

Breast Cancer

Genetic Risk

When and what should be tested?

- Upon or before presentation
- Peripheral blood, saliva or buccal mucosa swab

Who should be tested?

- Blood relative with known pathologic/likely pathologic variant in a cancer susceptibility gene
- Individuals meeting criteria but tested negative with a limited panel
- Personal history of breast cancer
 - Diagnosed at 50 years or younger
- Diagnosed at any age with
 - An additional breast cancer primary (at any age)
 - At least 1 close blood relative with breast, ovarian, pancreatic, or high-grade prostate (Gleason 7 or higher) or intraductal prostate cancer at any age
 - Unknown family history
 - Triple negative breast cancer
 - Lobular breast cancer with personal or family history of diffuse gastric cancer
 - At least 1 close blood relative with:
 - Breast cancer diagnosed ≤ 50 yrs.; or
 - Ovarian cancer; Stage 4 prostate cancer, or high or very high-risk prostate cancer; pancreatic cancer; or intraductal prostate cancer
 - ≥ 3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
 - Ashkenazi Jewish ancestry
 - Personal history of ovarian cancer
 - Male breast cancer
 - Any patient with mutation identified on tumor genomic testing that has clinical implications if also identified as germline
 - To aid in systemic therapy decision making
 - An affected or unaffected individual with first- or second-degree relatives meeting any of the above criteria(except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)
 - An affected or unaffected individual who does not otherwise meet criteria but has $>5\%$ probability of a BRCA 1/2 variant based on probability models

→ FDA/NCCN Approved

- Recommend genetic counseling referral and consider testing:
- ATM, BRCA 1/2, BARD1, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53
- Genes typically tested for pancreatic Risk: ATM, BRCA1/2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53
- For individuals who require confirmatory testing for a BRCA1/BRCA2 or other high penetrance pathogenic variant or mutation(s) detected by an FDA-authorized direct-to-consumer (DTC) test report or pathogenic mutation or variant identified on tumor testing (tissue NGS or ctDNA liquid bx)

→ Emerging

- Hereditary germline testing to include gBRCA should be considered for all high risk, early stage, HER-2 negative breast cancer patients

Breast Cancer

Early stage

When and what should be tested?

- At initial work-up
- Post-surgery
- Before adjuvant therapy
- Tissue sample

Who should be tested?

- If patient fit and appropriate for adjuvant chemotherapy
- ER+, HER2-, T1b-T3, N0-N1mi

FDA/NCCN approved

- To determine Adjuvant therapy, multi-gene genomic assay- such as
 - Oncotype Dx – Category 1 NCCN Preferred
 - (for pN0) Category 1 preferred, for pN1 (1-3 positive nodes) Postmenopausal Category 1 Preferred, premenopausal category 2A - other.
 - Mammaprint – Category 1 – Other
 - ProSigna – Category 2A
 - EndoPredict – Category 2A
 - Breast Cancer Index – Category 2A
- MRD

Emerging

- Possible emerging prognostic/predictive role of CTCs, cfDNA etc. AI predictive models
- Stromal disruption

Breast Cancer

Diagnostic testing for initial or recurrent disease - non metastatic

When and what should be tested?

- At initial work-up
- Upon progression if negative/equivocal at initial
- Tissue sample preferred
- Consider re-biopsy of metastases if negative initially

Appropriate Path assessment

- Histopathology
- ER/PR/HER2-
- Margins
- IDC vs ILC vs other
- Grade
- Emerging role of genomic sequencing in advanced stage or at progression

FDA/NCCN approved

- ER/PR expression
- HER2 by IHC for all patients
- PD-L1 in advanced TNBC
- gBRCAm
- PIK3CA/AKT1/PTEN
- ESR1
- MRD

Emerging

- sHRR
- HRD
- sBRCA 1/2

Breast Cancer

Stage IV – Metastatic - (recurrent or de novo)

When and what should be tested?

- At initial metastatic diagnosis – tissue sample preferred
 - TNBC
 - At presentation of MBC or at progression on first line therapy in ER+ or HER2+, or at presentation with advanced disease
 - The distinction between HER2 IHC 0 with no membrane staining from IHC 0+ with faint, partial membrane staining in ≤10%, 1+, or 2+/ISH negative results (on primary or metastatic samples) is currently clinically relevant since patients with metastatic disease may be eligible for treatment targeting non-amplified levels of HER2 expression.
- Consider re-biopsy of metastases if negative initially

Who should be tested?

- Treatment eligible
- Consider in all advanced stage patients at presentation
- Repeat serial/longitudinal testing with tissue or liquid at progression to assess for resistance mechanisms, mutational evolution, and/or clonal evolution/selection
- If NGS done on primary tumor, consider potential value of tissue NGS from metastatic site or liquid ctDNA

FDA/NCCN approved

- Germline mutation testing if not done prior
- BRCA if a history of relapsed/refractory HER2 negative, MBC previously treated with chemotherapy and is a candidate for PARP inhibitor therapy
- Somatic mutation analysis by NGS, at minimum should include assessment of TMB/MSI, PIK3CA
- Panel should include tumor agnostic actionable genomic variants (NTRK 1/2/3 fusions by NGS DNA + RNA, MSI, dMMR, TMB, RET fusion, BRAF V600E, germline PALB2)
- PDL-1 for mTNBC
- For all recurrent MBCs that are HR positive and HER2 negative
 - PIK3CA/AKT1/PTEN
 - ESR1
 - MRD

Emerging

- Emerging role of sBRCA, other HRR mutations, and HRD, HER2 activating mutations, germline PALB2, FGFR1-3 fusion/ mutation
- EphA5 in TNBC