CANCER THERAPY AND PREVENTION

Model based evaluation of long-term efficacy of existing and alternative colorectal cancer screening offers: A case study for Germany

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Abstract
For individuals willing to minimize their lifetime risk of colorectal cancer (CRC), the most effective screening approach remains unclear. Here, we sought to compare the long-term performance of existing and alternative CRC screening offers in a case study for Germany. Applying the perspective of a perfectly adhering man or woman at average risk, we used COSIMO, a validated Markov-based multistate model, to simulate the effects of current CRC screening offers in Germany. These include age- and sex-dependent offers for fecal immunochemical testing (FIT) or screening colonoscopies, which may be used twice starting at age 50 in men and age 55 in women. For comparison, we modeled screening colonoscopies at ages 50, 60 and 70, screening colonoscopies at ages 50 and 60, followed by biennial FITs and conventional FIT-based strategies at varying intervals. We found that the highest reductions in lifetime risks of developing (76%-84%) and dying from CRC (82%-90%) were achieved by three colonoscopies, followed by annual FIT screening and strategies combining both modalities. In men, additional screening from age 70 onwards reduced the risk of dying from CRC by another 9% units and resulted in 32 to 39 additional life-years gained per 1000 individuals. Among women, three colonoscopies outperformed current screening offers in all outcomes, at little risk of screening-related complications. In summary, several FIT- and colonoscopy-based offers yield comparably high CRC risk reductions, including approaches combining both modalities. German screening offers may be optimized by lowering the eligibility age for screening colonoscopy for women, along with additional offers for the elderly.

Keywords: colonoscopy, colorectal cancer, fecal immunochemical testing, modeling, screening

What’s new?
Endoscopy- and fecal test-based colorectal cancer screening strategies have been introduced in population-based screening programmes around the world. However, it remains unclear which...
screening strategy may be most effective. Using a validated simulation tool, here the authors compare the long-term performance of the age- and sex-dependent screening strategies currently offered in Germany to potential alternatives. This case study illustrates strong potential for improvement of the currently-offered German screening options. In particular, screening colonoscopy could be offered from age 50 to both sexes and complementary screening options could be made available at older ages, preferably based on fecal testing.

1 | INTRODUCTION

Observational and randomized studies have consistently demonstrated that screening reduces colorectal cancer (CRC) incidence and mortality in the average-risk population.\(^1\) As therefore widely recommended, endoscopy-based or fecal test-based CRC screening offers have been introduced in population-based screening programs around the world.\(^6\) However, although each modality is acknowledged to be effective per se, it remains unclear how the long-term efficacy of these options compares to each other. While a number of head-to-head studies are underway,\(^7\) these are inevitably limited in terms of assessed strategies, populations, outcomes and follow-up.\(^1\)\(^1\)

These evidence gaps are particularly relevant in settings where various strategies are already offered to the screening-eligible population. For instance, in Germany, people can choose between several options: either fecal immunochemical testing (FIT) only, FIT and colonoscopy in sequence or, only for men, only colonoscopy (Table 1). Individuals willing to minimize their lifetime CRC risk will be concerned about which strategy may be the most effective. In particular, sequencing FIT and colonoscopy may be ineffective, as it implies a high number of colonoscopies to detect one case of cancer after several negative FITs.\(^1\)\(^2\) Men who opt for the colonoscopy-only strategy starting at age 50 face an upper age limit at age 60, which contradicts guideline recommendations to continue screening at least until age 75.\(^1\)\(^3\) In both cases, more rational and effective alternatives may exist, that is, by reversing the sequence of tests, or by offering additional screening.

Potential differences in the efficacy of screening strategies are of central importance for health authorities seeking to design and optimize screening programs, as well as for screening-interested individuals offered several pathways. We set up a simulation model to evaluate the long-term impact of currently implemented and potential alternative screening offers in a case study for perfectly adhering men and women in Germany.

2 | MATERIALS AND METHODS

2.1 | Multistate Markov model

We used the validated Markov-based Colorectal Cancer Multistate Simulation Model (COSIMO) to simulate effects of screening for CRC in a hypothetical German population.\(^1\)\(^4\) Briefly, COSIMO simulates the natural history of CRC based on the process of precursor lesions developing into preclinical and then clinical cancer in a hypothetical population. Screening can interfere with the natural history of CRC (Figure 1).

The model’s natural history assumptions were derived step-by-step in several previous analyses using data from the German screening colonoscopy registry, the world’s largest registry of its kind.\(^1\)\(^5\)\(^-\)\(^1\)\(^7\) CRC mortality rates were estimated using data from a German case-control study and German registry data.\(^1\)\(^8\)\(^-\)\(^1\)\(^9\) General mortality rates and average life expectancy were extracted from German population life tables.\(^2\)\(^0\) A comprehensive documentation on the model's structure and data sources is given in Appendix S1, including overviews on all model parameters (Tables S1-S3). The model's source code is available from our website.\(^2\)\(^1\)

2.2 | Simulations

2.2.1 | Modeled strategies

We performed simulations for the currently possible maximum use of screening offers within the organized screening program in Germany.

| Screening test | Offers for men | Offers for women |
|----------------|----------------|------------------|
| Colonoscopy    | Start of eligibility: age 50 | Start of eligibility: age 55 |
|                | Up to two screening colonoscopies 10 years apart if first screening colonoscopy was used before age 65 | Up to two screening colonoscopies 10 years apart if first screening colonoscopy was used before age 65 |
| Fecal immunochemical test\(^b\) | Annually from age 50 to 54 if no screening colonoscopy is used | Annually from age 50 to 54 |
|                | Biennially from age 55 onwards if no screening colonoscopy is used | Biennially from age 55 onwards if no screening colonoscopy is used |

\(^a\)After a positive fecal immunochemical test, diagnostic colonoscopy is warranted.

\(^b\)From October 2002 to March 2019, screening colonoscopy was offered from aged 55 on for both sexes. In April 2019, the eligibility age was lowered for men to age 50, while the offer for women remained unchanged.
For each strategy, the simulated population consisted of 100,000 previously unscreened, perfectly adhering men or women aged 50 at model start. Models were run for 50 years, that is, up to age 100. Alternative scenario (4) was chosen as increasing age is a key determinant for CRC incidence and mortality, and an additional colonoscopy might contribute to further reduce absolute CRC risks. Scenario (5) reverses the sequence of the current offer (scenario 2), which may be a more efficient approach to using screening capacities. Ab i e n n i a l F I T interval was used as most evidence on fecal testing is based on biennial screening. Scenarios (6-10) allow a comparison to typically recommended, purely FIT-based strategies. Age 75 was chosen in line with general average-risk screening recommendations.

### 2.2.2 | Outcomes

For each scenario, we assessed the cumulative incidence, mortality and years of potential life lost (YPLL) due to CRC deaths after 50 years and determined the corresponding absolute and relative reductions vs a scenario without screening. YPLL is a weighted metric taking the average remaining life expectancy at premature death into account. The corresponding benefit of screening are the life-years-gained (LYG), which were calculated per 1000 individuals. In addition, we derived the cumulative numbers of screening and surveillance tests. The expected number of complications was calculated by multiplying the number of colonoscopies with age-specific complication rates at screening colonoscopy in Germany for the year 2018.

### 2.3 | Sensitivity analyses

To explore the impact of uncertainty related to model key parameters, all point estimates of the starting prevalence and transition rates were replaced by either the lower or upper limits of the 95% confidence intervals (CIs). As well, in the base-case analysis, FITs were adjusted to yield 10% positivity to adequately reflect the current German testing landscape (see Appendix S1 for details including positivity cut-offs). Therefore, we re-run the analyses with FITs adjusted to yield 5% positivity, which will allow to assess the effect of a potential variation in diagnostic performance parameters.

### 3 | RESULTS

All strategies resulted in marked reductions of CRC incidence, mortality and YPLL when compared to no screening (Table 3; Figures 2 and 3). Overall, least incident cancer cases were found for the scenario using...
three colonoscopies (scenario 4), followed by annual FIT (scenario 6) and the dual modality strategies (scenarios 1 and 5). These four screening strategies also yielded very high, very similar reductions in CRC mortality and YPLL across both sexes, with estimated LYG per 1000 individuals ranging from 595 to 623 in men and 481 to 510 in women.

Although the effects of annual FIT screening (scenario 6) clearly outperformed the effects of biennial FIT screening (scenario 7), the gap between both scenarios could approximately be halved by annual FIT screening at ages 50 to 54 only, followed by biennial FIT screening (scenario 2). Further prolongation of FIT screening intervals yielded substantially lower reductions in all incidence and mortality outcomes.

For men, who have the option of two colonoscopies at ages 50 and 60 since the year 2019 (scenario 3), use of this option provides substantially less protection than the previously and still available alternative option of having two colonoscopies at ages 55 and 65 after preceding annual FIT testing at ages 50 to 54 (scenario 1) with respect to all three assessed outcomes (CRC incidence: 76% vs 78%, CRC mortality; 81% vs 86%, YPLL: 84% vs 86%). However, offers of an additional screening colonoscopy at age 70 (scenario 4) or additional biennial FIT screening at ages 70 to 78 (scenario 5), which are currently not available, would provide even stronger protection from all assessed outcomes and result in an additional 32 to 39 LYG per 1000 individuals.

### Table 3
Comparison of current screening offers to potential alternatives in terms of colorectal cancer risk reductions and burden of testing after 50 simulated years

| Incidence reduction (%) | Prev. cases (per 1000) | Mortality reduction (%) | Prev. deaths (per 1000) | YPLL reduction (%) | LYG (per 1000) | No. of FITs (per 1000) | No. of colonoscopies (per 1000) |
|------------------------|------------------------|-------------------------|-------------------------|-------------------|----------------|------------------------|--------------------------|
| **Men**                |                        |                         |                         |                   |                |                        |                          |
| Current maximal offer  |                        |                         |                         |                   |                |                        |                          |
| (1) FIT50-54, CS55 + 65| 78                     | 106                     | 86                      | 53                | 86             | 595                    | 5066                     | 2742                     |
| (2) FIT50-54, FIT55-75 | 73                     | 99                      | 84                      | 52                | 83             | 580                    | 8399                     | 2187                     |
| (3) CS55 + 60a         | 76                     | 103                     | 81                      | 50                | 84             | 584                    | —                        | 2868                     |
| Potential alternatives |                        |                         |                         |                   |                |                        |                          |                          |
| (4) CS50 + 60 + 70     | 84                     | 115                     | 90                      | 55                | 90             | 623                    | —                        | 3376                     |
| (5) CS50 + 60, FIT70-78| 81                     | 110                     | 89                      | 55                | 89             | 616                    | 1534                     | 3119                     |
| FIT50-75               |                        |                         |                         |                   |                |                        |                          |                          |
| (6) Annually           | 79                     | 107                     | 88                      | 54                | 86             | 602                    | 10 358                   | 2448                     |
| (7) Biennially         | 69                     | 94                      | 82                      | 50                | 80             | 556                    | 7211                     | 1987                     |
| (8) Every 3 years      | 61                     | 83                      | 76                      | 46                | 74             | 513                    | 5747                     | 1704                     |
| (9) Every 4 years      | 54                     | 73                      | 69                      | 42                | 67             | 468                    | 4730                     | 1489                     |
| (10) Every 5 years     | 49                     | 67                      | 66                      | 40                | 63             | 437                    | 4242                     | 1387                     |
| **Women**              |                        |                         |                         |                   |                |                        |                          |                          |
| Current maximal offer  |                        |                         |                         |                   |                |                        |                          |                          |
| (1) FIT50-54, CS55 + 65| 76                     | 84                      | 82                      | 40                | 85             | 481                    | 5279                     | 2530                     |
| (2) FIT50-54, FIT55-75 | 67                     | 74                      | 79                      | 38                | 81             | 458                    | 11 415                   | 1457                     |
| (3) CS55 + 60a         | 70                     | 78                      | 75                      | 36                | 81             | 458                    | —                        | 2596                     |
| Potential alternatives |                        |                         |                         |                   |                |                        |                          |                          |
| (4) CS50 + 60 + 70     | 84                     | 93                      | 89                      | 43                | 90             | 510                    | —                        | 3297                     |
| (5) CS50 + 60, FIT70-78| 78                     | 87                      | 86                      | 42                | 88             | 500                    | 2617                     | 2822                     |
| FIT50-75               |                        |                         |                         |                   |                |                        |                          |                          |
| (6) Annually           | 76                     | 84                      | 85                      | 41                | 86             | 488                    | 15 737                   | 1730                     |
| (7) Biennially         | 63                     | 70                      | 75                      | 36                | 77             | 437                    | 95 28                     | 1309                     |
| (8) Every 3 years      | 54                     | 60                      | 68                      | 33                | 69             | 394                    | 7131                     | 1082                     |
| (9) Every 4 years      | 46                     | 52                      | 61                      | 29                | 62             | 354                    | 5693                     | 928                      |
| (10) Every 5 years     | 42                     | 47                      | 58                      | 28                | 58             | 328                    | 5000                     | 859                      |

Note: All scenarios were simulated for a hypothetical cohort of perfectly adherent 100 000 men and women aged 50 years for up to 50 cycles of each 1 year.
Abbreviations: CS, screening colonoscopy; FIT, fecal immunochemical test; LYG, life years gained (the reverse of YPLL); Prev., Prevented; YPLL, years of potential life lost.

*aOnly offered for men.*
FIGURE 2 Predicted colorectal cancer risk reductions, prevented events and test burden per prevented event and screening-related complications for maximal screening offers in Germany and alternatives after 50 simulated years (CS50 and 60 is currently only offered for men).

(A) Risk reduction; (B) Prevented events per 1000 individuals; (C) Colonoscopies per prevented event; (D) Complications per 1000 individuals.

CRC, colorectal cancer; CS, colonoscopy; FIT, fecal immunochemical testing.
**FIGURE 3**  Expected cumulative incidence (A) and cumulative mortality (B) of colorectal cancer within 50 years for maximal screening offers in Germany and alternatives (CS50 and 60 is currently only offered for men). CS, colonoscopy; FIT, fecal immunochemical testing.

**FIGURE 4**  Comparison of expected number of additional complications in prescreened screening participants using biennial FITs from ages 70 to 78 vs screening colonoscopy at age 70. Events per 1000 participants aged 50 at start of simulation who used screening colonoscopy at ages 50 and 60 (scenario 3). Shown is the expected number of additional complications occurring from age 70 to the end of simulation (age 100) when using additional biennial FIT screening from ages 70 to 78 (scenario 4) and an additional screening colonoscopy at age 70 (scenario 5).
Among women, both of these currently not available screening options, in particular the option of three colonoscopies at ages 50, 60 and 70 would also clearly outperform the currently offered maximum use of screening, consisting of annual FIT at ages 50 to 54, followed by screening colonoscopy at ages 55 and 65.

Intensive FIT-based strategies (scenarios 2, 6 and 7) implied the highest numbers of screening tests. Numbers of expected complications were overall low and in proportion to the numbers of required colonoscopies, which were highest for the most effective strategies (Figure 2). While deviations in numbers of colonoscopies between both strategies were modest (by ~10%), sequencing FIT and colonoscopy (scenario 1) required two to three times the number of FITs vs sequencing colonoscopy and FIT (scenario 5). In individuals screened with colonoscopies at ages 50 and 60, the expected total number of additional complications in subjects above 70 years of age was approximately 40% (men) and 60% (women) lower when biennial FITs from ages 70 to 78 were used instead of a third colonoscopy (Figure 4).

3.1 Sensitivity analyses

Overall, sensitivity analyses for starting prevalences and annual transition rates yielded similar findings as compared to the base case (Tables S4 and S5). FITs adjusted to yield a lower positivity resulted in markedly reduced estimates for incidence and mortality reductions (Table S6).

4 DISCUSSION

This case study provides estimates on the comparative long-term efficacy of screening strategies for CRC as offered in Germany, along with potential alternative approaches. From the perspective of an individual facing the options currently provided by the German early cancer detection program, all offers provide strong protection from developing or dying from CRC. Nevertheless, men making use of the screening colonoscopy offer at start of eligibility would substantially benefit from complementary screening offers at older ages, at little risk of screening-related complications. Additional screening from age 70 onwards would imply an approximately 9% units higher reduction of the risk of dying from CRC and result in 32 to 39 additional LYG per 1000 individuals. In women, three colonoscopies at 10-yearly intervals starting at age 50 clearly outperformed current maximum screening offers in all assessed outcomes. Taken together, these aspects suggest large potential for optimizing the design of screening offers in Germany.

4.1 Findings in context

Screening offers for CRC in Germany have evolved historically. While stool-test based screening has been offered since 1977, screening colonoscopy was introduced as another, alternative primary screening modality in 2002. This made the German CRC screening landscape rather unique, as, which few exceptions, worldwide typically only one modality is offered as primary screening test.6 Only in April 2019, different starting ages for colonoscopy screening for men and women were introduced (age 50 for men; age 55 for women).23

So far, no direct comparisons of the performance of FIT vs colonoscopy-based strategies have been completed. The long-term outcomes of ongoing head-to-head studies are not expected before the late 2020s.7-9 Evidence from previous modeling studies likewise using a lifelong timeframe, predominantly in hypothetical US-American populations, suggest that 10-yearly screening colonoscopy may be the most efficacious screening strategy, but common FIT-based strategies do not fall much behind in terms of achievable CRC mortality reductions.25,26 A previous study also found the Germany-specific sequential offer of FIT and colonoscopy to be an effective option.27 Estimated CRC incidence reductions reach from 57% to 72% with annual FIT from ages 50 to 75 and from 62% to 88% with 10-yearly screening colonoscopy. Corresponding mortality reductions reach from 72% to 81% and from 77% to 90%, respectively.26,28 Overall, these estimates are in line with those from our study, which though yielded slightly higher CRC incidence reductions (76%-79% and 84%, respectively), and mortality reductions (85%-88% and 89%-90%, respectively).

Differences in risk reduction estimates likely result from two factors. First, COSIMO was developed for the German screening-eligible population,14 thereby reflecting correspondingly higher absolute lifetime CRC risks than, for instance, in the US population.29,30 Higher absolute risks may imply greater benefits of screening, which is also mirrored in the larger absolute numbers of LYG in our study compared to modeling for the US population.26 Second, differing diagnostic performance parameters used to inform the models likely matters. For instance, for modeling FIT-based strategies, in the base case analysis COSIMO was adjusted to match the comparably high positivity rates in Germany (at 10%), resulting in higher FIT sensitivity and lower specificity parameters as compared to previous models.

4.2 Implications for colorectal cancer screening

Our study adds several points to the literature. First, sequences of colonoscopy and FIT screening may be similarly effective as commonly recommended single modality strategies, for example, annual FIT or 10-yearly colonoscopy.6 This confirms and expands on the results of a previous Germany-centered model, which was mainly focused on a blood-based biomarker test.27 Our finding underpins the value of implementing screening programs with flexible design options. In Germany, the overall adherence to CRC screening steeply increased after the introduction of the dual screening offer.31 Further flexibility, for example, by allowing to choose between stool tests or another screening colonoscopy at older ages, might have further positive effects on the uptake of screening offers on a population level, while offering each individual similar levels of protection from CRC risks.

Second, our analyses illustrate an unintended long-term effect of a logical fallacy induced by the design of CRC screening offers in
Germany. A study in German physicians reported that the overwhelming majority (88%) were advising patients to undergo screening colonoscopy, the gold standard screening test, rather than other screening modalities.32 Men willing to minimize their CRC risk may therefore opt to undergo screening colonoscopy directly when eligible at age 50, followed by a repeat examination 10 years later. However, this may in fact not be the most effective pathway through German screening offers, as alternative strategies possibly imply higher CRC risk reductions and more LYG.

Third, in men, limiting the offer to only two screening colonoscopies imposes an upper age limit for screening at age 60 in those choosing the most effective screening modality directly at start of eligibility. Our study suggests that these subjects would substantially benefit from complementary screening from age 70 onwards. Even though the German system is not restrictive (as even prescreened individuals may undergo a reimbursed diagnostic colonoscopy, eg, for the clarification of symptoms, at any time), such complementary examinations should ideally be offered in a systematic and regular fashion to increase reach also in those asymptomatic. However, introducing an offer of a third screening colonoscopy may raise concerns regarding a further increase of demand for colonoscopy capacities (as also predicted by our model), which is already substantial due to recent implementation of an organized screening program and demographic aging.

Offering additional FIT screening in older age groups may, therefore, be an elegant alternative approach. On the one hand, such offer was predicted to imply a similar number of colonoscopies as the current FIT-colonoscopy sequencing offer. On the other, as suggested by the significantly reduced number of required FITs, capacities would likely be used in a more efficient manner, due to longer test intervals and age-specific higher prevalences. Lastly, although rare, colonoscopy can cause complications, which occur at higher frequency and bear higher potential for harm in the elderly.33 For instance, while the severity of colonoscopy-induced bleedings very seldom require inpatient care regardless of age (in 0.02%-0.03% of all screening colonoscopies in Germany in 2018), bleedings overall tend to occur more frequently in those aged ≥75 years (0.18%-0.20%) as compared to younger age groups (0.12%-0.17%).24 As well, the frequency of perforations, typically a severe complication, tends to increase significantly with older age (aged 70 or older, 0.03%-0.05%, aged 55-69, 0.01%-0.02%),24 Our study therefore suggests that FIT may be more appropriate in those above 70 years due to the noninvasive mode of delivery, thereby reducing the colonoscopy burden.

Finally, COSIMO predicted similar benefits of screening for men and women, which is consistent with sex-stratified findings by previous models covering a lifelong timeframe.26 Sex-dependent screening offers, as currently in place in Germany, should therefore be carefully reconsidered. Most importantly, women would benefit significantly from lowering the eligibility age for screening colonoscopy, along with additional offers for the elderly. Of note, some of the so far available evidence suggests a possibly greater34, smaller35,36 or even no effect37 of screening in women. However, chance findings due to underpowered studies for sex-stratified analyses cannot be ruled out, and overall, the CRC risk strongly increases with age in both sexes. Along with the long life-expectancy in Germany, which is already above 80 years on average for women,37 it appears plausible that screening would benefit both sexes on a similar magnitude over a lifelong timeframe.

4.3 | Limitations

Specific limitations of COSIMO have been described previously.12,14 Briefly, major limitations concern simplifying model assumptions and uncertainties related to input parameters. For instance, as the true adenoma miss rate at colonoscopy in Germany is unknown, we used representative estimates derived from a comprehensive systematic review and metaanalysis using data not limited by geographic region.38 As well, although the German national screening colonoscopy registry was a particularly well-suited data source to calibrate the model to the German population,14 the registry did not include sufficiently detailed data to calculate specific transition rates for proximal and distal neoplasms. Thus, no distinction according to cancer subsite can be made by the model.

Furthermore, all simulated scenarios assumed perfect adherence. From a societal perspective, the assumption of a perfectly adhering population is highly unrealistic, as, in practice, full coverage to all screening and diagnostic related procedures as well as surveillance remains far out of reach even in countries with well-organized screening programs.39,40 However, population-based adherence is a very complex matter involving differential patterns of screening behavior, for example, consistent or sporadic uptake,41-42 which vary across populations, tests and considered timeframes. Analyses from the societal perspective would require comprehensive analyses going far beyond the scope of our study, which sought to address the perspective of an individual willing to undergo maximum screening and facing several possibilities, as is the case in Germany. This perspective was tantamount to a simulated 100% uptake of offers, an assumption which also allows decision-takers to understand a strategy’s performance under perfect conditions and may therefore inform population guidelines and medical-decision making on designing screening programs. Finally, as our study was limited to considerations on clinical effectiveness, harms and test burden, further study assuming a health economic point-of-view is warranted.

5 | CONCLUSION

From the perspective of an individual man or woman willing to minimize the lifetime CRC risk, several strategies will yield comparatively high reductions of the risks of developing or dying from colorectal cancer: annual or age-dependent FIT screening from ages 50 to 75, screening colonoscopies at ages 50, 60 and 70, as well as dual modality approaches, such as screening colonoscopies at ages 50 and 60 followed by biennial FITs from age 70 onwards. Men making use of screening colonoscopies at ages 50 and 60, as offered in Germany since April 2019, would benefit substantially from additional screening...
offers at older ages. Screening offers for women may be optimized by lowering the eligibility age for screening colonoscopy to age 50 along with additional offers for the elderly.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Hermann Brenner and Thomas Heisser designed the study and developed the methodology. Thomas Heisser conducted the statistical analyses and drafted the manuscript. All authors critically reviewed the manuscript, contributed to its revision and approved the final version submitted. The researchers are independent from funders. All authors had full access to all of the data (including statistical reports and tables) used for the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT
All analyses relevant to the study are included in the article or uploaded as supplementary information. The model source code is available from https://www.dkfz.de/en/klinepi/download/index.html. Further information is available from the corresponding author upon request.

ETHICS STATEMENT
The corresponding author affirms that the article is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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