HEALTH BENEFITS AND COST-EFFECTIVENESS OF PRIMARY GENETIC SCREENING FOR LYNCH SYNDROME IN THE GENERAL POPULATION

Appendix

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1. Introduction and Overview

The Archimedes Model is a large-scale simulation model of physiology, diseases, and healthcare systems that has been described in the literature (1-4). While a number of modeling frameworks exist (e.g. Markov models), the Archimedes Model is relatively distinct. For example, unlike Markov models in which individuals probabilistically transition from one disease state to another at discrete time intervals (e.g. annually), and in which there may be no "memory" of prior disease states, the Archimedes Model is built up from the underlying anatomy, physiology, and biological variables. Diseases and outcomes are defined in terms of these underlying variables, and can therefore occur and progress in a continuous fashion. Interventions and treatments act on the underlying variables to modify or prevent disease progression. The model has been validated against studies such as the Cancer Prevention Study II Nutrition Cohort and the Veterans Affairs Cooperative Study Group on colorectal cancer screening (5), and a number of model validations have appeared in the literature (6, 7).

1.1 Scope of the Archimedes Lynch syndrome model

Lynch syndrome (also known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC)) is a disease caused by mutations in mismatch repair genes. The current Lynch syndrome (LS) component of the Archimedes Model focuses on colorectal cancer (CRC) and endometrial cancer (EC) in Lynch syndrome patients and consists of the followings:

(A) A detailed model of colorectal cancer (CRC) in carriers of mismatch repair (MMR) gene mutations, which describes the **natural history of CRC** in mutation carriers, and (ii) the **healthcare processes** associated with surveillance for and treatment of CRC in mutation carriers.

(B) A phenomenological description of endometrial cancer (EC) in mutation carriers, which describes **the incidence and mortality of EC** in mutation carriers, and (ii) the **health care processes** associated with surveillance for and treatment of EC in mutation carriers.

(C) A model of prevalence of mutation carriers and their associated family history in the U.S. population.

1.2 Sources of data

The Lynch syndrome model was built from the following types of data sources:

- ***Summary data of small studies:*** Small studies involving tens to hundreds of individuals, which are designed to evaluate a specific aspect of Lynch syndrome, such as location of cancer or distribution of adenoma size in mutation carriers. These include clinical trials, autopsy studies, colonoscopy screening studies, and retrospective studies.
- ***National surveys and databases:*** Information from national surveys and databases was used to model various aspects of the general population. The

Surveillance Epidemiology and End Results (SEER) database(8) was used to construct incidence of Lynch syndrome-associated cancers in non-carriers. Data from the National Center for Health Statistics were used to generate family structures for the Family History Model (9, 10).

- ***Lynch syndrome registry:*** The Dutch Lynch Syndrome-HNPCC Registry(11) (also known as the Leiden registry) was used to validate the Family History Model.

1.3 Model features

1.3.1 Risk factors

- Age
- Gender
- MMR mutation (*MLH1, MSH2, MSH6*, or *PMS2*)

1.3.2 Interventions

- CRC surveillance by colonoscopy
- Removal of colorectal adenomas by polypectomy
- Surgery for CRC: segmental colectomy with colorectal anastomosis, subtotal colectomy with ileorectal anastomosis, sigmoidectomy with colorectal anastomosis, proctosigmoidectomy or proctectomy with colostomy, proctocolectomy with ileal pouch-anal anastomosis
- Pharmacological and radiation therapy for CRC
- EC surveillance by transvaginal ultrasound (TVU) and endometrial aspirate biopsy
- Treatment and prophylaxis of EC: Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO)

1.3.3 Testing

- Genetic testing: four-gene testing, three-gene testing, single-gene testing, single site (mutation-specific) testing
- Microsatellite instability (MSI) tumor testing: not used to inform genetic testing
- Immunohistochemistry (IHC) tumor testing

1.3.4. Primary health outcomes

- CRC incidence/mortality
- EC incidence/mortality

1.3.5 Logistic outcomes

- Number of colonoscopies
- Number of colorectal surgeries

- Number of TAHBSOs
- Number of genetic tests
- Number of genetic tests needed to identify an additional mutation carrier
- Number of first-degree relatives tested and identified with mutations

1.3.6 Cost and utility outcomes

- Cost of genetic screening
- Cost of surveillance/treatment
- Cost of cancer treatment for CRC/EC
- Total medical costs Life years
- Quality-adjusted life years (QALYs)
- Average cost-effectiveness ratio (ACER)
- Incremental cost-effectiveness ratio (ICER)

2 Sporadic colorectal and endometrial cancers

The colorectal cancer model within the Archimedes Model was developed in collaboration with the American Cancer Society (ACS). This model provides a comprehensive description of colorectal cancer at the clinical level. It consists of (i) ***a natural history component*** that tracks cancer progression, including adenoma development, tumor growth, and symptoms, as a function of non-modifiable risk factors such as age, gender, ethnicity, family and personal history, and modifiable risk factors such as obesity (BMI) and exercise, (ii) a ***screening component*** that allows for detection and removal of adenomas and diagnosis of preclinical CRC, (iii) a ***treatment component*** that predicts survival following diagnosis of CRC as a function of tumor stage, size, and type, and (iv) a ***cost component*** that tracks the cost of diagnosis, prevention measures, screening, complications of screening, follow-up in the event of a positive screening, and treatment.

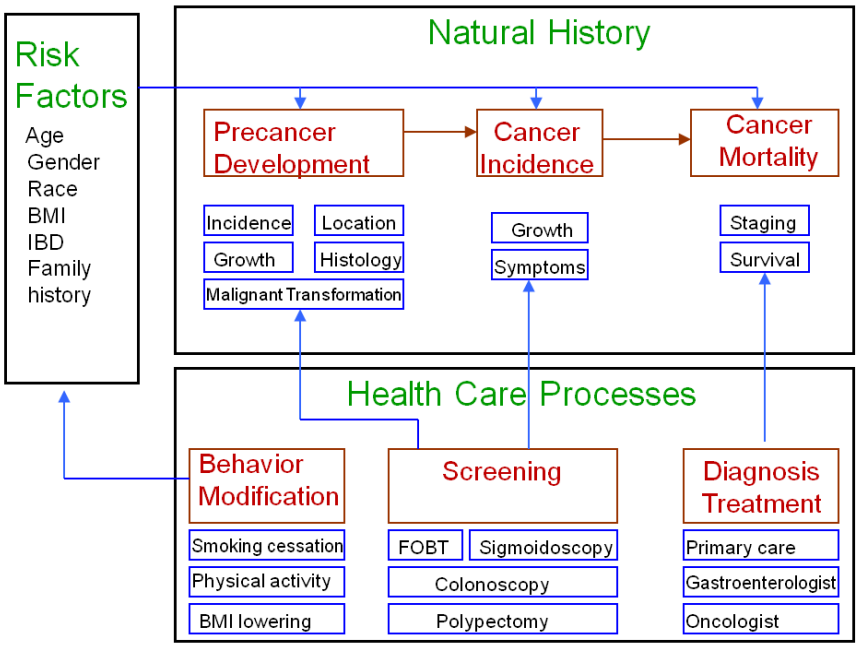

Figure 1. Overview of sporadic colorectal cancer model. BMI is body mass index. IBD is inflammatory bowel disease. FOBT is fecal occult blood test.

We model three types of pre-cancerous lesions, namely (i) ***benign polyps*****,** which will never become cancer, (ii) ***adenomatous polyps (i.e. adenomas)***, which have the potential for malignant transformation, and (iii) ***IBD-associated dysplasia,*** which is the precursor of cancer in patients with inflammatory bowel diseases.
The category “benign polyp” includes hyperplastic, inflammatory and other non-neoplastic polyps and accounts for 1/3 of the total number of polyps (12). Polyps are modeled to occur in the colon and the rectum stochastically through a non-homogenous Poisson process.(13) The rate of polyp occurrence increases exponentially with age and is a function of various risk factors including gender, BMI, and family history. Some of the risk factors, such as BMI and smoking, may change over time. For instance, weight loss can reduce the rate of polyp occurrence. Polyps can occur at eight different anatomical sites along the colon-rectum, namely cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. The distribution of anatomical sites of polyps as function of age and gender are extracted from the Clinical Outcomes Research Initiative (CORI) database (14).
The model allows individuals to develop multiple clinically detectable malignancies, with morbidity and mortality risks associated with each. The propensity of an adenoma for malignant transformation increases with age and adenoma size. The location of an adenoma also affects the rate of malignant transformation. When the malignant transformation probability of an adenoma reaches a pre-defined value (randomly chosen from a uniform distribution between 0 and 1), the adenoma becomes cancerous. We assume that the initial size of malignancy is equal to the size of the adenoma at the time of malignant transformation. The tumor grows exponentially with growth

parameters based on an author-conducted meta-analysis of the literature (15-18). The distribution of tumor size at diagnosis by symptoms is adapted from early SEER data (8), when the effect of screening is minimal. If there is screening, cancer is detectable before the symptoms surface. The survival of a patient following CRC diagnosis is modeled based on current SEER survival data and is a function of age, gender, stage, and tumor size. The sporadic CRC model has been validated against a number of studies including the Cancer Prevention Study-II Nutrition Cohort (19) and Veterans Affairs Cooperative Study Group (5).

The sporadic EC model t is a simple representation of the disease and was built specifically for this study. It was built from the SEER database and consists of (i) an ***incidence component,*** describing the risk of developing EC as function of age, (ii) a ***survival component***, describing the survival of EC patients following diagnosis, (iii) ***a treatment component***, describing the effects of TAHBSO on future incidence of EC and (iv) ***a cost component*** that tracks costs of treatment of endometrial cancer.

3 Colorectal cancer in carriers of MMR mutation

3.1 Model structure

The Lynch syndrome CRC model consists of three major components (see Figure 2), namely, ***the risk factors*** (which describes the input of the model), ***the natural history model*** (which describes the natural history of colorectal cancer) and ***the model of health care processes*** (which describes the interactions of the patients with health care systems via screening, diagnosis, surveillance, and treatment).

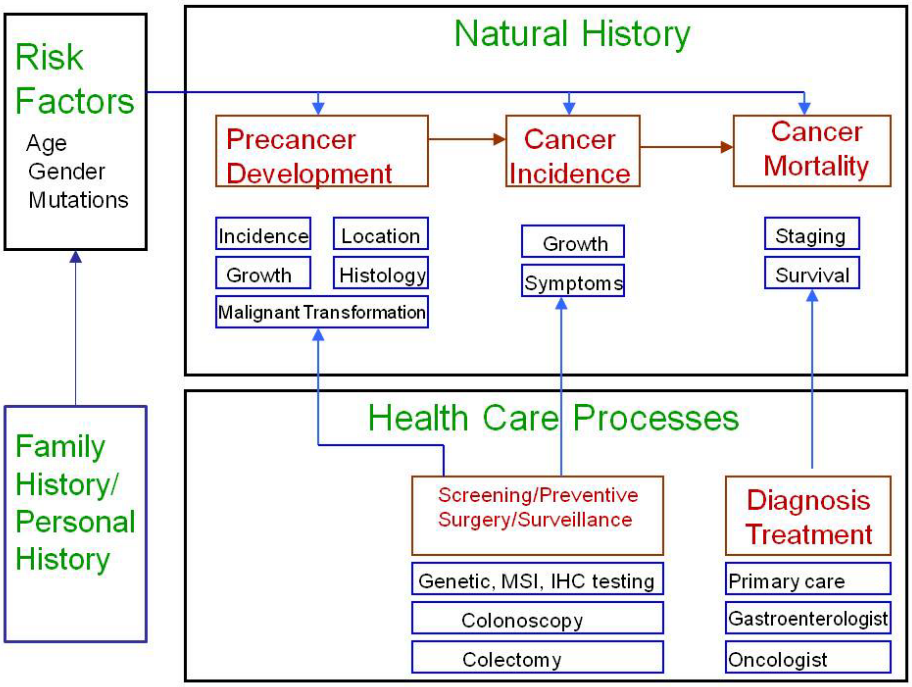

Figure 2. Structure of the model for CRC in mutation carriers. MSI is microsatellite instability. IHC is immunohistochemistry

The ***risk factor*** component describes the inputs of the model including age, gender, and type of mutation carrier (e.g. *MLH1*, *MSH2*, *MSH6*, *PMS2,* and non-carrier). The ***natural history component*** tracks progression of pre-cancerous lesions and cancers in Lynch syndrome patients, including

- adenoma development (*i.e.* incidence, anatomical distribution, growth, and malignant transformation of adenomas),
- tumor development (*i.e.* growth, symptoms, recurrence) and
- patient survival following diagnosis,

The component describing ***health care processes*** consists of

- a testing module that describes sensitivity and specificity of diagnostic tests used in Lynch syndrome
- a surveillance module that describes colonoscopic surveillance of at-risk individuals
- a surgery model that describes effects of segmental/total colectomy

Information on family history and personal history is used to predict the risk of carrying mutations. Development of CRC and EC in mutation carriers are assumed to occur independently of each other.

3.2 Natural history

The model of the natural history of CRC is designed to capture the following key characteristics of CRC in mutation carriers(20):

- CRC in mutation carriers has earlier average age of onset than sporadic CRC.
- Adenoma-carcinoma sequence in mutation carriers is accelerated.
- Proximal colon involvement (approximately 70% of CRCs in mutation carriers are located in the proximal colon).
- There is a high risk of recurrence.
- Lynch syndrome patients have better CRC survival than sporadic CRC patients.

In the current model, colorectal carcinomas in mutation carriers arise from colorectal adenomas. Removal of adenomas by polypectomy during colonoscopy screening will reduce risk of developing CRC.

3.2.1 Adenoma incidence

Literature review

There are relatively few studies quantifying the incidence of adenomas in mutation carriers. One of the most notable publications is Mecklin *et al.*(21) In this study, the authors reviewed colonoscopy data from the Finnish Hereditary Colorectal Cancer Registry electronic database on 420 Lynch syndrome mutation carriers without previous colorectal tumors. Based on the colonoscopy results, the cumulative risk of adenoma by age 60 was estimated to be 68% (95% confidence interval [CI]: 50%-80%) in men and 48% (95% CI: 29%-62%) in women.

Lindgren *et al.*(22) estimated that the relative risk for mismatch repair gene mutation carriers to develop an adenoma was 4.5 times greater than that of the general population.

Liljegren *et al.*(23) determined the prevalence of adenomatous and hyperplastic polyps in a large cohort of mutation carriers. The frequency of an adenoma at first colonoscopy increased from 5.0% (95% CI, 2.8% to 8.3%) in individuals younger than 35 years old to 18.9% (95% CI, 9.4% to 32.0%) in individuals 55 and older. They found no differences regarding prevalence of adenomas between persons harboring mutations in *MLH1, MSH2*, or *MSH6* (p>0.6).
De Jong *et al.*(24) studied risk of developing adenomas in 249 carriers and 247 controls. They reported that the proportion of subjects free of an adenoma at the age of 60 years was 29.7% for carriers and 70.8% for controls ($p < 0.05$).
Burn *et al.*(25) used a two-by-two design to investigate the effects of aspirin and resistant starch (Novelose) in reducing the risk of adenoma and carcinoma among persons with Lynch syndrome. About 19% of participants developed colonic adenoma or carcinoma over a mean follow-up of 29 months.

Modeling approach

- We assume that there is no difference in adenoma incidence between *MLH1, MSH2, MSH6,* and *PMS2* mutation carriers. This is supported by Liljegren *et al.*(23), who did not find statistically significant differences in prevalence of adenomas among persons harboring mutations in *MLH1, MSH2*, or *MSH6* (p>0.6). Note that the risk of developing *cancer* does depend on type of mutation; only the risk of developing *adenomas* is independent of mutation type.
- Adenoma occurrence is assumed to follow a non-homogenous Poisson distribution, which has been found to adequately describe incidence of adenomas the general population (13).
- Annual risk that an individual *i* will get a new adenoma is given by

$$\lambda_i^{AI} = \exp\left(\theta_0^{AI} + \theta_1^{AI} age_i\right)$$

  where θ_0^{AI} is the baseline risk and θ_1^{AI} describes the increase of adenoma risk as function of age.
- A person can develop no adenomas, one adenoma, or several adenomas in his or her lifetime.
- Adenomas can also occur and give rise to second primary cancers after CRC has been diagnosed and treated.
- We use data from Mecklin *et al.*(21) to estimate values for θ_0^{AI} and θ_1^{AI} separately for males and females (see Figure).

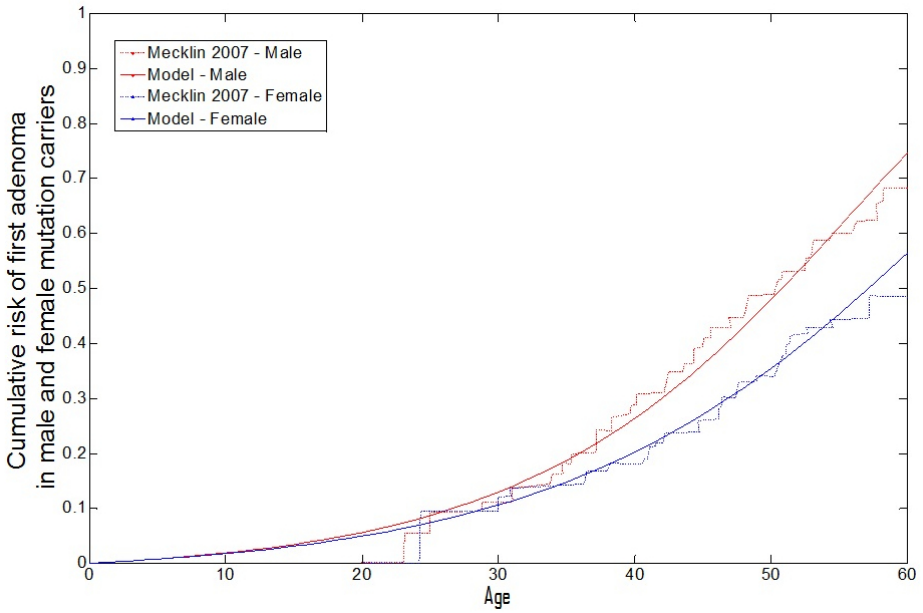

Figure 3. Fitting of adenoma incidence model to cumulative risk of first adenoma in male and female mutation carriers reported by Mecklin *et al.* (2007).(21)

Validation

- We validate the adenoma incidence model against data published in Burn *et al.*(25) See Table 1.

Time	Outcomes	Trial	Simulation
At entry	Presence of neoplasia at colonoscopic examination	14.1%	13.6%
	Number of adenomas found in colonoscopic examination at study entry among those with adenomas		
	1	83.8%	85.7%
	2	12.4%	10.1%
	3	2.9%	2.1%
End of study	No neoplasia	81.1%	79.2%
	Neoplasia (both adenomas and carcinomas)	18.9%	20.8%
	Carcinomas	3%	2.1%
	Number of adenomas found in colonoscopic examination at study entry among those with adenomas		
	1	75.8%	72.9%
	2	15.6%	12.6%
	3	4.7%	3.7%

Table 1. Validation against Burn *et al.*(25): Comparisons of predicted outcomes on adenoma incidence with those of the trial.

3.2.2 Adenoma location

Literature review

Table 2 summarizes the anatomical distribution of adenomas in mutation carriers. Most studies only report the proportion of adenomas in the proximal, transverse, distal colon, and the rectum, and do not specify how adenoma location may depend on age, gender, race/ethnicity, or type of mutation.

Reference	Number of adenomas	Rectum	Distal Colon	Proximal Colon
Liljegren *et al.*(23)	94	25%	33%	41%
Mecklin *et al.*(21)	116	23%	27%	50%
Lindgren *et al.*(22)	42	31%	26%	43%
Rijcken *et al.*(26)	100	20%	30%	50%
Pino *et al.(27)*	42		30%	70%
de Jong *et al.*(24)	116	18%	30%	52%
Weighted average by number of adenomas	**510**	**22.2%**	**29%**	**48.8%**

Table 2. Anatomical distribution of adenomas in Lynch syndrome patients. Pino *et al.*(27) only reported locations of adenomas in colon.

Modeling approach

- We assume that adenoma location is independent of age, gender, race, and type of mutation.
- The model for anatomical distribution of adenomas in mutation carriers is built based on summary data from colonoscopy studies of mutation carriers (Table 2).
- For sporadic colorectal cancers, it is established that adenoma location trends towards a more proximal site as a function of increasing age. Although adenomas and carcinomas in MMR mutation carriers have a preponderance in the proximal colon, an age dependency is not well established for Lynch syndrome, and we therefore assume that adenoma location in mutation carriers is independent of age.
- Using the summary data from colonoscopy studies of mutation carriers (Table 2), we construct the cumulative distribution $P_{AL}(l_A)$ for the location index l_A, which indicates whether an adenoma is located in the rectum, the distal colon (splenic flexure to rectum), or the proximal colon (cecum to the splenic flexure).
- The location of a new adenoma is sampled from $P_{AL}(l_A)$.

3.2.3 Adenoma growth

Literature review

To the authors' knowledge, there are no longitudinal studies of adenoma growth in individuals with MMR mutations. Table 3 summarizes data on adenoma size reported in different colonoscopy studies. Data from Burn *et al.*(25) are excluded here because they represent aggregated data of adenomas and carcinomas. The most relevant data is from Liljegren *et al.*,(23) reporting the distribution of adenoma size for adenomas found during first-ever colonoscopy. Other publications (e.g. de Jong *et al.*(24)) reported size of adenomas found in both first-ever and subsequent colonoscopies. Both Mecklin *et al.*(21)and Pino *et al.*(27) reported average size of adenomas to be 7.2-7.4 mm.

Publications	**Number of adenomas**	**Size distribution**		**Mean or median size (mm)**	**Size range (mm)**
		<5 mm	≥ 5 mm		
Liljegren *et al.*(23)	77	41.6%	58.4%		
Mecklin *et al.*(21)	116	Not available		Mean: 7.4	1-40
Rijcken *et al.*(26)	100	70%	30%	Median: 2.0	0.5-34
Pino *et al.*(27)	42	Not available		Mean: 7.2	2-22
de Jong *et al.*(24)	116	< 7mm, 66%	≥7mm, 34%		

Table 3. Distribution, mean/median and range of adenoma sizes in mutation carriers.

Modeling approach

- We assume that growth of adenomas in mutation carriers is independent of age, gender, and mutation type.
- We model adenoma growth using a log-linear growth model (28).
- We assume that adenomas are spherical and the initial size of any adenoma is equal to 1 mm.
- The growth parameters for adenomas are fitted to reproduce the size distribution reported by Liljegren *et al*.(23).
- The growth model is validated against average adenoma size reported by Mecklin *et al.* (21) and Pino *et al.* (27) and against a size distribution reported by de Jong *et al.* (24).

3.2.4Cancer risk/Malignant transformation

Literature review

Table 4 summarizes studies that estimate the risk of developing CRC with different types of MMR mutation. These studies are used to construct a cumulative risk of CRC as function of age. Quehenberger(29) reported the cumulative risk of CRC in mutation carriers at age 70 to be 27% for males and 22% for females, rates substantially lower than those of previous studies. It is likely that previous studies are biased toward families with many affected members, whose risks are therefore elevated in comparison to mutation carriers with an average number of affected family members (29, 30).
Risk of developing CRC in males is higher than in females. Based on available data, Palomaki *et al.*(30) estimated penetrance by age 70 to be 45% for men and 35% for women. In a more recent study, Barrow *et al.* estimated the cumulative risk of CRC at age 70 for mutation carriers to be 54.3% for males and 45.6% for females (31).

Several studies investigated the difference between *MLH1* and *MSH2* in terms of risk of developing CRC and EC. The difference in CRC risk between *MLH1* and *MSH2* mutation carriers is either not statistically significant or small. Therefore, we assume that the risks of developing CRC in *MLH1* and *MSH2* mutation carriers are similar.
There is little information on cumulative risk of CRC in carriers of *MSH6* and *PMS2* gene mutations. Jenkins *et al*. suggested that the risk of developing CRC in *PMS2* and *MSH6* mutation carriers is 10% lower than in *MLH1* and *MSH2* mutation carriers (32). Buttin *et al.* (33) and Wagner *et al*. (34) estimated the risk of developing CRC in *MSH6* carriers to be 58% at age 70 and 32% at age 80, respectively. Senter *et al.* provided estimates for CRC and EC in a sample of 99 *PMS2* carrying probands (35).

Modeling approach

- Risk of developing CRC in mutation carriers is estimated based on a meta-analysis of existing data on penetrance of CRC among mutation carriers.
- Risk of developing CRC depends on mutation type, gender, and age.
- We assume that CRC risk is similar between *MLH1* and *MSH2* mutation carriers, and can be estimated together.
- CRC risks for *MSH6* and *PMS2* are estimated separately.
- We use a hazard equation to model the transition from adenomas to preclinical cancer. First, we introduce the hazard rate, h_{ij}^{A}, which represents the rate that an adenoma *j* in an individual *i* becomes cancer. The probability that the transition has occurred by time *t,* $P_{ij,A\to C}(t)$, is given by the following propensity function

$$P_{ij,A\to C}(t) = 1 - \exp\left(-\int_{t_0}^{t} h_{ij}^{A}\, d\tau\right)$$

  where the subscript $A \to C$ denotes the transition from adenomas to cancer, and t_0 is the time of adenoma inception. For a mutation type, h_{ij}^{A} depends on adenoma size d_A, adenoma location l_A (see section 3.2.5), age, and gender. For each mutation-gender combination, h_{ij}^{A} is fitted to match the risk of developing colorectal cancer as function of age derived from the meta-analysis and anatomical distribution of tumors.
- The following data were excluded from the meta-analysis:
  - Data from Mecklin *et al.*(21) were not used because mutation carriers underwent regular colonoscopic surveillance, which potentially reduced CRC incidence.
  - Data from Goecke *et al.*(36) and Vasen *et al.*(37) were not used because the authors reported CRC risk for males and females together.
  - Data from Jenkins *et al.*(32) were not used because the authors reported CRC risk for *MLH1, MSH2, MSH6* and *PMS2* together.
  - Data from Aarnio *et al.*(38) were excluded because the estimated risk of developing CRC by age 70 of 100% in male *MLH1/MSH2* mutation carriers is a substantial outlier relative to other studies.

- Figure shows an example of the model fit to a weighted average of existing data.

References	*MLH1*	*MSH2*	*MSH6*	*PMS2*

Hendriks *et al.*(39)	X	X	X	
Buttin *et al.*(33)			X	
Dunlop *et al.*(40)	X			
Quehenberger *et al.*(29)	X			
Hampel *et al.*(41)	X			
Barrow *et al.*(31)	X	X		
Wagner *et al.*(42)			X	
Senter *et al.*(35)				X
Stoffel *et al.*(43)	X	X		

Table 4. References used to estimate cancer risk in mutation carriers.

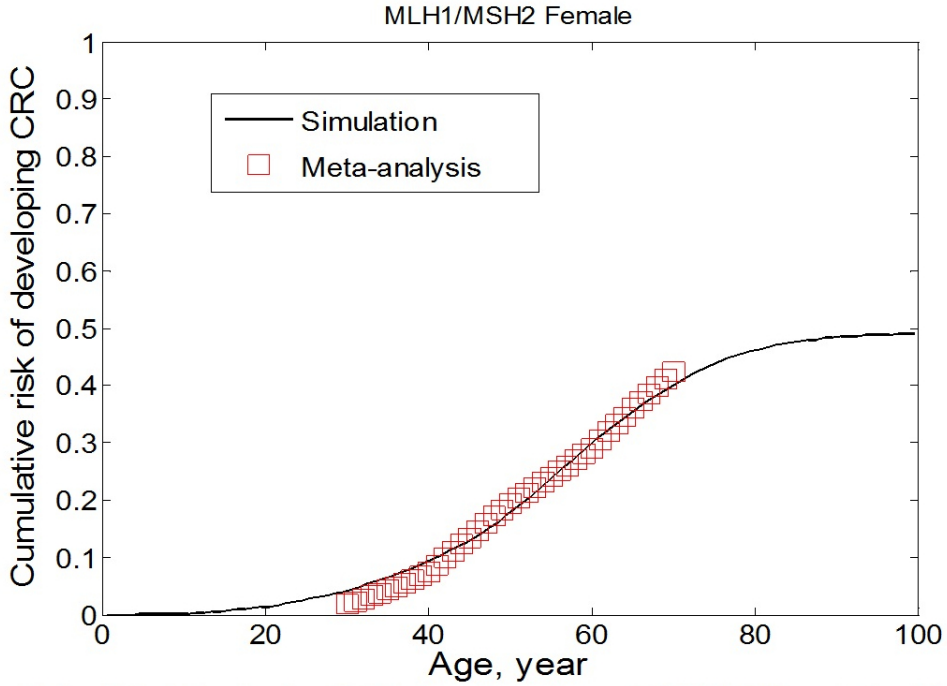

Figure 4. Fit to cumulative risk of developing CRC in female carriers of MLH1/MSH2 mutation. The square symbol represents the result of a meta-analysis of existing data. The solid line represents the model fit to the data.

3.2.5Cancer location

Literature review

- Table 5 below summarizes the anatomical distribution of colorectal carcinomas in mutation carriers. Colorectal carcinomas in mutation carriers are located predominantly in the proximal colon (44).
- Proximal adenomas in mutation carriers account for roughly 50% of the total number of adenomas, while proximal carcinomas account for approximately 70% of all colorectal carcinomas in mutation carriers.

Modeling approach

- We assume that cancer location is independent of age, gender, race, and mutation type.
- To capture the distribution of malignancy location in mutation carriers, the hazard rate h_{ij}^{A} for malignant transformation (see section 3.2.4) is a function of adenoma location.
- The hazard rate h_{ij}^{A} is fitted to reproduce the anatomical distribution of tumors obtained from the meta-analysis of data summarized in Table 5.

Publication	**Number of carci-nomas**	**Distal**			**Proximal**		
		Rectum	***Sigmoid***	***Descending***	***Transverse***	***Ascending***	***Cecum***
Mecklin *et al.*(21)	41	5%	20%		24%	51%	
Lindgren *et al.*(22)	15	14%	30%		56%		
Aaltonen *et al.*(45)	63	22%			78%		
de Vos Tot Nederveen Cappel *et al.* (46)	21	5%	5%	5%	19%	19%	38%
Weighted average by number of carcinomas	**140**	**6%**	**18%**		**76%**		

Table 5. Anatomical distribution of cancers in Lynch syndrome patients.

3.2.6 Survival

Literature review

Sankila *et al.*(47) reported that the overall five-year cumulative relative survival rate was 65% for Lynch syndrome patients with colorectal cancer and 44% for patients with sporadic colorectal cancer. The relative survival rates of patients with Lynch syndrome were better in every stratum analyzed. They concluded that *MLH1*-associated colorectal cancer has a natural history different from that of sporadic colorectal cancer. According to Sankila *et al,*(47) the five-year survival rates are 98% in the case of Dukes' A, 80% for Dukes' B, and 60% for Dukes' C staging classification.

Watson *et al.*(48) compared the survival of an unselected series of CRC patients with Lynch syndrome and showed that LS patients had lower stage disease ($p < 0.001$), and fewer had distant metastases at diagnosis ($p < 0.001$ in an analysis stratified by T classification). In stage-stratified survival analysis, the LS cases had a significant overall

survival advantage regardless of adjustment for their younger age. Watson *et al.*(48) estimated the hazard ratio (of LS cases relative to the unselected series) to be 0.67 ($p < 0.0012$).

Aarnio *et al.*(49) compared 43 members of LS colorectal cancer families with a control group including 122 sporadic CRC patients and found that cumulative five-year survival in LS was significantly better than in sporadic colorectal cancer (86% vs. 59%, hazard ratio 0.41, $p = 0.02$).

Barnetson *et al.*(50) showed that after adjusting for stage, the difference in cancer survival between mutation carriers and non-carriers is not statistically significant. They found no significant difference in survival either between patients who had no previous cancers and those who had previous cancers. They also found no significant difference in survival between carrier groups according to the extent of tumor spread at diagnosis: the five year survival rate among patients with localized disease (stages I and II) was 95% for carriers and 87% for non-carriers. For those with metastatic disease (stages III and IV), the five-year survival rate was 42% for both carriers and non-carriers.
Barrow *et al.*(31) reported a five-year survival of 56.2%, with females surviving slightly better than males. Gryfe *et al.*(51) studied 607 CRC patients under age 50 (17% had high-frequency MSI) and reported that microsatellite instability was associated with a significant survival advantage independent of all standard prognostic factors, including tumor stage (hazard ratio, 0.42; 95 percent confidence interval, 0.27 to 0.67; $p< 0.001$).

Modeling approach

- The difference in survival between mutation carriers with CRC and patients with sporadic CRC is characterized by a hazard ratio. The hazard ratio is derived from an author-conducted meta-analysis of publications on CRC survival in mutation carriers, separately for males and females, and is assumed to be independent of age and cancer stage.
- The survival rate of sporadic CRC is derived from the Surveillance Epidemiology and End Results (SEER) database (8).
- Based on data from Gryfe *et al.* (51), Barnetson *et al.* (50), Watson *et al.* (48), Sankila *et al.*(47), and Aarnio *et al.* (49), we estimate the hazard ratio to be 0.53.

3.2.7 Second primary tumor

Literature review

De Vos tot Nederveen Cappel *et al.*(46) estimated the risk of developing a second colon tumor after treatment of a primary CRC in Lynch syndrome to be 16% after ten years of follow-up. Lin *et al.*(52) estimated the annual rates of metachronous CRC among *MLH1* and *MSH2* mutation carriers to be 2.1% and 1.7% respectively. Mecklin *et al.*(53) estimated the risk of a metachronous tumor after partial colectomy to vary from 15% to 30%.
Rodriguez-Bigas *et al.*(54) estimated the risk of rectal cancer in patients with LS after an abdominal colectomy to be approximately 12% at 12 years. Age at first surgical procedure and surveillance correlated with rectal cancer risk. On the other hand, de Vos

tot Nederveen Cappel *et al.*(46) estimated the risk of developing rectal cancer to be 3.4% in ten years.

Modeling approach

- Second primary CRCs arise from second primary adenomas after treatment of the initial cancer.
- Occurrence of adenomas that give rise to second primary CRCs are predicted according to the adenoma incidence model.
- Adenomas can only appear in the sections of the colon and the rectum that have not been removed during surgical treatment (either by segmental resection or total colectomy) of the primary CRC.

Validation

- The risk of developing a second colon tumor after treatment of a primary CRC in LS patients, was validated against de Vos tot Nederveen Cappel *et al.*(46)

3.3 Health care processes

The model of health care processes describes the interactions of unaffected and affected MMR mutation carriers with the health care system. It consists of:

(i) a ***diagnosis component***, in which individuals with symptoms are examined in primary care settings and subsequently sent to testing,
(ii) a ***testing component***, in which individuals at increased risk for Lynch syndrome are tested by either MSI, IHC, and/or genetic testing,
(iii) a ***surveillance component*** that describes surveillance by colonoscopy and its preventive effects on CRC incidence,
(iv) a ***preventive surgery component*** that describes polypectomy to prevent CRC in mutation carriers with low grade adenomas,
(v) a ***treatment component*** involving surgical (segmental and total colectomies) as well as pharmacological/radiation therapy that uses the survival model described to output the survival length and the time of CRC death, and
(vi) a ***cost component*** that tracks cost of diagnosis, prevention measures, screening, follow-up following positive testing, and treatment.

Testing for mutations will be discussed separately in section 5. Costs are shown in Table 12. All values are adjusted to 2009 values using the medical care component of the Bureau of Labor Statistics Consumer Price Index (55). In this section, we discuss colonoscopic surveillance, polypectomy and treatment of LS.

3.3.1. Colonoscopic surveillance and polypectomy

Literature review

Guidelines on Lynch syndrome recommend colonoscopy for mutation carriers every one to two years, with a starting age of 25 years old or ten years younger than earliest diagnosis in the family (56, 57). The National Comprehensive Cancer Network (NCCN) and other professional organizations have similar recommendations: colonoscopic surveillance every one to two years starting at age 20-25 and annual screening after age 40 (58-60).

Surveillance by colonoscopy has been shown to reduce CRC incidence and mortality. Jarvinen *et al.*(61) reported that colonoscopy screening at three-year intervals in a 15-year follow-up of Lynch syndrome patients reduces the risk of CRC by 56%, and mortality by 65%. Mecklin *et al.*(21) reported a similar reduction as a result of surveillance at an interval of two to three years. Colonoscopy at an interval of two years or less leads to the detection of colon cancer at earlier stages, in comparison to a surveillance frequency of greater than two years (46). De Jong *et al.*(62) followed 2788 members from 146 Lynch syndrome families in the Netherlands to assess mortality caused by CRC. When comparing the subjects who did or did not have surveillance colonoscopies, a significant difference in standardized mortality ratio was observed (6.5 vs. 23.9, respectively), suggesting a reduction of 70% in mortality.
Compliance to colonoscopy surveillance in identified mutation carriers is high and has been shown to reach 100% in a Finnish population (63). On the other hand, based on seven studies with a total of 168 patients, Palomaki *et al.*(30) estimated the proportion of mutation carriers complying with colonoscopic surveillance recommendations to be 79-81%.

Modeling approach

- Colonoscopy surveillance reduces CRC incidence by removing adenomas that might become carcinomas.
- Sensitivity and specificity of colonoscopy for adenomas in Lynch syndrome patients are assumed to be similar to those for adenomas in patients with sporadic CRC.
- Compliance to colonoscopic surveillance is based on estimates provided by Palomaki *et al.*(30) because these estimates, unlike those of Pylvanainen *et al.*(63) which are for a Finnish population only, are homogeneous and span several populations including U.S. populations.
- Based on author estimates of current U.S. practice patterns, 20% of known asymptomatic carriers diagnosed with advanced adenoma during annual colonoscopy screening have total colectomy. The remaining 80% with advanced adenomas have them removed endoscopically. One hundred percent of adenomas graded lower than advanced are removed endoscopically.
- Sensitivity and specificity of colonoscopy as a function of size and location of adenoma are based on a meta-analysis by Rex *et al.*(64) and Loeve *et al.*(65, 66).
- We neglect morbidity associated with colonoscopy and only include surgery-related mortality.
- Surgical mortality rate is based on Palomaki *et al.*(30).

3.3.2. Treatment of CRC

Literature review

Lynch syndrome patients who develop CRC are at high risk for recurrent CRC. The American Society of Colon and Rectal Surgeons recommends the following for individuals with Lynch syndrome who develop CRC or one or more advanced

adenomas, and optionally for unaffected mutation carriers who are unwilling or unable to undergo regular colonoscopy(59, 67, 68):

- Subtotal colectomy with ileorectal anastomosis and annual rectal surveillance, or
- Hemicolectomy with annual colonoscopy

It should be noted that although favored, subtotal colectomy with ileorectal anastomosis has not been proven to be superior to segmental resection with annual colonoscopic surveillance (30).

With respect to chemotherapy, although a few studies found that MSI-H tumors in Lynch syndrome patients are resistant to 5-FU based chemotherapy and are more sensitive to CPT11 (irinotecan), the evidence is not strong enough to support changes in chemotherapy recommendations (30).
Guillem *et al.*[46] estimated the 30-day mortality rate of subtotal colectomy with ileorectal anastomosis to be 0.9%. This agrees well with the mortality rate used by Syngal *et al.*(69) in an earlier cost-effectiveness analysis of prophylactic surgery in mutation carriers.

Modeling approach

- Survival of LS patients diagnosed with CRC is captured by the survival model described in section 3.2.6.
- The effects of colectomy are captured by not allowing future adenomas to appear in sections of the colon that have been removed by surgery.
- Following total proctocolectomy, we assign 50% of patients to continue annual surveillance in the form of examination up to the anal verge.
- The type of segmental resection for sporadic CRC following a diagnosis as a function of cancer location is given in Table 6 below.

Malignancy location	Type of surgery
Proximal colon (cecum to splenic flexure)	Right hemicolectomy with ileo-descending anastomosis
Descending colon	Left hemicolectomy with transverse-sigmoid anastomosis
Sigmoid colon	Sigmoidectomy with colorectal anastomosis
Rectum	Proctosigmoidectomy (70%) with ileal pouch anal anastomosis or proctectomy with colostomy (30%)

Table 6. Type of segmental resection as function of CRC location.

4. Endometrial cancer in carriers of MMR mutations

4.1 Model structure

The Lynch syndrome EC model consists of three major components namely, ***the risk factors*** (which describes the input of the model), ***the natural history model*** (which describes the natural history of endometrial cancer) and ***the model of health care processes*** (which describes the interactions of the patients with health care systems via screening, diagnosis, surveillance and treatments) (See Figure 5).
The ***risk factor*** component describes the inputs of the model including age, and type of mutation carrier (e.g. MLH1, MSH2, MSH6, PMS2, and non-carrier).
The ***natural history component*** tracks incidence and mortality of endometrial cancer in Lynch syndrome patients.
The component describing ***health care processes*** consists of medical interventions, such as TAHBSO, which can alter the incidence and mortality of endometrial cancer.

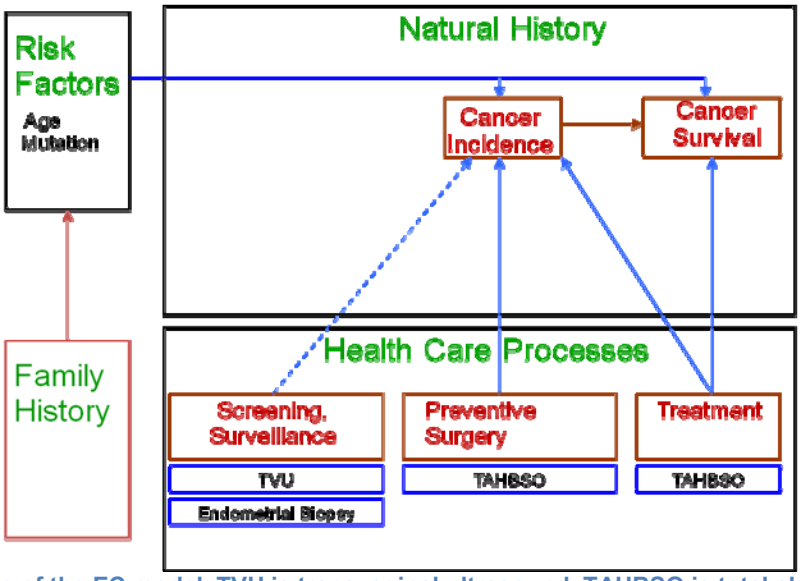

Figure 5. Structure of the EC model. TVU is transvaginal ultrasound. TAHBSO is total abdominal hysterectomy and bilateral salpingo-oophorectomy.

4.2 Natural history

4.2.1. Incidence

Literature review

Approximately 3-5% of endometrial cancer may be attributed to Lynch syndrome (70). Table 7 summarizes studies quantifying the risk of developing EC in mutation carriers. Schmeler *et al.*(71) performed a retrospective cohort analysis of women with germline mutations. While none of 61 the women who underwent hysterectomy developed endometrial cancer, about 70% of the 210 women who did not undergo hysterectomy developed endometrial cancer.

Study	Year	Population	Mutation
Buttin *et al.* (33)	2004	59	*MSH6*
Jenkins *et al.*(32)	2006	17	*MLH1, MSH2*
Schmeler *et al.*	2006	210	*MLH1, MSH2*
Hendricks *et al.*(39)	2004	87	*MSH6*
Vasen *et al.*(72)	2001	309	*MLH1, MSH2*
Aarnio *et al.*	1999	183	*MLH1, MSH2*
Hampel *et al.*	2005	183	*MLH1, MSH2*
Dunlop *et al.*	1997	35	*MLH1, MSH2*
Quehenberger *et al.*(29)	2005	152	*MLH1, MSH2*
Stoffel *et al.*(43)	2009	300	*MLH1, MSH2*
Senter *et al.*(35)	2008	99	*PMS2*

Table 7. Studies of incidence of endometrial cancer in mutation carriers.

Modeling approach

- Incidence of endometrial cancer is modeled as a function of age and mutation type, based on a meta-analysis of data provided in the Table 7.
- We assume that EC risk is similar between *MLH1* and *MSH2* mutation carriers, and can be estimated together.
- EC risks for carriers of *MSH6* and *PMS2* mutations are estimated separately.

4.2.2. Survival

Literature review

There are relatively few studies reporting the survival rates of EC in LS patients. Boks *et al.*(73) showed that the survival rate of individuals with Lynch syndrome-associated EC appears to be not statistically different from that of patients with sporadic EC.

Modeling approach

- Referencing Boks *et al.* (73), we assume that the survival of mutation carriers with endometrial cancer is not significantly different from the survival of women with endometrial cancer in the general population. The survival rate is built from SEER data (8).
- Survival is a function of age and time since cancer diagnosis.
- We used the SEERstat software package (8) to construct Kaplan-Meier survival estimates as a function of time since diagnosis, binned by age in five-year increments.

4.3 Health care processes

4.3.1. Surveillance

Literature review

The value of endometrial surveillance for women with MMR mutations is not well-established. Lindor *et al.*(60) performed a review of care recommendations for

individuals with Lynch syndrome. With regard to endometrial surveillance, they recommend (i) annual endometrial biopsy starting at age 30-35 or (ii) annual transvaginal ultrasound (TVU) starting at age 30-35. Lindor *et al.*(60) noted, however, that there exists "insufficient evidence to recommend for or against" each strategy. Vasen *et al.*(56) conducted a detailed review of literature regarding clinical management of Lynch syndrome, and summarized a panel of experts' clinical recommendations. They stated that "Surveillance by gynecological examination, TVU, and aspiration biopsy starting from age 30-35 years may lead to the detection of premalignant lesions and early cancers." Like Lindor *et al.,*(60) they noted that "the value of surveillance for endometrial cancer is unknown."

Renkonen *et al.*(74) performed an analysis of the effect of surveillance on endometrial cancer survival in women with Lynch syndrome. While they found higher survival rates in women who underwent surveillance, the surveillance group had only 14 members, and the effects of surveillance on cancer survival are not statistically significant.

Based on existing literature, Kwon *et al.*(75) estimated a minor improvement of stage distribution of EC at the time of diagnosis due to surveillance. The proportions of stages I, II, III, and IV in the no-prevention no-screening strategy are 78%, 8%, 13% and 1% respectively, while the proportions of stages I,II, III, and IV in the screening strategy are 79%, 10%, 10% and 1% respectively. The small changes in stage distribution do not affect the overall survival significantly.

Existing evidence indicates that screening for endometrial cancer in Lynch syndrome patients has a high false-positive rate and lacks efficacy. Rijcken *et al.*(76) screened 41 women (35 premenopausal and 6 postmenopausal) diagnosed with Lynch syndrome via gene mutation or by fulfilling Amsterdam criteria with annual TVU and serum CA-125 analysis for a median follow-up of five years (76) In 0.9% of ultrasounds, further evaluation via endometrial sampling was suggested. From this, only three premalignant lesions were discovered. One endometrial cancer was detected through symptoms. Similarly, Dove-Edwin *et al.*(77) performed a study of TVU screening in 269 women who either had Lynch syndrome or came from Lynch syndrome-like families. For a total of 825.7 person-years of risk, only two cases of endometrial cancer were reported; both were detected by symptoms, not by ultrasound screening.

Stoffel *et al.*(78) reported only three of 12 (25%) women who had family history of LS underwent appropriate endometrial surveillance with either yearly ultrasound or yearly endometrial biopsy. On the other hand, Wagner *et al.* and Collins *et al.* reported higher compliance to endometrial cancer screening: 69% and 53%, respectively (79, 80).

Modeling approach

- Based on Dijkhuizen *et al.* (81), we assume the sensitivity and specificity of endometrial aspirate biopsy to be 91% and 98%, respectively.

- We assume that detection of precancerous endometrial lesions during asymptomatic surveillance by TVU is negligible (Dove-Edwin *et al.*(77)).

- Surveillance does not have any effect on endometrial cancer incidence or survival according to literature review.

- Although surveillance for EC is assumed to have no effects on incidence and mortality of EC, a model of annual screening by TVU and endometrial biopsy enables accurate estimation of costs due to EC surveillance.
- Women who are positive for MMR mutation but are asymptomatic undergo TVU and endometrial aspirate biopsy surveillance with a compliance of 57% based on a meta-analysis of data from Stoffel *et al.* (78), Wagner *et al.*(79) and Collins *et al.(*80).
- Women with known Lynch syndrome manifesting with EC undergo TAHBSO with 100% compliance, as recommended by guidelines.
- Women with known Lynch syndrome manifesting with CRC have the option for elective prophylactic TAHBSO (i.e. no EC is present yet) at an age-dependent compliance rate (see next section). Those individuals not electing a TAHBSO have annual TVU and endometrial biopsy, with compliance of 57%, based on the author-conducted meta-analysis described above.

4.3.2. Preventive and interventional surgery

Literature review

According to Vasen *et al.*(56) and Palomaki *et al.*(30), risk reduction by TAHBSO after the completion of childbearing should be presented as an elective option for mutation carriers. It is expected that a cancer-free woman who has learned of a positive mutation carrier status but who has not completed child bearing might elect to defer a purely prophylactic TAHBSO until completion of child bearing.

Schmeler *et al.*(71) performed a retrospective cohort analysis of women with germline mutations, a portion of whom had TAHBSO. They noted that none of 61 the women who underwent TAHBSO developed endometrial cancer, whereas about 70% of the 210 women who did not undergo hysterectomy developed endometrial cancer. It should be noted that a decrease in the incidence of endometrial cancer alone might not improve survival, because five-year survival rates are greater than 90% for both early-stage sporadic and Lynch syndrome-associated endometrial cancers (82).

Mortality associated with TAHBSO is estimated to range from 0 to 0.04% (Palomaki *et al.*(30)). Chen *et al.*(83) reported surgical hysterectomy mortality as a function of age as drawn from the SEER database. The rate of surgical mortality increases with age and reaches 2% for 80 years old and older.

Modeling approach

- We assume that a woman diagnosed with endometrial cancer will have TAHBSO.
- Following hysterectomy, the hazard rate for developing endometrial cancer is set to zero. Therefore, recurrence of endometrial cancer is not possible in the model.
- We account for mortality risk due to TAHBSO, but neglect morbidity. We also neglect the costs and morbidities–if any–of women initiating and taking estrogen therapy following TAHBSO.
- TAHBSO is assumed to have a mortality risk of 0.02%, which is a weighted-average of mortality rates reported in nine studies summarized in Table 11 of Palomaki *et al.*(30)

- Compliance to purely elective TAHBSO when a woman has learned that she is a mutation carrier is modeled as a sigmoidal function of age (Table 8). These figures are not reported in the literature and are therefore estimated by the authors C.R.B., R.W.B., S.B.G, and S.S. who have clinical expertise in LS.

Parameter	Value
Compliance to TAHBSO surgery in asymptomatic mutation carriers	< 30 year old: 0% 40 years old: 40% 50 years old: 60% 80 years old: 75%
Compliance to TAHBSO surgery in mutation carriers diagnosed with CRC, but not yet with EC	< 30 year old: 5% 40 years old: 60% 50 years old: 80% 80 years old: 90%

Table 8. Modeled compliance to TAHBSO surgery as function of age.

5. Testing for mutations

5.1. Microsatellite instability (MSI) and immunohistochemical (IHC) analyses

Literature review

Based on their review of several prospective studies of sensitivity of MSI and IHC analyses, Vasen *et al.* (56) concluded that:

- The sensitivity of MSI analysis is slightly higher than that of IHC analysis.
- In families with a high probability of having a mutation, IHC is the best first step because it may direct mutation analysis.

Shia *et al.*(84) conducted a comprehensive review of existing literature on sensitivity of IHC and MSI testing. They estimated that the sensitivity for predicting all *MLH1, MSH2, MSH6*, and *PMS2* mutations is 94% for IHC and 83% for MSI (84).

In a recent publication, Palomaki *et al.*(30) conducted a similar review of sensitivity and specificity of MSI and IHC analyses. Palomaki *et al.*(30) estimated the sensitivity of MSI for *MLH1/MSH2* to be 91% and for *MSH6/PMS2* to be 77% and the sensitivity of IHC to be 83%. Specificity for MSI was estimated to be 90.2%, while specificity for IHC was estimated to be 88.8%.(30)

Modeling approach

- Since results of MSI do not specifically inform genetic testing, for the purpose of capturing appropriate testing costs, MSI testing is bundled with IHC testing in the current practice patterns arm of the study.

- Analytic sensitivity and analytic specificity for IHC testing are set to 83% and 88.8%.(30)

5.2. Genetic sequence testing

Literature review

There exist uncertainties in estimating the analytic specificity and sensitivity for genetic testing. Based on subjective opinion, Palomaki *et al.*(30) estimated the sequencing/MLPA sensitivity and specificity to be 99.5% and 99.97% respectively. On the other hand, Bonis *et al.*(85) estimated the sensitivity and specificity of genetic testing to be 95% and 99.5%, respectively. Furthermore, these sensitivities may not allow for variants of uncertain significance that are encountered clinically. There are also uncertainties associated with estimating sensitivity of genetic testing for *PMS2* mutations due to complex interactions between *PMS2* and *MSH1* genes.

Modeling approach

- Sensitivity of genetic testing for *MLH1, MSH2* and *MSH6* is set to a conservative estimate of 90%, based on clinical expertise of authors C.R.B., R.W.B., S.B.G., and S.S.
- Sensitivity of genetic testing for *PMS2* is based on Senter *et al*.(35). Specificity of genetic testing is based on Palomaki *et al.*(30).
- Sensitivity and specificity of genetic testing are summarized in Table 9.

Mutation	Analytic sensitivity	Analytic specificity
MLH1	90%	99.97%
MSH2	90%	99.97%
MSH6	90%	99.97%
PMS2	62%	99.97%

Table 9. Sensitivity and specificity of genetic testing.

6. Population generation

Generation of a population representative of the U.S. general population consists of the following steps:

- Step 1: Generate natural history of CRC and EC for mutation carriers.
- Step 2: Generate natural history for non-carriers.
- Step 3: Generate family history for mutation carriers.
- Step 4: Generate family history for non-carriers.
- Step 5: Mix populations of carriers and non-carriers in appropriate proportion.

6.1. Prevalence of mutation carriers

Literature review

Chen *et al.*(86) used the following Bayes' rule to estimate the frequency of mutations of MMR genes in the general population:

$$\text{carrier prevalence} = \frac{\text{carrier prevalence among cases} \cdot \text{cancer incidence}}{\text{cancer incidence among carriers}}$$

Chen *et al.*(86) considered only colorectal cancers diagnosed before age 50 and estimated the numbers in the right-hand side of the equation as follows:

- The prevalence of *MLH1* and *MSH2* mutation carriers among CRC cases younger than 50 is 0.28.
- The overall cancer incidence by age 50 in the general population is 0.00215, from the SEER database (8).
- The CRC risk among carriers of *MLH1* and *MSH2* (by age 50) is 0.32.

This leads to a carrier frequency of 0.0019 for *MLH1* and *MSH2* mutations combined, or 0.0009 and 0.0010 for the two gene mutations individually. Since less information is available on *MSH6* mutation prevalence, Chen *et al.*(86) assumed that it accounts for 15% of all LS mutations; that is, 0.00036. In summary, Chen *et al.*(86) estimated that the frequency of mutations of *MLH1* is one in 1100, *MSH2* is one in 1000, and *MSH6* is one in 2800. Overall, roughly one in 440 people carry mutations in *MLH1, MSH2* or *MSH6*.

DeLaChappele *et al.*(87) used a similar approach to estimate the frequency of MMR mutations. However, rather than using data for CRC before age 50, they used all CRCs and estimated a carrier frequency between 1:2000 and 1:660.
Dunlop *et al.*(88) conducted a similar analysis based on Scottish data and estimated carrier prevalence in the population aged 15–74 years to be 1:3139 (95% CI = 1:1247–1:7626).

It should be noted that all estimates suffer from several uncertainties, including(87):

- Estimates often ignore *MSH6* and *PMS2* mutations,
- Neither MSI nor mutation detection is 100% sensitive, and
- The estimates are based solely on CRC.

Palomaki *et al.*(30) estimated the prevalence of LS CRC among newly CRC diagnosed to be 3% (see Table 13 of Palomaki *et al.*(30)). This number is consistent with the figure of 2.2% reported by Hampel *et al.* (41), considering that 10-20% of LS families have a mutation of undefined type.
Palomaki *et al.*(30) also estimated the proportions of mutations among mutation carriers to be 32% *MLH1*, 39% *MSH2*, 14% *MSH6*, and 15% *PMS2*.

Modeling approach

- Based on Palomaki *et al.* (30), the proportion of mutations among mutation carriers are distributed as follows: 32% *MLH1*, 39% *MSH2*, 14% *MSH6*, and 15% *PMS2*.
- To estimate the frequency of mutation carriers in the general population, we use the following information:
    - Incidence of CRC in the general population
    - CRC penetrance among mutation carriers
    - Prevalence of LS CRC among newly diagnosed CRC in the U.S. population

- We use SEER data (8) to model the incidence of CRC in the general population.
- We use data from section 3.2.4 to estimate CRC penetrance among mutation carriers.
- Based on Palomaki *et al.* (30), and Hampel *et al*. (41) we set the prevalence of LS CRC among newly diagnosed CRC in the U.S. population to be 3%.
- We then run the simulation and adjust the frequency of mutation to reproduce the 3% prevalence of LS CRC among all diagnosed CRC. Using this method, we estimate the prevalence of MMR mutation in the general U.S. population to be one in 255.

6.2. Family history in non-carriers

Literature review

Ramsey *et al.*(89) analyzed data from the 2000 National Health Interview Survey (NHIS), a national cross-sectional interview survey of approximately 36,000 U.S. households. They showed the prevalence of family history for CRC increases with age. The prevalence of people with positive family history of CRC reaches the "steady state" value of 10% around age 60-69. In addition, the proportion with two or more first-degree relatives with history of CRC is roughly 7% of those reporting at least one relative with colorectal cancer.

Modeling approach

- Family history of colorectal cancer and endometrial and other LS cancers in non-carriers is generated from the Family History Model, as described in section 6.3.
- The Family History Model is validated against data on family history of CRC in the U.S. population reported by Ramsey *et al.*(89) (see section 6.3).

6.3 Family history in mutation carriers

Literature review

The $PREMM_{126}$ model (90) , which is an update of the $PREMM_{12}$ model (91), requires information on cancer history of first- and second-degree relatives. Therefore, to generate this information, we first constructed a family pedigree structure representative of U.S. families (9, 10), and then distributed mutations and cancers among these family pedigrees at prevalence and incidence rates previously described.

To address the sparsity of appropriate family history data for unaffected mutation carriers without prevalence bias from LS registries, we use Monte-Carlo simulation of families with Lynch syndrome, adapting techniques described elsewhere (92-94). The familial data produced by the simulation is used to create surrogate parameters which represent family history data of interest, and which provide input into the $PREMM_{126}$ model for risk-assessment.

Modeling approach

- All births are considered singleton (i.e. we neglect twins, triplets, etc.).

- For the generation of offspring, parental pairings are modeled as monogamous.
- We neglect the homozygous dominant MMR mutation case.
- The details of family structure can be captured by two parameters: the distribution of mother's age at birth as a function of birth number (Figure 6), and the distribution of the number of children per nuclear family (Figure 7). Mother's age at birth provides the inter-birth interval, and number of children provides the size of each generation.
- In addition to EC and CRC, we have also constructed models of incidence for other LS-associated cancers in first- and second-degree relatives. Information on these cancers is required for risk assessment using $PREMM_{126}$. The additional cancers include biliary cancer, brain cancer, gastric cancer, ovarian cancer, pancreatic cancer, sebaceous carcinoma, small bowel cancer, and urologic cancer. Table 10 summarizes the cancer model's data sources.
- Figure 8 describes the steps involved in generating first-degree and second-degree relatives for a proband. Each relative's birth, cancer incidence, and death are tracked relative to the proband's age.
- The model accounts for misattributed paternity and spontaneous mutation by not assigning mutation carrier status to 3% of parents of probands, based on an estimate from Le Roux (95).

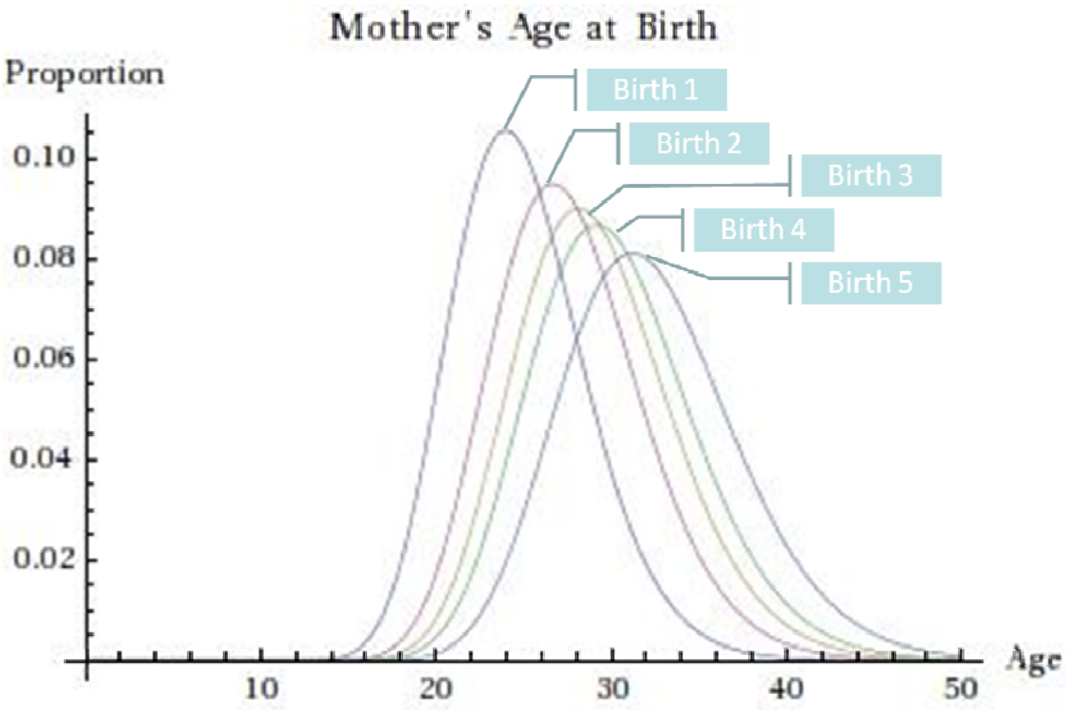

Figure 6: Distributions of mother's age at birth for each birth interval (Mathews *et al.*(9)).

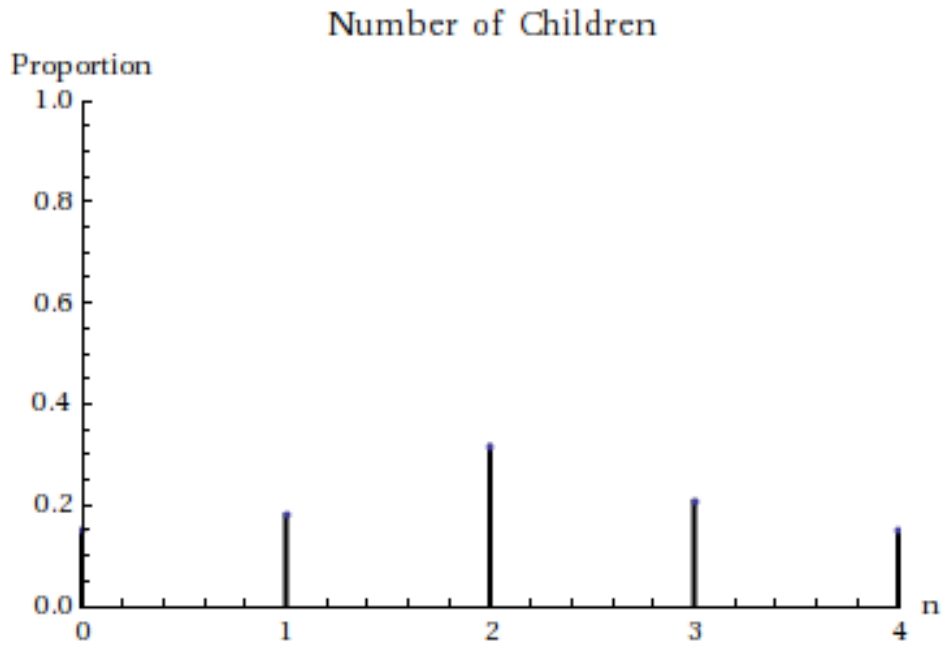

Figure 7: Distribution of number of children per nuclear family (Chandra *et al.*(10)).

Cancers	Population	Data Source
• Biliary Cancer • Brain Cancer • Gastric Cancer • Ovarian Cancer • Small Bowel Cancer • Urologic Cancer	Mutation carriers	Watson *et al.*(96)
	Non-carriers	SEER(8)
• Pancreatic Cancer	Mutation Carriers	Kastrinos *et al.*(97)
	Non-carriers	SEER(8)
• Sebaceous Carcinoma	Mutation Carriers	Ponti *et al.*(98)
	Non-carriers	Doris *et al.*(99)

Table 10: Family History Model's cancer data sources.

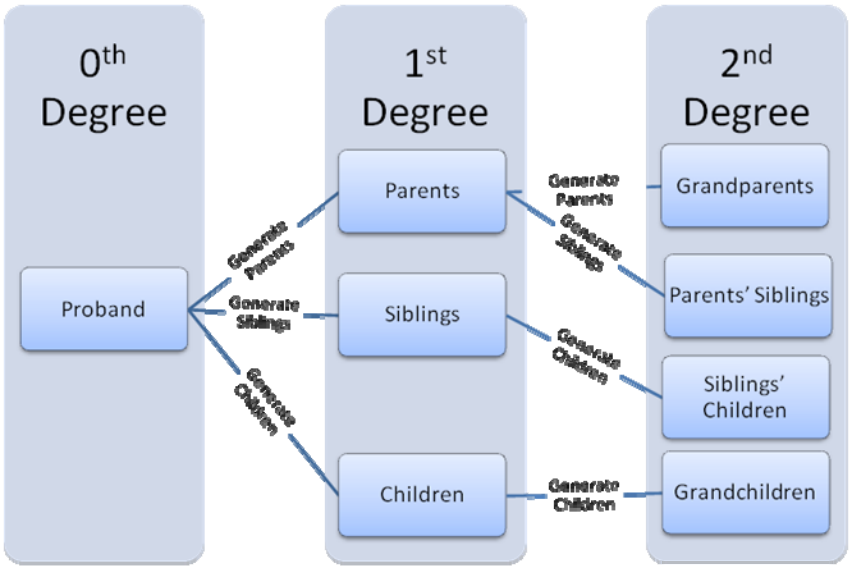

Figure 8: Generation of a proband's family out to second-degree relatives.

Validation

Validation of family history of CRC in general population

We validated the Family History Model against the data provided by Ramsey *et al.*(89). This study contains data on the prevalence of first-degree CRC family history as a function of proband age, as well as the distribution of the number of first-degree relatives affected among families with CRC history in the general population. We produced a set of general-population families via the Family History Model for comparison (see Figure and Figure 10).

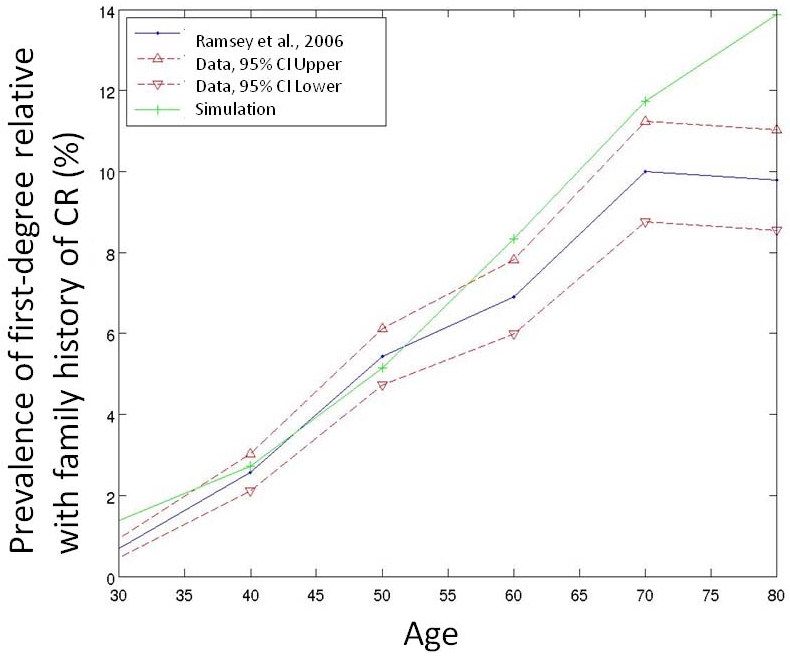

Figure 9: Prevalence of first-degree family history of CRC as a function of proband age. The figure compares predicted prevalence of first-degree family history of CRC in the general population (green line) against data reported by Ramsey *et al.*(89) The dashed lines with triangle symbols represent the 95% confidence interval of the data.

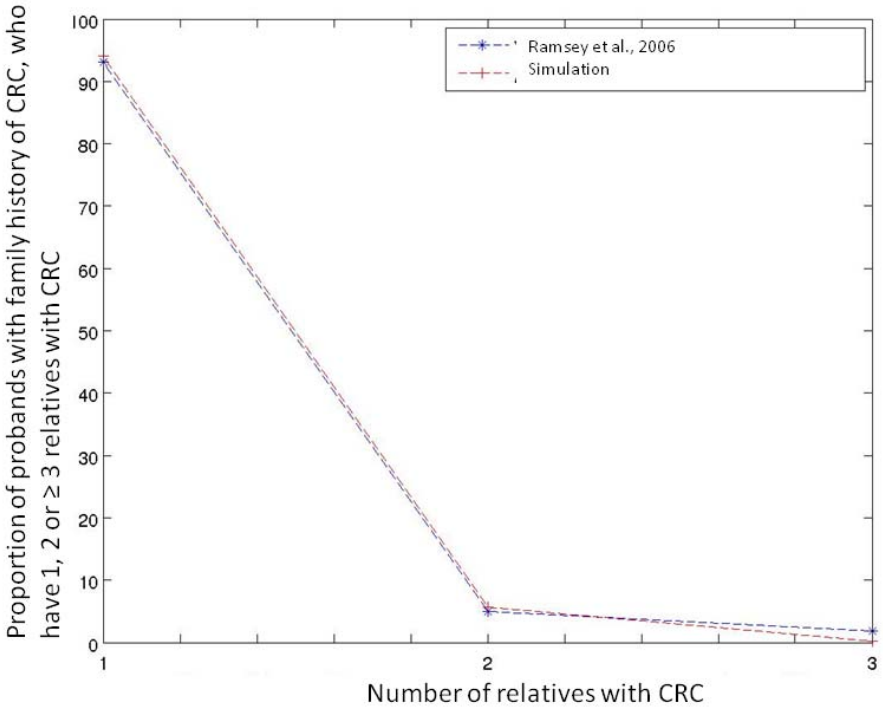

Figure 10: The distribution of the number of first-degree relatives affected among families with CRC history (Ramsey *et al.*(89)).

Validation of family history of CRC in carriers of MMR mutations

We used the the Dutch Lynch Syndrome-HNPCC Registry (i.e. the Leiden registry)(11) to validate the output of the Family History Model for carriers of MMR mutations. The registry was selected for its large sample size, rich family structure, and cancer incidence data. The purpose of the validation is to determine whether the Family History Model reproduces the outcomes of the Leiden registry, when the Family History Model's pedigree structure is set to match Leiden's. Specifically, we ensure that the family structure and cancer history of the Family History Model and Leiden registry match (Figures 12-16), and then compare the family history of CRC-related outcomes detailed above. Missing values from the registry were imputed using an algorithm adapted from van Asperen *et al.* (100), which has been previously used with the registry data. Validations of the Archimedes model of family history were ascertained by comparing to Leiden registry data on mother's age at the birth of each child, the number of children per nuclear family, cumulative incidence of CRC and EC, prevalence of first-degree family history of CRC, and proportion of probands as a function of the number of relatives with CRC, as shown in Figures 11-18.

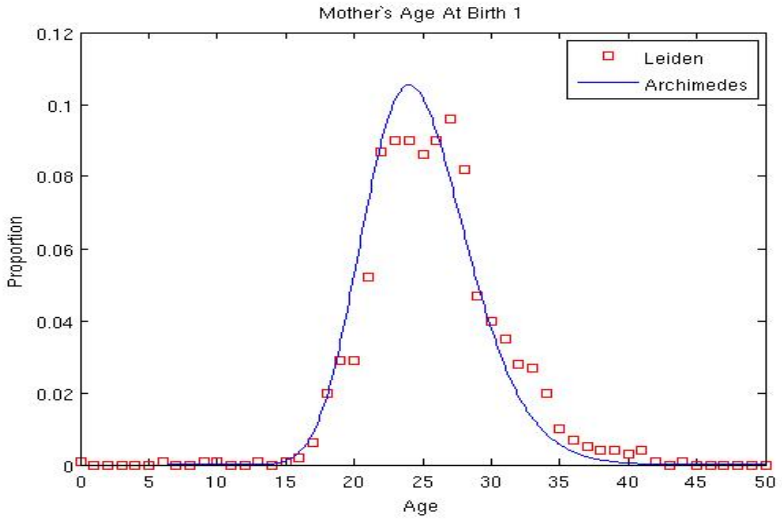

Figure 11: Calibration of the Archimedes Family History Model to the Leiden dataset for the distributions of mother's age at first birth.

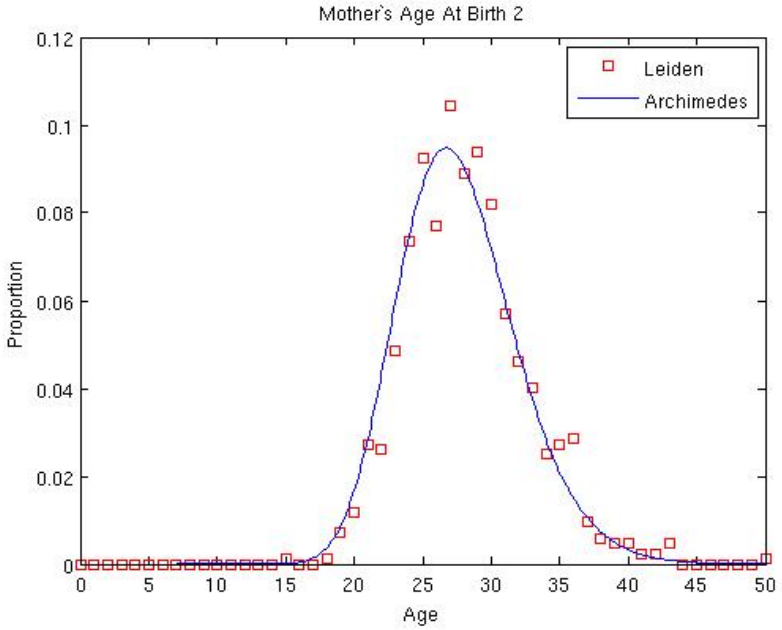

Figure 12: Calibration Archimedes Family History Model to Leiden data for the distributions of mother's age at second birth. (Comparisons of subsequent births omitted for brevity.)

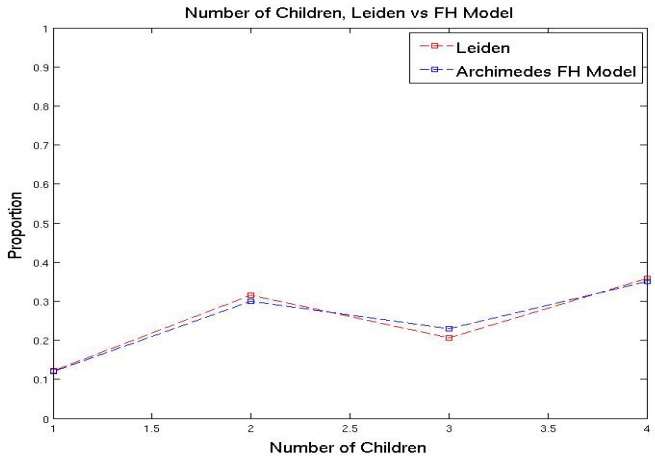

Figure 13: Calibration of and the Archimedes Family History Model to Leiden data for the distributions of number of children per nuclear family.

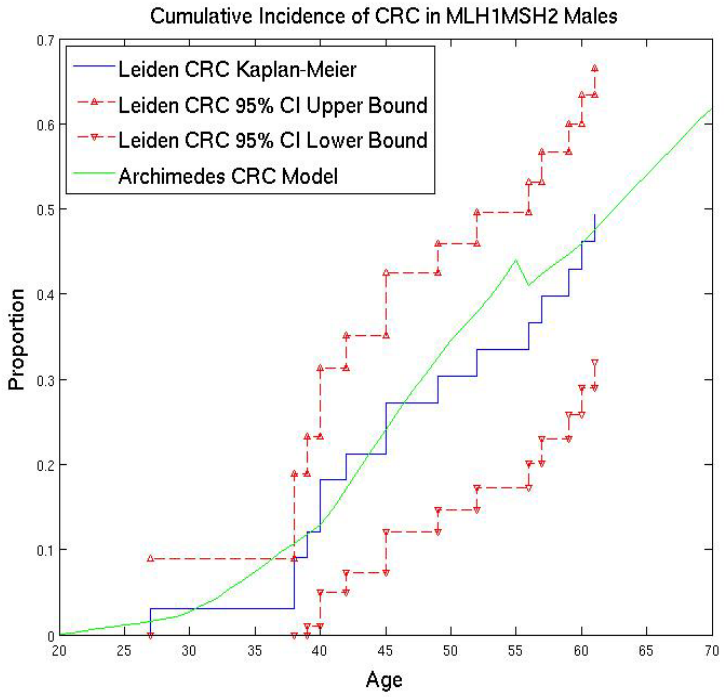

Figure 14: Comparison of Kaplan-Meier estimate of Leiden CRC cumulative incidence in confirmed *MLH1 / MSH2* carrier males with Archimedes CRC model for male *MLH1 / MSH2* mutation carriers.

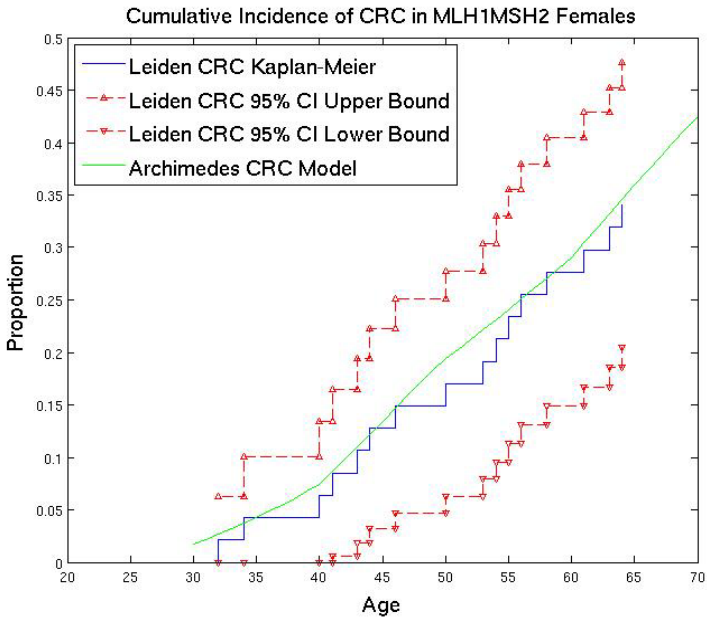

Figure 15: Comparison of Kaplan-Meier estimate of Leiden CRC cumulative incidence in confirmed *MLH1 / MSH2* carrier females with Archimedes CRC model for female *MLH1 / MSH2* mutation carriers.

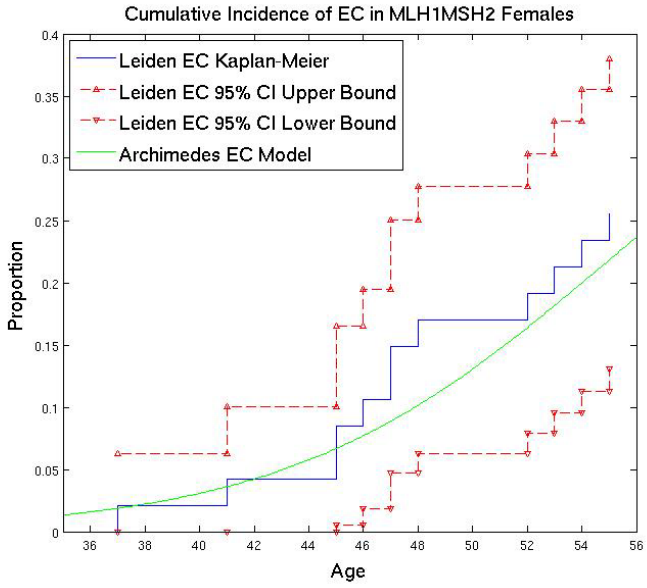

Figure 16: Comparison of Kaplan-Meier estimate of Leiden EC cumulative incidence in confirmed *MLH1 / MSH2* carrier females with Archimedes EC model for female *MLH1 / MSH2* mutation carriers.

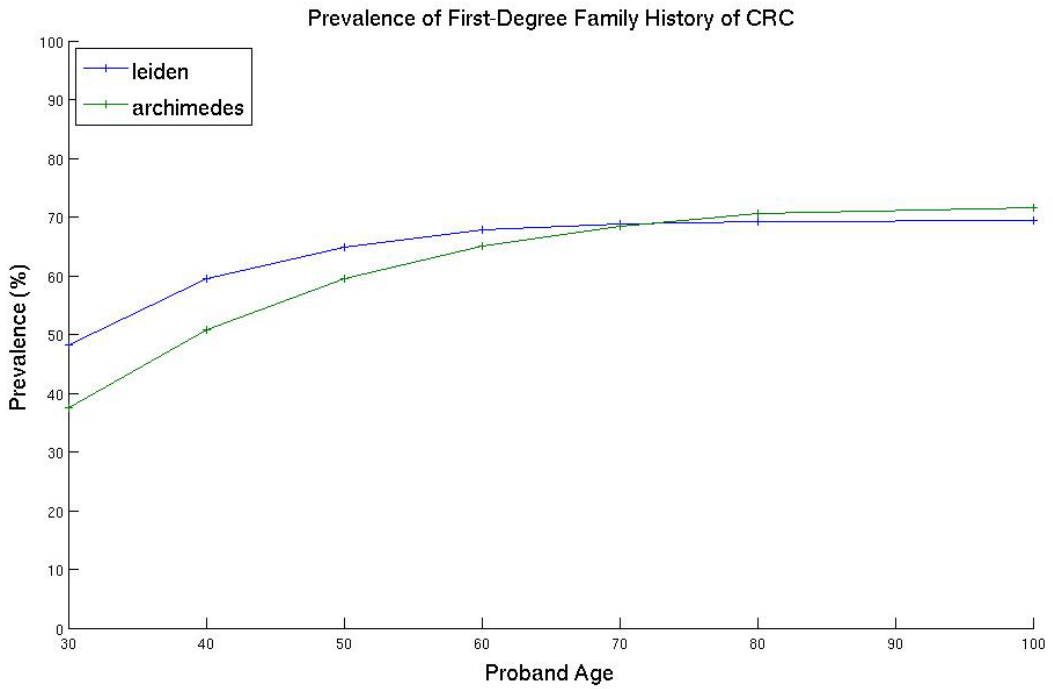

Figure 17: Leiden Validation: Proportion of probands with some family history of CRC as a function of proband age.

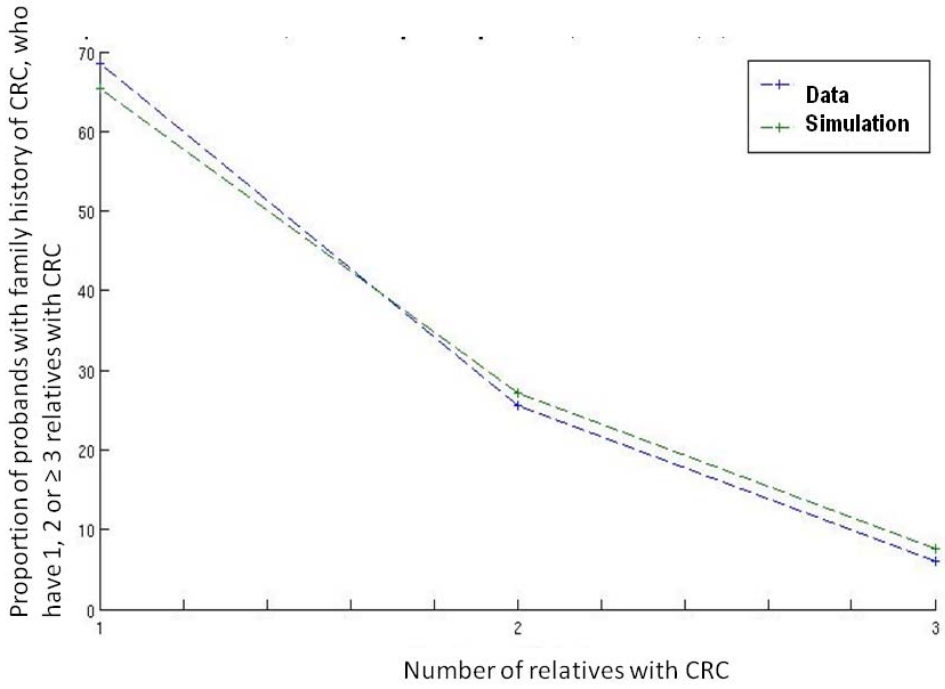

Figure 18: Leiden Validation: Distribution of number of affected first degree relatives among probands with some family history of CRC.

7. Study Design

We conducted a virtual clinical trial in which 100,000 simulated individuals, representative of the general U.S. population, were tracked from the age of 20, and were exposed to each of twenty primary screening strategies (Screening Strategy Arms). These strategies (Table 11), involved risk-assessment at different ages (20, 25, 30, 35, or 40) using $PREMM_{126}$, followed by four-gene mutation testing of those individuals whose risks for carrying a mutation exceeded a given threshold (0%, 2.5%, 5.0%, or 10%). A threshold of 0% was considered equivalent to universal screening in which all individuals received genetic testing without preceding risk assessments. The $PREMM_{126}$ model was chosen for risk assessment because it is well-validated and usable for individuals who have not necessarily developed malignancies.

Cloned cohorts were given current care (Current Practice Arm) in which testing was performed in individuals with appropriate clinical risk factors after a malignancy was detected (101).

In the Screening Strategy Arms, individuals with negative genetic test results were presumed not to carry a mutation, and received future screening for sporadic colorectal cancer according to NCCN Practice Guidelines (101). Individuals with positive genetic test results were thereafter screened annually with colonoscopy, and with endometrial biopsy and transvaginal ultrasound, or were given prophylactic TAHBSO.

In the Current Practice Arm, individuals with colorectal or endometrial cancer meeting certain clinical criteria (colorectal or endometrial cancer at age < 50, or ≥2 Lynch syndrome-associated cancers in the same proband, or a proband with ≥2 first or second-degree relatives with Lynch syndrome-associated cancers) were offered either testing by immunohistochemistry followed (when positive) by single-gene testing, or direct genetic testing for *MLH1, MSH2, and MSH6*, followed optionally by *PMS2*, at utilization rates reflective of current practice (Figure 19 and Grover *et al.*(102)). The effect of testing individuals at 100% physician adherence to current recommendations was studied through sensitivity analysis (see Figure 2 of manuscript).

In both the Screening Strategy Arms and the Current Practice Arm, individuals testing positive at the time of a malignancy were offered appropriate surgical and/or medical intervention and ongoing surveillance. In addition, single-site (mutation-specific) testing was performed on first-degree relatives of known mutation carriers at reported compliances (Table 12). As simulated individuals aged, their family histories of Lynch syndrome-associated cancers evolved naturally. In the simulation, people became aware of updates in cancer diagnoses among relatives at rates described in the literature, and sought physician reassessment of their own updated risks as appropriate (103, 104).

Screening Strategy	Screening start-age (yrs)	Risk threshold above which to implement 4-gene test (%)
#1	20	0.0
#2	25	0.0
#3	30	0.0
#4	35	0.0
#5	40	0.0
#6	20	2.5
#7	25	2.5
#8	30	2.5
#9	35	2.5
#10	40	2.5
#11	20	5.0
#12	25	5.0
#13	30	5.0
#14	35	5.0
#15	40	5.0
#16	20	10.0
#17	25	10.0
#18	30	10.0
#19	35	10.0
#20	40	10.0

Table 11: Experimental screening strategies.

7.1. Genetic Screening Arms

Individuals who fall above the risk threshold for genetic testing (See Figure) Individuals whose $PREMM_{126}$-calculated risk is above the risk threshold for genetic testing for a given screening strategy receive genetic testing for four MMR mutations, generating either a positive or negative result.

- Those receiving a negative result (true negative + false negative) from four-gene panel testing are presumed *not* to carry a mutation, and receive future screening according to NCCN Practice Guidelines(105) for sporadic colorectal cancer, consisting of colonoscopy starting at the age of 50 (age 40 for those with a first degree relative with a history of CRC), and recurring as follows:
    - Once every ten years for normal colonoscopy results (every five years for those with a first-degree relative with CRC)
    - Once every five years for low-risk adenoma findings
    - Once every three years for advanced or multiple adenoma findings (neglecting polyposis syndromes)

  These individuals continue to undergo screening for sporadic CRC. If or when a sporadic polyp or tumor is detected, these individuals receive treatment for CRC. Similarly, if or when a sporadic endometrial cancer is detected based on an individual becoming symptomatic (rather than screening), an aggregated treatment is modeled. Survival rates following these treatments are based on section 3.2.6 for CRC, section 4.2.2 for EC, and costs of treatment are given in Table 12.
  - For women whose genetic testing results indicate an MMR mutation, elective TAHBSO is modeled to occur according to age-dependent compliance rates previously described.
  - All unaffected, MMR positive individuals (men and women) undergo pre-disease surveillance at described compliance rates, consisting of annual colonoscopy, as per NCCN Practice Guidelines for HNPCC. Furthermore, women who have not had a hysterectomy undergo annual TVU and endometrial aspirate biopsy at compliance rates listed in Table 12 starting at age 30,.
  - A positive result following genetic testing for *MLH1, MSH2, MSH6* and *PMS2* mutations, as shown in Figure 19, triggers testing of one or more first-degree family members of the mutation-carrying proband. Testing of each first-degree relative is based on a random draw relative to each individual's probability of complying (see Section 5 of Table 12.).
  - Based on Ramsey *et al.(106)* and author expertise, compliance to genetic testing of first-degree relatives of MMR mutation-positive probands is set to 60% for siblings, 70% for children, and 60% for parents. Only one parent of a proband is tested. If positive, then only family members on that parent's side are eligible for testing (in the case of sensitivity analyses conducted involving testing of second-degree relatives). If negative, then the other parent is an obligate carrier (and is not tested), and only family members on that parent's side are eligible for testing. If a randomly selected first-degree relative is less than 18 years of age, she or he is given a genetic test at 18 years old, in accordance with generally accepted genetic testing practice for adult-onset genetic diseases.
  - 20% of known asymptomatic carriers diagnosed with advanced adenoma during annual colonoscopy screening receive total colectomy. The remaining 80% of individuals with advanced adenomas have them removed endoscopically. One hundred percent of adenomas graded lower than advanced are removed endoscopically.
  - If endometrial cancer is detected in a known MMR positive individual, then TAHBSO is implemented for endometrial tumors.

- Among individuals who have had a total proctocolectomy, 50% continue surveillance up to the anal verge, and 50% no longer participate in annual CRC surveillance.
- Compliance to surveillance of colorectal cancer and endometrial cancer is based on estimates provided in Table 12.
- Surveillance of colorectal cancer and endometrial cancer continue until a person dies.

Individuals who fall below the risk threshold for genetic testing (See Figure) Individuals in the current practice strategy who do not meet the $PREMM_{126}$-calculated risk threshold for genetic testing are subjected to CRC screening later in life according to NCCN guidelines for sporadic CRC. Any such patient who develops a CRC or EC tumor is considered an affected patient (as opposed to an unaffected patient for screening). Therefore, such patients who develop a tumor and who meet clinical criteria (See Figure , and Section 7.3 below for definition), AND who have not had a prior genetic test, will be subjected to the testing sequence (IHC/MSI and/or single gene/multi-gene test).
As simulated individuals age, they accumulate family and personal history of diseases. To capture the rates at which real people are re-evaluated by their physicians for personal and family history, we assume that a person will report changes in his or her personal and family histories for re-evaluation of $PREMM_{126}$ score, with a delay of one year and a compliance of 70%.

7.2. Current Practice Arm

Health care processes for the Current Practice Arm are designed to represent current U.S. practice patterns for LS (see Figure 19).

- Although the Amsterdam II and the Revised Bethesda criteria, as well as a number of risk engines, are described in the literature for screening purposes, clinical application of these tools is limited. Instead, common clinical practice when a person presents with a tumor is to suspect Lynch syndrome and consider testing when the proband presents with colorectal or endometrial cancer at age < 50, or the proband has ≥2 Lynch syndrome-associated cancers, or a proband has ≥2 first or second-degree relatives with Lynch syndrome-associated cancers.
- A person with a tumor who meets these clinical criteria is subjected to a testing sequence as diagrammed in Figure . Briefly, it is recognized that to capture current practice patterns, some percentage of patients (83%) see physicians who do not consider LS (Grover *et al.*(102)). These patients have their CRC treated, but are presumed to have sporadic CRC. Furthermore, some percentage of patients seen by the 17% of physicians who do consider LS (70%) are seen in non-institutional settings where it is more common to do genetic testing than IHC. Finally, because *PMS2* mutation testing is not widely adopted, 20% of patients with negative *MLH1, MSH2*, and *MSH6* test results receive a *PMS2* test. (These parameters were informed by C.R.B, R.W.B., S.B.G, and S.S., authors with clinical expertise in LS).

- Although BRAF testing for methylation in IHC negative individuals is an emerging test that might mitigate the need for *MLH1* sequence testing in individuals whose CRC tumor is sporadic in nature, its place in standard clinical practice has not yet been well established (30), and it is not modeled as standard of care in the Current Practice Arm.
- Individuals with positive results from IHC (true positive and false positive) subsequently have single-gene sequence testing. Patients undergoing IHC testing in the current practice group, by definition, have a tumor. Therefore, those with positive MMR mutation by genetic test, are given the diagnosis of Lynch syndrome (i.e. tumor plus confirmation by testing), and receive treatment as previously described. A woman with only a CRC tumor is offered an elective TAHBSO at the same time as colectomy with an age-dependent compliance to TAHBSO as previously described.
- Post surgery, patients have ongoing annual surveillance for Lynch syndrome consisting of annual colonoscopy (or proctoscopy if they have had total colectomy),(30) and TVU with endometrial aspirate (if they still have a uterus).
- Finally, patients entering the Current Practice Arm with a first tumor but who do not meet the clinical criteria that cause suspicion for Lynch syndrome are presumed to have sporadic CRC or EC. Some of these patients are true negatives for Lynch and some are false negatives for Lynch, yet all of them receive aggregated treatment for sporadic CRC consisting of surgery, chemotherapy, and radiation as is currently represented in the Archimedes Model. The true negatives have morbidity and mortality rates consistent with sporadic CRC, while the false negatives likely have recurrence of a tumor due to the nature of Lynch syndrome. Therefore, any recurrence of a tumor causes a patient to meet one of the clinical criteria of two or more tumors, and this prompts for genetic testing.

7.3. Cost-Effectiveness

Utility parameters for calculating quality-adjusted life-years (QALYs) are shown in Table 12. A societal perspective was used, with costs, benefits, and life-years discounted 3%, and with adherence to other recommendations of the Panel on Cost-Effectiveness in Health and Medicine (107). We defined the average cost-effectiveness ratio as cost per QALY saved of a given screening strategy relative to current practice, and calculated incremental cost-effectiveness ratio as cost per QALY saved of a given strategy relative to the nearest strategy on the efficient frontier (manuscript Figure 1a). We considered a strategy to be “cost-effective” if the cost per QALY was below the often-quoted benchmark of $50,000/QALY (108), although others have argued for higher thresholds (109).

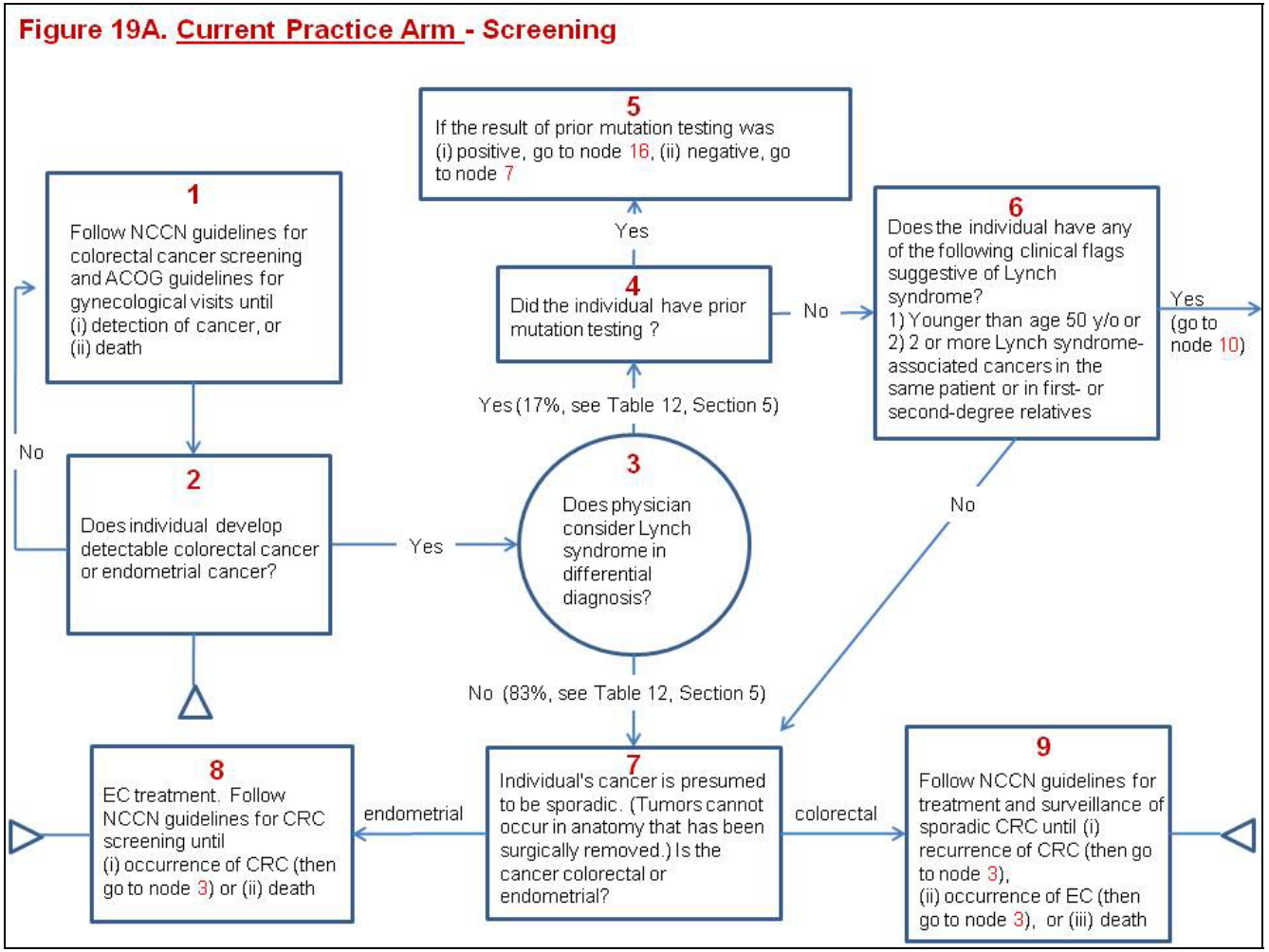

Figure 19. Flow chart of health care processes and sequences in Current Practice Arm (control group). Abbreviations: NCCN – National Comprehensive Cancer Network, ACOG – American College of Obstetricians and Gynecologists, CRC – colorectal cancer, EC – endometrial cancer, IHC – immunohistochemistry, MSI – microsatellite instability, MMR – mismatch repair, TAHBSO – total abdominal hysterectomy and bilateral salpingo-oophorectomy.

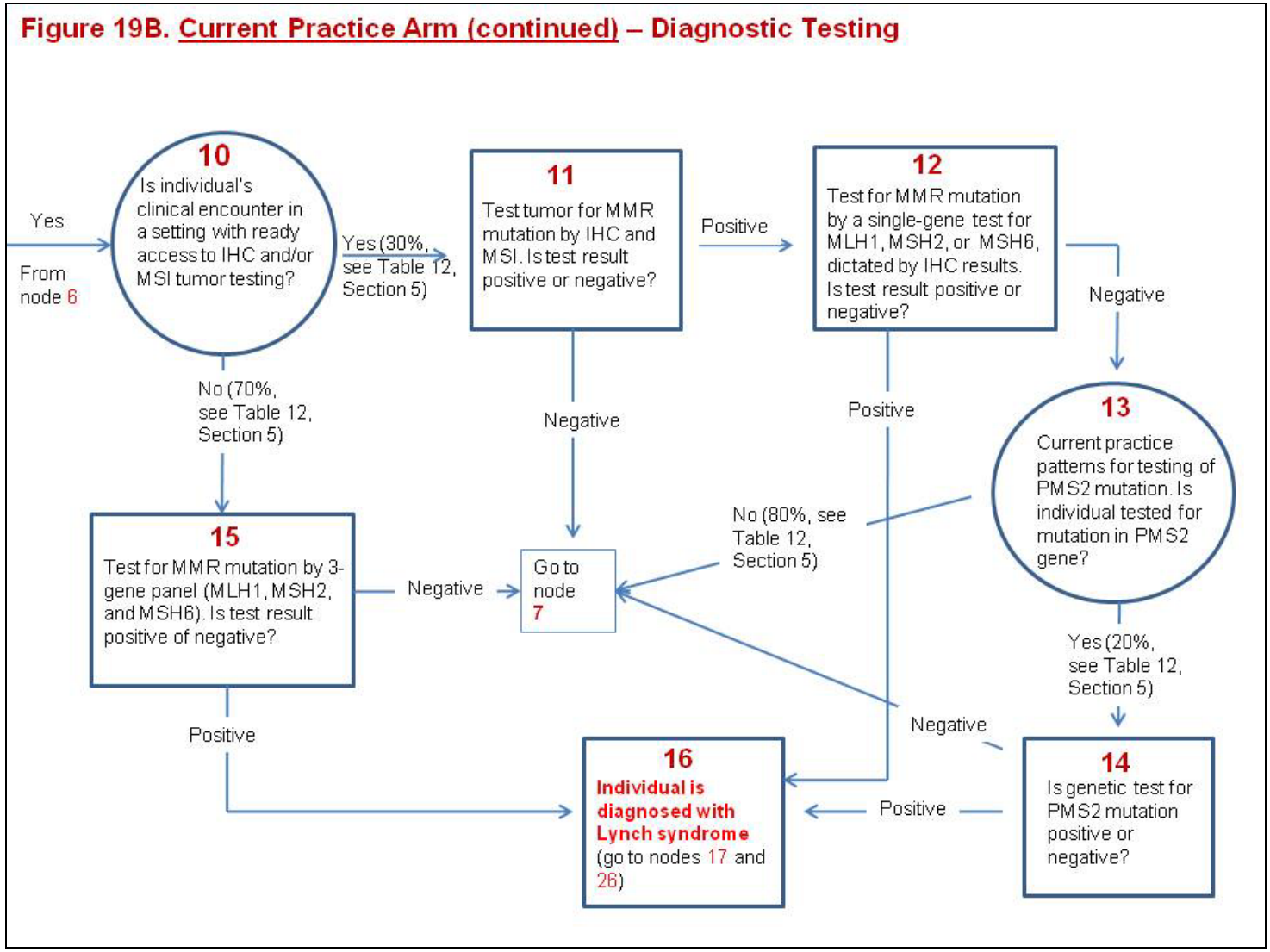

Figure 19. Flow chart of health care processes and sequences in Current Practice Arm (control group).

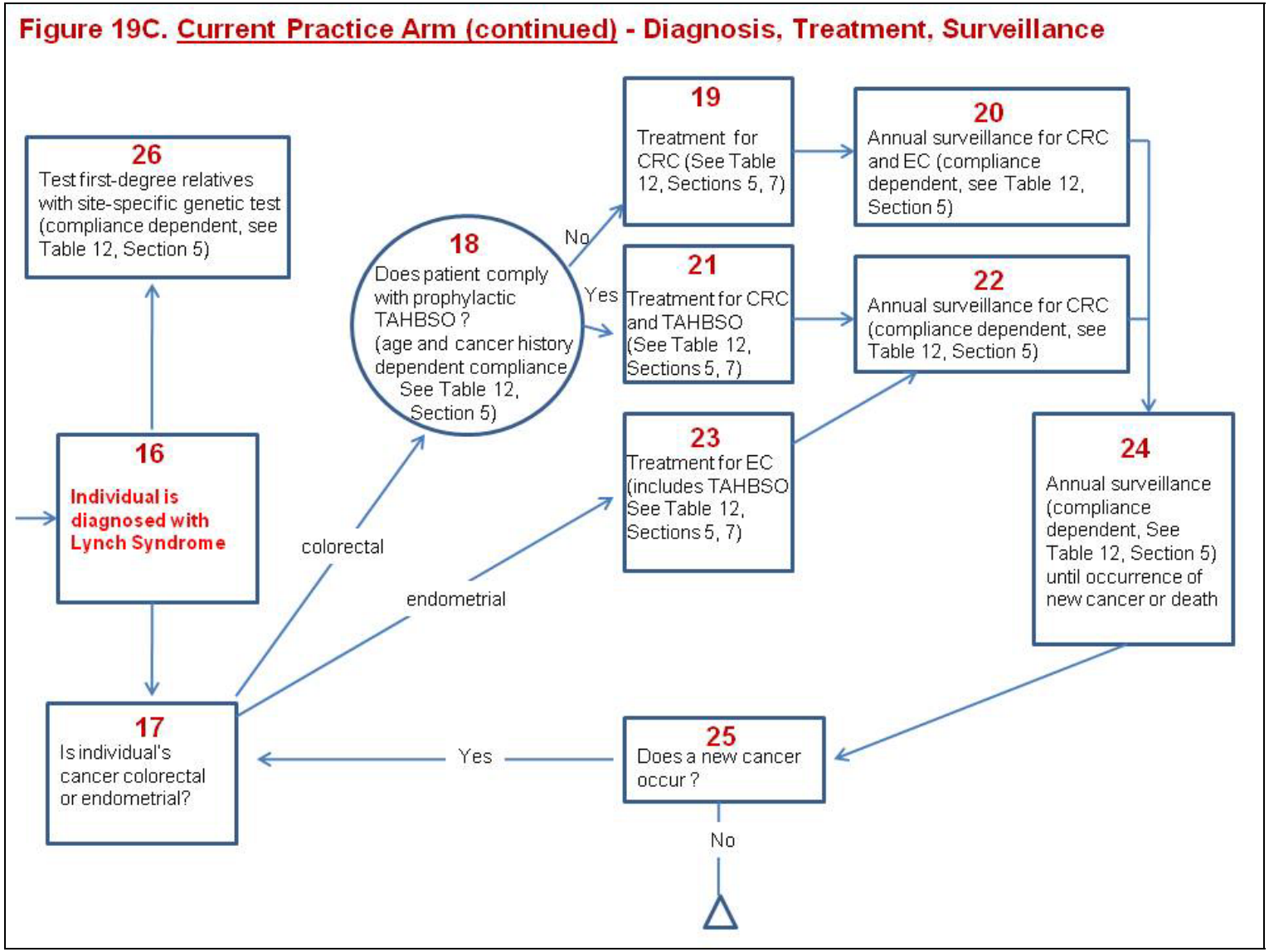

Figure 19. Flow chart of health care processes and sequences in Current Practice Arm (control group).

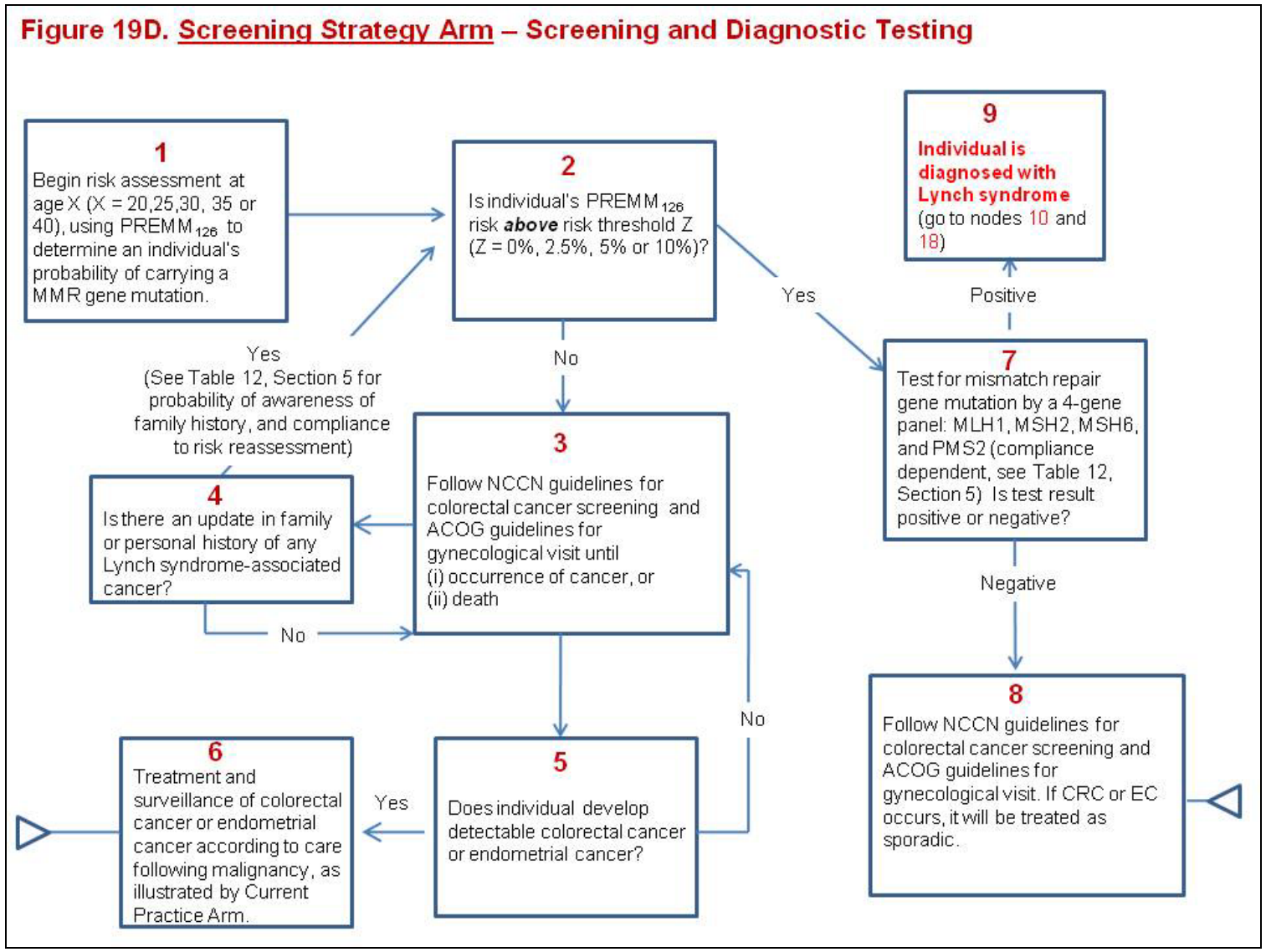

Figure 19. Flow chart of health care processes and sequences in the Screening Strategy Arm (experimental group).

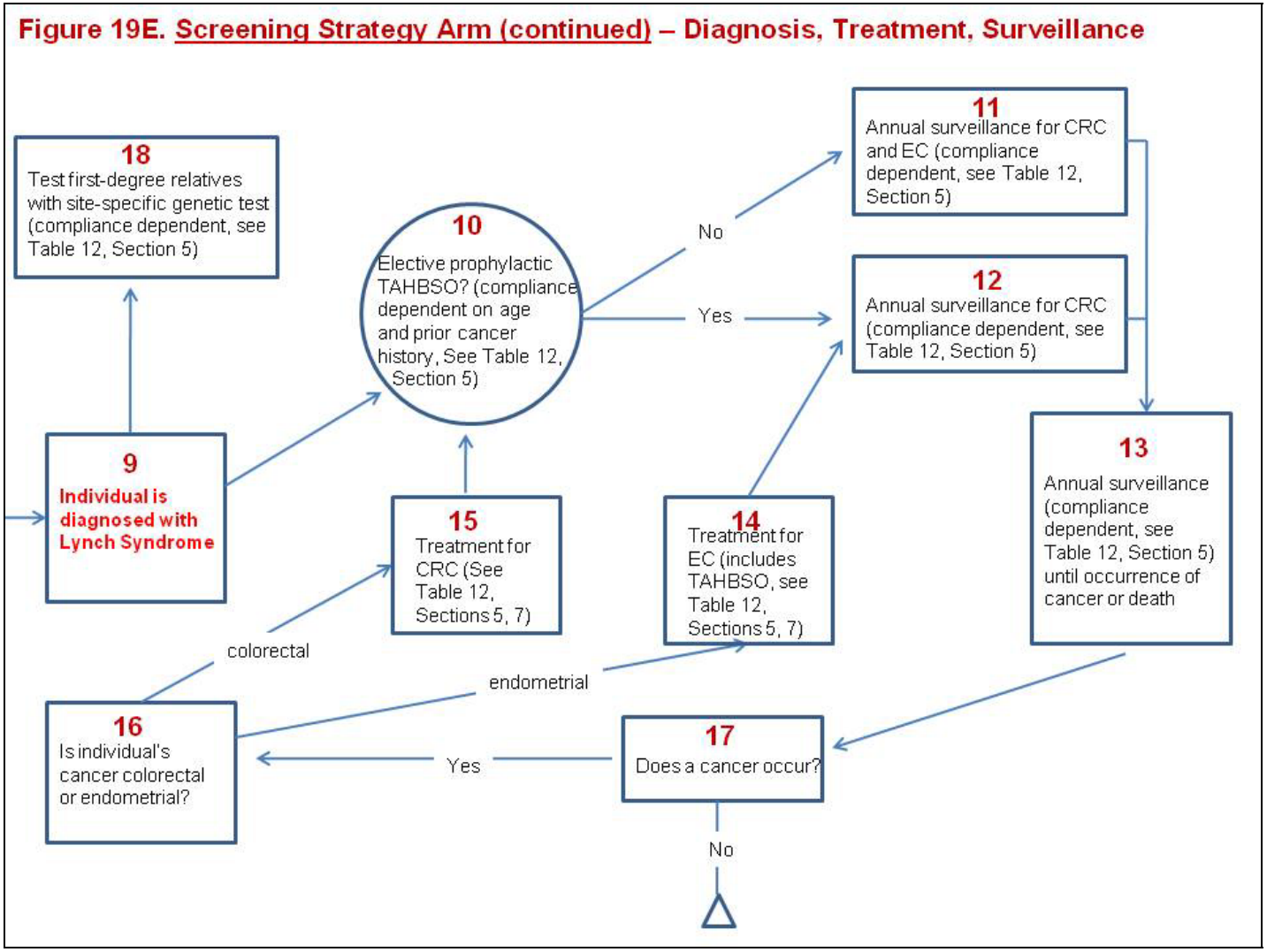

Figure 19. Flow chart of health care processes and sequences in the Screening Strategy Arm (experimental group).

8. Model Parameter Summary

Table 12. Key parameters, assumptions, modeling approaches, and sources.

Model Parameter	Assumptions and Approaches	List of Sources
Section 1: Colorectal Cancer Natural History in Lynch Syndrome		
Adenoma incidence, location, and growth	-Adenoma development was assumed to follow a non-homogenous Poisson distribution. -Adenoma growth was described by a log-linear growth equation. -Anatomical distribution of adenomas in mutation carriers were derived from an author-conducted meta-analysis.	Liljegren *et al.* (23) Mecklin *et al.* (21) Lindgren *et al.* (22) Rijcken *et al.*((26) de Jong *et al*.,(24) Pino *et al.*(27)
Cancer risk/malignant transformation	-Cancer risk as a function of age and gender in mutation carriers was derived from an author-conducted meta-analysis. -The malignant transformation rate of adenomas was a function of age, gender, and adenoma location.	Hendriks *et al.*(39), Buttin *et al.*,(33), Dunlop *et al.*,(40), Quehenberger *et al.*(29), Hampel *et al.*(41), Wagner *et al.*(42), Senter *et al.*(35), Barrow *et al.*(31) , Stoffel *et al.(*43)
Cancer location	-Cancer location was based on an author-conducted meta-analysis.	Mecklin *et al*.,(21) Lindgren *et al*.,(22) Aaltonen *et al*.,(45) de Vos Tot Nederveen Cappel *et al*.(46)
Survival	-Difference in colorectal cancer survival between non-carriers and carriers was characterized by a hazard ratio derived from an author-conducted meta-analysis.	SEER (8), Gryfe *et al*.,(51), Barnetson *et al*.,(50), Watson *et al*.,(48), Sankila *et al*.,(47), Aarnio *et al*.,(49), Barrow *et al*.(31)

Cancer recurrence	-Second primary colorectal cancers occurred as they arose from new adenomas after treatment of primary cancer.	Lin *et al.*(110), Mecklin and Jarvinen (53), Rodriguez-Bigas *et al*.(54)
Section 2: Endometrial Cancer Natural History in Lynch Syndrome		
Endometrial cancer incidence	-Risk of developing endometrial cancer in mutation carriers was based on an author-conducted meta-analysis.	Hampel *et al*.(111), Senter *et al*.(35) Buttin *et al*.(33), Hendriks *et al.*(39), Stoffel *et al.*(43), Dunlop *et al.*(40), Quehenberger *et al.*(29), Aarnio et al. (38), Jenkins et al. (32) Schmeler et al. (112)
Survival	-Survival was assumed to be the same for sporadic and Lynch-associated endometrial cancer and was derived from the SEER database.	SEER (8), Boks *et al*.(73)
Section 3: Prevalence		
Lynch syndrome prevalence among all colorectal cancer diagnoses (used to estimate mutation prevalence)	-Based on a conservative estimate of 2.2% from Hampel *et al.,*(41) and on author estimates of rates of Lynch syndrome in families with no defined mutation, this value was set to 3.0%, in concordance with Table 13 in Palomaki.(30)	Hampel *et al*.(41) Palomaki *et al.(30)*
Mutation type	- The distribution of different mutation types was taken to be: 32% *MLH1*, 39% *MSH2*, 14% *MSH6* and 15% *PMS2*.	Palomaki *et al*.(30)
Section 4: Tests and Procedures	**Values**	
Genetic test analytic sensitivity**	*MLH1*: 90% *MSH2*: 90%	Palomaki *et al*.(30) Senter *et*

	MSH6: 90% *PMS2*: 62%	*al*.(35)
Genetic test analytic specificity	*MLH1*: 99.97% *MSH2*: 99.97% *MSH6*: 99.97% *PMS2*: 99.97%	Palomaki *et al*.(30)
Immunohistochemistry analytic sensitivity, specificity	83%, 88.8%	Palomaki *et al*.(30)
Colonoscopy: sensitivity, specificity of adenoma detection	Adenoma size 0-5mm: sensitivity – 75%, specificity – 95% 5-10mm: sensitivity – 85%, specificity – 95% >10mm: sensitivity – 95%, specificity – 95%	Rex *et al*.(113) Loeve *et al.(66)*
Colonoscopy: segments screened	95% reach ascending colon, 70% reach cecum	Rex *et al*.(113) Loeve *et al.(66)*
Endometrial cancer surveillance	Endometrial aspirate biopsy: sensitivity – 91%, specificity – 98% Transvaginal ultrasound: limited detection in asymptomatic patients	Dijkhuizen *et al*.(114) Dove-Edwin *et al*.(77)
Section 5: Compliances and Practice Patterns		
Compliance to annual colonoscopy screening for known unaffected mutation carriers	81%	Palomaki *et al*.(30)
Compliance to annual endometrial biopsy for known unaffected mutation carriers	57%	Stoffel *et al*.(78) Wagner *et al*.(79) Collins *et al*.(80)
Compliance to genetic testing of first-degree relatives of mutation-positive probands	60% for siblings 70% for children 60% for parents (Only one parent of a proband was tested. If negative, then the other parent was considered an obligate carrier.)	Ramsey *et al*.(106)
Percent of patients with malignancy who are seen by a physician who considers Lynch	17%	Grover *et al*.(102)

syndrome and the clinical criteria for testing for Lynch syndrome		
Compliance to CRC screening in the general population and in unidentified unaffected mutation carriers	57%	Behavioral Risk Factor Surveillance System(115)
Minimum age for genetic testing of FDRs of probands who have tested positive for mutation	18 years old	Consensus C.R.B, R.W.B, S.B.G., S.S.
Compliance to prophylactic TAHBSO in unaffected mutation carriers	< 30 year old: 0% 40 years old: 40% 50 years old: 60% 80 years old: 75%	Consensus C.R.B, R.W.B, S.B.G., S.S.
Compliance to prophylactic TAHBSO in mutation carriers diagnosed with CRC, but not yet with EC	< 30 year old: 5% 40 years old: 60% 50 years old: 80% 80 years old: 90%	Consensus C.R.B, R.W.B, S.B.G., S.S.
Compliance to TAHBSO if diagnosed with EC	100%	Consensus C.R.B, R.W.B, S.B.G., S.S.
Percent of patients who were evaluated based on clinical criteria for LS risk that do not begin the testing process with IHC, but instead directly receive multi-gene testing	70%	Consensus C.R.B, R.W.B, S.B.G., S.S.
Percent of patients following positive IHC and a negative result for *MLH1, MSH2*, and *MSH6*, who subsequently get *PMS2* testing	20%	Consensus C.R.B, R.W.B, S.B.G., S.S.
Percent of known unaffected carriers diagnosed with advanced adenoma during annual colonoscopy screening who choose to have total colectomy	20% (Remaining 80% of advanced adenomas are removed endoscopically. One hundred percent of adenomas graded lower than advanced are removed endoscopically.)	Consensus C.R.B, R.W.B, S.B.G., S.S.

Current practice patterns: surgery following diagnosis of CRC in known carriers	90% total colectomy, 10% segmental resection	Consensus C.R.B, R.W.B, S.B.G., S.S.
Current practice patterns: surgery following diagnosis of CRC in which mutation status is not known (or not considered) at the time of surgery	10% total colectomy, 90% segmental resection	Consensus C.R.B., R.W.B, S.B.G., S.S.
Type of segmental resection surgery following a diagnosis of CRC as function of cancer location: **Proximal colon (cecum, ascending, and transverse)** **Descending colon** **Sigmoid colon** **Rectum**	 Right hemicolectomy with ileo-descending anastomosis Left hemicolectomy with transverse-sigmoid anastomosis Sigmoidectomy with colorectal anastomosis Proctosigmoidectomy (70%) or proctectomy with colostomy (30%)	Consensus C.R.B., R.W.B, S.B.G., S.S.
Compliance to annual colorectal surveillance by colonoscopy following surgery for sporadic CRC	50% for total proctocolectomy (rectal/anal surveillance), and 95% for other types of surgeries	Consensus C.R.B., R.W.B, S.B.G., S.S.
Standard gynecological visit for healthy women of unknown mutation carrier status	Age 20-30: annual exam with a compliance of 18.3% Age 30-65: gynecological visit every three years with a compliance of 83.3% Above age 65: no gynecological visit	Mehrotra *et al.* (116) American College of Obstetricians and Gynecologists Guideline (117)
Gynecological visit for known mutation carriers	Annually, with a compliance of 81%	Consensus opinion, based on compliance to annual colonoscopy among known

		mutation carriers
Probability of proband's awareness of family cancer history	First-degree relative: 84% Second-degree relative: 44%	Murff, *et al.* (118), Mitchell *et al*.(104)
Delay and compliance for reevaluation of the pre-test probability following updates in personal and family history	1 year and 70%	Consensus C.R.B, R.W.B, S.B.G., S.S.
Section 6: Surgical Mortalities		
Mortality associated with colonoscopy (occurring within 30 days after the procedure)	0.008%	Palomaki *et al*.(30)
Mortality associated with total colectomy with ileorectal anastomosis (occurring within 30 days after the procedure)	0.9%	Palomaki *et al*.(30)
Mortality associated with TAHBSO (occurring within 30 days after the procedure)	0.02%	Palomaki *et al*.(30)
Section 7: Costs		
Multiple gene testing for *MLH1, MSH2, MSH6,* and *PMS2*	$3,495	Calculated from a 2009 author survey of U.S. commercial genetic test providers. A similar approach was used by Mvundura et al. (119).
Multiple gene testing for *MLH1, MSH2, MSH6*	$2,618	Averaged from a 2009 author survey of U.S. commercial genetic test providers
Single gene testing for *MLH1*	$860	
Single gene testing for *MSH2*	$771	
Single gene testing for	$933	

MSH6		
Single gene testing for *PMS2*	$884	
Single-site testing	$298	
Immunohistochemistry	$281	2009 Medicare reimbursement rates
Microsatellite instability	$457	Palomaki *et al*.(30)
Biopsy/polypectomy	$160	2007 CMS reimbursement projected to 2009
Colonoscopy	$532	2007 CMS reimbursement projected to 2009
Total colectomy for mutation carriers with advanced adenomas (costs for colorectal surgery for those with carcinoma are accounted for in the cost of colorectal cancer treatment)	$22,800	2009 Medicare reimbursement rate
Transvaginal ultrasound	$110	Kwon *et al*.(75)
Endometrial biopsy	$201	Kwon *et al*.(75)
Gynecology visit	$154	Kwon *et al*.(75)
Prophylactic TAHBSO	$20,445	Kwon *et al*.(75)
Treatment of endometrial cancer	$24,291	Kwon *et al*.(75)
Treatment of colorectal cancer by stages and phases **Stage I, Initial/Continuing/Terminal** **Stage II, Initial/Continuing/Terminal** **Stage III, Initial/Continuing/Terminal** **Stage IV, Initial/Continuing/Terminal**	 $27,221/$2,166/$48,791 $37,563/$2,024/$48,662 $45,804/$2,883/$51,276 $59,812/$8,945/$68,809	1998-2003 Medicare reimbursement rate(120)
Section 8: Health Utility Parameters		

Colorectal cancer Stage I	0.74	Ness *et al*.(121)
Colorectal cancer Stage II	0.67	Ness *et al*.(121)
Colorectal cancer Stage III	0.50	Ness *et al*.(121)
Colorectal cancer Stage IV	0.25	Ness *et al*.(121)
Endometrial cancer	0.83	Kwon *et al*.(75)
MMR mutation detected in an unaffected (tumor-naïve) individual	1.0 (Based on two studies of quality of life in women following genetic testing for BRAC1/2. Both studies concluded that perceived quality of life after a positive genetic test result for BRCA1/2 returned to normal within 6-12 months.)	Beran *et al*.(122) Smith *et al*.(123)
Total colectomy with ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis for patients with advanced adenoma (Surgical disutility for those with colorectal cancer is accounted for in disutility due to colorectal cancer diagnosis)	0.84	van Duijvendijk *et al*.(124)
TAHBSO	0.86	Kwon *et al*.(75)
Proctocolectomy	0.83	Fazio *et al*.(125)
Colostomy	0.85	Boyd *et al*.(126)

References

1. Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. Lancet 2010; 375:1365-74.
2. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med 2005; 143:251-64.
3. Schlessinger L, Eddy DM. Archimedes: a new model for simulating health care systems--the mathematical formulation. J Biomed Inform 2002; 35:37-50.
4. Computer modeling of diabetes and its complications: a report on the Fourth Mount Hood Challenge Meeting. Diabetes Care 2007; 30:1638-46.
5. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000; 343:162-8.
6. Eddy DM, Schlessinger L. Validation of the archimedes diabetes model. Diabetes Care 2003; 26:3102-10.
7. Eddy DM, Schlessinger L. Archimedes: a trial-validated model of diabetes. Diabetes Care 2003; 26:3093-101.
8. Surveillance Epidemiology and End Results (SEER) Program Populations (1969-2006) (www.seer.cancer.gov/popdata) NCI, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released February 2009. .
9. Mathews TJ, Hamilton BE. Mean age of mother, 1970-2000. Natl Vital Stat Rep 2002; 51:1-13.
10. Chandra A, Martinez GM, Mosher WD, Abma JC, Jones J. Fertility, family planning, and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth. Vital Health Stat 23 2005:1-160.
11. The Dutch Lynch Syndrome-HNPCC Registry. Accessed December 28, 2009.
12. Tobi M. Polyps as biomarkers for colorectal neoplasia. Front Biosci 1999; 4:D329-38.
13. Rutter CM, Yu O, Miglioretti DL. A hierarchical non-homogenous Poisson model for meta-analysis of adenoma counts. Stat Med 2007; 26:98-109.
14. Radhakrishnan K, So EL, Silbert PL, et al. Prognostic implications of seizure recurrence in the first year after anterior temporal lobectomy. Epilepsia 2003; 44:77-80.
15. Bolin S, Nilsson E, Sjodahl R. Carcinoma of the colon and rectum--growth rate. Annals of Surgery 1983; 198:151-8.
16. Umetani N, Masaki T, Watanabe T, Sasaki S, Matsuda K, Muto T. Retrospective radiographic analysis of nonpedunculated colorectal carcinomas with special reference to tumor doubling time and morphological change. Am J Gastroenterol 2000; 95:1794-9.
17. Matsui T, Tsuda S, Yao K, Iwashita A, Sakurai T, Yao T. Natural history of early colorectal cancer: evolution of a growth curve. Dis Colon Rectum 2000; 43:S18-22.
18. Welin S, Youker J, Spratt JS, Jr. The Rates and Patterns of Growth of 375 Tumors of the Large Intestine and Rectum Observed Serially by Double Contrast Enema Study (Malmoe Technique). The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine 1963; 90:673-87.
19. Chao A, Connell CJ, Cokkinides V, Jacobs EJ, Calle EE, Thun MJ. Underuse of screening sigmoidoscopy and colonoscopy in a large cohort of US adults. Am J Public Health 2004; 94:1775-81.
20. Vasen HF. Review article: The Lynch syndrome (hereditary nonpolyposis colorectal cancer). Aliment Pharmacol Ther 2007; 26 Suppl 2:113-26.
21. Mecklin JP, Aarnio M, Laara E, et al. Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. Gastroenterology 2007; 133:1093-8.
22. Lindgren G, Liljegren A, Jaramillo E, Rubio C, Lindblom A. Adenoma prevalence and cancer risk in familial non-polyposis colorectal cancer. Gut 2002; 50:228-34.

23. Liljegren A, Barker G, Elliott F, et al. Prevalence of adenomas and hyperplastic polyps in mismatch repair mutation carriers among CAPP2 participants: report by the colorectal adenoma/carcinoma prevention programme 2. J Clin Oncol 2008; 26:3434-9.
24. de Jong AE, Morreau H, Van Puijenbroek M, et al. The role of mismatch repair gene defects in the development of adenomas in patients with HNPCC. Gastroenterology 2004; 126:42-8.
25. Burn J, Bishop DT, Mecklin JP, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. N Engl J Med 2008; 359:2567-78.
26. Rijcken FE, Hollema H, Kleibeuker JH. Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. Gut 2002; 50:382-6.
27. Pino MS, Mino-Kenudson M, Wildemore BM, et al. Deficient DNA mismatch repair is common in Lynch syndrome-associated colorectal adenomas. J Mol Diagn 2009; 11:238-47.
28. Wilson LS, Lightwood J. Model of estimated rates of colorectal cancer from polyp growth by year of surveillance. Journal of medical screening 2001; 8:187-96.
29. Quehenberger F, Vasen HF, van Houwelingen HC. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. J Med Genet 2005; 42:491-6.
30. 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; 11:42-65.
31. Barrow E, Alduaij W, Robinson L, et al. Colorectal cancer in HNPCC: cumulative lifetime incidence, survival and tumour distribution. A report of 121 families with proven mutations. Clin Genet 2008; 74:233-42.
32. Jenkins MA, Baglietto L, Dowty JG, et al. Cancer risks for mismatch repair gene mutation carriers: a population-based early onset case-family study. Clin Gastroenterol Hepatol 2006; 4:489-98.
33. Buttin BM, Powell MA, Mutch DG, et al. Penetrance and expressivity of MSH6 germline mutations in seven kindreds not ascertained by family history. Am J Hum Genet 2004; 74:1262-9.
34. Wagner A, Barrows A, Wijnen JT, et al. Molecular analysis of hereditary nonpolyposis colorectal cancer in the United States: high mutation detection rate among clinically selected families and characterization of an American founder genomic deletion of the MSH2 gene. Am J Hum Genet 2003; 72:1088-100.
35. Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008; 135:419-28.
36. Goecke T, Schulmann K, Engel C, et al. Genotype-phenotype comparison of German MLH1 and MSH2 mutation carriers clinically affected with Lynch syndrome: a report by the German HNPCC Consortium. J Clin Oncol 2006; 24:4285-92.
37. Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology 1996; 110:1020-7.
38. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999; 81:214-8.
39. Hendriks YM, Wagner A, Morreau H, et al. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterology 2004; 127:17-25.
40. Dunlop MG, Farrington SM, Carothers AD, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. Hum Mol Genet 1997; 6:105-10.
41. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005; 352:1851-60.
42. Wagner A, Hendriks Y, Meijers-Heijboer EJ, et al. Atypical HNPCC owing to MSH6 germline mutations: analysis of a large Dutch pedigree. J Med Genet 2001; 38:318-22.

43. Stoffel E, Mukherjee B, Raymond VM, et al. Calculation of Risk of Colorectal and Endometrial Cancer Among Patients with Lynch Syndrome. Gastroenterology 2009.
44. Ivanovich JL, Read TE, Ciske DJ, Kodner IJ, Whelan AJ. A practical approach to familial and hereditary colorectal cancer. Am J Med 1999; 107:68-77.
45. Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998; 338:1481-7.
46. de Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G, et al. Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. Dis Colon Rectum 2002; 45:1588-94.
47. Sankila R, Aaltonen LA, Jarvinen HJ, Mecklin JP. Better survival rates in patients with MLH1-associated hereditary colorectal cancer. Gastroenterology 1996; 110:682-7.
48. Watson P, Lin KM, Rodriguez-Bigas MA, et al. Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. Cancer 1998; 83:259-66.
49. Aarnio M, Mustonen H, Mecklin JP, Jarvinen HJ. Prognosis of colorectal cancer varies in different high-risk conditions. Ann Med 1998; 30:75-80.
50. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med 2006; 354:2751-63.
51. Gryfe R, Kim H, Hsieh ET, et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. N Engl J Med 2000; 342:69-77.
52. Lin KM, Shashidharan M, Ternent CA, et al. Colorectal and extracolonic cancer variations in MLH1/MSH2 hereditary nonpolyposis colorectal cancer kindreds and the general population. Dis Colon Rectum 1998; 41:428-33.
53. Mecklin JP, Jarvinen HJ. Clinical features of colorectal carcinoma in cancer family syndrome. Dis Colon Rectum 1986; 29:160-4.
54. Rodriguez-Bigas MA, Vasen HF, Pekka-Mecklin J, et al. Rectal cancer risk in hereditary nonpolyposis colorectal cancer after abdominal colectomy. International Collaborative Group on HNPCC. Ann Surg 1997; 225:202-7.
55. Consumer Price Index. 2009 [cited 2009 Dec. 1]; Available from: http://www.bls.gov/cpi/
56. Vasen HF, Moslein G, Alonso A, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 2007; 44:353-62.
57. Burt RW. Colon cancer screening. Gastroenterology 2000; 119:837-53.
58. Desch CE, McNiff KK, Schneider EC, et al. American Society of Clinical Oncology/National Comprehensive Cancer Network Quality Measures. J Clin Oncol 2008; 26:3631-7.
59. Giardiello FM, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. Gastroenterology 2001; 121:198-213.
60. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006; 296:1507-17.
61. Jarvinen HJ, Aarnio M. Surveillance on mutation carriers of DNA mismatch repair genes. Ann Chir Gynaecol 2000; 89:207-10.
62. de Jong AE, Hendriks YM, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology 2006; 130:665-71.
63. Pylvanainen K, Kairaluoma M, Mecklin JP. Compliance and Satisfaction with Long-Term Surveillance in Finnish HNPCC Families. Fam Cancer 2006; 5:175-8.
64. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997; 112:24-8.
65. Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res 1999; 32:13-33.
66. Loeve F, Brown ML, Boer R, van Ballegooijen M, van Oortmarssen GJ, Habbema JD. Endoscopic colorectal cancer screening: a cost-saving analysis. J Natl Cancer Inst 2000; 92:557-63.

67. Church J, Simmang C. Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer). Dis Colon Rectum 2003; 46:1001-12.
68. Guillem JG, Wood WC, Moley JF, et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. J Clin Oncol 2006; 24:4642-60.
69. Syngal S, Weeks JC, Schrag D, Garber JE, Kuntz KM. Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. Ann Intern Med 1998; 129:787-96.
70. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control 2009; 16:14-22.
71. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006; 354:261-9.
72. Vasen HF, Stormorken A, Menko FH, et al. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. J Clin Oncol 2001; 19:4074-80.
73. Boks DE, Trujillo AP, Voogd AC, Morreau H, Kenter GG, Vasen HF. Survival analysis of endometrial carcinoma associated with hereditary nonpolyposis colorectal cancer. Int J Cancer 2002; 102:198-200.
74. Renkonen-Sinisalo L, Butzow R, Leminen A, Lehtovirta P, Mecklin JP, Jarvinen HJ. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer 2007; 120:821-4.
75. Kwon JS, Sun CC, Peterson SK, et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. Cancer 2008; 113:326-35.
76. Rijcken FE, Mourits MJ, Kleibeuker JH, Hollema H, van der Zee AG. Gynecologic screening in hereditary nonpolyposis colorectal cancer. Gynecol Oncol 2003; 91:74-80.
77. Dove-Edwin I, Boks D, Goff S, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer 2002; 94:1708-12.
78. Stoffel EM, Garber JE, Grover S, Russo L, Johnson J, Syngal S. Cancer surveillance is often inadequate in people at high risk for colorectal cancer. J Med Genet 2003; 40:e54.
79. Wagner A, van Kessel I, Kriege MG, et al. Long term follow-up of HNPCC gene mutation carriers: compliance with screening and satisfaction with counseling and screening procedures. Fam Cancer 2005; 4:295-300.
80. Collins V, Meiser B, Gaff C, St John DJ, Halliday J. Screening and preventive behaviors one year after predictive genetic testing for hereditary nonpolyposis colorectal carcinoma. Cancer 2005; 104:273-81.
81. Dijkhuizen FP, De Vries LD, Mol BW, et al. Comparison of transvaginal ultrasonography and saline infusion sonography for the detection of intracavitary abnormalities in premenopausal women. Ultrasound Obstet Gynecol 2000; 15:372-6.
82. Offit K, Kauff ND. Reducing the risk of gynecologic cancer in the Lynch syndrome. N Engl J Med 2006; 354:293-5.
83. Chen LM, Yang KY, Little SE, Cheung MK, Caughey AB. Gynecologic cancer prevention in Lynch syndrome/hereditary nonpolyposis colorectal cancer families. Obstet Gynecol 2007; 110:18-25.
84. Shia J. Immunohistochemistry versus microsatellite instability testing for screening colorectal cancer patients at risk for hereditary nonpolyposis colorectal cancer syndrome. Part I. The utility of immunohistochemistry. J Mol Diagn 2008; 10:293-300.
85. Bonis PA, Trikalinos TA, Chung M, et al. Hereditary nonpolyposis colorectal cancer: diagnostic strategies and their implications. Evid Rep Technol Assess (Full Rep) 2007:1-180.

86. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA 2006; 296:1479-87.
87. de la Chapelle A. The incidence of Lynch syndrome. Fam Cancer 2005; 4:233-7.
88. Dunlop MG, Farrington SM, Nicholl I, et al. Population carrier frequency of hMSH2 and hMLH1 mutations. Br J Cancer 2000; 83:1643-5.
89. Ramsey SD, Yoon P, Moonesinghe R, Khoury MJ. Population-based study of the prevalence of family history of cancer: implications for cancer screening and prevention. Genet Med 2006; 8:571-5.
90. Kastrinos F, Steyerberg EW, Mercado R, et al. The PREMM 1,2,6 Model Predicts Risk of MLH1, MSH2, and MSH6 Germline Mutations Based on Cancer History. Gatroenterology 2010 (in press).
91. Balmana J, Stockwell DH, Steyerberg EW, et al. Prediction of MLH1 and MSH2 mutations in Lynch syndrome. JAMA 2006; 296:1469-78.
92. Sibert A, Goldgar DE. The effect of disease penetrance, family size, and age of onset on family history with application to setting eligibility criteria for genetic testing. Fam Cancer 2003; 2:35-42.
93. Bajdik CD, Raboud JM, Schechter MT, McGillivray BC, Gallagher RP. A computer model to simulate family history of breast/ovarian cancer in BRCA1 mutation carriers. Math Biosci 2001; 171:99-111.
94. Bajdik CD, Raboud JM, McGillivray BC, Schechter MT, Gallagher RP. Implications of the age range in a population-based BRCA1 testing program with eligibility based on family history of breast and ovarian cancer. Genet Test 2004; 8:229-34.
95. Le Roux MG, Pascal O, David A, Moisan JP. Non-paternity rate and screening in genetic disease analysis. Lancet 1993; 341:57.
96. Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 2008; 123:444-9.
97. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009; 302:1790-5.
98. Ponti G, Losi L, Di Gregorio C, et al. Identification of Muir-Torre syndrome among patients with sebaceous tumors and keratoacanthomas: role of clinical features, microsatellite instability, and immunohistochemistry. Cancer 2005; 103:1018-25.
99. Dores GM, Curtis RE, Toro JR, Devesa SS, Fraumeni JF, Jr. Incidence of cutaneous sebaceous carcinoma and risk of associated neoplasms: insight into Muir-Torre syndrome. Cancer 2008; 113:3372-81.
100. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005; 42:711-9.
101. Burt RW, Barthel JS, Dunn KB, et al. NCCN clinical practice guidelines in oncology. Colorectal cancer screening. J Natl Compr Canc Netw 2010; 8:8-61.
102. Grover S, Stoffel EM, Bussone L, Tschoegl E, Syngal S. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004; 2:813-9.
103. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA 2004; 292:1480-9.
104. Mitchell RJ, Brewster D, Campbell H, et al. Accuracy of reporting of family history of colorectal cancer. Gut 2004; 53:291-5.
105. NCCN. NCCN colorectal cancer screening practice guidelines. National Comprehensive Cancer Network. wwwnccnorg 2008.
106. Ramsey SD, Burke W, Clarke L. An economic viewpoint on alternative strategies for identifying persons with hereditary nonpolyposis colorectal cancer. Genet Med 2003; 5:353-63.
107. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996; 276:1339-41.

108. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. Med Decis Making 2000; 20:332-42.
109. Braithwaite RS, Meltzer DO, King JT, Jr., Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care 2008; 46:349-56.
110. Lin KM, Shashidharan M, Thorson AG, et al. Cumulative incidence of colorectal and extracolonic cancers in MLH1 and MSH2 mutation carriers of hereditary nonpolyposis colorectal cancer. J Gastrointest Surg 1998; 2:67-71.
111. Hampel H, Stephens JA, Pukkala E, et al. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. Gastroenterology 2005; 129:415-21.
112. Schmeler KM, Lu KH. Gynecologic cancers associated with Lynch syndrome/HNPCC. Clin Transl Oncol 2008; 10:313-7.
113. Rex DK. Colonoscopy: a review of its yield for cancers and adenomas by indication. Am J Gastroenterol 1995; 90:353-65.
114. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer 2000; 89:1765-72.
115. Behavioral counseling to prevent sexually transmitted infections: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008; 149:491-6, W95.
116. Mehrotra A, Zaslavsky AM, Ayanian JZ. Preventive health examinations and preventive gynecological examinations in the United States. Arch Intern Med 2007; 167:1876-83.
117. ACOG Practice Bulletin no. 109: Cervical cytology screening. Obstet Gynecol 2009; 114:1409-20.
118. Murff HJ, Byrne D, Syngal S. Cancer risk assessment: quality and impact of the family history interview. Am J Prev Med 2004; 27:239-45.
119. 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; 12:93-104.
120. Zauber AG, Lansdorp-Vogelaar I., Wilschut J., Knudsen, A.B., van Ballegooijen M., Kuntz, K.M. Cost-effectiveness of DNA stool testing to screen for colorectal cancer: Report to AHRQ and CMS from the Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN and SimCRC Models. 2007.
121. Ness RM, Holmes AM, Klein R, Dittus R. Utility valuations for outcome states of colorectal cancer. Am J Gastroenterol 1999; 94:1650-7.
122. Beran TM, Stanton AL, Kwan L, et al. The trajectory of psychological impact in BRCA1/2 genetic testing: does time heal? Ann Behav Med 2008; 36:107-16.
123. Smith AW, Dougall AL, Posluszny DM, Somers TJ, Rubinstein WS, Baum A. Psychological distress and quality of life associated with genetic testing for breast cancer risk. Psychooncology 2008; 17:767-73.
124. Van Duijvendijk P, Slors JF, Taat CW, et al. Quality of life after total colectomy with ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg 2000; 87:590-6.
125. Fazio VW, O'Riordain MG, Lavery IC, et al. Long-term functional outcome and quality of life after stapled restorative proctocolectomy. Ann Surg 1999; 230:575-84; discussion 84-6.
126. Boyd NF, Sutherland HJ, Heasman KZ, Tritchler DL, Cummings BJ. Whose utilities for decision analysis? Med Decis Making 1990; 10:58-67.