Genetics in Breast Cancer

Screening guidelines and Risk Reducing Strategies

→ Hereditary Breast cancers 5–10% of all Breast CA

Common germ line mutations leading to BC

Gene	Location	Tumours	Risk breast cancer (%)	Incidence	
BRCA1	17q	Breast, ovary	60-90	1 in 1000	High Penetrance
BRCA2	13q	Breast, ovary, prostate, pancreas	40-60	1 in 800	
TP53 (Li-Fraumeni)	17p	Breast, sarcoma, glioma	95	1 in 30,000	
PTEN (Cowden)	10q	Breast, thyroid, endometrial, colorectal	60	1 in 200,000	intermediate
STK11 (Peutz-Jeghers)	19p	Breast, gastrointestinal	40	1 in 25,000	
CDH1 (E-cadherin)	16q	Breast, gastric	20-40	Rare	low

TNBC
Similar to sporadic CA
Her-2 +ve

BRCA 1 & 2 → Autosomal dominant
- variable penetrance.
- life time risk of Breast cancer 26-85%
- lifetime risk of ovarian cancer
  BRCA-1 - 16-63%
  BRCA-2 - 10-27%

* ♀ from high risk family

| (2 breast cancer < 50 years |
| > 2 breast cancer @ any age)

↓

10.1. BRCA Negative

may be positive in larger gene panel mutation testing

↓

4 x increased risk of breast cancer.

But ♀ from BRCA +ve family is tested Negative for mutation → No risk of CA Breast

→ Hereditary vs familial

↓ Known specific genetic mutation

↓ "unnatural cluster of cancer patients without known specific genetic mutation"

TABLE 53.1

Guidance for Hereditary Genetic Panel Testing in Women with Breast Cancer

1. Patients with family members with known deleterious mutations in *BRCA1/2*, *PALB2*, *CHEK2*, *ATM*, or other genes associated with hereditary breast cancer
2. Patients with early-onset breast cancer (usually age <50 y)
3. Patients with triple-negative breast cancer (up to age 65 y)
4. Patients with personal history of second breast cancer, or ovarian cancer, or male breast cancer
5. Patients with one or more first-degree relatives with breast cancer, ovarian cancer, or male breast cancer
6. Patients with multiple family members with cancers that may be associated with hereditary breast cancer syndromes including pancreatic, prostate, colorectal, or uterine cancers, or cancers associated with Li-Fraumeni syndrome
7. Patients who are potential candidates for adjuvant PARP inhibitor therapy (see the following text)
8. Patients with metastatic breast cancer

→ High risk individual

↓

Risk assessment through scores

1. Gail model — Based on:
   - Age at menarche
   - Age at 1st child birth
   - No. of previous Breast Bx
   - H/o 1st degree relatives c Breast cancer
   - +/- of Atypical hyperplasia
2. Claus model
3. BRCA Pro
4. Tyrer Cuzik — Best currently

↓

Lifetime risk > 20% significant

Intensive surveillance

- Monthly SBE
- Yearly CBE
- Yearly
  - Mammo — for risk < 15%
  - MRI — for risk > 20%
  - 15% - 20% No consensus

Chemoprevention

Premenopausal → Tamoxifen 20mg PO × (5) years

Red risk by 49%

Post menopausal → Tamoxifen / AI

Exemestane 25mg OD 3rd

risk by 65%

Retrospective Data only for both

Prophylatic Surgeries

- B/L mastectomy c reconstruction
  - 90-95% risk reduction
  - BSO in pre menopausal women

BRCA and Breast cancer

→ PARP inhibitors in BRCA positive – olaparib

OLYMPIA trial.

OLAPRIB – Mechanism of action

Germline BRCA 1/2 mutated cells

↓

Rely on PARP (Poly ADP ribose polymerase) enzyme for DNA repair

olaparib (–) → ↓

Accumulation of defective DNA → Apoptosis

OLYMPIA trial

BRCA 1/2 +ve | HER 2 –ve

TNBC or ER +ve | metastic disease – OLYMPIAD trial

6 months of NACT / ACT

↓ ↓

Olaparib 300mg BD × 1 year

Placebo

↓

Improved 3yr DFS (87.1% vs 80.1%)

→ Surgical options in BRCA positive patients :

* Non metastatic CA Breast → OS and Local recurrence are same in BCS / mastectomy in BRCA 1/2 positive compared to general population.

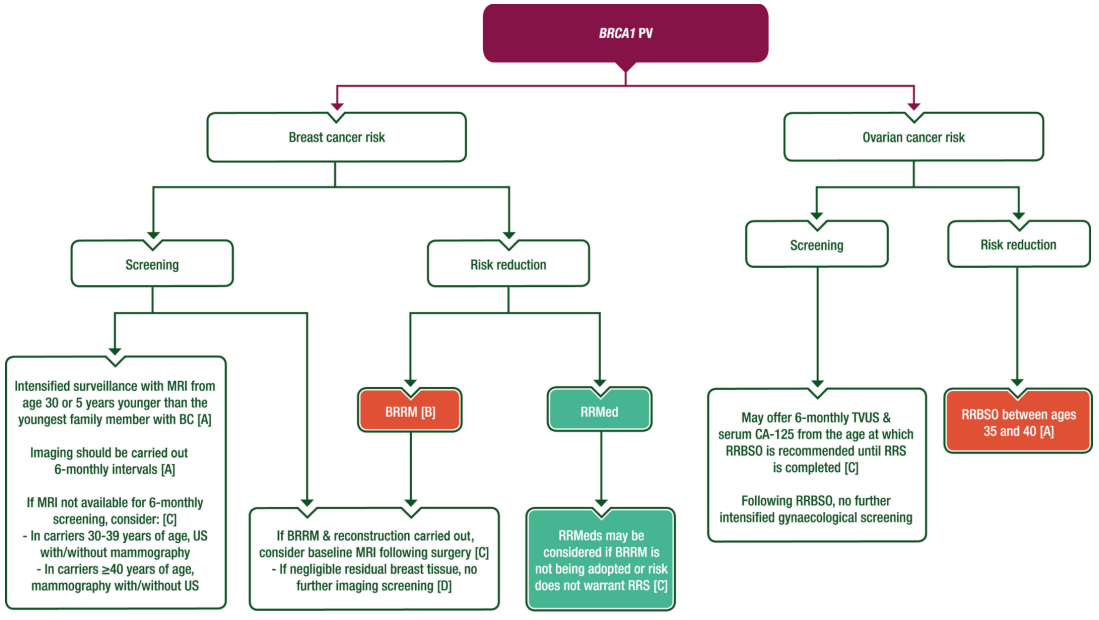
* Factors to be considered for prophylactic risk reducing contralateral mastectomy: (CRRM)

  . Mutations in high Penetrance genes
    - BRCA 1/2
    - p53
    → strongly advice CRRM. Reduces risk by 90%.
  . Age at diagnosis (Strongest predictor of future C/L breast cancer)
  . Family H/O Breast CA
  . Ability of pt. to undergo MRI surveillance
  . Co-morbidities
  . Life expectance > 10 years.

Genes with moderate / low penetrance → No data except for CHEK 1100 del gene for CRRM.

* Patients ~ BRCA 1/2 positive
  - Can undergo BCS
  - Can undergo post op RT
  - Can undergo Nipple sparing CRRM.
  - Platinum (Carboplatin) better than taxanes (Docetaxel) chemotherapy.
  - PARP inhibitors should be offered to metastatic BRCA 1/2 positive in 1st line (OLYMPIAD trial) to 3rd line (EMBRACE trial)
  - Adjuvant PARP inhibitors in non metastatic BRCA 1/2 → OLYMPIA trial
  - Neoadjuvant PAPP inhibition ~ Talazoparib in BRCA mutated TNBC → ongoing trials.

→ Individuals ī BRCA1/2 germline mutation without current Breast/ ovarian cancers:



→ Fertility issues in BRCA 1/2 carriers:

- Complete family before RRBSO, or oocyte/ovarian preservation.
- Counselled about Prenatal diagnosis and Pre implantation Genetic testing to prevent passing on defective gene to next generation.

Screening Recommendations

