Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management

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INTRODUCTION

Individuals with Lynch syndrome have an increased risk of colorectal and endometrial cancer [1,2]. Other sites of cancer include the ovary, stomach, small bowel, pancreatobiliary system, genitourinary system (urothelial cancer), prostate, brain, and skin [3-12]. There may also be an increased risk of breast cancer in individuals with Lynch syndrome (table 1) [7,13-20].

This topic will review recommendations for screening and surveillance of individuals with Lynch syndrome and their families. Guidelines for cancer screening in patients diagnosed with Lynch syndrome have been proposed by several groups including: the American College of Gastroenterology, United States Multi-Society Task Force on Colorectal Cancer, European Hereditary Tumor Group, the Manchester International Consensus Group, the British Society of Gastroenterology, the European Society of Medical Oncology, American Society of Clinical Oncology, and National Comprehensive Cancer Network [21-34]. Our recommendations are largely consistent with these guidelines. The clinical manifestations and diagnosis of Lynch syndrome, the management of patients and families with other hereditary colon cancer syndromes, and screening in patients with a family history of colorectal cancer or polyps who are not known to have one of the above conditions are discussed elsewhere. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis" and "Familial adenomatous polyposis: Screening and management of patients and families" and "Juvenile polyposis syndrome" and "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp".)

TERMINOLOGY

- Lynch syndrome refers to individuals and families with a pathogenic germline mutation in one of the DNA mismatch repair genes (*MLH1, MSH2, MSH6*, and *PMS2)* or the *EPCAM* gene.
- Hereditary nonpolyposis colorectal cancer refers to individuals and/or families who fulfill Amsterdam criteria (table 2). Approximately one-half of families that fulfill Amsterdam criteria have Lynch syndrome. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Family history-based criteria'.)

MANAGEMENT

General measures

Health maintenance — Several important measures are appropriate for all patients with Lynch syndrome including:

- Annual physical examination beginning at age 25 to 30 years with a clinician familiar with the clinical manifestations of Lynch syndrome. Family cancer history should be reviewed and updated with new cancer diagnoses and individuals newly tested at annual visits.
- Patient education on cancer risk factor reduction strategies include avoiding tobacco, being physically active, maintaining a healthy weight, eating a healthy diet (high in vegetables and fruits and lower in red meats), limiting or eliminating alcohol, protecting against sexually transmitted infections, vaccinations such as human papillomavirus (HPV) vaccination, avoiding sun exposure, and obtaining appropriate cancer screening [31,33,35]. These are general recommendations for cancer prevention; data are limited on how lifestyle modification may modify cancer risks in patients with Lynch syndrome in particular.
- Females with Lynch syndrome, especially those who are premenopausal and/or females over 40 years of age who opt for surveillance rather than preventive surgery should have annual follow-up with a gynecology clinician with knowledge of Lynch syndrome. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Screening and prevention of endometrial and ovarian cancer".)

Reproductive counseling — In individuals of reproductive age, we discuss carrier testing and prenatal testing options including preimplantation genetic diagnosis. Lynch syndrome is an autosomal dominant disorder and can be transmitted by either parent to approximately 50

percent of their offspring. In addition, couples should be advised of the possibility and risks associated with both partners being carriers of pathogenic variants in the same mismatch repair (MMR) gene, leading to a 25 percent chance of having a child with constitutional MMR deficiency syndrome or constitutional MMR deficiency (biallelic mutations of the DNA MMR genes) [36]. Carrier testing can be offered to the partner to determine if they are carriers of pathogenic variants in the same MMR gene. This is particularly relevant as *MSH6* and *PMS2* mutations, which can be associated with a more moderate penetrance phenotype, are common in the population and may not be associated with a strong family history of cancer. (See "Inheritance patterns of monogenic disorders (Mendelian and non-Mendelian)" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Differential diagnosis'.)

Screening for Lynch-associated cancers — Our approach to cancer screening is based on the personal and family cancer history, the gene affected, and the mode of ascertainment of the familial mutation. Experts have increasingly advocated for screening recommendations tailored to the MMR gene alone based on estimates of lower lifetime cancer risk for carriers of germline *PMS2* mutations and a later mean age of colorectal cancer (CRC) onset in germline *MSH6* carriers. Our practice recommendations have begun to incorporate these screening options, in line with society guidelines (National Comprehensive Cancer Network [NCCN], European Society for Medical Oncology [ESMO]) [33]. However, it must be acknowledged that the understanding of penetrance of each MMR gene and unique MMR gene mutations for cancer at the individual and family level remains limited, and cancer risk may be impacted by unmeasured gene-gene (ie, modifying genes) and gene-environment interactions. In addition, reported risk estimates are influenced by both immediate family history as well as ascertainment-related factors.

Candidates for screening — We typically screen for Lynch-associated cancers in individuals with any of the following:

- Pathogenic germline mutation in the DNA MMR genes or *EPCAM* deletions that can inactivate *MSH2.*
- Risk factor(s) for Lynch syndrome (eg, known familial mutation in a close relative) in the absence of genetic testing. Identifying individuals who are at risk for Lynch syndrome and would benefit from genetic testing is discussed separately. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Diagnostic approach'.)

Persons at risk for Lynch syndrome should be urged to pursue diagnostic genetic testing to confirm whether they have Lynch syndrome. Confirmatory genetic testing is critical for several

reasons. If Lynch syndrome is present, it allows clinicians to make accurate medical recommendations related to cancer screening, surgical prophylaxis, and chemoprevention. If Lynch syndrome is not identified, this would almost certainly lead to substantially altered medical recommendations, focusing on CRC risk rather than extra-colonic Lynch syndrome cancer risks. Finally, once a hereditary risk mutation is identified in a family, it makes determination of risk easier in close family members. In individuals with indeterminate genetic test results, medical recommendations must be tailored to their personal and family history and the possible underlying hereditary cancer syndrome. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Diagnostic approach'.)

Colorectal cancer — The optimal colonoscopy screening interval in Lynch syndrome is uncertain and is best tailored to MMR gene affected, age, and family history. In our practice, we suggest that individuals with *MLH1* and *MSH2* associated Lynch syndrome undergo CRC screening with colonoscopy every one to two years beginning at age 20 to 25 years, or two to five years prior to the earliest age of CRC diagnosis in the family (whichever comes first). For *MSH6* carriers and *PMS2* carriers, CRC screening can be delayed until age 30 to 35 years and conducted every one to three years if there is no family history of early-onset CRC or other Lynch syndrome cancers that would otherwise suggest the familial mutation may be exhibiting higher penetrance than usual.

Several guidelines support differential screening for CRC depending on the MMR gene affected, or at least consider starting screening in *MSH6* and *PMS2* carriers later [23,32,33,35], with greater allowances for an extended screening interval in *MSH6* carriers and *PMS2* carriers. The efficacy of these recommendations has not been prospectively evaluated [37,38]. Nonetheless, while there is some risk of early-onset cancers in both *MSH6* and *PMS2* carriers, it is likely small. Rare *MSH6* and *PMS2* families with early-onset CRC (<35 years of age) have been reported, particularly in clinic-based series where penetrance estimates are often the highest [39]. Additional studies in Lynch syndrome mutation carriers may help determine the optimal gene-specific colonoscopy screening intervals. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Genotype phenotype correlation'.)

CRC screening has been demonstrated to decrease mortality in individuals with Lynch syndrome [40,41]. A prospective study of 22 families with Lynch syndrome compared cancer incidence and mortality between 133 at-risk members who had been screened regularly over 15 years and 119 members who had declined screening [42]. Individuals who had undergone colonoscopy on an average of every three years had a lower CRC incidence (6 versus 16 percent)

and overall mortality (8 versus 22 percent) as compared with the unscreened group. A decision analysis model estimated that colonoscopy surveillance in Lynch syndrome family members would be associated with a gain of approximately 14 quality-adjusted life years per screened individual as compared with no screening [43].

The recommendation for annual CRC surveillance is based on the observation of interval cancers in some series of Lynch syndrome families and rapid progression of the adenoma-carcinoma sequence in Lynch syndrome patients [44-46]. A prospective cohort study that included 1126 individuals from families with Lynch syndrome evaluated the efficacy of annual colonoscopies in detecting adenomas and CRC [40]. In this study, 99 CRCs were found in 90 individuals; 71 were diagnosed by surveillance colonoscopies. The median time between the CRCs detected through follow-up colonoscopy and the preceding colonoscopy was 11.3 months. However, conflicting data have suggested that shorter CRC screening intervals (<1.5 years) provide no advantage over longer screening intervals (>3.5 years) in terms of greater rate of cancer diagnosis or increased detection of lower-stage versus advanced-stage disease [47]. Similarly, a study from Europe compared one-year, one- to two-year, and three-year colonoscopy screening intervals in patients with Lynch syndrome and found no difference in CRC incidence when the three groups were compared [48]. Factors associated with increased risk of CRC included a history of prior CRC, male sex, *MLH1/MSH2* mutation, age >40 years, and an adenoma identified at the index colonoscopy. Accumulating data suggested *MLH1*-associated CRC may be less likely than other Lynch-associated CRCs to develop through a classic polyp pathway, and that *MLH1* carriers may be less likely to manifest adenomas (compared with *MSH2* and *MSH6* carriers) and advanced adenomas (compared with *MSH2* carriers) [49].

Gastric cancer — We screen for gastric cancer by upper gastrointestinal endoscopy (esophagogastroduodenoscopy) and biopsy every two to four years starting at 30 to 35 years of age. Upper endoscopy can be paired with every other colonoscopy, or performed more frequently if patient/family demonstrates features suggesting high risk (eg, advanced atrophic gastritis, autoimmune gastritis, extensive or incomplete intestinal metaplasia, family history of gastric cancer, especially early-onset [<50 years] or multiple gastric cancers, or East Asian descent) [50-52].

We treat *Helicobacter pylori* infection when it is detected. *H. pylori* infection may interact with hereditary predisposition syndromes to increase risk of gastric cancer, although this risk was linked to homologous-recombination genes rather than the MMR genes [53].

Our recommendations are largely consistent with guidelines from the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), United States Multi-Society Task Force (MSTF), the Japanese Society for Cancer of the Colon and Rectum (JSCCR), and

American College of Gastroenterology (ACG) [21,22,25,26,33,34,54]. However, it should be noted that several groups refrain from explicitly recommending gastric cancer screening due to a lack of evidence [28,32,35,55].

There are limited data regarding the efficacy of screening for gastric cancer in individuals with Lynch syndrome. In one study of 73 MMR gene mutation carriers and 32 mutation-negative family members who underwent a screening upper endoscopy, one duodenal cancer was diagnosed in one MMR gene mutation carrier, but no gastric cancers were detected in either group [50]. The prevalence of precursor lesions was not significantly different in mutation-positive and negative individuals. However, in other large cohort studies, upper endoscopy performed for gastric cancer screening detected predominantly early-stage cancers (80 to 83 percent of screening-detected cancers were stage I). In contrast, upper endoscopy performed for evaluation of symptoms or started later in life was more likely to detect advanced cancers [56,57]. More studies are needed to demonstrate cost effectiveness and survival benefit of gastric cancer screening [58]. (See "Association between *Helicobacter pylori* infection and gastrointestinal malignancy", section on 'Role of H. pylori in carcinogenesis' and "Metaplastic (chronic) atrophic gastritis" and "Gastric intestinal metaplasia", section on 'Risk factors'.)

Small intestinal cancer — Screening for small intestinal cancer is not routinely recommended in patients with Lynch syndrome given that the lifetime risk of small intestinal cancer in Lynch syndrome is small (0.4 to 12 percent) and screening is not likely to be cost-effective [59]. However, we carefully inspect the distal duodenum and terminal ileum for small intestinal cancers during upper endoscopy and colonoscopy, respectively [23,28].

Lynch syndrome-related cancers of the small intestine occur most frequently in the duodenum but may also occur throughout the small bowel. In one cohort of 10 patients with Lynch syndrome and small bowel adenocarcinoma, five patients had duodenal cancers while three patients had jejunal cancers and two patients had ileal cancers [60]. In a cohort of 2015 patients with Lynch syndrome, 47 patients were diagnosed with 49 duodenal cancers, and 10 percent of patients were under the age of 35 years at the time of diagnosis. Patients undergoing routine endoscopic surveillance had higher rates of early-stage disease compared with no surveillance (77 versus 29 percent) [61].

If a patient has a family history that clearly includes a small bowel cancer, we offer the option for wireless capsule endoscopy surveillance on a three- to five-year basis. Beyond these patients/families, we reserve the use of wireless capsule endoscopy for evaluation of the small bowel in mutation carriers with unexplained abdominal pain or iron deficiency anemia [59,62].

Endometrial and ovarian cancer — There is no proven effective screening strategy for early detection of endometrial or ovarian cancer. It is important to counsel patients regarding their cancer risk and the early nonspecific symptoms of ovarian cancer. Females with Lynch syndrome should also be advised to promptly seek medical attention for abnormal uterine bleeding, which is the typical presentation for endometrial cancer in both premenopausal and postmenopausal patients. Screening and prevention of endometrial and ovarian cancer is discussed separately. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Screening and prevention of endometrial and ovarian cancer".)

Skin cancer — All patients with Lynch syndrome should undergo at least one baseline skin examination for Lynch-associated skin lesions. We usually perform the initial exam between the ages of 40 and 50 years, unless there is a family history of Lynch syndrome-associated skin lesions occurring at an earlier age. Skin manifestations are most frequently found in *MSH2* families but can be associated with all the MMR genes. The frequency of follow-up skin exams in patients with no findings at baseline should be determined as needed by a dermatologist, but we suggest a minimum of every one to three years. In those individuals with proven Lynch-associated skin findings (previously known as Muir-Torre variant Lynch syndrome), skin examinations at least annually to detect sebaceous tumors (benign and malignant) and cutaneous keratoacanthomas should be performed, but may be performed even more frequently if skin manifestations are numerous [63]. Lynch syndrome may also predispose to other skin cancers, but given their high prevalence in the general population, we counsel patients on protection from ultraviolet exposure (avoid excessive sun exposure, use of a high-strength sunscreen, and sun-protective measures). (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Extracolonic manifestations'.)

Additional screening in selected patients

Urinary tract cancer — We screen for urothelial cancers with urinalysis and urine cytology in all individuals with *MSH2/EPCAM* disease variants. We also offer screening for urothelial cancers in individuals with *MLH1, MSH6, and PMS2* disease variants if they have additional risk factors for urothelial cancer (male sex, smoking history, or family history of urothelial malignancies after age 30 years). Multiple studies have reported that the risks of urothelial cancers in Lynch syndrome are higher in males, particularly those with *MSH2* variants [64-67]; however, urothelial cancers have also been documented in *MLH1* and *MSH6* families. Family history of urothelial cancer is also a risk factor [68].

However, screening for urothelial cancer is controversial due to low sensitivity of screening and the relatively low risk of urothelial cancers in Lynch syndrome [21-23,25,28,33-35,54,69]. One

retrospective study of 977 individuals from families suspected to have Lynch syndrome who had undergone a total of 1868 screening urine cytology tests diagnosed 14 individuals with a urinary cancer; of these, five had interval cancers [69]. Only two urine cytology tests (0.1 percent) led to a diagnosis of an asymptomatic urothelial tumor and 22 (1.2 percent) of the tests were false positive. The sensitivity and specificity of urine cytology in diagnosing asymptomatic urinary tumors was 29 and 96 percent, respectively. Of the 14 tumors diagnosed, 11 were in *MSH2* mutation carriers.

Prostate cancer — For males with Lynch syndrome, we discuss the initiation of prostate cancer screening by prostate-specific antigen test at age 40 years and, if available, follow-up in a high-risk cancer screening clinic. Data suggest that prostate screening in males with Lynch syndrome has potential to detect tumors that are highly likely to need treatment. In a prospective screening study that includes 828 males from families with pathogenic variants in mismatch repair genes (644 carriers of mismatch repair pathogenic variants and 184 non-carrier controls) who underwent prostate-specific antigen screening, the incidence of prostate cancer detected in males with *MSH2* and *MHS6* pathogenic variants was significantly higher as compared with age-matched non-carrier controls [70]. *MSH2* carriers had more clinically significant (intermediate- or high-risk) prostate cancer at diagnosis as compared with non-carriers. The mean age of prostate cancers diagnosed in *MSH2* carriers was 55 years (range 40 to 69 years) and in *MSH6* carriers was 63 years (55 to 67 years). Family history of prostate cancer was reported in a minority of patients (two of the 13 *MSH2* carriers, none of the four *MSH6* carriers). None of the three *MSH2* carriers with age of diagnosis <50 years reported a family history of prostate cancer.

Pancreatic cancer — Routine screening for pancreatic cancer is not recommended in all individuals with Lynch syndrome, only for Lynch syndrome mutation carriers with one or more affected first-degree relatives with pancreatic cancer [21,22,35,71]. Screening for pancreatic cancer in patients with Lynch syndrome is discussed in detail separately. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Lynch syndrome' and "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Our approach'.)

Other cancer prevention strategies

Prophylactic surgery — Prophylactic colectomy for mutation carriers who have an endoscopically normal colon is not routinely recommended but is reserved for patients who are unable or unwilling to undergo routine CRC surveillance.

Strategies for reducing the risk of endometrial and ovarian cancer are discussed separately. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Screening and prevention of endometrial and ovarian cancer".)

Chemoprevention — We suggest the use of aspirin in patients with Lynch syndrome as it may reduce the incidence of CRC. In our practice, in patients with a personal and family history consistent with high penetrance risk, we initiate aspirin at a dose of 81 mg per day or 325 mg per day. *In MLH1, MSH2*, and more penetr*ant MSH6* carriers, we discuss increasing the aspirin dose to 650 mg per day after several months if it is tolerated without side effects. In patients who carry *PMS2* pathogenic variants or have side effects to aspirin or those with a personal and family history suggestive of less penetrant cancer risk, we use a lower dose of aspirin (81 mg daily). A placebo-controlled trial that included 937 individuals with Lynch syndrome initially found that neither aspirin nor resistant starch provided a benefit for adenoma or CRC prevention after a mean of 29 months of follow-up [72]. In a subsequent analysis of 861 patients followed for a longer period of time (mean of 10 years), the intention-to-treat time-to-event analysis showed a nonsignificant protective effect of aspirin. However, a per-protocol analysis in individuals treated with 600 mg aspirin per day for more than two years showed a reduction in incidence of all Lynch-associated cancers (incidence rate ratio [IRR] 0.65, 95% CI 0.44-0.94). Further studies are needed to clarify the net benefits in CRC prevention and to find the optimal dose for chemoprevention for individuals with Lynch syndrome [73-77]. (See "NSAIDs (including aspirin): Role in prevention of colorectal cancer", section on 'Aspirin trials'.)

ADDITIONAL CONSIDERATIONS FOR COLORECTAL NEOPLASIA

Surgery — Lynch syndrome has important implications for management of colorectal neoplastic lesions due to increased risk of metachronous colorectal cancer (CRC). Females undergoing colectomy should undergo counseling with a gynecologic oncologist or surgeon familiar with Lynch syndrome to discuss the option of concurrent prophylactic hysterectomy and bilateral salpingo-oophorectomy to prevent endometrial and ovarian cancer, taking into account age and childbearing status. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Screening and prevention of endometrial and ovarian cancer", section on 'Strategies for cancer risk reduction'.)

- **Colon neoplasia** – In individuals with Lynch syndrome with colon cancer or an endoscopically unresectable adenoma, total abdominal colectomy with ileorectal anastomosis is the risk-reducing procedure of choice, with continued annual endoscopic surveillance of the retained rectum. We reserve segmental colectomy with annual postoperative colonoscopic surveillance for individuals who are not candidates for total

colectomy or who have strong preference to not undergo total colectomy [22,26]. However, if a second colon cancer develops despite adherence to intensive screening, total colectomy should be performed. Individuals with Lynch syndrome who undergo segmental colectomy for the first colon cancer diagnosis have an increased risk of subsequent adenoma or CRC as compared with individuals who undergo subtotal colectomy with ileorectal anastomosis [78-80]. In a study of 382 carriers of an MMR gene mutation (172 *MLH1*, 167 *MSH2*, 23 *MSH6,* and 20 *PMS2*) who underwent surgery for their first CRC, none of the 50 carriers who had had extensive colectomy was diagnosed with a metachronous CRC [79]. However, of 332 carriers who had had segmental resections, 74 (22 percent) were diagnosed with a metachronous CRC (incidence rate 23.6; 95% CI 18.8-29.7 per 1000 person-years). The cumulative risk of metachronous CRC for carriers with segmental colectomy at 10, 20, and 30 years was estimated to be 16, 41, and 62 percent, respectively. Risk of metachronous CRC was reduced by 31 percent for every 10 cm of bowel removed [79].

Studies suggested that patients with *MLH1* and *MSH2* mutations who underwent segmental colon resection appeared to be at increased risk of metachronous cancer compared with those who underwent extended resection [81]. However, for patients with *MSH6* or *PMS2* mutations, the risk of metachronous cancer was not significantly different after partial colectomy compared with extended colectomy. While most studies have been small, data have suggested that there was no mortality benefit with extended colectomy, provided that patients had access and adhered to surveillance colonoscopy. Additional considerations include the morbidity of repeat abdominal surgeries for metachronous cancers and the emerging role of managing MMR cancers with immunotherapy.

- **Rectal neoplasia** – In individuals with Lynch syndrome with rectal cancer, total proctocolectomy with an ileal pouch anal anastomosis is the most definitive risk-reducing operation given the high risk for metachronous colon cancer in those with proctectomy [23]. However, this surgery may also be associated with more postoperative complications and long-term issues with continence compared with a permanent ileostomy or a low-anterior resection followed by ileorectal anastomosis to the rectal stump. A multi-disciplinary team including gastroenterology, radiation oncology, medical oncology, and clinical cancer genetics should be involved in the decision on extent of surgery, which should be guided by the age at diagnosis, factors that may increase the likelihood of a poor functional outcome, and patient preferences. If a rectal remnant is preserved for continence, it is important to ensure at least annual colonoscopic surveillance of the retained colon.

Individuals with Lynch syndrome who undergo proctectomy for the first rectal cancer are found to have an increased risk of metachronous colon cancer as compared with those who undergo total proctocolectomy with a permanent ileostomy or a restorative ileal pouch anal anastomosis [82,83]. In a retrospective cohort study of 79 carriers of a germline mutation in an MMR gene (18 *MLH1*, 55 *MSH2*, 4 *MSH6*, and 2 *PMS2*) who had undergone a proctectomy for rectal cancer, 21 (27 percent) were diagnosed with a metachronous colon cancer (incidence rate 24.3 per 1000 person-years) over a median observation of nine years [83]. Most were early-stage cancers: 72 percent were stage I and 22 percent stage II. The cumulative risk of metachronous colon cancer at 10, 20, and 30 years after proctectomy for rectal cancer was estimated to be 19, 47, and 69 percent, respectively. These risks were evident despite an apparent one to two yearly colonoscopic surveillance interval after rectal surgery.

Chemotherapy — The presence of high level of microsatellite instability (MSI-H), a characteristic of CRCs associated with Lynch syndrome, has implications for adjuvant chemotherapy and immunotherapy. Studies suggest that single-agent, fluoropyrimidine-based chemotherapy is less beneficial, or even potentially harmful, for patients with MSI-H tumors when used in the adjuvant setting. However, adjuvant therapy with leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX) has been beneficial in this setting [84-89]. Negative implications of fluorouracil alone or FOLFOX have not been observed in the metastatic setting.

In contrast, immunotherapy with an immune checkpoint inhibitor that targets the programmed death receptor-1 (PD-1) has been shown effective in the front-line treatment of MSI-H metastatic CRC [90] and for advanced MSI-H metastatic CRC that has progressed following conventional chemotherapy [91,92]. Dual blockade of anti-PD-1 and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) in MSI-H tumors has also been shown to increase the rate of disease control without compromising toxicity rates [93]. Finally, immunotherapy with anti-PD-1/L1 monoclonal antibodies and anti-CTLA-4 monoclonal antibodies is being examined in a number of clinical settings including adjuvant therapy, maintenance therapy, and prevention (no diagnosis of cancer) among patients with Lynch syndrome. Also of note, MSI-H non-CRCs have also been shown to be highly responsive to anti-PD-1/PD-L1 therapy [94]. (See "Initial systemic therapy for metastatic colorectal cancer", section on 'DNA mismatch repair deficient/microsatellite unstable tumors' and "Overview of advanced unresectable and metastatic solid tumors with DNA mismatch repair deficiency or high tumor mutational burden", section on 'Response to immunotherapy'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary colorectal cancer syndromes".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Colon and rectal cancer screening (The Basics)" and "Patient education: Colonoscopy (The Basics)")
- Beyond the Basics topics (see "Patient education: Screening for colorectal cancer (Beyond the Basics)" and "Patient education: Colonoscopy (Beyond the Basics)" and "Patient education: Flexible sigmoidoscopy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Background** – Lynch syndrome is an autosomal dominant disorder caused by a germline mutation in one of the DNA mismatch repair genes (*MLH1, MSH2, MSH6*, and *PMS2)* or deletion in the *EPCAM* gene. Lynch syndrome is characterized by an increased risk of colorectal cancer (CRC). Individuals with Lynch syndrome also have an increased risk of extracolonic malignancies, the most common of which is endometrial cancer. Other sites of cancer include the ovary, stomach, small bowel, pancreatobiliary system, genitourinary system (urothelial cancers), prostate, brain, and skin. There may also be an increased risk of breast cancer in individuals with Lynch syndrome. Screening guidelines by expert groups are valuable but should be tailored to the history of cancer seen within the family.

(See 'Terminology' above and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Clinical features'.)

- **Screening for Lynch-associated cancers** – In individuals with Lynch syndrome, we suggest the following approach to screening:

  - For patients with pathogenic variants in *MLH1* and *MSH2*, annual to biennial (every one to two years) colonoscopy starting between the ages of 20 and 25 years, or two to five years prior to the earliest age of CRC diagnosis in the family (whichever comes first). For carriers of *MSH6* and *PMS2* mutations, screening can potentially start later (at age 30 to 35 or two to five years prior to the earliest CRC in the family), unless an early-onset CRC has been diagnosed in a given family, and examinations occur every one to three years. Decisions related to age of initiation of CRC screening and the interval of time between screenings should be made after careful review of the family history and discussion of the pros and cons of intensive screening with the patient. (See 'Colorectal cancer' above.)

  - Screening and prevention of endometrial and ovarian cancer are discussed in detail separately. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Screening and prevention of endometrial and ovarian cancer", section on 'Strategies for cancer risk reduction'.)

  - Upper endoscopy with biopsy of the stomach starting at 30 to 35 years and treatment of *Helicobacter pylori* infection when detected. We have typically paired upper endoscopy with every other colonoscopy, so individuals receive this screening on a two- to four-year basis. *MSH6* and *PMS2* carriers who have colonoscopy screening every three years have upper endoscopy paired with every colonoscopy. In addition, we carefully inspect the distal duodenum and terminal ileum for small intestinal cancers during upper endoscopy and colonoscopy, respectively.

  - We perform annual urinalysis and urine cytology examination beginning at age 30 to 35 years for all patients with Lynch syndrome after thoroughly reviewing the limitations and lack of data supporting this screening. Higher-risk patients for Lynch-associated urothelial cancers including *MSH2* carriers, smokers, males, and those patients with a family history of urothelial cancer are urged to consider screening. Patients with an abnormal screen are referred to urology for further evaluation.

  - Annual physical examination performed by a primary care clinician starting at age 20 to 25 years.

- At least one thorough skin survey performed by a dermatologist to be certain that the patient does not have any Lynch syndrome skin manifestations. We initiate screening for patients between the ages of 40 and 50 years, unless Lynch syndrome skin manifestations started earlier in the family. The frequency of follow-up exams should be determined as needed by a dermatologist, but at a minimum of every one to three years.

- **Patients with colorectal neoplasia** – For those with colon cancer or an unresectable adenoma, total colectomy with ileorectal anastomosis is an option. In individuals with Lynch syndrome with rectal cancer, total proctocolectomy with an ileal pouch anal anastomosis is the most definitive risk-reducing operation given the high risk for metachronous colon cancer. However, the extent of surgery should be guided by the age at diagnosis, factors that may increase the likelihood of a poor functional outcome, and patient preference. Patients who undergo segmental colon resection, especially *MLH1* and *MSH2* carriers, will be at risk of metachronous colon cancer, with risk up to about 20 percent at 10 years. More extensive surgery decreases incidence of metachronous cancers but has not been associated with improvement in other outcomes.

  Following surgery for CRC, patients should continue to undergo annual endoscopic surveillance of the remaining colon given the high risk of metachronous cancer.

- **Chemoprevention** – For patients with Lynch syndrome we suggest the use of aspirin as it may reduce the incidence of CRC (**Grade 2C**). Further studies are needed in this population to clarify the impact of aspirin on CRC risk reduction, and to identify its optimal dose and duration of use. (See 'Chemoprevention' above.)

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Topic 15804 Version 35.0

GRAPHICS

Lifetime cancer risk related to Lynch genotypes

Cancer site	MLH1		MSH2*		MSH6		PMS2	
	Female	Male	Female	Male	Female	Male	Female	Male
Any Lynch cancer	**80.2%**	**68.5%**	**83.4%**	**80.5%**	**55.2%**	**28.5%**	**40.1%**	**57.3%**
Colorectal	48.3%	56.0%	42.6%	55.8%	17.3%	16.4%	8.5%	32.8%
Endometrial	37.2%	–	44.1%	–	45.7%	–	21.2%	–
Gastric	4.3%	8.9%	4.0%	8.3%	0.7%	0.7%	¶	2.7%
Ovarian	8.0%	–	13.4%	–	6.3%	–	2.5%	–
Ureter/kidney	2.9%	4.5%	19.5%	15.8%	3.9%	3.3%	¶	¶
Bladder	4.8%	5.6%	9.4%	13.1%	2.6%	9.0%	¶	¶
Prostate	–	15.6%	–	24.0%	–	7.0%	–	3.3%
Breast[Δ]	12.4%	–	15.5%	–	15.1%	–	12.4%	–
Brain	1.4%	0.6%	2.2%	6.6%	1.2%	0.8%	¶	¶
Small bowel	4.5%	8.3%	3.7%	7.0%	0.6%	2.8%	2.1%	3.3%
Pancreas	3.7%	3.1%	3.5%	3.3%	2.2%	1.2%	¶	¶
Bile duct/gallbladder	1.5%	4.0%	2.4%	4.6%	¶	¶	¶	¶

This table includes cumulative incidences of cancer in respective organs for males and females at 75 years of age.

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* Cancer risks in individuals with a pathogenic *EPCAM* variant are similar to those with a pathogenic *MSH2* variant.

¶ Data are insufficient to make a determination.

Δ There is ongoing debate as to whether breast cancer is a Lynch syndrome-associated cancer.

Data from: Dominguez-Valentin M, Haupt S, Seppälä TT, et al. Mortality by age, gene and gender in carriers of pathogenic mismatch repair gene variants receiving surveillance for early cancer diagnosis and treatment: A report from the prospective Lynch syndrome database. EClinicalMedicine 2023; 58:101909.

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Amsterdam II criteria for Lynch syndrome

There should be at least three relatives with any Lynch syndrome-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
One should be a first-degree relative of the other two
At least two successive generations should be affected
At least one should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any
Tumors should be verified by pathological examination

Adapted from Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999; 116:1453.

Graphic 59832 Version 7.0

Contributor Disclosures

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