Economic evaluation of genetic screening for Lynch syndrome in Germany

Running title: Economic evaluation of Lynch syndrome screening

Authors

Franziska Severin[1*], PD Dr. Björn Stollenwerk[1], Prof. Dr. Elke Holinski-Feder[2], Dr. Elisabeth Meyer[1], Prof. Dr. Volker Heinemann[3], Dr. Clemens Giessen-Jung[3], PD Dr. Wolf Rogowski[1]

[1]Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Ingolstädter Landstrasse 1, 85764 Neuherberg, Germany

[2]MGZ - Medizinisch Genetisches Zentrum, Bayerstraße 3-5, 80335 Munich, Germany

[3]Department of Medical Oncology and Comprehensive Cancer Center, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377 Munich, Germany

*corresponding author (Tel.: 0049 89 3187 2346, Fax: 0049 89 3187 3375, E-mail: franziska.severin@helmholtz-muenchen.de)

Abstract

Purpose: Lynch syndrome screening among patients with newly diagnosed colorectal cancer can decrease mortality in their affected first-degree relatives. In Germany, it is not yet clinical practice and the cost-effectiveness of different testing strategies is unknown.

Methods: We set up a decision-analytic model to analyze the cost-effectiveness of Lynch syndrome screening from the perspective of the German Statutory Health Insurance system. A total of 22 testing strategies considering family history assessment, analysis of tumor samples (i.e. immunohistochemistry (IHC), microsatellite instability and BRAF testing) and genetic sequencing were analyzed. Life years gained in relatives by closed-meshed colonoscopy and aspirin prophylaxis were estimated by Markov models. Uncertainty was assessed deterministically and probabilistically.

Results: On average, detected mutation carriers gained 0.52 life years (undiscounted 1.34) by increased prevention. Most strategies were dominated except three: family assessment by the Bethesda criteria followed by IHC and BRAF testing and genetic sequencing; IHC and BRAF testing and genetic sequencing; and direct sequencing of all index patients. Their incremental cost-effectiveness was € 77,268, € 253,258 and € 4,188,036 per life year gained, respectively.

Conclusion**:** The results were less favorable than those of previous models. Chemoprevention appears to provide comparably low additional benefit and improves cost-effectiveness only slightly.

Keywords: Individualized health care; Lynch syndrome; screening; cost-effectiveness; Germany

INTRODUCTION

In Germany, colorectal cancer (CRC) is the second most commonly diagnosed form of cancer for both women and men, with over 69,000 cases reported in 2012.[1] Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer (HNPCC), accounts for ca. 3% of all newly diagnosed CRC cases which makes it the most common hereditary colon cancer syndrome.[2] It is caused by autosomal-dominant mutations in DNA mismatch-repair (MMR) genes (*MSH2*, *MLH1*, *MSH6*, and *PMS2*), which leads to an accumulation of genetic changes furthering tumor growth[3]. Individuals who inherit the autosomal-dominant mutation have an approximately 40% lifetime risk of developing CRC[4] , compared with ca. 6% in the German population[1].

In Germany, patients with LS are recommended to undergo colonoscopy every year from age 25, along with physical examinations.[5, 6] Colonoscopic surveillance has shown effective at preventing progression (of polyps) to CRC as well as detecting the disease at an early stage, thus reducing CRC incidence and mortality.[7] In addition to increased colonoscopic surveillance, long-term aspirin intake has been proposed as an effective way to reduce CRC risks.[8] Although aspirin prophylaxis is internationally discussed as a promising approach it is not generally recommended by the German guidelines for the prevention of CRC in LS patients, as data regarding appropriate dosage is still missing.[5]

Given the high CRC risk in LS carriers, it is important to define appropriate diagnostic procedures for the identification of LS patients. Traditionally, clinical criteria such as the revised Bethesda guidelines or Amsterdam II criteria have been used to guide further genetic testing in patients suspected for LS.[5] These criteria include information about cancer cases

among family members. However, many patients might not be identified by family criteria, e.g. because of small family sizes, incomplete penetrance of the MMR mutation, or because patients are simply unaware about cancer cases in their families.[9] Therefore alternative screening algorithms which do not include family history data might be desirable.[10, 11]

International studies have shown, that genetic screening among patients with newly diagnosed CRC to detect mutations and offer testing and increased prevention to relatives may be an effective approach, resulting in very favorable cost-effectiveness ratios of less than $40,000 per life year gained (LYG) [12-17] or less than $60,000 per quality-adjusted LYG [18, 19]. We would expect similar favorable results also for Germany, however, given international differences in medical reimbursement rates and health care provision this still needs to be assessed. In particular, the German guidelines foresee yearly colonoscopic surveillance whereas existing cost-effectiveness models assume surveillance intervals of two or even three years.[12, 14-17] Also, costs of testing for LS appear to be higher in Germany than for example reported in US models. [13-16, 18, 19] Both might possibly increase the costs per LYG of LS screening in Germany.

To our knowledge there is currently only one study assessing the cost-effectiveness of LS screening in Germany.[20] Although this study concludes that the most cost-effective approach involves testing first-degree relatives (FDR) of newly diagnosed CRC cases that have been found to be mutation carriers[20] it does not compare different testing strategies to detect LS in CRC patients.

Therefore this study aims to assess the expected cost-effectiveness of different screening strategies for LS from the perspective of the German Statutory Health Insurance (SHI)

system. The SHI system is the most important payer in the German health care system with approximately 85% of the German population seeking insurance within the system.[21] We also aimed to assess the cost-effectiveness of adding aspirin chemoprevention to colonoscopic surveillance in LS carriers. Existing studies do not account for the presumably favorable effect of aspirin chemoprevention in LS carriers and thus the potential role of aspirin in LS remains unclear. Moreover we aimed to identify key variables that could improve the cost-effectiveness of LS screening and thus should be further considered by German public policy.

MATERIALS AND METHODS

Model structure

We set up a probabilistic decision-analytic model analyzing effects in LYG and costs financed by the SHI. We used a cohort model consisting of two parts: First, the genetic testing strategies were represented as a decision tree. This allowed evaluating various testing strategies in terms of the number of detected mutations and related costs. Second, Markov models were used to estimate cancer-related mortality and life expectancy in FDR without LS, in undetected FDR who inherited LS but undergo normal colonoscopic surveillance only, and in FDR with LS who were detected and thus can benefit from increased surveillance and prophylactic aspirin. To illustrate the consequences for the SHI, we assume a cohort size of 69.400 individuals diagnosed with CRC, which corresponds with the CRC incidence projected for Germany in 2012.[1]

Testing strategies

Once CRC is identified in an index patient genetic counselling and testing for LS is offered. In those patients that agree to be tested, analysis of tumor material and genetic sequencing is performed. Genetic sequencing involves testing of a blood sample to identify mutations in the MMR genes by means of sequencing and deletion. Tumor screening involves microsatellite instability (MSI) and immunohistochemistry (IHC) analysis and testing for the BRAF V600 mutation. In contrast to MSI testing, IHC can predict which of the MMR genes may be defective resulting in lower testing costs as genetic sequencing can be targeted on the relevant MMR gene. If the MLH1 protein is absent in the IHC analysis, BRAF testing can be used as a further step to exclude sporadic CRC cases: detection of the BRAF V600 mutation strongly argues for a sporadic tumor.

Figure 1 provides an overview of the screening strategies considered. In strategy 1-6, tumor-tissue analysis is used as a preceding step to increase the likelihood of identifying a germline mutation in an MMR gene. Strategy 7 assumes direct sequencing of all MMR genes without prior tumor analysis. The seven baseline strategies may be combined with the Amsterdam II[22] (A) or revised Bethesda[23] (B) criteria. Testing is then offered only to patients who fulfil the clinical criteria. The resulting testing strategies are termed A 1-7 and B 1-7. Strategy B-4 and B-6 are the two screening strategies currently recommended by the German guideline for CRC treatment and prevention.[5]

If a causative mutation is detected in an index patient, targeted DNA testing for this mutation can be offered to the person's FDR. FDR who inherited the family mutation are offered increased prevention opportunities.

Markov model

Markov models were used to estimate cancer-related mortality and life expectancy in FDR. Following the recommendation of the German guideline for CRC[5], LS positive FDR were assumed to be offered annual colonoscopic surveillance starting at age 25. In addition, although not yet recommended by the German guideline, they receive aspirin prophylaxis. Mutation-negative relatives are offered standard prevention consisting of colonoscopy every 10 years between age 55 and 75. Standard prevention would also be offered to false-negative mutation carriers and those whose mutation status was unknown (e.g. relatives that decline genetic testing).

Each Markov model consists of the 5 main states well, CRC, metachronous CRC, well after cancer and death (see Figure 2). Cancer stages were classified according to the Union Internationale Contre le Cancer (UICC) stages I-IV and survival was assumed to depend on cancer stage at tumor detection. Evidence suggests that the stage distribution is more favorable in individuals with intensified screening and that colonoscopic surveillance is effective by detecting the disease at an early stage.[6]

Once CRC is diagnosed, FDR could progress to metachronous cancer state. We assumed that individuals could develop CRC not more than twice in their lifetime.[13, 14] For both, initial and metachronous cancer, FDR progressed to the well after cancer state if they had survived CRC for more than ten years.

The model used 1-year cycle length to capture short and long term costs and effects associated with CRC. The Markov process continued until age of 120 years assuming that virtually all cohort members will have died by this age.

Analysis was performed using TreeAge Pro 2014 (TreeAge Software Inc., Williamstown, MA, USA) with a discount rate of 3%. Half cycle correction was applied to both costs and effects.

Parameters

We obtained input parameters (see Supplementary Material S1 for an overview) from the published literature using PubMed searches and reference tracking.

Family information and test uptake

Data on the number of FDR per index patient and relatives' sex and age were obtained from German studies.[6, 24, 25] Family mutation prevalence among FDR was assumed 50%, reflecting the autosomal-dominant inheritance. Data on the MMR genes affected were taken from a meta-analysis.[2]

The uptake of genetic testing among index patients was assumed to be 85% as reported by Dutch study.[26] Uptake of genetic testing among FDR was estimated to be 29.5% as reported by a German study.[25] Based on a meta-analysis of international studies, adherence to regular colonoscopy among mutation positive relatives was assumed to be 82%.[2] Patients who adhere to colonoscopic prevention are also assumed to comply with aspirin prevention.

Test quality

Sensitivity and specificity of laboratory tests were taken from a systematic review.[2] Performance of clinical criteria was taken from a recent international study.[27] The family mutation test in relatives was assumed to have 100% sensitivity and specificity.[14]

Disease epidemiology

Data on the risk of CRC for mutation carriers was taken from a recent French study.[4] The cumulative risk was estimated at 42% by age 80 years, averaged over different MMR genes. This number is comparable to a recent consensus estimate.[2] The cumulative risks for the different age categories reported in the study were converted into 1-year probabilities via conversion to rate.[28] Cumulative CRC risks for the general population were obtained from the Centre for Cancer Registry Data at Robert-Koch-Institute[29] and also transferred to 1-year risks.

Survival rates by UICC stage and year after cancer diagnosis were taken from the Munich Tumor Registry. Compared with sporadic CRC, MSI associated tumors are characterized by better survival. Following the evidence generated by Popat et al.[30], the model assumes a relative risk of 67% for overall survival associated with MSI.

Effectiveness of screening

Data on the distribution of CRC stages in the general population were obtained from the Munich Cancer Registry. The stage distribution for LS carriers, with and without increased prevention, was taken from a German study among LS patients.[6]

The study by Stupart et al.[7] provides an odds ratio of colon cancer incidence for patients with LS who undergo regular colonoscopy, compared with non-adherent mutation carriers. This odds ratio corresponds with a median follow-up time of 5 years in a population with an average age of 34 years. Based on the exponential distribution, this corresponds with an average follow-up time of 7.21 years. To convert this odds ratio to a hazard rate we applied

the incidence rates of Bonadona et al.[4], as the colon cancer incidence has not been reported by Stupart et al..

Recent data from the CAPP2 study showed that daily aspirin use (600mg) for 4 years had a protective effect on CRC in LS patients.[8] In accordance with this study, our model assumes a 63% hazard ratio of CRC for a maximum of 11 years which corresponds to the observation period of the study.

Costs

Costs are calculated in 2012 euros (€). Costs for the genetic testing process and colonoscopic prevention were calculated from the German ambulatory fee schedule, based on fixed points per type of service multiplied by a baseline point value. Costs for aspirin are based on data reported by Bayer HealthCare.

To estimate the costs of complications from colonoscopy and aspirin prevention, ICD codes for the main adverse events, bleeding and perforation (as complication of colonoscopy) and nontrivial gastrointestinal bleeding (as complication of aspirin prevention), were identified. From the German Diagnosis Related Groups (DRG) Report Browser (Version 2012)[31], the most common DRGs for these ICDs were extracted. The average case costs for these DRGs were taken as a proxy for the costs of hospitalization and were multiplied with the probability of being hospitalized after an adverse event. Potential ambulatory costs were considered negligible.

Costs for treating CRC at different UICC stages were taken from Mvundura et al.[14] and transferred based on purchasing power parities (PPP) data provided by the OECD.

Uncertainty

Probabilistic

Input parameters were assigned statistical distributions by fitting beta distributions for probabilities, gamma distributions for cost, Dirichlet distribution for multinomial data and lognormal distributions for parameters associated with risk reductions. A probabilistic sensitivity analysis for the non-dominated strategies with 1,000 iterations was conducted.

Decision uncertainty is presented by means of cost-effectiveness acceptability curves. Additionally the impact of uncertainty associated with single parameter values on the cost-effectiveness was assessed by analysis of covariance (ANCOVA) methods.[28] The potential value of collecting further evidence on uncertain parameter was quantified using expected value of perfect information (EVPI) analysis.

Scenario analysis

We performed a deterministic one-way sensitivity analysis to assess the impact of systematically varying one single input parameter at a time across wider intervals. Furthermore we performed extensive scenario analysis assessing the impact of different assumptions on testing uptake, performance of revised Bethesda criteria, aspirin prophylaxis, screening intervals, decreasing testing costs and discount rates.

RESULTS

Costs per mutation detected

Assuming a LS prevalence of 3%, 2,082 out of 69,400 newly diagnosed CRC cases are affected with LS. In the base case analysis, the number of detected mutations among CRC cases ranges between 383 in strategy A-5 and A-6 and 1,646 in strategy 7.

Overall testing costs in index patients range between € 11,308,328 in strategy B-2 and € 257,044,078 in the direct sequencing strategy (strategy 7). Strategy B-2 has the lowest cost per index mutation detected resulting in € 17,935 per mutation detected.

Effects of LS screening

The expected undiscounted number of LYG through prevention in LS carriers is 1.61 years for men and 1.98 years for women when prevention is started at age 25 years, and decrease with the patient's age at the time prevention was started. Women gain more life years through prevention than men because of their overall higher life expectancy. The average gain by increased prevention is 1.34 (1.20 for men and 1.52 for women and LYG discounted at 3% are 0.49 and 0.58, respectively).

Mean costs and effects of prevention for a relative with LS are shown in Table 1. Total costs of care with increased prevention for relatives aged 25 years and older outweigh the cost associated with standard prevention in undetected LS carriers by € 1,192 per person. The major part of the costs of increased prevention is due to colonoscopic surveillance (€4,300 out of € 4,896).

Cost-effectiveness of LS screening

All screening strategies reduce cancer incidence and death and yield more life years than the no screening strategy. The vast majority of screening strategies is dominated or subject to extended dominance. Table 2 displays the costs, effects and incremental cost-effectiveness ratios (ICER) as compared to the next most cost-effective strategy of the remaining screening strategies. The ICERs range from € 77,268 per LYG in strategy B-2 to € 4,188,036 per LYG in strategy 7.

Probabilistic sensitivity analysis

Figure 3 displays the cost-effectiveness acceptability curve for the non-dominated screening strategies. At a threshold of € 50,000 per LYG used for illustration, the no screening strategy has a probability of 87% of being considered cost-effective. At the same threshold, strategy B-2 is the optimal strategy in 13% of iterations.

A summary of the ANCOVA results for strategy B-2 applied separately to LYG and incremental costs is presented in Supplementary Material S2. This analysis suggests that stage distribution of CRC in LS carriers who do not adhere to colonoscopic surveillance and the prevalence of LS are most important in explaining variation in the overall effects. In Germany, the ambulatory care fee schedule includes a floating evaluation factor. Uncertainty about the parameter distribution of this value has the largest impact on the overall distribution of costs.

The EVPI is plotted in Supplementary Material S3 for willingness to pay thresholds between € 0 and € 500,000 per LYG and a time horizon of 5 years. The EVPI indicates that further

research to inform decisions could be worthwhile. At a threshold of € 50,000 and a time horizon of 5 years, the EVPI amounts to € 3,360,954. Extending the analysis to an infinite time horizon increases the EVPI to € 23,750,152.

Scenario analyses

To identify important drivers of cost-effectiveness of LS screening, a number of scenarios were explored which are fully reported in Supplementary Material S4. Variables concerning uptake of testing appear to be critical drivers of cost-effectiveness. Increasing the uptake rate among FDR to 52%[32] changes the ICER of strategy B-2 to € 45,169 per LYG compared with no screening. Assuming an ideal uptake of 100% in index patients and FDR results in an ICER of €24,979 per LYG.

Omitting aspirin chemoprevention from the model is associated with only a small reduction in health benefits. When compared to the baseline analysis average remaining life expectancy of LS carriers only decreases by 0.01 years. Also, aspirin prophylaxis only has a small influence on the cost-effectiveness of LS screening. If aspirin is omitted from the model, the ICERs increase slightly with, for example, strategy B-2 resulting in € 79,812 per LYG.

Supplementary Material S5 additionally reports the results of a deterministic one-way sensitivity analysis systematically varying all input parameters across wider intervals. The number of relatives per index patient has the highest impact on model results. Strategies become more cost-effective as more relatives are tested. The prevalence of LS is another influential variable. As the prevalence decreases calculated cost per life year gained increase.

DISCUSSION

In this study, we evaluated the effectiveness and cost-effectiveness of LS screening as a potential strategy for individualized CRC prevention. The cost-effectiveness of the included strategies ranges between € 77,268 per LYG in strategy B-2 and € 4.188.036 per LYG in strategy 7.

Implication of this study

LS screening recommendations in Germany foresee that patients who seek genetic counselling are assessed by the revised Bethesda criteria followed by either a MSI analysis (strategy B-6) or a sequential IHC and MSI analysis (strategy B-4).[5] In our analysis, both strategies were dominated. This means that other strategies considered in this analysis are both less expensive and more effective in detecting LS carriers. To improve the health benefits derived from available budget, a revised version of the German recommendations for LS screening might take these results into account and promote the increased use of more cost-effective strategies involving IHC and BRAF testing in newly diagnosed CRC patients.

To our knowledge this is the first cost-effectiveness analysis which accounts for the presumably favorable effect of aspirin chemoprevention as “add on” to colonoscopic surveillance in LS carriers. According to our results, aspirin chemoprevention only makes a small contribution to CRC risk reduction. In mutation carriers who adhere to recommended colonoscopic screening, aspirin use provides relatively low additional health effects. Despite the additional costs associated with aspirin use and the treatments of aspirin related complications, aspirin chemoprevention slightly improves the cost-effectiveness of LS

screening. However, we only analyzed the role of aspirin when it is used as add on and not its impacts when it is used instead of colonoscopic surveillance. Because colonoscopic surveillance is unpleasant in preparation, time-consuming, and not without risk some LS carriers might prefer solely aspirin prevention despite the uncertainty surrounding its effects. Further studies which assess the effectiveness and cost-effectiveness LS screening in a population solely adhering to aspirin chemoprevention would thus be desirable. Given that the effectiveness of aspirin in reducing CRC is uncertain and given that it is associated with additional adverse effects, CRC prophylaxis should take individual patient preferences into account.

Deterministic sensitivity analysis demonstrated that variables concerning uptake of testing appear to be critical drivers of cost-effectiveness. If all index patients and their FDR were tested for LS the calculated ICER could be decreased to € 24,979 per LYG. Although this is an unrealistic scenario it illustrates a key determinant of cost-effectiveness. Because costs of testing index patients occur regardless how many FDR are tested subsequently, low uptake by index cases is relatively less important than by FDR. This indicates that further research into factors that could enhance FDR' willingness to undergo testing would be desirable. If tested index cases are reluctant to share relevant genetic information with their family members, relatives cannot benefit from screening and intervention. The cost-effectiveness of screening could be increased if physicians routinely report genetic information to increased-risk family members. However, for such a strategy, legal and ethical restrictions regarding the protection of confidential patient information need to be considered carefully.

Comparison with other studies

The results from this study differ substantially from the favorable results of previous cost effectiveness models used to evaluate LS screening in patients with newly diagnosed CRC.[12-19] Based on current screening recommendations in Germany we assume that mutation positive patients undergo colonoscopy once a year whereas previous studies assumed screening intervals of two or even three years.[12, 14-17] The sensitivity analysis shown in supplementary material 4 shows however, that the closed-meshed surveillance foreseen by the German guidelines does not explain the differences in the model results. Rather, this might be explained by the following factors:

First, we assume that only a small proportion of relatives are tested for LS. This is due to the low probability of relatives being interested in the screening program. Other studies assume higher uptake ranging between 52% and 100% for FDR.[13, 14, 17, 18] In Germany, however, experience has shown that the number of relatives who are tested for LS and thus can benefit from screening is likely to be smaller which tends to increase the costs per LYG.

Second, other studies also assume more FDR per index patient, with the studies by Ladabaum et al.[13] and Wang et al. [18]assuming up to eight FDR per index patient, all of whom are 25 years when prevention starts. In this study we assume less than four FDR per index patient based on German evidence.[25] This is because family size in Germany tends to be smaller than in the US. Results from deterministic and probabilistic sensitivity analysis have shown that the number of relatives tested is a critical driver of cost-effectiveness. Also, assumptions made by Ladabaum et al.[13] and Wang et al.[18] relating to relatives' age is likely to

improve cost-effectiveness as health gains decrease with the patient's age at the time prevention was started.

The differences in life expectancy between LS carriers that adhere to increased prevention and those that do not adhere to prevention are slightly higher in earlier studies.[13, 14, 18] This can be explained by different assumptions relating to cancer stage distributions and cancer risks in LS patients. Mvundura et al.[14] assume ultimately less favorable stage distributions and cancer stage related survival for LS patients as compared to this study. This might have overestimated the degree of benefit derived from increased prevention. Also, the study by Mvundura and colleagues[14] assumes better cancer stage related survival for those LS patients adhering to colonoscopic prevention compared to those that do not adhere to prevention. The studies by Ladabaum et al.[13] and Wang et al.[13, 18] assumed ultimate high CRC risk based on earlier studies assessing risks in mutation carriers. However, there is evidence from more recent studies that CRC risks are lower than previously reported.[2, 4] Again, this is likely to underestimate the costs per LYG of CRC prevention.

Limitations

Our study has a number of limitations. First, we did not model the risk of other forms of cancer. In particular women face an increased risk for gynecological cancers (e.g. endometrial or ovarian cancer). Although the German guidelines foresee gynecological surveillance the efficiency of such examinations is still uncertain.[33] To our knowledge, the studies by Ladabaum et al.[13] and Dinh et al.[19] are the only cost-effectiveness studies addressing the critical issue of screening for gynecological cancers. Due to the uncertain

benefit derived from such screening, the studies assume that gynecological surveillance results in additional costs without comprising any benefits.

We did not assume different CRC risks and prevention intervals based on the MMR gene involved. MSH6 carriers have found to be at lower risk for CRC with a higher age of tumor onset compared to MLH1 and MSH2 carriers.[4] This probably means that no general prevention protocol is suitable for all MMR mutation carriers. Also we did not model CRC risk associated with the EPCAM gene, another gene that has recently found to impact LS.[34]

We did assume that mutation carriers adhering to regular colonoscopy also adhere to aspirin prevention. This might have biased our results for or against screening. However, reported adherence rates in clinical trials valuating aspirin for the prevention of colorectal adenomas are high and range between 76% and 92%.[35] In mutation carriers aspirin compliance might even be higher as these patients might be aware of their predisposition. Also, like other studies[12-16, 18], we did not model ongoing adherence rates for CRC prevention. If relatives decide to stop prevention, this would reduce LYG and calculated ICERs might be underestimated. However, studies have found that lifetime compliance is high[14] and that 95% of mutation positive relatives would consider lifetime surveillance.[36]

Furthermore, risks for complications of increased prevention in mutation carriers might be underestimated. Our estimates concerning the risk of complications derived from colonoscopy are based on data from the German screening program.[37] This program is, however, aimed at the general population aged 55 years and older. It might be that estimates are too optimistic and that in reality risk of complications are higher in the LS group. Risk of bleeding after aspirin intake was taken from a recent meta-analysis assessing

the effect of aspirin on vascular outcomes.[38] However, patients analyzed in this study in general received lower aspirin dose than assumed in this study. Patients taking high-dose aspirin might have higher risks for adverse events. As reported risks are low, we assume a zero risk of death from colonoscopy and aspirin prevention. Between 2003 and 2008, only 5 fatalities from colonoscopy were reported with 1 million colonoscopies performed in Germany. Death from gastrointestinal bleeding is also rare. A review on aspirin prevention for CRC reported only one death associated with gastrointestinal bleeding.[39] We also did not model increased risk for hemorrhagic stroke in patients taking aspirin. However, any increase in risk for hemorrhagic stroke might be compensated by a risk reduction for ischemic stroke.[40]

We did not calculate outcomes in terms of quality-adjusted LYs (QALYs). We would expect that by including QALY weights, the cost-effectiveness of LS screening would become less favorable. Mvundura et al.[14] showed that including QALYs raises the costs per health outcome reflecting the fact that most people are not in perfect health. This result is confirmed by the study of Wang et al.[18] which incorporated preference data from an own quality of life study.

Conclusion

Within this study we evaluated the cost-effectiveness of LS screening. Results have shown that LS screening provides clinical benefit but at high cost. The most cost-effective strategy involves family history assessment with the revised Bethesda criteria followed by IHC testing, BRAF testing and genetic sequencing with an ICER of 77.268 € per life year gained. A revised version of the German recommendations for CRC might wish to take these results into

account and promote IHC and subsequent BRAF testing instead of MSI testing. To improve the cost-effectiveness of LS screening, further research should address factors that could enhance FDR' willingness to undergo testing.

To our knowledge, this is the first economic evaluation which also considers aspirin prophylaxis as "add on" to intensified colonoscopic screening for CRC prevention in LS patients. In our analysis, aspirin chemoprevention provides comparatively low additional health effects and improves the cost-effectiveness of screening only slightly. Given uncertainty surrounding its long term effects and side effects, the economic case for recommending chemoprevention as adjunct to colonoscopy is rather weak. Physicians might thus wish to consider other factors such as individual patient preferences when prescribing chemoprevention.

ACKNOWLEDGEMENT

We are grateful to Scott Grosse, Verena Steinke-Lange and two anonymous reviewers for their valuable comments on earlier versions of this manuscript.

Supplementary information is available at the Genetics in Medicine website.

References

1. RKI. Beiträge zur Gesundheitsberichterstattung des Bundes: Krebs in Deutschland 2007/2008. Available at: http://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsB/KID2012.html. Accessed December 2, 2013.
2. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN**.** EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med* 2009;11(1):42-65.
3. Laghi L, Malesci A**.** Microsatellite instability and therapeutic consequences in colorectal cancer. *Digestive Diseases* 2012;30(3):304-9.
4. 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(22):2304-10.
5. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Kolorektales Karzinom, Langversion 1.1, 2014, AWMF Registrierungsnummer: 021-007OL, http://leitlinienprogramm-onkologie.de/Kolorektales-Karzinom.62.0.html. Accessed July 29, 2014.
6. Engel C, Rahner N, Schulmann K, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. *Clin Gastroenterol Hepatol* 2010;8(2):174-82.
7. Stupart DA, Goldberg PA, Algar U, Ramesar R**.** Cancer risk in a cohort of subjects carrying a single mismatch repair gene mutation. *Fam Cancer* 2009;8(4):519-23.

8. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 2011;378(9809):2081-7.

9. Tan YY, McGaughran J, Ferguson K, et al. Improving identification of lynch syndrome patients: a comparison of research data with clinical records. *Int J Cancer* 2013;132(12):2876-83.

10. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genet Med* 2009;11(1):35-41.

11. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Genetic/Familial High-Risk Assessment: Colorectal. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed: 17.09.2014.

12. Kievit W, de Bruin JH, Adang EM, et al. Cost effectiveness of a new strategy to identify HNPCC patients. *Gut* 2005;54(1):97-102.

13. Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. *Ann Intern Med* 2011;155(2):69-79.

14. Mvundura M, Grosse SD, Hampel H, Palomaki GE**.** The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. *Genet Med* 2010;12(2):93-104.

15. Ramsey SD, Burke W, Clarke L**.** An economic viewpoint on alternative strategies for identifying persons with hereditary nonpolyposis colorectal cancer. *Genet Med* 2003;5(5):353-63.

16. Ramsey SD, Clarke L, Etzioni R, Higashi M, Berry K, Urban N**.** Cost-effectiveness of microsatellite instability screening as a method for detecting hereditary nonpolyposis colorectal cancer. *Ann Intern Med* 2001;135(8 Pt 1):577-88.

17. Wang VW, Koh PK, Chow WL, Lim JF**.** Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary non-polyposis colorectal cancer in Singapore. *Fam Cancer* 2012;11(2):279-89.

18. Wang G, Kuppermann M, Kim B, Phillips KA, Ladabaum U**.** Influence of patient preferences on the cost-effectiveness of screening for lynch syndrome. *J Oncol Pract* 2012;8(3 Suppl):e24s-30s.

19. Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. *Cancer Prev Res (Phila)* 2011;4(1):9-22.

20. Hagen A, Hessabi HK, Gorenoi V, Schonermark MP**.** [Cost-effectiveness evaluation of predictive molecular diagnostics using the example of hereditary non-polyposis colorectal cancer (HNPCC)]. *Gesundheitswesen* 2008;70(1):18-27.

21. Busse R, Blümel M. Germany: health system review. Health Systems in Transition, 2014, 16(2):1–296. Available at :http://www.euro.who.int/en/about-us/partners/observatory/health-systems-in-transition-hit-series/countries-and-subregions/germany-hit-2014. Accessed: 09.10.2014.

22. Vasen HF, Watson P, Mecklin JP, Lynch HT**.** New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999;116(6):1453-6.

23. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004;96(4):261-8.

24. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J Clin Oncol* 2008;26(35):5783-8.

25. Schneider R, Rummele P, Dechant S, Hofstadter F, Lorenz W, Furst A**.** Familial non-polyposis colorectal carcinoma (Lynch syndrome) in Germany - analysis of information, advisory service and family screening. *Dtsch Med Wochenschr* 2011;136(1-2):17-22.

26. Ramsoekh D, van Leerdam ME, Tops CM, et al. The use of genetic testing in hereditary colorectal cancer syndromes: genetic testing in HNPCC, (A)FAP and MAP. *Clin Genet* 2007;72(6):562-7.

27. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. *JAMA* 2012;308(15):1555-65.

28. Briggs A, Claxton C, Sculpher M**.** *Decision modelling for health economic evaluation*. Oxford: Oxford Univerity Press; 2006.

29. Centre for Cancer Registry Data, Robert-Koch-Institute. Available at: http://www.rki.de/EN/Content/Health_Monitoring/Cancer_Registry/cancer_registry_node.html. Accessed March 12, 2012.

30. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol* 2005;23(3):609-18.

31. Institut für Entgeldsysteme im Krankenhaus. Available from http://www.g-drg.de/cms. Accessed July 30, 2013.

32. Sharaf RN, Myer P, Stave CD, Diamond LC, Ladabaum U. Uptake of genetic testing by relatives of lynch syndrome probands: a systematic review. *Clin Gastroenterol Hepatol* 2013;11(9):1093-100.

33. Vasen HF, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* 2013;62(6):812-23.

34. Kuiper RP, Vissers LE, Venkatachalam R, et al. Recurrence and variability of germline EPCAM deletions in Lynch syndrome. *Hum Mutat* 2011;32(4):407-14.

35. Cole BF, Logan RF, Halabi S, et al. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. *Journal of the National Cancer Institute* 2009;101(4):256-66.

36. Lynch HT, Watson P, Shaw TG, et al. Clinical impact of molecular genetic diagnosis, genetic counseling, and management of hereditary cancer. Part II: Hereditary nonpolyposis colorectal carcinoma as a model. *Cancer* 1999;86(11 Suppl):2457-63.

37. Zentralinstitut für die kassenärztliche Versorgung in der Bundesrepublik Deutschland. Projekt wissenschaftliche Begleitung von Früherkennungs-Koloskopien in Deutschland. 2008.

38. Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J**.** Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *American Journal of Medicine* 2011;124(7):621-9.

39. Dube C, Rostom A, Lewin G, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* 2007;146(5):365-75.

40. Thorat MA, Cuzick J**.** Role of Aspirin in Cancer Prevention. *Current Oncology Reports* 2013.

Figure legends:

Figure 1: Overview screening strategies

Figure 2: Markov Model

Figure 3: Cost-effectiveness acceptability curves

Table 1: Discounted costs and effects of prevention in mutation carriers

	Costs of CRC	Costs of colonoscopic prevention	Costs of aspirin prevention	Total costs	Discounted LYs men	Discounted LYs women	Discounted LYs average
Standard prevention	5,023	245	0	5,268	20.26	21.77	20.90
Annual colonoscopy and aspirin prevention	1,561	4,300	596	6,460	20.75	22.35	21.42
- Increment to standard prevention	-3,462	4,055	596	1,192	0.49	0.58	0.52

Table 2: Cost-effectiveness without dominated screening alternatives (compared to the next most cost-effective strategy)

Strategy		Total costs	Total LY	Incremental costs	Incremental LY	Incremental costs per life year gained
0	No screening	218,581,280	5,703,154	-	-	-
B-2	Counseling incl. Bethesda, IHC, BRAF, sequencing	242,028,209	5,703,458	23,446,929	303	77,268
2	Counseling, IHC,BRAF, sequencing	252,442,654	5,703,499	10,414,444	41	253,258
7	Counseling, direct sequencing	476,882,146	5,703,552	224,439,493	54	4,188,036

Figure 1

Click here to download high resolution image

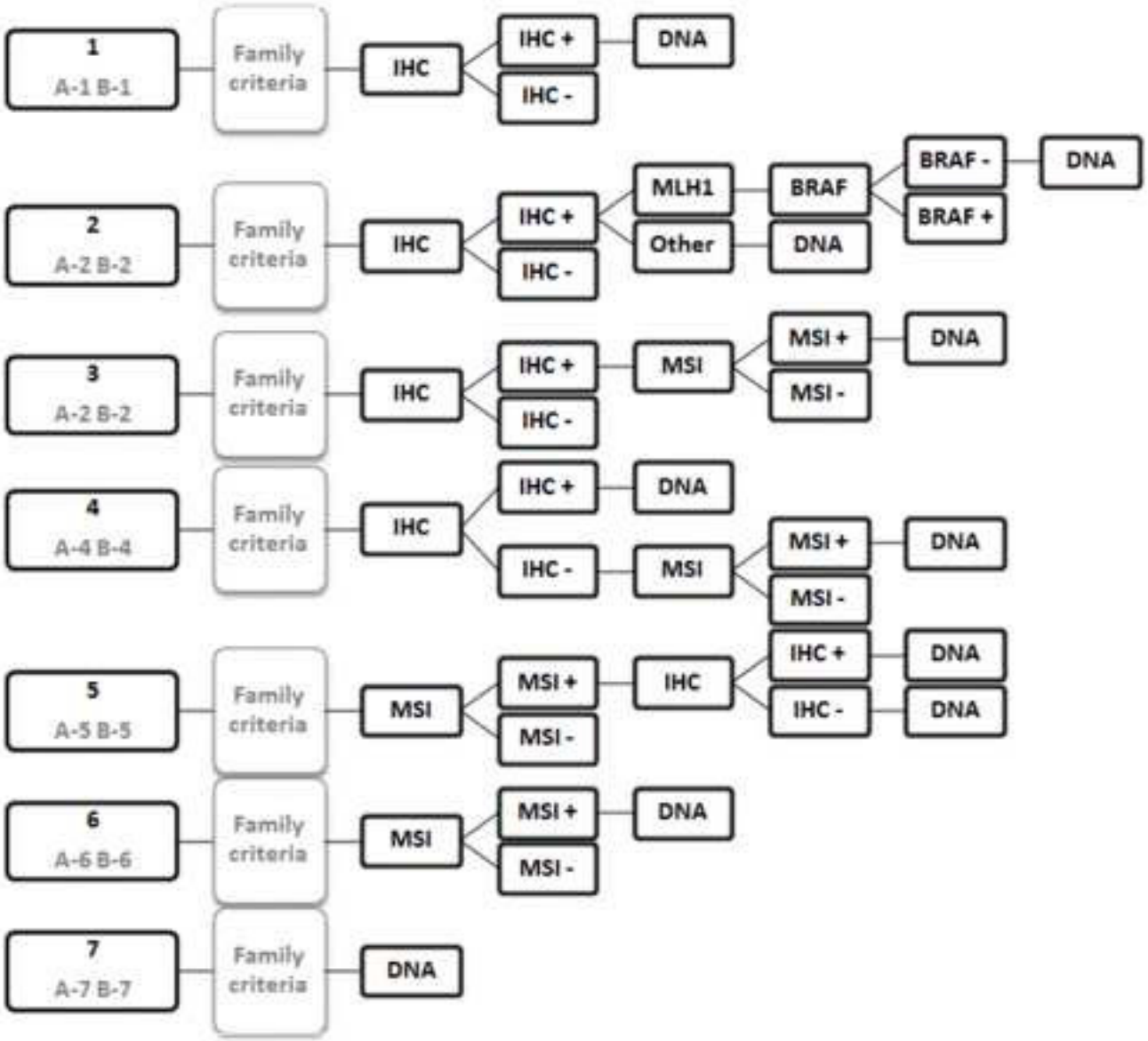


Figure 2
Click here to download high resolution image

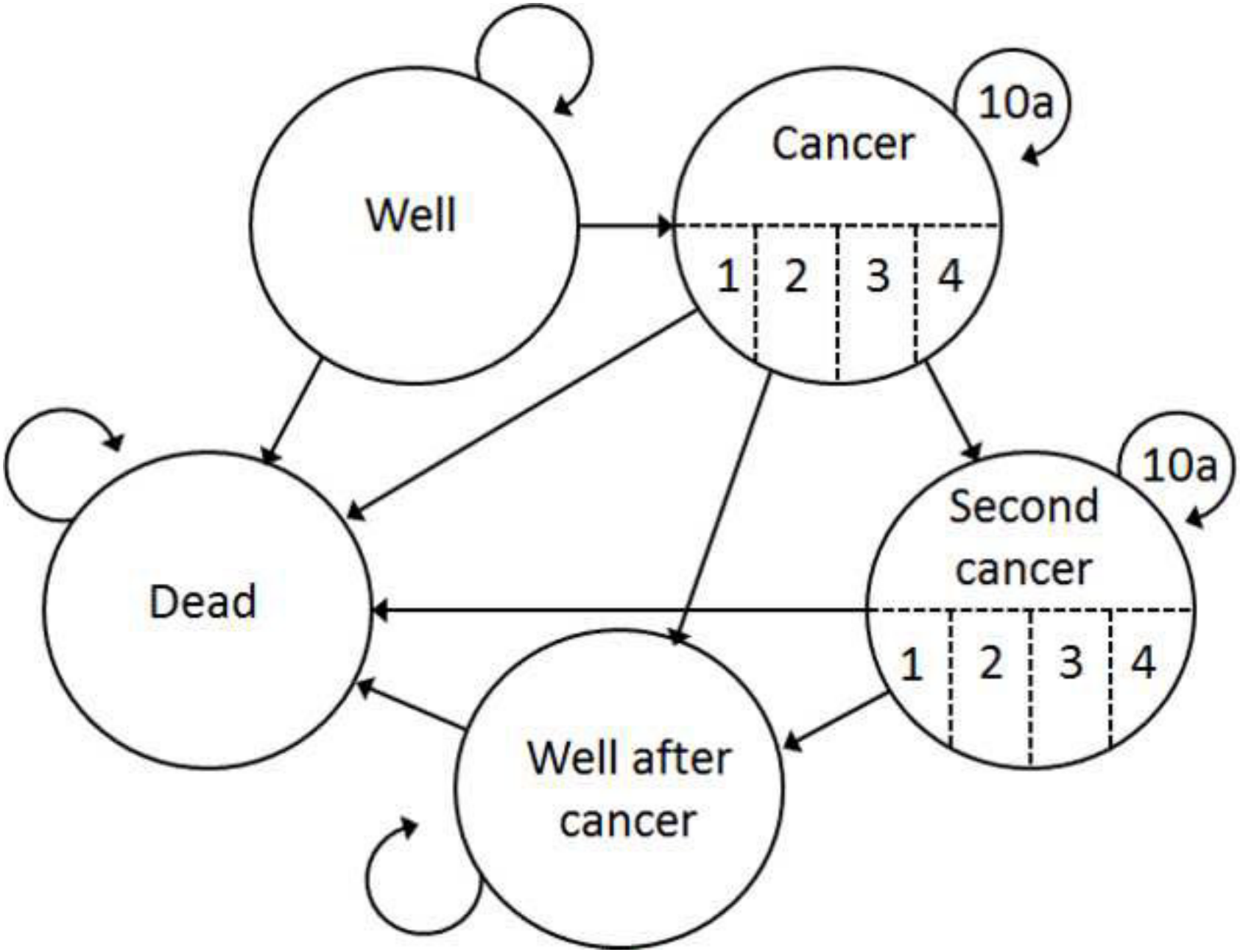
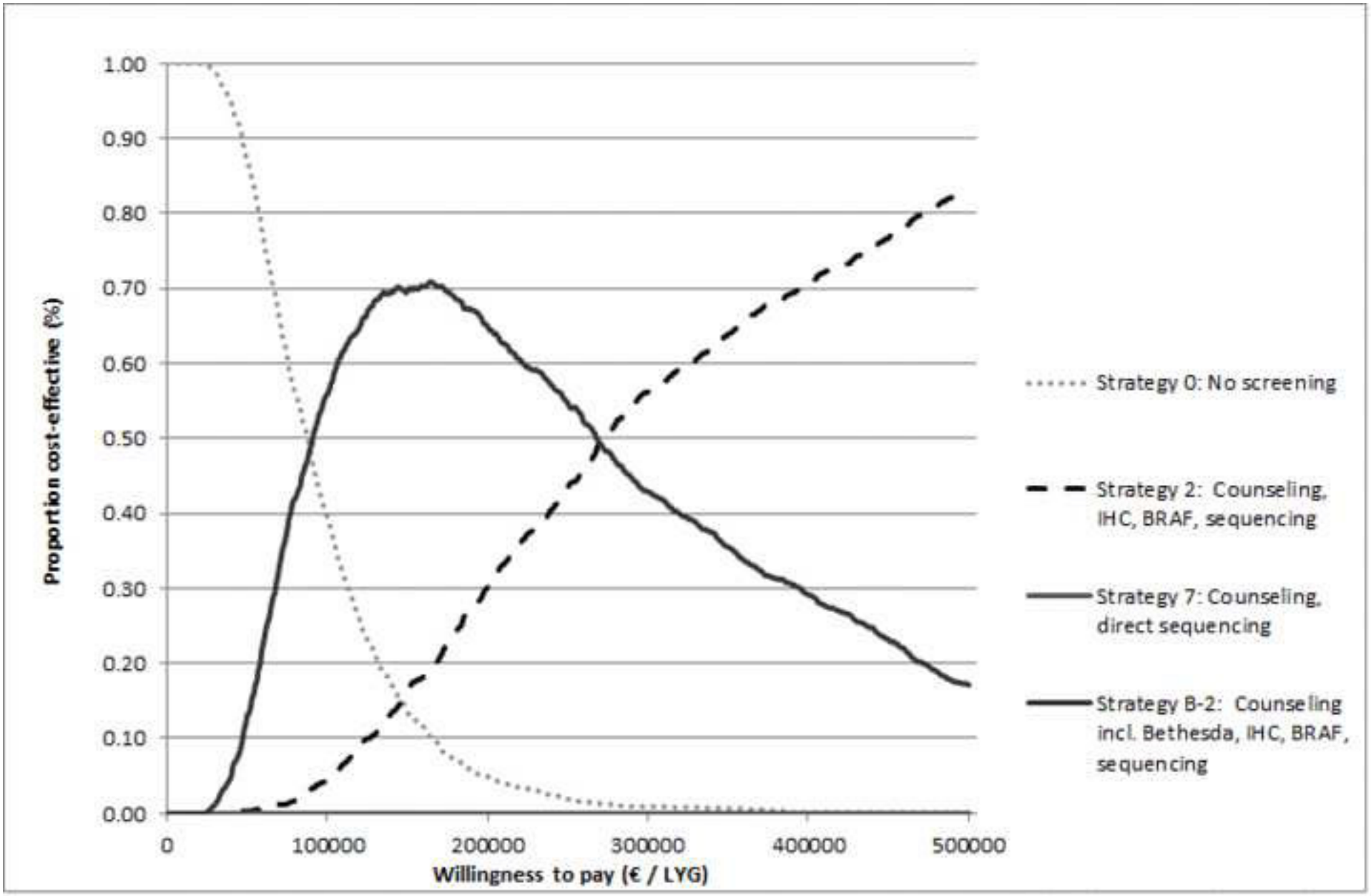


Figure 3
Click here to download high resolution image



Supplementary Material 1: Model parameters and distributions

Parameter	Value	SE	Source
Population			
Number index patients with CRC 2012	69,400	-	RKI [1]
Number of FDR per CRC patient	3.833	0.564	Schneider et al. 2011 [2]
Prevalence of LS among CRC patients	0.0281	0.000105	Hampel et al. 2008 [3]
Proportion of relatives with mutation	0.5	-	given
Proportion of female relatives	0.423	0.00629	Schneider et al. 2011 [2]
Distribution of MMR mutations:			Palomaki et al. 2009 [4]
MSH2	0.384	0.144	
MLH1	0.324	0.121	

MSH6	0.144	0.054	
PMS2	0.148	0.055	
Age distribution of relatives at screening			Engel et al. 2010 [5]
25 years	0.136	0.0173	
35 years	0.328	0.0236	
45 years	0.278	0.0225	
55 years	0.149	0.0180	
65 years	0.0783	0.0135	
75 years	0.0303	0.0086	
Uptake and adherence			
Uptake index: counseling and test	0.848	0.00320	Ramsoekh et al. 2007 [6]
Uptake relatives: counseling and test	0.295	0.00581	Schneider et al. 2011 [2]
Proportion of relatives with	0.818	0.00233	Palomaki et al. 2009

Lynch syndrome who comply with surveillance			[4]
Test quality			
MSI test			
sensitivity (MLH1, MSH2)	0.893	0.00220	Palomaki et al. 2009 [4]
sensitivity (MSH6, PMS2)	0.761	0.00202	Palomaki et al. 2009 [4]
specificity	0.907	0.0000754	Palomaki et al. 2009 [4]
IHC test			
sensitivity	0.868	0.00235	Palomaki et al. 2009 [4]
specificity	0.910	0.000157	Palomaki et al. 2009 [4]
BRAF test			
sensitivity	0.700	0.00304	Palomaki et al. 2009 [4]

specificity	0.990	0.00577	Palomaki et al. 2009 [4]
Sequencing			
sensitivity	0.995	0.00289	Palomaki et al. 2009 [4]
specificity	1.000	0.000173	Palomaki et al. 2009 [4]
False-positive results/IHC only			
Loss of MSH2 (and possibly MSH6) indicated	0.15	0.0563	Palomaki et al. 2009: PC [4]
Loss of MLH1 (and possibly PMS2) indicated	0.7	0.263	Palomaki et al. 2009: PC [4]
Loss of MSH6 (only) is indicated	0.1	0.0375	Palomaki et al. 2009: PC [4]
Loss of PMS2 (only) is indicated	0.05	0.018	Palomaki et al. 2009: PC [4]
False-positive results/IHC after MSI			
IHC is true positive | MSI false positive	0.850	0.144	Mvundura et al. 2010 [7]

IHC is true negative | MSI false positive	0.12	0.0450	Mvundura et al. 2010 [7]
Correlation of results: MSI after IHC			
MSI true positive | IHC true negative	0.99	0.00577	Engel et al. 2006 [8]
MSI false positive | IHC false positive	0.970	0.00175	Engel et al. 2006 [8]
MSI negative | IHC negative	0.928	0.000321	Engel et al. 2006 [8]
Amsterdam II criteria			
sensitivity	0.272	0.00142	Moreira et al. 2012 [9]
specificity	0.979	0.3671	Moreira et al. 2012 [9]
Revised Bethesda criteria			
sensitivity	0.881	0.00133	Moreira et al. 2012 [9]
specificity	0.544	0.367	Moreira et al. 2012 [9]
Disease epidemiology			
1-year CRC risk for LS carriers			Bonadona et al. 2011 [10]
25 - 34 years	0.00202	0.000757	

35 - 44 years	0.00310	0.00116	
45 – 54 years	0.00876	0.0033	
55 – 64 years	0.0134	0.0050	
65 -74 years	0.0155	0.0058	
75 and older	0.0113	0.0042	
Hazard of CC incidence for patients with LS who undergo regular colonoscopy, compared with non-adherent mutation carriers	log(HR)=-1.077	SE(log(HR))=0.448	Stupart et al. 2009 [10, 11]
Hazard of CC incidence for patients with LS who adhere to aspirin intake, compared with non-adherent mutation carriers.	log(HR)=-0.462	SE(log(HR))=0.299	Burn et al. 2011 [12]
1-year CRC risk for non-carriers (general population)			RKI [13]
Men			
25 - 34 years	0.000011	0.00000422	

35 - 44 years	0.000055	0.0000208
45 – 54 years	0.000215	0.0000805
55 – 64 years	0.000830	0.000311
65 -74 years	0.00206	0.000772
75 and older	0.00338	0.001269
Women		
25 - 34 years	0.000012	0.00000440
35 - 44 years	0.000047	0.0000176
45 – 54 years	0.000185	0.0000694
55 – 64 years	0.000551	0.000207
65 -74 years	0.00114	0.000428
75 and older	0.00210	0.000789
Stage distribution (for first and second CRC diagnosis)		
LS carriers with biennial colonoscopy		Engel et al. 2010[5]
Stage 1	0.694	0.0126
Stage 2	0.250	0.0119

Stage 3	0.0556	0.00628	
Stage 4	0	0	
General			Munich Tumour Registry
Stage 1	0.212	0.00002511	
Stage 2	0.297	0.0000280	
Stage 3	0.267	0.0000272	
Stage 4	0.224	0.0000256	
LS carriers symptomatic, no-annual colonoscopy			Engel et al. 2010 [5]
Stage 1	0.267	0.0285	
Stage 2	0.533	0.0322	
Stage 3	0.133	0.0219	
Stage 4	0.067	0.0161	

Relative risk for overall survival (LS carriers vs. general population)	log(RR)=-0.400	SE(log(RR))=0.290	Popat et al. 2005 [14]
1-year relative survival by UICC stage and year after cancer diagnosis	Depending on UICC cancer stage and time individual has spent in the cancer state For example stage 2, first year after cancer diagnosis: 0.941	0.00000148	Munich Tumour Registry
Probability second cancer: LS	0.0173	0.00648	Parry et al. 2011 [15]
Probability second cancer: average risk	0.00314	0.00118	Mulder et al. 2012 [16]
Costs			
EBM point value	0.0351	0.00506	KVB [17]

GOÄ point value	0.0583	0.00841	GOÄ [18]
Genetic testing			
Microsatellite analysis	12,755	point value	EBM [17]
Immunohistochemistry	3,450	point value	EBM[17]
BRAF test	3,400	point value	GOÄ [18]
Sequencing MLH1/PMS2 or MSH2/MSH6	109,305	point value	EBM [17]
Test for family mutation	5,825	point value	EBM [17]
Sequencing 4 genes without tumor material	120,050	point value	EBM [17]
Counseling			
Baseline payment for genetic counselling	1,175	point value	EBM [17]
Detailed genetic counselling, family history assessment, risk assessment	3,335	point value	EBM [17]

Administration			
Informing about screening: baseline	0.860	0.323	Caluculated on bases of leaflet
Informing relatives: baseline	0.860	0.323	Caluculated on bases of leaflet
Prevention in LS carriers			
Coloscopy	192.764	72.287	EBM [17]
Polypectomy (with colonoscopy)	28.564	10.712	EBM [17]
Histology (with polypectomy)	12.968	4.863	EBM [17]
Probability of polypectomy (LS, all cases)	0.276	0.104	Engel et al. 2010 [5]
Costs of aspirin prevention per year	95.049	35.643	On request from BayerHealth Care
CRC treatment costs			Mvundura et al. 2010 [7]
stage 1, first diagnosis	21,750.657	8,156.496	

stage 2, first diagnosis	24,009.602	9,003.601	
stage 3, first diagnosis	27,198.550	10,199.457	
stage 4, first diagnosis	38,694.445	14,510.419	
stage 1, second diagnosis	23,692.497	8,884.687	
stage 2, second diagnosis	24,611.419	9,229.282	
stage 3, second diagnosis	28,691.159	10,759.185	
stage 4, second diagnosis	42069.228	15775.960	
Complications of prevention			
Colonoscopy			
Cost of hospital treatment of complications bleeding	1,856.89	1624.7788	DRG: X06C [19]
Cost of hospital treatment of complications perforation	5,501.52	4813.8300	DRG: X06A [19]
Probability of hospital treatment of complications bleeding	0.262	0.0982	ZI Berlin [20]

Probability of hospital treatment of complications perforation	0.99	0.0100	ZI Berlin [20]
Risk of bleeding	0.00161	0.00000000533	ZI Berlin [20]
Risk of perforation	0.000226	0.0000000142	ZI Berlin [20]
Aspirin			
Cost of hospital treatment of complication gastrointestinal bleeding	2,243.57	1963.123	DRG: G73Z[19]
Probability of hospital treatment of complications gastrointestinal bleeding	0.525	0.197	UK-TIA Study Group (1988) [21]
Risk of gastrointestinal bleeding	0.0410	0.00000418	Raju et al. (2011) [22]

Table References

1. RKI**.** Beiträge zur Gesundheitsberichterstattung des Bundes: Krebs in Deutschland 2007/2008. Available at: http://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsB/KID2012.html. Accessed December 2, 2013.

2. Schneider R, Rummele P, Dechant S, Hofstadter F, Lorenz W, Furst A**.** Familial non-polyposis colorectal carcinoma (Lynch syndrome) in Germany - analysis of information, advisory service and family screening. *Dtsch Med Wochenschr* 2011;136(1-2):17-22.

3. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J Clin Oncol* 2008;26(35):5783-5788.

4. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN**.** EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med* 2009;11(1):42-65.

5. Engel C, Rahner N, Schulmann K, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. *Clin Gastroenterol Hepatol* 2010;8(2):174-182.

6. Ramsoekh D, van Leerdam ME, Tops CM, et al. The use of genetic testing in hereditary colorectal cancer syndromes: genetic testing in HNPCC, (A)FAP and MAP. *Clin Genet* 2007;72(6):562-567.

7. Mvundura M, Grosse SD, Hampel H, Palomaki GE**.** The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. *Genet Med* 2010;12(2):93-104.

8. Engel C, Forberg J, Holinski-Feder E, et al. Novel strategy for optimal sequential application of clinical criteria, immunohistochemistry and microsatellite analysis in the diagnosis of hereditary nonpolyposis colorectal cancer. *International Journal of Cancer* 2006;118(1):115-122.

9. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. *JAMA* 2012;308(15):1555-1565.

10. 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(22):2304-2310.

11. Stupart DA, Goldberg PA, Algar U, Ramesar R**.** Cancer risk in a cohort of subjects carrying a single mismatch repair gene mutation. *Fam Cancer* 2009;8(4):519-523.

12. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 2011;378(9809):2081-2087.

13. Centre for Cancer Registry Data R-K-IAfhwrdECHMCRcrnha.

14. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol* 2005;23(3):609-618.

15. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. *Gut* 2011;60(7):950-957.

16. Mulder SA, Kranse R, Damhuis RA, Ouwendijk RJ, Kuipers EJ, van Leerdam ME. The incidence and risk factors of metachronous colorectal cancer: an indication for follow-up. *Diseases of the Colon and Rectum* 2012;55(5):522-531.

17. KVB Kassenärtzliche Bundesvereinigung. Available at: http://www.kbv.de. Accessed September 17, 2013.

18. GOÄ - Gebührenordnung für Ärzte. Available at:http://www.e-bis.de. Accessed March 12, 2013.

19. Institut für Entgeldsysteme im Krankenhaus. Available at: http://www.g-drg.de/cms. Accessed July 30, 2013.

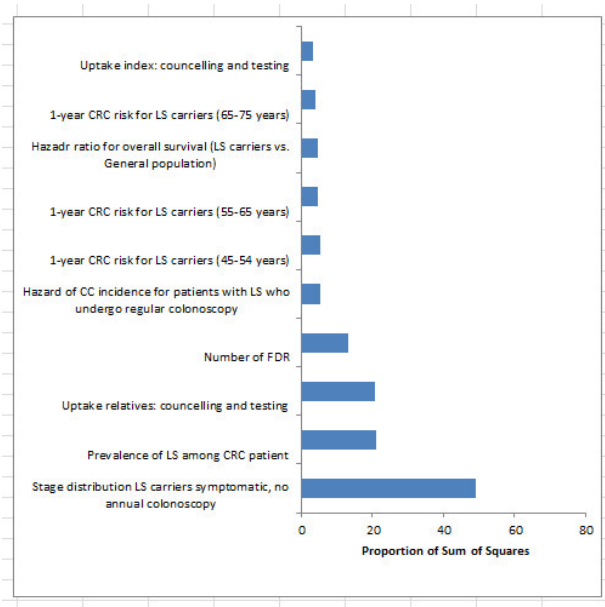
20. Zentralinstitut für die kassenärztliche Versorgung in der Bundesrepublik Deutschland. Projekt wissenschaftliche Begleitung von Früherkennungs-Koloskopien in Deutschland. 2008.

21. UK-TIA Study Group. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. UK-TIA Study Group. *British Medical Journal (Clinical Research Edition)* 1988;296(6618):316-320.

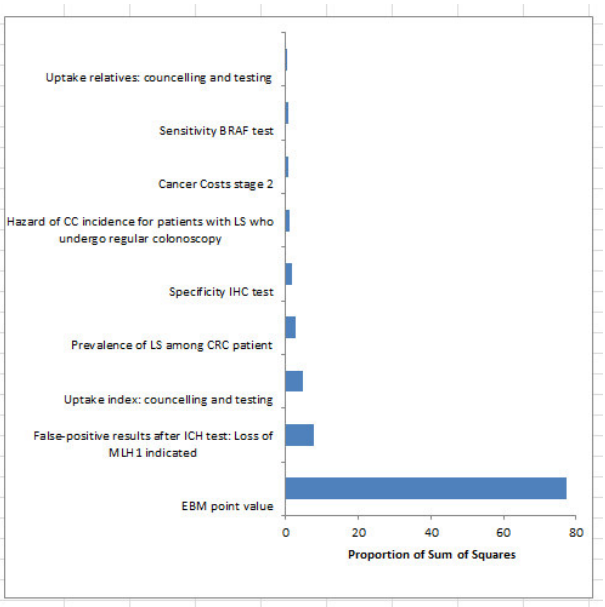
22. Raju N, Sobieraj-Teague M, Hirsh J, O'Donnell M, Eikelboom J. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *American Journal of Medicine* 2011;124(7):621-629.

Supplementary Material 2: Summary of individual parameter contributions to model sum of squares (ANCOVA) for strategy "counselling incl. Bethesda, IHC, BRAF, sequencing" (strategy B-2) compared to the no screening strategy for (a) LYG and (b) incremental costs

(Only the 10 most influential parameters are presented)

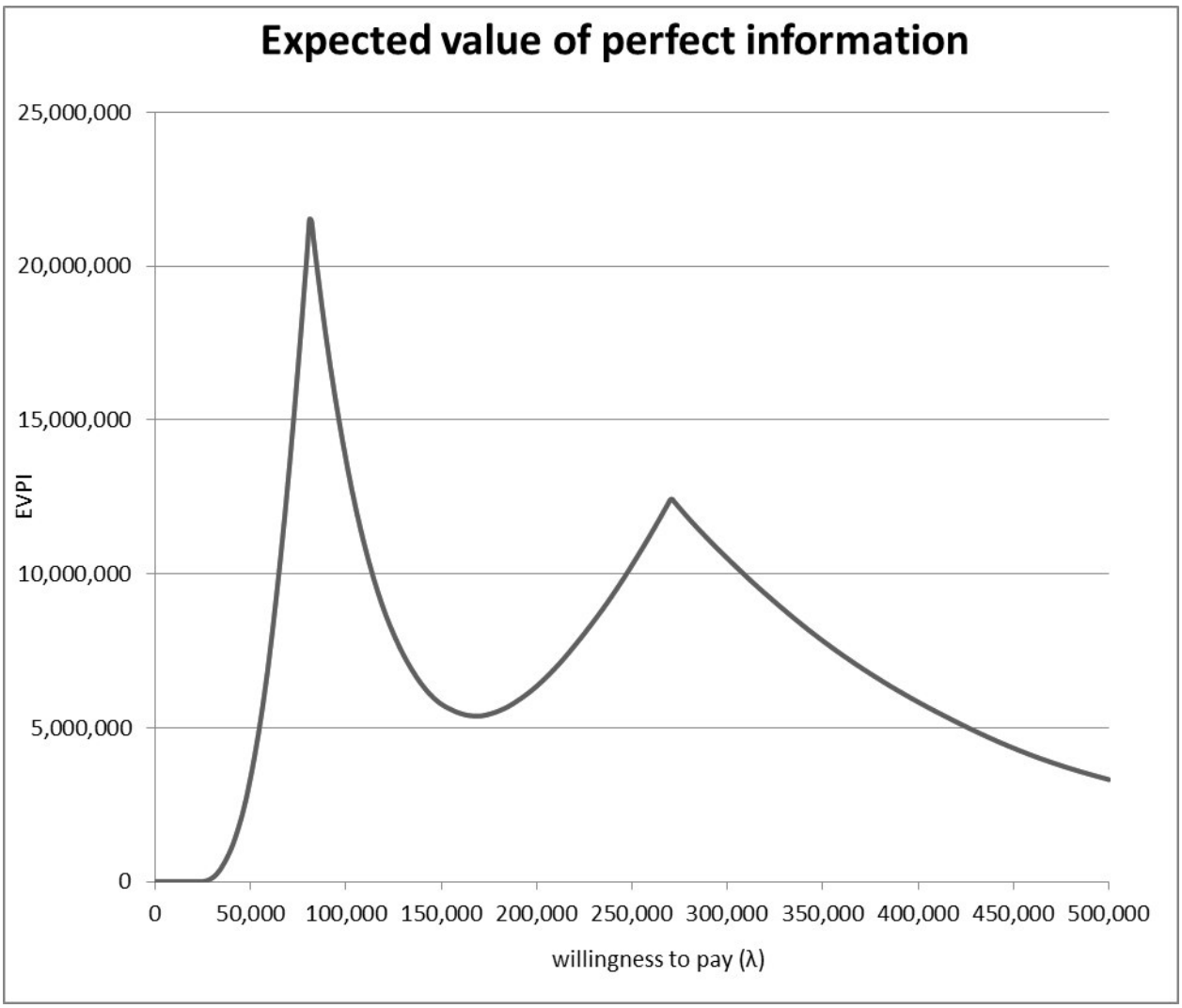


(a) LYG



(b) incremental costs

Supplementary Material 3: Expected value of perfect information



Supplementary Material 4: Scenario Analyses

Uptake of genetic counselling and testing

The estimate of uptake and adherence of LS screening had to be based on weak evidence, first, because the published literature on this topic is limited; and second, because genetics and genetic testing is a highly sensitive topic in the German society so that it is unclear to what extent international evidence is transferable. As with other screening programs the clinical benefit increases as the compliance with genetic counselling and testing increases. In a first analysis we evaluated how calculated ICERs change if uptake of testing and counselling in index patients and FDR increases to 100%. For each strategy the calculated ICERs decrease dramatically. For instance, strategy "counseling incl. Bethesda, IHC, BRAF, sequencing" (strategy B-2) results in an ICER of € 24,979 per life year gained compared with the no screening strategy. A recent literature review found that up to 52% of FDR receive genetic testing (30). This might be a more realistic scenario although these high uptake rates might still be overestimated for the German context. Again for each strategy the calculated ICERs decrease with strategy "counseling incl. Bethesda, IHC, BRAF, sequencing" (strategy B-2) results in an ICER of € 45,169 per life year gained compared with the no screening strategy.

Performance of Bethesda criteria

The revised Bethesda guidelines are probably the most commonly used criteria to select patients with CRC for further molecular analysis. However, in clinical practice they are often criticized for missing many families with the mutations as performance of the criteria might strongly depended on the clinician's recognition of patients' family and understanding of the criteria. In an alternative scenario we therefore evaluate how cost-effectiveness changed if estimates of sensitivity and specificity are lower than previously reported. In an unselected population Trano et al (31) reported a sensitivity of 50% and a specificity of 75% for the Bethesda criteria. If these values are used in the

analysis the most cost effective strategy is “counseling, IHC, BRAF, sequencing” (strategy 2) resulting in an ICER of € 98,271 per life year gained compared with the no screening strategy.

Effect of aspirin chemoprevention

To address the uncertainty that is associated with aspirin chemoprevention we analyzed alternative scenarios based on conservative and optimistic assumptions. When aspirin was assumed to occur costs without providing any benefit, costs of prevention in mutation carriers increase by 195 € compared to the base case. This is due to the increased occurrence of CRC that could not be prevented by aspirin use. The conservative scenario was associated with a reduction of 0.01 years in life when compared to the base case scenario. This leads to an increase in the ICERs with, for example, strategy “counseling incl. Bethesda, IHC, BRAF, sequencing” (strategy B-2) resulting in € 80,119 per life year gained when compared to the no-screening strategy.

In the optimistic scenario, cost of CRC prevention increases by € 2,048. Although prevention reduces expenditure for CRC treatment the additional costs of aspirin use far exceeds the savings. The high costs come with an increase in remaining life years. When comparing the optimistic scenario to the base case scenario remaining life expectancy rises by 0.03 years. Calculated ICERs slightly decrease with strategy “counseling incl. Bethesda, IHC, BRAF, sequencing” (strategy B-2) resulting in a calculated ICER of € 74,399 per life year gained.

We also evaluate how cost effectiveness changed if aspirin prophylaxis was not considered as cancer prevention. Calculated ICERs increase slightly with, for example, “counseling incl. Bethesda, IHC, BRAF, sequencing” (strategy B-2) resulting in € 79,812 per life year gained when compared to the no-screening strategy.

Frequency of colonoscopic screening

The current screening recommendations in Germany foresee that mutation positive patients undergo colonoscopy once a year. However, best screening intervals are internationally discussed

(28). Therefore, in an alternative scenario we evaluated how cost-effectiveness changed if colonoscopy surveillance is performed once in two years instead of once a year. Because of the lack of evidence for risk reduction of regular colonoscopy, biannual colonoscopy was assumed to yield the same benefit as annual colonoscopy but to incure less cost. ICER ranges from € 73,154 per LYG in strategy "counseling incl. Bethesda, IHC, BRAF, sequencing" (strategy B-2) to € 4,183,922 per life year gained in strategy "councelling, sequencing" (strategy 7).

Fully personalized scenario

In an alternative scenario we assumed that results of tumour tissue analysis (IHC; MSI and BRAF tests) are already routinely available and can be used for decision to test for LS without incurring additional costs. Again the most cost-effective strategy incorporates the use Bethesda criteria, followed by IHC and BRAF testing and genetic sequencing (strategy B-2). The calculated ICER results in € 64,956 per life year gained. We also incorporated in this scenario the prospect of falling DNA testing costs assuming that genetic sequencing will be available for € 100. This resulted in a calculated ICER of € 31,004 per live year gained for strategy "counselling incl. Bethesda, IHC, BRAF, sequencing" (strategy B-2).

Discount rate

We also evaluate how applied discount rates influence calculated ICERs. Fist we increase discount rate to 10% for effects only, for costs only and for both. This results in an ICER of € 378,909, 76,712 and 376,181 per live year gained for the most cost effective strategy ("counseling incl. Bethesda, IHC, BRAF, sequencing" (strategy B-2)). Second we delete discounting (discount rate 0%), for effects only, for costs only and for both which resulted in an ICER of € 30,294, 77,769 and 30,491 per life year gained.

Supplementary Material 5: One-Way Sensitivity Analyses for strategy "counselling incl. Bethesda, IHC, BRAF, sequencing" (strategy B-2) versus the no screening strategy