

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER: HNPCC (also known as Lynch syndrome)

A Guide for people with HNPCC and their family and friends.

This Information Guide is aimed at helping you to understand Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome, a rare condition that tends to run in some families.

This Guide does not replace your discussions with doctors, genetic counsellors, nurses and other health professionals.

We suggest that you read this Guide in the order in which it is written, as each new section builds upon information in previous sections.

Some medical terms that may be unfamiliar are explained in the glossary.

BACKGROUND TO THIS GUIDE

- This Guide is based on Cancer Council NSW booklet 'Understanding Hereditary Non-Polyposis Colorectal Cancer (HNPCC) Syndrome', published in June 2004.



I. What is HNPCC?

Hereditary non-polyposis colorectal cancer syndrome (HNPCC) leads to a very high risk for colorectal cancer. The name explains what it is:

H stands for Hereditary. This means that it can be passed from a parent to their child (inherited). People with this condition have not inherited cancer, but have inherited a high risk of developing colorectal cancer and a risk of developing some other cancers. Sometimes people are the first in their family to develop HNPCC.

NP stands for Non-Polyposis. This indicates that HNPCC is different from another hereditary condition called Familial Adenomatous Polyposis (FAP). People with FAP usually have hundreds of small growths, called polyps, on the lining of their bowel wall. Polyps do occur in HNPCC but usually in much smaller numbers than in FAP.

CC stands for Colorectal Cancer – that is, cancer of the colon or rectum, also known as large bowel cancer.

HNPCC is also known as **Lynch syndrome**, named after Dr Henry T. Lynch who described families with the condition.

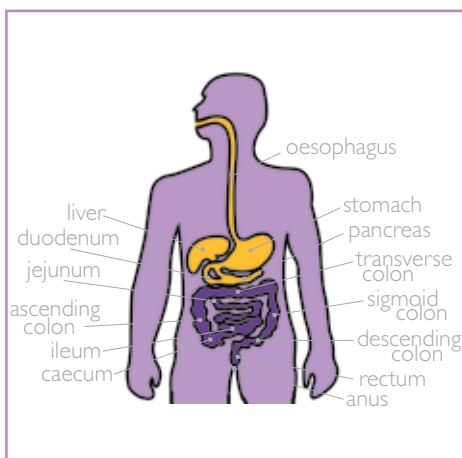
The bowel

The bowel is part of the digestive system, or gut.

The gut is the long tube that runs from your mouth, via your stomach and bowel, to your back passage (anus).

Food passes through the bowel, is digested and absorbed and the waste products are passed out as bowel motions.

- The gut includes: The oesophagus, stomach and small bowel (the duodenum, jejunum and ileum) where food is digested and absorbed.
- The large bowel (the colon and rectum) where only water and salts are absorbed. The colon has different sections – caecum, ascending colon, transverse colon, descending colon and the sigmoid colon. The rectum leads to the outside of the body via the anus.



What causes HNPCC?

Every cell of the body carries a full set of instructions for growth and development called genes.

Occasionally some genes do not work properly because there is a change in them. This change is called a mutation.

HNPCC arises when a gene contains a mutation that reduces its ability to prevent the growth of polyps and cancer in certain parts of the body.

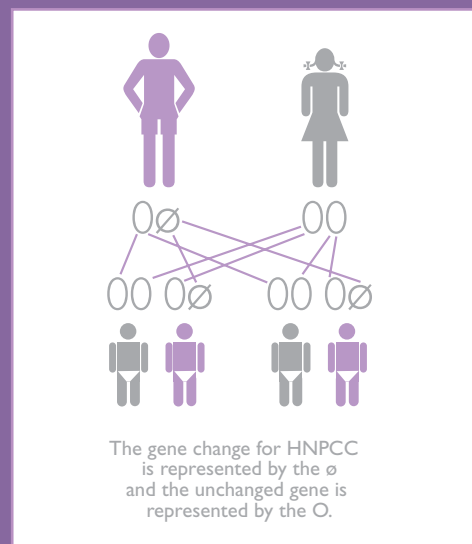
There are several known genes in which mutations can lead to HNPCC. These genes are known as the 'mismatch repair' genes. HNPCC is due to an inherited mutation in one of the mismatch repair genes.

How is HNPCC inherited?

Genes come in pairs. You inherit one copy of every gene from your mother and the other copy from your father. This is how a gene mutation can be passed on in a family.

If someone has a HNPCC mutation, each of their children, regardless of their sex, has a 50% (one in two) chance of inheriting the mutation. This does not mean that 50% of the children will necessarily be affected, but that each child has a 50% chance of being affected.

This diagram shows the chance that each child has of inheriting the mutation. In this example, the father is carrying the HNPCC mutation. When a baby is conceived, each parent passes on one copy of each of their genes to the baby. When one of the parents is carrying a mutation in one of the HNPCC genes, represented here by the "ø" symbol, we see that there is a 50% chance that the baby will also carry this mutation.



How is HNPCC inherited ?

(cont'd...)

If a person does not inherit the family HNPCC mutation, then they cannot pass it on to their children.

If someone has HNPCC, it is possible that their brothers and sisters also have the condition. One of their parents could have the condition but may not know about it because they have not had any symptoms. The family should seek advice from genetic counselling professionals who know about HNPCC and can advise the family on screening and testing.

Your family may be at risk of having HNPCC syndrome if any of the following features are present:

- At least three family members have had bowel cancer or one of the other associated cancers (eg. womb, renal pelvis, ureter, small bowel – see next section), and one person is a close relative of the other two (i.e. parent/child/sibling).
- At least two successive generations are affected.
- At least one person was diagnosed at under 50 years of age.
- A person in the family with two or more bowel cancers, or bowel cancer and one of the other associated cancers.
- Familial Adenomatous Polyposis (FAP) has been excluded from the diagnosis.

If you have a relative with HNPCC you may be at risk. You might find it useful to contact your Familial Cancer

Clinic to discuss your family history and find out whether your family is at risk of HNPCC. Contact details of your nearest Familial Cancer Clinic are listed at the end of this information Guide.

Cancers associated with HNPCC

Some other forms of cancer are linked with HNPCC. Cancer of the uterus/womb is the only one that occurs nearly as often as bowel cancer in HNPCC families.

Cancers shown in bold (below) are by far the most common in HNPCC.

Men	Women
- Large bowel	- Large bowel
- Small bowel	- Endometrium (inner lining of uterus/womb)
- Stomach	<i>*this is not cancer of the cervix</i>
- Renal pelvis (part of the kidney)	- Small bowel
- Ureter (tube from kidney to bladder)	- Stomach
- Pancreas	- Renal pelvis
	- Ureter
	- Pancreas
	- Ovary

Tumour tissue testing may assist the diagnosis of HNPCC

If HNPCC syndrome is suspected in your family then tests can be done on tissue from a bowel cancer of a family member. These tests are looking for changes in the genetic information within a cancer cell and include:

- microsatellite instability (MSI) testing and
- immunohistochemistry (IHC) testing. IHC is a staining test to check which genes are working in the tumour tissue.

If the MSI test shows that the tumour cells are stable (no microsatellite instability) then it is less likely that the person has a mutation in one of the known HNPCC genes. If the MSI shows that tumour cells are unstable, then HNPCC is more likely, and IHC testing can help identify which gene should be tested for the presence of a HNPCC mutation.

What can be done if someone has HNPCC?

People with HNPCC are at increased risk of developing cancer. A person with a proven diagnosis of HNPCC has about an 80% chance of developing cancer.

There is much that can be done to reduce cancer risk if someone has HNPCC. This includes regular check-ups and, sometimes, individuals may consider preventative surgery.

2. Genetic testing for HNPCC

What does genetic testing involve?

Genetic testing is usually offered to families where there is a cancer history suggesting HNPCC. If it is possible, tumour tissue testing may be done first to clarify whether genetic testing is appropriate and which gene is likely to be affected. The particular mutation in the HNPCC gene varies from one family to another.

The first step in each family is to try and find the family-specific HNPCC gene mutation by first testing a blood sample from an affected person. This process of a "mutation search" may take considerable time, and it is not always possible to find the mutation that causes HNPCC for a family. For this reason, a mutation search may be inconclusive.

If, however, the family-specific gene mutation can be identified, then other at-risk relatives can have a blood test to see if they have inherited the family HNPCC mutation. This is called predictive testing. Results for predictive tests are available more quickly because we already know the family's specific HNPCC mutation, so we know exactly where to look in the gene.

Genetic testing usually involves giving a small blood sample after written, informed consent is provided. Genetic counselling is offered before and after genetic testing by your Familial Cancer Clinic.

If you have not inherited the family mutation, then you do not have HNPCC syndrome. If you have not inherited the mutation, then you do not need intensive screening and your children are not at risk of inheriting HNPCC syndrome from you.

Genetic testing in Australia is done through Familial Cancer Clinics, where professionals make sure that people receive all the support and help they may need to make decisions about testing. Genetic testing done through a Familial Cancer Clinic is free.

- Genetic testing examines the information in a gene.
- Genetic testing can identify gene mutations.
- A blood sample is needed for genetic testing

Search for the family mutation

Begin genetic testing with an affected family member (results may take several months).

Positive result:
The family mutation is identified.

Inconclusive result:
The family mutation is unable to be identified.

Predictive testing
can be offered to at-risk family members (takes about 8 weeks to get a result).

No genetic test is available for at-risk family members. Family should continue with screening as per guidelines in section 3 as there is continued risk of HNPCC.

Positive result: has HNPCC and needs regular screening. See guidelines in Section 3.

Negative result: does not have HNPCC. Cannot pass it onto children.**

** People found not to have their family's HNPCC mutation have the same risk of bowel and other cancers as the general population. They need to consult their doctor about any symptoms and be screened for colorectal cancer in the same way as the general population.

Genetic testing FAQs

Can all families have the HNPCC genetic test?

Not all families can have the HNPCC genetic test because:

- HNPCC genetic testing is only offered to families when the family history suggests the possibility of HNPCC.
- Sometimes a family thought to have HNPCC syndrome has no living affected family member to test, or has some affected family members who are not interested in having genetic testing. This means that the family mutation cannot be identified, and at-risk relatives therefore can not be offered predictive testing.
- In some families, even though a blood sample is available, the laboratory may not be able to find the family-specific HNPCC gene mutation. This may be due to a type of mutation that is difficult to find and/or the possibility of a genetic change on an as yet unidentified gene associated with HNPCC.

What happens if I can't be gene tested?

If you are at risk of HNPCC syndrome but you can't be gene tested, you will need to have regular bowel examinations to check for polyps. Your treatment options then are the same as for everyone else with HNPCC syndrome.

What if I don't have the family's HNPCC gene mutation?

If you don't have the gene mutation found in other members of your family, you do not have HNPCC and do not have the same high risk of developing bowel cancer.

Your children are not at risk of inheriting HNPCC syndrome because you don't have the mutation to pass on to them.

Your children do not need to have the genetic test. You and your children no longer need to have screening for HNPCC syndrome.

If you have not inherited the family mutation it does not, however, mean that you will never develop bowel cancer, but that your chance of developing bowel cancer is the same as for the general population – about a 1 in 20 chance in your lifetime.

What if I do have the family HNPCC gene mutation?

If the test finds that you carry the family HNPCC mutation then you have a high risk of developing bowel cancer and an increased risk of some other cancers throughout your lifetime. You need to have regular check-ups to reduce your risk of developing cancer or to find cancer early if it has already developed. For details about regular screening, see section 3.

When can the test be done?

If the family-specific HNPCC mutation is identified, family members (18 years and older) can have the test as soon as they wish. For people under the age of 18, parental consent may be required.

There is no immediate benefit from genetic testing in childhood, so it is usually preferable for the individual to be old enough to have a say in whether they want to have the test or not. If you are concerned about this, talk it over with your genetic counsellor.

Who will know my test result?

Your personal test result is shared only with persons or organisations for whom you give consent.

The importance of talking it over

Before you have a genetic test, it is important to talk with a professional such as your doctor or genetic counsellor about the pros and cons of genetic testing. This may help you decide if genetic testing is right for you.

Insurance policies and genetic testing

If you are planning to have genetic testing, it is wise to discuss insurance issues with a genetic counsellor before testing.

I'M NOT SURE I WANT TO KNOW

This is a common reaction. It may be helpful to consider the following points.

- If the test shows you do not have the family HNPCC gene mutation, you will know that you have the same risk of developing bowel cancer as the general population but not the high risk associated with being an HNPCC mutation carrier. You will not need to have screening until the age recommended for the general population, unless symptoms arise.
- If the test shows you do have the family gene mutation, remember that people who have regular screening and removal of polyps have a lower risk of bowel cancer than those who do not have screening. Additional cancer screening tests may be advised. Also, cancers of the bowel and uterus diagnosed early can be treated very successfully.

3. Regular check-ups

Regular check-ups are recommended to detect and treat polyps and cancers early.

Regular check-ups should begin at age 25 or five years earlier than the youngest age at diagnosis of an affected relative (whichever comes first). Check-ups should continue throughout life.

Men and women with proven HNPCC:

- Colonoscopy every 12 months

Screening of other organs depends upon family history and may include:

- Endoscopy of upper gastrointestinal system every 24 months.
- Urinalysis and cytology every 12 months.
- Abdominal ultrasound.

Additional check-ups for women:

Removal of the uterus and cervix (hysterectomy) and removal of the ovaries (oophorectomy) are options which aim to prevent cancer from developing in the uterus or ovaries. Women with HNPCC may consider risk-reducing surgery from the age of 30-35 or once they have completed their families, particularly where there is a family history of uterine or ovarian cancers. Alternatively, screening of the uterus and ovaries every 12 months may be offered, although it is not clear how effective this screening is in detecting these cancers early. Women should talk these options over with their doctor or Family Cancer Clinic.

If you have had bowel surgery:

- Endoscopic check of any remaining bowel every 12 months

Men and women at risk of (but not with proven) HNPCC

- Colonoscopy every 24 months.
- Faecal occult blood testing (FOBT) may be offered in intervening years.
- Other tests depend on the strength of family history of cancers in those organs.

Evidence shows that regular colonoscopy and removal of polyps improves outcomes in HNPCC patients.

Tests that may be used during regular check-ups

Colonoscopy

A colonoscopy is an examination using video technology, in which the inner lining of the large bowel is inspected using a flexible tube with a light at the end. The tube is passed through the anus and moved through the bowel to enable the doctor to see along its full length. The bowel has to be empty, so some medication is usually given the day before to help you to empty your bowel. The examination generally takes about 30 minutes. It is done under sedation as a day procedure. If any polyps are seen, they can usually be removed at this time.

Upper gastrointestinal endoscopy

An upper gastrointestinal endoscopy examines the lining of the upper part of the gut using a similar type of technology to the colonoscopy. A tube is inserted through the mouth. Light sedation is often given to the patient. To ensure the stomach and upper gut are empty, no food or drink should be taken for several hours before the procedure.

Gene positive and at-risk people should immediately tell their doctor or Familial Cancer Clinic about any symptoms of bowel problems such as rectal bleeding, indigestion, abdominal pain, changes to bowel habits (like prolonged constipation or diarrhoea) or genito-urinary symptoms such as blood in the urine or abnormal bleeding from the vagina. In general, any persistent new symptoms should be discussed with your doctor or Familial Cancer Clinic.

Surgery

Surgery for bowel cancer

Some people from a family with HNPCC syndrome do not see a doctor until bowel cancer has already developed and it needs to be removed with surgery. The type of surgery will depend on the location of the cancer. Follow-up screening of the remaining bowel will be needed to detect any possible future abnormalities.

The option of preventative surgery

There is no clear agreement about the necessity for preventative bowel surgery in HNPCC. Ask your specialist and the team at the local familial cancer service about your particular situation.

4. Support and information

The NSW & ACT Hereditary Cancer Registry

The Hereditary Cancer Registry (HCR) was established to provide information and support to people affected by hereditary cancer, their family members who may be at risk, and their doctors in NSW and the ACT. While there are a number of hereditary related cancers, the conditions focussed on by the HCR include:

- Hereditary Non-Polyposis Colorectal Cancer – HNPCC
- Familial Adenomatous Polyposis – FAP
- Peutz-Jeghers Syndrome – PJS
- Juvenile Polyposis
- Other polyposis syndromes (i.e. Hyperplastic, Mixed Polyposis, MYH Associated Polyposis)

What does the Hereditary Cancer Registry do?

The HCR aims to assist people from families with a high risk of hereditary cancer to understand and manage their risk. It does this by:

- Building a complete picture of the condition in a family, assisting doctors to assess risks and plan screening and treatment.
- Developing knowledge about the incidence of hereditary cancer conditions in NSW and ACT.
- Contributing to better information, services and support for patients and their families.
- Providing a screening reminder service to registrants and their doctors.

The HCR offers an optional screening reminder service to assist registrants with keeping up to date with screening appointments. The HCR records registrants' contact details, family history, treatment, screening test results and details of any surgery that has been performed. All the information kept at the HCR remains strictly confidential. It is not given to anyone else, including family members, without permission.

The information on the HCR database is an excellent starting point for national and international research into hereditary cancer syndromes such as HNPCC. Information that is recorded on people or families is only used in statistical reports in which individuals cannot be identified. The HCR receives advice from a committee of clinical experts.

Why should I register and how do I register?

People from high-risk families are encouraged to register with the HCR to take advantage of the up-to-date information, screening reminder service and support provided by the registry. Registration is voluntary, and personal information is held confidentially under the Health Information and Records Privacy Act.

Registration can be completed using the registration form provided by your doctor or genetic counsellor, or contact the HCR for more information.

Other services offered by the NSW & ACT Hereditary Cancer Registry include:

- Current information about hereditary cancer, its prevention, treatment and management.
- A newsletter to keep you up to date with new developments.

- Booklets and pamphlets about hereditary cancer conditions
- Information about genetic services and tests.
- Assistance with informing relatives of their risk by providing letters and other information about the family cancer condition.
- Assistance with contacting interstate and overseas registries for the benefit of family members.
- Information events.
- Access to confidential telephone counselling.
- Assistance with contacting support groups (cancer/genetics/ostomy).
- Assistance with education and research.

For more information contact the NSW & ACT Hereditary Cancer Registry:

Phone: 1800 505 644

Fax: 02 8374 5744

E-Mail: hcr@cancerinstitute.org.au

Mail:

NSW & ACT Hereditary Cancer Registry

c/o Cancer Institute NSW
Locked Bag 9014

Alexandria NSW 1435

Website: www.cancerinstitute.org.au/cancer_inst/programs/hcr.html

Familial Cancer Clinics

The staff at familial cancer clinics are trained to assist you with concerns about your family's history of cancer and can organise for you and your family to be seen by specialists who provide clinical advice, screening recommendations and, if appropriate, organise genetic testing.

The staff at familial cancer clinics can assist you with information about your family's history of cancer. They can organise for your history to be assessed by professionals and/or can give you contact details for the nearest Familial Cancer Clinic

Centre for Genetics Education

Information fact sheets and other information about hereditary cancer is also available from the Centre for Genetics Education. You can call 02 9926 7324 or visit the website

www.genetics.edu.au

Newcastle	Hunter Family Cancer Service Cnr Turton & Tinonee Roads Waratah 2298	02 4985 3132
Randwick	Hereditary Cancer Clinic Prince of Wales Hospital High Street, Randwick 2031	02 9382 2577
Westmead	Familial Cancer Service Westmead Hospital Westmead 2145	02 9845 6947
Darlinghurst	Family Cancer Clinic St Vincent's Hospital Darlinghurst 2010	02 8382 3395
Camperdown	Hereditary Cancer Clinic Royal Prince Alfred Hospital Missenden Road, Camperdown	02 9515 5080
St Leonards	Family Cancer Service Royal North Shore Hospital Pacific Highway, St Leonards 2065	02 9926 6502
Kogarah	Hereditary Cancer Clinic St George Hospital Gray Street, Kogarah 2217	02 9350 3815

For other locations in NSW phone the Hereditary Cancer Registry on 1800 505 644 or visit the HCR website page: http://www.cancerinstitute.org.au/cancer_inst/programs/hcr.html

Cancer Council Helpline 13 11 20

Cancer Council Helpline is a telephone information service provided by Cancer Council NSW for people affected by cancer.

For the cost of a local call, you can talk about your concerns and needs confidentially with oncology health professionals. Helpline consultants can also put you in touch with appropriate services in your area.

Call the Cancer Council Helpline on **13 11 20**

AGSA – The Association of Genetic Support of Australasia

For information about support groups contact the Association of Genetic Support of Australasia on 02 9211 1462 or visit the website:

www.agsa-geneticsupport.org.au/

5. Glossary

Adenoma

A non-cancerous tumour. It may turn into a cancer if not treated.

Anus

The back passage. The opening of the bowel through which bowel motions are passed.

Benign

Not cancer.

Colon

The part of the large bowel between the end of the small intestine (the ileum) and the rectum. It is about 1.5 metres long.

Colonoscopy

Examination of the large bowel using a thin flexible tube with a light at the end, called a colonoscope. It is passed through the anus and gently moved around so that, through it, the doctor can see the full length of the large bowel.

Duodenum

The first 30 centimetres of the small bowel. The stomach empties into the duodenum.

Gene

The elements of a cell that carry instructions on how the cell should grow and function. Each person has a set of

many thousands of genes inherited from both parents. This set is found in every cell of the body.

Ileum

The lower half of the small bowel, which joins up with the colon.

Jejunum

The part of the small bowel below the duodenum and leading into the ileum.

Large bowel

The colon and rectum.

Malignant

Cancerous. Malignant cells can spread (metastasise) and eventually cause death if not treated.

Mismatch repair genes

A set of genes whose job is to repair errors in DNA when cells divide. If one of the mismatch repair genes is not working properly, DNA errors accumulate in the cell, increasing the risk of cancer.

So far, four mismatch repair genes have been found to be associated with HNPCC. The names of these four genes are *hMLH1*, *hMSH2*, *hMSH6* and *PMS2*. There may be other genes associated with HNPCC not yet discovered by scientists.

Mutation

A change in a gene causing it to show a new characteristic.

Polyp

An abnormal growth or lump in the bowel, often on a stalk, like a mushroom. Polyps are usually benign but can turn cancerous.

Rectum

The last 12-15 centimetres of the large bowel, which opens to the outside of the anus. The faeces collect in the rectum before they are passed as a bowel motion.

Sigmoid colon

The last 20-25 centimetres of the colon, which leads into the rectum.

Sigmoidoscopy

Examination of the rectum and sigmoid colon using a sigmoidoscope. This is a narrow lighted tube. It is inserted gently through the anus, and gives a view of the lining of the bowel.