Genetic Counseling and Surveillance Focused on Lynch Syndrome

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Abstract:
Lynch syndrome is a hereditary cancer syndrome caused by germline mutations in one of several DNA mismatch repair genes. Lynch syndrome leads to an increased lifetime risk of various cancers, particularly colorectal, and endometrial cancers. After identifying patients suspected of having Lynch syndrome by clinical criteria, computational prediction models, and/or universal tumor testing, genetic testing is performed to confirm the diagnosis. Before and after genetic testing, genetic counseling should be provided. Genetic counseling should involve a detailed personal and family history, information on the disorder and genetic tests, discussion of the management and surveillance of the disease, career plan, family plan, and psychosocial support. Surveillance of colorectal cancer and other malignancies is of paramount importance for properly managing Lynch syndrome. This review focuses on important considerations in genetic counseling and the latest insights into the surveillance of individuals and families with Lynch syndrome.

Keywords:
Lynch syndrome, colorectal cancer, genetic counseling, surveillance, next-generation sequencing

Introduction
Lynch syndrome is the most common cause of inherited colorectal cancer (CRC), accounting for 2%-4% of newly diagnosed CRC cases. This syndrome is characterized not only by CRC but also by common development of extracolonic malignancies, including cancers in the endometrium, ovaries, gastrointestinal tract, and urinary tract. This hereditary cancer syndrome is transmitted through an autosomal dominant pattern caused by germline mutations in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2, or in the epithelial-cell adhesion molecule (EpCAM) gene.

Lynch syndrome is traditionally suspected when a patient fulfills the clinical criteria for the disease such as the Amsterdam II criteria or the revised Bethesda guidelines. The Amsterdam II criteria are based on the patient or family history of cancer. The revised Bethesda guidelines are based on typical patient and/or family history and tumor pathologic features showing high DNA microsatellite instability. Despite these clinical criteria, Lynch syndrome is often under-diagnosed, even when patients meet these criteria because of their low sensitivity. Therefore, recent diagnostic approaches have focused on molecular genetics. Current standard guidelines endorsed by the National Comprehensive Cancer Network (NCCN) and the American College of Medical Genetics and Genomics recommend universal tumor testing for all patients with newly diagnosed CRC, which includes a polymerase chain reaction-based test for microsatellite instability and immunohistochemistry (IHC) for MMR proteins.

After identification of suspected Lynch syndrome patients based on clinical criteria and/or universal tumor testing, confirmative diagnosis is typically made by genetic tests. The traditional method of genetic testing for Lynch syndrome is direct sequencing of a specific MMR gene or of EpCAM at the germline level by the Sanger method. Traditionally, IHC of 4 MMR proteins is performed on the CRC tissue. In
A. Definition

Genetic counseling is the process through which specially trained healthcare providers assess genetic or hereditary diseases of affected or at-risk individuals and families based on a combination of personal medical history and family history to support them in understanding and adapting to the clinical, psychosocial, economical, and ethical issues raised during the diagnostic process\(^\text{19-21}\). Counseling processes focus on giving unbiased, essential information and non-directive assistance in the decision-making process of the patient and his or her family. Components of genetic counseling should include (1) an investigation of the personal medical history and collection of family history in a detailed format, (2) education regarding the inheritance, genetic testing, and management options of the hereditary disease, (3) assistance for psychosocial dimensions, (4) informed consent, (5) disclosure of genetic test results with at-risk relatives, (6) discussion of the career plan and family plan, and (7) discussion of the management and surveillance of patients and affected or at-risk relatives\(^\text{15}\). Table 1 shows a summary of the components of genetic counseling before and after genetic testing.

B. Personal and family history

In the first step of genetic counseling, a detailed medical history of colorectal cancer, endometrial cancer, and extracolonic malignancies should be investigated in suspected patients and their families of at least two generations. A de-
tailed family pedigree should be drawn, which is useful for assessing familial cancer risk and analyzing the inheritance patterns of diseases with possible determination of the proband\(^2\). A family pedigree is of crucial importance from several perspectives. First, a family pedigree can provide a clinical basis regarding whether or not the individual meets clinical criteria such as the Amsterdam II criteria or the revised Bethesda guidelines, thereby aiding the decision on undergoing confirmative genetic testing. Computational prediction models, such as PREMM\(_{1,2}\), REMM, and MMRpro, which assess the probability of Lynch syndrome, are particularly helpful when direct sequencing of the tumor tissue is not possible. These computational models also require information regarding the family members\(^7\). Second, a family pedigree can distinguish candidates who may benefit from genetic testing from those who will not (due to no risk of inheriting Lynch syndrome). Thus, a family pedigree can provide time- and cost-effective guidance for genetic testing of the family members. Lastly, a family pedigree can be used as educational material for the patient and family members.

**C. Counseling on genetic testing**

Before genetic testing, a genetic counselor should inform the individual who will undergo genetic testing of the advantages and disadvantages of this procedure, the implications of the test results, and limitations of the test. The counselor should inform the patient that the genetic variation detected by genetic testing does not always reflect a causative mutation. A genetic variation is typically classified as pathogenic, likely pathogenic, variants of unknown significance (VUS), likely benign, or benign\(^26,27\). Genetic testing may provide large amounts of information such as regarding VUS, and its interpretation can be difficult, which should be informed during genetic counseling. Additionally, the results of genetic testing are sensitive information, which should be shared among families and can affect family members. Genetic testing may reveal unexpected results or be costly. Thus, extensive counseling and informed consent are required before any genetic testing is performed in accordance with the relevant laws\(^28\).

**D. Targeted single-gene test vs. NGS multi-gene panel**

Traditionally, genetic testing for Lynch syndrome is conducted using a targeted single-gene test. In the targeted single-gene test, a specific MMR gene suggested by IHC of MMR proteins in CRC tissue is investigated. Recently, the NGS multi-gene panel test has been introduced and adopted in clinical practice. The foremost advantage of NGS technologies is their massively parallel sequencing capability, which allows for simultaneous screening of multiple targeted genomic regions. Thus, this approach may identify additional germline mutations by using a larger genetic pool. Another important advantage is the reduced turnaround time of the analysis\(^8,29,30\). Technical advances in genetic engineering have led to drastic reductions in the costs of multi-gene panel testing\(^31\). Because of these advantages, NGS multigene panel testing may be more cost- and time-effective than the traditional targeted single-gene test. Furthermore, more comprehensive interpretation through multiple gene analysis can be conducted. Additionally, unlike the targeted single-gene test in which testing fatigue can develop due to subsequent testing of other target genes after negative findings in one target gene, testing fatigue can be decreased in the NGS multi-gene panel test because multiple genes are analyzed simultaneously. Therefore, the NGS multi-gene panel test has broadened the scope of clinical application with increases in the number of target genes for hereditary CRC, genetic heterogeneity, and diverse phenotypes. Lynch syndrome can be also an indication for NGS multi-gene panel test due to the nature of the disease such as the involvement of multiple MMR genes\(^32\).

Despite these advantages, there are some important disadvantages to NGS multi-gene panel testing. Notably, it is difficult to interpret incidental findings such as unexpected mutations and VUS\(^29\). In one study in which an NGS multi-gene panel test was performed for 1,260 patients with suspected Lynch syndrome, genetic variants were detected in 182 patients. Of these, 71 (39%) showed non-Lynch mutations\(^33\). These incidental variations may be clinically significant or associated only with benign polymorphisms. Also, the patient may show a tendency for developing other late-onset diseases with recessive inherited patterns or other common diseases\(^34\). Accurately interpreting these possibilities is not always straightforward. Misclassification of an insignificant abnormality as a significant mutant allele can cause uncertainty and excessive emotional stress to the patient and family members. Some of these findings can lead to unreasonable additional tests and/or prophylactic surgical procedures due to errors in and a lack of medical studies as well as inaccuracies in prediction algorithms for VUS. Therefore, detailed explanations of both the advantages and limitations of genetic tests, including NGS multi-gene panel testing, should be provided during genetic counseling to ensure informed consent by the patients.

**E. Family counseling**

If a genetic testing detects pathogenic mutations, a counseling team should provide the best management and surveillance plan for the patient. Additionally, because of the hereditary nature of Lynch syndrome, counseling of the family members should be considered\(^35\). Based on the detailed pedigree of the family, at-risk family members can be differentiated from those without risk. Education of at-risk family members is of paramount importance so that they can make voluntary decisions regarding their own care, including ge-
netic testing for confirmative diagnosis of the presence or absence of Lynch syndrome. An interesting issue regarding family counseling is the family relationship. If the family relationship breaks down, the results of genetic testing may remain undisclosed, whereas if the family relationship is good, the family members may encourage each other to undergo genetic testing. This clinically interesting finding indicates that the family relationship may be more important than professional counseling. Another issue is the psychosocial aspect of the affected families. The family members of patients diagnosed with Lynch syndromes are under more stressful conditions than those in a normal family. A genetic counseling team should be aware of psychosocial issues before and after genetic testing and during surveillance for a large group of patients and their family members.

F. Family plan

Patients with Lynch syndrome can pass the causative mutation on to their offspring. Therefore, most patients with Lynch syndrome are interested in their family plan. A genetic counselor should inform patients of the most current knowledge regarding family plans of patients with Lynch syndrome. As medical technologies have progressed, prenatal diagnosis and preimplantation genetic diagnosis have become technically feasible. In a survey of 161 patients with Lynch syndrome in the US, 66% of the patients strongly agreed or agreed that prenatal diagnosis and preimplantation genetic diagnosis are ethical. Approximately 42% of the patients strongly agreed or agreed that they would consider prenatal testing. Approximately 20% of the patients would consider having children earlier before prophylactic surgery to reduce the risk of gynecological cancers. During genetic counseling, clinicians should thoroughly discuss the legal, ethical, practical, and psychosocial aspects of family planning, including prenatal diagnosis and preimplantation genetic diagnosis. Despite the technical feasibility of prenatal diagnosis and selective implantation of unaffected zygotes, there is no consensus regarding the performance of these practices. A legal and ethical consensus should be reached through sufficient discussion among various social parties, including the patients, clinicians, government, non-government organizations, legal circles, and religious circles.

G. Multi-disciplinary team approach for genetic counseling

Because of the complexity and diversity of genetic counseling, in-depth counseling should be approached as a team. The ideal counseling team can consist of clinicians including a gastroenterologist, surgeon, oncologist, obstetrician-gynecologist, and psychiatrist, medical geneticist, molecular diagnostic specialist, genetics nurses, and ancillary staffs. A leader should comprehensively manage and supervise this multi-disciplinary team. The multi-disciplinary team should systematically approach and manage the patient and family members according to the cutting-edge knowledge by each professional on the team. The multi-disciplinary team should provide the patient and family members with updated information about the disease when available.

Surveillance and Management of Lynch Syndrome

A. Surveillance guidelines

Patients with Lynch syndrome are at an increased risk of CRC as well as extracolonic malignancies at a young age. Therefore, appropriate surveillance programs are of paramount importance for the prevention, early detection, and effective management of CRC and other malignancies. The aim of this section is to describe the current literature and provide evidence-based recommendations for surveillance strategies for Lynch syndrome. Many recommendations in this review are based on the US Multi-Society Task Force (USMSTF), American College of Gastroenterology (ACG), Mallorca group, European Society for Medical Oncology (ESMO), and NCCN guidelines. Table 2 summarizes the current recommendations for the surveillance of Lynch syndrome.

B. Colorectal cancer

CRCs associated with Lynch syndrome have distinctive features such as a younger age at presentation, predominance in the right colon, flat rather than polyoid precursor adenomas, and rapid progression from adenoma to cancer (estimated progression of 35 months compared to 10-15 years for sporadic cancers in the average risk population). Regular colonoscopy is the only surveillance protocol demonstrated to be effective. A prospective observational study reported that colonoscopy surveillance resulted in a 72% decrease in mortality from CRC in Lynch syndrome. Thus, most guidelines recommend that colonoscopy should be performed at least every 2 years beginning at the age of 20-25 years for all patients with a molecular confirmative diagnosis of Lynch syndrome. In several other studies, more frequent colonoscopy surveillance with less than 2-year intervals was associated with an earlier stage of CRC at diagnosis compared with less frequent colonoscopy. Some guidelines such as those of ACG and USMSTF suggest that annual colonoscopy should be considered for the surveillance of MMR germline mutation carriers, as several previous studies demonstrated CRC development between 1-2 years in this population. The incidence of CRC varies according to the target mutation of MMR genes in Lynch syndrome. The lifetime risk of CRC in MLH1- and MSH2-mutation carriers ranges from 22% to 74%, whereas a lower CRC risk has been found in women that are MSH6- (but not in men, 30% vs. 69%) or PMS2-
mutation carriers (15%-20%). Therefore, a more active 1-2 year surveillance interval can be recommended in patients with MLH1 and MSH2 mutations at an earlier age, and surveillance may begin at the age of 25-30 years in those with MSH6 and PMS2 mutations. The USMSTF guidelines proposed beginning colonoscopy screening at the age of 30 years in MSH6-mutation carriers and 35 years in PMS2-mutation carriers, unless an early onset cancer exists in a given family. Colonoscopy may also begin 2-5 years before the youngest age at diagnosis of CRC in an affected family member if diagnosed before the age of 25 years.

If CRC and/or premalignant polyps that cannot be controlled by endoscopic procedures are detected during surveillance colonoscopy, subtotal colectomy with ileorectal anastomosis is the preferred treatment regardless of the patient age according to the ACG, USMSTF, and NCCN guidelines. The reason for subtotal colectomy is the high rate of metachronous CRC after segmental resection of the initial CRC in patients with Lynch syndrome (16%-19% at 10 years; 41%-47% at 20 years). However, the post-colectomy overall survival is similar between patients with subtotal colectomy and those with segmental colon resection followed by intensive colonoscopy surveillance. Therefore, the most appropriate type of CRC surgery in patients with Lynch syndrome remains unclear, although subtotal colectomy is the preferred surgery. Particularly, less extensive surgery can be considered in patients older than 60-65 years.

C. Endometrial and ovarian cancer

Endometrial cancer is the second most common cancer that develops in Lynch syndrome. The cumulative lifetime risk of this cancer is approximately 15%-71% in Lynch syndrome patients and it develops earlier than sporadic endometrial cancer. Ovarian cancer also shows an increased incidence, with the cumulative lifetime risk ranging from 4% to 20% and the average age of emergence of 40-50 years in women with Lynch syndrome. The risk of developing ovarian cancer is approximately 9% in MLH1- and MSH2-mutation carriers, with the lowest risk observed in MSH6-mutation carriers.

There is currently insufficient evidence to support surveil-
lance protocols for endometrial and ovarian cancers in Lynch syndrome. Few studies of surveillance for endometrial cancer in Lynch syndrome have been conducted. The screening methods used in these studies varied from transvaginal or transabdominal ultrasound alone to a combination of transvaginal ultrasound and endometrial biopsy. The surveillance intervals also varied for 1 to 3 years. Despite the lack of good evidence, several annual surveillance modalities have been proposed by many professional societies because of concerns regarding the cumulative risk of endometrial and ovarian cancers. The suggested surveillance modalities include gynecological exams, transvaginal ultrasound, endometrial sampling, and CA-125 analysis starting at the age of 30-35 years.

Most current guidelines suggest that prophylactic hysterectomy with bilateral salpingo-oophorectomy is an option in women with Lynch syndrome who have completed child-bearing and are approximately 40 years of age. A cost-effectiveness study comparing gynecological surveillance and prophylactic gynecological surgery in women of childbearing age with Lynch syndrome showed that prophylactic surgery was less costly compared to surveillance. Another retrospective study of women with Lynch syndrome showed that women undergoing hysterectomy with or without bilateral salpingo-oophorectomy did not develop endometrial and ovarian cancers compared to matched women who did not undergo these surgeries. However, the morbidity of surgery and risk of menopausal symptoms should be fully considered in the decision-making. The advantages and disadvantages of all prophylactic surgeries must be discussed with the patients.

**D. Cancer in parts of the gastrointestinal tract other than the colorectum**

The cumulative lifetime risk of gastric cancer in patients with Lynch syndrome ranges from 0.2% to 13%. In Eastern Asia, where approximately half of all new cases of gastric cancer worldwide occur, the risk of gastric cancer in Lynch syndrome is much higher compared to that in North America and Western Europe. How to cluster gastric cancer in families with Lynch syndrome remains unclear. Additionally, current studies regarding the efficacy of surveillance for gastric cancers in Lynch syndrome are insufficient. Therefore, current guidelines suggest different recommendations for endoscopic surveillance of gastric cancer. The guidelines of the NCCN, USMSTF, and ESMO recommend that screening for gastric cancer should be considered in individuals at risk of or affected by Lynch syndrome by esophagogastroduodenoscopy starting at the age of 30-35 years, with surveillance every 2-3 years considered based on individual risk factors. In comparison, the Mallorca group does not recommend ongoing surveillance for this cancer. Despite different opinions on gastric cancer surveil-

The lifetime risk of small bowel cancer in Lynch syndrome is approximately 0.4%-12%. The major sites of small bowel cancers in Lynch syndrome are the duodenum and the ileum. Most current guidelines do not recommend routine surveillance for small bowel cancer except for the NCCN guidelines, which suggest that capsule endoscopy can be considered starting at the age of 30-35 years and every 2-3 years.

**E. Other extracolonic cancers**

The lifetime risk of urinary tract cancer, including ureter, renal pelvis, and bladder cancers, in Lynch syndrome patients is approximately 0.2%-25%. Screening for urinary tract cancer by urinalysis and urine cytology is ineffective in the general population due to the low sensitivity and high false-positive results of these tests. Thus, the Mallorca group does not recommend routine screening for urinary tract cancers in Lynch syndrome. However, the USMSTF consensus suggests that annual urinalysis should be considered for individuals at risk for or affected by Lynch syndrome starting at the age of 30-35 years because urinalysis is a non-invasive, easily accessible, and inexpensive screening method.

The lifetime risk of pancreatic cancer in Lynch syndrome is also increased (~4% by the age of 70 years). Most current guidelines do not recommend surveillance for pancreatic cancer in Lynch syndrome. However, an international expert consensus panel recommended magnetic resonance imaging or endoscopic ultrasonography for the surveillance of pancreatic cancers in Lynch syndrome-associated gene-mutation carriers who have at least one first-degree relative with pancreatic cancer.

Few studies have examined the risk of several other malignancies associated with Lynch syndrome, including prostate, breast, skin, and central nervous system cancers. There are also no standard guidelines concerning the surveillance of these extracolonic cancers. Routine surveillance of prostate and breast cancers is not recommended above the level of the general population.

**Conclusion**

Lynch syndrome is the most common hereditary CRC
syndrome with an autosomal dominant inheritance pattern. This syndrome is characterized by early onset CRC and other extracolonic malignancies. Great advances in molecular technologies, including more accurate, efficient genome sequencing such as NGS multi-gene panel testing, have increased the understanding of the complex pathogenesis of Lynch syndrome. Because of the complicated nature of this disease, a multi-disciplinary team approach is critically important for successfully managing Lynch syndrome. As an important process in the multi-disciplinary approach, professional genetic counseling is mandatory. Detailed information regarding genetic testing, including both the advantages and limitations of the test, should be provided. Comprehensive family counseling is also important. Proper discussion of the patient’s career and family plans should be also conducted. Regular surveillance for CRC and other malignancies is pivotal for the appropriate management of Lynch syndrome, although the evidence used for the surveillance recommendations is not sufficient. Further international studies are needed to investigate the benefits of surveillance strategies in patients with Lynch syndrome to provide evidence-based surveillance guidelines.

Conflicts of Interest
There are no conflicts of interest.

References
1. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med. 2003 Mar; 348(10): 919-32.
2. Sinicrope FA. Lynch syndrome-associated colorectal cancer. N Engl J Med. 2018 Aug; 379(8): 764-73.
3. Burt RW, DiSario JA, Cannon-Albright L. Genetics of colon cancer: impact of inheritance on colon cancer risk. Annu Rev Med. 1995 Feb; 46: 371-9.
4. Lynch HT, Lynch PM, Lanspa SJ, et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet. 2009 Jul; 76(1): 1-18.
5. Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med. 1998 May; 338(21): 1481-7.
6. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med. 2005 May; 352(18): 1851-60.
7. Lynch HT, Snyder CL, Shaw TG, et al. Milestones of Lynch syndrome: 1895-2015. Nat Rev Cancer. 2015 Mar; 15(3): 181-94.
8. Vasen HF, Mecklin JP, Khan PM, et al. The international collaborative group on hereditary non-polyposis colorectal cancer (ICG-HNPCC). Dis Colon Rectum. 1991 May; 34(5): 424-5.
9. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPPC, Lynch syndrome) proposed by the international collaborative group on HNPCC. Gastroenterology. 1999 Jun; 116(6): 1453-6.
10. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004 Feb; 96(4): 261-8.
11. 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. 2005 Apr; 293(16): 1986-94.
12. Rubenstein JH, Enns R, Heidelberg J, et al. American gastroenterological association institute guideline on the diagnosis and management of Lynch syndrome. Gastroenterology. 2015 Sep; 149(3): 777-82; quiz e16-7.
13. Giardiello FM, Allen JJ, Axibald JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US multi-society task force on colorectal cancer. Am J Gastroenterol. 2014 Aug; 109(8): 1159-79.
14. Julie C, Tresalet C, Brouquet A, et al. Identification in daily practice of patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer): revised Bethesda guidelines-based approach versus molecular screening. Am J Gastroenterol. 2008 Nov; 103(11): 2825-35; quiz 36.
15. Perez-Carbonell L, Ruiz-Ponte C, Guarinos C, et al. Comparison between universal molecular screening for Lynch syndrome and revised Bethesda guidelines in a large population-based cohort of patients with colorectal cancer. Gut. 2012 Jun; 61(6): 865-72.
16. Provenzale D, Gupta S, Ahnen DJ, et al. Genetic/familial high-risk assessment: colorectal version 1.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2016 Aug; 14(8): 1010-30.
17. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012 Oct; 308(15): 1555-65.
18. Tafe LJ. Targeted next-generation sequencing for hereditary cancer syndromes: a focus on Lynch syndrome and associated endometrial cancer. J Mol Diagn. 2015 Sep; 17(5): 472-82.
19. Heald B, Rybicki L, Clements D, et al. Assessment of clinical workload for general and specialty genetic counsellors at an academic medical center: a tool for evaluating genetic counselling practices. NPJ Genom Med. 2016 May; 1: 16010.
20. Hampel H. Genetic counseling and cascade genetic testing in Lynch syndrome. Fam Cancer. 2016 Jul; 15(3): 423-7.
21. Loikema MP, Gadella-van Hooijdonk CG, Bredenoord AL, et al. Ethical, legal, and counseling challenges surrounding the return of genetic results in oncology. J Clin Oncol. 2013 May; 31(15): 1842-8.
22. Zhen JT, Syed J, Nguyen KA, et al. Genetic testing for hereditary prostate cancer: current status and limitations. Cancer. 2018 Aug; 124(15): 3105-17.
23. Green RC, Parfrey PS, Woods MO, et al. Prediction of Lynch syndrome in consecutive patients with colorectal cancer. J Natl Cancer Inst. 2009 Mar; 101(5): 331-40.
24. Kastrinos F, Steyerberg EW, Mercado R, et al. The PREMM (1,2,6) model predicts risk of MLH1, MSH2, and MSH6 germline mutations based on cancer history. Gastroenterology. 2011 Jan; 140(1): 73-81.
25. Weissman SM, Bellcross C, Bittner CC, et al. Genetic counseling considerations in the evaluation of families for Lynch syndrome—a review. J Genet Couns. 2011 Feb; 20(1): 5-19.
26. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013 Jul; 15(7): 565-74.
27. Richards CS, Bale S, Bellissimo DB, et al. ACMG recommendations for standards for interpretation and reporting of sequence variations: revisions 2007. Genet Med. 2008 Apr; 10(4): 294-300.
28. Egalite N, Groisman IJ, Godard B. Genetic counseling practice in next generation sequencing research: implications for the ethical oversight of the informed consent process. J Genet Couns. 2014 Aug; 23(4): 661-70.
29. Luthra R, Chen H, Roy-Chowdhuri S, et al. Next-generation sequencing in clinical molecular diagnostics of cancer: advantages and challenges. Cancers (Basel). 2015 Oct; 7(4): 2023-36.
30. Machini K, Douglas J, Braxton A, et al. Genetic counselors’ views and experiences with the clinical integration of genome sequencing. J Genet Couns. 2014 Aug; 23(4): 496-505.
31. Gallego CJ, Shirts BH, Bennette CS, et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: a cost-effectiveness analysis. J Clin Oncol. 2015 Jun; 33(18): 2084-91.
32. Lorans M, Dow E, Macrae FA, et al. Update on hereditary colorectal cancer: Improving the clinical utility of multigene panel testing. Clin Colorectal Cancer. 2018 Jun; 17(2): e293-305.
33. Yurgelun MB, Allen B, Kaldate RR, et al. Identification of a variety of mutations in cancer predisposition genes in patients with suspected Lynch syndrome. Gastroenterology. 2015 Sep; 149(3): 604-13 e20.
34. Leenen CH, Heijer M, van der Meer C, et al. Genetic testing for Lynch syndrome: family communication and motivation. Fam Cancer. 2016 Jan; 15(1): 63-73.
35. Dewanwala A, Chittenden A, Rosenblatt M, et al. Attitudes toward childbearing and prenatal testing in individuals undergoing genetic testing for Lynch syndrome. Fam Cancer. 2011 Sep; 10(3): 549-56.
36. Clancy T. A clinical perspective on ethical arguments around pre-natal diagnosis and preimplantation genetic diagnosis for later onset inherited cancer predispositions. Fam Cancer. 2010 Mar; 9(1): 9-14.
37. Vasan HF, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPPC): recommendations by a group of European experts. Gut. 2013 Jun; 62(6): 812-23.
38. Palter VN, Baker NA, Rabeneck L, et al. A framework to build capacity for a reflex-testing program for Lynch syndrome. Genet Med [Internet]. 2018 Oct 22 [cited 2019 Jan 14]. Available from: https://dx.doi.org/10.1038/s41436-018-0342-8
39. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015 Feb; 110(2): 223-62; quiz 63.
40. Balmana J, Balague F, Cervantes A, et al. Familial risk-colorectal cancer: ESMO clinical practice guidelines. Ann Oncol. 2013 Oct; 24(Suppl 6): vi73-80.
41. Kanth P, Grimmett J, Champine M, et al. Hereditary colorectal polyposis and cancer syndromes: a primer on diagnosis and management. Am J Gastroenterol. 2017 Oct; 112(10): 1509-25.
42. Jass JR, Stewart SM, Stewart J, et al. Hereditary non-polyposis colorectal cancer—morphologies, genes and mutations. Mutat Res. 1994 Oct; 310(1); 125-33.
43. Edelstein DL, Axilbund J, Baxter M, et al. Rapid development of colorectal neoplasia in patients with Lynch syndrome. Clin Gastroenterol Hepatol. 2011 Apr; 9(4): 340-3.
44. Dove-Edwin I, Sasieni P, Adams J, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ. 2005 Nov; 331(7524): 1047.
45. Vasan HF, Abdirahman M, Brohet R, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. Gastroenterology. 2010 Jun; 138(7): 2300-6.
46. Engel C, Rahner N, Schulmann K, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. Clin Gastroenterol Hepatol. 2010 Feb; 8 (2): 174-82.
47. Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line MFS2 mutations. Gastroenterology, 2008 Aug; 135(2): 419-28.
48. Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst. 2010 Feb; 102(3): 193-201.
49. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011 Jun; 305(22): 2304-10.
50. 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. 2002 Dec; 45 (12): 1588-94.
51. 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 Jul; 60(7): 950-7.
52. Win AK, Parry S, Parry B, et al. Risk of metachronous colon cancer following surgery for rectal cancer in mismatch repair gene mutation carriers. Ann Surg Oncol. 2013 Jun; 20(6): 1829-36.
53. Kim TJ, Kim ER, Hong SN, et al. Survival outcome and risk of metachronous colorectal cancer after surgery in Lynch syndrome. Ann Surg Oncol. 2017 Apr; 24(4): 1085-92.
54. Barrow E, Robinson L, Alduaj W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. Clin Genet. 2009 Feb; 75(2): 141-9.
55. Watson P, Vasan HFA, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer. 2008 Jul; 123(2): 444-9.
56. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand. 2011 May; 90(5): 437-44.
57. 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. 2002 Mar; 94(6): 1708-12.
58. Renkonen-Sinisalo L, Butzow R, Leminen A, et al. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer. 2007 Feb; 120(4): 821-4.
59. Gerrritzen LH, Hoogerbrugge N, Oei AL, et al. Improvement of endometrial biopsy over transvaginal ultrasound alone for endometrial surveillance in women with Lynch syndrome. Fam Cancer. 2009 Dec; 8(4): 391-7.
60. Yang KY, Caughey AB, Little SE, et al. A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPPC) Families. Fam Cancer. 2011 Sep; 10(3): 535-43.
61. 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 Jan; 354(3): 261-9.

62. Capelle LG, Van Grieken NC, Lingsma HF, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology. 2010 Feb; 138(2): 487-92.

63. Schulmann K, Brasch FE, Kunstmann E, et al. HNPPC-associated small bowel cancer: clinical and molecular characteristics. Gastroenterology. 2005 Mar; 128(3): 590-9.

64. Haanstra JF, Al-Toma A, Dekker E, et al. Prevalence of small-bowel neoplasia in Lynch syndrome assessed by video capsule endoscopy. Gut. 2015 Oct; 64(10): 1578-83.

65. Saurin JC, Filleul F, Soussan EB, et al. Small-bowel capsule endoscopy diagnoses early and advanced neoplasms in asymptomatic patients with Lynch syndrome. Endoscopy. 2010 Dec; 42(12): 1057-62.

66. Myrhøj T, Andersen MB, Bernstein I. Screening for urinary tract cancer with urine cytology in Lynch syndrome and familial colorectal cancer. Fam Cancer. 2008 Dec; 7(4): 303-7.

67. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA. 2009 Oct; 302(16): 1790-5.

68. Canto MI, Harinck F, Hruban RH, et al. International cancer of the pancreas screening (CAPS) consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013 Mar; 62(3): 339-47.