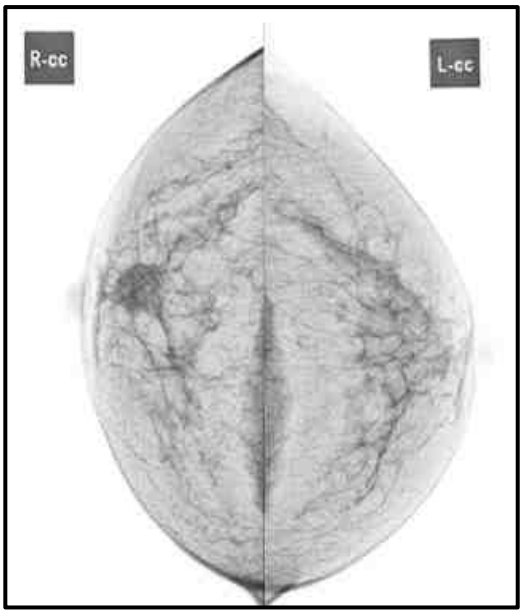
Advanced Molecular Diagnosis of Breast Cancer Diseases



PBM-Spain has developed high-complexity laboratory developed tests (LDTs) providing a molecular subtyping of breast cancer, with the final goal of enhancing diagnosis and therapy in the following major areas:

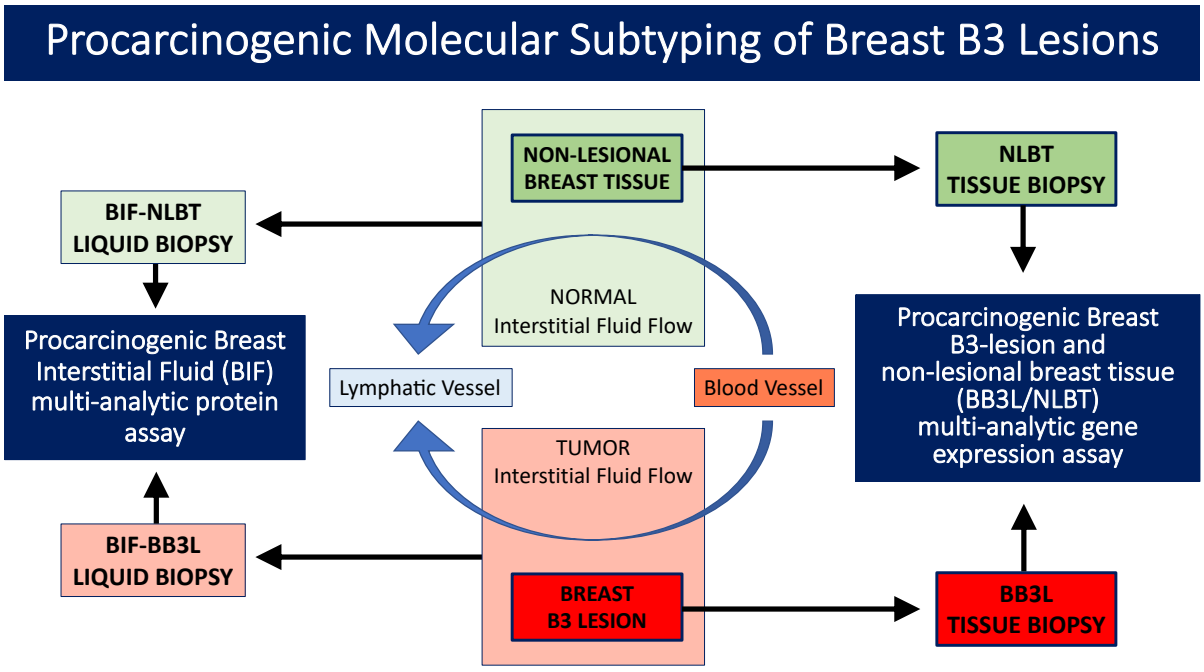
- **Breast B3 lesions with a high malignant potential.**
- **Breast cancer HER2 phenotypes.**
- **Residual disease after invasive breast cancer neoadjuvant therapy**

For all clinical cases, the value proposition is that multi-analytic molecular and genetic assays, with algorithmic analysis, and their digital integration with routine histopathological, radiological, and clinical diagnosis, will facilitate a cost/effective personalized healthcare monitoring and therapy of patients with breast cancer, which may result in an average 60% cost saving, improved healthcare outcomes and, ultimately, less suffering for the patient.

Procarcinogenic Screening of Breast B3-Lesions with a high malignant potential

- Breast B3 lesions are very heterogeneous and of uncertain malignant potential, leading up to 7-fold increase of cancer risk and up to 40% risk underestimation in the initial biopsy because histological diagnosis is usually made on needle core (NCB) and vacuum-assisted (VAB) biopsies.
- Its inherent diagnostic complexity leads to questionable, non-standardized and cost inefficient interventions (including annual follow-up with multimodal imaging, re-biopsy and even surgery), demanding a Quality Improvement (QI) opportunity using a molecular diagnostic approach.
- Main goal is to get a more precise predictive diagnosis of cancer risk, avoiding stressful interventions and over-treatments, while simplifying clinical management of patients, which in turn saves healthcare expenses and a long follow-up.

PERSONA BIOMED of Spain SL
Calle Valle de la Ballestera 64, 46015 Valencia, Spain; Office Phone: (34) 96 348-8196;
Email: ana.perez@personabiomedspain.com; www.personabiomedspain.com



- On this basis, PBM-Spain is offering a combined Procarcinogenic Molecular Subtyping of Breast B3-Lesions based on NLBT & BIF multianalytic gene and protein assays (as shown above). The purpose is to target the very challenging biological variation in breast cancer risk (Pathway 2), ensuring lower ratios of both “malignancy overdiagnosis” (Pathway 1), and “redundant interventions to breast cancer deaths prevented” (Pathway 3), which may save resources while improving woman’s life quality by decreasing morbidity and mortality.

- In summary, adoption of the offered **Procarcinogenic Molecular Screening** in the clinical management of B3 breast lesions should better define risk of malignancy, in turn providing two cost/effective healthcare benefits:
    - **Avoidance of unnecessary surgeries when patients with "high risk" lesions (HDA and papillomas with atypia) test negative for the Procarcinogenic assays.**
    - **Avoidance of unnecessary imaging studies and follow-up interventions when patients with "low risk" lesions (such as Flat Epithelial Atypia, Lobular Neoplasia, radial scar, etc) test negative for the Procarcinogenic assays.**

- Definitely, the **Procarcinogenic Molecular Screening** may not just save healthcare resources, but also may better support the quality of woman’s life by reducing their clinical consultations and interventions.

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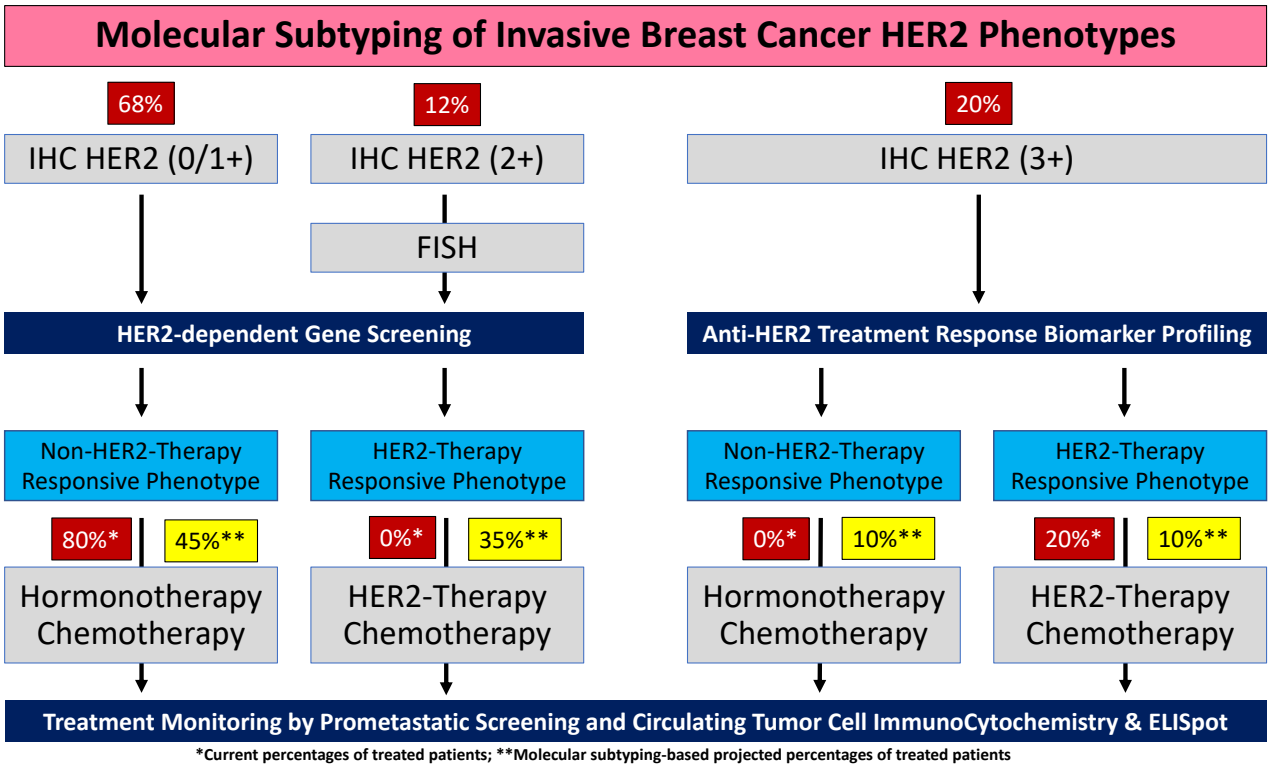
Complementary Diagnostic Test for the Molecular Subtyping of Invasive Breast Cancer HER2 Phenotypes

- Breast cancer overexpression of HER2 correlates with aggressive malignant behavior and short overall survival, but at a time breast cancer becomes sensitive to HER2-targeted therapies improving overall survival in patients with both localized and metastatic tumors.
- HER-2 assessment by immunohistochemistry (IHC), with and without additional in situ hybridization (FISH), allows sorting patients into various therapeutic response categories: Non-responders (IHC 0/1+); Responders (IHC 3+ expression); and patients with undefined HER2-overexpression (IHC 2+) requiring combined IHC and FISH assessment.
- Neither separately nor together, IHC and FISH correctly sort patient responders and non-responders to HER2-targeted therapies. This includes a large number of potential responders from the low-HER2 overexpression patient subgroup (IHC 0/1+/2+), and of non-responders from the high-HER2 overexpression patient subgroup (IHC 3+).



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- This suboptimal therapeutic selection has an important cost for both patients and healthcare entities, which is also demanding a QI opportunity using complementary diagnostic tests that help improving patient selection for HER2-targeted therapies.
- On this basis, PBM-Spain is offering a **multianalytic assay, targeting HER2-dependent gene expression,** for the reassessment of both IHC 0/1+ (68%) and IHC 2+ (12%) breast cancers with the main goal of identifying potential responders. And another **multianalytic assay targeting HER2 treatment response biomarkers** in order to identify those IHC 3+ breast cancers that may not respond to HER2 therapy.
- Altogether, it represents an attempt to rescue potential HER2 therapy responders **(up to 35% of breast cancer patients)** from the non-responder and undefined HER2-expression subgroups, while we identify potential non-HER2 therapy responders **(up to 10% of breast cancer patients)** from the high HER2 overexpressing subgroup.

- In summary, using the proposed multi-analytical assays for the molecular subtyping of HER2 phenotypes and HER2 treatment response potential should provide two cost-effective healthcare benefits:
    - **Limit morbidity associated with ineffective HER2 therapy and save unnecessary and expensive HER2 therapies for up to 50% of IHC 3+ breast cancers having non-responsive HER2-phenotype, while allowing them an earlier access to more effective therapies.**
    - **Provide HER2 therapy to those non-IHC&FISH detectable IHC- 0/1+/2+ patients of responsive HER2-phenotype, resulting in longer disease-free interval, greater overall survival and lower metastatic recurrence rate for these patients.**

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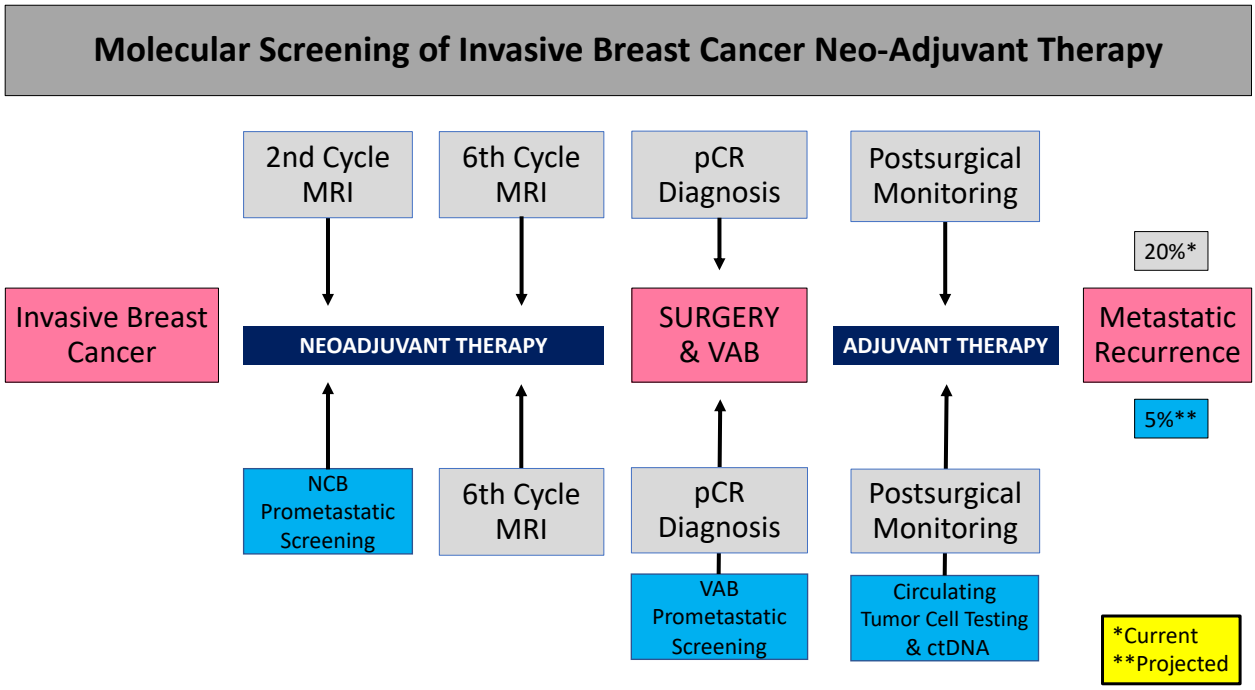
Residual Disease Molecular Screening for Breast Cancer Post-Neoadjuvant Therapy

- Neoadjuvant therapy (NAT) is a standard treatment strategy for locally advanced and inflammatory breast cancers of help to reduce tumor size and re-staging, and in turn leading to more conservative surgery.
- MRI-based response monitoring during and at the end of treatment, provides around 65% sensitivity and pathological study is still considered gold standard of pathologic Complete Response (pCR) assessment. However, recurrence rates after pCR is unacceptably high in patients undergoing a conservative surgery to avoid overtreatment, stressing the urgent need of better assessing pCR.
- Therefore, identification of reliable and accurate biomarkers is important for improving response assessment and risk stratification of patients before and after NAT, for selecting appropriate candidates of NAT, and for avoiding unnecessary drug toxicity in patients who just slightly respond to NAT.



- There is a QI opportunity for better screening residual cancer disease and providing biological information for better estimating benefits of supplementary post-NAT.

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- PBM-Spain is now offering a molecular screening for post-NAT breast cancers with the help of a multi-analytical assay of the VAB focused on prometastatic genes and proteins whose expression level and interrelationships are tumor-specific, in combination with Circulating Tumor Cell (CTC) detection in peripheral blood. The final goal is a more accurate diagnosis of the residual submicroscopic disease leading to tumor recurrence in pCR patients.

- In summary, using the offered multi-analytic assays on primary breast cancer prometastatic biomarkers and circulating tumor cells, as a complementary diagnostic test for the molecular screening of patient with pathological Complete Response (pCR) to Neoadjuvant Therapy, should provide two valuable and cost-effective healthcare benefits:

    - **Earlier detection of patients with residual subclinical (occult) disease and high metastatic recurrence potential.**

    - **Anticipated redesign of the treatment strategy to reduce unnecessary palliative interventions while improving patient's chances of survival.**

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