General appendix

MISCAN-COLON MODEL OVERVIEW

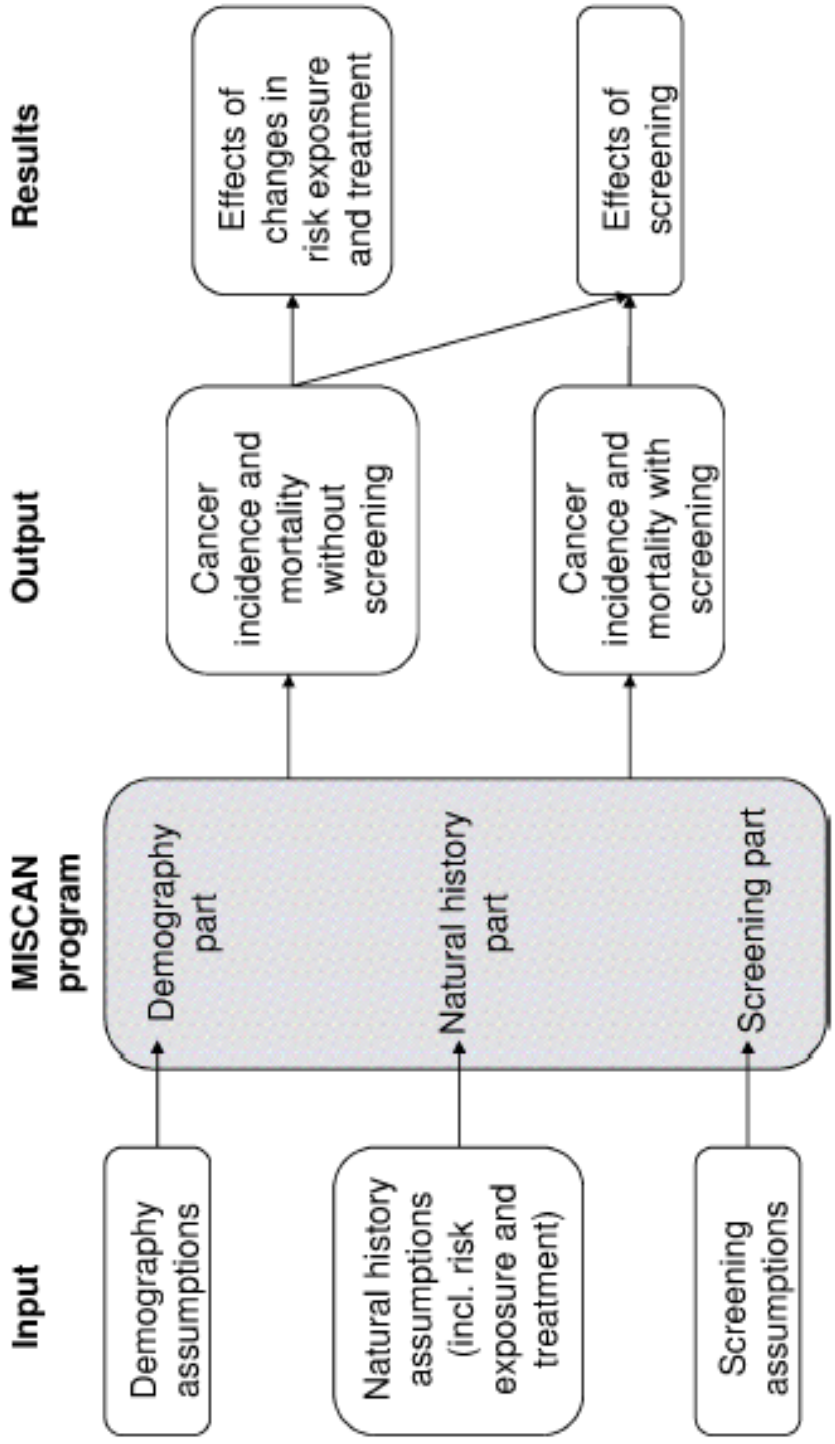
MISCAN-Colon is a stochastic, semi-Markov microsimulation model. In a microsimulation model, individuals are simulated one at a time instead of as proportions of a cohort. The advantage of this is that new events can be dependent on past events of that individual, giving the model a 'memory'. The model is stochastic, which means that sequences of events are simulated by drawing from distributions of probabilities and durations instead of using fixed values. Therefore, the outcomes of the model are subject to random variation. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are birth and death of a person, adenoma incidence and transitions from one state of disease to another. MISCAN–Colon consists of three parts (Appendix Figure 1): demography; natural history; and screening part. These parts are not physically separated in the program, but it is useful to consider them separately.

Demography part

MISCAN–Colon first generates a series of individual life histories in the demography part to form a population according to the Demography Parameters. Each person in the population consists of a date of birth and a date of death from other causes than colorectal cancer. These dates are drawn from birth and life tables that are representative for the population under consideration. The maximum age that a person can reach in the model is set to 100 years.

Natural history part

The natural history part of MISCAN–Colon simulates colorectal cancer histories (natural histories) for each individual life history separately. We based our natural history model on the adenoma–carcinoma sequence of Morson and Vogelstein.[20, 287] This means that adenomas are generated according to a personal risk index and an age specific incidence rate. For each person, a risk index is generated at the beginning of the simulation. Based on the risk index and the age specific incidence rate, the ages at which adenomas develop are generated. This results in no adenomas for most persons and one or more adenomas for others. Some of these adenomas develop into colorectal cancer.

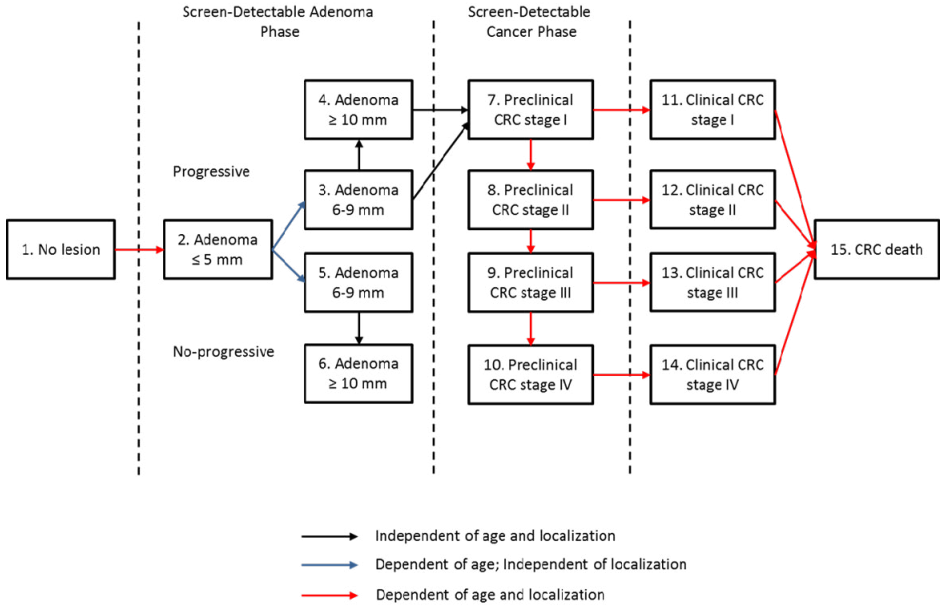


Appendix Figure 1. Structure of MISCAN-Colon

The development from adenoma into cancer covers different stages and depends on the type of adenoma (non–progressive/progressive), the transition probabilities and the duration distribution. During each invasive preclinical stage, a cancer may be clinically detected because of symptoms before it progresses to a higher stage.

The average duration of the preclinical cancer stages and average duration between the adenoma onset and the progression into preclinical cancer (adenoma dwell time) were calibrated using data obtained from randomized, controlled trials (RCTs) evaluating screening[29, 31, 112, 236, 238] and recently validated using the NORCCAP trial results.[182]In addition, the model assumes: an equal overall dwell time for adenomas to develop into cancer from medium (30% of all CRCs) and from large size adenomas (70% of all CRCs); an exponential distribution for durations in the adenoma and preclinical cancer states; a perfect correlation between durations within adenoma and preclinical cancer states (quicker growing from small adenoma to medium/large adenoma, faster progression into preclinical CRC); and no correlation between durations within adenoma states and duration in the preclinical cancer states.

Adenomas and cancers are modelled to be continuously distributed over the colorectum. The possible transitions between the different states are represented in Appendix Figures 2. Once an adenoma has developed into clinical colorectal cancer, the corresponding survival time is dependent on age-, stage-, and localization-specific survival probabilities based on Cancer Registry data. The life history of each person is altered according to the colorectal cancer histories (natural history) that is simulated for that person. This means that the state a person is in is the same as the state of the most advanced adenoma or carcinoma he has. If he dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly. This procedure is explained in Appendix Figure 3. In this example the life history of a person is shown who develops two adenomas. One of these adenomas develops into a cancer and causes death before the age of death from other causes. The combination of life history without colorectal cancer and the development of adenomas is shown in the bottom line: combined life history for colorectal cancer.



Appendix Figure 2. Model structure with adenoma-carcinoma sequence for progressive adenomas and non-progressive adenoma sequence

Screening part

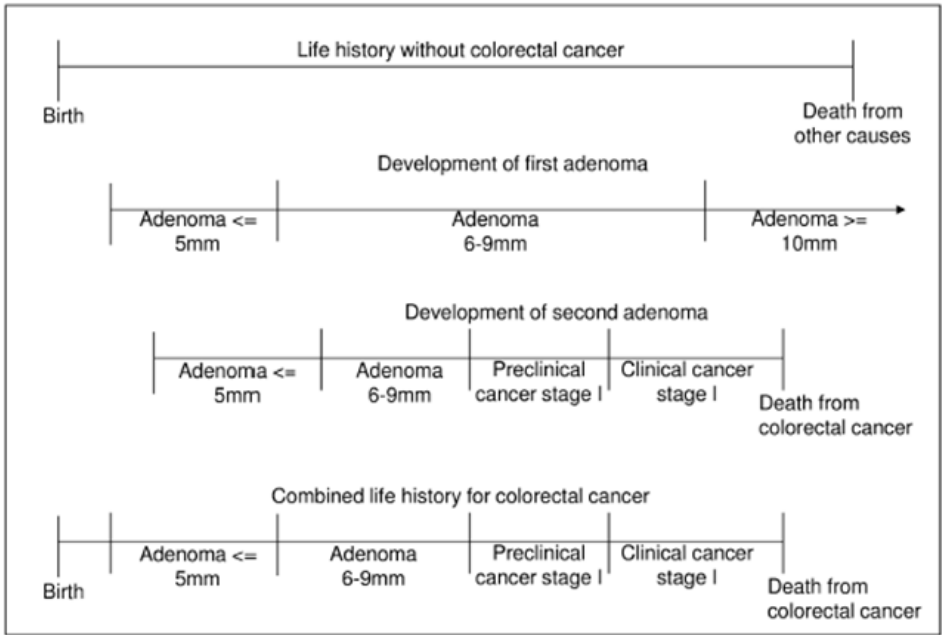
In the third part of the program, screening for colorectal cancer is simulated. After the life history of a person is adjusted for colorectal cancer, the history will now be adjusted for the effects of screening. The screening part is simultaneously run with the natural history part, making detection of adenomas and carcinomas in different states possible. Persons can be invited to participate in screening at specified ages as defined in the screening policy. Depending on the test used and the presence of adenomas and/or carcinomas at the moment of the screening test, there is a probability of a positive test result. Screening may detect all non-invasive adenomas and invasive carcinomas, but individual lesions may also be missed. A positive screening test will result either in removal of an adenoma and preventing CRC or early detection of a preclinical carcinoma, possibly in an earlier stage than when it would have been clinically detected, resulting in a favorable stage shift and potentially improved prognosis. The model also incorporates colonoscopy-related complications,[253] over-diagnosis, and overtreatment.

An example of the effect of screening, screening benefit, or over-diagnosis on the life history of an individual is explained in Appendix Figure 4. In the case of patient A in Appendix Figure 4, the natural history part generates an adenoma. This adenoma progress into preclinical cancer and is diagnosed at stage II due to symptoms. This patient dies from CRC before its pre-generated date of death of other causes. The red arrow shows the moment that a screening examination is introduced. In this case the adenoma will be detected, removed,

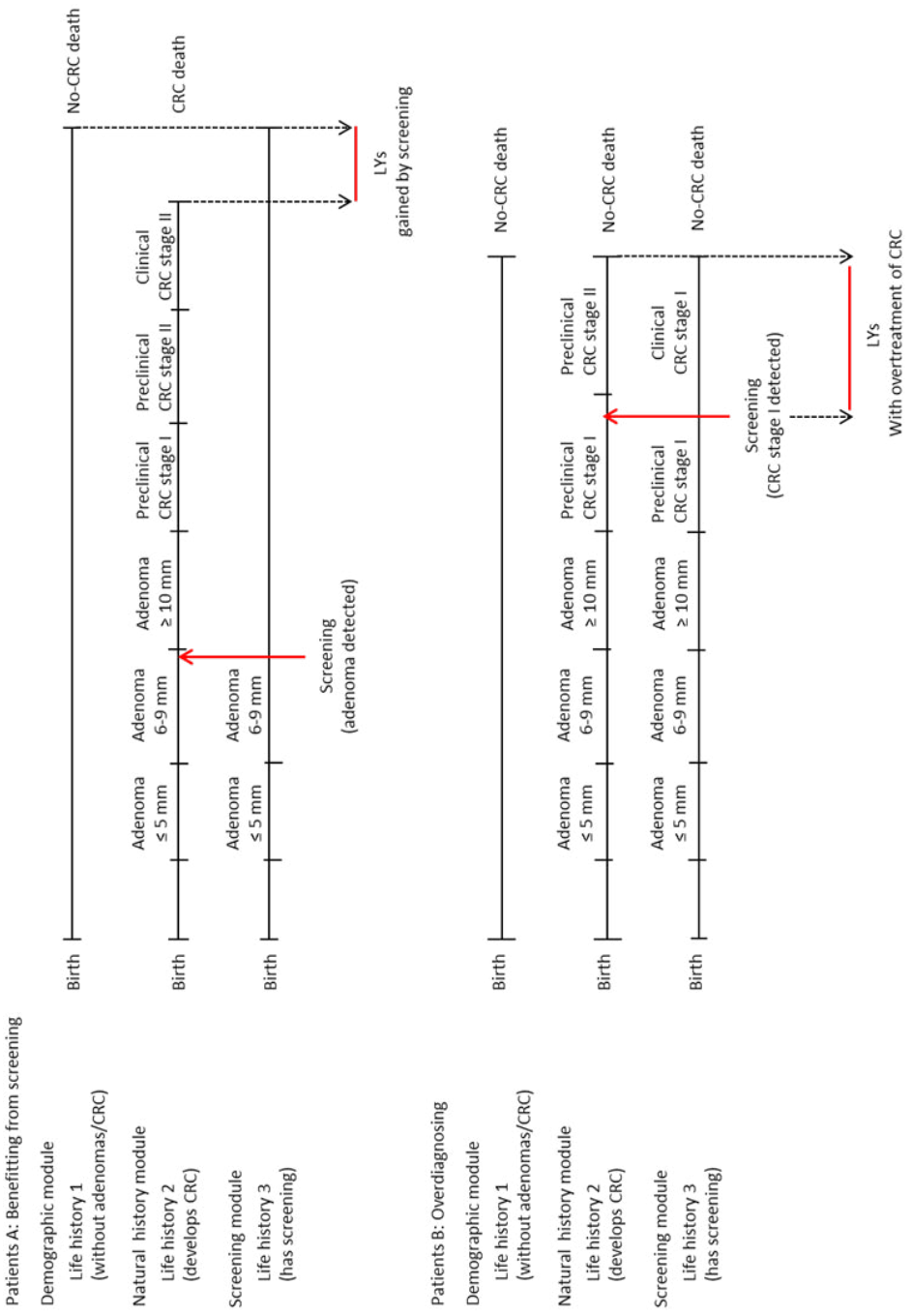
and CRC death is averted. The positive effect of the screening is represented by the red horizontal line, indicating the increase in life years that is gained with the introduction of screening. However, screening might also result in overdiagnosis and overtreatment of CRC (no LYs gained, but only additional LYs with CRC care) as reported in the patient B example.

He develops an adenoma that would never have been diagnosed in a no screening scenario. However, during the screening examination, CRC is detected in stage I, resulting in unnecessary treatment.

Besides, an improvement in survival because of stage-shift (i.e. a cancer diagnosed in an earlier stage with screening than without screening), we also assume the possibility for improved survival because of a shift within stage. This is because, as seen in RCTs on guaiac fecal occult blood testing, stage-specific survival in screen-detected CRC, even after the lead-time bias correction, results more favorable compared to clinically detected CRC.[156] In the model, we assign those screen-detected cancer cases that would have been clinically detected in the same stage a survival corresponding to a cancer that is one stage less progressive. Hence, a cancer screen-detected in stage II that would also have been clinically diagnosed in stage II is assigned the survival of a clinically diagnosed stage I cancer. The only exception is made for the screen-detected stage IV cancer cases: we assigned a survival of clinically diagnosed stage IV CRC in those cases.



Appendix Figure 3. Modelling natural history into life history



Appendix Figure 4. Modelling screening into life history

Model parameters overview

Demography part

1. Number of birth cohorts
2. Proportion of the population in each birth cohort
3. For each birth cohort parameters of its birth table
4. For each birth cohort the parameters of its life table

Natural history part

1. Adenoma-carcinoma sequence states
2. Age specific adenoma incidence rate by birth cohort
3. Parameters for the distribution of the individual risk index
4. Distribution of adenomas over the colorectal sites
5. Probability for adenomas to be progressive
6. Parameters for the transition probability of non-progressive adenomas for each state
7. Parameters for the duration distribution of non-progressive adenomas for each state
8. Parameters for the transition probability of progressive lesions for each state
9. Parameters for the duration distribution of progressive lesions for each state
10. Correlation between duration in subsequent states
11. Parameters for survival after clinical diagnosis by age at diagnosis, year of diagnosis, stage of disease and localization of the cancer.

Screening part

1. Parameters for the dissemination of screening
2. Reach, sensitivity, specificity of different screening tests
3. Dependency of test outcomes on previous test outcomes of the same individual
4. Parameters for survival after screen detected diagnosis
5. Surveillance after screen-detected adenomas

Parameter nature and distinction

The parameters reported in the previous section can be divided into three categories (Appendix Table 1):

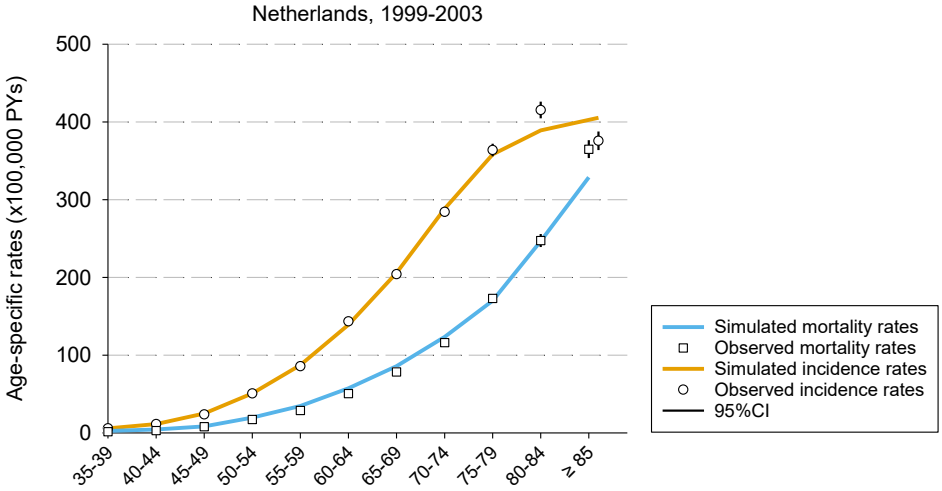
- Parameters that are directly estimated from available data
- Parameters for which no data (or limited data) are available
- Parameters that will be varied to fit reference data

Appendix Table 1. Parameters division

Parameters that are directly estimated from available data	**Parameters for which no data (or only limited data are available)**	**Parameters that will be varied to fit reference data (calibrated)**
Demography	Transition probabilities from preclinical non-invasive states	Probability for an adenoma to be progressive
Distribution of lesions over large bowel	Correlation between durations in subsequent states	Individual risk index
Survival after clinical diagnosis	Survival after screen detected diagnosis	Incidence rate of adenomas
Distribution of cancers over invasive stages	-	Duration distribution in preclinical states
Sensitivity, specificity and reach of screening tests	-	Transition probabilities from preclinical invasive states to clinical states
Participation in screening, diagnostic follow-up and surveillance	-	Dependency of test outcomes
Relative risk associated with risk and protective factors	-	-

DUTCH MISCAN-COLON MODEL VERSION

The Dutch version of the MISCAN-Colon model was first calibrated to age- and stage-specific (UICC TNM stage classification) CRC incidence rates observed in the Netherlands in 1999-2003 (Appendix Figure 5).[106] Survival rates were based on data from the South of the Netherlands,[106] since nationwide data were not available. The model parameters not directly observable in epidemiological studies, such as adenoma dwell time and the preclinical duration of CRC, were calibrated replicating outcomes of CRC screening RTCs[29, 31, 112, 236, 238] and, subsequently, validated to the results of the NORCCAP trial (**Chapter 3**).[182] The Dutch MISCAN-Colon model version has been used to inform the Dutch FIT CRC screening programme[160] and to assess cost-effectiveness of CRC screening.[86, 165, 262, 288-290]



Appendix Figure 5. Model predicted and observed colorectal cancer (CRC) incidence and mortality rates in The Netherlands, 1999-2003.

US MISCAN-Colon model version

In the US version of the MISCAN-Colon model, the age-specific probability of adenoma progressivity and the age-, localization-specific transition between preclinical and clinical cancer stages were calibrated to SEER data on age-, stage- and localization-specific incidence of CRC in pre-screening years (i.e., 1975-1979, Appendix Figure 6).[36] The personal risk index and the age-specific onset of adenomas were calibrated to adenoma prevalence data obtained in several autopsy studies (Appendix Figure 7).[36, 114, 129, 131, 134, 244-249] The distribution of adenoma over the colon and rectum was assumed equals to the distribution of cancer cases seen in SEER before the introduction of screening.[36] The average duration of the preclinical cancer stages were calibrated according to data obtained from randomized, controlled trials (RCTs) evaluating screening using guaiac fecal occult blood tests.[29, 31, 238] The average duration between the adenoma onset and the progression into preclinical cancer (adenoma dwell time) was calibrated and validated to the data on interval cancer seen in sigmoidoscopy screenings RCT.[236]

The Italian MISCAN-Colon model

We used the IARC cancer incidence in five continents databases (vol. IX, period 1998-2002) to inform and to calibrate the Italian model.[63] Cancer registry data from Turin, Milan, Genoa, Florence, and Prato were excluded due to early introduction of population-based screening programmes or pilot studies in those areas.[91, 92, 181] Stage distribution parameters were calibrated using data from the Cancer Screening National Monitoring reports.[291] We modelled the age distribution of the Italian population in 1998 using data from the Human Mortality Databases.[105] CRC survival rates were adjusted based on data published by the

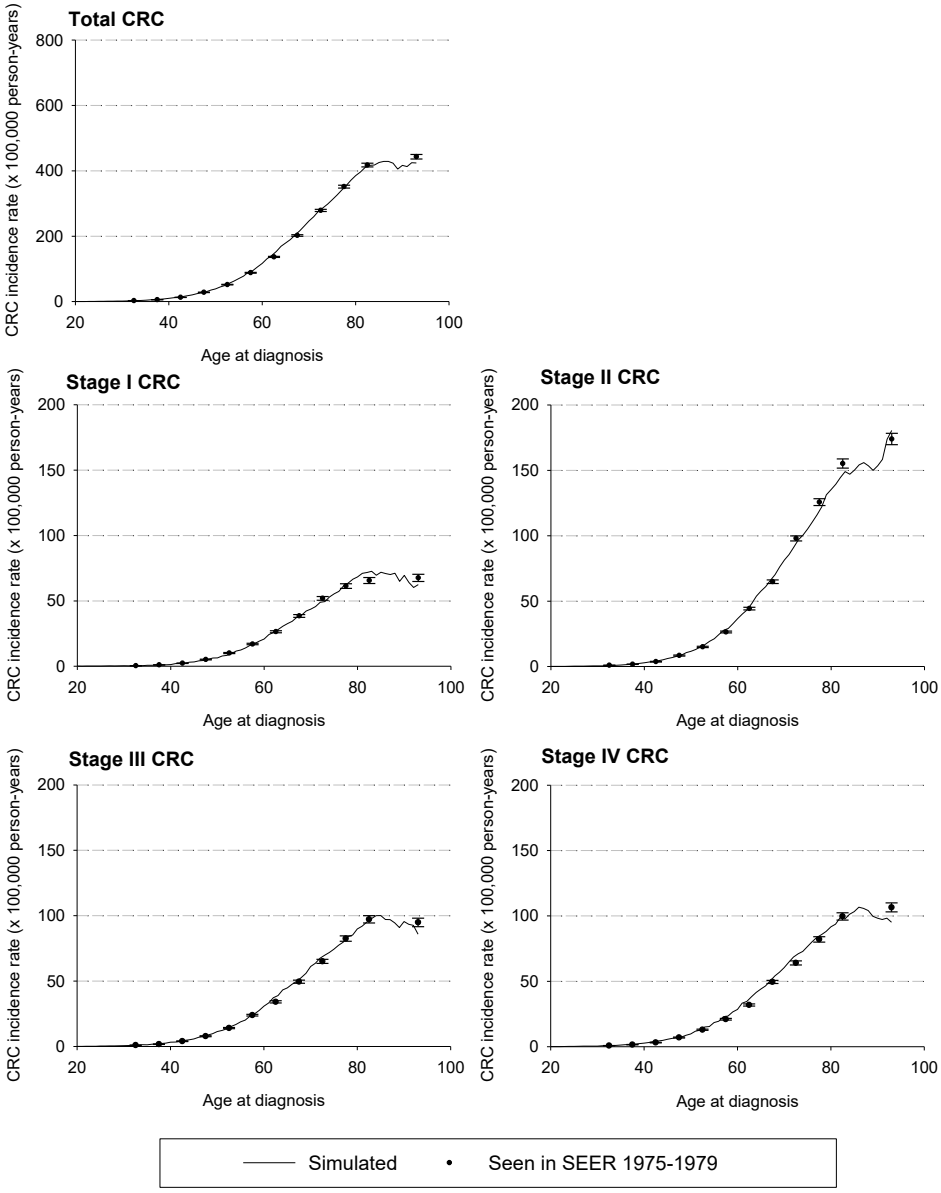
EURO-CARE V project.[105, 169] The model was used to replicate CRC incidence and mortality rates observed in Italy during the period 1998-2002 and CRC stage distribution in the pre-screening period (internal validation).[63, 291] Calibration results are reported in Chapter 4.

The Slovenian MISCAN-Colon model

We calibrated the Slovenian model using CRC incidence and stage distribution data from the cancer registry of Slovenia (2004-2008, period before implementation of the FIT organized screening).[156] The model was adjusted to simulate the Slovenian population in 2008 (based on data from the Human Mortality Databases).[105] CRC survival was adjusted using the results of the EURO-CARE V project.[105, 169] The model was internally validated replicating the CRC incidence rates, mortality rates, and stage distribution observed in Slovenia during 2004-2008.[156] Calibration results are reported in Chapter 4.

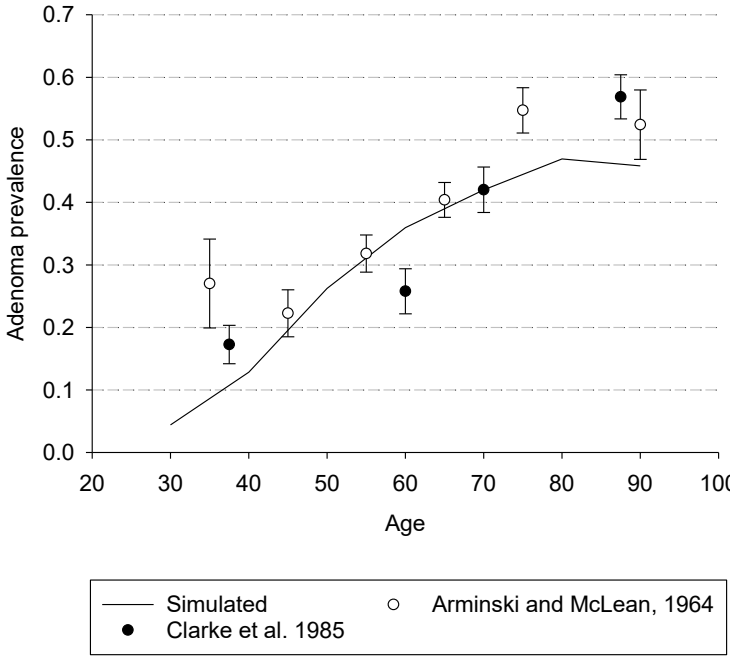
The Finnish MISCAN-Colon model

As a population-based screening pilot study investigating effectiveness of gFOBT screening was performed in 2004 in Finland,[62] we calibrated the Finnish MISCAN-Colon version using CRC incidence and stage distribution data observed in the Finnish Cancer Registry between 1999 and 2003.[292] However, CRC stage distribution data was converted before performing the model calibration due to the different CRC staging classification (not conform the UICC TNM stage classification). The conversion was performed as follows: Localized CRCs were assumed for 1/3 as TNM stage I and for 2/3 as TNM stage II (based on the CRC stage proportions observed in The Netherlands, Italy and Slovenia); regional (CRCs non-localized, only regional lymph node metastases or with no information on extent) as TNM stage III; and distant (CRCs metastasized further than regional lymph nodes) as TNM stage IV. We used the model to simulate the 1999 age-specific Finnish population based on data from the Human Mortality Databases.[105] Survival rates after CRC diagnosis were adjusted based on data published by the EURO-CARE V project.[105, 169] The model was used to replicate CRC incidence rates, mortality rates, and CRC stage distribution observed in Finland in the pre-screening period (1999-2003, internal validation).[292] Calibration results are reported in Chapter 4.



Bars indicate 95% CIs. CRC = colorectal cancer; SEER = Surveillance, Epidemiology, and End Results.

Appendix Figure 6. Colorectal cancer incidence seen before the introduction of screening versus incidence simulated by Microsimulation Screening Analysis-Colon model.



Appendix Figure 7. Adenoma prevalence seen in selected autopsy studies versus prevalence simulated by Microsimulation Screening Analysis-Colon model. Observed results are shown only for the 2 largest studies on which the model has been calibrated. The model has additionally been calibrated to 8 other autopsy studies. Bars indicate 95% CIs.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018.
2. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018;103:356-387.
3. Huxley RR, Ansary-Moghaddam A, Clifton P, et al. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. Int J Cancer 2009;125:171-80.
4. Arnold M, Karim-Kos HE, Coebergh JW, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. Eur J Cancer 2015;51:1164-87.
5. Cancer Stat Facts: Colorectal Cancer - National Cancer Institute - Surveillance, Epidemiology, and End Results Program. Available at: https://seer.cancer.gov/statfacts/html/colorect.html. Last access: October 7th 2019.
6. Jasperson KW, Tuohy TM, Neklason DW, et al. Hereditary and familial colon cancer. Gastroenterology 2010;138:2044-58.
7. Baglietto L, Jenkins MA, Severi G, et al. Measures of familial aggregation depend on definition of family history: meta-analysis for colorectal cancer. J Clin Epidemiol 2006;59:114-24.
8. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer 2006;42:216-27.
9. Daly PE, Samiee S, Cino M, et al. High prevalence of adenomatous colorectal polyps in young cancer survivors treated with abdominal radiation therapy: results of a prospective trial. Gut 2017;66:1797-1801.
10. Henderson TO, Oeffinger KC, Whitton J, et al. Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. Ann Intern Med 2012;156:757-66, W-260.
11. Maisonneuve P, Marshall BC, Knapp EA, et al. Cancer risk in cystic fibrosis: a 20-year nationwide study from the United States. J Natl Cancer Inst 2013;105:122-9.
12. Nottage K, McFarlane J, Krasin MJ, et al. Secondary colorectal carcinoma after childhood cancer. J Clin Oncol 2012;30:2552-8.
13. Teepen JC, Kok JL, van Leeuwen FE, et al. Colorectal Adenomas and Cancers After Childhood Cancer Treatment: A DCOG-LATER Record Linkage Study. JNCI: Journal of the National Cancer Institute 2018:djx266-djx266.
14. Starr TK, Allaei R, Silverstein KA, et al. A transposon-based genetic screen in mice identifies genes altered in colorectal cancer. Science 2009;323:1747-50.
15. Garcia MA, Yang N, Quinton PM. Normal mouse intestinal mucus release requires cystic fibrosis transmembrane regulator-dependent bicarbonate secretion. J Clin Invest 2009;119:2613-22.
16. Velcich A, Yang W, Heyer J, et al. Colorectal cancer in mice genetically deficient in the mucin Muc2. Science 2002;295:1726-9.
17. Billings JL, Dunitz JM, McAllister S, et al. Early colon screening of adult patients with cystic fibrosis reveals high incidence of adenomatous colon polyps. J Clin Gastroenterol 2014;48:e85-8.
18. Rigter LS, Spaander MCW, Aleman BMP, et al. High prevalence of advanced colorectal neoplasia and serrated polyposis syndrome in Hodgkin lymphoma survivors. Cancer 2019;125:990-999.
19. Holmqvist AS, Chen Y, Berano Teh J, et al. Risk of solid subsequent malignant neoplasms after childhood Hodgkin lymphoma-Identification of high-risk populations to guide surveillance: A report from the Late Effects Study Group. Cancer 2019;125:1373-1383.

20. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319:525-32.
21. Morson B. The polyp-cancer sequence in the large bowel. Proc R Soc Med 1974;67:451-7.
22. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315-29; quiz 1314, 1330.
23. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 5th ed. Philadelphia: Lippincott - Raven Publishers; 1997: http://cancerstaging.org/references-tools/deskreferences/Documents/AJCC5thEdCancerStagingManual.pdf.
24. Sobin LH, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 7 ed: Wiley-Blackwell; 2009.
25. Dukes C.E. The classification of cancer of the rectum. Journal of Pathological Bacteriology 1932;35(323).
26. Kuntz KM, Lansdorp-Vogelaar I, Rutter CM, et al. A systematic comparison of microsimulation models of colorectal cancer: the role of assumptions about adenoma progression. Med Decis Making 2011;31:530-9.
27. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 2010;116:544-73.
28. Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. Lancet 2017;389:1299-1311.
29. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472-7.
30. Holme O, Loberg M, Kalager M, et al. Long-Term Effectiveness of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality in Women and Men: A Randomized Trial. Ann Intern Med 2018;168:775-782.
31. Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-32.
32. Kronborg O, Jørgensen OD, Fenger C, et al. Randomized study of biennial screening with a faecal occult blood test: Results after nine screening rounds. Scand J Gastroenterol 2004;39:846-851.
33. Scholefield JH, Moss SM, Mangham CM, et al. Nottingham trial of faecal occult blood testing for colorectal cancer: A 20-year follow-up. Gut 2012;61:1036-1040.
34. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: Follow-up findings of the italian randomized controlled trial - SCORE. J Natl Cancer Inst 2011;103:1310-1322.
35. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med 2013;369:1106-14.
36. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg 2008;95:1029-1036.
37. Rossi PG, Vicentini M, Sacchettini C, et al. Impact of Screening Program on Incidence of Colorectal Cancer: A Cohort Study in Italy. Am J Gastroenterol 2015;110:1359-1366.
38. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97.
39. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. Jama 2014;312:606-15.

40. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. Lancet Oncol 2012;13:55-64.
41. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007;99:1462-70.
42. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008;135:82-90.
43. Guittet L, Bouvier V, Mariotte N, et al. Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. Gut 2007;56:210-4.
44. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010;59:62-8.
45. Smith A, Young GP, Cole SR, et al. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. Cancer 2006;107:2152-9.
46. Kaminski MF, Bretthauer M, Zauber AG, et al. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. Endoscopy 2012;44:695-702.
47. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706.
48. European Commission, 2010. P7_TA(2010) 0152 — Commission Communication on Action Against Cancer: European Partnership Committee on the Environment. Public Health and Food Safety — PE438.367 European Parliament Resolution of 6 May 2010 on the Commission Communication on Action Against Cancer: European Partnership Texts adopted Thursday, 6 May 2010 — Brussels.
49. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. Jama 2016;315:2564-2575.
50. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2018.
51. Hadjiliadis D, Khoruts A, Zauber AG, et al. Cystic Fibrosis Colorectal Cancer Screening Consensus Recommendations. Gastroenterology 2018;154:736-745 e14.
52. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancer. Version 5.0 - October 2018. Available at: http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf. Last access: 26 November 2018.
53. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008;58:130-60.
54. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. Jama 2006;296:1507-17.
55. Council of the European Union (2003). Council Recommendation of 2 December 2003 on cancer screening (2003/878/EC), Off J Eur Union no. L 327, pp. 34-38.
56. Malila N, Senore C, Armaroli P, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Organisation. Endoscopy 2012;44 Suppl 3:SE31-48.

57. Altobelli E, Lattanzi A, Paduano R, et al. Colorectal cancer prevention in Europe: burden of disease and status of screening programs. Prev Med 2014;62:132-41.
58. Selby K, Cornuz J, Gachoud D, et al. Training primary care physicians to offer their patients faecal occult blood testing and colonoscopy for colorectal cancer screening on an equal basis: a pilot intervention with before-after and parallel group surveys. BMJ Open 2016;6:e011086.
59. Ponti A, Anttila A, Ronco G, Senore C, Basu P, Segnan N, et al. (2017). Against Cancer. Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening. Brussels, Belgium: European Commission. Available from: https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf. .
60. Altobelli E, D'Aloisio F, Angeletti PM. Colorectal cancer screening in countries of European Council outside of the EU-28. World J Gastroenterol 2016;22:4946-57.
61. Scepanovic M, Jovanovic O, Keber D, et al. Faecal occult blood screening for colorectal cancer in Serbia: a pilot study. Eur J Cancer Prev 2017;26:195-200.
62. Pitkaniemi J, Seppa K, Hakama M, et al. Effectiveness of screening for colorectal cancer with a faecal occult-blood test, in Finland. BMJ Open Gastroenterol 2015;2:e000034.
63. Zorzi M, Da Re F, Mantellini P, et al. Screening for colorectal cancer in Italy: 2011-2012 survey. Epidemiol Prev 2015;39:93-107.
64. Shapiro JA, Klabunde CN, Thompson TD, et al. Patterns of colorectal cancer test use, including CT colonography, in the 2010 National Health Interview Survey. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2012;21(6):895-904.
65. Howard DH, Guy GP, Jr., Ekwueme DU. Eliminating cost-sharing requirements for colon cancer screening in Medicare. Cancer 2014;120:3850-2.
66. Gini A, Zauber AG, Cenin DR, et al. Cost Effectiveness of Screening Individuals With Cystic Fibrosis for Colorectal Cancer. Gastroenterology 2018;154:556-567 e18.
67. Senore C, Ederle A, Benazzato L, et al. Offering people a choice for colorectal cancer screening. Gut 2013;62:735-40.
68. Vogelaar I, van Balegooijen M, Zauber AG, et al. Model profiler of the MISCAN-Colon microsimulation model for colorectal cancer. Deparment of Public Health, Erasmus MC. 2004; available from: http://cisnet.flexkb.net/mp/pub/cisnet_colorectal_sloankettering_profile.pdf
69. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. Jama 2016;315:2595-609.
70. Peterse EFP, Meester RGS, Siegel RL, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: Microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. Cancer 2018;124:2964-2973.
71. Caglayan C, Terawaki H, Chen Q, et al. Microsimulation Modeling in Oncology. JCO Clin Cancer Inform 2018;2:1-11.
72. EU-TOPIA (Towards improved screening for breast, cervical and colorectal cancer in all of Europe) project, a five year project (2015-2020) funded by the European Commission's Horizon 2020 programme. Online website: https://eu-topia.org/about-eu-topia/about-eu-topia/.
73. Elmunzer BJ, Singal AG, Sussman JB, et al. Comparing the effectiveness of competing tests for reducing colorectal cancer mortality: a network meta-analysis. Gastrointest Endosc 2015;81:700-709 e3.
74. Malila N, Anttila A, Hakama M. Colorectal cancer screening in Finland: details of the national screening programme implemented in Autumn 2004. J Med Screen 2005;12:28-32.

75. Leuraud K J-SD, Saline E. Evaluation épidémiologique du programme de dépistage organisé du cancer colorectal en France. Première évaluation depuis la généralisation du programme pour 46 départements sur la période 2008-2009. Saint-Maurice : Institut de veille sanitaire ; 2012. 29 p.
76. Libby G, Brewster DH, McClements PL, et al. The impact of population-based faecal occult blood test screening on colorectal cancer mortality: A matched cohort study. Br J Cancer 2012;107:255-259.
77. van Rijn JC, Reitsma JB, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343-50.
78. Rácz I, Szabó, A., Goda, M., & Oláh, A. Preliminary colorectal cancer screening program model in Hungary. . Gastrointestinal Oncology 2002;4(2-3):119-121.
79. Tepes B, Bracko M, Novak Mlakar D, et al. Results of the FIT-based National Colorectal Cancer Screening Program in Slovenia. J Clin Gastroenterol 2016.
80. Cancer Screening in the European Union (2017). Report on the implementation of the Council Recommendation on cancer screening. 09 February 2017. Available at: https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf.
81. European Colorectal Cancer Screening Guidelines Working G, von Karsa L, Patnick J, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy 2013;45:51-9.
82. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
83. Zielonke N, Gini A, Jansen EEL, et al. Evidence for cancer specific and all-cause mortality reduction due to screening for breast, cervical and colorectal cancer: a systematic review. PROSPERO 2016: CRD42016042433
84. Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. Stat Med 1997;16:1017-29.
85. Multilingual Thesaurus of the European Union (EUROVOC). Available at: http://eurovoc.europa.eu/drupal/?q=request&uri=http://eurovoc.europa.eu/100277 .
86. van der Meulen MP, Lansdorp-Vogelaar I, van Heijningen EM, et al. Nonbleeding adenomas: Evidence of systematic false-negative fecal immunochemical test results and their implications for screening effectiveness-A modeling study. Cancer 2016;122:1680-8.
87. Higgins JP GS. Cochrane Handbook for Systematic Review of Interventions v5.1.0. Available at: http://training.cochrane.org/handbook. Accessed April, 2016.
88. Hamza S, Cottet V, Touillon N, et al. Long-term effect of faecal occult blood screening on incidence and mortality from colorectal cancer. Dig Liver Dis 2014;46:1121-1125.
89. Malila N, Hakama M, Pukkala E. A 25-year follow-up of a population screened with faecal occult blood test in Finland. Acta Oncol 2007;46:1103-1106.
90. Bjerrum A, Andersen O, Fischer A, et al. Colorectal cancer mortality 10 years after a single round of guaiac faecal occult blood test (gFOBT) screening: experiences from a Danish screening cohort. BMJ Open Gastroenterol 2016;3.
91. Bertario L, Russo A, Crosignani P, et al. Reducing colorectal cancer mortality by repeated faecal occult blood test: A nested case-control study. Eur J Cancer 1999;35:973-977.
92. Zappa M, Castiglione G, Grazzini G, et al. Effect of faecal occult blood testing on colorectal mortality: Results of a population-based case-control study in the district of Florence, Italy. INT J CANCER 1997;73:208-210.
93. Faivre J, Tazi MA, El Mrini T, et al. Faecal occult blood screening and reduction of colorectal cancer mortality: A case-control study. Br J Cancer 1999;79:680-683.

94. Ventura L, Mantellini P, Grazzini G, et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. Dig. Liver Dis. 2014;46:82-86.
95. Thiis-Evensen E, Kalager M, Bretthauer M, et al. Long-term effectiveness of endoscopic screening on incidence and mortality of colorectal cancer: A randomized trial. United Eur Gastroenterol J 2013;1:162-168.
96. Manser CN, Bachmann LM, Brunner J, et al. Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: A closed cohort study. Gastrointest Endosc 2012;76:110-117.
97. Chiu SY, Malila N, Yen AM, et al. Predicting the effectiveness of the Finnish population-based colorectal cancer screening programme. J Med Screen 2017:969141316684524.
98. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49.
99. Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM). NCT01239082, available at: https://clinicaltrials.gov/ct2/show/NCT01239082, last access: Febraury 1, 2017.
100. Hol L, Wilschut JA, van Ballegooijen M, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. Br J Cancer 2009;100:1103-10.
101. van der Vlugt M, Grobbee EJ, Bossuyt PM, et al. Adherence to colorectal cancer screening: four rounds of faecal immunochemical test-based screening. Br J Cancer 2017;116:44-49.
102. Crotta S, Segnan N, Paganin S, et al. High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test. Clin Gastroenterol Hepatol 2012;10:633-8.
103. Liang PS, Wheat CL, Abhat A, et al. Adherence to Competing Strategies for Colorectal Cancer Screening Over 3 Years. Am J Gastroenterol 2016;111:105-14.
104. Coebergh JW. Colorectal cancer screening in Europe: first things first. Eur J Cancer 2004;40:638-42.
105. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. Eur J Cancer 2015;51:2158-2168.
106. Lemmens V, van Steenbergen L, Janssen-Heijnen M, et al. Trends in colorectal cancer in the south of the Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival. Acta Oncol 2010;49:784-96.
107. Angell-Andersen E, Tretli S, Coleman MP, et al. Colorectal cancer survival trends in Norway 1958-1997. Eur J Cancer 2004;40:734-42.
108. Minicozzi P, Walsh PM, Sanchez MJ, et al. Is low survival for cancer in Eastern Europe due principally to late stage at diagnosis? Eur J Cancer 2018;93:127-137.
109. U. S. Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. Jama 2016;315:2564-75.
110. European Commission. European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis: LuxembourgPublications Office of the European Union., 2010.
111. Van Hees F, Zauber AG, Van Veldhuizen H, et al. The value of models in informing resource allocation in colorectal cancer screening: the case of the Netherlands. Gut 2015;64:1985-1997.
112. Rutter CM, Knudsen AB, Marsh TL, et al. Validation of Models Used to Inform Colorectal Cancer Screening Guidelines: Accuracy and Implications. Med Decis Making 2016;36:604-14.
113. Tuscany Cancer Registry, http://www.ispo.toscana.it/rtt. Last access: February 22, 2017.
114. Clark JC, Collan Y, Eide TJ, et al. Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. Int J Cancer 1985;36:179-86.

115. Caro JJ, Eddy DM, Hollingworth W, et al. ISPOR-SMDM task force's recommendations for good modeling practices-reply to letter to the editor by Corro Ramos. Value Health 2013;16:1108.
116. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. Value Health 2012;15:843-50.
117. Bretthauer M, Gondal G, Larsen K, et al. Design, organization and management of a controlled population screening study for detection of colorectal neoplasia: attendance rates in the NORCCAP study (Norwegian Colorectal Cancer Prevention). Scand J Gastroenterol 2002;37:568-73.
118. Gondal G, Grotmol T, Hofstad B, et al. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. Scand J Gastroenterol 2003;38:635-42.
119. Hoff G, Grotmol T, Skovlund E, et al. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. Bmj 2009;338:b1846.
120. Loeve F BR, van Ballegooijen M, van Oortmarssen GJ, Habbema JDF. Final Report MISCANCOLON, Microsimulation Model for Colorectal Cancer: Report to the National Cancer Institute Project. No. NO1-CN55186. ed. Rotterdam, The Netherlands: Department of Public Health, Erasmus University, 1998.
121. Loeve F, Boer R, Zauber AG, et al. National Polyp Study data: evidence for regression of adenomas. Int J Cancer 2004;111:633-9.
122. van Hees F, Habbema JD, Meester RG, et al. Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis. Ann Intern Med 2014;160:750-9.
123. Rutter CM, Johnson EA, Feuer EJ, et al. Secular Trends in Colon and Rectal Cancer Relative Survival. Journal of the National Cancer Institute 2013.
124. Neddermeijer H.G. et al. Adaptive Extensions of the Nelder and Mead Simplex Method for Optimization of Stochastic Simulation Models. Econometric institue report EI2000-22/A.
125. Blatt LJ. Polyps of the colon and rectum. Diseases of the Colon & Rectum 1961;4:277-282.
126. Arminski TC, McLean DW. Incidence and distribution of adenomatous polyps of the colon and rectum based on 1,000 autopsy examinations. Diseases of the Colon & Rectum 1964;7:249-261.
127. Bombi JA. Polyps of the colon in barcelona, Spain. An autopsy study. Cancer 1988;61:1472-1476.
128. Chapman I. Adenomatous Polypi of Large Intestine: Incidence and Distribution. Annals of Surgery 1963;157:223-226.
129. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. Gut 1992;33:1508-14.
130. Johannsen LGK, Momsen O, Jacobsen NO. Polyps of the Large Intestine in Aarhus, Denmark. Scandinavian Journal of Gastroenterology 1989;24:799-806.
131. Rickert RR, Auerbach O, Garfinkel L, et al. Adenomatous lesions of the large bowel: an autopsy survey. Cancer 1979;43:1847-57.
132. Surveillance, Epidemiology, and End Results (SEER) Program SEER* Stat Database: Incidence—SEER 9 Regs Limited-Use, Nov 2002 Sub (1973–2002). National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch. Released April 2003, based on the November 2002 submission, 2003. Bethesda, MD: National Cancer Institute, 2003.
133. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: An autopsy study. Cancer 1982;49:819-825.
134. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut 1982;23:835-42.

135. Hardcastle JD, Chamberlain JO, Robinson MHE, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. The Lancet 1996;348:1472-1477.
136. Jørgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-32.
137. Mandel JS, Church TR, Ederer F, et al. Colorectal Cancer Mortality: Effectiveness of Biennial Screening for Fecal Occult Blood. Journal of the National Cancer Institute 1999;91:434-437.
138. Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, et al. A novel hypothesis on the sensitivity of the fecal occult blood test. Cancer 2009;115:2410-2419.
139. Maklin S, Hakama M, Rissanen P, et al. Use of hospital resources in the Finnish colorectal cancer screening programme: a randomised health services study. BMJ Open Gastroenterol 2015;2:e000063.
140. Hoff G, Sauar J, Hofstad B, et al. The Norwegian guidelines for surveillance after polypectomy: 10-year intervals. Scand J Gastroenterol 1996;31:834-6.
141. Van Rijn JC, Reitsma JB, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. The American journal of gastroenterology 2006;101:343-350.
142. Atkin WS, Cook CF, Cuzick J, et al. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet 2002;359:1291-300.
143. Holme O, Schoen RE, Senore C, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. Bmj 2017;356:i6673.
144. Koleva-Kolarova RG, Zhan Z, Greuter MJ, et al. Simulation models in population breast cancer screening: A systematic review. Breast 2015;24:354-63.
145. de Koning HJ, Alagoz O, Schechter CB, et al. Reply to Koleva-Kolarova et al. The Breast 2016;27:182-183.
146. Urban N, Drescher C, Etzioni R, et al. Use of a stochastic simulation model to identify an efficient protocol for ovarian cancer screening. Control Clin Trials 1997;18:251-70.
147. Havrilesky LJ, Sanders GD, Kulasingam S, et al. Development of an ovarian cancer screening decision model that incorporates disease heterogeneity: implications for potential mortality reduction. Cancer 2011;117:545-53.
148. Raji OY, Duffy SW, Agbaje OF, et al. Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. Ann Intern Med 2012;157:242-50.
149. Tammemagi CM, Pinsky PF, Caporaso NE, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal And Ovarian Cancer Screening Trial models and validation. J Natl Cancer Inst 2011;103:1058-68.
150. Ten Haaf K, Jeon J, Tammemagi MC, et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS Med 2017;14:e1002277.
151. Katki HA, Kovalchik SA, Berg CD, et al. Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. Jama 2016;315:2300-11.
152. Brenner H, Niedermaier T, Chen H. Strong subsite-specific variation in detecting advanced adenomas by fecal immunochemical testing for hemoglobin. Int J Cancer 2017;140:2015-2022.
153. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8.
154. Brenner H, Hoffmeister M, Arndt V, et al. Protection From Right- and Left-Sided Colorectal Neoplasms After Colonoscopy: Population-Based Study. JNCI: Journal of the National Cancer Institute 2010;102:89-95.

155. Holme O, Bretthauer M, Fretheim A, et al. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. Cochrane Database Syst Rev 2013:CD009259.
156. Lansdorp-Vogelaar I, van Ballegooijen M, Boer R, et al. A novel hypothesis on the sensitivity of the fecal occult blood test: Results of a joint analysis of 3 randomized controlled trials. Cancer 2009;115:2410-9.
157. Church TR, Ederer F, Mandel JS. Fecal occult blood screening in the Minnesota study: sensitivity of the screening test. J Natl Cancer Inst 1997;89:1440-8.
158. Doubeni CA. The Impact of Colorectal Cancer Screening on the United States Population: is it time to celebrate? Cancer 2014;120:2810-2813.
159. Robertson DJ, Ladabaum U. Opportunities and Challenges in Moving From Current Guidelines to Personalized Colorectal Cancer Screening. Gastroenterology 2019;156:904-917.
160. van Hees F, Zauber AG, van Veldhuizen H, et al. The value of models in informing resource allocation in colorectal cancer screening: the case of The Netherlands. Gut 2015;64:1985-97.
161. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--6. Value Health 2012;15:835-42.
162. Finnish Cancer Registry. Available at: https://cancerregistry.fi/. Last Access: 3 July 2017. .
163. Slovenian Cancer Registry. Available at: http://www.slora.si/en/register-raka-rs. Last Access: 4 July 2017.
164. Buskermolen M, Gini A, Naber SK, et al. Modeling in Colorectal Cancer Screening: Assessing External and Predictive Validity of MISCAN-Colon Microsimulation Model Using NORCCAP Trial Results. Med Decis Making 2018:272989X18806497.
165. Wilschut JA, Hol L, Dekker E, et al. Cost-effectiveness analysis of a quantitative immunochemical test for colorectal cancer screening. Gastroenterology 2011;141:1648-55 e1.
166. Human Mortality Database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org or www.humanmortality.de (data downloaded on 15 November 2017). .
167. Curado. M. P. E, B., Shin. H.R., Storm. H., Ferlay. J., Heanue. M. and Boyle. P., eds (2007). Cancer Incidence in Five Continents, Vol. IX IARC Scientific Publications, No. 160, Lyon, IARC. .
168. Zorzi M, Mangone L, Sassatelli R, et al. Screening for colorectal cancer in Italy: 2011-2012 survey. Epidemiol Prev 2015;39:115-25.
169. Brenner H, Bouvier AM, Foschi R, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. Int J Cancer 2012;131:1649-58.
170. Istituto Superiore di Sanitá/ISTAT. Availabe at: https://www.iss.it/site/mortalita/Scripts/SelCause.asp. Last access: 22 February 2017.
171. Ventura L, Mantellini P, Grazzini G, et al. The impact of immunochemical faecal occult blood testing on colorectal cancer incidence. Dig Liver Dis 2014;46:82-6.
172. DEMO-ISTAT. Databases available at: http://demo.istat.it/archivio.html. Last access: 21 February 2017.
173. Segnan N, Senore C, Andreoni B, et al. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy"--SCORE. J Natl Cancer Inst 2002;94:1763-72.
174. Pedersen JK, Engholm G, Skytthe A, et al. Cancer and aging: Epidemiology and methodological challenges. Acta Oncol 2016;55 Suppl 1:7-12.
175. Brenner H, Hoffmeister M, Arndt V, et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst 2010;102:89-95.

176. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345-57.
177. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327-34.
178. Giovannucci E, Colditz GA, Stampfer MJ, et al. Physical activity, obesity, and risk of colorectal adenoma in women (United States). Cancer Causes Control 1996;7:253-63.
179. Giovannucci E, Stampfer MJ, Colditz GA, et al. Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. Ann Intern Med 1998;129:517-24.
180. Giovannucci E, Stampfer MJ, Colditz GA, et al. Folate, methionine, and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst 1993;85:875-84.
181. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst 2011;103:1310-22.
182. Buskermolen M, Gini A, Naber SK, et al. Modeling in Colorectal Cancer Screening: Assessing External and Predictive Validity of MISCAN-Colon Microsimulation Model Using NORCCAP Trial Results. Med Decis Making 2018;38:917-929.
183. Dutch Cancer Registry. Available at: https://www.cijfersoverkanker.nl/?language=en. Last access: 15 August 2019.
184. Gini A, Jansen EEL, Zielonke N, et al. Impact of colorectal cancer screening on cancer-specific mortality in Europe: A systematic review. Eur J Cancer 2020.
185. Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al. Real-Time Monitoring of Results During First Year of Dutch Colorectal Cancer Screening Program and Optimization by Altering Fecal Immunochemical Test Cut-Off Levels. Gastroenterology 2017;152:767-775 e2.
186. van der Steen A, Knudsen AB, van Hees F, et al. Optimal colorectal cancer screening in states' low-income, uninsured populations-the case of South Carolina. Health Serv Res 2015;50:768-89.
187. Jansen EEL, Zielonke N, Gini A, et al. Effect of organised cervical cancer screening on cervical cancer mortality in Europe: a systematic review. Eur J Cancer 2020.
188. Zielonke N, Gini A, Jansen EEL, et al. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. Eur J Cancer 2020.
189. Gini A, Buskermolen M, Senore C et al. Development and validation of three regional microsimulation models for predicting colorectal cancer screening benefits in Europe. Manuscript submitted.
190. Csanadi M, de Kok IM, Heijnsdijk EA, et al. Key indicators of organized cancer screening programs: Results from a Delphi study. J Med Screen 2019:969141318820362.
191. American Cancer Society. Cancer Statistics Center, Colorectum: at a glance [Internet]. Atlanta (GA): ACS; c 2017 [cited 2017 Oct 11]. Available from: https://cancerstatisticscenter.cancer.org/?_ga=1.33682849.1877282425.1465291457#!/cancersite/Colorectum.
192. Jones RM, Woolf SH, Cunningham TD, et al. The relative importance of patient-reported barriers to colorectal cancer screening. Am J Prev Med 2010;38:499-507.
193. Senore C, Inadomi J, Segnan N, et al. Optimising colorectal cancer screening acceptance: a review. Gut 2015;64:1158-77.
194. Sommers BD, Gunja MZ, Finegold K, et al. Changes in Self-reported Insurance Coverage, Access to Care, and Health Under the Affordable Care Act. Jama 2015;314:366-74.
195. Fedewa SA, Goodman M, Flanders WD, et al. Elimination of cost-sharing and receipt of screening for colorectal and breast cancer. Cancer 2015;121:3272-80.
196. Hamman MK, Kapinos KA. Affordable Care Act Provision Lowered Out-Of-Pocket Cost And Increased Colonoscopy Rates Among Men In Medicare. Health Aff (Millwood) 2015;34:2069-76.

197. Hamman MK, Kapinos KA. Colorectal Cancer Screening and State Health Insurance Mandates. Health Econ 2016;25:178-91.
198. Richman I, Asch SM, Bhattacharya J, et al. Colorectal Cancer Screening in the Era of the Affordable Care Act. J Gen Intern Med 2016;31:315-20.
199. Wharam JF, Zhang F, Landon BE, et al. Colorectal Cancer Screening in a Nationwide High-deductible Health Plan Before and After the Affordable Care Act. Med Care 2016;54:466-73.
200. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, et al. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. J Natl Cancer Inst 2009;101:1412-22.
201. National Cancer Institute. Cancer Intervention and Surveillance Modeling Network: colorectal cancer model profiles [Internet]. Bethesda (MD): NCI; [cited 2017 Sep 27]. Available from: https://cisnet.cancer.gov/colorectal/profiles.html.
202. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, et al. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:659-69.
203. National Center for Health Statistics. National Health Interview Survey [Internet]. Hyattsville (MD): NHIS; [last updated 2017 Sep 21; cited 2017 Sep 27]. Available from: http://www.cdc.gov/nchs/nhis.htm.
204. Sabatino SA, White MC, Thompson TD, Klabunde CN. Cancer screening test use—United States, 2013. MMWR Morb Mortal Wkly Rep. 2015;64(17):464–8.
205. Centers for Disease Control and Prevention. Vital signs: colorectal cancer screening test use—United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(44):881–8. .
206. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844-57.
207. CMS.gov Clinical laboratory fee schedule files [Internet]. Baltimore (MD): Centers for Medicare and Medicaid Services; [last modified 2016 Sep 29; cited 2017 Sep 27]. Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files.html.
208. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst 2008;100:630-41.
209. Colquhoun P, Chen HC, Kim JI, et al. High compliance rates observed for follow up colonoscopy post polypectomy are achievable outside of clinical trials: efficacy of polypectomy is not reduced by low compliance for follow up. Colorectal Dis 2004;6:158-61.
210. Khatami S, Xuan L, Roman R, et al. Modestly increased use of colonoscopy when copayments are waived. Clin Gastroenterol Hepatol 2012;10:761-766 e1.
211. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert Rev Pharmacoecon Outcomes Res 2008;8:165-78.
212. Oliphant R, Brewster DH, Morrison DS. The changing association between socioeconomic circumstances and the incidence of colorectal cancer: a population-based study. Br J Cancer 2011;104:1791-6.
213. Cubanski J, Swoope C, Boccuti C, Jacobson G, Casillas G, Griffin S, et al. A primer on Medicare: key facts about the Medicare program and the people it covers [Internet]. Menlo Park (CA): Henry J. Kaiser Family Foundation; 2015 Mar 20 [cited 2017 Sep 27]. Available from: http://kff.org/report-section/a-primeron-medicare-what-types-ofsupplemental-insurance-dobeneficiaries-have/.
214. Cooper GS, Kou TD, Schluchter MD, Dor A, Koroukian SM. Changes in receipt of cancer screening in Medicare beneficiaries following the Affordable Care Act. J Natl Cancer Inst. 2015;108(5).

215. Han X, Robin Yabroff K, Guy GP, Jr., et al. Has recommended preventive service use increased after elimination of cost-sharing as part of the Affordable Care Act in the United States? Prev Med 2015;78:85-91.
216. Mehta SJ, Polsky D, Zhu J, et al. ACA-mandated elimination of cost sharing for preventive screening has had limited early impact. Am J Manag Care 2015;21:511-7.
217. Medina GG, McQueen A, Greisinger AJ, Bartholomew LK, Vernon SW. What would make getting colorectal cancer screening easier? Perspectives from screeners and nonscreeners. Gastroenterology Research and Practice [serial on the Internet]. 2012 [cited 2017 Sep 27]. Available from: https://www.hindawi.com/journals/grp/2012/895807/.
218. Meissner HI, Klabunde CN, Breen N, et al. Breast and colorectal cancer screening: U.S. primary care physicians' reports of barriers. Am J Prev Med 2012;43:584-9.
219. Mehta SJ, Jensen CD, Quinn VP, Schottinger JE, Zauber AG, Meester R, et al. Race/ethnicity and adoption of a population health management approach to colorectal cancer screening in a community-based healthcare system. J Gen Intern Med. 2016;31(11):1323–30.
220. Subramanian S, Bobashev G, Morris RJ. When budgets are tight, there are better options than colonoscopies for colorectal cancer screening. Health Aff (Millwood) 2010;29:1734-40.
221. Doubeni CA, Corley DA, Zauber AG. Colorectal cancer health disparities and the role of US law and health policy. Gastroenterology. 2016; 150(5):1052–5.
222. Henry J. Kaiser Family Foundation. Status of state action on the Medicaid expansion decision [Internet]. Menlo Park (CA): KFF; 2017 Jan 1 [cited 2017 Sep 27]. Available from: http://www.kff.org/health-reform/state-indicator/state-activityaround-expanding-medicaid-underthe-affordable-care-act.
223. Schoen C, Osborn R, Squires D, et al. Access, affordability, and insurance complexity are often worse in the United States compared to ten other countries. Health Aff (Millwood) 2013;32:2205-15.
224. HealthyPeople.gov. Disparities [Internet]. Washington (DC): Department of Health and Human Services; [last updated 2017 Sep 26; cited 2017 Sep 27]. Available from: https://www.healthypeople.gov/2020/about/foundation-health-measures/Disparities.
225. Ness RM, Holmes AM, Klein R, et al. Utility valuations for outcome states of colorectal cancer. Am J Gastroenterol 1999;94:1650-7.
226. Centers for Disease Control and Prevention. National Health interview Survey, 2015.
227. Sabatino SA, White MC, Thompson TD, et al. Cancer screening test use - United States, 2013. MMWR Morb Mortal Wkly Rep 2015;64:464-8.
228. Centers for Disease C, Prevention. Vital signs: colorectal cancer screening test use--United States, 2012. MMWR Morb Mortal Wkly Rep 2013;62:881-8.
229. Lo SH, Halloran S, Snowball J, et al. Predictors of repeat participation in the NHS bowel cancer screening programme. Br J Cancer 2015;112:199-206.
230. Kapidzic A, van Roon AHC, van Leerdam ME, et al. Attendance and diagnostic yield of repeated two-sample faecal immunochemical test screening for colorectal cancer. Gut 2015.
231. Parkins MD, Parkins VM, Rendall JC, et al. Changing epidemiology and clinical issues arising in an ageing cystic fibrosis population. Ther Adv Respir Dis 2011;5:105-19.
232. Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cyst Fibros 2008;7:450-3.
233. Knapp EA, Fink AK, Goss CH, et al. The Cystic Fibrosis Foundation Patient Registry. Design and Methods of a National Observational Disease Registry. Ann Am Thorac Soc 2016;13:1173-9.
234. Meyer KC, Francois ML, Thomas HK, et al. Colon cancer in lung transplant recipients with CF: increased risk and results of screening. J Cyst Fibros 2011;10:366-9.

235. Niccum DE, Billings JL, Dunitz JM, et al. Colonoscopic screening shows increased early incidence and progression of adenomas in cystic fibrosis. J Cyst Fibros 2016;15:548-53.
236. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010;375:1624-33.
237. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687-96.
238. Mandel JS, Church TR, Ederer F, et al. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999;91:434-7.
239. Holme Ø, Løberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: A randomized clinical trial. JAMA 2014;312:606-615.
240. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. New Engl J Med 2012;366:2345-2357.
241. Hadjiliadis D; Khoruts A; Zauber AG; Hempstead SE; Maisonneuve P; Lowenfels AB, for the CF Colorectal Cancer Screening Taskforce. Cystic Fibrosis Colorectal Cancer Screening Consensus Recommendations. Work in progress 2017.
242. Vogelaar I, van Balegooijen M, Zauber AG, et al. Model profiler of the MISCAN-Colon miscosimulation model for colorectal cancer. Deparment of Public Health, Erasmus MC. 2004; available from: http://cisnet.flexkb.net/mp/pub/cisnet_colorectal_sloankettering_profile.pdf
243. Rutter CM, Johnson EA, Feuer EJ, et al. Secular trends in colon and rectal cancer relative survival. J Natl Cancer Inst 2013;105:1806-13.
244. Arminski TC, McLean DW. Incidence and Distribution of Adenomatous Polyps of the Colon and Rectum Based on 1,000 Autopsy Examinations. Dis Colon Rectum 1964;7:249-61.
245. Bombi JA. Polyps of the colon in Barcelona, Spain. An autopsy study. Cancer 1988;61:1472-6.
246. Chapman I. Adenomatous polypi of large intestine: incidence and distribution. Ann Surg 1963;157:223-6.
247. Johannsen LG, Momsen O, Jacobsen NO. Polyps of the large intestine in Aarhus, Denmark. An autopsy study. Scand J Gastroenterol 1989;24:799-806.
248. LJ B. Polyps of the colon and rectum: incidence and distribution. Dis Colon Rectum 1961;4:277-82.
249. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. Cancer 1982;49:819-25.
250. Belli EV, Landolfo K, Keller C, et al. Lung cancer following lung transplant: single institution 10 year experience. Lung Cancer 2013;81:451-4.
251. Gatto NM, Frucht H, Sundararajan V, et al. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst 2003;95:230-6.
252. Schroy PC, 3rd, Coe A, Chen CA, et al. Prevalence of advanced colorectal neoplasia in white and black patients undergoing screening colonoscopy in a safety-net hospital. Ann Intern Med 2013;159:13-20.
253. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 2009;150:849-57, W152.
254. Leffler DA, Kheraj R, Garud S, et al. The incidence and cost of unexpected hospital use after scheduled outpatient endoscopy. Arch Intern Med 2010;170:1752-7.
255. The United States Department of Labor. Bureau of Labor Statistics. Consumer Price Index. Available from: http://www.bls.gov/cpi/tables.htm.
256. Nick JA, Chacon CS, Brayshaw SJ, et al. Effects of gender and age at diagnosis on disease progression in long-term survivors of cystic fibrosis. Am J Respir Crit Care Med 2010;182:614-26.
257. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. Jama 2011;305:2304-10.

258. MacKenzie T, Gifford AH, Sabadosa KA, et al. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the Cystic Fibrosis Foundation patient registry. Ann Intern Med 2014;161:233-41.
259. Kelly T, Buxbaum J. Gastrointestinal Manifestations of Cystic Fibrosis. Dig Dis Sci 2015;60:1903-13.
260. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 2001;19:3163-72.
261. Blom J, Yin L, Lidén A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: Importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-1168.
262. van der Meulen MP, Lansdorp-Vogelaar I, Goede SL, et al. Colorectal Cancer: Cost-effectiveness of Colonoscopy versus CT Colonography Screening with Participation Rates and Costs. Radiology 2018;287:901-911.
263. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. N Engl J Med 2016;374:833-42.
264. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271-89.
265. Mark DH. Visualizing cost-effectiveness analysis. Jama 2002;287:2428-9.
266. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. Jama 2016;315:2564-2575.
267. Youn P, Li H, Milano MT, et al. Long-term survival among Hodgkin's lymphoma patients with gastrointestinal cancer: a population-based study. Ann Oncol 2013;24:202-8.
268. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2008;100:1368-79.
269. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355:1572-82.
270. Barton GR, Briggs AH, Fenwick EA. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). Value Health 2008;11:886-97.
271. Turner KO, Genta RM, Sonnenberg A. Lesions of All Types Exist in Colon Polyps of All Sizes. Am J Gastroenterol 2018;113:303-306.
272. Reulen RC, Frobisher C, Winter DL, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. Jama 2011;305:2311-9.
273. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018;68:250-281.
274. Minister of Health of the Netherlands, 2016. Available at: http://www.rivm.nl/en/Topics/B/Bowel_cancer_screening_programme (Accessed July 27, 2016).
275. Nathan PC, Ness KK, Mahoney MC, et al. Screening and surveillance for second malignant neoplasms in adult survivors of childhood cancer: a report from the childhood cancer survivor study. Ann Intern Med 2010;153:442-51.
276. van Eggermond AM, Schaapveld M, Janus CP, et al. Infradiaphragmatic irradiation and high procarbazine doses increase colorectal cancer risk in Hodgkin lymphoma survivors. Br J Cancer 2017;117:306-314.
277. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. N Engl J Med 2015;373:2499-511.
278. Lassman D, Sisko AM, Catlin A, et al. Health Spending By State 1991-2014: Measuring Per Capita Spending By Payers And Programs. Health Aff (Millwood) 2017;36:1318-1327.

279. EU-TOPIA towards improved cancer screening. url: http://eu-topia.org/about-eu-topia/about-eu-topia/, last access: Febrary 1, 2017.
280. Csanadi M, de Kok IM, Heijnsdijk EA, et al. Key indicators of organized cancer screening programs: Results from a Delphi study. J Med Screen 2019;26:120-126.
281. Scottish Intercollegiate Guidelines Network (SIGN). Long term follow up of survivors of childhood cancer. Edinburgh: SIGN; 2013. (SIGN publication no. 132). [March 2013]. Available from URL: http://www.sign.ac.uk. Last access: 05 May 2017.
282. Swedish Working Group for Long-term Follow-up after Childhood Cancer (SALUB). Version 5.0, 2010. Available at: http://www.blf.net/onko/page6/page14/files/Salub_5_2010_Eng.pdf. Last access: July 28 2017.
283. Cystic Fibrosis Foundation Patient Registry 2015 Annual Data Report. Bethesda, Maryland. Available on: https://www.cff.org/Our-Research/CF-Patient-Registry/2015-Patient-Registry-Annual-Data-Report.pdf 2016. Cystic Fibrosis Foundation.
284. Gini A, Meester RGS, Keshavarz H, et al. Cost-Effectiveness of Colonoscopy-Based Colorectal Cancer Screening in Childhood Cancer Survivors. J Natl Cancer Inst 2019;111:1161-1169.
285. Goede SL, Rabeneck L, Lansdorp-Vogelaar I, et al. The impact of stratifying by family history in colorectal cancer screening programs. Int J Cancer 2015;137:1119-27.
286. Ykema B, Rigter L, Spaander M, et al. Diagnostic Accuracy of Stool Tests for Colorectal Cancer Surveillance in Hodgkin Lymphoma Survivors. J Clin Med 2020;9.
287. Morson B. President's address. The polyp-cancer sequence in the large bowel. Proc R Soc Med 1974;67:451-7.
288. Goede SL, van Roon AH, Reijerink JC, et al. Cost-effectiveness of one versus two sample faecal immunochemical testing for colorectal cancer screening. Gut 2013;62:727-34.
289. Lansdorp-Vogelaar I, Goede SL, Bosch LJW, et al. Cost-effectiveness of High-performance Biomarker Tests vs Fecal Immunochemical Test for Noninvasive Colorectal Cancer Screening. Clin Gastroenterol Hepatol 2018;16:504-512 e11.
290. Wilschut JA, Habbema JD, van Leerdam ME, et al. Fecal occult blood testing when colonoscopy capacity is limited. J Natl Cancer Inst 2011;103:1741-51.
291. Zorzi M, Mangone L, Anghinoni E, et al. Screening for colorectal cancer in Italy: 2011-2012 survey. Epidemiol Prev 2015;39:108-14.
292. Finnish cancer registry. Available at: https://cancerregistry.fi/. Last Access: 3 July 2017.