BIOMARKER TESTING
in Gynaecological Cancers

Finding the tumour's weakness or target

Why do biomarkers matter?

Cancer treatment is changing. For many years, treatment decisions were based mainly on where the cancer started, how advanced it was, and how it looked under the microscope. These factors are still very important. But today, doctors can often look deeper. We can study the biology of the tumour.

Two patients may have the same cancer diagnosis, the same stage, and even a very similar pathology report. But their tumours may behave differently. One tumour may respond well to a certain treatment, while another may respond less well, or not at all. This can happen because the tumours have different biological features.

These biological features are called **biomarkers**.

A biomarker is a measurable sign from the tumour. It may be found in tumour tissue, in DNA, or sometimes in blood. Biomarkers can help doctors understand how the tumour behaves and whether it has a weakness or a target that can be used for treatment.

Biomarker testing is one of the foundations of personalised medicine. This means choosing treatment not only according to the name of the disease, but also according to the individual biology of the tumour.

We do not treat only "ovarian cancer" or "endometrial cancer".
We try to understand the biology of each patient's tumour.

Figure 1.

Two patients may have the same cancer diagnosis, but their tumours have different biology. Biomarker testing helps doctors understand these differences and choose the most appropriate treatment.

A tumour is more than cancer cells

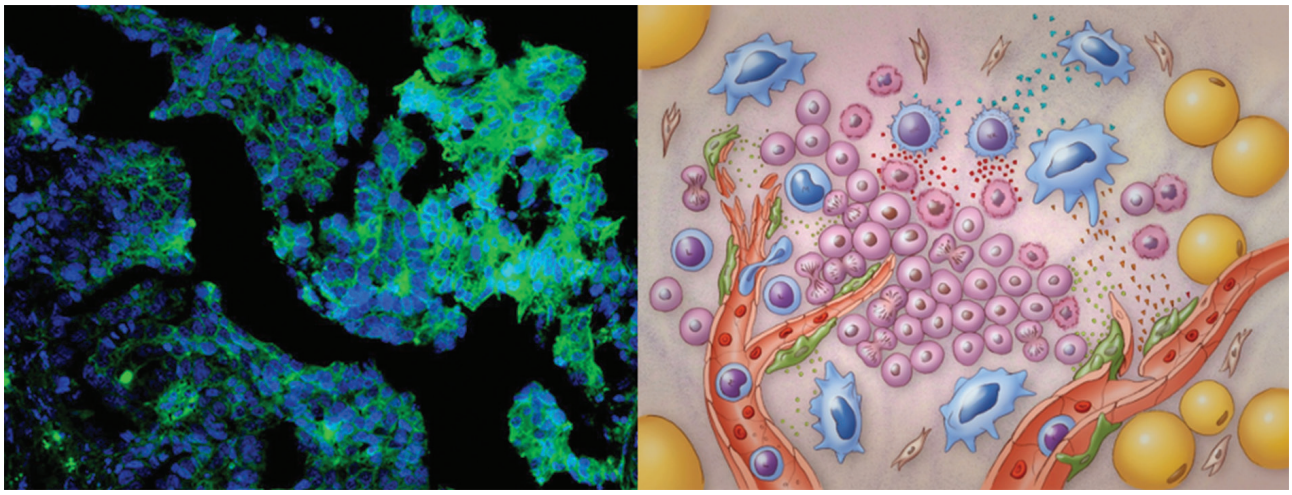
A tumour is not made only of cancer cells. It also contains blood vessels, immune cells, support cells and many signalling molecules. These cells communicate with each other. Some may help the body fight the cancer. Others may help the tumour grow, survive or spread. This complex environment is sometimes called the **tumour microenvironment**. Under the microscope, two tumours may look similar. But biomarker testing can reveal important hidden differences. These differences may influence which treatment is most likely to work.

In simple terms, biomarkers help doctors look for one of three things: a weakness inside the tumour cell, a target on the tumour surface, or a biological feature that may help guide treatment.

Figure 2.

A tumour is more than cancer cells. *The image on the left shows tumour tissue under a special microscope: the blue areas show cell nuclei, and the green highlights one biological component of the tumour tissue. It may resemble a lively city seen from above at night.*

***The picture on the right shows** the tumour microenvironment — cancer cells, immune cells, blood vessels, support tissue and signalling molecules — interacting like pedestrians, cars, streets and traffic in a busy city.*



How is biomarker testing done?

To test biomarkers, doctors usually need a sample of the tumour. This sample may be obtained during surgery or by biopsy. In some patients, especially when treatment is planned before surgery or when the cancer comes back, a biopsy can provide very important information.

Depending on the location of the tumour, a biopsy can be taken through a direct sample or, in some cases, using imaging tests such as a CT scan or ultrasound. One common method is an **ultrasound-guided core needle biopsy**. In this procedure, a thin needle is guided into the tumour using ultrasound imaging. A small sample of tissue is taken and sent to the laboratory.

The procedure is usually short, outpatient, and well tolerated. The tumour sample is first examined by a pathologist to confirm the type of cancer. Additional tests may then look for specific biomarkers, such as defects in DNA repair, markers of immune sensitivity, or targets on the surface of cancer cells. The results can help guide decisions about chemotherapy, maintenance treatment, targeted therapy, immunotherapy in selected patients, antibody-drug conjugates, or treatment at recurrence. A small tumour sample can provide important information for major treatment decisions.

Important biomarker examples

Different biomarkers matter in different types of gynaecological cancer. Not every patient needs every test. The choice of testing depends on the tumour type, stage of disease, previous treatment, available tissue and available treatment options. The following examples show how biomarker testing may help doctors understand the tumour and choose treatment more precisely.

1. BRCA and HRD: A weakness in DNA repair

Where is this most relevant?

BRCA and HRD testing is especially important in **ovarian, fallopian tube and primary peritoneal cancer**, particularly in high-grade serous ovarian cancer. DNA is the genetic information inside our cells. It is damaged all the time, and healthy cells have repair systems that fix this damage. Some ovarian cancers have problems with one of the important DNA repair systems. This may happen when genes such as **BRCA1** or **BRCA2** are altered. It can also happen through other mechanisms.

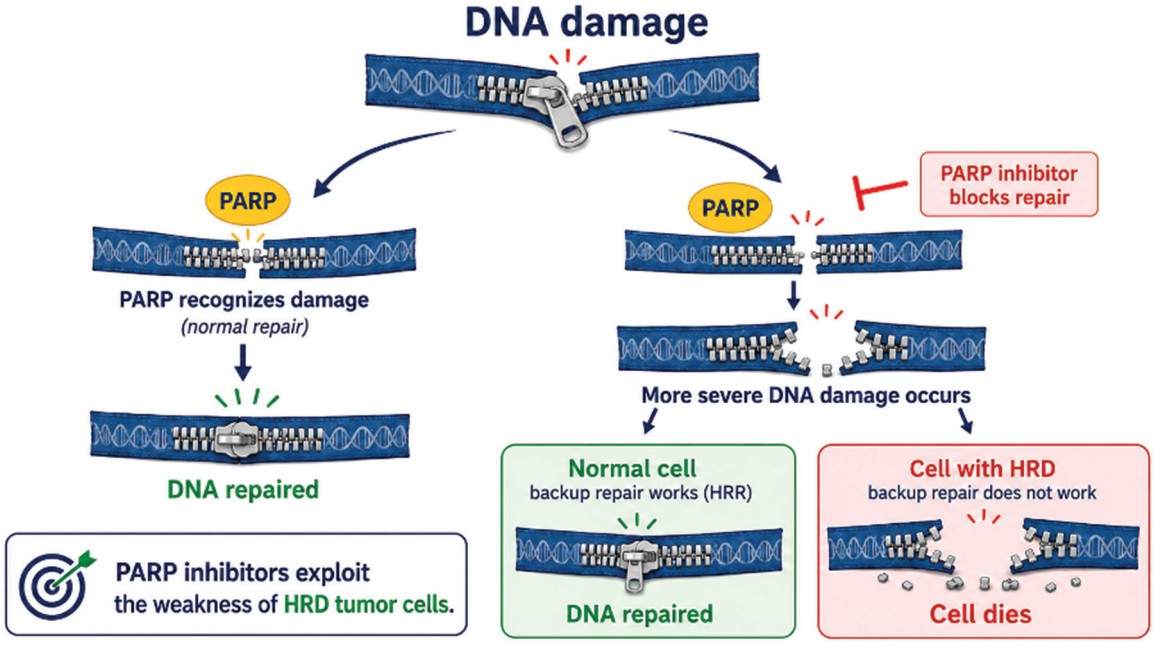
A broader term for this type of DNA repair weakness is **HRD**, which stands for **homologous recombination deficiency**. You can imagine this repair system as a zipper. When the zipper works, the DNA can be repaired. When the zipper is broken, the cell cannot repair DNA properly. For the cancer cell, this is a weakness.

Doctors may be able to use this weakness with a group of medicines called **PARP inhibitors**. These treatments are often used as maintenance treatment in ovarian cancer. They increase DNA damage in cancer cells. If the tumour already has defective DNA repair, the cancer cell may not be able to survive the additional damage. This principle is called **synthetic lethality**. In simple words, the tumour has a weakness, and the treatment uses that weakness against the cancer cell. BRCA testing is very important because some BRCA changes are inherited. If an inherited BRCA mutation is found, genetic counselling is recommended. This can be important not only for the patient, but also for family members.

BRCA and HRD can show that the tumour has a weakness in DNA repair. This may help guide treatment with PARP inhibitors and may also identify inherited cancer risk.

Figure 3.

BRCA/HRD and PARP inhibitors. *Some tumour cells have a weakness in DNA repair. PARP inhibitors increase DNA damage further. Normal cells can often repair this damage, but cancer cells with HRD may not be able to survive.*



2. MMRd and MSI: When DNA spell-checking does not work

Where is this most relevant?

MMRd and MSI are especially important in endometrial cancer, where they may help guide immunotherapy and identify patients who may need genetic counselling. In selected ovarian cancers, especially endometrioid and clear-cell types, they may also provide useful information.

Another DNA repair system is called the **mismatch repair system**. Its job is to correct small mistakes that occur when DNA is copied. You can imagine it as a spell-checking system for DNA. When this system works, most mistakes are corrected. When it does not work properly, mistakes accumulate. The tumour becomes full of DNA errors. This is called **MMRd**, which means **mismatch repair deficient**. A related term is **MSI-high**, or **microsatellite instability-high**.

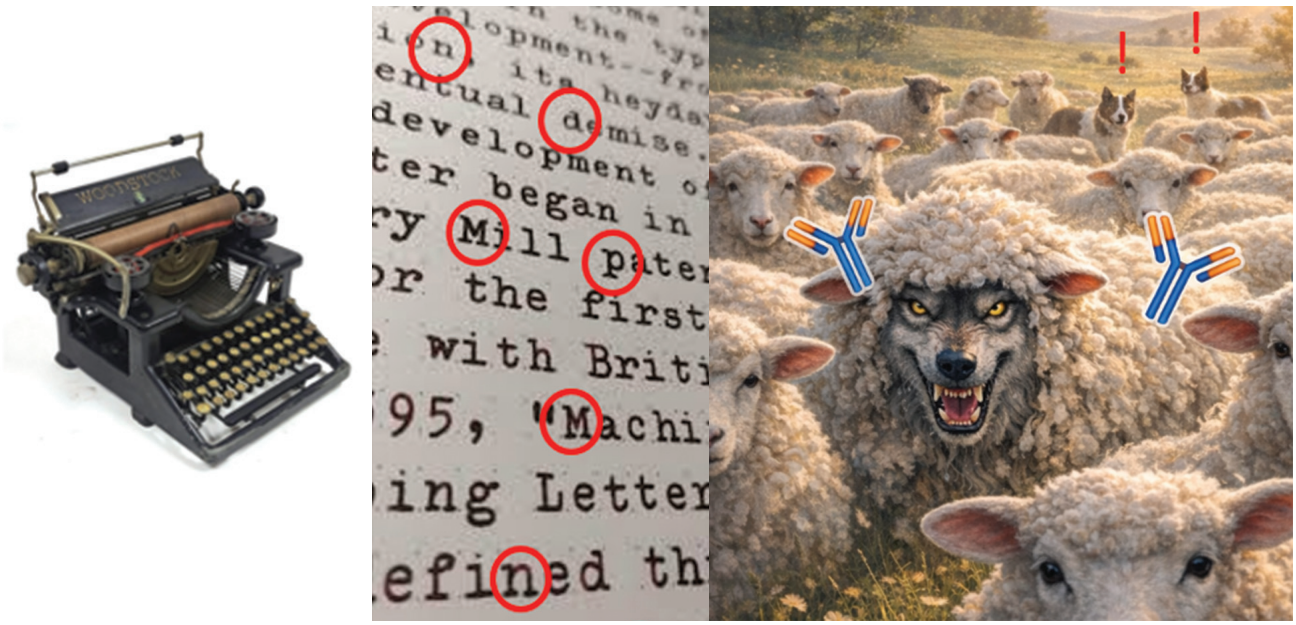
This biomarker can matter for two main reasons. First, tumours with MMRd or MSI-high may be more visible to the immune system. In some patients, this may help doctors consider **immunotherapy**. Immunotherapy does not attack the cancer directly like chemotherapy. Instead, it helps the immune system recognise and fight the tumour. Second, MMRd or MSI-high may sometimes be connected with **Lynch Syndrome**, an inherited condition that increases the risk of several cancers. If this is suspected, doctors may recommend genetic counselling and further testing.

MMRd/MSI means that the tumour has a problem correcting small DNA errors. It is especially important in endometrial cancer, where it may help guide immunotherapy and identify patients who may need genetic counselling. In selected ovarian cancers, especially endometrioid and clear-cell types, it may also provide useful information.

Figure 4.

MMRd/MSI and the immune system. *DNA copying can be imagined as typing a long text. When the proofreading system works, most mistakes are corrected. When mismatch repair is deficient, many errors remain. These errors can make the tumour easier for the immune system to recognise.*

In the picture, the tumour is shown as a wolf hidden among sheep: immunotherapy can help the immune system recognise the danger and attack it.



3. Folate receptor alpha - FRα: A target on the tumour surface

Where is this most relevant?

FRα testing is mainly relevant in ovarian cancer, particularly in recurrent high-grade serous ovarian cancer. There are many possible targets on the surface of cancer cells. One current clinically important example in ovarian cancer is folate receptor alpha, often shortened to FRα.

You can imagine FRα as an address label on the cancer cell. If this address label is present, certain treatments may be able to find the cancer cell more precisely.

This is important for a type of treatment called an antibody-drug conjugate, or ADC. An ADC has two main parts. The first part is an antibody. The antibody recognises and binds to a specific target on the cancer cell. The second part is a drug payload, which is designed to damage or kill the cancer cell after the ADC enters the cell.

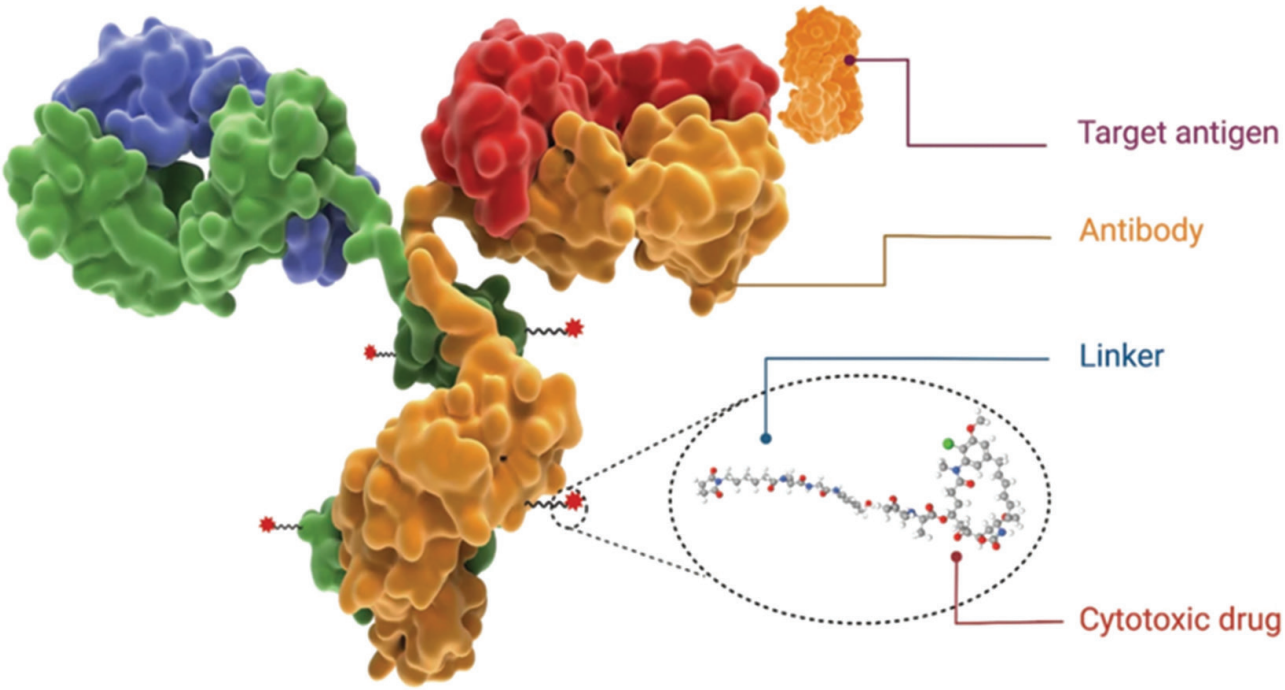
This treatment can be compared to a Trojan horse. The antibody finds the target on the cancer cell and brings the drug inside. Once inside, the drug is released and can destroy the cancer cell. In some cases, the released drug may also affect nearby cancer cells.

FRα testing can help doctors identify whether this treatment approach may be relevant. FRα is used here as an example of a surface target; other targets may also become important as new treatments are developed.

FRα can act as a target on the surface of ovarian cancer cells. If the target is present, an antibody-drug conjugate may be able to deliver treatment more directly to the tumour cell.

Figure 5.

Antibody-drug conjugate, or ADC. *The Y-shaped structure is an antibody. It recognises a target on the cancer cell, such as folate receptor alpha. The antibody is connected by a linker to a small but powerful drug. Like a Trojan horse, the antibody helps deliver the drug into the cancer cell, where it can be released.*



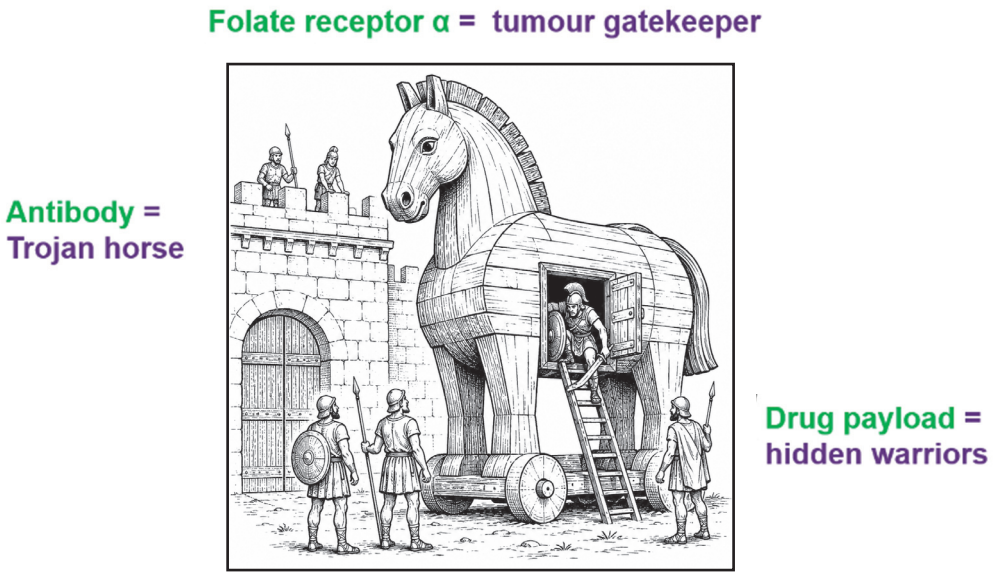
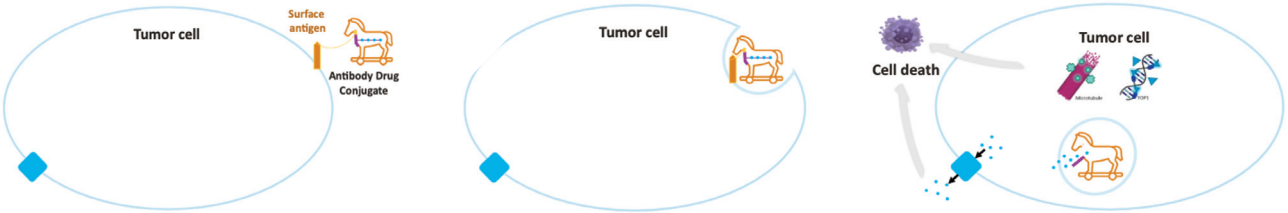


Figure 6.

Step-by-step action of an antibody-drug conjugate. *The antibody binds to a target on the cancer cell, the treatment enters the cell, the drug is released, and the cancer cell dies.*



4. PD-L1: A "stop sign" for the immune system

Where is this most relevant?

PD-L1 testing is especially important in **cervical cancer**, where it helps doctors determine if **immuno-therapy** is a suitable treatment option. While the immune system is designed to find and destroy cancer cells, some tumours can develop a protein on their surface called **PD-L1**.

You can imagine PD-L1 as a **"stop sign"** or a **"fake handshake"**. When an immune cell approaches the tumour to attack it, the PD-L1 protein sends a signal that says, "I am a healthy cell, do not harm me." This allows the cancer to stay hidden and continue growing.

Testing for PD-L1 helps your doctor see how many of these "stop signs" the tumour is using. If the level is high, certain medicines can be used to block this signal—essentially taking the blindfold off your immune system so it can recognise and fight the cancer cells more effectively.

PD-L1 testing can show if a cervical tumour is hiding from the immune system. This information helps doctors choose immunotherapy treatments that "un-mask" the cancer cells.

Other biomarkers may also be important.

Some other biomarkers are relevant in selected patients. For example, POLE and p53 are important in endometrial cancer classification, and HER2 may be relevant in some endometrial cancers. Your doctor will decide which tests are useful according to the tumour type and treatment situation.

What does biomarker testing mean for patients

Biomarker testing does not replace standard diagnosis or treatment. It adds more information.

It can help doctors answer important questions.

- **Can we identify a weakness in the tumour?**
- **Can we find a target on the tumour cell?**
- **Is there a treatment that may be more likely to work?**
- **Is there a treatment that is unlikely to help?**
- **Is genetic counselling needed?**
- **Should the tumour be tested again if the cancer comes back?**

Not every biomarker leads directly to a specific treatment. Not every patient needs every test. Sometimes a biomarker result helps immediately. Sometimes it becomes useful later, for example if the disease returns or if a new treatment becomes available. The aim is to make treatment decisions as precise and safe as possible.

Questions you may want to ask your doctor

Has my tumour been tested for important biomarkers?

If I have ovarian cancer, have BRCA and HRD testing been performed or considered?

If I have ovarian cancer, should my tumour be tested for folate receptor alpha?

If I have endometrial cancer, has MMR or MSI testing been performed?

Could any biomarker result affect my treatment options?

Do I need genetic counselling?

Would a new biopsy be useful if the cancer comes back?

How will the biomarker results influence my treatment plan?

Summary

Biomarkers are clues from the tumour. They help doctors understand how the cancer behaves and whether it has a specific weakness or target.

BRCA and HRD are especially important in ovarian cancer. They show a weakness in DNA repair and may help guide treatment with PARP inhibitors.

MMRd and MSI are especially important in endometrial cancer and may also be relevant in selected ovarian cancers. They may help guide immunotherapy or genetic counselling.

FRα is mainly relevant in ovarian cancer. It is a target on the tumour surface and may help guide treatment with antibody-drug conjugates.

PD-L1 is especially important in cervical cancer. It acts as a signal that hides the tumour from the immune system and may help guide treatment with immunotherapy.

Tumours may look similar, but their biology can be very different. Biomarker testing helps doctors understand each patient's tumour more precisely.

**We test the tumour, look for its weakness or target,
and use this information to choose the most appropriate treatment.**

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ENGAGe recommends contacting your local patient association!