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SHORT COMMUNICATION

Successful implementation of Lynch syndrome screening in a safety net institution

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Abstract Lynch syndrome (LS) is the most common cause of hereditary colorectal cancer (CRC), and national guidelines recommend screening patients with CRC for LS. However, there is a paucity of data related to Lynch syndrome in the underserved population, in which unique issues of access, cultural beliefs regarding cancer, language barriers, immigration status, and financial restraints exist. We performed a descriptive, retrospective review of a selective LS screening protocol at an urban safety net hospital between 2009 and 2014 with the aim of describing the detected prevalence of LS as well as reporting the high quality and suboptimal screening rates. A total of 154 cases of CRC were identified over the 5-year period, of which 57 met selective LS screening criteria. Eleven patients had a positive screen, and three patients were diagnosed with LS, leading to an overall detected LS prevalence of 1.9 %. The rate of high quality screen was greater than 90 %, consistent with prior studies. Thus, we show that screening for LS in a safety net hospital can be successful in achieving high quality screening and provide an example for other public hospitals considering implementation of hereditary cancer screening.

Keywords Lynch syndrome · Hereditary colon cancer · Immunohistochemistry · Underserved screening

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death in the USA (Siegel et al. 2014). CRC incidence and mortality can be reduced by screening but the underserved population, including the uninsured, recent immigrants, and minority groups, has suboptimal screening rates (Gupta et al. 2014). At least 5–10 % of CRC cases are hereditary, and Lynch syndrome (LS), an autosomal dominant disorder caused by mutations in DNA mismatch repair (MMR) genes, is the most common hereditary cause of CRC (Giardiello et al. 2014; Syngal et al. 2015; Lynch and de la Chapelle 2003; Markowitz and Bertagnolli 2009). Identifying LS can confer cancer-related survival benefit for the patient and their affected family through intensive cancer surveillance programs and prophylactic surgery (Jarvinen et al. 2000; Schmeler et al. 2006). Studies evaluating LS prevalence and surveillance have been performed in North American white and western European populations (Hall and Olopade 2006), which limit the generalizability of published data to the underserved US population.

Two validated methods for LS screening have similar sensitivity and specificity: (1) microsatellite instability (MSI) testing or (2) immunohistochemistry (IHC) staining to identify absent MMR protein expression of the tumor (Hampel et al. 2008; Terdiman 2005). A positive screen is followed by genetic counseling and germline testing for MMR mutations to establish the diagnosis of LS.

Recently, universal screening of all CRC patients under the age of 70 years has been shown to be feasible (Hampel et al. 2005) and cost-effective (Ladabaum et al. 2011) prompting guideline recommendations (Giardiello et al. 2014; Syngal et al. 2015) for universal screening of all newly diagnosed patients with CRC. However, implementation requires a multidisciplinary approach with close integration of clinical

services and genetic testing is a complex and delicate matter (Ladabaum 2014). Furthermore, in resource-limited settings, screening only higher risk patients may be practical and there is considerable variation in the implementation of genetic screening in community hospitals (Cohen 2014; Karlitz et al. 2015). With the passage of the Affordable Care Act and the expansion of health insurance coverage, an increasing number of previously underserved patients seek medical care at safety net hospitals and further understanding of LS in this patient population is critical.

The aims of this study were to describe the implementation of LS screening at San Francisco General Hospital (SFGH), report the detected prevalence of LS and associated DNA mutations in the MMR genes, and to assess the quality in implementation of the LS screening protocol to identify barriers and challenges to success.

Methods

Screening protocol

SFGH is a safety net institution (i.e., provides a significant level of care to low income, uninsured and vulnerable populations) affiliated with the University of California, San Francisco (UCSF). Patients are ethnically diverse (20 % African American, 20 % Asian/Pacific Islander, 25 % Caucasian, and 30 % Hispanic), and many are immigrants with more than 20 different languages spoken by patients. Approximately, 36 % of outpatients at SFGH lack insurance, 34 % have MediCal (California's Medicaid program), 16 % have Medicare, and 14 % report commercial payers or other sources.

SFGH began screening for LS in January 2009; IHC screening was initiated by the pathology department in patients with surgically resected CRC who were 50 years or younger, had tumors with histological characteristics suggestive of MSI, or had synchronous CRC detected on surgical pathology. These selective screening criteria included some of the Revised Bethesda Guidelines (Umar et al. 2004) and were similar to criteria used by UCSF (Kidambi et al. 2015). Informed consent from patients to screen their tumors for Lynch syndrome was not required to be obtained per institution protocol. A positive screen (absent IHC staining for MSH2, MSH6, or PMS2 or absent MLH1 staining with negative BRAF V600E mutation testing) was indicated on the surgical pathology report with a statement regarding the interpretation and was available in the patients' electronic medical record to the treating oncologists, surgeons, and gastroenterologists. Patients were identified as candidates for genetic counseling either during tumor board presentations, or the treating clinicians were responsible for following up on abnormal screens.

At SFGH, two genetic counselors working through UCSF were available for counseling services once per week on-site at SFGH. Once referrals were forwarded to the genetic counselor, patients were contacted via telephone to schedule genetic counseling. Patients who accepted were counseled and offered germline testing. Telephone interpreters were used for counseling non-English speaking patients, and written educational materials in the patient's spoken language were utilized. Genetic counseling was offered free of charge, and genetic testing was typically covered by the patient's health insurance, such as MediCal or Healthy San Francisco (San Francisco's health insurance for low-income patients not qualifying for MediCal). Patients without health insurance qualified for Myriad's Hardship Program, which offered free CRC genetic panel testing to low-income patients.

Study design

A retrospective study examining implementation of LS screening from January 2009 through December 2014 at SFGH was performed. The medical records of all patients with surgically resected CRC at SFGH between January 2009 and December 2014 were reviewed to identify patients that met LS screening criteria; CRC tumors referred from an outside hospital and neuroendocrine tumors were excluded. Each patient's medical chart was reviewed to determine whether the patient met LS screening criteria.

Outcome

Demographic and CRC data was collected on all patients and, for positively screened patients, the outcomes of genetic counseling were gathered. Utilizing previously described (Marquez et al. 2013) definitions for LS screening metrics, a "high quality screen" was defined as either completion of IHC screening with a normal result in a patient meeting screening criteria, or completion of IHC screening with an abnormal result, followed by genetic counseling and germline testing. A "suboptimal screen" was defined as either failure to complete IHC screening in a patient meeting screening criteria or failure to complete genetic counseling or genetic testing after an abnormal IHC screen. The prevalence of LS in this study was the number of cases of LS as a proportion of the total cases of CRC included in the study.

Results were reported as mean (standard deviation) for continuous data or number of patients (percentage by screening method or result) for categorical data. Descriptive data was analyzed using the SPSS statistical software (version 21, Chicago, IL). This study was approved by the UCSF institutional review board.

Results

A total of 163 cases of CRC were surgically resected between January 2009 and December 2014, and nine cases met exclusion criteria. Of the remaining 154 cases, 57 (37.0 %) met screening criteria (17 cases met age criteria, 33 tumors had MSI histology, and seven cases had synchronous CRC). Figure 1 depicts the outcomes of screening and genetic counseling follow-up. Of the 97 cases that did not meet screening criteria, 83 patients (85.6 %) were between the ages of 50 and 70 years. Three cases of LS were diagnosed; thus, the overall prevalence of LS was 1.9 % amongst all patients with CRC with a detection rate of 5.2 % amongst those who underwent screening.

Table 1 shows demographic and CRC characteristics for included patients. As expected, patients who were screened were younger than those who were not (mean age 55.9 vs 62.2 years, respectively). Across all groups, patients of Asian ethnicity formed the majority, though an equal percentage of Hispanics had a positive screen.

The characteristics of the 11 patients with a positive IHC screen are shown in Table 2. Patients were seen by a genetic counselor on average (mean) 5 months after diagnosis of CRC (range of 1 to 19 months, median of 4 months). All three patients with LS had a family history of early CRC in a first-degree relative, and two patients had multiple family members with LS-related cancers. One patient who tested negative for LS was diagnosed with MYH-associated polyposis, a known hereditary colon cancer syndrome. One patient with a positive screen was not referred for counseling as CRC was diagnosed during a hospitalization for bowel obstruction requiring colectomy, and the patient passed away shortly thereafter from end stage acquired immunodeficiency syndrome (AIDS).

The rate of high quality screening was 91.2 %. Of the suboptimal screens (8.8 %), two patients were not referred for genetic counseling by the treating clinicians, two patients who received genetic counseling did not follow up for germline testing as recommended during their visit to the genetic counselor, and one patient refused germline testing after

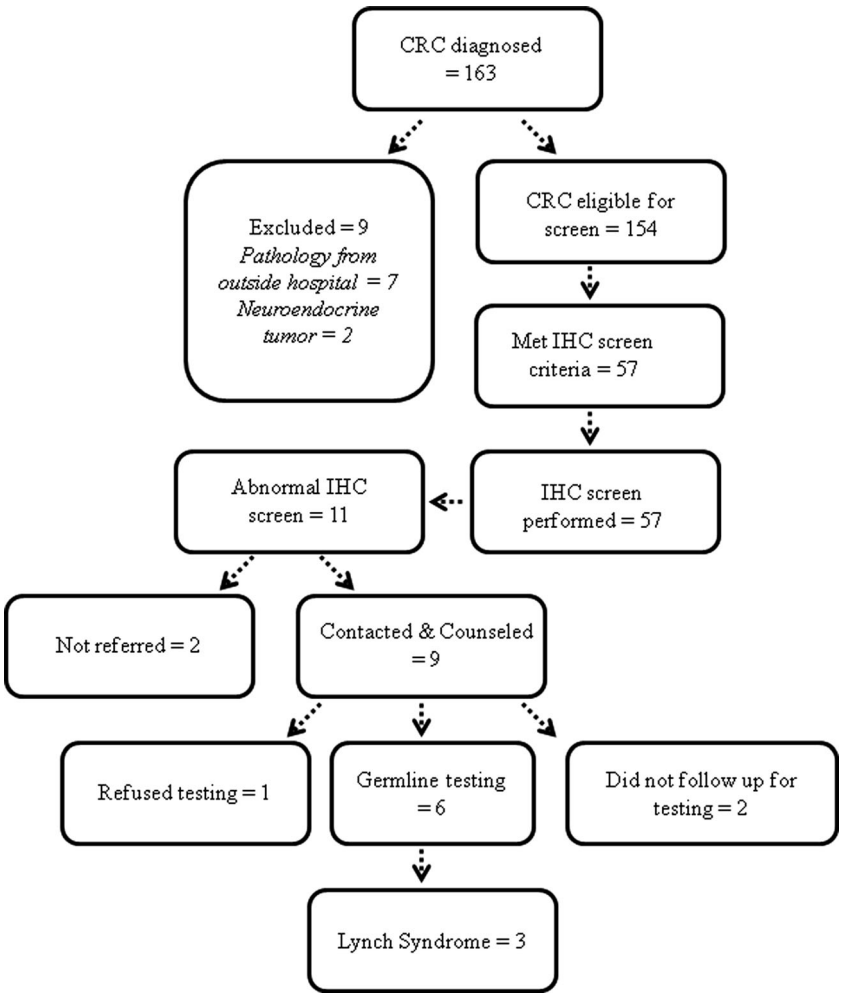

Fig 1 Lynch syndrome screening protocol and outcomes. *CRC* colorectal cancer, *IHC* immunohistochemistry

Table 1 Baseline characteristics of screened and unscreened patients with colon cancer

	Not screened ($N = 97$)	Normal screen/negative IHC screen ($N = 46$)	Positive screen for IHC ($N = 11$)
Age (SD)	62.2 (7.0)	55.9 (10.7)	55.5 (7.9)
Male sex	51 (52)	25 (54)	7 (63.6 %)
Race			
White	18 (18.6)	9 (19.6)	2 (18.2)
Black	18 (18.6)	5 (10.9)	1 (9.1)
Hispanic	5 (5.2)	10 (21.7)	4 (36.4)
Asian	56 (57.6)	22 (47.8)	4 (36.4)
Birthplace			
USA	20 (20.6)	10 (21.7)	4 (36.4)
Central/South America	14 (14.4)	10 (21.7)	2 (18.1)
Europe	5 (5.2)	4 (8.7)	0 (0)
Asia	54 (55.7)	20 (43.5)	4 (36.3)
Unknown	4 (4.1)	2 (4.3)	1 (9.1)
Insurance			
County-funded	16 (16.5)	12 (26.1)	4 (36.3)
Medicare	22 (22.7)	8 (17.4)	1 (9.1)
Medicaid	22 (22.7)	11 (23.9)	2 (18.2)
HMO/PPO	30 (30.9)	10 (21.7)	3 (27.3)
Self-pay	2 (2.1)	2 (4.3)	1 (9.1)
Unknown	5 (5.1)	3 (6.5)	0 (0)
Colon cancer site			
Ascending	22 (22.7)	13 (28.3)	3 (27.3)
Transverse	13 (13.4)	8 (17.4)	4 (36.3)
Descending	14 (14.4)	1 (2.2)	2 (18.2)
Sigmoid	48 (49.5)	24 (52.2)	2 (18.2)
TNM stage			
I	37 (38.1)	6 (13.0)	1 (9.1)
II (A–C)	22 (22.7)	13 (28.3)	6 (54.5)
III (A–C)	25 (25.8)	17 (40.0)	4 (36.3)
IV (A–B)	13 (13.4)	10 (21.7)	0 (0)

Unless otherwise noted, listed as number of cases (%N). *SD* standard deviation, *IHC* immunohistochemistry

counseling due to minimal contact with siblings and lack of children that he perceived would benefit from the knowledge of a diagnosis of LS.

Discussion

This is the second study (Marquez et al. 2013) to report on the outcomes of LS screening in a safety net hospital, and the primary outcome showing a high quality screening rate over 90 % confirms that implementation of screening for hereditary CRC in the safety net setting can be successful. The prevalence of LS in our diverse patient population was 1.9 %, which is similar to the prevalence in the largest pooled screening study (Pinol et al. 2005), though because less than 40 % of patients met LS screening criteria in our study this likely leads to a low estimate of the true prevalence. Furthermore, given the results of a recent state-level database study from Louisiana (Karlitz et al. 2015) showing public hospitals were the least likely to test for MSI in young CRC patients, the favorable outcomes we demonstrate provide a framework for LS screening implementation that may be applicable to other safety net hospitals.

The issue of screening for CRC in the underserved population has been described in detail previously (Gupta et al. 2014), but there is a paucity of data when it comes to screening for hereditary CRC syndromes. Unique factors include access, cultural beliefs regarding cancer, language barriers, immigration status, and financial restraints [Gupta et al. 2014; Hall and Olopade 2006), and the protocol at SFGH sought to address

Table 2 Characteristics of patients with positive immunohistochemistry screen for Lynch syndrome

Age	Sex	Race	Language	Insurance	CRC location	Stage	IHC results	Notes	Germline test results
52	Male	Hispanic	Spanish	Medicaid	Ascending	IIIB	MSH2PMS2	Father CRC	Positive for LS: MSH2 2393del4
63	Male	Hispanic	Spanish	Medicare	Ascending	IIIA	MSH2MSH6	Family history of multiple Lynch-related cancers	Positive for LS: MSH6 c 3103C>T (p. Arg1035)
68	Female	Hispanic	Spanish	Medicaid	Transverse	IIIB	MLH1PMS2	3 synchronous CRC; Family history of multiple Lynch-related cancers	Positive for LS: MLH1 Exon 14 del
45	Male	Hispanic	Spanish	County-funded	Sigmoid	IIIC	PMS2	No family history	Negative for LS
44	Male	White	English	County-funded	Transverse	IIA	MLH1PMS2	Grandfather melanoma, father small cell lung cancer	Negative for LS
51	Female	Chinese	Cantonese	HMO/PPO	Sigmoid	I	MLH1PMS2	No family history of cancers	Negative for LS. Positive for MutY Homolog c934-2A>G
49	Male	Chinese	Chinese	Self-pay	Ascending	IIA	PMS2	No family history of cancers	Did not want germline testing
62	Female	Chinese	Chinese	County-funded	Descending	IIA	MSH2 MSH6	No family history	Did not follow up for testing
56	Male	Black	English	HMO/PPO	Descending	IIA	MSH2MSH6	Mother pancreatic cancer	Did not follow up for testing
57	Male	Chinese	Cantonese	County-funded	Transverse	IIA	MLH1	No referral placed for genetic counseling	–
63	Female	White	English	HMO/PPO	Transverse	IIB	MLH1PMS2	Patient passed away of end stage AIDS	–

LS Lynch syndrome

these issues. Genetic counseling was provided on-site to mitigate geographical access barriers. Language barriers were addressed using telephone interpreters and providing educational materials in the patients' native language. Financial restraints were alleviated by offering free genetic counseling and either ordering germline tests covered by the patients' insurance or enrolling the patient in the Myriad Hardship Program, which offered free testing to qualified patients. Cultural barriers were the most challenging to address and relied on the expertise of the genetic counselors and clinicians caring for the patients.

Other important aspects of the screening protocol deserve mention. Screening criteria were limited to "high risk" CRC patients utilizing criteria from the Revised Bethesda Guidelines due largely to limited financial resources; this was confirmed in the analysis, which showed that implementing guideline recommended screening of all CRC patients 70 years or younger would have increased the number of patients screened by 150 %.

Referrals for genetic counseling were initiated by physicians, and this was successfully performed in all but one case, in which an indicated referral was not placed. A previous study showed automatic referrals, in which genetic counselors took the responsibility for follow-up, most likely to lead to patients receiving counseling and germline testing (Heald et al. 2013), but this strategy was not utilized in our protocol because a mechanism for automatic referrals was not available when the screening protocol was initially implemented. Six of the nine patients who were counseled agreed to germline testing, which is lower than the results of research protocol-based studies in which over 90 % of patients underwent germline testing [Hampel et al. 2005; Hampel et al. 2008), but is consistent with results from studies of routine clinical practice (Heald et al. 2013; Kidambi et al. 2015a) adding to the observation that future efforts in LS screening implementation must focus on educating and engaging all positively screened patients (Kidambi and Terdiman 2015). We are currently investigating quality improvement measures such as utilizing a newly created electronic ordering system to incorporate electronic referrals to genetic counseling and creating a mechanism to better follow up with patients who do not return for genetic counseling.

The results of this study are consistent with those of Marquez et al. (2013), who reported 1-year outcomes of IHC-based screening in CRC patients 70 years or younger pooled from an academic medical center and a safety net hospital (Parkland Health and Hospital). Our selective screening protocol achieved a slightly better high quality screening rate

than that of Parkland's universal protocol (90 vs 78 %), which may be due to a larger sample size or differences in the demographics of the patients with Asians and Hispanics accounting for the majority of SFGH patients and blacks making up the majority of Parkland's cohort. In both studies, nearly all patients received counseling, though all patients in the Parkland study who were counseled underwent testing as opposed to just 67 % in our study and the reasons for this difference are not clear, but may be due to differences in the cultural backgrounds of our largely immigrant patient population. Ultimately, the results of both studies confirm that LS screening in the safety net setting is feasible and has the potential to satisfy quality metrics. Given the positive results of this study, we hope to improve the screening process at SFGH with the goal of a 100 % high quality screening rate.

There were limitations to our study. The sample size was small, but because the results were generated as a part of routine clinical practice they are interpretable and potentially generalizable to other safety net settings serving a similar patient population. Additionally, like many urban safety net county hospitals, SFGH is affiliated with an academic center, which may limit the findings to similar hospitals. Larger, multi-center studies in the safety net setting would better address this issue of generalizability.

In conclusion, we report a successful framework for implementation of LS screening in the safety net setting and confirm that high quality screening for LS is possible. The prevalence of LS in our diverse population of patients with CRC was at least 1.8 %. We believe critical components of a successful LS screening protocol in a safety net setting include automatic pathology testing of tumor samples that meet screening criteria, strong communication between clinicians treating patients, genetic counseling available near the clinical treatment facilities (i.e., hospital or clinic) to mitigate geographical barriers to access, educational materials in the patient's native language, and close attention to financial barriers experienced by the patient. This is only the second study in this patient population and adds to the sparse literature on this important topic.

Compliance with ethical standards This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of interest The authors declare that they have no conflicts of interest.

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