What is hereditary breast cancer?
Breast cancer is the most common cancer in the UK. Unfortunately 1 in 8 women will develop breast cancer; with 80% being diagnosed after the age of 50. This means that in the general population women have a 12.5% risk of breast cancer. 1 in 868 men will also be diagnosed with breast cancer.

Most breast cancer occurs by chance, however approximately 5-10% is hereditary and in some families ovarian cancer can be genetically related to breast cancer. In families where breast cancer is hereditary it may be possible to find the genetic change (mutation) which is responsible for the cancer. This allows for appropriate cancer screening and risk-reducing options.

What are genes?
Genes are the body’s instructions and they 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 this causes an increased risk of cancer.

Mutations in at least 9 genes can cause an increased risk of breast cancer and other cancers. However, we know that there are other genes which are also associated with breast cancer and research is attempting to understand these other genes.

How do I know if I am at risk?
Families with hereditary breast cancer generally show one or more of the following clues:

• Several relatives with breast cancer
• Breast cancer diagnosed before the age of 45
• Bilateral breast cancer (cancer in both breasts)
• Ovarian cancer
• Increased frequencies of other cancers such as prostate and pancreatic cancer
• Male breast cancer
• Triple negative breast cancer
• Jewish ancestry and breast or ovarian cancer

It is important to be aware that hereditary breast cancer can be present on either the maternal (mother’s) or paternal (father’s) side of the family.

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.

What is BreastGene?
BreastGene is a test for hereditary breast cancer which examines the code for 9 genes known to cause a significant risk of breast cancer. The following genes are tested:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Risk of breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>ATM associated breast cancer</td>
<td>17 - 60%</td>
</tr>
<tr>
<td>BRCA1</td>
<td>HBOC</td>
<td>&lt; 85%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>HBOC</td>
<td>&lt; 90%</td>
</tr>
<tr>
<td>CDH1</td>
<td>HDGC</td>
<td>39-60%</td>
</tr>
<tr>
<td>CHEK2</td>
<td>Hereditary breast cancer</td>
<td>25%</td>
</tr>
<tr>
<td>PALB2</td>
<td>Hereditary breast cancer</td>
<td>35-57%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden’s syndrome</td>
<td>85%</td>
</tr>
<tr>
<td>TP53</td>
<td>Li Fraumeni syndrome</td>
<td>85% by age 60</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz jegers</td>
<td>45%</td>
</tr>
</tbody>
</table>
Hereditary Breast and Ovarian Cancer (HBOC)

Mutations in BRCA1 & BRCA2 cause hereditary breast and ovarian cancer. In the general population 0.25% of people will have a BRCA mutation.

The estimated cancer risks associated with BRCA mutations vary however; BRCA1 mutations are estimated to cause up to an 85% lifetime risk of breast cancer and a <60% risk of ovarian cancer. Men with BRCA1 mutations may have a slightly increased risk of male breast cancer as well as approximately a 20% risk of prostate cancer.

Women with BRCA2 mutations have up to a 90% lifetime 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.

Women with BRCA gene mutations should have annual MRI from age 30 years and annual mammogram from 35 years. Ovarian cancer screening has not been shown to be beneficial and therefore some women may consider risk-reducing surgery. Men may benefit from prostate cancer screening.

Occasionally, a baby will inherit two BRCA2 mutations and will therefore have the congenital condition known as Fanconi Anemia.

PTEN Hamartoma Tumor Syndrome / 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 an increased risk of melanoma (5%). Colonoscopy as well as breast MRI and mammograms, renal MRI, skin examination and thyroid ultrasounds will be recommended. Risk reducing surgery may be considered.

Peutz Jeghers Syndrome (PJS)

PJS causes polyps in the large and small bowel, as well as ovarian tumours and abnormal colouring of the skin, particularly on the lips in childhood. PJS causes an increased risk of bowel (39%), breast (45%), pancreatic (11%) and other cancers. Mammography, colonoscopy and other cancer screening tests will be recommended.

Hereditary diffuse Gastric Cancer (HDGC)

HDGC causes a high risk of stomach cancer (estimated to be 70% in men and 46% in women) and lobular breast cancer (39-60%) as well as a possible increased risk of bowel cancer. Individuals with HDGC will be treated at a centre with expertise in the condition. Increased breast screening with annual breast MRI and mammograms will be recommended. Some people also consider gastrectomy (removal of the stomach) due to the increased risk of stomach cancer and bowel screening may be suggested.

Li Fraumeni Syndrome (LFS)

Li Fraumeni syndrome is a very rare condition which causes a high risk of cancer in childhood and adulthood: approximately 1 in 5000 to 1 in 20000, people will have LFS. Li Fraumeni syndrome causes an increased risk of sarcomas, brain tumours, breast cancer (85% risk by age 60), adrenal cortical carcinomas and other cancers. Individuals with TP53 mutations have a 50% risk of developing cancer by age 30 and a lifetime risk of up to 90%. Breast screening with MRI will be recommended. Individuals are also advised to avoid radiation as they have an increased sensitivity.

ATM associated breast cancer

Approximately 1 in 200 people (0.5%) will carry a mutation in the ATM gene. Individuals with a mutation in the ATM gene have a moderately increased risk of breast cancer, as well as possible increased risk of radiation-sensitivity. Increased breast screening is recommended.

Rarely a baby may inherit an ATM mutation from their mother AND their father, in which case they will have the congenital condition called Ataxia-Telangiectasia (AT). AT causes uncontrollable movements (ataxia), immune defects, and an increased risk of leukemia and lymphoma.
CHEK2
Mutations in the CHEK2 gene are found in 4% of families with hereditary breast cancer and cause a moderately increased risk of breast cancer as well as a possibly increased risk of bowel cancer. Very rarely, individuals have been shown to carry 2 mutations in the CHEK2 gene which seems to cause a higher risk of breast cancer. Increased breast screening, and in some situations, bowel screening will be recommended.

PALB2
Mutations in PALB2 have been shown to cause a moderately high risk of breast cancer. The risk is estimated to be approximately 35% although the risk is greater if there is a strong family history of breast cancer (up to 57%) and our knowledge of PALB2 is rapidly increasing. Increased breast screening with mammography and MRI is recommended. PALB2 also causes a possible increased risk of pancreatic cancer. Occasionally, a baby will inherit two PALB2 mutations and will therefore have the congenital condition known as Fanconi Anemia.

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 breast 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 breast cancer can be inherited from either side of the family. The diagram illustrates this.

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

BreastGene uses state of the art technology known as NextGeneration sequencing to examine the code for each of the 9 genes in detail. Dosage analysis is used to look for large deletions (missing parts) and duplications (extra parts). BreastGene is a comprehensive way to assess a person’s risk for hereditary breast and associated cancers. However, no test is 100% and it is possible that someone could have a genetic mutation in one of these genes or in a currently unknown gene which is not detected by this test.

It is most accurate to perform genetic testing on a family member who has had breast 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 breast 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 breast cancer and possibly other cancers. Your exact risk(s) 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 breast cancer it is usual for them to have screening-mammography and often breast MRI scans. The frequency and timing of breast screening will depend on which genetic mutation is found.

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

Risk-reducing surgery
Unfortunately no screening is 100% effective and in some situations, people may wish to consider risk-reducing surgery. In particular, risk-reducing mastectomy to remove healthy breast tissue may be considered by some women. This is very much an individual decision and obviously needs careful consideration. If a woman wishes to consider this option, her breast surgeon can provide further information.

Additionally, women with a BRCA mutation may consider bilateral salphingo-oophorectomy (removal of the ovaries and tubes).

Breast awareness
It is important for all women to be ‘breast aware’ which means becoming familiar with how your breasts look and feel. Many women have lumpy breasts, which naturally change depending upon the time in your menstrual cycle and therefore it is best to check yourself at the same time each month (mid-cycle). If you notice a change in your breasts it is important to seek medical advice.

Signs of breast cancer are:
- lumps, thickening or bumpy areas
- changes in appearance, like puckered or dimpled skin
- bloodstained nipple discharge
- a rash or red area on the nipple or areola that won’t heal,
- a change in your nipple position (pointing differently or pulled in).

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

Other risk factors
Some hormonal factors have been suggested as breast cancer risk factors. In particular, it is known that early menarche (first period) and late menopause increase the risk of breast cancer. Breast-feeding lowers the risk of breast cancer, as does early childbirth (before the age of 30).

It is known that the pill lowers the risk of ovarian cancer when taken for 5 or more years. However, there may be a slightly increased chance of developing breast cancer for women who take the pill for prolonged periods; this risk decreases once women stop taking the pill.

Hormone replacement therapy (HRT) increases the risk of breast cancer when used after a natural menopause however it may be helpful for women who have an early surgically induced menopause.

Lifestyle factors
It is known that a healthy diet can promote good general health and lower the risk of cancer. In particular, maintaining a normal body weight and avoiding abdominal weight gain will lower the risk of breast cancer. Limiting alcohol intake and doing regular physical exercise will also lower the risk of breast cancer.

Insurance & financial information
Obtaining insurance coverage following genetic testing need not be a concern as the Code on Genetic Testing and Insurance ensures that individuals do not have to disclose cancer predictive test results. More information can be found at https://www.abi.org.uk/globalassets/files/publications/public/genetics/code-on-genetic-testing-and-insurance_embargoed.pdf

Further information and support can be found at:-
www.breastcancergenetics.co.uk
www.menagainstbreastcancer.org
www-facingourrisk.org
www.youngsurvival.org
www.cancercare.org
www.cancerresearchuk.org
www.lbdc.org
www.cancerbacup.org.uk
www.brcaumbrella.ning.com

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.

GeneHealth UK is part of Check4Cancer Ltd.