

# Lynch Syndrome: An Explanation for Families

## *Hope for the Future*



This article is dedicated to the memory of Dr. Jeremy Jass

Teacher, mentor, colorectal cancer pathologist, and researcher in the Colon Cancer Family Registry

And as a tribute to my friend Lynn, whose family history has led to countless presentations on Lynch Syndrome

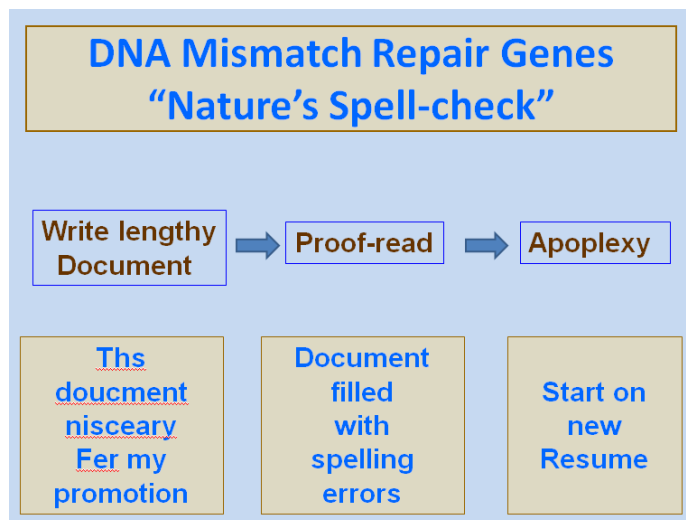
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Recently, a friend and I were discussing the details of a medical procedure that both of us had undergone at the same hospital, and even more coincidentally, with the same gastroenterologist. Although my colonoscopy had been clean, she asked if I might explain the significance of the polyp that she had been diagnosed with. To my surprise, her pathology report revealed seven polyps, and moreover, they ranged throughout the colon – from her cecum to her rectum - that is, from one end to the other. To a molecular oncologist, seven polyps were far more interesting than a solitary polyp! When I asked about her family history of polyps and cancer, she was only able to recall one case - her father's colon cancer. Since some cancers, including colon cancer, tend to aggregate in certain high-risk families, I offered to help her develop her own family tree, albeit a family tree of cancers. Her job was to start questioning every living relative on her father's side of the family. As she began to hone her investigative skills, the process became both rewarding and intriguing. Long-lost family history was slowly unraveled and, moreover, her dogged questioning inspired others in the family to query even more relatives in a sort of generational cascade of questions. After a number of weeks, we were able to reconstruct the cancer family history for many generations. Relatives continued to offer information, which enabled us to fill in the missing ages at diagnosis of cancer in some relatives. Her family history was significant in that six successive generations on her father's side had one or more cases of colon or other cancers, including some that were diagnosed before age 50 (a young age for cancer and seen much more often in high-risk families). The youngest, a cousin, was diagnosed with colon cancer at age 34. He died within two years.

My friend's family history is typical for Lynch Syndrome, the most common form of hereditary colon cancer. First described by Dr. Warthin in 1913, the syndrome remained both unacknowledged and unappreciated by the medical community for over 60 years, when Dr. Henry Lynch started exploring the family trees of some of his high risk patients. To his surprise, one of his families was the initial family (Family G) reported by Warthin. Dr. Lynch's early publications garnered international interest in what appeared to be a hereditary syndrome associated with increased risk for cancers of the intestines. The syndrome was initially termed Hereditary Non-Polyposis Colorectal Cancer (HNPCC). It is now known that the syndrome encompasses a broad spectrum of cancers, including those of the colon (large intestine), small intestine, endometrium (lining of the uterus), ureter and renal pelvis (parts of the urinary system), kidney, bladder, stomach, pancreas, ovary, brain, liver - including the gallbladder and its bile duct, skin (sebaceous adenomas, sebaceous cancers and keratoacanthomas), possibly breast and prostate cancers, as well as cancers of connective tissues called sarcomas. In recognition of Dr. Lynch's contribution, this complex pattern of familial cancers was renamed Lynch Syndrome. Lynch Syndrome is caused by a hereditary mutation in a family of genes known as DNA Mismatch Repair (MMR) genes.

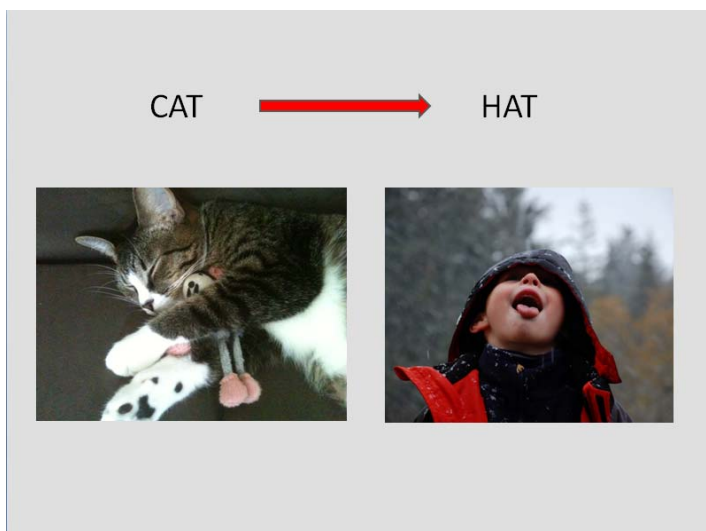
### Role of DNA Mismatch Repair Genes

The biologic function of MMR genes is to repair genetic mistakes that sometimes occur in the DNA when cells divide. The proteins produced by the MMR genes peruse the DNA, looking for any "spelling" errors in the genetic sequence. If an error is detected, the proteins can remove the faulty segment of DNA and replace it with the correct sequence. Genetic mutations in a MMR gene disable the gene and its protein; this results in the accumulation of unrepaired errors throughout the remainder of the DNA. In cells that frequently divide, such as those lining the body cavities of the stomach, intestines, uterus, and other hollow organs,



the unrepaired DNA errors can accumulate to critical levels, affecting normal cell function. In many ways, the genes serve as a “spell-check” protein for DNA. An analogy is to envision typing a lengthy but important document on a computer with a broken spell-check function; for most of us, the longer we type, the higher the number of spelling errors.

However, to better understand the significance of mutations in Lynch syndrome, it is helpful to go back to molecular biology 101. In the English language, there are 26 letters which can spell any word used in the Western World depending on how the letters are arranged. The genetic alphabet is shorter, consisting of only four letters or nucleotides, abbreviated as C, T, A, and G. Despite the limited number of genetic letters, nature has ingeniously found a way for these four nucleotides to spell out not words, but rather the recipe for any protein needed by the human body. Just as for words, the genetic letters in our DNA must be arranged in a highly specific sequence in order for proteins to be properly synthesized. Even one improper letter in the DNA sequence can cause a protein to become misshaped, completely dysfunctional, or even missing. Spelling errors in the DNA are referred to as mutations. Mutations in MMR genes are especially serious because the abnormal protein made by the mutated MMR gene will no longer be able to function properly as a “spell-check” for the remainder of the DNA, resulting in an accumulation of mutations in many other genes over time. Unfortunately in human beings (as in all living organisms), when unrepaired mutations occur in critical genes that control cell growth or other biologic functions, the affected cells may begin to grow unabated, resulting in tumor formation.



A HAT will never sit in your lap and purr. Yet it is only one letter different from CAT. That one spelling error makes all the difference!

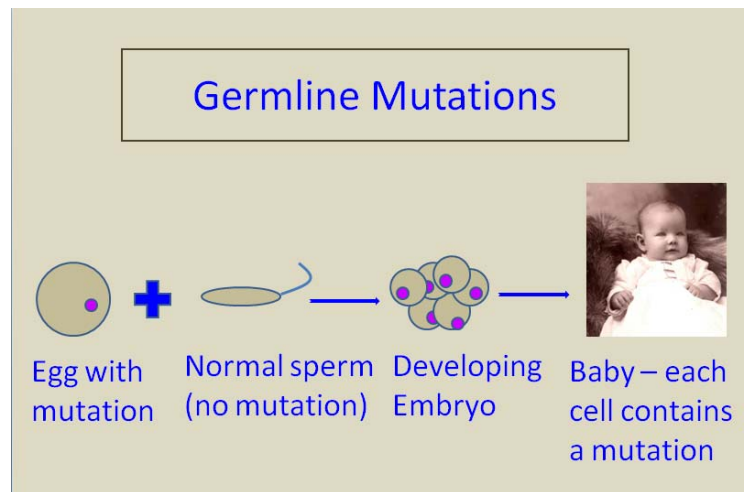
### [DNA Mismatch Repair Genes in Lynch Syndrome](#)

The Mismatch Repair genes consist of a family of genes, each of which has a slightly different role in the DNA repair process. The genes were first identified in yeast cells, and the names were coined as a reflection of their biologic roles in those cells. The four genes that contribute to Lynch Syndrome in humans are MLH1, MSH2, MSH6, and PMS2. Other MMR genes exist, but none is believed at this time to play a major role in Lynch Syndrome. The most commonly mutated genes are MLH1 and MSH2, followed by MSH6. PMS2 is the least commonly mutated gene. Although much research remains to be done on how mutations in these four genes contribute to cancer development, it has been observed that the types of cancers and the age of diagnosis can vary depending on the specific gene that is mutated. For instance, patients with a mutation in PMS2 on average do not develop cancer until later in life, perhaps in their 60s, 70s, or later. This is in contrast to those with MLH1 or MSH2 mutations, in whom cancers often occur in early adulthood. Those with a mutation in MSH6 may be at higher risk for development of endometrial (lining of the uterus) cancer. A subset of Lynch families are at higher

risk for certain types of skin cancers (these families often have mutations in MSH2). Regardless of which MMR gene is mutated in a Lynch family, those who inherit the mutated gene are at higher risk for development of cancer.

### Pattern of Inheritance in Lynch Syndrome

The mutations found in Lynch Syndrome are *germline*, meaning that at conception, the mutation is present in either the sperm or the egg. As the fertilized egg divides, each cell will contain one copy of the mutated gene. At the time of birth, the newborn infant has  $10^{13}$  (1 followed by 13 zeroes) mutations, one individual mutation in each cell. The mutated gene in each cell is unable to produce a normal MMR protein. Fortunately, each cell contains two copies of each MMR gene, one from each parent. The normal copy (inherited from the parent who does not



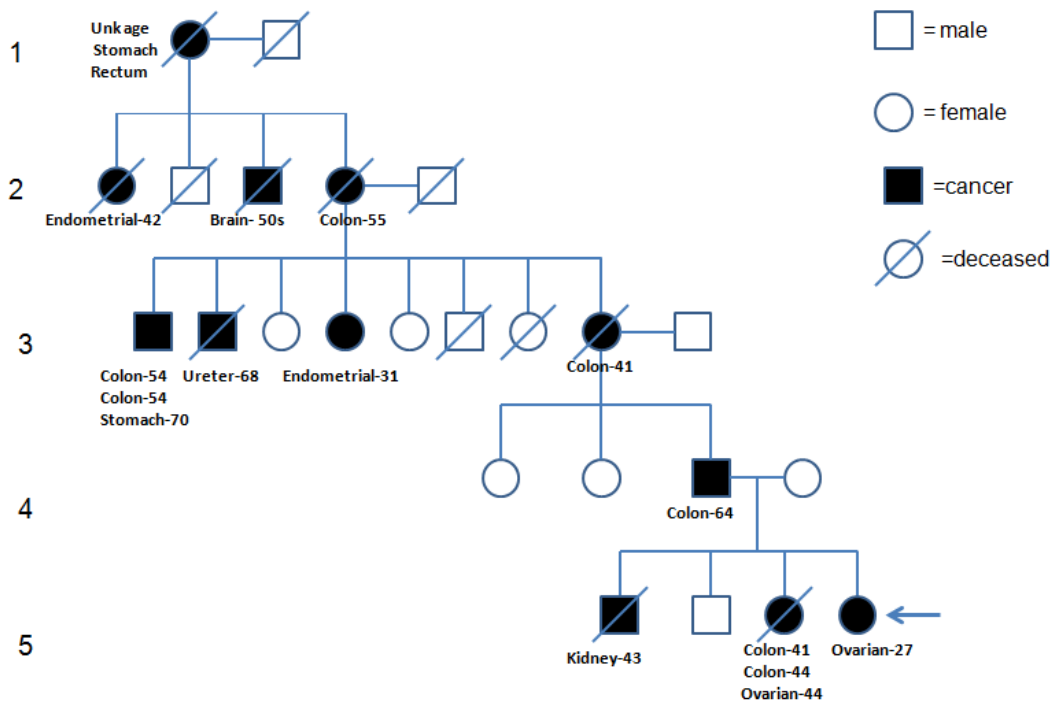
have Lynch Syndrome) can perform the spell-check functions of the MMR gene and maintain the integrity of the DNA genome. Cancers arise when a mutation knocks out the remaining normal copy of the MMR gene in a given cell. That cell, regardless of type - stomach cell, colon cell, or any other cell - now has no MMR defenses against genetic damage or changes in the sequence of the DNA. This is the mechanism by which cancers arise in individuals who are affected with Lynch Syndrome.

In some genetic diseases, a patient must inherit a mutated gene from both parents in order to develop the disease (this is called *recessive* inheritance). These patients generally develop disease very early in life because neither mutated gene is able to produce a normal protein. As a consequence, the cells cannot function normally and disease ensues.

However, the pattern of inheritance in Lynch Syndrome is described as *dominant*, meaning that inheriting a mutated gene from just one affected parent will cause the disease. Because each cell in an affected person has a copy of the mutated gene, the affected mother or father would pass the mutated gene on through egg or sperm cells respectively. Hence, regardless of which parent is affected, the mutated gene can be passed on with equal chance to sons and daughters. This means that each child has a 50% chance of inheriting the mutated gene and a 50% chance of inheriting a normal gene from the affected parent. Of course, each child will also inherit one normal gene from the unaffected parent (remember that each cell contains two copies of the gene - one from each parent). Having said that, the actual proportion of children in a given Lynch family who inherit the gene is not quite so straight forward. When flipping a coin, there is a 50/50 chance that it will be tails. We all know, however, that if you flip a coin 10 times, it is highly unlikely that you will get tails on exactly five of the flips. This is because each flip starts over again with a 50/50 chance. In many Lynch families, roughly half of the children inherit the gene. But just as we sometimes see only one or two tails or, in contrast, nine or ten tails out of ten tosses of the coin, Lynch families can defy the odds. In our studies on Lynch Syndrome, we have a number of families in which the majority of children (for example, 5 of 6) are diagnosed with Lynch Syndrome, while in others only one child in a relatively large family inherits the gene.

## Family Trees/Pedigrees in Lynch Syndrome

Because of the substantial lifetime cancer risk for individuals who do inherit a mutated gene, plotting those with cancer on a pedigree or family tree often results in a striking cancer history. Below is an example of a pedigree for a Lynch family. In the pedigree, males are depicted as squares, females as circles, darkened circles/squares are those with cancer, the age of diagnosis (if known) is listed, slashes indicate individuals who have died. Note that cancers are observed in each generation of this family, that multiple types of cancers are present in the family, that ages when cancer was diagnosed vary, that some individuals develop multiple cancers (including multiple cancers in the same organ), and that in some families, the number of affected children may be much higher (or lower) than 50%. In presenting a pedigree, the current generations are always listed at the bottom (in this pedigree, generation 5), and the earlier generations (grandparents, great-grandparents, and so on) are found above, one line per generation. In this family, the cancer history was traced back five generations. The arrow indicates the patient first diagnosed with Lynch.



## Amsterdam Criteria

The Amsterdam Criteria, developed by an international consortium of scientists interested in Lynch Syndrome, capitalized on the striking pattern of family history in Lynch families. These criteria were used to facilitate the diagnosis of Lynch Syndrome before molecular diagnostic tools such as DNA testing were available. A typical “Amsterdam I” family will have the following criteria:

- at least 3 relatives with colorectal cancer (CRC)
- one relative must be a first-degree relative of the other two
- at least two successive generations are affected
- at least 1 case must be diagnosed before age 50
- the family is known not to have a different hereditary syndrome called Familial Adenomatous Polyposis (FAP)

A biologic parent, sibling, or child is defined as a first-degree relative. An essential feature in Amsterdam I families is the presence of a “triad” of CRC cases – each triad consists of 3 cases meeting the above criteria. Examples of triads are two siblings and a biologic parent - each diagnosed with CRC; a child, father, and paternal grandparent with CRC; a child, mother, and maternal aunt with CRC. Of course, one of the CRC cases must be less than age 50 at diagnosis. It should be pointed out that an affected child with two affected parents does not constitute a triad because although the parents are both first-degree relatives to their child, they are not first-degree relatives of each other. In the pedigree above are many examples of triads, which indicate that this Lynch family fulfills the Amsterdam I criteria. Later, when it was understood that Lynch Syndrome encompasses many types of cancers, the criteria were loosened. Currently, there are a variety of pattern-detecting tools (Amsterdam I, Amsterdam II, modified Amsterdam, and revised Bethesda criteria) with somewhat different criteria, all of which assist the physician and the genetic counselor in determining if the family should be tested for Lynch Syndrome. It should be noted that meeting the Amsterdam criteria is not a diagnosis of Lynch Syndrome, only a diagnostic tool. Conversely, not all Lynch Syndrome families meet the criteria above, and this can be misleading for clinicians and patients alike when the diagnosis of Lynch is being considered.

Skipping of generations (a generation with no cancers), although uncommon, can be attributed to a number of factors. In some cases, death of undiagnosed mutation carriers at young ages (accidents, war, and at different times and places, infectious diseases) before cancers would normally develop produces what looks like a skipped generation. This can also be observed when undiagnosed carriers undergo surgical procedures such as hysterectomy (removal of the uterus) or gastrectomy (removal of the stomach), which fortuitously prevents the development of cancer in these organs. More recently, routine clinical exams or procedures may result in the removal of suspicious lesions such as colon polyps at an early phase of growth, thus thwarting eventual cancer development. And some individuals, despite being mutation-positive, never develop cancer. Relatives in Lynch families who do not develop cancer are assumed to be an “obligate carrier” (the mutation carrier status cannot be confirmed, but is assumed) when his or her children are diagnosed with Lynch Syndrome. Thus, although there may be no cancer within a given generation, there is essentially always a mutation carrier if someone in a subsequent generation is diagnosed with Lynch Syndrome.

### [Cancer Risk in Lynch Syndrome](#)

#### **Lifetime Cancer Risks**

	<u>Lynch Risk</u>	<u>General Public Risk</u>
Colorectal:	52-82%	5.5%
Endometrial:	25-60%	2.7%
Stomach:	6-13%	<1%
Ovarian:	4-12%	1.6%
Small intestine:	3-6%	<1%
Urinary tract:	1-4%	<1%
Hepatobiliary tract:	1-4%	<1%
Brain:	1-3%	<1%
Sebaceous skin lesions:	1-9%	<1%

Kohlmann W, Gruber SB; Lynch Syndrome  
[www.ncbi.nlm.nih.gov/books/NBK1211](http://www.ncbi.nlm.nih.gov/books/NBK1211)

#### **Mean age of diagnosis of Lynch Cancers**

Colorectal:	44-61 years
Endometrial:	48-62 years
Stomach:	56 years
Ovarian:	42.5 years
Small intestine:	49 years
Urinary tract:	55 years
Hepatobiliary tract:	not reported
Brain:	50 years
Sebaceous skin lesions:	not reported

Kohlmann W, Gruber SB; Lynch Syndrome  
[www.ncbi.nlm.nih.gov/books/NBK1211](http://www.ncbi.nlm.nih.gov/books/NBK1211)

All individuals diagnosed with Lynch Syndrome are at higher risk for development of cancer during their lifetime compared to the general public. Risk levels are reported as a range, since risks reported vary between published studies, and may be dependent on the particular MMR gene, the specific mutation, race/ethnic background, gender (whether you are male or female) and other factors not yet understood. The lifetime risk for developing a cancer of the colon or rectum in Lynch carriers can approach 80% or higher; the lifetime risk for endometrial cancer ranges from 20-60%. Lifetime risks for developing other cancers are generally considered to be less than 20%. The risk for developing cancer at an early age is also elevated. Although some individuals may develop first cancers in their 60s, 70s, or even 80s, it is more common for carriers to develop cancer at younger ages, sometimes even in the third decade of life (20s). One of the hallmarks of Lynch syndrome is an elevated risk (up to 30%) for mutation carriers to develop more than one cancer. These *metachronous* (happening at different times) cancers can be limited to one organ (for instance, tumors that develop in different parts of the colon over a period of time), but are also observed to occur in different organs (e.g., colon cancer followed later by endometrial cancer). Multiple cancers can also be diagnosed at the same time, either in the same or in different organs. These are known as *synchronous* (happening at the same time) cancers. The colon of one of our study patients was found to contain four separate cancers when it was removed! This patient fortunately decided to have his entire colon removed, which facilitated the detection of the other cancers. Very rarely, Lynch patients will develop many new primary (unrelated independent) cancers. Two other study participants each developed more than seven primary cancers. One died relatively young, while the other lived to see multiple grandchildren. This tendency for multiple cancers can help direct treatment once a cancer is detected, including more aggressive surgical resection, which is done to help prevent future cancers in the organ(s) affected.

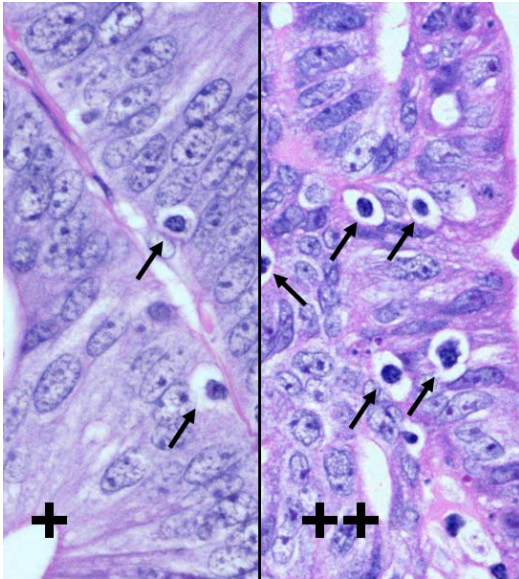
### Colon Cancer in Lynch Syndrome

Cancers of the colon or rectum are the most common cancers diagnosed in Lynch patients. Approximately 1/35 individuals diagnosed with colorectal cancer has Lynch Syndrome, or, looking at this from a different perspective, about 3-5% of all newly diagnosed colorectal cancers can be attributed to Lynch mutations. Onset tends to be early, often before age 50, and occasionally as early as age 20. Colorectal cancers arise from precursor polyps, mushroom-like protrusions developing on the inner surface of the colon or rectum. Although Lynch carriers (unlike some other genetic syndromes that result in colorectal cancer) do not tend to have a large number of colorectal polyps, it is thought that the progression time from initial polyp formation to the development of cancer is shortened. This accelerated transition from polyp into cancer can be less than 2-3 years, compared to 10-15 years for those with non-hereditary colorectal cancer. Lynch carriers who develop colorectal cancer may have a better prognosis compared to patients who develop non-hereditary colorectal cancer. The reason for this is unknown.



Despite being a common Lynch cancer, many colorectal cancer cases are never explored for possible hereditary causes. In an effort to remedy this, a great deal of effort in the past decade has focused on describing the clinical and pathological features of Lynch-associated cancers. From a medical viewpoint, Lynch colorectal cancers tend to be "right-sided" (diagnosed in the cecum, ascending colon, or transverse colon), are "adenocarcinomas" (a pathological type of colorectal cancer), may be "poorly differentiated" (cells look very primitive, not like the fully functional cells that normally line the colorectum), and often have a unique pattern of infiltration of white blood cells called lymphocytes (immune cells) - looking, under the microscope, as if someone had taken a salt shaker and sprinkled the tumor with small, blue-stained cells. Some tumors may also develop abundant mucinous material; the tumor cells in these types of colorectal tumors may appear to be floating in mucus-like pools. These

features can alert the pathologist, generally the first physician to examine the tumor tissue microscopically after a biopsy or a cancer surgery, that the tumor may have a higher likelihood of being a Lynch cancer. Appropriate testing for Lynch Syndrome may then be recommended by the pathologist, especially if the patient is younger than age 50, has been diagnosed with multiple cancers, or has a strong family history for colorectal or other cancers. Often, genetic counselors will work with the pathologist to determine which tests are needed.



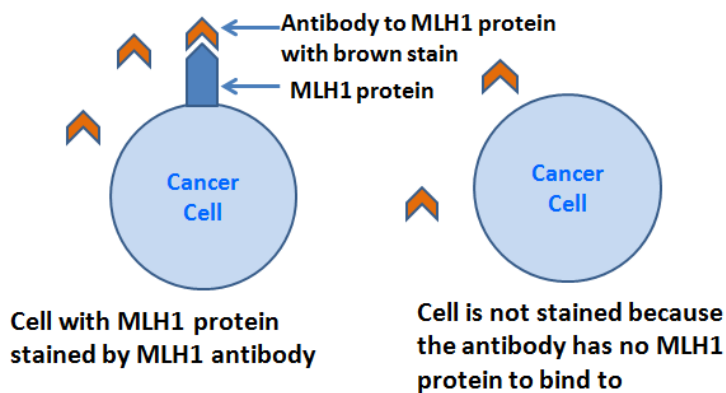
Examples of colorectal cancers that are “peppered” with white blood cells (indicated by arrows). The cells look like they are surrounded by a white halo, and indeed, some scientists think that these cells may help to protect the patient.

(Photos courtesy of Dr. Jeremy Jass and the Colon Cancer Family Registry)

### Laboratory Tests used on Lynch Syndrome Tumors

Two methods are primarily used in the pathology laboratory to test cancerous tumor tissue for Lynch Syndrome markers. Immunohistochemistry (IHC) allows the tumor tissue to be evaluated for the presence of the MMR proteins. To run this test, the pathologist stains four different slices (sections) of tumor tissue with brown-stained antibodies to each of the four MMR proteins. If the MMR protein is present in the tumor, the section will stain dark brown. The brown stain suggests that the MMR gene is not mutated, and is able to produce a normal MMR protein which can bind with the stained antibody. In most patients with Lynch Syndrome, the mutated MMR gene produces an abnormal or misshapen protein that cannot complex with the antibody and as a result, the tissue section will appear pale in color. The tumor tissue slides are carefully examined under the microscope by the pathologist to determine if the tumor tissue is stained or unstained. IHC is useful because it may indicate which MMR gene is mutated. However, in a small percentage of cases (usually less than 10%), tumors from Lynch patients will not have abnormal IHC. The second test performed on potential Lynch cancers is evaluation for microsatellite instability, or MSI. This test compares DNA in non-cancerous (normal) tissue to DNA extracted from the cancerous tumor tissue. Usually, a blood sample is used as the source of normal DNA, but occasionally normal tissue removed during a surgical procedure is used. In Lynch mutation carriers, there are normally many more DNA spelling errors in the tumor tissue compared to that of the normal tissue. The presence of microsatellite instability suggests that one of the MMR genes is not functioning properly, but does not indicate which gene might be mutated. In addition, about 15-20% of non-hereditary colorectal tumors will show microsatellite instability.



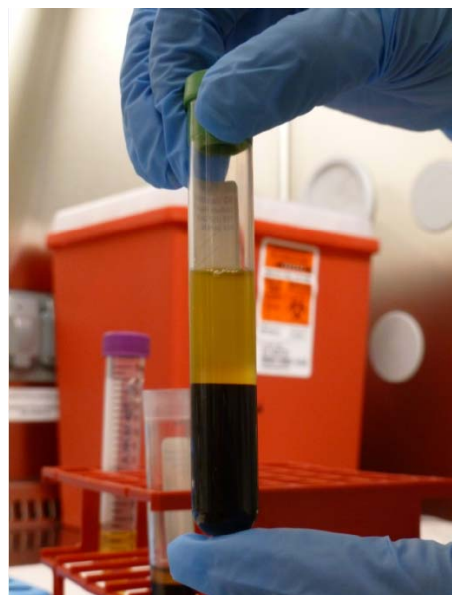


### Immunohistochemistry

The antibody to the MMR protein is tagged with a brown dye. Its shape is reciprocal to the MMR protein, so that it exactly fits. If the MMR protein is missing, or is misshaped, the antibody cannot bind, and the cell will appear unstained. Shape is everything in IHC !

### Genetic Counseling and Mutation Testing in Lynch Syndrome

Samples of DNA from a patient's blood may be sent for genetic testing for Lynch syndrome in the following cases: 1) a patient's tumor tissue showed abnormal IHC staining or abnormal MSI testing (or both); 2) the family history is highly suggestive of Lynch Syndrome; 3) the cancerous tumor showed some of the hallmark features of Lynch Syndrome when the tissue was examined microscopically by a pathologist; 4) the patient was diagnosed at a very early age. Before genetic testing is done, however, the patient is often referred to a genetic counselor. Genetic counselors work closely with physicians and medical staff in hospitals and in many ways, can be the best advocate for potential or confirmed Lynch carriers. The genetic counselor may assist physicians in ordering additional medical tests. The counselors also will help the patient to secure medical records from past medical or surgical procedures in order to obtain a complete medical history and will work with the patient on construction of a family tree of cancer cases, with ages of diagnosis if possible. The genetic counselor may be able to verify cancer details in relatives who are no longer living. Perhaps most importantly, the genetic counselor will spend considerable time addressing the concerns of the patient, answering questions, and outlining the advantages and disadvantages of being tested for an MMR mutation, which for many patients can be a somewhat frightening experience. Only when the patient feels completely comfortable with having his or her DNA tested for Lynch Syndrome, and has signed the appropriate consent forms, will a fresh blood sample be collected. The DNA from the blood will be sent to a clinical laboratory for genetic testing for a mutation in one of the four MMR genes (only a few laboratories have the facilities to test for MMR mutations). In many cases, the gene that will be tested (at least first) will be the gene whose protein was not observed in the IHC testing done on the tumor tissue.



### Mutation Tests Results

After the testing is completed, the results will be provided to the physician or genetic counselor who ordered the test. For patients who are confirmed to harbor an MMR mutation, the information will include which gene is mutated, as well as the specific name of the mutation. There are many types of mutations that can be detected by genetic analyses, including deletions, insertions, point mutations, missense, nonsense, frameshift, and splice-site mutations (see Box). Each type of mutation impairs the ability of the MMR gene to produce a normal protein. Most of these mutations will either result in a protein that is so abnormal that it degrades and disappears

(resulting in a missing protein), or a protein that is misshapen and completely dysfunctional. An example of a MMR mutation is: MLH1 73A>T. In this example, at the 73<sup>rd</sup> nucleotide (or letter) of the MLH 1 gene, a spelling error occurred in which the nucleotide “A” was replaced by the nucleotide “T”. This simple spelling error results in the production of a faulty MMR protein. Another example of a MMR mutation is MSH6 741delA. This mutation occurred because the nucleotide “A” was inadvertently deleted (del) from the DNA at position 741 in the MSH6 gene. Because the gene is missing one nucleotide, the protein produced by the gene is deformed and unable to function properly. Sometimes, a mutation is found, but the biologic effects are unclear. These mutations are referred to as “unclassified” mutations or “variants of unknown significance” (VUS), and it is not currently understood if these increase the risk for Lynch cancers. Unclassified mutations are being studied globally by many scientists, and eventually these mutations will be reclassified as either deleterious (Lynch mutations) or as benign (harmless).

Example of a point mutation  
in which one “letter” differs

Normal MSH2 gene: **CTTACG**  
Mutated MSH2 gene: **ATTACG**

Example of a frameshift mutation  
in which one “letter” is missing

Normal spelling: **She saw Tom**  
Missing letter “h”: **Ses awt om**

The missing letter results in a biologically  
incomprehensible section of DNA

- **Deletions**: one or more “letters” missing in the DNA
- **Insertions**: one or more extra “letters” in the DNA
- **Point mutation**: a change in one “letter” of the DNA sequence
- **Missense**: a change in the amino acid encoded by the DNA resulting from a change in the DNA sequence
- **Nonsense**: a change in the DNA sequence which results in a very short, non-functional protein
- **Frameshift**: missing or extra DNA which causes the DNA sequence to become continuously misread
- **Splice-site**: a change in where the reading begins – and therefore how the chains of amino acids that make up the protein are joined together

See references: cancer.gov for more information on proteins/amino acids

### Follow-up Care for Lynch Patients

It is important for all confirmed or suspected mutation carriers, regardless of cancer status, to be followed closely by a physician/team of physicians for the rest of their life. This team will be responsible for ordering appropriate screening procedures, e.g., medical procedures designed to 1) prevent cancers by detecting and treating growths while they are still precancerous; and 2) reduce mortality by detecting cancers at an early stage of development when treatment is most effective. Providing a list of all familial cancer diagnoses to the physician(s) can facilitate a tailored screening approach, particularly if less common Lynch cancers such as brain, renal pelvis (the part of the ureter that drains urine from the kidney towards the bladder), gall bladder and bile duct, or pancreas are part of the spectrum of cancers observed in the family.

The most common screening procedure for Lynch patients is a colonoscopy, a procedure in which a lighted tube

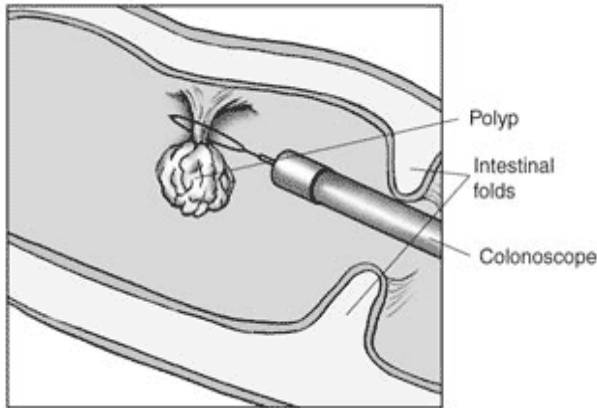


Diagram from the National Institutes of Health

with a camera is inserted into the entire length of the colon. During a colonoscopy, the physician carefully examines the inner surface of the large intestine and, most importantly, removes and/or biopsies any suspicious areas. All tissue that is removed is examined by the pathologist to determine whether it is benign (harmless), precancerous, or cancer. Colonoscopies are recommended every 1-2 years starting at age 20-25; in families in which a colon cancer was diagnosed prior to age 25, colonoscopies should begin 2-5 years earlier than the youngest case. Studies have shown that regular screening colonoscopies can reduce the incidence of colorectal cancer in Lynch carriers by up to 62%, and

decrease overall mortality by 65%. Other clinical procedures designed to examine the colorectum, including sigmoidoscopy, barium enema, and computed tomographic colonography, are available but are thought to be less optimal for those with Lynch Syndrome. My friend with the seven polyps encouraged her young adult children (late teens and early 20's) to have colonoscopies, and each child was diagnosed with asymptomatic polyps. Had these colonoscopies been delayed by 10, 20 or 30 years (as often happens when individuals are unaware of the presence of a Lynch mutation in the family), these children may well have been diagnosed with advanced-stage colorectal cancer instead!

Screening recommendations for cancers of the stomach, small intestine, endometrium, ovary, urinary tract (kidney, ureters and bladder) and other organs have been proposed by various investigators, but have not yet been universally adopted by the global community (hence are not yet considered to be the standard of care). Because of this, it is important for patients with Lynch syndrome to work with their physicians to ensure that regular physical exams are being scheduled. A summary of the current status of screening guidelines in the U.S. can be viewed on the National Comprehensive Cancer Network website (NCCN), but this website is primarily designed for physicians and requires registration for access (website is available below under references). More extensive screening procedures may be advised for individuals who develop brain cancers or certain skin cancers (see below).

**Muir-Torre Syndrome** is a variant of Lynch syndrome in which individuals are also at risk for skin tumors, including sebaceous adenomas, sebaceous epitheliomas, sebaceous adenocarcinomas, and keratoacanthomas (a type of squamous cell skin carcinoma). Regular, full-body skin exams conducted by a qualified dermatologist are necessary for individuals with Muir-Torre to reduce the risk of debilitating or metastatic skin cancers. A second variant of Lynch Syndrome is **Turcot Syndrome**. Those with Turcot Syndrome have been observed to have a higher incidence of tumors in the central nervous system (CNS) in addition to other Lynch cancers. The CNS tumors are usually manifested as brain tumors, with glioblastoma being the most common cancer. The panel of screening physicians for these families *may* include a neurologist (although again, with the caveat that universally accepted screening recommendations for Turcot Syndrome are not yet available).

### [Surgical Options in Lynch Syndrome](#)

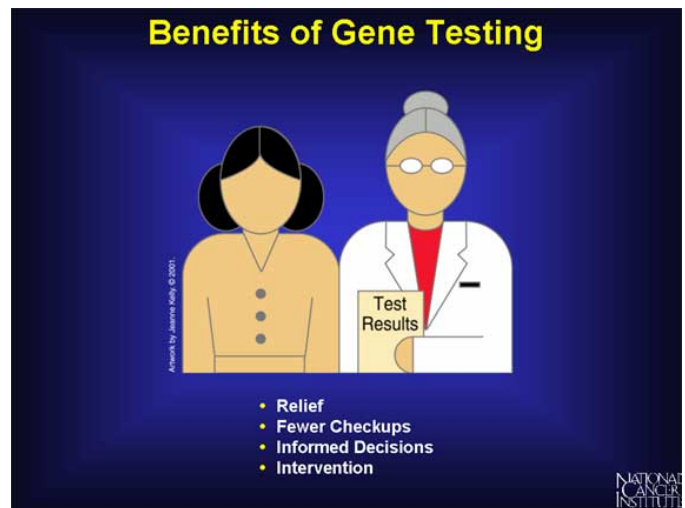
Patients with Lynch Syndrome have a higher lifetime risk for the development of multiple cancers. Because of this, treatment options for cancers that do arise should include procedures that lessen or minimize the risk for subsequent cancers. For colorectal cancers, removal of most/all of the colon rather than just the segment of colon

in which the cancer occurred may be considered or recommended, especially in young people. Although this might seem like radical treatment, each new cancer brings with it the risks associated with additional surgery, including debilitating complications. For women, elective removal of the uterus, uterine (fallopian) tubes, and ovaries after completing childbearing has been shown to reduce the incidence of cancers in these organs. Treatment options for patients with Lynch Syndrome should be discussed with a surgeon who has experience with the disorder and who can help patients better understand the long-term risks for multiple cancers. In many communities, especially those with academic medical centers (those associated with medical schools), hereditary cancer clinics are available; these provide counseling, screening recommendations, treatment, and follow-up care by physicians with extensive expertise in Lynch and other hereditary conditions.

### Testing of Family Members

Testing of family members can prove to be a life-saving measure for an entire extended family, as screening procedures in newly identified mutation-positive individuals can begin immediately. For those who are young adults, this translates into decades of additional screening. Sadly, many if not most deaths in Lynch families, especially in older generations, occur in patients who are completely oblivious of the risk present in the family; when medical intervention is sought only after symptoms appear, treatment has been needlessly delayed and is often less effective. A second benefit is that the testing of one person often initiates a cascade of interest in other family members.

Within a matter of months, a family with no knowledge of Lynch Syndrome can transition into a family with scores of relatives who now are aware of their mutation status. This cascade brings a cycle of hope to families that have suffered from generations of cancer diagnoses and deaths. And for those who are mutation negative, there is no longer the anxiety that their children will suffer the same fate as aunts, uncles, and grandparents (mutation-negative individuals have the same risk for cancer as the general public). Genetic counselors are trained to work with extended families to ensure that all relevant family members receive an opportunity for mutation testing, and can facilitate the process in cases where strained family relationships exist. For families that have not yet received testing (but are concerned that the family might harbor a Lynch mutation), testing is optimally conducted first in a family member diagnosed with a Lynch-related cancer. In many cases, insurance will cover the cost for testing of relatives once Lynch Syndrome has been confirmed in a family. Confirming the mutation in a relative is less expensive and less time consuming than the original testing done in a family because, now, instead of searching across all possible mutations, the test merely seeks to confirm or exclude the known specific mutation in that family. Indeed, finding an unknown mutation is like looking for one misspelled word in a 900 page book. Once the mutation is known however, the testing lab can go to the specific location in the DNA (e.g., in our lengthy book - page 743, 2<sup>nd</sup> paragraph from the top) and look for the genetic misspelling. Generally, testing is not conducted on children who are younger than 18 years of age. However, rare exceptions may be made when cancer in a relative was diagnosed at a very young age. In these families, it is sometimes recommended that minor children be considered for genetic testing and/or for other clinical tests. It should be noted that some cancers in Lynch families are sporadic cancers; these develop as a consequence of mutations that were acquired over a long period of time in the tissue from which the cancers arose. Sporadic cancers generally, but not always, are diagnosed in family members who do not carry the mutation.



## [Gaining a Sense of Control in Lynch Syndrome](#)

Although one cannot be cured of Lynch Syndrome, there are steps that one can take to gain a sense of self-control. Having an up-to-date family pedigree is a powerful tool for persuading insurance companies or reluctant physicians to comply with recommended procedures (see below). This is best accomplished when it becomes a family endeavor. Specific individuals in each generation, usually those who have good rapport with extended family members or those with good technical/computer skills, can be tasked with collecting medical history of close relatives and with providing updates as new diagnoses are confirmed. For deceased relatives, death certificates not only shed light on the date of death, but more importantly, may list all cancer diagnoses in addition to the immediate cause of death. These can be sought from the Departments of Vital Statistics in most states and next of kin may have copies stashed away with long-forgotten papers. It is also helpful to develop a well organized filing system for Lynch-related medical records, including genetic counseling reports, mutation results, medical/surgical procedures, biopsy reports, imaging results (X-rays, CAT scans, etc), and relevant laboratory test results - and with permission from all relatives - keeping family members up to date. Keeping abreast of current knowledge on Lynch Syndrome also empowers members of Lynch families. A few of the plethora of websites available are listed below, and each provides a different approach on Lynch Syndrome information.

If a Lynch support group does not exist in your community, consider starting one as a legacy for your family or as a tribute to a cherished relative. In the last few years, a national Lynch organization was started in Australia, which provides education for physicians, patients, and communities, resources for emotional support, and opportunities to volunteer. The information provided on their website (below) can be used as a template to implement similar programs on a local level, regardless of the size of your town. In Kauai, where I had some early training in dermatology, we started what we jokingly referred to as the "Mole-watching Club of Kauai". Although the title was facetious, the principle was sound. Every hairdresser, barber, massage technician and physical therapist became aware of the fact that they had the potential to save the life of another human being by simply having the courage to point out a "funny-looking mole". Having the courage to share your experience with Lynch Syndrome with other at-risk families in your community can enable you and your family to indirectly save the lives of countless individuals in generations to come.

## **Community Genetic Testing**



**Enabling life for a new generation of mischief makers**

### [Some Resources for Lynch Syndrome](#)

National Cancer Institute (NCI): [www.cancer.gov](http://www.cancer.gov) (for general information about cancer and amino acids)

NCI : [www.cancer.gov/cancertopics/pdq/genetics/colorectal/HealthProfessional/Page3#Section\\_89](http://www.cancer.gov/cancertopics/pdq/genetics/colorectal/HealthProfessional/Page3#Section_89)

U.S. National Library of Medicine, Genetics Home Reference: [www.ghr.nlm.nih.gov/condition/lynch-syndrome](http://www.ghr.nlm.nih.gov/condition/lynch-syndrome)

National Library of Medicine, NIH: [www.ncbi.nlm.nih.gov/books/NBK1211](http://www.ncbi.nlm.nih.gov/books/NBK1211)

Cancer.Net: [www.cancer.net/cancer-types/lynch-syndrome](http://www.cancer.net/cancer-types/lynch-syndrome)

Lynch Syndrome Screening Network: [www.lynchscreening.net](http://www.lynchscreening.net)

Mayo Clinic: [www.mayoclinic.com/health/lynch-syndrome](http://www.mayoclinic.com/health/lynch-syndrome)

UCSF Medical Center: [www.ucsfhealth.org/conditions/lynch\\_syndrome/](http://www.ucsfhealth.org/conditions/lynch_syndrome/)

Lynch Syndrome International: [www.lynchcancers.com/](http://www.lynchcancers.com/)

Lynch Syndrome Australia: [www.lynchsyndrome.org.au/](http://www.lynchsyndrome.org.au/)

NCCN (this is primarily a resource for physicians, and contains screening and treatment guidelines, but there are also patient resources): [http://www.nccn.org/professionals/physician\\_gls/pdf/colorectal\\_screening.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf)

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Hawaii's children and pets, and the author's grandmother (baby photo, circa 1890) are to be credited with many of the photos in this presentation. The beach photos are credited to Sara Sameshima (cover photo) and Dan Harmon (turtle photo below).

