CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Lynch Syndrome–Associated Colorectal Cancer

Frank A. Sinicrope, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

From the Divisions of Oncology and of Gastroenterology and Hepatology, Mayo Clinic and Mayo Comprehensive Cancer Center, Rochester, MN.

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A 48-year-old man presents with intermittent lower abdominal pain on his right side and reports a weight loss of 4.5 kg (10 lb). He is married and has two healthy teenage children. The physical examination is remarkable for the presence of blood in the stool on digital rectal examination. The hemoglobin level is 11.4 g per deciliter. His mother had a gynecologic cancer at 45 years of age, and his maternal grandfather had colorectal cancer at 63 years of age. Computed tomography of the abdomen and pelvis shows thickening of the cecal wall and pericecal adenopathy. A colonoscopy reveals a polypoid cecal mass, and a biopsy shows poorly differentiated adenocarcinoma. How should this patient be further evaluated and treated?

THE CLINICAL PROBLEM

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Colorectal cancer is the fourth most common cancer in the United States; the median age at diagnosis is 68 years. Of all new cases of colorectal cancer, 3% are attributable to the Lynch syndrome.[1] It is critical to recognize inherited syndromes that are associated with colorectal cancer, of which the Lynch syndrome is the most common. Colorectal cancer occurs at a younger age among patients who have the Lynch syndrome than among patients who have sporadic colorectal cancer (45 to 60 vs. 69 years of age),[2] although the age at onset varies according to genotype. Although colorectal cancer is the most common cancer associated with the Lynch syndrome, extracolonic cancers, including cancers of the endometrium (the most common), small bowel, ureter and renal pelvis, stomach, hepatobiliary tract, and ovary, can occur.[3] Variants of the Lynch syndrome include the Muir–Torre syndrome, which is characterized by sebaceous adenomas and other skin tumors (such as keratoacanthomas), and Turcot's syndrome, which includes glioblastoma.[3,4]

The Lynch syndrome phenotype is characterized by a predominance of cancers on the right side of the colon and a propensity for synchronous and metachronous colorectal cancers.[4,5] These tumors typically show poor differentiation that may include mucinous features or a medullary growth pattern, as well as abundant infiltrating lymphocytes in the tumor that represent a response to neoantigens generated by a high mutational burden.[6,7] Hypermutation results from deficient mismatch repair that compromises the ability to repair base-pair mismatches in DNA, which in turn confers a predisposition to colorectal cancer and other cancers over the course of a person's lifetime. Colorectal cancers with deficient mismatch repair are associated with an earlier stage at diagnosis and a lower propensity for metastases than proficient mismatch repair tumors; the incidence of deficient mis-

KEY CLINICAL POINTS

LYNCH SYNDROME–ASSOCIATED COLORECTAL CANCER

- The Lynch syndrome is the most common inherited syndrome associated with colorectal cancer, accounting for 3% of new diagnoses; it is also associated with extracolonic cancers, the most common of which is endometrial cancer.
- The Lynch syndrome phenotype includes a propensity for cancers of the proximal colon, poor tumor differentiation with mucinous or signet-ring cell histologic features or a medullary growth pattern, abundant infiltrating lymphocytes in the tumor, and synchronous and metachronous colorectal cancers.
- Criteria for the diagnosis of the Lynch syndrome on the basis of specific features of family history of cancer fail to detect the syndrome in many affected patients. Confirmation of the diagnosis requires the detection of a germline mutation in a mismatch-repair gene or in epithelial-cell adhesion molecule (*EpCAM*).
- Guidelines recommend universal testing of all patients with newly diagnosed colorectal cancer for deficient mismatch repair to determine whether the cancer is associated with the Lynch syndrome.
- A diagnosis of the Lynch syndrome should prompt consideration of subtotal colectomy rather than segmental resection owing to the high risk of metachronous colorectal cancers. Immune checkpoint inhibitors can produce durable responses in patients with the Lynch syndrome who have metastatic colorectal cancer.

match repair is reported to be 20% in stage II colorectal cancer, 11% in stage III, and 3.5% in stage IV.[8] Multiple studies, including a meta-analysis,[9] have shown that patients who have nonmetastatic colon cancers and deficient mismatch repair have a significantly better prognosis than patients with stage-matched proficient mismatch-repair tumors; this advantage is observed in untreated patients and in patients who receive the standard regimen of FOLFOX (fluorouracil, leucovorin, and oxaliplatin).[10] In the case of patients with recurrent or metastatic colorectal cancer, studies show that outcomes in patients who have tumors with deficient mismatch repair are similar or worse than outcomes in those with proficient mismatch repair, a finding that remains unexplained, although the oncogenic *BRAF* V600E mutation may be contributory in sporadic cases.[11,12]

The diagnosis of the Lynch syndrome is made by identification of a germline mutation in a mismatch-repair gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) or a germline deletion in *EpCAM* (epithelial-cell adhesion molecule) (which leads to epigenetic inactivation of *MSH2*).[4,13] When one of the mismatch-repair genes is mutated in the germline, there is a high probability that a second "hit" of somatic mutation will occur in the other copy of that gene that disables mismatch-repair function and can lead to cancer. Resultant deficient mismatch repair leads to microsatellite instability in cancers, which is characterized by alterations in lengths of repetitive regions within DNA known as microsatellites.[14] The risk of cancer depends on the affected gene. Mutations in *MLH1* or *MSH2* have been reported to account for 60 to 80% of all Lynch syndrome–associated cancers; other cases are attributable to *MSH6* or *PMS2* and, rarely, to *EpCAM*.[4,15] Mutations in *MSH2* are associated with a higher risk of extracolonic cancers, particularly endometrial cancer.[16] Recent population-based data indicate a higher carrier frequency of germline mutations in *MSH6* and *PMS2* than in *MLH1* or *MSH2* but with lower penetrance for cancers, including colorectal cancer.[1] Carriers of *MSH6* mutations present with colorectal cancer and endometrial cancers at later ages than do carriers of *MLH1* or *MSH2* mutations.[15,16] Deficient mismatch repair and microsatellite instability are not exclusive to the Lynch syndrome; they are more likely to occur in sporadic cases of colorectal cancer that are caused by *MLH1* promoter hypermethylation[17] or, less commonly, double somatic mismatch-repair mutations.[18] Sporadic colorectal cancers with deficient mismatch repair are more likely to occur in women and in patients who are older at the time of diagnosis than cancers associated with the Lynch syndrome.[17]

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

The diagnosis of the Lynch syndrome is often missed in clinical practice owing to a lack of knowledge of the syndrome and failure to obtain

Table 1. Amsterdam II Criteria and Revised Bethesda Guidelines for Diagnosis of the Lynch Syndrome.

Amsterdam II criteria
1. Three or more relatives with histologically verified Lynch syndrome–associated cancer, one of whom is a first-degree relative of the other two*
2. Cancer involving at least two generations
3. One or more cancer cases diagnosed before 50 years of age
Revised Bethesda guidelines
1. Diagnosis of colorectal cancer or endometrial cancer in a patient younger than 50 years of age
2. Presence of synchronous colorectal cancers, metachronous colorectal cancers, or other Lynch syndrome–associated tumors, regardless of patient age
3. Diagnosis of colorectal cancer with a high frequency of microsatellite instability on the basis of histologic findings (Crohn's-like lymphocytic reaction, mucinous or signet-ring cell differentiation, or medullary growth pattern) in a patient younger than 60 years of age
4. Diagnosis of colorectal cancer in one or more first-degree relatives with a Lynch syndrome–related tumor, with one of the diagnoses occurring before 50 years of age
5. Diagnosis of colorectal cancer in two or more first- or second-degree relatives with Lynch syndrome–related tumors, regardless of patient age

* Lynch syndrome–associated tumors include cancers of the colon and rectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, and sebaceous glands, as well as keratoacanthomas.

a complete family history that includes the types of cancers and ages at diagnoses in first- and second-degree relatives. The Lynch syndrome is autosomal dominant; a clinical diagnosis is suspected when a patient history and a family history fulfill the Amsterdam I criteria or the less stringent Amsterdam II criteria[19] (Table 1). However, only 50% of affected patients meet these criteria. To facilitate the diagnosis of the Lynch syndrome, the Bethesda guidelines were developed to identify patients to test for microsatellite instability; these guidelines were later revised to include tumor pathologic features[20] (Table 1). Recently, guidelines supported by multiple organizations have recommended universal testing of all patients with newly diagnosed colorectal cancer for deficient mismatch repair or microsatellite instability to determine whether the cancer is associated with the Lynch syndrome.[21]

TESTING FOR DEFICIENT DNA MISMATCH REPAIR

The identification of the Lynch syndrome involves initial evaluation of tumor tissue to test for deficient mismatch-repair proteins by means of immunohistochemical analysis or to test for microsatellite instability with the use of a polymerase-chain-reaction–based test. Loss of a mismatch-repair protein can direct germline testing of that gene. MLH1 and PMS2 proteins bind and function as a stable heterodimer; loss of expression of MLH1 and PMS2 together indicates an alteration in *MLH1* by somatic methylation of the *MLH1* promoter (sporadic case of colorectal cancer) or by *MLH1* germline mutation (Lynch syndrome–associated colorectal cancer). Loss of expression of MSH2 or MSH6 (or both) or PMS2 is typically caused by a germline mutation. Results of immunohistochemical analysis and tumor testing for microsatellite instability have been shown to be highly concordant. With the use of a panel of microsatellite markers, tumors are classified as having a high frequency of microsatellite instability (on the basis of the number of abnormal microsatellite markers) if instability is found in more than 30% of the microsatellites examined.[22] A high frequency of microsatellite instability indicates deficient mismatch repair, whereas a low frequency of microsatellite instability or no microsatellite instability indicates proficient DNA mismatch repair. In colorectal cancers with deficient mismatch repair, a finding of loss of expression of MLH1 and PMS2 or a finding of a high frequency of microsatellite instability is followed by *BRAF* V600E testing or analysis of *MLH1* methylation status (Fig. 1). Detection of a somatic *BRAF* V600E mutation is closely associated with *MLH1* hypermethylation, which is the most common cause of deficient mismatch repair (approximately 70% of cases), and the presence of either of these alterations in

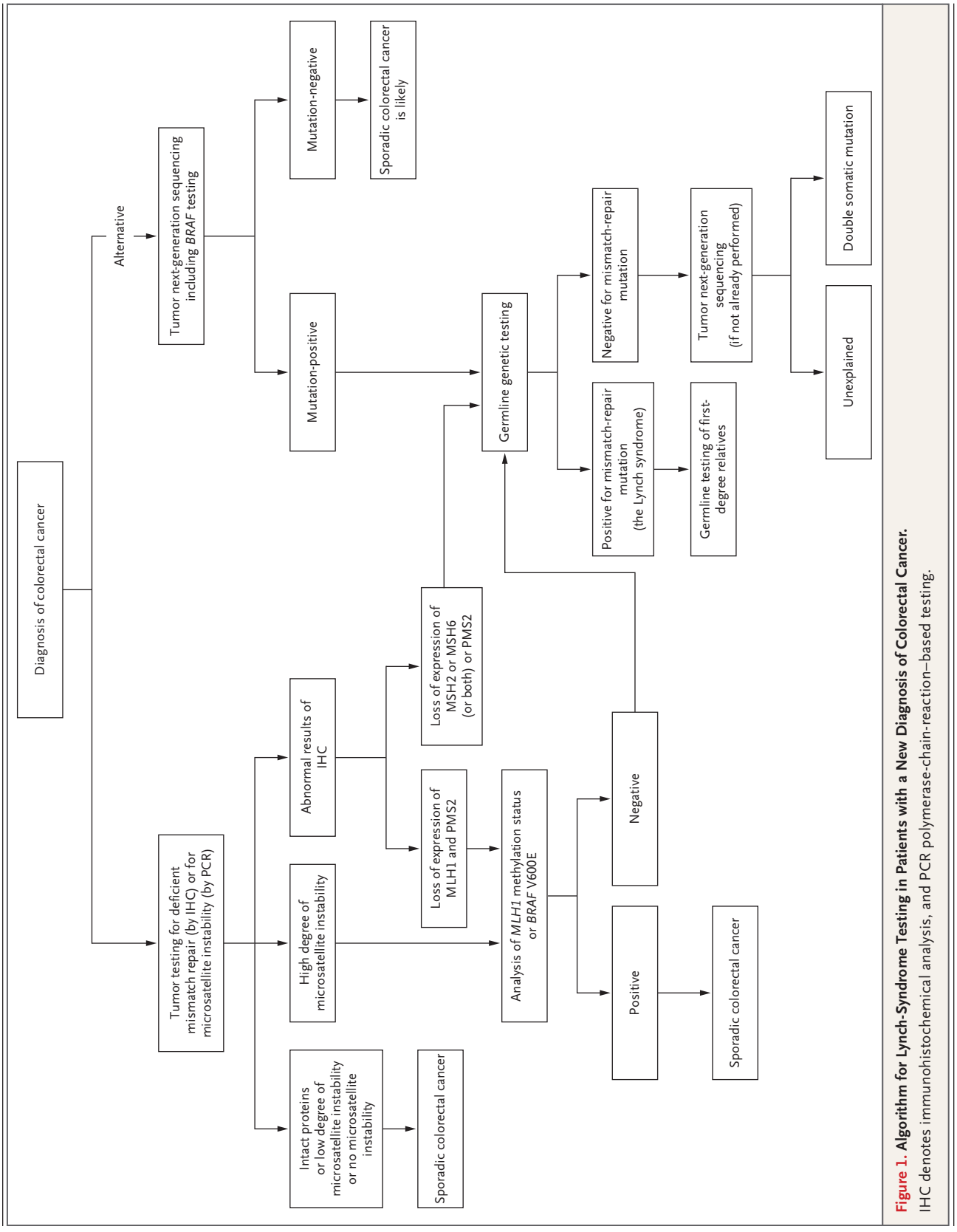


Figure 1. Algorithm for Lynch-Syndrome Testing in Patients with a New Diagnosis of Colorectal Cancer.
IHC denotes immunohistochemical analysis, and PCR polymerase-chain-reaction–based testing.

a tumor indicates a sporadic origin and rules out the Lynch syndrome.[23] Patients whose colorectal cancer shows loss of *MLH1* and lacks a *BRAF* V600E mutation or *MLH1* hypermethylation, as well as patients whose cancer shows loss of *MSH2* or *MSH6* (or both) or *PMS2* or whose tumors are found to have a high frequency of microsatellite instability, should be referred for cancer genetic counseling and should be offered germline genetic testing to confirm the Lynch syndrome (Fig. 1).

The evaluation of patients with colorectal cancer can be simplified with the use of up-front next-generation sequencing of tumor tissue to determine the mismatch-repair status.[24] This test is increasingly performed as the initial test to identify the Lynch syndrome, and results are concordant with those obtained by microsatellite-instability testing or immunohistochemical analysis.[24,25] Next-generation sequencing detects somatic mutational burden and also identifies actionable therapeutic targets such as mutations in genes related to the RAS pathway. For all patients who are found to have a suspected germline mutation on next-generation sequencing tumor testing, the mutation should be confirmed by germline sequencing, which may be performed with the use of the less expensive single-mutation test rather than a full gene sequence or a next-generation germline sequencing panel.

Tumor sequencing is useful in the evaluation of "Lynch-like" syndrome, in which colorectal cancer or other Lynch syndrome–associated tumors show deficient mismatch repair, but no mutation in a mismatch-repair gene or in *EpCAM* is detected. Many of these cases have double somatic mismatch-repair mutations or a somatic mutation with loss of heterozygosity of the other allele (Fig. 1).[18,26,27] A rare mechanism of deficient mismatch repair is constitutional mismatch-repair deficiency, which is characterized by biallelic germline mutations in a mismatch-repair gene that has recessive inheritance and is associated with café au lait spots and a wide spectrum of childhood cancers.[28]

In recent years, multigene panel tests for germline testing have become widely available and represent an alternative to traditional, syndrome-specific germline genetic testing. Multigene panel testing has shown that many patients with a germline mutation in a mismatch-repair gene do not fulfill the Amsterdam or Bethesda criteria. A benefit of multigene panels is the potential identification of germline cancer-susceptibility gene mutations that are associated with inherited syndromes other than the Lynch syndrome.[29] However, the tests also commonly detect potentially uninformative germline findings, including variants of unknown significance,[29] that create challenges for determining their pathogenicity and underscore the need for genetic counseling of patients to interpret molecular test results. Patients who are not found to have a germline mutation may still have a cancer that is associated with deficient mismatch repair, and immunotherapy may provide clinical benefit (discussed below); therefore, germline genetic testing should not replace the evaluation of tumor tissue for mismatch-repair deficiency or microsatellite instability.

SCREENING OF FAMILY MEMBERS

Once the diagnosis of the Lynch syndrome is confirmed in a proband by the identification of a germline mutation in a mismatch-repair gene, genetic testing is recommended for at-risk family members, beginning with first-degree relatives. The Lynch syndrome can be identified or ruled out by analysis of a blood sample for the specific mutation identified in the proband. Persons with the mutation, regardless of whether cancer develops in them, have a 50% chance of passing the mutation on to their offspring. For family members who lack an identified germline mutation, routine screening for colorectal cancer is recommended according to guidelines for the general population. For carriers of the mutation, colonoscopy every 1 to 2 years is recommended beginning at 20 to 25 years of age or 2 to 5 years before the youngest age at which colorectal cancer was diagnosed in the family if the diagnosis occurred before 25 years of age; for carriers of *MSH6* or *PMS2*, colonoscopy every 1 to 2 years should begin at 30 years of age and 35 years of age, respectively.[30]

SURGICAL MANAGEMENT

The possibility of the Lynch syndrome should be considered before surgical resection of colon cancer since it may influence the extent of colon resection performed. Tumor tissue obtained by colonoscopic biopsy can potentially be analyzed

for mismatch repair protein expression before surgery in cases in which the Lynch syndrome is suspected. In a retrospective cohort study, the risk of metachronous colorectal cancer among patients with the Lynch syndrome increased over time (rates of 16%, 41%, and 62% at 10, 20, and 30 years, respectively).[31] Observational studies have shown that the risk of metachronous colorectal cancer was lower among patients with the Lynch syndrome who had undergone subtotal colectomy at the diagnosis of a first colon cancer than among those who had undergone segmental resection.[5,31,32] In a meta-analysis of six studies (mean duration of follow-up, 106 months [approximately 9 years]), rates of metachronous cancers were 3.4 times as high among patients who underwent segmental resection as among patients who underwent subtotal colectomy, although a survival benefit among those who underwent subtotal colectomy was not found among the studies that had a minimum median follow-up of 60 months.[32] Factors that favor treatment with more extensive surgical resection for colon cancer include a younger patient age and a more severe Lynch syndrome phenotype. Guidelines of the U.S. Multi-Society Task Force on Colorectal Cancer include colectomy with ileorectal anastomosis as the primary procedure for the treatment of patients with the Lynch syndrome and colorectal cancer.[30] Less extensive surgery is considered in patients older than 60 to 65 years of age and in patients who have underlying sphincter dysfunction, given the risks of chronic diarrhea, incontinence, or both. After subtotal colectomy, endoscopic surveillance of the remaining rectum is generally recommended to be performed every 6 or 12 months.

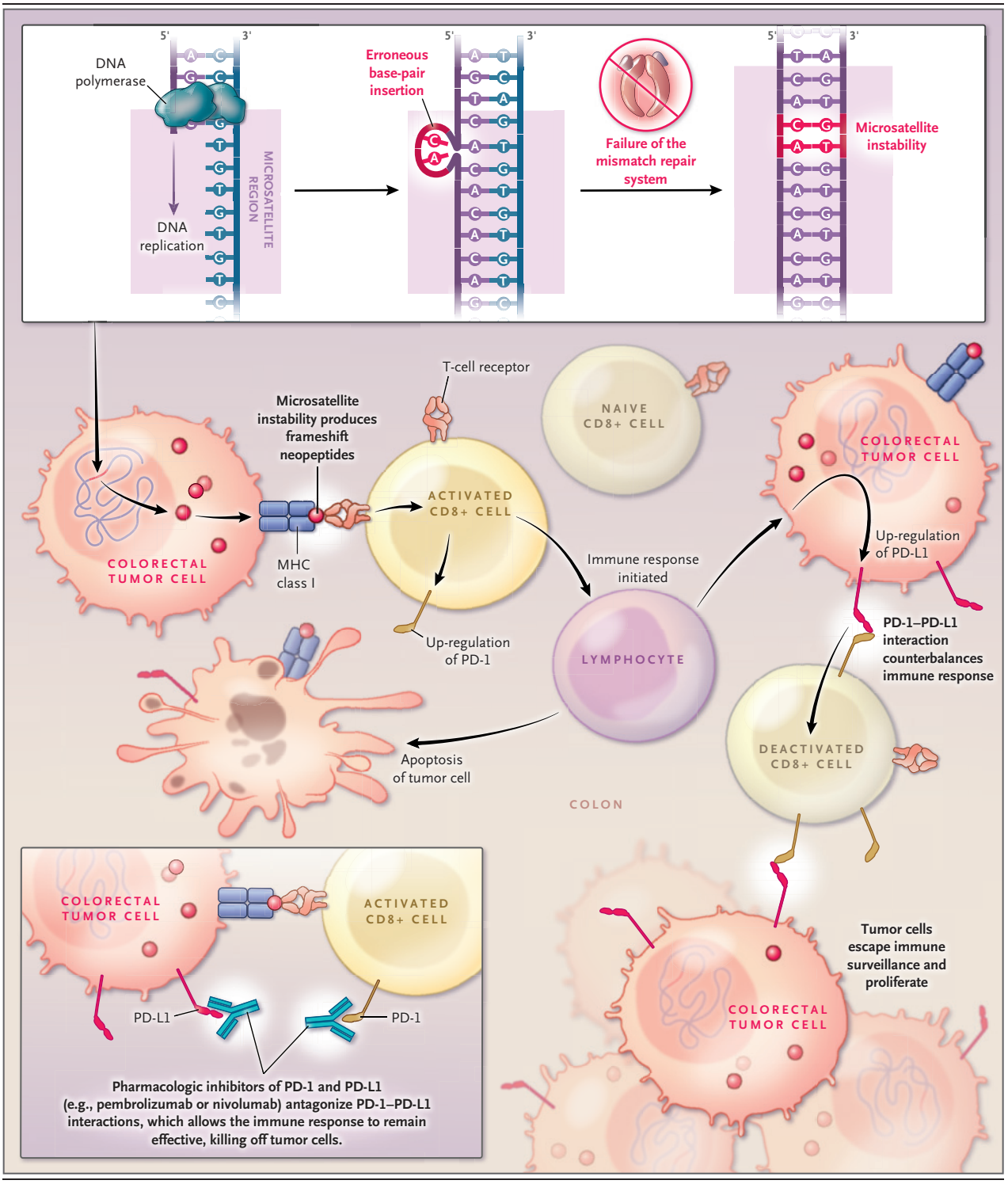
CHEMOTHERAPY AND IMMUNOTHERAPY

Adjuvant chemotherapy with 5-fluorouracil did not result in a survival benefit in subgroup analyses of patients with stage II colon cancer with deficient mismatch repair.[33] Adjuvant chemotherapy with a regimen of FOLFOX or CAPOX (capecitabine and oxaliplatin) is the standard of care in patients with stage III (node-positive) colon cancer, irrespective of tumor mismatch-repair status. Among patients with stage III colon cancer who received adjuvant FOLFOX in clinical trials, survival was significantly longer among those who had deficient mismatch repair than among those who had proficient mismatch repair.[10,34] Similar results were observed in a cohort of consecutively treated patients with stage III colon cancer.[35]

Colorectal cancers with deficient mismatch repair have abundant frameshift mutation–specific neoantigens that trigger an increased density of tumor-infiltrating lymphocytes.[7,36] Despite this enhanced immunogenicity, T cells are unable to eradicate these tumors owing, in part, to overexpression of immune checkpoint proteins[37] that can be antagonized by checkpoint inhibitors (Fig. 2). The anti–programmed death 1 (PD-1) antibodies pembrolizumab[38,39] and nivolumab[40] have been evaluated in patients with metastatic colorectal cancer and deficient mismatch repair in whom previous treatment with cytotoxic agents had failed. Pembrolizumab monotherapy and nivolumab monotherapy resulted in objective response rates that ranged from 31 to 52% (median follow-up time, 12 to 12.5 months) and that were durable; median progression-free survival and overall survival were not yet reached.[39,40] Response rates were similar in patients with Lynch syndrome–associated colorectal cancers and those with non–Lynch syndrome–associated colorectal cancers. In a subsequent trial, the combination of nivolumab plus ipilimumab, an anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, resulted in response rates and disease-control rates that were higher than those previously reported with nivolumab alone.[41] Pembrolizumab received the first Food and Drug Administration (FDA) approval for the treatment of metastatic solid tumors with deficient mismatch repair or with a high frequency of microsatellite instability regardless of cancer site, on the basis of observed efficacy after failure of at least one previous therapy. Nivolumab and more recently its combination with ipilimumab have been approved by the FDA for the treatment of colorectal cancer with deficient mismatch repair or with a high frequency of microsatellite instability after the occurrence of disease progression during treatment with standard chemotherapy.

AREAS OF UNCERTAINTY

Previous studies that attributed a majority of cases of the Lynch syndrome to *MLH1* and *MSH2* germline mutations typically involved patients



who fulfilled the Amsterdam or Bethesda criteria (i.e., patients who had a personal history or family history [or both] of colorectal cancer or endometrial cancer). These studies were probably biased against the detection of *MSH6* or *PMS2* mutations because these mutations are associated with lower penetrance for cancer, a reduced risk of cancer, and a later age at cancer onset.[1,15,16]

Figure 2 (facing page). Targeting of Colorectal Cancers in Patients with Deficient Mismatch Repair with the Use of Immune Checkpoint Inhibitors.

Deficient DNA mismatch repair results in tumors with microsatellite instability that are characterized by extensive insertions and deletions in coding regions that lead to frameshift mutations. These mutations generate immunogenic peptides (i.e., neoantigens) that are unique to the tumor and trigger an immune response that can be enhanced by immune checkpoint blockade. As shown, cytotoxic T-lymphocytes (CD8+ T cells) can recognize neoantigens displayed on major histocompatibility complex (MHC) class I molecules at the surface of tumor cells, which in turn can trigger an immune response with an increased density of tumor-infiltrating lymphocytes. This response is counterbalanced by up-regulation of immune checkpoint proteins, including programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1), that allow tumors to escape immune surveillance. Antibodies against PD-1 and PD-L1 block immune tolerance, which results in an enhanced antitumor effect.

Recent population-based data indicate that the prevalence of carriers of *MSH6* and *PMS2* exceeds that of *MLH1* and *MSH2* carriers.[1] Furthermore, multigene panel testing has suggested an association between germline mutations in *MSH6* and *PMS2* and breast cancer, ovarian cancer, or both,[42] mostly among patients who did not meet established criteria for the Lynch syndrome or among patients in whom the criteria for *BRCA1* and *BRCA2* testing were more frequently met than the criteria for the Lynch syndrome. In one study, the presence of a germline mutation in *MSH6* or *PMS2* doubled a woman's risk of breast cancer by 60 years of age.[43] These data suggest important limitations of clinical testing criteria to identify the Lynch syndrome and indicate the need for further investigation of the spectrum of cancer risks among carriers of mismatch-repair mutations.

In a prospective study involving 450 patients who had received a diagnosis of colorectal cancer before 50 years of age, a spectrum of mutations that included pathogenic germline variants were found in 16% of screened patients, half of whom had the Lynch syndrome.[27] On the basis of these data, it was suggested that genetic counseling and multigene panel testing be considered at the time of diagnosis for all patients with early-onset colorectal cancer. Important caveats are that gene panel tests will identify many germline mutations for which penetrance and appropriate management remain unknown, particularly variants associated with modestly increased cancer risks.

The use of immune checkpoint inhibitors in patients with colorectal cancer is currently limited to patients with metastatic disease; it is unknown whether this therapy can be of benefit in the case of earlier-stage cancers with deficient mismatch repair. An ongoing phase 3 trial is evaluating whether the anti–programmed death ligand 1 (PD-L1) antibody atezolizumab in combination with adjuvant FOLFOX, as compared with FOLFOX alone, can improve survival in patients with resected stage III colon cancers with deficient mismatch repair.[44]

GUIDELINES

Guidelines for the evaluation and treatment of patients with the Lynch syndrome have been published.[45] Universal testing of all newly diagnosed colorectal cancers for deficient mismatch repair or microsatellite instability is recommended by the American Society of Clinical Oncology, the American Society for Clinical Pathology, the Association for Molecular Pathology, the College of American Pathologists, the National Comprehensive Cancer Network (NCCN),[21] and the European Society for Medical Oncology. In addition, NCCN guidelines recommend the use of pembrolizumab or nivolumab for second-line or later treatment of metastatic colorectal cancers with deficient mismatch repair.[46] Recommendations in this article are consistent with published guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has early onset of colon cancer, and his family history suggests the diagnosis of the Lynch syndrome. If the gynecologic cancer in the patient's mother was endometrial cancer, the Amsterdam II criteria are satisfied. Prompt testing of tumor tissue for deficient mismatch repair or a high frequency of microsatellite instability is indicated, and referral for genetic counseling is indicated because testing to detect a germline mutation in a mismatch-repair gene is needed to confirm the diagnosis of the Lynch syndrome. If the diagnosis is confirmed, subtotal colectomy is recommended,

with endoscopic surveillance of the remaining rectum every 6 or 12 months, given the high risk of metachronous colorectal cancer. Evaluation of at-risk family members, beginning with first-degree relatives, is warranted. Patients with stage III colon cancer with deficient mismatch repair can be considered for participation in a clinical trial of immunotherapy, whereas immune checkpoint inhibitors are a standard treatment for patients with metastatic colorectal cancer and deficient mismatch repair.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and penetrance of major genes and polygenes for colorectal cancer. Cancer Epidemiol Biomarkers Prev 2017;26:404-12.
2. Møller P, Seppälä T, Bernstein I, et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 2017;66:464-72.
3. Watson P, Vasen HFA, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 2008;123:444-9.
4. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895-2015. Nat Rev Cancer 2015;15:181-94.
5. Kalady MF, McGannon E, Vogel JD, Manilich E, Fazio VW, Church JM. Risk of colorectal adenoma and carcinoma after colectomy for colorectal cancer in patients meeting Amsterdam criteria. Ann Surg 2010;252:507-11.
6. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012;487:330-7.
7. Schwitalle Y, Kloor M, Eiermann S, et al. Immune response against frameshift-induced neopeptides in HNPCC patients and healthy HNPCC mutation carriers. Gastroenterology 2008;134:988-97.
8. Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer 2009;100:266-73.
9. Popat S, Houlston RS. A systematic review and meta-analysis of the relationship between chromosome 18q genotype, DCC status and colorectal cancer prognosis. Eur J Cancer 2005;41:2060-70.
10. Zaanan A, Shi Q, Taieb J, et al. Role of deficient DNA mismatch repair status in patients with stage III colon cancer treated with FOLFOX adjuvant chemotherapy: a pooled analysis from 2 randomized clinical trials. JAMA Oncol 2018;4:379-83.
11. Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer 2011;117:4623-32.
12. Sinicrope FA, Shi Q, Allegra CJ, et al. Association of DNA mismatch repair and mutations in BRAF and KRAS with survival after recurrence in stage III colon cancers: a secondary analysis of 2 randomized clinical trials. JAMA Oncol 2017;3:472-80.
13. Ligtenberg MJ, Kuiper RP, Chan TL, et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3′ exons of TACSTD1. Nat Genet 2009;41:112-7.
14. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. Science 1993;260:816-9.
15. Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304-10.
16. Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst 2010;102:193-201.
17. Poynter JN, Siegmund KD, Weisenberger DJ, et al. Molecular characterization of MSI-H colorectal cancer by MLHI promoter methylation, immunohistochemistry, and mismatch repair germline mutation screening. Cancer Epidemiol Biomarkers Prev 2008;17:3208-15.
18. Haraldsdottir S, Hampel H, Tomsic J, et al. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. Gastroenterology 2014;147(6):1308-1316.e1.
19. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 1991;34:424-5.
20. Laghi L, Bianchi P, Roncalli M, Malesci A. Re: Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:1402-3.
21. NCCN clinical practice guidelines in oncology: genetic/familial high-risk assessment: colorectal version I.2015. Fort Washington, PA: National Comprehensive Cancer Network, 2016.
22. Murphy KM, Zhang S, Geiger T, et al. Comparison of the Microsatellite Instability Analysis System and the Bethesda panel for the determination of microsatellite instability in colorectal cancers. J Mol Diagn 2006;8:305-11.
23. Jin M, Hampel H, Zhou X, Schunemann L, Yearsley M, Frankel WL. BRAF V600E mutation analysis simplifies the testing algorithm for Lynch syndrome. Am J Clin Pathol 2013;140:177-83.
24. Hampel H, Pearlman R, Beightol M, et al. Assessment of tumor sequencing as a replacement for Lynch syndrome screening and current molecular tests for patients with colorectal cancer. JAMA Oncol 2018;4:806-13.
25. Nowak JA, Yurgelun MB, Bruce JL, et al. Detection of mismatch repair deficiency and microsatellite instability in colorectal adenocarcinoma by targeted next-generation sequencing. J Mol Diagn 2017;19:84-91.
26. Mensenkamp AR, Vogelaar IP, van Zelst-Stams WA, et al. Somatic mutations in MLH1 and MSH2 are a frequent cause of mismatch-repair deficiency in Lynch syndrome-like tumors. Gastroenterology 2014;146(3):643-646.e8.
27. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. JAMA Oncol 2017;3:464-71.
28. Durno CA, Sherman PM, Aronson M, et al. Phenotypic and genotypic characterisation of biallelic mismatch repair deficiency (BMMR-D) syndrome. Eur J Cancer 2015;51:977-83.
29. Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. J Clin Oncol 2017;35:1086-95.
30. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. Am J Gastroenterol 2014;109:1159-79.
31. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut 2011;60:950-7.
32. Heneghan HM, Martin ST, Winter DC. Segmental vs extended colectomy in the management of hereditary nonpolyposis colorectal cancer: a systematic review

and meta-analysis. Colorectal Dis 2015; 17:382-9.
33. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-26.
34. André T, de Gramont A, Vernerey D, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol 2015;33:4176-87.
35. Tougeron D, Fauquembergue E, Rouquette A, et al. Tumor-infiltrating lymphocytes in colorectal cancers with microsatellite instability are correlated with the number and spectrum of frameshift mutations. Mod Pathol 2009;22:1186-95.
36. Maby P, Tougeron D, Hamieh M, et al. Correlation between density of CD8+ T-cell infiltrate in microsatellite unstable colorectal cancers and frameshift mutations: a rationale for personalized immunotherapy. Cancer Res 2015;75:3446-55.
37. Llosa NJ, Cruise M, Tam A, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discov 2015;5:43-51.
38. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20.
39. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.
40. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-91.
41. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018;36:773-9.
42. Espenschied CR, LaDuca H, Li S, McFarland R, Gau C-L, Hampel H. Multigene panel testing provides a new perspective on Lynch syndrome. J Clin Oncol 2017;35: 2568-75.
43. Roberts ME, Jackson SA, Susswein LR, et al. MSH6 and PMS2 germ-line pathogenic variants implicated in Lynch syndrome are associated with breast cancer. Genet Med 2018 January 18 (Epub ahead of print).
44. Sinicrope FA, Ou FS, Shi Q, et al. Randomized trial of FOLFOX alone or combined with atezolizumab as adjuvant therapy for patients with stage III colon cancer and deficient DNA mismatch repair or microsatellite instability (ATOMIC, Alliance A021502). J Clin Oncol 2017;15: Suppl:35. abstract.
45. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110:223-62.
46. Benson AB III, Venook AP, Al-Hawary MM, et al. NCCN guidelines insights: colon cancer, version 2.2018. J Natl Compr Canc Netw 2018;16:359-69.

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