Review Article

The evolution of colorectal cancer genetics—Part 2: clinical implications and applications

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Abstract: The genetic understanding of colorectal cancer (CRC) continues to grow, and it is now estimated that 10% of the population has a known hereditary CRC syndrome. This article will examine the evolving surgical and medical management of hereditary CRC syndromes, and the impact of tumor genetics on therapy. This review will focus on the most common hereditary CRC-prone diseases seen in clinical practice, which include Lynch syndrome (LS), familial adenomatous polyposis (FAP) & attenuated FAP (AFAP), MutYH-associated polyposis (MAP), and serrated polyposis syndrome (SPS). Each section will review the current recommendations in the evaluation and treatment of these syndromes, as well as review surgical management and operative planning. A highly detailed multigeneration cancer family history with verified genealogy and pathology documentation whenever possible, coupled with germline mutation testing when indicated, is critically important to management decisions. Although caring for patients with these syndromes remains complex, the application of this knowledge facilitates better treatment of both individuals and their affected family members for generations to come.

Keywords: Surgical oncologic management; medical oncologic management; hereditary colorectal cancer (hereditary CRC)

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Introduction

A historical review and summary of the molecular basis of hereditary colorectal cancer (CRC) has been previously discussed in part 1 of this volume. This article will examine the evolving surgical and medical management of hereditary CRC syndromes, and the potential impact of tumor genetics on therapy. CRC is the third most common cause of cancer death in the world with an estimated incidence of over one million cases per year (1). Advancements in colonoscopy have reduced the incidence of CRC by 45-77% and have recently been reported to have reduced mortality by greater than 30% since 1990 (2). The genetic understanding of CRC also continues to grow, and it is now estimated that 2-10% of the population has a known hereditary CRC syndrome. In addition, there are 20-30% of CRC cases with evidence of a familial component, but without a clear hereditary disease identified (1,3,4). Prior to identifying genetic mutations, the diagnosis of a familial cancer syndrome was based on highly-targeted clinical and family history alone (5,6). Now that surgical and medical management of this disease can often be based on pathological variants in the patient's DNA, the physician's suspicion for a hereditary component of CRC in high-risk patients should be greater (6). This knowledge provides the

indication for early endoscopic and/or surgical intervention, and plays a role in guiding adjuvant chemotherapy. This approach may not only prevent or treat CRC for the individual, but also allows for the care of the entire family (7).

This review will discuss the indications and recommendations for the surgical and medical oncologic management of hereditary colorectal cancer syndromes. It will emphasize how this knowledge can be used in formulating an operative plan, and decision making for adjuvant therapy. We will focus upon the most common hereditary diseases seen in clinical practice, which include Lynch syndrome (LS), familial adenomatous polyposis (FAP) and attenuated FAP (AFAP), MutYH-associated polyposis (MAP), and serrated polyposis syndrome (SPS).

Lynch syndrome (LS)

LS is an autosomal dominant condition that results from a defect in one of the mismatch repair (MMR) genes and in the past was also referred to as Hereditary Nonpolyposis Colorectal Cancer (HNPCC). It is the most common hereditary CRC syndrome, and is characterized by the early presentation of colorectal, endometrial, and various other cancers (8). The MMR genes clearly involved in the development of LS are *MLH1*, *MSH2*, *MSH6* and *PMS2*, with other gene candidates such as *EPCAM* and epimutations being evaluated. The surgical options for CRC in the setting of LS previously ranged from segmental colectomy, to subtotal colectomy, and even total proctocolectomy (TPC). Presently, our preferred option is total colectomy for a colonic cancer or endoscopically unresectable advanced adenoma, and TPC for patients with the less frequent presentation of a primary rectal neoplasm.

Prior to the early 1990's when pathologic variants were discovered, some of which were distinctive of LS, the diagnosis and management of LS was based on a clinical assessment using the Amsterdam criteria, which have been modified over time (8,9). However, identifying patients preoperatively who are not parts of a known LS family is often challenging. These patients are typically young, often present with locally advanced tumors, with associated bleeding, or obstruction, and not infrequently harbor multiple primary extracolonic cancers, particularly endometrial cancer. These patients frequently require timely operative intervention without the ability to wait for genetic testing (10,11). LS associated cancer has been reported in 15% of CRC patients less than 50 years old (11). Baiocchi *et al*. used immunohistochemical (IHC) testing to retrospectively compare patients with CRC both above and below the age of 50 (10). They analyzed previous specimens for *MLH1*, *MSH2* and *MSH6* expression and determined that 51% of CRC patients did not express at least one of these MMR proteins, and therefore were a likely LS carrier. Furthermore, after establishing a diagnosis of LS by IHC, retrospectively, only 31% of the LS patients met the Amsterdam II criteria, and only 50% met the Bethesda criteria, findings which demonstrate the importance of molecular analysis. This study may even underestimate the incidence of LS due to not analyzing PMS2 and microsatellite instability (MSI). However, an abnormal test for *MLH1* should be interpreted with caution. Based on a false negative rate of 5-10% by using IHC, the current National Comprehensive Cancer Network Guidelines recommend that abnormal *MLH1* IHC should be followed by testing the tumor for BRAF V600E or hypermethylation of the *MLH1* promoter, as this pattern has been identified in spontaneous colon tumors (12,13). Germline genetic analysis should always be performed; however, IHC is a simple, cheap, and rapid way of determining LS in a patient who may not have the time to wait for the germline testing to be completed (10).

CRC surgical implications

There are three main groups of patients who would require a colectomy: (I) newly diagnosed colon cancer patients with or without a known personal or family history of LS; (II) patients with a LS affected family member; and (III) LS patients considering prophylactic colectomy, particularly those harboring MMR deleterious mutations and who decline recommended colonoscopy. The complex decision making process for the surgical options in LS must consider the risk of a synchronous and/or metachronous CRC, the risk of the operation, and the expected alteration of the patient's quality of life (QOL) particularly with a rectal primary cancer.

The risk of synchronous CRC in LS has been reported to be approximately 6-18%. The risks of metachronous tumors are reported to be 16% at 10 years, 41% at 20 years and 62% at 30 years after segmental resection (14,15). More recently Cirillo *et al.* identified a risk of at least one metachronous CRC after a median of 6 years. This was broken down into colon and rectal cancers with a risk of a metachronous tumor of 22.2% and 27.7% respectively. A proportional hazards model in the development of a metachronous CRC showed a 6-fold increase in the risk of death, with the metachronous cancer at a greater risk of being diagnosed at either stage III or IV (16).

Colon cancer is identified more commonly than rectal cancer in LS. However, rectal cancer occurs approximately 11-35% of the time, when one includes both synchronous and metachronous lesions (16,17). It is our opinion that a newly diagnosed CRC is best managed by a total abdominal colectomy. However, in the setting of significant metastatic disease a segmental colectomy may be offered. A low anterior resection, abdominoperineal resection or ileal pouch-anal anastomosis can be performed for rectal cancer, but the operation should be tailored to the patient (14,18). Total abdominal colectomy can be considered both therapeutic and prophylactic, given the high rate of metachronous CRC (16,18). Furthermore, removing the entire colon allows for easier outpatient intensive surveillance of the rectum. Parry and colleagues demonstrated that with every 10 cm of bowel removed in a LS patient, there is a reduction in their risk of metachronous CRC by 31% (15). Although a survival benefit has yet to be shown, multiple studies now advocate for an extended resection for patients with LS (10,15,16,19,20).

To further support the indication for extended resection, Natarajan and colleagues compared prophylactic colectomy, or extended resection, at the time of an initial CRC diagnosis, with a segmental resection (19). There was a longer time period to develop a second CRC after extended resection compared to segmental resection, (16-175 *vs.* 6-160 months respectively). In addition, the segmental resection group required a second operation sooner, (4-195 *vs.* 7-275 months). Subsequent operations were due to complications from the initial operation, treatment of a second primary or metachronous lesion, or endometrial/ovarian cancer. Although the risk of a metachronous lesion was less with subtotal colectomy, this study also did not demonstrate a survival difference (19).

The QOL following subtotal colectomy versus segmental resection is also a significant patient concern. Haanstra *et al.* in 2012 evaluated the effect of extended resection on functional outcomes and QOL. This study excluded cases of rectal cancer, end ileostomy, and ileal pouch-anal anastomosis. Patients were evaluated with QOL questionnaires. To assess generic QOL the Short Form-36 health survey was used; to evaluate disease-specific QOL the European Organization for Research and Treatment of Cancer Colorectal Cancer-specific Quality of Life Questionnaire Module was used; and to determine functional QOL the Colorectal Functional Outcome questionnaire was used. Subtotal colectomy patients had a significantly greater frequency of bowel movements as well as a worse functional outcome; however there was no difference in QOL impacted by multiple bowel movements. This study supports the use of an extended resection for a LS associated colon cancer (21).

The management of postoperative patients who received a segmental colectomy for a Lynch related colon cancer is often encountered in situations where LS was not suspected pre-operatively, or when a resection was the patient's preference. It is critical to counsel the patients on their risk of metachronous tumors, with the current options being frequent colonoscopic surveillance or completion colectomy (14,22). For patients who do not receive a completion colectomy, postoperative endoscopic surveillance is critical to survival, and close interval follow up is important since the transition from adenoma to carcinoma in LS is faster (3 *vs.* 8-15 years in sporadic CRC) (18). A subsequent study demonstrated that the median time from the diagnosis of CRC and the most recent colonoscopy was 11.3 months; therefore, this data supports surveillance at least once a year with a full clearing colonoscopy (23). It is our practice to add narrow band imaging to the surveillance colonoscopy, as it has been shown to increase the detection of additional adenomas by 27%, and to improve the detection rate of flat adenomas from 12% to 45% when compared to standard colonoscopy (24).

The risk of CRC in LS is approximately 60-85% depending on which MMR gene is involved. Patients with *MLH1* and *MSH2* mutations have a higher risk of cancer, with diagnosis at a younger age, compared to *MSH6* and *PMS2* mutations (25,26). *MLH1* mutation carriers have a higher risk of CRC, while *MSH2* carriers have a higher rate of multiple primary extracolonic cancers, to include brain (glioblastoma), ovarian, stomach, hepatobiliary, urinary tract, breast, and prostate cancers (27-32). Colonoscopy screening decreases the risk of a second CRC by 62% when patients have routine surveillance (33). It is rare for colonoscopy to miss a polyp >10 mm. However, for polyps between 1-5 mm, up to 35% can be overlooked (34). With this knowledge, prophylactic colectomy may be ideal for some patients, requiring only a subsequent yearly rectal surveillance. Prophylactic colectomy before the age of 25 has been associated with the greatest increase in life expectancy when compared to older patients and those where surgery was performed after a CRC diagnosis (35). It is still widely debated about recommendations for a prophylactic colectomy. It is important to evaluate the patient for both emotional and physical perspectives, understand his or her MMR mutation status, and ensure that a genetic counselor is actively engaged with the decision making process. In women who present with uterine cancer,

prophylactic colectomy can be considered in addition to the surgical treatment of gynecologic diseases, if the patient is being managed in a comprehensive manner (36). Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a prudent option given limited endometrial and extremely poor ovarian cancer screening (36).

Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant syndrome found in less than 1% of all CRCs, but will progress on to colon cancer nearly 100% of the time (26). FAP results from a mutation of the adenomatous polyposis coli (*APC*) gene located on chromosome 5q21-22 (37). The genotypic understanding of the APC mutation is clinically relevant to the phenotypic presentation. Classic FAP occurs when there are mutations between codons 168-1,580 with severe disease between codons 1250-1464 (38). Classical FAP is defined clinically if there are 100 or more adenomatous colon and rectal polyps, and typically occurs in patients younger than age 40. AFAP is generally defined in individuals with 10-99 colonic adenomatous polyps, or those with 100 or more colonic polyps occurring at an older age, or those with a history of CRC before age 60 and a family history of multiple adenomatous polyps (39,40). The latter group of patients will usually have rectal sparing, have right-sided colonic adenomas, and lack extra colonic manifestations (37). Because of the greater genotypic and phenotypic variability in AFAP, a high clinical suspicion and thorough family history is critical for the diagnosis, as these patients frequently, if not always, progress on to a colon cancer (37). Although there have been multiple studies describing the sequence and the location of the APC gene, the significance of a single amino acid missense variants in the APC gene is difficult to interpret (37). With the advent of genetic testing, it has become important to characterize these variants in order to properly counsel and treat FAP patients, particularly those patients with AFAP.

The treatment for FAP is surgical removal of the colon and rectum. The options for surgery include abdominal colectomy with ileorectal anastomosis (IRA), restorative proctocolectomy with either ileal J-pouch anal anastomosis (IPAA), and TPC and ileostomy (14,41). Patients are recommended to undergo this procedure during their teens or early twenties. Initial screening colonoscopy has been recommended to begin at age 10 years, but Kennedy and colleagues recommends that the ideal time at 7 years old. In their series the average age for colectomy was at 15.4 years old with the youngest patient being four. The majority of operations performed in this group were IPAA, with 88% having a hand sewn anal anastomosis with a mucosectomy. This series had no recurrences following IPAA and routine surveillance pouchoscopy was recommended (42).

If there is limited rectal polyposis, then IRA is a feasible option. This is also recommended in woman of child-bearing age, as this operation can be converted to an IPAA once child bearing has been completed (43). The risk of developing rectal cancer in a patient undergoing IRA increases from 4% at 5 years to up to 25% at 20 years. This data has even lead to recommendations of patients having their IRA converted to IPAA before the age of 50 (44). The number of rectal polyps and the presence of rectal cancer should be the main factor in the determination of whether or not to perform a proctectomy. As with LS, the functional outcomes following IPAA are of a significant concern for patients when making these operative decisions. In a meta-analysis performed by Aziz *et al.*, no difference was found in postoperative compilations, though IRA required a significantly lower rate of reoperations within 30 days (44). IPAA demonstrated superior results in cancer reduction: 0% *vs.* 5.5% following IRA. There was a decrease in the long-term need for reoperation in IPAA group. There was no difference in dietary restrictions or sexual dysfunction, although patients with IRA had a lower incidence of social restrictions compared to IPAA, 4% *vs.* 14%. Furthermore the frequency of daily stools, need for night defecation, and incontinence over 24 hours, was greater in IPAA (44). Recent studies advocate for a laparoscopic approach, and have demonstrated an association with fewer postoperative complications, better overall outcomes, and shorter length of stay. However, this operation requires technical expertise, and a large volume of cases to maintain this skill. Future studies are needed to further elucidate these findings (45-48).

MutYH-associated polyposis (MAP)

MAP was discovered in 2002 when studying patients who appeared to meet clinical criteria for FAP but tested negative for a defect in the *APC* gene. Further testing identified a biallelic mutation in the *MYH* gene, which produced an autosomal recessive polyposis syndrome. *MYH* mutations can vary with ethnicity, and phenotypically this disease can mimic FAP. It has been shown that 7.5% of classical FAP that was negative for an APC mutation had a biallelic *MYH* mutation (49). Biochemically, the MYH gene repairs DNA mutations damaged by reactive oxygen species. It typically presents as FAP with multiple colon adenomas, though it can also result in a MMR gene mutation and present

similar to LS. The diagnostic confusion makes the surgical recommendations challenging (50). Due to the rarity and complexity of the diagnosis of this disease, referral to a genetic counselor is recommended for the optimal care of these patients.

Leite *et al.* evaluated the incidence of germline *MYH* mutations in 19 APC-mutation negative patients. They found 69% of patients registered as classical FAP and 17% registered as AFAP to actually have a *MYH* mutation. All ten patients in this series with a *MYH* mutation had surgical resection, which included: five total colectomies, four restorative proctocolectomies and one left partial colectomy. The patient with a partial colectomy eventually underwent a completion colectomy. Two patients had a prophylactic colectomy prior to the diagnosis of cancer. Ten patients had a diagnosis of CRC and three of these patients also had a synchronous or metachronous lesion. The mean age to the development of CRC cancer was 50.6 years, which is about 10 years later than classical FAP. Although the number of patients identified in this study is low, the data suggests that screening alone with polypectomy is not sufficient for these patients, and they should be treated as AFAP including consideration for a prophylactic colectomy. The timing of prophylactic colectomy, however, may be later than AFAP based on this study (51).

Serrated polyposis syndrome (SPS)

Serrated polyps, previously called hyperplasic polyps, are characterized by the serrated appearance of the crypt epithelium on histology. These lesions were previously thought to be benign, but recent data shows a 15-20% risk of CRC arising through this serrated neoplasia pathway. Gene inactivation through hypermethylation of a promoter region, BRAF mutations, or MSI is thought to be the molecular etiology of this syndrome (52). SPS is characterized by: (I) ≥5 serrated polyps proximal to the sigmoid colon with at least 2 greater than 10 mm; (II) a least one serrated polyp proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis; (III) >20 serrated polyps of any size but distributed throughout the colon (53,54).

Jasperson *et al.* analyzed 51 patients with SPS. The average age of diagnosis was 49 years old. The average number of serrated polyps identified was 35, and 71% had at least one greater than 10 mm. Adenomas were identified in 82% of patients, and CRC in 16%, with the earliest age of onset at 22 years. This study advocates for full colonoscopy every 1-2 years for surveillance and endoscopic treatment as needed due to the development of cancer. Surgical management is considered when polyps cannot be endoscopically controlled, or if there are numerous large serrated lesions in the proximal aspect of the colon (52,53).

Hazewinkel *et al.* also supports annual surveillance colonoscopy for serrated polyposis. Recurrence rates were 80% if the serrated polyp was ≥3 mm. It took, on average, two procedures to completely clear the colon. Advanced adenomas were detected in 9% of patients, with a median interval of 13 months between detection and the previous clearing colonoscopy. Prophylactic resection was performed in 8% of SPS patients after clearing colonoscopy. These patients received a subtotal colectomy with IRA, which is the recommended resection (52,53,55,56).

Familial CRC-type X

Familial CRC-type X or "syndrome X" involves patients who clinically meet all criteria for LS, but have neither MSI nor an expression of a MMR mutation, and therefore are not genetically defined LS (3,6,25). These patients have a lower incidence of CRC than LS patients, but a greater incidence than the general population (25). The mean age of diagnosis is later than in LS patients, but approximately 10 years younger than in spontaneous cases (57,58). Tumors are found mainly in the left colon or rectum, and there is a lower association of tumors with mucinous features (3). There are no current reports of extracolonic neoplasia in these patients (5). Without more knowledge of the molecular nature of this disease, there are no genetically based current guidelines or recommendations for surgical management.

Chemotherapy implications

CRC genetics has the potential to influence screening, prevention, treatment and survivorship. At this juncture, the current knowledge of CRC genetics has an impact on the therapy of both adjuvant and metastatic disease. While multiple molecular markers and gene expression assays have been studied, only MSI has prognostic value. A survival benefit has been demonstrated when comparing hereditary CRC, to include FAP and LS to sporadic cases, and this benefit is more pronounced for patients with LS. This benefit was previously thought to be due to selection bias, younger age and/or more aggressive screening (59-62). Bertario *et al.* demonstrated in a study group of over two thousand patients no survival difference in LS and FAP compared to sporadic cases (62). This study further analyzed

patients under 60 years old, which again showed comparable outcomes between the groups. To counter these findings, Stigliano and colleagues retrospectively compared survival between LS and sporadic CRC. This study demonstrated an improved five year survival with LS CRC compared to spontaneous cases (94.2% *vs.* 75.3%; P>0.01). Interestingly this study was able to show that all tumors that demonstrated MSI had a 100% survival, suggesting that MSI plays a critical role in the prognosis of colon cancer (63).

MSI may result from germline mutations in MMR genes *MLH1*, *MSH2*, *MSH 6* or *PMS2* and EpCam. Somatic mutations in these genes may occur in up to 20% of sporadic CRC patients and hypermethylation of *MLH1* results in gene inactivation in 50% of cases. These mutations will result in LS and these cases are classified as either MSI-H or MSI-L (high or low).

MSI-H tumors are more common in stage II patients (20%) and proximal colon (29%). Evidence suggests that MSI-H stage II colon cancer patients do not benefit for adjuvant chemotherapy with a fluoropyrimidine, and tumors treated with these agents may even have a worse outcome (64-66). Stage II MSI-H patients with adverse clinicopathologic features such as obstruction and perforation should be counseled regarding the benefit of adjuvant chemotherapy. However, a recent analysis of the Mosaic Trial demonstrated a benefit to the combination of oxaliplatin and infusional 5-FU/leucovorin in stage III MSI-H patients (67).

Five gene expression profiling assays are marketed in the US. Of these the 12 gene recurrence score (oncotype-DX Colon Cancer Assay) has the most data and validation (68). This assay has prognostic but not predictive value, and unlike MSI-L is not endorsed by the NCCN for routine decision making in stage II patients. This assay may, however, be useful in the counseling of MSI-L patient who have other risk factors.

Genetic based treatment has been established and widely accepted in patients with metastatic CRC. Epidermal growth factor receptor (EGFR) overexpression is seen in more than 50% of patients. This however, does not correlate with response to treatment with targeted inhibitors against a downstream EGFR signaling pathway (69). Tumors that are KRAS exon 2 wild types have a higher response rate to the EGFR inhibitors cetuximab and panitumumab. KRAS activating mutations are associated with resistance to these agents and are seen in approximately 40% of patients with metastatic CRC (70,71). Due to these findings, the American Society of Clinical Oncology issued a provisional clinical opinion that testing for KRAS gene mutations in patients with metastatic colorectal carcinoma should be performed to predict response to anti-EGFR monoclonal antibody therapy. Furthermore, metastatic CRC patients with KRAS exon 2 codon 12 or 13 mutations should not receive an EGFR inhibitor as part of their treatment (72).

Even though wild type KRAS is necessary for a response to anti-EGFR agents, it may not be sufficient in up to 20-40% of cases. In the PRIME study, 17% of patients without KRAS exon 2 mutations had mutations in KRAS exons 3 and 4 or exons 2.3 and 4 on NRAS. Panitumumab based treatment had an inferior progression free and overall survival in combination with FOLFOX versus the chemotherapy arm alone. A recent meta-analysis looked at 22 studies that included 2,395 patients. It concluded that further examination of downstream mutations in KRAS exons 3 and 4, NRAS, BRAF and PIK3CA and non-functional PTEN are able to demonstrate resistance to anti-EGFR therapies. This study suggests that biomarker analysis beyond KRAS exon 2 should be implemented for prediction of a clinical benefit of anti-EGFR antibodies in metastatic CRC (73). NCCN currently recommends performing genotyping for RAS mutations to include the exon 2 and non-exon 2 for KRAS, and NRAS. The guidelines further state that there was insufficient information in the use of BRAF V600E mutation, which is downstream of KRAS, as a status to guide anti-EGFR therapy. BRAF can be prognostic for adverse overall progression free and overall survival in the adjuvant setting but are less predictive for response to treatment (74).

Conclusions

Advances made in screening, diagnosing and treating CRC, progressively increases our understanding of CRC tumors with respect to their genome, biome, and proteome, and ultimately clinical outcomes. With further study and subsequent elucidation of the molecular basis and biologic mechanisms of CRC, the application of this knowledge holds the promise to better treat not just a general disease, but each individual disease. In essence, a molecular based prescription for optimal care. Furthermore, the application of a multidisciplinary approach to the evaluation and management of these syndromes has fundamentally changed the best practices used to help not just a single individual, but entire families for generations to come.

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References

1. Patel SG, Ahnen DJ. Familial colon cancer syndromes: An update of a rapidly evolving field. Curr Gastroenterol Rep 2012;14:428-38.
2. Lieberman D. Screening for colorectal cancer in individuals at average risk: Current methods and emerging issues. JAMA Intern Med 2014;174:10-11.
3. Perea J, Justo I, Alvaro E, et al. Surgical management of hereditary colorectal cancer: Surgery based on molecular analysis and family history. Rev Esp Enferm Dig 2009;101:536-40.
4. Schrader K, Offit K, Stadler ZK. Genetic testing in gastrointestinal cancers: a case-based approach. Oncology (Williston Park) 2012;26:433-6, 438, 444-6 passim.
5. Gallagher DJ, Smith JD, Offit K, et al. Diagnosing hereditary colorectal cancer. Clin Colorectal Cancer 2010;9:205-211.
6. Boland CR, Lynch HT. The history of Lynch syndrome. Fam Cancer 2013;12:145-57.
7. Ahnen DJ, Wade SW, Jones WF, et al. The increasing incidence of young-onset colorectal cancer: A call to action. Mayo Clin Proc 2014;89:216-24.
8. Vasen HF, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of lynch syndrome (HNPCC): Recommendations by a group of european experts. Gut 2013;62:812-23.
9. Kalady MF. Surgical management of hereditary nonpolyposis colorectal cancer. Adv Surg 2011;45:265-74.
10. Baiocchi GL, Portolani N, Vermi W, et al. Lynch syndrome from a surgeon perspective: Retrospective study of clinical impact of mismatch repair protein expression analysis in colorectal cancer patients less than 50 years old. BMC Surg 2014;14:9.
11. Warrier SK, Yeung JM, Lynch AC, et al. Managing young colorectal cancer: A UK and irish perspective. World J Surg 2014;38:1827-33.
12. National Comprehensive Cancer Network. Genetic/familial high-risk assessment: Colorectal (version 1.2014). National Comprehensive Cancer Network Web site. Available online: http://www.nccn.org. Updated 2014. Accessed 03/27, 2014.
13. Hendriks YM, de Jong AE, Morreau H, et al. Diagnostic approach and management of lynch syndrome (hereditary nonpolyposis colorectal carcinoma): A guide for clinicians. CA Cancer J Clin 2006;56:213-25.
14. Rodriguez-Bigas MA, Moeslein G. Surgical treatment of hereditary nonpolyposis colorectal cancer (HNPCC, lynch syndrome). Fam Cancer 2013;12:295-300.
15. 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.
16. Cirillo L, Urso ED, Parrinello G, et al. High risk of rectal cancer and of metachronous colorectal cancer in probands of families fulfilling the amsterdam criteria. Ann Surg 2013;257:900-4.
17. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to lynch syndrome: A systematic review. JAMA 2006;296:1507-17.
18. Baucom RB, Wise PE. Endoscopic and surgical management of hereditary nonpolyposis colorectal cancer. Clin Colon Rectal Surg 2012;25:90-6.
19. Natarajan N, Watson P, Silva-Lopez E, et al. Comparison of extended colectomy and limited resection in patients with lynch syndrome. Dis Colon Rectum 2010;53:77-82.
20. Kalady MF, McGannon E, Vogel JD, et al. Risk of colorectal adenoma and carcinoma after colectomy for colorectal cancer in patients meeting Amsterdam criteria. Ann Surg 2010;252:507.
21. Haanstra JF, de Vos Tot Nederveen Cappel WH, Gopie JP, et al. Quality of life after surgery for colon cancer in patients with lynch syndrome: Partial versus subtotal colectomy. Dis Colon Rectum 2012;55:653-9.
22. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: An analysis from the CAPP2 randomised controlled trial. Lancet 2011;378:2081-7.
23. Engel C, Rahner N, Schulmann K, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. Clin Gastroenterol Hepatol 2010;8:174-82.
24. East JE, Suzuki N, Stavrinidis M, et al. Narrow band imaging for colonoscopic surveillance in hereditary non-polyposis colorectal cancer. Gut 2008;57:65-70.
25. Celentano V, Luglio G, Antonelli G, et al. Prophylactic surgery in Lynch syndrome. Tech Coloproctol 2011;15:129-34.
26. Jarry J, Brunet JS, Laframboise R, et al. A survey of APC mutations in quebec. Fam Cancer 2011;10:659-65.
27. Lin-Hurtubise KM, Yheulon CG, Gagliano RA Jr, et al. Excess of extracolonic non-endometrial multiple primary cancers in MSH2 germline mutation carriers over MLH1.

J Surg Oncol 2013;108:433-7.
28. Bauer CM, Ray AM, Halstead-Nussloch BA, et al. Hereditary prostate cancer as a feature of Lynch syndrome. Fam Cancer 2011;10:37-42.
29. Lotsari JE, Gylling A, Abdel-Rahman W, et al. Breast carcinoma and Lynch syndrome: molecular analysis of tumors arising in mutation carriers, non-carriers, and sporadic cases. Breast Cancer Res 2012;14:R90.
30. Raymond VM, Mukherjee B, Wang F, et al. Elevated risk of prostate cancer among men with Lynch syndrome. J Clin Oncol 2013;31:1713-8.
31. Raymond VM, Everett JN, Furtado LV, et al. Adrenocortical carcinoma is a Lynch syndrome-associated cancer. J Clin Oncol 2013;31:3012-8.
32. Risinger JI, Barrett JC, Watson P, et al. Molecular genetic evidence of the occurrence of breast cancer as an integral tumor in patients with the hereditary nonpolyposis colorectal cancer syndrome. Cancer 1996;77:1836-43.
33. Järvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000;118:829-34.
34. van Rijn JC, Reitsma JB, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: A systematic review. Am J Gastroenterol 2006;101:343-50.
35. Syngal S, Weeks JC, Schrag D, et al. Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. Ann Intern Med 1998;129:787-96.
36. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the lynch syndrome. N Engl J Med 2006;354:261-9.
37. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): A review of the literature. Crit Rev Oncol Hematol 2007;61:153-61.
38. Rozen P, Macrae F. Familial adenomatous polyposis: The practical applications of clinical and molecular screening. Fam Cancer 2006;5:227-35.
39. Jasperson KW, Burt RW. APC-associated polyposis conditions. In: Pagon RA, Adam MP, Bird TD, et al. eds. GeneReviews(R). Seattle (WA): University of Washington, 1993.
40. Nielsen M, Hes FJ, Nagengast FM, et al. Germline mutations in APC and MUTYH are responsible for the majority of families with attenuated familial adenomatous polyposis. Clin Genet 2007;71:427-33.
41. Smith KD, Rodriguez-Bigas MA. Role of surgery in familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (lynch syndrome). Surg Oncol Clin N Am 2009;18:705-15.
42. Kennedy RD, Potter DD, Moir CR, et al. The natural history of familial adenomatous polyposis syndrome: A 24 year review of a single center experience in screening, diagnosis, and outcomes. J Pediatr Surg 2014;49:82-6.
43. Rozen P, Macrae F. Familial adenomatous polyposis: The practical applications of clinical and molecular screening. Fam Cancer 2006;5:227-35.
44. Aziz O, Athanasiou T, Fazio VW, et al. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg 2006;93:407-17.
45. Talebinejad S, Hicks TC, Margolin DA, et al. Restorative proctocolectomy: the current ochsner experience. Ochsner J 2013;13:512-6.
46. Chokshi RJ, Abdel-Misih S, Bloomston M. Surgical management of colorectal cancer: A review of the literature. Indian J Surg 2009;71:350-5.
47. Maartense S, Dunker MS, Slors JF, et al. Hand-assisted laparoscopic versus open restorative proctocolectomy with ileal pouch anal anastomosis: A randomized trial. Ann Surg 2004;240:984-91; discussion 991-2.
48. Keller DS, Khorgami Z, Swendseid B, et al. Laparoscopic and converted approaches to rectal cancer resection have superior long-term outcomes: a comparative study by operative approach. Surg Endosc 2014;28:1940-8.
49. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 2003;348:791-9.
50. Church J, Heald B, Burke C, et al. Understanding MYH-associated neoplasia. Dis Colon Rectum 2012;55:359-62.
51. Leite JS, Isidro G, Martins M, et al. Is prophylactic colectomy indicated in patients with MYH-associated polyposis? Colorectal Dis 2005;7:327-31.
52. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012;107:1315-29; quiz 1314, 1330.
53. Jasperson KW, Kanth P, Kirchhoff AC, et al. Serrated polyposis: Colonic phenotype, extracolonic features, and familial risk in a large cohort. Dis Colon Rectum 2013;56:1211-6.
54. Snover DC, Ahnen D, Burt R, et al. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman T, Carneiro F, Hruban R. eds. WHO classification of tumours of the digestive system. Lyon: World Health Organization, 2010:160-5.

55. Hazewinkel Y, Reitsma JB, Nagengast FM, et al. Extracolonic cancer risk in patients with serrated polyposis syndrome and their first-degree relatives. Fam Cancer 2013;12:669-73.
56. Hazewinkel Y, Tytgat KM, van Eeden S, et al. Incidence of colonic neoplasia in patients with serrated polyposis syndrome who undergo annual endoscopic surveillance. Gastroenterology 2014;147:88-95.
57. Goel A, Xicola RM, Nguyen TP, et al. Aberrant DNA methylation in hereditary nonpolyposis colorectal cancer without mismatch repair deficiency. Gastroenterology 2010;138:1854-62.
58. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in amsterdam-I criteria families without mismatch repair deficiency: Familial colorectal cancer type X. JAMA 2005;293:1979-85.
59. Fujita S, Moriya Y, Sugihara K, et al. Prognosis of hereditary nonpolyposis colorectal cancer (HNPCC) and the role of japanese criteria for HNPCC. Jpn J Clin Oncol 1996;26:351-5.
60. Percesepe A, Benatti P, Roncucci L, et al. Survival analysis in families affected by hereditary non-polyposis colorectal cancer. Int J Cancer 1997;71:373-6.
61. Myrhøj T, Bisgaard ML, Bernstein I, et al. Hereditary non-polyposis colorectal cancer: clinical features and survival. Results from the Danish HNPCC register. Scand J Gastroenterol 1997;32:572-6.
62. Bertario L, Russo A, Sala P, et al. Survival of patients with hereditary colorectal cancer: Comparison of HNPCC and colorectal cancer in FAP patients with sporadic colorectal cancer. Int J Cancer 1999;80:183-7.
63. Stigliano V, Assisi D, Cosimelli M, et al. Survival of hereditary non-polyposis colorectal cancer patients compared with sporadic colorectal cancer patients. J Exp Clin Cancer Res 2008;27:39.
64. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 2005;23:609-18.
65. Guastadisegni C, Colafranceschi M, Ottini L, et al. Microsatellite instability as a marker of prognosis and response to therapy: A meta-analysis of colorectal cancer survival data. Eur J Cancer 2010;46:2788-98.
66. Merok MA, Ahlquist T, Royrvik EC, et al. Microsatellite instability has a positive prognostic impact on stage II colorectal cancer after complete resection: Results from a large, consecutive norwegian series. Ann Oncol 2013;24:1274-82.
67. Poindessous V, Ouaret D, El Ouadrani K, et al. EGFR- and VEGF(R)-targeted small molecules show synergistic activity in colorectal cancer models refractory to combinations of monoclonal antibodies. Clin Cancer Res 2011;17:6522-30.
68. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. J Clin Oncol 2011;29:4611-9.
69. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-45.
70. Bos JL, Fearon ER, Hamilton SR, et al. Prevalence of ras gene mutations in human colorectal cancers. Nature 1987;327:293-7.
71. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757-65.
72. Allegra CJ, Jessup JM, Somerfield MR, et al. American society of clinical oncology provisional clinical opinion: Testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol 2009;27:2091-6.
73. Therkildsen C, Bergmann TK, Henrichsen-Schnack T, et al. The predictive value of KRAS, NRAS, BRAF, PIK3CA and PTEN for anti-EGFR treatment in metastatic colorectal cancer: A systematic review and meta-analysis. Acta Oncol 2014;53:852-64.
74. French AJ, Sargent DJ, Burgart LJ, et al. Prognostic significance of defective mismatch repair and BRAF V600E in patients with colon cancer. Clin Cancer Res 2008;14:3408-15.

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