What is hereditary bowel cancer?

Bowel cancer (also known as colorectal cancer) is the fourth most common cancer in the UK. Unfortunately 1 in 19 women and 1 in 14 men will develop bowel cancer during their lifetime, with most being diagnosed after the age of 50. This means that in the general population men have a 7% lifetime risk of developing bowel cancer and women have a 5% risk.

Most bowel cancer occurs by chance, however 2-5% of bowel cancer is inherited and up to 30% is familial. In some families stomach, womb and ovarian cancer can also be genetically related to bowel cancer. In families where bowel cancer is hereditary it may be possible to find the genetic change (mutation) which is responsible for the cancers. This allows appropriate cancer screening and risk-reducing options.

What are genes?

Genes are the body’s instructions and determine how the body develops and is maintained. Some genes prevent cancer developing: if there is a mutation in one of these cancer genes, then the gene doesn’t work correctly and causes an increased risk of cancer.

Mutations in at least 11 genes can cause an increased risk to bowel cancer and other cancers. However, we know that there are other genes which are also associated with bowel cancer.

How do I know if I am at risk?

Families with hereditary bowel cancer generally show one or more of the following clues:

- Bowel cancer diagnosed at a young age (before the age of 50)
- Bowel cancer that has screened positive for Lynch syndrome
- Several relatives with bowel cancer
- Relatives with bowel cancer and related cancers (such as womb or ovarian cancer)
- Multiple bowel polyps* in an individual
- Multiple generations with cancer

* Cancer usually starts as a benign growth known as a polyp. Not all polyps will become cancerous and they can often be removed during screening.

How can genetic testing help?

Genetic testing can help determine the risk of cancer within a family and guide appropriate cancer screening. Depending on the specific genetic risk different screening tests can be arranged and risk-reducing strategies considered. Colonoscopies have particularly been shown to lower the risk of bowel cancer in families with an inherited risk.
What is BowelGene?
BowelGene looks at 11 genes which cause an increased risk of bowel cancer. The following genes are tested:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Estimated bowel risk by age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>Lynch syndrome</td>
<td>35-65%</td>
</tr>
<tr>
<td>MSH2</td>
<td>Lynch syndrome</td>
<td>35-75%</td>
</tr>
<tr>
<td>MSH6</td>
<td>Lynch syndrome</td>
<td>10-70%</td>
</tr>
<tr>
<td>PMS2</td>
<td>Lynch syndrome</td>
<td>15-20%</td>
</tr>
<tr>
<td>EPCAM</td>
<td>Lynch syndrome</td>
<td>35-75%</td>
</tr>
<tr>
<td>MUTYH</td>
<td>MUTYH associated Polyposis</td>
<td>43-100%</td>
</tr>
<tr>
<td>APC</td>
<td>FAP</td>
<td>~100%</td>
</tr>
<tr>
<td></td>
<td>AFAP</td>
<td>70%</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>Juvenile Polyposis Syndrome</td>
<td>38-68%</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Juvenile Polyposis Syndrome</td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden syndrome</td>
<td>9-16%</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz Jeghers Syndrome</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>Cowden syndrome</td>
<td></td>
</tr>
</tbody>
</table>

**Lynch syndrome (LS)**
Lynch syndrome is the most common hereditary bowel cancer syndrome and is the cause of approximately 1–3% of all bowel cancer. LS causes an increased risk of bowel (25-70%), stomach (5%), womb (30-70%), prostate (18-30%) and other cancers. It has been estimated that in Europe approximately one million people have LS.

Some hospitals now automatically screen bowel tumours for Lynch syndrome. For individuals who screen positive further genetic testing on a blood sample is recommended. If a mutation is identified on the blood test then the person is said to have Lynch syndrome.

If someone has LS, regular bowel screening with colonoscopy is vital and other risk-reducing strategies will be considered. These strategies include detecting and treating an infection called Helicobacter Pylori as well as taking aspirin, and in women, consideration of risk-reducing surgery.

**Familial Adenomatous Polyposis (FAP) and Attenuated Familial Adenomatous Polyposis (AFAP)**
FAP and AFAP are inherited conditions which cause many bowel polyps (over 100 in classical FAP), as well as an increased risk of bowel, small bowel (4-12%) and other cancers.

These conditions are rare: approximately 2-3 people in 100 000 will have FAP. However, about 25% of people with FAP will have a new mutation in the APC gene: this means that it occurred for the first time in them and so they usually won’t have a family history of cancer. If someone has FAP they usually consider having their bowel and rectum removed, while people with AFAP need increased bowel screening.

**MUTYH Associated Polyposis (MAP)**
MAP is unusual in that it is inherited in a recessive pattern. This means that someone must inherit a mutation from their mother AND father to be affected. MAP causes multiple bowel polyps, an increased risk of bowel cancer and possibly other cancers. Someone with MAP would be advised to have regular bowel screening and may consider more extensive surgery if they have been diagnosed with bowel cancer.

**Juvenile Polyposis syndrome (JPS)**
Juvenile polyposis causes many polyps in the bowel and most people will develop some polyps by the age of 20. As well as an increased risk of bowel cancer JPS also increases the risk of stomach cancer (21%) and possibly other cancers. Colonoscopy and endoscopy screening will be recommended. 22% of people with SMAD4 mutations will also have hemorrhagic telangiectasia (malformations of the veins).

**Peutz Jeghers Syndrome (PJS)**
PJS causes polyps in the large and small bowel, as well as ovarian tumours and abnormal colouring of the skin in childhood, particularly on the lips. PJS causes an increased risk of bowel (39%), breast (45%), pancreatic (11%) and other cancers. Mammograms, colonoscopies and other cancer screening will be recommended.
PTEN Hamartoma Tumor Syndrome (PHTS)/ Cowden syndrome
Cowden syndrome causes bowel polyps, benign skin lesions, benign breast disease, autism and other features. Individuals with Cowden syndrome have an increased risk of bowel (9%), breast (85%), kidney (34%), thyroid (35%), and womb (28%) cancers as well as a risk of melanoma (5%). Colonoscopy as well as mammograms, renal MRI, skin examination and thyroid ultrasounds will be recommended. Risk reducing surgery may be considered.

How are these conditions inherited?
Genes come in pairs; we get one copy from our mother and one copy from our father. Currently most bowel cancer syndromes are inherited in a dominant pattern. This means that if someone has a mutation in one copy of a gene then there is a 50% chance that they will pass this onto their children. The diagram opposite illustrates this.

How does the test work?
BowelGene is performed on a blood or saliva sample and it takes 4 weeks to obtain the results.

BowelGene uses state of the art NextGeneration sequencing to examine the code for each of the 11 genes in detail. In addition, dosage analysis is used to look for large deletions (missing parts) and duplications (extra parts) of the genes. It is a comprehensive way to assess a person’s risk for hereditary bowel and associated cancers. However, no test is 100% and it is possible that someone could have a genetic mutation which is not detected by this test.

It is most accurate to perform genetic testing on someone who has had bowel cancer so that a possible genetic cause can be found in the family. If this is not possible, genetic testing can be performed on someone who has not had cancer, although if the results are normal this will not be as informative.

What will the test show?
There are 3 possible results:

1. A mutation is found in one of the genes which is known to increase the risk of bowel cancer. Increased screening and/or risk-reducing techniques will be recommended.

2. A genetic variation is found, but whether or not this is the definite cause of cancer is unknown. Screening will be recommended based on the family history.

3. No mutation is found. It is possible that there may be an undetectable mutation or a mutation in a different gene. Cancer screening may still be beneficial.
What does it mean if I have a mutation?
If you have a mutation this means that you have an increased risk of bowel cancer and possibly other cancers. Your exact risks will depend on which gene mutation has been found. Extra screening and/or risk-reducing strategies will be discussed. It will also be possible to offer predictive testing to other people in your family to see if they also have the mutation.

Screening
When someone has an increased risk of bowel cancer it is usual for them to have colonoscopies. A colonoscopy is when a flexible telescope is inserted into the anus to examine the entire bowel (rectum and colon). If any polyps are found these can usually be removed to prevent them developing into cancer. The frequency of colonoscopy will depend on which gene mutation is found.

Screening for other cancers may also be needed and will be discussed if necessary.

Aspirin has been shown to lower the risk of bowel cancer in some circumstances and is currently recommended for LS carriers.

Risk-reducing surgery
In some situations, people may wish to consider risk-reducing surgery. This is dependent on the condition.

In Lynch syndrome women have an increased risk of womb and ovarian cancer and may therefore consider hysterectomy and removal of the ovaries.

Colectomy (removal of the colon) may be considered if an individual has FAP or when an individual has been diagnosed with colorectal cancer.

Bowel awareness
It is important for everyone to be bowel aware and inform their doctor if they notice any signs that they are concerned about.

Signs of bowel cancer are:
- Bleeding from the anus and/or blood in the stool
- A change in bowel habit (needing to go to the toilet more or less often) lasting for 3 weeks, and particularly looser stools
- Unexplained weight loss
- Extreme tiredness for no obvious reason
- A pain or lump in the tummy

Most of the time people with these signs will not have cancer but is always important to get them checked out.

Other risk factors
The risk of bowel cancer increases as a person becomes older which is why bowel screening for the general population currently starts at 55. A personal history of bowel polyps, type 2 diabetes, ulcerative colitis, Crohn’s, and a condition called Acromegaly also increase the risk of bowel cancer and you should consult your doctor regarding screening if you have these.

Lifestyle factors
Smoking and drinking alcohol have both been shown to increase the risk of bowel cancer. Your GP can help with smoking cessation and/or discuss your alcohol intake if you are concerned. Red meat, processed meat, abdominal and body fatness also increase the risk of colorectal cancer

A diet high in dietary fibre, garlic, milk, and calcium lower the risk of colorectal cancer, as does physical activity.

Financial Issues
Some individuals may be concerned about difficulties with obtaining insurance coverage following genetic testing. Currently, there is a moratorium ensuring that individuals do not need to disclose predictive genetic tests. This moratorium is valid until 2019. More information about insurance can be found at: [http://www.abi.org.uk](http://www.abi.org.uk)

Further information and support can be found at:-
- [http://www.lynchcancers.com](http://www.lynchcancers.com)
- [http://community.macmillan.org.uk/cancer_types/hereditary_nonpolyposis_colorectal_cancer_hnpcc_or_lynch_syndrome/f/33346/t/51150.aspx](http://community.macmillan.org.uk/cancer_types/hereditary_nonpolyposis_colorectal_cancer_hnpcc_or_lynch_syndrome/f/33346/t/51150.aspx)
- [www.corecharity.org.uk 020 7486 0341](http://www.corecharity.org.uk 020 7486 0341)
- [www.hereditarycc.org](http://www.hereditarycc.org)
- [www.researchuk.org 0808 800 4040](http://www.researchuk.org 0808 800 4040)
- [www.macmillan.org.uk 0808 808 0000](http://www.macmillan.org.uk 0808 808 0000)
- [www.bowelcanceruk.org.uk 0800 8403540](http://www.bowelcanceruk.org.uk 0800 8403540)

Our knowledge of cancer genetics is rapidly growing, and the information given summarises this to date. Please keep us informed of any significant changes in your family in the future as this may alter our advice to you. Please do not hesitate to contact us if you have any questions or concerns.
GeneHealth UK is the leading provider of genetic tests and offers national and international counselling and testing services. We have designed our services to be comprehensive and to detect all of the clinically relevant mutations, however no genetic test will pick up all genetic mutations. If your results are abnormal you may be eligible for referral to an NHS clinic via your GP, or to a consultant in one of our private clinics throughout the UK. This may be funded by either self-pay or private medical insurance.

Please visit www.GeneHealthUK.com for more information and advice.

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