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Cost-effectiveness analysis of colorectal cancer screening strategies in Germany

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Colorectal cancer (CRC) screening has been shown to contribute to the reduction in CRC incidence and mortality. To inform the CRC screening recommendations, it usually relies on models that are flexible to predict the effectiveness of various screening modalities and strategies from a lifetime perspective. To date, there are only two CRC microsimulation models considering the two CRC carcinogenesis pathways (adenoma-carcinoma and serrated neoplasia pathways). However, both are calibrated with grid search optimization methods, limiting their capability to account for parameter uncertainty. Furthermore, there is no cost-effectiveness analysis from a microsimulation model to assess the current German CRC screening program and to explore alternative strategies under different invitation approaches to improve screening participation.

The aims of the present thesis are two-fold: (1) To construct an individual-level model encompassing both CRC development pathways, and to explore a Bayesian calibration method for CRC disease modeling; (2) To conduct an up-to-date cost-effectiveness analysis for evaluating the cost-effectiveness of various CRC screening strategies in the current German organized CRC screening program, and to thereby inform future CRC screening policies in Germany.

A discrete event simulation model, DECAS, was thus developed in the R software. DECAS simulates the CRC natural history from the state of no lesions to precancerous lesions (adenoma or serrated polyps) and to pre-clinical and clinical CRCs in individuals with an average CRC risk and follows them up from the age of 20 to 90 or death, whichever occurs first. The rates of event happening were lesion-, age-, sex- and location-specific, and they were calibrated with a likelihood-free approximate Bayesian computation method, adaptive population Monte Carlo (APMC). The calibration took advantage of 74 prevalence data points from the German screening colonoscopy program, which consisted of 5.2 million average-risk screening participants in 2003-2014. The Bayesian calibration rendered 1,000 sets of posterior parameter samples, with which DECAS successfully reproduced the CRC incidence data from the German national cancer registry.

After DECAS natural history model validation, the screening component was added to the DECAS model. If any lesions prior to the clinical cancer state are detected by the screening tests, individuals can be referred to or directly removed by colonoscopy. To further validate the predictive ability of DECAS regarding the CRC screening effects, external validations against two large randomized control trials on flexible sigmoidoscopy and guaiac fecal occult blood test and a large colonoscopy cohort study were performed. Additionally, cross validation against the three most widely used CRC screening models, the CISNET models, was conducted. DECAS demonstrated accurate predictions for CRC incidence and mortality reduction in the validation studies.

The validated DECAS model was then used to evaluate the benefits, burdens, and harms of CRC screening strategies in Germany, including annual fecal immunochemical tests (FIT) for aged 50-54 years followed by two 10-yearly colonoscopies or biennial FIT from age 55-75 years for both sexes, and the new strategy allowing men to start the two 10-yearly colonoscopies from the age of 50 years. Alternative strategies including biennial FITs or 10-yearly colonoscopies from the age of 45 or 50 years, and combined strategies with annual FIT from the age of 45 followed by 10-yearly colonoscopies from the age of 50 were also evaluated. All strategies were evaluated under four scenarios: perfect adherence, low adherence under the current organized program with an invitation letter, improved adherence with an invitation letter and mail-out FITs, high (but imperfect) adherence with an invitation letter, mail-out FITs, and an additional reminder.

All strategies were found to be cost-effective compared to no-screening across all four scenarios. Assuming perfect adherence and compared to no-screening, the screening strategies brought about a

34-75% CRC incidence reduction, a 52-80% CRC mortality reduction, 57-97 life-years gained, and 36-98 quality-adjusted life-years gained per 1,000 40-year-olds. All strategies were cost-saving, and they resulted in 809-3,240 colonoscopies needed and 1-4 colonoscopy complication cases per 1,000 40-year-olds. In scenarios with imperfect adherence, the benefits, burdens, and harms decreased with the participation rates. In the two mail-out FIT scenarios, the sent but unused FITs could amount up to 9,967 kits and caused an additional cost of €93,323 per 1,000 40-year-olds in the biennial FIT strategy starting at age 45 in the lower adherence scenario.

Additionally, the strategy with sex-differentiated starting age for colonoscopy appeared to be more cost-effective than the equal-starting-age strategy. Both pure colonoscopy and FIT-colonoscopy combined strategies appeared to be more cost-effective than pure FIT ones. Three-time 10-yearly colonoscopies strategy starting from the age of 45 was deemed the most cost-effective across scenarios given the willingness-to-pay thresholds of €5,000-100,000. Overall, strategies starting from the age of 45 provided the best balance between benefits, burdens, and harms, which is consistent with recent recommendation changes from major US guidelines.

The modeling evidence from the present thesis can, despite the uncertainty, serve as a basis to inform future policy making for CRC screening in Germany in the absence of long-term evidence for FIT and colonoscopy screening from clinical trials. Future research directions include a recalibration of DECAS with more efficient Bayesian algorithms and with more robust serrated polyp data when available. Moreover, the cost-effectiveness for more risk-stratified screening strategies other than sex-specific ones (e.g., with a priori individual risks) and alternative screening modalities (e.g., multitarget stool DNA test or computed tomography colonography) can be explored. Lastly, DECAS can also be used to analyze the public health and economic impacts of delayed CRC screening due to disruption by external forces, e.g., the COVID-19 pandemic.