Fact sheet **33**

BOWEL CANCER & INHERITED SUSCEPTIBILITY

This fact sheet talks about when bowel cancer is considered to be a hereditary or familial condition. A small number of families have an increased chance of developing cancer because they have inherited a DNA change in a cancer protection gene.

IN SUMMARY

- Cancer is very common in the community and mostly occurs just by chance
- A small proportion of families have an inherited susceptibility to developing some cancers.
- Inherited bowel cancer conditions (syndromes) include:
  1. Familial Adenomatous Polyposis (FAP)
  2. Lynch Syndrome (previously also known as Hereditary Non Polyposis Colorectal Cancer (HNPCC)).
  3. MUTYH-Associated Polyposis (also known as MAP or MYH-Associated Polyposis)

WHAT IS BOWEL CANCER?

Cancer occurs when cells in the body continue to divide uncontrollably. This can happen in any tissue or organ in the body. Cancerous cells have the potential to spread to other parts of the body. Bowel cancer generally refers to cancer of the large bowel, which is made up of the colon and rectum, and is therefore also known as colorectal cancer.

Bowel cancer is a common disease in the community. About 1 in 14 (7%) men and women will develop bowel cancer by the age of 85 years.

WHAT CAUSES BOWEL CANCER?

There is no single cause. There are, however, several risk factors which can influence someone's chance of developing bowel cancer. The most important are:

- Getting older. Most people who develop bowel cancer are over the age of 50, although it can occur at any age.
- Having a family history of bowel cancer.

WHAT IS MEANT BY A FAMILY HISTORY OF BOWEL CANCER?

A family history of bowel cancer means having one or more close blood relatives who have, or have had, bowel cancer.

The closest blood relatives (not relatives by marriage) are parents, siblings and children and are called first-degree relatives. Aunts, uncles, nephews, nieces and grandparents are second-degree relatives.

A family history of cancer can be due to:

- Chance, because cancer is common
- Common environmental and lifestyle influences among family members
- Having shared genetic factors, such as a non-working 'cancer protection' gene in the family.

Many people know of a relative with bowel cancer just because bowel cancer is common. Such people may still be at average or slightly above the average risk for developing bowel cancer.

Some people have a stronger family history where a number of their close blood relatives have had bowel cancer, and /or they were diagnosed at a young age.

Depending on the pattern of cancers in the family, these people may be considered at moderate or potentially high risk of developing bowel cancer.

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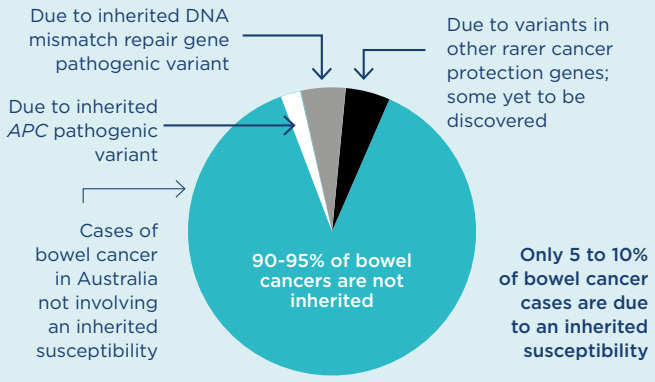
Figure 33.1:
Chance of having bowel cancer due to an inherited susceptibility.



CELLS, DNA AND GENES

Our bodies are made up of billions of cells. Each cell contains a complete copy of our genetic information or DNA. Our DNA contains the instructions for growth and development and is packaged into chromosomes that contain all our genes. Genes provide a code for the proteins our body needs to function.

We all have two copies of every gene, one that is inherited from the mother, and one from the father. As we age and grow, our cells are continually dividing to form new cells by the process of cell division. This means our DNA is copied over and over again.

INHERITED SUSCEPTIBILITY TO BOWEL CANCER

Most bowel cancers are not due to an inherited susceptibility. However a small number of cases (about 5%-10%) in Australia involve an inherited susceptibility to develop the cancer (*Figure 33.1*). In these cases, a person has inherited a non-working copy of a bowel 'cancer protection' gene. A spelling mistake in the gene that stops it working properly is called a **pathogenic variant** or **mutation**.

We all have many different 'cancer protection' genes that control growth and division of our cells throughout life.

Pathogenic variants in these 'cancer protection' genes may cause cells to grow and divide in an uncontrolled way. For a cell to become cancerous, multiple variants have to occur in a number of different 'cancer protection' genes within a cell, over time.

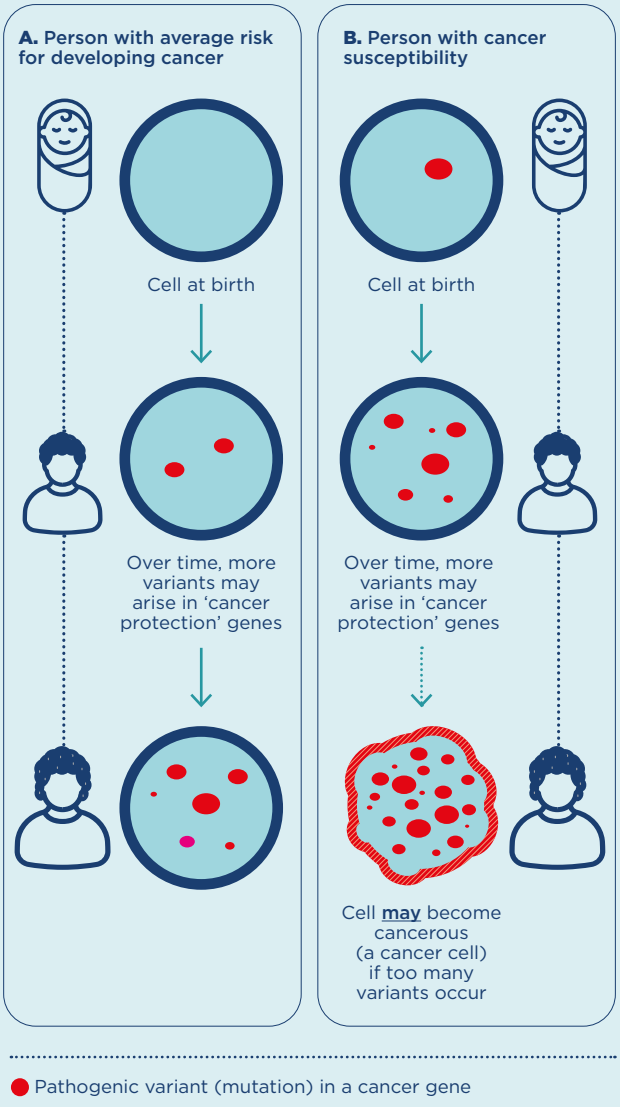
It can take many years for a cancer to develop, and this is the reason why the risk of cancer increases with age and most cancers occur in older people. The reason why these variants occur is thought to be a combination of genetic factors, environmental factors and the process of ageing.

Figure 33.2 shows a stylised image of a cell from a person with average risk of developing cancer (left hand side) and the cell of someone with an inherited pathogenic variant at birth (right hand side). Over time, as we age, we accumulate variants in genes that may increase the 'burden' or risk for developing cancer. If enough of these variants arise over time, the cell becomes cancerous (a 'cancer cell'). The person with the inherited pathogenic variant is more likely to have a cancer develop in their lifetime, because their cells started with a pathogenic variant already present at birth. This means that fewer variations need to happen to the cells' protective genes for a cancer to develop.

WHAT IS A STRONGER FAMILY HISTORY THAT SUGGESTS AN INHERITED SUSCEPTIBILITY?

Documenting the health history of family members over several generations helps work out if a person has a strong family history, and therefore greater chance for an inherited cause. It is important to record how the person is related, the type of cancer they have had and the age when cancer was first diagnosed. It is also useful to ask whether any relatives have already had genetic testing performed (usually performed by blood test) or tumour testing (a type of test performed on a tumour looking at genetic markers). Tumour testing is commonly performed on bowel cancer tumours as a first step because it may inform genetic testing.

Figure 33.2:
Increased chance of cancer cell development in those born with a cancer susceptibility compared with the average person



Characteristics of a family that may suggest an inherited pathogenic variant include:

- Two close relatives with bowel cancer diagnosed before the age of 50.
- Three Lynch syndrome-related cancers (e.g. bowel, endometrial, ovary, stomach, renal tract or brain cancer) in close relatives diagnosed at any age.
- Young onset or multiple (more than 20) pre-cancerous polyps in the bowel.

People with a strong family history can be referred by their doctor to a family cancer service. When meeting certain criteria for testing, genetic testing may be covered by Medicare or by the hospital. For those who have had cancer, they may seek this advice from their specialist (such as an oncologist).

WHAT ARE THE BOWEL CANCER SYNDROMES?

There are a number of conditions in which inherited pathogenic variants in 'cancer protection' genes can increase the risk of bowel cancer and some other types of cancer.

Three of these conditions are:

1. Familial Adenomatous Polyposis (FAP)
2. Lynch Syndrome
3. MUTYH-Associated Polyposis (MAP)

1. Familial Adenomatous Polyposis (FAP)

FAP is a rare condition that accounts for less than 1% of all bowel cancer (*Figure 33.1*). People with FAP develop many pre-cancerous growths called polyps (also called adenomas), usually more than 100, in their large bowel.

FAP stands for:

- **Familial** because it runs in families (i.e. it is hereditary)
- **Adenomatous** because the polyps that develop in FAP are adenomas. Adenomatous polyps have the potential to develop into cancer
- **Polyposis** which means multiple polyps.

Most people with FAP develop bowel polyps during their late teens, however they may start at any age. Rarely do they happen before the age of 10 years. If left untreated, these polyps will eventually develop into bowel cancer. The chance of developing bowel cancer is high. People with FAP may also develop cancer in the upper part of the gastro-intestinal tract (especially of the duodenum, the first part of the intestine) and rare non-cancerous tumours such as desmoid tumours (fibrous tissue tumour).

FAP develops as a result of an inherited pathogenic variant in the adenomatous polyposis coli (*APC*) gene. The *APC* 'cancer protection' gene is known as a **tumour suppressor gene** and its role is to act as 'brakes' on uncontrolled cell growth in the large bowel. Polyps form when cell growth is uncontrolled.

About one third of people with FAP have no known family history of the condition. There are two possible explanations for this: one of the parents had FAP but it was never recognised, or a new *APC* pathogenic variant occurred spontaneously in one copy of the *APC* gene causing a new pathogenic variant at the time of conception. The parent who passed on the variant in the egg or sperm does not have FAP.

There is a milder form of FAP, also caused by *APC* variants, called **Attenuated FAP (A-FAP)**. People with A-FAP usually develop less polyps than people with A-FAP.

Some people who have a clinical picture that looks similar to attenuated FAP have two pathogenic variants in the *MUTYH* gene. This condition is called *MUTYH*-Associated Polyposis (MAP) and is inherited in an autosomal recessive pattern, meaning parents are usually unaffected, but siblings may be affected by polyposis.

2. Lynch Syndrome

Lynch syndrome is a rare condition that accounts for between 1% and 4% of all bowel cancers (*Figure 33.1*).

People with Lynch syndrome develop bowel cancer at a younger age, usually before the age of 50 years. They often have one or more polyps (**adenomas**) in the bowel but do not have the large numbers of polyps occurring in people with FAP.

In addition, people with Lynch syndrome are at increased risk of some types of cancers outside of the large bowel most commonly endometrial (cancer of the lining of the uterus), ovarian cancer, as well as a smaller risk for other cancers (including stomach, small bowel, renal, and brain cancer).

Lynch syndrome develops as a result of an inherited pathogenic variant in mismatch repair (MMR) genes, specifically *MLH1*, *MSH2*, *MSH6* and *PMS2*. MMR genes are involved in the repair of genetic 'spelling' mistakes that can occur when the genes are copied to make new cells. The chance of developing cancer varies according to which of the MMR genes have a pathogenic variant.

3. *MUTYH*-Associated Polyposis (MAP)

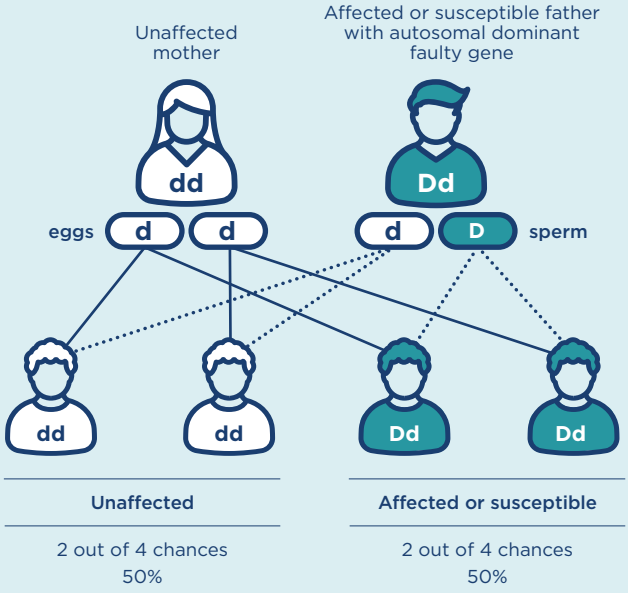
Some people who have a clinical picture that looks similar to attenuated FAP have two pathogenic variants in the *MUTYH* gene. This condition is called *MUTYH*-Associated Polyposis (MAP) and is inherited in an **autosomal recessive** pattern, meaning parents are usually unaffected, but siblings may be affected by polyposis. MAP is inherited in a different pattern to FAP and Lynch Syndrome. See below about inheritance for MAP.

HOW IS FAP AND LYNCH SYNDROME INHERITED?

FAP and Lynch syndrome (but not MAP) follow an autosomal dominant pattern of inheritance (*Figure 33.3*).

1. The *APC* and MMR genes are located on the **autosomes (numbered chromosomes). Each person has 2 copies of these genes, one inherited** from the mother, one inherited from their father.
2. The effects of the pathogenic variants in the *APC* and MMR genes are **dominant** over the information in the working copy of the genes.

Figure 33.3:
Autosomal dominant inheritance when one parent has a non-working *APC* or MMR gene. The non-working gene is represented by 'D'; the working copy by 'd'.



Where one parent has an *APC* or MMR gene variant, in every pregnancy each of their children has a:

- 1 in 2 (50%) chance of inheriting the gene variant
- 1 in 2 (50%) chance of not inheriting the gene variant and inheriting a working copy of the gene from both parents.

An *APC* or MMR gene variant can be inherited from either the mother or the father and passed on to either a son or a daughter.

People who have *not* inherited the pathogenic variant are not at increased risk of cancer and cannot pass it on to their children. However, they still have the same risk for developing cancer as the average person in the Australian population.

WHAT IS THE PATTERN OF INHERITANCE IN FAMILIES WITH MAP?

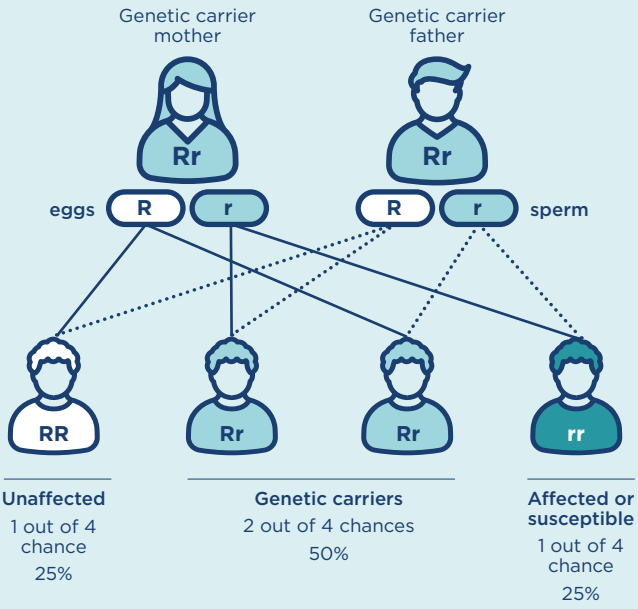
MAP follows an autosomal recessive pattern of inheritance (*Figure 33.4*).

This is because:

1. The *MUTYH* gene is located on one of the autosomes (numbered chromosomes). Each person has 2 copies of this gene, one inherited from the mother, one inherited from their father.
2. The effects of a pathogenic variant in a *MUTYH* gene copy is **recessive** over the information in the working copy of the gene. Where both parents have a *MUTYH* gene variant, in every pregnancy each of their children has a:

- 1 in 4 (25%) chance of inheriting the gene variant from the mother and the gene variant from the father. This person will have or be susceptible for developing MAP
- 1 in 2 (50%) chance of inheriting a gene variant from one parent but not the other. They will have one working and one non-working copy of the gene
- 1 in 4 (25%) chance of not inheriting the father's or mother's gene variants and instead inheriting working copies of the gene from both parents. They have not inherited the increased risk of cancer and therefore cannot pass the pathogenic variants to their children.

Figure 33.4:
Autosomal recessive inheritance when both parents are unaffected genetic carriers for the condition. The non-working copy of the gene containing a recessive variant is represented by 'r'; the working copy of the gene by 'R'.



Whilst individuals who do not have two pathogenic variants (one on each gene copy) in the *MUTYH* gene will not develop MAP, they will still have the same risk for developing cancer as the average person in the Australian population.

GENETIC COUNSELLING AND TESTING

The genetic counselling team or specialist (such as oncologist) may be able to:

- Work out the chance of developing bowel cancer based on a person's family history and any previous testing performed in the family
- Work out whether genetic testing is likely to be helpful
- Talk about the limitations, potential benefits and disadvantages of genetic testing
- Talk about cancer screening and ways of reducing the chance of developing cancer.

Table 33.1:
Chance of developing bowel and other cancers for people with FAP, Lynch syndrome or MAP when not having screening. Information extracted from eviQ Risk Management Guidelines.

Condition	Chance (risk) for **women** developing bowel cancer and other cancers up until age 70 years	Chance (risks) for **men** developing bowel cancer and other cancers up until age 70 years
FAP	Greater than 95% for bowel cancer About 5% (approximate) for duodenal cancer (by age 60)	Greater than 95% for bowel cancer About 5% for duodenal cancer (by age 60)
Lynch syndrome* *Ranges are listed because cancer risk depends on which MMR gene is involved	About 10-37% for bowel cancer About 15-30% for endometrial cancer (lining of the uterus) Up to 15% ovarian cancer Slightly increased chance of developing cancer of the stomach, small bowel, renal tract, and brain	About 20-47% for bowel cancer Slightly increased chance of developing cancer of the stomach, small bowel, renal tract, and brain
MAP	About 86% for bowel cancer Extra-intestinal cancers about 38% Duodenal polyps 17-34%; gastric polyps 11% Small risk of duodenal cancer	Similar risks for men as for women with MAP
Risk for the general population (to age 85 years)	About 7% for bowel cancer About 1.5% for endometrial cancer About 1% for ovarian cancer	About 7% for bowel cancer

Genetic testing for pathogenic variants in the *APC*, MMR, and *MUTYH* genes is complex and involves:

- First identifying the gene variant(s) via a blood sample in a family member who has or had bowel cancer or a related cancer (a **variant search**). A **variant search** is often performed on a group of selected genes (known as a panel). This group may include some additional genes depending on the cancer types present in the family.

  Results can show:

  1. The pathogenic variant(s) was found
  2. No pathogenic variant was found
  3. A variant of uncertain significance (VUS) was found. This is an unclear result. Further information to understand different types of results is available at www.genetics.edu.au.
- Then, and only if a pathogenic variant is found, testing other family members to determine if they have inherited the same variant (**predictive genetic testing**).

WHAT ARE THE CHANCES OF DEVELOPING CANCER FOR SOMEONE WITH AN INHERITED SUSCEPTIBILITY?

People with FAP, Lynch syndrome and MAP have an increased chance of developing bowel cancer and some other types of cancer (*Table 33.1*).

There are some other rarer inherited bowel cancer syndromes, which present with different types of bowel polyps and other clinical features which your specialist will examine you for, if required.

MANAGING AN INCREASED CHANCE OF DEVELOPING BOWEL CANCER

Genetic counselling and risk management

It is recommended that people with FAP, Lynch syndrome or MAP and their relatives seek management advice from a family cancer clinic or medical specialist. National guidelines for health care professionals exist at the Cancer Institute NSW eviQ website.

FAP

People who have an *APC* gene variant need regular bowel check-ups (called sigmoidoscopy or **colonoscopy**) from their early teenage years and eventually an operation to remove the bowel and prevent bowel cancer. It is also important for the upper gastrointestinal tract to be checked (called an endoscopy) from the age of 25 years.

Lynch syndrome

It is strongly recommended that people who have a MMR gene variant have regular check-ups (including a bowel test called **colonoscopy**). Surgery to reduce the risk of endometrial and ovarian cancer may also be recommended for some women and should be discussed with a specialist doctor.

Some medications, such as Aspirin may lower the risk of bowel cancer and studies in people at high risk are ongoing. Taking risk-reducing medication should be discussed with an experienced medical professional.

MAP

People with MAP (*MUTYH*-Associated polyposis) need regular bowel check-ups (colonoscopy) from the age of 20 years. If a large number of polyps are found and these cannot be managed by regular colonoscopy screening, an operation to remove the bowel and prevent cancer may be considered. From the age of 35 years a check of the upper gastrointestinal tract (called an endoscopy) is required to check for polyps in the duodenum.

It is recommended that people with FAP, Lynch syndrome and MAP are enrolled by their doctor on a local hereditary cancer registry for information and surveillance reminders. Further information is available at the NSW Hereditary Cancer Registry (www.cancerinstitute.org.au).

Lifestyle may help

Most cancers occur due to a combination of genetic factors, environmental factors and the process of ageing.

Maintaining a balanced diet high in fibre and low in fat, no smoking and living a healthy lifestyle can reduce the risk of many cancers.

Planning a pregnancy

Testing may be available for inherited breast cancer during a pregnancy. Genetic testing in a pregnancy for genetic causes of breast cancer is optional and should be talked about in full with your doctor, midwife or genetic counsellor. It may also be possible to have preimplantation genetic diagnosis (PGD) to look for inherited causes in an embryo made using *in vitro* fertilisation (IVF). Some people also investigate egg, sperm or embryo donation. Others choose to have a natural pregnancy with no testing.

Reproductive genetic carrier screening for a range of genetic conditions that follow a recessive pattern of inheritance is also available for couples who are planning pregnancy, or are in early pregnancy.

When planning a family, options for testing are best talked about and considered before pregnancy.

More support and information is available for individuals and families through support organisations including Bowel Cancer Australia, Lynch Syndrome Australia, Cancer Council and Genetic Alliance Australia.