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Review article

Historical review of Lynch syndrome

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ABSTRACT

Lynch syndrome was formerly known as Hereditary Nonpolyposis Colorectal Cancer. Currently, these two nomenclatures each have their unique definitions and are no longer used interchangeably. The history of hereditary nonpolyposis colorectal cancer was first recognized formally in the literature by Henry Lynch in 1967. With advances of molecular genetics, there has been a transformation from clinical phenotype to genotype diagnostics. This has led to the ability to diagnose affected patients before they manifest with cancer, and therefore allow preventative surveillance strategies. Genotype diagnostics has shown a difference in penetrance of different cancer risks dependent on the gene containing the mutation. Surgery is recommended as prevention for some cancers; for others they are reserved for once cancer is noted. Various surveillance strategies are recommended dependent on the relative risk of cancer and the ability to intervene with surgery to impact on survival. Risk reduction through aspirin has shown some recent promise, and continues to be studied.

Revisão histórica da síndrome de Lynch

Palavras-chave:
Síndrome de Lynch
Câncer colorretal hereditário sem polipose
Câncer colorretal
Critérios de Amsterdam
Critérios de Bethesda
Instabilidade de microssatélites: MSI

RESUMO

A síndrome de Lynch era anteriormente conhecida como "câncer colorretal hereditário não polipose". Atualmente, essas duas nomenclaturas têm, cada uma, sua própria definição original e já não são empregadas de forma intercambiável. O histórico de câncer colorretal hereditário não polipose foi formalmente reconhecido pela primeira vez na literatura por Henry Lynch em 1967. Com os avanços da genética molecular, verificou-se uma mudança do fenótipo clínico para o diagnóstico genotípico. Esse fato levou à capacidade de diagnosticar pacientes afetados antes que o câncer se manifestasse, e, portanto, à utilização de estratégias preventivas de rastreamento. O diagnóstico genotípico mostrou a diferença na penetrância de diferentes riscos de câncer dependendo do gene que contem a mutação.

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Imunohistoquímica: IHQ
Câncer familial
Síndrome de Muir-Torre
Síndrome de Turcot
Família X
Reparação de incompatibilidade

A cirurgia é recomendada para a prevenção de alguns tipos de câncer; para outros, ela é reservada quando há o aparecimento da doença. Várias estratégias de rastreamento são recomendadas, dependendo do risco relativo de câncer, bem como a capacidade para intervir com a cirurgia objetivando um impacto na sobrevivência. A redução do risco através do uso de aspirina recentemente mostrou ser promissor e continua a ser estudada.

Introduction

Lynch syndrome is a hereditary disorder with an autosomal dominant transmission. In addition to colorectal cancer (CRC), those affected are at increased risk of secondary cancers such as: ovarian, uterine, renal urinary collecting system (transitional cell of renal pelvis and ureter), gastric, sebaceous gland adenomas /adenocarcinomas and brain. Since 1967, when Dr. Lynch first described the association of inheritance and adenocarcinoma of the colon in 1967,[1] there have been many advances, and many of these just in the past 10 years.

History

Dr. Warthin, a University of Michigan pathologist, first described a family affected with multiple cancers. His seamstress would lament her inevitable death due to cancer, as had occurred with many of her family members. She did succumb to endometrial cancer. Dr. Warthin drew her family tree and labeled it as Family G, as the family immigrated to America from Germany.[2] See Fig. 1.[3]

This information laid somewhat dormant until Dr. Henry Lynch had met with a later generation of University of Michigan pathologists who reintroduced this family tree to him. He found it similar to other families he had been following in Nebraska (Family N) since he was a second year medicine resident.[4]

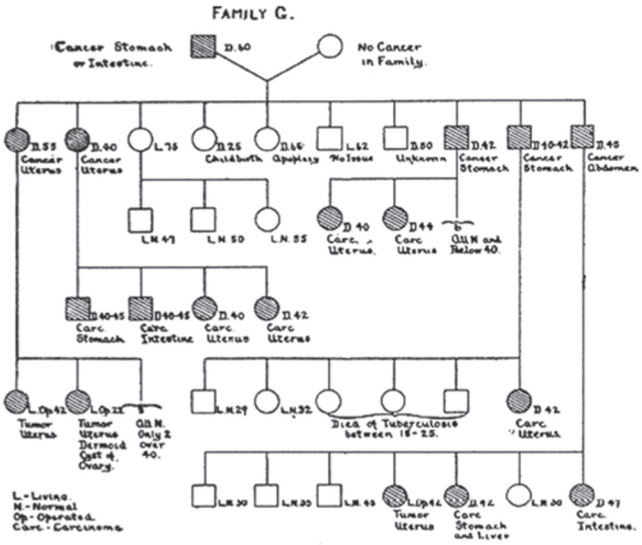

Fig. 1 – Amsterdam I criteria.

Dr. Lynch met a lot of skepticism as he presented a hereditary link, as at that time the focus was on the environment and its relationship with cancer. The strong consensus at that time was that the familial occurrences were due to similar carcinogen exposures.

Patterns emerged as Lynch continued to follow the family. He noted in this Nebraska family that the offspring of affected parents had a cumulative risk of 54.1%, compared to 3.6% amongst offspring of unaffected parents. He also noted a predilection for the proximal colon in his families vs. the general population. Out of the 14 that were successfully treated for their colon cancer by local resection, 11 developed a second colon cancer 2-23 years later, with a mean of 8 years. Therefore, Dr. Lynch dutifully noted the autosomal transmission, the proximal location and propensity for multiple cancers over 30 years ago.[5]

The terminology describing this syndrome has undergone transformations throughout the years. Therefore, caution is recommended as you read earlier manuscripts, as the cohorts of patients were not always a homogenous group. The terminology Hereditary Nonpolyposis Colorectal Cancer and Lynch syndrome was first used in 1985.[6,7,8] These two terms were used interchangeably until Dr. Jass' 2006 article better defined Lynch syndrome as a disease with a proven mismatch repair gene mutation with vertical transmission regardless of age. Prior to 2006 the terminologies were used interchangeably, and at times studies compared apples to oranges. As we know now and will discuss later there are other families with patterns similar to Lynch syndrome but that are not proven to have a mismatch repair gene as their cause for their cancer predilection. In this review we will reserve Lynch syndrome to describe those with a proven mismatch repair gene mutation.[9]

Transforming from phenotype diagnosis to genotype diagnosis

In the 1970's and 1980's, the gene mutations giving rise to Lynch syndrome were unknown. The diagnosis was made only by family history. It was not until 1990 that a collaborative effort was made to make consensus criteria for diagnosis. In 1990 the Amsterdam criteria were decided on by a group of scientists with special interests on hereditary disorders at the International Collaborative Group meeting in Amsterdam. It was published in 1991 (Table 1). The goal was to use this definition to then place these families with common patterns in collaborative studies.[10]

To allow for the incorporation of many of the secondary cancers noted in these families (cancers of the endometrium,

Table 1 – Amsterdam I criteria.

Amsterdam I
3 FDR with CRC, one of whom is FDR relative to the other two; and 2 generations affected; and 1 of the affected <50 years of age; and Familial Adenomatous Polyposis has been ruled out

small bowel or pelvic-ureter system), the criteria were later revised as Amsterdam II.[11] See Table 2.

With each variation that followed, the goal was to increase awareness. Therefore newer criteria accepted a higher sensitivity for lower specificity. Newer criteria also began to incorporate common histopathological findings that were noted in these colon cancers. The role of pathologists to help identify these patients emerged. As early as 1986, Mecklin and Järvinen noted certain features in the histology of the colon cancers in these families. This included features such as poor differentiation, and abundant mucin secretion marked lymphocytic infiltrations. The adenomas were also noted to transform to cancer within a shorter time frame.[12]

It was not until 1996 that a formal evaluation of these histopathological findings was reviewed. In Bethesda, The Early Detection Branch of the National Cancer Institute convened in a workshop entitled "The intersection of Pathology and Genetics in the Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Syndrome". From this ensued a list of guidelines to identify those who should be tested for microsatellite instability. This became known as the Bethesda Guidelines.[13] See Table 3.

NCI held another workshop in 2002 that led to the Revised Bethesda Criteria[14] (Table 4). In this interim the standard panels for microsatellite instability testing were agreed upon. Also at this time three mismatch repair genes were found to be the cause of Lynch: *MLH1 MSH2*, and *MSH6*. The main difference in these two guidelines was that the evaluation of polyps in young patients was discarded, the age range was expanded to incorporate more testing, and second degree relatives histories were included as a risk assessment.

The University of Pittsburgh showed that the incorporation of the pathologist aided in the increase of identification of high-risk patients in comparison to relying only on clinical family history information. This allowed more pathologists to then undergo further testing such as IHC and/or genetic testing. While 8 out of 75 CRC patients were identified with earlier criteria, this increased to 17/75 using the revised guidelines. In the additional 9 that were identified 3 had absent *MSH2* on IHC, 6 had absent *MLH1*. This was an earlier study and IHC on *MSH6* and *PMS2* were not yet incorporated in their IHC algorithm. Therefore this is a minimum identification.[15]

Table 2 – Amsterdam II criteria.

Amsterdam II
3 or more relatives with a Lynch associated cancer (colorectal, endometrial, small intestine, ureter, renal pelvis); and 2 or more successive generations affected, one is a first-degree relative of the other two; and 1 or more relatives is diagnosed before the age of 50; and Familial Adenomatous Polyposis has been ruled out Tumors should be verified by pathologic examination.

Table 3 – Bethesda guidelines.

Individuals with cancer in families that meet the Amsterdam criteria
• Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers[a] • Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at age < 45 y, and the adenoma diagnosed at age < 40 y • Individuals with colorectal cancer or endometrial cancer diagnosed at age < 45 y • Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed at age < 45 y[b] • Individuals with signet ring cell type colorectal cancer diagnosed at age < 45 y[c] • Individuals with adenomas diagnosed at age < 40 y

[a] Endometrial, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional cell carcinoma of the renal pelvis or ureter.
[b] Solid/cribriform defined as poorly differentiated or undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces.
[c] Composed of > 50% signet ring cells.

This concept of testing tumors in an automatic sequence by pathologists had mixed implementation. Many clinicians and pathologists had concerns that PCR and IHC testing on the specimens were considered genetic testing and should not be performed without consent. Therefore, some institutions did incorporate this testing on their consent forms for colon resections. Other institutions felt that this was testing on the tumor and therefore no more indicative of labeling someone as Lynch short of taking a family history. It was the combination of Heather Hampel's landmark study in 2005[16] which was revisited in 2008,[17] and the EGAPP group,[18] Dr. Jass' definition of Lynch,[9] and the passage of the Genetic Information Nondiscrimination Act (GINA)[19] that led to the groundwork for the ability to do universal screening. These will be discussed in more details later in the paper.

History of microsatellite instability (MSI) and immunohistochemistry (IHC) testing

Microsatellites are stretches of DNA with a repetitive sequence of nucleotides (e.g., CCCCC or CGACCACGA). These areas are susceptible to errors when a mismatch repair gene (i.e. *MLH1*, *MSH2*, *MSH6*, *PMS2*) function is impaired. The mismatch repair genes function is to repair these errors. Without repair there is an accelerated accumulation of single nucleotide mutations and alterations in the length of simple repetitive microsatellites. Cancers arising in cells with defective mismatch repair (MMR) gene function exhibit an inconsistent number of microsatellite nucleotide repeats when compared to normal tissue, a finding referred to as "microsatellite instability". This can be tested by polymerase chain reaction (PCR). In 1992, three groups independently published results that recognized the link between microsatellite instability and Lynch syndrome.[20,21,22] Thibodeau[20] noted that there was a preponderance of cancer in the proximal location and also

Table 4 – Revised Bethesda guidelines.

Tumors from individuals should be tested for MSI in the following situations:

- Colorectal cancer diagnosed in a patient who is less than 50 years of age
- Presence of synchronous, metachronous colorectal, or other HNPCC- associated tumors[a] regardless of age
- Colorectal cancer with the MSI-H[b] histology[c] diagnosed in a patient who is less than 60 years of age[d]
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under 50 years of age
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age
- Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors including colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel

[a]Hereditary Nonpolyposis Colorectal Cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot Syndrome), sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.
[b]MSI-H, microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.
[c]Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.
[d]There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.

Table 5 – Recommendations for the evaluation of MSI-H and MSI-L.

The original National Cancer Institute (NCI) microsatellite panel included BAT25, BAT26, D2S123, D5S346 and D17S2507; however, the following caveats may apply:

- If only dinucleotide repeats are mutated, test a secondary panel of microsatellite markers with mononucleotide repeats (e.g., BAT40 and/or MYCL) to exclude MSI-L.
- Dinucleotide repeats are less sensitive than mononucleotide repeats for MSI-H; however, they provide an internal control for the prevention of sample mix-up
- A pentaplex panel of five quasimonomorphic mononucleotide repeats may be more sensitive for MSI-H tumors than other microsatellite markers and may obviate the need for normal tissue for comparison; this approach requires three or more mutant alleles to indicate MSI-H

[a]MSI-H, microsatellite instability–high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers in tumors. MSI-L, microsatellite instability–low in tumors refers to changes in only one of the five NCI-recommended panels of microsatellite markers in tumors.

noted enhanced survival in patients with Lynch syndrome when compared to sporadic cases. Peltomaki[21] referred to it as replication error (RER) phenotype. Alltonen[22] linked the locus that would later help to identify the actual MMR genes responsible.

To facilitate communication among investigators, The Early Detection Branch sponsored a third workshop entitled the "International Workshop on Microsatellite Instability and RER Phenotypes in Cancer Detection and Familial Predisposition" on December 8-9th, 1997. Over 120 investigators attended. The goal was to define uniform criteria for MSI; to propose technical guidelines for its detection; to review the literature pertaining to the implications of this phenotype; and to develop a research agenda for future research. In particular, their high priority was to identify potential areas of clinical application to cancer detection, prognosis, and therapeutic response. At this meeting, MSI was defined as a change of any length due to either insertion or deletion of repeating units in a microsatellite within a tumor when compared to normal tissue. It was at this meeting that the Bethesda Panel was proposed. These were to be the specific markers for MSI assessment, including BAT25, BAT26, D5S346, D2S123 and D17S250. If two or more of the five microsatellites tested in the tumor were mutated it was termed MSI-high (MSI-H). If one was mutated it was termed MSI-Low (MSI-*L*) and *if none, MS-Stable (MSS)*.[23] See Table 5.

Boland's article[23] that summarized the proceedings stressed that MSI-H in itself was not to be diagnostic of Lynch syndrome. While MSI-H was noted in 95% of those with HNPCC cancers that met Amsterdam criteria, and in 47% of cancers in families considered high risk but not meeting Amsterdam criteria, it was also noted in 13% of those with sporadic cancers. In fact, in Hampel's 2005 paper (24), only 28.1% of their patients who were MSI-H were found to carry a Lynch-associated mutation.

In 1993, the same year that the link between MSI and Lynch syndrome was reported, mutations discovered in the mismatch repair gene, *MSH2*, were found to be associated with the syndrome.[24,25] Mutations in *MLH1* and *PMS2* were reported in 1994[26-29] and *MSH6* in 1997.[30,31] The discovery of these genes led the way for IHC testing and then to guide gene testing.

IHC allows one to use antibodies to stain for the proteins produced by the MMR genes. A lack of staining is suggestive, but not indicative, of a mutation in the corresponding gene. MMR protein can be present but non-functional, and therefore can present with false positive results.[32] In fact, there were reports of *MSH2* being absent on IHC testing, but no *MSH2* mutation could be found. It is now known that this is due to an epimutation that leads to a silencing of *MSH2*. Chan[33] noted this linked deletion of 3' terminal end of epithelial cell adhesion molecule, EPCAM gene (formerly TACSTD1) to Lynch syndrome. *EPCAM* is located upstream from *MSH2*. Gross deletions that disrupt the 3' end of *EPCAM* deletion leads to methylation induction of the promoter regions of *MSH2*. This has been reported in up to 19-30% of individuals with MSI and absence of *MSH2* on IHC.[34,35,36] As commercial testing for each gene became available, the corresponding proteins were added to IHC panels.

MSI testing can be complementary to IHC testing, as false negatives can occur when the MMR protein is present but non-functional. MSI testing can be done with very little tissue and is highly reproducible.[32]

But because it requires microdissection and molecular analysis it is not readily available at all centers. Additionally,

in tumors with high levels of mucin, false negatives can occur.[16] False negatives also can occur with *MSH6* germline mutations, as they may have MSI-L results.[37] And unlike with IHC testing, an abnormal MSI test results does not suggest which gene to test.

Absence of *MLH1* on IHC was also noted to have a low gene mutation detection rate. In time it became possible to distinguish sporadic from a hereditary etiology in individuals with absent expression of *MLH1* on IHC testing. This abnormal IHC result is frequently due to two somatic events: BRAF mutation Val600Glu (V600E) or *MLH1* promoter hypermethylation. They both are common explanations of absent *MLH1* expression in patients without a germline *MLH1* mutation, particularly among those diagnosed with CRC after age 50. *BRAF* mutations and *MLH1* promoter hypermethylation are thought to be rare in Lynch syndrome-related cancers, though each has been seen in individuals with Lynch syndrome. In spite of these reported cases, the presence of a *BRAF* mutation or *MLH1* promoter hypermethylation essentially rules out the diagnosis of Lynch syndrome.[38-43]

Remember, as abnormalities in IHC are suggestive, confirmatory diagnosis of Lynch is only by positive mutation on gene sequencing. The first patents for gene sequencing of *MLHH-1* and *MSH2* were filed in 1997 and 1999. Commercial launching then ensued in 2000.[44] Commercial testing for *MSH6* soon followed. Due to technical complexity of *PMS2* testing, commercial testing of the *PMS2* gene did not become available until 2009.

An estimated 50% of Lynch syndrome mutations are found in *MLH1*,[45] 40% in the *MSH2* gene[45] 7%-10% in the *MSH6* gene,[30,33,46] 5% in the *PMS2* gene[47] and 1-3% *EPCAM*.[36,48,49]

Screening for Lynch syndrome

From 2000-2005 many centers were using family histories and pathological criteria by the Revised Bethesda Criteria to guide testing on tumors for MSI and or IHC. If these were abnormal, genetic counseling and then gene testing were performed. There was much controversy during this time whether MSI and IHC could be performed without patients' consent. There was concern that these studies themselves could lead to a diagnosis of a hereditary disorder, which could have insurance implications. With Heather Hampel's study on all colorectal cancers,[17] the new definition of Lynch syndrome (confirmed by a proven MMR gene mutation),[9] *EGAPP*[18] and GINA[19] led the movement towards universal screening. The finding that a family history (a standard on initial history and physicals) that met Amsterdam criteria led to a diagnosis of Lynch syndrome with the same frequency as documenting abnormal MSI/IHC testing (about 60% of the time) also added to the defense to perform MSI and IHC without formal consent.[17,50] Therefore, patients were only defined to have the Lynch mutation once mutation was noted by gene sequencing. There is consensus that once germline testing is to be considered, genetic counseling is a standard.[51]

The United States Law began to recognize the importance and consequences of gene testing. GINA, passed in 2008 and enacted in 2009, prohibits health insurers from using genetic information (e.g., genetic test results, family history) to determine insurability. It does have shortcomings that genetic counselors explain as part of their normal consenting process. If patients have a lapse of coverage, genetic diseases can be considered a pre-existing condition. It does not prevent companies from using the diagnosis of Lynch syndrome to help underwrite their disability, life insurance, and long-term policies. Since its inception, The Affordability Care Act of 2010 also allowed new coverage options to individuals who have been uninsured for at least six months because of a pre-existing condition. This program will serve as a bridge to 2014, when rejecting insurance coverage due to pre-existing conditions will be prohibited.[52]

Hampel's and De la Chappelle's 2005 study[16] on all colorectal cancers resected amongst the major hospitals in Ohio led to some very important discoveries and the feasibility of screening for Lynch syndrome on all CRC patients. It was then updated in 2008.[17] In 2005, initially all colorectal cancers underwent MSI testing. If they were MSI-H or MSI-L they underwent IHC for *MLH1, MSH2, MSH6* and *PMS2*-, sequencing of *MLH1, MSH2*, and *MSH6*, and methylation analysis of *MLH1* promoter region if IHC for *MLH1* was abnormal. If IHC revealed a lack of *PMS2* and a presence of *MLH1, PMS2* gene mutation was analyzed. In addition, those that were MSS but met Bethesda or Amsterdam criteria underwent IHC testing.

In 2008 an additional 500 CRC patients were screened, this time with MSI and IHC. Another 372 patients who were MSS and had normal IHC (or IHC not completed secondary to lack of tissue) underwent gene testing for two of the most common MMR gene mutations in their series. One is American Founder Mutations (*MSH2*) and the other was another common mutation in *MSH2*.

Combining the findings of the 2005 with the 2008 study patients, it was noted that the MSI-H prevalence was 12.7% in all colorectal cancers, and the prevalence of Lynch syndrome was at a minimum of 2.8%. In 2005, 10 out of the 23 identified Lynch syndrome patients were over 50 years of age and 5 out of 23 did not meet Bethesda or Amsterdam criteria. Testing only by MSI or IHC would each have missed two probands. MSI lacked sensitivity if there was significant mucin in the specimen and therefore careful dissection by pathology was recommended. For each proband, 5.79 at-risk family members were contacted; over 3 members per proband were diagnosed with Lynch.

Not only was prevalence now established, it also illustrated the feasibility of testing all colon cancers for Lynch syndrome. 1566 patients out 1700 patients agreed to participate. Only 2 out of 23 probands from 2005 study refused contact to be made with at-risk family members. Of the 199 members who were contacted and received counseling, only two of these refused to undergo gene testing. These findings led to discussion about health care policy and Lynch syndrome. The Evaluation of Genomic Applications in Practice and Prevention Group (EGAPP) published its position statement in 2009, concluding with moderate certainty that testing newly diagnosed CRC patients could provide moderate population benefit. It did not address the cost-effectiveness of a universal screening program.[18]

In 2009, Myundura et al.[53] reported that universal testing would detect nearly twice as many Lynch patients as targeting only those with younger age of onset of CRC. Also, the

incremental cost effectiveness ratio was comparable to other preventive services. Their decision model looked at 4 main strategies:1. IHC testing for all MMR genes and utilizing *BRAF* if *MLH1* was abnormal 2. IHC testing for all 4 MMR genes and proceeding to gene sequencing if abnormal, or 3. MSI-H testing and proceeding to gene sequencing if abnormal or strategy 4, testing all CRC with gene sequencing.

For each of the four strategies the models calculated costs and outcomes using many of the data from Hampel's papers, i.e. average relatives contacted, tested, calculating costs of testing, surveillance and treatment for CRC. For each strategy the cost-effectiveness ratios (in US dollars) were $23,206, $23,221, $28,291 and $ 79,651, respectively. See Table 6 below.

Cost-effectiveness ratios associated with Lynch syndrome testing strategies among new diagnosed colorectal cancer patients and testing and surveillance for CRC among their first-degree relatives. See Table 7.

Analyzing the incremental cost-effectiveness ratio (ICER) using strategy 1. the incremental cost-effectiveness comparing to the next best strategy varies from about $18,000 to $50,000. Comparing this to colonoscopy screening (individuals older than 50 and at every 10-year intervals) is $25,000 per LY saved. They note in these same articles that many analysts use a critical value of $50,000 or $100,000 per LY or QALY as a criterion of cost-effectiveness. They concluded that universal testing for Lynch syndrome is well within the range of acceptable ICERs for preventive services in the United States. As with many studies looking at cost effectiveness of genetic testing, the true saving come to those which operate in a hereditary center module, as there is active attempts to reach out to at-risk family members. The cost savings is truly made with the site specific testing of the at-risk relatives once a mutation is known. Site specific testing is much cheaper, frequently one tenth of the cost for diagnosing the proband's mutation.

Current diagnostic strategies

As the preceding text shows, there are many ways to arrive at a diagnosis of Lynch syndrome, from going straight to germline genetic testing of all Lynch genes to targeting the germline testing based on results from IHC, *BRAF* and *MLH1* hypermethylation testing. According to their availability and policies, individual institutions follow a host of algorithms. Some hospitals only perform MSI or IHC on specimens as requested by clinicians on a case-by-case basis. Some institutions follow Bethesda Criteria and may perform MSI, IHC, or both. There is a trend after the EGAPP working group papers that more institutions are performing universal screening on ALL colorectal cancers (and some performing IHC on endometrial), with MSI or IHC or both. Some sites have expanded to IHC on all or a subset of endometrial cancers.

Imperative in these strategies is that the abnormal values are reported to a clinician or counselor who can appropriately interpret these results. At Duke University we currently perform MSI and IHC on all colorectal cancers, by endoscopic biopsy or surgical resection specimen, with all results being sent to our genetic counselors. Clinicians in gastroenterology, surgery and medical oncology all agreed to allow the counselors to contact their patients as an extension of their practice. This allows the treating clinician to maintain "ownership" over the follow-up of abnormal results, removes pathologists from a position of directly influencing patient care, and maintains HIPAA compliance.

Many institutions begin Lynch syndrome evaluation by performing IHC testing based on the rationale that an abnormal IHC test will lead to cheaper germline genetic testing. Cost of gene sequencing and deletion/duplication testing for all 4 genes varies by laboratory, but is at least $4500. Testing a single gene, as directed by an abnormal IHC result, can decrease this cost by at least $2000. Cost of site-specific genetic testing for a known familial mutation ranges from about $150-$500. This illustrates the cost saving as hereditary centers reach out to at-risk family members.

For those found to lack *MLH1* staining on IHC, centers vary whether reflexively *BRAF/MLH1* hypermethylation is performed or whether genetic counseling ensues prior to performing *BRAF*. The presence of *BRAF* mutation/*MLH1* hypermethylation virtually excludes Lynch syndrome. But if the individual has a strong family history or early onset cancer, heightened surveillance may still prevail. This is because

Table 6 – Incremental cost-effectiveness ratios of the 4 testing strategies of universal to no testing, of age-targeted testing to no testing, age-targeted testing to previous strategy in dollars per life-year saved.

Strategies	Description of testing strategy[a]	Incremental cost-effectiveness ratio of universal testing relative to no testing and relative to previous strategy, dollars per life-year saved	Incremental cost-effectiveness ratio of age-targeted testing relative to no testing and relative to previous strategy, dollars per life-year saved	Incremental cost-effectiveness ratio of universal testing relative to age-targeted testing and relative to previous strategy, dollars per life-year saved
1	IHC, BRAF testing and sequencing	$22,552 and $22,552	$7,832 and $7,832	$37,010 and $37,010
2	IHC testing and sequencing	$23,321 and $273,915	$7,944 and $60,569	$38,411 and $429,973
3	MS1 testing and sequencing	$41,511 and $764,917	$11,680 and $168,905	$70,792 and $1,192,575
4	Genetic sequencing for 4 genes	$142,289 and $737,025	$44,902 and $252,643	$237,278 and $1,192,575

[a]Sequencing includes detection of large deletions and rearrangements.

Table 7 – Interval cost-effectiveness ratios relative to next most effective strategy and relative to no Lynch syndrome testing for detecting Lynch syndrome in newly diagnosed patients with colorectal cancer.

Change made to baseline model assumptions	Incremental cost-effectiveness ratios relative to next most effective strategy and relative to no Lynch syndrome testing (in parentheses) strategy for detecting Lynch syndrome in newly diagnosed patients with colorectal cancer[a]			
	IHC, BRAF testing and then sequencing (strategy 1)	IHC testing and then sequencing (strategy 2)	MSI testing and then sequencing (strategy 3)	Genetic sequencing for four genes (strategy 4)
Median laboratory list price – universal vs. no testing	$30,331 ($30,331)	$170,300 ($30,740)	$786,030 ($49,272)	$1,082,378 ($200,037)
Median laboratory list price – universal vs. age-targeted testing	$50,563 ($50,563)	$280,003 ($51,359)	$1,435,324 ($85,391)	$1,803,950 ($341,837)
Cascade testing (12 relatives) – universal vs. no testing	$12,332 ($12,332)	$129,346 ($12,663)	$340,298 ($20,470)	$329,869 ($63,773)
Cascade testing (12 relatives) – universal vs. age-targeted testing	$18,778 (18,778)	$181,543 ($19,379)	$579,096 ($33,291)	$508,402 ($104,909)

[a]Sequencing includes detection of large deletions and rearrangements.

while it is rare, *MLH1* hypermethylation can be present in a Lynch syndrome patient as the second hit.[36,39] On the contrary, *MSH2* methylation has been found to be the second hit in approximately 24% of *MSH2* related cancers. It has not been found in sporadic cancers.[54]

Because of the proteins of the MMR are frequently present as complexes/dimers, loss of one is often associated with a loss of the partner MMR protein. Loss of expression of *MLH1* is almost always associated with loss of *PMS2* expression. Loss of *MSH2* expression is almost always accompanied by loss of *MSH6* expression. On the other hand, loss of *PMS2* expression or *MSH6* expression is frequently seen without the accompanying loss of *MLH1* or *MSH2*, respectively. Loss of *MSH2* and *MSH6* usually indicates a germline *MSH2* mutation. Loss of *MSH6*, only, usually indicates a mutation in *MSH6*. Non-sporadic loss of *MLH1* and *PMS2* (i.e., normal *BRAF* and *MLH1* hypermethylation testing) is typically due to an *MLH1* or *PMS2* mutation. Loss of *PMS2*, only, usually represents a *PMS2* mutation. Because of this relationship with paired complexes, some centers strategize by performing IHC first for *PMS2* and *MSH6*. If both are present, no further testing is done. If one is absent, the other partner of the dimer is tested. For example, absent expression of *MSH6* would lead to IHC testing of *MSH2*.

Although there are clearly benefits to beginning the Lynch syndrome evaluation with MSI and IHC screening on an affected individual's colon or endometrial tumor, or even an adenoma with high-grade dysplasia,[55,56] this is not always possible. When another tumor within the Lynch syndrome spectrum is available, MSI and IHC testing can still guide further testing when abnormal. The same logic applies to performing MSI and IHC on metastases from a colorectal primary. When no Lynch spectrum tumor, adenoma or metastasis is available for MSI and IHC testing, direct germline genetic testing of the Lynch-associated genes is the next step. However, interpretation of germline results is not always straightforward. Variants of uncertain clinical significance can confound interpretation. And normal germline results in an individual with high prior probability of detecting a mutation (e.g., because of meeting Amsterdam II criteria or having colon cancer with histologic features noted in the revised Bethesda criteria) still leave the possibility of an undetectable germline mutation. This complicates risk management for the patient and their first-degree relatives, as it is unclear whether they should be managed as if they have Lynch syndrome.

There are various mathematical models that have been devised using patient's personal cancer history and family members to predict risks of gene mutations in Lynch syndrome. Some have found these helpful to determine if gene sequencing (with its inherent short-coming without tissue availability) is worthwhile. When IHC MSI cannot be performed on tissue due to inavailability, these are PREMM$_{1,2,6}$, MMRpredict, and MMRpro.

PREMM$_{1,2,6}$

The model is based on data from 4539 individuals undergoing genetic testing of *MSH2, MLH1,* and *MSH6* through a commercial laboratory. This model uses the proband's and second-degrees relatives history of Lynch syndrome-related cancers (colon, endometrial, stomach, ovarian, small intestine, urinary tract/kidney, bile ducts, glioblastoma, sebaceous gland tumors, and pancreas) and age of onset of colon and endometrial cancers. MSI and IHC testing is not included. Based on genotype/phenotype data, this model provides specific likelihood estimates for detecting a mutation in each of the MMR genes (*MLH1, MSH2, MSH6*). Using a 5% mutation probability as a standard for MMR testing, the model has an estimated sensitivity of 90% and a specificity of 54%.[57] Using family history it can also estimate risk of MMR gene mutation in an unaffected individual.

MMRpredict

Uses a population-based cohort diagnosed with CRC before age 55 years who were tested for *MLH1, MSH2*, and *MSH6* mutations. Data from MSI and IHC testing and the presence of CRC and/or endometrial cancer in first-degree relatives can be incorporated. This model can only be used in affected individuals. Because the model is based on those diagnosed before 55 years of age, it is unclear how accurate the model is for tumors diagnosed in older individuals.[58]

MMRpro

Uses the data obtained from clinic and population available in the literature with cancer risk estimates based on penetrance from a meta-analysis of five large Lynch syndrome studies. It uses the presence of CRC and other cancers in the proband, first- and second-degree relatives, age of onset, and IHC and MSI testing to estimate the likelihood of identifying a germline mutation in *MLH1*, *MSH2*, or *MSH6*. It allows calculation of a family member's risk to inherit the germline mutation and the risk to develop colon or endometrial cancer.[59]

Risks of CRC

In the early 20th century, at the time Warthin' first described Family G, gastric cancer was a common cancer in Lynch syndrome families. Just as sporadic cancer has seen a decline, so has gastric cancer in Lynch syndrome. The more common secondary cancers are colorectal, ovarian, gastric, and renal system (transitional cell of renal pelvis and ureter) and sebaceous cysts adenoma and adenocarcinomas. A mnemonic quite useful to remember these is COUGaRS: Colorectal, Ovarian, Uterine, Gastric and Renal(Urinary-transitional cell), Sebaceous tumors. Other cancers include medulloblastoma brain cancers, biliary cancers, and small bowel. More recent small increases in prostate and breast has been reported. Currently, colorectal cancer is overall the most common cancer in Lynch syndrome.

Earlier in the history of Lynch syndrome, the mean age for CRC was thought to be 43 years old. Lynch describes average age of 44.6 years in his Family R.[5] We now know this is a false low average due to selection bias. As we all had a higher degree of concern for the younger patients with CRC it falsely lowered the mean age of occurrence. When Hampel excluded the probands in her study, and with aggressive discovery of relatives with Lynch who already had CRC, the average age of cancer in the nonprobands was 61 years.[60]

Previously patients with Lynch syndrome were thought to have a ~80% risk of cancer by the age of 80. As our knowledge and diagnostic capabilities have been augmented, our numbers are tempered. Also, looking at risks based on specific mutations, more individualized risks can be predicted. These risks also vary by sex. For example, *MLH1* and *MSH2* mutations have CRC risks of 66-69% in men, 43-53% in women with average age of 61 years.[60,61] Overall, *MSH6* and *PMS2* have an attenuated risk. CRC cancer risks for patients with *MSH6* mutations are 44% for males and 20% for females.[62] Patients with *MSH6* mutations also present with later ages of onset and a more distal distribution. They are also associated with MSI-L tumors.[46,63] The risk in a patient with a *PMS2* mutation was 15%-20% by 70 years of age.[47] The newly noted mutation in *EPCAM* has higher penetrance for CRC. Kempers estimated from a cohort of 194 individuals with *EPCAM* mutations that the cumulative risk of CRC by 70 is 75%.[64]

Risks of non-colonic cancers

See Table 8.[65]

Table 8 – Comparative risks of cancer types of general population and patients with MLH1 and MSH2 mutation, and mean age of onset of each cancer with patients with MLH12 and MSH2 mutations.

Cancer Type	General population risk	Lynch syndrome (MLH1 and MSH2 heterozygotes)	
		Risk	Mean age of onset
Colon	5.5%	52-82%	44-61 years
Endometrium	2.7%	25-60%	48-62 years
Stomach	< 1%	6-13%	56 years
Ovary	1.6%	4-12%	42.5 years
Hepatobiliary tract	< 1%	1.4-4%%	Not reported
Urinary tract	< 1%	1-4%	~55 years
Small bowel	< 1%	3-6%	49 years
Brain/central nervous system	< 1%	1-3%	~50 years
Sebaceous neoplasms	< 1%	1-9%	Not reported

Endometrial cancer

Endometrial cancer (EC) is the second most common cancer in Lynch syndrome. Women have a 25-60% lifetime risk (Table 8).[60,61,66,67] Just as studies on high-risk families found a younger age of onset for colon cancer that was reputed in population studies, the same occurred with EC. Early studies reported average age of 48 years old; the population-based studies now show average age is 62.[60,67]

Also similar to colon cancer, endometrial cancer has various risks based on mutation site. *MLH1, MSH2, MSH6*[32] have approximately a 44% risk for endometrial CA. Others have noted a slight increase risk of endometrial for *MSH6* vs. *MLH1,* and *MSH2*.[46] Kemper[64] found a 12% risk for *EPCAM* mutations. Women who in their lifetime have both colon and endometrial cancer have an equal chance of having either cancer first.[69,62] For those women who are diagnosed with their colorectal cancer first, their subsequent risk of later EC is 26% within 10 years of their CRC diagnosis.[70] The lifetime risk (70 years) for a woman to have colon or endometrial cancer was noted to be 73% in Stoffel's study.[61]

Gastric cancer

Gastric cancer in Lynch patients is usually intestinal type adenocarcinoma, though Capelle has reported that in the Netherlands, up to 20% can present with a diffuse gastric carcinoma histology.[71,72,73] Microsatellite instability is noted in these tumors.[74]

Overall, estimates for gastric cancer risk in heterozygotes for an *MLH1* or an *MSH2* mutation range from 6% to 13%. Men with *MSH2* mutation have the highest risks.[72,73] A high incidence of H pylori infection, or Asian populations also have increased incidence.[75] The mean age of diagnosis is 56 years old.[71]

Ovarian cancer

The risk for ovarian cancer is roughly twice in *MSH2* (8%-11%) versus *MLH1* mutation (4-6%). The mean age is 42.5 years with

30% diagnosed before the age of 35.[72] The histology distribution is similar to those with sporadic ovarian cancer, though borderline does not seem to be associated with Lynch syndrome.[76] One metanalysis paper noted ovarian cancers with mismatch repair deficiency presented in earlier stages.[77] The only study that compared survival did not reveal a survival advantage for Lynch patients with ovarian cancer versus the sporadic ovarian cancer.[78]

Renal-urinary tract cancers

The urinary tract cancers most associated with Lynch syndrome are transitional carcinomas of the ureter and renal pelvis. One Dutch study suggested an increased risk with bladder cancer. Their Lynch patient with bladder cancer did show MSI and/or loss of stain on IHC that corresponded to the germline mutation. Bladder cancer, however, is not listed as one of the Amsterdam or Bethesda criteria.[76,79] Watson notes a smallest risk estimate of 1% in women with *MLH1* mutation and then up to 27% in men with *MSH2* mutation.[72]

Small bowel cancer

Lifetime risk of small bowel cancer is 3-6%, though >100 times the risk of the general population.[72] 50% of the small bowel cancers are within the duodenum and jejunum, within the reach of an upper endoscopy.[80] The majority in adenocarcinoma[80] incidence is similar between *MLH1* and *MSH2* mutations and rare in *MSH6* and *PMS2*.[81]

Pancreatic and biliary cancer

A few studies have revealed an increased risk of pancreatic cancer, and family clustering is noted. Geary noted a sevenfold increase risk in their Lynch syndrome patients over the general population.[82,83] However, other studies have not demonstrated an increased risk.[84]

Brain tumors

The risk for brain tumors is estimated at approximately 2%.[16] Risks may be underestimated as 26% of the time when the age of onset is before 25 years of age.[72] The most common histology is glioblastoma, and is rarely associated with microsatellite instability.[85] It is the third cause of cancer death for Lynch patients in a large Dutch cohort.[86]

Sebaceous skin neoplasias

This includes sebaceous adenomas, sebaceous epitheliums, sebaceous carcinomas, and keratoacanthomas.[87,88] Sebaceous neoplasms associated with Lynch syndrome exhibit MSI and IHC.[89,90] The data on the frequency of sebaceous neoplasms in individuals with Lynch syndrome are limited. Studies have found that between 1% and 9% of individuals with a germline mutation in an MMR gene have a sebaceous neoplasm.[91,92] Individuals with Lynch syndrome and a sebaceous neoplasm have Muir-Torre syndrome, which was initially thought to be a separate entity. IHC testing of sebaceous adenomas has shown that a significant proportion is sporadic. Among those with abnormal IHC testing in a sebaceous neoplasm, Lynch syndrome mutation carriers are more likely than those with sporadic presentation to have multiple sebaceous neoplasms and a personal or family history of a Lynch spectrum cancer.[93]

Additional cancer risks

Hematologic cancers, laryngeal cancer and sarcomas have been suggested. Due to rarity of presentations, it is difficult to determine the magnitude of risks.[94,95] Nilbert[96] did note defective MMR in the histopathology of six of eight sarcomas in individuals with Lynch syndrome.

Breast cancer

The relationship between breast cancer and Lynch syndrome is unresolved.[97,98,99] Studies have not consistently demonstrated a higher than expected incidence. Walsh, however, did demonstrate that in breast cancer of patients with a mutation in a MMR gene, 51% did demonstrate a loss of immunohistochemical staining for the protein corresponding to the gene in which a germline mutation occurs.[100]

Variants of Lynch

Muir-Torre syndrome is the terminology used to describe a Lynch syndrome patient who also has sebaceous neoplasms of the skin. The types of sebaceous skin neoplasias described include: sebaceous adenomas, sebaceous epitheliomas, sebaceous carcinomas, and keratoacanthomas.[87,88] *MSH2* mutation is the most common mutation noted.[92]

Turcot syndrome is defined as CRC or colorectal adenomas in addition to tumors of the central nervous system. This can be due to APC gene mutation as seen in FAP, or due to MMR gene mutation associated as a Lynch syndrome.[101] Therefore, the clinical colonic presentation varies from numerous colonic polyps to a single polyp or CRC. The brain cancer associated with APC mutation tends to be medulloblastomas; mutations of the MMR gene tend to present with glioblastomas. The brain tumors associated with mutations in a mismatch repair gene exhibit MSI.[101,102]

Homozygous mismatch repair mutations: rare individuals who are homozygous for mutations in *MLH1*, *MSH2*, *MSH6,* and *PMS2* have been reported. Affected individuals often have onset of colon or small bowel cancer prior to the second decade of life. One third of children with biallelic mutations have been reported to have more than ten polyps. Also associated is Hematologic cancer, brain tumors, and *café-au-lait* macules.[103,104]

Survival

When matched stage for stage, colon cancers in individuals with Lynch syndrome are associated with a better prognosis than sporadic colon cancer.[105] This is an unexpected finding because the poorly differentiated histology of Lynch syndrome-related colon cancers is typically associated with a

poor prognosis. Due to the mutation in the MMR genes, Lynch syndrome cancers do not respond to typical chemotherapeutic agents like 5-fluorouracil, in fact, they may do worse.[106]

Surveillance

Surveillance is an important part of the management of a patient with Lynch syndrome. Optimal surveillance requires a multidisciplinary approach involving primary care physicians, gastroenterologists, gynecologists and colorectal surgeons. An excellent resource for surveillance is available on the National Comprehensive Cancer Network website (www.nccn.org). There are no strong data for surveillance for many of the Lynch syndrome associated cancers and recommendations outside of colon and endometrium are based on expert opinion.

CRC Surveillance

Since 1977 Dr. Lynch proposed starting colonic surveillance as early as 20 years of age.[5] Current surveillance recommendations also start in Lynch patients as early as age 20-25 (or 10 years prior to family member's cancer diagnosis, whichever is earlier) with colonoscopy. Intervals are every two years, until 40, then yearly afterwards. The short interval is due to the accelerated progression of polyp to cancer as noted by Jass in 1992.[107] Some recommend starting surveillance at the age of 30 in patients with *MSH6* or *PMS2* mutations since the average age of onset of colon cancer is somewhat later. Colonoscopy is repeated every 1-2 years. After diagnosis of CRC and subsequent resection, surveillance should occur on a yearly basis. Regular surveillance is proven to reduce both incidence (11% vs 27%) and death (2% vs 12%) from CRC.[108]

Gynecological Surveillance

There is no clear evidence to support routine screening or surveillance for endometrial or ovarian cancer. Some recommend annual transvaginal US and endometrial sampling at 30-35 years of age.[46,47] Studies on the effectiveness of transvaginal ultrasound examination and endometrial biopsy have had conflicting results. In most screening studies, patients presented with symptoms before or during their surveillance with transvaginal ultrasound or endometrial sampling.[109,110]

Ovarian cancer

No specific ovarian cancer screening trials have been conducted in women with Lynch syndrome. Of note, screening for ovarian cancer using CA-125 blood tests and transvaginal ultrasound examination has not been effective in other high-risk populations such as women with a *BRCA1* or *BRCA2* mutation.[111]

Gastric cancer

There are no strong data for gastric cancer surveillance. Schulmann has noted that 50% of his patients with small bowel cancer were noted proximally within the reach of an upper endoscope.[80] While there are no studies on the efficacy of surveillance, enteroscopy is a consideration noted by the NNCN starting at age 30-35 and performing every 2-3 years. More frequent intervals can be considered if chronic inflammation, atrophic gastropathy and/or intestinal metaplasia is noted. Many insurance companies are now covering this procedure. Also capsule endoscopy every 2-3 years starting at 30-35 years of age can be considered for surveillance of the distal small bowel.

Urinary collecting system

A urinalysis can be performed on an annual basis starting at 30-35 years of age (NCCN 2011). There are no studies to prove efficacy and survival. As it is a noninvasive test, recommendations remain.

Other cancers

Lindor et al.[46] recommend beginning annual examination at age 21 for features of sebaceous. The National Comprehensive Cancer Network recommends beginning annual physical exam for such features at 25-30.[112] There is no current data to make a standard recommendation in the case of pancreaticobiliary cancers. There are programs that are embarking as a research study to perform surveillance for Lynch and other high-risk patients for pancreatic cancer.[113,114]

Surgery for prophylaxis and for treatment

Gynecological cancer

Women with Lynch syndrome who are undergoing colon cancer are usually offered the choice of prophylactic hysterectomy and bilateral salpingo-oophorectomy. Also, once the patient is past childbearing age or post-menopausal, prophylactic hysterectomy and bilateral salpingo-oopherectomy can be considered as a risk-reducing measure. Schmeler[115] noted in their case-control study of 315 women with Lynch syndrome, 1/3 had prophylactic hysterectomy with bilateral salpingo-oophorectomy. After 10 years of follow-up, there were no gynecological cancers in the women with prophylactic surgery, though there was 33% incidence of endometrial cancer and 5% ovarian cancer in the control group. Chen and colleagues[116] also noted the efficacy of prophylactic surgery. They concluded that one diagnosis of endometrial cancer was prevented for every 6 surgeries, and one ovarian cancer for every 28 surgeries. Most would recommend for the pre-menopausal women who choose prophylactic surgery to be placed on hormonal replacement until the age of 50.[30,46,47,117]

CRC

Dr. Lynch first described that, with good family history, recommendations of colon removal may decrease the incidence of cancer.[5] This was prior to significant use of colonoscopy in the prevention of colon cancer as the snare was just invented

in 1969.[118] Currently prophylactic colon resection is not recommended. The extent of surgery to be performed once a CRC is diagnosed is still under investigation (NCCN 2011). There are pros and cons to consider in regards to segmental vs. total or subtotal colectomy. There is a balance of quality of life, and the risks of metachronous disease.

The initial risks of CRC as stated earlier are substantially decreased with frequent surveillance by colonoscopy. There is no reason not to believe that metachronous cancers are not also reduced with frequent surveillance. Engel noted in their Lynch patients that if a metachronous cancer was found during yearly surveillance colonoscopy it was earlier in stage, with 95% discovered in Stage I and Stage II.[119]

Parry[120] notes in their comparison of segment versus extensive resection that the metachronous risk was reduced by 31% for each 10cm of bowel removed. While they state there was no difference in the frequency of endoscopy in the two groups, the interval was truly only estimated and not recorded. The weakness in this study is the frequency of scoped was assumed to be distributed uniformly in the period between the first and last age of endoscopy. Those metachronous cancers that were discovered, as in Engel' study, were predominantly in early stages: 27 (47%) at stage I, 20 (35%) at stage II and 10 (18%) at stage III. Of the 10 patients who developed AJCC stage III metachronous CRC (mean follow-up 12 [SD 10] years), six reported 1-2 yearly lower endoscopy, one reported no endoscopy and for three it was unknown. At 5 years after surgical resection, 49 (98%) who had extensive colectomy and 327 (98%) who had segmental colectomy were alive (p1⁄40.8). At 10 years, 49 (98%) who had extensive colectomy and 322 (97%) who had segmental colectomy were alive (p1⁄40.7). Therefore one can conclude a more substantial resection may limit second surgery but no proof in increased survival can be gathered by this study.

Maeda[121] constructed a state-transition (Markov) model based on assumptions obtained from available data sources and published literature. They compared segmental colectomy (SEG) to a total abdominal colectomy (TAC) for quality adjusted life years (QALYs). They concluded that, for young (30-year-old) patients with Lynch syndrome, mean survival was slightly better with TAC than with SEG (34.8 v 35.5 years). Their QALYs were approximately equivalent, with QALYs per patient of 21.5 for SEG and 21.2 for TAC. With advancing age, SEG becomes a more favorable strategy.

There have been no studies to date that prove that a more extensive resection will translate to greater colon cancer survival. Therefore, case by case management based on patients' age of presentation, stage of initial cancer presentation, current bowel habits and continence, willingness to undergo close surveillance and patient desires need to be considered and discussed with the patient.

Risk adjustments

We are all aware that there is always an interplay between environment and genetics. We at this time cannot change our genes, but can we decrease the risks that our genes have in store for us through our environment? There are many reasons to stop smoking. We encourage our Lynch syndrome patients to stop smoking as it was one of the three risks factors CRC noted by Watson et al.[122] The other two factors were male sex and *MLH1* mutation. The hazard ratio of being a male was 1.58, *MLH1* vs. *MSH2* was 2.07 and tobacco use, 1.43.

Chemoprevention

Women who take a combined oral contraceptive pill can lower their risk of endometrial and ovarian cancer. This risk seems to decrease with longer duration. While the ovaries enjoy a permanent protective effect, this affect persists for about 5 years after stopping oral contraceptives. While there is no evidence to suggest oral contraceptives in Lynch syndrome patients, its use is not contraindicated in Lynch syndrome patients. Other risks factors such as smoking and history of thromboembolism need to be considered prior to prescribing.[117,122]

Professor Burn and team have been looking over the years at the use of aspirin and starch to prevent CRC in patients with known mutations. His study was a two by two double blinded randomized study of starch/ASA, Starch/placebo, placebo/ASA, placebo/placebo. Patients received 30 g of starch (novelose) and 600 mg of aspirin. The study was designed to note if this decreased the incidence of advanced adenomas or carcinomas. Initial results of 746 Lynch patients after 4 years did not reveal a decreased risk with the use of aspirin. In 2011, after a few patients had reached 10 years of follow-up, the results were reviewed once more in regards to their risks of CRC and other Lynch related cancers. Post-intervention review revealed 13 of 342 allocated aspirin and 27 of 329 allocated had CRC. 38 participants developed cancer at a site other than the colorectal (additionally, two participants had CRC and another Lynch syndrome cancer) of which 16 were randomly assigned to aspirin and 22 to aspirin-placebo. The study does not comment on the compliance of colonoscopy but interestingly even for non-CRC the risks decreased. From this they recommend 600 mg of ASSA per day for patients who can tolerate the regimen. CAPP3 is underway to evaluate different dosages as doses <600 have been implied in their study to be also effective. The optimum dose and duration is to be studied in CAPP3.[123,124]

Family X

At the beginning of the paper we discussed the importance of Lynch to be diagnosed with confirmation of MMR gene mutation. It is now known that not all patients who meet the Amsterdam Criteria are Lynch syndrome patients. This is best illustrated with Family X. Family X was first described by Lindor.[125] In her large database of patients that met Amsterdam criteria, there were two groups. One group was MSI, the other was MSS. Comparing these patients and their at-risk relatives (3422 first- and second-degree relatives) in these two groups, a few striking differences were noted. A standardized incidence ratio was calculated and compared to the general population. The families that were MSI-H had a greatly increased risk of CRC with a SIR 6.1. Also increased were cancers of the uterus, stomach, urinary tract, ovary,

and small bowel, pancreas and liver. The MSS family had a CRC risk with a SIR of 2.3. There were no other cancers noted with increased risk in this group. The onset of cancer in the MSI0H group was also earlier (48.7) vs. 60.7 in the second group. The lower risk ratio for CRC and the absent risk of the secondary cancers. In retrospect this is the Lynch syndrome I patients that were discussed many years ago.

Lindor dispelled the notion that all families meeting Amsterdam I criteria are a distinct homogenous group and could now be further subdivided by their MSI status. The families that do not have an MMR defect (MSI-L/MSS in this study) have a lower risk of CRC, and a later onset. Therefore colonoscopy recommendations are to start colonoscopies for the at-risk family members at 5-10 years earlier than the earliest diagnosis of CRC in the family and occur every 5 years, if normal.

During the same year Llor et al.[126] studied 1309 newly diagnosed CRC in Spain in which 25 probands fit Amsterdam I or II criteria. Fifteen (60%) of the tumors were MSS with the remaining MSI-H. All MSS tumors expressed *MLH1*, *MSH2* or *MSH6*. MSS probands were older at diagnosis (67.8 vs. 64.8), had more left sided colon cancers (86.7 v evenly spread), were well differentiated (33% vs. 0%), and lacked lymphocytic infiltrate (0% vs. 50%). There was no difference in synchronous or metachronous cancers. When looking at relatives, more families in the MSS group had less affected members than in the MSI-H group (18% vs. 31.5%) and were diagnosed at a later age (60.2vs 53.8). All extracolonic tumors found in both groups were endometrial and this occurred more frequently in the MSI group than in the MSS group (5.1% v3.3%). These findings echoed Lindor's study that MSS families fulfilling Amsterdam criteria appear to be representing a syndrome separate from Lynch syndrome. Later studies, including a 2007 study by Valle et al.,[127] continue to bolster this important distinction.

Summary

Much has been learned since the Human Genome Project, and much more is to be discovered. As more variants of unknown significance are categorized as deleterious mutations, more patients will be properly diagnosed as Lynch syndrome. As we have better definitions of the mutations, and long-term follow-up on the affected patients, we will become better in tailoring patients' risks and therefore tailoring their management. With a better understanding of their pathophysiology we may then be able to intervene with better prevention strategies. To meet the goals of increasing the diagnosis of Lynch syndrome to then in turn decrease incidence of cancer in these families, a group of institutions formed the Lynch Syndrome Surveillance Network in the United States in 2011. Through universal screening and a common shared database these goals can be met.

Conflict of interest

The authors declare no conflicts of interest.

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