

# Diagnosis and management of hereditary colorectal cancer syndromes: Lynch syndrome as a model

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Previously published at [www.cmaj.ca](http://www.cmaj.ca) on Aug. 3, 2009.

This article deals exclusively with the hereditary forms of colorectal cancer. Clinical examples of hereditary colorectal cancer syndromes abound; of these, familial adenomatous polyposis and Lynch syndrome are the most common and well known (Figure 1).<sup>1</sup> In this review, we use Lynch syndrome as an example for the diagnosis, testing of germ cells for mutations, surveillance and management of hereditary colorectal cancer.

Lynch syndrome is the most common hereditary syndrome that predisposes patients to colorectal cancer. It accounts for 2%–5% of the total burden of colorectal cancer.<sup>2</sup> The estimated number of new colorectal cancer cases in Canada in 2008 was 21 500.<sup>3</sup> Thus, Lynch syndrome accounted for as many as 1075 cases in Canada in 2008. Each patient with Lynch syndrome may represent a family in which multiple family members can be expected to develop colorectal cancer or an integral extracolonic cancer. Clearly, these families have an important impact on public health policy.

The second most common hereditary colorectal cancer syndrome is familial adenomatous polyposis, which is responsible for less than 1% of all colorectal cancer cases.<sup>4</sup> Other identified syndromes that predispose patients to colorectal cancer are even less common (Figure 1). However, we still have much to learn about the basis of “familial” colorectal cancer.

In 1966, our team described 2 large families from the mid-western United States with an apparent excess number of members with colorectal cancer that lacked multiple colonic adenomas.<sup>5</sup> This disorder involved a variety of extracolonic cancer sites and was therefore initially referred to as the “cancer family syndrome.” It was subsequently renamed hereditary non-polyposis colorectal cancer syndrome. Since the identification of mismatch repair mutations in this syndrome, it has become known as Lynch syndrome<sup>6,7</sup> (Online Mendelian Inheritance in Man database no. 120435).<sup>8</sup> The name hereditary nonpolyposis colorectal cancer syndrome is given to disorders that have similar phenotypes but that lack the specific mutations involved in Lynch syndrome (e.g., familial colorectal cancer type X).<sup>9,10</sup>

Advances in molecular diagnostics in the last 15 years have changed the landscape of Lynch syndrome. It is now quite common to identify a germline mutation in one of the mismatch repair genes. The most common mutations are those in *MLH1* and *MSH2*.<sup>4</sup> Microsatellite instability testing and immunohistochemistry are useful tools to determine

## Key points

- A number of hereditary syndromes may predispose patients to colorectal cancer.
- The most common is Lynch syndrome, followed by familial adenomatous polyposis.
- The primary care physician has a vital role in recognizing the possibility of a hereditary syndrome that predisposes patients to colorectal cancer.
- Targeted surveillance and management based on the syndrome’s natural history may reduce mortality.

whether a patient is a candidate for testing for mutations in the mismatch repair genes.<sup>4,11</sup>

Advances in molecular genetics, particularly in the identification of cancer-causing mutations in germ cells, have made it possible to establish whether patients are at high risk of hereditary cancers. In this review, we discuss some of the distinguishing features of hereditary colorectal cancer syndromes and outline the role that primary care physicians play in the detection of hereditary colorectal cancer syndromes and the care of affected patients.

## A recently identified mutation: *MYH*

The *MYH* gene plays an active role in protecting genomic integrity during transcription. Although most hereditary cancer syndromes have an autosomal dominant inheritance pattern, *MYH* mutations are autosomal recessive, which means that a mutation must occur in both alleles of the gene in order for disease to develop. The effect of a monoallelic mutation in *MYH* is unclear. There is phenotypic overlap between milder, attenuated forms of familial adenomatous polyposis and *MYH*-associated polyposis. However, *MYH*-associated polyposis typically results in a different pattern of extracolonic cancers, including breast cancer,<sup>12</sup> sebaceous adenocarcinoma and endometrial cancer.<sup>13</sup> The possibility of sebaceous adeno-

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Cite as *CMAJ* 2009. DOI:10.1503/cmaj.071574

carcinoma in this syndrome overlaps with Muir–Torre syndrome, which is a variant of Lynch syndrome.<sup>14,15</sup>

Expanded testing, screening and management criteria are being developed for *MYH*-associated polyposis. *MYH* mutation testing is indicated for patients with multiple colonic adenomas who do not have an *APC* mutation. Based on their study that included 453 patients with multiple colorectal adenomata and no *APC* mutation, Olschwang and coworkers<sup>16</sup> suggested an early screening program, beginning between ages 25 and 30, that includes endoscopy of the upper digestive tract and colorectum every 2 years.

As with any hereditary colorectal cancer syndrome, screening and management recommendations are based on the natural history of the disorder along with the results of genetic testing (Table 1, Table 2).

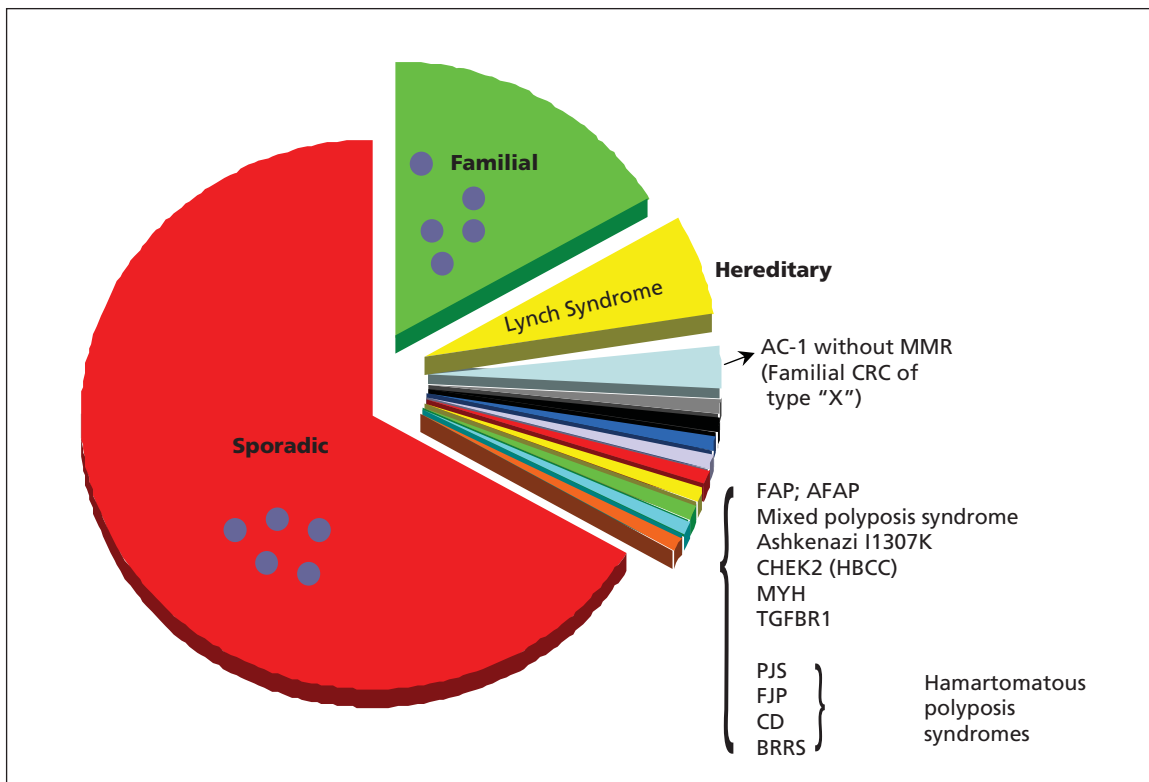
### Family history

A family history that includes most, if not all, relevant details can be collected at the time of patient intake or registration by use of a structured questionnaire that can be reviewed and addressed during the clinic visit. An alternative to a printed questionnaire is the online tool for recording family medical history provided by the United States Department of Health and Human Services ([www.hhs.gov/familyhistory/](http://www.hhs.gov/familyhistory/)) as part of the

United States Surgeon General’s Family History Initiative. The suspicion of a hereditary cancer syndrome often results from recognition of a familial pattern of disease, such as a constellation of early colorectal, genitourinary, breast and selected types of other cancers.<sup>20</sup> Ideally, the patient’s family history will include information about cancers of all anatomic sites, with approximate ages of onset, for the patient’s first-degree relatives (parents, siblings, children) and, whenever possible, second-degree relatives (maternal and paternal aunts, uncles and grandparents). Figure 2 shows the family members who should, whenever possible, be included in this modified nuclear pedigree. Older family members will have often passed the cancer risk age and, therefore, will be more genetically informative.

### Referral to a geneticist or cancer centre

Referral to a medical geneticist or a hereditary cancer centre can be made at any time during the family workup process, depending on the complexity of the clinical or genetic problem, the physician’s individual expertise and the resources available. The rates of referral for DNA testing for cancer-causing mutations are low throughout the world, even among patients with a family history of cancer. For example, Murff and colleagues<sup>22</sup> reported that, of 6 candidates at high risk for breast cancer, only 1 was referred for *BRCA* testing.



**Figure 1:** Circle graph depicting the marked genotypic and phenotypic heterogeneity in hereditary colorectal cancer syndromes. Circles indicate as yet undiscovered variants of hereditary cancers. Note: AC-1 = Amsterdam Criteria I, MMR = mismatch repair, FAP = familial adenomatous polyposis, AFAP = attenuated familial adenomatous polyposis, HBCC = hereditary breast and colorectal cancer, PJS = Peutz–Jeghers syndrome, FJP = familial juvenile polyposis, CD = Cowden disease, BRRS = Bannayan–Rauvalcaba–Riley syndrome. Modified with permission from The American Cancer Society, Inc.<sup>1</sup>

Guttmacher and colleagues<sup>23</sup> reported that only 17% of patients who would be considered as candidates for genetic testing were referred for testing. It is unfortunate that so many patients are not receiving the many benefits of molecular genetic testing. Knowledgeable primary care physicians are key to improving these numbers.

## Comprehensive family pedigree

If a hereditary cancer syndrome is suspected, a comprehensive family history for cancer can supplement a patient-reported family history. Patient-reported family histories for cancer are accurate and valuable for assessing the risk of breast cancer and colorectal cancer but are less accurate for more rare types of cancer.<sup>24</sup> Primary care physicians may wish to construct the more detailed comprehensive family history, but this is more commonly done by a genetic counsellor or a medical geneticist after referral.

The comprehensive family pedigree incorporates all of the available cancer findings in the family, including cancer of all anatomic sites with age of onset<sup>25</sup> and pathology documentation (if available) as well as pertinent noncancer phenotypic features, such as perioral pigmentation in Peutz–Jeghers syndrome, multiple colonic adenomas in familial adenomatous polyposis, a paucity of polyps in its attenuated familial adenomatous polyposis counterpart, and the presence of sebaceous adenomas, sebaceous carcinomas and multiple keratoacanthomas in Muir–Torre syndrome (a variant of Lynch syndrome).<sup>4,26</sup> Table 1

shows the characteristics of hereditary polyposis syndromes, and those of Lynch syndrome are listed in Box 1.

## Genetic testing

It is essential to determine which patients need to be tested for hereditary cancer syndromes.<sup>27</sup> We recommend that the following criteria be met before a patient is referred to a medical geneticist or a hereditary cancer centre or before genetic testing: a family history consistent with the hereditary cancer syndrome of concern; a mutation for which testing exists that has been identified as causal to the syndrome; availability of comprehensive genetic counseling,<sup>28</sup> with risks and benefits understood to have truly informed patient consent; and the existence of useful surveillance or management options, or both, for carriers of the mutation that would affect the patient's care.

The most genetically informative family member is one with an early-onset syndrome cancer who is in the patient's direct line of hereditary descent (e.g., a parent, sibling or child affected by a syndrome cancer). This family member would be the most likely family member to carry the family's deleterious mutation, if there is one present in the family. If a mutation is identified in a likely carrier, it is possible for other family members to undergo "mutation-specific testing," which has lesser cost and higher accuracy than the initial testing needed to identify the specific mutation.

Once a family's cancer-causing mutation has been identified, it is necessary to decide which other family members

**Table 1:** Characteristics of hereditary polyposis syndromes

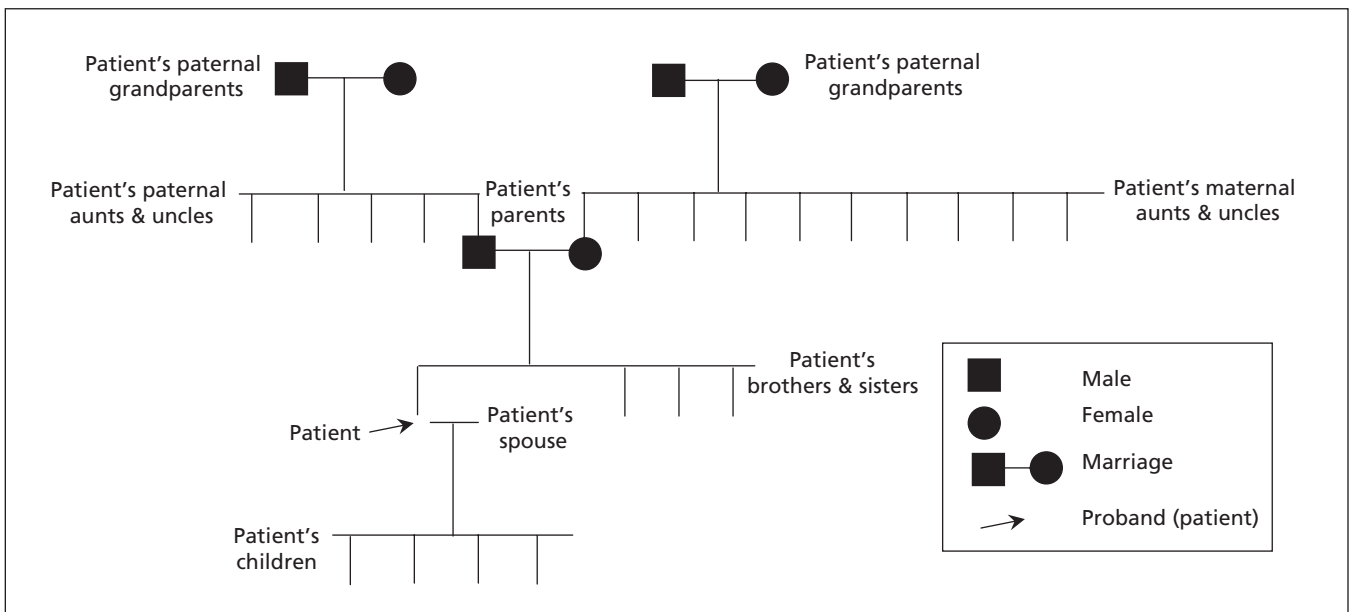
Characteristic	Familial adenomatous polyposis	Attenuated familial adenomatous polyposis	<i>MYH</i> -associated polyposis	Juvenile polyposis	Peutz–Jeghers
Adenomatous polyp burden	50 to thousands	< 50	< 100	A significant proportion of syndromic juvenile polyps will harbor areas of adenomatous transformation. <sup>17</sup>	
Hamartomatous polyps	None	None	None	Variable, mainly colorectal*	Variable colorectal and gastric; typically small intestinal involvement
Age of polyp onset	In the 2nd decade of life	Variable, often 3rd decade	Variable, usually after 50	Variable, usually 1st, 2nd decades of life	Variable, usually 1st, 2nd decades of life
Average age of cancer onset	Hepatoblastoma in 1st decade; thyroid in 1st and 2nd; brain in latter half of the 1st decade; colon in the 3rd decade.	55	Variable (unknown)	Variable (> 30% by 60 years of age)	Variable
Extracolonic cancers	Small bowel, gastric, periampullary, duodenal, pancreas, brain tumours (Turcot syndrome), hepatoblastoma	Small bowel, gastric, periampullary, duodenal, pancreas, brain tumours (Turcot syndrome), hepatoblastoma	Sebaceous gland tumours (skin), breast	Gastric, small bowel	Testicular (sertoli cell), ovarian (granulosa cell) pancreatic
Germline mutations	<i>APC</i> (mutation unknown in 20% of patients)	<i>APC</i> (mutation unknown in 20% of patients)	<i>MYH</i>	<i>BMPR1A</i> , <i>SMAD</i> (mutation unknown in 40%–60% of patients)	<i>PTEN</i> , <i>STK11</i> (mutation unknown in 50% of patients)

\*Gastric hamartomatous polyps are more common in patients harboring a *SMAD4* gene mutation.

**Table 2:** Screening and surveillance recommendations by age for patients with hereditary polyposis syndromes<sup>17-19</sup>

Age, yr	Syndrome; screening and surveillance measure			
	Familial adenomatous polyposis	Familial juvenile polyposis	Peutz–Jeghers syndrome	PTEN hamartoma syndrome*
< 10	<ul style="list-style-type: none"> <li>• <math>\alpha</math>-Fetoprotein and abdominal ultrasound annually from birth to age 10</li> </ul>			
10–20	<ul style="list-style-type: none"> <li>• Annual colonoscopy from age 10–12</li> <li>• Annual upper endoscopy, as soon as colonic polyps appear or at age 15</li> <li>• There is no consensus on thyroid screening but clinical examination and ultrasound of suspicious lesions needs to be part routine health care management visits</li> </ul>	<ul style="list-style-type: none"> <li>• Colonoscopy with polypectomy, annually if not all polyps removed, otherwise every 3 yr from age 15</li> <li>• Upper endoscopy every 3–5 yr from age 15; repeated annually if the patient has polyps</li> <li>• Annual clinical exam and baseline ultrasound of the thyroid from adolescence</li> </ul>	<ul style="list-style-type: none"> <li>• Upper endoscopy (esophageal gastroduodenoscopy and enteroscopy) and small bowel follow through, every 2–3 yr</li> <li>• Annual testicular exam, ultrasound if the condition is clinically suspected</li> </ul>	<ul style="list-style-type: none"> <li>• Colonoscopy and upper endoscopy every 2 yr</li> <li>• Small bowel follow through from age 15</li> <li>• Monthly breast self-exam from age 18</li> <li>• Baseline thyroid ultrasound at age 18, annual neck exam</li> </ul>
> 20	<ul style="list-style-type: none"> <li>• Annual upper and lower endoscopy (including post-colectomy)</li> </ul>	<ul style="list-style-type: none"> <li>• Monthly breast self-exam, clinical exam every 6–12 mo from age 21</li> </ul>	<ul style="list-style-type: none"> <li>• Mammography every 2 yr</li> <li>• Annual breast exam, Papanicolaou smear, endometrial biopsy and transvaginal ultrasound</li> <li>• Colonoscopy every 2 yr from age 25</li> </ul>	<ul style="list-style-type: none"> <li>• Annual breast exam and mammography</li> <li>• Endometrial suction biopsy beginning at age 35–40</li> <li>• Annual urinalysis (if there is a history of renal cancer)</li> <li>• Dermatologic screening exam (melanoma)</li> </ul>

\*Also known as Cowden syndrome and Bannayan–Riley–Ruvalcaba syndrome.



**Figure 2:** Patient's modified nuclear pedigree, which depicts the minimal amount of information required for a comprehensive family history of colon cancer. This involves detailed description of the patient (arrow), her siblings, children, parents, maternal and paternal aunts, uncles and grandparents. Reproduced with permission Karger.<sup>21</sup>

should receive mutation-specific testing. Considerations include whether cancer-causing mutation is known to segregate in the family; whether the mutation has been identified in a candidate family member; whether the individual patient is at high risk of cancer because of his or her position in the pedigree or has a syndrome-associated cancer; and whether the patient has a cancer syndrome stigmata (phenotype) (e.g., multiple polyposis in familial adenomatous polyposis).

Patients should be encouraged to take responsibility for informing their relatives who may be at risk about the hereditary disorder and the opportunities available to them. Educational materials should be made available. A 14-page booklet for patients, entitled *Living with Hereditary Colorectal Cancer*, has been developed by our team at Creighton (copies of the booklet and information about reprinting are available from the corresponding author). In addition, there are several websites with useful information. The American Society for Clinical Oncology sponsors Cancer.net, which has information for patients with Lynch syndrome ([www.cancer.net/patient/Cancer+Types/Hereditary+Non-Polyposis+Colorectal+Cancer](http://www.cancer.net/patient/Cancer+Types/Hereditary+Non-Polyposis+Colorectal+Cancer)). The Colorectal Cancer Coalition's website also has information for patients (<http://fightcolorectalcancer.org/awareness/patients/prevention/risk>). When possible, family members should be given the opportunity to participate in a family information service,<sup>29</sup> which can be effective in enhancing cancer control through its informal group educational and therapeutic benefits.

## Surveillance and management

Once Lynch syndrome has been diagnosed, medical management involves a highly targeted screening and management program, which is based on the syndrome's natural history (Box 1). Table 3 shows the level of evidence for the most common screening and management modalities.<sup>30</sup> Lindor and colleagues<sup>30</sup> note that evidence from many studies is insufficient to recommend for or against most of these practices. It is therefore necessary to base recommendations, at least in part, on the characteristics and natural history of the disorder.

Colonoscopic screening has been shown to significantly improve survival among carriers of a mutation associated with Lynch syndrome.<sup>31,32</sup> Lindor and colleagues<sup>30</sup> reported that the available evidence strongly supports colonoscopic surveillance for patients with Lynch syndrome, and they recommended this procedure every 1–2 years, starting between the ages of 20 and 25. Those with a mutation in *MSH6* should start screening at age 30. Features of Lynch syndrome-associated colorectal cancer that are addressed by these recommendations include early age of cancer onset, accelerated carcinogenesis of adenomas into carcinomas, and predilection to cancer of the proximal colon (about 70% of Lynch syndrome-related colorectal cancers occur in the right colon, which is not accessed through sigmoidoscopy).<sup>4,7</sup> There is continuing research into improvements in colonoscopic detection of polyps and adenomas, such as chromoscopic colonoscopy<sup>33,34</sup> and the use of narrow band imaging.<sup>35</sup>

Lindor and colleagues<sup>30</sup> recommend subtotal colectomy for patients with Lynch syndrome who have colorectal cancer,

### Box 1: Features of Lynch syndrome<sup>4,26</sup>

- Autosomal dominant inheritance pattern
- Earlier average age of onset of colorectal cancer than in the general population (45 years in Lynch syndrome v. 63 years in the general population)
- Proximal (right-sided) colonic cancer predilection (70%–85% of colorectal cancers in Lynch syndrome are proximal to the splenic flexure)
- Accelerated carcinogenesis (tiny adenomas can develop carcinomas within 2–3 years in Lynch syndrome v. 8–10 years in the general population)
- High risk of additional colorectal cancers (25%–30% of patients who have surgery for a Lynch syndrome-associated colorectal cancer have a second primary colorectal cancer within 10 years of surgical resection if they received a less than subtotal colectomy)
- Increased risk of malignant disease at certain extracolonic sites:<sup>20</sup>
  - endometrium (40%–60% lifetime risk for female mutation carriers)
  - ovary (12%–15% lifetime risk for female mutation carriers)
  - stomach (higher risk in people of Asian descent)
  - small bowel
  - hepatobiliary tract
  - pancreas
  - upper uroepithelial tract (transitional cell carcinoma of the ureter and renal pelvis)
  - brain (in the Turcot syndrome variant of Lynch syndrome)
- Sebaceous adenomas, sebaceous carcinomas and multiple keratoacanthomas in Muir–Torre syndrome (variant of Lynch syndrome)
- Pathology of colorectal cancer is more often poorly differentiated, with an excess of mucoid and signet-cell features, a Crohn-like reaction and an excess of infiltrating lymphocytes within the tumour
- Increased survival from colorectal cancer
- Germline mutation in a mismatch repair gene (most commonly *MLH1*, *MSH2* or *MSH6*) that segregates in the patient's family (i.e., members who carry the mutation show a much higher rate of syndrome-related cancers than those who do not carry the mutation.)

and they also recommend urinalysis with cytology beginning between age 25 and 35.

Following colorectal cancer, the second most frequent cancer in Lynch syndrome is endometrial carcinoma (occurs in 40%–60% of women with the mutation), followed by carcinoma of the ovary (occurs in about 12%–15% of women with the mutation).<sup>20</sup> Based on their study of the evidence, Lindor and colleagues<sup>30</sup> recommend endometrial sampling and transvaginal ultrasonography of the uterus beginning between age 30 and 35. They also recommend transvaginal ultrasonography of the ovaries beginning at the same age. We agree with these recommendations, with the caveat that the patient must be fully apprised of the screening limitations for early detection of ovarian cancer, as well as the lack of evidence of a reduction in mortality through endometrial and ovarian screening.

**Table 3:** Recommended management for at-risk members of families with Lynch syndrome (Reproduced with permission from the American Medical Association.<sup>30</sup>)

Type of intervention	Recommendation	Quality of evidence regarding intervention	Strength of recommendation*
Screening colonoscopy	Every 1–2 yr beginning at age 20–25 yr (age 30 yr in <i>MSH6</i> families), or 10 yr younger than the youngest age at diagnosis in the family, whichever comes first	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes†	Strongly recommended There is good evidence that the guideline improves important health outcomes and concludes that benefits substantially outweigh harms
Endometrial sampling	Every year beginning at age 30–35 yr	Evidence is insufficient to assess the effects on health outcomes‡	Insufficient evidence to recommend for or against Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined
Transvaginal ultrasound for endometrial and ovarian cancer	Every year beginning at age 30–35 yr	Evidence is insufficient to assess the effects on health outcomes‡	Insufficient evidence to recommend for or against Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined
Urinalysis with cytology	Every 1–2 yr beginning at age 25–35 yr	Evidence is insufficient to assess the effects on health outcomes‡	Insufficient evidence to recommend for or against Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined
History and examination with detailed review of systems, education, and counselling regarding Lynch syndrome	Every year beginning at age 21 yr	Evidence is insufficient to assess the effects on health outcomes‡	Insufficient evidence to recommend for or against Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined
Prophylactic surgery Colorectal resection (segmental v. subtotal colectomy v. complete proctocolectomy)	For at-risk persons without colorectal neoplasia: generally not recommended, discuss as alternative to regular colonoscopy, with preferences of well-informed patient actively elicited  For persons with a diagnosed cancer or polyp not resectable by colonoscopy,§ subtotal colectomy favoured with preferences of well-informed patient actively elicited	Evidence is insufficient to assess the effects on health outcomes‡	Insufficient evidence to recommend for or against Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined
Hysterectomy or oophorectomy	Discuss as option after childbearing completed	Good–fair¶	No recommendation for or against There is at least fair evidence that the guideline can improve health outcomes but the balance of benefits and harms is too close to justify a general recommendation

\*Adapted from the US Preventive Services Task Force's 2-tier system to assess the quality of evidence and to assign strength of recommendations in support of each guideline.

†While the quality of evidence supporting colon examination is good, the optimal frequency and initiation age have not been adequately studied.

‡Because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

§Resection of a colon neoplasm is therapeutic, not prophylactic. At issue is the extent of resection — if greater than otherwise required by usual surgical considerations, then it carries an element of prophylaxis. Because all persons in this group will be undergoing surgery, there is opportunity to consider prophylactic removal of much or all of the colon. For women, the discussion should include option of having a hysterectomy or oophorectomy at the same time.

¶Defined as evidence that includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

The efficacy of prophylactic hysterectomy and bilateral salpingo-oophorectomy in women who have a Lynch syndrome–related germline mutation is supported by evidence-based findings, and this should be offered as an option for cancer prevention after a woman’s family is completed.<sup>36</sup>

Screening for more uncommon cancers integral to Lynch syndrome varies depending on specific family history; therefore, this is best addressed by a genetic counselor.

Hereditary colorectal cancer syndromes provide a wealth of opportunities for highly targeted clinical management and prevention. The key to prevention is early diagnosis through a comprehensive family history, followed by germline mutation testing if appropriate, and targeted surveillance and management for patients with mutations.

An extremely useful set of guidelines is that of the National Comprehensive Cancer Network,<sup>37</sup> which can be ordered in print or used as an interactive tool on the Network’s website. The network offers colorectal cancer screening guidelines for patients at average or increased risk, including algorithms to assist in recognizing the likely presence of various hereditary colorectal cancer syndromes, deciding if a referral for genetic testing is warranted, and providing management after diagnosis. An advantage of the interactive tool on the website is that physicians can find detailed information and recommendations for the set of variables presented by a specific patient without needing to wade through similar material for the myriad other possible situations.

The American Gastroenterological Association also publishes guidelines that are periodically updated on colorectal cancer screening and surveillance for patients at average and high risk.<sup>38</sup> These provide an excellent background and overview, but, because of their nature, they are not as comprehensive as those by the National Comprehensive Cancer Network.

## Lynch syndrome as a model for clinical cancer control

The characteristic clinical features of Lynch syndrome are shown in Box 1. This information is often extremely helpful in establishing a diagnosis and determining who should be tested. For a more detailed discussion, see the articles by Lynch and de la Chapelle.<sup>4,11</sup>

The original Amsterdam criteria<sup>39</sup> were designed to provide uniformity in collaborative research studies and looked at only personal and familial histories of colorectal cancer. When these criteria were determined to be too stringent, the Amsterdam Criteria II<sup>40</sup> were developed. These criteria considered the extracolonic cancers in the Lynch syndrome tumour spectrum, thereby making the diagnosis more specific. Both sets of Amsterdam criteria were used before the development of molecular-based diagnostic tools such as microsatellite instability and immunohistochemistry testing. More recently, the Bethesda Guidelines (Box 2)<sup>41,42</sup> were developed, which make use of new molecular and pathologic knowledge and have proven to be of even greater use in determining who should receive genetic testing.<sup>43</sup> Microsatellite instability testing is indicated when any one of the guideline criteria is met.<sup>44</sup>

### Box 2: Bethesda guidelines for testing colorectal tumours for microsatellite instability<sup>41</sup>

The following groups of patients should receive testing for microsatellite instability:

- Patients aged less than 50 years with a diagnosis of colorectal cancer.
- Patients with synchronous or metachronous colorectal or other syndrome-associated tumours,\* regardless of age.
- Patients aged less than 60 years with colorectal cancer with microsatellite instability–high† histology.†
- Patients with at least 1 first-degree relative with a diagnosis of colorectal cancer or a syndrome-associated tumour\* under age 50 years.
- Colorectal cancer or syndrome-associated tumour\* diagnosed at any age in 2 first- or second-degree relatives.

\*Includes colorectal, endometrial, stomach, ovarian, pancreas, ureter or renal pelvis, biliary tract and brain (usually glioblastoma as seen in Turcot syndrome) tumours, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome and carcinoma of the small bowel.

†Presence of tumour infiltrating lymphocytes, Crohn disease–like lymphocytic reaction, mucinous or signet-ring differentiation, or medullary growth pattern.

Although the original Amsterdam criteria are no longer used to diagnose Lynch syndrome, they have more recently proved useful in the identification of another subset of possibly hereditary colorectal cancers. Lindor and colleagues,<sup>9</sup> as well as some other researchers, have described families that fulfill the original Amsterdam criteria but lack the mismatch repair mutation findings necessary for diagnosis of Lynch syndrome; such families have what is referred to as “familial colorectal cancer type X.”

## Summary

Increased knowledge of genetics and molecular pathophysiologic pathways holds the promise for the development and timing of screening measures, such as colonoscopy, which may facilitate detection of presymptomatic cancer and potentially a reduction of mortality. Insight into the molecular genetic mechanisms of hereditary cancer syndromes may improve targeted cancer control measures and pharmacologic therapy. Thus, it may one day become possible to select therapy based on genomic or proteomic profiles for targeted molecular-based pharmacologic therapy. Physicians must attain a better grasp of hereditary cancer syndromes and, when more expertise is needed, make appropriate referrals to experienced medical geneticists or a centre with expertise in hereditary cancer. Lives can be saved through cancer prevention using genetic knowledge.

This article has been peer reviewed.

**Competing interests:** None declared.

**Contributors:** Henry Lynch, Jane Lynch and Thomas Attard each made substantial contributions to the analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and gave final approval of the version to be published. In addition, Henry Lynch and Thomas Attard made substantial contributions to conception and design and acquisition of data.

**Funding:** This paper was supported by revenue from Nebraska cigarette taxes awarded to Creighton University by the Nebraska Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the State of Nebraska or the Nebraska Department of Health and Human Services.

Support was also given by the National Institutes of Health through grant #1U01 CA 86389.

Henry Lynch's work is partially funded through the Charles F. and Mary C. Heider Chair in Cancer Research, which he holds at Creighton University.

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