What is hereditary prostate cancer?
Prostate cancer is the most common cancer among men in the UK. Unfortunately, 1 in 8 men will be diagnosed with prostate cancer, with 75% being diagnosed over the age of 65. This means that men have a 12.5% lifetime risk of prostate cancer. The majority of prostate cancer occurs by chance however approximately 5-9% of all prostate cancer and 12% of metastatic prostate cancer is estimated to be hereditary.

In general, men with 1 first degree relative (father or brother) have twice the risk of prostate cancer, while men with 2 first degree relatives have 5 times the risk compared to the general population.

What are genes?
Genes are the instructions that 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 several genes have been linked to prostate cancer; of these 10 genes are known to increase the risk of prostate cancer and possibly other cancers. Importantly we know that there are other genes which are associated with prostate cancer.
How do I know if I am at risk?
You may be at increased risk of prostate cancer if you have any of the following signs in your family:

- Early onset prostate cancer (diagnosed before age 55)
- 3 first degree relatives (brother, son, father) diagnosed with prostate cancer
- Ashkenazi Jewish ancestry and breast, ovarian or prostate cancer
- Prostate cancer and 2 relatives with breast or ovarian cancer
- Prostate cancer and male breast cancer or ovarian cancer or bilateral breast cancer
- Prostate Cancer and early onset bowel or womb cancer (before 50)
- Prostate cancer and 2 relatives with bowel or womb cancer

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 can be considered. However, it is important to be aware that even if testing is normal you may still have an increased risk of prostate cancer based on your family history.

What is ProstateGene?
ProstateGene looks at 10 genes which cause an increased risk of prostate cancer. The following genes are tested:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Lifetime Risk of prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>HBOC</td>
<td>~20% (7-26%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>HBOC</td>
<td>~40% (19-61%)</td>
</tr>
<tr>
<td>HOXB13</td>
<td>Hereditary Prostate cancer</td>
<td>33 - 60%</td>
</tr>
<tr>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPCAM</td>
<td>Lynch syndrome</td>
<td>18% - 30%</td>
</tr>
<tr>
<td>ATM</td>
<td>Hereditary Prostate Cancer</td>
<td>Significantly increased risk</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Hereditary Prostate Cancer</td>
<td>2-3 times general population risk</td>
</tr>
</tbody>
</table>

Hereditary Breast and Ovarian Cancer (HBOC)
Mutations in BRCA1 & BRCA2 cause hereditary breast and ovarian cancer as well as prostate cancer. 2% of men diagnosed with prostate cancer before the age of 55 will have a BRCA2 mutation. In the general population 0.25% of Non Jewish people and 2% of Ashkenazi (Eastern European) Jewish people will have a BRCA mutation.

The estimated cancer risks associated with BRCA mutations vary however; BRCA1 mutations are estimated to have up to an 85% risk of breast cancer and up to 60% risk of ovarian cancer. While men with BRCA1 mutations have a slightly increased risk of male breast cancer and approximately a 20% risk of prostate cancer.

Women with BRCA2 mutations have up to a 90% risk of breast cancer and up to a 30% risk of ovarian cancer. Men with BRCA2 mutations have a 5-10% lifetime risk of developing breast cancer and approximately a 40% risk of prostate cancer.

Individuals with BRCA2 mutations also have an increased risk of pancreatic cancer and possibly other cancers.

Studies have shown that prostate cancer caused by BRCA1 and BRCA2, tends to be of a higher grade and therefore more likely to benefit from treatment. In particular it may respond better to platinum based chemotherapy and PARP inhibitors.

Women with BRCA gene mutations should have annual MRI from age 30 years and annual mammogram from 40 years. Ovarian screening has not been shown to be beneficial and therefore some women may consider risk-reducing surgery. Men may benefit from prostate cancer screening.

Very rarely, a baby may inherit two BRCA2 mutations. In this situation the baby will have the congenital condition known as Fanconi Anaemia.
Lynch syndrome (LS)
It has been estimated that in Europe approximately one million people have Lynch Syndrome. LS causes an increased risk of bowel (25-70%), stomach (5%), womb (30-70%), prostate (18-30%) and other cancers.

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.

Studies have shown that prostate cancer caused by LS tends to be of a higher grade and therefore more likely to benefit from treatment. There are also clinical trials looking into a new immunotherapy drug known as PD1 which appears to be particularly effective in Lynch syndrome related cancers.

HOXB13
This gene has been found in 5% of prostate cancer families and causes an estimated 33-60% risk of prostate cancer.

ATM
This gene has been shown to cause a significantly increased risk of prostate cancer. Prostate cancer is also likely to be of a higher grade and therefore to benefit from treatment.

CHEK2
Mutations in CHEK2 cause an increased risk of prostate cancer (2-3 times that of the general population).

How are these conditions inherited?
Genes come in pairs; we get one copy from our mother and one copy from our father. At present all known prostate 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 risk of prostate cancer can be inherited from either side of the family. The diagram above illustrates this.

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

ProstateGene uses state of the art NextGeneration Sequencing to examine the code for each of the 10 genes in detail. In addition, dosage analysis is used to look for large deletions (missing parts) and duplications (extra parts) in the genes.

However, no test is 100% accurate and it is possible that someone could have a genetic mutation which is not detected by this test. It is important to be aware that a normal result on ProstateGene does not rule out the risk of hereditary prostate cancer.

Where possible, it is most accurate to perform genetic testing on someone who has had cancer so that a possible genetic cause can be found in the family.
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 prostate 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 a 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 prostate 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 a mutation.

Screening
We recommend that men with an inherited mutation in an associated prostate cancer gene have annual PSA tests from age 40. It is important to be aware that screening aims to diagnose prostate cancers at an earlier more treatable stage however screening for prostate cancer is still imprecise and, in some situations, may lead to unnecessary biopsies or false reassurance.

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

Prostate awareness
It is important for all men to be prostate aware and inform their doctor if they notice any signs that they are concerned about.

Signs of prostate cancer include;

- Needing to urinate often, especially at night
- Difficulty in starting to urinate
- Straining to urinate or taking a long time to finish
- Pain when urinating or ejaculating
- Pain in the lower back, hips or pelvis
- Blood in the urine.

Most men with these signs will not have cancer but is always important to get them checked out.

Other risk factors
It is known that ethnicity influences the risk of prostate cancer: black men have the highest risk of prostate cancer, then white men and Asian men have the lowest risk.

Height is also associated with prostate cancer: the taller a man the higher his risk.

A personal history of some types of cancer (kidney, bladder, melanoma, lung, thyroid) also increases the risk of prostate cancer as does exposure to radiation.

Warfarin, Acetaminophen and diabetes have been shown to lower the risk of prostate cancer.

Lifestyle Factors
Lycopenes (from tomatoes and tomato based products), a diet rich in vegetables and low in red meat may lower the risk of prostate cancer, whilst diets high in calcium may increase the risk.

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 test results. This moratorium is valid until 2019. More information about insurance can be found at:
http://www.abi.org.uk

Further information and support can be found at:
http://www.prostatecancersupport.co.uk/treatments.htm
http://prostatecanceruk.org
http://www.lynchcancers.com
http://community.macmillan.org.uk/cancer_types/hereditary_non-polyposis_colorectal_cancer_hnpcc_or_lynch_syndrome/f/33346/t/51150.aspx
http://community.macmillan.org.uk/cancer_experiences/brca_positive/default.aspx
http://facingourrisk.org

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.
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Please visit our website www.GeneHealthUK.com/Clinics for an up-to-date list of clinic locations and directions. Please be aware that most genetic counselling sessions are undertaken by phone so a clinic may not be needed.

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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