Risk Assessment and Screening for Lynch Syndrome

Introduction
The increased risks for breast and ovarian cancers associated with the genetic mutation of the BRCA1/BRCA2 genes is relatively well known among clinicians. Knowledge regarding other hereditary cancer syndromes, however, is comparatively low. For example, Lynch syndrome, also known as nonpolyposis colon cancer, develops from an inherited genetic mutation and is associated with colorectal, gynecologic, and other cancers. Studies have demonstrated that although Lynch syndrome has a similar prevalence to that of BRCA1/BRCA2 mutational syndromes, clinicians often fail to conduct adequate screening for the disorder. This article discusses a novel and simple screening system to identify patients with Lynch syndrome and thereby facilitate appropriate management and improve outcomes.

Characteristics of Lynch Syndrome
Lynch syndrome is the most common inherited form of colorectal cancer and accounts for 2% to 3% of all colorectal cancer cases. Individuals with Lynch syndrome have an estimated lifetime risk for developing colon cancer as high as 80%. Endometrial and ovarian cancers also are associated with Lynch syndrome. Patients also have an elevated risk for developing cancer of the ureter, renal pelvis, stomach, biliary tree, and small bowel (Figure). Lynch syndrome is caused by germline defects in the mismatch repair genes MLH1, MSH2, MSH6, and PMS2, which result in microsatellite instability in tumors, loss of expression of the associated protein, or both.

Early identification of an individual with Lynch syndrome allows for the application of intensive screening for the detection of cancers as well as consideration of primary and secondary preventative measures, such as total colectomy, hysterectomy, and/or oophorectomy.

Screening for Lynch Syndrome
Because screening and other interventions can have a profound effect on outcomes and survival, identification of patients with Lynch syndrome is critical. The benefits of genetic testing also extend to at-risk family members, who may use the information as a primary means to monitor for or prevent cancer.

Definitive identification of Lynch syndrome can be achieved through genetic testing. However, costs make universal screening with genetic testing unfeasible. Furthermore, the optimal manner to target a subpopulation that would benefit from genetic testing for Lynch syndrome continues to be a challenge. Traditionally, several clinical systems and algorithms (e.g., Bethesda system, Amsterdam II system) have been used for this purpose, but these systems are plagued by poor positive and negative predictive values. Indeed, Syngal and colleagues reported that the sensitivity and specificity of the Amsterdam II criteria were 72% and 78%, respectively, and those of the Bethesda criteria were 94% and 25%, respectively.

The poor utility of those systems has prompted investigators to develop other models that more accurately determine an individual's risk for Lynch syndrome in order to guide appropriate targeting for genetic testing.

Hereditary Colon Cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Risk with hereditary colon cancer</th>
<th>General population risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>≤82%a</td>
<td>2% by age 70 y</td>
</tr>
<tr>
<td>Stomach</td>
<td>≤13%b</td>
<td>&lt;1% by age 70 y</td>
</tr>
</tbody>
</table>

Although the following cancers are rare, risk is also increased with Lynch syndrome: small intestine, 7.2%; urinary tract, 4%; brain, 3.7%; biliary tract, 2% all by age 70 y.

Hereditary Colon Cancer

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<th>Risk with hereditary colon cancer</th>
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</thead>
<tbody>
<tr>
<td>Uterine (Endometrial)</td>
<td>≤71%b</td>
<td>1.5% by age 70 y</td>
</tr>
<tr>
<td>Ovary</td>
<td>≤12%b</td>
<td>&lt;1% by age 70 y</td>
</tr>
</tbody>
</table>

Risk for a second cancer ≤50%

General population risk 5% within 15 y

Known Family Histories Associated With Hereditary Colon Cancer

- Colon or rectal cancer before age 50
- Endometrial cancer before age 50
- Two or more Lynch syndrome cancersa at any age in the same person
- Two or more family members with a Lynch syndrome cancer on the same side of the family, one before age 50
- Three or more family members with a Lynch syndrome cancer on the same side of the family at any age
- Personal or family history of 10 or more cumulative colorectal polyps (adenomas) at any age
- A previously identified hereditary colon cancer mutation in the family

The PREMM1,2,6 Model
One such system is the multivariable polytomous logistic regression model PREMM1,2,6, a Web-based computerized personal and family history risk assessment (Table). It is designed to allow health care professionals to estimate the cumulative and individual probabilities that an individual is an MLH1, MSH2, or MSH6 mutation carrier.

Several studies have examined the utility of the PREMM1,2,6 model. In the original study of the model by Kastrinos and colleagues, the areas under the receiver operating characteristic curves for prediction of genetic mutation were 0.86 for MLH1 mutation carriers, 0.87 for MSH2, and 0.81 for MSH6. This corresponded to an area under the curve of 0.88 for the overall cohort, indicating that this model can successfully predict an individual's risk for mismatch repair mutations in these genes.

Recently, DiSario and colleagues conducted a study to determine the feasibility of performing screening with the PREMM1,2,6 model for patients within a community gastroenterology practice. In their study, English-speaking patients presenting to a gastroenterology clinic or ambulatory endoscopy center for any reason were

Figure. Hereditary colon cancer significantly increases risks for colon, uterine, and other cancers.

a Risk related to Lynch syndrome, attenuated familial adenomatous polyposis, or MYH-associated polyposis.
b Risk related to Lynch syndrome.

*Assessment criteria based on medical society guidelines.

Lynch syndrome cancers include colon, endometrial, ovarian, stomach, kidney/urinary tract, pelvis, biliary tract, small bowel, pancreas, brain, and sebaceous adenoma/carcinoma.

Based on references 6-12.
administered the PREMM1,2,6 Model questionnaire on a tablet computer. Patients were advised to obtain family history of colon, uterine, and ovarian cancers during the initial scheduling call, in mailings of registration materials, and during a confirmation telephone call. Patients with a PREMM1,2,6 model score of at least 5% were then directed to watch a 4-minute video regarding Lynch syndrome followed by counseling by the provider. These patients also were offered genetic testing. Patients referred for genetic testing submitted buccal mucosal and/or blood samples for genetic testing at a central commercial laboratory (Myriad Genetic Laboratories, Inc). This included DNA sequencing and/or large rearrangement analysis in a panel that included genes associated with Lynch syndrome.

In all, 3,134 patients agreed to participate in the study, and 177 (5.6%) had a PREMM1,2,6 model score of at least 5%. Ultimately, 173 of the 3,134 patients underwent genetic testing, and 6 (3.5%) were positive for Lynch syndrome–associated mutations. A post-study survey of patients and clinicians showed high satisfaction with the implementation of cancer risk assessment and subsequent genetic testing. The majority of providers indicated that this process was easy to implement and functioned well within their existing practices without overly burdensome time demands.

In another study that tested the cost–benefit of predictive models to identify patients for genetic screening, Dinh and colleagues reported that this strategy was cost-effective at $26,000 per quality-adjusted-life-year. This estimate is well below the accepted health care cost-effectiveness threshold of $50,000 per quality-adjusted-life-year and is comparable to the cost-effectiveness of other common cancer screening protocols. Furthermore, this strategy resulted in improved health outcomes for mutation carriers, including significant decreases in cases of colorectal and endometrial cancers and early detection of existing cancers.

### Table. PREMM1,2,6 Model: Prediction Model for MLH1, MSH2, and MSH6 Gene Mutations

<table>
<thead>
<tr>
<th>Relatives Information—First Degree</th>
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<tbody>
<tr>
<td>How many first-degree relatives have had colorectal cancer?</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>One</td>
</tr>
<tr>
<td>How many first-degree relatives have had endometrial cancer?</td>
<td></td>
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<tr>
<td>None</td>
<td>One</td>
</tr>
<tr>
<td>Have any first-degree relatives had another Lynch syndrome–associated cancer?</td>
<td></td>
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<tr>
<td>No</td>
<td>Yes</td>
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</table>

<table>
<thead>
<tr>
<th>Relatives Information—Second Degree</th>
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<tbody>
<tr>
<td>How many second-degree relatives have had colorectal cancer?</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>One</td>
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<tr>
<td>How many second-degree relatives have had endometrial cancer?</td>
<td></td>
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<tr>
<td>None</td>
<td>One</td>
</tr>
<tr>
<td>Have any second-degree relatives had another Lynch syndrome–associated cancer?</td>
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<td>No</td>
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</table>

### References

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