Published in final edited form as:

J Natl Compr Canc Netw. 2010 January ; 8(1): 98–105.

Risk Assessment, Genetic Testing and Management of Lynch Syndrome

Shilpa Grover, MD, MPH^{1,2,3,4} and Sapna Syngal, MD, MPH^{1,2,3}

¹Division of Gastroenterology, Department of Medicine, Brigham and Women's Hospital, Boston, MA

²Harvard Medical School, Boston, MA

³Dana-Farber Cancer Institute, Boston, MA

⁴Program in Cancer Outcomes Research and Training, Massachusetts General Hospital, Boston, MA

Abstract

Of the estimated 150,000 colorectal cancer (CRC) cases diagnosed annually, approximately 30% have a familial basis and 3–5% are due to high penetrance inherited cancer syndromes. Lynch syndrome or hereditary non polyposis colorectal cancer (HNPCC), caused by inherited germline mutations in mismatch repair (MMR) genes, is the most commonly inherited CRC syndrome. It is characterized by young onset CRC and an increased risk for extra-colonic tumors, including gynecologic, urinary tract and other gastrointestinal cancers. Commercial testing is available for mutations in the MMR genes but testing all CRCs would be economically prohibitive. Therefore a comprehensive evaluation of a multigenerational family cancer history is essential for the identification of at-risk individuals. The presence of tumors diagnosed at a young age, multiple first- and second-degree relatives with cancer or 2 or more primary cancers may be indicative of an inherited cancer syndrome and such individuals should undergo genetic evaluation. Genetic test results, when conclusive, can guide management for both patients and their families. However, indeterminate test results may provide false reassurance to patients who continue to be at higher than average risk. With on-line risk assessment tools and commercial genetic testing, there is potential to identify a greater number of at-risk individuals at an earlier age. However, for these measures to improve outcomes, patients must receive screening recommendations and counseling appropriate for their cancer risk.

Keywords

Lynch syndrome; hereditary non polyposis colorectal cancer; HNPCC; mismatch repair genes; familial colorectal cancer

Background

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. Approximately 65% of all CRC cases are sporadic. These CRCs may be associated with environmental factors or may be polygenic in inheritance from multiple low penetrance susceptibility genes and do not exhibit familial clustering of cancer.

Corresponding Author: Sapna Syngal, MD, MPH, Associate Professor of Medicine, Harvard Medical School, Dana-Farber Cancer Institute, 44 Binney Street, Smith 209, Boston, MA 02114, Tel: (617) 632-5022, Fax: (617) 632-4088, ssyngal@partners.org.

Disclosures: The authors have no disclosures

Nearly 30% of CRC cases arise from moderately penetrant, inherited susceptibility genes, possibly interacting with environmental factors.^{1, 2} In families with moderately penetrant, inherited susceptibility genes there is a clustering of CRC cases in excess of that expected by chance.³ Studies have demonstrated that the risk of CRC is two- to three-fold higher than expected in the general population if a first-degree relative is diagnosed with CRC. The risk increases to three-fold or higher if two first-degree relatives have CRC or a single first-degree relative is diagnosed with CRC prior to 50 years of age. An individual's risk of CRC is also increased if a second- or third-degree relative have CRC or a first-degree relative has a colorectal adenoma.^{4, 5}

Three to five percent of CRC cases are due to highly penetrant inherited syndromes. These include Lynch syndrome or hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), *MYH* associated polyposis (MAP) and rare hamartomatous polyposis syndromes. This review focuses on the diagnostic features, evaluation and management of Lynch Syndrome with a brief discussion about other inherited CRC syndromes.

Lynch Syndrome

Lynch syndrome, the most common familial CRC syndrome, results from a mutation in one of the mismatch repair genes *MLH1*, *MSH2*, *MSH6* or *PMS2*. After being initially described by Aldred Warthin in a family with endometrial and CRC, Henry Lynch subsequently broadened the syndrome to include a spectrum of malignancies.^{6, 7} Lynch syndrome is now known to be associated with early onset of CRC and a predisposition to cancers of the endometrium, ovary, stomach, small bowel, biliary tract, urinary tract, and brain.

Clinical Features of Lynch Syndrome

Individuals with Lynch syndrome have a 60–80% lifetime risk of CRC.^{89–11} Cancer risk varies based on gender and the mismatch repair mutation.^{8, 11–14} CRCs in Lynch syndrome arise from adenomatous polyps. Although individuals with Lynch syndrome develop adenomas more frequently than controls,¹⁵ they do not present with hundreds to thousands of polyps as seen in classic Familial Adenomatous Polyposis (FAP). A large proportion of adenomas in individuals with Lynch syndrome demonstrate advanced histology. In addition, the progression from adenoma to carcinoma may occur over a shorter interval of 2–3 years, in contrast to 8–10 years in sporadic CRC cases.^{16, 17}

CRC in Lynch syndrome has an early age of onset with an average age of 45 years at diagnosis. Individuals with Lynch syndrome are at risk for both synchronous and metachronous CRC.¹⁶ These CRCs are frequently located in the proximal colon (70%) and on histology have an intense Crohn's like lymphocytic reaction, a mucinous component or are poorly differentiated.¹⁸ After adjusting for stage, CRC patients with Lynch syndrome have a better prognosis than sporadic cases, however the reasons remain unclear.^{19–21}

Individuals with Lynch syndrome are also at risk for a number of extracolonic malignancies. In women with Lynch syndrome, endometrial cancer is the second most common malignancy, with an estimated lifetime risk of 40–60%. In addition, women have a 10–12 % lifetime risk of ovarian cancer.^{10, 13, 22} Brain tumors are the third leading cause of cancer death in individuals with Lynch syndrome.²³ The Turcot variant of Lynch syndrome is associated with astrocytomas, glioblastomas, and oligodendrogliomas of the brain.²⁴ Sebaceous neoplasms of the skin including sebaceous adenoma, sebaceous epithelioma, basal cell epithelioma with sebaceous differentiation, sebaceous carcinoma, and squamous cell cancer (keratoacanthoma type) are associated with Muir-Torre syndrome.²⁵ The

spectrum of Lynch associated malignancies is also known to include stomach, small intestine, biliary tract and urothelial carcinoma of the renal pelvis and ureter.

Genetics of Lynch Syndrome

Lynch syndrome is inherited in an autosomal dominant pattern. Germline mutations in mismatch repair (MMR) genes *MLH1* and *MSH2* account for 90% of cases.¹⁶ Mutations in *MSH6* have been found in 6–10% of Lynch syndrome families and in 1%, mutations in *PMS2* have been identified.

The MMR system is responsible for correcting errors that occur during DNA replication. Slippage of DNA occurs frequently during the replication of short mononucleotide or dinucleotide repeat sequences (microsatellites) resulting in too few or too many copies. These errors are normally corrected by DNA polymerase. Errors that are not corrected by DNA polymerase are corrected by the MMR mechanism. In individuals with Lynch syndrome, due to failure of the MMR mechanism, errors in microsatellite repeat sequences are not corrected. This phenomenon is referred to as microsatellite instability. Tumorigenesis results when the second copy of the affected MMR gene is somatically mutated and microsatellites are located in the coding regions of genes involved in tumor initiation and progression.

Genetic Evaluation for Lynch syndrome

Genetic evaluation allows for confirmation of the suspected clinical diagnosis of Lynch syndrome in an individual and in risk stratification of family members. Initial evaluation in families without a known mutation should start with molecular analysis of the colorectal tumor.

(1) Tumor Molecular Evaluation

a. Microsatellite Instability Testing—Assessment for microsatellite instability (MSI) is most commonly performed with a NCI recommended, five microsatellite marker panel. The MSI phenotype is defined on the basis of the number of markers that demonstrate instability.²⁶ Tumors are considered microsatellite high (MSI-H) if two or more of the five microsatellite sequences are mutated; microsatellite low (MSI-L) if one microsatellite sequence is mutated and microsatellite stable (MSS) if none of the five microsatellite sequences in tumor DNA are mutated.

b. Immunohistochemistry Testing—Immunohistochemistry (IHC) testing analyses the expression of MMR proteins. Tumors in Lynch syndrome frequently reveal loss of staining for the antibodies to mismatch repair proteins.²⁷ Loss of expression of a MMR protein according to IHC is an alternate marker of MMR mutations.²⁸ Guidelines recommend germline testing for MMR mutations in individuals with abnormal MSI or IHC results.

Both MSI and IHC testing have limitations. IHC analysis is a faster and less expensive test than MSI analysis, but mutations associated with immunoreactive, but non-functional, proteins can result in false negative IHC results. Studies have also demonstrated slightly lower sensitivity of IHC compared to MSI testing.^{29–32} With regard to MSI testing, although 90% of Lynch-related cancers demonstrate MSI, up to 15% of sporadic CRCs may have MSI abnormalities due to epigenetic mechanisms, i.e. inactivation of *MLH1* by promoter methylation.³³ Therefore, it may be reasonable to perform *BRAF* mutation analysis for the p. V600E mutation associated with sporadic *MLH1* promoter methylation, prior to germline testing, in tumors that demonstrate loss of MLH1 staining on IHC.

(2) Germline Testing

The presence of a pathogenic/deleterious germline mutation in one of four MMR genes identifies individuals positive for Lynch syndrome or true positive. Once a pathogenic mutation is identified in the proband, at risk relatives can be tested for the same mutation. If the identified family mutation is not found, the results are considered true negative and these individuals can be managed as average risk. In cases where there is no identified family mutation and no pathogenic mutation is detected or a mutation of unclear pathogenic significance is found, genetic test results are considered indeterminate or uninformative. Individuals with indeterminate results are still considered at higher than average risk and recommendations for surveillance must be based on personal and family cancer history.

Identification of Individuals at Risk for Lynch Syndrome

(1) Clinical Criteria

In 1991, the Amsterdam criteria were proposed to identify individuals who were likely to be mutation carriers. The Amsterdam criteria required the presence of young onset CRC, in addition to a family history of three CRCs involving two successive generations. As these criteria are stringent, they are limited in sensitivity.¹⁹ The Amsterdam II criteria include other Lynch associated malignancies³⁴ and therefore have a higher sensitivity than the Amsterdam criteria. With the introduction of tumor molecular analysis for Lynch Syndrome, the Bethesda guidelines were proposed to guide the identification of patients for MSI testing.³⁵ Studies evaluating the performance of clinical criteria in populations at high-risk for Lynch Syndrome, have demonstrated that the Bethesda guidelines have a higher sensitivity compared to the Amsterdam I and II criteria.³⁶ Recently, the revised Bethesda guidelines were proposed to improve the accuracy of identifying patients with Lynch syndrome.³⁷ Limitations of these criteria were highlighted in a study by Hampel et al. that noted that in a population based cohort of 1066 patients with CRC, 5 of 23 mutation carriers did not meet the Bethesda and revised Bethesda criteria and would otherwise been missed if genetic evaluation was limited to individuals who met these criteria.³⁸ In light of these limitations, an alternative strategy of universal MSI/IHC testing of all individuals with CRC has been proposed. Even if such a strategy were found to be cost-effective, it may still fail to identify cases where MMR mutations disrupt MMR function but do not result in MSI, as seen with *MSH6* mutations or where IHC results are normal despite a non-functional MMR protein.

B. Prediction Models—Prediction models have been developed to identify individuals at risk for Lynch syndrome and to quantify the risk of germline MMR mutations. Three such models by Barnetson et al.²¹, the PREMM_{1,2}³⁹ and the MMRpro are noteworthy.⁴⁰

Barnetson et al. analyzed a population based cohort of 870 patients diagnosed with CRC prior to 55 years of age. Multivariable regression analysis was used to develop a 2 stage model to predict *MLH1*, *MSH2* and *MSH6* mutations. The model included patient age, gender, tumor location, presence of synchronous and metachronous CRCs, family history of endometrial cancer and CRC, the age of the youngest relative with CRC (stage 1) and tumor MSI and IHC results (stage 2). The model was then validated in 155 patients with CRC diagnosed prior to 45 years of age. The model sensitivity of 62%, specificity of 97% and positive predictive value of 80% were superior to the performance of the Bethesda and Amsterdam criteria. The ability of the model to separate mutation carriers from those without a MMR mutation (model discrimination), was similar between the derivation and validation cohort. However, it is important to note that this model was developed and validated in patients with young onset CRC and did not include Lynch associated cancers other than endometrial cancer.

The PREMM_{1,2} model (Prediction of mutations in *MLH1* and *MSH2*) was developed in a cohort of 1914 individuals at moderate risk for Lynch syndrome.³⁹ Clinical data from 898 probands was used for model derivation. The model was then validated in 1016 unrelated probands. The final multivariable logistic regression model included proband diagnosis of CRC, colonic adenomas, extracolonic Lynch associated cancers and a family history of Lynch cancers. The PREMM_{1,2} model showed good discrimination with an area under the receiver operating curve of 0.80. The PREMM_{1,2} model has also been validated in a large population based cohort.⁴¹ Strengths of the model included its ability to incorporate extracolonic Lynch associated neoplasms and to provide individualized risk prediction using an easy to use web-based calculator. However, the PREMM_{1,2} model does not consider family size or unaffected family members.

The MMRpro model estimates the probability of carrying a deleterious mutation in *MLH1*, *MSH2* and *MSH6* genes by using estimates of mutation prevalence and the penetrance of MMR genes.⁴⁰ The model can also estimate the probability of developing CRC or endometrial cancer in unaffected relatives. In the validation group, the MMRpro model performed better at identifying mutation carriers than the Bethesda guidelines, although it slightly over predicted the number of carriers. Advantages of the MMRpro model include its ability to account for family size by including unaffected relatives and to incorporate MSI data. For individuals with indeterminate or uninformative genetic testing results, the MMRpro model can provide post-sequencing probability of a deleterious mutation. These estimates are particularly valuable given that genetic testing has limitations in sensitivity and that uninformative results may lead to false reassurance and poor adherence to recommended cancer screening.⁴²

Studies have demonstrated that these three prediction models have comparable sensitivities to the revised Bethesda criteria. They can also provide quantitative risk assessment and streamline genetic testing by identification of the family member with the highest probability of being a mutation carrier. But before prediction models can be widely incorporated into more advanced management decisions, such as deciding the extent of surgical resection in an operative setting, external validation studies are needed to assess the transportability of model cut-offs in population-based and high-risk cohorts. An approach to the genetic evaluation for Lynch syndrome is outlined in Figure 1.

Management of Individuals with Lynch Syndrome

(1) Screening and Management of CRC

Among individuals with Lynch syndrome, screening for CRC, has been demonstrated to decrease CRC incidence and mortality.^{43, 44} In a prospective screening study that followed individuals over a 15 year period, colonoscopies at 3 year intervals decreased CRC mortality by 63%.⁴⁴ Observational studies have however reported interval cancers in individuals undergoing colonoscopies at 3 year intervals.⁴⁵ Therefore, current screening guidelines take into account the early age of CRC onset, the predisposition for proximal and metachronous cancer, the rapid progression from adenoma to carcinoma and the incidence of interval cancers. It is recommended that individuals with Lynch syndrome undergo CRC screening with colonoscopy every 1–2 years beginning between the ages of 20–25 years.^{46, 47}

In patients with Lynch syndrome who develop CRC, given the risk of synchronous CRCs, evaluation of the entire colon is necessary prior to surgical resection. Microsatellite stability may affect the response to chemotherapy and patients who have MSI-H cancers are less likely to respond to alkylating agents or 5-FU^{48,49} but are more likely to respond to irinotecan than patients who have MSI-L CRCs.⁵⁰ In patients undergoing surgery, subtotal colectomy should be considered as the cumulative risk of a second CRC at 10 year follow-

up is significantly higher after a partial colectomy compared to a subtotal colectomy. (15.7% and 3.4% respectively).⁵¹

(2) Screening for Endometrial Cancer

Guidelines recommend that women at risk for Lynch Syndrome undergo endometrial cancer screening with annual transvaginal ultrasound and endometrial biopsy beginning at 25–35 years of age. Although screening for endometrial cancer has not been demonstrated to improve survival in women with Lynch syndrome, data suggest that screening may lead to the detection of premalignant lesions or detection of endometrial cancer at an early stage.⁵²

An alternative strategy to endometrial cancer screening is prophylactic hysterectomy and bilateral salpingo-oophorectomy. In a case control study, Schmeler et al. examined the occurrence of endometrial and ovarian cancer in women with Lynch syndrome who had undergone prophylactic hysterectomy alone or with bilateral salpingo-oophorectomy, as compared to controls.⁵³ No endometrial cancers occurred in the 61 women who underwent hysterectomy as compared to 69 endometrial cancers in 210 controls. In addition, no ovarian or peritoneal cancers were diagnosed in the 47 women who had undergone bilateral salpingo-oophorectomy, as compared to 12 of 223 controls. Although this study supported prophylactic surgery to reduce the risk of endometrial and ovarian cancer, it is important to note that the protective effect against ovarian cancer after surgery was not statistically significant. Therefore, discussion of prophylactic hysterectomy and bilateral salpingo-oophorectomy should be part of the management for women, particularly those who have completed childbearing.

(3) Screening for Other Cancers

Annual physical examinations with total body dermatologic examinations are recommended for individuals with Lynch syndrome.⁹ The incidence of brain tumors and cancers of the small bowel, stomach, and biliary tract are too low to warrant routine screening.⁵⁴ However, experts have suggested that if there is clustering of gastric cancers in the family or if there is a high incidence of gastric cancer in the individual's country of origin, screening for gastric cancer with esophagogastroduodenoscopy can be considered. Screening for urothelial cancers in families with clustering of these tumors by annual urine analysis with cytology and renal ultrasounds starting at 30–35 years have been proposed, but there are no data regarding the effectiveness of these approaches yet; therefore, screening for these cancers is generally approached on a family-by-family basis and individualized based on the specific spectrum of tumors.

Differential Diagnosis

Familial Colon Cancer Type X has been used to describe families that meet Amsterdam criteria due to clustering of CRCs, but with no DNA mismatch repair mutation. Studies have suggested that the incidence of CRC may be lower in these families as compared to those with Lynch syndrome and these individuals may not be at an increased risk of extra-colonic cancers.⁵⁵

Attenuated familial adenomatous polyposis (AFAP) and *MYH* associated polyposis (MAP) should also be considered in the differential diagnosis. FAP is caused by an inherited mutation in the adenomatous polyposis coli (*APC*) gene. FAP follows an autosomal dominant pattern of inheritance, but approximately one-third of cases arise from de novo mutations. Unlike patients with classic FAP who may present with greater than a thousand polyps, patients with AFAP have an average of 30 polyps and can present in the fourth or fifth decade. These patients have a 70–80% lifetime risk of CRC and are at risk for polyps of the upper gastrointestinal tract.

MAP should be considered in patients with colorectal adenomas and CRC whose family history is suggestive of an autosomal recessive inheritance. Biallelic pathogenic mutations in the *MYH* gene may account for 30% of families with multiple adenomas who do not have a pathogenic *APC* mutation.⁵⁶ As with Lynch syndrome, genetic testing for AFAP and MAP permits an assessment of the patient's cancer risk and identification of at-risk and affected family members. Although there are no clear guidelines for the frequency of endoscopic surveillance in MAP, current recommendations include upper endoscopy and colonoscopy—the frequency of which should be based on the size, number and pathology of polyps.⁵⁷

In conclusion, a comprehensive assessment of family cancer history is essential in determining an individual's risk of developing CRC. More frequent screening is recommended in patients with familial cancer risk than the average-risk individual. For patients with a family history that meet criteria for an inherited cancer syndrome (based on clinical criteria or with a score above the pre-specified prediction model cut off), genetic testing should be performed. As other low penetrance genes that contribute to familial risk are identified and gene-gene and gene-environment interactions are more clearly defined, the interpretation and estimation of cancer risk is likely to become more complex. Testing should therefore be performed in a specialized setting so that risk counseling and recommendations for future screening can be made in accordance with an individual's cancer risk.

References

1. Tenesa A, Farrington SM, Prendergast JG, et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on 11q23 and replicates risk loci at 8q24 and 18q21. *Nat Genet.* May; 2008 40(5):631–637. [PubMed: 18372901]
2. Tomlinson IP, Webb E, Carvajal-Carmona L, et al. A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3. *Nat Genet.* May; 2008 40(5):623–630. [PubMed: 18372905]
3. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med.* Jul 13; 2000 343(2):78–85. [PubMed: 10891514]
4. Slattery ML, Kerber RA. Family history of cancer and colon cancer risk: the Utah Population Database. *J Natl Cancer Inst.* Nov 2; 1994 86(21):1618–1626. [PubMed: 7932826]
5. Winawer SJ, Zauber AG, Gerdes H, et al. Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. *N Engl J Med.* Jan 11; 1996 334(2):82–87. [PubMed: 8531963]
6. Warthin AS. The further study of a cancer family. *J Cancer Res.* 1925; 9:279–286.
7. Lynch HTKA. Cancer family “G” revisited: 1895–1970. *Cancer.* Jun; 1971 27(6):1505–1511. [PubMed: 5088221]
8. Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology.* Apr; 1996 110(4):1020–1027. [PubMed: 8612988]
9. Jenkins MA, Baglietto L, Dowty JG, et al. Cancer risks for mismatch repair gene mutation carriers: a population-based early onset case-family study. *Clin Gastroenterol Hepatol.* Apr; 2006 4(4):489–498. [PubMed: 16616355]
10. Quehenberger F, Vasen HF, van Houwelingen HC. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. *J Med Genet.* Jun; 2005 42(6):491–496. [PubMed: 15937084]
11. Stoffel E, Mukherjee B, Raymond VM, et al. Calculation of risk of colorectal and endometrial cancer among patients with Lynch syndrome. *Gastroenterology.* Nov; 2009 137(5):1621–1627. [PubMed: 19622357]

12. Aarnio M, Mecklin JP, Aaltonen LA, Nystrom-Lahti M, Jarvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. *Int J Cancer*. Dec 20; 1995 64(6):430–433. [PubMed: 8550246]
13. Dunlop MG, Farrington SM, Carothers AD, et al. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum Mol Genet*. Jan; 1997 6(1):105–110. [PubMed: 9002677]
14. Vasen HF, Stormorken A, Menko FH, et al. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. *J Clin Oncol*. Oct 15; 2001 19(20):4074–4080. [PubMed: 11600610]
15. De Jong AE, Morreau H, Van Puijenbroek M, et al. The role of mismatch repair gene defects in the development of adenomas in patients with HNPCC. *Gastroenterology*. Jan; 2004 126(1):42–48. [PubMed: 14699485]
16. Lynch HT, de la Chapelle A. Genetic susceptibility to non-polyposis colorectal cancer. *J Med Genet*. Nov; 1999 36(11):801–818. [PubMed: 10544223]
17. Jass JR, Stewart SM. Evolution of hereditary non-polyposis colorectal cancer. *Gut*. 1992; 33(6): 783–786. [PubMed: 1624160]
18. Jass JR, Walsh MD, Barker M, Simms LA, Young J, Leggett BA. Distinction between familial and sporadic forms of colorectal cancer showing DNA microsatellite instability. *Eur J Cancer*. May; 2002 38(7):858–866. [PubMed: 11978509]
19. Vasen HFA, Mecklin J-P, Meera Khan P, Lynch HT. The International Collaborative Group on hereditary nonpolyposis colorectal cancer (ICG-HNPCC). *Dis Col Rectum*. 1991; 34:424–425.
20. Watson P, Lin KM, Rodriguez-Bigas MA, et al. Colorectal carcinoma survival among hereditary nonpolyposis colorectal carcinoma family members. *Cancer*. Jul 15; 1998 83(2):259–266. [PubMed: 9669808]
21. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *N Engl J Med*. Jun 29; 2006 354(26):2751–2763. [PubMed: 16807412]
22. Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer*. Apr 12; 1999 81(2):214–218. [PubMed: 10188721]
23. de Jong AE, Hendriks YM, Kleibeuker JH, et al. Decrease in mortality in Lynch syndrome families because of surveillance. *Gastroenterology*. Mar; 2006 130(3):665–671. [PubMed: 16530507]
24. Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot's syndrome. *N Engl J Med*. 1995; 332(13):839–847. [PubMed: 7661930]
25. Ponti G, Ponz de Leon M. Muir-Torre syndrome. *Lancet Oncol*. Dec; 2005 6(12):980–987. [PubMed: 16321766]
26. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res*. Nov 15; 1998 58(22):5248–5257. [PubMed: 9823339]
27. Hendriks Y, Franken P, Dierssen JW, et al. Conventional and tissue microarray immunohistochemical expression analysis of mismatch repair in hereditary colorectal tumors. *Am J Pathol*. Feb; 2003 162(2):469–477. [PubMed: 12547705]
28. Niessen RC, Berends MJ, Wu Y, et al. Identification of mismatch repair gene mutations in young patients with colorectal cancer and in patients with multiple tumours associated with hereditary non-polyposis colorectal cancer. *Gut*. Dec; 2006 55(12):1781–1788. [PubMed: 16636019]
29. Pinol V, Castells A, Andreu M, et al. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. *Jama*. Apr 27; 2005 293(16):1986–1994. [PubMed: 15855432]
30. Cunningham JMKC, Christensen ER, et al. The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. *Am J Hum Genet*. 2001; 69(4):780–790. [PubMed: 11524701]
31. Debniak T, Kurzawski G, Gorski B, Kladny J, Domagala W, Lubinski J. Value of pedigree/clinical data, immunohistochemistry and microsatellite instability analyses in reducing the cost of determining hMLH1 and hMSH2 gene mutations in patients with colorectal cancer. *Eur J Cancer*. Jan; 2000 36(1):49–54. [PubMed: 10741294]

32. Hampel H, Frankel W, Panescu J, et al. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. *Cancer Res.* Aug 1; 2006 66(15):7810–7817. [PubMed: 16885385]
33. Wang L, Cunningham JM, Winters JL, et al. BRAF mutations in colon cancer are not likely attributable to defective DNA mismatch repair. *Cancer Res.* Sep 1; 2003 63(17):5209–5212. [PubMed: 14500346]
34. Vasen HFA, Watson P, Mecklin J-P, Lynch HT. ICG-HNPCC at. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch Syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology.* 1999; 116:1453–1456. [PubMed: 10348829]
35. Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute workshop on hereditary nonpolyposis colorectal cancer syndrome: meeting highlights and Bethesda Guidelines. *JNCI.* 1997; 89:1758–1762. [PubMed: 9392616]
36. Syngal S, Fox EA, Eng C, Kolodner RD, Garber JE. Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1 [In Process Citation]. *J Med Genet.* 2000; 37(9):641–645. [PubMed: 10978352]
37. Umar ABC, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst.* Feb 18; 2004 96(4):261–268. [PubMed: 14970275]
38. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med.* May 5; 2005 352(18):1851–1860. [PubMed: 15872200]
39. Balmana J, Stockwell DH, Steyerberg EW, et al. Prediction of MLH1 and MSH2 mutations in Lynch syndrome. *Jama.* Sep 27; 2006 296(12):1469–1478. [PubMed: 17003395]
40. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. *Jama.* Sep 27; 2006 296(12):1479–1487. [PubMed: 17003396]
41. Balaguer F, Balmana J, Castellvi-Bel S, et al. Validation and extension of the PREMM1,2 model in a population-based cohort of colorectal cancer patients. *Gastroenterology.* Jan; 2008 134(1):39–46. [PubMed: 18061181]
42. Grover S, Stoffel EM, Mercado RC, et al. Colorectal Cancer Risk Perception on the Basis of Genetic Test Results in Individuals at Risk for Lynch Syndrome. *J Clin Oncol.* Jul 20.2009
43. Jarvinen HJ, Mecklin J-P, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary non-polyposis colorectal cancer. *Gastroenterology.* 1995; 108:1405–1411. [PubMed: 7729632]
44. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology.* May; 2000 118(5):829–834. [PubMed: 10784581]
45. Renkonen-Sinisalo LAM, Mecklin J, Järvinen HJ. Surveillance Improves Survival of Colorectal Cancer in Patients with Hereditary Nonpolyposis Colorectal Cancer. *Cancer Detection and Prevention.* 2000; 24(2):137–142. [PubMed: 10917133]
46. Burke W, Petersen G, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. *Cancer Genetics Studies Consortium.* *Jama.* 1997; 277(11):915–919. [PubMed: 9062331]
47. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: Clinical guidelines and rationale-Update based on new evidence. *Gastroenterology.* Feb; 2003 124(2):544–560. [PubMed: 12557158]
48. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med.* Jul 17; 2003 349(3):247–257. [PubMed: 12867608]
49. Jover R, Zapater P, Castells A, et al. Mismatch repair status in the prediction of benefit from adjuvant fluorouracil chemotherapy in colorectal cancer. *Gut.* Jun; 2006 55(6):848–855. [PubMed: 16299036]

50. Fallik D, Borriani F, Boige V, et al. Microsatellite instability is a predictive factor of the tumor response to irinotecan in patients with advanced colorectal cancer. *Cancer Res.* Sep 15; 2003 63(18):5738–5744. [PubMed: 14522894]
51. de Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G, et al. Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. *Dis Colon Rectum.* Dec; 2002 45(12):1588–1594. [PubMed: 12473880]
52. Dove-Edwin I, Boks D, Goff S, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer.* Mar 15; 2002 94(6):1708–1712. [PubMed: 11920532]
53. 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.* Jan 19; 2006 354(3):261–269. [PubMed: 16421367]
54. Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer.* Jul 15; 2008 123(2):444–449. [PubMed: 18398828]
55. 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.* Apr 27; 2005 293(16):1979–1985. [PubMed: 15855431]
56. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. *N Engl J Med.* Feb 27; 2003 348(9):791–799. [PubMed: 12606733]
57. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol.* Mar; 2009 104(3):739–750. [PubMed: 19240699]
58. Grover S, Syngal S. Genetic testing in gastroenterology: Lynch syndrome. *Best Pract Res Clin Gastroenterol.* 2009; 23(2):185–196. [PubMed: 19414145]

Figure 1. Algorithm for Genetic Evaluation of Individuals with CRC Based on Revised Bethesda Guidelines and PREMM_{1,2} Score⁵⁸

* If loss of MLH1 expression, *BRAF* analysis should be performed.

\$ Other models may be used. Each model has its own pre-specified cut-off.

PREMM_{1,2} <http://www.dana-farber.org/pat/cancer/gastrointestinal/crc-calculator/default.asp>

Barnetson <https://hnpccpredict.hgu.mrc.ac.uk/>

MMRpro <http://astor.som.jhmi.edu/BayesMendel/>

Surveillance recommendations based on personal and family history