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Recommendations on Surveillance and Management of Biallelic Mismatch Repair Deficiency (BMMRD) Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer

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The US Multi-Society Task Force on Colorectal Cancer, with invited experts, developed a consensus statement and recommendations to assist health care providers with appropriate management of patients with biallelic mismatch repair deficiency (BMMRD) syndrome, also called constitutional mismatch repair deficiency syndrome. This position paper outlines what is known about BMMRD, the unique genetic and clinical aspects of the disease, and reviews the current management approaches to this disorder. This article represents a starting point from which diagnostic and management decisions can undergo rigorous testing for efficacy. There is a lack of strong evidence and a requirement for further research. Nevertheless, providers need direction on how to recognize and care for BMMRD patients today. In addition to identifying areas of research, this article provides guidance for surveillance and management. The major challenge is that BMMRD is rare, limiting the ability to accumulate unbiased data and develop controlled prospective trials. The formation of effective international consortia that collaborate and share data is proposed to accelerate our understanding of this disease.

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The US Multi-Society Task Force on Colorectal Cancer has produced a series of consensus statements, guidelines, and recommendations on topics related to the diagnosis and management of colorectal cancer (CRC) (1). Traditionally, the guidelines use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to evaluate the strength of evidence in the development of guidelines and recommendations (2). Prior guidelines addressed issues such as the optimal approaches to screening for CRC, management of patients with adenomatous polyps of the colon, guidelines for the performance of colonoscopy, and the optimal approach to bowel preparation for colonoscopy (3,4). In each instance, prospective controlled clinical trials were considered the gold standard for high-quality evidence.

Recently, the Task Force published guidelines for the evaluation and management of Lynch syndrome (LS), some of which were drawn from high-quality evidence, but others were developed from expert opinions because of the absence of optimal prospective clinical trials (1). The strength of evidence is based on the science at any point in time, but clinical decisions must be made at all times in the context of the available studies. High-quality studies and evidence require the availability of a large number of research subjects.

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Table 1. Estimated Penetrance and Age of Onset of Neoplasms in BMMRD

Organ	Estimated penetrance, %	Age at diagnosis, median (range), y	References
Small-bowel adenomas[a]	50	12 (10–20)	(12,33)
Colorectal adenomas[a]	>90	9 (6–15)	(12,33)
Small-bowel cancer	10	28 (11–42)	(12,17,18,25)
Colorectal cancer[b]	70	16 (8–48)	(12,17,18)
Low-grade brain tumors	Unknown	Unknown	
High-grade brain tumors[c]	70	9 (2–40)	(17,18,25)
Lymphoma	20–40	5 (0.4–30)	(17,18,25)
Leukemia	10–40	8 (2–21)	(17,18,25)
Endometrial cancer	<10	(19–44)	(17,18,25)
Urinary tract cancer	<10	(10–22)	(17,18,25)
Other sites[d]	<10	(1–35)	(17,18,25,33)

[a]Low- and high-grade adenomas with probable rapid progression.
[b]Patients undergo subtotal colectomy and ileal–rectal anastomosis, resulting in a decreased risk of colorectal cancer.
[c]High-grade glioma, medulloblastoma, and primitive neuroectodermal tumors.
[d]Fewer than 5 cases of each of the following neoplasms have been reported: neuroblastoma, Wilms tumor, rhabdomyosarcoma, osteosarcoma, breast cancer, melanoma, ovarian neuroectodermal tumor, pilomatricoma, and hepatic adenoma.

METHODS

A computer-aided search of MEDLINE from 1999 to March 2016 was performed focusing on biallelic mismatch repair deficiency (BMMRD) syndrome and constitutional mismatch repair deficiency (CMMRD) syndrome. The search was restricted to English language articles. In addition, a search was conducted using references from accessed articles. Publications were retrieved, and the authors synthesized and assessed the available data. There were no controlled trials in BMMRD. Experts pooled their collective experiences to develop consensus guidelines as an initial attempt to produce more uniform approaches to patient management, and prioritize areas in greatest need of research. The Multi-Society Task Force is composed of gastroenterology specialists with a special interest in CRC, representing the following major gastroenterology professional organizations: American College of Gastroenterology, the American Gastroenterological Association Institute, and the American Society for Gastrointestinal Endoscopy. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition, and representatives of the Collaborative Group of the Americas on Inherited Colorectal Cancer also reviewed this article. This document was approved by the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition.

BMMRD CHARACTERISTICS

LS is the autosomal-dominant disease caused by a monoallelic germline mutation in a DNA mismatch repair (MMR) or *EPCAM* gene, and is the most common cause of inherited CRC (5). LS is caused by a large number of heterozygous germline mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*, and the tumor DNA is characterized by microsatellite instability (microsatellite instability–high [MSI-H], or, by convention, MSI). Penetrance for cancer is incomplete in LS; the cumulative lifetime risk of CRC is variable depending on the gene mutated and sex, and ranges from 40 to 70% for women and men, respectively, for the genes *MSH2*, *MLH1*, and *MSH6* (5). Penetrance for CRC is reduced substantially for LS associated with mutations in *PMS2*, ranging from 10 to 20% (6–8). Patients with LS also are predisposed to extracolonic malignancies, primarily endometrial cancer (40% in women with mutations in *MSH2* and *MLH1*), and, to a lesser extent, other gastrointestinal and genitourinary cancers. These syndromes can be managed adequately by annual colonoscopy and appropriate gynecologic surgery (1).

A rare and far more virulent cancer syndrome occurs in the setting of biallelic MMR gene mutations (biallelic MMR deficiency [BMMRD]) (OMIM database accession no. 2763000). This disorder also is called *constitutional MMR deficiency* (CMMRD), because those born with biallelic inactivation of any one of the MMR genes have no DNA MMR activity in any tissue. In contrast, in LS, gene expression from the one wild-type allele is sufficient for adequate DNA MMR activity until a second hit inactivates the wild-type allele from the unaffected parent. The consequent tumor tissue is DNA-MMR deficient, which permits MSI to ensue.

BMMRD is characterized by the absence of DNA-MMR activity from birth, and results in brain tumors, colonic polyposis, colorectal and small-bowel cancers, leukemias, and lymphomas (**Table 1**). Patients often have café-au-lait macules and other stigmata that can be mistaken for neurofibromatosis type 1 (9,10). Somatic mutations in the *NF1* gene as a consequence of constitutional absence of MMR activity are the presumed explanation for this occurrence (11).

The lifetime risk of gastrointestinal cancer among BMMRD patients is the highest reported of all gastrointestinal cancer

predisposition syndromes as a function of age, with tumors often diagnosed in the first decade of life (12). The rate of progression of adenomas among BMMRD patients appears to be accelerated and more rapid than in LS. This may occur because BMMRD tumors acquire early somatic mutations in the polymerase proofreading genes *DNA polymerase* ε and δ (*POLE* and *POLD1*), and together with the underlying DNA-MMR defect, develop ultrahypermutated tumors with a massive number of substitution mutations and an unprecedented rate of progression (13). This contrasts with the distinctly smaller numbers of mutations seen in most childhood malignancies compared with adult-onset cancers (14).

In view of the striking cancer and mortality risk in these patients, close surveillance of affected individuals is important for early cancer detection. Over the past 15 years, BMMRD patients have been followed up with a clinical surveillance protocol (15) designed to diagnose tumors in asymptomatic patients amenable to surgical resection. Gastrointestinal and brain tumors are the most common malignancies described in BMMRD, occurring in more than half of these patients (16–18). Unfortunately, no consensus exists on the optimal screening and surveillance guidelines, which confounds managing physicians, and can lead to inappropriate refusal to pay for reasonable care by insurers.

BMMRD will occur in 25% of the offspring of 2 individuals who have LS involving the same gene; consequently, BMMRD is quite rare. The mutations may be homozygous or compound heterozygotes, and the various combinations of mutations can lead to clinical pleiotropy. Patients with colon cancer and café-au-lait macules presumed to have familial adenomatous polyposis with no APC mutation identified should be re-evaluated for BMMRD (19).

BMMRD probably is under-recognized. Moreover, the rarity of this disease, accompanied by childhood presentation, has led to limited research and the absence of controlled trials in the management of this disorder. Nevertheless, clinicians are confronted with difficult management decisions without guidelines based on data or consensus. Consequently, several experts have pooled collective experiences to develop consensus guidelines as an initial attempt to identify more uniform approaches to patient management, and to prioritize areas in greatest need of research.

DIAGNOSTIC CHALLENGES IN BMMRD

BMMRD is an under-recognized syndrome with pleiotropic presentations. Clues to guide clinicians to suspect BMMRD and increase recognition of BMMRD are included in **Table 2**. Patients may be children or young adults diagnosed with early onset CRC, brain tumors, leukemias, lymphomas, or uterine cancer. Any child or young adult with cancer plus parental consanguinity or features of neurofibromatosis not explained by other confirmed germline mutations should be suspected. Raising awareness among gastroenterologists, oncologists, dermatologists, internists, gynecologists, and pediatricians is paramount for improving the characterization of BMMRD patients and outcomes for patients and families with this disorder.

In contrast to other cancer predisposition syndromes, most patients with BMMRD have no immediate family history of LS-related cancers because their parents are young and not yet phenotypically affected despite harboring a monoallelic mutation in a DNA-MMR gene. In addition, small family sizes will make autosomal-recessive diseases appear to be sporadic (16). An important clue in the family history that may suggest BMMRD is parental consanguinity. Therefore, because the family history of cancers often is noncontributory, a high index of suspicion is required.

Table 2. Clinical and Laboratory Features to Raise Suspicion for Possible BMMRD

Child or young adult with a Lynch syndrome cancer (colorectal, small bowel, ureter, endometrial, and so forth)
Child or young adult with colonic adenomatous polyposis not explained by a known polyposis syndrome mutation (familial adenomatous polyposis, *MUTYH*-associated polyposis)
Any child or young adult with cancer plus parental consanguinity, café-au-lait macules, or features of neurofibromatosis, not explained by other confirmed germline mutation (ie, neurofibromatosis)
Any cancer with abnormal immunohistochemistry for the DNA-MMR proteins in normal and tumor tissue
History of brain cancer, lymphoma, or leukemia without history of radiation
Any child or adult with hypermutated tumor

One reason for the negative family history is that biallelic germline mutations in *PMS2* are the most common cause of BMMRD. The penetrance for LS-associated cancers is relatively low in monoallelic carriers of mutation in *PMS2* (ie, the parents). The combination of the early onset cancer in the proband, later-onset cancer in the parents, and incomplete penetrance for *PMS2*-LS leads to a family history that often is negative (7,20,21).

Biallelic germline mutations in *MSH6* also are over-represented in BMMRD (22). In *MSH6*-LS, the onset of LS-associated tumors occurs at a high frequency, but later in life than with the more common types: *MSH2*-LS and *MLH1*-LS. Consequently, the child with biallelic MMR gene mutations most often will develop neoplasia before either parent. As a possibly related observation, when CRC develops in a person younger than age 50 in the absence of a strong family history, again, the *PMS2* and *MSH6* genes are the most frequently involved (23,24).

The phenotypic and genotypic characterization of a patient with BMMRD can be challenging even when the diagnosis is being considered. Diagnostic criteria are proposed for the evaluation of a child or young adult cancer patient based on the phenotypic presentation (25,26). The diagnosis requires confirmation of biallelic deleterious germline MMR gene mutations. This situation creates constitutional DNA-MMR deficiency, and nonexpression of the MMR protein usually is observed in all normal, non-neoplastic tissues as well as tumor tissues, which can be confusing in the pathologic interpretation of the immunohistochemistry of the tumor tissue and surrounding tissues where the pathologist expects full protein expression in non-neoplastic cells, as was shown in a recent case study (27). The family history frequently is negative, and because of the broad implications for the patient and family, it is reasonable to recommend universal testing for immunohistochemistry and MSI on all small- and large-bowel cancers in children.

Table 3. Recommendations for Screening At-Risk or Affected Persons With BMMRD (1,12,15,18)

Intervention	Recommendation	Alternative approach
Upper endoscopy and video capsule endoscopy	Annually beginning at 8 years	--
Colonoscopy	Annually beginning at 6 years	--
Brain MRI	Every 6 months beginning at 2 years	Head ultrasound starting at 6 months until fusion of fontanel
Complete blood count	Every 6 months beginning at 1 year	--
Pelvic examination with endometrial sampling	Annually beginning at age 20 years	--
Urinalysis	Annually beginning at age 10 years	MRI
Total-body MRI	Uncertain	--

In addition, identifying 2 MMR mutations in the germline and confirming they are on separate alleles can be difficult. Patients are identified with homozygous biallelic alterations of MMR genes and compound heterozygous alterations. Variants of unknown functional significance also have been reported in the MMR genes. Making matters worse, the majority of BMMRD patients carry *PMS2* mutations (17,18), which is complicated by the presence of 20 *PMS2* pseudogenes, which are nonfunctional, in the human genome, all of which have wild-type sequences that can obscure finding true mutations, depending on the DNA sequencing strategies used. Functional assays such as lymphocyte tolerance to methylating agents and mutation signatures among BMMRD individuals ultimately may become diagnostic for BMMRD (13,14,28).

BMMRD SURVEILLANCE

The management of BMMRD is based on the current estimates of neoplasia risk and the early age of onset for the cancers (**Table 1**), which have led to tentative guidelines for the management of these patients (**Table 3**).

Colorectal cancer

Evidence-based CRC screening and surveillance recommendations in LS were developed based on prospective but uncontrolled trials with large numbers of patients. Colorectal screening with colonoscopy decreases the CRC mortality in patients with LS (29–31). Frequent colonoscopy screening (every 1 or 2 years) was associated with earlier-stage diagnosis of CRC and a reduction in the number of CRCs in LS patients. Guidelines recommend that patients at risk for LS, or with confirmed LS, undergo colonoscopy every 1–2 years, beginning between ages 20–25 years or 2–5 years before the youngest age at diagnosis of CRC in the family if diagnosed before age 25 years (1,32).

Patients with BMMRD are at risk for extremely early onset CRC. Among BMMRD patients presenting with CRC, the median age at diagnosis was 16 years (range, 8–48 y) and more than half of cases are classified as pediatric-onset CRC. Colonic adenomatous oligopolyposis typically is diagnosed between 5 and 10 years of age, which may lead to an erroneous diagnosis of familial adenomatous polyposis. As more BMMRD patients are identified and undergo colonoscopy, additional data will help determine the age spectrum for onset of adenomas. In contrast to the right-sided predominance of CRC in LS, left-sided CRC appears more prevalent in BMMRD patients, perhaps owing to the frequent involvement of *PMS2* gene mutations (33). The progression of adenomas to malignancy in BMMRD is the most rapid of any inherited colorectal cancer syndrome (12,13,34).

A surveillance program initiated for a kindred with homozygous germline mutations in *MLH1* resulting in BMMRD led to the detection of 15 tumors in the 2 surviving siblings over 10 years of follow-up evaluation (15,35). Both sisters in this program underwent ileal–rectal anastomosis and have endoscopic surveillance of the rectum every 6 months with adenomas, often with high-grade dysplasia resected at every examination.

The International BMMRD Consortium and The European Consortium Care for CMMRD both recommend annual colonoscopy starting in the first decade of life (12,15,18,25). The International BMMRD Consortium recommends starting at 6 years of age and the European Consortium recommends starting at 8 years of age. We do not know what the optimal or most cost-effective surveillance is, and this is a topic for future research.

Recommendation

1. In patients with BMMRD, surveillance for CRC by colonoscopy is recommended annually beginning at age 6.

Once polyps are identified, colonoscopy every 6 months is recommended. *Weak recommendation, low-quality evidence.*

Small-bowel cancer

Patients with BMMRD are at increased risk of very early onset small-bowel cancers. The median age at diagnosis of small-bowel cancer was 28 years, with a range of 11–42 years (12,22). The prevalence of small-bowel cancer ranges from 10 to 16% in BMMRD patients (33). Prospective data are scant, but insights have been derived from single kindreds followed up for extended periods. Malignant tumors have included an asymptomatic jejunal cancer amenable to complete resection and the other identified lesions showed low-grade to high-grade dysplasia. This kindred continues in the surveillance program, and 2 malignancies (duodenal and jejunal cancers) have been diagnosed over the past 5 years, after a total of 15 years of surveillance.

Because patients are living longer with BMMRD, the prevalence of small-bowel cancer likely will increase. The age of onset of small-bowel adenomas is later than for colonic adenomas in BMMRD; they typically develop in the second decade of life. Cancers have been identified in the duodenum, jejunum, and ileum. Five small-bowel cancers were diagnosed in 4 patients from a group of 35 patients followed up prospectively using the International BMMRD Consortium guidelines (12). Video capsule endoscopy (VCE) and magnetic resonance enterography have been the modalities used for small-bowel surveillance. To date, no deaths related to gastrointestinal cancer have occurred among patients in the surveillance program. All of the small-bowel malignancies were identified in asymptomatic patients undergoing small-bowel surveillance and were amenable to complete resection. Removal of small-bowel polyps is recommended. An additional 11-year-old boy presented with weight loss, abdominal pain, anemia, metastatic duodenal cancer, and subsequently was diagnosed with BMMRD (35).

Upper endoscopy and VCE are the diagnostic modalities currently recommended for evaluating the small bowel in BMMRD patients. The sensitivity of VCE for small-bowel polyps in BMMRD has not been evaluated. In addition to VCE, we recommend monitoring hemoglobin levels in BMMRD individuals. Prospective monitoring of BMMRD individuals after resection of small-bowel cancers is required to rigorously determine the long-term outcome.

The International BMMRD Consortium and The European Consortium Care for CMMRD both recommend annual upper endoscopy and video capsule endoscopy starting in the first decade of life (12,15,18,25). The International BMMRD Consortium recommends starting at 8 years of age and the European Consortium recommends starting at 10 years of age.

Recommendation

2. In patients with BMMRD, annual surveillance for small-bowel cancer by upper endoscopy and video capsule endoscopy is suggested beginning at 8 years of age.

Monitoring of hemoglobin levels every 6 months also is suggested, beginning at 8 years of age. *Weak recommendation, very low quality evidence.*

Central nervous system tumors

Brain tumors are frequent among BMMRD patients, and often diagnosed in the first decade of life. The penetrance for these tumors is unknown. High-grade gliomas are most common, followed by primitive neuroectodermal tumors and medulloblastoma. Similar to gastrointestinal adenomas, the rate of progression among BMMRD individuals appears to be rapid in the brain tumors. The median age at diagnosis in patients with BMMRD is 9 years (range, 2–40 y) (22). Surveillance magnetic resonance imaging (MRI) identified an asymptomatic anaplastic astrocytoma amenable to complete resection with long-term disease-free survival (15,35). Prognosis depends on the possibility of complete resection, making early detection paramount. Asymptomatic low-grade tumors have been identified on MRI and completely resected (15).

The current literature suggests surveillance including MRI starting at 2 years of age with repeat MRI every 6 months. There is a high frequency of unrecognized BMMRD among young patients with high-grade gliomas in populations in which consanguinity is common (36). As more patients with BMMRD undergo brain MRI, a central nervous system phenotype is emerging that includes agenesis of the corpus callosum, vascular changes, and gray matter heterotopias (37–39). Prospective surveillance with systematic data collection of BMMRD patients undergoing MRI will add to our understanding of this disease.

Recommendation

3. In patients with BMMRD, surveillance for brain tumors by brain MRI every 6 months is suggested, commencing at 2 years of age.

Weak recommendation, low-quality evidence.

The age of onset and frequency of MRI in this guideline is in agreement with both The International BMMRD Consortium and The European Consortium Care for CMMRD (15,18).

Lymphomas/Leukemias

All major types of leukemias and lymphomas occur in BMMRD. However, there is a high prevalence of lymphoid malignancies, most commonly T-cell non-Hodgkin lymphomas. Currently, no proven surveillance modalities for leukemia or lymphoma have been identified. Data collected by the International BMRRD consortium and other case series expand the tumor spectrum of BMMRD to include osteosarcoma and tumors of embryonal tissue origin such as neuroblastoma, Wilms tumor, and rhabdomyosarcoma (40). The natural history of these tumors in BMMRD patients is unknown.

Recommendation

4. Complete blood count is suggested every 6 months beginning at 1 year of age.

Weak recommendation, very low quality evidence.

The European Consortium suggests optional abdominal ultrasound every 6 months, beginning at 1 year of age (18).

Endometrial cancer

Endometrial cancer is the second most common cancer occurring in LS, with a cumulative lifetime risk ranging from 10 to 70% related to the specific gene mutation (1). Expert consensus recommends offering screening for endometrial cancer in LS by pelvic examination and endometrial sampling annually starting at age 30–35 years (1). Endometrial cancer has been reported in fewer than 10 BMMRD individuals diagnosed between 19 and 44 years (22,41). Currently, the prevalence of endometrial cancer among BMMRD patients appears to be low but may increase as these patients live longer.

Clinicians managing patients with early onset uterine cancer should assess patients for café-au-lait macules because diagnosing BMMRD would allow implementation of an appropriate surveillance protocol.

Recommendation

5. In women with BMMRD, surveillance for endometrial cancer is suggested by transvaginal ultrasound, pelvic examination, and endometrial sampling annually starting at age 20 years.

Weak recommendation, very low quality evidence.

The age of onset and frequency of surveillance in this guideline is in agreement with both The International BMMRD Consortium and The European Consortium Care for CMMRD (15,18).

Urinary tract cancers

Patients with LS are at risk of transitional cell carcinomas of the ureter, renal pelvis, and bladder (1). The risk is greatest in males with *MSH2* mutations. The evidence for effectiveness in screening the urinary tract in LS patients is weak. Urinalysis starting at age 30–35 years is recommended (1). Urinary cytology examinations are of no value for screening in high-risk individuals (42,43). Among BMMRD patients reported to date, fewer than 10 individuals have been reported with urinary tract tumors. The age at diagnosis has ranged from 10 to 22 years. As patients with BMMRD transition into adulthood, we recommend annual urinalysis starting at 10 years of age and consideration of MRI.

Recommendation

6. In patients with BMMRD, surveillance for cancer of the urinary tract is suggested, with annual urinalysis starting at age 10 years

Weak recommendation, very low quality evidence.

The age of onset of urinalysis is recommended at 10 and 20 years by The International BMMRD Consortium and The European Consortium, respectively (15,18).

Hepatic adenomas

Hepatic adenomas were reported in 3 unrelated patients with BMMRD (44). Awareness of the association of hepatic adenoma with BMMRD is important so that benign adenomas are not misdiagnosed as metastatic disease, resulting in inappropriate interventions, including surgery or chemotherapy. Hepatic imaging techniques including abdominal MRI should be used to differentiate liver metastases from hepatic adenomas. Hepatic adenomatosis may occur in BMMRD with nodules up to 5 cm, but the natural history of this situation is not yet understood.

Recommendation

7. Given the rarity with which these lesions have been described in BMMRD, no routine surveillance for hepatic adenoma is recommended.

Weak recommendation, very low quality evidence.

Surveillance for the asymptomatic relatives

In contrast to other cancer predisposition syndromes, the majority of BMMRD kindreds have no immediate family history of LS-related cancers and most parents are clinically unaffected. In contrast to typical LS, *PMS2* mutations are the most common mutations identified among BMMRD patients. *PMS2* mutations in the heterozygous state have low penetrance, which probably explains the paucity of LS cancers in the extended family. Consequently, asymptomatic parents may receive a diagnosis of LS after the diagnosis of BMMRD is made in a child. Therefore, we recommend that all heterozygous family members follow the LS screening guidelines (1).

Recommendation

8. Screening for LS-associated cancers is recommended in persons at risk (first-degree relatives of those affected), or affected with LS following the evidence-based guidelines (1).

Weak recommendation, moderate-quality evidence.

Surveillance in adult BMMRD patients and risks of LS-associated tumors

Because patients with BMMRD undergo intensive surveillance programs, malignancies will be detected and treated, and patients will enjoy longer lives. It is unclear what tumor spectrum will emerge among adults with BMMRD. No specific recommendations for adults with BMMRD exist, and it is not certain whether particular tumors will continue to increase with age among BMMRD survivors. In addition, clinical heterogeneity related to different mutations in the 4 DNA-MMR genes is likely, but currently undefined.

BMMRD MANAGEMENT

Synchronous and metachronous tumors

Synchronous gastrointestinal and/or extraintestinal cancers occur frequently in BMMRD. Therefore, oncologists and gastroenterologists managing BMMRD patients need to assess the entire gastrointestinal tract for synchronous tumors before determining treatment plans. In one review, 20% of patients had multiple synchronous CRCs, ranging from 2 to 10 malignancies (33). Similarly, synchronous small-bowel cancers commonly occur in BMMRD. Among 17 BMMRD patients reported with small-bowel cancers by consortia, approximately one third had multiple synchronous small-bowel tumors (12,33). BMMRD patients with concomitant extraintestinal cancers are reported, including rectal cancer with mediastinal non-Hodgkin lymphoma diagnosed during preoperative staging.

Metachronous cancers occur frequently in BMMRD patients. In a literature review, 132 tumors were reported among 92 patients (12,22), although this could represent reporting bias. Among 24 patients followed in the International BMMRD Consortium, half developed metachronous gastrointestinal cancers (12). As more patients are followed up prospectively and undergo surveillance with earlier diagnosis of tumors, our appreciation of metachronous cancer will increase.

Gastrointestinal surgery

The risk of metachronous CRC in monoallelic LS after partial colectomy is substantial (10-year cumulative risk, 16–19%). Consequently, colectomy with ileorectal anastomosis is the primary treatment for patients known to be affected with LS who have CRC or colonic neoplasia not amenable to resection at endoscopy (1). Given the greater risk of CRC among BMMRD individuals and

the high prevalence of metachronous gastrointestinal cancers, an aggressive management approach is recommended. In BMMRD patients with colonic polyps containing high-grade dysplasia or cancer, or when there are too many polyps to remove endoscopically, total or subtotal colectomy with ileorectal anastomosis is recommended, although proctocolectomy with ileal pouch–anal anastomosis may be necessary in the case of rectal cancer. Close monitoring of the rectum with endoscopy every 6–12 months is crucial after ileorectal anastomosis.

Small-bowel resection is the treatment of choice for tumors amenable to resection. The survival rate of patients with tumors amenable to complete resection appears to be favorable, much as it is for CRC in LS (45). Prospective long-term follow-up evaluation of patients will be important as we define the natural history of BMMRD. Aggressive surveillance of the small bowel after resection is important because of the extremely high rate of metachronous gastrointestinal tumors.

Pharmacologic intervention

Studies have shown that LS patients experience a significant reduction in the risk of CRC and possibly other noncolonic LS-related cancers by taking aspirin (46). The initial prospective placebo-controlled studies were conducted in Europe using 600 mg of aspirin per day in adults, and those who took the aspirin for at least 2 years had a reduction in CRC incidence of >60%. The median age of the treated patients was 45 years, and there was no excess aspirin-related toxicity in the treatment group compared with patients taking placebo. It is unknown whether a beneficial pharmacologic effect will be seen in individuals with BMMRD because the biology of this disease is different from that in ordinary LS. However, it would seem reasonable to propose a controlled prevention trial of aspirin in BMMRD patients.

Immunologic considerations

CRCs with MSI generate a large number of frame-shift neopeptides that are immunogenic (47–49). This may explain the large number of tumor-infiltrating lymphocytes in CRCs with MSI and the large number and size of regional lymph nodes in resection specimens of patients undergoing surgery for CRC in LS. The clinical survival in patients with CRC in LS is significantly better than that for sporadic CRCs (45,50,51). One interpretation of this is that the immunologic response to antigenic neopeptides helps contain the CRC and limits metastasis. Patients with CRCs in the setting of LS may develop metastases and die of their cancer despite this, because some tumors manage to escape immunologic containment.

Two theoretical approaches have emerged from this information. One way tumors escape immunologic detection and cell death is by expressing programmed death-1 ligands (PD-L1 or PD-L2), a molecule that engages programmed death-1 (PD-1) on immune cells, which represses the cytotoxic immune-mediated response to the tumor. Administration of the anti–PD-1 monoclonal antibody, pembrolizumab, resulted in a significant improvement in clinical outcome in 78% of patients with MSI CRCs (52). Anti–PD-1 therapy provides no benefit for the treatment of CRC without MSI. This was a preliminary observation, not fully evaluated in LS or BMMRD. This therapy has not been applied systematically to BMMRD, but this may be an ideal setting for this type of treatment(53). Additional antibodies and drugs are under development that target the immune checkpoints, and BMMRD patients are potential candidates for these new approaches.

A second theoretical consideration stems from the observation that defective DNA-MMR activity results in a hypermutable phenotype in the DNA of these tumors (13,14). There is a particular tendency for the defective MMR phenotype to generate single base-pair deletion mutations at mononucleotide repeats. There are a small number of genes that have mononucleotide repeats in a coding exon, and deletions in single base-pair repeats will lead to recursive extended downstream frameshift mutations in those genes (49,54). Some of these mutated genes are recognized "drivers" of CRC, including the genes *TGFβR2* and *ACVR2A*, which are mutated in most MMR-deficient CRCs (55,56). Moreover, these mutations occur repeatedly at the exact same sequences, generating the same downstream frameshift neopeptides. Furthermore, these mutations commonly are found in normal, non-neoplastic colonic crypts of resection specimens of LS-associated CRC, and the frameshift peptides are antigenic (47). LS patients have been shown to have antibodies to these frameshift peptides in their blood (57). This has led investigators to consider the possibility of vaccinating LS patients with synthetic frameshift peptides in an attempt to enhance the immune response and possible immune-editing–based eradication of early neoplasia (58). The concept has been explored in adults with monoallelic LS, but not in cases of BMMRD.

Genetic counseling

Young patients diagnosed with cancer always should raise the suspicion of a possible underlying cancer predisposition. Any young patient with cancer plus consanguinity and/or features of neurofibromatosis should be evaluated for an underlying BMMRD. Clues to guide clinicians to suspect BMMRD are included in **Table 2**. Genetic counseling plays a crucial role in the management of kindreds with BMMRD. Genetic counseling can offer support and education for this complex diagnosis that has implications for the entire family. Siblings of the proband would be at risk of having BMMRD, Lynch syndrome, or neither condition, and testing is required to determine the surveillance protocol, which differs in the type of screening and the age to start. Both parents of the proband have Lynch syndrome, and a genetic counselor can review cancer risk and surveillance recommendations for what most often are lower penetrance LS genes. A counselor also can identify other family members at risk (grandparents, aunts, uncles, cousins), as well as offer options such as prenatal and preimplantation genetic diagnosis for future children who may be at risk. As life expectancy increases for patients with BMMRD, family planning considerations based on risk of LS for the children should be reviewed.

Table 4. Knowledge Gaps Requiring Research in the Field

What is the prevalence of BMMRD, and do we understand the full spectrum of disease associated with BMMRD?
What are the genotype–phenotype correlations in BMMRD, and how do we interpret novel compound heterozygous mutations?
Is total-body MRI an effective surveillance modality in BMMRD?
Is there a role for chemoprevention using aspirin, what dose is optimal, and beginning at what age in BMMRD?
What is the role of immune checkpoint therapy for patients with cancer and BMMRD?
Is there a role for immunizing BMMRD patients with frameshift peptides before the development of any cancer?
What is the explanation for the greater number of biallelic mutations in PMS2 and MSH6 compared with MSH2 and MLH1 (as occurs in Lynch syndrome)? Are biallelic mutations in MSH2 and MLH1 more likely to be embryonic lethal, or is the population prevalence of low-penetrance PMS2 and MSH6 mutations much greater than currently is appreciated?
Why do some cancers in BMMRD often fail to show MSI?

FUTURE DIRECTIONS

Over time, as BMMRD becomes better recognized and more patients are characterized and enter surveillance programs, systematic data collection will allow for a more comprehensive understanding of the cancer spectrum, and genotype–phenotype correlations. Surveillance of adult BMMRD survivors may expand the tumor spectrum in BMMRD, and additional LS-associated tumors may emerge among adults with BMMRD. As we intervene clinically in this disease, the natural history will change and evolve.

Rapid whole-body MRI might be considered as a potential diagnostic test among patients with BMMRD. MRI has the potential to identify urinary tract cancers, endometrial cancer, osteosarcoma, and many intra-abdominal tumors. The risk of brain tumors is not yet clear for adult survivors of BMMRD, but as these patients reach adult life, this may become a major concern. International collaboration will help advance our understanding of the tumor spectrum in BMMRD and ultimately understand genotype–phenotype correlations.

BMMRD is a disease with a desperate need for more research (**Table 4**). International consortia are needed to accelerate the acquisition of data on the natural and treated history of BMMRD. Over time, patients may have whole-genome sequencing with detection of BMMRD before the tumors develop. The efficacy of screening programs needs careful examination to ensure the use of appropriate tests at optimal intervals, and that zeal to detect early treatable tumors does not produce more harm than benefit. Studies to determine whether aspirin (or other anti-inflammatory drugs) can play a beneficial role in BMMRD are needed. Finally, we need to determine whether immune checkpoint therapies or other manipulations of the immune system are useful in this disease, which is one of the most virulent cancer-predisposing syndromes ever described.

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CONFLICT OF INTEREST

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