TRANSCRIPT:

Understanding my tests: Molecular classification of womb cancer

Womb cancer, also known as **endometrial cancer**, is the 4th most common cancer in women and people with wombs in the UK. Almost 10,000 new cases are diagnosed each year.

Womb cancer is typically treated by surgery. This involves removing the womb, including the cervix, the tubes, and the ovaries. This procedure is known as total hysterectomy with bilateral salpingo-oophorectomy. In selected cases, additional tissues, in particular lymph nodes, may also need to be removed.

In most cases, surgery is curative and no further treatment is required. In a few cases, there is a chance that the cancer may not have been completely removed. This is known as **residual disease**. Or that it comes back despite being removed. This is known as **recurrence**.

When there is residual disease or a significant chance of recurrence, additional non-surgical treatments may be offered before or after surgery. These non-surgical treatments include radiotherapy, including brachytherapy, and/or external beam radiotherapy, chemotherapy, and hormone or endocrine therapy. In some instances, most commonly after recurrence, new treatments such as immune therapy may also be offered. This may be through participating in a clinical trial investigating new treatments.

The chance of recurrence and the decision whether or not to give additional treatment largely depends on two things. Firstly, what the cancer cells look like down the microscope to the pathologist, features such as cancer **type** and **grade**, and secondly, how far the cancer has spread, also known as the cancer **stage**.

The cancer stage is decided by examining the tissues removed during surgery and additional information from scans. This helps to place each cancer into a particular group depending on the chance of recurrence. Recent research has shown that examining the gene changes in cancer cells using various tests gives additional important information.

Let us look more closely at these tests.

Genes are short sections of DNA inside cells that form the instruction manual for our body. Research shows that womb cancers are caused by specific changes in some of these genes. By looking for these changes, we can place these cancers into one of four groups. Each of these groups has completely different behaviour, response to treatment, and chance of recurrence.

These groups are **POLE-mutated**, **MMR-defective**, **p53-abnormal** and **NSMP**. Cancers in this group have **N**o **S**pecific **M**olecular **P**rofile.

When pathologists look down the microscope, it can sometimes be difficult to decide which group each cancer belongs to because cancers of different groups can look similar to each other. However, when what the pathologist sees down the microscope is combined with the results of the genetic tests, each cancer is placed in the correct group. This ensures that each person receives the most appropriate treatment.

Let us look at the four groups.

POLE:
Although written as “pole”, this is pronounced “po-lee”, which is short for DNA **POL**ymerase **E**psilon. Womb cancers with changes in the POLE gene make up less than one-tenth of all womb cancers. POLE-mutated cancers may not require additional treatment after surgery. For POLE testing, DNA is taken from cancer cells in the biopsy or hysterectomy samples. This testing is carried out in one of a few specialised centres in the UK and may take several weeks to process.

MMR:
MMR stands for mismatch repair. Womb cancers with defective mismatch repair make up about one-third of all womb cancers. A small proportion of these may be due to Lynch syndrome, which may affect other family members. These cancers respond well to different treatments and may be eligible to receive immune therapy. MMR is tested using immunohistochemistry or IHC, a technique which may be carried out in a local or regional laboratory. Test results may take up to two weeks.

p53:
p53 is a protein made by the TP53 gene. This is abnormal in just over one-tenth of womb cancers. These cancers respond to chemotherapy and some may be eligible for new therapies, often as part of a clinical trial. p53 is also tested using IHC, which may be carried out in a local or regional laboratory. Test results may take up to two weeks.

NSMP:
The fourth category makes up about half of all womb cancers. In these, all three tests; POLE, MMR, and p53 are normal. These are therefore classified as womb cancers with **N**o **S**pecific **M**olecular **P**rofile or **NSMP**. Cells recognise and respond to hormones such as **oestrogen** through structures known as **receptors**. In some womb cancers, the oestrogen receptors, or **ER**, may be low or entirely absent. In NSMP womb cancers, the ER status gives valuable

information. ER is also tested using IHC, which may be carried out in a local or regional pathology laboratory. Test results may take up to two weeks.

The tests POLE, MMR, p53 and ER are carried out in all cases of womb cancer as needed. The results of these tests, along with the cancer stage and what pathologists see down the microscope, place each womb cancer in the correct category. This ensures that the patient, their family, and the cancer multidisciplinary team can together decide the ideal treatment for the best possible outcome.

Thank you for watching. We hope that this has helped you understand why these additional tests are carried out. You can find out more information about womb cancer in our other videos in this series and on our website.