FLEX: From Genomic Profiling to Real-World Insights in 30,000 Patients with Early-Stage Breast Cancer

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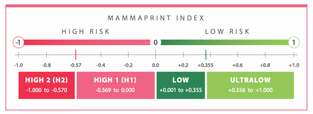
Introduction

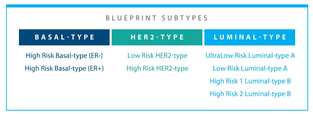
Treatment approaches for early-stage breast cancer (EBC) have advanced significantly in recent decades, with the addition of HER2-targeted therapies, immunotherapy, and personalized chemotherapy. However, despite these advances, many questions related to treatment cannot be practically or ethically addressed due to limitations of prospective, randomized, clinical trials, including:

- Extended follow-up in EBC treatment trials may delay the dissemination of practice-changing results.
- Poor representation of less common tumors (such as invasive lobular carcinoma)
- Limited enrollment of patients of diverse racial/ethnic backgrounds.

Hence, observational registry Real-World Data clinical trials, such as FLEX, which analyze clinical and pathologic data, treatment history, outcomes, and whole transcriptomics can provide actionable evidence that can inform clinical practice.

The ongoing, multi-center, FLEX study (NCT03053193) seeks to enroll 30,000 EBC patients to create a large-scale, diverse, population-based registry of whole transcriptome data matched with clinical data with 10 years of follow-up to investigate new gene expression signatures of prognostic and/or predictive value in a real-world setting. Efforts are focused on enriching enrollment of diverse racial/ethnic minorities, historically underrepresented groups, and uncommon EBC tumor histologies. An additional objective is supporting investigator-initiated sub-studies to address clinically relevant questions in EBC with up to 10 years of follow-up.



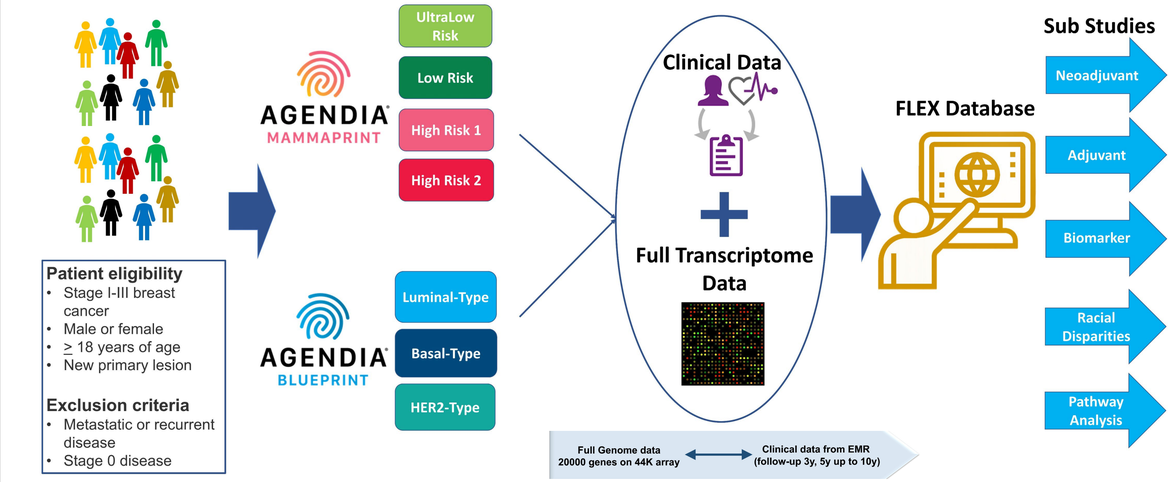


Methods

FLEX is a large prospective, observational trial that enrolls patients (male or female) who are ≥ 18 years old with stage I-III breast cancer. Patients who receive standard of care MammaPrint® (70-gene signature risk of recurrence), with or without BluePrint® (80-gene signature molecular subtype) on their primary breast tumor and consent to clinically annotated whole transcriptome data collection are eligible for enrollment. Within 7 years of trial initiation, FLEX has enrolled over 21,000 patients across 102 sites in the US, 3 sites in Canada, and 1 site each in Greece and Israel. Of the total FLEX population, 9495 (47%) have reached 3 years of follow-up, and 4047 (20%) have reached 5 years of follow-up. To address racial/ethnic disparities in clinical trials, a concerted effort has led to the inclusion of 1892 Black/African American, 1722 Latin American/Hispanic, and 490 Asian American Pacific Islander EBC patients of self-reported racial/genetic ancestry, making FLEX a highly diverse study of EBC patients. Similarly, FLEX represents one of the largest cohorts of ILCs, composed of 2196 ILC and 649 mixed ILC/ductal histology tumors. Studies from FLEX have led to 3 peer-reviewed publications, with 3 submitted in 2025 currently under review. Fourteen FLEX investigator-initiated sub-study abstracts have been presented in 2025. Additionally, over 53 FLEX abstracts have been accepted at congresses internationally (2018-2025), including 11 presentations focused on therapy selection, 12 on differences in tumor biology and clinical outcomes by race/ethnicity, and 2 on ILC, among others.

Data generated from FLEX include important new findings in EBC management. Among these findings are the prediction of absolute chemotherapy benefit in genomically high-risk patients, prediction of survival benefit from adjuvant anthracyclines, associations of genomic signatures that predict resistance to CDK4/6 inhibition, and overrepresentation of aggressive ER+ basal-type tumors in Black/African American patients.

FLEX Schema



Patient eligibility
- Stage I-III breast cancer
- Male or female
- ≥ 18 years of age
- New primary lesion

Exclusion criteria
- Metastatic or recurrent disease
- Stage 0 disease

MammaPrint, BluePrint, and Full-genome Data Linked with Clinical Data to Evaluate New Gene EXpression Profiles

FLEX Sub-studies & MammaPrint/BluePrint Studies

Ancestry and Racial Disparities

- Association of MammaPrint and Clinical Outcomes by Race Among 5,000 Individuals with HR+HER2- Early-stage Breast Cancer Enrolled in FLEX. *ASCO* 2025
- Identification of racial disparities across MammaPrint and BluePrint subtypes in HR+HER2- breast cancer. *ESMO* 2024
- Impact of race on BluePrint genomic subtyping in HER2+ breast cancer. *ASCO* 2023
- Racial disparities in breast cancer and effect of obesity: MammaPrint, BluePrint and whole transcriptome analyses of tumors in Latin American patients in FLEX trial. *SABCS* 2023 (Poster spotlight)
- MammaPrint and BluePrint identify racial disparities among women with HR+HER2- EBC. *SABCS* 2023

Predicting Chemotherapy Benefit & Treatment Selection

- MammaPrint predicts chemotherapy benefit in HR+/HER2- early breast cancer: FLEX Registry real-world data. *JNCI Cancer Spectrum* 2025
- Association of MammaPrint index and 3-year outcome of patients in the FLEX Registry trial with HR+HER2- early-stage breast cancer treated with chemotherapy with or without anthracycline. *ASCO* 2024
- Association of MammaPrint with Gene Expression Pathways Predictive of Resistance to Cyclin-Dependent Kinase 4/6 (CDK) Inhibition. *SABCS* 2024

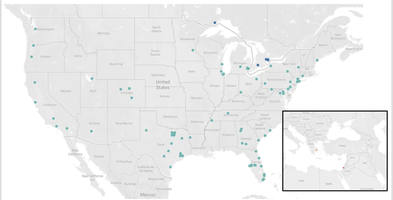
Invasive Lobular Carcinoma

- Impact of Neoadjuvant Chemotherapy on Surgical Outcomes and Conversion to Node-Negativity in Invasive Lobular Breast Cancer: Analysis of Molecularly High-risk tumors by Histologic Subtype on the I-SPY2 Clinical Trial. *ASBrS* 2025
- Distribution of MammaPrint, BluePrint, and Response Predictive Subtypes based on ImPrint and RePrint in Lobular tumors – A FLEX Substudy. *SABCS* 2023
- Differential gene expression in Luminal-type invasive lobular carcinoma and invasive ductal carcinoma by MammaPrint risk stratification. *SABCS* 2020

Age, HER2+ Disease

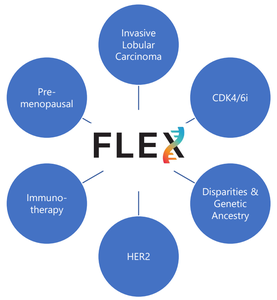
- Real-World Evidence from FLEX: Utility of MammaPrint in guiding treatment planning for patients aged 70 and older with early-stage breast cancer. *ASCO* 2025
- Molecular Insights into HR+/HER2+ Early-stage Breast Cancer: Neoadjuvant Therapy Responses by MammaPrint and BluePrint genomic subtypes. *ASCO* 2025
- Genomic Landscape of ER+/HER2-low early-stage breast cancers in the FLEX Study: MammaPrint, BluePrint and whole transcriptome analysis. *SABCS* 2023

FLEX Network



- >21,000 participants enrolled
- >100 actively enrolling sites in FLEX Network (US, Canada, Greece, Israel)
- >400 FLEX Investigators

FLEX Working Groups



Accrual & Output

21k >21,000 Participants enrolled	**>4k** Non-white participants enrolled	**3** 2025 Peer-reviewed publications
>4k Participants with 5-year follow-up data	**>3k** Lobular tumors enrolled	**14** FLEX Substudy abstracts accepted (2025)

Conclusions

- FLEX continues to drive innovation in the management, prognostication, and subclassification of early-stage breast cancers, attributed to its enrollment of >21,000 participants of diverse races/ethnicities, tumor histologies, and clinical histories.
- Real-world studies like FLEX include patients more representative of the general EBC population and can answer questions not feasible or ethically answerable in randomized controlled trials[1], including the ability of MammaPrint to predict chemotherapy benefit in genomically high-risk tumors[2].
- Accrual towards the target of 30,000 patients continues, with clinical follow-up of at least 10 years planned.

References: [1]Bar Y *JNCI Cancer Spectrum* 2025, [2]Brufsky AM *JNCI Cancer Spectrum* 2025