Inherited Predisposition For Breast Cancer In Diverse Hereditary Cancer Syndromes

Strategies For Syndrome Specific Genetic Testing & Risk Management.

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Inherited predisposition to Breast Cancer

Diverse manifestations and diverse genetic basis

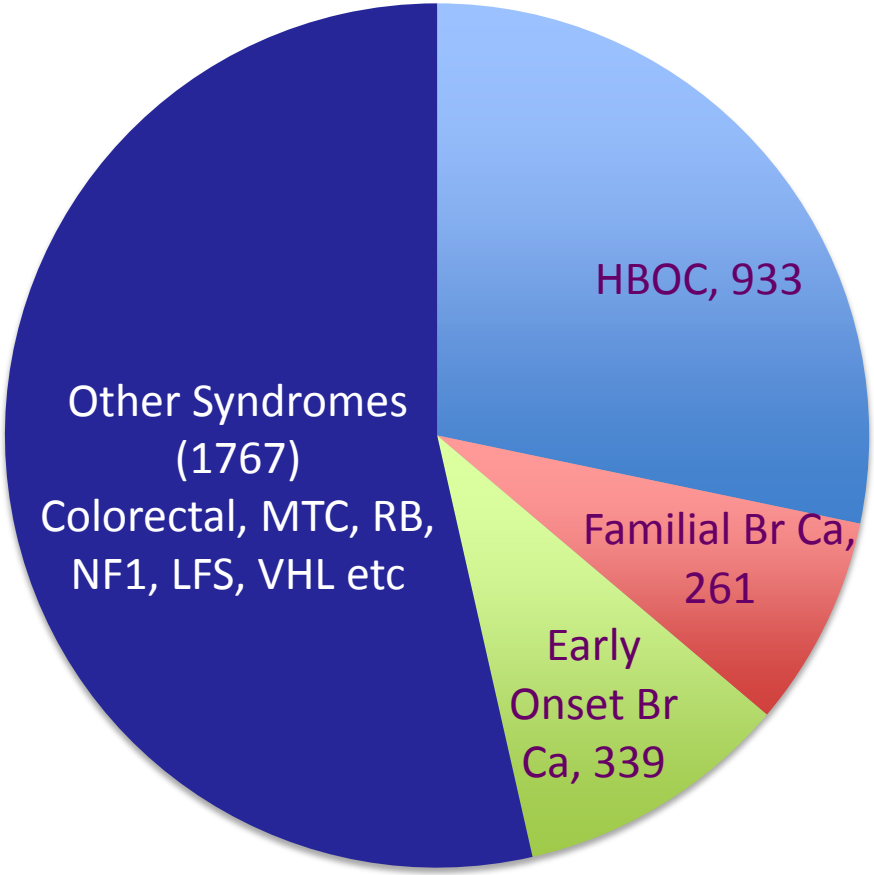
- Hereditary Breast Ovarian Cancer (BRCA1/2) is the most common syndrome
- Several other diverse syndromes associated with breast cancer predisposition
  - Li-Fraumeni (TP53)
  - Peutz Jeghers Syndrome (STK11)
  - Cowden's syndrome (PTEN)
  - Lynch Syndrome (MMR genes)
  - Other rare syndromes
- Accurate identification of the syndrome aids genetic counselling, testing and risk management

TMC cohort of 3700 families with Inherited Cancer Predisposition (2003-16)

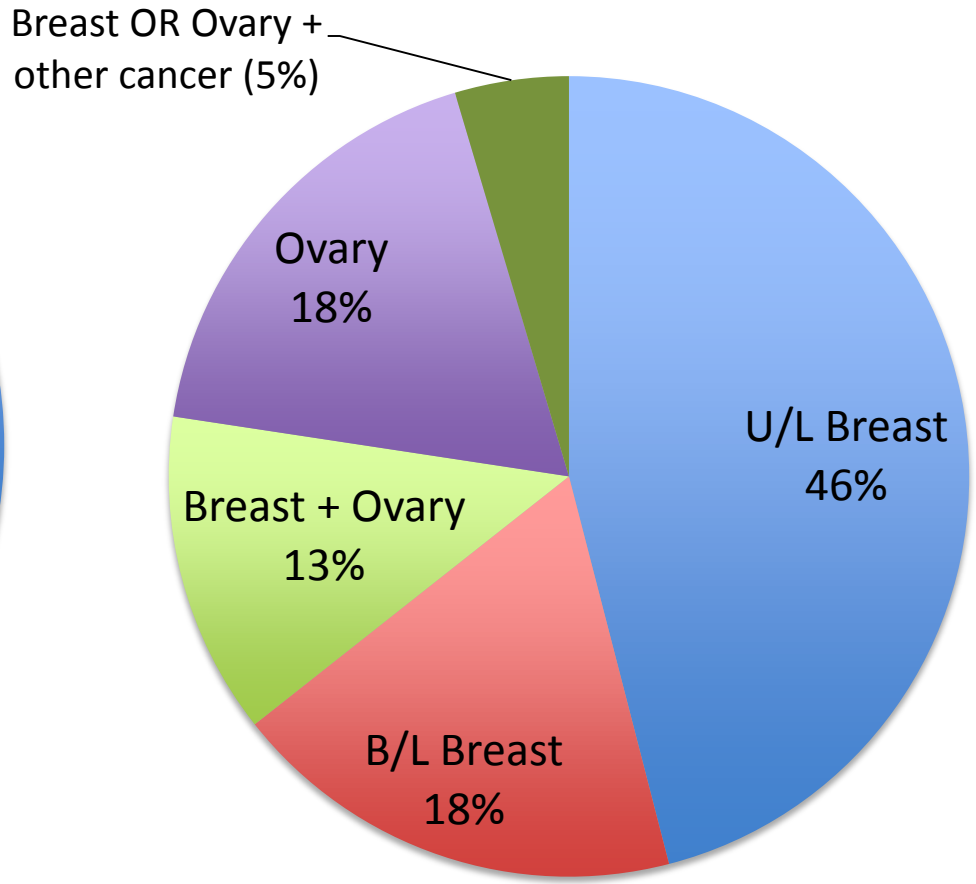
Hereditary Breast Ovarian Cancer Syndrome/ Familial Breast Ca	1012
Hereditary Non-Polyposis Cancer Syndrome	242
Familial Adenomatous Polyposis	66
Li-Fraumeni/Li-Fraumeni Like Syndrome	261
Familial cancers (not fitting in to a specific syndrome)	152
Multiple Endocrine Neoplasia	59
Neurofibromatosis Type 1 / 2	58
Oculo Cutaneous Albinism Type 1 / 2	07
Xeroderma Pigmentosum	31
Tuberous Scelorosis	06
Retinoblastoma	39
VHL	30
Others syndromes: Cowden, PJS, Gorlin's, RCC, Paraganglioma etc	60

Breast cancer in Proband / Relatives seen in HBOC and several other syndromes

HBOC/FBC/ Early Onset Breast Ca is the most common syndrome in 3300 families registered (2003-15)



In 261 BRCA1/2 carriers with cancer Uni / Bilateral Breast Cancer in 2/3rd Ovarian +/- Breast cancer in 1/3rd



High Throughput Cost Effective Strategy to detect maximum number of germline mutations in a common hereditary cancer like HBOC

BRCA1/2 full gene sequencing (Sanger / NGS) + MLPA in 125 HBOC cases with high mutation probability (BOADECIA)

VUS (Splice Site & Missense)

Co-Segregation, In-Silico &

Structure Function studies

<u>Specific Mutation identified in > 1 unrelated family, tested in</u>

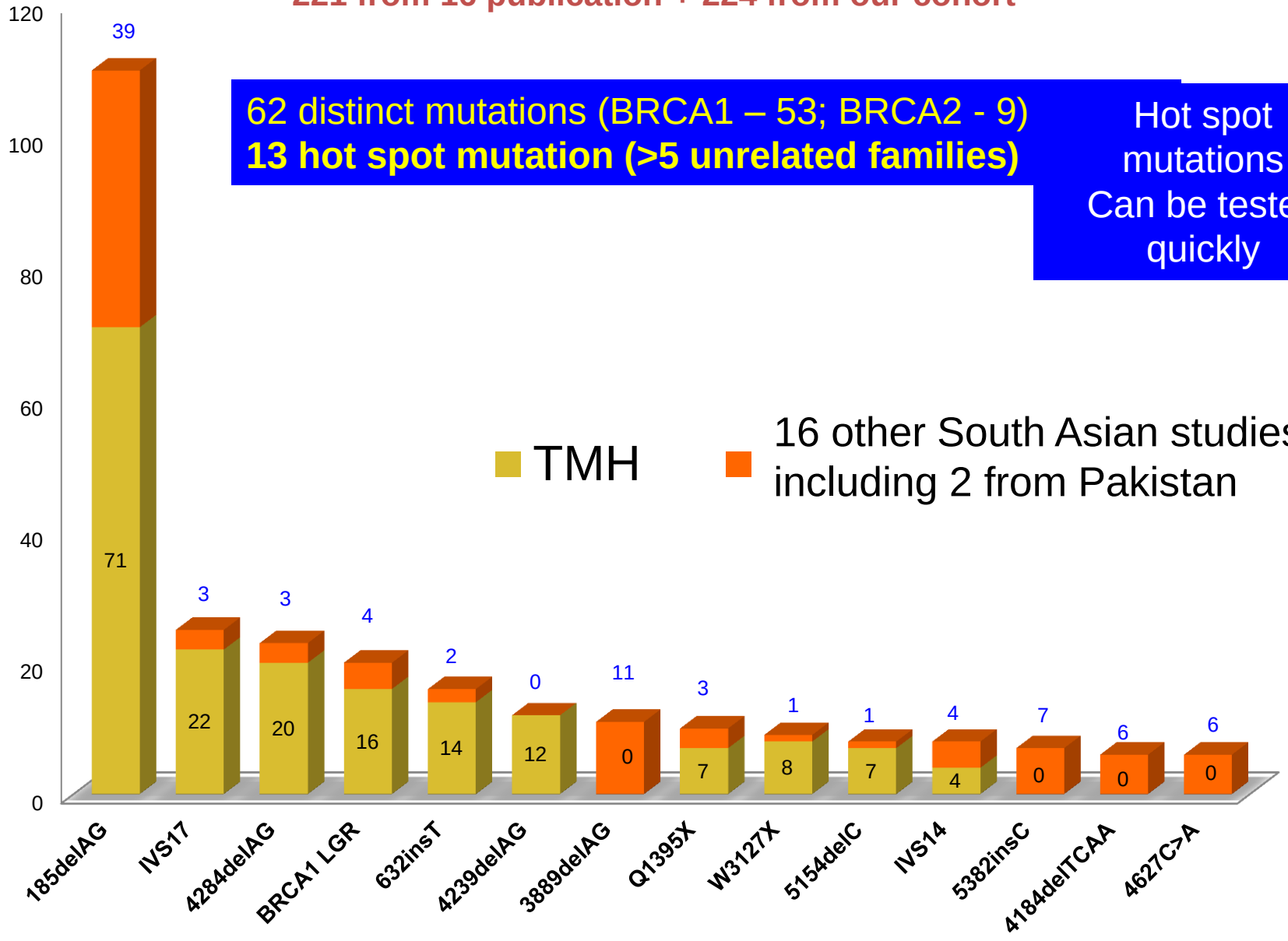
1) All 700 HBOC cases (or specific communities)

2) Founder effect confirmed by haplotyping

3) Founder / Recurrent mutations tested in early onset sporadic cases of same region / community

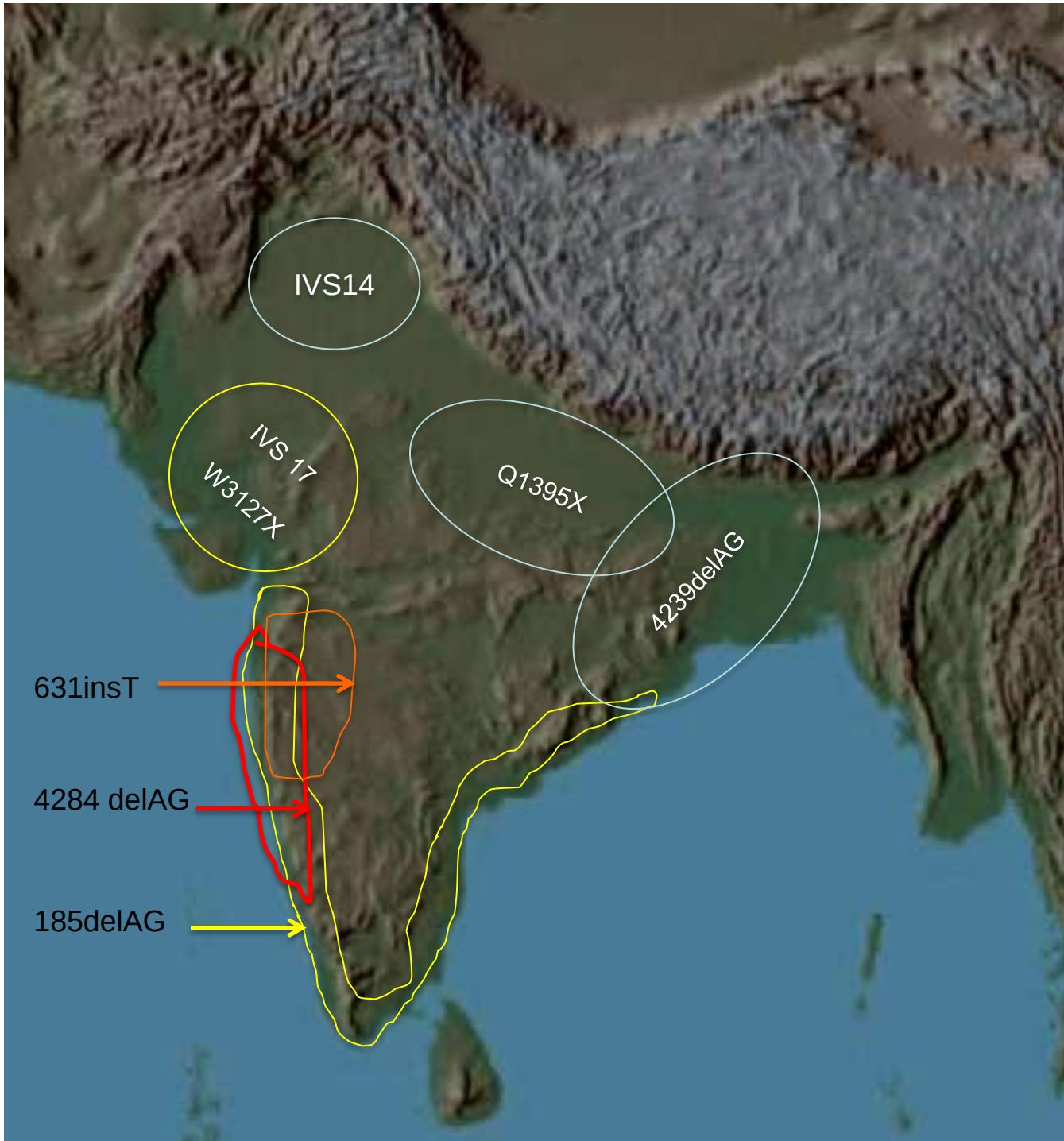
445 South Asians families with BRCA1/2 mutations Reported from anywhere including Indians, Pakistanis in subcontinent or outside (

221 from 16 publication + 224 from our cohort



Unrelated carriers of Specific BRCA 1/2 mutations usually are from a region and community.

Founder effect of recurrent mutations confirmed by Haplotyping analysis

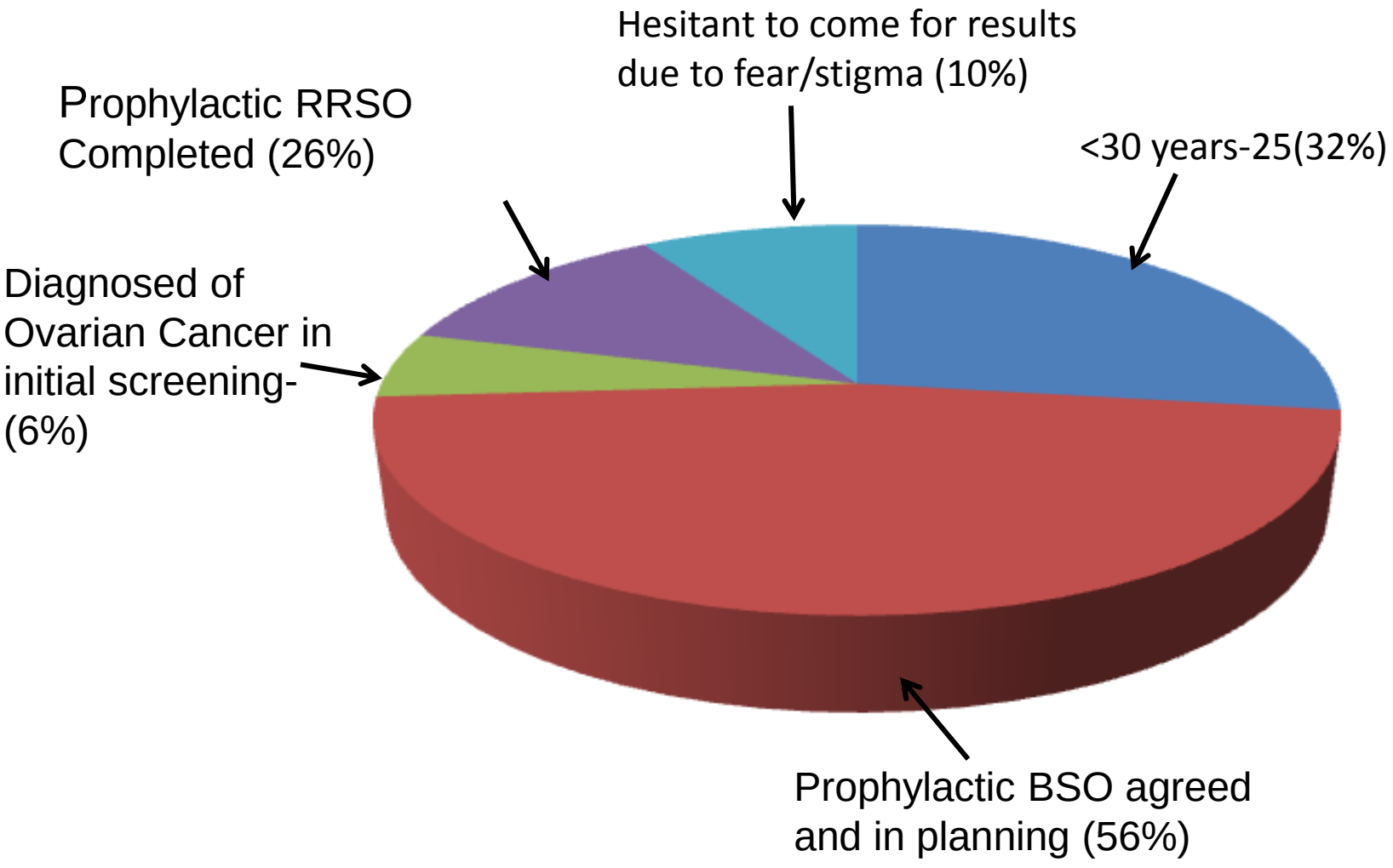


High Uptake of Risk Reducing Salpingo-Oopherectomy (RRSO) in BRCA1 mutation +ve Healthy Women (n=77)

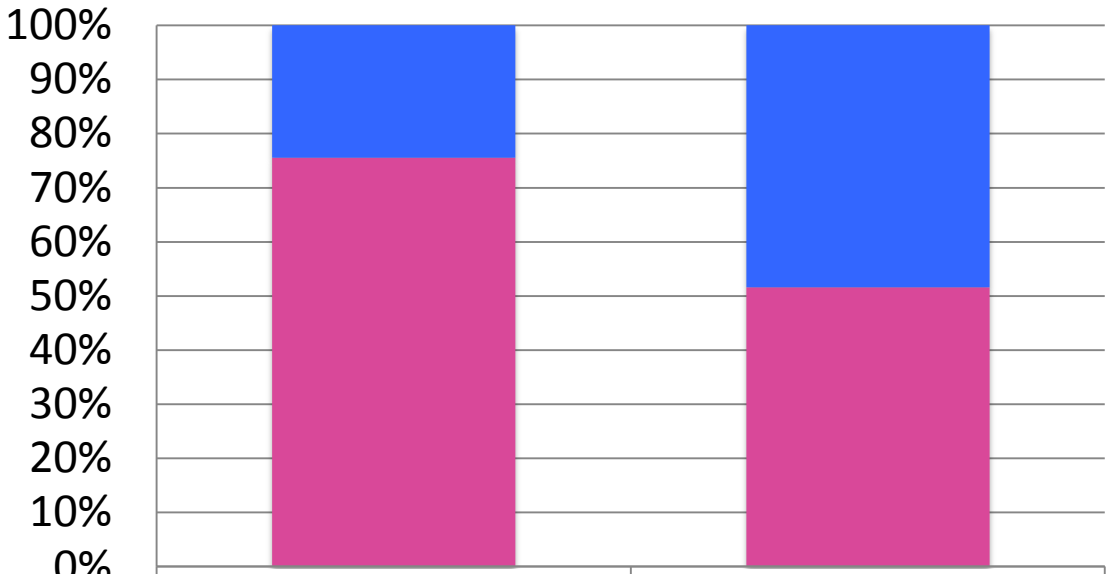
RRSO not advised due to age (<30) to 25 women

Post Test Counselling due in 9 women

RRSO Advised to 43 women



Breast Cancer in Li-Fraumeni Syndrome or 'Li-Fraumeni Like' families (n=223) with or without Germline TP53 mutation



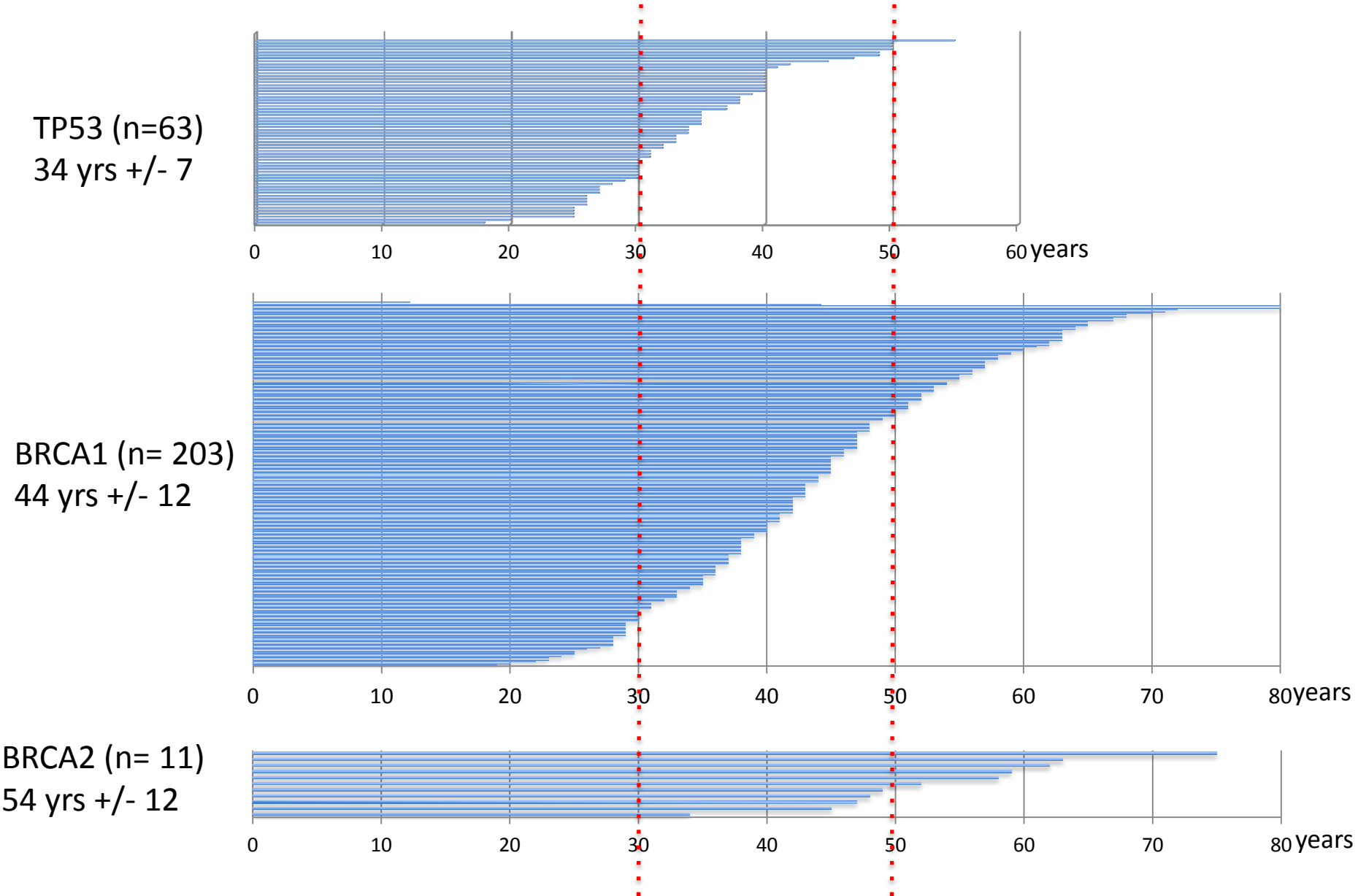
	TP53 +ve	TP53 -ve
No Breast Ca	11	90
Breast Ca *	34	96

P<0.03

*8 TP53 +ve families had 4 breast cancer cases & did not fulfill criteria for LFS/LFL

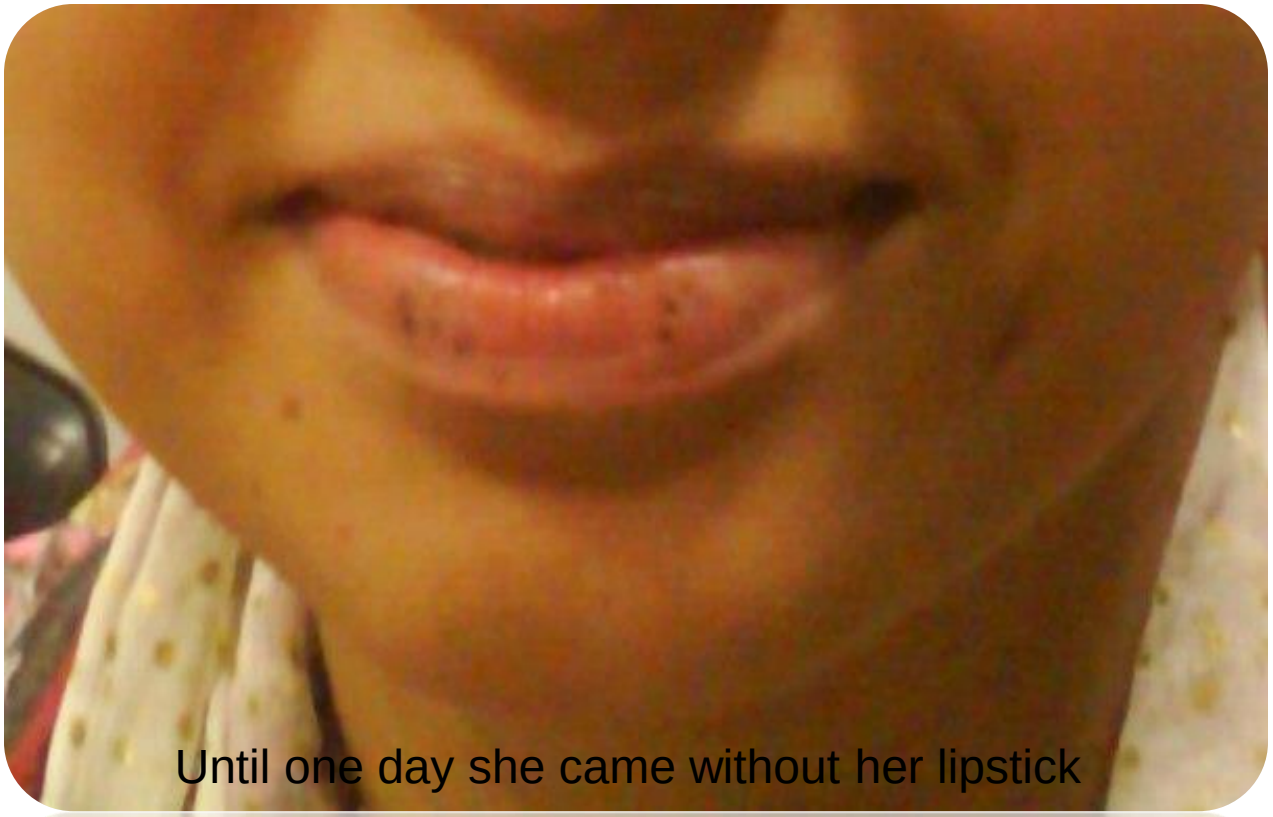
*Unlike TNBC of BRCA1 carriers, majority of TP53 mutation carriers have ER / PR +ve Breast Ca

Age at Breast Cancer diagnosis
TP53, BRCA1 & BRCA2 mutation carriers



Very Early onset bilateral breast cancer in a University Student with no family history of cancer and no Syndromic features

Missed diagnosis of Peutz Jegher's Syndrome

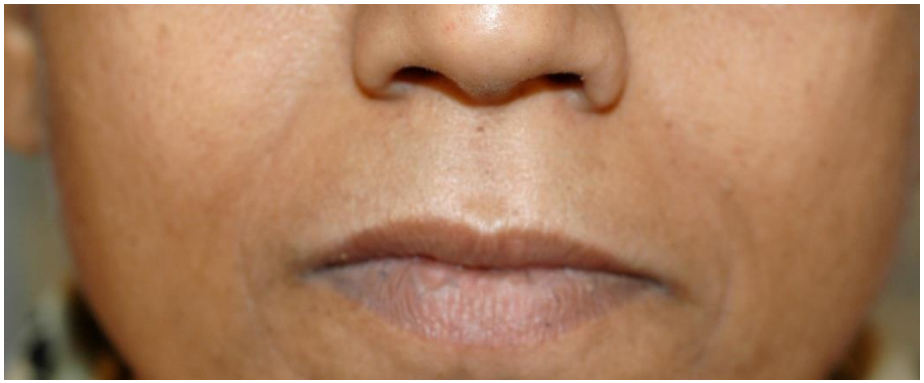


Until one day she came without her lipstick

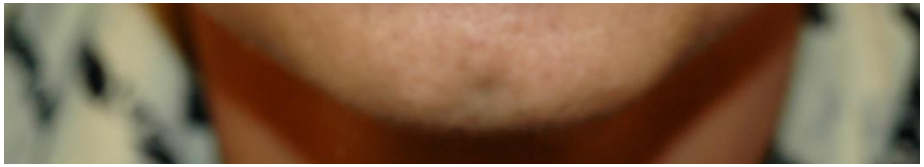
And her mother & uncle later developed stomach / bowel cancer

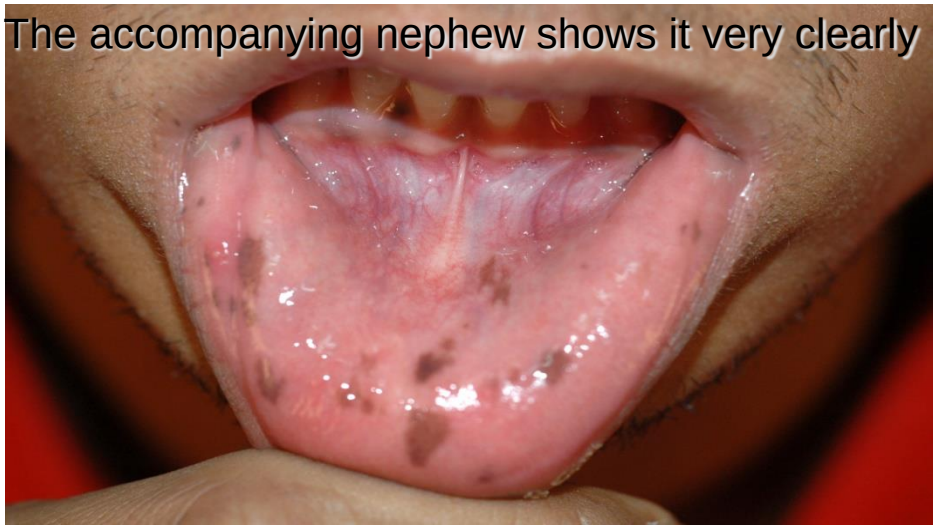
STK 11 (Serine Threonine Kinase) gene: Tumour suppressor function by acting on other kinases, maintains cell polarity & inhibits abnormal cell growth

Early onset bilateral breast cancer in a lady with no family history of cancer and no Syndromic features



A missed diagnosis of Peutz Jegher Syndrome





Several family members underwent abdominal surgery in childhood for acute abdomen

Breast cancer risk and its characteristics in diverse syndromes & Risk management

Syndrome (Gene)	Breast Cancer risk	Ovarian Cancer risk	Other Cancer risk	Mean Age & ER/PR	High risk Screening	Risk reducing surgery
HBOC (BRCA1)	++++	+++	+/-	44 yrs +/- 12 TNBC	Breast	RRSO
HBOC (BRCA2)	++++	++	+	54 yrs +/- 12 ER +ve	Breast	RRSO
LFS/LFL (TP53)	++++	+	++++	34 yrs +/- 7 ER +ve	Breast, CNS, Whole body etc.	?
PJS (STK11)	++	+	++	(25-50 yrs)	Breast + GI	?
Lynch (MMR)	+	+/-	++++	(30-60 yrs)	?	No

Suspect syndrome based on type of cancers, ER/PR, and age at cancer diagnosis
Single Gene or Gene Panel Test → Gene Specific screening / prevention advice