The **Advocate's Guide** to Genomics, Genetics and Personalised Medicine in **Breast Cancer**

EUROPA DONNA
The European Breast Cancer Coalition

Why do advocates need to understand the role of genetics and genomics in breast cancer?

Genetics and genomics hold the key to unlocking unique combinations lying within individuals and within tumours. Once identified, they can be used for **prevention, prognosis, risk stratification**, and, ultimately, to **guide personalised therapy**. It will be imperative for advocates and patients to understand this information as it could hold the **future of breast cancer therapy**.

Why is this topic important to Europa Donna?

Genomic markers will drive breast cancer management in the future and will be fundamental to achieving the mission and many of the **goals of the Coalition**: furthering education and promoting the advancement of breast cancer research, promoting prevention, early diagnosis and optimal management, and ensuring **equal access** to prevention, diagnosis and treatment. It also addresses the objectives of **Europe's Beating Cancer Plan,** which aims to improve approaches to cancer care across the full disease spectrum.

Europa Donna Mission

Europa Donna — The European Breast Cancer Coalition is an independent non-profit organisation whose members are affiliated groups from countries throughout Europe. The Coalition works to raise awareness of breast cancer and to mobilise the support of European women in pressing for improved breast cancer education, appropriate screening, optimal treatment and increased funding for research. Europa Donna represents the interests of European women regarding breast cancer to local and national authorities as well as to institutions of the European Union.

Genetics and Genomics: What does this mean?

Genetics is the study of heredity and individual genes, while **genomics** refers to the study of all genes, as a whole or part of a genetic sequence, and how they interact and function.

In terms of breast cancer, **genetic and genomic testing** is used to identify **molecular alterations or mutations**. They can indicate the **future risk** of breast cancer in those who take the test before they are diagnosed. In those with breast cancer, they are used for **identifying the tumour subtype,** the **prognosis**, choosing **therapy**, monitoring the **response** to therapy, and predicting **side effects** of treatment.

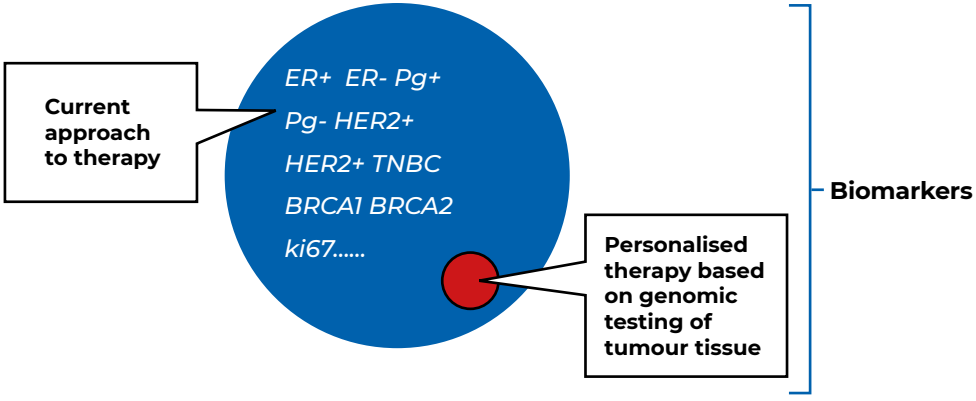
Globally, these molecular alterations are referred to as **biomarkers**, which the European Medicines Agency defines as 'A **biological molecule** found in **blood, other body fluids, or tissues** that can be used to follow body processes and diseases in humans and animals.'

Genetic and Genomic Testing

In breast cancer, **genetic testing** is used primarily in healthy people to identify specific gene mutations that have **high risk for cancer** and are **inherited** (eg, BRCA1 or BRCA2). This is to predict the risk of having breast cancer in the future. These genetic tests can also be used in people with cancer to determine if they have these hereditary mutations in order to plan **risk-reducing strategies** or treatments to avoid a second breast or ovarian cancer.

Genomic testing is performed on the breast **tumour tissue** to determine the genetic 'signature' of a cancer and identify genomic drivers that may be relevant to possible **management approaches**. For example, studies have shown that some women with specific **low-risk gene signatures** have little added benefit from chemotherapy and may be spared this treatment. It can also identify certain genes or mutations that indicate that a specific therapy may be effective.

As more genetic and genomic information is gathered, there will be increasing opportunities for highly **personalised targeted therapies**.



Genetics and Hereditary Breast Cancer

About 5% to 10% of breast cancers are considered to be hereditary, ie, running in families. Abnormalities (or mutations) in two genes in particular, **BRCA1 and BRCA2**, account for most high-risk hereditary breast cancers. BRCA1/2 mutations or variants are uncommon and cause about 3% to 5% of breast cancers overall (and 10% to 15% of ovarian cancers). Yet it is estimated that women who carry these mutations have a cumulative **risk of having breast cancer** of 72% for BRCA1 and 69% for BRCA2 by the time they are 80 years old.

There are **other higher risk mutations**, such as in TP53 and CHEK2, which are rare but are included in **familial breast cancer management**. There are at least 200 other genetic variants associated with an altered risk of breast cancer. In certain combinations, they could be responsible for additional hereditary breast cancers.

Based on their family history, some healthy women may choose to undergo **genetic testing** to find out if they carry – or do not carry – any high-risk mutations. According to the European Breast Cancer Council, any such testing should be provided with access to **clinical geneticists** and **genetic counsellors**, with the guidance of appropriate healthcare professionals to give people an accurate understanding of risk; to inform evidence-based interventions; and to avoid possible harm, both physical and psychological, through unnecessary interventions and anxiety. People should always be referred to **breast cancer services** with the appropriate genetic specialists.

Genetic Testing for Hereditary Breast Cancer Risk

In Healthy People

Genetic risk testing should be performed in national health services and breast cancer services/centres according to the latest evidence-based guidelines, with access to genetic counselling and informed consent. Tests are carried on a blood sample, or a sample from the mouth or saliva.

In **healthy people**, testing for BRCA1/2 and certain other mutations is only indicated when there is a **high index of suspicion**, such as a mutation identified in a close relative with breast cancer, or a broader family history of breast cancer.

Even among those **without a family history**, certain groups, such as women of Ashkenazi **Jewish descent**, those with breast cancer at a **younger age** (50 years or younger), and those with **triple-negative breast cancer**, are more likely to have BRCA1/2 gene mutations and can be offered genetic testing.

Undergoing testing by **recognised centres** within the national health services is the preferred approach. The **European Breast Cancer Council Manifesto** on genetic risk prediction testing states that any direct-to-consumer tests must be used with the appropriate caution, and include **informed consent**, **counselling** and **medical supervision.**

Women who are found to carry **high-risk genes** may choose to undergo frequent **monitoring**, or **prophylactic approaches** such as ovarian suppression of oestrogen production and prophylactic mastectomy. It is important to discuss the reasons for wanting the test and potential implications of any results on a woman's future **physical and psychological health**.

In Women With Breast Cancer

Among women with breast cancer, identifying the presence of BRCA variations can help to provide more **options for therapy**.

The **European Commission Initiative on Breast Cancer** (ECIBC)'s quality assurance scheme for breast cancer services states that centres must offer access to **genetic testing and counselling** for all women diagnosed with breast cancer who are at a high risk of having genetic mutations.

The St. Gallen 2021 meeting recommendations published in 2022 concluded that **genetic panels for hereditary cancer** should be offered to women if they have a more than 10% risk for a hereditary mutation in algorithms based on family history, age at diagnosis, and tumour subtype. Testing should use a gene panel including BRCA1 and 2, ATM, BARD1, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, STK11, RAD51D, and TP53.

Breast Cancer Subtypes and Biomarkers: The Foundation of Management

Before embarking on genomic testing in women with breast cancer, it is important to identify the **characteristics of the cancer** and **biomarkers** using what is known to date. There are **five main cancer subtypes** that are fundamental to any management decisions at the current time:

Luminal A-like	Luminal B-like (HER2 negative)	Luminal B-like (HER2 positive)	HER2	Basal like/triple negative
ER and PgR positive, HER2 negative, and low Ki67	ER positive, HER2 negative, and either high Ki67 or low PgR, plus a high-risk molecular signature, if available	ER positive, HER2 positive, and any Ki67 or PgR level	HER2 positive and ER and PgR absent	HER2 negative and ER and PgR absent

ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; Ki67 = a proliferation marker that provides prognostic information; PgR = progesterone receptor

Women should receive results of the pathology testing, including these findings, in the **pathology report** describing the **tumour characteristics** based on the biopsy, and evaluation of tissue removed at surgery. It includes the tumour subtype and stage, size and various prognostic factors.

The most **important prognostic factors** in early breast cancer are the expression of oestrogen (ER) and progesterone (PgR) receptors, HER2, proliferation markers such as Ki67, the number of regional lymph nodes involved, tumour histology, the size, grade and the presence of tumour cells in the vascular tissue surrounding the tumour area. The presence of clear margins, with no tumour cells in the area surrounding the removed tumour tissue, is also very important.

These established breast cancer subtypes are the current **foundation of management** approaches. However, breast cancer is very heterogeneous, ie, tumours can have a wide array of characteristics. As biomarkers are identified and their relevance to the disease or its treatment is determined, specific testing and management approaches will become increasingly personalised.

Genetic and Genomic Testing of Tumour Tissue

Tumour samples can be tested for mutations/alterations that guide prognosis and treatment decisions, as part of the **standard pathological evaluation**, and as complementary information.

Techniques and Tests to Identify Biomarkers

Test	Description
Immunohistochemistry (IHC)	Staining method used on a biopsy or tumour specimen to detect HER2, HER and Pg
FISH (fluorescence in situ hybridization)	Test performed in tissue to identify chromosomes; used to detect HER2
PCR (polymerase chain reaction)	Test for changes in a gene or chromosome (eg, PIK3CA) in tissue and with liquid biopsies; also used in gene sequencing to detect BRCA mutation
Liquid biopsy	Test in a blood sample that checks for circulating cancer cells or tumour DNA. Still under investigation and preliminary, but is used to detect PIK3CA in MBC
Next-generation sequencing (NGS)	Used to identify novel and rare mutations, familial genes (eg, BRCA), and potential treatment targets based on test of tumour tissue

Genomic Molecular Assays: Next-Generation Sequencing

Genomic molecular assays include **gene array panels** or gene expression profiles. Gene or genomic signature tests of tumour tissues have been widely studied in clinical trials to identify their **predictive value** and are gradually becoming available for wider use. These prognostic assays can indicate, based on a **high-risk score**, whether or not a woman with an ER-positive and HER-negative tumour and other specific characteristics would benefit from chemotherapy before or after surgery (or those with a low risk who may be spared chemotherapy). Some tests indicate who might benefit from extended endocrine therapy or identify genes that can be targeted with biological drugs and different combinations of therapies. Some of these tests include: Oncotype DX®, MammaPrint®, Breast Cancer Index®, EndoPredict® and Prosigna®.

The ECIBC's **European Guidelines on Breast Cancer Screening and Diagnosis**, which are updated on a regular basis, currently recommend using a **21-gene recurrence score** in women with ER-positive, HER2-negative, lymph-node negative or up to 3 lymph-node positive invasive breast cancer to guide the use of chemotherapy. They suggest using the 70-gene signature test for women with high clinical risk of cancer recurrence.

It is important that the information obtained from these tests be **relevant to prognosis**, management decisions and/or provide a target for therapy. Women should be informed about the possible benefits of this type of testing. **Accessibility** to testing without national, geographical or socioeconomic limitations is a key factor to consider (see page 8).

Genomics and Biomarkers in Metastatic Breast Cancer

As in women with early breast cancer, those with **advanced or metastatic breast cancer** (MBC) should be treated by a multidisciplinary team, according to the latest evidence and guidelines (eg, the Advanced Breast Cancer (ABC) and ESO-ESMO guidelines). **Biomarker testing** of the new tumour site/sites should be performed because the characteristics (eg, hormone receptor status, HER2 status) may be different from the primary tumour and they can also change over time from positive to negative and vice versa.

The treatment approach may involve hormone therapy, anti-HER2 therapy or chemotherapy, depending on the **tumour characteristics**. Novel approaches based on biomarkers are now available and this area continues to evolve. **ABC guidelines** recommend evaluating:

- ER and HER2 status
- BRCA germline mutation status
- PI3CA mutation status in ER+/HER2- cancer
- PD-L1 status in triple-negative breast cancer

This is because some **newer targeted therapies** have shown advantages in tumours exhibiting these characteristics. Conversely, the ABC guidelines do not recommend using **NGS multigene panels** in routine practice, except where there is **access to a drug** to target any biomarkers identified.

HER2 Low

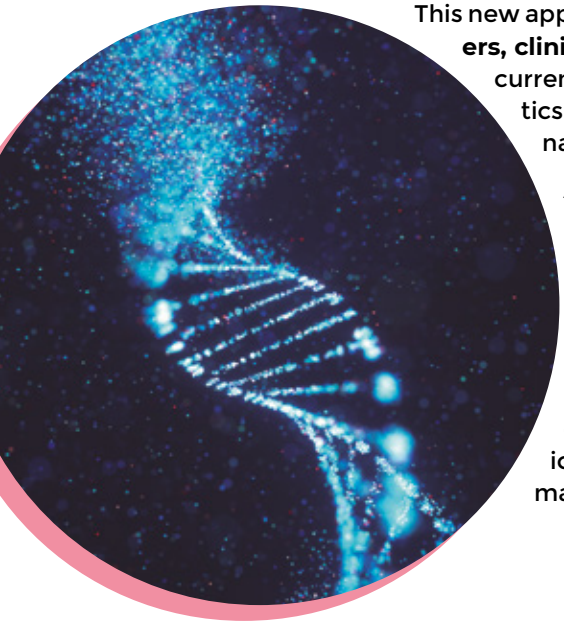
In recent years, the concept of a subgroup of **HER2-low tumours**, where HER2 is detected in low levels in a tissue biopsy, has emerged. In the past, these were considered HER2-negative because therapies were not effective in treating them. New therapy can now target this lower level of HER2. This demonstrates how biomarkers evolve as new therapies are designed to target them.

Looking to Precision Medicine

Precision medicine is a step beyond the current single biomarker approach to targeted therapy. Precision medicine is a **personalised approach** to breast cancer prevention and management that involves a combination of **genetics/genomics, environment and lifestyle** to identify a therapy or approach that will work best for each individual.

Next-generation sequencing can sequence entire genomes or examine specific areas of interest using **multiple biomarker tests**, which is a great leap from single biomarker tests. In the short-term, ideally all patients with breast cancer should undergo **clinically relevant biomarker testing** with the use of certain extended panels where appropriate. In the long-term view, all patients will undergo comprehensive genomic testing.

Current research in this approach is in the area of **MBC**. According to this concept, genomic testing is used to identify genetic drivers of **tumour progression** as targets for treatment. It can be used to identify which women may experience toxicity, who would benefit/not benefit from a certain treatment, and address resistance to therapy. As many genetic alterations are identified, treatment will become increasingly personalised. **Rare mutations** may mean that a woman is treated with a therapy that is unique to her cancer.



This new approach will require **advocates, researchers, clinicians and policy makers** to reconsider current approaches to clinical trials, diagnostics, treatment, regulatory processes, to name a few.

As data accumulate, **artificial intelligence** may play a role in prognosis, diagnosis and therapy. **National data registers and standardised data gathering** will be fundamental for this approach going forward.

For now, this remains in the research domain or in the future for routine clinical practice, as access to common biomarker testing remains a challenge.

Access to Biomarker Testing: Inequalities and Areas for Action

Single Biomarker Tests

While **precision medicine** may be the goal for the future, access to even ***single* biomarker testing** is limited in many countries. A **study published in late 2022** on the access to biomarker testing for all cancers across the EU-27 plus the United Kingdom* revealed that 18 countries had medium access, seven had high access, and three had low access to *single* biomarker tests. In those with low access, this was attributed to an **underdeveloped or inefficiently organised laboratory infrastructure**. In Southern and Eastern Europe, **lack of reimbursement** impeded access to these single biomarker tests, which many **patients pay out of pocket**.

Next-Generation Sequencing

The situation is similar for NGS, which have an uptake of 0% in some countries and more than 50% in others. Overall, **less than 10% of cancer specimens** requiring molecular testing are analysed using NGS. Low uptake is due to **lack of access to NGS technology** in laboratories in some countries and **lack of funding** in others. In Northern and Western European countries the uptake is generally high.

Quality Assurance

The quality of biomarker testing tends to be high in Northern and Western Europe, with more than 90% of laboratories participating in **external quality assurance schemes**. In Southern and Eastern Europe, participation is lower, mainly due to **lack of funding**. In some Eastern European countries, low participation occurs because the quality assurance schemes are not required for public funding or participation in clinical trials.

What do patients report?

The **European Cancer Patient Coalition** was a collaborator in this study, which also surveyed almost 1600 patients. Only about **30% of patients** reported undergoing biomarker testing. One-third of those who underwent testing **did not receive adequate information** about the tests from physicians. This indicates a need for **further education** about biomarkers for everyone involved.

Key Messages

Improved **regulatory and reimbursement approval** of precision medicines and associated tests, and **increased funding** for biomarkers could help guarantee more **equal access to new therapies** for all patients in Europe, which is an objective of **Europe's Beating Cancer Plan**. The biomarker report also includes a ranking of countries in their access to precision medicines and the percentage of reimbursement.

**See Normanno N, et al. Eur J Cancer. 2022;176:70-77.*

What to advocate for regarding genetics, genomics and personalised medicine in breast cancer:

- Access to biomarker testing and genetic and genomic tests according to European guidelines
- High-quality standardised genetic/genomic tests and histopathology
- Access to pathology reports
- Genetic risk testing performed in national health services and breast cancer services in women at high risk of hereditary breast cancer and in those with breast cancer who are at a high risk of having genetic mutations
- Access to genetic counselling and informed consent
- Improved coordination of the regulatory process for precision medicines and molecular tests
- Improved public funding for research on and access to biomarker testing
- High-quality data registries for clinical and real-world data
- Education for health care providers
- Education for patients and patient advocates
- Education for policymakers

Resources

ABC Guidelines. https://www.abcglobalalliance.org/abc-hub#abc-guidelines

European Breast Cancer Council Manifesto 2018: Genetic Risk Prediction Testing in Breast Cancer. European Journal of Cancer 2019;106:45-53.

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