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RECENTLY IDENTIFIED COLON CANCER PREDISPOSITIONS: MYH AND *MSH6* MUTATIONS

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Abstract

Single-gene germline mutations conferring a high lifetime risk of CRC account for up to 6% of all CRC cases. The most widely studied monogenic colorectal cancer syndromes include Familial Adenomatous Polyposis (FAP) and Lynch syndrome. However, additional syndromes continue to be defined and new predisposition genes are continuing to be identified.

Most recently, MYH associated polyposis (MAP) and an "Atypical Lynch syndrome" related to the presence of *MSH6* mutations have been linked to an increased risk of CRC. In this review, we summarize basic information related to these newly recognized gene mutations, including the accumulating data on the prevalence and penetrance of deleterious mutations, as well as the management options for identified carriers and their families.

Recognizing these heritable syndromes is essential and predictive genetic testing will continue to transform the field of cancer risk assessment by offering the opportunity to focus on more precise risk management and cancer prevention.

Colorectal cancer (CRC) is a common malignancy affecting over 148,000 new patients each year in the United States and is estimated to have caused 55,170 deaths in the year 2006.[2] Multiple risk factors have been studied, and one of the most sophisticated advances made to date has been related to the use of molecular genetics in identifying heritable colorectal cancer syndromes.

Although the majority of patients with CRC have sporadic disease without evidence of an inherited disorder, up to 30% have a familial component and a potentially definable genetic basis.[2,3] Over the last decade single-gene germline mutations conferring high lifetime risk of CRC have been identified and account for 5–6% of all colorectal cancer cases.[4–6] Other genes with more subtle or modifying effects continue to be characterized.

Readily identifying populations with hereditary CRC syndromes, such as Familial Adenomatous Polyposis (FAP) and Lynch syndrome (also known as Hereditary Nonpolyposis Colorectal Cancer or HNPCC), is of great importance given the known benefit of intensive endoscopic surveillance and prophylactic surgery on morbidity and mortality. Recognizing these syndromes also has an impact on referral for predictive genetic testing where identifying

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gene carriers improves the efficiency of cancer surveillance and helps identify which other family members require intense management versus those who can receive the standard of care.[7–9]

Genetic information has the potential not only to inform but also transform cancer risk identification, risk reduction, and treatment practices. The incorporation of careful genetic testing into oncology practice is an important step toward more precise risk management and prevention.

Familial Adenomatous Polyposis: Classic and Attenuated

FAP is the most easily identified form of hereditary colorectal cancer. It is an autosomal dominant condition with a prevalence of one in 8000 individuals. It is classically characterized by multiple (>100) adenomatous polyps in the colon and rectum that develop after the first decade of life. The age of onset of colonic adenomas is variable; by age 10 approximately 15% of patients manifest adenomas, by age 20 the probability increases to 75%, and by age 30, 90% will have presented with FAP.[10] Without intervention, FAP confers a risk of colorectal cancer of nearly 100% in affected individuals at a mean age of 39 years.

Although total colectomy can drastically reduce colorectal cancer risk in patients with FAP, they remain at risk for other manifestations of the disorder that require frequent medical follow-up and have the potential for considerable morbidity. These associated conditions include polyps in the upper gastrointestinal tract, extraintestinal manifestations such as desmoid tumors, osteomas, epidermoid cysts, congenital hypertrophy of retinal pigment epithelium, and other malignant lesions such as thyroid tumors, small bowel adenocarcinoma, central nervous system tumors, and in children, hepatoblastoma.

Most cases of FAP are due to mutations of the APC gene on chromosome 5q21. APC gene testing has been commercially available since 1994 and has led to changes in management guidelines. Genetic evaluation for individuals fulfilling clinical criteria for FAP is recommended, and presymptomatic genetic testing removes the necessity of annual endoscopic screening of family members who do not inherit the gene mutation present in the family.

While patients affected with classic FAP can be easily identified, a subset of patients has a less obvious phenotype. Patients with 10 or more cumulative colorectal adenomas but less than 100 are at risk for attenuated FAP (AFAP), which arises from APC mutations at the 5′ or 3′ ends of the gene or in certain areas of exon 9.[11,12] With this phenotype, adenomas and CRC occur later in life than in classic FAP, extraintestinal manifestations are uncommon, and cases may appear to be sporadic.

MYH-Associated FAP

Inherited mutations in the recently described human analogue of the *Escherichia coli muty* gene, MYH, have been shown to predispose individuals to multiple colorectal adenomas and carcinoma. Patients with MYH-associated polyposis (MAP) present with clinical features similar to FAP or AFAP but in the absence of a strong multigenerational family history of polyposis. Patients typically present between the ages of 40–60 years with a variable number of colorectal adenomatous polyps.[13] However, MYH mutation carriers do not usually present with multiple polyps before the age of 30 years.[14] There are limited reports on the prevalence of extracolonic tumors associated with MAP. In one study, where 16 MAP patients underwent upper gastrointestinal endoscopy, duodenal adenomas or gastric fundic gland polyps were found in 31%.[15]

The Gene

MYH is a base excision repair (BER) gene located on chromosome 1p35 and is involved in repairing DNA that is damaged by reactive oxygen species generated during aerobic metabolism as well as by exogenous stimuli such as various chemical oxidants and ionizing radiation. Loss of MYH activity leads to an unusually high frequency of G:C to T:A transversions resulting in nonsense or splicesite mutations in APC. This suggests faulty repair of 7,8-dihydro-8-oxo-2′deoxyguanosine (8-oxoG), one of the most deleterious products of oxidative DNA damage, where 8-oxoG readily mispairs with adenine residues leading to transversion mutations in the daughter strand. When effective, MYH glycosylase provides defense against such damage by scanning the daughter strand after replication and removing the mispaired nucleoside.

Estimated CRC risk

Biallelic Mutation Carriers—The contribution of MYH to the multiple adenoma phenotype was first described in a Welsh kinship with multiple colorectal adenomatous polyps and carcinoma but no inherited APC mutation or mismatch repair gene.[16] In the mutational analysis of MYH in this family, all three affected siblings were noted to be compound heterozygotes for the missense mutations, Y165C and G382D. Unaffected family members were either homozygous wildtype or heterozygous for one of the mutations, and this finding suggested an autosomal recessive pattern of inheritance. Subsequent studies have revealed that this family was not an isolated instance and further demonstrated the prevalence of biallelic MYH mutations in populations with multiple colorectal adenomas. Sieber et al[17] noted that in 259 APC mutation negative British patients with five to hundreds of adenomas, 5.4% (14/259) were found to be mutation carriers, and the two original mutations described, Y165C and G382D, accounted for the majority (82%) of mutant alleles. Overall, 30% of patients with 15–100 adenomas were biallelic mutation carriers. In another similar British cohort of 111 probands with more than 10 adenomas, Sampson et al[18] found that 23% were biallelic MYH carriers. In these studies the mean age of MAP presentation was about 50 years, and almost all patients had multiple adenomas (5–100) or a mild classical FAP phenotype with fewer than 1000 polyps. CRC was present in about 50% of patients at the time of diagnoses.

These studies have assessed the contribution of MYH to colorectal carcinoma in patients selected for multiple colorectal adenomas and do not account for its role in cases not associated with multiple polyps. To gain insight into the contribution of MYH to the overall CRC burden on the population level, Enholm et al[19] conducted a case-control study of 1042 Finnish CRC patients, regardless of their polyp phenotype, and 424 cancer-free controls and found that MYH-associated CRC appeared as common as CRC associated with FAP. Fleischmann et al[20] appreciated similar findings when examining the gene in a total of 358 affected individuals with CRC diagnosed before age 55 years and 354 controls. These data[20] suggest that up to 2.8 % (upper limit of 95% CI) of early onset CRC could be ascribed to biallelic MYH mutations. Therefore, biallelic mutation carriers not only have some clinical features similar to those with polyposis resulting from APC mutations, but MYH confers a near equal contribution to early onset CRC comparable to that of germline APC mutations.

The role of MYH in early onset CRC has been confirmed in multiple larger case-control studies.[21,22] The following studies assessed the magnitude of the increased risk attributable to MYH regardless of polyp phenotype. In the largest cohort studied to date, Farrington et al[22] screened a series of 2239 CRC cases and 1845 controls for germline variants of MYH mutations and found that biallelic MYH defects impart a 93-fold excess risk of CRC, which accounts for 0.8% of cases greater than 55 years and 0.54% of the entire cohort. Additionally, penetrance for homozygous carriers was almost complete by age 60 years.[22] In a recent meta-analysis pooling the data of all published case-control studies assessing CRC risk in biallelic MYH carriers,

Tenesa et al[23] validated these findings showing an estimated genotype relative risk (GRR) of 117 (95% CI: 74–184). Jenkins et al[24] reported that biallelic carriers were 53 times more likely to be diagnosed with CRC compared with the general population with a cumulative risk of 80% by age 70 years (Table 1).

Monoallelic Mutation Carriers

While the risk of developing CRC is appreciated in biallelic mutation carriers, the question of whether individuals known to carry monoallelic MYH mutations are at increased risk of CRC remains greatly debated and unanswered. The studies to date suggest that monoallelic carriers have a slight increase in CRC risk. Jenkins et al[24] reported that monoallelic carriers were on average 2.9 times more likely to be diagnosed with CRC compared to the general population and that there is an 8% cumulative risk to age 70 years. In two recent meta-analyses examining the contribution of monoallelic carriers on CRC risk, the pooled estimated odds ratio has been noted to be 1.26[23,25] (Figure 1). However, the available data,[14,19,21,22,26–28] even when combined, are underpowered to detect an association. This problem is in part due to the low allele frequency of the MYH mutations in all populations studied thus far.

Genetic Testing

Appropriate candidates for MYH mutational analysis testing include individuals who exhibit features of classic or attenuated FAP in the absence of a germline APC mutation and those who have a family history of adenomas or CRC compatible with a recessive pattern of inheritance. Routine screening techniques fail to identify pathogenic APC mutations in an estimated 10–30% of classic FAP cases and in up to 70–90% of AFAP patients, and this situation makes it necessary to consider the possibility of an existing MYH mutation.[29–32] Additionally, MYH testing should be considered in patients with young onset of CRC whose tumors do not exhibit defective DNA MMR[14,33] (Table 2).

Genetic testing for MYH mutations is done first by mutation specific testing since two of the most common MYH mutations, Y165C and G382D, account for approximately 85% of MAP cases.[34] If one of these mutations is present, then sequencing is done to identify an inactivating mutation on the opposite allele, because if both alleles are mutated to inactivate the gene, disease ensues and CRC risk increases. If neither of the two most common mutations is found and a MAP etiology is strongly suspected, then primary sequencing can be done to detect other less common mutations. Screening of APC and MYH may be considered and performed in parallel in some patients, such as those with isolated cased of multiple adenomas.

Whether it is worthwhile to undertake genetic testing in the partners of patients with biallelic MYH mutations is uncertain, but it is important to consider because a biallelic carrier will produce affected children with a partner who carriers a single mutation. In such cases the disease will appear to be inherited in an autosomal dominant manner.

Clinical Management

To date, no specific screening guidelines for MAP have been established. However, given the established increased CRC risk associated with biallelic mutation carriers, these individuals should be managed similarly to those persons with classic FAP due to APC gene mutations.[14,17] This includes screening endoscopies of the upper and lower GI tracts, with consideration for colectomy if the polyp burden makes endoscopic surveillance improbable. Since most data support a later age of polyposis onset than that seen in FAP, suggestions have been made to initiate surveillance at age 25 years.

Baseline endoscopic screening is also recommended for first-degree relatives of biallelic mutation carriers, particularly in siblings, since they carry the highest risk (25%) of also

harboring biallelic mutations. Parents and children of biallelic mutation carriers are obligate carriers of at least one of the mutations, and the risk in monoallelic carriers to date is not fully defined. However, given the slight increase in adenoma and CRC likelihood in monoallelic mutation carriers, baseline colonoscopy is suggested, and intense lifetime surveillance should be pursued if colorectal adenomas are noted. In the absence of adenomatous polyps on initial colonoscopy, repeat screening is recommended every 3–5 years[14] (Table 3).

Lynch Syndrome

In 1966 Dr Henry Lynch and colleagues[35] described an aggregation of colorectal and endometrial cancers in two large midwestern kindreds, inherited in an autosomal dominant manner. Subsequently, investigators have termed this inherited condition “Lynch syndrome” and expanded the constellation of associated malignancies. Lynch syndrome is estimated to account for about 3–5% of all CRC and is caused predominantly by mutations in one of four of the DNA mismatch repair (MMR) genes: *MSH2, MLH1, MSH6*, and *PMS2*. Mutation carriers have an increased risk of CRC (60–80%), as well as an increased risk for a wide variety of extracolonic malignancies, most notably endometrial cancer (40–60%).[4–6]

There are several classification systems for the clinical diagnosis of Lynch syndrome, ranging from the most restrictive Amsterdam criteria[36,37] to the most inclusive revised Bethesda Guidelines,[38,39] all relying on personal and/or family medical histories. In families that do fulfill the Amsterdam criteria, the chance of identifying a germline mutation in *MLH1* and *MSH2* ranges from 45–85%.[40–43] However, when families with multiple colon cancers do not fulfill the Amsterdam criteria but do fulfill the less stringent Bethesda Criteria, a mutation is detected in approximately 15–30%.[41–43]

MSH6-Associated “Atypical Lynch Syndrome”

In 1996 it was discovered that germline mutations in *MSH6* cause an “atypical” form of Lynch syndrome.[44,45] *MSH6* defects account for about 7–15% of all Lynch syndrome-associated mutations, but the majority of families with *MSH6* mutations do not meet Amsterdam criteria.[45–47] Although the link between Lynch syndrome and *MSH2* and *MLH1* has been firmly established, our understanding of the exact role of *MSH6* in inherited cancer susceptibility continues to evolve. *MSH6*-related Lynch syndrome has a reduced occurrence of CRC that tends to occur at a later age compared to *MSH2* and *MLH1* carriers as well as an increased prevalence of endometrial cancer.[45,48–51] The reported mean age of onset of CRC and endometrial cancer in *MSH6* mutation-positive families was 50 years (compared to 44 years in *MSH2* and 41 in *MLH1*) and 53 years (compared to 49 in *MSH2* and 48 in *MLH1*), respectively.[45,47] The apparently later age of onset has been confirmed by a more recent study of 20 families (146 carriers) with a truncating mutation in *MSH6*.[52] However, despite the delay in the age of CRC onset, *MSH6* mutation carriers are at the same high lifetime risk of cancer (up to 70%) as those individuals with *MLH1* and *MSH2* mutations (Table 4).

The Gene

The general finding of an older age at diagnosis in *MSH6* mutation carriers when compared with carriers of a mutation in *MSH2* or *MLH1* may be explained from the functional level of the MMR proteins. MLH1 and MSH2 proteins are involved in MMR of both single nucleotide mismatches and insertion-deletion loops, and repair is impaired in the absence of either MLH1 or MSH2. Likewise, the MSH6 protein is involved in the repair of both single-base mismatches and insertion-deletion loops, but it is not absolutely required for DNA MMR activity. In the absence of MSH6, MSH3 protein (the product of a closely related gene) can partially replace MSH6 repair function and may represent a protecting factor against accumulation of DNA damage.[53–55]

Genetic Testing

The use of microsatellite instability (MSI) testing in the evaluation of Lynch syndrome improves the cost-effectiveness of the molecular strategy for diagnosing these families. MSI analysis gives an indication of abnormal MMR in general, irrespective of the MMR gene and type of mutation involved. It detects length variations of simple, repetitive sequences (microsatellites) distributed throughout the genome as a consequence of faulty MMR. A set of five markers has been developed to test for MSI and includes the markers D2S123, D5S346, D17S250, BAT25, and BAT26. When tumors score MSI-high, there are at least 30% of markers that show instability. This phenotype is reported in 85–92% of CRC associated with Lynch syndrome and in 10–15% of sporadic CRC cases.[41,56,57] A distinguishing feature of *MSH6*-associated Lynch syndrome is that many cancers arising in mutation carriers exhibit an MSI-low or microsatellite stable (MSS) tumor phenotype.[49,52,58] This feature may be due in part to the limited number of markers used by most investigators. It is proposed that a more extensive panel of markers be utilized in order to improve the sensitivity of the test.[59,60]

Given this limitation and the broad variability regarding penetrance associated with *MSH6* germline mutations, multiple studies have emphasized the concomitant use of immunohistochemistry (IHC) with MSI analysis as a preselection tool for *MSH6* DNA analysis.[61,62] IHC offers additional information on which MMR gene should be selected for DNA analysis. Hendricks et al[52] have shown that applying IHC to CRC tumors increases the sensitivity in predicting *MSH2* mutations to 92% and in *MSH6* to 90%. For *MLH1*, IHC has a sensitivity of 48% when using *MLH1* specific antiserum but increases to 71% when *PMS2* staining is also applied.[52] Since the mismatch repair proteins form heterodimeric complexes, distinct IHC patterns can be expected and patients can thereafter be selected for DNA mutation analysis. If a tumor is found to exhibit MSI with loss of specific protein expression, the targeted germline testing of an affected patient for *MLH1*, *MSH2*, or *MSH6* mutations can be offered.

It is important to emphasize that IHC is not always diagnostic. It is most useful in identifying particular protein expression loss when MMR mutations result in protein truncation (which includes nonsense, frameshift, and splicesite mutations) and large genomic rearrangements. In cases of missense mutations, IHC can show expression of a protein despite its being functionally abnormal. For individuals with a family history suggestive of atypical Lynch syndrome, but with tumors that are MSS or MSI-L and inconclusive IHC testing, *MSH6* germline mutation analysis should be pursued. In addition, screening for *MSH6* mutations is recommended for kindreds with suspected Lynch syndrome who are negative for *MSH2* and *MLH1* germline mutations.[4]

Clinical Management

Individuals with Lynch syndrome who have a known or a suspected *MLH1* or *MSH2* mutation, as well as family members who are at increased risk based on an identified mutation in their family, should undergo colonoscopy every 1 to 2 years starting at age 25 years (Table 3). Given the later onset for CRC in *MSH6* mutation carriers, it is recommended that colonoscopic screening be initiated at age 30 years and continued every 1 to 2 years thereafter.[63] Prophylactic colectomy for at-risk individuals without a history of CRC, as an alternative to screening colonoscopy, is generally not recommended given the insufficient evidence to assess the impact on health outcomes.

With respect to endometrial cancer screening in women with Lynch syndrome, future studies are necessary to determine the most appropriate and effective screening modalities and intervals. At present, it is recommended that women with a known or suspected MMR mutation, or who are at increased risk due to a documented mutation in the family, should undergo annual endometrial biopsy and transvaginal ultrasound beginning at 30 to 35 years. Transvaginal

ultrasound is used to assess for ovarian abnormalities but is believed not to have a role in endometrial cancer screening in premenopausal women. Although a general recommendation has not been made regarding prophylactic hysterectomy and oophrectomy, this option should be discussed with postmenopausal women and women who have completed childbearing.[64]

Cancers other than those of the colon and endometrium account for about 30% of cancers in *MLH1* and *MSH2* carriers, and perhaps up to 50% of cancers seen in *MSH6* carriers.[46] However, no standard screening recommendations have been created and to date, there are no studies to support additional surveillance. An empiric approach has been to offer site-specific screening for non-endometrial cancers that appear to be overrepresented in families with Lynch syndrome.

For individuals with a diagnosed CRC or colorectal polyp not amenable to endoscopic resection, a subtotal colectomy should be favored but has not been proven to be superior to annual colonoscopic surveillance. Issues that should be taken into consideration in such patients when recommending subtotal colectomy versus segmental resection include compliance with endoscopic surveillance and personal preference.[65]

Considerable advances have been made over the last decade in the understanding of genetic predispositions to colorectal cancer. Translating new findings made in molecular genetics has been challenging, and many questions still remain unanswered. However, the potential beneficial impact on the clinical care and well-being of affected patients and their susceptible families is well recognized, and future research is underway to better define associated CRC risk and optimal screening and surveillance strategies. Determining the appropriate candidates for predictive genetic testing and managing cancer risk after testing are critical functions for healthcare providers as exciting and new opportunities emerge in cancer risk and prevention.

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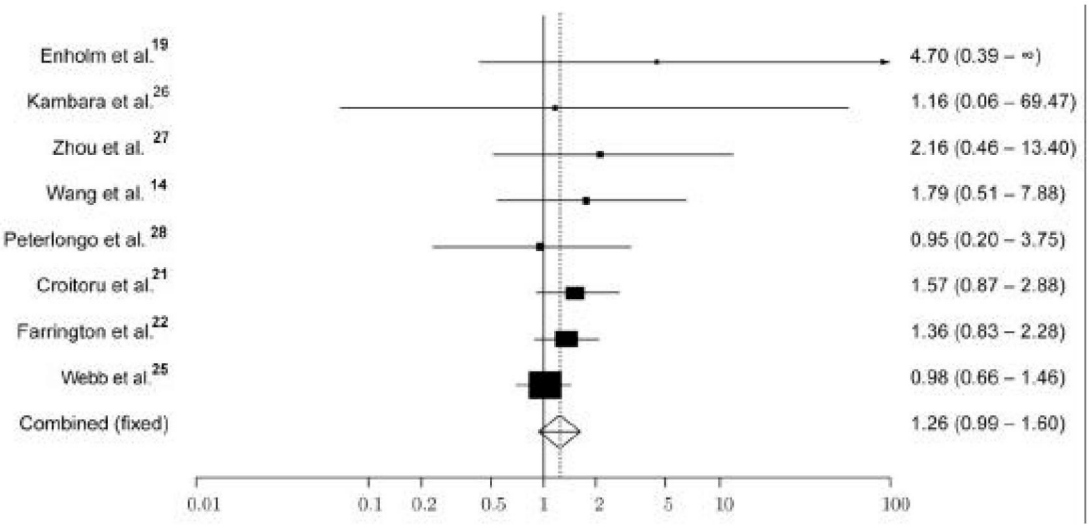

Figure 1. CRC Risk associated with monoallelic MYH variants*

*Funnel plot of OR of CRC risk associated with monoallelic Y165C and G382D *MYH* variants, under a fixed-effects model. Studies are plotted in order of decreasing variance of the log (Odds Ratio). Horizontal lines represent 95% Confidence Intervals (CI). Each box represents the Odds Ratio (OR) point estimate, and its area is proportional to the weight of the study. The diamond and broken line represent the overall summary estimate, with the 95% CI given by the width of the diamond. The unbroken vertical line is at the null value (OR 1.0). Reprinted with permission.[25]

Table 1

Risk of Colorectal Cancer in MYH carriers

Carrier	Lifetime Risk*
Monoallelic	8% (4–19%)
Biallelic	80% (35–100%)

* Cumulative risk by age 70 years [24]

Table 2

Indications for MYH gene testing

Recommended:	
•	*APC* gene negative individuals with features of classic FAP/AFAP
•	Autosomal recessive inheritance of CRC or multiple adenomas
•	Siblings of known MYH mutation carriers*
Suggested:	
•	Young onset CRC with negative MMR gene mutation[14]
•	Partners of known biallelic MYH mutation carriers**

Abbreviations: APC=Adenomatous Polyposis Coli, FAP=Familial Adenomatous Polyposis, AFAP=Attenuated Familial Adenomatous Polyposis, CRC=colorectal cancer, MMR=mismatch repair.

* Siblings have highest risk of carrying biallelic mutations (25%) amongst all first-degree relatives

** Biallelic mutation carriers produce affected offspring if partner is monoallelic mutation carrier

Table 3

Recommended Management for MYH and *MSH6* Mutation Carriers and At-Risk Family Members[14, 63, 64]

Mutation	Type of Intervention	Recommendation
MYH		
Biallelic	Colonoscopy/EGD	Start at age 25 years; perform every 1–2 years
	Colectomy (total or subtotal based on presentation)	For CRC diagnosis or if endoscopic surveillance improbable due to polyp burden
Monoallelic	Colonoscopy	Start at age 25 years; If adenomatous polyps present: perform every 1–2 years; otherwise perform every 3–5 years [14]
MSH6*	Colonoscopy	Start at age 30 years (or 10 years earlier than youngest age of CRC diagnosis in family); perform every 1–2 years[63]
	Endometrial sampling/ transvaginal ultrasound	Start at age 30–35 years; perform annually
	Colectomy (subtotal vs segmental resection)	For CRC diagnosis or if polyp nonresectable by colonoscopy**
		Prophylactic colectomy not recommended***
	Hysterectomy + bilateral salpingo-oophorectomy	For endometrial or ovarian cancer or abnormal endometrial sampling/ transvaginal ultrasound
		Option of prophylactic surgery should be discussed after childbearing completed[64]

Abbreviations: EGD=esophagogastroduodenoscopy, CRC=colorectal cancer.

* Consider cancer specific screening for affected individuals/family members if presence of overrepresented non-endometrial Lynch syndrome-associated cancers

** Subtotal colectomy preferred over segmental resection. Segmental resection requires annual colonoscopy given increased risk of metachronous cancers

*** Prophylactic colectomy can be discussed as alternative to annual colonoscopy in noncompliant patients

Table 4

Cancer Risk in *MSH6* Mutation Carriers [46,51,52]

	Colorectal Cancer	Endometrial Cancer
Age at diagnosis (years)		
Mean	53.1	53.5
Range	32–84	43–65
Lifetime Risk*	60–70%	52–71%

*Cumulative risk by age 80 years