way of simulating leads to similar results as a Markov model with yearly transition probabilities. However, the advantage of the MISCAN approach is that durations in a certain state do not need to be a discrete value but can be continuous. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, Barrett’s incidence, and transitions from one state of disease to another.

The basic structure of the Dutch MISCAN-EAC model is separated in three main parts:

* Demography part
* Natural history part
* Screening, surveillance and treatment part

**Demography Part**

The individual life histories are simulated in the demography part of the model. For each person, a birth date and death date for other causes than EAC is simulated. The distribution of births and deaths can be adjusted to represent the simulated population.

**Natural history part**

The natural history part of Dutch MISCAN-EAC simulates the development of EAC in the population. The model used in this study was calibrated to the Dutch EAC incidence rates per age group, averaged over years 2012-2017 (**Figure 1**).(1)

**Figure 1**. Average esophageal adenocarcinoma (EAC) incidence in the Netherlands in years 2012-2017

We assume that EAC develops through precursor Barrett’s esophagus (BE). For each individual in the simulated population, a personal risk index is generated. A minority of the population has symptomatic gastro-esophageal reflux disease (GERD), giving them a higher risk of developing BE during their lifetime.(2, 3) The development of BE is generated according to this personal risk index and an age-specific incidence of onset. Furthermore we distinguish short-segment (SS) and long-segment (LS) BE. The sequence from the onset of BE to EAC diagnosis is governed by sojourn times between the different states. BE starts in a state with no dysplasia (ND), thereafter dysplasia can develop. Two states of dysplasia are defined: low-grade dysplasia (LGD) and high-grade dysplasia (HGD). Indefinite dysplasia was considered as LGD in our model. There is a possibility that regression from HGD to LGD and from LGD to ND occurs. The probability to regress or progress depends on a transition rate matrix, and it is therefore also influenced by the sojourn time. The probability of regression, progression, and the according sojourn times can be calculated as follows:

$Probability of regression in state i =\frac{R\_{ir}}{R\_{ir}+R\_{ip}}$, where *i*: current state LGD or HGD, *r*: regress, *p*: progress, *R*: rate

$Probability of progression in state i=\frac{R\_{ip}}{R\_{ir}+R\_{ip}}$, where *i*: current state LGD or HGD, *r*: regress, *p*: progress, *R*: rate

$Sojourn time in state i=\frac{1}{R\_{ir}+R\_{ip}}$, where *i*: current state LGD o*r* HGD: regress, *p*: progress, *R*: rate

From HGD, malignant cells can arise that can transform to cancer state T1a. From this state, preclinical malignant cancer stage 1 can develop, which can sequentially progress into preclinical malignant states 2, 3, and 4. In each of these four states, there is a probability of the cancer being clinically diagnosed (*i.e.*, because of symptoms). The sojourn times between these described states are exponentially distributed. Because most sojourn times extend beyond the demography-generated age of death from other causes, only a small proportion of the population develops EAC from BE.

The survival after EAC diagnosis depends on the cancer stage. We used data on survival of EAC patients in the Netherlands diagnosed in years 2010-2013 to inform the modeled survival rates at 1, 3, and 5 years after diagnosis.(4) A graphical representation of the model structure is shown in **Figure 2**.

**Figure 2.** *MISCAN-EAC Model structure*

EAC: esophageal adenocarcinoma, LSBE: long-segment Barrett’s esophagus, SSBE: short-segment Barrett’s esophagus, T1a: esophageal adenocarcinoma T1a

**Surveillance and treatment part**

The development of EAC can be interrupted by surveillance. Surveillance can detect BE, dysplasia and preclinical cancer. When BE or dysplasia are detected, they can be removed using treatment. Cancer may be detected in an earlier stage than it would have been otherwise (i.e., in case of clinical diagnosis). In this way surveillance can reduce EAC incidence and EAC death. Endoscopic eradication treatment (EET) can be used for treatment of BE patients. We assume that duration of initial EET is 2 years and BE patients receive endoscopic mucosal resection (EMR) and/or radiofrequency ablation. The EET success and recurrence rates are assumed based on the pre-treatment state of the patients (ND, LGD, HGD/T1a EAC).

For each individual patient, the outcome of the 2-year endoscopic treatment is randomly drawn based on the disease state at the start of the treatment (**Manuscript Table 2**). In case of treatment failure, the patient remains in endoscopic surveillance at an interval based on their pre-treatment dysplastic grade. In case of treatment success, the patient transits to the state of complete eradication of dysplasia with persistent metaplasia (CE-D) or complete eradication of dysplasia and intestinal metaplasia (CE-IM) after 2 years. In the former case, we assume that the patient in the recurrent NDBE phase having the same assumptions as our natural history model, only without the distinction between short-segment and long-segment. In the latter case, the patient stays in the CE-IM state for a sojourn time randomly selected from an exponential distribution. If the patient transits to the next state (recurrence/progression), he immediately would transit to the state of histological recurrence and a new RFA is applied followed by surveillance according to post-treatment surveillance intervals described in ***Appendix Table 1.***

**Integration of the three model components**

For each individual, the demography part of the model simulates a time of birth and a time of death of other causes than EAC, creating a life history without EAC. Subsequently the onset of BE is simulated for some of the individuals. Most individuals do not develop any dysplasia. In case of progressive BE, dysplasia may develop and HGD transforms into a malignant state, causing symptoms and eventually resulting in death from EAC. If a person dies from EAC before he would die from other causes, his death age is adjusted accordingly.

After the life history of a person has been adjusted for the natural history of disease, it can also be adjusted for the effects of screening. During screening and surveillance, BE with or without dysplasia can be removed by treatment. BE is removed at the time of treatment and this individual does not develop cancer according to the original life history because the precursor has been removed. In case of successful treatment, the individual may die from other cause or the individual may develop BE again and EAC later. The effect of surveillance is the difference in life-years between the simulation without surveillance and the simulation with surveillance.

**MODEL QUANTIFICATION AND CALIBRATION**

In this part, the parameters that we use in the different parts of the model and the methods that we have used to calibrate them, are described. The main source that we used for the calibration process was the ProBar study, which is a multicenter prospective cohort study in the Netherlands.(5) In this study, 783 patients with NDBE (≥2 cm) were included and followed under endoscopic surveillance according to the guidelines of the American College of Gastroenterology with a median follow-up of 7.6 years. In this study, neoplastic progression of BE patients (development of HGD or EAC) was determined during follow-up.

**Demography parameters**

There are two types of demography parameters: birth tables and life tables. For the birth tables, we assumed that all individuals were born at 1957. The life tables were derived from the life tables published by Statistics Netherlands.(6) We assumed everyone to die before age 100.

**Natural history parameters**

The prevalence rate of symptomatic GERD is around 20%.(7-10) Therefore we assumed that 20% of the total population suffers from symptomatic GERD. Another fixed parameter in the model was the proportion of the BE patients who had symptomatic GERD. We assumed that individuals with GERD symptoms make up 60% of the BE patient population.(11, 12)

One of the calibration targets in our model is the maximum BE prevalence at ages 50-70, which was set to 12% in the male population and 7% in the female population. There is limited evidence available on precise prevalence of BE in the Netherlands, but based on the expert opinion and available studies we do feel it would not be higher than these percentages.(13)

Using the ProBar study, we estimated that from the male BE patients, 1.4% were HGD, 13.1% were LGD, and 85.5% were NDBE. From the female BE patients, we estimated that 0.5% were HGD, 9.7% were LGD, and 89.8% were NDBE. Both distributions were used as calibration targets in the model.(5) SSBE and LSBE were assumed to have similar proportions of LGD and HGD. Furthermore, the EAC incidence was calibrated to the EAC incidence rates in the Netherlands in years 2012-2017.(1) EAC was assumed to be diagnosed in stages 1, 2, 3, and 4 in 17%, 15%, 30%, and 38% of cases in women, and 17%, 13%, 31%, and 40% of cases in men, respectively.(5)

We adjusted the screening part of the model in order to reproduce the characteristics of the ProBar study design by implementing realistic surveillance and diagnostic inaccuracy as observed in this study.(5) BE with or without LGD was detected at index endoscopy. Surveillance was stopped when HGD or EAC was found. As the SSBE population in the ProBar cohort does not cover the total SSBE population in our model (ProBar only included ≥2cm), the progression rates were taken as an upper bound for these populations. The calculation of the annual progression rates as calibration targets was calculated after a follow-up of 13 years using a weighted average of follow-up years (**Figure 6**).

**Calibration process**

During the optimization the Pearson chi-square Goodness of fit function was minimized. The deviation of each of the four calibration targets (EAC incidence rates per age group, annual progression rate from BE to HGD and EAC, proportions of dysplasia and average BE prevalence at ages 50-70) were summed to calculate the overall Goodness of fit of the model given a certain set of parameters. The search for new parameters was performed following the Nelder-Mead simplex method.

**CALIBRATION RESULTS**

Calibration results are presented in **Figures 3-6**. **Figures 3** and **4** show the age-specific EAC incidence calibration targets in years 2012-2017 in the black diamonds,(1) and the results of the model in the blue (male) and red (female) lines, respectively.

**Figure 3**. *Age-specific EAC incidence in Dutch male population (Observed[1] vs simulated) in the absence of screening and surveillance (natural history)*

**Figure 4.** *Age-specific EAC incidence in Dutch female population (Observed[1] vs simulated) in the absence of screening and surveillance (natural history)*

**Figure 5** presents the prevalence of BE in Dutch male and female population in absence of screening or surveillance for BE (natural history).

At baseline in the ProBar study, the median age was 59 for men, and 65 for women. When replicating the ProBar study, we could assess the progression rate in a 59-year-old male and 65-year-old female BE (ND+LGD) cohort towards HGD and EAC. The results are presented in **Figure 6**.

**Figure 6.** *Annual progression rate from short-segment (SS) or long-segment (LS) Barrett’s esophagus towards high-grade dysplasia or esophageal adenocarcinoma (EAC) in men and women*

The other optimized or fixed parameters used in the model are presented in **Table 1**.

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| **Table 1.** *Parameters used in the model* |  |
| **Model parameter** | **Male model** | **Female model** | **Parameter characteristics** |
| Symptomatic GERD prevalence | 20% (7-10) | 20% (7-10) | Fixed input |
| BE developed from symptomatic GERD population | 60% of BE from GERD population(11, 12) | 60% of BE from GERD population(11, 12) | Fixed input |
| BE prevalence age 50-70 | 4-10% | 4-7% | Optimized |
| Average duration between one state to the next state (years) |  |
| SSBE to SSLGD | 18.6 | 38.1 | Optimized |
| SSLGD to SSHGD | 3.3 | 6.7 | Optimized |
| SSHGD to T1a  | 2.6 | 5.4 | Optimized |
| LSBE to LSLGD | 11.3 | 23.1 | Optimized |
| LSLGD to LSHGD | 2.0 | 4.1 | Optimized |
| LSHGD to T1a  | 1.6 | 3.3 | Optimized |
| T1a to preclinical stage 1 EAC | 1.4 | 1.4 | Optimized |
| Regression transition probabilityLGD to NDBEHGD to LGD | 79.5%24.4% | 79.5%24.4% | OptimizedOptimized  |
| BE: Barrett’s esophagus; EAC: esophageal adenocarcinoma; GERD: Gastroesophageal Reflux disease; HGD: high grade dysplasia; LGD: low grade dysplasia; LS: long-segment; NDBE: non-dysplastic Barrett’s esophagus; SS: short-segment |

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