

Every Cancer is a genetic disease BUT Cancer is rarely inherited. Why?

- Cancers develop due to the accumulation of **somatic** mutations. **Germline** mutations are usually lethal.
- Cancer is a multi-step process
- **Heterozygosity** at specific loci can predispose people to develop cancer

SIX DIABOLICAL SUPERPOWERS OF CANCER

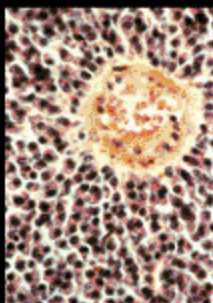
1. GROWTH EVEN IN THE ABSENCE OF NORMAL "GO" SIGNALS

Most normal cells wait for an external message before dividing. Cancer cells (*image*) often counterfeit their own pro-growth messages.



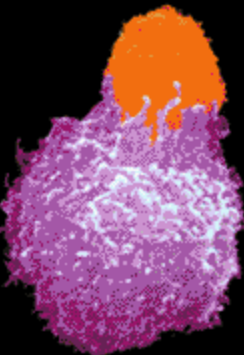
2. GROWTH DESPITE "STOP" COMMANDS ISSUED BY NEIGHBORING CELLS

As the tumor (*yellow*) expands, it squeezes adjacent tissue, which sends out chemical messages that would normally bring cell division to a halt. Malignant cells ignore the commands.



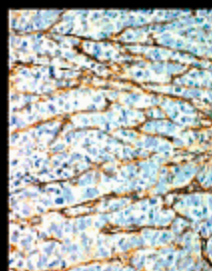
3. EVASION OF BUILT-IN AUTODESTRUCT MECHANISMS

In healthy cells, genetic damage above a critical level usually activates a suicide program. Cancerous cells (*magenta*) bypass this mechanism, although agents of the immune system (*orange*) can sometimes successfully order the cancer cells to self-destruct.



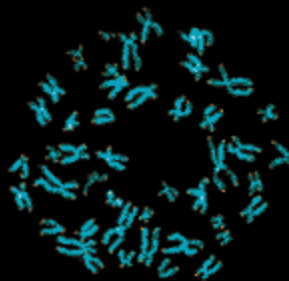
4. ABILITY TO STIMULATE BLOOD VESSEL CONSTRUCTION

Tumors need oxygen and nutrients to survive. They obtain them by co-opting nearby blood vessels to form new branches (*brown streaks*) that run throughout the growing mass.



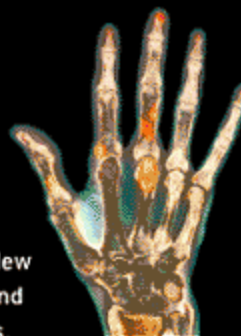
5. EFFECTIVE IMMORTALITY

Healthy cells can divide no more than 70 times. Malignant cells need more than that to make tumors. So they work around systems—such as the telomeres (*yellow*) at the end of chromosomes (*blue*)—that enforce the reproductive limit.



6. POWER TO INVADE OTHER TISSUES AND SPREAD TO OTHER ORGANS

Cancers usually become life-threatening only after they somehow disable the cellular circuitry that confines them to a specific part of the particular organ in which they arose. New growths (*orange and yellow*) appear and eventually interfere with vital systems.



Clockwise from top right: CHRIS JONES Corbis; PETER LANSDORP University of British Columbia; SCIENCE PHOTO LIBRARY; FRANK LYNCH QualTek Molecular Laboratories; ANDREJS LIEPINS/SPL; CNRI/SPL; SPL

Cancer Cells have altered Chromosome Numbers

Karyotype from Breast Cancer Cell

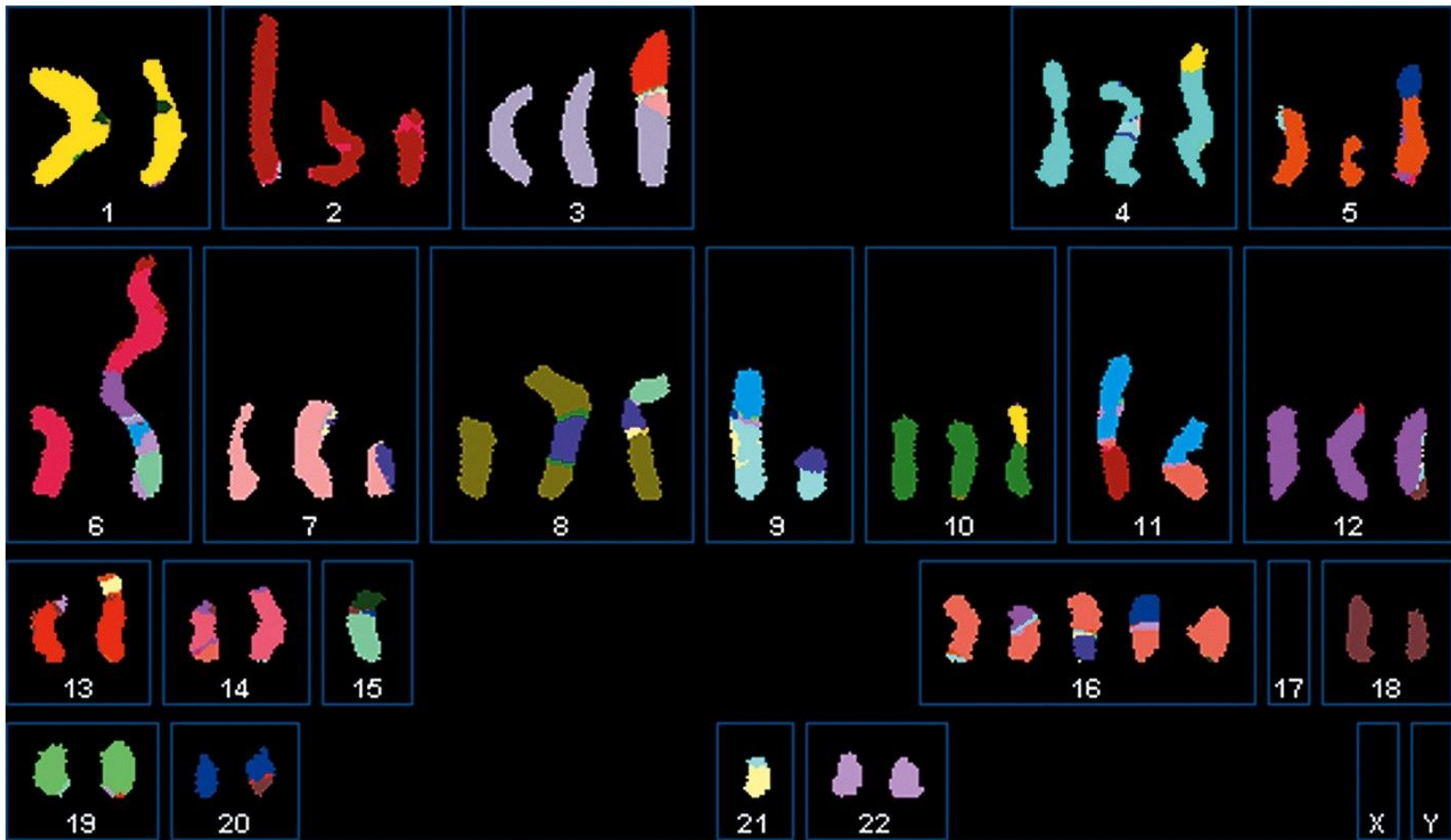


Figure 16-5 Cell and Molecular Biology, 5/e (© 2008 John Wiley & Sons)

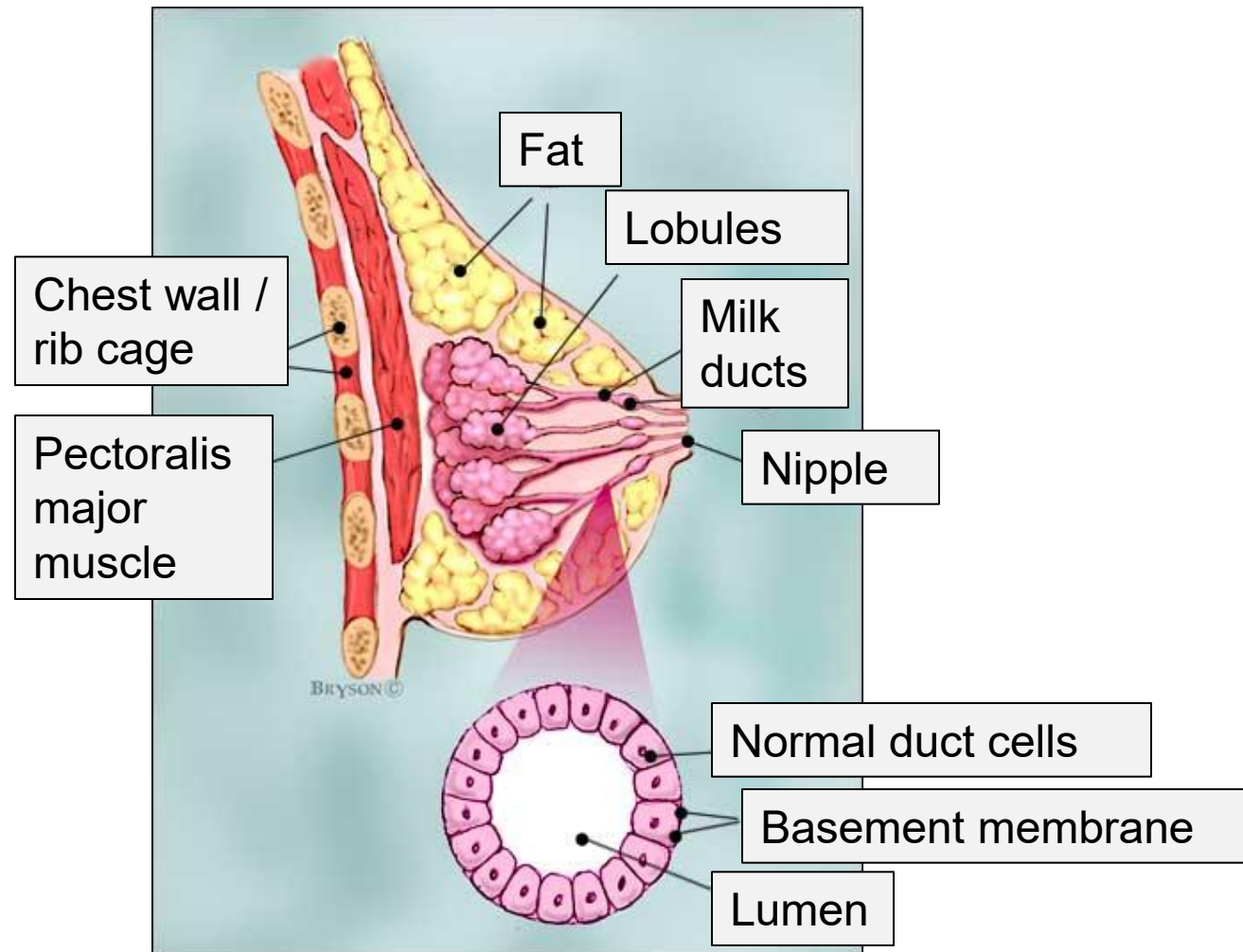
***Loss of checkpoint control = faulty
chromosome segregation***

Cancer is *Extremely* Heterogeneous

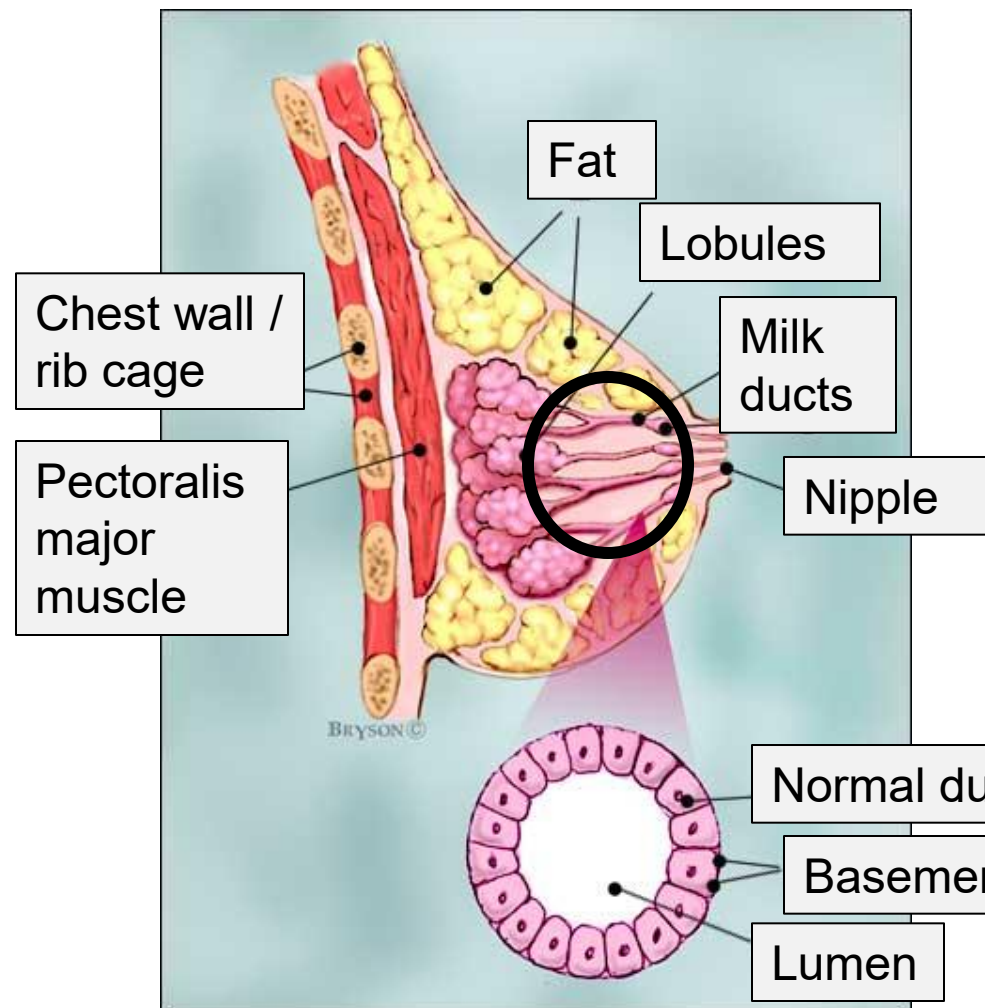
- Neoplasm* – Greek *neo* = new, *plasm* = creation, formation
– a.k.a. tumor (Latin "tumere" to swell), suffix “-oma”
- **Hematopoietic cancers** (i.e., individual cells) versus **solid tumors** (masses)
 - Lymphoid & myeloid neoplasms vs. breast, colon, etc
 - Transformed **mesenchymal** cells (sarcomas) vs. transformed **epithelial** cells (carcinomas).
 - Muscle, vascular & hematopoietic neoplasms vs. most breast, colon and lung neoplasms

Classification of a disease is paramount in understanding its **etiology** and how to **effectively treat it**.

Understanding Breast Anatomy



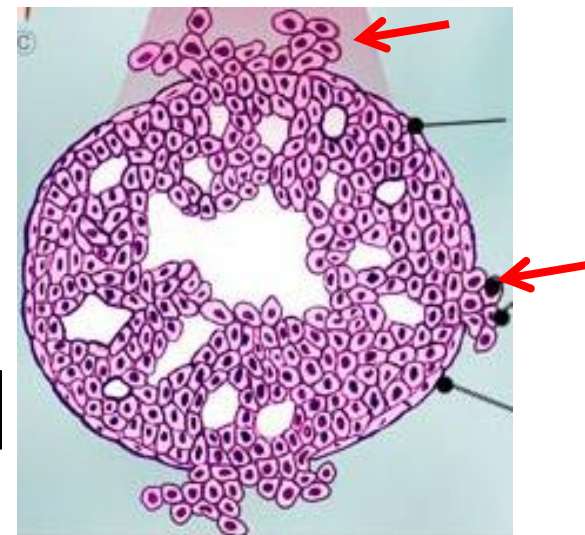
Cancer in the Milk Ducts: Ductal Carcinoma



"in situ"
means
"in its
original
place"

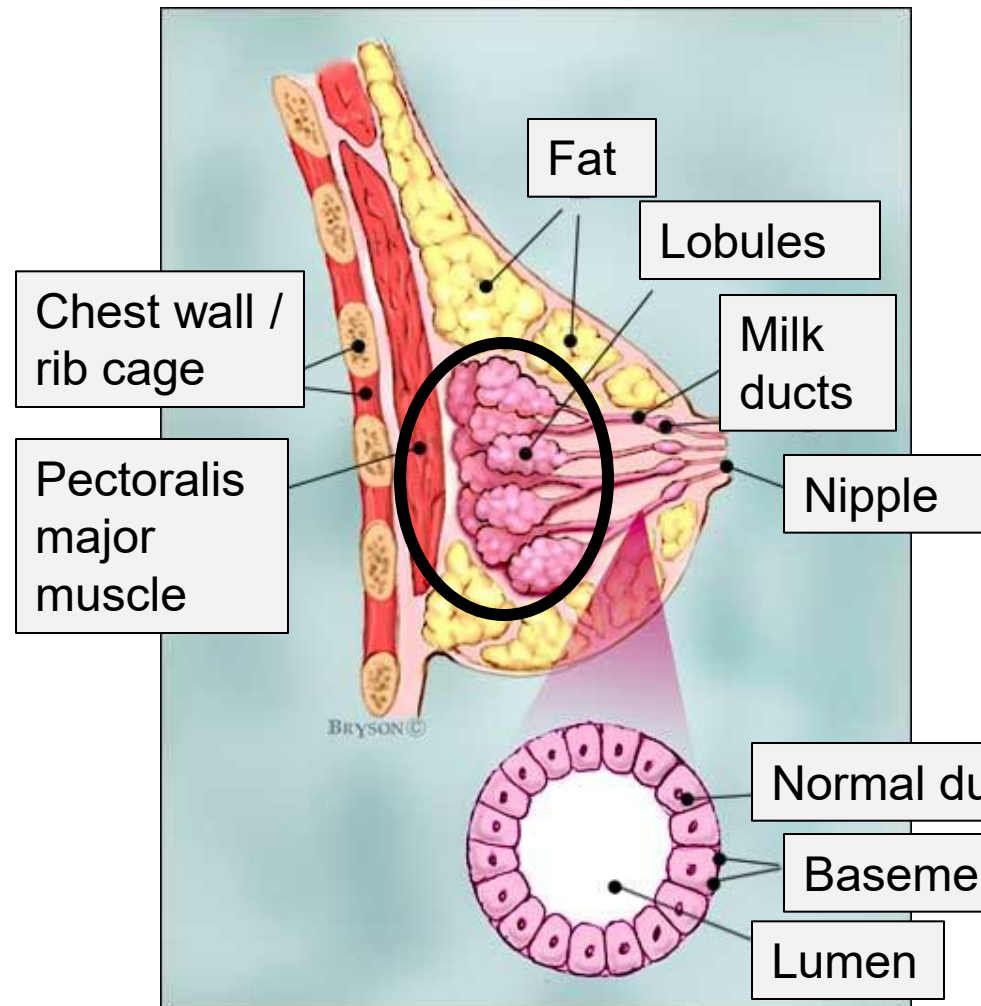


Ductal Carcinoma *in situ* (DCIS)

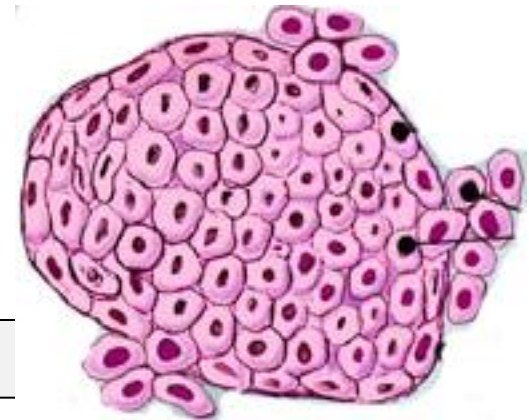


Invasive Ductal Carcinoma (IDC)

Cancer in the Breast Lobules: Lobular Carcinoma



Lobular Carcinoma *in situ* (LCIS)



Invasive Lobular Carcinoma (ILC)

Pathological Grade of Neoplasm

Microscopic examination of histology (usu. biopsy)

How much of the tissue looks like it should?

Linked to prognosis. Scale: 3-9.

- Histologic Grade: How many cells still look like normal [tissue] cells? (1, 2 or 3) *Aberrant differentiation*
- Nuclear Grade: What is the size and shape of the nucleus? (1, 2 or 3) *Aneuploidy*
- Replication Grade: How many cells are actively dividing? (1, 2 or 3) *Cell cycle dysregulation*

Bigger Picture:

Clinical Stages of Cancer

How big is the tumor?

Has it spread to the lymph nodes or beyond?

- Stage 0: Noninvasive cancer (DCIS, LCIS)
- Stage 1: Invasive cancer ≤ 2 cm, but no lymph nodes
- Stage 2a/b: Invasive cancer 2-5 cm +/- lymph nodes
- Stage 3: Invasive cancer ≥ 5 cm, + lymph nodes, sometimes attached to chest wall
- Stage 4: Cancer has spread to other organs (metastasis)

Modern Cancer Treatment

LOCAL: (at the site of the tumor)

- **Surgery:** to remove the tumor
 - Ex: Lumpectomy (removal of the tumor + margin)
 - Ex: Mastectomy (removal of the breast)
- **Radiation:** kill any cells missed during surgery.
Reduces recurrence by 50-66%.

SYSTEMIC: (throughout the body)

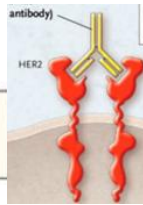
- **Chemotherapy:** kill or inhibit any cancer cells that may remain after surgery or have moved to other parts of the body

Classes of Chemotherapy Agents

“Targeted”

Ex: Trastuzumab
(Herceptin)

Monoclonal antibodies



Ex: Tamoxifen

Hormone inhibitors

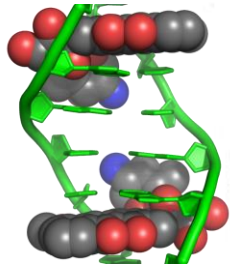


Ex: Adriamycin

Topoisomerase inhibitors

Antibiotics

Anthracyclines



Centrioles

Microtubule inhibitors

Vinca alkaloids
Taxanes

Plant-deived anti-microtubule agents
Ex: docetaxel, vincristine

Ex: Methotrexate, 5-fluorouracil

Antimetabolites

Folate
Purine
Pyrimidine analogs

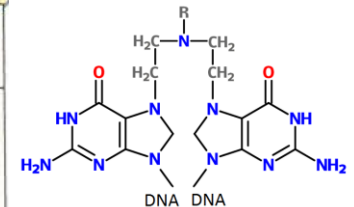
“Non-specific”

Transcription

Alkylating agents

Mustards
Nitrosoureas
Platinum compounds

Ex: Cyclophosphamide



N7 interstrand crosslinked DNA

Targeted Cancer Treatments

- Receptor Inhibitors
- Inhibition of specific proteins / pathways
- Inhibition of angiogenesis

Characteristics of Breast Tumors: Hormone Receptors

14th Century, breast cancer is known as “nuns’ disease”

The New England Journal of Medicine

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Volume 332

JUNE 15, 1995

Number 24

THE USE OF ESTROGENS AND PROGESTINS AND THE RISK OF BREAST CANCER IN POSTMENOPAUSAL WOMEN

GRAHAM A. GOLDITZ, M.B., B.S., SUSAN E. HANKINSON, S.G.D., DAVID J. HUNTER, M.B., B.S.,
WALTER C. WILLETT, M.D., JOANN E. MANSON, M.D., MEIR J. STAMPFER, M.D.,
CHARLES HENNEKENS, M.D., BERNARD ROSNER, Ph.D., AND FRANK E. SPEIZER, M.D.

ORIGINAL CONTRIBUTION

JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative
Randomized Controlled Trial

Writing Group for the
Women's Health Initiative
Investigators

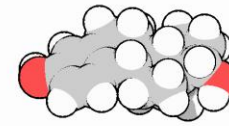
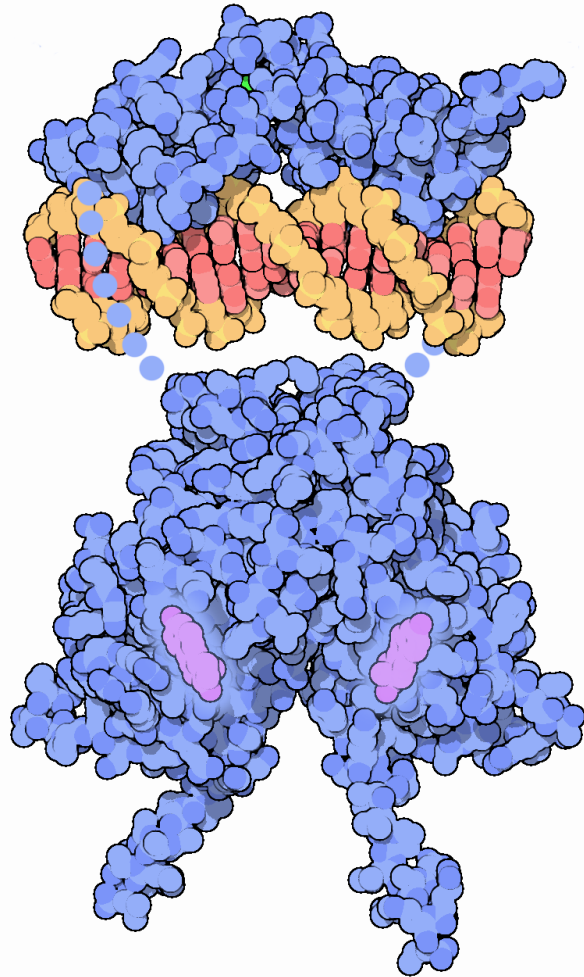
Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used

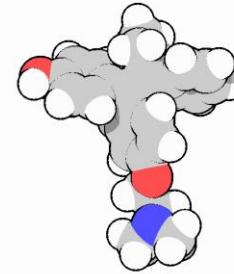
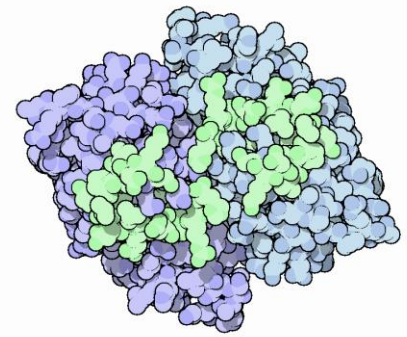
Hormone Receptor-Positive Tumors (ER+ / PR+)

- Normal breast tissue responds to the hormones via Estrogen Receptor (ER) & Progesterone Receptor (PR) → growth signal
- Cancerous cells make more ER & PR, and grow more
- About 75% of breast cancers are hormone-receptor positive

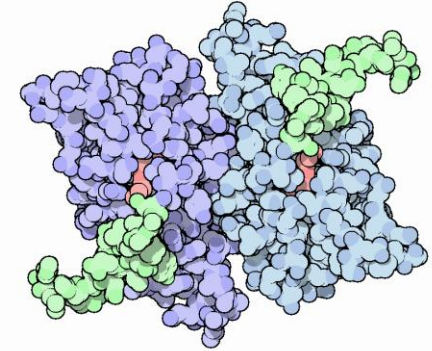
Blocking ER Receptors



estradiol



tamoxifen



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The Lancet, [Volume 351, Issue 9114](#), Pages 1451 - 1467, 16 May 1998
doi:10.1016/S0140-6736(97)11423-4 [Cite or Link Using DOI](#)

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Tamoxifen for early breast cancer: an overview of the randomised trials

Early Breast Cancer Trialists' Collaborative Group

Collaborators listed at end of paper

1998 Meta-analysis of clinical trials:
reduced mortality 12-26%

Left, top: PDB ID 1hcq. bottom: PDB ID 1a52
Right, top: PDB ID 1qku. bottom: PDB ID 3ert
<http://www.rcsb.org/pdb/101/motm.do?momID=45>

Characteristics of Breast Tumors: Growth Factor Receptors

HER2 Positive Tumors (HER2+)

- Human Epidermal growth factor Receptor (HER)2 is found in normal breast tissue
- Sometimes the gene overexpresses or duplicates
 - more HER2 protein
 - more cell growth
- 15-20% of breast cancers are HER2 +

Blocking Growth Factor Receptors

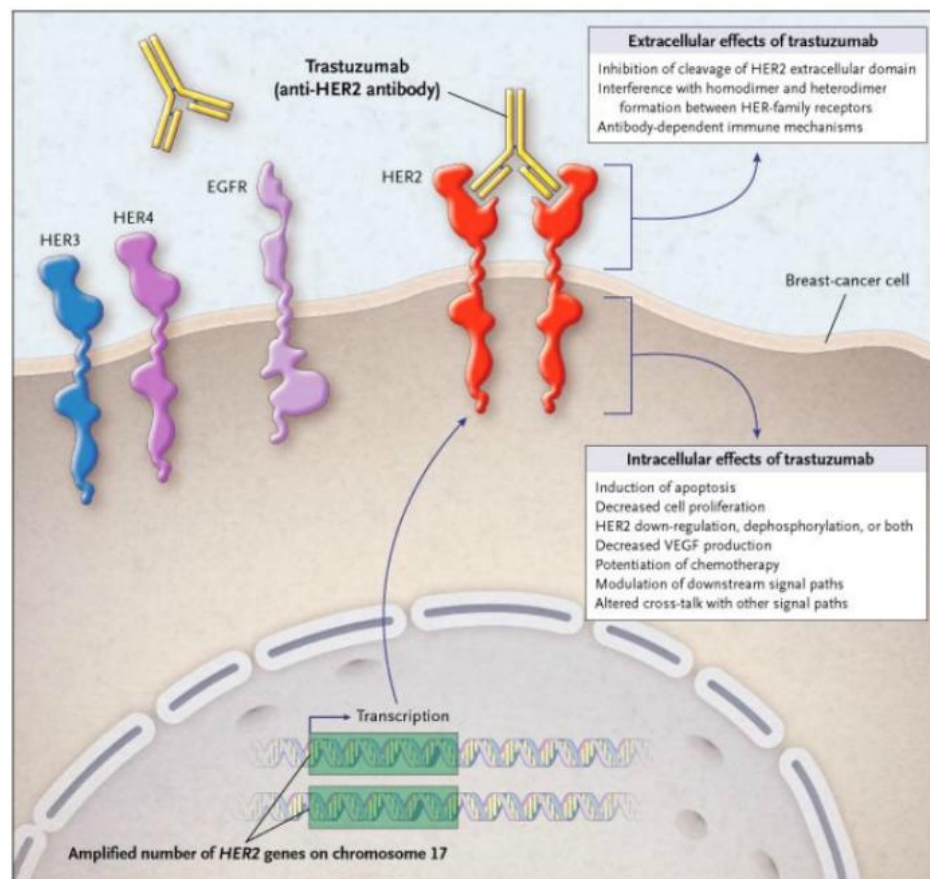
2005: 12% increase in disease-free survival and **33% reduction in risk of death**

The NEW ENGLAND JOURNAL of MEDICINE

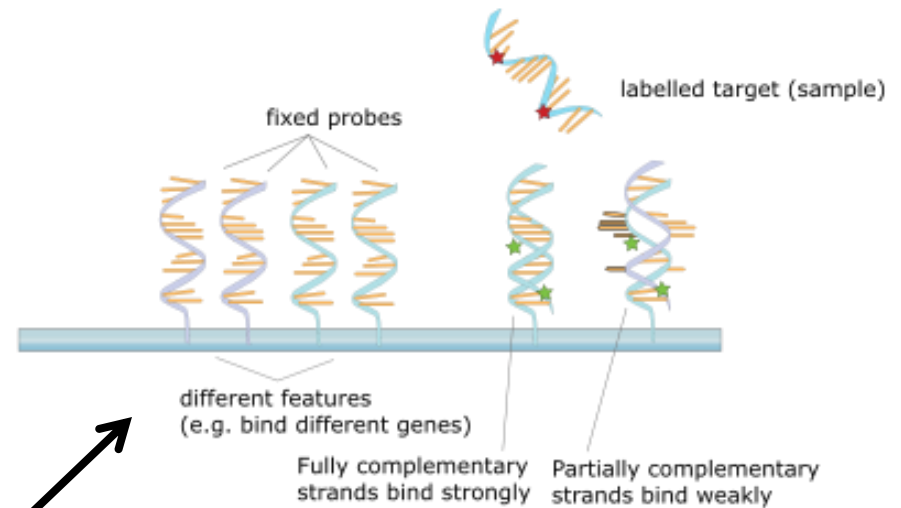
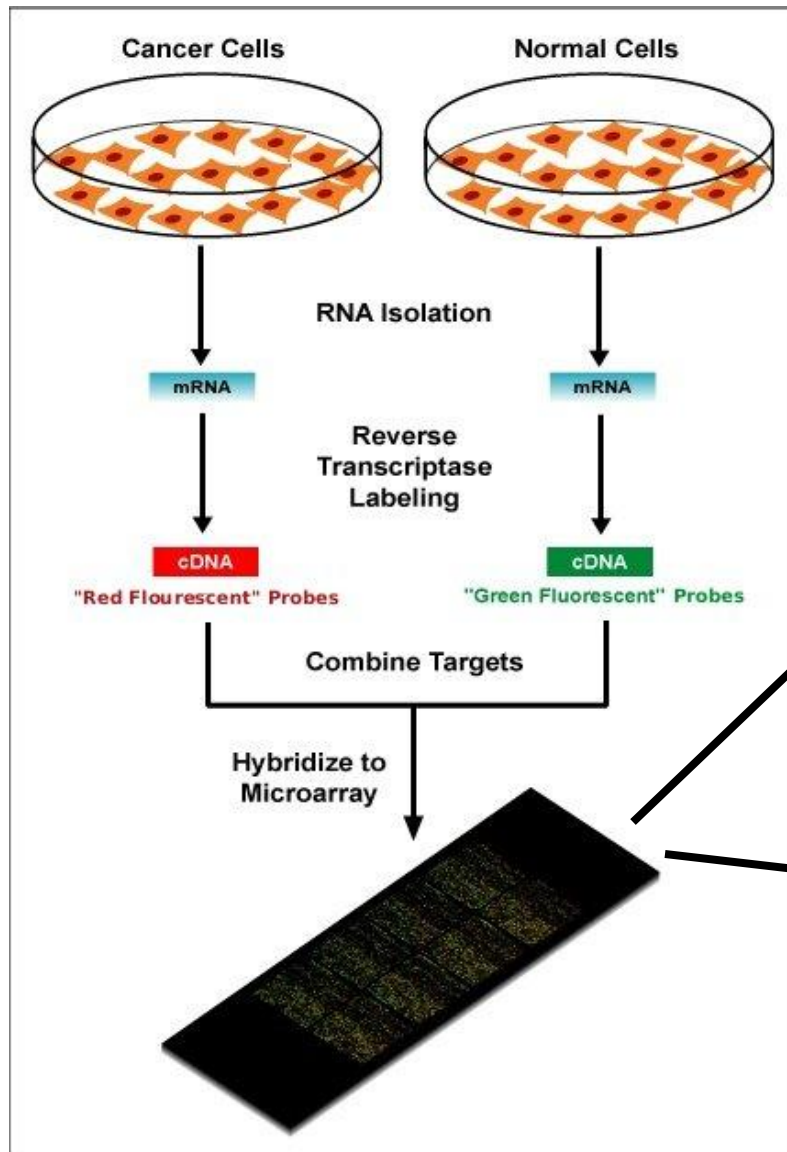
ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D., Vera J. Suman, Ph.D., Charles E. Geyer, Jr., M.D., Nancy E. Davidson, M.D., Elizabeth Tan-Chiu, M.D., Silvana Martino, D.O., Soonmyung Paik, M.D., Peter A. Kaufman, M.D., Sandra M. Swain, M.D., Thomas M. Pisansky, M.D., Louis Fehrenbacher, M.D., Leila A. Kutteh, M.D., Victor G. Vogel, M.D., Daniel W. Visscher, M.D., Greg Yothers, Ph.D., Robert B. Jenkins, M.D., Ph.D., Ann M. Brown, Sc.D., Shaker R. Dakhil, M.D., Eleftherios P. Mamounas, M.D., M.P.H., Wilma L. Lingle, Ph.D., Pamela M. Klein, M.D., James N. Ingle, M.D., and Norman Wolmark, M.D.

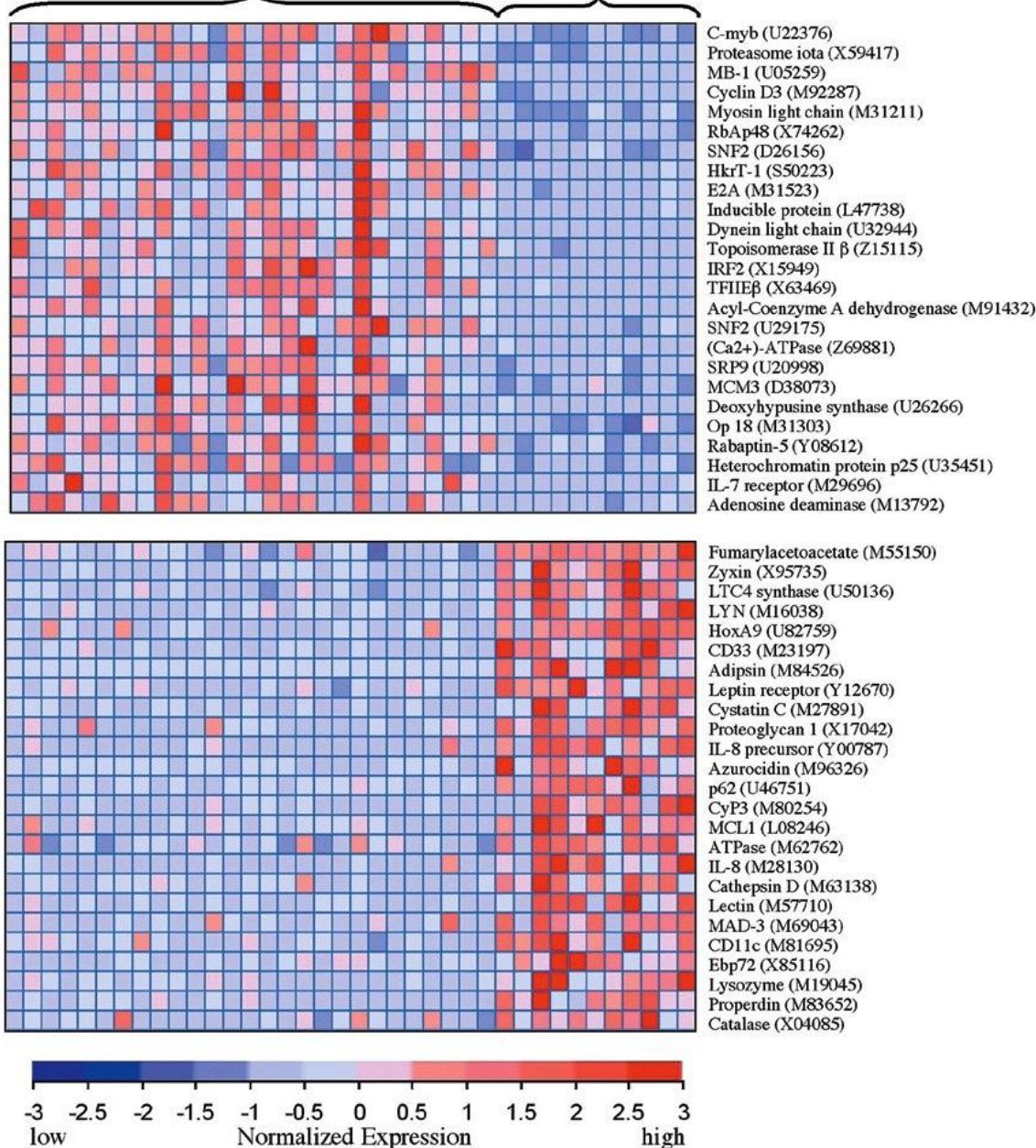


DNA Microarrays Assay Gene Expression



Acute Lymphoblastic Leukemia ALL

Acute Myeloid Leukemia AML



Microarrays: Determine whether specific mRNAs are expressed at higher (**red**) or lower (**blue**) levels than expected (i.e., compared to “housekeeping” genes like GAPDH, actin or tubulin monomers, 18s / 28s rRNA).

Differences in Gene Expression of two types of Leukemia

- mutations don't just result in a loss of function of that gene, but can also have downstream affects on target gene i.e., mutation of transcription factors

The Cancer Genome Atlas



Understanding genomics
to improve cancer care



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Four Subtypes of Stomach Cancer Identified

Researchers with the TCGA Research Network have found that stomach cancers, also called gastric cancers or gastric adenocarcinomas, fall into four distinct molecular subtypes.

[Learn More ▶](#)

Stomach
Cancer
Subtypes IDed



Lung Cancer
Research
Published



Cancers
Selected for
Study



About TCGA

Leadership Update



July 2014
**Steps Towards Precision Medicine:
Utilizing FFPE Specimens for
Comprehensive Genomic**

Research Briefs

June 2014
**MTOR Gene Unlocks Two Approaches to Targeted
Therapies**

[Launch Data Portal](#) ▶

The Cancer Genome Atlas (TCGA) Data Portal provides a platform for researchers to search, download, and analyze data sets generated by TCGA.

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How It Works

Learn more about the components of The Cancer Genome Atlas and how it works through this interactive tool. Select a vertical tab to read more about a specific topic or let the slides change automatically. You can also [download the PDF](#).

TISSUE PROCESSING

01

Tissue Processing

- Cancer patients are asked to donate a portion of tumor tissue that has been removed as part of their cancer treatment along with a sample of normal tissue, usually blood. Tissue and fluid used for analysis are called biospecimens.
- Biospecimen samples used for genomic research need to meet a stringent set of criteria so that the genetic material (DNA and RNA) removed from them can be used by advanced genomic analysis and sequencing technologies.
- The TCGA [Biospecimen Core Resources](#) laboratories process samples to ensure they meet the TCGA biospecimen criteria and prepare them for analysis. Part of the process includes coding the biospecimens to remove any information that might connect a sample with a patient's private information



RESEARCH AND DISCOVERY

02

DATA SHARING

03

COMMUNITY RESEARCH AND DISCOVERY

04

[Download the PDF](#).

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TISSUE PROCESSING

RESEARCH AND DISCOVERY

01

02

Research and Discovery

TCGA researchers analyze tumor and normal tissue from hundreds of patients for each cancer selected for study. This provides the statistical power needed to produce a complete genomic profile of each cancer, which is crucial to identifying those genomic changes that offer the greatest opportunities for therapeutic development.



TCGA **Genome Characterization Centers** analyze many of the genetic changes involved in cancer including how the genome is rearranged or how gene expression changes in tumors compared to normal cells.



High-throughput TCGA **Genome Sequencing Centers** identify the changes in DNA sequence associated with specific types of cancer. Newly developing sequencing technologies will be used to increase the scope of DNA sequencing efforts on TCGA samples.



Immense amounts of data from characterization and sequencing platforms are integrated across thousands of samples. The TCGA **Genome Data Analysis Centers** will provide new information-processing, analysis and visualization tools to the entire research community to facilitate broader use of TCGA data.

Copy Number Alteration
Epigenomics
mRNA Expression
miRNA Analysis
DNA Sequencing
Proteomics



Data Integration and Analyses

DATA SHARING

COMMUNITY RESEARCH AND DISCOVERY

03

04

How It Works

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TISSUE PROCESSING

01

RESEARCH AND DISCOVERY

02

DATA SHARING

03

Data Sharing

- The information that is generated by the TCGA Research Network is centrally managed at the TCGA [Data Coordinating Center](#) and entered into public databases as it becomes available, allowing scientists to continually access the information.
- Scientists search, download and analyze datasets generated by the TCGA Research Network through the TCGA [Data Portal](#). Essentially, the Data Portal contains the genetic profiles of specific cancer types.



COMMUNITY RESEARCH AND DISCOVERY

04

TCGA Collecting Samples from 11 Different Cancers

CANCER TISSUES BEING COLLECTED FOR POTENTIAL STUDY

Last Updated: May 16, 2014

[Expand All](#) | [Collapse All](#)

► Breast

► Central Nervous System

► Endocrine

► Gastrointestinal

► Gynecologic

► Head and Neck

► Hematologic

► Skin

► Soft Tissue

► Thoracic


► Urologic

Selection Criteria:


- * Poor prognosis and overall public health impact
- * Availability of human tumor and matched-normal tissue samples that meet TCGA standards for patient consent, quality and quantity

Up to 500 samples per cancer

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Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

We analysed primary breast cancers by genomic DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, microRNA sequencing and reverse-phase protein arrays. Our ability to integrate information across platforms provided key insights into previously defined gene expression subtypes and demonstrated the existence of four main breast cancer classes when combining data from five platforms, each of which shows significant molecular heterogeneity. Somatic mutations in only three genes (*TP53*, *PIK3CA* and *GATA3*) occurred at >10% incidence across all breast cancers; however, there were numerous subtype-associated and novel gene mutations including the enrichment of specific mutations in *GATA3*, *PIK3CA* and *MAP3K1* with the luminal A subtype. We identified two novel protein-expression-defined subgroups, possibly produced by stromal/microenvironmental elements, and integrated analyses identified specific signalling pathways dominant in each molecular subtype including a HER2/phosphorylated HER2/EGFR/phosphorylated EGFR signature within the HER2-enriched expression subtype. Comparison of basal-like breast tumours with high-grade serous ovarian tumours showed many molecular commonalities, indicating a related aetiology and similar therapeutic opportunities. The biological finding of the four main breast cancer subtypes caused by different subsets of genetic and epigenetic abnormalities raises the hypothesis that much of the clinically observable plasticity and heterogeneity occurs within, and not across, these major biological subtypes of breast cancer.

Nature, 2012

Integration of Multiple Data Types

- Genomic DNA copy number arrays
 - Testing gene duplications / amplifications
- DNA methylation
 - Epigenetics / chromatin remodeling / silencing
- Exome sequencing
 - Sequencing all protein coding genes
- messenger RNA arrays
- microRNA sequencing
- Reverse-phase protein arrays
 - Analysis of protein expression

Note from Dina: As all of my brilliant students know, a missense mutation is actually a mutation that changes the amino acid, not the reading frame.

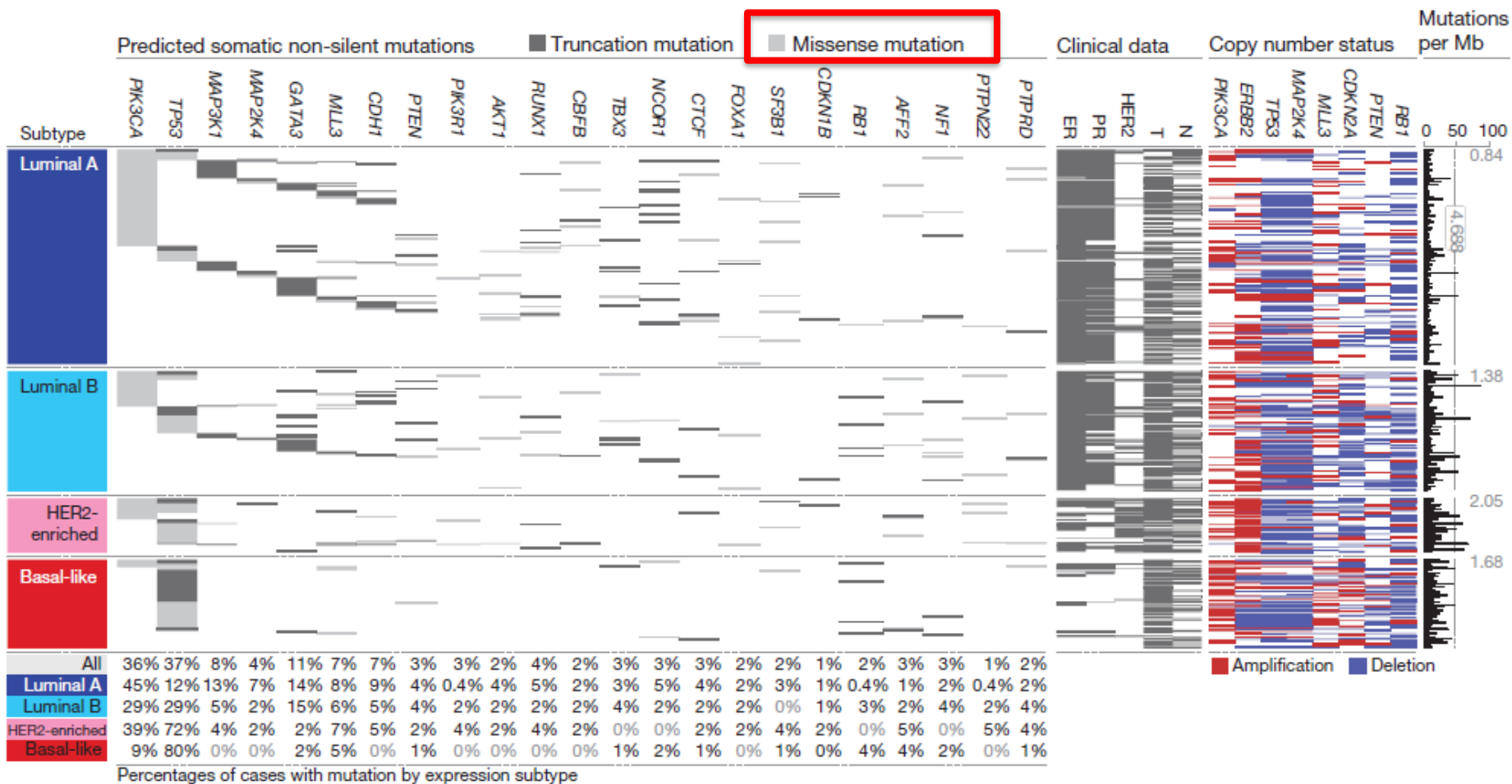
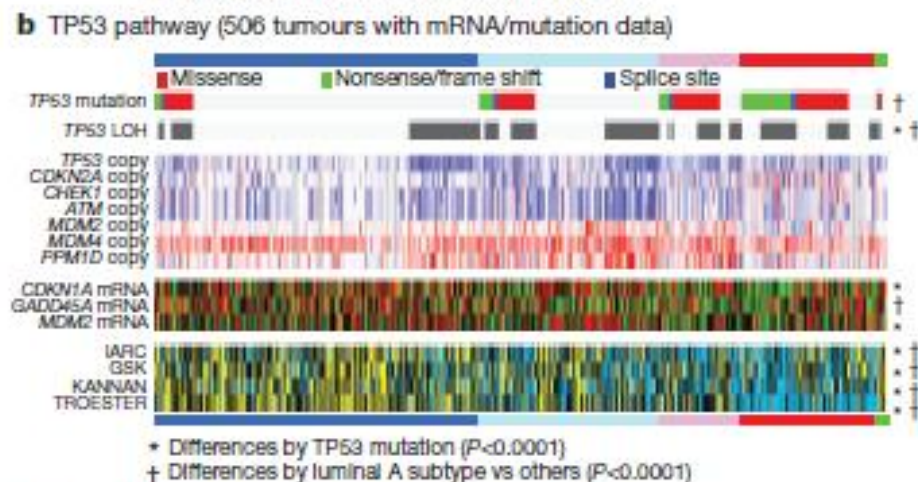
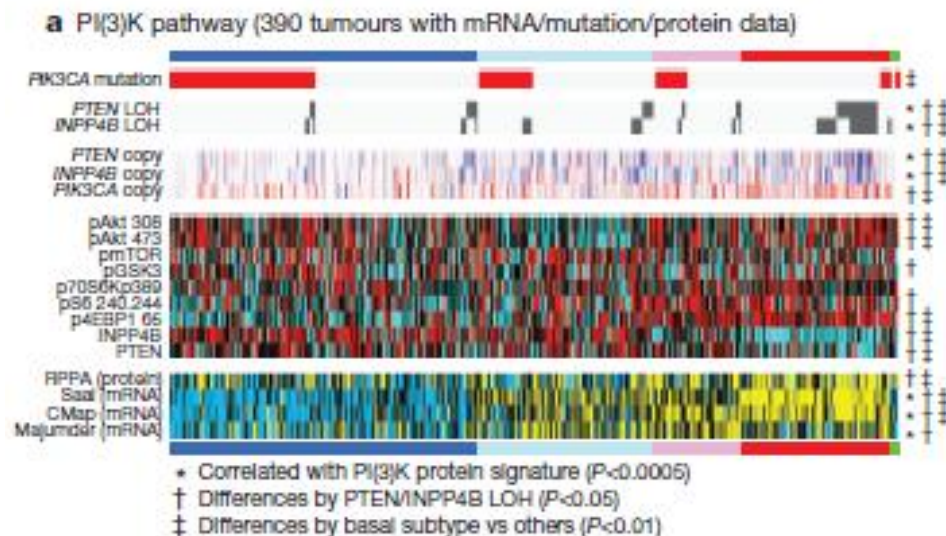


Figure 1 | Significantly mutated genes and correlations with genomic and clinical features. Tumour samples are grouped by mRNA subtype: luminal A

N, node status; T, tumour size. The right panel shows significantly mutated genes with frequent copy number amplifications (red) or deletions (blue). The



* Differences by RB1 mutation ($P < 0.003$)
† Differences by RB1 LOH ($P < 0.005$)
‡ Differences by luminal A subtype vs others ($P < 0.0001$)

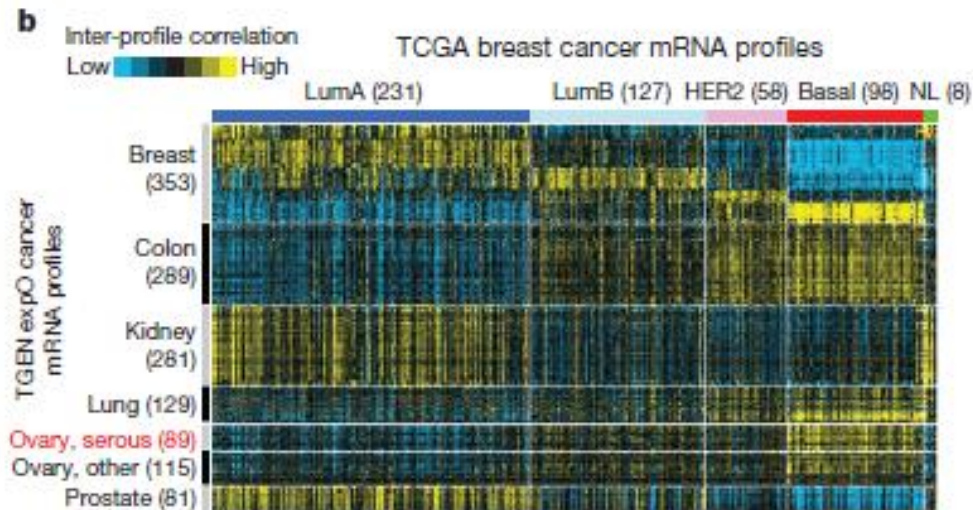
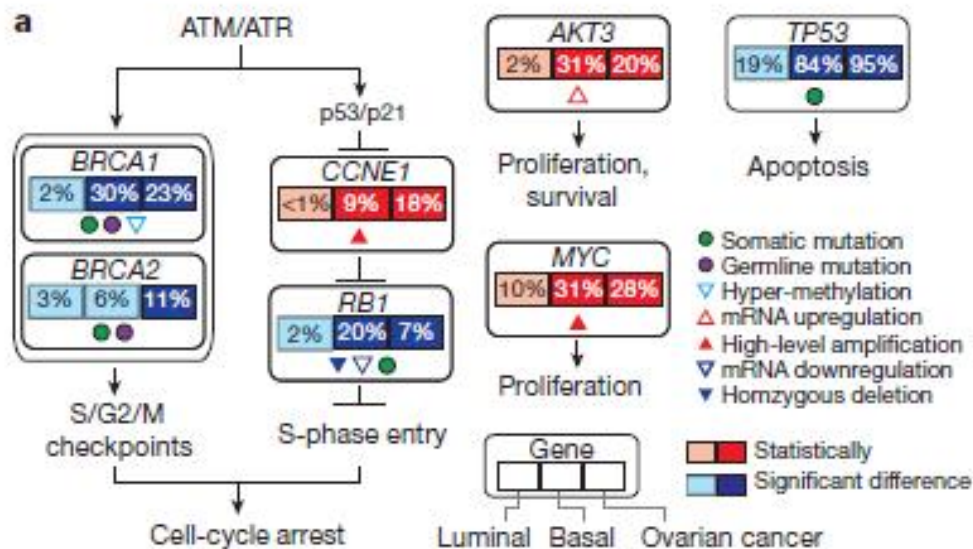
Copy change mRNA expression Protein expression Gene signature activity
Loss Gain Low High Low High Less More
mRNA subtype: Luminal A Luminal B HER2-enriched Basal-like Normal-like



Figure 3 | Integrated analysis of the PI(3)K, TP53 and RB1 pathways. Breast

Triple Negative Breast Cancer

- ER-
- PR-
- HER2-
- Few treatment options
- Poor prognosis



Luminal A

Luminal B

HER2

Basal

Figure 5 | Comparison of breast and serous ovarian carcinomas.

a, Significantly enriched genomic alterations identified by comparing basal-like or serous ovarian tumours to luminal cancers. **b**, Inter-sample correlations (yellow, positive) between gene transcription profiles of breast tumours (columns; TCGA data, arranged by subtype) and profiles of cancers from various tissues of origin (rows; external "TGEN expO" data set, GSE2109) including ovarian cancers.

We systematically looked for other common features between serous ovarian and basal-like tumours when each was compared to luminal. We identified: (1) *BRCA1* inactivation; (2) *RB1* loss and cyclin E1 amplification; (3) high expression of *AKT3*; (4) *MYC* amplification and high expression; and (5) a high frequency of *TP53* mutations (Fig. 5a). An additional supervised analysis of a large, external multitumour type transcriptomic data set (Gene Expression Omnibus accession GSE2109) was performed where each TCGA (The Cancer Genome Atlas) breast tumour expression profile was compared via a correlation analysis to that of each tumour in the multitumour set. Basal-like breast cancers clearly showed high mRNA expression correlations with serous ovarian cancers, as well as with lung squamous carcinomas (Fig. 5b). A PARADIGM analysis that calculates whether a gene or pathway feature is both differentially activated in basal-like versus luminal cancers and has higher overall activity across the TCGA ovarian samples was performed; this identified comparably high pathway activity of the HIF1- α /ARNT, MYC and FOXM1 regulatory hubs in both ovarian and basal-like cancers (Supplementary Fig. 20C). The common findings of *TP53*, *RB1* and *BRCA1* loss, with *MYC* amplification, strongly suggest that these are shared driving events for basal-like and serous ovarian carcinogenesis. This suggests that common therapeutic approaches should be considered, which is supported by the activity of platinum analogues and taxanes in breast basal-like and serous ovarian cancers.

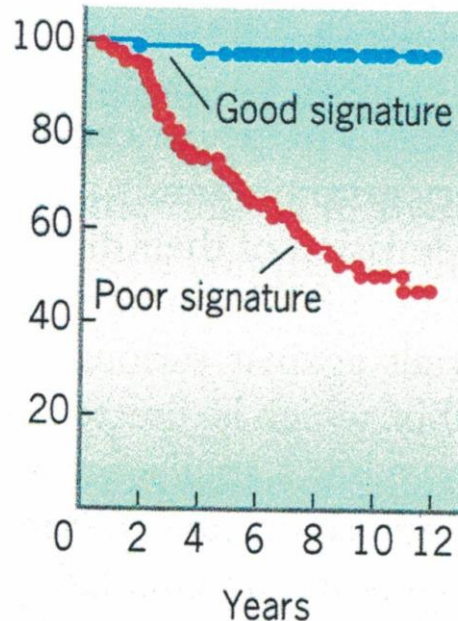
Genetic Signatures can Inform Treatment Choice

N- patients
(esp over age
50) on average
have good
prognosis.

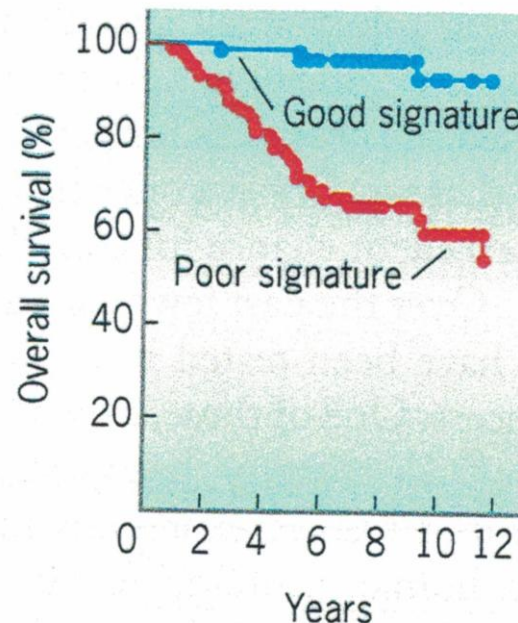
These patients
are treated
less
aggressively,
sometimes no
chemo at all.

But “Poor
signature”
group needs
more TMT

Lymph-Node-Negative Patients



Lymph-Node-Positive Patients



N+ patients on
average have
poorer
prognosis
(Stage II v III).

These patients
are treated
very
aggressively,
causing severe
side effects –
including
secondary
cancers.

Figure 16.21 (6th ed): The use of DNA microarray data in determining the choice of treatment.

An ounce of prevention is worth a pound of cure...

- Screening:
 - mammograms, Pap smears + HPV testing, colonoscopy, PSA
- Genetic Testing:
 - *BRCA1/2*
 - Only 10% of breast cancer is inherited
 - Only 50% of inherited breast cancer is positive for germline *BRCA1* or *BRCA2* mutations
 - ‘Comprehensive panels’

GTR: GENETIC TESTING REGISTRY

All GTR

Tests

Conditions/Phenotypes

Genes

Labs

GeneReviews

[Advanced search for tests](#)

Search Conditions/Phenotypes

Find conditions and phenotypes by searching for disease names, traits, drugs, proteins and analytes.

You  [GTR Tutorials](#)

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NIH thanks labs for registering over 24,000 tests for 5,000 conditions and 3,600 genes!

[YouTube basic search video](#)

(3/5) << || >>

Molecular Resources

[ClinVar](#)

Information about sequence variation and its relationship to human health, NIH.

[Genetics & Medicine](#)

NCBI's molecular medicine databases and tools, NIH. [See tips.](#)

Clinical Resources



Welcome to **GeneTests**, a medical genetics information resource.

[NEW TESTS](#)

Welcome

The GeneTests website

Welcome to GeneTests. From its start in 1992, GeneTests has grown to reflect the advances in genetic testing capabilities and to address the needs of our ever widening user community. We invite you to explore, try some of your favorite searches, and let us know what you think. Your feedback will help shape GeneTests into the indispensable tool you want for your practice.

What's New

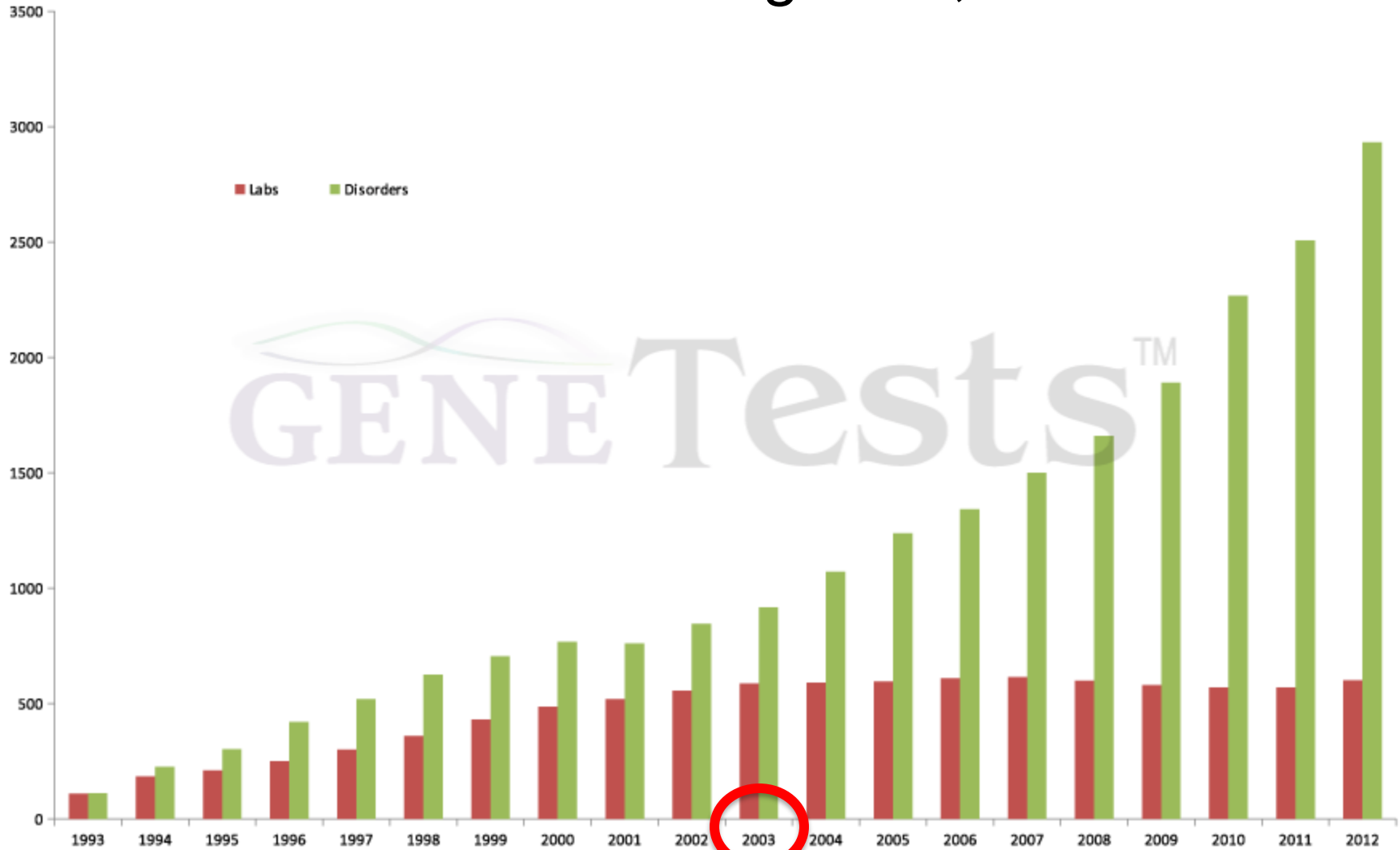
See you at Booth 316 in San Diego!

We will be in San Diego at the American Society of Human Genetics so plan to visit to learn what's new at GeneTests or give us feedback. While at our booth, sign up to become a GeneTests™ member to improve your search experience and facilitate professional connections. As a registered member, you will have access to all newly added features. Membership is free and easy to...

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Disorders for which genetic tests are available and laboratories offering tests, 1993-2012



Note from Dina: Actually, the Human Genome Project was “declared completed in 2003 (Wikipedia).

<https://www.genetests.org/img/content/chart1.png>

BROCA - Cancer Risk Panel

BROCA Gene List

Gene	Function/Pathway	Heterozygote Cancer risk*	Associated syndrome	References (PMID)
<i>AKT1</i>	AKT signaling	Breast, Thyroid	Cowden-like	23246288
<i>APC</i>	WNT signaling	Colon	Familial adenomatous polyposis	20301519

<i>ATM</i>	Double stranded break repair	Breast, Pancreatic	<i>GEN1</i>	Double stranded break repair	Breast	2052659
<i>ATR</i>	Double stranded break repair	Oropharyngeal	<i>GREM1</i>	BMP antagonist	Colon	22561515
<i>BAP1</i>	BRCA1-associated protein complex	Uveal Melanoma, Mesothelioma	<i>HOXB13</i>	transcription factor	Prostate	22236224
<i>BARD1</i>	BRCA1-associated protein complex	Breast, Ovarian	<i>MEN1</i>	Gene expression regulation	Endocrine	9215689

<i>BMPR1A</i>	TGF-beta signaling	Colon	<i>MLH1</i>	Mismatch DNA repair	Colon, Ovarian, Endometrial
<i>BRCA1</i>	BRCA1-associated protein complex	Breast, Ovarian	<i>MRE11A</i>	Double stranded break repair	Breast
<i>BRCA2</i>	Fanconi/BRCA	Breast, Ovarian	<i>MSH2 (+EPCAM)</i>	Mismatch DNA repair	Colon, Ovarian, Endometrial
<i>BRIP1</i>	Fanconi/BRCA	Breast, Ovarian	<i>MSH6</i>	Mismatch DNA repair	Colon, Endometrial
<i>CDH1</i>	Cell adhesion	Breast, Gastric	<i>MUTYH</i>	DNA repair	Colon (homozygous)
<i>CDK4</i>	Cell cycle	Melanoma	<i>NBN</i>	Double stranded break repair	Breast
<i>CDKN2A</i>	Cell cycle	Pancreatic, Melanoma	<i>PALB2</i>	Fanconi/BRCA	Breast, Pancreatic
<i>CHEK1</i>	Double stranded break repair	Unknown	<i>PIK3CA</i>	AKT signaling	Breast, Thyroid
<i>CHEK2</i>	Double stranded break repair	Breast	<i>PMS2</i>	Mismatch DNA repair	Colon, Endometrial
<i>CTNNA1</i>	Beta-catenin, e-cadherin complex	Gastric	<i>POLD1</i>	DNA Polymerase	Colon, Endometrial
<i>FAM175A/Abraxas</i>	Double stranded break repair	Breast	<i>POLE</i>	DNA Polymerase	Colon
<i>GALNT12</i>	O-glycosylation	Colon	<i>PRSS1</i>	Digestion (Trypsin 1)	Pancreatic
			<i>PTEN</i>	PI3K/MAPK Signaling	Breast
			<i>RAD51B</i>	Double stranded break repair	Unknown
			<i>RAD51C</i>	Fanconi/BRCA	Ovarian, Breast
			<i>RAD51D</i>	Fanconi/BRCA	Ovarian, Breast
			<i>RET</i>	Receptor Tyrosine Kinase	Endocrine

<i>SDHB</i>	Succinate dehydrogenase complex	Pheochromocytoma, Paraganglioma	Hereditary paraganglioma-pheochromocytoma	11404820
<i>SDHC</i>	Succinate dehydrogenase complex	Pheochromocytoma, Paraganglioma	Hereditary paraganglioma-pheochromocytoma	11062460
<i>SDHD</i>	Succinate dehydrogenase complex	Pheochromocytoma, Paraganglioma	Hereditary paraganglioma-pheochromocytoma	10657297
NEW SLX4	Fanconi/BRCA	Unknown	Fanconi anaemia (recessive)	23840564
<i>SMAD4</i>	TGF-beta signaling	Colon	Juvenile polyposis	20301642
<i>STK11</i>	Cell Cycle/p53 regulation	Breast, Pancreatic	Peutz-Jeghers syndrome	20301443
<i>TP53</i>	Cell growth	Breast, Ovarian	Li-Fraumeni syndrome	22006311,20301488
<i>VHL</i>	p53 regulation	Kidney, Neuroendocrine	von Hippel-Lindau syndrome	20301636
<i>XRCC2</i>	Double stranded break repair	Breast	Fanconi anaemia (recessive)	22464251,22232082

*Only the most commonly associated cancer types are listed. A more detailed description of cancer risk for some BROCA genes can be found at [GeneReviews](#).

Methods

This assay sequences all exons and flanking intronic sequences of *AKT1*, *APC*, *ATM*, *ATR*, *BAP1*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK1*, *CHEK2*, *CTNNA1*, *FAM175A* (Abraxas), *GALNT12*, *GEN1*, *GREM1*, *HOXB13*, *MEN1*, *MLH1*, *MRE11A*, *MSH2* (+EPCAM), *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIK3CA*, *PMS2*, *POLD1*, *POLE*, *PRSS1*, *PTEN*, *RAD51B*, *RAD51C*, *RAD51D*, *RET*, *SDHB*, *SDHC*, *SDHD*, *SLX4*, *SMAD4*, *STK11*, *TP53*, *VHL*, and *XRCC2*. A total of 1.1 Mb (1.1 Million base pairs) are sequenced and the average coverage ranges from 320 to >1,000 sequencing reads per bp. Genomic regions are captured using biotinylated RNA oligonucleotides (SureSelect), prepared in paired-end libraries with ~200 bp insert size, and sequenced on an Illumina HiSeq2000 instrument with 100 bp read lengths, in a modification of a procedure described by Walsh et al. 2010 (1) and 2011 (2). Large deletions and duplications are detected using methods described by Nord et al. 2011 (3).

Next generation DNA
sequencing:
320- to >1000-fold coverage

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*113705

BREAST CANCER 1 GENE; **BRCA1**

HGNC Approved Gene Symbol: **BRCA1**


Cytogenetic location: **17q21.31** *Genomic coordinates (GRCh37):* **17:41,196,311-41,277,499** (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype	Phenotype MIM number	Phenotype mapping key
17q21.31	{Breast-ovarian cancer, familial, 1}	604370	3
	{Pancreatic cancer, susceptibility to, 4}	614320	3

TEXT

Description

BRCA1 plays critical roles in DNA repair, cell cycle checkpoint control, and maintenance of genomic stability. **BRCA1** forms several distinct complexes through association with different adaptor proteins, and each complex forms in a mutually exclusive manner (Wang et al., 2009). 

Cloning and Expression

Miki et al. (1994) identified cDNA sequences corresponding to the **BRCA1** gene by positional cloning of the region on 17q21 implicated

Table of Contents for *113705

- [Title](#)
- [Gene-Phenotype Relationships](#)
- [Text](#)
 - [Description](#)
 - [Cloning and Expression](#)
 - [Gene Structure](#)
 - [Mapping](#)
 - [Gene Function](#)
 - [Molecular Genetics](#)
 - [Genotype/Phenotype Correlations](#)
 - [Evolution](#)
 - [Animal Model](#)
- [Allelic Variants](#)
- [Table View](#)
- [See Also](#)
- [References](#)
- [Contributors](#)
- [Creation Date](#)
- [Edit History](#)

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BRCA1 breast cancer 1, early onset [*Homo sapiens* (human)]

Gene ID: 672, updated on 5-Nov-2014

☒ Summary

Official Symbol	BRCA1 <small>provided by HGNC</small>
Official Full Name	breast cancer 1, early onset <small>provided by HGNC</small>
Primary source	HGNC:HGNC:1100
See related	Ensembl:ENSG00000012048 ; HPRD:00218 ; MIM:113705 ; Vega:OTTHUMG00000157426
Gene type	protein coding
RefSeq status	REVIEWED
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	IRIS; PSCP; BRCAI; BRCC1; PNCA4; RNF53; BROVCA1; PPP1R53
Summary	This gene encodes a nuclear phosphoprotein that plays a role in maintaining genomic stability, and it also acts as a tumor suppressor. The encoded protein combines with other tumor suppressors, DNA damage sensors, and signal transducers to form a large multi-subunit protein complex known as the BRCA1-associated genome surveillance complex (BASC). This gene product associates with RNA polymerase II, and through the C-terminal domain, also interacts with histone deacetylase complexes. This protein thus plays a role in transcription, DNA repair of double-stranded breaks, and recombination. Mutations in this gene are responsible for approximately 40% of inherited breast cancers and more than 80% of inherited breast and ovarian cancers. Alternative splicing plays a role in modulating the subcellular localization and physiological function of this gene. Many alternatively spliced transcript variants, some of which are disease-associated mutations, have been described for this gene, but the full-length nature of only some of these variants has been described. A related pseudogene, which is also located on chromosome 17, has been identified. <small>[provided by RefSeq, May 2008]</small>

Table of contents

- Summary
- Genomic context
- Genomic regions, transcripts, and products
- Bibliography
- Phenotypes
- Variation
- HIV-1 interactions
- Pathways from BioSystems
- Interactions
- General gene information
 - Markers, Related pseudogene(s), Potential readthrough, Homology, Gene Ontology
- General protein information
- NCBI Reference Sequences (RefSeq)
- Related sequences
- Additional links
 - Locus-specific Databases

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