Screening for Germline Mismatch Repair Mutations Following Diagnosis of Sebaceous Neoplasm

Jessica N. Everett, MS, CGC; Victoria M. Raymond, MS; Monica Dandapani, MS; Monica Marvin, MS; Wendy Kohlmann, MS; Anu Chittenden, MS; Erika Koeppe, MPH; Shanna L. Gustafson, MS, MPH; Tobias Else, MD; Douglas R. Fullen, MD; Timothy M. Johnson, MD; Sapna Syngal, MD; Stephen B. Gruber, MD, PhD, MPH; Elena M. Stoffel, MD, MPH

IMPORTANCE Sebaceous neoplasms (SNs) define the Muir-Torre syndrome variant of Lynch syndrome (LS), which is associated with increased risk for colon and other cancers necessitating earlier and more frequent screening to reduce morbidity and mortality. Immunohistochemical (IHC) staining for mismatch repair (MMR) proteins in SNs can be used to screen for LS, but data on subsequent germline genetic testing to confirm LS diagnosis are limited.

OBJECTIVE To characterize the utility of IHC screening of SNs in identification of germline MMR mutations confirming LS.

DESIGN, SETTING, AND PARTICIPANTS Retrospective study at 2 academic cancer centers of 86 adult patients referred for clinical genetics evaluation after diagnosis of SN.

MAIN OUTCOMES AND MEASURES Results of tumor IHC testing and germline genetic testing were reviewed to determine positive predictive value and sensitivity of IHC testing in diagnosis of LS. Clinical variables, including age at diagnosis of SN, clinical diagnostic criteria for LS and Muir-Torre syndrome, and family history characteristics were compared between mutation carriers and noncarriers.

RESULTS Of 86 patients with SNs, 25 (29%) had germline MMR mutations confirming LS. Among 77 patients with IHC testing on SNs, 38 (49%) had loss of staining of 1 or more MMR proteins and 14 had germline MMR mutations. Immunohistochemical analysis correctly identified 13 of 16 MMR mutation carriers, corresponding to 81% sensitivity. Ten of 12 patients (83%) with more than 1 SN had MMR mutations. Fifty-two percent of MMR mutation carriers did not meet clinical diagnostic criteria for LS, and 11 of 25 (44%) did not meet the clinical definition of Muir-Torre syndrome.

CONCLUSIONS AND RELEVANCE Immunohistochemical screening of SNs is effective in identifying patients with germline MMR mutations and can be used as a first-line test when LS is suspected. Abnormal IHC results, including absence of MSH2, are not diagnostic of LS and should be interpreted cautiously in conjunction with family history and germline genetic testing. Use of family history to select patients for IHC screening has substantial limitations, suggesting that universal IHC screening of SNs merits further study. Clinical genetics evaluation is warranted for patients with abnormal IHC test results, normal IHC test results with personal or family history of other LS-associated neoplasms, and/or multiple SNs.
Lynch syndrome (LS) is caused by germline mutations in genes involved in the DNA mismatch repair (MMR) pathway (MLH1 [OMIM 120436], MSH2 [OMIM 609309], MSH6 [OMIM 600678], PMS2 [OMIM 600259], and TACSTD1/EPCAM [OMIM 185535]) and is associated with increased risk for several cancers including colorectal, endometrial, ovarian, gastric, biliary tract, pancreatic, urinary tract, and central nervous system tumors.1 The association of sebaceous neoplasms (SNs) of the skin, including sebaceous carcinomas and sebaceous adenomas, with internal malignancies was first described in the dermatology literature in 1967 and referred to as Muir-Torre syndrome (MTS).2,3 In 1981, Lynch et al reported SNs in 3 kindreds with LS with pathogenic germline mutations, further defining MTS as a clinical variant of LS.

Identification of patients with LS is clinically valuable given availability of risk-reducing strategies, including earlier and more frequent colonoscopy and prophylactic hysterectomy and bilateral salpingo-oophorectomy, to reduce cancer-related morbidity and mortality.5,6 Routine screening of colorectal and endometrial cancers for evidence of MMR deficiency, including presence of microsatellite instability (MSI) and/or absent expression of the MMR proteins by immunohistochemical (IHC) analysis, has shown that 2% to 4% of colorectal cancers and 2% to 5% of endometrial cancers are associated with LS.7,8 This universal tumor-screening approach has better sensitivity than clinical criteria for identifying patients with LS and has the potential to be cost-effective if individuals and their at-risk relatives can be identified and screened to reduce morbidity and mortality.9 Given the experience with colorectal and endometrial cancers, routine screening of SNs for MMR deficiency to identify LS has been proposed.10-12 Several studies have examined the use of MSI and IHC testing to screen unselected SNs and have shown prevalence of MMR deficiency ranging from 25% to 60%.13-16 However, most of these studies had limited or no information on germline genetic test results; thus, data regarding the prevalence of germline MMR mutations confirming LS among individuals with SNs, as well as sensitivity and specificity of SN tumor testing, are limited.

Our objective was to characterize the utility of MSI and IHC screening of SNs in identification of germline MMR mutations confirming LS. We analyzed data on all patients with SNs evaluated at 2 large clinical cancer genetics programs to examine outcomes of tumor screening and germline genetic testing.

Methods

Permission for research was approved by the institutional review boards of the University of Michigan Comprehensive Cancer Center (UMCCC) and the Dana-Farber Cancer Institute (DFCI). Patients provided written consent to participate in DNA-banking registries, granting access to deidentified medical and family history and use of this information for publication. Participants were identified through review of patients enrolled in research registries of the cancer genetics clinics at UMCCC and DFCI from January 2000 through September 2012. Individuals with diagnoses of sebaceous carcinoma, sebaceous adenoma, sebacea, and sebaceous epithelioma were included in the analysis; patients with sebaceous hyperplasia were excluded. Clinical demographic information including age, SN location and subtype, and other cancer diagnoses was recorded for each participant. Results from clinically performed tumor testing, including MSI and IHC testing for DNA MMR proteins and germline genetic testing for mutations in the MLH1, MSH2, MSH6, PMS2, and/or TACSTD1/EPCAM genes, were reviewed. All clinical testing was completed over the 12-year study period in laboratories with College of American Pathologists accreditation and Clinical Laboratory Improvement Amendments licensure, in accordance with accepted standards. Four-generation family histories were evaluated for cancer diagnoses among relatives and categorized according to Amsterdam I and II clinical diagnostic criteria for LS.17,18 For patients not meeting Amsterdam criteria, PREMM1,2,6 risk scores19 were calculated to estimate risk for MMR mutation on the basis of personal and family history of LS-related cancers. Colon adenomas were not incorporated. Cancers in relatives were confirmed where records were available.

To evaluate differences in demographic, clinical, and familial characteristics between groups, we conducted t tests and Wilcoxon-Mann-Whitney tests for continuous variables and χ² and Fisher exact tests for categorical variables. Bonferroni corrections were applied to P values to adjust for multiple comparisons.

Results

Eighty-six patients with SN from 86 independent families presented for genetic evaluation during the study period (66 at UMCCC, 20 at DFCI). A total of 107 SNs were diagnosed among the 86 patients, including 52 sebaceous adenomas, 45 sebaceous carcinomas, 5 sebaceomas, 3 sebaceous epitheliomas, and 2 SNs without further information. Twelve patients had more than 1 sebaceous lesion. Pathogenic or suspected pathogenic germline MMR mutations confirming LS were identified in 25 (29%) of 86 patients with SN referred for genetic evaluation. Mutations identified included 18 in MSH2, 5 in MLH1, 1 in MSH6, and 1 in PMS2. Two variants of uncertain significance (VUSs) were identified (1 in MSH2, 1 in MSH6).

Nine patients presenting on the basis of SN diagnosis were found to carry MMR mutations without any testing of their SN tumors. Reasons that testing of SNs was not completed included known MMR mutation in the family (3 of 9), tumor testing performed on a different LS-related tumor (4 of 9), and family history meeting Amsterdam I or II clinical diagnostic criteria warranting direct germline genetic testing (2 of 9).

The remaining 77 patients underwent tumor analysis for MMR deficiency on a single SN. The MSI testing could not be completed in 37 SN tumors (48%) because of insufficient sample (individual MSI results are reported in Table 1 and Table 2); IHC analysis was completed on all 77 SN tumors. Immunohistochemical analysis revealed that 38 of 77 SNs (49%) had absent expression of 1 or more MMR proteins. Twenty-
seven had absent expression of MSH2 or MSH2/MSH6; 9 (33%) of these were found to carry germline MSH2 mutations. Nine had absent expression of MLH1 or MLH1/PM2; 4 (44%) of these had germline MLH1 mutations. Two patients had equivocal IHC staining for MSH6 only; 1 had a pathogenic MSH6 mutation and 1 had a VUS in MSH6. None of the samples demonstrated isolated absence of PMS2 expression. In total, 14 of 38 patients with abnormal IHC test results on SN were confirmed to carry pathogenic germline MMR mutations, for a positive predictive value of 37% for IHC screening (Figure, Table 1, Table 2).

Several significant differences were noted between those with pathogenic germline MMR mutations (n = 25) and those with abnormal IHC expression but without germline MMR mutations (n = 23) (Table 3). Mean age at diagnosis of SN among mutation carriers was significantly younger than in those without mutations (54.8 vs 67.2 years; P < .001, t test). Patients with MMR mutations were significantly more likely to have more than 1 SN (40% vs 0%; P < .001, Fisher exact test), and 10 of 12 patients (83%) with more than 1 SN had pathogenic germline MMR mutations, making this a strong predictor of mutation status. One patient with more than 1 SN had a VUS in MSH6. Family history differences, as measured by adherence to clinical diagnostic family history criteria and risk model scores, were also noted. Of patients with MMR mutations, 48% met Amsterdam I or II criteria, compared with 4% in the group without mutations (P < .001). Among individuals with family his-

Abbreviations: ACC, adrenocortical carcinoma; BL, bladder cancer; CRC, colorectal cancer; DCIS, ductal carcinoma in situ; ellipses, not applicable; EN, endometrial adenocarcinoma; FA, father; FH, fibrous histiocytoma; GBM, glioblastoma multiforme; IHC, immunohistochemical; LS, Lynch syndrome; MA, maternal aunt; MA, maternal uncle; MG, maternal grandmother; MO, mother; MSI, microsatellite instability; MU, maternal uncle; OV, ovarian cancer; PA, paternal aunt; PGF, paternal grandfather; PGM, paternal grandmother; PU, paternal uncle; question mark, unknown; RCC, renal cell carcinoma; S, sister; SA, sebaceous adenoma; SC, sebaceous carcinoma; SN, sebaceous neoplasm; UR, ureteral cancer; VUS, variant of uncertain significance.

aLS-associated cancers include colorectal, endometrial, ovarian, stomach, small intestine, urinary tract or kidney, bile duct, GBM, sebaceous gland, and pancreas.

bHigh, stable, and low indicate that >30%, 1%-30%, and 0% of markers demonstrate instability, respectively.

cAmsterdam I or II indicates 3 or more individuals with a diagnosis of LS-associated tumor, 2 successive generations affected, at least 1 individual receiving the diagnosis before age 50 years.

dPMS2 stain read as “weak”; germline testing was completed for all mismatch repair genes.

eMSH6 stains read as equivocal or uninterpretable; MLH1 and MSH2 stains had normal results.

fReported as “suspected pathogenic” by clinical laboratory.
Table 2. Patients With No Germline Mismatch Repair Mutations Detected

<table>
<thead>
<tr>
<th>Sex</th>
<th>SN</th>
<th>Other*</th>
<th>Cancer History, Type (Age at Diagnosis, y)</th>
<th>Family History of LS-Associated Cancers, Relationship: Type (Age at Diagnosis, y)</th>
<th>PREMM1,2,6, %c</th>
<th>Tumor Analysis Result</th>
<th>MSIe</th>
<th>IHC Test Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>SC (77)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>5.1</td>
<td>High</td>
<td>MLH1/PMS2</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>SC (60)</td>
<td>...</td>
<td>...</td>
<td>MG: CRC (88)</td>
<td>&lt;5</td>
<td>...</td>
<td>MLH1</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA (60)</td>
<td>...</td>
<td>...</td>
<td>MG: CRC (70s); MU: PAN (73)</td>
<td>&lt;5</td>
<td>Stable</td>
<td>MLH1/PMS2</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA (62)</td>
<td>...</td>
<td>MO: CRC (75)</td>
<td>...</td>
<td>&lt;5</td>
<td>High</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SC (63)</td>
<td>CRC (25); BL (61)</td>
<td>Amsterdam I</td>
<td>...]</td>
<td>...</td>
<td>5.1</td>
<td>High</td>
<td>MSH2/MSH6</td>
</tr>
<tr>
<td>F</td>
<td>SA (70)</td>
<td>...</td>
<td>MO: RCC (63); MGF: STO (57)</td>
<td>...</td>
<td>&lt;5</td>
<td>...</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>SA (45)</td>
<td>...</td>
<td>FA: CRC (71); PGM: CRC (92)</td>
<td>...</td>
<td>&lt;5</td>
<td>...</td>
<td>MSH2</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA (77)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>5.1</td>
<td>High</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SN (50)</td>
<td>...</td>
<td>PA: CRC (30s)</td>
<td>...</td>
<td>9.6</td>
<td>...</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SC (61)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>5.1</td>
<td>High</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SC (59)</td>
<td>...</td>
<td>MO: EN (82)</td>
<td>...</td>
<td>10.1</td>
<td>...</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SN (77)</td>
<td>CLL/SLL (73)</td>
<td>S: PAN (56)</td>
<td>...</td>
<td>6.9</td>
<td>High</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>SN (81)</td>
<td>...</td>
<td>PU: STO (?)(?)(?)</td>
<td>...</td>
<td>&lt;5</td>
<td>...</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SN (73)</td>
<td>BL (64)</td>
<td>MO: PAN (70)</td>
<td>...</td>
<td>6.9</td>
<td>...</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA (75)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>5.1</td>
<td>High</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>F*</td>
<td>SA (71)</td>
<td>...</td>
<td>S: CRC (70); BL (70)?</td>
<td>...</td>
<td>&lt;5</td>
<td>...</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SN (68)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>5.1</td>
<td>...</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SC (60)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>5.1</td>
<td>High</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>SA (76)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>5.1</td>
<td>...</td>
<td>MSH2/MSH6f</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SC (63)</td>
<td>RCC (52)</td>
<td>MGM: STO (80s)</td>
<td>...</td>
<td>5.9</td>
<td>High</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA (75)</td>
<td>...</td>
<td>MO: BL (80s)</td>
<td>...</td>
<td>8.1</td>
<td>High</td>
<td>MSH2/MSH6</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SC (69)</td>
<td>...</td>
<td>MU: BL (?)(?)</td>
<td>...</td>
<td>5.9</td>
<td>...</td>
<td>MLH1/PMS2</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA (74)</td>
<td>PRO (60)</td>
<td>B: CRC (50); MU: CRC (73)</td>
<td>...</td>
<td>&lt;5</td>
<td>High</td>
<td>MLH1/PMS2</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA (62)</td>
<td>SCC (51)</td>
<td>MO: CRC (63); MGM: RCC (70s)</td>
<td>...</td>
<td>6.4</td>
<td>...</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>SA (73)</td>
<td>...</td>
<td>S: CRC (54); MO: CRC (52)</td>
<td>...</td>
<td>15.4</td>
<td>Stable</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SC (73)</td>
<td>CRC (69)</td>
<td>...</td>
<td>...</td>
<td>6.6</td>
<td>Stable</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>SC (85)</td>
<td>CRC (69); ES (79)</td>
<td>...</td>
<td>...</td>
<td>12.3</td>
<td>Stable</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA (51)</td>
<td>...</td>
<td>PA: OV (50); PGM: PAN (82)</td>
<td>...</td>
<td>8.1</td>
<td>Stable</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>SN (51)</td>
<td>...</td>
<td>B: CRC (56)</td>
<td>...</td>
<td>&lt;5</td>
<td>Stable</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SA, SN (73)</td>
<td>...</td>
<td>B: CRC (62); BL (61); PGM: CRC (62)</td>
<td>...</td>
<td>&lt;5</td>
<td>Stable</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SC (32)</td>
<td>...</td>
<td>MA: EN (63)</td>
<td>...</td>
<td>7.1</td>
<td>Low</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: B, brother; BL, bladder cancer; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; CRC, colorectal cancer; ellipses, not applicable; EN, endometrial adenocarcinoma; ES, endometrial sarcoma; FA, father; IHC, immunohistochemical; MA, maternal aunt; MGF, maternal grandfather; MGM, maternal grandmother; MO, mother; Msi, microsatellite instability; MU, maternal uncle; PA, paternal aunt; PAN, pancreatic cancer; PGM, paternal grandmother; PRO, prostate cancer; PU, paternal uncle; question mark, unknown; RCC, renal cell carcinoma; S, sister; SA, sebaceous adenoma; SC, sebaceous carcinoma; SCC, squamous cell carcinoma; SN, sebaceous neoplasm; STO, stomach cancer.

*Ellipses indicate no other cancer history.

1LS-associated cancers include colorectal, endometrial, ovarian, stomach, small intestine, urinary tract or kidney, bile duct, glioblastoma multiforme, sebaceous gland, pancreas. Ellipses indicate no family history.

2Ellipses indicate not applicable.

3High, stable, and low indicate that greater than 30%, 1% to 30%, and 0% of markers demonstrate instability, respectively. Ellipses indicate MSI test not completed.

4Organ transplant recipient.

5Partial loss of MSH2.

6Cancer not meeting Amsterdam I or II criteria, the mean PREMM1,2,6I risk score was 31.2% for mutation carriers and 6.4% for the group with no mutations identified (P = .002).

Thirty-nine of 77 patients (51%) had normal expression of all 4 MMR proteins in their SNs. Eleven (28%) went on to undergo germline genetic testing of all MMR genes because of suspicious personal or family histories. Two of these 11 patients (18%) were found to carry germline mutations: 1 pathogenic mutation in MSH2 and 1 suspected pathogenic mutation in PMS2 (Table 1). One patient had a VUS in MSH2. Twenty-eight
patients did not undergo germline testing after receiving normal IHC test results. Fourteen of these 28 (50%) had no personal or family history of any other LS-associated cancer. Mean age at diagnosis and strength of family history were not significantly different between the group untested for germline mutations and the group who underwent germline genetic testing with no mutation found (Table 3).

Among the 16 patients with MMR mutations found after tumor screening of SNs and germline testing, 9 (56%) had a personal history of atypical LS cancers not accounted for in risk models or diagnostic criteria (adenocortical cancer, fibrous histiocytoma), and 1 had more than 1 SN. Two carriers reported a history of classic LS cancers in first cousins, not captured by the PREMM1,2,6 model, which incorporates only diagnoses in first-degree and second-degree relatives.

Discussion

In this clinical series of patients with SN selected on the basis of referral for genetic evaluation, IHC test result was concordant with the MMR gene mutation identified in 13 of 16 patients (81% sensitivity) and had a positive predictive value for identifying germline MMR mutations of 37%. To our knowledge, our series is the first to have germline genetic test results available for all individuals with abnormal results of IHC testing for diagnosing LS. Prospective study of universal IHC screening in SN would be useful to determine how performance compares to universal IHC screening in colorectal cancer, which is gaining acceptance and estimated to be cost-effective at a positive predictive value of 23.9%.20,21 Our re-
We acknowledge that our study has certain limitations. Patients were evaluated through 2 different clinics over a 12-year period, with variability in referral practices and in clinical testing practices and standards. Germline genetic testing was completed in only 11 of 39 patients (28%) with normal IHC test results. Without confirmation of normal germline results, specificity cannot be accurately estimated and sensitivity may be overestimated because unidentified mutation carriers could exist in the untested group with normal IHC test results. However, mean age at diagnosis of SN and strength of family history as measured by PREMM1,2,6 scores among patients with normal IHC test results who did not undergo germline testing did not differ significantly from the characteristics of the tested group who did not carry germline mutations (Table 3). It is also possible that some patients with abnormal IHC test results but no germline mutations may have a germline mutation that could not be identified with currently available testing. Mutation carriers had earlier onset of SN, higher prevalence of multiple SNs, and stronger family histories and risk model scores compared with patients with abnormal IHC test results and no germline mutation found (Table 3). Finally, this series represents a selected population of patients who were identified as having risk for MTS and referred for clinical genetics evaluation at tertiary referral centers, sometimes solely on the basis of SN and sometimes because of additional suggestive personal or family history. There are institutional differences in patient demographic characteristics and referral patterns, and this series does not represent a universal screening approach. Defining the true prevalence of LS among all patients with SNs will require additional prospective study. However, our finding of MMR gene mutations in nearly 1 in 3 patients presenting on the basis of SN suggested that IHC testing of SN may be used as a first-line screening test in patients with suspected LS.

These findings also support previous recommendations for routine IHC screening of all SNs, regardless of strength of the personal or family history. The majority of mutation carriers identified after IHC testing of SN and germline testing did not meet Amsterdam I or II clinical diagnostic family history criteria for LS (13 of 16 [81%]), and 44% (7 of 16) did not meet the clinical definition of MTS. Presence of 2 or more relatives with colorectal cancer has been suggested as a threshold for offering IHC testing and would have identified 6 of 16 mutation carriers (38%) in this series. A PREMM1,2,6 risk model threshold of greater than 5% has been suggested for consideration of germline testing and would have identified 10 carriers (62%). Whereas a detailed pedigree including third-degree relatives and incorporating all cancer diagnoses remains useful to help interpret IHC test results, the low sensitivity of family history alone limits its utility as a prescreen to select patients for IHC screening.

The majority (61%) of patients with abnormal IHC test results in an SN had no germline mutation identified, indicating that MMR phenotype in SNs is not diagnostic of LS. This is particularly striking in the subgroup of patients with absent MSH2/MSH6 expression in SNs, of whom only 33% had germline MSH2 mutations and no TACSTD1/EPCAM mutations were identified (Figure). In colorectal and endometrial cancer, absent MSH2/MSH6 staining is widely considered to be diagnostic of LS, with 85% of patients having identifiable germline MSH2 or TACSTD1/EPCAM mutations. Results suggest that a substantial number of patients with abnormal IHC test results but without germline MMR mutations could have developed SN through somatic, nonheritable molecular events. Caution should be used in interpreting the clinical implications of abnormal IHC test results in SN in the absence of germline genetic test results.

### Conclusions

We propose a clinical practice algorithm for patients with SN (Box) to optimize identification of LS after diagnosis of sebaceous adenoma or carcinoma, beginning with consideration of IHC screening of SNs to be ordered by pathologist or clinician, excluding patients with sebaceous hyperplasia or known LS diagnosis. Family history screening for LS-associated cancers in at least first-degree and second-degree relatives is also warranted for all patients with SN. Genetics referral should be recommended for patients with SN and any of the following: absent MMR protein expression (abnormal result) on IHC screen, normal MMR protein expression and personal or family history of any LS-associated cancer, or more than 1 SN. Our findings suggest that a combination of routine tumor testing and family history assessment would optimize identification of patients with LS in the dermatology setting.

---

**Box. Clinical Practice Algorithm for Sebaceous Neoplasm (SN)**

1. Immunohistochemical screening of SN to be ordered by pathologist or clinician
2. Family history screen for Lynch syndrome (LS)-associated cancers in first-degree or second-degree relatives
3. Genetics clinic referral for patients with SN and any of the following:
   1. Absent mismatch repair protein expression (abnormal result) on immunohistochemical testing
   2. Normal mismatch repair protein expression and personal or family history of LS-associated cancer
   3. More than 1 SN

*Classic LS-associated cancers include colorectal, endometrial, stomach, small bowel, ovarian, pancreatic, and urinary tract cancers and glioblastoma multiforme. Atypical LS-associated cancers include adrenocortical and hepatobiliary cancers and sarcoma.*

---

**ARTICLE INFORMATION**

Accepted for Publication: May 2, 2014.

Published Online: July 9, 2014.

Author Contributions: Ms Everett and Dr Stoffel 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.

Study concept and design: Everett, Dandapani,
Mismatch Repair Mutations and Sebaceous Neoplasm

Original Investigation Research

Marvin, Kohlmann, Gustafson, Johnson, Gruber, Stoffel.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Everett, Raymond, Marvin, Chittenden, Johnson, Stoffel.

Critical revision of the manuscript for important intellectual content: Raymond, Dandapani, Kohlmann, Koepe, Gustafson, Else, Fullen, Johnson, Syngal, Gruber, Stoffel.

Statistical analysis: Everett, Koepe, Gruber, Stoffel. Stoffel.

Obtained funding: Syngal, Gruber.

Administrative, technical, or material support: Everett, Raymond, Dandapani, Marvin, Chittenden, Else, Syngal, Gruber.

Study supervision: Johnson, Syngal, Gruber, Stoffel.

Conflict of Interest Disclosures: Ms Everett and Gustafson and Dr Gruber have served as paid consultants to Myriad Genetic Laboratories, Inc. No other disclosures are reported.

Funding/Support: This study was supported in part by National Institutes of Health grants P30 CA042414 (Dr Kohlmann), T32-DK007425 (Dr Else), SRO1CA132829-04 (Dr Syngal), K24-K24CA13433-08 (Dr Syngal), P30 CA04089 (Dr Gruber), P30 CA046592 (Dr Gruber), and K07CA120448-5 (Dr Stoffel).

Role of the Sponsor: The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentation: This study was presented at the 16th Annual Meeting of the Collaborative Group of the Americas on Inherited Colon Cancer; October 29, 2012, Boston, Massachusetts.

REFERENCES


