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ORIGINAL REPORT

Testing Women With Endometrial Cancer to Detect Lynch Syndrome

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A B S T R A C T

Purpose
Women with endometrial cancer as a result of Lynch syndrome may not be identified as such by Amsterdam II criteria. We estimated the costs and benefits of different testing criteria to identify Lynch syndrome in women with endometrial cancer.

Methods
We developed a Markov Monte Carlo simulation model to compare six criteria for Lynch syndrome testing for women with endometrial cancer: Amsterdam II criteria; age younger than 50 years with at least one first-degree relative having a Lynch-associated cancer at any age (FDR); immunohistochemistry (IHC) triage if age younger than 50 years; IHC triage if age younger than 60 years; IHC triage at any age if 1 FDR; and IHC triage of all endometrial cancers. Net health benefit was life expectancy, and primary outcome was the incremental cost-effectiveness ratio (ICER). The model estimated the number of new colorectal cancers associated with each strategy.

Results
IHC triage of women with endometrial cancer having at least 1 FDR yielded a favorable ICER of $9,126 per year of life gained. This strategy would subject fewer cases to IHC but identify more mutation carriers than age thresholds of 50 or 60 years. IHC triage of all endometrial cancers could identify the most mutation carriers and prevent the most colorectal cancers but at considerable cost ($648,494 per year of life gained).

Conclusion
IHC triage of women with endometrial cancer at any age having at least 1 FDR with a Lynch-associated cancer is a cost-effective strategy for detecting Lynch syndrome.

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INTRODUCTION

The lifetime risk of endometrial cancer among women with Lynch syndrome may be as high as 60%, and this risk may be greater than their lifetime risk of colorectal cancer.[1] Endometrial cancer may be the sentinel cancer among women with Lynch syndrome, being diagnosed at an earlier age than colorectal cancer.[2] Therefore, women with endometrial cancer represent an important subgroup for Lynch syndrome testing, because if a mutation is identified, they can undergo risk-reducing interventions for colorectal cancer, which may prolong their overall life expectancy.[3,4] Furthermore, their family members can be tested for known mutations and have the opportunity to undergo risk-reducing interventions for both gynecologic and colorectal cancers.

Testing all women with endometrial cancer for Lynch syndrome has the potential to identify a significant number of mutation carriers, but this would incur substantial cost to the health care system, as endometrial cancer is the most common gynecologic cancer in North America and the fourth most common cancer among all women.[5,6] In general, genetic testing for Lynch syndrome is encouraged in women with endometrial cancer if their family history fulfills Amsterdam II criteria.[7-9] This guideline implies that they must have at least two other relatives with a Lynch syndrome-associated cancer (for a total of three affected individuals), within two successive generations, and one of them must have been diagnosed younger than the age of 50 years.[10] However, not all women with Lynch syndrome will fulfill these criteria.[11-16] Recognizing that a significant proportion of women with Lynch syndrome are diagnosed with endometrial cancer under the age of 50 and many of them will have at least one first-degree relative with a Lynch-associated cancer, it may be reasonable to include this specific subgroup of women when offering genetic services for Lynch syndrome.[17-20] A more inclusive option is to test all

Table 1. Lynch Syndrome Prevalence by Testing Strategy

Testing Strategy	Proportion of All Endometrial Cancer Patients		Prevalence of Lynch Syndrome	
	%	Range	%	Range
Amsterdam II criteria	1[18,37]	0-2.3	30[18,37]	21-39
Endometrial cancer younger than 50 years with at least 1 FDR	4*[17,19,20]	2.2-5.3	35[17,19,20]	23-43
Endometrial cancer younger than 50 years	14[28]	12-20	9[17-20]	4.9-18
Endometrial cancer younger than 60 years	36.5[28]	30-45	4[18,37]	0.2-8
Endometrial cancer at any age with at least 1 FDR	12[38]	10-15	17[38]	15-20
All endometrial cancers, any age	100		2[17,18,38,39]	1-3

Abbreviation: FDR, first-degree relative with a Lynch-associated cancer at any age.
*Approximately 16% to 38% of all women with endometrial cancer younger than 50 years have at least one FDR, and 14% of all endometrial cancers are diagnosed at younger than 50 years.

women with endometrial cancer younger than the age of 50 or 60 years, regardless of family history, beginning with immunohistochemistry (IHC) triage, then referring those with abnormal results for genetic testing. In the absence of a direct comparison of these different testing criteria, we developed a cost-effectiveness analysis to compare the benefits and costs of each testing strategy.

METHODS

We developed a Markov Monte Carlo simulation model to estimate the costs and benefits of Lynch syndrome testing for a hypothetical cohort of women diagnosed with endometrial cancer in the general population. We compared six criteria for Lynch syndrome testing by determining the incremental cost-effectiveness ratio (ICER), defined as the additional cost of a specific strategy divided by its health benefit compared with an alternate strategy. The numerator of the ICER was the average lifetime cost in United States dollars (USD) in the year 2010, and the denominator was the average life expectancy gain in years. A strategy that was less effective (lower life expectancy gain) and more costly than an alternate strategy was considered strongly dominated. A strategy that was more costly but more effective than an alternate strategy was considered cost-effective if its ICER was below $50,000 per year of life gained, a commonly used willingness-to-pay threshold for cost-effectiveness analyses evaluating preventive health measures.[21] In keeping with recommendations of the US Panel on Cost-Effectiveness in Health and Medicine, we adopted a societal perspective and discounted all costs and health benefits at a rate of 3% per year.[22]

In the model, we assumed that women with endometrial cancer were still at risk for colorectal cancer. They were comparable across testing strategies with respect to demographics, stage, and histologic type of endometrial cancer, and risk factors for colorectal cancer. For those who were directly referred for genetic counseling and testing, four mismatch repair genes would be sequenced (*MLH1, MSH2, MSH6, PMS2*). For those who underwent IHC triage, this would be performed on formalin-fixed, paraffin-embedded sections from hysterectomy specimens, and abnormal IHC results would prompt referral for genetic counseling and relevant DNA sequencing. For those who were confirmed mutation carriers, we assumed that they would undergo annual colonoscopy, as recommended by several consensus guidelines.[8,9,23-25] For those who were confirmed noncarriers, approximately 50% would have at least one colonoscopy over the next 10 years, as expected in the US population.[26,27] Risks of colorectal cancer and associated mortality rates were governed by mutation status and the presence or absence of screening, which were estimated from published literature. The proportion of all endometrial cancer cases diagnosed at younger than age 50 and 60 years were estimated from the Surveillance, Epidemiology, and End Results database of 12 geographic regions in the United States from 1988 to 2001.[28] Health care costs were also estimated from a number of sources, including published literature on genetic counseling, IHC for mismatch repair proteins, gene sequencing, colonoscopy, and colorectal cancer treatment costs.[29-36] Selected data are presented in Tables 1, 2 through 3.[37-48]

Women with endometrial cancer comprise a hypothetical cohort residing in one of five Markov health states: well; at risk for colorectal cancer, colorectal cancer, unscreened; colorectal cancer, screened; dead. All of them begin in the at-risk for colorectal cancer health state. If they are diagnosed with colorectal cancer, they transition to the colorectal cancer state, depending on whether or not they underwent screening. In this health state, they may die of colorectal cancer or age-dependent mortalities according to United States life tables.[49] If they are alive at the end of a 1-year cycle, they remain in that health state and are subject to cancer-related and competing mortalities. If they are alive 10 years after their colorectal cancer diagnosis, they transition to the well state where they are still subject to age-dependent mortality risks. The process continues in yearly cycles until all women in the cohort reach the dead state, because of cancer or other causes.

The model was programmed using TreeAge Pro 2009 (TreeAge Software, Williamstown, MA). Six criteria (ie, strategies) for Lynch syndrome testing were defined for women with endometrial cancer in the general population, including two criteria for direct referral for genetic counseling and testing, and four criteria for IHC triage of endometrial cancers, followed by referral for genetic counseling and testing if the IHC results were abnormal. Direct referral for genetic counseling and testing would be offered to women with endometrial cancer who fulfilled: Amsterdam II criteria; or diagnosis younger than age 50 with at least one first-degree relative having a Lynch syndrome-associated cancer at any age (1 FDR). IHC triage would be offered

Table 2. Probability Estimates

Subgroup	Lifetime Risk of CRC		5-Year Mortality From CRC	
	%	Range	%	Range
Lynch syndrome, screened[3,4,40,41,42]	15	10-20	6	3-10
Lynch syndrome, unscreened[41,43]	40	30-50	47	35-60
Sporadic, screened[44-46]	3	2-4	15	10-20
Sporadic, unscreened[47]	5	4-6	37	20-50
Test Characteristic	**Sensitivity**		**Specificity**	
	%	Range	%	Range
Amsterdam II criteria[11-16,48]	62	41-78	62	45-78
Immunohistochemistry[17-19]	92	80-100	70	60-83

Abbreviations: CRC, colorectal cancer; Lynch syndrome, screened, women with endometrial cancer and Lynch syndrome who undergo annual colonoscopy; Sporadic, screened, women with sporadic endometrial cancer who have at least one colonoscopy over the next 10 years.

Table 3. Cost Estimates

Item	CPT Code	Estimated Cost in US$	Range
Immunohistochemistry triage for four mismatch repair genes[30,34]	88342	540	400-700
Genetic counseling, initial consult[30]	96040	83	41-164
Genetic counseling, follow-up[30]	96040	41	20-83
Physician counseling for genetic testing and screening[30]	99203	100	40-200
DNA sequencing of each gene[31,35]	83890	1,200	600-1,800
Colonoscopy[29]	45378, HCPSC level II code G0105	950	382-979
Average total lifetime cost of colorectal cancer treatment[29,33,36]		35,000	30,000-40,000

Abbreviations: CPT, Common Procedural Terminology (American Medical Association); HCPCS, Healthcare Common Procedure Coding System (Medicare).

to women diagnosed with endometrial cancer who fulfilled one of the following: age younger than 50 years; age younger than 60 years; any age if 1 FDR; or any age, regardless of family history.

We performed one-way and two-way sensitivity analyses to account for uncertainty around various parameters, including the probability of identifying Lynch syndrome according to specific testing criteria, risks of colorectal cancer, mortality rates, compliance with colorectal cancer screening, and costs. We conducted a Monte Carlo simulation using tracker variables within a Markov model to estimate the number of women who would be identified as having Lynch syndrome, and the subsequent number of colorectal cancer cases expected with each testing strategy.

RESULTS

The average discounted costs, life expectancy, and incremental cost-effectiveness ratios (ICERs) are provided in Table 4. Life expectancy was highest with the most inclusive testing strategy (IHC triage of all women with endometrial cancer). However, the ICER associated with this strategy was unfavorable ($648,494 per year of life gained). Testing by Amsterdam II criteria, IHC triage younger than age 50, and IHC triage younger than age 60 were all strongly dominated by IHC triage at any age if there was at least 1 FDR. The latter strategy had an ICER of $9,126 per year of life gained relative to the least costly testing strategy (genetic testing for all women younger than age 50 with at least 1 FDR). Therefore, we would consider IHC triage of all women with endometrial cancer having at least 1 FDR with a Lynch-associated cancer at any age to be a cost-effective testing strategy for detecting Lynch syndrome.

Our results were stable within a wide range of plausible costs and probability estimates. Even when compliance with genetic testing and colorectal cancer surveillance was estimated to be as low as 50%, the ICERs remained fairly stable. The sensitivity and specificity of Amsterdam II criteria both had to exceed 95% before this became a cost-effective testing strategy. If the sensitivity of IHC was lower than 70%, then IHC triage would no longer be cost-effective, and genetic testing for all women younger than age 50 with 1 FDR (without IHC triage) would be the most favorable testing strategy.

In the United States there will be approximately 45,000 women diagnosed with endometrial cancer in the year 2010.[50] Our model predicts that 827 women (1.84%) would be identified as having Lynch syndrome if we triaged all of these cases with IHC. By applying IHC triage to those with endometrial cancer and at least 1 FDR, 755 carriers (1.68%) would be identified. If we applied Amsterdam II criteria to this cohort, only 539 carriers (1.2%) would be identified. IHC triage based on the diagnosis of endometrial cancer and 1 FDR would subject fewer cases to IHC but identify more mutation carriers than using age thresholds of 50 or 60 years. In general, the more mutation carriers identified, the lower the potential number of subsequent colorectal cancers, as seen in Table 5.

DISCUSSION

IHC triage of all women with endometrial cancer who have at least 1 FDR with a Lynch-associated cancer at any age is a cost-effective

Table 4. Average Discounted Lifetime Costs, Life Expectancy, and ICERs

Testing Strategy	Average Lifetime Cost (US$)	Average Discounted Life Expectancy (years)	ICER
Age < 50, at least 1 FDR	2,254	14.52708	—
IHC triage < age 50	2,255	14.52686	Dominated
IHC triage any age, at least 1 FDR	2,277	14.52971	$9,126
IHC triage < age 60	2,484	14.52792	Dominated
IHC triage all endometrial cancers	3,131	14.53077	$648,494
Amsterdam II criteria	4,045	14.52733	Dominated

NOTE. Dominated strategies are more costly and less effective than an alternate (preceding) strategy.

Abbreviations: ICER, incremental cost-effectiveness ratios; FDR, first-degree relative with a Lynch-associated cancer at any age; IHC triage, immunohistochemistry triage, then referral for genetic testing if abnormal IHC results.

Table 5. Monte Carlo Simulation of Women With Endometrial Cancer in the United States

Testing Strategy	No. Cases Subject to IHC Triage	No. Identified With Lynch Syndrome	No. of Subsequent CRC Cases
Amsterdam II criteria	NA	539	2,582
Age < 50, at least 1 FDR	NA	530	2,470
IHC triage < age 50	6,285	520	2,442
IHC triage < age 60	16,226	548	2,450
IHC triage any age, at least 1 FDR	5,786	755	2,442
IHC triage all endometrial cancers	45,000	827	2,413

Abbreviations: IHC triage, immunohistochemistry triage, then referral for genetic testing if abnormal IHC results; CRC, colorectal cancer; NA, not applicable, as women who fulfill these criteria are directly referred for genetic testing; FDR, first-degree relative with a Lynch-associated cancer at any age.

strategy for identifying those who should be referred for genetic testing. Amsterdam II criteria are still provided as guidelines for selecting individuals for Lynch syndrome testing,[8,9] although it is well recognized that the sensitivity and specificity of these criteria are not high.[9,16,51] This may be partly attributed to the fact that cancers in family members tend to be under-reported, even by individuals with personal histories of cancer.[52,53] It has been suggested that those with personal histories of synchronous or metachronous Lynch-associated cancers, with the first diagnosed before age 50, should be referred for testing.[54] However, the ideal scenario is that Lynch syndrome testing takes place before an individual is diagnosed with two cancers. The revised Bethesda criteria have a higher sensitivity than Amsterdam II criteria for detecting Lynch syndrome, but these are applicable only to those with a diagnosis of colorectal cancer.[55] Testing all women with endometrial cancer younger than the age of 50 has been suggested as a potential strategy for identifying Lynch syndrome, as the estimated mutation prevalence in these women is approximately 9%.[17,19] However, if the average age at diagnosis of endometrial cancer is 48,[1] then almost 50% of women with Lynch syndrome are diagnosed with endometrial cancer after the age of 50. Furthermore, fewer than 20% of all endometrial cancers in the population are diagnosed at younger than age 50, and therefore this age threshold may be too restrictive in identifying potential carriers. Similarly, while the prevalence of Lynch syndrome is high in those with lower uterine segment cancers[56] and those younger than age 50 with a normal body mass index,[19] these subgroups are too small to identify a significant number of carriers at a population level.

Evidence of microsatellite instability (MSI) or abnormal IHC in one of the mismatch repair genes has been recommended as an indication for genetic testing,[54] as these tests have been proven to be highly sensitive and specific in detecting Lynch syndrome, both in colorectal and endometrial cancers.[15,17-19,57-62] We did not include MSI testing in our model because MSI and IHC have comparable sensitivities for detecting Lynch syndrome in endometrial cancer,[17-19] and IHC can be done in any pathology lab whereas MSI requires a more sophisticated analysis including polymerase chain reaction for DNA amplification and electrophoresis, which may not be readily available at all centers. Regardless of methodology for triage, using age thresholds of 50 or 60 years will miss a significant proportion diagnosed with endometrial cancer after age 60, especially those with *MSH6* mutations.[18] While IHC testing of all endometrial cancers regardless of age would identify the highest number of mutation carriers, we did not find this strategy to be cost effective. Furthermore, IHC triage is not necessarily practical because it would require discussion and informed consent from all of these women about the implications of an abnormal result, even if only a small subgroup has abnormal IHC and is selected for genetic testing. If IHC triage were limited to those diagnosed with endometrial cancer younger than age 60, this would still represent almost 40% of all endometrial cancers in our population. However, IHC triage for those with 1 FDR having a Lynch-associated cancer would apply to only 10% to 15% of all patients with endometrial cancer, and fewer than 20% of these women would be referred for genetic testing.

The incremental benefit of IHC triage of all women with endometrial cancer having at least 1 FDR with a Lynch-associated cancer at any age is an average life expectancy gain of 1 day compared to Amsterdam II criteria. This is comparable to the life expectancy gain from triennial cervical cancer screening (compared to less frequent screening),[63] which is the current recommendation by the American College of Obstetricians and Gynecologists for women older than age 30 in the general population.[64] Because the benefit of testing is averaged across the entire target population, the average life expectancy gain is dependent on the proportion of individuals having the condition within that population. The less prevalent the condition (ie, only 2% of all women with endometrial cancer having Lynch syndrome), the lower the average life expectancy gain from testing. The average life expectancy gain may appear to be very low, but it is very significant for those individuals identified as having Lynch syndrome who might have died prematurely without undergoing surveillance for colorectal cancer.

The advantage of this analysis is that we can estimate the costs and benefits of Lynch syndrome testing in a large cohort of women with endometrial cancer, which would be difficult to evaluate in the context of a clinical trial. The major disadvantage of this analysis is the uncertainty relating to various parameters, including the prevalence of Lynch syndrome within specific age subgroups, their colorectal cancer risks and mortality rates, and total lifetime costs for colorectal cancer treatment. We assumed that women allocated to each strategy were comparable with respect to other risk factors for colorectal cancer, including body mass index, smoking, diet, comorbidities such as diabetes, and alcohol consumption. We also assumed that they had comparable risks of other Lynch-associated cancers, such as gastric, small bowel, ureter and renal pelvis, although these were not modeled in this analysis. Our base case model results were based on 100% compliance with colonoscopic surveillance in confirmed mutation carriers,[65] but much lower rates have also been observed, which underscores the need to improve screening rates across this population.[66-68]

If Amsterdam II criteria continue to be utilized to guide genetic testing for Lynch syndrome, a significant proportion of individuals with Lynch syndrome may be missed. The proportion of women with endometrial cancer and Lynch syndrome who fulfill Amsterdam II criteria may be as low as 30%.[18] In contrast, the proportion of women with endometrial cancer and Lynch syndrome who have at least 1 FDR with a Lynch-associated cancer may be as high as 80% to 100%.[17-19] These women should be triaged with IHC, then offered the opportunity to undergo genetic counseling and testing. If they are identified as carriers, they can undergo more frequent surveillance to prevent colorectal cancer. Furthermore, their unaffected FDRs have the opportunity to undergo genetic testing and risk-reducing interventions to prevent colorectal and gynecologic cancers, which will contribute to reducing the total cancer burden among families affected by Lynch syndrome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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REFERENCES

1. Lu HK, Broaddus RR: Gynecologic cancers in Lynch syndrome/HNPCC. Fam Cancer 4:249-254, 2005

2. Lu KH, Dinh M, Kohlmann W, et al: Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol 105:569-574, 2005

3. Syngal S, Weeks JC, Schrag D, et al: Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. Ann Intern Med 129:787-796, 1998

4. Vasen HF, van Ballegooijen M, Buskens E, et al: A cost-effectiveness analysis of colorectal screening of hereditary nonpolyposis colorectal carcinoma gene carriers. Cancer 82:1632-1637, 1998

5. Estimated New Cases for the Most Common Cancers by Sex and Province, Canada, 2010, in Canadian Cancer Society's Steering Committee (ed): Canadian Cancer Statistics 2010. Canadian Cancer Society, Toronto, Ontario, Canada, 2010

6. Altekruse SF, Kosary CL, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2007. National Cancer Institute, Bethesda, MD, 2010

7. BC Cancer Agency: Lynch syndrome criteria. http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/HereditaryCancerProgram/referralinformation/lynchcriteria.html

8. 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 296:1507-1517, 2006

9. Vasen HF, Moslein G, Alonso A, et al: Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 44:353-362, 2007

10. Vasen HF, Watson P, Mecklin JP, et al: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 116:1453-1456, 1999

11. Aaltonen LA: Molecular epidemiology of hereditary nonpolyposis colorectal cancer in Finland. Recent Results Cancer Res 154:306-311, 1998

12. Cunningham JM, Kim CY, Christensen ER, et al: The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. Am J Hum Genet 69:780-790, 2001

13. Debniak T, Kurzawski G, Gorski B, et al: Value of pedigree/clinical data, immunohistochemistry and microsatellite instability analyses in reducing the cost of determining hMLH1 and hMSH2 gene mutations in patients with colorectal cancer. Eur J Cancer 36:49-54, 2000

14. Hampel H, Stephens JA, Pukkala E, et al: Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: Later age of onset. Gastroenterology 129:415-421, 2005

15. Pinol V, Castells A, Andreu M, et al: Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA 293:1986-1994, 2005

16. Syngal S, Fox EA, Eng C, et al: Sensitivity and specificity of clinical criteria for hereditary nonpolyposis colorectal cancer associated mutations in MSH2 and MLH1. J Med Genet 37:641-645, 2000

17. Berends MJ, Wu Y, Sijmons RH, et al: Toward new strategies to select young endometrial cancer patients for mismatch repair gene mutation analysis. J Clin Oncol 21:4364-4370, 2003

18. Hampel H, Frankel W, Panescu J, et al: Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res 66:7810-7817, 2006

19. Lu KH, Schorge JO, Rodabaugh KJ, et al: Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer. J Clin Oncol 25:5158-5164, 2007

20. Walsh MD, Cummings MC, Buchanan DD, et al: Molecular, pathologic, and clinical features of early-onset endometrial cancer: Identifying presumptive Lynch syndrome patients. Clin Cancer Res 14:1692-1700, 2008

21. Neumann PJ, Sandberg EA, Bell CM, et al: Are pharmaceuticals cost-effective? A review of the evidence. Health Aff (Millwood) 19:92-109, 2000

22. Weinstein MC, Siegel JE, Gold MR, et al: Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 276: 1253-1258, 1996

23. Desch CE, Benson III AB, Somerfield MR, et al: Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 23:8512-8519, 2005

24. NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening V.1.2010. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection

25. World Gastroenterology Organisation/International Digestive Cancer Alliance Practice Guidelines: Colorectal cancer screening. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/06_colorectal_cancer_screening.pdf

26. Richardson LC, Rim SH, Plescia M: Vital Signs: Colorectal cancer screening among adults aged 50-75 years, United States. Morbidity and Mortality Weekly Report 59:1-5, 2010. www.cdc.gov/mmwr/preview/mmwrhtml/mm59e0706a1.htm

27. National Cancer Institute: Screening and Risk Factors Report: Had a sigmoidoscopy or colonoscopy in past 10 years—2008, all races, female, ages 50+. http://statecancerprofiles.cancer.gov/risk/index.php?risk=23&sex=2&type=risk&stateFIPS=00&sortVariableName=default&sortOrder=default

28. Kosary CL: Cancer of the corpus uteri, in Ries LAG, Young JL, Keel GE, et al (eds): SEER Survival Monograph: Cancer Survival Among Adults—U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, Bethesda, MD, 2007

29. Ferro SA, Myer BS, Wolff DA, et al: Variation in the cost of medications for the treatment of colorectal cancer. Am J Manag Care 14:717-725, 2008

30. AMA: 2010 CPT codes and Medicare payment information. American Medical Association, Chicago, IL, 2010

31. Cook-Deegan R, DeRienzo C, Carbone J, et al: Impact of gene patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: Comparing breast and ovarian cancers with colon cancers. Genet Med 12:S15-38, 2010

32. Henry SG, Ness RM, Stiles RA, et al: A cost analysis of colonoscopy using microcosting and time-and-motion techniques. J Gen Intern Med 22: 1415-1421, 2007

33. Lang K, Lines LM, Lee DW, et al: Lifetime and treatment-phase costs associated with colorectal cancer: Evidence from SEER-Medicare data. Clin Gastroenterol Hepatol 7:198-204, 2009

34. Mayo Clinic: Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen, Immunostains. Mayo Clinic, Rochester, MN, 2010. http://www.mayomedicallaboratories.com/test-catalog/Fees+and+Coding/83015

35. Mayo Clinic: Hereditary Non-Polyposis Colorectal Cancer (HNPCC) Mutation Screen. Mayo Clinic, Rochester, MN, 2010. http://www.mayomedicallaboratories.com/test-catalog/Fees+and+Coding/83015

36. Yabroff KR, Warren JL, Schrag D, et al: Comparison of approaches for estimating incidence costs of care for colorectal cancer patients. Med Care 47:S56-63, 2009

37. Resnick K, Straughn JM Jr, Backes F, et al: Lynch syndrome screening strategies among newly diagnosed endometrial cancer patients. Obstet Gynecol 114:530-536, 2009

38. Ollikainen M, Abdel-Rahman WM, Moisio AL, et al: Molecular analysis of familial endometrial carcinoma: A manifestation of hereditary nonpolyposis colorectal cancer or a separate syndrome? J Clin Oncol 23:4609-4616, 2005

39. Goodfellow PJ, Buttin BM, Herzog TJ, et al: Prevalence of defective DNA mismatch repair and MSH6 mutation in an unselected series of endometrial cancers. Proc Natl Acad Sci U S A 100:5908-5913, 2003

40. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al: Ten years after mutation testing for Lynch syndrome: Cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol 27:4793-4797, 2009

41. Jarvinen HJ, Aarnio M, Mustonen H, et al: Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 118:829-834, 2000

42. Vasen HF, Abdirahman M, Brohet R, et al: One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. Gastroenterology 138:2300-2306, 2010

43. de Jong AE, Hendriks YM, Kleibeuker JH, et al: Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology 130:665-671, 2006

44. Cotterchio M, Manno M, Klar N, et al: Colorectal screening is associated with reduced colorectal cancer risk: A case-control study within the population-based Ontario Familial Colorectal Cancer Registry. Cancer Causes Control 16:865-875, 2005

45. Boursi B, Halak A, Umansky M, et al: Colonoscopic screening of an average-risk population for colorectal neoplasia. Endoscopy 41:516-521, 2009

46. Rundle AG, Lebwohl B, Vogel R, et al: Colonoscopic screening in average-risk individuals ages 40 to 49 vs 50 to 59 years. Gastroenterology 134:1311-1315, 2008

47. National Cancer Institute/SEER: Lifetime Risk Tables, SEER Cancer Statistics Review, 1975-2007. Statistical Research and Applications Branch DoCCaPS, National Cancer Institute, Bethesda, MD, 2010

48. Salovaara R, Loukola A, Kristo P, et al: Population-based molecular detection of hereditary nonpolyposis colorectal cancer. J Clin Oncol 18: 2193-2200, 2000

49. Arias E, Rostron BL, Tejada-Vera B: United States life tables, 2005. Natl Vital Stat Rep 58:1-132, 2008

50. National Cancer Institite/SEER: Endometrial cancer home page. http://www.cancer.gov/cancertopics/types/endometrial

51. Lipton LR, Johnson V, Cummings C, et al: Refining the Amsterdam Criteria and Bethesda Guidelines: Testing algorithms for the prediction of mismatch repair mutation status in the familial cancer clinic. J Clin Oncol 22:4934-4943, 2004

52. Glanz K, Grove J, Le Marchand L, et al: Underreporting of family history of colon cancer: Correlates and implications. Cancer Epidemiol Biomarkers Prev 8:635-639, 1999

53. Mitchell RJ, Brewster D, Campbell H, et al: Accuracy of reporting of family history of colorectal cancer. Gut 53:291-295, 2004

54. Lancaster JM, Powell CB, Kauff ND, et al: Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol 107:159-162, 2007

55. Umar A, Boland CR, Terdiman JP, et al: Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96:261-268, 2004

56. Westin SN, Lacour RA, Urbauer DL, et al: Carcinoma of the lower uterine segment: A newly described association with Lynch syndrome. J Clin Oncol 26:5965-5971, 2008

57. Caldes T, Godino J, Sanchez A, et al: Immunohistochemistry and microsatellite instability testing for selecting MLH1, MSH2 and MSH6 mutation carriers in hereditary non-polyposis colorectal cancer. Oncol Rep 12:621-629, 2004

58. Halvarsson B, Lindblom A, Rambech E, et al: Microsatellite instability analysis and/or immunostaining for the diagnosis of hereditary nonpolyposis colorectal cancer? Virchows Arch 444:135-141, 2004

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

60. 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 10:293-300, 2008

61. Cohn DE, Frankel WL, Resnick KE, et al: Improved survival with an intact DNA mismatch repair system in endometrial cancer. Obstet Gynecol 108:1208-1215, 2006

62. Modica I, Soslow RA, Black D, et al: Utility of immunohistochemistry in predicting microsatellite instability in endometrial carcinoma. Am J Surg Pathol 31:744-751, 2007

63. Goldie SJ, Kim JJ, Wright TC: Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. Obstet Gynecol 103:619-631, 2004

64. ACOG Practice Bulletin no. 109: Cervical cytology screening. Obstet Gynecol 114:1409-1420, 2009

65. Collins VR, Meiser B, Ukoumunne OC, et al: The impact of predictive genetic testing for hereditary nonpolyposis colorectal cancer: Three years after testing. Genet Med 9:290-297, 2007

66. Hadley DW, Jenkins JF, Steinberg SM, et al: Perceptions of cancer risks and predictors of colon and endometrial cancer screening in women undergoing genetic testing for Lynch syndrome. J Clin Oncol 26:948-954, 2008

67. Halbert CH, Lynch H, Lynch J, et al: Colon cancer screening practices following genetic testing for hereditary nonpolyposis colon cancer (HNPCC) mutations. Arch Intern Med 164:1881-1887, 2004

68. 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 4:295-300, 2005

