

1 **Additional File 1**

2 **Natural history parameter calibration**

3 Calibration parameters (Table 11) were transition probabilities from adenoma to advanced
4 adenoma, advanced adenoma to preclinical UICC stage I and from preclinical UICC stage I to
5 stage II, III and IV as well as probabilities of being symptomatic (from any preclinical stage).

6 Primary calibration target was the cumulative incidence of colorectal cancer at age 75 (i.e., the
7 risk to develop cancer by the age of 75). Secondary targets were age-specific lifetime incidence
8 and the cancer stage distribution (detected UICC I-IV cases).

9 First, these target parameters were derived from an unscreened population in Austria (1995-
10 1999) (1). Age-specific lifetime incidence was given in 5-year age groups with a peak at age
11 70-75. It was assumed that cancer cases reported as death certificate only (DCO cases) are
12 severe cases and therefore, they were proportionally distributed among UICC III-IV stages.
13 Cases with undefined cancer stages were proportionally distributed among UICC I-IV cases.
14 Stage distribution from the US Surveillance, Epidemiology, and End Results Program (SEER)
15 database and other modeling studies were applied for plausibility checks (2).

16 Age-specific adenoma incidence was derived from a calibration study of the MISCAN CRC
17 screening model for the Netherlands (3). In this study, observed adenoma prevalence data
18 estimated from international autopsy studies and Dutch epidemiological target data were
19 used (3). No published Austrian data on adenoma prevalence are available.

20 In the second step (automated calibration), the calibration parameters were first fitted to the
21 cumulative cancer incidence at age 75 and age-specific lifetime-risk was checked. Thereafter,

22 the algorithm was adapted using a weighted set of two target parameters (cumulative incidence,
 23 UICC stage distribution) as a goodness-of-fit measure.

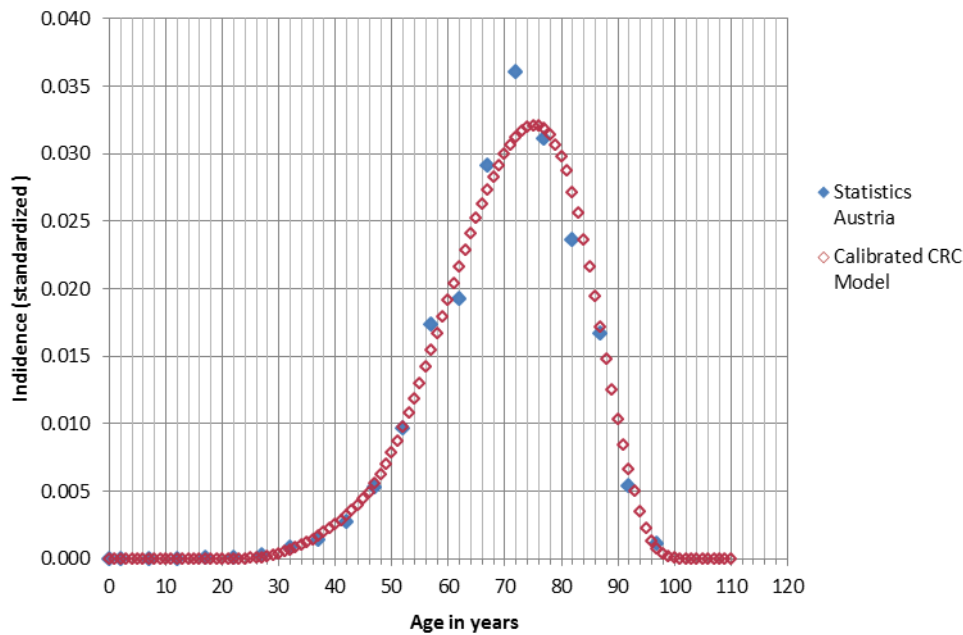
24 In the third step (non-automated), marginal adjustments were performed to obtain stage
 25 distribution of UICC II-IV cancer cases. Detailed results of the calibration are reported in the
 26 Additional file 1 (see Table 6, Figure 3 and Figure 4).

27 **Table 6. Stage distribution of incident CRC cases according to the calibrated model**
 28 **compared to other sources.**

| Stage distribution of incident CRC cases | UICC I | UICC II | UICC III | UICC IV |
|---|--------|---------|----------|---------|
| Calibrated Model | 21% | 25% | 30% | 24% |
| Statistics Austria (1995-1999) | 21% | 25% | 30% | 24% |
| Statistics Austria without DCO cases | 25% | 26% | 26% | 24% |
| SEER (1975-1979)* | 18% | 33% | 24% | 25% |
| MISCAN* | 18% | 34% | 24% | 25% |

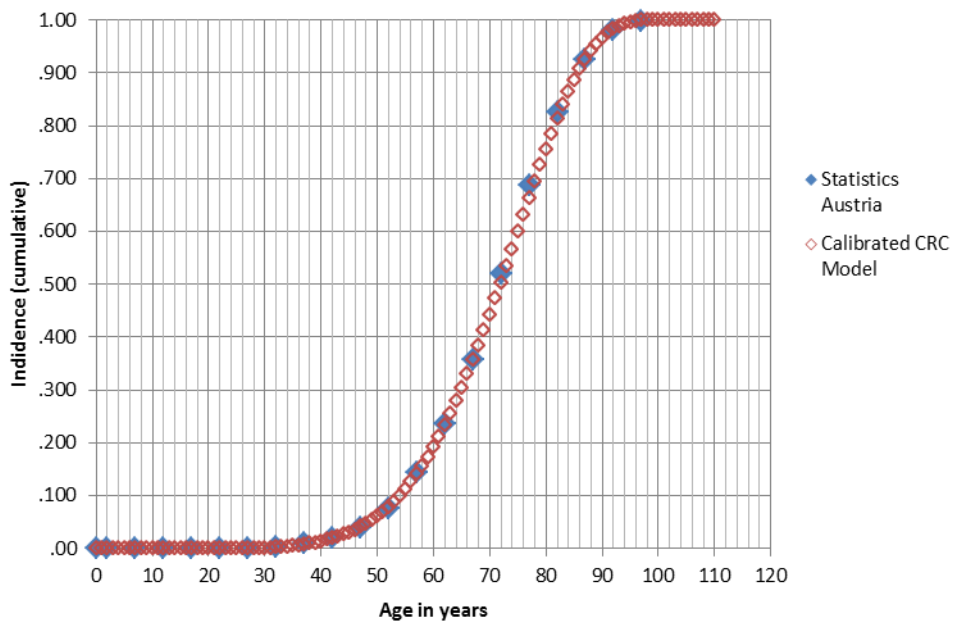
29 SEER - Surveillance, Epidemiology, and End Results Program, DCO - death certificate only, MISCAN -
 30 Microsimulation Screening Analysis, * validation

31 **Figure 3: Age distribution of incident cases (standardized incidence).**



32 CRC – colorectal cancer

33 **Figure 4: Age distribution of incident cases (cumulative incidence).**



34 CRC – colorectal cancer

35 **Test Accuracy**

36 **Table 7. Tests accuracy data of screening tests.**

| Test | Value | Source |
|-------------------------------|--------------|--------------------------|
| Colonoscopy | | |
| Sensitivity Adenomas | 69.0% | Bundo et al. 2017(4) |
| Sensitivity Advanced adenomas | 86.7% | Bundo et al. 2017(4) |
| Sensitivity Cancer | 94.7% | Pickhardt et al. 2003(5) |
| Specificity | 100.0% | Austrian Expert Panel |
| gFOBT | | |
| Sensitivity Adenomas | 9.5% | Zauber et al. 2008(6) |
| Sensitivity Advanced adenomas | 23.9% | Zauber et al. 2008(6) |
| Sensitivity Cancer | 72.2% | Hirai et al. 2016(7) |
| Specificity | 90.0% | Hirai et al. 2016(7) |
| FIT | | |
| Sensitivity Adenomas | 7.6% | Imperiale et al. 2014(8) |
| Sensitivity Advanced adenomas | 36.7% | Launois et al. 2014(9) |
| Sensitivity Cancer | 87.2% | Launois et al. 2014(9) |
| Specificity | 92.8% | Launois et al. 2014(9) |

37 gFOBT - guaiac-fecal occult blood test, FIT - fecal immunochemical test.

38 **Economic data**

39 Direct-medical costs were derived from the perspective of the Austrian public health care
40 system. Both medical outpatient- and inpatient-care costs were based on original data from the
41 Main Association of Austrian Social Security Institutions (10). These costs are explained in
42 more detail below taking into account the relative frequency distribution of cancer location,
43 cancer stage and medication options, which is reported in Table 9 (1).

44 *Costs of tests*

45 The costs of a colonoscopy includes the cost of colonoscopy without polypectomy as well as
46 lump compensation, outpatient visits, clinical report, the medical consultation and digital rectal
47 examination, each as a national average of charges of internists and surgeons. The costs of
48 polypectomy are measured as the mean costs for an endoscopic removal of polyps of the colon
49 and the rectum.

50 The costs for the guaiac-based fecal occult blood test include lump compensation, outpatient
51 visits, the medical consultation and digital rectal examination. The costs are measured as
52 national average of charges of internists and surgeons.

53 The costs for the immunochemical fecal occult blood test additionally include the reagents for
54 the examination, the laboratory examination, the transport costs and the physician's fee per
55 patient. The costs for both types of fecal occult blood test kit are listed separately.

56 *Staging costs*

57 The staging costs were collected separately for colorectal cancer (i.e., cancer location ICD-10
58 C18 and ICD-10 C19) and rectal cancer (i.e., cancer location ICD-10 C20). These costs include
59 in both cases the outpatient visit, laboratory work with the tumor marker (carcinoembryonic
60 antigen), sonography of the upper abdomen and computed tomography (CT) of the abdomen
61 and thorax. In addition, the costs for the staging of rectal cancer include also both a magnetic
62 resonance tomography (MR) of the lesser pelvis and a rectal endosonography (10).

63 The staging costs were used to produce a weighted mean of these two cancer types. For this
64 purpose, they were multiplied with the mean relative frequency of colorectal cancer and the

65 mean relative frequency of rectal cancer in the years 2010 to 2014 (70.31% and 29.69%
66 respectively) (10).

67 *Inpatient-care costs*

68 The inpatient-care costs are provided separately for the three different cancer locations (ICD-
69 10 C18, ICD-10 C19, ICD-10 C20) and the four cancer stages (UICC I, UICC II, UICC III and
70 UICC IV). Thus, only patients with an identified cancer stage were considered in the available
71 economic data. These costs were calculated using the corresponding points of the Diagnosis
72 Related Groups (DRG) of a treatment multiplied with the estimated mean value of a DRG point
73 (value of DRG point = EUR 1.4), separately for each UICC level and cancer location (10).

74 For the decision-analytic model, we aggregated this data on the four cancer stages UICC I-IV
75 by taking into account the relative frequency of the cancer location (i.e., ICD-10 C18, ICD-10
76 C19 and ICD-10 C20) at each cancer stage between 2010 and 2014. Thus, we include the
77 inpatient-care costs at UICC level as weighted mean of the three considered cancer locations.

78 *Medication costs*

79 The medication costs are provided for three types of medication for cancer stage UICC IV.
80 58.46 % of the patients receive a tyrosine kinase inhibitor (drug 1, i.e., Regorafenib
81 (Stivarga®)) and 30.84 % of the patients an antineoplastic nucleoside analog (drug 2, i.e.,
82 Trifluridin/Tipiracil (Lonsurf®)). Additionally, 10.70 % of the patients receive Regorafenib
83 (drug 1) plus Trifluridin (drug 2). The cost for this latter medication is calculated as the sum of
84 the costs of the two drugs. The medication costs are further calculated for the model as weighted
85 average of the three medication types using the above mentioned proportional shares.

86 *Follow-up costs*

87 The follow-up costs were provided separately for colorectal cancer (ICD-10 C18 and ICD-10
88 C19) and rectal cancer (ICD-10 C20). Timelines are presented in Table 10.

89 *Follow-up costs for colorectal cancer*

90 In the first year, the follow-up costs for colorectal cancer include a quarterly medical
91 consultation (after 3, 6, 9 and 12 months), the tumor marker laboratory four times a year (after
92 3, 6, 9 and 12 months), a colonoscopy and an annual CT of the abdomen (after 12 months). In
93 the second and the third year, the follow-up costs are similar, though no further colonoscopies
94 are conducted.

95 The follow-up costs in the fourth and fifth year include a medical consultation and the
96 measurement of tumor markers twice a year (after 42, 48, 54 and 60 months). The costs for a
97 CT of the abdomen were further considered once in the fourth and once in fifth year (after 48
98 and 60 months). Moreover, the costs for a further colonoscopy were included in the fourth year
99 (after 48 months). After the fifth year following surgery, the follow-up costs for colorectal
100 cancer include a medical consultation and colonoscopy every five years (every 60 months).

101 *Follow-up costs for rectal cancer*

102 In the first year, the follow-up costs for rectal cancer include a quarterly medical consultation
103 (after 3, 6, 9 and 12 months), the tumor marker laboratory four times a year (after 3, 6, 9 and
104 12 months), a rectoscopy after 6 months, a colonoscopy after 12 months and a CT of the
105 abdomen after 6 months for 30% of the patients and after 12 months for all patients. In the
106 second and third year, the follow-up costs are similar, though again no further colonoscopies
107 are conducted. The rectoscopy is repeated after 24 months and for 25-30 % of the patients again
108 after 36 months.

109 Similarly to the follow-up of the colorectal cancer, the follow-up costs in the fourth and fifth
110 year include a medical consultation and measurement of tumor markers twice a year (after 42,
111 48, 54 and 60 months). Moreover, the abdomen was scanned with computed tomography once
112 in the fourth and once in fifth year (after 48 and 60 months). The costs for a further colonoscopy
113 were included in the fourth year (after 48 months). After the fifth year, the follow-up costs for
114 colorectal cancer and rectal cancer are the same and include medical consultation and a
115 colonoscopy every five years (i.e., every 60 months).

116 The overall follow-up costs in the model are calculated for each year after diagnosis as a
117 weighted mean of colorectal cancer and rectal cancer using the relative frequency distribution
118 (cf. staging costs).

119 *Costs for colonoscopy screening program*

120 The estimated annual costs for the colonoscopy screening program provided include costs for
121 the coordinating office, management of the invitation (i.e., print and shipping of reminders),
122 service line, evaluation, data management, quality management and public relations.

123 The costs for the reminders were calculated based on all people between 50 and 70 years of age
124 in 2016. Following data provided by Statistics Austria to the HVB, these were 2369510 people
125 in Austria on Jan 1, 2017. As the reminders for a colonoscopy screening are sent every 10 years,
126 the costs for the invitation management are calculated for a tenth of these people, i.e.,
127 236951 (11).

128 *Costs for stool-based screening program*

129 The estimated annual costs for the stool-based screening program provided include the same
130 costs as for the colonoscopy screening, i.e., coordinating office, the management of the
131 invitation (i.e., print and shipping of reminders), service line, evaluation, data management,
132 quality management and public relations.

133 However, the costs for the management of screening invitation are higher as the reminders are
134 sent out to all people between 40 and 75 years of age on an annual basis. Thus, the costs include
135 screening invitations sent annually to 4016937 people in Austria (as per January 1, 2017,
136 Statistics Austria) (11).

137 *Costs of complications*

138 For the calculation of the costs, only those complications of colonoscopies which result in an
139 inpatient stay are considered. This can be further differentiated into complications followed by
140 a surgical procedure (0.013 % of all screening colonoscopies) and complications without a
141 surgical procedure, but still with an inpatient stay (0.03 % of all screening colonoscopies).
142 These costs were calculated using data from the Documentation and Information System for
143 Analyses in Healthcare (12).

144 *End-of-life costs*

145 End-of-life costs applied to cancer death of patients staged UICC I or UICC II include the
 146 inpatient-care costs for cancer stage UICC III and UICC IV as well as the medication costs for
 147 UICC IV. The end-of-life costs of patients staged UICC III dying from cancer include the
 148 inpatient-care costs and the medication costs for UICC IV. These end-of-life costs are
 149 calculated by taking into account the distribution of the cancer location.

150 **Table 8. Aggregated costs of tests, staging, inpatient, medication, follow-up, screening,**
 151 **complications and end-of-life of colorectal and rectal cancer (Index year 2017) -**
 152 **Extended.**

| Item | Costs at index year 2017, EUR |
|---|-------------------------------------|
| Costs for tests | |
| Colonoscopy | 228.21 |
| Polypectomy | 63.97 |
| gFOBT | 36.52 |
| iFOBT | 41.11 |
| gFOBT (stool test only) | 0.83 |
| iFOBT (stool test only) | 0.89 |
| Staging costs | |
| Colorectal cancer | 404.38 |
| Rectal cancer | 595.86 |
| Aggregated staging costs | 461.22 |
| Inpatient-care costs (cancer location- cancer stage) | |
| ICD-10 C18 UICC I | 14094.73 |
| ICD-10 C18 UICC II | 19665.00 |
| ICD-10 C18 UICC III | 19342.20 |
| ICD-10 C18 UICC IV | 24069.73 |
| ICD-10 C19 UICC I | 13839.35 |

| Item | Costs at index year 2017, EUR |
|--|--|
| ICD-10 C19 UICC II | 13745.38 |
| ICD-10 C19 UICC III | 14897.63 |
| ICD-10 C19 UICC IV | 18379.95 |
| ICD-10 C20 UICC I | 13353.12 |
| ICD-10 C20 UICC II | 16699.57 |
| ICD-10 C20 UICC III | 19057.20 |
| ICD-10 C20 UICC IV | 24867.53 |
| Aggregated inpatient costs UICC I | 13830.58 |
| Aggregated inpatient costs UICC II | 18699.11 |
| Aggregated inpatient costs UICC III | 19037.65 |
| Aggregated inpatient costs UICC IV | 24059.44 |
| Medication costs (UICC IV) | |
| Regorafenib (Stivarga®) | 12373.50 |
| Trifluridin/Tipiracil (Lonsurf®) | 9327.70 |
| Stivarga® plus Lonsurf® | 21701.20 |
| Aggregated medication costs | 12433.00 |
| Follow-up costs | |
| Year 1 (colorectal cancer) | 531.05 |
| Year 2 (colorectal cancer) | 346.01 |
| Year 3 (colorectal cancer) | 346.01 |
| Year 4 (colorectal cancer) | 418.95 |
| Year 5 (colorectal cancer) | 233.91 |
| Year 9, year 14, lifelong every 60 months (colorectal cancer) | 228.21 |
| Year 1 (rectal cancer). | 600.82 |
| Year 2 (rectal cancer) | 415.68 |
| Year 3 (rectal cancer) | 355.09 |
| Year 4 (rectal cancer) | 418.95 |
| Year 5 (rectal cancer) | 242.99 |

| Item | Costs at index year 2017, EUR |
|---|--|
| Year 9, year 14, lifelong every 60 months (rectal cancer) | 228.21 |
| Aggregated follow-up costs: year 1 | 551.76 |
| Aggregated follow-up costs: year 2 | 366.69 |
| Aggregated follow-up costs: year 3 | 348.71 |
| Aggregated follow-up costs: year 4 | 418.95 |
| Aggregated follow-up costs: year 5 | 236.61 |
| Aggregated follow-up costs: year 9, 14, lifelong every 60 months | 228.21 |
| Costs for screening program | |
| Costs for colonoscopy screening program | 1950353.17 |
| Costs for stool-based screening program | 4118142.33 |
| Costs of complications | |
| Surgical procedures | 23258.11 |
| Inpatient stay | 5250.33 |
| End-of-life costs | |
| One-time costs, cancer death at UICC I and UICC II | 55530.09 |
| One-time costs, cancer death at UICC III | 36492.45 |

153 gFOBT - guaiac-fecal occult blood test, FIT - fecal immunochemical test, EUR - Euro, ICD-10 C18 - malignant
154 neoplasm of colon, ICD-10 C19 - malignant neoplasm of rectosigmoid junction, ICD-10 C20 - malignant
155 neoplasm of rectum, UICC - Union for International Cancer Control classification.

156 **Table 9. Relative frequency distribution of cancer stage, cancer location, and medication**
 157 **options used for cost calculations.**

| Item | Relative frequency | Source |
|---|---------------------------|------------------------|
| Cancer location per cancer stage* | | |
| <i>UICC I</i> | | |
| ICD-10 C18 | 0.6182 | Statistics Austria (1) |
| ICD-10 C19 | 0.0391 | Statistics Austria (1) |
| ICD-10 C20 | 0.3427 | Statistics Austria (1) |
| <i>UICC II</i> | | |
| ICD-10 C18 | 0.7109 | Statistics Austria (1) |
| ICD-10 C19 | 0.0368 | Statistics Austria (1) |
| ICD-10 C20 | 0.2524 | Statistics Austria (1) |
| <i>UICC III</i> | | |
| ICD-10 C18 | 0.6400 | Statistics Austria (1) |
| ICD-10 C19 | 0.0486 | Statistics Austria (1) |
| ICD-10 C20 | 0.3115 | Statistics Austria (1) |
| <i>UICC IV</i> | | |
| ICD-10 C18 | 0.6902 | Statistics Austria (1) |
| ICD-10 C19 | 0.0397 | Statistics Austria (1) |
| ICD-10 C20 | 0.2701 | Statistics Austria (1) |
| Cancer location | | |
| Colorectal cancer (ICD-10 C18 + ICD-10 C19) | 0.7032 | Statistics Austria (1) |
| Rectal cancer (ICD-10 C20) | 0.2968 | Statistics Austria (1) |
| Medication options** | | |
| Option 1 - Regorafenib (Stivarga®) | 0.5846 | HVB (10) |
| Option 2 - Trifluridin (Lonsurf®) | 0.3084 | HVB (10) |
| Option 3 - Regorafenib + Trifluridin | 0.1071 | HVB (10) |

158 *mean values for the years 2010-2014, ** values for the year 2016, HBV - Main Association of Austrian Social
 159 Security Institutions, ICD-10 C18 - malignant neoplasm of colon, ICD-10 C19 - malignant neoplasm of
 160 rectosigmoid junction, ICD-10 C20 malignant neoplasm of rectum, UICC - Union for International Cancer Control
 161 classification.

Table 10. Timeline of follow-up cost elements for colorectal and rectal cancer.

| Year | Follow-up cost elements | Months after surgery |
|--|---|---|
| Colorectal and rectal cancer | | |
| 1, 2, 3, 4, 5, 9, 14, lifelong every 5 years | Medical consultation | 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36 42, 48, 54, 60 108, 168, 228, ... |
| 1, 2, 3, 4, 5 | Tumor marker laboratory ("Tumormarker-Labor") | 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36 42, 48, 54, 60 |
| 1, 4, 9, 14, lifelong every 5 years | Colonoscopy | 12, 48, 108, 168, 228, ... |
| Colorectal cancer | | |
| 1, 2, 3 | CT of the abdomen | 12, 24, 36, 48, 60 |
| Rectal cancer | | |
| 1, 2, 3, 5 | Rectoscopy | 6, 24, 36 (25-30%) 60 (25-30%) |
| 1, 2, 3, 4, 5 | CT of the abdomen | 6 (30%), 12, 18 (30%), 24, 36, 48, 60 |

CT - computed tomography.

164 **Further model parameters**

165 **Table 11. Natural history model parameters and screening adverse effects**

| Transition From | To | Age (years) | Annual probability (annual rate) | Source |
|----------------------------------|-------------------------------|-------------|----------------------------------|------------------------------------|
| No lesion | Adenoma | 0-19 | 0.00200* | Goede et al. 2013 (3) |
| | | 20-29 | 0.00400* | |
| | | 30-39 | 0.00600* | |
| | | 40-44 | 0.02400* | |
| | | 45-49 | 0.02900* | |
| | | 50-54 | 0.03000* | |
| | | 55-59 | 0.03400* | |
| | | 60-64 | 0.04100* | |
| | | 65-69 | 0.04700* | |
| | | 70-74 | 0.05700* | |
| | | 75-79 | 0.03800* | |
| | | 80-84 | 0.03600* | |
| | | 85-120 | 0.01000* | |
| Adenoma | Advanced adenoma | | 0.016273 | calibrated |
| Advanced adenoma | UICC I undetected | | 0.027150 | calibrated |
| UICC I undetected | UICC II undetected | | 0.500000 | calibrated |
| UICC II undetected | UICC III undetected | | 0.600000 | calibrated |
| UICC III undetected | UICC IV undetected | | 0.700000 | calibrated |
| UICC I undetected | UICC I detected by symptoms | | 0.105000 | calibrated |
| UICC II undetected | UICC II detected by symptoms | | 0.205000 | calibrated |
| UICC III undetected | UICC III detected by symptoms | | 0.450000 | calibrated |
| UICC IV undetected | UICC IV detected by symptoms | | 1.000000 | calibrated |
| Screening adverse effects | | | | |
| Death from colonoscopy | | | 0.002900 | Reumkens et al. 2016 (13) |
| Hospitalization | | | 0.000420 | Austrian Colonoscopy Registry (14) |

166 *calibrated to autopsy studies.

167 Calibrated - to cumulative and age-specific incidence of colorectal cancer and UICC stage distribution of incident cases in Austria - Statistics Austria 1995-1999(1), UICC - Union for International Cancer Control classification.

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Table 12. Relative survival probability for symptomatic-detected colorectal cancer patients.

| Year post first diagnosis | Relative survival probability for symptomatic-detected colorectal cancer patients with first CRC diagnosis | | | |
|---------------------------|--|---------|----------|---------|
| | UICC I | UICC II | UICC III | UICC IV |
| 1-year | 0.915 | 0.892 | 0.851 | 0.470 |
| 2-year | 0.980 | 0.961 | 0.888 | 0.615 |
| 3-year | 0.983 | 0.967 | 0.905 | 0.645 |
| 4-year | 0.978 | 0.964 | 0.911 | 0.721 |
| 5-year | 0.991 | 0.966 | 0.939 | 0.806 |
| 6-year | 0.993 | 0.972 | 0.950 | 0.840 |
| 7-year | 0.994 | 0.977 | 0.959 | 0.869 |
| 8-year | 0.995 | 0.981 | 0.966 | 0.896 |
| 9-year | 0.996 | 0.985 | 0.973 | 0.920 |
| 10-year | 0.997 | 0.989 | 0.980 | 0.942 |
| 11-year | 0.998 | 0.992 | 0.985 | 0.963 |
| 12-year | 0.999 | 0.995 | 0.991 | 0.982 |
| 13-year | 1.000 | 0.997 | 0.995 | 1.000 |
| 14-year | 1.000 | 1.000 | 1.000 | 1.000 |

171 Recalculated based on averaged relative survival probabilities from Statistics Austria 2010-2014 for first diagnosis
 172 (ICD 10 C18 - malignant neoplasm of colon, ICD 10 C19 - malignant neoplasm of rectosigmoid junction, ICD 10
 173 C20 - malignant neoplasm of rectum) including screen and non-screen detected patients.
 174 CRC - colorectal cancer, UICC - Union for International Cancer Control classification.

175 **Table 13. Relative survival probability for screen-detected colorectal cancer patients.**

| Year post first diagnosis | Relative survival probability for screen-detected colorectal cancer patients with first CRC diagnosis | | | |
|---------------------------|---|---------|----------|---------|
| | UICC I | UICC II | UICC III | UICC IV |
| 1-year | 0.975 | 0.967 | 0.948 | 0.675 |
| 2-year | 0.994 | 0.989 | 0.961 | 0.777 |
| 3-year | 0.995 | 0.990 | 0.968 | 0.796 |
| 4-year | 0.994 | 0.989 | 0.970 | 0.843 |
| 5-year | 0.997 | 0.990 | 0.979 | 0.894 |
| 6-year | 0.998 | 0.992 | 0.983 | 0.913 |
| 7-year | 0.998 | 0.993 | 0.986 | 0.930 |
| 8-year | 0.999 | 0.994 | 0.989 | 0.944 |
| 9-year | 0.999 | 0.996 | 0.991 | 0.958 |
| 10-year | 0.999 | 0.997 | 0.993 | 0.970 |
| 11-year | 1.000 | 0.998 | 0.995 | 0.981 |
| 12-year | 1.000 | 0.998 | 0.997 | 0.991 |
| 13-year | 1.000 | 0.999 | 0.999 | 1.000 |
| 14-year | 1.000 | 1.000 | 1.000 | 1.000 |

176 Recalculated based on averaged relative survival probabilities from Statistics Austria 2010-2014 for first diagnosis
 177 (ICD 10 C18 - malignant neoplasm of colon, ICD 10 C19 - malignant neoplasm of rectosigmoid junction, ICD 10
 178 C20 - malignant neoplasm of rectum) including screen and non-screen detected patients.
 179 CRC - colorectal cancer, UICC - Union for International Cancer Control classification.

180 **Table 14. Relative survival probability for patients diagnosed with colorectal cancer**
 181 **(screen and symptomatic detected).**

| Year post first diagnosis | Relative survival probability for patients with first CRC diagnosis | | | |
|------------------------------|---|---------|----------|---------|
| | UICC I | UICC II | UICC III | UICC IV |
| 1-year | 92.9 | 91.0 | 87.4 | 51.8 |
| 2-year | 98.3 | 96.8 | 90.5 | 65.3 |
| 3-year | 98.6 | 97.2 | 92.0 | 68.0 |
| 4-year | 98.2 | 97.0 | 92.5 | 75.0 |
| 5-year | 99.2 | 97.1 | 94.9 | 82.7 |
| 6-year | 99.4 | 97.6 | 95.8 | 86.0 |
| 7-year | 99.5 | 98.1 | 96.6 | 88.8 |
| 8-year | 99.6 | 98.4 | 97.2 | 91.2 |
| 9-year | 99.7 | 98.8 | 97.8 | 93.3 |
| 10-year | 99.8 | 99.1 | 98.3 | 95.2 |
| 11-year | 99.9 | 99.3 | 98.8 | 97.0 |
| 12-year | 99.9 | 99.6 | 99.2 | 98.5 |
| 13-year | 100.0 | 99.8 | 99.6 | 100.0 |
| 14-year | 100.0 | 100.0 | 100.0 | 100.0 |

182 Averaged data from Statistics Austria 2010-2014 for diagnosis (ICD-10 C18-C20) including screen and non-screen
 183 detected patients for 1-year-to 5-year, 6-year and following data were extrapolated applying logarithmic functions
 184 to mortality probabilities.

185 CRC - colorectal cancer, UICC - Union for International Cancer Control classification.

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187 **Base-case analysis screening-related benefits and harms**

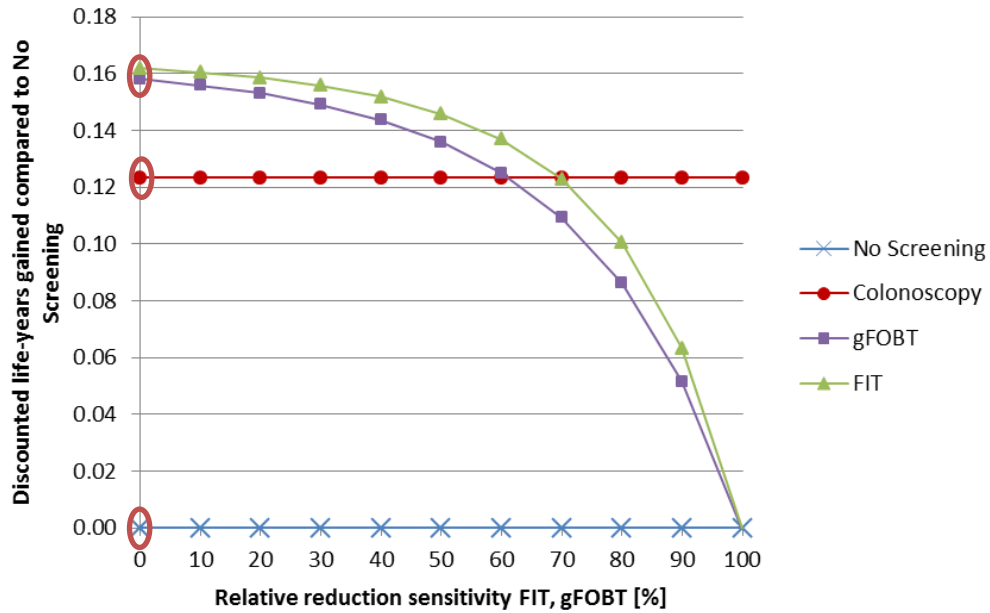
188 **Table 15. Outcome of screening programs to prevent colorectal cancer.**

| Outcome | Screening strategy: | 10-yearly colonoscopy | Annual gFOBT | Annual FIT |
|--|----------------------------|----------------------------------|-------------------------|-----------------------|
| Life-years gained | | 394 | 480 | 491 |
| CRC-related deaths averted | | 31 | 35 | 35 |
| CRC cases averted | | 62 | 66 | 69 |
| Additional complications due to colonoscopy (hospital admissions) | | 1.17 | 1.49 | 1.23 |
| Total positive test results | | 679 | 2797 | 2206 |

189 Numbers pertain to a cohort of 1000 persons 40 years of age who were followed until death in comparison to No
 190 Screening, CRC -colorectal cancer, gFOBT - guaiac-fecal occult blood test screening strategy, FIT - fecal
 191 immunochemical test screening strategy. FIT and gFOBT: 40-75 years old average - risk men and women.
 192 Colonoscopy: 50-70 years old average - risk men and women, all screening strategies include index testing, further
 193 diagnostics (including colonoscopy), surveillance (colonoscopy), treatment and follow up interventions.

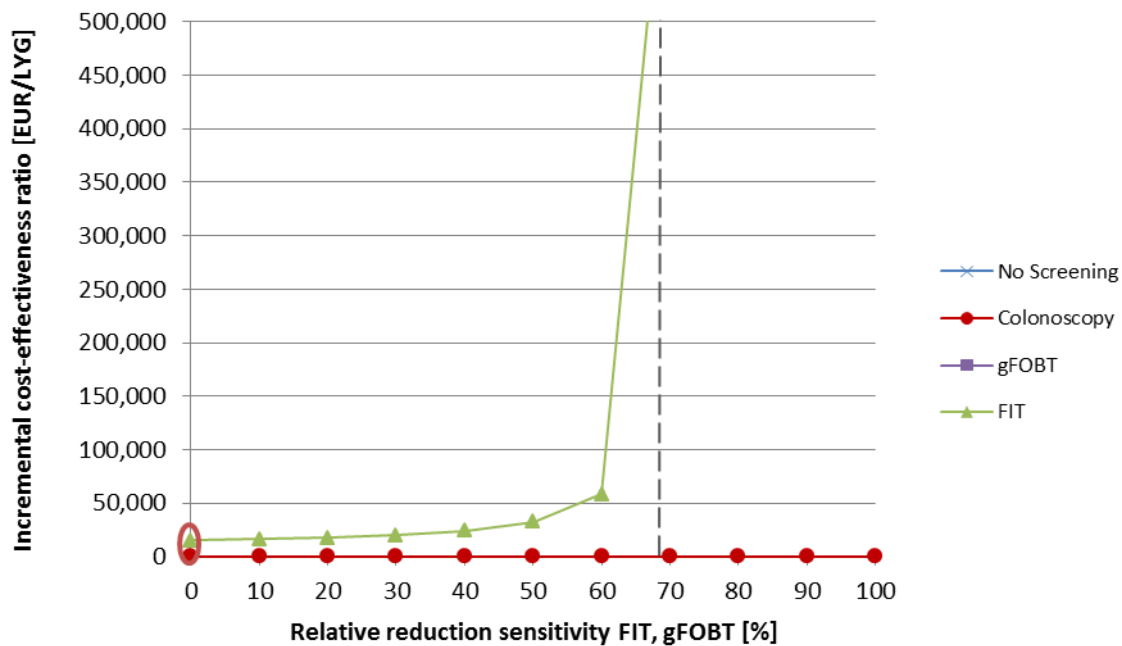
194 **Sensitivity analyses test accuracy**

195 **Figure 5. Sensitivity analysis on test accuracy for gFOBT and FIT impact on life years.**



196
 197 gFOBT - guaiac-fecal occult blood test strategy, FIT - fecal immunochemical test strategy. FIT and gFOBT: 40-
 198 75 years old average - risk men and women, annual. Colonoscopy: 50-70 years old average - risk men and women,
 199 10-yearly, all screening strategies include index testing, further diagnostics (including colonoscopy), surveillance
 200 (colonoscopy), treatment and follow up interventions.
 201 Red circles represent base case.

202 **Figure 6. Sensitivity analysis on test accuracy for gFOBT and FIT impact on ICER.**



203
 204 gFOBT - guaiac-fecal occult blood test strategy, FIT - fecal immunochemical test strategy, EUR - Euro, LYG -
 205 life-years gained. FIT and gFOBT: 40-75 years old average - risk men and women, annual. Colonoscopy: 50-70
 206 years old average - risk men and women, 10-yearly, all screening strategies include index testing, further
 207 diagnostics (including colonoscopy), surveillance (colonoscopy), treatment and follow up interventions.
 208 Red circle represents base case. gFOBT and No Screening are dominated strategies. Therefore, they are not shown
 209 in the graphic.

210 **Table 16. Calculative 10-year sensitivity of fecal blood tests in comparison to sensitivity**
 211 **of colonoscopy.**

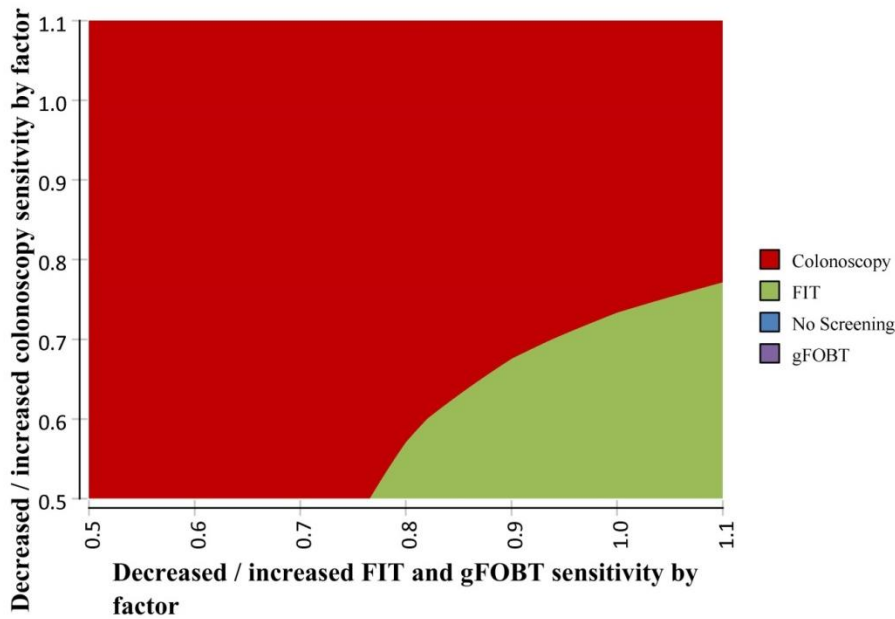
| | Sensitivity FIT | 10-year sensitivity* FIT | Sensitivity gFOBT | 10-year sensitivity* gFOBT | Sensitivity colonoscopy |
|---------------------|--------------------|--------------------------------|----------------------|----------------------------------|----------------------------|
| Adenoma | 0.076 | 0.546 | 0.095 | 0.631 | 0.690 |
| Advanced adenoma | 0.367 | 0.990 | 0.239 | 0.935 | 0.867 |
| Cancer | 0.872 | 1.000 | 0.647 | 1.000 | 0.947 |

212 *assuming independent test sensitivities for repeated screening tests.
 213 gFOBT - guaiac-fecal occult blood test strategy, FIT fecal immunochemical test strategy, FIT and gFOBT: 40-75
 214 years old average - risk men and women. Colonoscopy: 50-70 years old average - risk men and women, all
 215 screening strategies include index testing, further diagnostics (including colonoscopy), surveillance (colonoscopy),
 216 treatment and follow up interventions.

217 **Two-way sensitivity analyses**

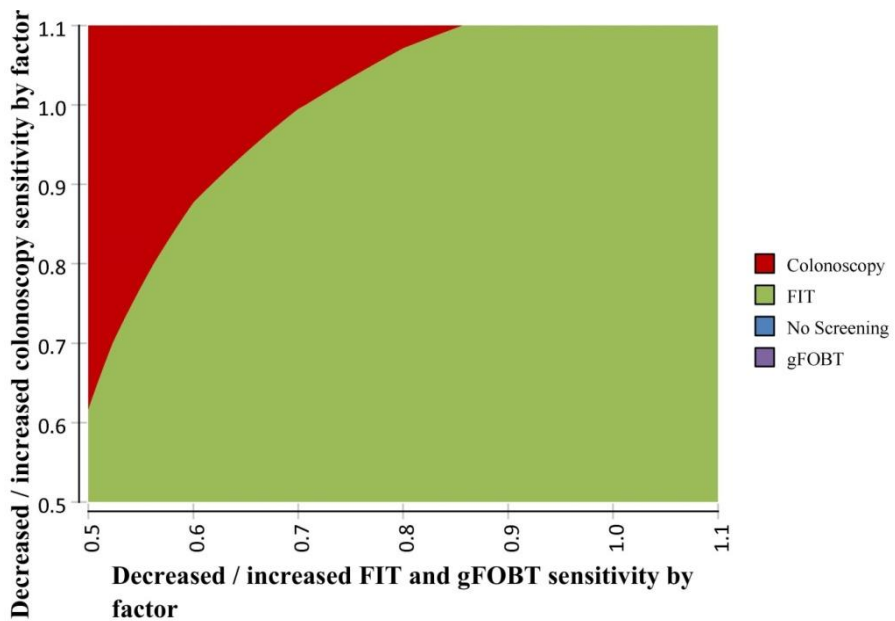
218 Figure 7, Figure 8 and Figure 9 show the results of the two-way sensitivity analyses when the
219 sensitivity of fecal occult blood tests (gFOBT, FIT) and the sensitivity of colonoscopy are
220 varied simultaneously assuming a willingness-to-pay thresholds of EUR 10000/LYG, EUR
221 20000/LYG and EUR 30000/LYG, respectively. The graphics read as follows: the sensitivity
222 parameters for the fecal occult blood tests are reduced by up to 50% and increased by up to
223 10% (x-axis). The same variation is assumed for the sensitivity of colonoscopy displayed on
224 the y-axis. Depending on the combinations of these two parameters on the x- and y-axis, the
225 shade of the area defines the cost-effective screening strategy given the respective willingness-
226 to-pay threshold. The combination of the factor 1 on the x-axis (sensitivity fecal occult blood
227 tests) and 1 on the y-axis (sensitivity colonoscopy) displays the base-case results. Assuming a
228 willingness-to-pay threshold of EUR 20000/LYG (Figure 8), FIT is cost-effective for the base-
229 case parameter set. Assuming a 20% reduction in the sensitivity of the fecal occult blood tests
230 and a 10% increase in the sensitivity of colonoscopy would lead to 10-yearly colonoscopy
231 screening being the cost-effective strategy.

232 **Figure 7. Two-way sensitivity analysis of test sensitivities with a WTP of EUR 10,000**
 233 **LYG.**



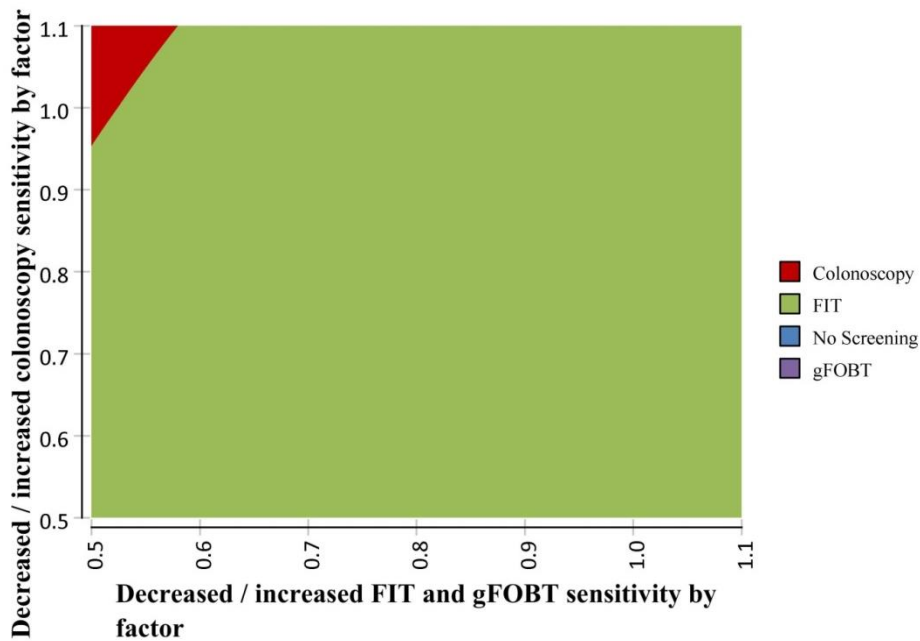
234 gFOBT - guaiac-fecal occult blood test screening strategy, FIT - fecal immunochemical test screening strategy,
 235 WTP willingness-to-pay, EUR - Euro, LYG - life-years gained.

236 **Figure 8. Two-way sensitivity analysis of test sensitivities with a WTP of EUR 20,000**
 237 **LYG.**



238 gFOBT - guaiac-fecal occult blood test screening strategy, FIT - fecal immunochemical test screening
 239 strategy, WTP willingness-to-pay, EUR - Euro, LYG - life-years gained.

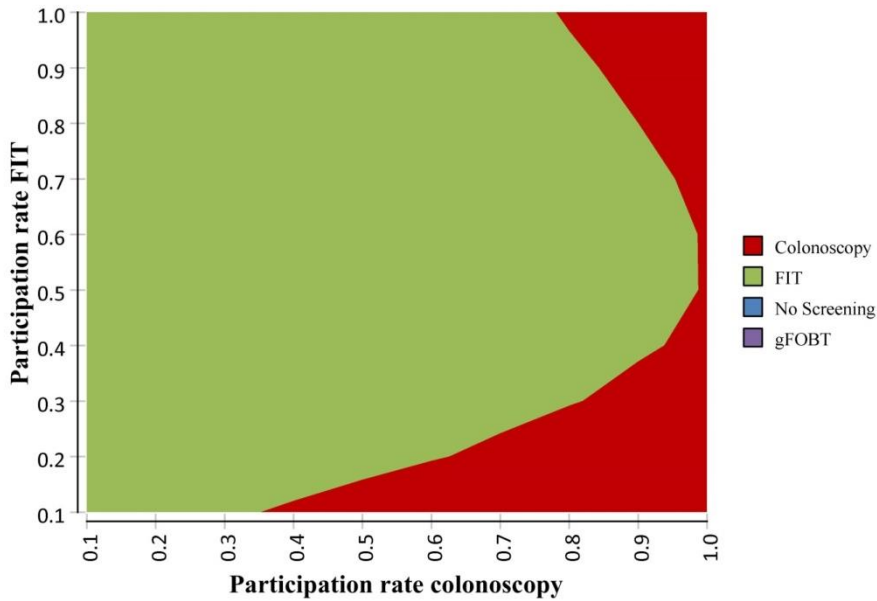
240 **Figure 9. Two-way sensitivity analysis of test sensitivities with a WTP of EUR 30,000**
 241 **LYG.**



242 gFOBT - guaiac-fecal occult blood test screening strategy, FIT - fecal immunochemical test screening strategy,
 243 WTP willingness-to-pay, EUR - Euro, LYG - life-years gained.

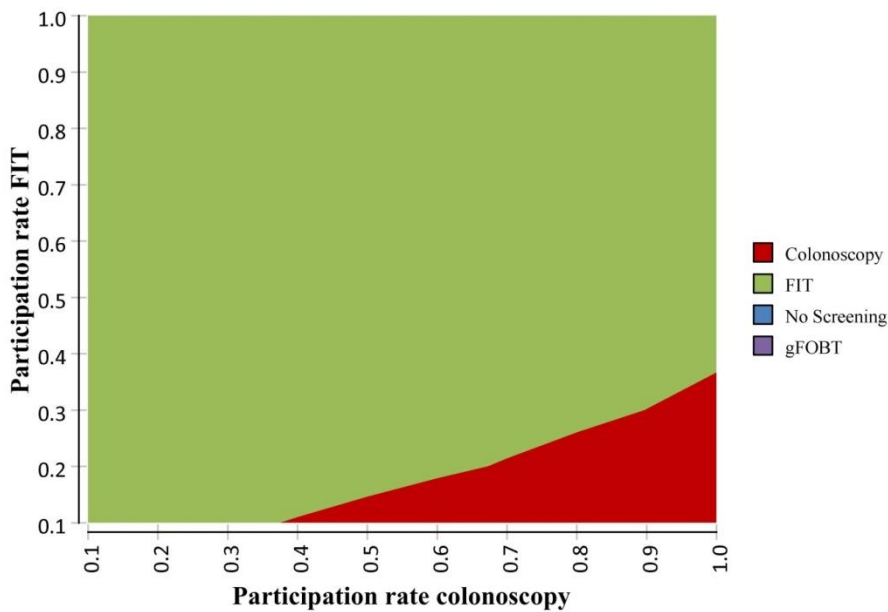
244 Figure 10, Figure 11 and Figure 12 show the results of the two-way sensitivity analyses when
 245 the participation rates of fecal occult blood tests (gFOBT, FIT) and colonoscopy are varied
 246 simultaneously assuming willingness-to-pay thresholds of EUR 10000/LYG, EUR 20000/LYG
 247 and EUR 30000/LYG, respectively. The participation rates for the both fecal occult blood tests
 248 are assumed to be equal. The graphics read as follows: the participation rates are assumed to
 249 vary between 10% and 100%. With increasing willingness-to-pay thresholds 10-yearly
 250 colonoscopy screening (symbolized by a red shaded area for the combinations of participation
 251 rates) would be the preferred option only for high participation rates of colonoscopy screening
 252 and low participation rates of the annual FIT screening.

253 **Figure 10. Two-way sensitivity analysis of test participation rates with a WTP of EUR**
 254 **10,000 LYG.**



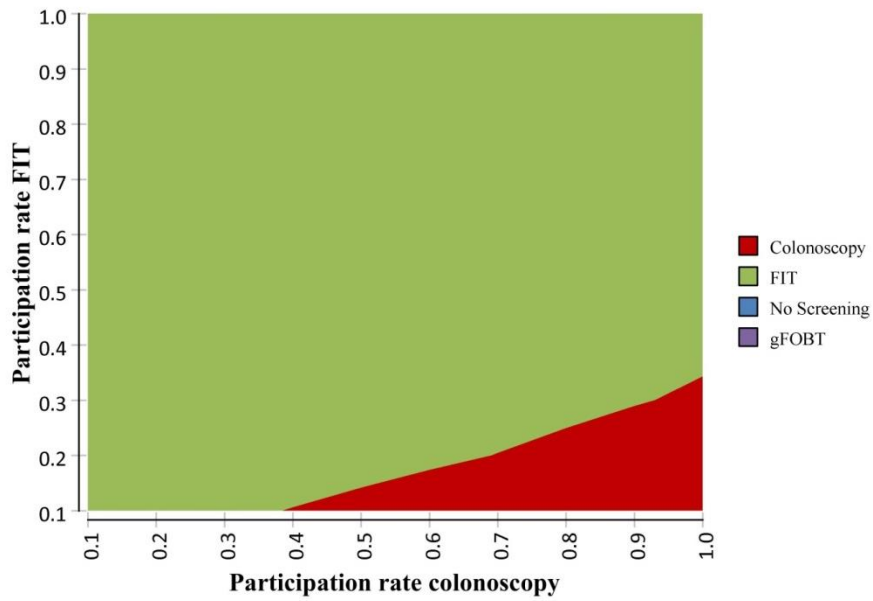
255 gFOBT - guaiac-fecal occult blood test screening strategy, FIT - fecal immunochemical test screening strategy,
 256 WTP willingness-to-pay, EUR - Euro, LYG - life-years gained.

257 **Figure 11. Two-way sensitivity analysis of test participation rates with a WTP of EUR**
 258 **20,000 LYG.**



259 gFOBT - guaiac-fecal occult blood test screening strategy, FIT - fecal immunochemical test screening strategy,
 260 WTP willingness-to-pay, EUR - Euro, LYG - life-years gained.

261 **Figure 12. Two-way sensitivity analysis of test participation rates with a WTP of EUR**
262 **30,000 LYG.**



263 gFOBT - guaiac-fecal occult blood test screening strategy, FIT - fecal immunochemical test screening strategy,
264 WTP willingness-to-pay, EUR - Euro, LYG - life-years gained.

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