Lynch Syndrome was described over a century ago but information on the medical consequences and optimal management of this disorder continue to amass and evolve. This brief overview highlights the gene-specific and site-specific cancer penetrance and management options for those with Lynch syndrome.

One hundred and one years ago, an astute pathologist from the University of Michigan, Aldred Scott Warthin MD, PhD, published a meticulously documented observational study of multiple families in which cancer appeared to aggregate.1 This was during an era that had not yet embraced the concept of cancer predisposition being heritable but Dr. Warthin laid out a case for this possibility, citing the recent recognition of certain strains of mice known to have different propensities to develop cancers. During the years of his work in Michigan (1895–1913) he studied 3,600 neoplasms, of which 1,600 were carcinomas on histologic diagnosis. Approximately 1,000 patients with these tumors provided some family history and 30% were able to give quite detailed histories; Dr. Warthin collected them all. The most famous family, known as Family G, was that of his seamstress, who Dr. Warthin predicted would die at a young age of a cancer based on her history: indeed, she died at age 35 of endometrial cancer. Dr. Warthin published an update of Family G in 1925,2 in which he described three generations descended from one man with cancer, among which 28 of 88 adults had cancer: 9 of the intestines, 3 of the stomach, 3 of unknown gastrointestinal origin, 12 in the uterus, and 1 in an ovary. The average age of 37.9 at diagnosis was unusual.

After Dr. Warthin, there was little written about the heritability of cancer until Dr. Henry Lynch began to report similar families in the 1960s. Dr. Lynch organized a reunion of Family G and in 1971 published his investigation of more than 650 Family G members, of which 95 had cancer.3 The medical community was overtly skeptical of the idea of cancer being hereditary, but eventually the evidence for this became overwhelming. This coincided with breakthroughs in molecular genetic technologies by the 1980s that confirmed the existence of constitutional mutations, such as mutations in the adenomatous polyposis coli (APC) gene that confer a high risk for cancers in patients with familial adenomatous polyposis. In 2000, Warthin’s Family G finally got an answer when a mutation in the MSH2 gene was reported in descendants of this family.4

WHAT DO WE KNOW TODAY?

Definition

Today, the preferred term of Lynch syndrome (LS) refers to an autosomal dominant predisposition to a specific list of cancers that are caused by the presence of a germline mutation that disturbs the function of a DNA mismatch repair (MMR) gene. As described by both Warthin and Lynch, the predominant cancers are those of colon and endometrium that arise at younger ages than are typical for these cancers in the general population.

Prevalence

The DNA mismatch repair genes in which mutations lead to LS are MLH1 and MSH2, which together account for approximately 85% of cases of LS in the United States, MSH6 (~10%), and PMS2 (~5%). The mutation frequencies are highly population-specific. In addition, germline deletions in the gene immediately upstream of MSH2, EPCAM (also known as TACSTD1), lead to epigenetic silencing of MSH2 and a LS-like phenotype. In the United States, LS accounts for approximately 2.2% of colon cancers5 and 2% to 4% of endometrial cancers.6-8 Unlike familial adenomatous polyposis with its dramatic polyposis phenotype, there is no obvious consistent phenotypic feature of LS to help clinicians recognize this disorder. Multiple guidelines, criteria, and models have been devised to assist in selecting patients for whom diagnostic studies for LS are indicated. The original Amsterdam criteria are helpful, but only approximately 50% of families fulfilling these pedigree criteria actually have LS. The Bethesda guidelines were designed to target patients for
whom tumor testing for DNA mismatch repair deficiency (see below) should be conducted but are fairly nonspecific and lack high sensitivity. Web-based models such as PREMM(1,2,6) (http://premm.dfci.harvard.edu/) can be used to set a threshold above which genetic testing might be reasonable.9

Penetrance and Tumor Spectrum

Most of the literature on cancer penetrance and age of onset in LS is based on studies that have combined results from families with mutations in all of the above genes. Over time, some differences between cancers associated with specific LS-causing genes have emerged, although more work in this area is needed. Broad generalizations include higher risks for gastrointestinal cancers for carriers of MSH2 for colorectal cancer, higher risks for extracolonic tumors in carriers of MSH2 mutations; later onset cancer risks for MSH6 mutation carriers; and overall lower risks for cancers in PMS2 mutation carriers. Tables 1 and 2 show the current tumor spectrums and cancer risks reported for each gene. Documented sites of increased risk are colorectum (two-thirds in the right colon), endometrium, urothelium, gastric, brain, pancreas, sebaceous gland (risks not quantitated), hepatobiliary system, and ovary. Many rare tumors have also occurred in individuals with LS, sometimes with evidence of mismatch repair deficiency, but there are insufficient data to conclude that lifetime risks for these tumors are meaningfully increased.

Recent work has focused on the risks for breast and prostate cancers in mutation carriers. Because these cancers are very common in the general population, differences in risks in LS were difficult to appreciate until sufficient statistical power could be generated from large enough datasets. The emerging picture is that there does appear to be an increased risk for breast and prostate cancer in patients with LS, especially in carriers of a MSH2 mutation.10,11 It is not clear whether the levels of risk warrant a change in surveillance strategies in patients with LS compared to the general population but this is an area that is likely to become clearer in the near future.

Clinical Management

Based on the established cancer risks in LS, several organizations have provided cancer surveillance guidelines for individuals with LS. The primary focus is on colorectal cancer and endometrial cancers because the risks are maximal for these cancers. Table 3 summarizes current recommendations. Regarding cancer prevention, there is good evidence that screening colonoscopy is an effective approach to preventing colorectal cancer deaths in LS (reviewed by Vasen et al, 2013).9 There is also evidence that endometrial and ovarian cancers can be prevented with hysterectomy and salpingo-oophorectomy.12 Although there is no evidence to support screening for gastric cancers, small bowel cancer, pancreatic or hepatobiliary cancers, or urothelial tumors, some experts do suggest efforts to detect tumors in these locations. Current American Cancer Society guidelines for breast and prostate cancer screening seem appropriate, and for carriers of MSH2 mutations the high risk guidelines (consideration of breast MRI and serum prostate antigen, respectively) may be indicated.

The Role of Surgery in Prevention in Lynch Syndrome

In general, there is agreement that hysterectomy/bilateral saphingo-oophorectomy should be offered to women with LS who have completed childbearing, and having this conversation is particularly relevant if they are having an operation for colon cancer, as is often the case. Regarding removal of the colon, because there is good evidence that colonoscopy is effective at preventing deaths by colon cancer in individuals with LS, there is not a groundswell of support for preventive colectomy. However, the extent of surgery when LS presents with a colon cancer is a different matter. It is intuitively obvious that removal of most of the colon will prevent most colon cancers. A heterogeneous group of 382 carriers of MMR gene mutations (172 MLH1, 167 MSH2, 23 MSH6, and 20 PMS2) with colorectal cancer who had surgery for their first colon cancer were analyzed using retrospective cohort analysis for age-dependent cumulative risks of metastatic colorectal carcinoma (CRC).13 Detailed information about interval screening was unavailable (although it should be noted that this was not a medically underserved cohort), yet of subjects who had segmental resections, 22% were diagnosed with metastatic CRC (incidence rate 23.6 per 1,000 person-years; 95% CI, 18.8 to 29.7). On the other hand, none of 50 subjects who had extensive colectomy was diagnosed with metastasized CRC. Furthermore, the risk of metastasized CRC was reduced by 31% (95% CI, 12% to 46%; p = 0.002) for every 10 cm of bowel removed. The cumulative risk of metastasized CRC was 16% (95% CI, 10% to 25%) at 10
years, 41% (95% CI, 30% to 52%) at 20 years, and 62% (95% CI, 50% to 77%) at 30 years after segmental colectomy. Patients with LS whose first colon cancer is treated with more extensive colonic resection have a lower risk of metachronous CRC than those receiving less extensive surgery. Cancer risk reduction of more extensive surgery must be weighed against the future likelihood of a noncurable CRC.

In 2013, Vasen et al. reviewed studies that reported the outcomes of colonoscopic surveillance in LS before surgery, and although cancers did arise, the vast majority were early stage and death rates were very low.14 Other important issues to consider are the functional results of subtotal colectomy versus segmental resection (surveys suggest worse functional outcomes but paradoxically not increased patient dissatisfaction), age (with much less to gain in older individuals than in those with many decades of expected life), and personal preference (which can vary substantially). Much like the issue of risk-reducing mastectomies in women with BRCA mutations, the highest patient satisfaction is likely to come from carefully educating the patient about the known risks and benefits, and then supporting the decision they make.

Chemoprevention

Perhaps the single most exciting recent event in the field of LS came in 2011, with a follow-up analysis of outcomes of the CAPP2 (Colorectal Adenoma/carcinoma Prevention Programme), a randomized controlled trial conducted on 1,071 carriers of LS from 34 centers in 17 countries (not including the United States) comparing 600 mg aspirin and/or 30 g of resistant starch to placebo over 2 to 4 years. At the first 4-year endpoint there was no significant reduction in cancer development,15 but after 4 years from randomization a 50% risk reduction emerged for the development of any new LS-related cancers, an effect that persisted for at least 5 years after cessation of aspirin therapy. Although there is a substantial body of literature regarding the preventive effects of aspirin and other COX-inhibitors on the development of colonic polyps and cancers, as well as several other tumors, in
the general population, the CAPP2 trial is the first to extend this evidence to people with LS. Based on this single study, those caring for individuals with LS are encouraged to discuss potential use of aspirin. A dose optimization and validation study, CAPP3, will be starting soon but the results will probably not be available for another 5 to 10 years.

DNA Mismatch Repair in Diagnosing and Understanding Lynch Syndrome

DNA mismatch repair genes are not tumor suppressor genes in the traditional sense (i.e., genes that limit the cell cycle), but when a second hit occurs in the normal allele of a cell that already contains a germline hit in a MMR gene, the two hits render the cell unable to repair misincorporation errors that occur during normal cell replication. The result of failure to repair DNA is the rapid accumulation of mutations within genes of all types, including tumor suppressor genes and proto-oncogenes. Thus, the loss of normal DNA mismatch repair greatly increases the likelihood of any cell arriving at the necessary constellation of mutations that defines malignant transformation.

Loss of DNA mismatch repair leads to a distinctive tumor phenotype known as microsatellite instability (MSI). Within our genome there are thousands of segments of DNA with simple sequence repeats called microsatellites. Most microsatellites are in noncoding regions of the genome. When a panel of microsatellites from a tumor with a DNA mismatch repair defect is compared to constitutional DNA from the same person, one can observe the nonfidelity of replication: the tumor microsatellites will have altered sizes compared to the germline microsatellites. When 30% or more of the microsatellites in a tumor are altered (usually 5 to 10 are assayed), that tumor is said to manifest a high level of microsatellite instability or to be MSI-H, which is diagnostic for defective DNA mismatch repair.

Immunohistochemistry offers an alternative and complementary method for assessing DNA mismatch repair status. Because of protein dimerization, a characteristic pattern of loss of expression is seen when genes are inactivated (Table 4). Analysis of this pattern can help guide genetic testing when LS is suspected.

Can Lynch Syndrome be Diagnosed by Demonstrating DNA Mismatch Repair in the Tumor?

Unfortunately this is not the case. The germline jumpstart toward the Knudson second hit is only one possible mechanism leading to a tumor with DNA mismatch repair deficiency (MSI-H phenotype). Studies of MSI in the general population demonstrated that approximately 15% to 17% of all colorectal cancers are MSI-H, but this is not evenly distributed. The percent of MSI-H tumors increases as a function of age, and this correlation is especially pronounced in women.16 The underlying mechanism involves hypermethylation of the promoter of the MLH1 gene. Until recently,
age-related hypermethylation presented a practical barrier to implementation of broader screening programs for detection of LS based on tumor DNA mismatch repair because most cases detected would not actually have LS. Recent advances in technology have opened up the possibility of universal screening for LS. These advances in testing include direct testing for tumor methylation of $MLH1$, the discovery that somatic $BRAF$ mutations are common in somatically methylated tumors and almost never seen in LS, and more rapid/less expensive mutation analysis for the germline mutations themselves. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group has recommended MSI or immunohistochemistry testing for LS in all newly diagnosed cases of colorectal cancer, after obtaining informed consent.\textsuperscript{17} The benefit of identification of LS is primarily for the relatives, and there is an acknowledged research gap in analysis of the cost-effectiveness of a universal screening approach. A group of European experts have

### TABLE 3. Surveillance or Management Recommendations for Individuals with Lynch Syndrome from the National Comprehensive Cancer Network (NCCN) Guidelines\textsuperscript{31}

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveillance for MLH1 and MSH2 Mutation Carriers</strong></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Colonoscopy at age 20-25 or 2-5 years prior to the earliest colon cancer if diagnosed before age 25, and repeat every 1-2 years. There are data suggesting that aspirin may decrease the risk of colon cancer in Lynch syndrome; however, at this time the data are not sufficiently robust to make a recommendation for its standard use.</td>
</tr>
<tr>
<td>Endometrial and ovarian</td>
<td>Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option that should be considered by women who have completed childbearing. Patients must be aware that dysfunctional uterine bleeding warrants evaluation. There is no clear evidence to support screening for endometrial cancer for Lynch syndrome. However, annual office endometrial sampling is an option. Although there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening for patients with Lynch syndrome. Transvaginal ultrasound for ovarian and endometrial cancer has not been shown to be sufficiently sensitive or specific to support a positive recommendation, but may be considered at the clinician’s discretion. Serum CA-125 is an additional ovarian screening test with caveats similar to those of transvaginal ultrasound.</td>
</tr>
<tr>
<td>Gastric and small bowel</td>
<td>There is no clear evidence to support screening for gastric, duodenal, and small bowel cancer in Lynch syndrome. Selected individuals or families, or those of Asian descent, may consider esophagogastroduodenoscopy with extended duodenoscopy (to distal duodenum or into the jejunum) every 3-5 years beginning at age 30-35.</td>
</tr>
<tr>
<td>Urothelial</td>
<td>Consider annual urinalysis starting at age 25-30.</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Annual physical examination starting at age 25-30; no additional screening recommendations have been made.</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore, no screening recommendation is possible at this time.</td>
</tr>
<tr>
<td>Breast</td>
<td>There have been suggestions of an increased risk for breast cancer in Lynch syndrome patients; however, because of limited data no screening recommendation is possible at this time.</td>
</tr>
<tr>
<td><strong>Surveillance for MSH6 Mutation Carriers</strong></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Colonoscopy every 2–3 years at age 30-35 (may need to be earlier in some families, depending on age when cancers are observed), and then every 1-2 years after age 40.</td>
</tr>
<tr>
<td>Extra Colonic</td>
<td>Consider prophylactic hysterectomy and bilateral salpingo-oophorectomy in women who have completed childbearing. The risk of other Lynch syndrome-related cancers is reportedly low; however, because of limited data no screening recommendation is possible at this time.</td>
</tr>
<tr>
<td><strong>Surveillance for PMS2 Mutation Carriers</strong></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Colonoscopy every 2–3 years at age 35-40 (may need to be earlier in some families, depending on age when cancers are observed), and then every 1-2 years after age 50.</td>
</tr>
<tr>
<td>Extra Colonic</td>
<td>The risk of other Lynch syndrome-related cancers is reportedly low; however, because of limited data no screening recommendation is possible at this time.</td>
</tr>
</tbody>
</table>

### TABLE 4. Relationship between Genes with Two Hits (Germline plus Somatic or Both Somatic) and Expression Pattern on Immunohistochemistry

<table>
<thead>
<tr>
<th>Gene</th>
<th>MLH1 Expression</th>
<th>MSH2 Expression</th>
<th>MSH6 Expression</th>
<th>PMS2 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>MSH2</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>MSH6</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>PMS2</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>
also assessed the option of universal screening and have recommended testing CRCs in individuals who are diagnosed under age 70, provided the tests are accompanied by methods that identify MLH1 promoter hypermethylation. The EGAPP Working Group found that the evidence was insufficient to consider universal testing of endometrial cancers and the European group stated that “this can be considered” in individuals under age 70 years.14

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References

1. Warthin AS. Heredity with reference to carcinoma as shown by the study of the cases examined in the pathological laboratory of the University of Michigan, 1895-1913. Arch Intern Med. 1913;XII:546-555.