FLEX: A Real-World Evidence, Full Transcriptome Study in 30,000 Patients with Early-Stage Breast Cancer

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Background

Subtype-specific treatments, especially hormone and HER2-targeted therapies, have greatly improved survival and quality of life for breast cancer (BC) patients. Over the past decade, genomic signatures have refined BC classification into distinct molecular subtypes, offering insights into metastatic potential beyond traditional clinicopathologic features. Despite these advancements, BC remains the leading cause of cancer death among women, with nearly 15.5% of new cases in the US. This underscores the need for deeper exploration of tumor heterogeneity and genomic signatures, particularly in ER-positive early-stage breast cancer (EBC).

The ongoing **FLEX Study (NCT03053193)** seeks to link full genomic data, including MammaPrint and BluePrint with comprehensive clinical data. This aims to identify new prognostic and predictive gene signatures while enhancing trial enrollment among racial and ethnic minorities to improve health equity and outcomes. The study encourages investigator-initiated sub-studies (IIS) addressing unresolved questions in EBC management over a 5-10 years follow-up.

Methods

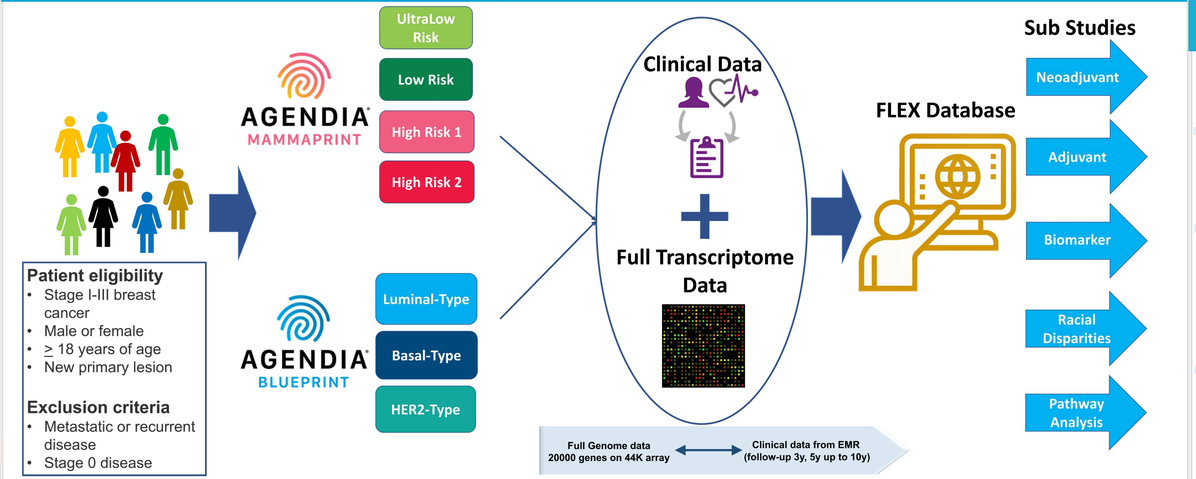
FLEX is a large, multi-center observational trial enrolling patients (male or female) ≥18 years with stage I-III EBC. It includes 95 sites in the US, 2 sites in Canada, 1 site in Greece, and Israel. As of September 2024, FLEX has enrolled ~18,000 EBC patients.

To address racial/ ethnic disparities in clinical trials, a concerted effort has led to the inclusion of 1,377 Black, 530 Latin American (LA)/Hispanic, 353 AAPI, out of 14,330 EBC patients with self-reported race and ethnicity, making FLEX the most diverse study on EBC patients to date.

The trial is currently supporting 42 active IIS and has presented over 45 abstracts internationally (2018-2024), including 11 presentations and 2 poster spot-light sessions that address the underlying differences in tumor biology and disparities in treatment in underrepresented populations.

Overall, as FLEX continues to grow, the study strives to leverage full transcriptome data to enhance precision medicine in EBC. By identifying molecular subtypes and predictive biomarkers, the trial intends to equip clinicians with enhanced tools for tailoring treatment strategies more effectively in EBC. The FLEX trial represents a pioneering effort in integrating genomic data and clinical information on a large scale to improve outcomes and reduce disparities in EBC. Its emphasis on diversity, comprehensive data collection, and collaborative research pursuits places it at the forefront of precision medicine in EBC.

FLEX Schema



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

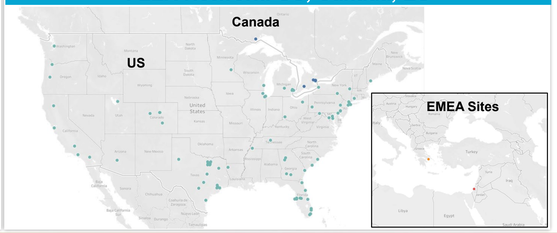
Exclusion criteria
- Metastatic or recurrent disease
- Stage 0 disease

FLEX Highlights

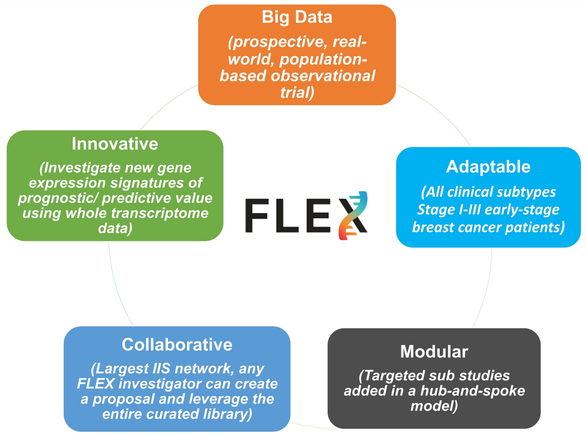
National FLEX PI: Dr. Joyce O'Shaughnessy

- ~18,000 patients now in FLEX, target goal of 30,000 enrolled
- >100 sites in the FLEX Network (US, Canada, Greece, Israel)
- >400 FLEX investigators
- Total: 42 active FLEX sub studies; 4 sub studies approved in 2024
- 45 abstracts (2018-24); ASCO 2023: 4, SABCS 2023: 5, ASCO 2024 4
- 3 FLEX publications, 6 FLEX manuscripts in progress

FLEX Network: US, Canada, EU



FLEX at a Glance



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

Key Areas of Collaborative Research

ER+ Basal Tumors
- 2 ongoing studies (2024)
- 5 presentations

Ethnic Disparities
- 5 active studies
- 10 presentations

CDK4/6i + ET for EBC
- New patient subset
- 1 active study
- Whole genome analysis of patient tumors

HER2 Positive Tumors
- 1 ongoing study (2024)
- Active investigators working group

Lobular Tumors
- 2 active studies
- 2 presentations

Biomarker
- 2 ongoing studies
- 4 presentations

Immune Signature
- 2 ongoing studies
- 2 presentations

Age
- 2 active studies (2024)
- 3 presentations

Investigator Initiated Sub-studies

New Molecular Signatures

- Distribution of MammaPrint, BluePrint, and Response Predictive Subtypes based on ImPrint and Reprint in Lobular tumors – A FLEX sub study. SABCS 2023 # PO4-02-03
- ImPrint immune signature in 10,000 EBC patients from the real-world FLEX database. SABCS 2022 #PD9-08
- Investigation of a genomic signature for transcription factor MAF gene amplification and lack of bisphosphonate benefit in early breast cancer. ASCO 2022

Neoadjuvant Therapy & Surgery

- MammaPrint index predicts neoadjuvant chemosensitivity in patients with HR+HER2- EBC in the real-world evidence FLEX study. SABCS 2023 # PO5-15-04
- MammaPrint Index as a predictive biomarker for neoadjuvant chemotherapy response and outcome in patients with HR+HER2- breast cancer in NBRST. ASCO 2023 # 521
- Identification of transcriptional changes with MammaPrint and BluePrint in EBC after neoadjuvant chemotherapy. ASCO 2022
- Impact of neoadjuvant endocrine therapy on tumor transcriptome in patients with EBC from the FLEX trial. SABCS 2022 #P5-09-02

Cancer Disparities: Biological, Genetic, Socioeconomic

- Impact of race on BluePrint genomic subtyping in HER2+ breast cancer. ASCO 2023 # 564
- 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 # PS 18-04 (Poster spotlight)
- MammaPrint and BluePrint identify racial disparities among women with HR+HER2- EBC. SABCS 2023 # PO1-28-01
- Whole transcriptomic analysis of HR+ breast cancer in Black women classified as basal-type by BluePrint. ASCO 2022

Breast Cancer Subtypes

- Characterization of MammaPrint UltraLow Risk tumors in more than 1400 patients from the real-world evidence FLEX study. SABCS 2023 # PO1-02-11
- Distribution of breast cancer molecular subtypes within receptor classifications: Lessons from the I-SPY2 Trial and FLEX Registry. ASCO 2022
- Defining transcriptomic profiles of early-stage mucinous breast cancers: A FLEX sub study. ASCO 2022

Optimizing Therapy Strategies

- Genomic risk classification and whole transcriptome analysis of HR+/HER2- Postpartum breast cancers - A FLEX sub study. ESMO 2024
- Genomic Landscape of ER positive HER2-low early breast cancers in the FLEX Study: MammaPrint, BluePrint and whole transcriptome analysis. SABCS 2023 # PO4-02-02
- Defining transcriptomic profiles of early-stage Mucinous Breast Cancers – A FLEX sub study. ASCO 2022 # 3134