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Under-utilization of Lynch Syndrome Screening in a Multisite Study of Colorectal Cancer Patients

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Abstract

Purpose—To examine Lynch Syndrome (LS) screening of metastatic colorectal cancer (mCRC) patients in integrated healthcare delivery organizations.

Methods—We determined the availability of LS screening criteria and actual LS screening in the medical records among 1,188 patients diagnosed with mCRC between 2004–2009 at seven institutions in the Cancer Research Network (CRN).

Results—We found infrequent use of LS screening (41/1188). Family history was available for 937 of the 1188 patients (79%). There was sufficient information to assess LS risk using family history based criteria in 719 of the 937 patients (77%) with family history documentation. In 391 individuals with a family history of a LS-associated cancer, 107 (27%) could not be evaluated due to missing information such as age of cancer onset. Eleven percent of patients who met Bethesda criteria and 25% of individuals who met the Amsterdam II criteria were screened for LS. When screening occurred, it followed recommended guidelines, but no testing method was preferred.

Conclusions—The information required for LS screening decisions is routinely collected but seldom utilized. There is a critical gap between collection of family history and its use to guide LS screening, which may support a case for implementation of universal screening guidelines.

Keywords

Lynch Syndrome; genetic testing; metastatic colorectal cancer; family history; hereditary cancer screening

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INTRODUCTION

Lynch Syndrome (LS), a hereditary cancer syndrome that accounts for 2–5% of the approximately 103,000 annual colorectal cancer (CRC) diagnoses in the US,[1–6] confers an increased risk of developing a number of other cancers including gastric, endometrial, ovarian, sebaceous gland, transitional carcinoma of the ureter, breast, prostate, and glioblastoma.[3,4,6–8]

Lynch syndrome is caused by autosomal dominant mutations in any one of 4 mismatch repair (MMR) genes (MLH1, MLH2, MLH6, and PMS2).[3,4] Individuals who harbor these germline mutations have an increased lifetime risk of developing CRC before age 50,[9,10] which is younger than the guideline-recommended age for initiating routine population-based screening.[3,4,11,12] CRC screening recommendations for individuals with LS include screening before age 50; possibly as young as age 20–25 or 2–5 years prior to the earliest diagnosis of cancer if under age 25,[6,12,13] and regular transvaginal ultrasound screening for endometrial and ovarian cancer beginning as early as age 30.[6,14] Additionally, it is recommended that females with LS consider prophylactic hysterectomy with bilateral salpingo-oophorectomy upon completion of childbearing. [6,13,14] Preliminary evidence also shows that individuals who are diagnosed with LS-associated cancers have a reduced response to fluorouracil chemotherapy treatment.[15–17] Therefore, identification of LS is important for developing appropriate screening and treatment regimens in affected individuals and for informing and identifying at-risk family members of this disease.

In order to facilitate identification of individuals with LS, a number of different clinical guidelines have been established. In 2009, the Evaluation of Genetic Applications in Practice and Prevention (EGAPP)[7] working group recommended universal screening of all patients newly diagnosed with CRC.[7] A joint guideline released in 2012 from the National Society of Genetic Counselors (NSGC) and the Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA-ICC) also supports the EGAPP recommendation and expands it to include all patients newly diagnosed with endometrial cancer,[5] based on recent cost-effectiveness studies.[18–20] In contrast, the current National Comprehensive Cancer Network (NCCN) and American Cancer Society (ACS) guidelines recommend LS screening once CRC is diagnosed [13,21] based on two established criteria that include family history elements, the Amsterdam II criteria[22] and the revised Bethesda criteria.[9]

A significant gap in the literature is how healthcare organizations currently screen for LS in individuals with newly diagnosed CRC. Here we describe LS screening frequency in integrated healthcare delivery settings using a multi-institutional cohort of individuals diagnosed with metastatic CRC between 2004 and 2009. We also examine 1) what, if any, patient factors are most likely to trigger LS screening; 2) whether physicians routinely collect all of the family history information necessary to assess LS risk using one of the recommended guidelines (Table 1); and 3) whether the family history information is used to guide LS screening decisions.

MATERIALS AND METHODS

Study Population

The study population includes 1,188 patients enrolled at any one of the seven participating Cancer Research Network (CRN) study institutions[23] as part of the Comparative Effectiveness Research in Genomics of Colon Cancer (CERGEN) study.[24] The seven study institutions are geographically distributed within the United States and represent diverse populations including Kaiser Permanente Northwest (Oregon and Washington), Kaiser Permanente Northern California, Kaiser Permanente Colorado, Kaiser Permanente Hawaii,

Marshfield Clinic (Wisconsin), Henry Ford Health System (Michigan), and HealthPartners Institute for Education and Research (Minnesota). Eligible patients were identified through tumor registries linked with electronic health information. We included patients aged 18 or older, diagnosed with Stage IV CRC between January 1, 2006, and December 31, 2009, and patients diagnosed with Stage III CRC between January 1, 2004, and December 31, 2008, who progressed to distant metastatic CRC. Only patients diagnosed with metastatic CRC were included in the study because the primary purpose of the study was to assess questions about treatment that is only indicated for patients with metastatic disease.[24] We included only cases diagnosed while in the health plan and excluded cases with incomplete treatment data or without pathology specimens. Because only individuals that were within an insurance health plan were included, all individuals did have insurance and 333 individuals were covered by Medicare/Medicaid.[24]

This study was approved by the Institutional Review Boards (IRB) at Kaiser Permanente Northwest, Kaiser Permanente Hawaii, Kaiser Permanente Colorado, Marshfield Clinic Research Foundation, and Henry Ford Health System, and did not require written informed consent. The IRBs for the remaining institutions ceded authority to the Kaiser Permanente Northwest IRB.

Electronic Data Collection

Data were extracted from the combined electronic medical records at each institution, using a model of distributed computer code through the Virtual Data Warehouse (VDW) and the local tumor registry to identify eligible cases and obtain electronic data. The VDW is a federated database that defines a standard specification for data contributed by each participating integrated healthcare delivery organization from clinical and administrative data sources.[25] Data elements extracted from the VDW included tumor registry information, vital signs, procedures, pharmacy, enrollment, and census data.

Manual Chart Abstraction

We performed manual chart abstraction of electronic medical records for information that is not typically documented in coded fields, but is available from physician notes and other text or scanned documents. Abstracted variables included verification of eligibility, patient characteristics (race, ethnicity, smoking, and alcohol use), a family history of cancer, cancer treatment history including surgery, radiation, and chemotherapy, palliative care, and imaging to assess disease progression. Genetic testing variables were manually abstracted in order to ensure that all records (even external documents) within a patient's medical record were captured. Any test ordered by physicians unaffiliated with the health care organizations or performed by an external laboratory were included, if they were present within a patient’s comprehensive medical record. These variables included genomic microsatellite instability (MSI) and protein immunohistochemistry (IHC) tests, germline mutation analysis of MLH1, MLH2, MLH6, and PMS2 genes, as well as MLH1 hypermethylation studies and BRAF testing to detect sporadic MMR defects.[5,11] Family history information was abstracted from coded and text fields, including the clinician notes in the medical chart and was recorded verbatim and codified in a study database. If a pedigree was available, it was de-identified and included with the chart abstraction.

LS Risk and Family History Analysis

Family history information was coded by a single investigator with a background in genetic counseling (AKR) with assistance from a research assistant (QAL). Positive family history included any family history of cancer and was further sub-classified into a family history of Lynch associated cancers or non-Lynch associated cancers. Negative family history was coded into “no family history of cancer,” “no family history of colon cancer,” “negative /

noncontributory family history," or "family history unknown" as documented in the medical record. Detailed text-based family history information was recoded for personal and family information about multiple primary colon cancers, additional personal history of other cancers, cancer in first and second degree relatives, cancer types, and ages of diagnoses.

We used algorithms, described in Table 1, to identify individuals with sufficient information eligible for LS screening via Amsterdam II,[22] revised Bethesda criteria,[9] MMRPredict,[26] or PREMM (1,2,6) model.[27] While the NSGC, GCA, and EGAPP, recommendations and the MMRPredict and PREMM models were not available at the time of diagnosis for all members of this cohort, we included them with the cut-off values suggested in the publications[26,27] to determine if sufficient information already existed in the medical record to assess individual risk using these guidelines.

Analysis

We compared patient characteristics in individuals selected for LS screening versus those with no LS screening. We defined LS screening to include any guideline-recommended combination of genomic microsatellite instability (MSI) and/or protein immunohistochemistry (IHC) tests, germline mutation analysis of MLH1, MLH2, MLH6, and PMS2 genes, as well as MLH1 hypermethylation studies and BRAF testing to detect sporadic MMR defects.[5,7,11] For individuals with and without documentation of LS screening tests, we compared the number who met the criteria for LS evaluation according to most available personal cancer history and family history-based guidelines (Table 1). All tests were conducted using SAS Release 9 (SAS Institute, Cary, NC). Reported P values were computed using Pearson's chi-square test (dichotomous variables) or Fisher's exact tests where cell size <5 or the two sample t test (quantitative variables).

RESULTS

The cohort consisted of 1188 individuals from 7 different institutions, 76% were diagnosed with metastatic CRC and 24% were diagnosed with stage III CRC and progressed to metastatic disease. The average age at diagnosis was 66.3 years, 74% were non-Hispanic white, and 50.7% were male. Overall, 41 patients (about 3% of the sample) were screened for LS via any testing method (MSI, IHC, or germline genetic testing) (Table 2). Individuals with LS screening had a younger age at diagnosis (58 versus 71 years; $p<0.0001$), were more likely to have family history documentation (88% versus 78%; $p=0.0035$), and were more likely to have a positive family history of CRC (22% versus 6%; $p<0.0001$). Screened individuals were also more likely to have documentation of ever using alcohol (68% versus 43%; $p<0.0001$) and less likely to have ever smoked (37% versus 52%; $p<0.0001$).

To determine how LS screening guidelines were applied to the 41 individuals screened, we compared the actual tests used with the recommended LS screening guidelines which indicate screening for either MSI or IHC or both before proceeding to germline sequencing (Figure l).[7] Thirty nine (95%) started with MSI or IHC tumor testing. All 13 patients with IHC tests first were negative for LS; however, 3 individuals (23%) were not tested for all 4 genes. Of the 14 patients starting with MSI tests, 12 (86%) were MSI-L; one was MSI-H and had no further testing, and one received MSI testing but lacked test results or follow-up. Of the 12 patients with concurrent MSI and IHC tests, all genes were present on IHC. One was also MSI-H and was subsequently found to have the BRAF v600E sporadic mutation.[5,11] One patient with MSI-L results also had BRAF testing; however, the BRAF test was conducted a year later which may indicate testing for anti-EGFR treatment rather than for LS risk. Two patients had selective genetic sequencing only with no mutations found; however, none were tested for all 4 genes, despite available testing at time of diagnosis (Figure 1).

Due to the low rate of LS screening, we investigated documentation of family history (ever documented in record/ no documentation found) as the first step towards hereditary cancer risk assessment. Overall, 937 (79%) patients had documentation of family history, with 719 individuals having sufficient information recorded to evaluate for LS risk using family history-based criteria, after excluding individuals with "family history unknown," "no family history of colon cancer," "negative/noncontributory family history," and individuals with family history recorded in relatives but without a recorded age of diagnosis (Figure 2). Of the 937, 577 (62%) described a family history of any cancer, 350 (37% of 937) were described as negative, and ten (1% of 937) had family history information that could not be determined. Of patients with a negative family history, 249 (71% of 350) were documented as "no family history of cancer," 62 (18% of 350) had "no family history of colon cancer" and 39 patients (11% of 350) were recorded as "negative/noncontributory family history" (Figure 2). Because we do not know what the patient was asked in these 39 people, we cannot accurately assess whether these family histories included any other LS-associated cancers or not.

Of the 577 patients with a family history of cancer, 186 (32%) noted a history of non-LS associated cancers only (Figure 2). Of those with a family history positive for CRC or LS-associated cancer, 261 (67% of 391) had sufficient information to determine the patient met Amsterdam or revised Bethesda Criteria for further LS screening (Figure 2). An additional 107 patients (27% of 391) with a family history of CRC or LS-associated cancer could not be accurately assessed for LS risk, usually due to missing age of diagnosis in family members.

Using family history and diagnosis information available in the chart and the algorithms for LS screening guidelines, we also examined percent eligible for LS screening vs. percent actually screened. By any of the nine standards for referral criteria evaluated, the majority of eligible patients were not screened for LS, ranging from 75% (Amsterdam II criteria) to 100% (individuals with multiple CRCs) (Table 3). Of the individuals who did receive LS screening, the majority were appropriate candidates based on the referral criteria evaluated including the revised Bethesda Criteria (28/41 =68%), the PREMM model (35/41=85%), the MMRPredict model (34/41 =83%), and the EGAPP recommendation or the NSGCA-ICC joint guideline (41/41=100%).

DISCUSSION

We found underutilization of LS screening (41/1188 patients across all sites). When LS screening was conducted, the majority of patients followed the recommended screening cascade. Initial screening for LS can occur through IHC or MSI testing of tumor tissue. Current guidelines agree the most cost effective process is utilizing tumor testing via IHC and/or MSI first to guide germline genetic testing with no consensus that one of these tests is better than the other and often both are performed.[19,20] Consistent with LS screening guidelines for no preference between MSI and/or IHC as a first step,[5,7] we observed approximately equal numbers screened with either test or both tests concurrently. Where the recommended LS screening process was not followed, it was due to incomplete testing of all the genes, lack of follow through on a positive MSI or IHC test result, or no confirmation of MSI/IHC testing in the chart. Because BRAF testing and other testing such as MSI may be conducted for treatment decisions rather than LS screening, we did investigate whether this may be occurring. In only one instance did we find a suspicion of BRAF testing that was likely ordered for treatment based on the temporal relationship between diagnosis, testing, and treatment.

We examined LS screening indicators such as family history, multiple primary colon cancers, and age at diagnosis. Lack of family history information does not appear to be the reason for the low rate of LS screening, as 79% of our population had some documentation of family history. In order to be informative for LS, a family history should document any history of LS associated cancers beyond CRC and include the cancer type, relative affected (including the lineage), and the age at diagnosis. Like Wood,[28] we found sufficient information to assess for LS risk in two-thirds of charts, and 67% of the charts with a positive cancer history included enough information indicating LS risk based on Amsterdam II or revised Bethesda criteria. Of those individuals we could not assess, the charts frequently lacked age at diagnosis information for relatives with a LS associated cancer. This observed lack of complete family history information is also consistent with other reports.[29–31] Several other studies have also found that insufficient family history information in the EMR was the limitation for implementation of the Bethesda and Amsterdam II criteria.[32,33] Singh and colleagues[33] found that there was no documentation of family history in 7.6% of the records within the tertiary care EMR at the VA hospital, with age at cancer onset incomplete in up to 49% of the population. Similarly, there was incomplete documentation within the EMR of the Penn State Hershey Cancer Institute in 38% of the patients diagnosed with a LS-associated cancer within the study period.[32]

We were able to determine that approximately 22% of our study population was eligible for LS screening using the revised Bethesda criteria;[9] and 1% of the study population fell into the more restrictive Amsterdam II criteria.[22] Yet, only 3% of the population had any LS screening. This is consistent with multiple studies reporting underutilization of screening and referrals,[29,30,32–35] ranging from 7% – 9% of study populations receiving LS screening. We determined that 89% of patients meeting Bethesda criteria and 91% of patients with a positive family history of CRC or LS-associated cancer in more than 2 relatives did not have LS screening despite their elevated risk status. Despite the availability of LS screening programs at these organizations, no cases of LS were identified, and the only patient with a MSI-H result did not receive further testing. If we consider that 3% of CRCs would have had LS,[3,4,6,7,11] then approximately 35 cases of LS were missed among the 1188 members in the study population.

To improve LS identification there is clearly a need for reflexive (automatic) or universal screening of all newly diagnosed CRC patients. Beamer and colleagues[36] determined that 71% of the NCI-Comprehensive Cancer Centers were conducting reflexive LS screening, while only 15% of the community hospital cancer programs regularly screened for LS. Similar to our results, there was no consensus on initial screening test method, with 48% of programs testing via IHC, 14% using MSI, and 38% utilizing both screening tests. Screening at these institutions was rarely universal and was often triggered by particular criteria such as young age at onset, especially in the community hospital cancer programs. However, it is estimated that one in 4 individuals with LS will be missed utilizing family history or age-based screening criteria[37] and recently, Moreira and colleagues[38] used pooled data from four large cohorts of newly diagnosed CRC patients to determine that universal MMR testing of newly diagnosed CRC patients had greater sensitivity to detect LS compared with all other strategies; further strengthening the argument for universal screening. None of the institutions in our study were Comprehensive Cancer Centers and none had institutional screening guidelines nor did they have universal screening programs at the time of the study; however several organizations are currently taking steps to either implement or evaluate such programs (personal communication: Goddard K., April 2012, re: 1R01CA140377-01A2 (R01) Integrating Genetic Testing for Lynch Syndrome in a Managed Care Setting; Cold C., May 2012 re: Plans for Lynch Syndrome Screening in the Marshfield Clinic Pathology Department).

Our study has several limitations. We examined only metastatic CRC cases in this analysis. Providers may not consider LS screening in patients with advanced cancer due to decreased relevance of recurrence risk and additional cancers in the patient. However, investigation of LS screening within 3 of the institutions did not show a difference in LS screening for earlier stage at diagnosis (data not shown). We may have also underestimated the number of patients eligible for LS screening because “negative” or “non-contributory” family history does not necessarily mean enough information was asked to determine LS risk, and “no family history of colon cancer” may indicate that family history of endometrial and other LS-associated cancer was not assessed. Although we captured any cancer history for family members, for study participants, we only collected information on multiple primary CRCs and did not assess whether any individuals had a previous diagnosis of other LS associated cancers; therefore our estimate of eligible individuals due to multiple LS associated cancers may also be low.

In summary, we found very low identification and screening of newly diagnosed cancer patients for LS. Family history of CRC is documented for most individuals although this varies by site. Despite the brevity in which family history is recorded, a significant proportion of patients in the study population had enough family history information recorded to assess risk status for LS. However, only 3% of patients meeting criteria were screened for LS, representing severe under diagnosis of this hereditary condition in patients and their families.

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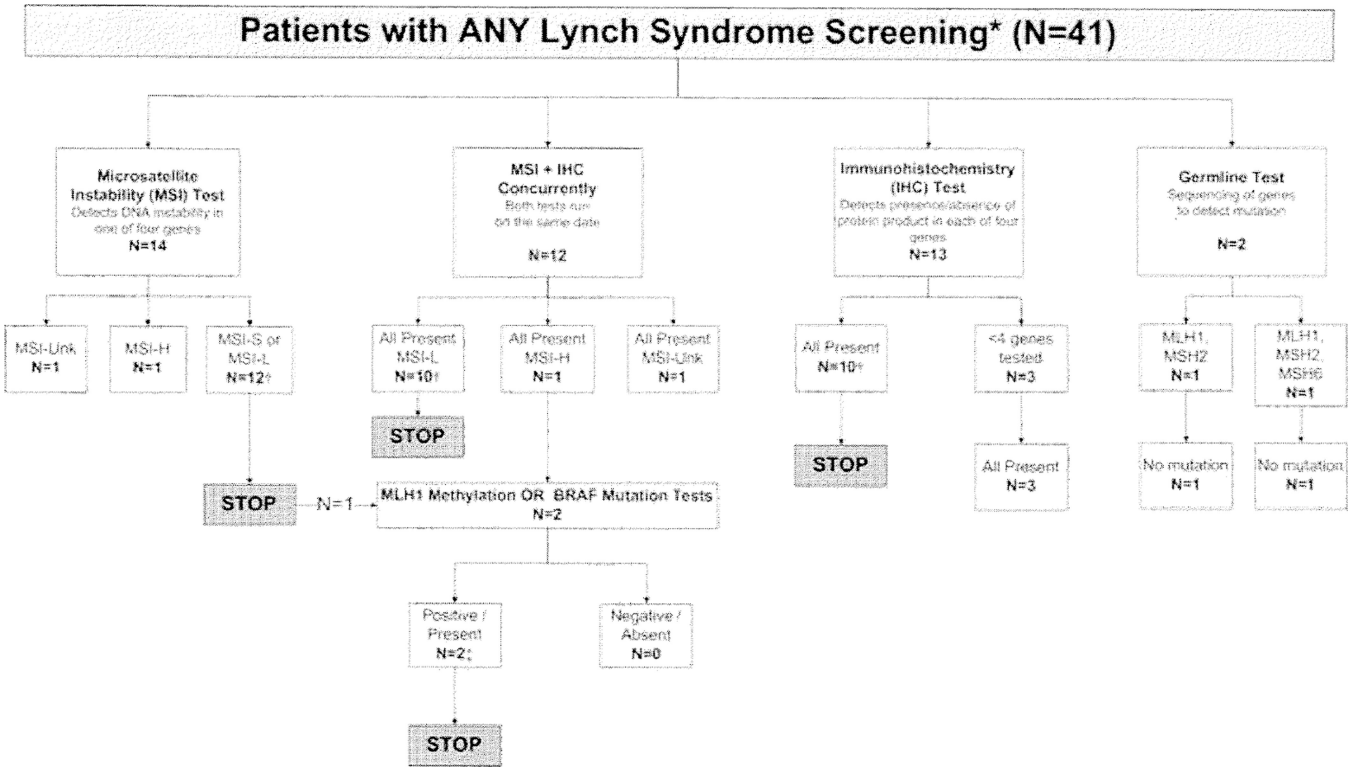

Figure 1. Flow Diagram of Lynch Syndrome Screening Conducted Among Patients in the Study Sample

Abbreviations: MSI-L indicates Microsatallite Instability Low; MSI-S indicates Microsatellite Instability Stable, MSI-H indicates Microsatellite Instability High

*Lynch Syndrome screening indicates any guideline-recommended combination of genomic microsatellite instability (MSI) and/or protein immunohistochemistry (IHC) tests, germline mutation analysis of MLH1, MLH2, MLH6, and PMS2 genes, as well as MLH1 hypermethylation studies and BRAF testing to detect sporadic MMR defects [5,7,11]

† Further testing is not indicated when tumors are MSI-L or MSI-S, or when all gene protein products are present on IHC because patients are assumed not to have Lynch Syndrome [4,20,37,38]

‡ Further testing is not indicated in the case of MLH1 methylation or BRAF v600E mutation because patients are assumed to not be at risk for Lynch Syndrome [3,5,7]

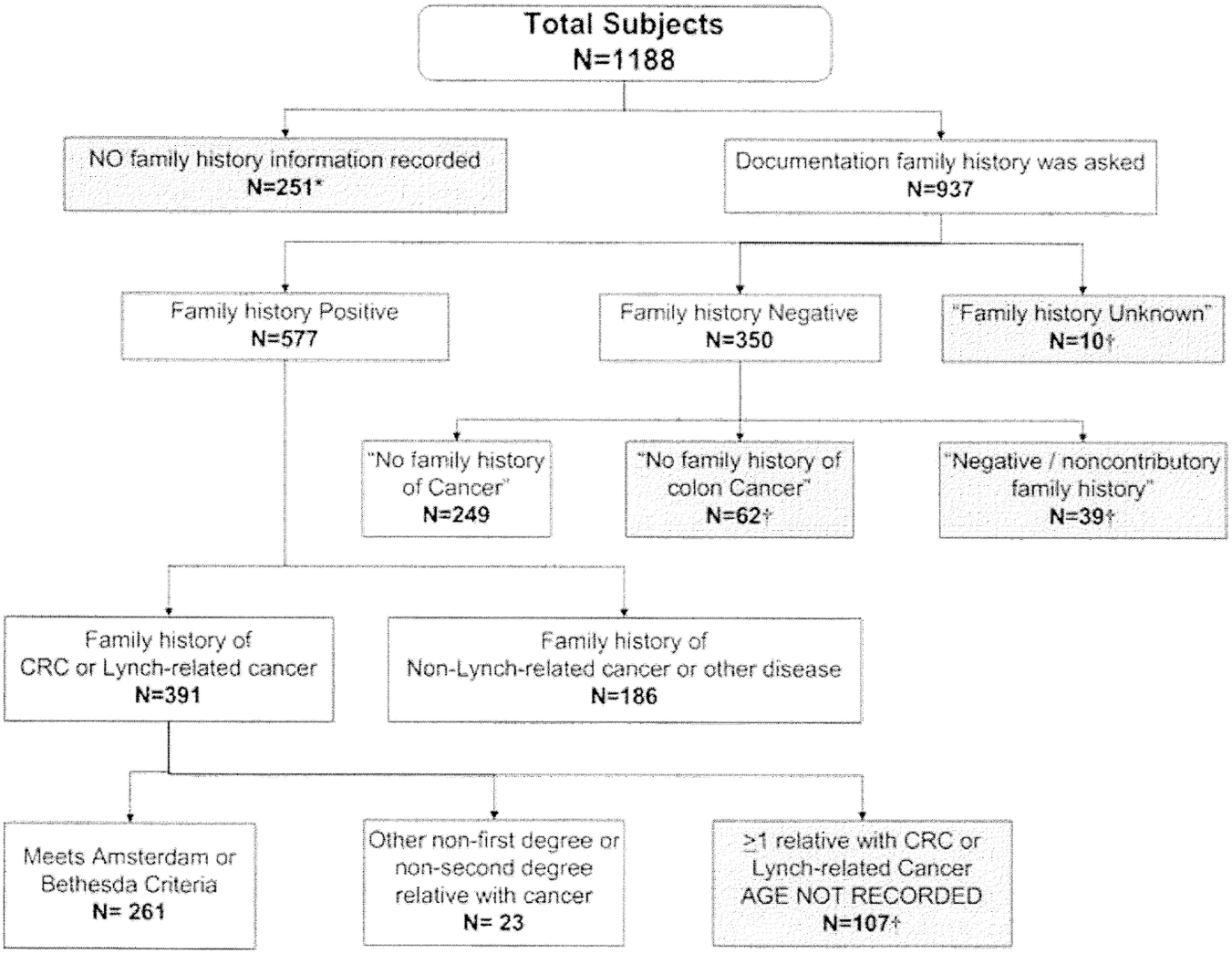

Figure 2. Availability and completeness of family history information recorded in patient medical records

Abbreviations: CRC = colorectal cancer

*No Family history information recorded (N=251) were not evaluated for Lynch Syndrome Risk

† Total N=719 (out of 937 with family history documentation) were evaluated for Lynch Syndrome risk: "Family history unknown" (N=10), "No family history of colon cancer" (N=62), "Negative/noncontributory family history" (N=39), and "≥1 relative with CRC or Lynch-related cancer AGE NOT RECORDED" (N=107) could not be evaluated for Lynch Syndrome risk due to insufficient information.

Table 1

Guidelines used to develop algorithms to evaluate cohort and recorded family history information

Guideline	Definition
≥ 1 first degree relative (FDR) with a LS associated tumor with diagnosis ≤ 50 years[6,9]	• A FDR is a parent, full sibling, or offspring. • A LS associated tumor is colon, gastric, endometrial, ovarian, sebaceous gland, transitional carcinoma of the ureter, glioblastoma, prostate or breast
≥ 2 FDR or second degree relative (SDR) with a LS associated tumor[6,9]	• A SDR is a grandparent, grandchild, uncle, aunt, nephew, niece, or half-sibling • The LS associated tumor can be diagnosed at any age
Amsterdam II criteria[22]	• 3 family members with LS-associated cancer, where one is a FDR of the other two AND • ≥2 generations have cancer diagnoses AND • ≥1 cancer diagnosed before age 50 AND • No Familial Adenomatous Polyposis (FAP)
Revised Bethesda Guidelines[8]	• CRC diagnosed in patient < 50 OR • Multiple CRC or LS-associated tumors present in one individual regardless of age OR • CRC with MSI-H histology diagnosed before age 60 OR • CRC in patient with ≥1 FDR with CRC or LS-associated tumor where at least one was diagnosed before age 50 OR • CRC in patient with ≥2 FDR or second degree relative (SDR) with CRC or LS-associated tumors regardless of age
MMRPredict[25]	• Age
Complex calculation to predict likelihood of MMR gene mutation that take into account information here	• Gender • Tumor location • Synchronous or metachronous tumor status • Diagnosis age before or after age 50 in FDRs • Family history of endometrial cancer
PREMM(1,2,6)[26]	• Patient age at diagnosis
Complex calculation to predict likelihood of MMR gene mutation that take into account information here	• Gender • Synchronous or metachronous tumor status of patient • Endometrial cancer or other LS-associated cancer in patient • CRC, Endometrial cancer or other LS-associated cancer in FDR and diagnosis age • CRC, Endometrial cancer or other LS-associated cancer in SDR and age of diagnosis
EGAPP Working Group recommendation[6]	• All newly diagnosed patients with CRC
NSGC /CGA-ICC Joint recommendation[5]	• All newly diagnosed patients with CRC or endometrial cancer

Table 2

Demographics of individuals who experienced Lynch Syndrome (LS) screening versus those who had no recorded LS screening

Demographic Characteristics	LS screening present*	LS screening absent	P[a]
Age at diagnosis, mean (sd)	58.3 (9.8)	71.2(10.9)	<0.0001
Female (%)	23 (56.1)	563 (49.1)	0.1873
White (%)	31 (75.6)	795 (69.3)	0.0769
Patient Asked about Family History (%)	36 (87.8)	897 (78.2)	0.0035
Family History Positive for Colon Cancer (%)	9 (22.0)	72 (6.3)	<0.0001
Ever Smoker (%)	15(36.6)	597 (52.0)	<0.0001
Ever Alcohol Use (%)	28 (68.3)	488 (42.5)	<0.0001
Metastatic Colon Cancer at diagnosis (%)	30 (73.2)	891 (77.7)	0.5318
Total N	41	1147	

Abbreviations: LS (Lynch Syndrome)

*LS screening indicates any guideline-recommended combination of genomic micro satellite instability (MSI) and/or protein immunohistochemistry (IHC) tests, germline mutation analysis of MLH1, MLH2, MLH6, and PMS2 genes, as well as MLH1 hypermethylation studies and BRAF testing to detect sporadic MMR defects [5,7,11]

[a]Reported *P* values were computed using Pearson's chi-square test (dichotomous variables) or the two sample t test (quantitative variables).

Table 3

Lynch Syndrome screening utilization by criteria

Criteria[a]	Total Fitting Criteria	LS screening present* (N=41)	LS Screening absent (N=1147)	P[b]
CRC Diagnosis ≤ 50[c]	138	31 (22%[d])	107 (78%)	<0.0001
Multiple primary CRCs[c]	32	0 (0.0%)	32 (100.0%)	<0.0001
≥ 1 FDR with LS associated tumor w/dx ≤ 50	18	3 (17%)	15 (83%)	<0.0001
≥ 2 FDR/SDR with LS associated tumor	106	10 (9%)	96 (91%)	<0.0001
Meets revised Bethesda Criteria	248	28(11%)	220 (89%)	<0.0001
Meets Amsterdam II Criteria	12	3 (25%)	9 (75%)	<0.0001
PREMM (1,2,6) model	238	35 (15%)	203 (85%)	<0.0001
MMRPredict model	194	34(18%)	160(82%)	<0.0001
EGAPP Working Group Criteria	1188	41 (3%)	1147(97%)	<0.0001
NSGC Criteria	1188	41 (3%)	1147(97%)	<0.0001

Abbreviations: LS (Lynch Syndrome)

*LS screening indicates any guideline-recommended combination of genomic microsatellite instability (MSI) and/or protein immunohistochemistry (IHC) tests, germline mutation analysis of MLH1, MLH2, MLH6, and PMS2 genes, as well as MLH1 hypermethylation studies and BRAF testing to detect sporadic MMR defects[5,7,11]

[a]Criteria are defined in Table 1.

[b]Reported *P* values were computed using Pearson's chi-square test comparing subjects with LS screening present / absent among those who met criteria, versus subjects with LS screening present / absent among those who did not meet criteria.

[c]CRC diagnosis ≤50 and Multiple primary CRCs refers to diagnoses in each individual patient in the cohort.

[d]All % are Row percentages.