Current Strategies for Understanding the Risk and Biology of Breast Cancer

33rd Annual Winter Refresher
New Mexico Academy of Family Physicians

Albuquerque, New Mexico
February 21, 2015

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Talk today

- Questions patients ask
  - What caused my breast cancer?
  - What kind of breast cancer do I have?
  - How can my specific cancer be treated?
- Question patients might not ask
  - How is breast cancer affecting women around the world?

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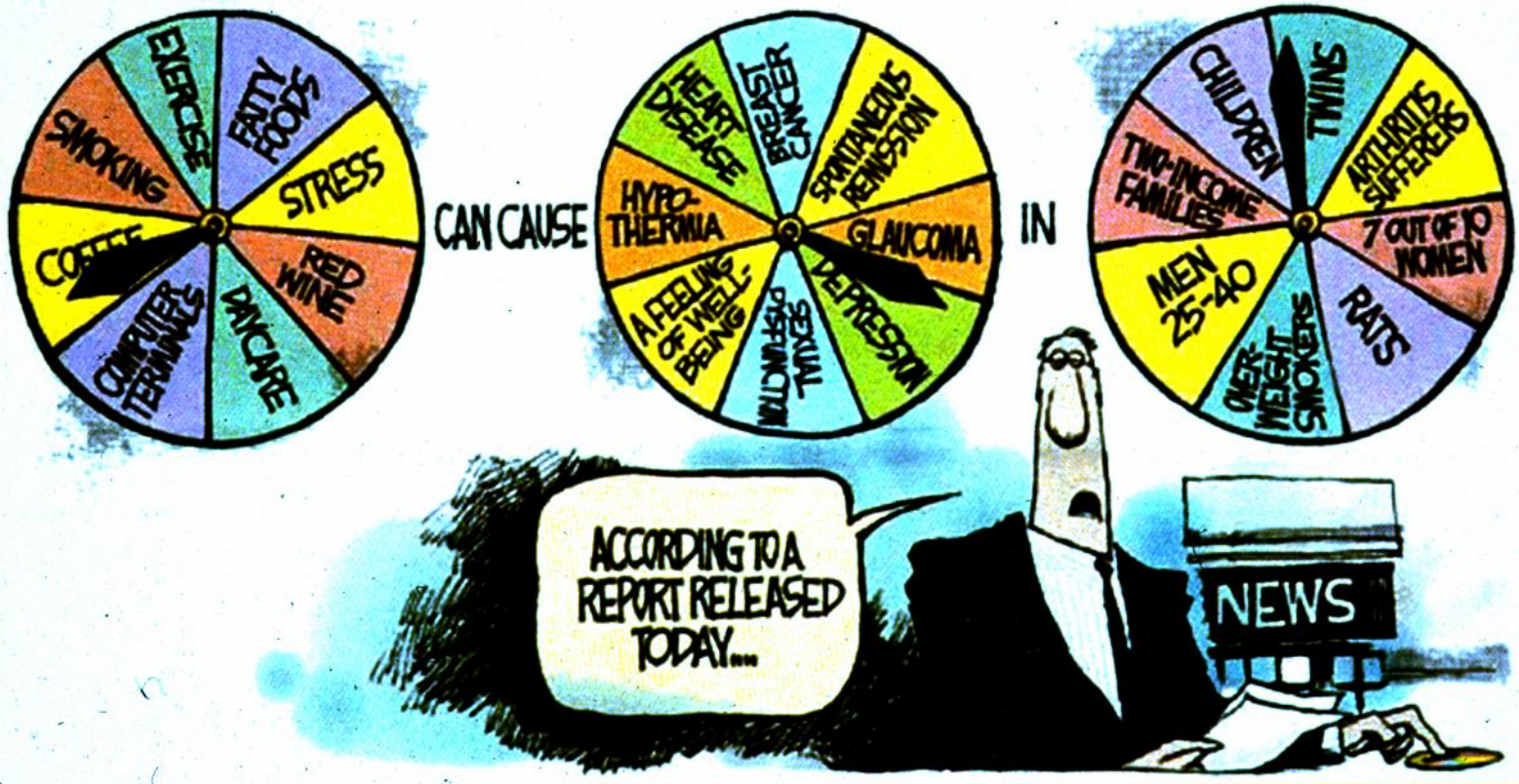
Today's Random Medical News

from the New England Journal of Panic-Inducing Gobbledygook

JIM BORGMAN



Risk factors for breast cancer

RR > 4.0

- Female
- Age (65+)
- Inherited BRCA 1/2
- Two or more first-degree relatives diagnosed <50 years
- History of breast cancer
- High breast density
- Previous benign biopsy

RR 2.1-4.0

- One first degree relative with breast cancer
- High dose radiation to chest
- High bone density
- Alcohol consumption

RR 1.1-2.0

- Late age at first full-term pregnancy (>30 years)
- Early menarche (<12 years)
- Late menopause (>55 years)
- No full-term pregnancies
- Never breast fed a child
- Recent oral contraceptive use
- Recent and long-term use of HRT
- Obesity (postmenopausal)

- Personal history endometrial, ovary or colon cancer
- Height (tall)
- High socioeconomic status

Multifactorial breast cancer etiology

- Both environmental and genetic contributions.
- Risk associated with individual factors does not cumulate in any simple mathematical way.
- Little is known about the interrelationships of risk factors.
- Many of these risk factors are believed to reflect cumulative exposure of the breast epithelium to hormones, both endogenous and exogenous.

The Challenge of Breast Cancer Prevention

Risk factors that are most modifiable are those most weakly associated with risk:

	RR > 4.0	**RR = 2.0-4.0**	**RR = 1.0-2.0**
Risk factors	Gender Age BRCA1/2	Family history Breast density	Pregnancy history Obesity Alcohol use Hormone use Physical activity

- In comparison the RR for smoking in relation to lung cancer is ~20.

Best evidence that lifestyle affects risk: Migration and lifestyle changes can alter incidence

Breast cancer incidence *			
	In Country		After Migration to U.S.
Shanghai	27.5	→	53.7
Hong Kong	37.7		
Miyagi, Japan	40.9	→	69.0
Osaka, Japan	28.9		

***Age standardized per 100,000 person years**
1983-1997 women aged 20-54

Zeigler, JNCI, 1993

Breast Cancer Risk Varies

- Race, ethnicity and ancestry
- Age and menopausal status
- Histological type
- Breast cancer subtype

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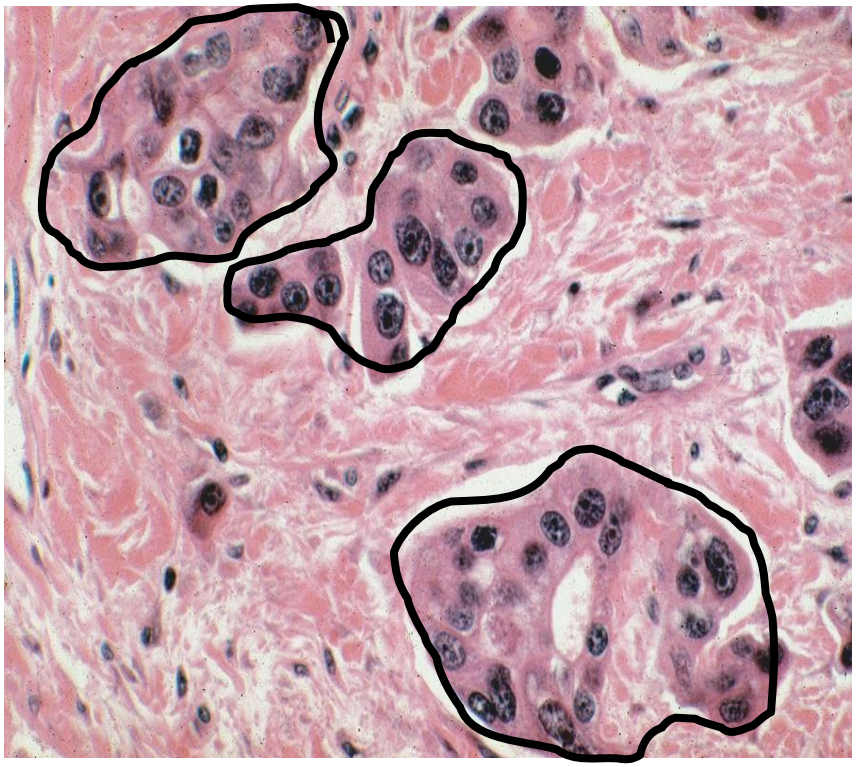
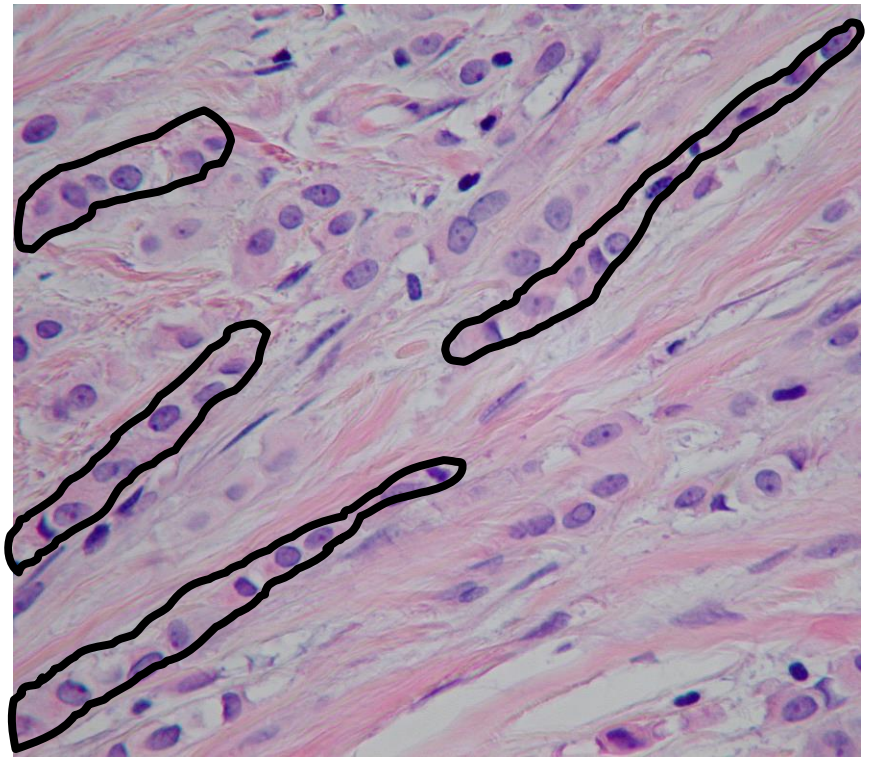
Invasive Ductal Carcinoma

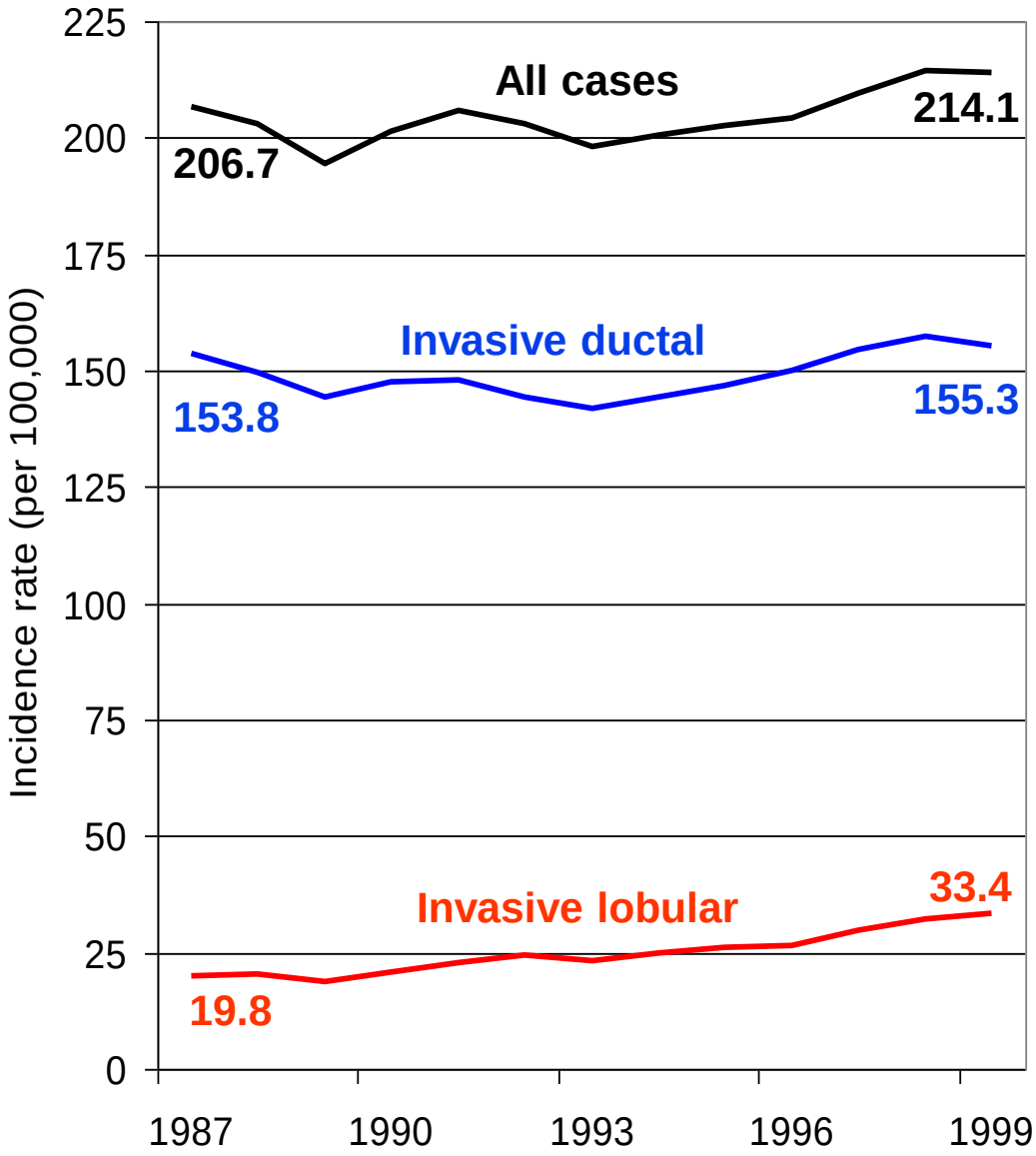


Invasive Lobular Carcinoma



Cornil, J Anat Physiol, 1865

U.S. incidence rates by histology



1987-2000:

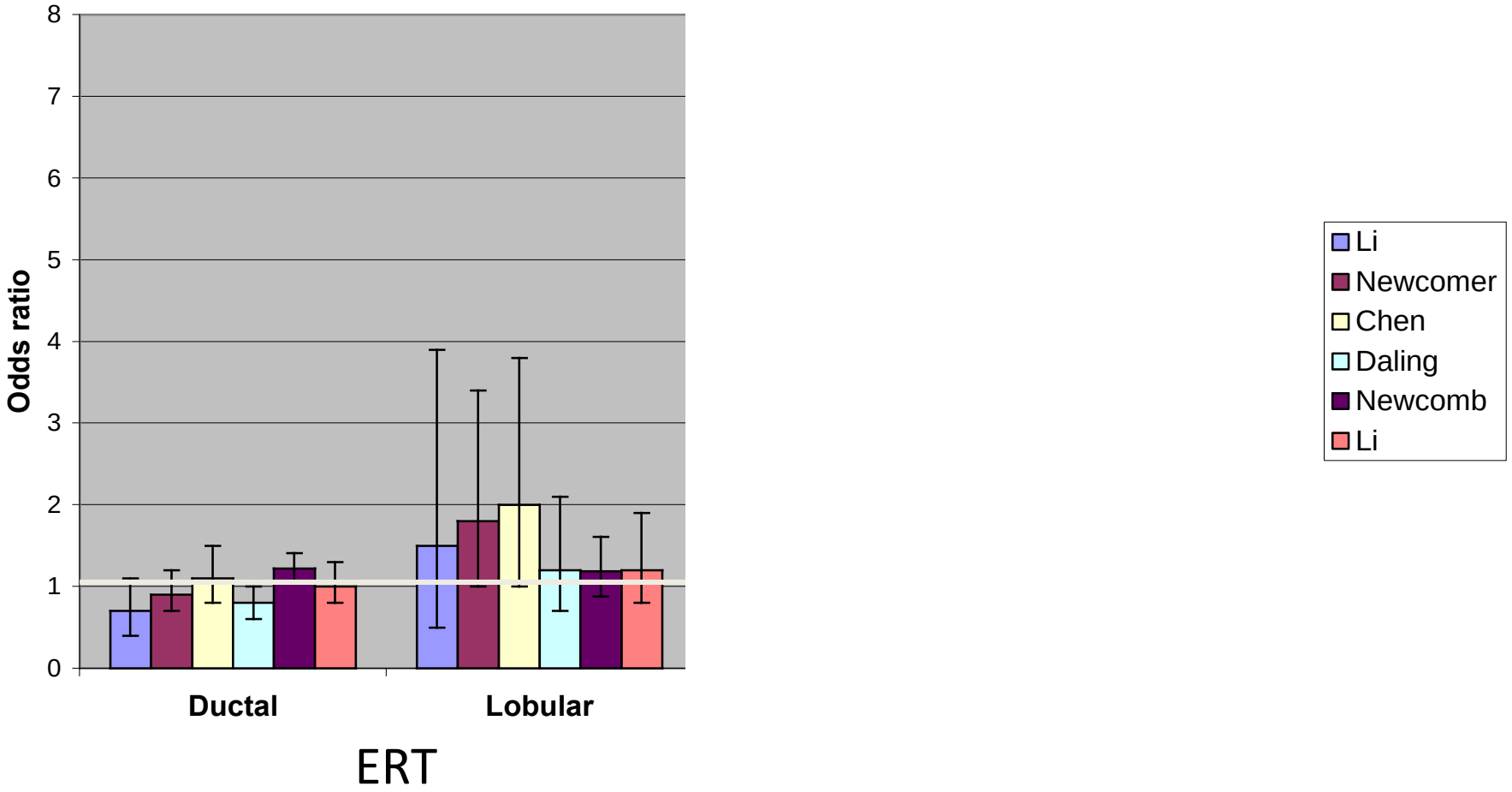
All cases: ↑4%

Ductal: ↑3%

Lobular: ↑65%

Li CI, et al. JAMA 2003;289:1421-24

Ever use of Estrogen Replacement Therapy (ERT) and Combined Hormone replacement Therapy (CHRT) by histology



Women's Health Initiative (WHI)

- Established in 1991 by the U.S. National Institutes of Health (NIH)
- Enrolled over 200,000 women in observational and randomized trials
- Menopausal Hormone Replacement Therapy (HRT) Trials (27,347):
  - Unopposed estrogen trial: BC RR = 0.77 (95% CI: 0.59-1.01)
  - Estrogen + progestin trial: BC RR = 1.26 (95% CI: 1.00-1.59)
- Before results were published:15 million HT users in the U.S., this dropped quickly to <9 million after the results were published

U.S. Breast Cancer Incidence decreases 2002-2003

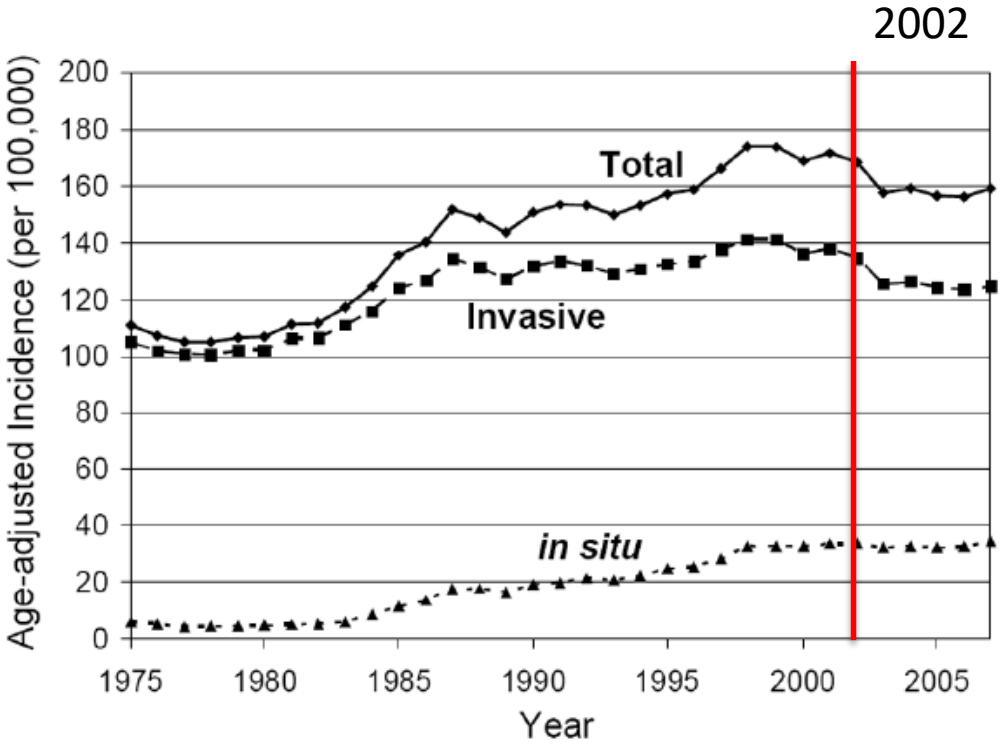


Figure 1. Female breast cancer incidence, 1975–2007
Female breast cancer incidence in SEER 9 registries (all ages), invasive vs. *in situ*, 1975–2007 [21].

Sprague et al, Cancer Causes Control 2011

Alcohol and Breast Cancer Risk

- Alcohol is the dietary factor most consistently associated with breast cancer risk.

- Modest relationship, compared to non-drinkers:

  1 drink per day increases breast cancer risk 10%

  2 drinks per day increases breast cancer risk 21%

- Hormones play a role:

  Controlled feeding study showed alcohol increases estrone sulfate levels in postmenopausal women.

  Alcohol shown to stimulate ER+, but not ER- cells.

Alcohol use and breast cancer risk by histology in the Women's Health Initiative

	Ductal (n=1,805)		Lobular (n=720)	
	HR	**95% CI**	**HR**	**95% CI**
Alcohol intake (drinks/week)				
Never drinker	1.0	(ref)	1.0	(ref)
Current drinker	1.0	(0.8-1.2)	**1.5**	**(1.1-2.1)**
1.0-3.9	1.0	(0.8-1.2)	**1.5**	**(1.1-2.2)**
4.0-6.9	1.1	(0.8-1.4)	**1.6**	**(1.0-2.4)**
7.0-13.9	1.2	(1.0-1.5)	**1.9**	**(1.3-2.8)**
≥14.0	1.0	(0.8-1.4)	**2.1**	**(1.4-3.3)**
p for trend		*0.055*		***0.002***

Li CI, et al. *J Natl Cancer Inst* 2010;102:1-10.

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The many clinical, morphological and molecular subtypes

Histological types

Inherited mutation status

Protein expression

Transcriptional

Genomic

miRNA

Epigenetic

Tumor microenvironment

Macroenvironment

Intratumoral heterogeneity

Advancing prevention, detection, therapy and improved survival depend on differentiating meaningful subgroups

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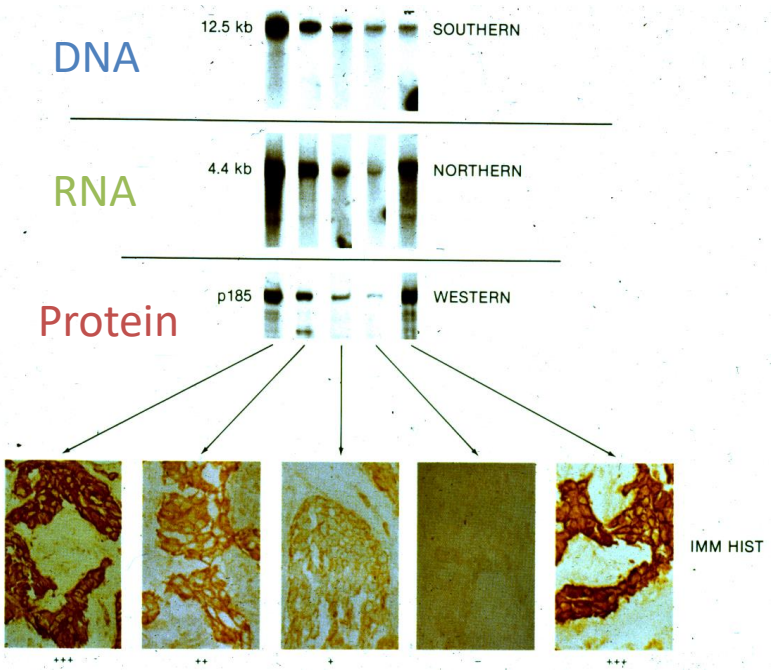
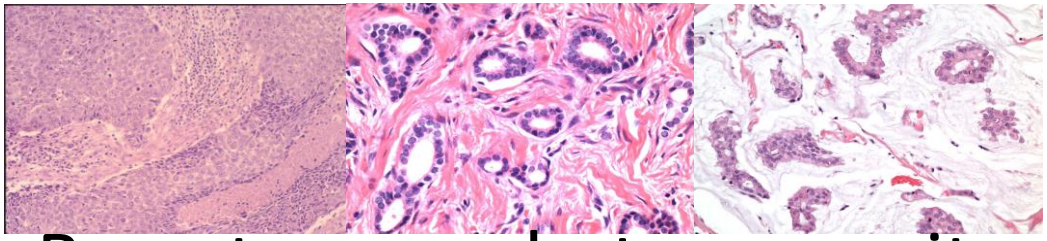
Advancing prevention, detection, therapy and improved survival depend on differentiating meaningful subgroups

Molecular markers define subtypes

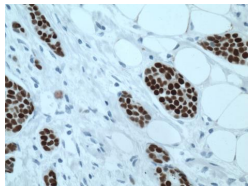
Molecular heterogeneity of breast cancer can be assessed at several levels:

Increase in Her2 in breast tumors can be observed at all three levels

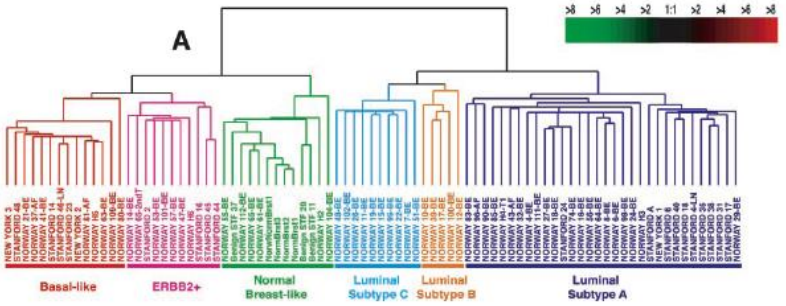




Breast cancer heterogeneity



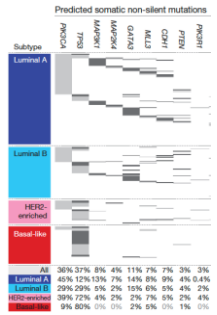
Define subtypes



Sorlie PNAS, 2001

Refine subtypes

Lehmann, et al., JCI, 2012

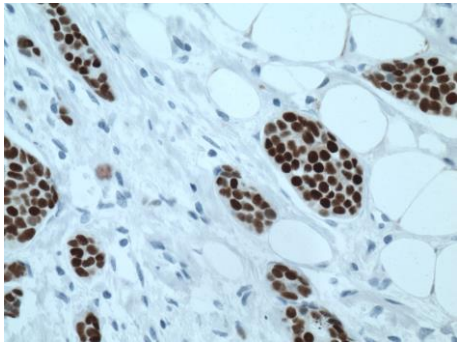


TCGA Network, Nature, 2012

Assess risk

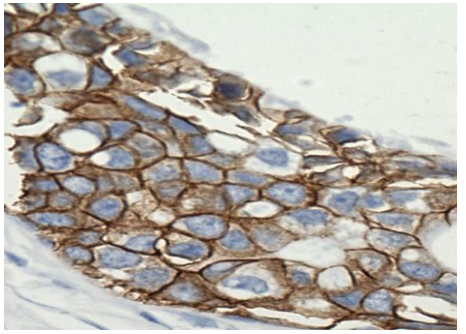
Adjust treatment/ management

Breast cancer subtypes offer opportunity for targeted therapy



Estrogen Receptor +

- 65-75% of breast tumors
- More common post-menopause
- Targeted treatment: anti-estrogens (AI/Tamoxifen)



HER2 +

- 12-15% of breast tumors
- Targeted treatment: trastuzumab/pertuzumab

Characteristics used to TREAT breast cancer

- Estrogen receptor
- HER2 oncogene amplification
- Tumor grade
- Ki-67 proliferation index

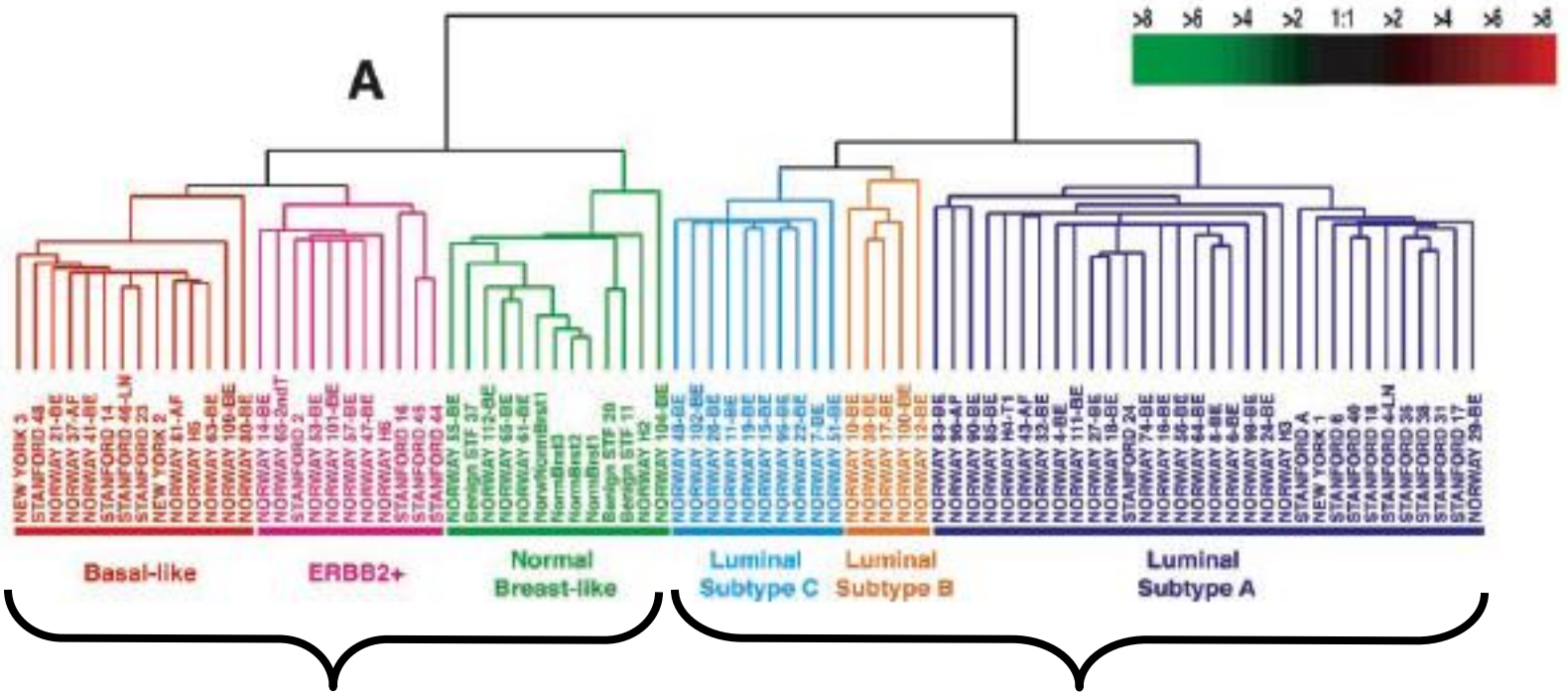
Characteristics used to define breast cancer subtypes

- Subtypes defined by protein expression (immunohistochemistry) and Tumor Grade
- Gene expression profiling
- Genomics

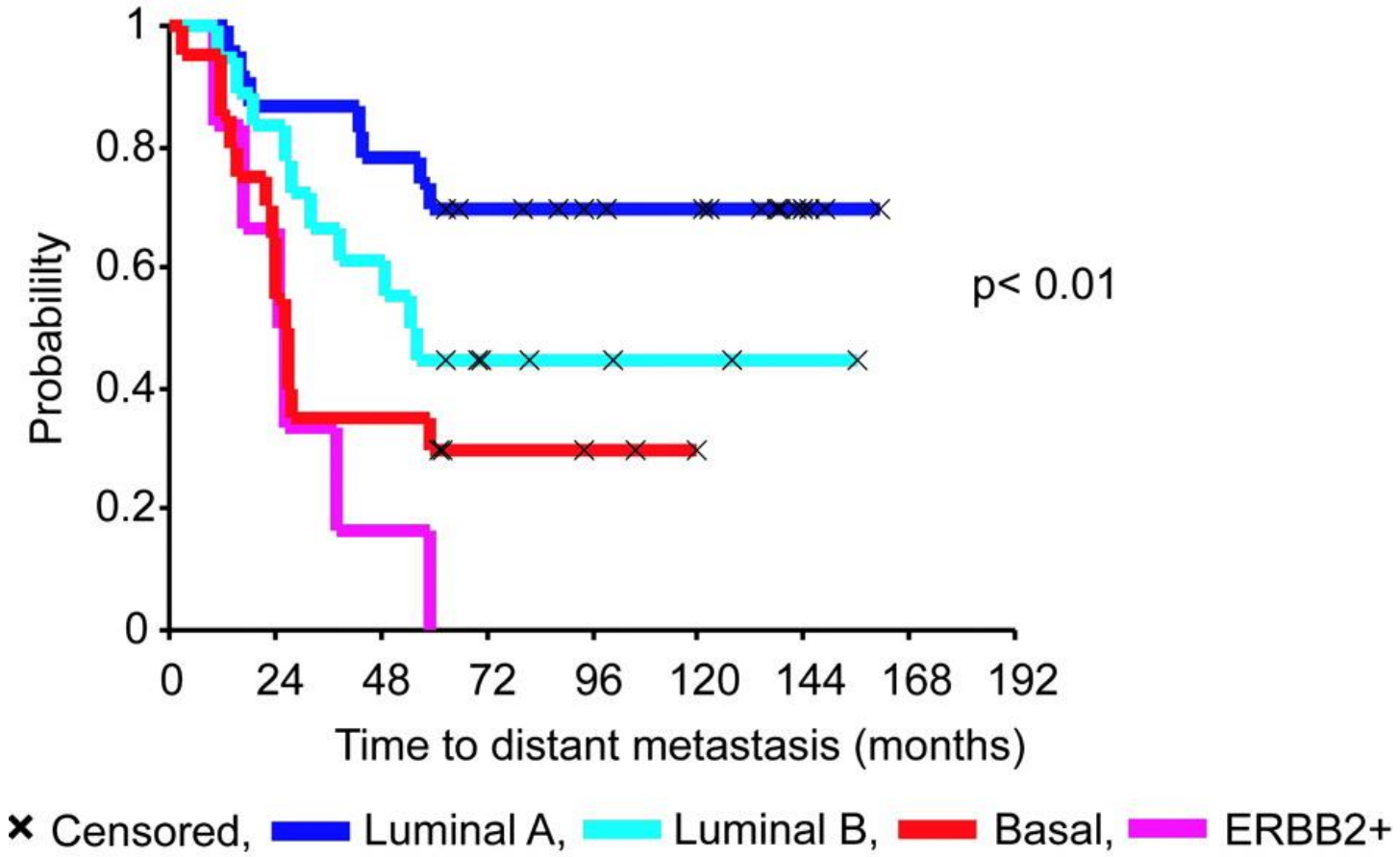
Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

PNAS, 2001

Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[b], Trevor Hastie[e], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[j], Thor Thorsen[k], Hanne Quist[l], John C. Matese[d], Patrick O. Brown[m], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[a,n]



Gene expression subtypes correlate with differences in prognosis



Consistent over multiple specimen sets

Sørlie T et al. PNAS 2003;100:8418-8423

Gene expression ➡ IHC subtype

RNA expression-based

Basal-Like

- Classified on basis of ~500 intrinsic genes
- Low expression: ER and HER2
- High expression: CK 5 and 17, Laminin, FABP7, EGFR
- p53 mutations (82%)

➡

Protein expression-based

Triple Negative

- ER negative
- PgR negative
- HER2 negative

Luminal A

- Low expression: HER2
- High expression: ERa, HNF3a, ER-LIV-1

➡

- ER and/or PgR positive
- HER2 negative
- Ki-67 <14%

Luminal B

- High expression: ATP5G1, PRNPIP, NSEP1, GGH, LAPTM4B, PRDX4

➡

- ER and/or PgR positive
- HER2 neg/Ki-67≥14%
- Her2 pos/any Ki-67

St. Gallen 2011 subtype recommendations

- **Luminal A** *Goldhircsh, Ann Oncol, 2011*
  - ER and/or PgR positive
  - HER2 negative
  - Ki-67 low (<14%)*
- **Luminal B1**
  - ER and/or PgR positive
  - HER2 negative
  - Ki-67 high
- **Luminal B2**
  - ER and/or PgR positive
  - HER2 positive
  - Ki-67 any
- **HER2 enriched**
  - HER2 over-expressed or amplified
  - ER and PgR absent
- **Basal/TN**
  - ER and PgR absent
  - HER2 negative

**Cheang JNCI, 2009; Ki-67 index threshold established with Pam50*

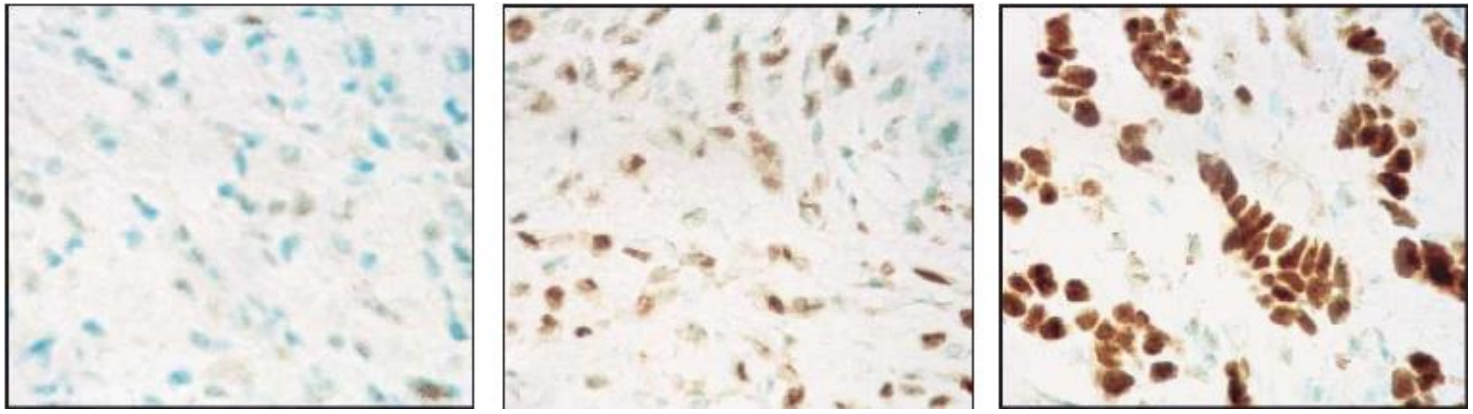
TNBC is heterogeneous collection of tumors with distinct phenotypes

	Lehmann	Prat & Perou
Basal-like	47%	49%
Luminal A	17%	5%
Luminal B	6%	6%
Normal-like	12%	1%
HER2	6%	9%
Unclassified	12%	
Claudin low		30%

Prat and Perou, Molec Oncol 2010 *Lehmann, et al., JCI, 2012*

Challenge: is the tumor really triple negative?

Effect of fixation time on Estrogen Receptor IHC results



3 hour **6 hour** **8 hour**

- **At least 8 hours fixation required to fully recognize ER/PR by IHC**

  Goldstein, Am J Clin Pathol, 2003

- **9% of core biopsies negative for ER and PR when compared with surgical biopsies**

  Hodi, J Clin Pathol, 2007

Research article

Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies

Brian D. Lehmann,[1] Joshua A. Bauer,[1] Xi Chen,[2] Melinda E. Sanders,[3] A. Bapsi Chakravarthy,[4] Yu Shyr,[2] and Jennifer A. Pietenpol[1]

2012

- **Analyzed gene expression profiles from 21 breast cancer data sets (3247 breast cancers)**
- **Filtered datasets for ER/PR/HER2 expression—identified 587 (18%) TNBC cases**
- **Six subtypes identified and confirmed in validation sets**

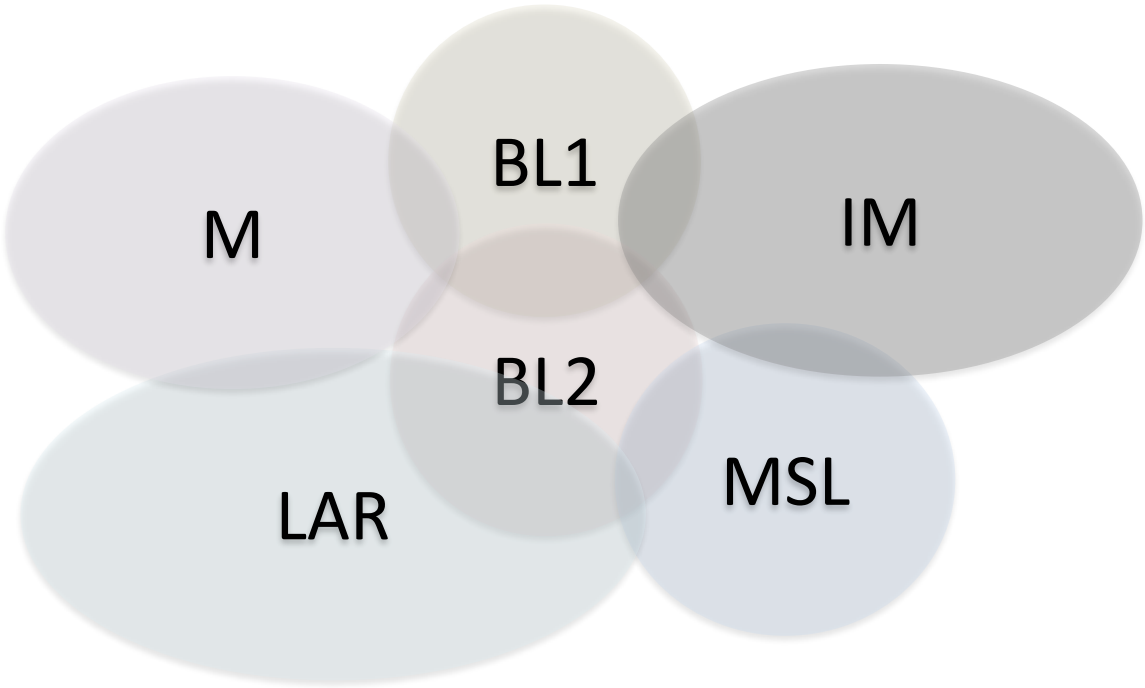
Molecular subtypes of TNBC

Basal-like 1 and 2: cell cycle and DNA damage response genes

Mesenchymal and MSL: enriched in cell differentiation, EMT and growth factor pathways

Luminal Androgen Receptor-driven by AR signalling

Immune Modulatory: Immune cell surface antigens, receptors and signal transduction genes

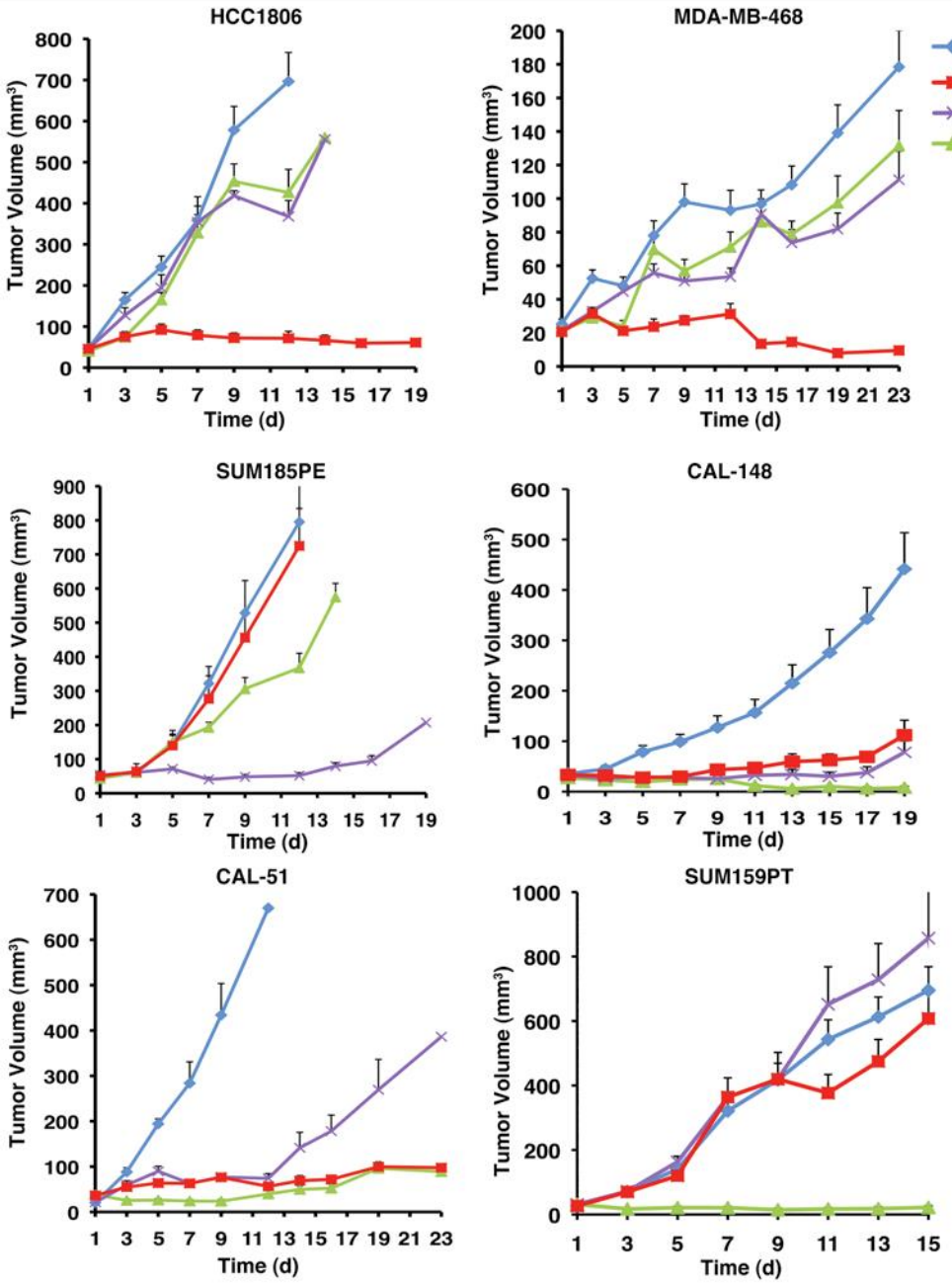


Varying sensitivity of representative cell lines to targeted therapies

Basal-Like

LAR

Mesenchymal-Like



Anti-androgen
PI3K/ mTOR kinase inhibitor

Lehmann, et al., JCI, 2012

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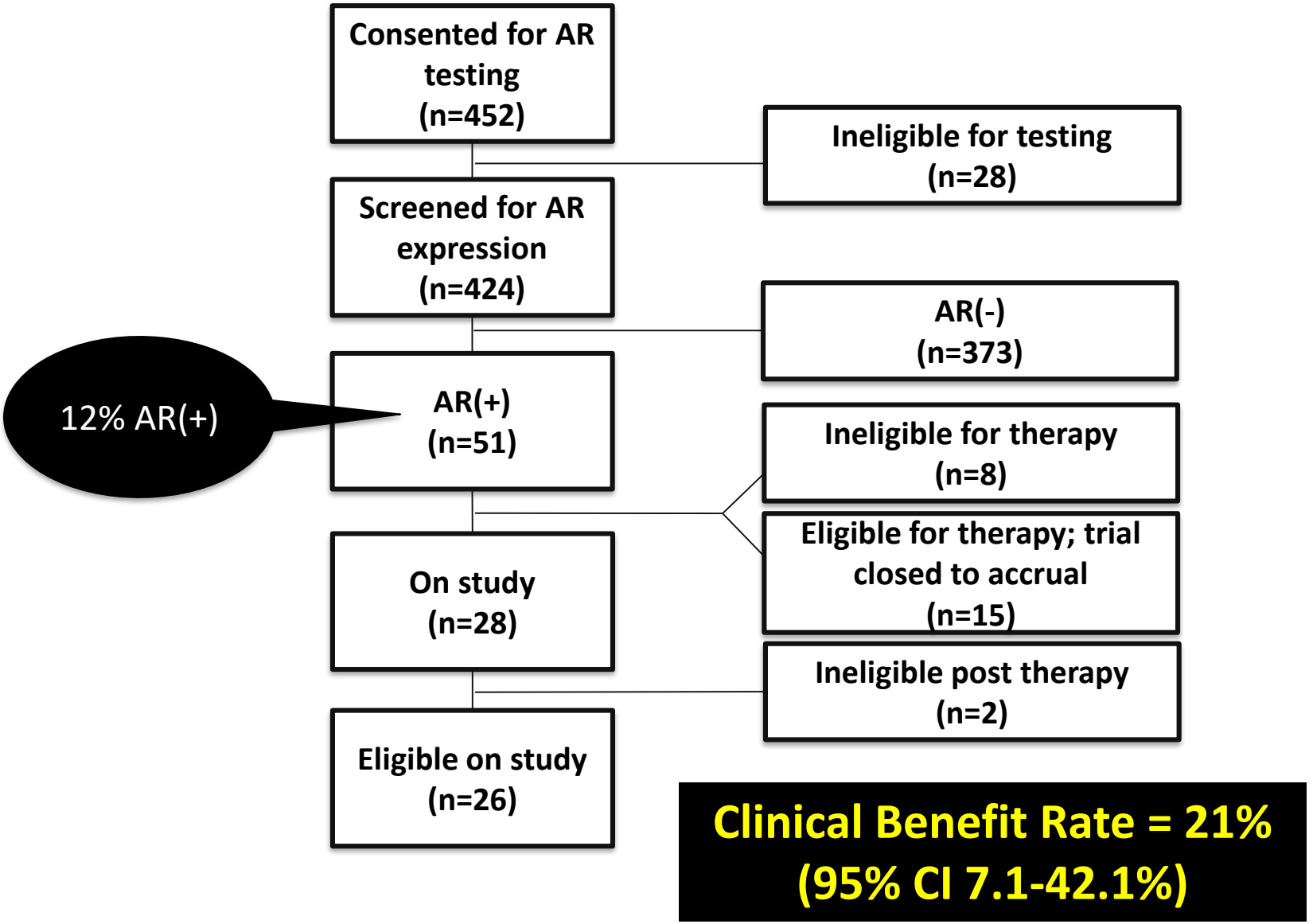
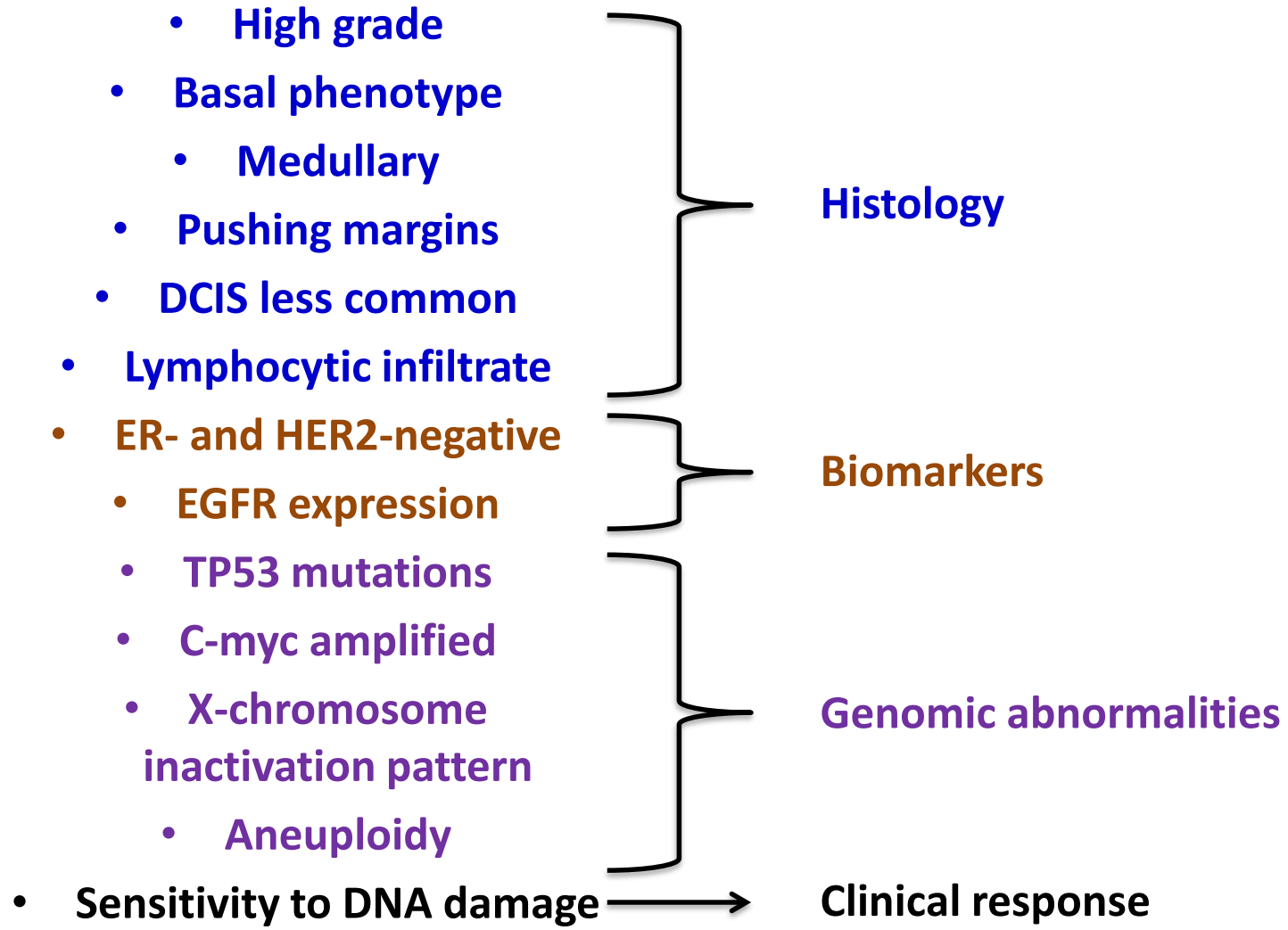
TBCRC 011: Bicalutamide in AR+ TNBC

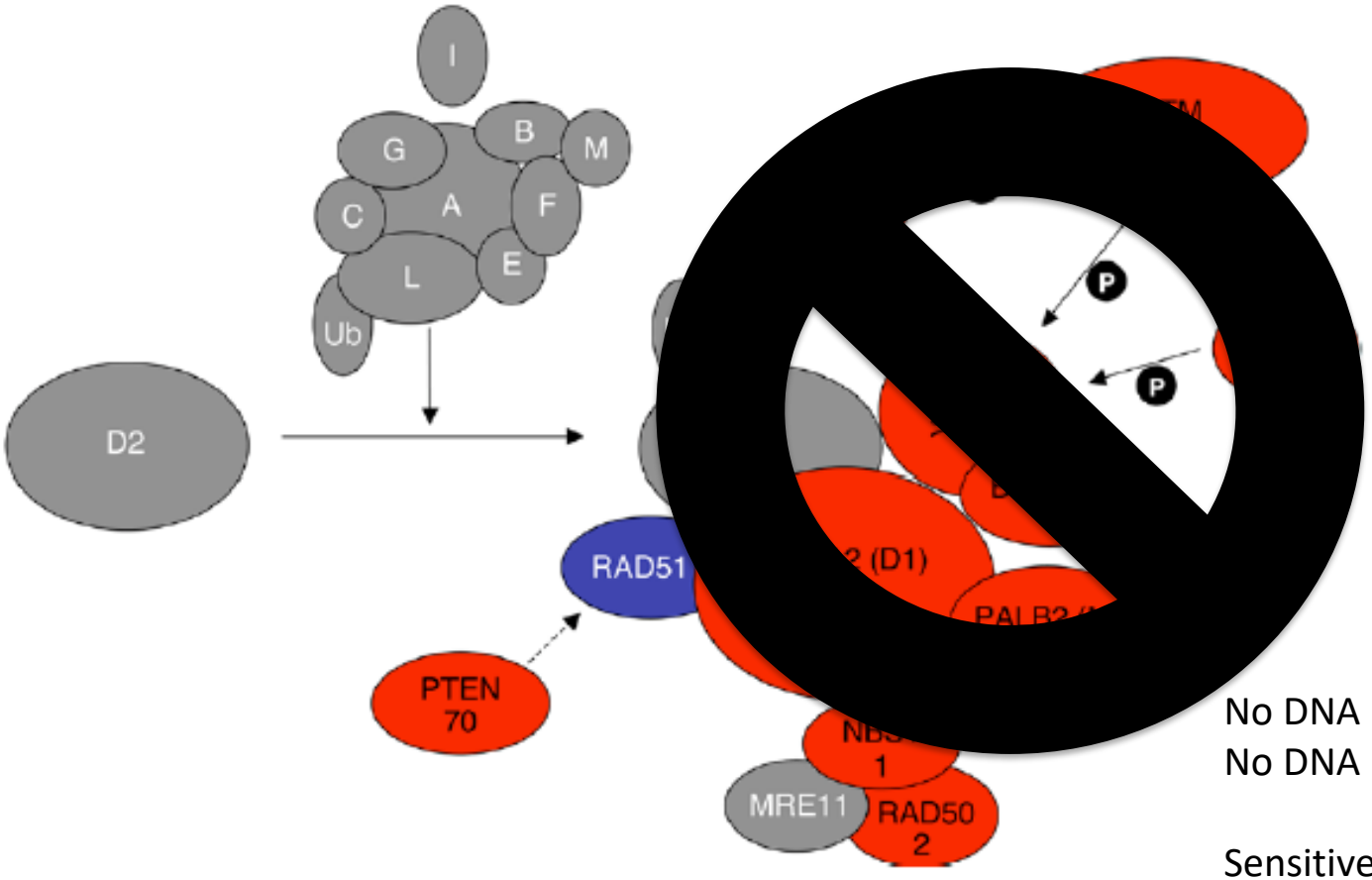


Gucalp et al, ASCO 2012

TNBC association with "BRCAness" = Characteristic of BRCA1 mutation



Inherited mutations in many DNA repair genes associated with Breast Cancer



No DNA damage checkpoint
No DNA damage repair

⬇

Sensitive to DNA damage agents

Figure 1. Interactions of Proteins Associated with Inherited Breast Cancer and with Fanconi Anemia

Walsh and King, Cancer Cell, 2007

Platinum Responsiveness in TNBC (Neoadjuvant)

Trial	Type	n	Drugs	Population	pCR
DFCI1	Single arm Ph 2	21	CDDP x 4	TNBC	21%
DFCI2	Single arm Ph 2	51	CDDP+bev	TNBC	15%
Polish	Retrospective	13	CDDP x 4	BRCA+	83%
GEICAM	Randomized Ph 2	94	EC-D EC-D+carbo	Basal-like (IHC)	30% 30%
GeparSixto	Randomized Ph 3	165	PM/bev PMCb/bev	TNBC (subset)	38% 59%
PreCOG0105	Single arm Ph 2	80	G/Carbo/iniparib	TNBC	36%
CALGB 40603	Randomized Ph 2	455	T-AC(bev) T/carbo-AC(bev)	TNBC	41% 54%

Silver et al, JCO 2012; Ryan et al, ASCO 2009; Byrski et al, JCO 2010; Alba et al, BCRT 2012; von Minckwitz et al, ASCO 2013 ; Telli et al, ASCO 2013; Sikov et al, SABCS 2013

PARP inhibition and DNA repair

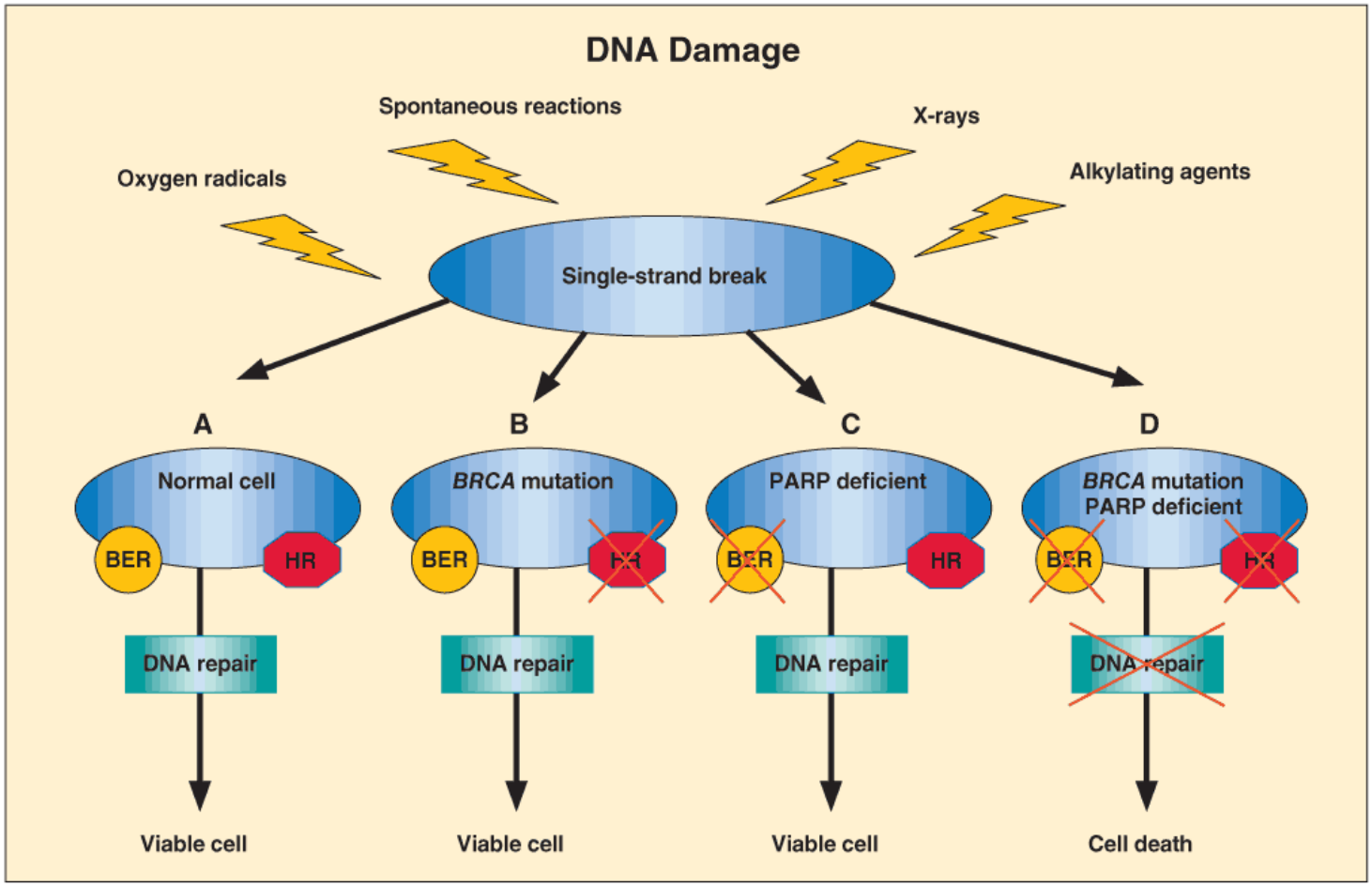
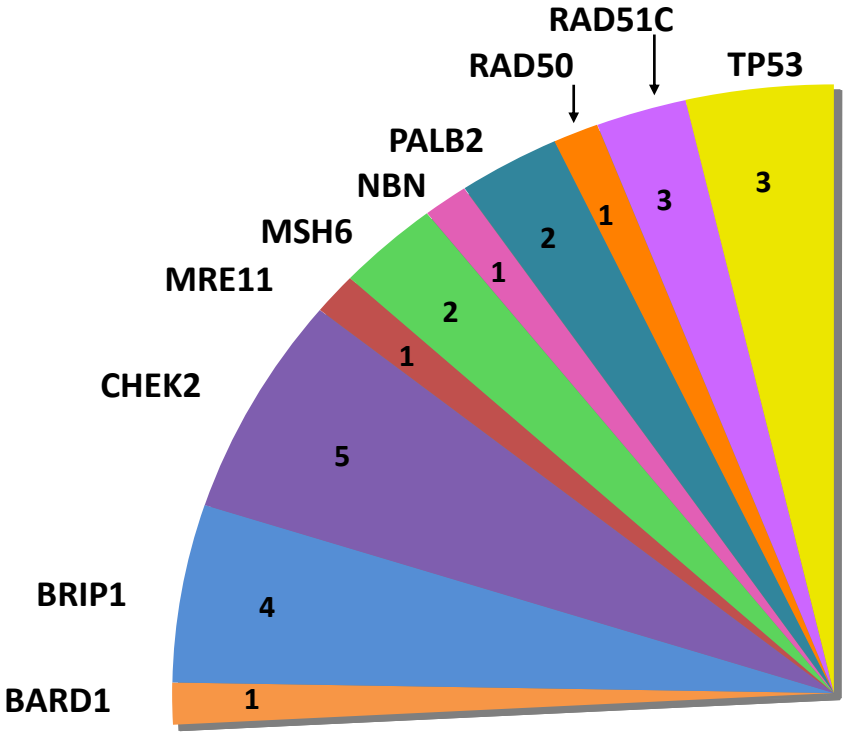


Figure 1: Schematic Illustration of Synthetic Lethality—BER = base excision repair (including single-strand break repair); HR = homologous recombination repair.

Comen and Robson, Oncology, 2010

Next Gen Sequencing 'BROCA' assay identifies Inherited Mutations in Gynecological Cancers



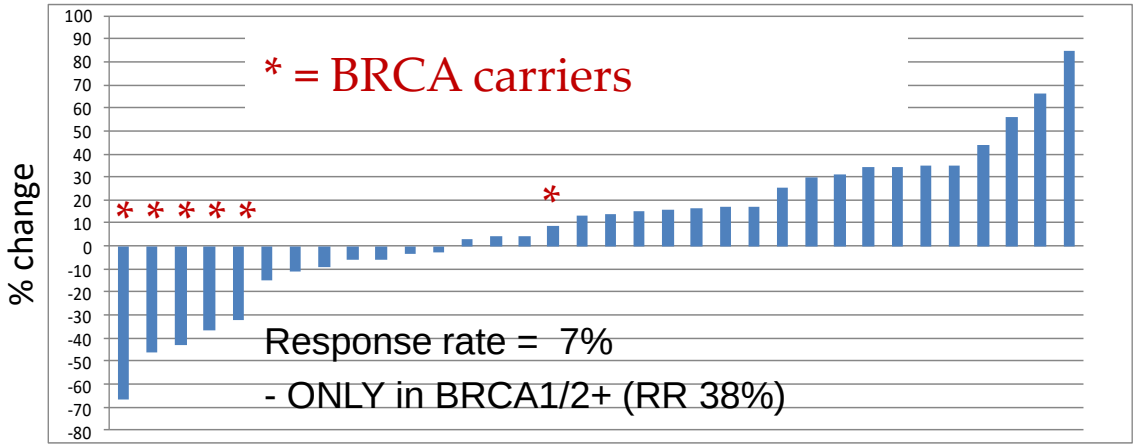
Walsh et al, PNAS, 2010
Walsh et al, PNAS, 2011

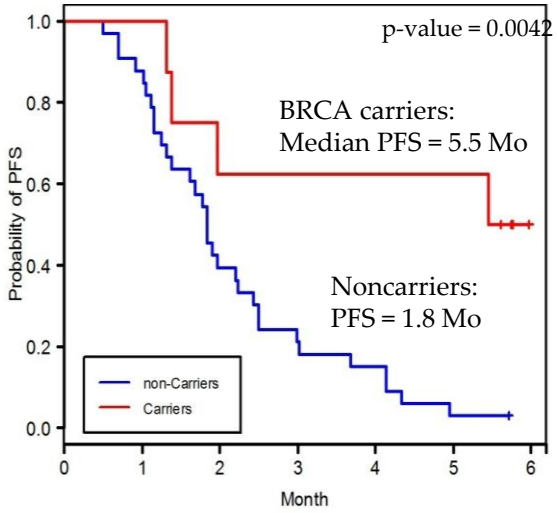
- >30% no family history of breast or ovarian cancer
- >35% were ≥60 y at diagnosis

Cases	BRCA1/2 mutation	Other Gene Mutation
N=360	64 (17.8%)	23 (6.4%)

Veliparib + Chemotherapy Combinations

Phase II Veliparib (ABT-888) + Temozolamide

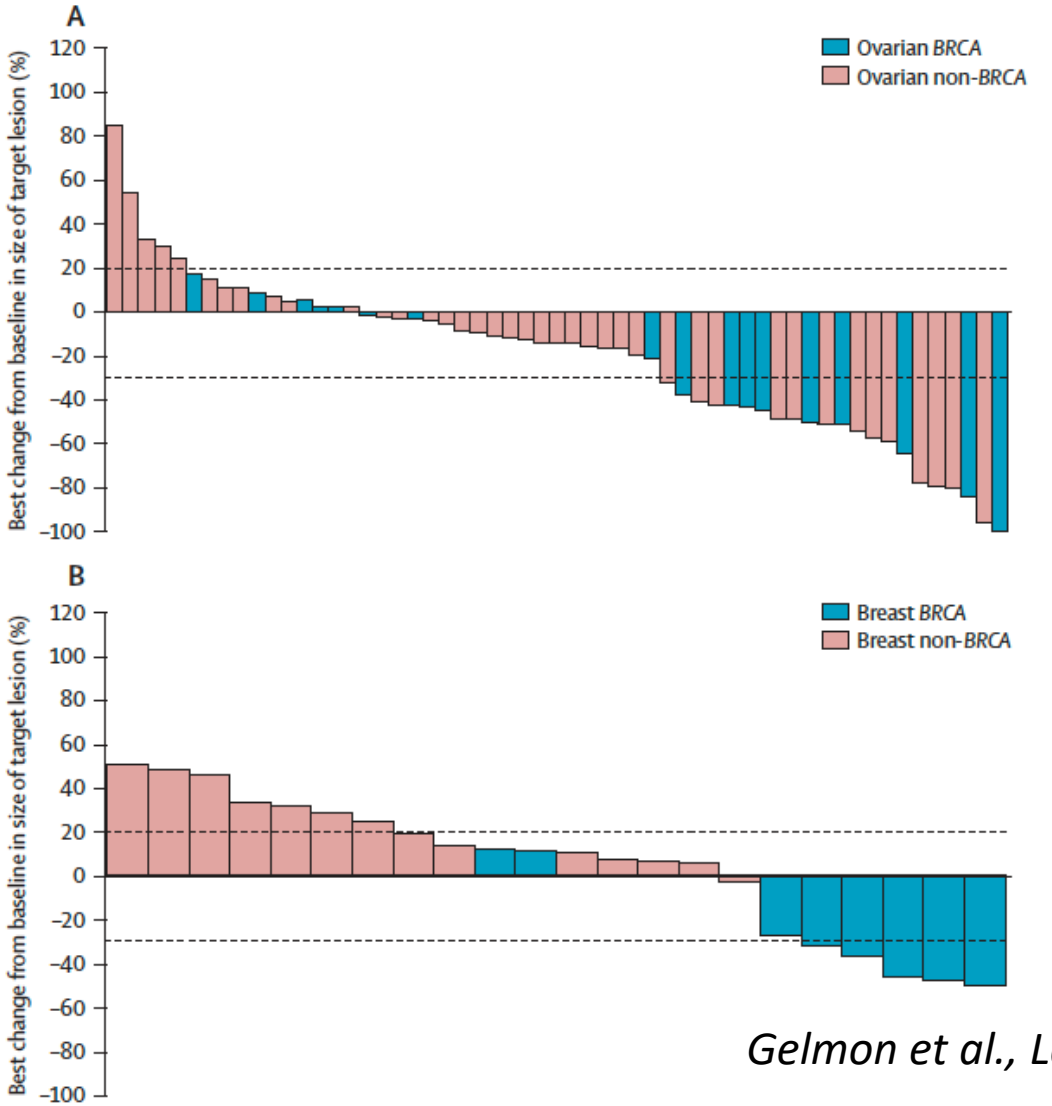




Phase II: Oliparib (AZD2281) Parp inhibition in ovarian and breast cancer

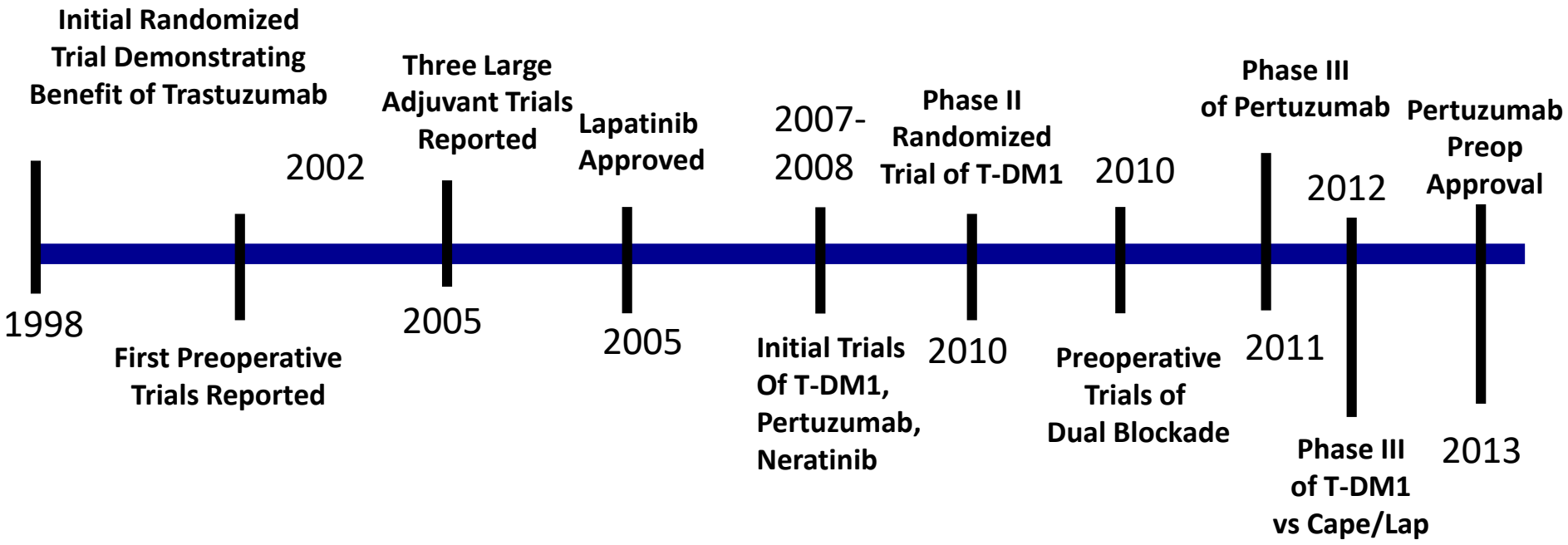
Ovarian

Breast



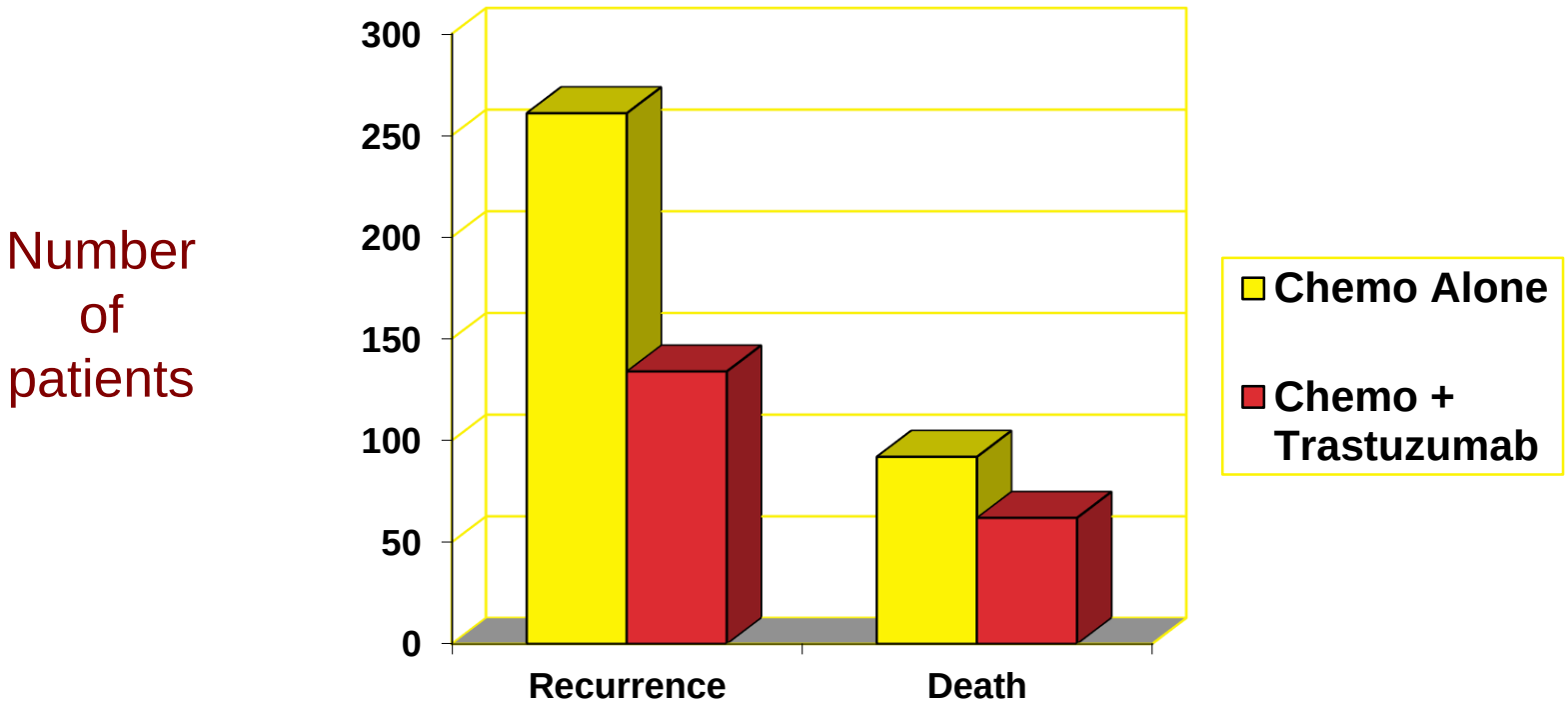
Gelmon et al., Lancet Oncol 2011

HER2+ Disease: Major Clinical Advances Over The Past 15 Years



Adjuvant (Early Stage) Trastuzumab: Combined Analysis of NSABP B-31 and N9831

Romond E et al, N Engl J Med 353, 2005



- Risk of breast cancer recurrence reduced by 52% at 3 yrs
- Risk of death decreased by 33%
- Increased risk of class III/IV CHF (absolute risk 3-4%)

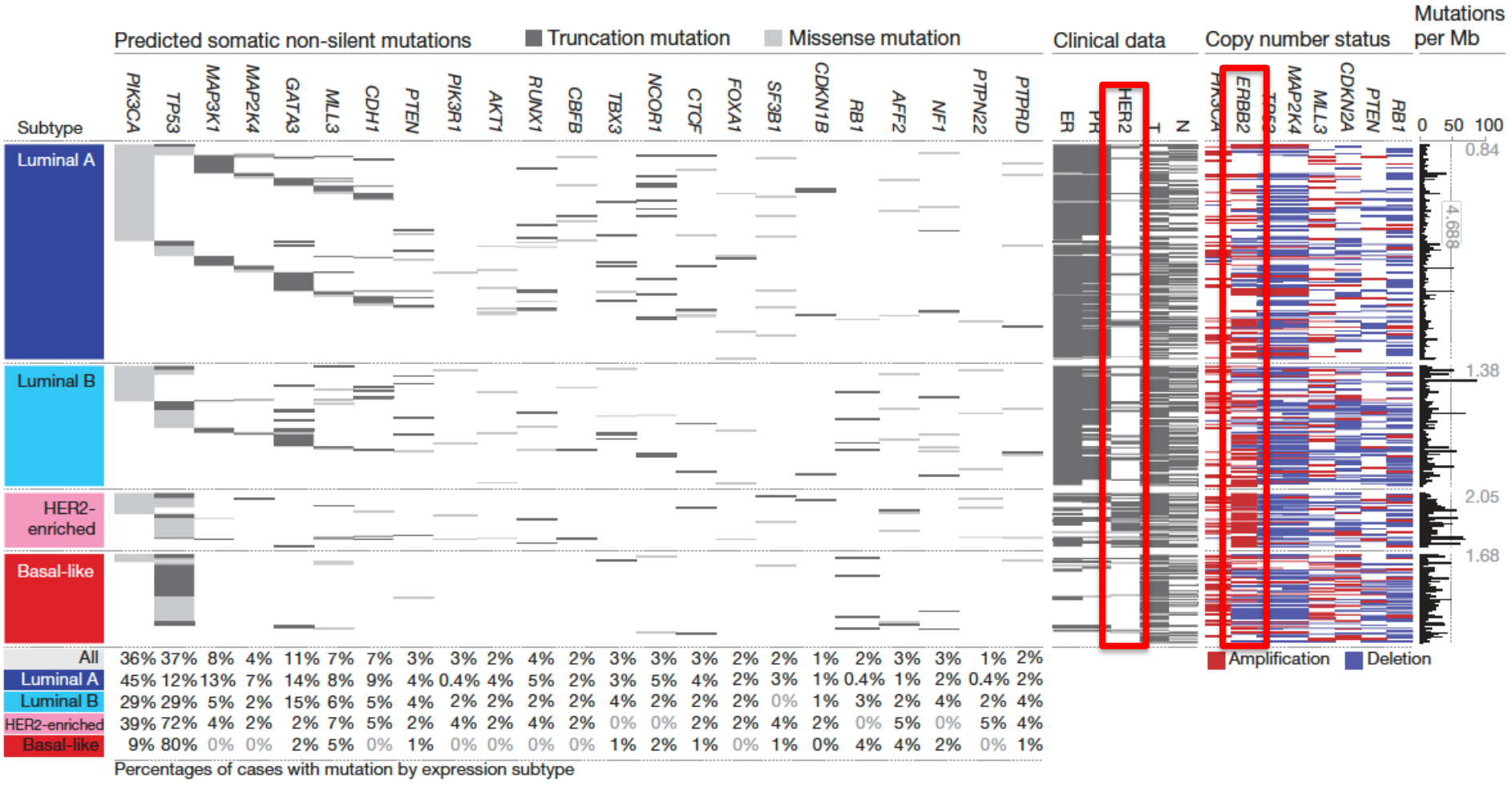
Clinical Challenges

1. **Heterogeneity of HER2+ Disease**
2. **Inadequacy of single agent blockade**
3. **Drug Resistance**
4. **Personalizing Approaches**

The Cancer Genome Atlas (TCGA)-Breast

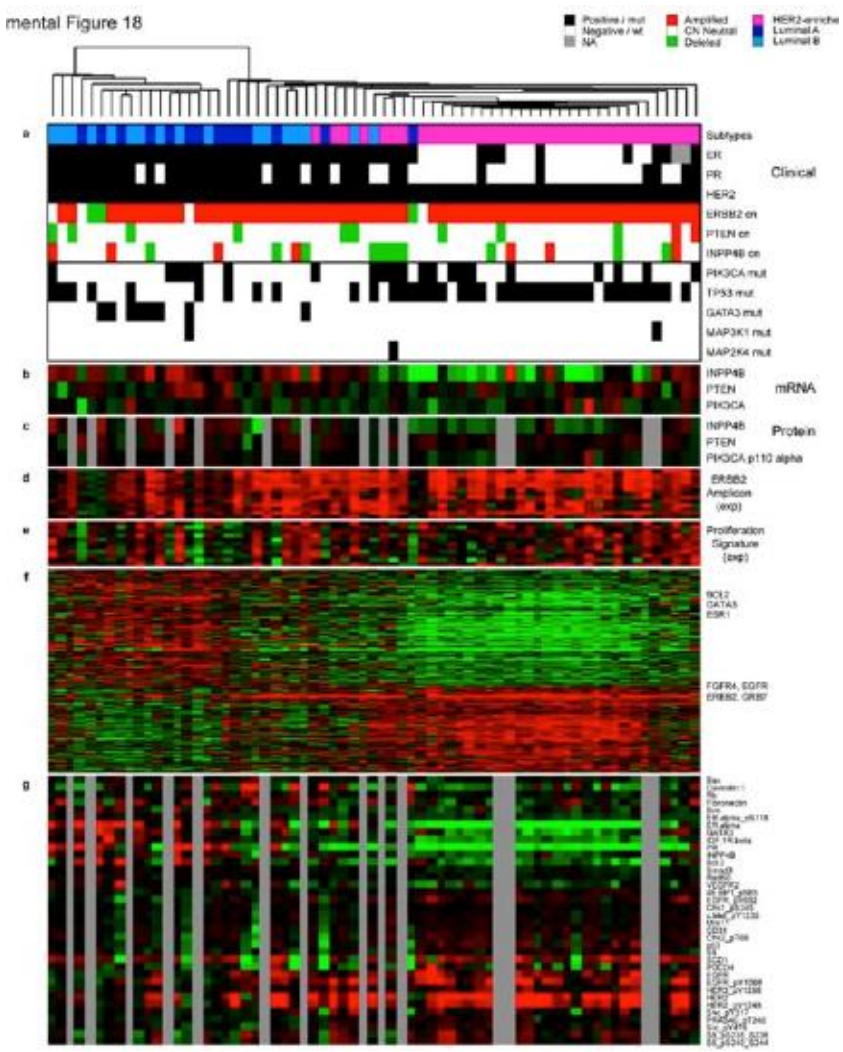
- Tumor and germline DNA samples from 825 patients; 466 tumors with data from 5 platforms
  - Agilent mRNA expression microarrays
  - Illumina Infinium DNA methylation chips
  - Affymetrix 6.0 SNP arrays
  - miRNAsequencing
  - whole-exome sequencing
  - 348 of the 466 samples also had reverse-phase protein array (RPPA) data
- 30,626 somatic mutations identified in 507 tumors by whole-exome sequencing
- Only three genes (TP53, PIK3CA and GATA3) occurred at >10% incidence across all breast cancers
- Novel significantly mutated genes identified: TBX3, RUNX1, CBFB, AFF2, PIK3R1, PTPN22, PTPRD, NF1, SF3B1 and CCND3

Significantly mutated genes and correlations with genomic and clinical features



The Cancer Genome Atlas Network, Nature, 2012

TCGA: Heterogeneity of HER2+ breast cancers



HER2-Luminal (hormone receptor positive):

express ER, PR, BCL2 and have GATA3 mutations but no ↑ in EGFR/pEGFR/HER2/pHER2 by protein or mRNA (High risk luminals?)

HER2-Enriched (hormone receptor negative):

Upregulation of RTKs: EGFR, FGFR

- **Amplification of EGFR, FGFR, CDK4, cyclin D1 and genes within the HER2 amplicon (GRB7, TOPO2)**
- **Strong EGFR/pEGFR/HER2/pHER2 expression**
- **Highest aneuploidy, highest somatic mutation rate**

HER2 overall:

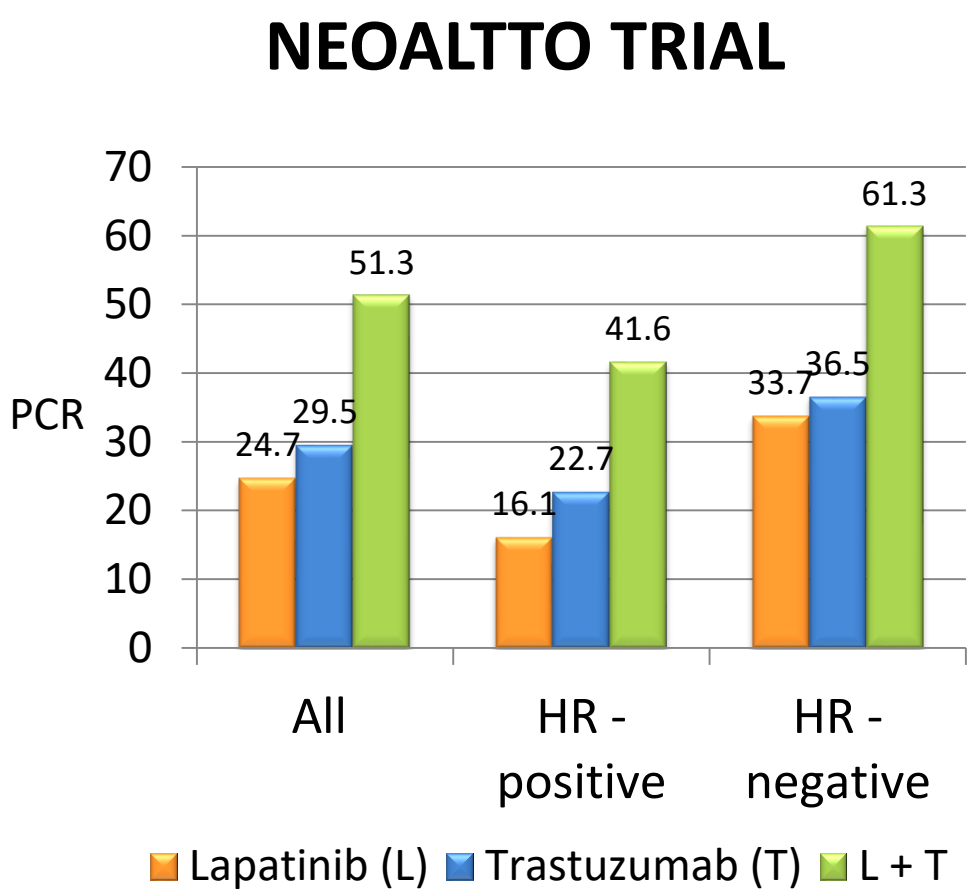
High rate of PIK3CA mutations (≈30%)

Pathologic CR Rates in NeoSphere Clinical Trial-417 patients

	Trast - Docetaxel	Pertuz – Docetaxel	Trast - Pertuz - Docetaxel
ITT (Overall)	29%	24%	46%
ER-	37%	30%	63%
ER+	20%	17%	26%

Gianni et al, Lancet Oncol 2012

Trastuzumab/Lapatinib dual therapy by hormone receptor

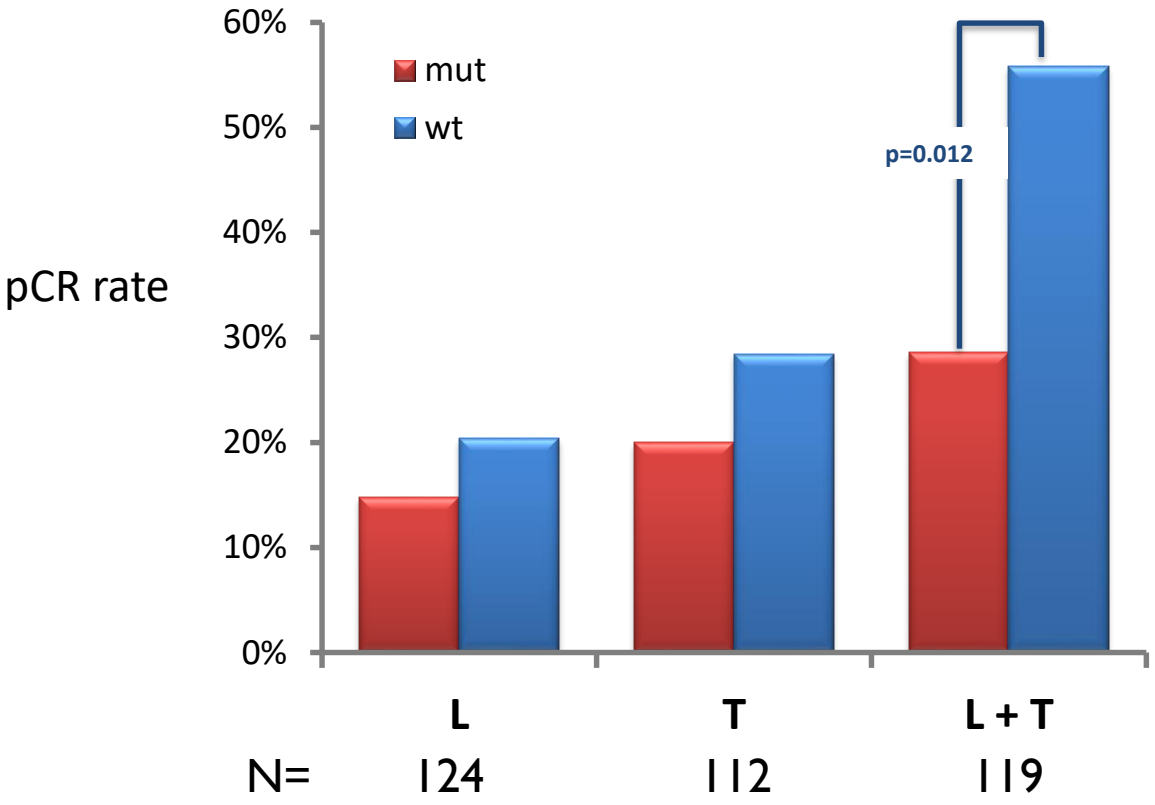


Neoadjuvant setting
455 women with
HER2+ breast cancer ≥ 2 cm

Baselga J et al; SABCS 2010; Lancet 2012

PIK3CA mutations are associated with resistance to anti-HER2 therapies (Neo-ALTTO)

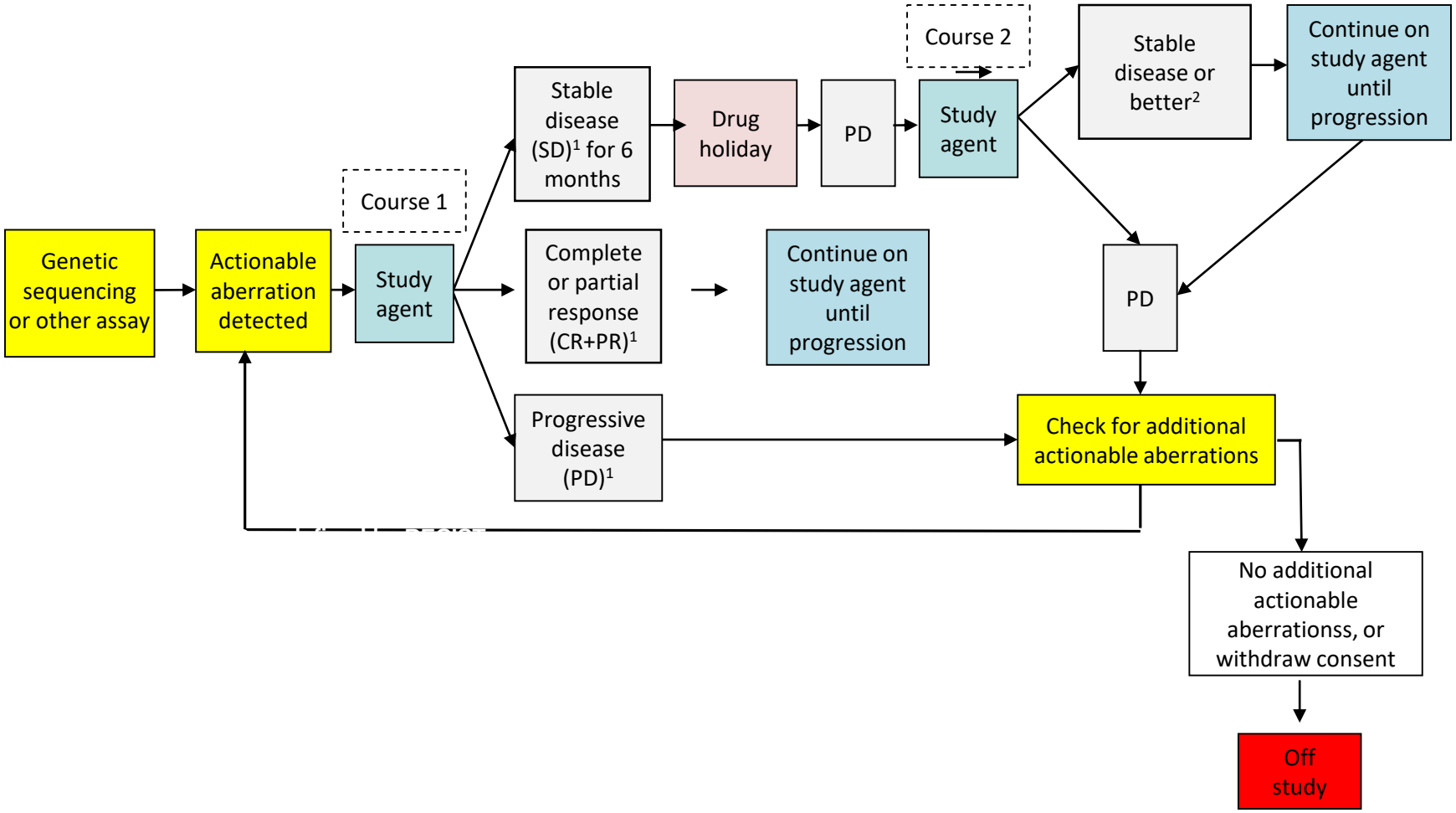
- For each treatment arm, the pCR rate was lower for patients with a PIK3CA mutation
- The difference was statistically significant in the combination arm



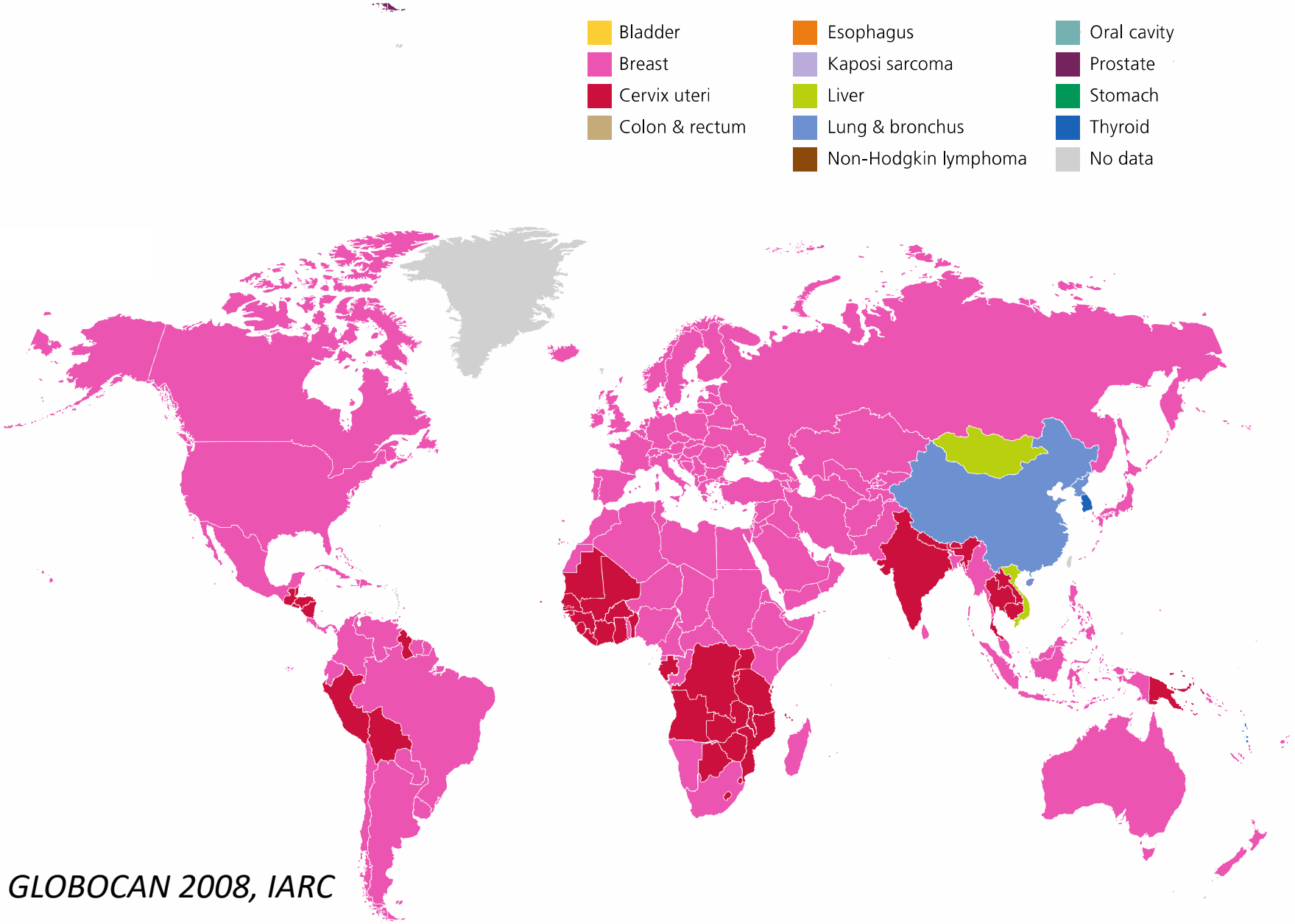
Baselga *et al.* ECCO 2013

“Genome-Forward” Trials: Integral Biomarkers in TNBC?

Proposed NCI-MATCH trial

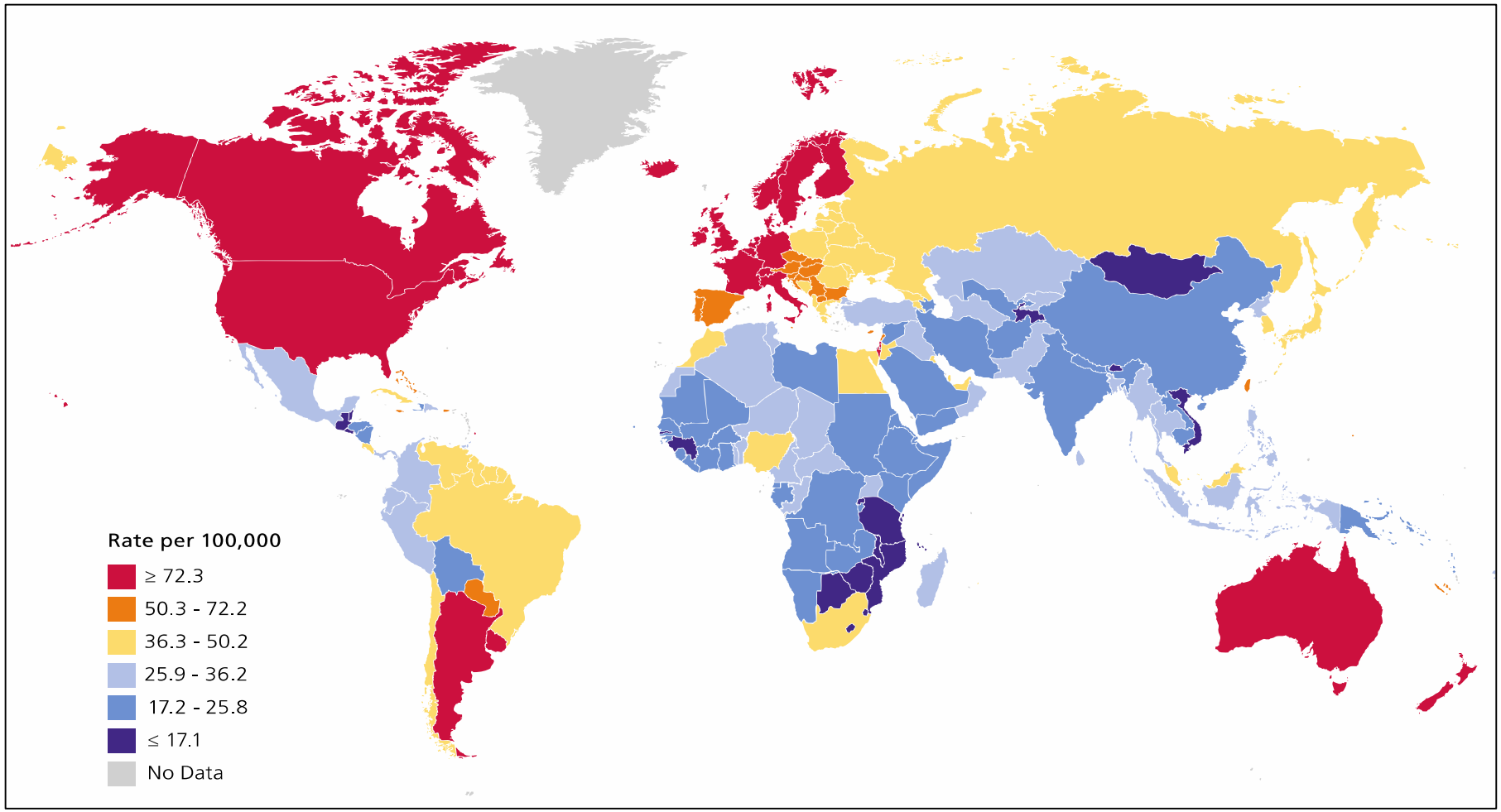


Most Common Cancer Sites Worldwide--Female, 2008



GLOBOCAN 2008, IARC

International Variation in Age-standardized Breast Cancer Incidence Rates, 2008



GLOBOCAN 2008, IARC

Worldwide Age-Standardized Breast Cancer Incidence, Mortality, Mortality-to-Incidence Ratios (1993-2001)

	Incidence		Mortality		MR:IR
	No.	Rate	No.	Rate	
WORLD	1,152,161	37.5	411,093	13.2	0.35
More developed	636,128	67.8	189,765	18.1	0.27
Less developed	514,946	23.8	221,028	10.4	0.44
CONTINENT					
North America	229,631	99.4	48,239	19.2	**0.19**
Oceania	13,507	84.6	3,338	19.4	0.23
Europe	360,746	62.3	129,010	19.7	0.32
Central/So America	90,147	41.0	30,361	14.0	**0.34**
Asia	385,853	22.1	152,967	8.8	0.40
Africa	65,197	23.4	44,399	16.2	**0.69**

Kamanger, JCO, 2006

The rate of triple negative breast cancer in Hispanic women is between that of Black women and White women

	Rate of TN breast cancer
African American	26%
Hispanic	22%
White	16%

Collaboration to study Hispanic Ancestry and Cancer: CHACO

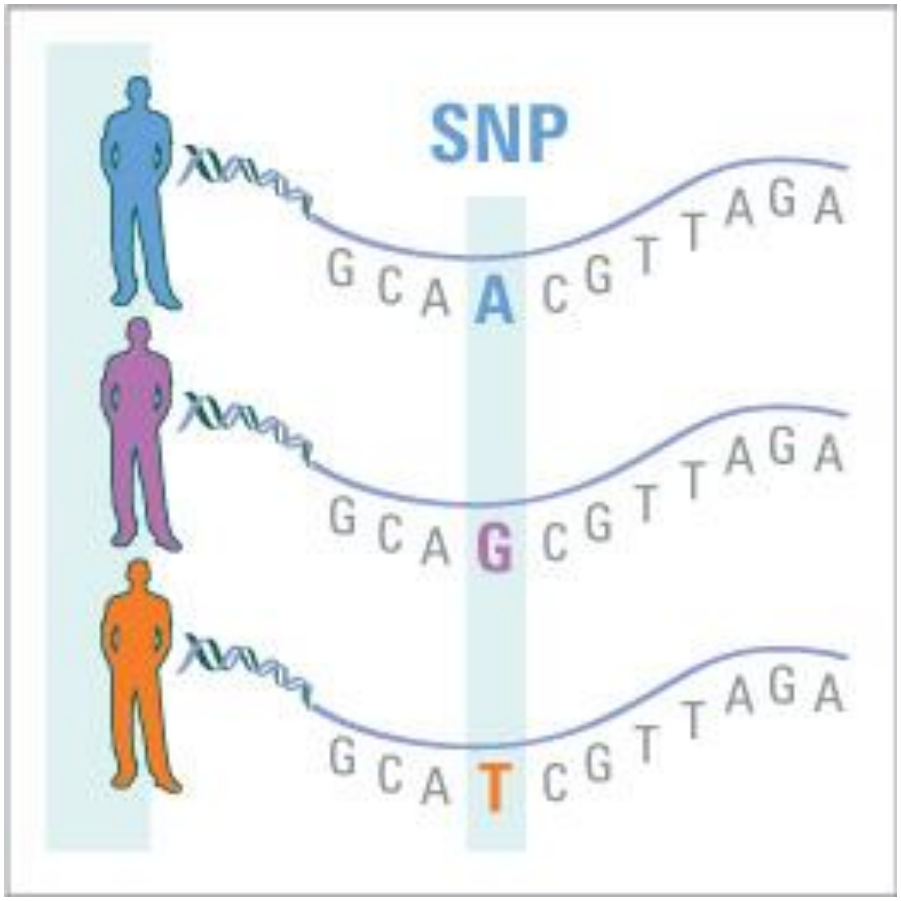
Peggy Porter MD, Linda Cook PhD, Chris Li MD PhD

Photo by: R.C. Lee, Dec 2011

Our hypothesis:

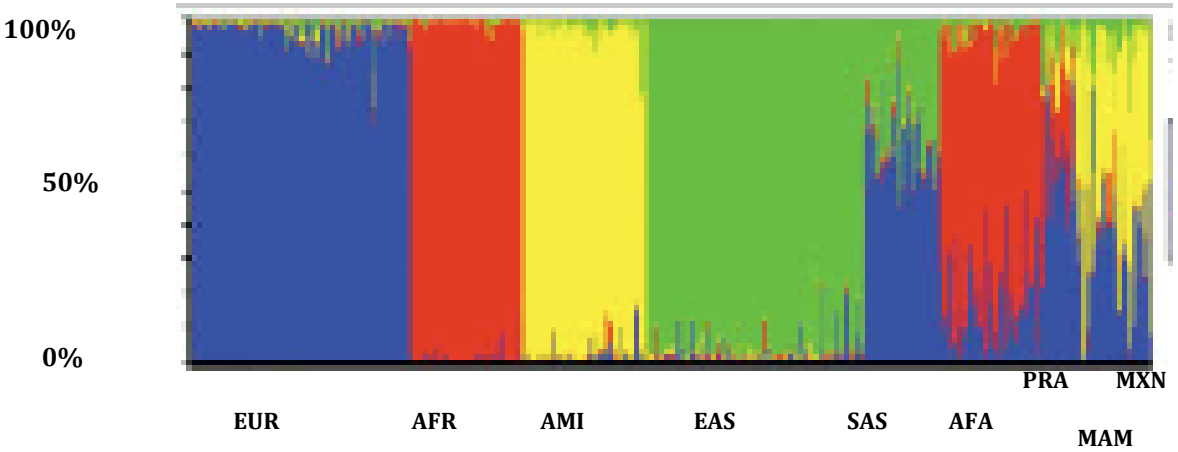
Ancestry is associated with specific breast cancer subtypes in Hispanic women

Ancestry mapping using differences in Single Nucleotide Polymorphisms

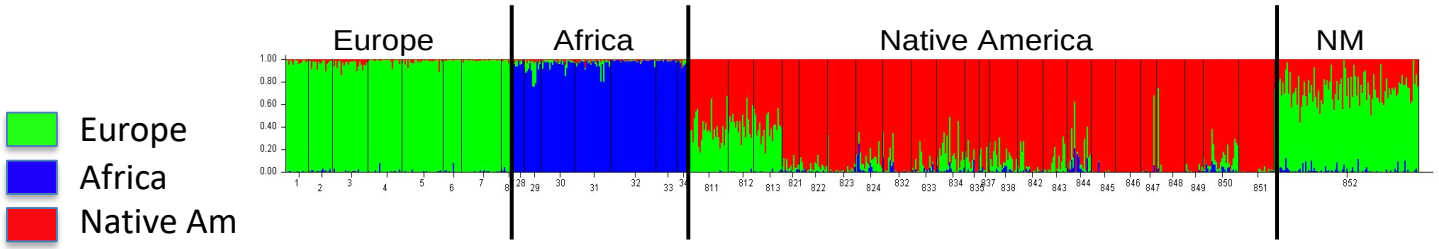


The genome sequences of any two people are 99.9% identical.
About one in 1,000 letters of human DNA can vary in the form of a SNP

Hispanic-Americans have a mixed European, Amer-Indian, and African ancestry



825 individuals using 128 ancestry informative markers (AIMs) and 4 population groups



78 NM residents and 37 ancestral populations

Acknowledgments

FHCRC

Epidemiology

Christopher Li

Kathleen Malone

Statistics

Li Hsu

Shawn Chai

UNM

Linda Cook

Porter Lab

Jamie Guenthoer

Carl Ton

Ming Gang Lin

Elizabeth Donato

Nicole Vartanian