## **SUPPLEMENTARY MATERIAL**

**Strongly Divergent Impact of Adherence Patterns**

**on Efficacy of Colorectal Cancer Screening:**

**The Need to Refine Adherence Statistics**

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### **Supplementary Appendix 1. COSIMO Model Documentation**

#### **Conceptual model structure**

Our Markov-based Colorectal Cancer Multistate Simulation Model (COSIMO) simulates the natural history of CRC based on the process of precursor lesions (non-advanced and advanced adenomas) developing into preclinical (asymptomatic) and then clinical (symptomatic) cancer. The simulation is performed on a hypothetical previously unscreened German population, with the number of simulated subjects and their corresponding baseline age (minimum 50 years) being variables to be chosen prior to model start. COSIMO can principally be used for simulating any population, provided updated or appropriately adjusted input parameters.

At start of the simulation, certain proportions of no neoplasm, non-advanced adenoma, advanced adenoma and preclinical CRC are assigned to the hypothetical population. The simulation runs up to a predefined number of cycles of each one year. Each year, people at each state have a certain probability (transition rate) to progress to the next state. Subjects with CRC may die from the disease, and at each state people may experience non-CRC death, reflecting the general background mortality from other causes.

Screening can alter the progression between states. People with adenoma will be moved backward to the state of no neoplasm, assuming removal of their adenoma at colonoscopy (for screening or diagnostic workup, e.g. after a positive fecal test). Subjects will then continue to have the probabilities to progress to the next states as those without findings at screening. We assume that, although these people are under a higher risk of developing adenomas or cancers than the general population,1 the excess risk will be effectively compensated through the protection provided by surveillance colonoscopies.2,3 Preclinical CRC detected at screening will be moved forward to the state of diagnosed cancer.

After each cycle where a screening test was applied, the model is able to differentiate the simulated population into a ‘screening negative’ and a ‘screening positive’ group, which allows for modelling different trajectories depending on the screening outcome. In such scenarios, subjects only receive the next screening round if they had a negative test result in the respective previous round. In the base case model, subjects with detected non-advanced adenomas or false-positive test results are assumed to undergo surveillance colonoscopies at predefined intervals of 10 years up to a predefined end age of 75 years. In case an advanced adenoma was detected, either at the primary screening test or at a surveillance colonoscopy, subjects are assumed to undergo periodic surveillance colonoscopies at 3-year intervals up to a predefined end age of 85.

#### **Model parameters**

**Starting prevalences and transition rates**

An overview of key model parameters is given in **Supplementary** **Table 1**.

*Data source*

The data basis of our analyses on model starting prevalences and transition rates was the nationwide screening colonoscopy registry run by the Central Research Institute of Ambulatory Health Care in Germany. The registry, which was built up along with the introduction of the screening colonoscopy offer in the year 2002, is a repository of all screening colonoscopies conducted in Germany. Reporting is virtually complete, as it is a prerequisite for physicians’ reimbursement by the health insurance funds. The registry includes only primary screening examinations (i.e., colonoscopies conducted for surveillance, work-up of symptoms or other screening tests are not included). Items reported include, besides basic sociodemographic variables, findings at colonoscopy, including number, size and histological characteristics of polyps. In case of multiple neoplasms, only the most advanced one (non-advanced adenoma, advanced adenoma, or cancer) is recorded. Advanced adenomas are defined as at least 1 adenoma ≥ 1 cm or at least 1 adenoma with villous components or high-grade dysplasia.

Noteworthy, the reporting for the screening colonoscopy registry does not differentiate by the class of lesion. Thus, the herein used term ‘adenoma’ refers to conventional or serrated adenomas (polyps) alike. While we preferred to refer to our model as being based on the adenoma-carcinoma pathway in previous publications 4–8 for the sake of simplicity and comprehensibility (as the grand majority of CRCs develops through this well-established pathway of cancer development 9,10), in fact COSIMO’s defining parameters were derived using polyp/adenoma prevalences as detected and reported at screening colonoscopy, regardless of their underlying mechanism or pathway of development. Therefore, it will be more precise to refer to the model as being based on the ‘natural history of CRC’, without restrictions on underlying CRC development pathways.

*Starting prevalence*

The proportions of no neoplasm, non-advanced adenoma, advanced adenoma and preclinical CRC at the beginning of simulation were calculated based on the data from 344,658 participants of the German screening colonoscopy program who had their first screening colonoscopy during 2003–2012 at the age of 55 years.6 To take into account that a certain proportion of neoplasms needs to be assumed to have been missed at colonoscopy screening, in particular for serrated or flat polyps,11,12 we re-calculated the previously reported prevalences,6 assuming representative miss rates of 25% for non-advanced adenomas and 5% for advanced neoplasms (advanced adenomas and preclinical cancers).

This was used as the best estimate for simulations starting with a 50-year-old population, which seems reasonable as selected regional programs which offer screening colonoscopy from age 50 on found similar prevalences of adenomas in age groups 50-54 and 55-59.13

*Transition rates*

Transition rates between states were estimated based on data from the nationwide screening colonoscopy registry by several separate birth cohort and mean sojourn time analysis. Details on the principles of these methods have been described previously.14–16 Briefly, sex- and age-specific annual incidence and transition rates were estimated from sex- and age-specific prevalences of adenomas among 3.6 – 4.3 million screening participants from the same birth cohorts in 2003–2011 (2003-2009) and 2004–2012 (2004 – 2010). The analysis on mean sojourn time of preclinical cancers additionally incorporated registry-reported colorectal cancer incidence and participation rates in screening colonoscopy from 2003-2006.

Similar as for the starting prevalences, as colonoscopy was shown to be less effective in detecting serrated lesions (and as the true proportions of missed conventional adenomas and serrated lesions in the registry-reported prevalences is unknown), we re-calculated previously reported transition rates 14–16 to adjust for representative colonoscopy miss rates.11,12 This adjustment resulted in slightly higher overall prevalences of adenomas, and therefore (when compared to previously reported rates) in slightly higher transition rates of incidence adenomas, as well as slightly lower transition rates from non-advanced to advanced adenomas and from adenomas to cancer. Age- and sex-specific annual transition rates between the states were estimated for age groups from 55-79 years in steps of 5 years. Estimates for age 50-54 and ≥ 80 (or ≥ 85) were assumed to be the same as those for age group 55-59 and 75-79 (or 80-84), respectively.

Confidence intervals for both starting prevalences and transition rates were derived by bootstrap analysis with resampling within sex- and age-specific subgroups. Ninety-five percent confidence intervals were determined as the 2.5th and 97.5th percentile of transition rate estimates obtained in 1,000 runs.

**Mortality rates**

Mortality rates for patients whose cancer was detected by screening or by symptoms were estimated in previous analyses.7,8 We combined data on the proportion of screening-detected cases among all CRC cases in Germany during 2003-2012 in people aged 55-79 years4,17 with the overall CRC-specific mortality rates by year after diagnosis in Germany in 2011-2012.17 We then used hazard ratios for patients detected by screening versus symptoms as obtained from a German population-based case-control study on CRC screening with long-term mortality follow-up of CRC patients7,18 to estimate CRC-specific mortality rates by mode of detection (**Supplementary** **Table 2**). Sex- and age-specific general mortality rates and average life expectancy of the population were extracted from German population life tables 2010/2012 (**Supplementary** **Table 3).**19

**Diagnostic performance**

*Fecal immunochemical testing (FIT)*

The sensitivity and specificity of FIT screening were adjusted for a positivity rate of 10% as reported by an analysis by Gies and colleagues who showed that the positivity rate is a very good proxy indicator for the diagnostic performance.20,21 We chose to use the sensitivity and specificity parameters (**Supplementary Table 1C**) as adjusted for a positive rate of 10% as this was the overall positivity rate of FITs used in Germany in 2018 22 and assumed an absolute difference of 5% in sensitivities (higher in men) and specificities (higher in women) based on evidence suggesting varying performance according to sex.23–26 For the base case scenario, due to the lack of evidence suggesting otherwise and in line with previous models on FIT screening,27,28 conditional independence between repeated rounds of FIT testing was assumed.

*Colonoscopy*

For colonoscopy, we assumed representative sensitivities (the proportion of detected cases among all subjects with the disease) of 75% and 95% for non-advanced adenomas and advanced neoplasms, respectively, based on evidence on the polyp and adenoma miss rates determined by tandem colonoscopy,11,12 with perfect specificity (the proportion of healthy people classified as such among all subjects without the disease) (100%). As our model follows a population-based approach which implies assigning global parameters to all subjects, this already incorporates differences in miss rates found according to polyp class.

### **Supplementary Appendix 2. Supplementary Tables and Figures**

**Overview**

**Supplementary Table 1.** Overview of model parameters

**Supplementary Table 2.** Annual CRC-specific mortality rates of CRC patients by mode of cancer detection

**Supplementary Table 3.** Sex- and age-specific general mortality rates

**Supplementary Table 4**. Differences in Long-term Outcomes for Screening with Annual FIT from Ages 50-75 given Varying Patterns of Adherence Yielding Identical Adherence Levels. Sensitivity Analysis using the lower limits of the 95% confidence intervals of starting prevalences and transition rates between model states.

**Supplementary Table 5**. Differences in Long-term Outcomes for Screening with Annual FIT from Ages 50-75 given Varying Patterns of Adherence Yielding Identical Adherence Levels. Sensitivity Analysis using the upper limits of the 95% confidence intervals of starting prevalences and transition rates between model states.

**Supplementary Table 6.** Differences in Long-term Outcomes for Screening Colonoscopy at Ages 50, 60 and 70 given Varying Patterns of Adherence Yielding Identical Adherence Levels. Sensitivity Analysis using the lower limits of the 95% confidence intervals of starting prevalences and transition rates between model states.

**Supplementary Table 7**. Differences in Long-term Outcomes for Screening Colonoscopy at Ages 50, 60 and 70 given Varying Patterns of Adherence Yielding Identical Adherence Levels. Sensitivity Analysis using the upper limits of the 95% confidence intervals of starting prevalences and transition rates between model states.

**Supplementary Table 8**. Differences in Long-term Outcomes for Screening with Annual FIT from Ages 45-75 given Varying Patterns of Adherence Yielding Identical Adherence Levels.

**Supplementary Table 9.** Differences in Long-term Outcomes Screening Colonoscopy at Ages 45-75 given Varying Patterns of Adherence Yielding Identical Adherence Levels.

#### **Supplementary Table 1.** Overview of model parameters

|  |
| --- |
| **A. Proportions of no neoplasm, non-advanced adenoma, advanced adenoma and preclinical CRC at the beginning of simulation1** |
|   |   | **Most advanced finding****% (95% confidence interval)** |
| **Sex** |  | **No neoplasm** | **Non-advanced adenoma** | **Advanced adenoma** | **Preclinical colorectal cancer** |
| Men |  | 71.5 (71.3 – 71.7) | 21.7 (21.5 – 21.9) | 6.3 (6.1 – 6.4) | 0.48 (0.45 – 0.52) |
| Women |  | 83.2 (83.0 – 83.3) | 13.2 (13.0 – 13.3) | 3.4 (3.3 – 3.5) | 0.26 (0.24 – 0.29) |
| 1 Estimates based on the German screening colonoscopy registry. Extracted and recalculated from reference 6 |
|   |   |   |   |   |   |
| **B. Sex- and age-specific annual transition rates between states²** |
|   |   | **Annual transition rates** **% (95% confidence interval)** |
| **Sex** | **Age**  | **No neoplasm tonon-advanced adenoma** | **Non-advanced adenoma toadvanced adenoma** | **Advanced adenoma topreclinical colorectal cancer** | **Preclinical colorectal cancer toclinical colorectal cancer** |
| Men | 50-54 | 3.1 (2.9 – 3.4) | 3.3 (2.8 – 3.9) | 2.6 (2.2 – 3.1) | 17.0 (16.0 – 18.2) |
|   | 55-59 | 3.1 (2.9 – 3.4)  | 3.3 (2.8 – 3.9) | 2.6 (2.2 – 3.1)  | 17.0 (16.0 – 18.2) |
|   | 60-64 | 3.1 (2.8 – 3.4) | 3.2 (2.6 – 3.7) | 3.1 (2.6 – 3.4) | 18.1 (17.2 – 19.1) |
|  | 65-69 | 3.2 (2.9 – 3.4)  | 3.2 (2.6 – 3.7) | 3.8 (3.4 – 4.3) | 20.1 (19.2 – 20.9) |
|  | 70-74 | 2.9 (2.6 – 3.3) | 3.3 (2.6 – 4.0) | 5.1 (4.5 – 5.8) | 19.4 (18.5 – 20.4) |
|  | 75-79 | 2.3 (1.8 – 2.9) | 3.0 (1.9 – 4.2) | 5.2 (4.2 – 6.2)  | 19.0 (17.9 – 20.1) |
|  | 80+ | 2.3 (1.8 – 2.9) | 3.0 (1.9 – 4.2) | 5.2 (4.2 – 6.2) | 17.2 (16.0 – 18.8) |
| Women | 50-54 | 1.8 (1.7 – 2.0) | 3.2 (2.6 – 3.8) | 2.5 (2.0 – 2.9) | 20.1 (18.6 – 21.8) |
|   | 55-59 | 1.8 (1.7 – 2.0) | 3.2 (2.6 – 3.8) | 2.5 (2.0 – 2.9) | 20.1 (18.6 – 21.8) |
|   | 60-64 | 2.0 (1.8 – 2.2) | 2.9 (2.2 – 3.4) | 2.7 (2.2 – 3.2) | 21.1 (19.7 – 22.5) |
|  | 65-69 | 2.1 (1.9 – 2.3) | 2.9 (2.3 – 3.5) | 3.8 (3.3 – 4.3) | 20.6 (19.5 – 21.8) |
|  | 70-74 | 2.0 (1.7 – 2.2) | 3.8 (3.0 – 4.6)  | 5.0 (4.2 – 5.7) | 19.6 (18.6 – 20.8) |
|  | 75-79 | 1.5 (1.1 – 2.0) | 3.0 (1.7 – 4.4) | 5.6 (4.4 – 6.8) | 18.2 (17.1 – 19.5) |
|  | 80+ | 1.5 (1.1 – 2.0) | 3.0 (1.7 – 4.4) | 5.6 (4.4 – 6.8) | 16.4 (15.3 – 17.8) |
| ² Estimates extracted and recalculated from references 14–16 |
|   |   |   |   |   |   |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| **Supplementary Table 1** Overview of model parameters (continued)

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| --- | --- | --- | --- | --- | --- |
|   |   |   |   |   |   |
| **C. Diagnostic performance parameters** |
|   |   | **Performance (%)** |
|  **Test (sex)** | **Parameter** | **No neoplasm** | **Non-advanced adenoma** | **Advanced adenoma** | **Preclinical colorectal cancer** |
| FIT (men) **³** | Sensitivity | - | 15.7 | 31.3 | 80.6 |
|  | Specificity | 91.2 | - | - | - |
| FIT (women) **³** | Sensitivity | - | 10.7 | 26.3 | 75.6 |
|  | Specificity | 96.2 | - | - | - |
|  Colonoscopy (both sexes)4 | Sensitivity | - | 75.0 | 95.0 | 95.0 |
| Specificity | 100 | - | - | - |
| 3 Estimates based on references 20,21 and 23–26.4 Estimates based on references 11,12FIT, fecal immunochemical test |
|  |

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#### **Supplementary Table 2.** Annual CRC-specific mortality rates of CRC patients by mode of cancer detection1

|  |  |
| --- | --- |
|   | **Annual CRC-specific mortality rates (%)** |
| **Year after diagnosis** | **Screeningcolonoscopy–detected cases** | **Symptom-detectedcases** |
| **Men** | **Women** | **Men** | **Women** |
| 1 | 4.6 | 3.7 | 19.7 | 20.6 |
| 2 | 2.2 | 1.9 | 9.3 | 10.7 |
| 3 | 2.1 | 1.3 | 8.8 | 7.4 |
| 4 | 1.5 | 0.9 | 6.3 | 4.8 |
| 5 | 1.2 | 0.6 | 5.0 | 3.3 |
| 6 | 0.8 | 0.3 | 3.5 | 1.7 |
| 7 | 0.4 | 0.3 | 1.8 | 1.8 |
| 8 | 0.4 | 0.3 | 1.9 | 1.8 |
| 9 | 0.4 | 0.0 | 1.9 | 0.0 |
| 10 | 0.0 | 0.0 | 0.0 | 0.0 |

1 estimates extracted from references7,8

CRC, Colorectal cancer.

#### **Supplementary Table 3.** Sex- and age-specific general mortality rates

|  |  |
| --- | --- |
|   | **General mortality rates from age to age +1 (%)**1 |
| **Age** | **Men** | **Women** |
| 50 | 0.4 | 0.2 |
| 51 | 0.4 | 0.2 |
| 52 | 0.5 | 0.3 |
| 53 | 0.6 | 0.3 |
| 54 | 0.6 | 0.3 |
| 55 | 0.7 | 0.4 |
| 56 | 0.7 | 0.4 |
| 57 | 0.8 | 0.4 |
| 58 | 0.9 | 0.4 |
| 59 | 1.0 | 0.5 |
| 60 | 1.0 | 0.5 |
| 61 | 1.1 | 0.6 |
| 62 | 1.2 | 0.6 |
| 63 | 1.3 | 0.7 |
| 64 | 1.4 | 0.7 |
| 65 | 1.5 | 0.8 |
| 66 | 1.7 | 0.9 |
| 67 | 1.8 | 0.9 |
| 68 | 1.9 | 1.0 |
| 69 | 2.1 | 1.1 |
| 70 | 2.2 | 1.2 |
| 71 | 2.4 | 1.3 |
| 72 | 2.7 | 1.4 |
| 73 | 3.0 | 1.6 |
| 74 | 3.3 | 1.8 |
| 75 | 3.7 | 2.1 |
| 76 | 4.1 | 2.4 |
| 77 | 4.6 | 2.7 |
| 78 | 5.2 | 3.1 |
| 79 | 5.8 | 3.6 |

*Continued on next page*

***Supplementary* Table 3.** *Sex- and age-specific general mortality rates (continued)*

|  |  |
| --- | --- |
|   | **General mortality rates from age to age +1 (%)**1 |
| **Age** | **Men** | **Women** |
| 80 | 6.5 | 4.1 |
| 81 | 7.2 | 4.7 |
| 82 | 8.0 | 5.4 |
| 83 | 8.9 | 6.2 |
| 84 | 9.9 | 7.1 |
| 85 | 11.1 | 8.2 |
| 86 | 12.3 | 9.3 |
| 87 | 13.7 | 10.7 |
| 88 | 15.3 | 12.1 |
| 89 | 16.9 | 13.7 |
| 90 | 18.7 | 15.4 |
| 91 | 20.7 | 17.2 |
| 92 | 22.7 | 19.1 |
| 93 | 24.8 | 21.1 |
| 94 | 27.0 | 23.2 |
| 95 | 29.1 | 25.3 |
| 96 | 31.2 | 27.4 |
| 97 | 33.2 | 29.6 |
| 98 | 35.1 | 31.7 |
| 99 | 37.2 | 34.0 |
| 100 | 39.2 | 36.2 |

1Estimates were extracted from German population life tables 2010/2012 (reference19).

**Supplementary Appendix 2. Supplementary Results.**

#### **Supplementary Table 4.** Differences in Long-term Outcomes for Screening with Annual FIT from Ages 50-75 given Varying Patterns of Adherence Yielding Identical Adherence Levels. Sensitivity Analysis using the lower limits of the 95% confidence intervals of starting prevalences and transition rates between model states.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **A. Men** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% annually | 82% | 90% | 88% |  | 100% annually | 82% | 91% | 88% |  | 1.0 | 1.0 | 1.0 |
| 50% annually | 41% | 45% | 44% |  | 100% every 2 years | 74% | 86% | 82% |  | 1.8 | 1.9 | 1.9 |
| 33% annually | 27% | 30% | 29% |  | 100% every 3 years | 66% | 80% | 76% |  | 2.4 | 2.7 | 2.6 |
| 25% annually | 21% | 23% | 22% |  | 100% every 4 years | 59% | 74% | 71% |  | 2.9 | 3.3 | 3.2 |
| 20% annually | 16% | 18% | 18% |  | 100% every 5 years | 54% | 70% | 66% |  | 3.3 | 3.9 | 3.8 |
| 17% annually | 14% | 15% | 15% |  | 100% every 6 years | 48% | 65% | 61% |  | 3.5 | 4.3 | 4.2 |
| 14% annually | 12% | 13% | 13% |  | 100% every 7 years | 44% | 59% | 56% |  | 3.8 | 4.6 | 4.5 |
| 13% annually | 10% | 11% | 11% |  | 100% every 8 years | 41% | 57% | 54% |  | 4.0 | 5.1 | 4.9 |
| 11% annually | 9% | 10% | 10% |  | 100% every 9 years | 38% | 50% | 49% |  | 4.1 | 5.0 | 5.0 |
| 10% annually | 8% | 9% | 9% |  | 100% every 10 years | 37% | 49% | 47% |  | 4.5 | 5.5 | 5.4 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| **B. Women** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% annually | 81% | 89% | 88% |  | 100% annually | 81% | 89% | 88% |  | 1.0 | 1.0 | 1.0 |
| 50% annually | 40% | 45% | 44% |  | 100% every 2 years | 69% | 81% | 80% |  | 1.7 | 1.8 | 1.8 |
| 33% annually | 27% | 30% | 29% |  | 100% every 3 years | 60% | 74% | 73% |  | 2.2 | 2.5 | 2.5 |
| 25% annually | 20% | 22% | 22% |  | 100% every 4 years | 52% | 67% | 66% |  | 2.6 | 3.0 | 3.0 |
| 20% annually | 16% | 18% | 18% |  | 100% every 5 years | 47% | 63% | 62% |  | 2.9 | 3.6 | 3.5 |
| 17% annually | 13% | 15% | 15% |  | 100% every 6 years | 42% | 57% | 56% |  | 3.1 | 3.9 | 3.8 |
| 14% annually | 12% | 13% | 13% |  | 100% every 7 years | 37% | 50% | 50% |  | 3.2 | 3.9 | 4.0 |
| 13% annually | 10% | 11% | 11% |  | 100% every 8 years | 35% | 50% | 49% |  | 3.5 | 4.5 | 4.4 |
| 11% annually | 9% | 10% | 10% |  | 100% every 9 years | 30% | 40% | 42% |  | 3.4 | 4.1 | 4.3 |
| 10% annually | 8% | 9% | 9% |  | 100% every 10 years | 30% | 41% | 41% |  | 3.7 | 4.6 | 4.7 |

CRC: colorectal cancer. YPLL: years of potential life lost. FIT: fecal immunochemical test.

#### **Supplementary Table 5.** Differences in Long-term Outcomes for Screening with Annual FIT from Ages 50-75 given Varying Patterns of Adherence Yielding Identical Adherence Levels. Sensitivity Analysis using the upper limits of the 95% confidence intervals of starting prevalences and transition rates between model states.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **A. Men** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% annually | 80% | 88% | 87% |  | 100% annually | 80% | 88% | 87% |  | 1.0 | 1.0 | 1.0 |
| 50% annually | 40% | 44% | 43% |  | 100% every 2 years | 72% | 83% | 81% |  | 1.8 | 1.9 | 1.9 |
| 33% annually | 27% | 29% | 29% |  | 100% every 3 years | 64% | 77% | 75% |  | 2.4 | 2.6 | 2.6 |
| 25% annually | 20% | 22% | 22% |  | 100% every 4 years | 57% | 71% | 69% |  | 2.8 | 3.2 | 3.2 |
| 20% annually | 16% | 18% | 17% |  | 100% every 5 years | 52% | 68% | 64% |  | 3.3 | 3.8 | 3.7 |
| 17% annually | 13% | 15% | 14% |  | 100% every 6 years | 47% | 62% | 59% |  | 3.5 | 4.2 | 4.1 |
| 14% annually | 11% | 13% | 12% |  | 100% every 7 years | 43% | 56% | 54% |  | 3.7 | 4.4 | 4.4 |
| 13% annually | 10% | 11% | 11% |  | 100% every 8 years | 40% | 54% | 52% |  | 4.0 | 4.9 | 4.8 |
| 11% annually | 9% | 10% | 10% |  | 100% every 9 years | 36% | 46% | 46% |  | 4.0 | 4.7 | 4.8 |
| 10% annually | 8% | 9% | 9% |  | 100% every 10 years | 35% | 46% | 45% |  | 4.4 | 5.2 | 5.2 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |
| **B. Women** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% annually | 77% | 85% | 86% |  | 100% annually | 77% | 85% | 86% |  | 1.0 | 1.0 | 1.0 |
| 50% annually | 39% | 42% | 43% |  | 100% every 2 years | 65% | 76% | 78% |  | 1.7 | 1.8 | 1.8 |
| 33% annually | 26% | 28% | 29% |  | 100% every 3 years | 56% | 69% | 70% |  | 2.2 | 2.4 | 2.4 |
| 25% annually | 19% | 21% | 22% |  | 100% every 4 years | 48% | 62% | 63% |  | 2.5 | 2.9 | 2.9 |
| 20% annually | 15% | 17% | 17% |  | 100% every 5 years | 44% | 58% | 58% |  | 2.9 | 3.4 | 3.4 |
| 17% annually | 13% | 14% | 14% |  | 100% every 6 years | 38% | 52% | 53% |  | 3.0 | 3.7 | 3.7 |
| 14% annually | 11% | 12% | 12% |  | 100% every 7 years | 34% | 45% | 47% |  | 3.1 | 3.7 | 3.8 |
| 13% annually | 10% | 11% | 11% |  | 100% every 8 years | 32% | 45% | 45% |  | 3.3 | 4.3 | 4.2 |
| 11% annually | 9% | 9% | 10% |  | 100% every 9 years | 27% | 36% | 38% |  | 3.2 | 3.8 | 4.0 |
| 10% annually | 8% | 8% | 9% |  | 100% every 10 years | 27% | 36% | 38% |  | 3.5 | 4.3 | 4.4 |

CRC: colorectal cancer. YPLL: years of potential life lost. FIT: fecal immunochemical test.

#### **Supplementary Table 6.** Differences in Long-term Outcomes for Screening Colonoscopy at Ages 50, 60 and 70 given Varying Patterns of Adherence Yielding Identical Adherence Levels. Sensitivity Analysis using the lower limits of the 95% confidence intervals of starting prevalences and transition rates between model states.

|  |
| --- |
| **A. Men** |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% at ages 50, 60 and 70 | 86% | 92% | 90% |  | 100% at ages 50, 60, and 70 | 86% | 92% | 90% |  | 1.0 | 1.0 | 1.0 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 67% at ages 50, 60, 70 | 57% | 61% | 60% |  | 100% at ages 50 and 60 | 78% | 84% | 85% |  | 1.4 | 1.4 | 1.4 |
|  |  |  |  |  | 100% at ages 50 and 70 | 75% | 83% | 80% |  | 1.3 | 1.4 | 1.3 |
|  |  |  |  |  | 100% at ages 60 and 70 | 69% | 78% | 66% |  | 1.2 | 1.3 | 1.1 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 33% at ages 50, 60, 70 | 28% | 30% | 30% |  | 100% at age 50 | 55% | 59% | 65% |  | 2.0 | 2.0 | 2.2 |
|  |  |  |  |  | 100% at age 60 | 59% | 67% | 59% |  | 2.1 | 2.2 | 2.0 |
|  |  |  |  |  | 100% at age 70 | 35% | 49% | 31% |  | 1.3 | 1.6 | 1.1 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |
| **B. Women** |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% at ages 50, 60 and 70 | 86% | 91% | 91% |  | 100% at ages 50, 60, and 70 | 86% | 91% | 91% |  | 1.0 | 1.0 | 1.0 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 67% at ages 50, 60, 70 | 57% | 60% | 60% |  | 100% at ages 50 and 60 | 74% | 79% | 83% |  | 1.3 | 1.3 | 1.4 |
|  |  |  |  |  | 100% at ages 50 and 70 | 76% | 83% | 81% |  | 1.3 | 1.4 | 1.3 |
|  |  |  |  |  | 100% at ages 60 and 70 | 74% | 81% | 71% |  | 1.3 | 1.3 | 1.2 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 33% at ages 50, 60, 70 | 28% | 30% | 30% |  | 100% at age 50 | 48% | 52% | 60% |  | 1.7 | 1.7 | 2.0 |
|  |  |  |  |  | 100% at age 60 | 60% | 66% | 61% |  | 2.1 | 2.2 | 2.0 |
|  |  |  |  |  | 100% at age 70 | 46% | 58% | 40% |  | 1.6 | 1.9 | 1.3 |

CRC: colorectal cancer. YPLL: years of potential life lost

#### **Supplementary Table 7.** Differences in Long-term Outcomes for Screening Colonoscopy at Ages 50, 60 and 70 given Varying Patterns of Adherence Yielding Identical Adherence Levels. Sensitivity Analysis using the upper limits of the 95% confidence intervals of starting prevalences and transition rates between model states.

|  |
| --- |
| **A. Men** |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% at ages 50, 60 and 70 | 83% | 89% | 89% |  | 100% at ages 50, 60, and 70 | 83% | 89% | 89% |  | 1.0 | 1.0 | 1.0 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 67% at ages 50, 60, 70 | 55% | 59% | 59% |  | 100% at ages 50 and 60 | 73% | 79% | 83% |  | 1.3 | 1.3 | 1.4 |
|  |  |  |  |  | 100% at ages 50 and 70 | 72% | 79% | 77% |  | 1.3 | 1.3 | 1.3 |
|  |  |  |  |  | 100% at ages 60 and 70 | 69% | 77% | 66% |  | 1.3 | 1.3 | 1.1 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 33% at ages 50, 60, 70 | 26% | 28% | 29% |  | 100% at age 50 | 48% | 52% | 60% |  | 1.8 | 1.8 | 2.1 |
|  |  |  |  |  | 100% at age 60 | 56% | 64% | 58% |  | 2.2 | 2.2 | 2.0 |
|  |  |  |  |  | 100% at age 70 | 37% | 49% | 32% |  | 1.4 | 1.7 | 1.1 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |
| **B. Women** |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% at ages 50, 60 and 70 | 81% | 86% | 89% |  | 100% at ages 50, 60, and 70 | 81% | 86% | 89% |  | 1.0 | 1.0 | 1.0 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 67% at ages 50, 60, 70 | 54% | 57% | 59% |  | 100% at ages 50 and 60 | 67% | 71% | 79% |  | 1.2 | 1.2 | 1.3 |
|  |  |  |  |  | 100% at ages 50 and 70 | 71% | 78% | 77% |  | 1.3 | 1.4 | 1.3 |
|  |  |  |  |  | 100% at ages 60 and 70 | 72% | 79% | 71% |  | 1.3 | 1.4 | 1.2 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 33% at ages 50, 60, 70 | 26% | 28% | 29% |  | 100% at age 50 | 40% | 43% | 53% |  | 1.5 | 1.5 | 1.8 |
|  |  |  |  |  | 100% at age 60 | 54% | 60% | 59% |  | 2.1 | 2.2 | 2.0 |
|  |  |  |  |  | 100% at age 70 | 46% | 56% | 40% |  | 1.8 | 2.0 | 1.4 |

CRC: colorectal cancer. YPLL: years of potential life lost

#### **Supplementary Table 8.** Differences in Long-term Outcomes for Screening with Annual FIT from Ages 45-75 given Varying Patterns of Adherence Yielding Identical Adherence Levels

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **A. Men** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% annually | 82% | 89% | 88% |  | 100% annually | 82% | 89% | 88% |  | 1.0 | 1.0 | 1.0 |
| 50% annually | 41% | 45% | 44% |  | 100% every 2 years | 76% | 86% | 84% |  | 1.9 | 1.9 | 1.9 |
| 33% annually | 27% | 30% | 29% |  | 100% every 3 years | 69% | 81% | 78% |  | 2.5 | 2.7 | 2.7 |
| 25% annually | 21% | 22% | 22% |  | 100% every 4 years | 62% | 75% | 72% |  | 3.0 | 3.4 | 3.3 |
| 20% annually | 16% | 18% | 18% |  | 100% every 5 years | 57% | 71% | 68% |  | 3.4 | 4.0 | 3.8 |
| 17% annually | 14% | 15% | 15% |  | 100% every 6 years | 51% | 66% | 63% |  | 3.7 | 4.5 | 4.3 |
| 14% annually | 12% | 13% | 13% |  | 100% every 7 years | 47% | 61% | 58% |  | 4.0 | 4.8 | 4.6 |
| 13% annually | 10% | 11% | 11% |  | 100% every 8 years | 43% | 55% | 53% |  | 4.1 | 4.9 | 4.8 |
| 11% annually | 9% | 10% | 10% |  | 100% every 9 years | 41% | 55% | 52% |  | 4.5 | 5.5 | 5.3 |
| 10% annually | 8% | 9% | 9% |  | 100% every 10 years | 39% | 54% | 50% |  | 4.7 | 6.0 | 5.7 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |
| **B. Women** |  |  |  |  |  |  |  |  |  |  |  |  |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% annually | 81% | 87% | 88% |  | 100% annually | 81% | 87% | 88% |  | 1.0 | 1.0 | 1.0 |
| 50% annually | 40% | 44% | 44% |  | 100% every 2 years | 71% | 81% | 82% |  | 1.8 | 1.9 | 1.9 |
| 33% annually | 27% | 29% | 29% |  | 100% every 3 years | 61% | 74% | 74% |  | 2.3 | 2.5 | 2.5 |
| 25% annually | 20% | 22% | 22% |  | 100% every 4 years | 53% | 66% | 66% |  | 2.6 | 3.0 | 3.0 |
| 20% annually | 16% | 17% | 18% |  | 100% every 5 years | 48% | 63% | 62% |  | 3.0 | 3.6 | 3.5 |
| 17% annually | 13% | 15% | 15% |  | 100% every 6 years | 43% | 58% | 57% |  | 3.2 | 4.0 | 3.9 |
| 14% annually | 12% | 12% | 13% |  | 100% every 7 years | 38% | 51% | 52% |  | 3.3 | 4.1 | 4.1 |
| 13% annually | 10% | 11% | 11% |  | 100% every 8 years | 34% | 44% | 46% |  | 3.3 | 4.0 | 4.1 |
| 11% annually | 9% | 10% | 10% |  | 100% every 9 years | 33% | 45% | 45% |  | 3.7 | 4.6 | 4.6 |
| 10% annually | 8% | 9% | 9% |  | 100% every 10 years | 32% | 45% | 44% |  | 3.9 | 5.2 | 5.0 |

CRC: colorectal cancer. YPLL: years of potential life lost. FIT: fecal immunochemical test.

#### **Supplementary Table 9.** Differences in Long-term Outcomes for Screening Colonoscopy at Ages 45-75 given Varying Patterns of Adherence Yielding Identical Adherence Levels

|  |
| --- |
| **A. Men** |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% at ages 45, 55, 65 and 75 | 86% | 92% | 90% |  | 100% at ages 45, 55, 65 and 75 | 86% | 92% | 90% |  | 1.0 | 1.0 | 1.0 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 50% at ages 45, 55, 65, 75 | 43% | 46% | 45% |  | 100% at ages 45 and 55 | 66% | 72% | 77% |  | 1.5 | 1.6 | 1.7 |
|  |  |  |  |  | 100% at ages 45 and 65 | 71% | 78% | 76% |  | 1.7 | 1.7 | 1.7 |
|  |  |  |  |  | 100% at ages 45 and 75 | 51% | 62% | 59% |  | 1.2 | 1.4 | 1.3 |
|  |  |  |  |  | 100% at ages 55 and 65 | 73% | 80% | 71% |  | 1.7 | 1.7 | 1.6 |
|  |  |  |  |  | 100% at ages 55 and 75 | 66% | 75% | 65% |  | 1.5 | 1.6 | 1.4 |
|  |  |  |  |  | 100% at ages 65 and 75 | 56% | 66% | 47% |  | 1.3 | 1.4 | 1.0 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |
| **B. Women** |
| **Selective adherence** |  | **Sporadic adherence** |  | **Ratio sporadic / selective** |
| **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |  | **Scheme** | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |   | **Incidence reduction** | **Mortality reduction** | **YPLL reduction** |
| 100% at ages 45, 55, 65 and 75 | 87% | 92% | 91% |  | 100% at ages 45, 55, 65 and 75 | 87% | 92% | 91% |  | 1.0 | 1.0 | 1.0 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| 50% at ages 45, 55, 65, 75 | 44% | 46% | 46% |  | 100% at ages 45 and 55 | 60% | 64% | 73% |  | 1.4 | 1.4 | 1.6 |
|  |  |  |  |  | 100% at ages 45 and 65 | 70% | 76% | 76% |  | 1.6 | 1.6 | 1.7 |
|  |  |  |  |  | 100% at ages 45 and 75 | 55% | 66% | 60% |  | 1.3 | 1.4 | 1.3 |
|  |  |  |  |  | 100% at ages 55 and 65 | 74% | 79% | 74% |  | 1.7 | 1.7 | 1.6 |
|  |  |  |  |  | 100% at ages 55 and 75 | 70% | 78% | 69% |  | 1.6 | 1.7 | 1.5 |
|  |  |  |  |  | 100% at ages 65 and 75 | 65% | 74% | 56% |  | 1.5 | 1.6 | 1.2 |

CRC: colorectal cancer. YPLL: years of potential life lost

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