Published in final edited form as:
Clin Gastroenterol Hepatol. 2010 June ; 8(6): 523–529. doi:10.1016/j.cgh.2010.03.010.

Underdiagnosis of Lynch Syndrome Involves More than Family History Criteria

Hardeep Singh, MD MPH[1], **Rachel Schiesser, MD**[2], **Gobind Anand**[3], **Pete Richardson, PhD**[4], and **Hashem B. El-Serag, MD, MPH**[4,5]

[1]Houston VA HSR&D Center of Excellence, and The Center of Inquiry to Improve Outpatient Safety Through Effective Electronic Communication, both at the Michael E. DeBakey Veterans Affairs Medical Center and the Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, Texas USA

[2]Department of Medicine, Baylor College of Medicine, Houston, Texas USA

[3]Johns Hopkins School of Medicine, Baltimore, MD

[4]Houston VA HSR&D Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center and the Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, Texas USA

[5]Section of Gastroenterology and Hepatology, Michael E. DeBakey Veterans Affairs Medical Center Department of Medicine, Baylor College of Medicine, Houston, Texas USA

Abstract

Background—Physicians' cancer-related family history assessment for Lynch syndrome is often inadequate. Furthermore, the extent to which clinicians recognize non-family history-related clues for Lynch syndrome is unclear. We reviewed an integrated electronic health record (EHR) to determine diagnostic evaluation for Lynch syndrome in patients diagnosed with colorectal cancer (CRC).

Methods—We conducted a retrospective cohort study of consecutive patients with CRC, newly diagnosed at a tertiary care VA facility, between 1999 and 2007. A detailed review of the EHR was conducted to evaluate the presence of family-history and non-family history-related criteria of the Bethesda guidelines. Patient outcomes (identification in clinical practice and referral for genetic testing) were also determined.

Address for Correspondence and Reprints: Hardeep Singh, MD, MPH VA Medical Center (152) 2002 Holcombe Blvd Houston, TX 77030 Phone (713) 794-8515 hardeeps@bcm.edu Fax: 713-748-7359.

Author Roles: Study concept and design: HS, HE, RS Acquisition of data: RS, GA Analysis and interpretation of data: HS, HE, RS, PR Drafting of the manuscript: HS, RS, HE, GA, PR Critical revision of the manuscript for intellectual content: HS, RS, GA, PR, HE Statistical analysis; PR; Obtained funding; HE, HS Administrative, technical, or material support; HS, HE Study supervision: HS, HE

Conflicts of Interest None

Data All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Results—We identified a total of 499 patients (mean age=65.4 years, 98.6% male, 51.1% non-Hispanic white). At least 1 of the Bethesda criterion was met for 57 patients (11.4%); none were met for 198 (39.7%); and there was uncertainty for 244 (48.9%) because of inadequate family history documentation and/or the patient was unsure about their family history. Forty-nine patients met criteria unrelated to family history. Only 4 of 57 patients (7%) that met the Bethesda guidelines had documentation of counseling. Among 244 patients with uncertainty, a suspicion for Lynch syndrome was documented in the EHR of 6 patients (2.5%); 3 received counseling.

Conclusions—Lynch syndrome is under-recognized, even when patients have clear criteria unrelated to family history. Multifaceted strategies focused on reducing providers' cognitive errors and harnessing EHR capabilities to improve recognition of Lynch syndrome are needed.

Keywords

Lynch syndrome; health outcomes; familial colorectal cancer; practice patterns; missed diagnosis; guideline non-adherence; genetic evaluation; delayed cancer diagnosis

Introduction

Lynch syndrome (previously referred to as Hereditary Nonpolyposis Colorectal Cancer or HNPCC) is an autosomal dominant disorder that is found in approximately 2-5% of all colorectal cancers (CRC) cases. It involves germline mutations in genes that encode DNA mismatch repair proteins.[1,2] Inactivation of the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) leads to microsatellite instability (MSI) and predisposes carriers to multiple malignancies including a 40-80% cumulative lifetime risk of developing CRC.[3-5] When carriers are identified, the morbidity and mortality from colorectal and endometrial cancers can be reduced by the implementation of early, aggressive screening measures.[3,6]

Other than family history, Lynch syndrome has no known specific phenotype or presentation, and therefore clinicians may not easily recognize patients with this syndrome even though it is the most common form of hereditary CRC.[7-9] To aid the identification of patients with Lynch syndrome, the Bethesda guidelines developed in 1996 and subsequently revised in 2004 because of modest specificity for identifying MSI-H tumors in high-risk populations.[2,10-12] The modified Bethesda guidelines included a spectrum of colonic and extracolonic cancers to identify *MSH2* and *MLH1* germline-mutation carriers in patients with cancers who may not fulfill the previously published Amsterdam II criteria.[13,14] Patients with CRC are recommended to undergo genetic testing if they fulfil the following revised Bethesda guidelines: 1) diagnosed with CRC before 50 years of age; 2) had synchronous or metachronous colorectal or other HNPCC-associated tumors, regardless of age; 3) had MSI-H histology under the age of 60 years; 4) had one or more first-degree relatives with CRC or other HNPCC-related tumor, with one of the cancers diagnosed by the age of 50 years; and 5) two or more first or second degree relatives with CRC or other HNPCC-related tumors, regardless of age.

Detailed family history, a component of the Amsterdam criteria and Bethesda guidelines, is essential in evaluating a patient for further genetic testing for Lynch syndrome. Previous studies have reported that cancer family history assessment is often inadequate in clinical practice, even in specialized cancer centers.[1,15,16] However, many patients qualify for further diagnostic workup for Lynch syndrome based on criteria unrelated to family history. These criteria include patient's age, presence of any HNPCC-related cancer, including synchronous and metachronous CRC or associated extracolonic cancer and if other pathological criteria specified in Bethesda guidelines are present. It is unknown if these "non-family history" criteria are appropriately recognized and if they lead to referral for further genetic testing among patients diagnosed with CRC in the United States. We therefore used a comprehensive

integrated electronic health record (EHR) to evaluate Lynch syndrome evaluation practices in patients with CRC diagnosed at a large tertiary care institution.

Methods

Setting

We conducted a retrospective cohort study of consecutive patients less than 80 years of age with pathologically confirmed CRC newly diagnosed at a tertiary care VA facility between 1999 and 2007. In this facility, patients are assigned to staff primary care practitioners (PCP) who have access to several specialties including gastroenterology, oncology and surgery. There were no specific clinical guidelines in place at the institution that addressed work up of Lynch syndrome during this study. At the time of the study genetic counseling and testing resources were available at a partnering academic institution. The study was approved by the local Institutional Review Board.

Chart review

We conducted a detailed review of the EHR to evaluate if patients met Bethesda guidelines and evaluated missed opportunities in diagnosis of Lynch syndrome in accordance with the standards available to providers at the time of their practice. Because the revised Bethesda guidelines were only released in Feb 2004, we did not apply them to "judge" practices at a time before that i.e. when only the original Bethesda guidelines were available. Therefore, we evaluated the presence of any criteria from the original Bethesda guidelines for patients whose date of CRC diagnosis was before March 2004 and any criteria from revised guidelines for patients whose date of CRC diagnosis was after March 2004. In addition, we evaluated the presence of Amsterdam II criteria in all study patients to identify possible additional patients. We also collected data on patient outcomes including referral for genetic testing and follow-up.

A structured data collection form was developed and pre-tested to determine three key elements: family history, non-family history criteria (such as age, presence of specified cancers *a*nd pathology results), and patient outcomes. The study team supervised and trained two reviewers (RS, GA) during pilot testing to ensure reliable and consistent data collection.

Identification of Family History

Because family history could be documented by multiple specialties in any number of electronic progress notes, we retrieved information about family history from several sources. First, to identify any progress note that might contain family history data, we used single-word searches containing one of the terms "FH", "fam", "FM" or "f/h" to conduct an automated text search of all progress notes of 15 patients in the study cohort. Next, we manually reviewed all progress notes in the EHR before and up to one year after CRC diagnosis for mention of family history in the same 15 patients. Initial automated text word searches identified approximately 80% of all notes identified manually as containing family history data. We subsequently strengthened text word searches by adding the following terms used as single-word searches: "mother," "father," "parent," "sister," "brother," "sibling," "child," "son," "daughter," "aunt," "uncle," "niece," "nephew," "maternal," "paternal," and "relative." Addition of these words identified all notes identified manually as containing family history data in 15 patients. We collected information needed to evaluate for presence of criteria to investigate further for Lynch syndrome such as relevant cancer history in first- and second-degree relatives and ages of diagnosis.

Non-Family History Criteria

In addition to age, we collected pathology data from the EHR, which contains designated detailed pathology reports menu since 1995 as well as selected progress notes containing past medical history. In addition to confirming CRC diagnosis, we evaluated the presence of any Lynch syndrome-related malignancies any time prior to the diagnosis or within one year after the CRC diagnosis. These malignancies included endometrial, ovarian, gastric, pancreatic, biliary tract, small-bowel, ureter and renal pelvis, brain, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome. To exclude polyposis, we reviewed all endoscopy procedure reports to evaluate for the number of polyps discovered.

Bethesda Guideline Determination

We used age, family history, and pathology information to determine if patients met Bethesda guidelines, did not meet Bethesda guidelines, or had uncertain Bethesda guideline status (either due to patient being unsure of their family history, or absent documentation of family history).

Referral for Further Genetic Testing and Other Outcomes

In all cases, we evaluated if any practitioner had suspected CRC related to a genetic or familial syndrome and if the patient had been counseled regarding familial CRC, if they were referred for genetic testing, and the outcome of the referral or testing, if any. All notes of primary care providers, gastroenterologists, surgeons and oncologists were reviewed for up to one year after CRC diagnosis. In addition, text searches using one of the terms “genetic,” “familial,” “hereditary,” “HNPCC,” or “Lynch” was used to supplement manual chart review.

Data Analysis

The study variables included one continuous variable (age) and several categorical variables (patient gender and ethnicity, mental health comorbid conditions, Bethesda guideline status and Amsterdam criteria, patient outcomes, tumor stage and family cancer history). Descriptive statistics included means and standard deviation for the continuous variables, and frequencies and proportions for categorical variables. .

Bethesda guidelines were summarized in three categories: [i] did not meet Bethesda guidelines (no criterion met) [ii] met Bethesda guidelines (at least one criterion was met) and [iii] Bethesda guideline status uncertain. Differences among the three patient groups were assessed for significance by the Wilcoxon test for the continuous variables and Fisher exact test for categorical variables.

Results

We identified a total of 499 patients with CRC (mean age of diagnosis 65.4 years (SD 9.0), 98.6% male, 51.1% non Hispanic white). At least one Bethesda criterion was met in 57 patients (11.4%); none were met in 198 (39.7%), and uncertain in 244 (48.9%) due to insufficient information (Fig. 1). The uncertainty was related to patient being unsure about family history in 69 (28.2%) cases, and absence of family history documentation by the provider in 214 [87.7%; percentages exceed 100 because information was obtained from notes from two or more different providers, one who documented uncertainty (i.e., the question was asked but the answer was uncertain) and another who did not document any family history at all (not known to us whether the question was asked or not)]. Two additional patients (0.4%) met the Amsterdam criteria.

Characteristics of Family History Documentation

Fig. 2 shows the content of family history documentation relevant to Lynch syndrome for 476 patients who had any family history documented in the EHR. Family history of some type of cancer was present in 263 (55.2%), absent in 154 (32.3%), patient was uncertain in 23 (4.8%), and there was no available documentation regarding cancer in 36 (7.6%). However, the age of the affected relative was not documented for 54 (56.2%) of 96 patients with history of Lynch syndrome-related malignancy in a first-degree relative. Similarly, age of affected relative was not documented for 17 (71%) of 24 patients with Lynch syndrome-related malignancy in 2nd degree relative. Overall, of 263 patients with documented positive family history of cancer, 154 (58.6%) did not contain information about Lynch syndrome-related malignancy in 2nd degree relative.

Lynch Syndrome Criteria

Original or Modified Bethesda guidelines were met in 57 patients (11.4%), not met in 189 (39.7%), whereas information was insufficient for definitive assessment in 244 (48.9%); the latter group constituted patients with "uncertain" Bethesda guideline status. Overall, 49 patients met non-family history criteria (total unique patients who met the non-family history criteria specified in Tables 1 and 2).

Of 254 patients diagnosed with CRC prior to 3/18/2004, during which time the original Bethesda guidelines were applied, 29 (11%) met criteria for further genetic testing (Table 1). The documentation necessary to evaluate the presence of "Individuals with CRC and a first-degree relative with colorectal cancer and/or HNPCC-related extracolocancer and/or a colorectal adenoma; one of the cancers diagnosed at age <50, and the adenoma diagnosed at age <40" was absent from the medical record in 55 of 254 patients (22%).

Of 245 patients diagnosed with CRC after 3/18/2004 (Table 2), during which time the revised Bethesda guidelines were available, 28 (11%) met criteria for further testing. However, close to half (n= 120) could not be evaluated fully secondary to lack of adequate family history documentation. For criterion #4 (CRC diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50), 26 patients (11%) had inadequate documentation to determine Bethesda guideline status, while for criterion #5, which relies on second-degree family history, 100 patients (41%) had inadequate documentation to determine the need for further genetic testing. Testing for MSI-H in CRC tissue was not available at the facility during the study period.

Differences among the three patient groups, [i] no criteria met, [ii] at least one criterion met and [iii] criteria status uncertain were assessed for significance. As expected, patients who met Bethesda guidelines were younger (p=0.03) compared to patients for whom no criteria were met (Table 3). There were no other significant differences between patients who met Bethesda guidelines and those in whom no criteria were met. We also compared patients with uncertain Bethesda guideline status and patients with certain Bethesda guideline status (at least one criterion met or no criteria met) and found no differences in any demographic or medical comorbidity variables except stage of cancer at diagnosis (p <0.001; data not shown in Table 3).

Outcomes

Outcomes were evaluated in groups with certain and uncertain guideline status (Fig. 3). Only 4 of 57 patients (7%) meeting Bethesda guidelines were counseled, of whom 2 were referred for further genetic testing. In 244 patients with uncertain status, 6 patients (2.5%) had documented evidence of being suspected for potential Lynch syndrome, of whom 3 were

counseled and 2 referred to a genetics clinic. None of the patients with unknown status received genetic testing (Fig 3).

Discussion

We evaluated diagnostic work-up for Lynch syndrome in a large cohort of CRC patients diagnosed in an integrated health care system. Information needed to evaluate risk for Lynch syndrome was missing in nearly half of these patients (48.9%), and referral for genetic evaluation was made in only 7% of those meeting Bethesda guidelines. We found under-recognition of Lynch syndrome involved patients with clear criteria (such as age<50, presence of synchronous and metachronous and/or extracolonic Lynch syndrome associated tumors) as well as subtle ones (detailed family history of cancer). Considerable information was missing from family history notably the age of 1st degree relative affected with Lynch syndrome related malignancy, and the mention of Lynch syndrome related malignancy 2nd degree relative.

Our study addresses the low recognition of Bethesda guidelines beyond family history of cancer.[9] For instance, the 49 patients who met non-family history related Bethesda criteria also had low documented suspicion, genetic referral and testing. All study patients were seen by multiple specialists in course of their treatment, including primary care, gastroenterologists, oncologists and surgeons. One explanation of this observation is “availability” heuristic”[17] or mental shortcut which refers to the tendency to recognize a diagnosis because of ease in recalling a past similar case. Providers who have not previously seen or encountered (i.e., availability) a case of missed or delayed Lynch syndrome diagnosis may be unlikely to think of it as a possibility, or stated differently “out of sight, out of mind”. This is especially relevant in that VA users undergoing colonoscopy are mostly older than 50 years where prevalence of Lynch syndrome is likely to be low. Another possible reason for the low referral rate for genetic counseling and testing could have been the providers’ knowledge that non-family history criteria for MSI testing are less predictive of a positive genetic test for Lynch syndrome in population with low prevalence for this syndrome.[18] Nevertheless, strategies to improve recognition require further understanding of the precise cognitive errors[19,20] that lead to missed Lynch syndrome diagnosis.

Our study confirms that family history continues to be poorly documented even in the presence of electronic health records that potentially facilitate such documentation. Our work thus builds on previous work which shows low referral rates for genetic evaluation for CRC syndromes because of non-recognition of familial cancer risk.[1,15,16] However, we also found specific areas where family history assessment needs improvement. For instance, documentation of age of affected relatives, and documentation of information on second degree relatives was mostly lacking, and both are essential details pertaining to evaluation of risk for Lynch Syndrome. Efforts to improve family history assessment[21,22] might need to specifically focus on this area.

The study provides insight on potential interventions to improve Lynch syndrome recognition. Multifaceted strategies to improve family history documentation in EHR systems are required. Currently this information is available in free-text format, often dispersed throughout the EHR in individual notes, and hence not easily accessible. This could be overcome by designing a structured stand-alone field in the EHR, where it would be possible for the family history to be documented, retrieved and updated by other providers.[23] Recognition of possibility of Lynch syndrome could also be improved by better computerized clinical decision-support in the EHR.[24] For instance, diagnosis of CRC in a patient less than 50 year of age could initiate an electronic reminder to future providers to pursue further diagnostic work-up for Lynch syndrome, or a trigger for more detailed personal and family history of cancer. Moreover, web-based models to assess risk for MMR mutations can be potentially incorporated into the EHR.[25,26] Lastly, our findings strengthen the need for specific programs on cancer genetics in the

medical education curriculum.[21] Most of the 14 Western European countries recently surveyed on strategies to identify individuals at high risk for CRC did not have such a program for such type of physician training.[21] Similar deficits are likely to be present in the United States.

Our study was conducted in a single VA facility with mostly male patients, and hence our findings may not be generalizable to other settings. However, given the existing literature on lack of family history recognition in other settings and cancers, we believe under-recognition of Lynch syndrome is likely pervasive in other clinical settings. It is possible that some veterans may have sought care outside the VA system and obtained this counseling elsewhere; this information would not have been captured by this study. However, being a relatively closed system, only few veterans with cancer diagnosed in the VA generally obtain outside care. Moreover, we searched the medical record extensively for such documentation. The absolute numbers of study patients affected are likely small. Although we may have missed patients that might potentially be recognized in the few settings that perform micro-satellite instability testing on all CRC patients, the strategy we used to identify potential cases may also over represent patients with Lynch syndrome, given the low 2-5% prevalence of Lynch syndrome in this population. Finally, it is not clear whether the deficits in the "process" of searching for Lynch syndrome-related cancer were necessarily linked to adverse outcomes, such as missed diagnoses of Lynch syndrome in relatives, or improved survival in the proband.

In summary, under-recognition of Lynch syndrome is quiet common and it involves cognitive errors related to clinicians' missing both family history and non-family history related clinical clues. The reasons and consequences of this under-recognition need to be further examined. This study provides insights on several potential multifaceted strategies to harness EHR capabilities to improve Lynch syndrome recognition.

Condensed Abstract

Lynch syndrome is under-recognized, even when patients have clear criteria unrelated to family history. Multifaceted strategies focused on reducing providers' cognitive errors and harnessing EHR capabilities to improve recognition of Lynch syndrome are needed.

Acknowledgments

Funding Source: The study was supported by an NIH K23 career development award (K23CA125585) to Dr. Singh, and in part by the Houston VA HSR&D Center of Excellence (HFP90-020). These sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. There are no financial disclosures from any authors.

Reference List

(1). Murff HJ, Greevy RA, Syngal S. The comprehensiveness of family cancer history assessments in primary care. Community Genet 2007;10:174–180. [PubMed: 17575462]

(2). Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997;89:1758–1762. [PubMed: 9392616]

(3). 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;74:233–242. [PubMed: 18554281]

(4). Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005;352:1851–1860. [PubMed: 15872200]

(5). Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology 1996;110:1020–1027. [PubMed: 8612988]

(6). Salovaara R, Loukola A, Kristo P, et al. Population-based molecular detection of hereditary nonpolyposis colorectal cancer. J Clin Oncol 2000;18:2193–2200. [PubMed: 10829038]

(7). Kaz AM, Brentnall TA. Genetic testing for colon cancer. Nat Clin Pract Gastroenterol Hepatol 2006;3:670–679. [PubMed: 17130877]

(8). Lynch HT, de la Chapelle A. Hereditary Colorectal Cancer. N Engl J Med 2003;348:919–932. [PubMed: 12621137]

(9). Lynch HT, Boland CR, Rodriguez-Bigas MA, Amos C, Lynch JF, Lynch PM. Who Should Be Sent for Genetic Testing in Hereditary Colorectal Cancer Syndromes? J Clin Oncol 2007;25:3534–3542. [PubMed: 17687158]

(10). Syngal S, Fox EA, Eng C, Kolodner RD, Garber JE. Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations inMSH2 and MLH1. Journal of Medical Genetics 2000;37:641–645. [PubMed: 10978352]

(11). Terdiman JP, Gum JR Jr. Conrad PG, et al. Efficient detection of hereditary nonpolyposis colorectal cancer gene carriers by screening for tumor microsatellite instability before germline genetic testing. Gastroenterology 2001;120:21–30. [PubMed: 11208710]

(12). Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261–268. [PubMed: 14970275]

(13). Umar A, Risinger JI, Hawk ET, Barrett JC. Testing guidelines for hereditary non-polyposis colorectal cancer. Nat Rev Cancer 2004;4:153–158. [PubMed: 14964310]

(14). Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116:1453–1456. [PubMed: 10348829]

(15). 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;2:813–819. [PubMed: 15354282]

(16). van Dijk D, Oostindier M, Kloosterman-Boele W, et al. Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Familial Cancer 2007;6:131–134. [PubMed: 17237905]

(17). Scott IA. Errors in clinical reasoning: causes and remedial strategies. BMJ 2009;338:b1860. [PubMed: 19505957]

(18). Terdiman JP, Levin TR, Allen BA, et al. Hereditary nonpolyposis colorectal cancer in young colorectal cancer patients: high-risk clinic versus population-based registry. Gastroenterology 2002;122:940–947. [PubMed: 11910346]

(19). Singh H, Petersen LA, Thomas EJ. Understanding diagnostic errors in medicine: a lesson from aviation. Qual Saf Health Care 2006;15:159–164. [PubMed: 16751463]

(20). Singh H, Sethi S, Raber M, Petersen LA. Errors in cancer diagnosis: current understanding and future directions. J Clin Oncol 2007;25:5009–5018. [PubMed: 17971601]

(21). Vasen HF, Moslein G, Alonso A, et al. Recommendations to improve identification of hereditary and familial colorectal cancer in Europe. Fam Cancer. 2009

(22). Yoon PW, Scheuner MT, Jorgensen C, Khoury MJ. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. Prev Chronic Dis 2009;6:A33. [PubMed: 19080039]

(23). Scheuner MT, de VH, Kim B, Meili RC, Olmstead SH, Teleki S. Are electronic health records ready for genomic medicine? Genet Med 2009;11:510–517. [PubMed: 19478682]

(24). Garg AX, Adhikari NKJ, McDonald H, et al. Effects of Computerized Clinical Decision Support Systems on Practitioner Performance and Patient Outcomes: A Systematic Review. JAMA 2005;293:1223–1238. [PubMed: 15755945]

(25). Balmana J, Stockwell DH, Steyerberg EW, et al. Prediction of MLH1 and MSH2 Mutations in Lynch Syndrome. JAMA 2006;296:1469–1478. [PubMed: 17003395]

(26). Pouchet CJ, Wong N, Chong G, et al. A comparison of models used to predict MLH1, MSH2 and MSH6 mutation carriers. Ann Oncol 2009;20:681–688. [PubMed: 19164453]

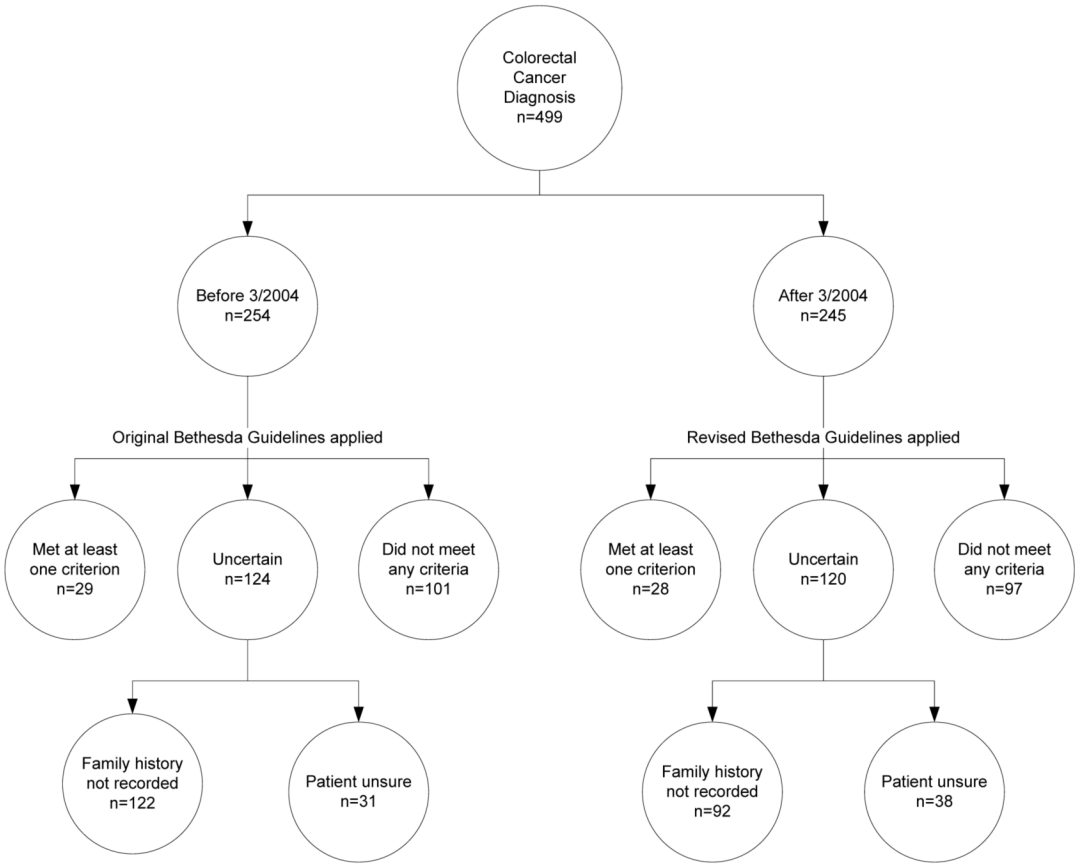

Figure 1.
Application and findings of clinical criteria for Lynch syndrome to all newly diagnosed colorectal cancer patients.

Figure 2.
Family history documentation and findings for 499 study patients with colorectal cancer.

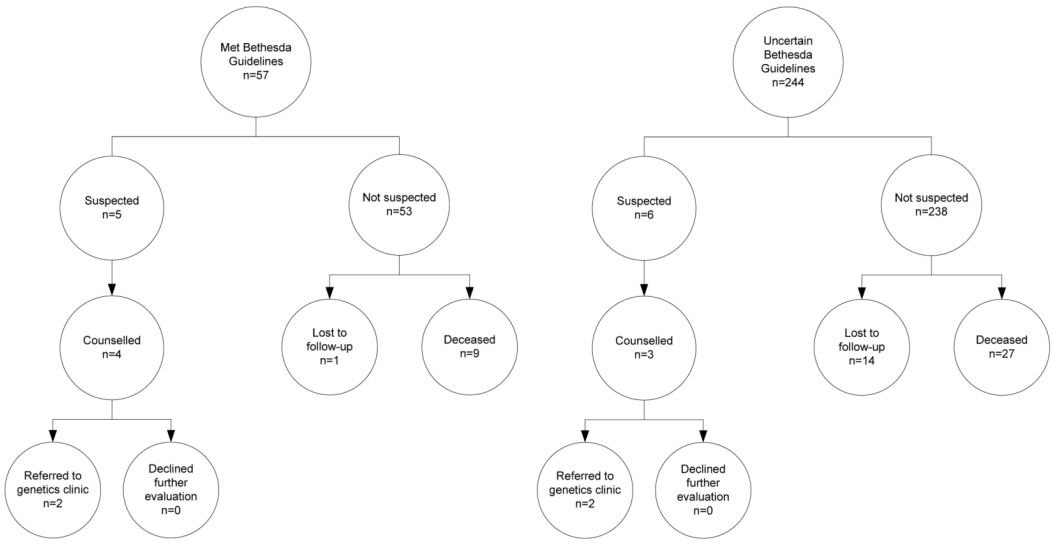

Figure 3.

Outcomes of patients who met Bethesda guidelines (at least onecriterion met) and patients with uncertain Bethesda guideline status* *Uncertain Bethesda guideline status = Information insufficient for assessment because family history was not documented and/or patient was unsure about family history

Table 1

Original Bethesda guidelines used for 254 patients diagnosed between 1999 and 3/18/2004

Criterion Number	Criteria	n
1	Individuals with cancer in families that meet the Amsterdam Criteria	
	No	105
	Yes	27
	not reported	122
2*	Individuals with two HNPCC-related cancers, including synchronous and metachronous CRC or associated extracolonic cancers [a]	
	No	234
	Yes	20
3	Individuals with CRC and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at age <50, and the adenoma diagnosed at age <40	
	No	162
	Yes	4
	not reported	55
	patient unsure	33
4*	Individuals with CRC or endometrial cancer diagnosed at age <50	
	No	250
	Yes	4
5*	Individuals with right-sided colorectal cancer with an undifferentiated pattern on histopathology diagnosed at age <50 years	
	No	254
6*	Individuals with signet-ring-cell type CRC diagnosed at age <50 years	
	No	254
7*	Individuals with adenomas diagnosed at age <40	
	No	254
	any Bethesda criterion = yes	29

[a] Endometrial, ovarian, gastric, hepatobiliary, small-bowel, or transitional cell carcinoma of the renal pelvis or ureter.

* Non-family history related criteria

Table 2

Revised Bethesda guidelines used for 245 patients diagnosed between 3/18/2004 and 2007 (N=245*)

Criterion Number	Criteria	n
1^	CRC diagnosed in a patient <50 years of age	
	No	240
	Yes	5
2^	Presence of synchronous, metachronous CRC or other HNPCC-associated tumors [b] regardless of age	
	No	224
	Yes	21
4	CRC diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50	
	No	184
	Yes	1
	patient unsure	34
	not documented	26
5	CRC diagnosed in two or more first- or second-degree relatives with a HNPCC-related tumors, regardless of age	
	No	117
	Yes	1
	patient unsure	27
	not documented	100
	any criterion = yes	28

[b] Endometrial, ovarian, gastric, pancreatic, biliary tract, small-bowel, ureter and renal pelvis, brain, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome

* Criteria 3 “CRC with MSI-H histology diagnosed in a patient who is <60 years old” was not used because none of the patients had this testing done.

^ Non-family history related criteria

Clin Gastroenterol Hepatol. Author manuscript; available in PMC 2011 June 1.

Table 3

Baseline characteristics of patients who met Bethesda guidelines (at least one criterion met), did not meet Bethesda guidelines (no criteria met) and uncertain Bethesda guideline status

	At least one criterion met N = 57	No criteria met N = 198	Uncertain* N = 244	p-value	
				Overall	At least one vs. no criteria
Age	61.3 (12.6)	65.3 (8.1)	65.6 (8.0)	0.07	0.03
Sex				0.76	0.53
Male	56 (98.2%)	196 (99.0%)	240(98.4%)		
Female	1 (1.8)	2 (1.0%)	4 (1.6%)		
Race				0.63	0.82
Whites	27 (47.4%)	102 (51.5%)	126 (51.6%)		
Blacks	20 (35.1%)	63 (31.8%)	62 (25.4%)		
Hispanics	5 (8.8%)	12 (6.0%)	22 (9.0%)		
Native Americans	0 (0.0%)	0 (0.0%)	1 (0.4%)		
Missing	5 (8.8%)	21 (10.6%)	33 (13.5%)		
Stage of CRC				0.0005	0.08
0	2 (3.5%)	28 (14.1%)	64 (26.2%)		
1	18 (31.6%)	41 (20.7%)	49 (20.1%)		
2	12 (21.0%)	33 (16.7%)	44 (18.0%)		
3	13 (22.8%)	38 (19.2%)	46 (18.8%)		
4	12 (21.0%)	58 (29.3%)	41 (16.8%)		
Medical Comorbidities				0.95	0.88
any	21 (36.8%)	69 (34.9%)	84 (34.4%)		
none	36 (63.2%)	129 (65.1%)	160 (65.6%)		
Diabetes				0.16	0.10
yes	10 (17.5%)	19 (9.6%)	35 (14.3%)		
no	47 (82.5%)	179 (90.4%)	209 (85.7%)		
Hypertension				0.67	0.41
yes	14 (24.6%)	61 (30.8%)	70 (28.7%)		

	At least one criterion met N = 57	No criteria met N = 198	Uncertain* N = 244	p-value	
				Overall	At least one vs. no criteria
no	43 (75.4%)	137 (69.2%)	174 (71.3%)		
Coronary Artery Disease				0.10	0.08
yes	1 (1.7%)	18 (9.1%)	25 (10.2%)		
no	56 (98.3%)	180 (90.9%)	219 (89.8%)		
Congestive Heart Failure				0.16	0.12
yes	0 (0.0%)	10 (5.0%)	7 (2.9%)		
no	57 (100.0%)	188 (95.0%)	237 (97.1%)		
Chronic Obstructive Pulmonary Disease				0.82	0.75
yes	4 (7.0%)	11 (5.6%)	13 (5.3%)		
no	53 (93.0%)	187 (94.4%)	231 (94.7%)		

*Uncertain status = Information insufficient for assessment because family history was not documented and/or patient was unsure about family history