Some Helpful Facts.....

1. Not all colorectal cancers are hereditary, but all colorectal cancers are caused by genetic mutations.
2. Approximately 70-75% of colorectal cancers are sporadic: these are cancers that occur in people who do not have a family history of that cancer or an inherited change in their genetic material (DNA) that would increase their risk for that cancer.

INTRODUCTION

All cancers are the result of gene mutations. The vast majority are sporadic occurrences with only some caused by hereditary genetic syndromes. Genetic conditions involve a largely unpredictable interplay of many factors and processes. Just because you hold a genetic mutation for something does not necessarily mean it will be expressed in your lifetime but knowing your risk can save your life. Please read on to learn more about the genetics behind colorectal cancer.

PART I: TYPES & PREVALENCE OF CANCERS

Sporadic Cancers (70-75%)
Sporadic cancers account for 70-75% of cancers. There is no family history with the same type of cancer and no identified inherited change in DNA. For most cancer patients, gene mutations are sporadic, caused by aging, exposure to chemicals, radiation, hormones or other factors in the body and the environment. Over time, a number of mutations may occur in a single cell, allowing it to divide and grow in an uncontrollable way that becomes a cancer. This usually takes many years and explains why most
cancers occur at a later age in life. Because people are not born with these acquired gene mutations, they cannot pass them on to their children.

**Familial Cancers (20-25%)**
Familial cancer account for 20-25% of colorectal cancers and there is a family history of the same type of cancer and no identified inherited change in DNA. Some families have more cases of colorectal cancer than would be expected by chance, but do not have an associated genetic syndrome. The cancer may be as a result of shared environmental or lifestyle factors.

**Hereditary Cancers (5-10%)**
Hereditary cancers account for 5-10% of colorectal cancers. There is an identified inherited genetic change in DNA that is passed down from parent to child. In some families, cancers are hereditary. This means that they are related to a specific gene mutation that was passed down (inherited) in a family. A person who is born with a mutation has it in every cell in his/her body. This means that it may be passed down when that person has children. People who inherit such gene mutations have a higher risk of developing certain forms of cancer compared to the general population. Inherited gene mutations help to explain why in some families, we see more people than expected with certain kinds of cancer and at a younger age. The next section will delve further into hereditary colorectal cancer syndromes.

**PART II: HEREDITARY COLORECTAL CANCER SYNDROMES**

The two most commonly inherited syndromes linked with colorectal cancer are:

A. **Lynch Syndrome (HNPCC) and**
B. **Familial Adenomatous Polyposis (FAP)**

**A. Lynch Syndrome (HNPCC)**

*Lynch Syndrome*, also referred to by some by its previous name Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is among the most inherited causes of cancers affecting about 1 in 279 people. Approximately 5% of all new colorectal cancers diagnosed each year are caused by Lynch Syndrome. It is caused by mutations in the *mismatch repair (MMR) genes* MLH1, MSH2, MSH6, PMS2, that correct mistakes when cells divide, and DNA is copied. Also, a mutated EPCAM gene can ‘turn off’ the MSH2 gene, therefore, leading to this cancer syndrome.

Lynch syndrome may be suspected if a person in their mid-40s develops colorectal cancer or has relatives who developed colorectal cancer around that age or earlier, compared to the general population average age of 72. In Lynch Syndrome polyps in the colon and rectum develop at an earlier age and grow faster than those in the general population. Although not everyone who inherits a mutated Lynch associated MMR gene will develop cancer, the risk is very high – up to 85% for colorectal cancer in their lifetime, for women there is also an increased lifetime risk of up to 60% for endometrial cancer and there is an increased risk over the general population of being diagnosed with other cancers including stomach, small intestine, pancreas, kidney, ureter, ovary, prostate, breast, bladder, bile duct, brain and sebaceous adenomas of the skin.

Lynch Syndrome is a highly under-diagnosed syndrome, in a released 2016 Blue Ribbon report (page 40) it states, “It is estimated that 1,000,000 people in the United States have Lynch syndrome; with less than
5% are aware of it.” [https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel/blue-ribbon-panel-report-2016.pdf](https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel/blue-ribbon-panel-report-2016.pdf)

Normally, colorectal cancer develops slowly, which is why doctors recommend a 2-year interval for a stool test in people at average risk who have a normal screening test. However, colorectal cancer develops rapidly in people with Lynch syndrome, so early and frequent screening is important. People with Lynch syndrome should undergo a colonoscopy every one to two years beginning at age 25 or 10 years prior to the earliest diagnosis of a family member. The development of colorectal cancer with these patients can be avoided or reduced by employing preventive surgery, removing a part or all of the colon. For women, doctors may recommend a hysterectomy if there are no plans for childbearing or if a woman is past the age for childbearing.

**(i) General Lifetime Cancer Risks for People with Lynch Syndrome (HNPCC):**

![DNA Image](https://via.placeholder.com/150)

Appearing below are the most common cancers that may develop from Lynch Syndrome. Other fewer common cancers are cited below.
Colorectal cancer: 20% to 80%
- Stomach cancer: 1% to 13%
- Hepatobiliary cancer (liver/bile duct): 1% to 13%
- Urinary tract (renal pelvis, ureter, kidney, bladder) cancer: 1% to 18%
- Small Intestine cancer: 1% to 6%
- Pancreatic cancer: 1% to 6%
- Brain or central nervous system tumour: 1% to 3%
- Skin: up to 9%

*Cancer risks for women with Lynch syndrome
- Endometrial cancer: 15% to 60%
- Ovarian cancer: 1% to 38%
- Breast: up to 18%

*Cancer risk for men with Lynch syndrome
- Prostate cancer: up to 30%

(ii) Is your Family a Lynch Family?
Families considered to be "Lynch families" must display certain criteria indicating a pattern of colon cancer throughout generations. These are referred to as the Amsterdam Criteria II (all criteria must be fulfilled), and include:
It is imperative that families with any of the above-mentioned guidelines share their medical histories within the family and if you feel these guidelines apply to you, consult your doctor and discuss seeking out genetic counselling. Only genetic testing can find out if you have a genetic mutation, and genetic counselors are trained to explain the risks and benefits of genetic testing. Genetic testing is complex, so the first test in a family is usually done on the person with the highest chance to have a mutation. This is called an index test. If the index test finds a mutation, other family members may choose to have carrier testing.

The definition of Lynch syndrome is still evolving. A person may still have Lynch syndrome even if the Amsterdam Criteria II guidelines do not fully match the family history. Therefore, meeting with a health professional who has training in genetic diseases and conditions is recommended for people who have a family history that suggests the possibility of Lynch syndrome.

The history of cancer in your close relatives is a clue to the chance of Lynch Syndrome in your family. Close relatives include your children, brothers, sisters, parents, aunts, uncles, grandchildren, and grandparents (on one side of the family). A history of cancer in cousins and more distant relatives may also be important and should be known. The absence of shared family medical histories is partially the cause of Lynch Syndrome being so underdiagnosed: An estimated 1 million people in the US have Lynch, and only 5% are aware. Keep in mind the general population lifetime risk for cancer is 1 in 2 women and 1 in 3 men. Learning you have Lynch Syndrome is not a sure case that you will get cancer, but it gives you the opportunity to be screened early and have preventative surgeries.
So please... talk to your families if you suspect a family cancer history and get the word out about Lynch Syndrome... you could save lives!

(iii) Screening and Lynch Syndrome:

Once Lynch Syndrome has been diagnosed, a highly targeted screening and medical management program is essential and may be lifesaving. During routine surveillance screening, tumours may be discovered and are more easily removed or treated before becoming life threatening. Furthermore, for colorectal cancer, which is the greatest risk in Lynch families, we know that cancer is 90% preventable through screening. Having polyps removed before they have a chance to develop into cancer will prevent the onset of the disease.

The following is recommended screening for people with Lynch Syndrome. It is important to discuss these options with your doctor, as each individual is different, based on the mismatch repair gene that is mutated and the family cancer history.
Screening options may change over time as new technologies are developed and more is learned about Lynch syndrome and its other forms. It is important to talk with your doctor about appropriate screening tests.

B. Familial Adenomatous Polyposis (FAP) and Attenuated Familial Adenomatous Polyposis (AFAP)
**Familial Adenomatous Polyposis (FAP)** is a very rare disorder that accounts for 1% of new colorectal cancers each year. The cause is the mutated *Adenomatous Polyposis Coli (APC)* gene. Affected patients with FAP can develop hundreds to thousands of polyps in the lining of the colon and rectum, the average onset of colon polyps in patients with FAP is age 16. People with untreated FAP have a greater than 90% chance of developing colon cancer. The average age of colorectal cancer diagnosis in FAP is 39 years, as compared to 72 years in the general population. **Attenuated Familial Adenomatous Polyposis (AFAP)** is a subtype of FAP, that is characterized by fewer colon polyps with an average age onset of 30 and a delay in the development of colon cancer (average age 50 to 55 years). The development of colorectal cancer with these patients can be avoided by employing preventive surgery to remove the colon. *(Note: The I1307K APC polymorphism/mutation is carried by 6-8% of those with Ashkenazi Jewish ancestry and increases the risk of colorectal cancer 1.5-2-fold for this group.)*

Several other cancers have been associated with FAP, including stomach, small intestine, pancreas, adrenal gland, papillary thyroid and periangiary (where the bile duct and pancreas empty into the small bowel). Risk for hepatoblastoma, a type of liver cancer, is increased in children with FAP. Desmoid tumours/desmoid fibromatosis, a locally aggressive tumour that does not spread (metastasize), are fibrous tumours that usually occur in the tissue covering the intestines, and a type of brain tumour called medullloblastoma can also occur in some individuals with FAP.

In addition, several other non-cancerous manifestations have been seen in FAP patients. Young FAP patients may develop cysts in the skin on the face, scalp, arms, and legs, often years before they develop colon polyps. Congenital hypertrophy of the retinal pigment epithelium (also called CHRPE) is an abnormality found in the retina of the eye that looks like a freckle and causes no symptoms for the patient. In FAP patients it can be present in both eyes. About 70% of FAP patients have dental abnormalities, including extra or missing teeth, fused roots, or non-cancerous tumours of the jawbone (osteomas). Although these manifestations are not harmful to the patient, they may be the first sign of FAP and prompt a patient to undergo testing for a mutation to the APC gene.

**PART III: TUMOUR TESTS FOR PREDICTING GERMLINE (INHERITED) MUTATIONS ASSOCIATED WITH LYNCH AND FAP**

Many institutions now perform a screening test on all colorectal cancers and endometrial (uterine) tumours at the time of surgery to predict germline (inherited) mutations in tumours, associated with Lynch syndrome and FAP. If you’re not sure if this test was done, ask your oncologist. If your surgery was not too long ago, it’s likely the test can still be performed if it wasn’t done. Most hospitals do one of these two screening tests appearing below, if not both.

**A. MICROsatellite INSTABILITY (MSI) TESTING**
A microsatellite instability (MSI) screening test looks for changes in the DNA sequence by comparing normal tissue and tumour tissue. Defects in the MMR genes result in an increased accumulation of DNA errors and stretches of DNA called microsatellites are especially prone to these errors. The presence of microsatellite instability (MSI) in colorectal tumour specimens is a hallmark feature of Lynch Syndrome and can be cause for suspicion of one of the germline mismatch repair (MMR) gene variants associated to the syndrome. If microsatellite testing shows mutations in 30% or more microsatellites it is called microsatellite instability-high (MSI-H). Knowing whether a cancer is microsatellite instability-high may also help plan the best treatment.

77-89% of Lynch-related tumours are MSI-H, but 10-15% of sporadic tumours also show it.

Given that both Lynch and sporadic tumours are MSI-H, additional IHC testing is needed to determine if it is truly Lynch syndrome.

**B. IMMUNOHISTOCHEMISTRY (IHC) TESTING**

An immunohistochemistry (IHC) test looks for missing proteins in tumour cells. The premise behind the test is that if the MMR genes are working properly, their protein products should be present in the tumour. However, if there is a mutation in one of the Lynch syndrome MMR genes, that gene’s protein will be absent in the tumour.

83-90% of Lynch-related tumours and 20% of sporadic tumours have at least one of these proteins absent.
Figure I: Workflow of Immunohistochemistry. I. Tissue collection; II. Fixation; III. Embedding; IV. Sectioning; V. mounting; VI. Antigen retrieval and blocking; VII. Primary antibody reaction; VIII. Labeled antibody reaction. IX. Staining and counterstaining. (Source: https://www.creative-diagnostics.com/Immunohistochemistry-guide.htm)

The figure above shows a typical immunohistochemistry workflow. Step I~V are sample preparation procedures, step VI~IX are analytical procedures.

PART IV: OTHER RARE INHERITED CONDITIONS ASSOCIATED WITH COLORECTAL CANCER

The following are other rare inherited conditions that can increase the risk of developing colorectal cancer, as well as other types of cancers:

A. **Gardner Syndrome** is a subtype of FAP, with a mutation in the APC gene. It is characterized by the presence of multiple polyps in the colon together with tumours outside the colon. Common symptoms of this condition include the development of extra teeth, bony tumours (osteomas) on the skull or other bones, and sebaceous cysts under the skin.

B. **Muir-Torre Syndrome (MTS)** is a subtype of Lynch syndrome with mutations of MSH2 or MLH1 genes. It can bring an increased risk of skin growths and cancers in addition to Lynch-related cancers. The most common characteristic is the finding of a skin tumour called a sebaceous adenoma. Other skin tumours associated are sebaceous epitheliomas, sebaceous carcinomas (which commonly occur on the eyelids) and keratoacanthomas. A finding of a sebaceous adenoma may be a marker of a visceral disease and warrants further investigation for internal malignancies including a colonoscopy.
C. **Turcot syndrome** is a subtype of both Lynch syndrome and FAP, it is either a mutation in the APC gene associated with FAP or a mutation in one of the mismatch repair genes associated with Lynch syndrome (predominantly MLH1 and PMS2). People with Turcot syndrome develop many polyps in the colon that can become cancerous and is also associated to primary brain tumours including gliomas, medulloblastomas, glioblastomas, ependymomas, and astrocytomas. The brain tumours in individuals with APC mutations are typically medulloblastoma, whereas those with Lynch mismatch repair mutations are usually glioblastoma multiforme.

D. **MYH-associated polyposis (MAP)** is caused by a mutation in the MUTYH DNA repair gene. People with MAP can develop hundreds of adenomatous polyps in the inner lining (mucosa) of the colon. In other cases, people with MAP can be diagnosed with fewer polyps (less than 20) and/or colorectal cancer at a young age. Some people with MAP have an increased risk of developing polyps in the upper gastrointestinal tract, such as the stomach and small intestine. The risk of thyroid cancer may also be increased in individuals with MAP.

E. **Juvenile Polyposis Syndrome (JPS)** is an inherited condition that causes polyps called hamartomas to develop. Hamartomas are usually non-cancerous, but they have the potential (10-50%) to develop into cancer. People with juvenile polyposis syndrome typically develop polyps before age 20; however, “juvenile” refers to the characteristics of the tissues that make up the polyp, not the age of the affected individual. Approximately 15 percent of people with Juvenile Polyposis Syndrome have other abnormalities, such as heart or brain abnormalities, twisting of the intestines (intestinal malrotation), an opening in the roof of the mouth (cleft palate), extra fingers or toes (polydactyly), and abnormalities of the genitalia or urinary tract. Based on current research, 2 genes have been linked to JPS, they are called BMPR1A and SMAD4.

F. **Peutz-Jeghers Syndrome (PJS)** is an inherited condition that involves a mutation of the STK11 gene (also known as LKB1). People with Peutz-Jeghers syndrome may develop large hamartomas in the digestive tract. Children with Peutz-Jeghers syndrome often have small freckles on the lips, around and inside the mouth, near the eyes and nostrils, and around the anus. These spots may also occur on the hands and feet. They develop during childhood and often fade as the person gets older. Peutz-Jeghers syndrome is also associated with a higher than average risk of developing other types of cancer, including breast, pancreatic, stomach, ovarian, lung and small intestine cancers. A small percentage of people with Peutz-Jeghers Syndrome do not have mutations in the STK11 gene. In these cases, the cause of the disorder is unknown.

G. **Hereditary Mixed Polyposis Syndrome (HMPS)** is an inherited condition that causes many different types of polyps to grow. The most common type of polyp to grow is a hamartoma. For most families with HMPS, a specific gene mutation causing the syndrome cannot be identified, although some families will have an inherited mutation in the GREM1 gene, but this is rare. Most, but not all, people with inherited GREM1 gene mutations are of Ashkenazi Jewish ancestry.

H. **Cowden Syndrome (CS)** and **Bannayan-Riley-Ruvalcaba Syndrome (BRRS)** represent a spectrum of overlapping features known as PTEN Hamartoma Tumour Syndrome, due to mutations in the PTEN gene. People with a PTEN mutation have a higher risk of developing non-cancerous hamartomatous polyps of the colon and cancers. CS patients also have increased risk for thyroid, breast, and endometrium cancer. While BRRS patients can have other physical findings, including larger-than-average head size (usually slows during childhood, so affected adults are of normal height and body size), dark freckles on the penis, skin lipomas, and delayed learning development.
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