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Gynaecology

- Breast cancer
- Ovarian cancer
- Endometrial cancer

Breast cancer

Breast cancer is the most common form of cancer in women. However, the prognosis of breast cancer is favorable, especialy when diagnosed and treated early. Treatment can include a combination of surgery (breast and axillary lymph node), radiotherapy, conventional chemotherapy, hormonal therapy and targeted therapy. There are two main histological types: ductal carcinoma and lobular carcinoma (in situ and invasive). Here, we will only discuss the treatment of invasive forms of breast cancer. HR (for hormonal therapy) and HER2 (for anti-HER2 therapy) status are the main indicators for which treatments to use: RH+/HER2-, RH-/HER2+, RH+/HER2+ (10 to 15%) and RH-/HER2- (or triple negative TN – 15%). Other markers (BRCA, PIK3CA, PDL-1, etc.) are new indicators used in the treatment of breast cancer.

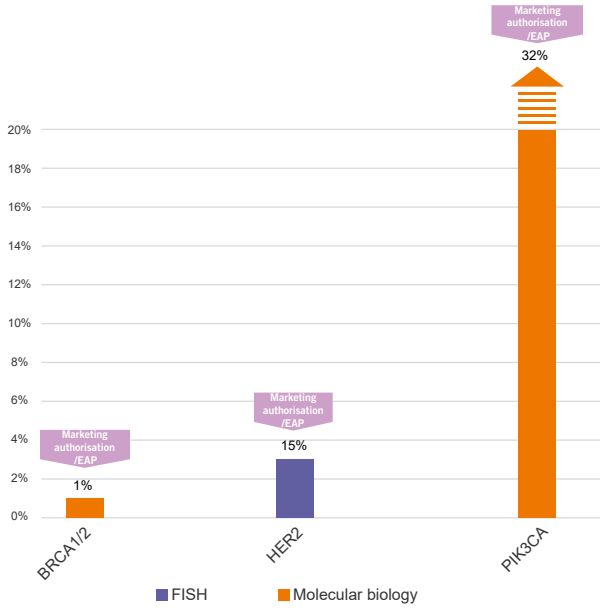
Eurofins Biomnis offers molecular tests for theranostic applications and establishing prognoses relating to breast cancers: HER2 FISH, identifying somatic BRCA1/2 and PIK3CA mutations, MSI testing and molecular signature testing for RH+/HER2- breast cancers.

DS85-INTGB – October 2020

“Targeted treatment: sensitivity and resistance”, “chemotherapy or no chemotherapy?” and “impact on prognosis” in breast cancer: What analyses are available? What techniques are used? What are potential targets for the future?

- FISH HER2 and plasma HER2
- Somatic BRCA1 and BRCA2 mutations
- PIK3CA mutation
- Prosigna – PAM50 – molecular signature
- Pan-organ NGS panel

Frequency of FISH or molecular abnormalities in breast cancer and targeted therapies available (marketing authorisation/EAP)



FISH HER2 and plasma HER2

In 2000, targeted anti-HER2 therapy (e.g. trastuzumab – herceptin – monoclonal antibodies) combined with chemotherapy revolutionised the treatment of HER2+ invasive breast carcinomas. HER2 status is determined using IHC (testing for expression of the HER2 protein: 0/+/++/+++) and FISH (testing for amplification of HER2) for IHC++ cases. IHC+++ and HER2 amplified cases are eligible for targeted therapy. New ASCO-CAP recommendations were introduced in 2018 for determining the HER2 status of invasive breast cancers. Combined therapies are being studied to improve the treatment of overexpressed or amplified HER2 tumours. Note that the HER2 marker is a marker of agressive disease, indicative of a poor prognosis if no targeted anti-HER2 therapy is administered. The HER2 extracellular domain assay (plasma HER2) may be of use in establishing prognoses.

Somatic BRCA1 and BRCA2 mutations

The efficacy of PARP inhibitors was first demonstrated in the treatment of ovarian cancer. The brief overview of the mechanisms for DNA repair and the role of PARP inhibitors is given in the paragraph on ovarian cancer.

Around 5% to 10% of breast cancers are genetic in origin and in 15% to 20% of cases this predisposition is linked to a BRCA1 or BRCA2 germline (constitutional) mutation. Oncogenetic consultations are key for screening patients that carry a BRCA mutation. Individual criteria (young woman – triple negative cancer) or family criteria can be used to target these patients. In some cases, however, only a somatic (and not constitutional) BRCA mutation is identified. In France, a number of different genetic oncology pathways for the prescription of a PARP inhibitor, dependent on the presence of a germline or somatic mutation, were proposed by INCa in 2019. Recently, authorisation was given for a PARP inhibitor (olaparib) for use in the treatment of locally advanced or metastatic HER2 negative breast cancers presenting with a BRCA1/2 mutation.

PIK3CA mutation

Breast cancer is associated with a number of gene mutations. Of the genes concerned, PIK3CA is mutated in around 32% of cases. This mutation is associated with old age, HR+/HER2 status and luminal A subtype. An association between the presence of a PIK3CA mutation and resistance to the targeted anti-HER2 therapy has been reported. A new targeted anti-PIK3CA therapy (alpelisib) has emerged recently (EAP in France for relapses and/or progression of HR+/HER2- metastatic cancers). It is highly likely that other targeted therapies will emerge for HER2- breast cancers, and in particular for TN cancers (HR-/HER2-).

PDL-1 and immunotherapy

A number of clinical trials are ongoing to validate the utility of immunotherapy (PDL-1 IHC or potentially in the near future the evaluation of tumour mutational burden (TMB)), in particular for TN breast cancers.

Prosigna – PAM50 – molecular signature

(*see* Prosigna-PAM50 brochure - ref. DS79 INTGB)

For breast cancer, a molecular signature or gene expression profile (based on quantitative RT-PCR) can be used for two purposes:

- To identify the intrinsic molecular subtype of the cancer (four subtypes: luminal A – luminal B – overexpressed HER2 – basal-like).
- To calculated the risk of recurrence at 10 years by combining lymph node status, the size of the tumour and the expression profile of 50 genes involved in HR+/HER2- cancers. This signature allows patients to be identified as low, intermediate or high-risk of recurrence and on this basis to determine whether to propose chemotherapy in combination with hormonotherapy.

Eurofins Biomnis offers the Prosigna™ - PAM50 test (Nanostring® Technology) which can be used for both purposes (FDA 2013).

Note: These molecular signatures do not provide therapeutic information on amplified HER2 or TN tumours and should not be prescribed for these types of cancer.

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Pan-organ NGS panel

(*cf.* Oncology- Other solid tumours - Sheet - ref. DS86-INTGB).

The routine use of NGS in oncology is leading to the emergence of promising molecular classifications for use in prognosis (e.g. association of TP53 mutations and basal-like subtype) and for the detection of resistance mechanisms against anti-HER2 therapy (e.g. AKT mutation). This new data will result in new treatment regimens. In view of these developments, we are offering the pan-organ NGS panel.

Ovarian cancer

Ovarian cancer is the seventh most common form of cancer in women. Ovarian cancer has a poor prognosis as it is often discovered late (fourth leading cause of death from cancer in women). In 90% of cases, it is an epithelial cancer (70% of cases are of the high-grade serous subtype). Treatment of this cancer has improved due to the revolutionary introduction of PARP inhibitors.

Somatic BRCA1 and BRCA2 mutations
MSI tests
Pan-organ NGS panel

Somatic BRCA1 and BRCA2 mutations

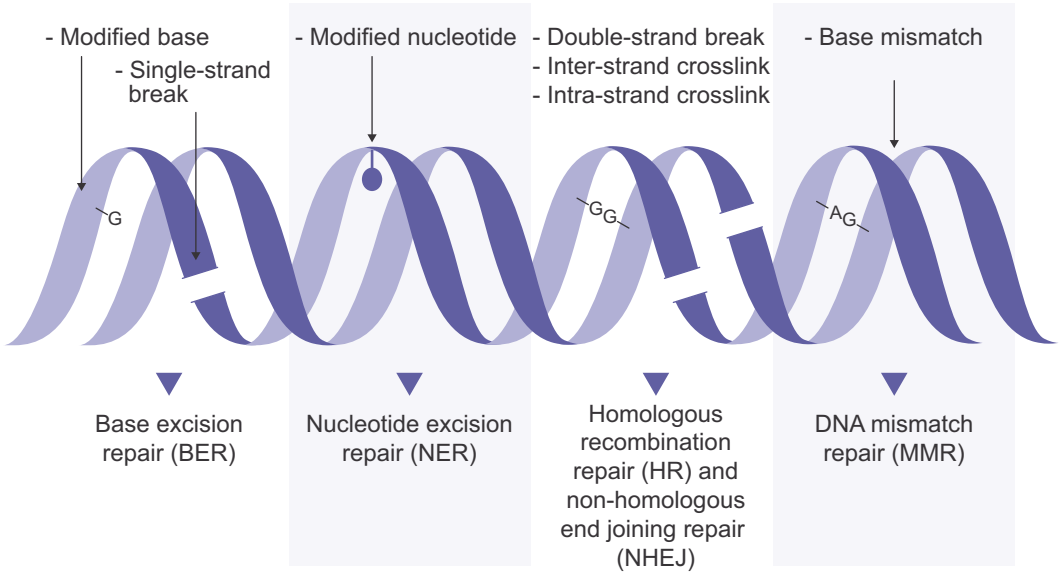
BRCA1 or BRCA2 mutations are reported in around 6% of ovarian cancers. They are associated with a good prognosis and improved response to platinum salts.

Brief overview of DNA repair mechanisms and how PARP inhibitors work:

In cells, DNA is constantly subject to physiological (e.g. replication errors) or environmental or chemical factors (e.g. ionising radiation, free radicals, alkylating agent, etc.) that impact its integrity.
It is therefore essential that this DNA is repaired. There are a number of processes by which a cell identifies and corrects damage to DNA: the DNA repair systems. Of these, five are of particular interest in oncology:

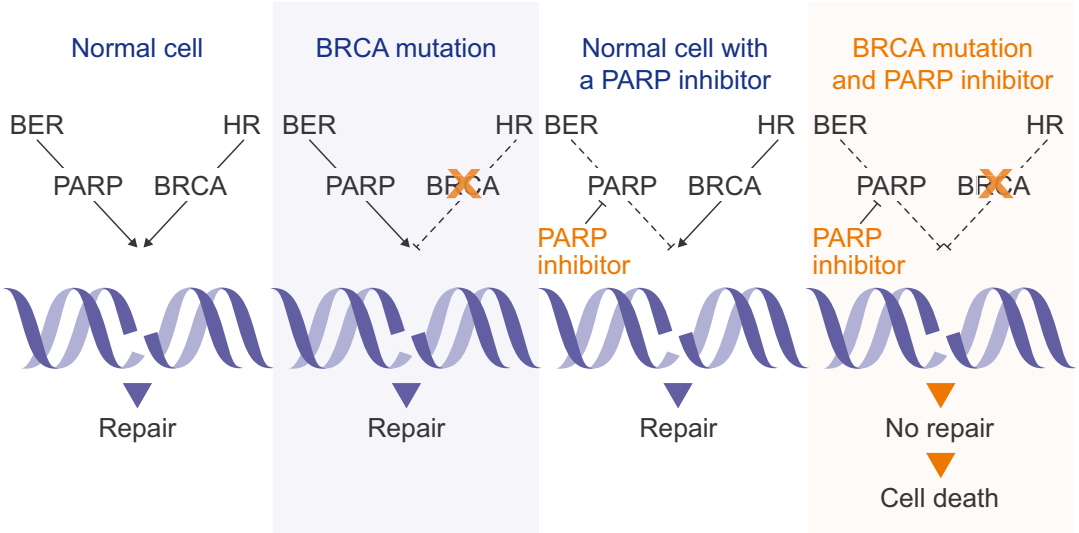
- Base Excision Repair (BER)
- Nucleotide Excision Repair (NER)
- Homologous Repair (HR)
- Non-Homologous End-Joining (NHEJ)
- Mismatch Repair (MMR)

The DNA repair systems



Each of these systems is associated with functional proteins (e.g. PARP for BER, BRCA or others (MRN, ATM, RAD51, PALB2, FANC, etc.) for HR, etc.). This means that the mutations of genes that code these proteins have a direct impact on the repair system.

Two systems in particular interact with each other: the BER and HR systems. If the BER mechanism is impaired, a single-strand break will become a double-strand break after passing through the replication fork. The double-strand break is then repaired by the HR system. If the HR system is dysfunctional (e.g. due to BRCA mutation), the repair does not take place and the cell is programmed for apoptosis (the NHEJ system is not effective enough on its own). As such, the effect of a PARP inhibitor in a mutated BRCA cell results in cell death: the term used is “synthetic lethality”.



PARP inhibitors (e.g. olaparib) represented a new class of targeted therapy. In 2014, olaparib received marketing authorisation for relapsed, platinum-sensitive high-grade serous epithelial ovarian cancer with BRCA mutation (germline or somatic).

Around 50% of high-grade serous carcinomas present with an HR deficit and around 15% to 20% of cases are explained by BRCA mutation alone (around 15% are germline and 5% somatic only). Note that in 10% of cases, BRCA promoter hypermethylation can be observed. In the future, comprehensive molecular screening or HR system operation tests will be key in the treatment tumours displaying “BRCAness” (ones that resemble mutated BRCA tumours). NGS HRD panels (HR system faults) or HRD molecular signatures could be offered as a means to better target patients with PARP inhibitors.

Note: As with ovarian cancer, oncogenetic consultations are key in determining individual and family treatment. In France, a number of different genetic oncology pathways for the prescription of a PARP inhibitor dependent on the presence of a germline or somatic mutation have been put forward by the INCa for ovarian cancer.

MSI tests

(see Oncology - Digestive system sheet - DS84-INTGB)

An MSI test is used in pre-screening for Lynch syndrome (constitutional oncogenetics with oncogenetic consultations). The MSI test, the PD-1/PDL-1 axis and the tumour mutational burden may also be investigated as part of innovative immunotherapies.

Note: The **pan-organ NGS panel** can be offered as part of clinical trials (*see* Oncology – Other solid tumours sheet – ref. DS86-INTGB).

Endometrial cancer

Endometrial cancer is the fifth most common form of cancer in women. The prognosis is good when it is diagnosed at a localised stage (70% of cases). The treatment is primarily surgical. Other treatments exist: brachytherapy, external radiotherapy and less commonly chemotherapy or hormone therapy for advanced forms. Due to its good prognosis, it is not often considered for targeted therapies.

MSI tests
Pan-organ NGS panel

MSI tests

(see Oncology – Digestive system sheet – ref. DS84-INTFR)

The indications for the MSI test are:

- Pre-screening for Lynch syndrome (constitutional oncogenetics with oncogenetic consultations). The molecular marker for sporadic cancer is MLH1 hypermethylation.
- Analysis of prognostic factors: An MSI+ status means it can be categorised in a molecular group with a good prognosis.
- In the near future, theranostic stratification using immunotherapy in advanced forms. The PD-1/PDL-1 axis and tumour mutational burden may also be investigated.

Note: The **pan-organ NGS panel** can be offered in connection with clinical trials (*see* Oncology - Other solid tumours - sheet DS86-INTGB).

In conclusion, the molecular biology and FISH approaches for gynaecological tumours are constantly changing. This document was written according to the state of knowledge in 2020.

Note: Alongside FISH and molecular analyses, Eurofins Biomnis can also test other biological parameters:

- In the field of breast cancer:
  - Evaluation of the toxic risk of fluoropyrimidines (5-FU).
  - Tumour markers such as ACE and CA15-3.
- In the field of ovarian cancer:
  - Tumour markers such as CA 125 – HE4 (ROMA score), ACE, CA 19.9 and CA 72.4.
- In the field of uterine, cervical and endometrial cancer:
  - Tumour markers such as SCC, Cyfra 21.1, CA 125, ACE and CA 19.9.
  - Detection of high-risk (HR) HPV genomes and HPV typing.

The evaluation of tumour mutational burden (TMB) as a predictive test for response to immunotherapy as a first-line treatment is also available from Eurofins Biomnis.

Before taking any samples, view the key information for each test (pre-analytical requirements, turnaround time, required documents*, etc.) on **www.eurofins-biomnis.com** > Test guide section > **Test Code**

Analysis codes

- HER2 FISH: **MOHC4**
- HER2 plasma: **ERBB2**
- Pan-organ NGS panel: **PAN**
- MSI test: **MICSA**
- PIK3CA mutation: **PIK3**
- Prosigna molecular signature: **PAM50**
- Somatic BRCA1/2: **BRCAS**
- TMB test: **TMB**

*Required documents

- Test request form - Oncology-Solid Tumours (ref. B9-INTGB)
- Histology report

Turnaround time (FISH and NGS): 10 days (one extra week if verification by Sanger is required)

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Literature references

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Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update.Wolff AC, et al. Arch Pathol Lab Med. 2018 Nov;142(11):1364-1382. PMID: 29846104

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Websites https://www.mycancergenome.org/
https://www.e-cancer.fr/
https://www.cancer.gov/

Abbreviations

BER Base Excision Repair

FDA Food and Drug Administration

HR Homologous Repair

HRD Homologous Recombination Defect

IHC Immunohistochemistry

TKI Tyrosine-Kinase Inhibitor

MMR MisMatch Repair

NER Nucleotide Excision Repair

NHEJ Non-Homologous End-Joining

PARP Poly(ADP-Ribose) Polymerase

HR Hormone Receptors

OR Oestrogen Receptors

PR Progesterone Receptors

TMB Tumour Mutational Burden

TN Triple Negative (for breast cancers: OR-/PR-/HER2-)

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