Laura Valle
Stephen B. Gruber
Gabriel Capellá *Editors*

Hereditary Colorectal Cancer

Genetic Basis and Clinical Implications

Springer

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Contents

Part I Genetic Causes and Associated Phenotypes: Hereditary Nonpolyposis CRC

1 Lynch Syndrome 3
Elena M. Stoffel, Matthew B. Yurgelun, and C. Richard Boland

2 The Molecular Basis of Lynch-like Syndrome 21
Gardenia Vargas-Parra, Matilde Navarro, Marta Pineda, and Gabriel Capellá

3 Constitutional Mismatch Repair Deficiency 43
Chrystelle Colas, Laurence Brugières, and Katharina Wimmer

4 Mismatch Repair-Proficient Hereditary Nonpolyposis Colorectal Cancer 55
Laura Valle

5 Genetic and Environmental Modifiers of Cancer Risk in Lynch Syndrome 67
Aung K. Win and Rodney J. Scott

Part II Genetic Causes and Associated Phenotypes: Gastrointestinal Polyposis Syndromes

6 Adenomatous Polyposis Syndromes: Introduction 93
Stefan Aretz

7 Familial Adenomatous Polyposis or APC-Associated Polyposis 99
Maartje Nielsen and Stephan Aretz

8 Adenomatous Polyposis Syndromes: Polymerase Proofreading-Associated Polyposis 113
Claire Palles, Andrew Latchford, and Laura Valle

9 Adenomatous Polyposis Syndromes: MUTYH-Associated Polyposis 135
Maartje Nielsen and Stephan Aretz

10 Adenomatous Polyposis Syndromes: NTHL1-Associated Polyposis / Tumor Syndrome 149
Maartje Nielsen and Stephan Aretz

11 Adenomatous Polyposis Syndromes: Germline Biallelic Inactivation of Mismatch Repair Genes 155
Stefan Aretz and Maartje Nielsen

12 Adenomatous Polyposis Syndromes: Unexplained Colorectal Adenomatous Polyposis 161
Stefan Aretz and Maartje Nielsen

13 Hamartomatous Polyposis Syndromes 165
Joanne Ngeow, Eliza Courtney, Kiat Hon Lim, and Charis Eng

14 Hereditary Mixed Polyposis Syndrome 185
Huw Thomas and Ian Tomlinson

15 Serrated Polyposis Syndrome 193
Sabela Carballal, Francesc Balaguer, and Antoni Castells

Part III Genetic Diagnostics and Clinical Management

16 Genetic Testing in Hereditary Colorectal Cancer 209
Conxi Lázaro, Lidia Feliubadaló, and Jesús del Valle

17 Universal Tumor Screening for Lynch Syndrome 233
Heather Hampel, Rachel Pearlman, and Deborah Cragun

18 Classification of Genetic Variants 257
Maurizio Genuardi, Elke Holinski-Feder, Andreas Laner, and Alexandra Martins

19 Prediction Models for Lynch Syndrome 281
Fay Kastrinos, Gregory Idos, and Giovanni Parmigiani

20 Surveillance Guidelines for Hereditary Colorectal Cancer Syndromes 305
Neda Stjepanovic, Leticia Moreira, Judith Balmaña, and Joan Brunet

21 Surgical Management of Hereditary Colorectal Cancer Syndromes 327
Johannes Dörner, Mahmoud Taghavi Fallahpour, and Gabriela Möslein

22 Chemoprevention in Hereditary Colorectal Cancer Syndromes 349
Reagan M. Barnett, Ester Borras, N. Jewel Samadder, and Eduardo Vilar

23 The Immune Biology of Microsatellite Unstable Cancer 367
Matthias Kloor and Magnus von Knebel Doeberitz

24 Hereditary Colorectal Cancer: Immunotherapy Approaches 385
David J. Hermel and Stephen B. Gruber

25 Medical Oncology Management of Hereditary Colorectal Cancer . . 401
Eduardo Vilar, Ramón Salazar, and Josep Tabernero

Part IV Registries and Databases

26 Databases: Intentions, Capabilities, and Limitations 417
Pål Møller, Sigve Nakken, and Eivind Hovig

27 The Colon Cancer Family Registry Cohort 427
Mark A. Jenkins, Aung K. Win, and Noralane M. Lindor

28 The Prospective Lynch Syndrome Database 461
Pål Møller, Sigve Nakken, and Eivind Hovig

29 The InSiGHT Database: An Example LOVD System 469
John Paul Plazzer, Johan den Dunnen, and Finlay Macrae

30 The International Mismatch Repair Consortium 479
Mark A. Jenkins, Jeanette C. Reece, and Aung K. Win

Index 497

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Laura Valle is a Principal Investigator of the Hereditary Cancer Program at the Catalan Institute of Oncology, IDIBELL, Barcelona (Spain). She obtained her bachelor degrees in Biology (2000) and Biochemistry (2001) from the University of Navarra (Spain) and carried out her Ph.D. thesis about hereditary colon cancer at the Spanish National Cancer Research Center (CNIO) (2006, Extraordinary Doctorate Award). Her interest in the genetic susceptibility to cancer led her to a postdoctoral stay with Dr. Albert de la Chapelle at the Comprehensive Cancer Center of the Ohio State University. In 2009, Dr. Valle joined the Hereditary Cancer Program of the Catalan Institute of Oncology to develop a research line focused on hereditary colon cancer. In 2009, she obtained the prestigious and highly competitive Ramón y Cajal contract for young researchers, and in 2016, funding from the I3 program for the stabilization of doctors (both funded by the Spanish Government). In 2012, she obtained the accreditation in human genetics and the National Award for the most outstanding young researcher in human genetics, both awarded by the Spanish Association of Human Genetics, and in 2013, a L'Oréal-UNESCO "For Women in Science – Spain" Research Award. Since 2017, she is elected member of the Executive Board of the Spanish Association of Human Genetics. Dr. Valle has dedicated her scientific career to the identification of the genetic causes of cancer predisposition and the better characterization of new hereditary colorectal cancer syndromes, which have led to her consolidation as world expert in the subject. In the last years, she has been invited lecturer to prestigious conferences in the field, such as the ones organized by the European Society of Human Genetics, the International Society of Gastrointestinal Hereditary Tumors, or the Collaborative Group of the Americas on Inherited Colorectal Cancer.

Stephen B. Gruber is a board certified medical oncologist, cancer geneticist, and epidemiologist whose research and clinical practice focuse on clinical cancer genetics and the molecular genetic and environmental contributions to colorectal cancer. Dr. Gruber earned his bachelor's degree from the University of Pennsylvania in 1984. He subsequently graduated with a Master of Public Health Degree from Yale University in 1986 and a Doctor of Philosophy in epidemiology at Yale in 1988.

Dr. Gruber graduated from the University of Pennsylvania Medical School earning his medical degree in 1992, where he also completed his internship and residency in internal medicine. He completed fellowships in medical oncology at Johns Hopkins Hospital and in clinical medical genetics at the University of Michigan. Following 14 years on the faculty at the University of Michigan, where he was the H. Marvin Pollard Professor of Medicine, he was appointed director of the USC Norris Comprehensive Cancer Center, H. Leslie and Elaine S. Hoffman Cancer Research Chair, and Professor of Medicine and Professor of Preventive Medicine at the Keck School of Medicine of the University of Southern California. In 2017 Dr. Gruber was named the Jane & Kris Popovich Chair in Cancer Research. Dr. Gruber is an elected member of the American Society of Clinical Investigation and was honored with the Lifetime Achievement Award, Collaborative Group of the Americas on Inherited Colorectal Cancer.

Gabriel Capellá obtained his MD degree from the University of Barcelona in 1983. He trained as a general and digestive surgeon at the Hospital de Sant Pau, Barcelona. His interest in translational cancer research led him to a postdoctoral stay with Dr. Manuel Perucho during 1989 and 1990. Back to Spain he spent 8 years at the Gastrointestinal Research Laboratory at the Hospital de Sant Pau where he focused his research on the molecular basis of pancreatic and colorectal cancer. Since 1998 he worked at the Catalan Institute of Oncology where he was director of the Translational Research Laboratory until 2011. Since 2010 he is serving as Director of the Hereditary Cancer Program. His main interest is the study of the genetic basis of gastrointestinal cancer focusing on novel technologies for the clinical management of patient at risk of developing GI cancer. He is coauthor of more than 230 publications in international peer-reviewed journals. He has served as vice-director for Research and Innovation, Health Department, Catalan Government, and he is currently the Director of the Bellvitge Biomedical Research Institute. He is cofounder of VCN Biosciences a spin-off aimed at developing new cancer therapies based on oncolytic adenoviruses. Since 2014 he is member of the Council of the International Society for Gastrointestinal Hereditary Tumors (InSiGHT).

Part I
Genetic Causes and Associated Phenotypes: Hereditary Nonpolyposis CRC

Chapter 1
Lynch Syndrome

Elena M. Stoffel, Matthew B. Yurgelun, and C. Richard Boland

Abstract Lynch syndrome is a highly penetrant hereditary cancer syndrome caused by pathogenic germline variants in DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*. Historically identified on the basis of family history of colorectal and endometrial cancers exhibiting autosomal dominant inheritance, universal screening of CRCs and endometrial cancers for features of MMR deficiency, together with cascade genetic testing in families, is at present the most effective approach for identifying individuals with Lynch syndrome. Here we review the history of Lynch syndrome, as well as the clinical and molecular investigations that have contributed to our understanding of Lynch syndrome and informed current approaches to diagnosis and clinical management.

Keywords Lynch syndrome · Genetic · Mismatch repair

1 Familial Colorectal Cancer: Polyposis or Nonpolyposis

Family history is one of the strongest determinants of colorectal cancer (CRC) risk [1], and one in three individuals diagnosed with CRC reports one or more affected relatives. The occurrence of CRC in multiple family members invokes the

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possibility of shared environmental and/or inherited risk factors, and the presence of an autosomal dominant inheritance pattern strongly suggests genetic predisposition. Also, early onset of cancer and multiple cancers in individuals raises the specter of a constitutional predisposition to cancer. In some cases, an obvious clinical phenotype such as colorectal polyposis (classically seen in familial adenomatous polyposis or FAP) can prompt the identification of individuals needing genetic evaluation. However, most cases of familial CRC lack a distinctive adenomatous polyposis phenotype. These families were historically designated as "hereditary nonpolyposis colorectal cancer (HNPCC)" as a means of distinguishing them from FAP; however, the term HNPCC has proven problematic as these cases are now known to comprise heterogeneous conditions associated with differences in disease spectrum and mechanisms of pathogenesis.

Lynch syndrome is the disease caused by pathogenic germline variants in DNA mismatch repair (MMR) genes and is the most common of the hereditary colorectal cancer syndromes. Although the Amsterdam criteria (≥3 individuals with CRC, involving ≥2 generations, with ≥1 diagnosed at age < 50) [2] were originally developed as a means to identify affected families, family history affords limited sensitivity and specificity for identifying individuals with Lynch syndrome. Molecular profiling of CRCs has helped elucidate relationships between germline variants and pathogenesis of these cancers. Implementation of universal screening of CRCs and endometrial cancers for features of DNA mismatch repair (MMR) deficiency, together with cascade genetic testing in families, is at present the most effective approach for identifying individuals with Lynch syndrome (Fig. 1.1) [3, 4]. Here we review the history of Lynch syndrome, as well as the clinical and molecular investigations that have contributed to our understanding of Lynch syndrome and informed current approaches to diagnosis and clinical management.

1.1 Lynch Syndrome: A History

Lynch syndrome is a highly penetrant inherited cancer predisposition syndrome caused by pathogenic germline variants in DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) and *EPCAM*. Lynch syndrome is named for Dr. Henry Lynch, whose characterization of families affected with CRC was instrumental in characterizing the broad spectrum of hereditary cancer syndromes [5]. The first known description of Lynch syndrome, however, occurred more than a century ago by Dr. Aldred Scott Warthin, Chairman of Pathology at the University of Michigan. In his report of a family disproportionately affected with endometrial, gastric, and intestinal cancers occurring at early ages, affecting individuals in multiple generations, Warthin hypothesized that the cancers resulted from inherited susceptibility [6]. Decades later, Lynch recontacted descendants from the family described by Warthin (known as Family G) and recruited dozens of additional families with

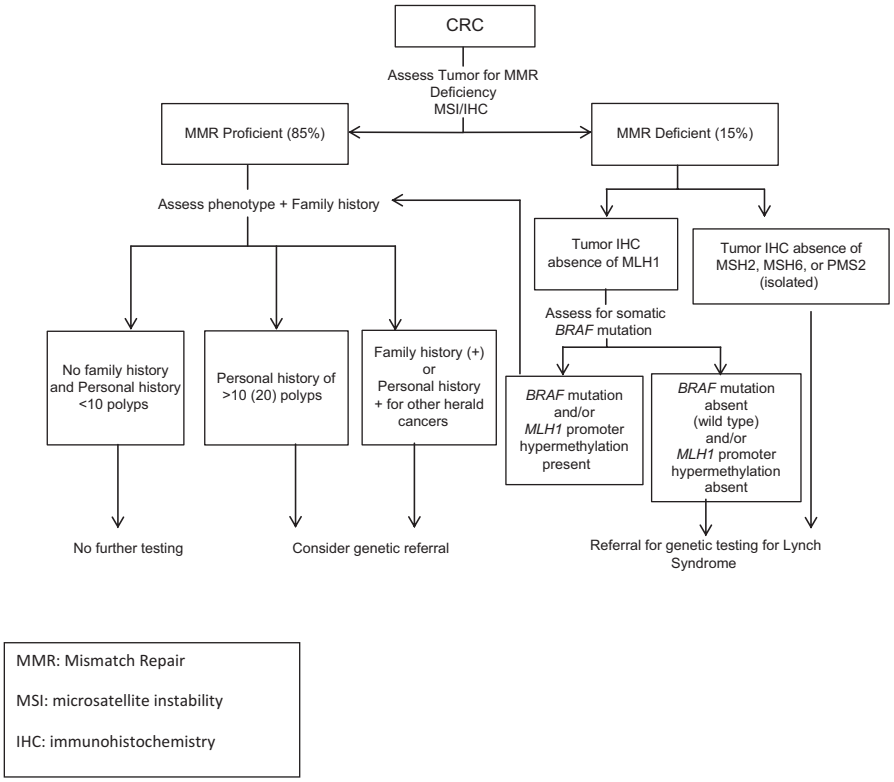

Fig. 1.1 Algorithm for assessing colorectal cancer patients for hereditary cancer syndromes

nonpolyposis colorectal cancer cases affecting multiple generations (Fig. 1.2). Collection of data and biospecimens from families identified in the United States and Europe made it possible to quantify increased incidence of not only colorectal but also gastric and endometrial cancers in these kindreds. Eventually, family history criteria (≥3 individuals with CRC, involving ≥2 generations, with ≥1 diagnosed at age < 50) were established as a means for identifying families to be recruited for study to ascertain biological basis of these familial cancers [7]. Examination of DNA from CRC tumors demonstrated an unusually large number of mutations in repetitive DNA sequences known as microsatellites, termed microsatellite instability-high (MSI-H), suggesting a novel mechanism of pathogenesis that differentiated these tumors from sporadic CRCs [8, 9]. Linkage analyses performed using germline DNA samples from affected families led investigators to chromosomes 2p and 3p, where germline variants in *MSH2* [10, 11] and *MLH1*

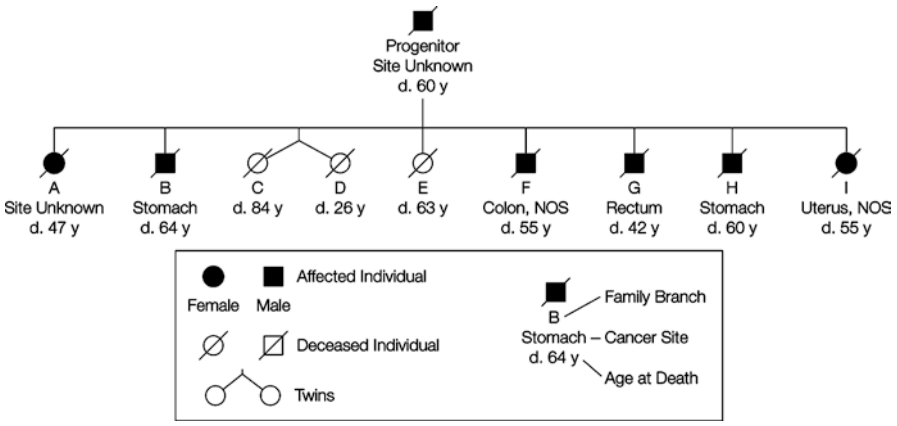

Fig. 1.2 Pedigree of Family G generations I and II (Fig. 2 reproduced from Douglas et al. [87])

[12–15], respectively, were identified. Shortly thereafter, germline variants in *PMS2* [16] and *MSH6* [17] were also discovered; later, deletions of the termination codon in *EPCAM* (also known as *TACSTD1*) associated with promoter methylation and epigenetic silencing of *MSH2*, which is immediately downstream of *EPCAM*, were implicated in a subset of affected families [18]. Today, clinical sequencing identifies pathogenic germline variants in *MLH1*, *MSH2*, *MSH6*, *PMS2*, *or EPCAM* in up to 90% of families with autosomal dominant MSI-H CRCs fulfilling clinical diagnostic criteria for Lynch syndrome.

1.2 Clinical Features and Epidemiology

Defining the biological basis of Lynch syndrome made it possible to identify affected families not only by clinical history but also by tumor molecular phenotype. Approximately 15% of all CRCs exhibit MSI-H phenotypes [19], with Lynch syndrome consistently implicated in 2.8–3.1% of all CRCs (roughly 20% of MSI-H CRCs) [20, 21], establishing it as the most common of the known hereditary colorectal cancer syndromes. Pathogenic variants in *MLH1* and *MSH2* account for the majority of germline pathogenic variants identified in Lynch syndrome families diagnosed in clinical settings. However germline variants in *MSH6* and *PMS2* are estimated to have higher prevalences in the general population, although lower disease penetrance and older ages at CRC diagnosis allow many *MSH6* and *PMS2* families to escape clinical diagnosis [22]. In a

recent population-based study from Iceland, pathogenic germline DNA MMR variants were discovered in 0.442%, or 1 in 225 unselected individuals [23], with founder mutations in *MSH6* and *PMS2* accounting for >90%. Other recent population-based data from the United States, Canada, and Australia have estimated a 1 in 279 combined population prevalence of germline MMR mutations with *MSH6* and *PMS2* variants being far more common than those in *MLH1* and *MSH2* [24].

Although Lynch syndrome is best known as a hereditary colorectal cancer syndrome, pathogenic germline variants in DNA MMR genes are also associated with increased risks for other extracolonic cancers, particularly endometrial adenocarcinoma. Variability in age of onset, as well as the diversity of cancer types, has led to a better understanding of the disease spectrum. While some of the variability in cancer risks may be attributed to genotype (Table 1.1), the range of clinical phenotypes, along with differences in penetrance and expressivity among relatives harboring the same germline variant, suggests additional genetic and environmental factors may act as modifiers of cancer risk (see Chap. 5).

1.2.1 Colorectal Cancer

CRC is the predominant cancer in most Lynch syndrome families, and the diagnosis of a MMR-deficient (MMRd) tumor is often the "red flag" that prompts genetic evaluation. Approximately 15% of CRCs exhibit MMRd/MSI-H phenotypes [19], and while most are sporadic cancers (developing through the CIMP-epigenetic serrated neoplastic pathway), 3% arise in the setting of germline mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, *or EPCAM*. The protein products of *MLH1*, *MSH2*, *MSH6*, and *PMS2* make up heterodimer complexes that have a critical role in DNA repair. The complex formed

Table 1.1 Estimated lifetime cancer risks (%) in Lynch syndrome, by gene [4, 26, 29, 30, 32–42]

Cancer type	Overall (%)	*MLH1* (%)	*MSH2* (%)	*MSH6* (%)	*PMS2* (%)	*EPCAM* (%)
Colorectal	10–75	25–70	30–60	10–22	10–20	70
Endometrial	14–71	14–54	20–52	34–71	15	12
Ovarian	1–20	4–15	5–17	1–15		
Gastric	1–13	4–11	2–14	1–10		
Small bowel	1–12	4–10	1–8	0–3		
Pancreatic	1–6					
Prostate	4–10					
Urinary tract	2–15	1–10	2–15	1–15		

between MSH2-MSH6 (MutSα) recognizes and binds to single nucleotide base pair mismatches, and small insertion-deletion abnormalities, after which a second heterodimer complex between MLH1-PMS2 (MutLα) binds to MutSα, and recruits exonuclease-1, triggering "long-patch excision" of newly synthesized DNA in the vicinity of the mismatched DNA. The DNA repair proteins quickly release from the DNA permitting resynthesis of the excised patch, usually correctly. Loss of DNA MMR activity results in the rapid accumulation of mutations and a hypermutated genome and eventually mutations in genes that are drivers of carcinogenesis [25]. Lynch-associated CRCs can be distinguished from sporadic MSI-H CRCs in that Lynch-associated tumors almost always lack the somatic *BRAF* mutations and *MLH1* promoter hypermethylation, which are hallmarks of serrated pathway neoplasms. Screening CRC tumors for MMRd, by PCR-based microsatellite analysis or immunohistochemistry (IHC) staining demonstrating loss of expression of MLH1, MSH2, MSH6, or PMS2 proteins, has been advocated as the most effective (and cost-effective) strategy for identifying individuals with Lynch syndrome [3, 4] (see Chap. 17).

Cumulative lifetime risk estimates for CRC in individuals with Lynch syndrome range from 10% to 75% [4, 26–42]. The variability may be explained in part by genotype, with risk for CRC highest for carriers of pathogenic germline variants in *MLH1* and *MSH2*, who also tend to be diagnosed at younger ages. Risk for CRC appears to be somewhat lower for carriers of pathogenic variants in *MSH6* and perhaps much lower for *PMS2* [33, 34, 43, 44]; however it is important to note that there remains significant variability and *MSH6*, *PMS2*, and *EPCAM* mutation carriers are underrepresented in published Lynch syndrome registries, resulting in lack of precision in cancer risk estimates. Consequently, it has been recommended that all Lynch syndrome mutation carriers adhere to intensive cancer surveillance recommendations, regardless of genotype [4, 32, 45].

Lynch-associated CRCs behave differently from sporadic CRCs, which has important implications for clinical management. With respect to oncologic treatment, the histopathologic and molecular characteristics of Lynch-associated CRCs are associated with differences in prognosis and therapeutic responses, in part because the DNA MMR system is involved in triggering cell death after chemotherapy-induced DNA damage, which is missing in CRCs with MSI (see Chaps. 23–25). Tumors arising as a result of defective mismatch repair are also hypermutated and generate neoantigenic peptides which can incite a brisk host immune response. Histopathologic examination of Lynch-associated CRCs often reveals abundant tumor infiltrating lymphocytes. Prognosis in patients with MMRd CRCs tends to be better, stage for stage, compared to MMR-proficient cancers [46]. With regard to oncologic therapies, patients with early-stage MMRd CRCs do not appear to benefit from adjuvant 5-FU monotherapy [47, 48]; however in some patients with metastatic MMRd CRCs, treatment with immune checkpoint inhibitors has been associated with excellent response [49, 50]. Clinical trials with other

novel agents are underway and promise to provide additional insights for treatment of Lynch-associated CRC.

The diagnosis of Lynch syndrome also has implications for surgical management of patients with colorectal neoplasia (see Chap. 21). As metachronous primary CRC tumors are common in Lynch syndrome [51, 52], more extensive colonic resections (e.g., subtotal colectomy) should be considered for patients with colorectal neoplasia who require surgery [4, 32, 45].

With regard to CRC prevention, early and frequent colonoscopic surveillance has been shown to be effective in reducing CRC incidence and mortality [53–55] justifying recommendations for colonoscopy every 1–2 years beginning at age 20–25 [4, 32, 45]. However it is important to note that colonoscopy may not afford perfect protection, as interval CRCs have been reported in patients compliant with intensive surveillance [44, 54–57]. While rapid progression and flat morphology of Lynch-associated polyps likely play a role in development of these interval cancers, reports of hypermutated aberrant crypt foci raise the question of whether some Lynch-associated CRCs arise from flat dysplasia rather than from discrete polyps [58]. Enhanced endoscopic technologies (e.g., chromoendoscopy, narrow band imaging/NBI) may help improve visualization of these lesions [59], and additional strategies for early detection are being investigated.

Chemoprevention of Lynch-associated neoplasia remains an area of active research. The Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) trial randomized subjects with Lynch syndrome to aspirin at a dose of 600 mg daily vs placebo and found approximately 60% reduction in incident CRCs and endometrial cancers in subjects randomized to aspirin, although the reductions were not detectable until a decade after the initial aspirin exposure [60]. Additional studies are currently underway to determine the optimum dose of aspirin and assess whether other nonsteroidal anti-inflammatory drugs may offer similar benefits (see Chap. 22).

1.2.2 Endometrial Cancer

Endometrial adenocarcinoma is the second most common cancer reported in families with Lynch syndrome. Lynch syndrome is implicated in approximately 3% of endometrial cancers, providing justification for screening all endometrial cancers diagnosed at age < 70 for MMRd phenotypes [32, 61, 62]. Approximately 20–30% of all endometrial cancers exhibit MMRd, and while most of these are sporadic tumors associated with somatic hypermethylation of the *MLH1* promoter, patients with MMRd endometrial cancers that do not exhibit *MLH1* promoter hypermethylation warrant referral for genetic evaluation for germline mutations in the MMR genes [62]. The cumulative lifetime risk for endometrial cancer in women with Lynch syndrome ranges from 14% to 71% [26–30, 34,

63]. While screening women for gynecologic cancers annually beginning at age 30–35 years using endometrial biopsy and/or transvaginal ultrasound has been endorsed by Lynch syndrome guidelines [4, 32, 45], prophylactic hysterectomy is the only intervention proven to be effective in reducing gynecologic cancer incidence [64] and should be discussed with women with Lynch syndrome who have completed childbearing.

1.2.3 Other Lynch Syndrome-Associated Cancers

Tumors other than CRC and endometrial cancer are overrepresented in families with Lynch syndrome (Table 1.1) [29, 30, 36, 65, 66]. Despite significant variability in disease penetrance and expressivity, risks for extracolonic tumors appear to be highest among *MSH2* mutation carriers [28, 35, 67]. While gastric cancers were among the most prominent tumors affecting Family G (when reported in 1913) and remain common in Lynch syndrome families in endemic areas such as Japan and Korea, the incidence of gastric cancer in families living in North America and Europe appears to be declining, with lifetime risk estimated between 5% and 13% [37]. Surveillance with upper endoscopy, with treatment for *Helicobacter pylori* infection if present, is recommended for MMR mutation carriers. With regard to ovarian cancer, lifetime risks range from 1% to 20%, and the lack of an effective screening test justifies consideration for prophylactic surgical oophorectomy at the time of hysterectomy. Although the absolute risk of cutaneous sebaceous neoplasms is small and likely varies widely family to family, routine dermatologic screening is recommended for Lynch syndrome carriers. Risks for small bowel, brain, urinary tract, hepatobiliary, and prostate cancers are also increased in Lynch syndrome; however, the benefit of surveillance for these cancers remains unproven and is not routinely recommended. Studies demonstrating a fourfold higher risk for pancreatic cancer in Lynch syndrome families compared with the general population [39] have led some to recommend MRI- and/or endoscopic ultrasound-based pancreatic cancer screening for MMR mutation carriers with a first degree relative affected with pancreatic cancer [68].

1.3 Approaches to Identifying Individuals at Risk for Lynch Syndrome

Strategies for identifying carriers of pathogenic germline variants in MMR genes include systematic assessment of family cancer history, molecular diagnostic testing of tumors, use of clinical prediction models, and germline DNA testing. While family history has historically been the cornerstone of genetic risk assessment, the variability in disease penetrance and expressivity can significantly limit its

sensitivity. Fewer than half of families with genetically confirmed Lynch syndrome have histories that meet the Amsterdam criteria. As most Lynch-associated CRCs exhibit phenotypes of DNA MMRd, the Bethesda guidelines were developed in 1997 [69] and subsequently modified and revised [70] to select which patients with CRC who should undergo MSI testing. However, studies employing screening of unselected CRC tumors for MMRd have demonstrated that algorithms employing the Bethesda guidelines miss up to one third of Lynch syndrome cases [20]. As a result, universal testing of all CRC tumors for MMRd has been advocated as the most effective approach for identification of individuals with Lynch syndrome [4, 71] (see Chap. 17).

1.3.1 Molecular Tumor Profiling

Multiple studies have employed universal testing of CRC tumors for MMRd with IHC and/or PCR-based MSI testing, demonstrating high sensitivity (77–90%) for identifying individuals with Lynch syndrome [72], surpassing that of family history-based diagnostic algorithms such as Amsterdam criteria and Bethesda guidelines [20, 73]. While the efficacy for universal testing of endometrial cancers for MMRd has been shown to be similarly effective, the sensitivity of molecular testing in other tumor types has not been extensively studied. It is important to note that tumor molecular profiling of CRCs and endometrial cancers is neither perfectly sensitive nor specific for Lynch syndrome. Some individuals with germline mutations in MMR genes (in particular *MSH6* and *PMS2*) have tumors that are MMR proficient. There are also MMRd CRCs and endometrial cancers in which the cause of the MMRd cannot be identified. While it had been assumed that MMRd tumors lacking somatic *BRAF* mutations or *MLH1* promoter methylation must harbor a germline MMR gene mutation, recent findings from comprehensive molecular profiling of these tumors suggest that as many as half of these have biallelic somatic mutations in DNA MMR genes in the tumor that are not present in the germline DNA, which has bome to be referred to as Lynch-like syndrome (see Chap. 2) [74, 75].

1.3.2 Computational Risk Models

While universal tumor molecular profiling has been proposed to be the most cost-effective strategy for identifying patients with cancer who require genetic evaluation for Lynch syndrome [76], not every patient will have a tumor available for testing. A number of computational models (e.g., MMRPro [77], PREMM1,2,6 [78], PREMM5 [79]) have been developed that incorporate data from individuals' personal and family history to calculate a predicted probability of a MMR gene mutation, with germline sequencing for MMR genes recommended for patients when there is a predicted probability ≥5%. Modeling of a

strategy screening asymptomatic young adults using PREMM1,2,6 model scores concluded this would be a cost-effective intervention for reducing morbidity and mortality related to Lynch-associated cancers [80]. The recently developed PREMM5 model, which is the only model to incorporate *PMS2* and *EPCAM* risk assessment, proposes lowering the threshold for germline sequencing to individuals with predicted probability of mutation of ≥2.5%; however the limited sensitivity of family history and/or computational models for identifying *PMS2* carriers remains a concern [79]. See Chap. 19 for detailed information on computational risk models.

1.4 Summary

While significant progress has been made over the past three decades in defining the biological basis of Lynch syndrome, there remains work to be done implementing clinical interventions to effectively diagnose and manage families affected with Lynch syndrome. The vast majority of at-risk individuals remain undiagnosed and operationalizing universal screening of CRCs and presymptomatic identification of individuals requiring intensive surveillance continue to present major challenges. Despite innovations in sequencing technologies, one in ten families with presumed Lynch syndrome undergoes germline genetic testing that yields clinical uninformative results. Sequencing of *PMS2* remains challenging due to the presence of 20 pseudogenes; series of *Alu* repeats in *MSH2* make the 5′ end of the gene and promoter region susceptible to large deletions that are difficult to detect. Germline variants of uncertain significance (VUS) are common in patients of non-European ancestry, and accurate reclassification of these has been challenging (see Chap. 29).

There are additional mechanisms that give rise to tumors with MMRd. Constitutional methylation of the *MLH1* promoter has been identified in individuals and in rare families may be caused by a single nucleotide variant near the transcriptional start site in the promoter of *MLH1* (c.-27C>A) which renders the promoter prone to methylation [81, 82]. The contributions of genetic, epigenetic, and/or environmental factors to modifying disease penetrance and expressivity both within and among families with Lynch syndrome remain to be elucidated.

Making the diagnosis of Lynch syndrome has immediate implications not only for the clinical management of cancer patients but also for care of their family members. While the importance of integrating cancer risk assessment for hereditary cancer syndromes into routine clinical care of patients (with and without cancer diagnoses) has been highlighted by many professional societies [4, 45, 62, 83–86], variability in genomic literacy among patients and providers and complexities of disease management present additional challenges. Cost-effectiveness models suggest the greatest benefit of genetic testing results from preventing cancers in the relatives of cancer patients [3]; however limited availability of genetics

expertise and the costs of genetic testing continue to present barriers to implementation.

Translating genetic test results into improved health outcomes requires interdisciplinary collaboration between oncologists, surgeons, geneticists, gastroenterologists, gynecologists, and primary care providers. Assuring that information gained through genetic testing is shared with close as well as more distant relatives, facilitating so-called cascade testing of at-risk family members, and ensuring that MMR mutation carriers comply with recommended surveillance tests will continue to be areas for intervention. Finally, even though it is becoming apparent that germline mutations in DNA MMR genes are much more common than previously thought, Lynch syndrome remains unrecognized in many patients because of variations in disease penetrance and expressivity. More data are needed to understand the contributions of modifiable risk factors and to maximize effectiveness of primary and secondary cancer prevention strategies for at-risk families.

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