Underdiagnosis of Lynch Syndrome Involves More Than Family History Criteria

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BACKGROUND & AIMS: 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 Veterans Affairs facility, between 1999 and 2007. A detailed review of the EHR was conducted to evaluate the presence of family history–related and non–family history–related criteria of the Bethesda guidelines. Patient outcomes (identification in clinical practice and referral for genetic testing) were also determined. **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 criteria was met for 57 patients (11.4%), none was 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%) who 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.

Lynch syndrome (previously referred to as hereditary nonpolyposis colorectal cancer [HNPCC]) is an autosomal dominant disorder that is found in approximately 2%–5% of all colorectal cancer (CRC) cases. It involves germline mutations in genes that encode DNA mismatch repair (MMR) proteins.[1,2] Inactivation of the DNA 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; therefore, clinicians might 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 were 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 might not fulfill the previously published Amsterdam II criteria.[13,14] Patients with CRC are recommended to undergo genetic testing if they fulfill 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 when younger than the age of 60 years; (4) had 1 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) had 2 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 family history of cancer assessment is often inadequate in clinical practice, even in specialized cancer centers.[1,15,16] However, many patients qualify for further diagnostic work up for Lynch syndrome on the basis of 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 pathologic criteria specified in Bethesda guidelines are present. It is unknown whether these "non–family history" criteria are appropriately recognized and whether they lead to referral for further genetic testing among patients diagnosed with CRC in the United States. We therefore used a compre-

Abbreviations used in this paper: CRC, colorectal cancer; EHR, electronic health record; HNPCC, hereditary nonpolyposis colorectal cancer; MMR, mismatch repair; MSI, microsatellite instability; VA, Veterans Affairs.

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hensive 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 younger than 80 years of age with pathologically confirmed CRC newly diagnosed at a tertiary care Veterans Affairs (VA) facility between 1999 and 2007. In this facility, patients are assigned to staff primary care practitioners 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 whether 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 February 2004, we did not apply them to "judge" practices at a time before that, ie, 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 pretested to determine 3 key elements: family history, non–family history criteria (such as age, presence of specified cancers, and pathology results), and patient outcomes. The study team supervised and trained 2 reviewers (R.S., G.A.) 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 1 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 contained a designated detailed pathology reports menu since 1995 as well as selected progress notes containing medical history. In addition to confirming CRC diagnosis, we evaluated the presence of any Lynch syndrome–related malignancies any time before the diagnosis or within 1 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 whether patients met Bethesda guidelines, did not meet Bethesda guidelines, or had uncertain Bethesda guideline status (as a result of either patients 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 whether any practitioner had suspected CRC related to a genetic or familial syndrome and whether the patient had been counseled regarding familial CRC, whether 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 1 year after CRC diagnosis. In addition, text searches with one of the terms "genetic," "familial," "hereditary," "HNPCC," or "Lynch" were 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 deviations for the continuous variables and frequencies and proportions for categorical variables.

Bethesda guidelines were summarized in 3 categories: (1) did not meet Bethesda guidelines (no criteria met), (2) met Bethesda guidelines (at least one criterion was met), and (3) Bethesda guideline status uncertain. Differences among the 3 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 (standard deviation, 9.0); 98.6% male; 51.1% non Hispanic white). At least one Bethesda criterion was