Q. Who in my team can consent patients for genetic testing, and what training is offered?
A. Consenting for genetic testing can be carried out by any doctor or nurse in the urology or oncology teams who have completed the formal training on germline consent procedure.. Instructions on how to consent can be found on the GM Cancer webpage, here.

Additionally, an E-Learning module will become available on the GM Cancer Academy.

The Prostate Cancer Genomics Lead at your Trust must be satisfied that you are adequately trained before you can consent patients for germline testing.

Q. How do I use the Manchester scoring system to calculate familial risk?
A. To calculate the familial risk, you can use the Manchester Scoring System. This was originally created to calculate familial risk for breast and ovarian cancers, but it can also be used for prostate cancer. You can find further instructions on using the Manchester Scoring System in the genomics toolkit on the Cancer Alliance webpage.

Q. How do I ensure I complete the request form correctly?
A. Please use the referral form titled 'NW GLH Genomic Testing Request Form – Rare Disease' which is available on the GLH website: Test Request Forms - Manchester University NHS Foundation Trust (mft.nhs.uk).

When completing the form, the clinical indication codes to be used are:

R430	Inherited prostate cancer
R444.2	PARP inhibitor treatment (only used when somatic testing has failed)

Please use one of these code instead of listing genes that are being tested.

The form must then be printed and given to the patient to the department taking their blood. The form and bloods will then be sent together to:

North West Genomic Laboratory Hub – Manchester Site
Manchester Centre for Genomic Medicine
Sample reception 6th Floor
St Mary's Hospital
Oxford Rd
Manchester
M13 9WL

Q. What about patients that do not want testing but would like to store their blood sample for their family to access in the future?
A. Some patients do not consent to have the genetic test but do choose to have their DNA sample stored to give their blood relatives the option to access this at a later date. In these circumstances, the sample would not be tested within that person's lifetime but could provide information for other family members in the future.

In this situation the consent form does not need to be completed. The referral form must be completed as follows:

- Clinical Details (type of test) – tick DNA Storage.
- Clinical Indication Code/Test Code: R430/R444.2 DNA storage only.

Further guidance on the North West Genomic Laboratory Hub can be found here: https://mft.nhs.uk/nwglh/

Q. What happens if a patient is found to have a variant of unknown significance?
A. It is recommended that patients with a VUS are flagged for a 5-year VUS review, using InfoFlex, or an alternative software tracking tool, through the urology team's aftercare programme (for example Personalised Stratified Follow Up programme). Once a patient qualifies for VUS review at 5 years, please contact the Genomic Laboratory Hub using this email address: mft.genomics@nhs.net

Q. What should I do if a patient has a negative germline variant test and is not eligible for referral to the clinical genetics team, but I am still concerned about their family history?
A. A regional cancer genomics MDT is held on the first Tuesday of the month at 11:00. Clinicians from around the region can request discussion of complex cases, for example, those with an unusual family history or if a clinician has questions about a test result.

If you wish to discuss a patient in more detail with the team please email: mft.nwglh-mdt@nhs.net

Q. For patient who require referral to the clinical genetics team, how long will they have to wait for their appointment?
A. Patients referred via the mainstreaming pathway will be fast-tracked and seen within three months. For routine referrals, the patient could wait over 12 months.

Q. Is there any support available to patients who have tested positive for the germline BRCA variant and are waiting to be seen by Clinical Genetics?

A. Whilst awaiting the appointment with Clinical Genetics, support would be provided to the patient by the Urology CNS. Should the CNS have any queries, they can contact the Clinical Genetics department directly.

Q. What is the difference between germline and somatic variants (mutations)?
A. There are two ways in which gene variant (also called a gene mutations) increase the risk of an individual developing cancer:

Somatic variants occur in the genes of an individual cell and when that cell divides there is a risk of cancer development. Somatic variants are not present when a child is conceived; they are acquired during the individual's lifetime. Smoking, aging, ultraviolet radiation and viruses are examples of causes of somatic variants. Somatic

variants can be important in decision-making for cancer treatment and a patient's prognosis, but they are not hereditary. They cannot be passed on to children and do not affect the risk of family members developing cancer.

Germline variants are far less common than somatic variants. They are inherited and therefore are present from the moment a person is conceived. Germline variants can influence whether, and when, an individual might get cancer, what cancer they might develop and what treatments are appropriate and most likely to be successful.

All cells have two copies of every gene (one inherited from each parent) so that there is a backup if one develops a variant and loses the correct function. For genes such as BRCA1 and BRCA2, when a person inherits a mutated variant they will have a normal copy inherited from their other parent. When that person has children themselves it is completely random whether their child inherits the normal or variant gene. There is a random chance each time a child is conceived so the affected individual may have both affected and unaffected children.

It is important to remember that a very small number of cancers are caused by germline gene variants. Although many families have multiple family members who have been affected by cancer, most of these cases are caused by the combined effects of multiple genetic and environmental factors, with only about 5-10 % being due to an error in a single high risk cancer gene.

Q. What is a BRCA gene variant?
A. Genes such as BRCA1 and BRCA2 give the instructions (code) to a cell to make proteins that protect against that cell turning cancerous. A variant is an error in the code so that abnormal proteins are made. These abnormal proteins do not function in the way they are supposed to and can mean that the cell loses protection against turning cancerous.

At birth, a patient with an inherited germline BRCA variant will still produce the normal protective BRCA protein via the normal copy they inherited from their other parent. However, they will be at a higher risk of cancer because if environmental factors damage their normal copy in cells then they do not have a backup to rely upon.

Q. What are the effects on the patient's family if they are found to have a BRCA germline gene variant?
A. If a patient is found to have a germline BRCA variant then they inherited an abnormal copy and can pass that abnormal copy to their children. As stated above, affected individuals also have a normal copy of the gene and this may be passed onto children instead of the abnormal copy. Every child of an affected individual has a 50:50 chance of inheriting the abnormal copy so a patient may have a mixture of children with and without the germline variant. The only way to test each family member's genetics is to give them a test. Therefore, it is important that affected patients are referred to the clinical genetics department so the risks of each family member can be quantified and offered a test. Proven affected family members would be at an increased risk of developing cancers (such as prostate/breast/ovarian) in their lifetime.