

CSBC Breast Cancer Overview

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Objectives

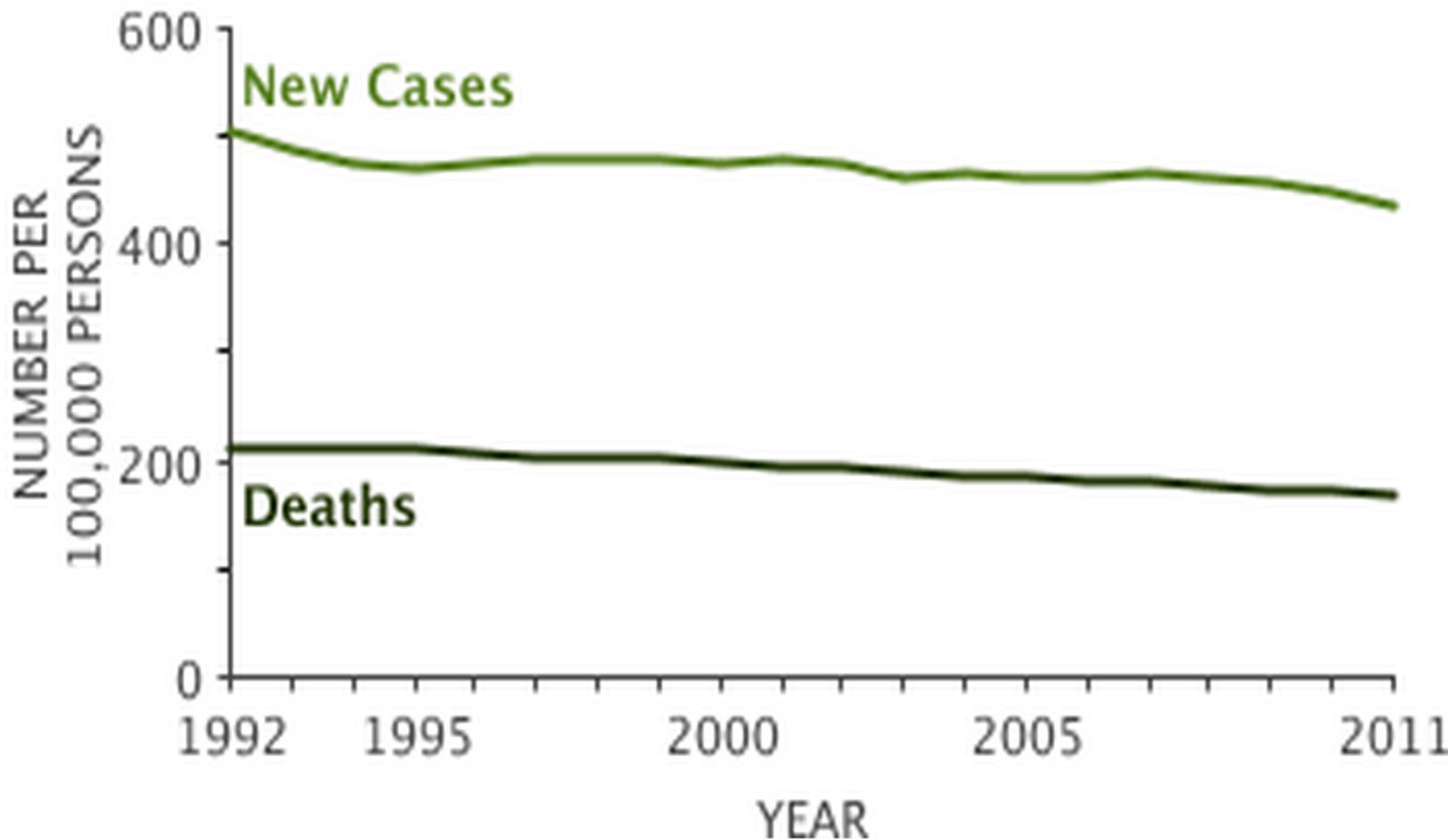
1. Breast cancer review.
2. Understand different genomic mechanisms that lead to aberrant signal transduction, including gene amplification/deletion, activating mutations and mutations that inhibit protein function.
3. Understand that molecular and genetic alterations in tumors are prognostic, diagnostic, and can be used in therapy decisions for patients.
4. Understand confounding factors in genomic analyses.

Breast Cancer Overview

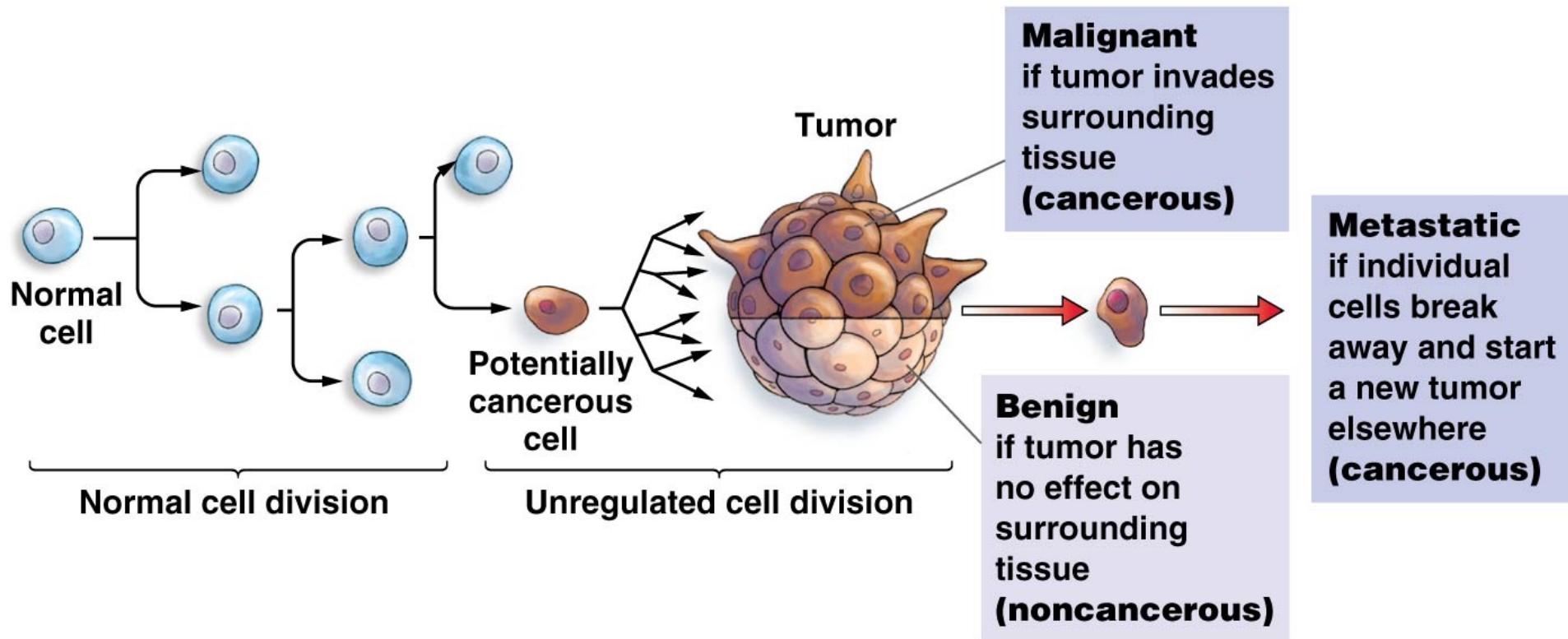
Most Common Cancer Types in U.S.

Common Types of Cancer	Estimated New Cases 2014	Estimated Deaths 2014
1. Prostate Cancer	233,000	29,480
2. Breast Cancer (Female)	232,670	40,000
3. Lung and Bronchus Cancer	224,210	159,260
4. Colon and Rectum Cancer	136,830	50,310
5. Melanoma of the Skin	76,100	9,710
6. Bladder Cancer	74,690	15,580
7. Non-Hodgkin Lymphoma	70,800	18,990
8. Kidney and Renal Pelvis Cancer	63,920	13,860
9. Thyroid Cancer	62,980	1,890
10. Endometrial Cancer	52,630	8,590

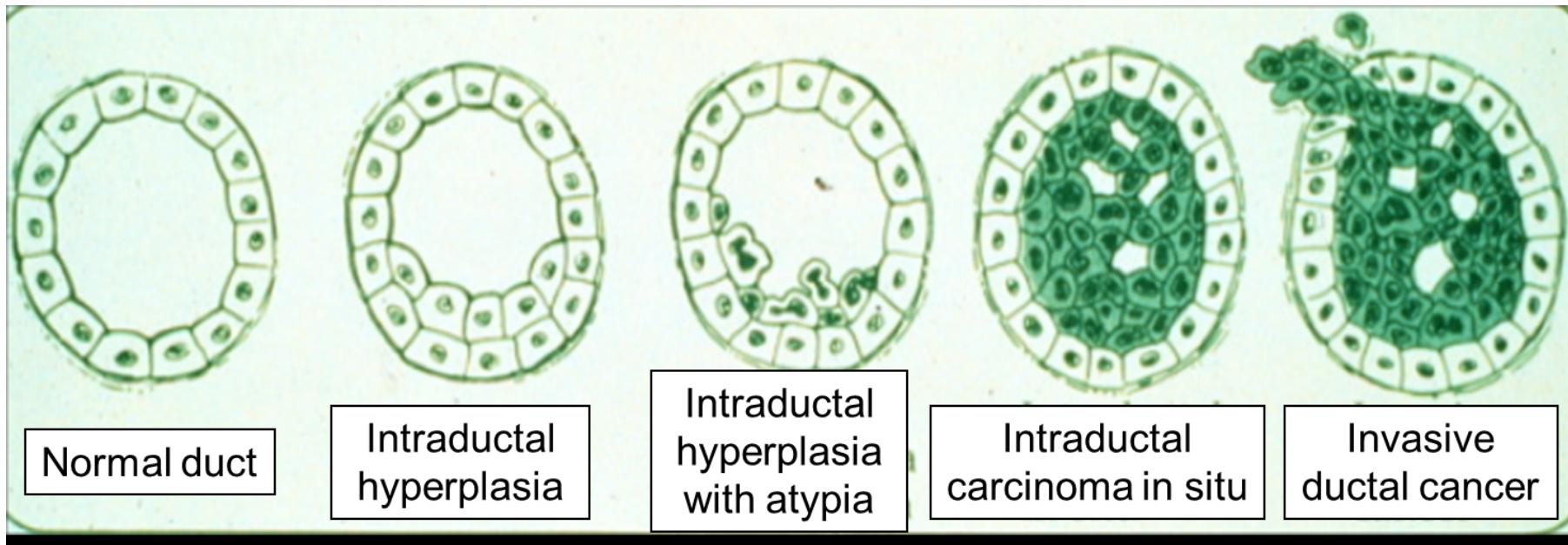
Current Progress in Cancer Diagnosis and Treatment



How do tumors develop?



Breast Cancer Development



Normal duct

Intraductal hyperplasia

Intraductal hyperplasia with atypia

Intraductal carcinoma in situ

Invasive ductal cancer

5 year survival:

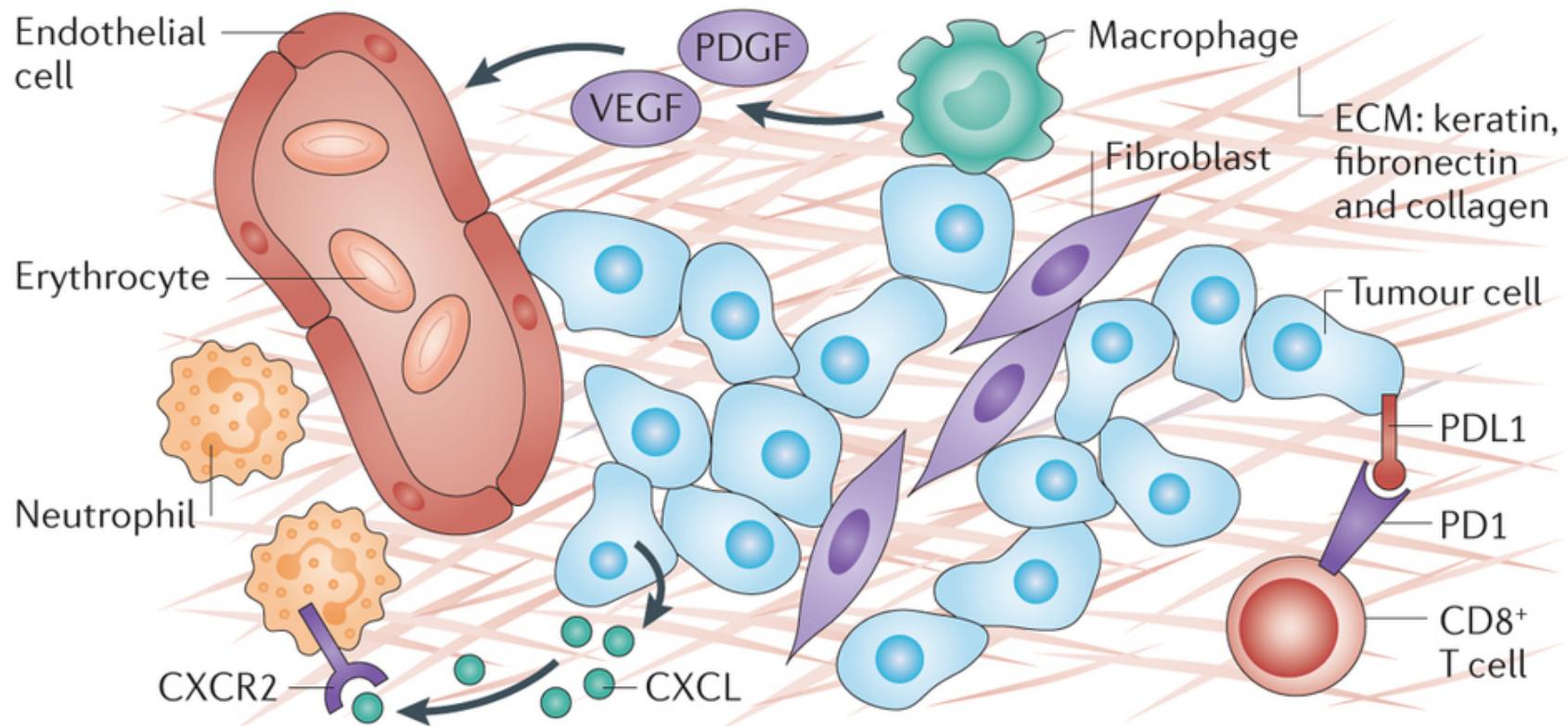
Stage 1: 95-100%

Stage 2: 86%

Stage 3: 57%

Stage 4: 20%

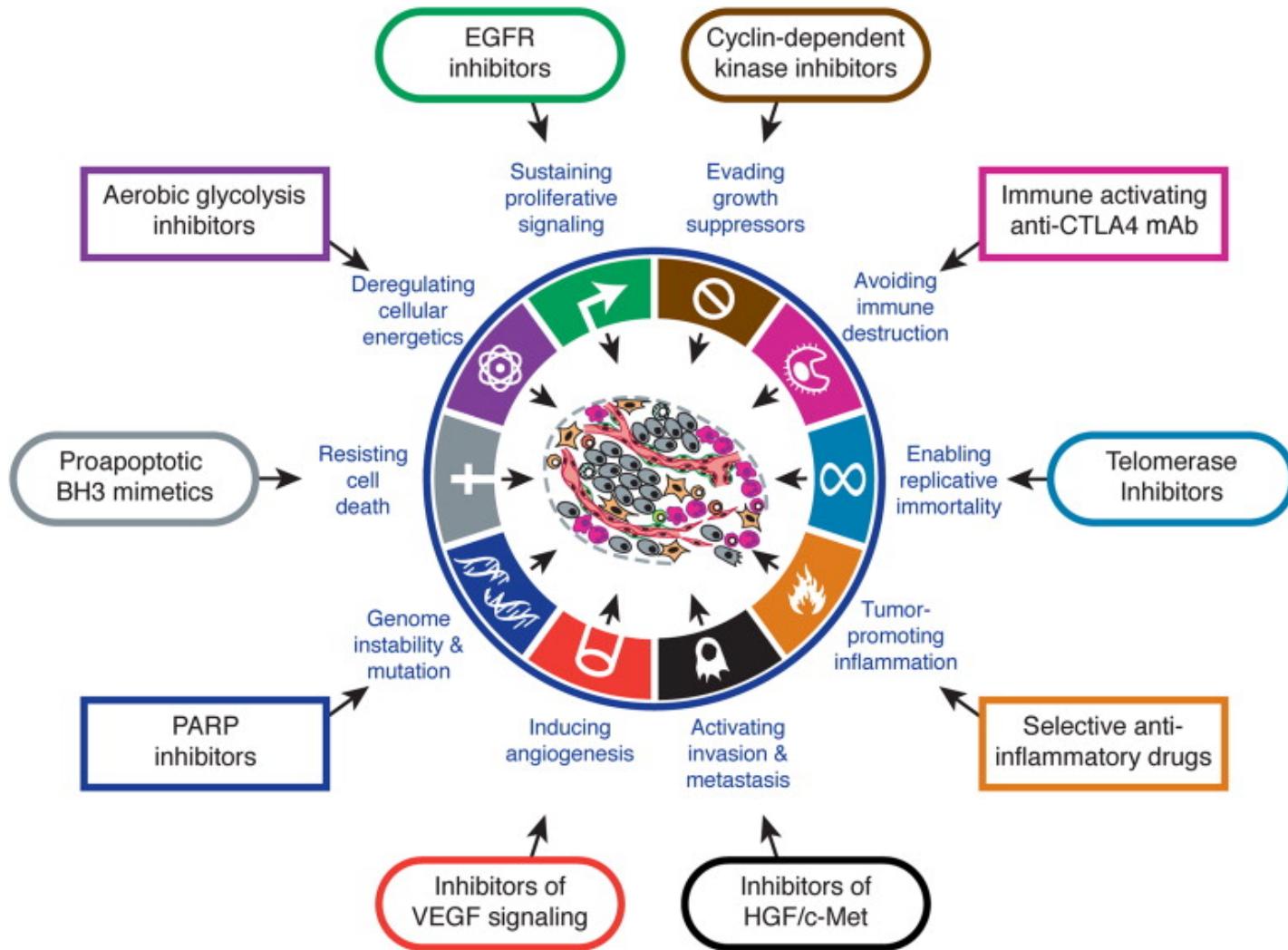
Tumor Composition



Nature Reviews | Cancer

Nature Reviews Cancer 14, 535–546 (2014)

Hallmarks of Cancer



Oncogenic Signaling Overview

Proto-oncogene



Oncogene

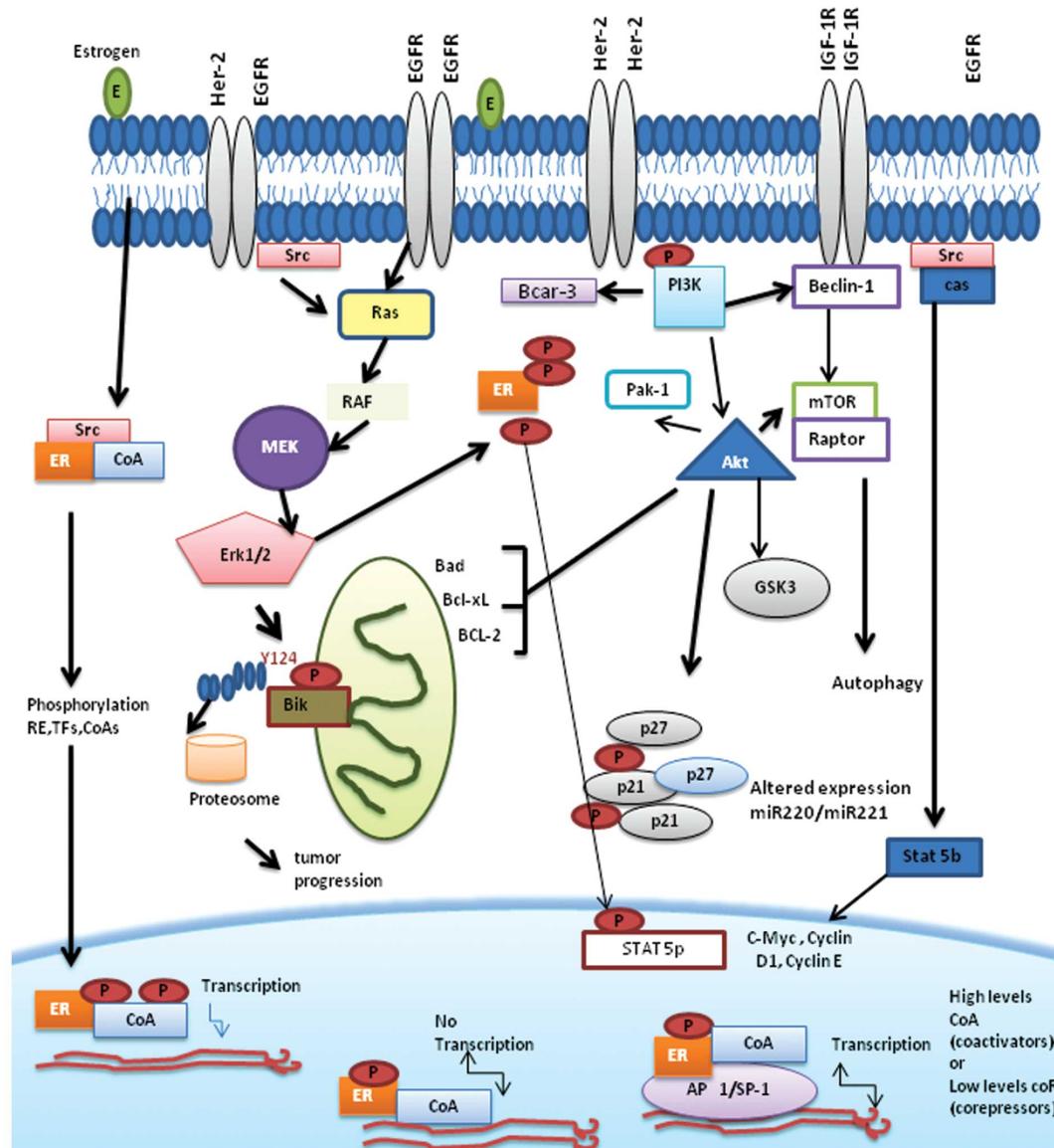


Tumor suppressor gene

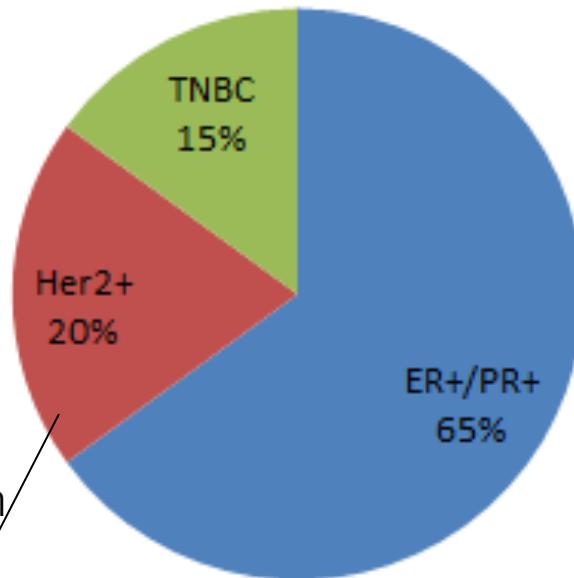


Courtesy: <http://www.tbo.com/news/education/crossing-guards-hit-the-streets-for-start-of-school-20150823/>

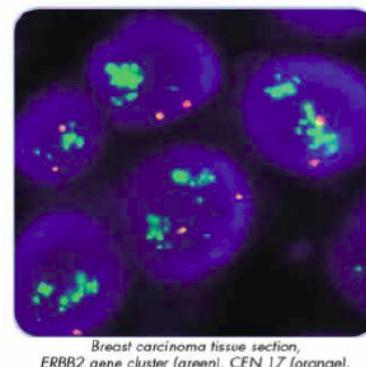
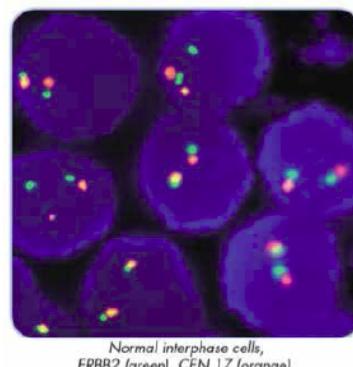
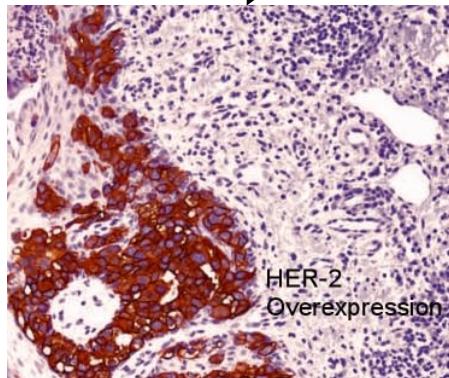
Oncogenic Signaling in Breast Cancer



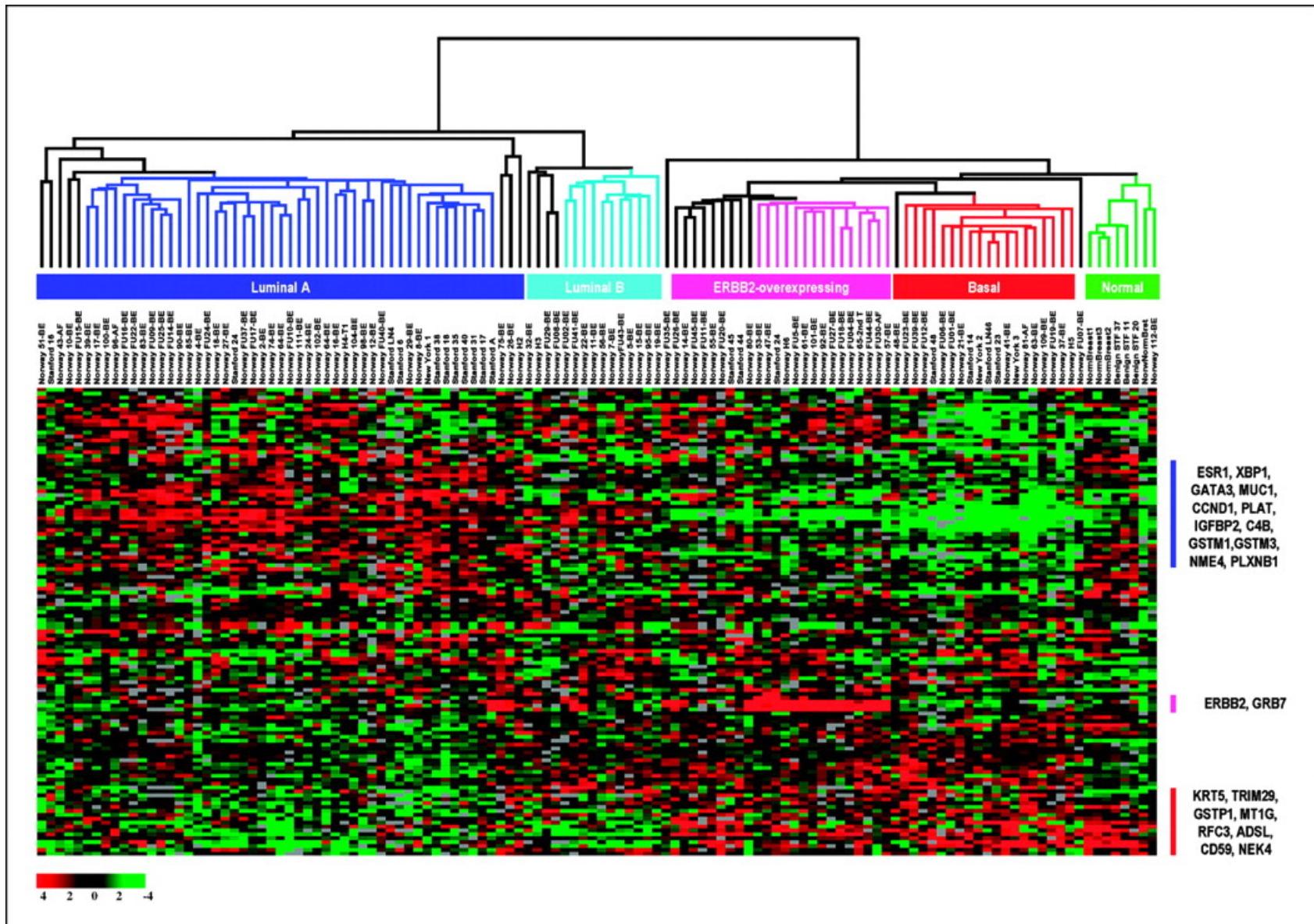
Breast Cancer by Tumor Subtype



Her2 amplification



Molecular Cancer Subtypes—Breast Cancer



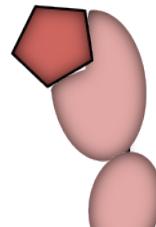
Question:

What are some of the consequences of HER2 amplification in a tumor?

Oncogenic Signaling in Breast Cancer- an example

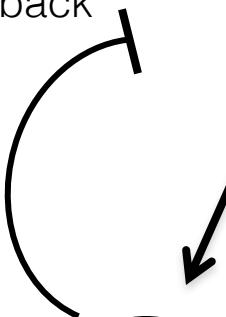
Ligand / Growth
Factor

Factor

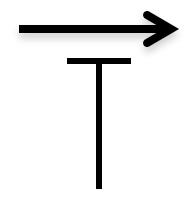


Receptor

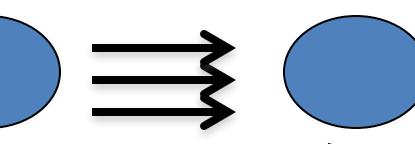
Negative
Feedback



Signal
Inhibitors



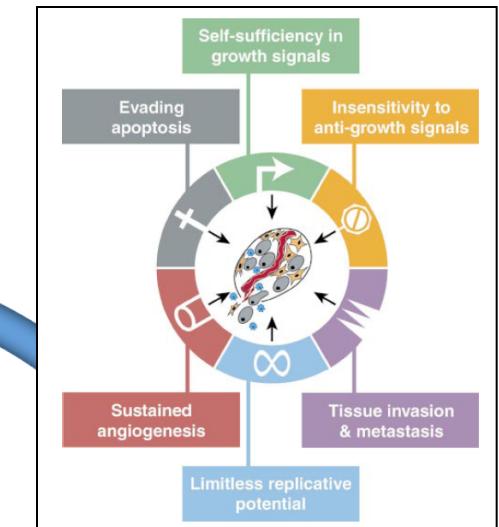
Signal transduction
can branch down
multiple pathways



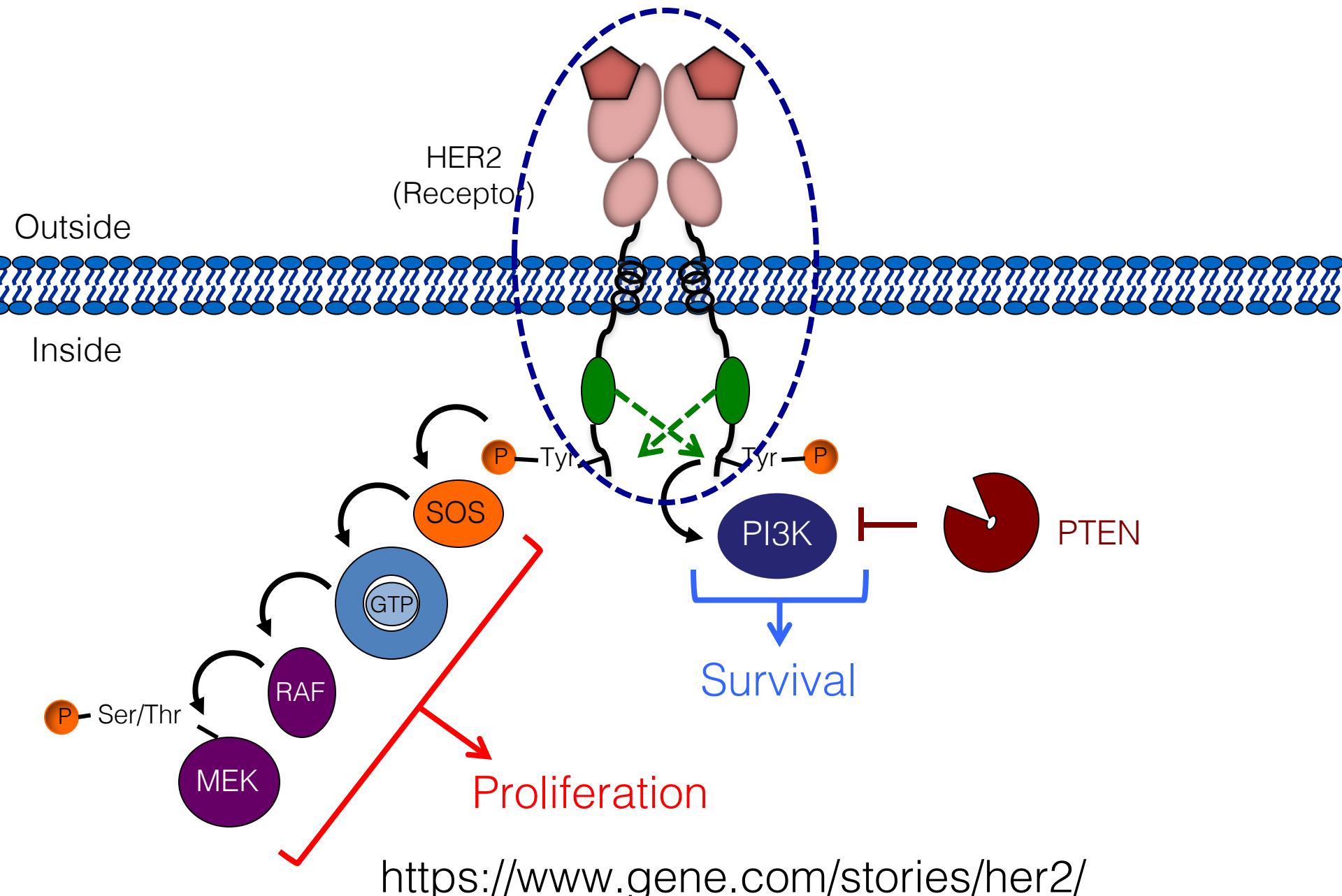
Amplification
of the signal

Cytoplasmic Effects

Genomic Effects



HER2 Oncogene



Questions:

Are the signaling pathways driving breast cancer cell growth/survival different from other cancers? What are some ways we can examine signaling across different cancers with limited patient tissue available?

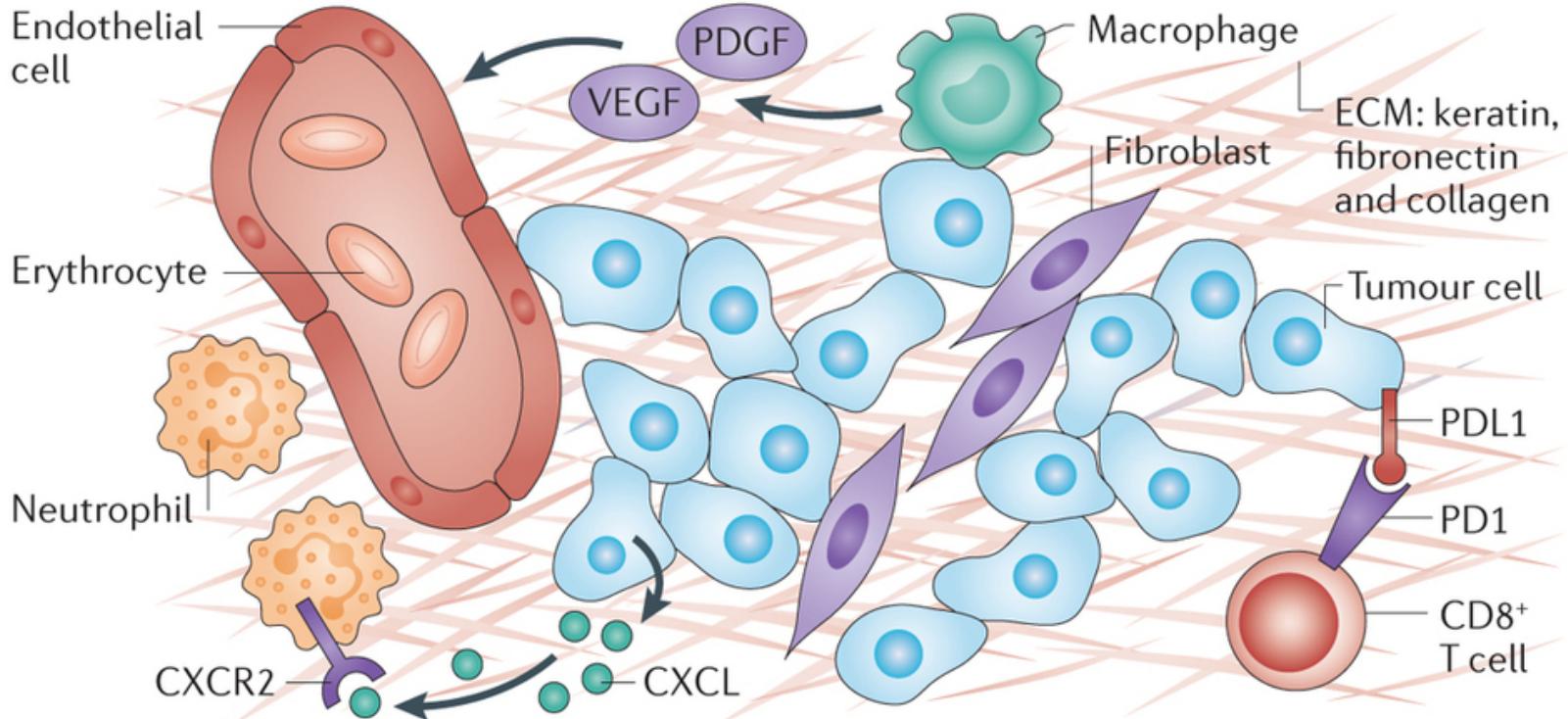
How can we assess the role of breast cancer pathways in patient survival?
Would a single gene test or a multigene test be more robust?

Confounding Variables

Confounding variables:

In statistics, a confounder (also **confounding** variable or **confounding factor**) is a variable that influences both the dependent variable and independent variable causing a spurious association.

Confounding variables (aka third **variables**) are **variables** that the researcher failed to control, or eliminate, damaging the internal validity of an experiment.

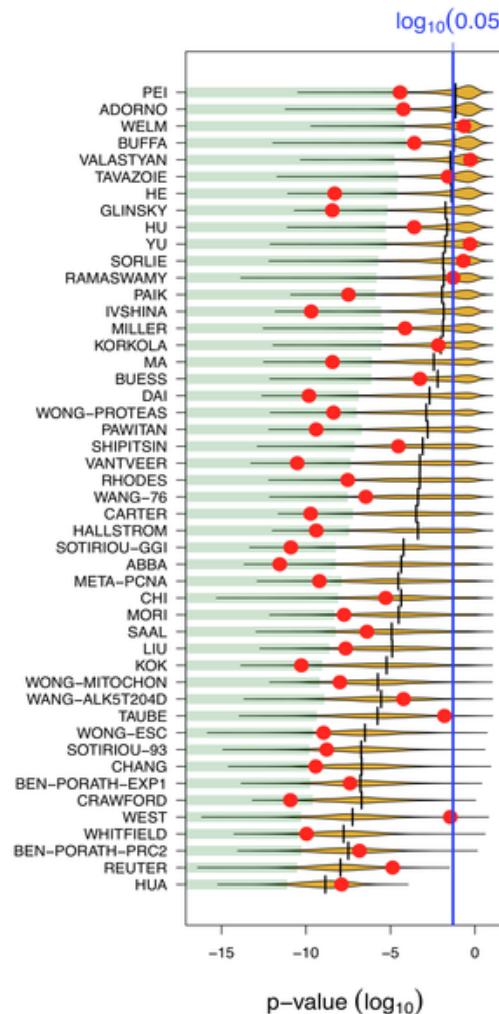


Nature Reviews | Cancer

Nature Reviews Cancer 14, 535–546 (2014)

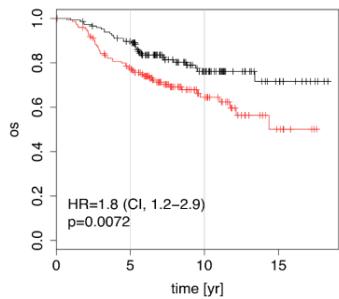
Most published signatures are not significantly better outcome predictors than random signatures of identical size

The x-axis denotes the p-value of association with overall survival. Red dots stand for published signatures, yellow shapes depict the distribution of p-values for 1000 random signatures of identical size, with the lower 5% quantiles shaded in green and the median shown as black line. Signatures are ordered by increasing sizes.

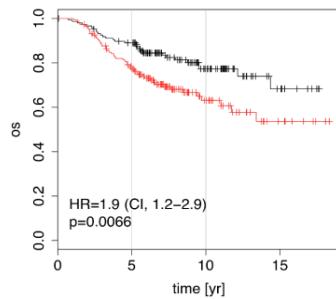


Association of negative control signatures with overall survival

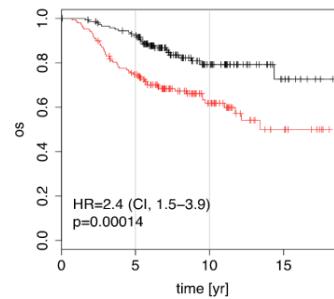
A



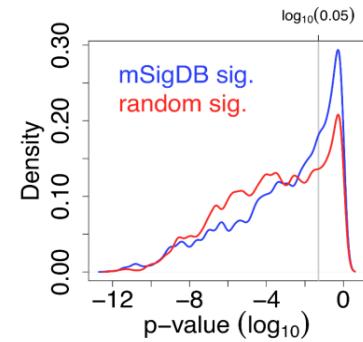
B



C



D



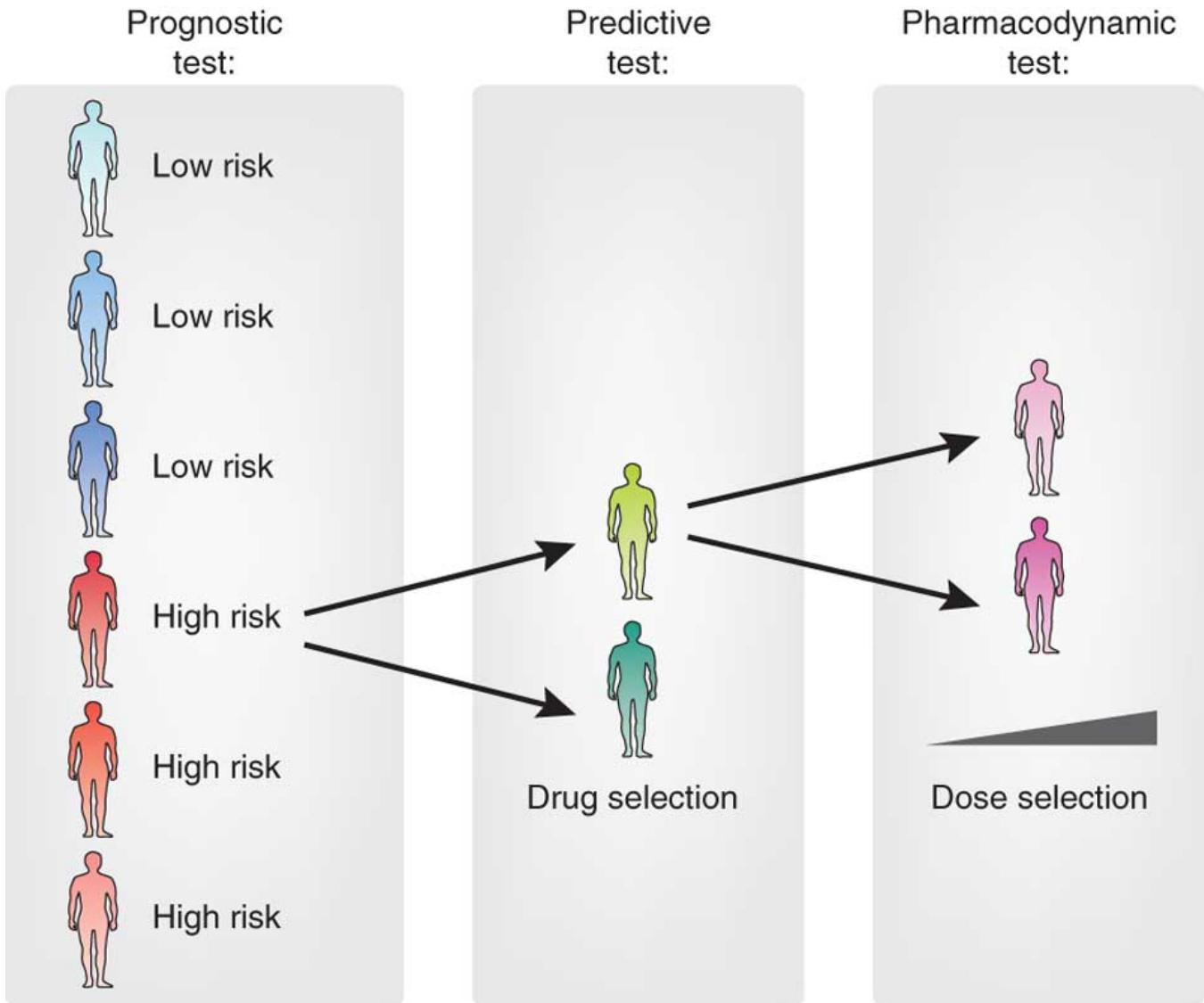
In plots A–C the NKI breast cancer cohort was split into two groups using a signature of post-prandial laughter (panel A), localization of skin fibroblasts (panel B), social defeat in mice (panel C). In panels A–C, the fraction of patients alive (overall survival, OS) is shown as a function of time for both groups. Hazard ratios (HR) between groups and their associated p-values are given in bottom-left corners. Panel D depicts p-values for association with outcome for all MSigDB c2 signatures and random signatures of identical size as MSigDB c2 signatures.

Question:

Given that ~26% of the genes are related to survival at $p<0.05$, what are some approaches you can take to develop a robust biomarker of response that is independent of confounding factors such as ER status and proliferation?

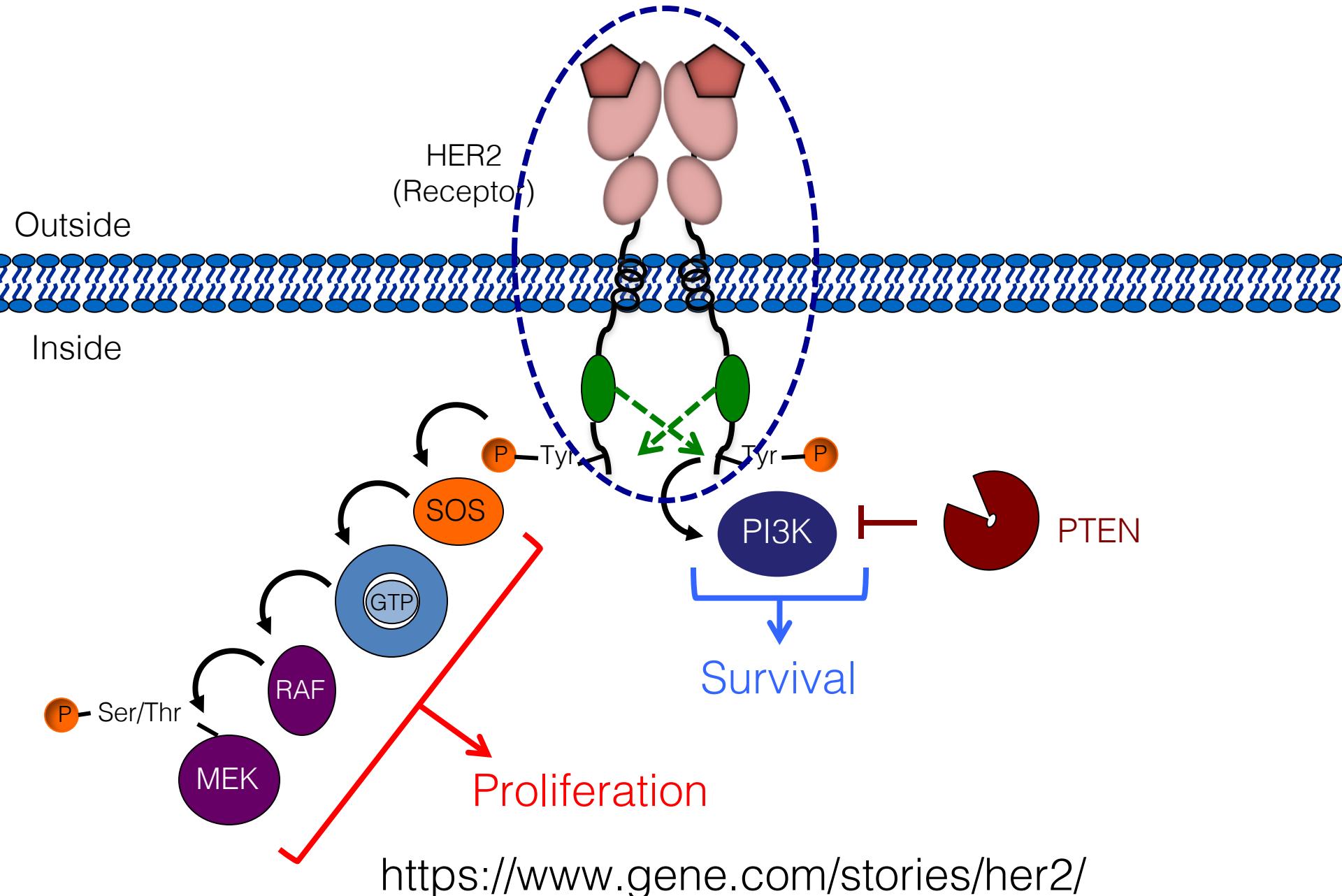
Biomarkers

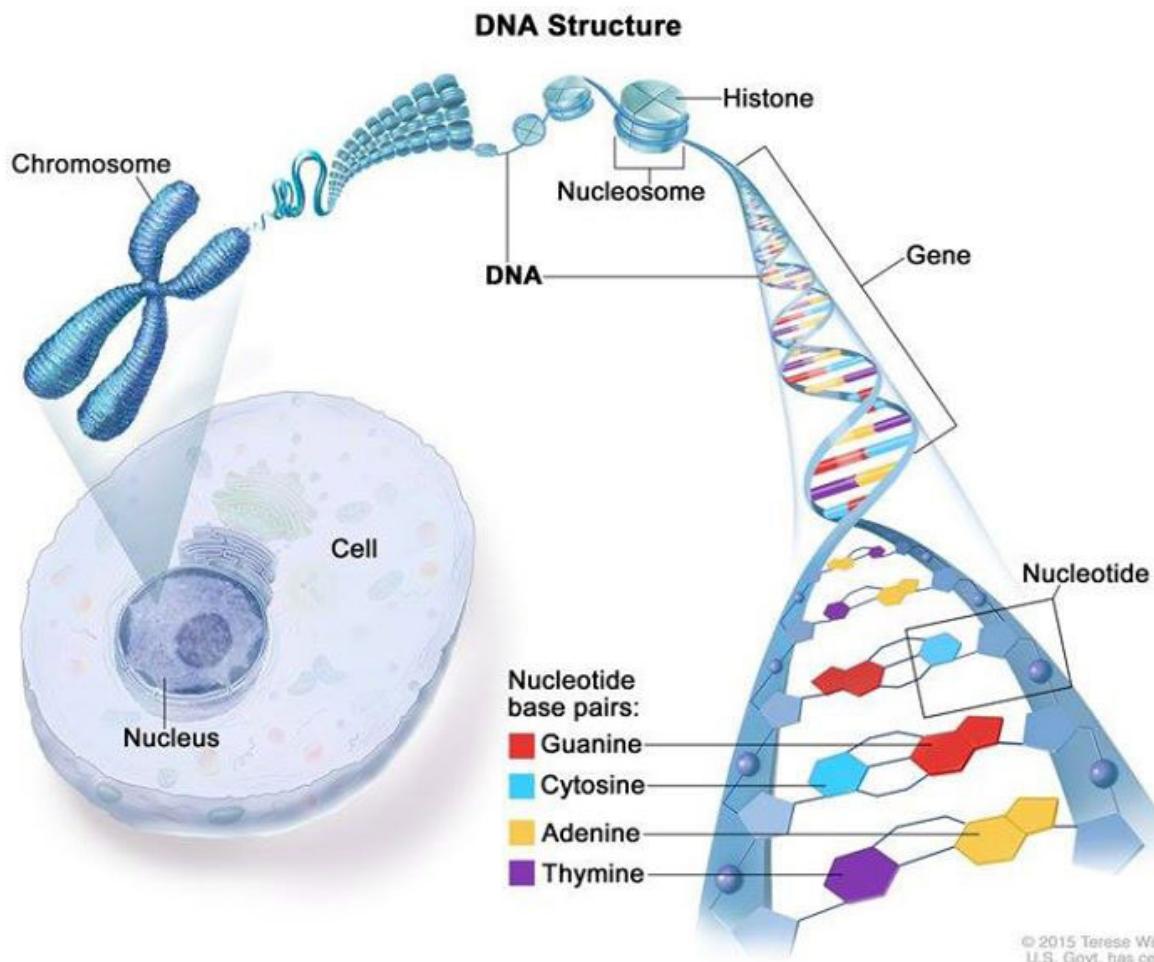
Biomarkers needed for a range of purposes



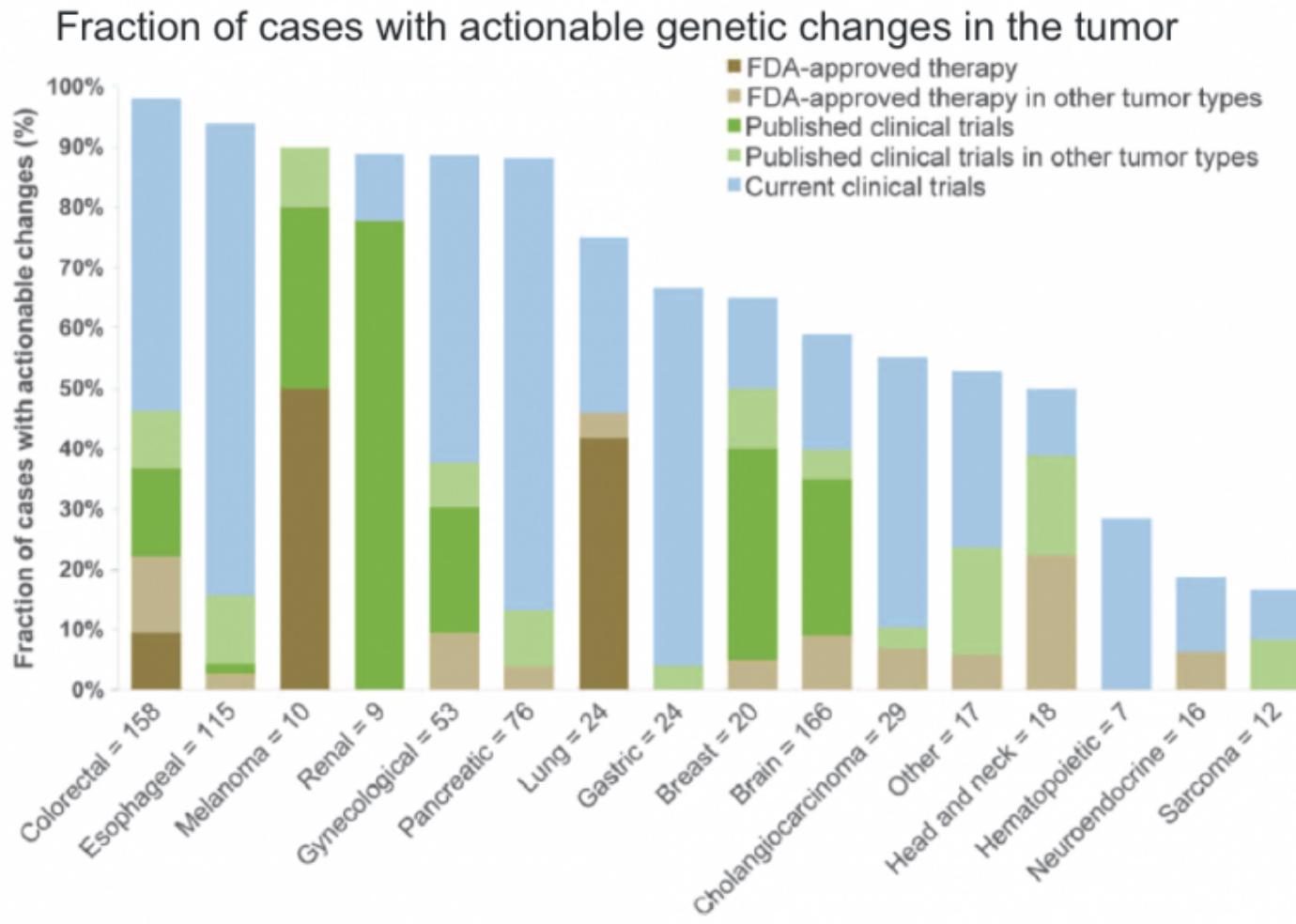
Also,
biomarkers
for pathway,
phenotype,
tumor
features

Gene, pathway, phenotype



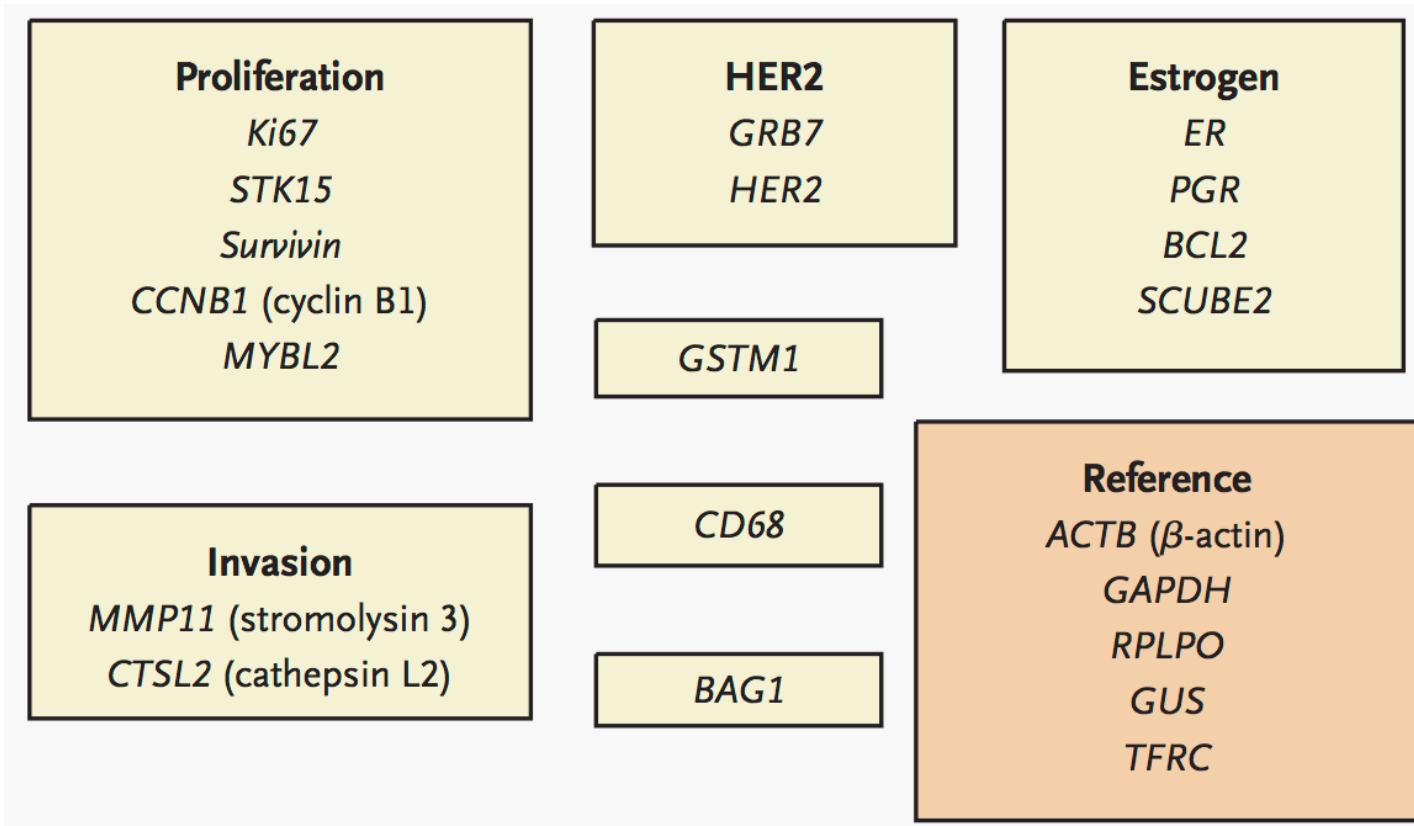


Do DNA-based tests provide actionable results?



Jones S, et al. Sci Trans Med 2015; 7(283):283ra53.

Oncotype DX: RNA based test



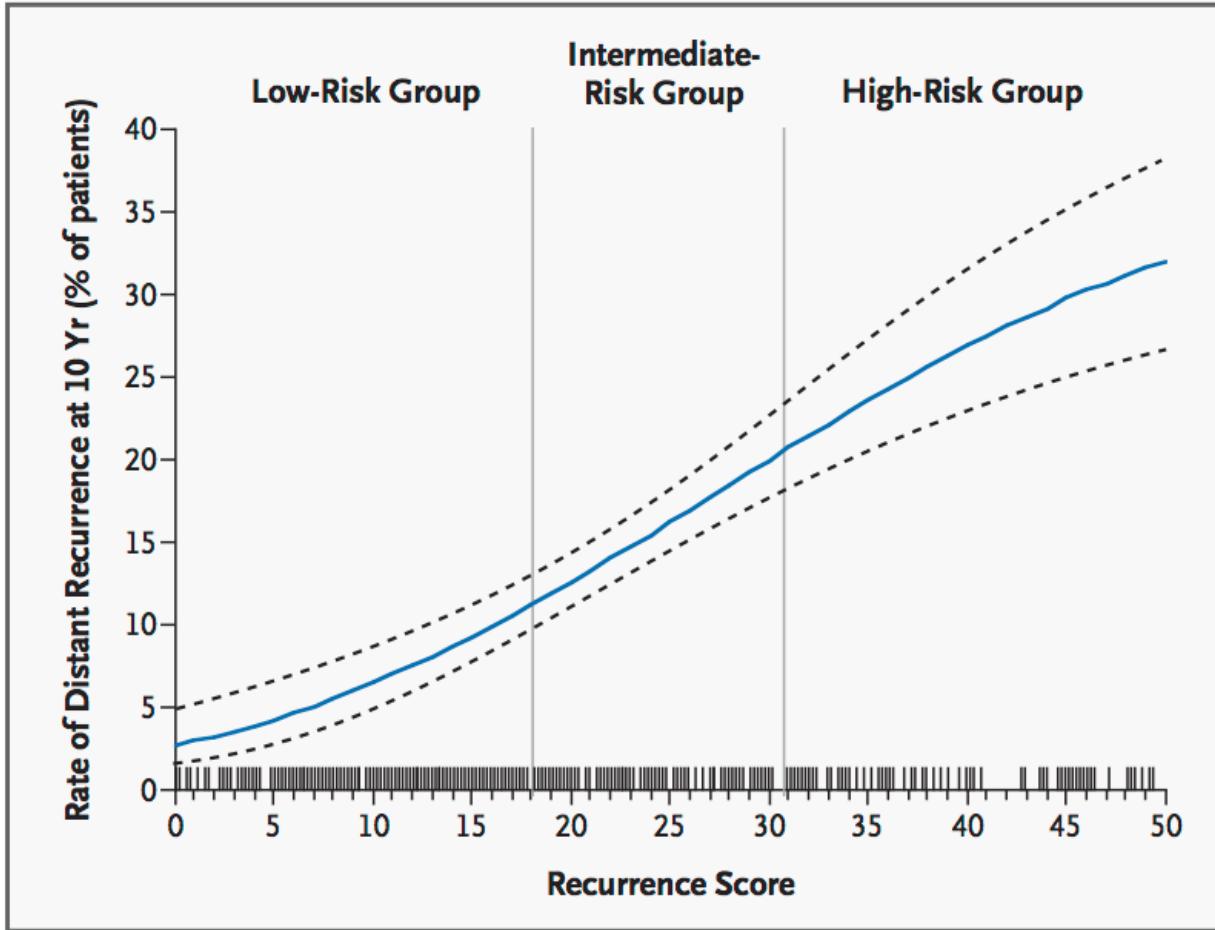
Development of the Oncotype DX Recurrence Score Assay: Formula

$$\begin{aligned}\text{Recurrence score} = & +0.47 \times \text{GRB7 group score} \\& -0.34 \times \text{ER group score} \\& +1.04 \times \text{Proliferation group score} \\& +0.10 \times \text{Invasion group score} \\& +0.05 \times \text{CD68} \\& -0.08 \times \text{GSTM1} \\& -0.07 \times \text{BAG1}\end{aligned}$$

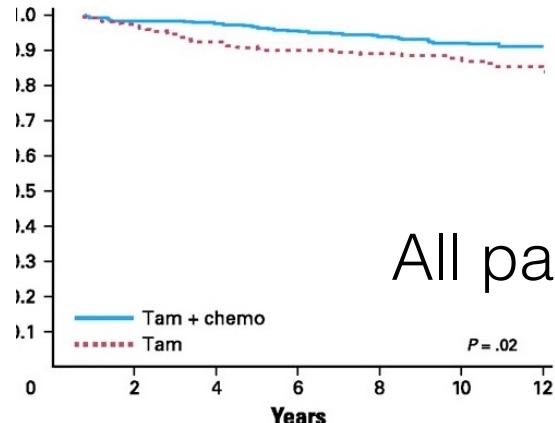
Category	Recurrence score (0 - 100)
Low risk of recurrence	<18
Intermediate risk of recurrence	≥18 to <31
High risk of recurrence	≥31

SOURCE: Paik S et al. *N Eng J Med* 2004;351:2817-26. [Abstract](#)

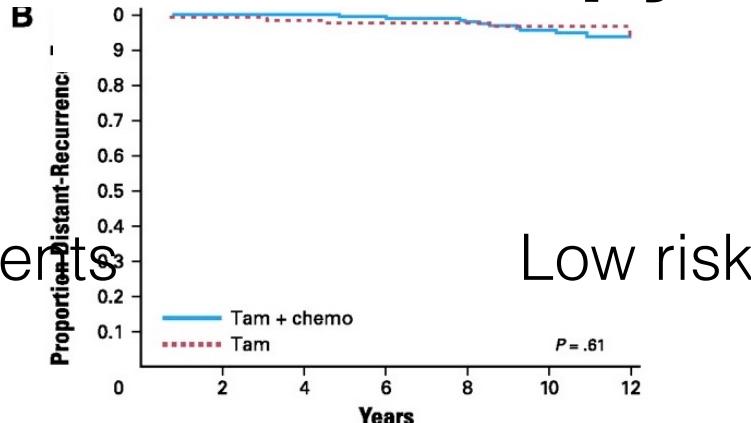
Recurrence Score Predicts Recurrence



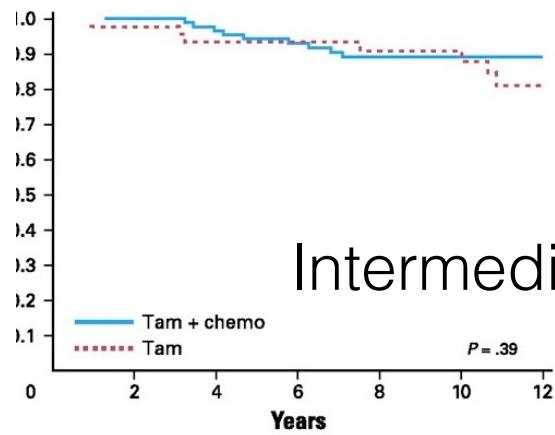
Biomarkers identify subpopulations that will respond to therapy



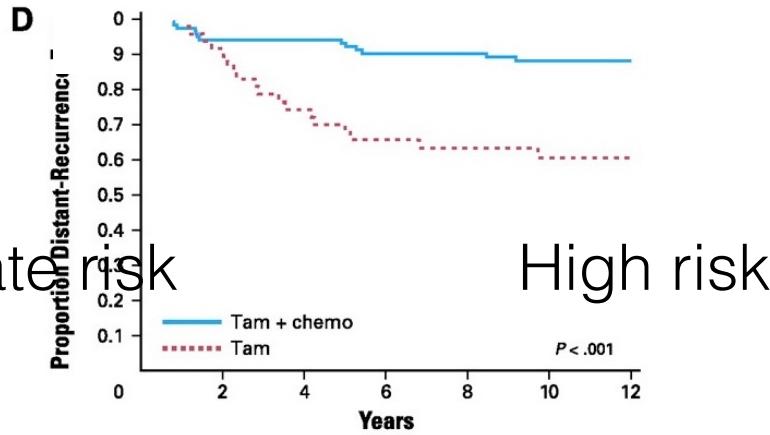
All patients



Low risk



Intermediate risk

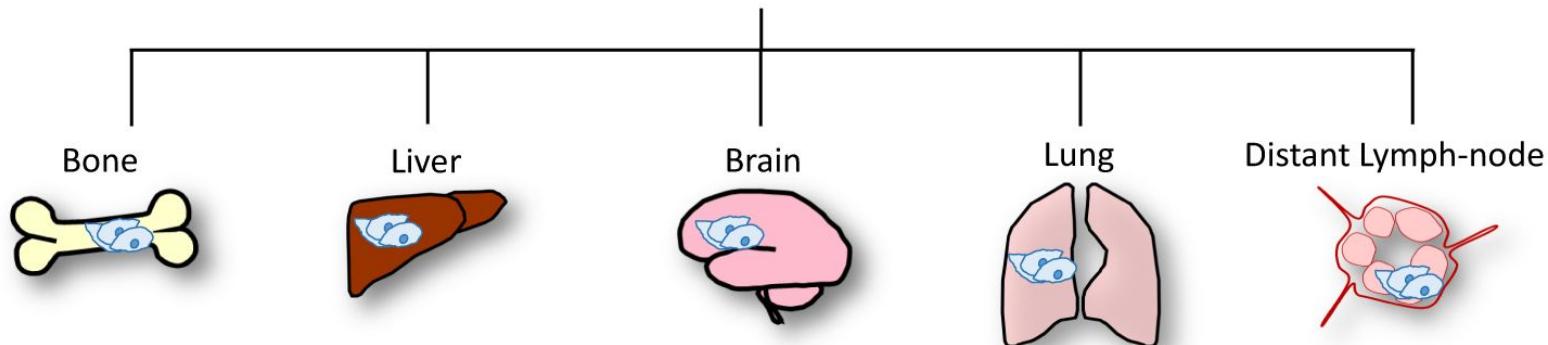


High risk

Question:

Oncotype Dx is a gene expression based biomarker of cancer recurrence and chemotherapy benefit. What other types of biomarkers may be useful?

Breast Cancer Distant Metastases



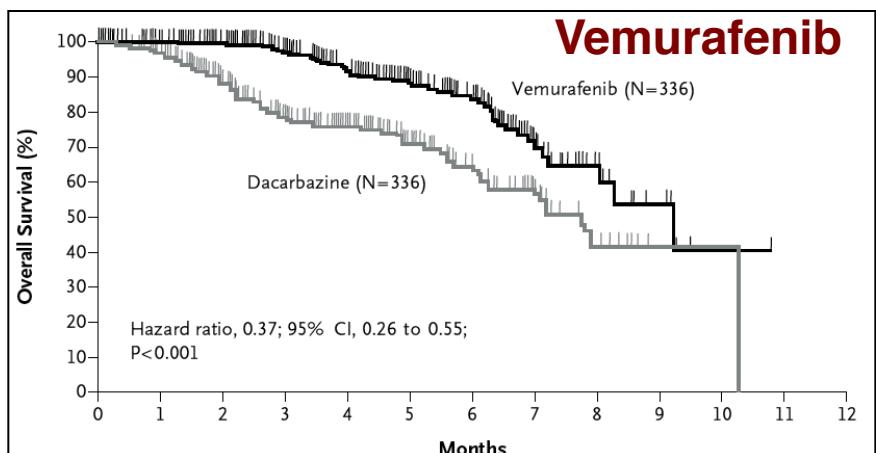
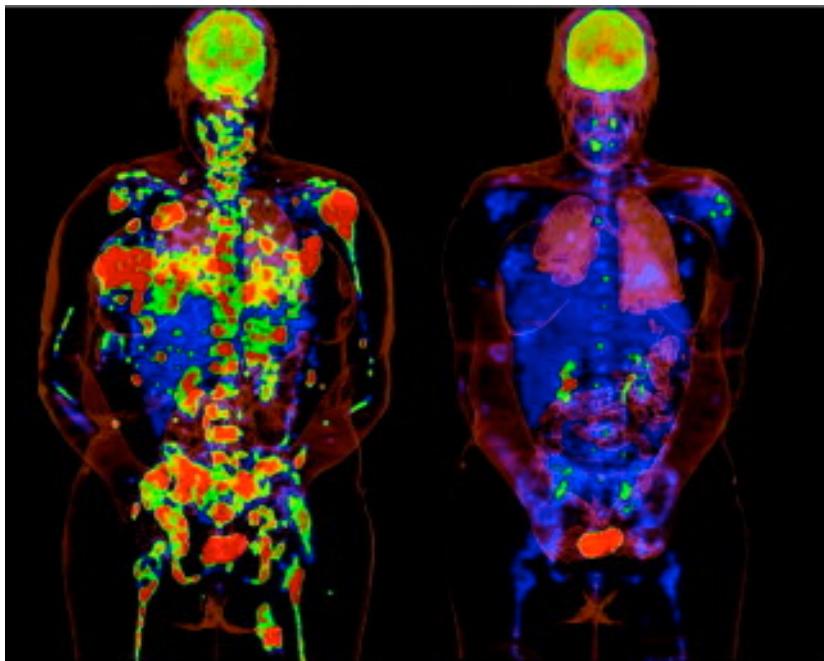
Associated subtypes

Molecular features

	Bone	Liver	Brain	Lung	Distant Lymph-node
Associated subtypes	Luminal-HER2	HER2-enriched ER-positive Luminal B Luminal-HER2	HER2-enriched Luminal-HER2 TN-nonbasal Basal-like	TN-nonbasal Basal-like Luminal B HER2+, HR-, p53-	Luminal type HER2-enriched
Molecular features	Growth factors: IGF1, PGE2, TGF β , PDGF and FGF2 Interleukins: IL-11, IL-1, IL-6 PTHRP OPN Heparanase RANKL-RANK pathway Src-dependent pathway	Chemokines and receptors: CXCR4/CXCL12 Interleukins: IL-6 Integrin complexes: α 2 β 1, α 5 β 1 N-cadherin HIF-regulated genes: LOX, OPN, VEGF, TWIST β -catenin-independent WNT signaling Downregulation of ECM (stromal) genes	ST6GALNAC5 CSC markers: Nestin, CD133, and CD44 Growth factors: VEGF and HBEGF Chemokines and receptors: CXCR4 Cytokines: CK5 MMP-1 and MMP-9 IL-8 Ang-2 COX2 L1CAM	Growth factors and their receptors: TGF β , EGFR, EREG, VEGF Matrix metalloproteinases: MMP-1 and MMP-2 COX2 LOX BMP inhibitors: GALNTs and Coco	Kallikreins: KLK10, KLK11, KLK12, and KLK13 Downregulation of BCR signal pathway

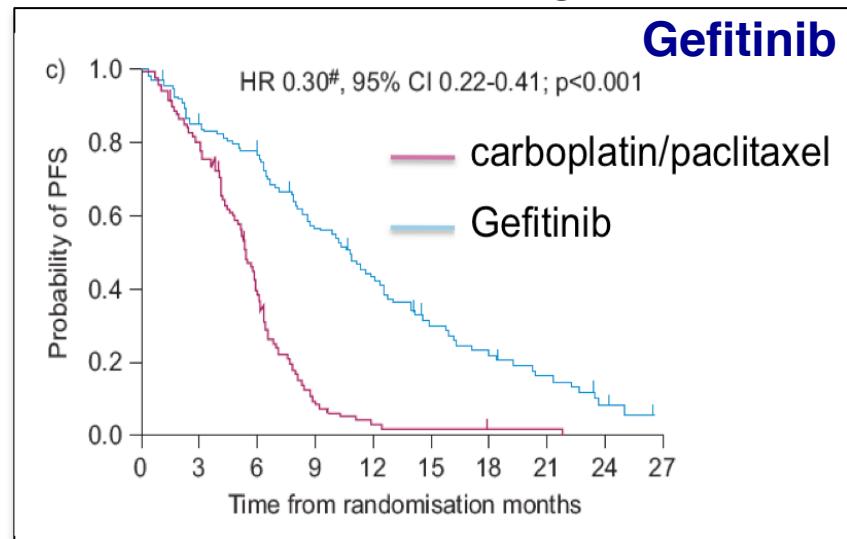
Targeted Therapies Improve Patient Outcome, But Often Fail to Cure Advanced Stage Cancer

Melanoma

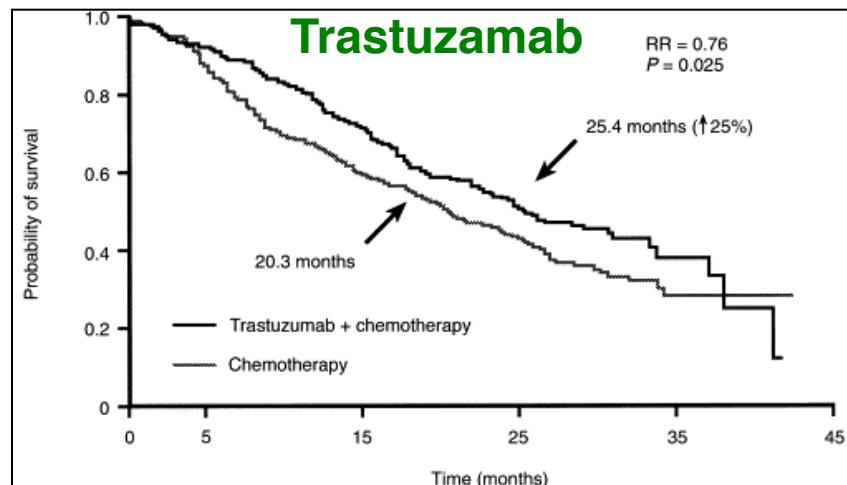


N Engl J Med 364;26 , 2011

Non Small Cell Lung Cancer



Her2+ Breast Cancer

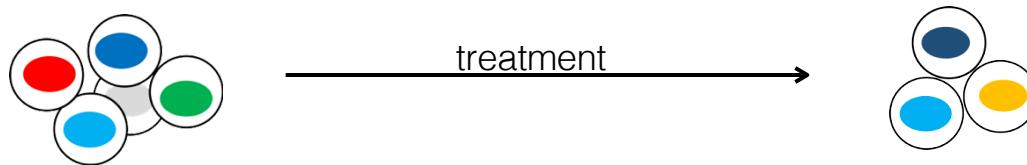


European Journal of Cancer, Vol 37. Supp 1.2001

Question:

Why aren't these drug regimens curing patients?

Tumor subclone heterogeneity and evolution



tumor heterogeneity evolves

each patient's tumor has the potential for a unique
evolutionary trajectory

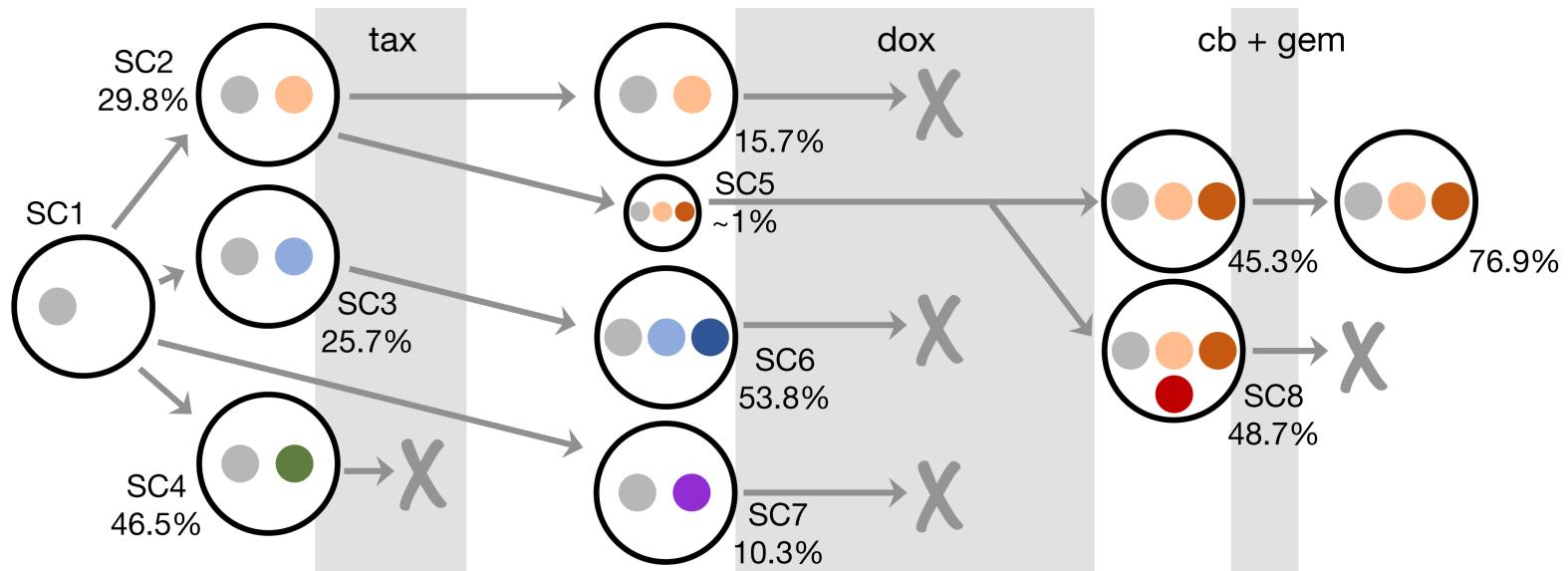
SUMMARY

1. Genomic data can predict patient outcomes
2. Confounding variables are important to control for in complex datasets
3. Biomarkers related to tumor subtypes can predict drug response
4. Future efforts need to account for additional cancer features, such as heterogeneity and plasticity

Thank You!

Please contact me with questions:
abild@coh.org

Longitudinal evolution of a breast cancer patient



Total of ~15000 variants, ~3,000 variants evolving over time (~26 total coding)