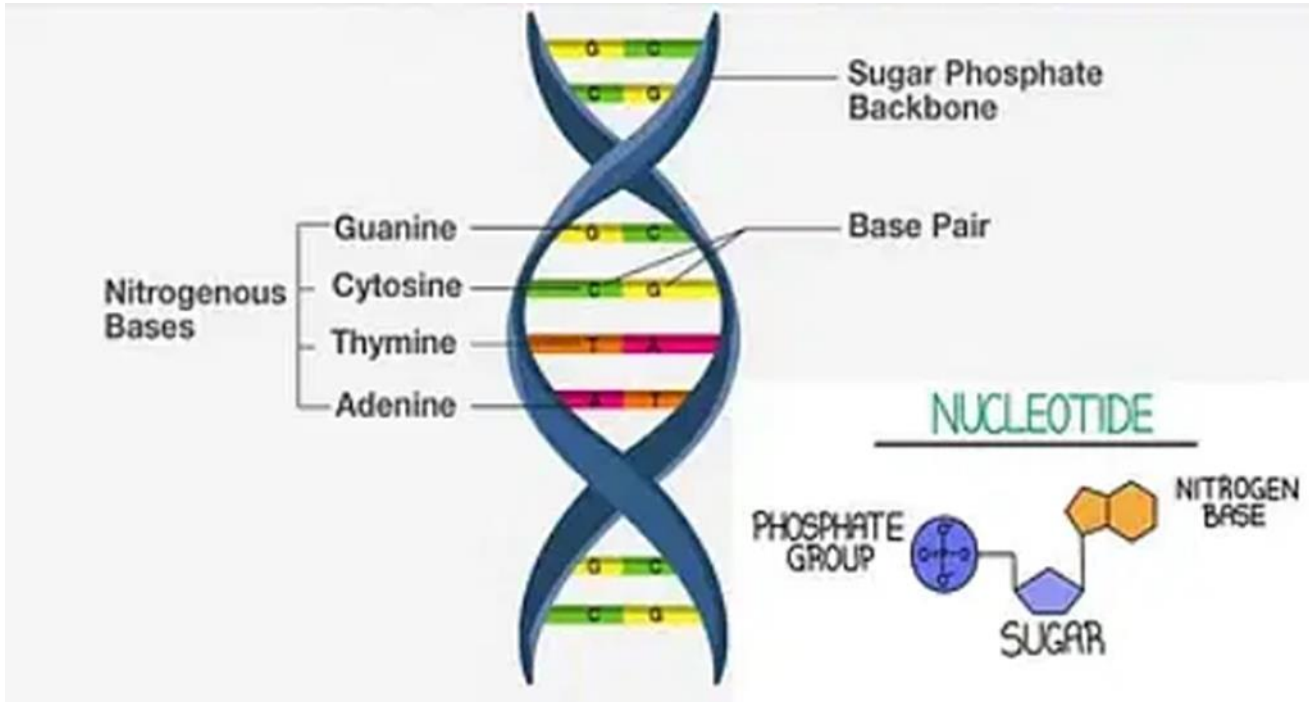
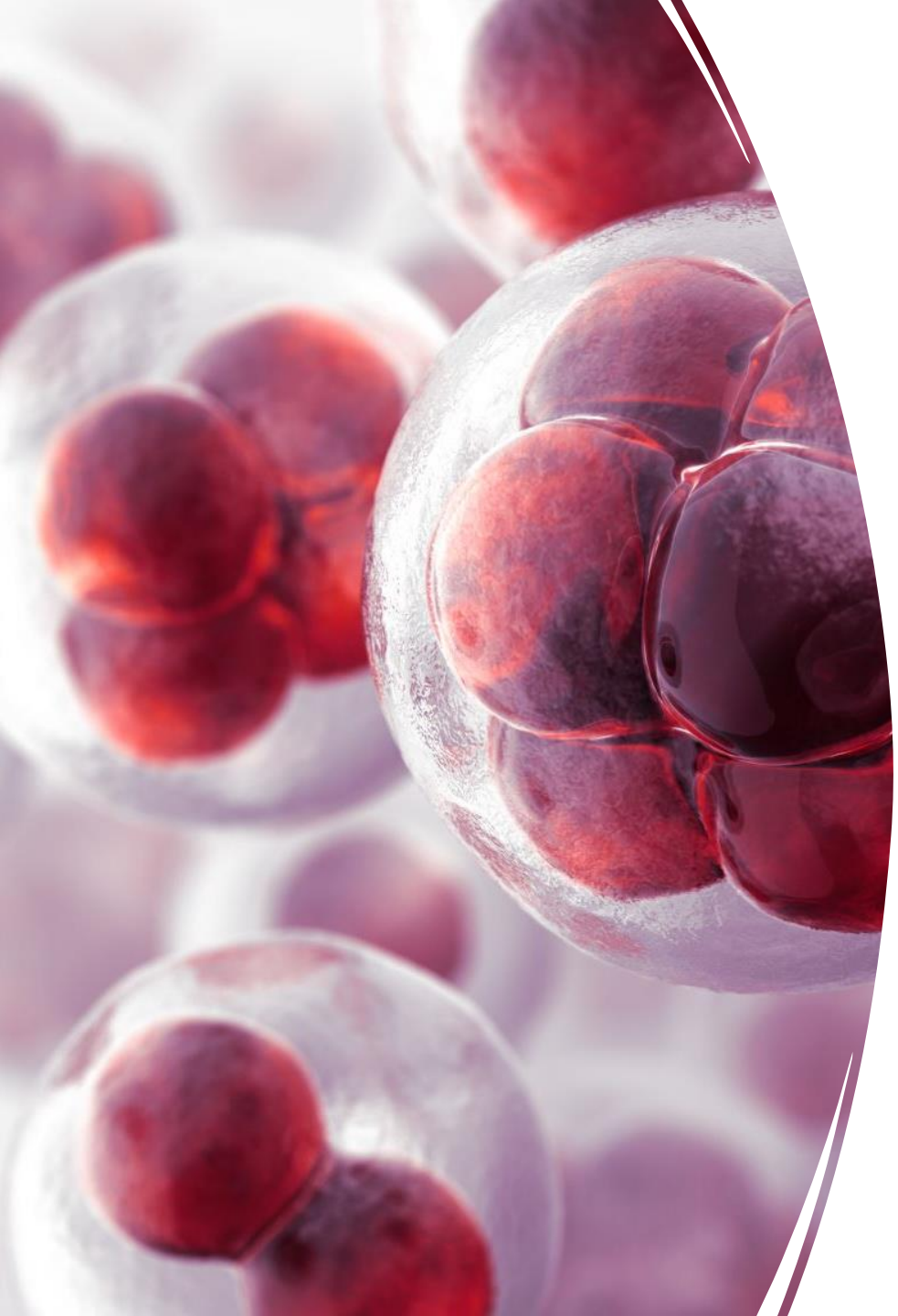
Hereditary Breast Cancers

Iram Khan


Sugar Phosphate Backbone
Base Pair
Guanine
Cytosine
Thymine
Adenine
Nitrogenous Bases
NUCLEOTIDE
PHOSPHATE GROUP
NITROGEN BASE
SUGAR



MECHANISMS OF ONCOGENESIS

- Insults DNA- Cell escapes the controlled processes of cell proliferation acquire new capabilities to permit unregulated cell division sustain tumour growth and to acquire metastatic potential

- Pro-oncogenes

- Tumor suppressor genes: checkpoints, apoptosis & DNA repair. Act recessively

MUTATIONS

This is an irreversible alteration to the DNA sequence

Can be:

- Point mutation
- Non-Synonymous: if it leads to a change in amino acid. Can be sense, nonsense or missense.
- Frameshift
- Copy number variations CNV/ chromosomal rearrangement

Mutations can be

- Constitutional/germline- in gametes…….Inherited Ca
- Somatic- post fertilization…….luckily the commonest form

Somatic Mutations:

Can be

- Driver

- Passenger…….once challenged by CT- Tumour recurrence.

- Fig 5.2

-A variant is change in DNA sequence which is different than accepted DNA sequence
-American college of medical genomics:

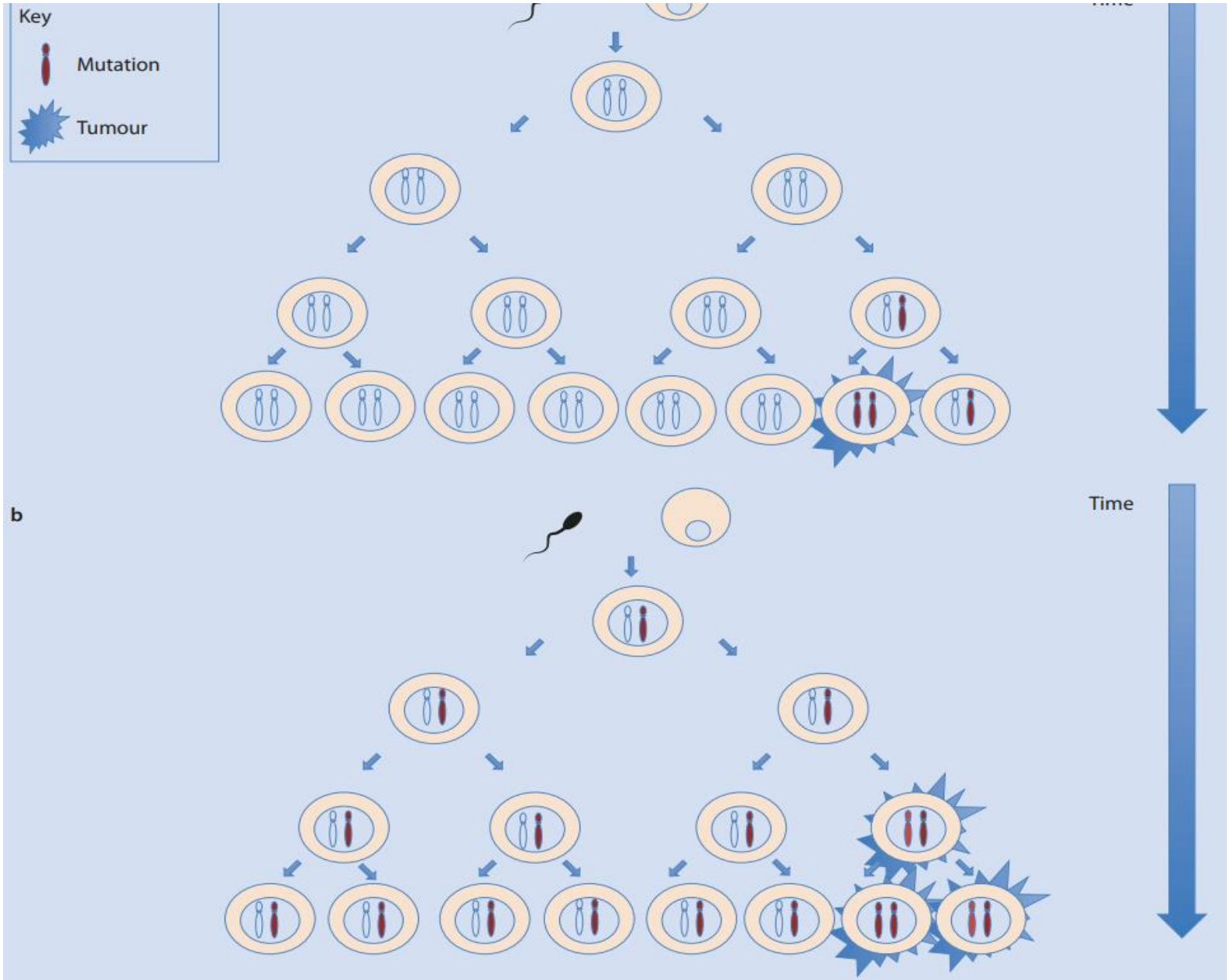
1. Pathogenic
2. Likely pathogenic
3. Uncertain significance
4. Likely benign
5. Benign

HEREDITARY BREAST CANCER SUSCEPTIBILITY

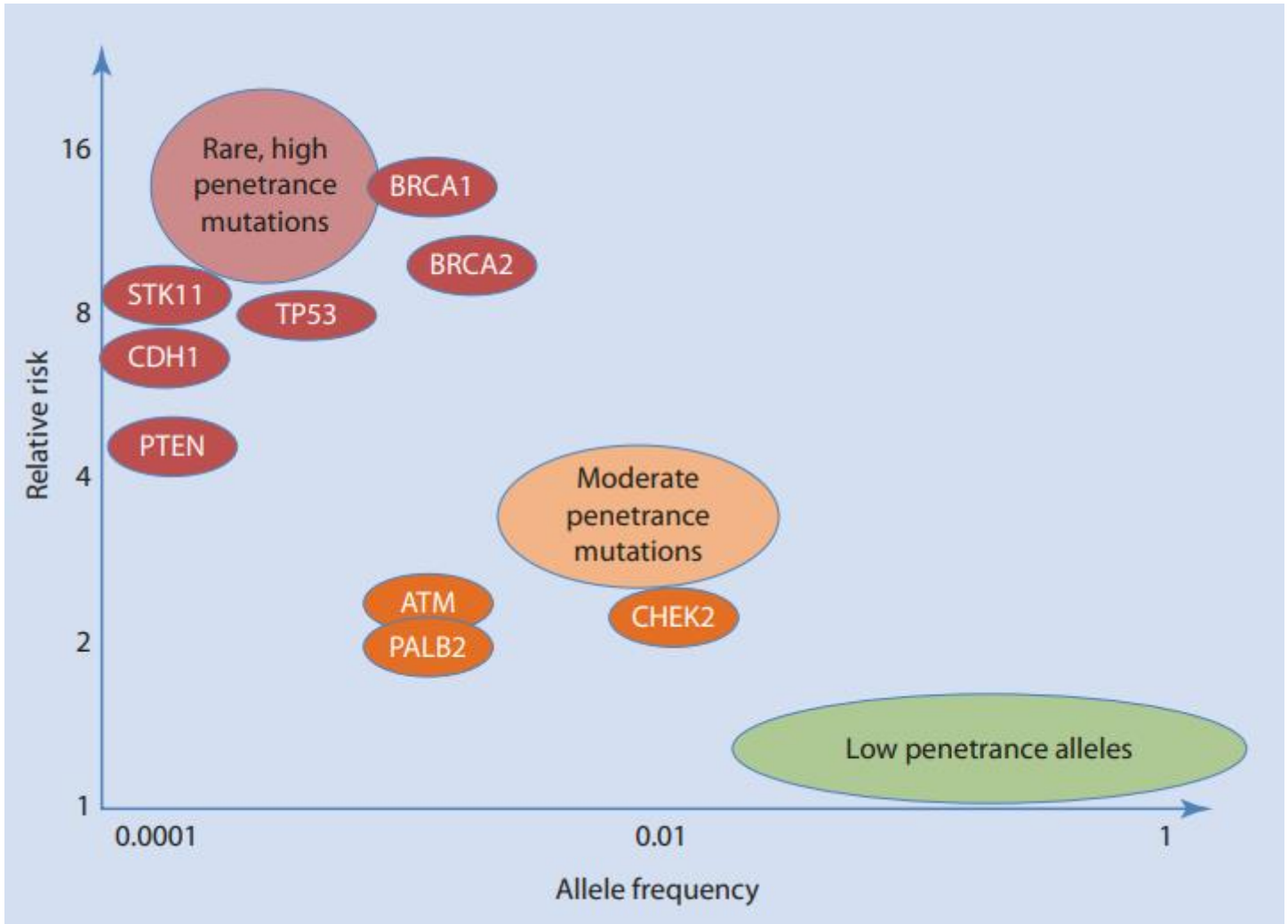
- High-penetrance genes- fourfold increased risk (NICE guidelines- >30% lifetime breast cancer risk)

- Moderate penetrance genes cause a two-to fourfold increased risk

(NICE guideline- 17-29% risk)


Key
Mutation
Tumour
b
Time

Gene	Syndrome	Population frequency	Breast cancer risk		Median age	Special tumour type	Other features
BRCA1 and BRCA2	Hereditary breast and ovarian cancer	1/400 to 1/800	High	BRCA1 60% by age 70 (95% CI 44–75%) BRCA2 55% by age 70 (95% CI 41–70%)	BRCA1 42 years BRCA2 45 years	BRCA1 triple-negative, basal tumours	Ovarian cancer Pancreatic cancer Prostate cancer (males)
TP53	Li-Fraumeni syndrome	1/5000 to 1/20,000	High	[a]	33 years	Often HER2 positive	Sarcoma Brain tumours Adrenocortical carcinomas May have multiple primaries
STK11	Peutz-Jeghers syndrome	1/155,000	High	45% by age 70 (95% CI 27–68%)	44 years		Mucocutaneous pigmentation Hamartomatous polyps Increased risk of GI, ovarian, pancreatic cancer and adenoma malignum of uterine cervix Gonadal tumours
PTEN	Cowden syndrome	1/200,000	High	77% by age 70 (95% CI 59–91%)	42 years	Increased incidence of benign breast disease	Macrocephaly Learning difficulties Thyroid cancer Endometrial cancer Gastrointestinal cancer Renal cell cancer
CDH1	Hereditary diffuse gastric cancer	Unknown	High	39% by age 80 (95% CI 12–84%)	53 years	Invasive lobular breast cancer	Gastric cancer


Rare, high penetrance mutations
BRCA1
BRCA2
STK11
TP53
CDH1
PTEN
Moderate penetrance mutations
ATM
PALB2
CHEK2
Low penetrance alleles
16
8
4
2
1
Relative risk
0.0001
0.01
1
Allele frequency

BRCA 1 and 2

These are DNA repair genes

- Commoner in Ashkenazi Jews- 1 in 40
- EMBRACE trial- median age of Dx is 42 and 45
- Her 2 enriched and oestnogen rich tumoun
- Dx by mammogram and MRE

P53

- TSG. Lf syndrome causing breast, brain, sarcomas, ACC tumors

- Lifetime risk of ca=100% in females and 73% in males.
- Ca breast : premenopausal; HER 2 enriched and 31% develope contra lateral breast ca.
- 30 % tumors develope secondary to radiation within 10 years.

CDH1

- Codes for E.Cadherin, required for cell to cell adhesion.
- Mutation causes GIST and lobular breast ca

- Risk of 39% by 80 years

STK11

-TSG, mutation causes peutz jeghers syndrome

-PJ associated with harmatomas polyps, breast ca, GIT tumors, pancreatic, gynae and gonadal tumors

-Average risk of breast ca= 44 yrs and lifetime risk of 32-54%

Risk assessment tools

- Gail
- Manchester scoring system
- Claus
- IBIS
- BRCAPro
- BOADICEA

Manchester Scoring System MSS

- Calculates probability of BRCA 1 and 2 mutation (MSS of more than 15%)

Uses pts family hx
simple and easy usage

- Gail

.Uses pts hx, hx of breast disorders and reproductive hx to assess pts risk of getting cancer
.modified Gail model
.Chemoprevention

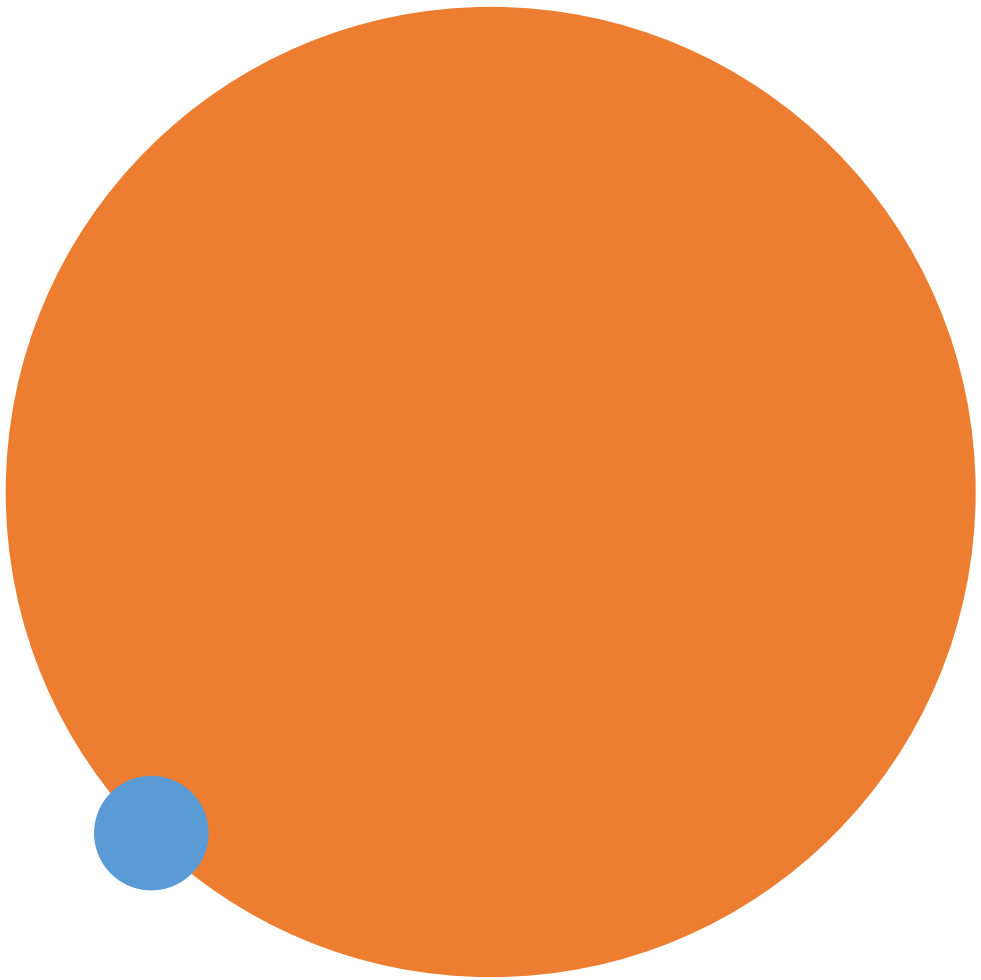
Claus

.Incorporates family hx for past few generations both paternal and maternal

· Includes ovarian ca hx in family

dataset restricted to whites and North Americans

.doesn’t include possibility of other genetic mutations.



IBIS

- Takes into account family hx of breast and other familial tumors includes reproductive hx , hx of hormonal exposures and pts BMI.

- Takes into accounts the Ashkenazi Jewish ancestry, male breast ca and other breast diseases such as atypical and carcinoma in situ

- Predicts lifetime risk of breast ca and risk of gene carriage

BOADICEA

Includes fx hx of breast and ovarian ca

Takes into account hx of other genetic mutations apart from BRCA1 & 2

includes hx of bilateral breast ca, male and ovarian breast ca

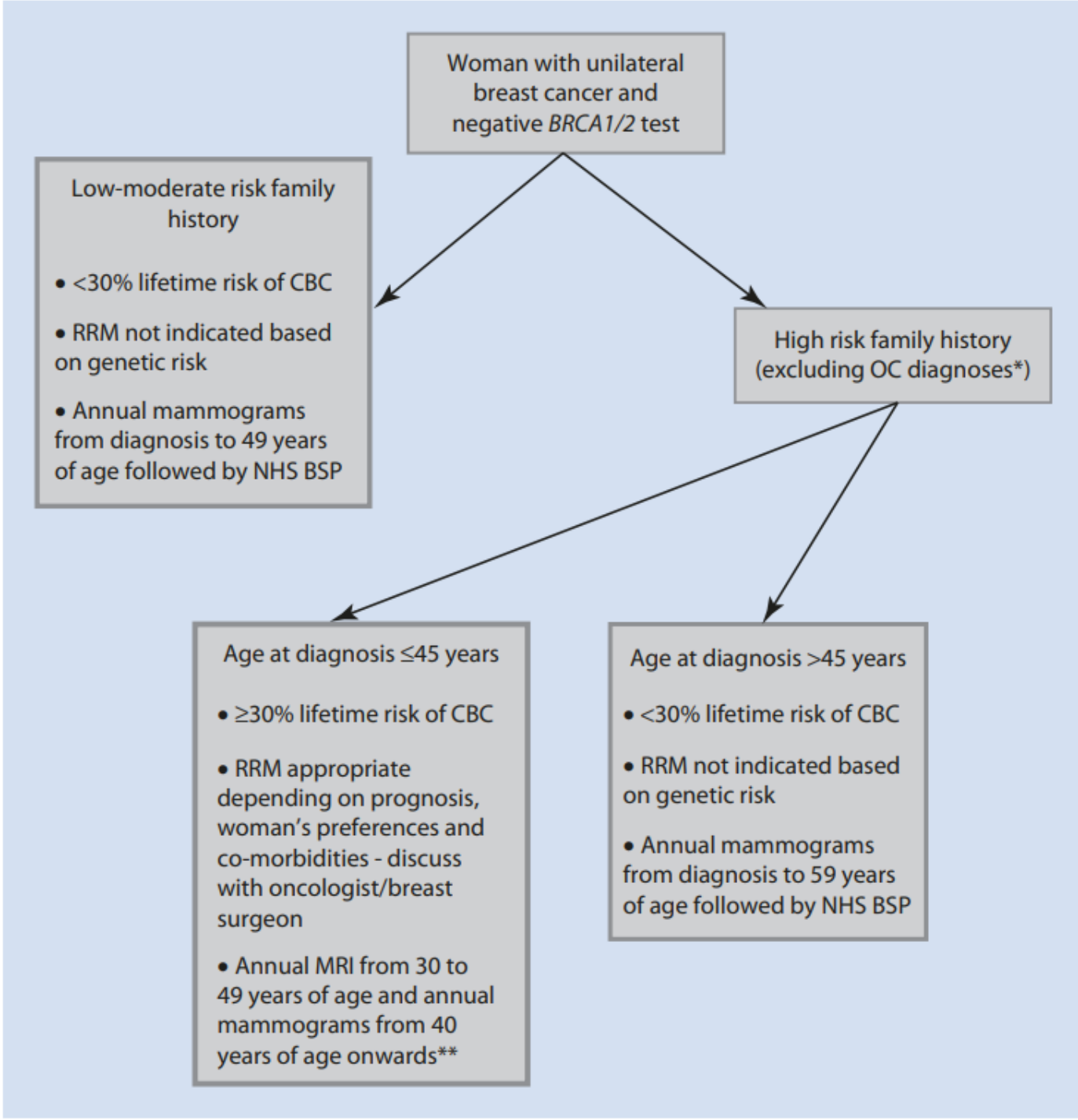
Gene sequensing

- Can be

-Diagnostic

-Predictive

.Pretest Counselling esp for VUS genes


Woman with unilateral breast cancer and negative *BRCA1/2* test
Low-moderate risk family history
• <30% lifetime risk of CBC
• RRM not indicated based on genetic risk
• Annual mammograms from diagnosis to 49 years of age followed by NHS BSP
High risk family history (excluding OC diagnoses*)
Age at diagnosis ≤45 years
• ≥30% lifetime risk of CBC
• RRM appropriate depending on prognosis, woman's preferences and co-morbidities - discuss with oncologist/breast surgeon
• Annual MRI from 30 to 49 years of age and annual mammograms from 40 years of age onwards**
Age at diagnosis >45 years
• <30% lifetime risk of CBC
• RRM not indicated based on genetic risk
• Annual mammograms from diagnosis to 59 years of age followed by NHS BSP