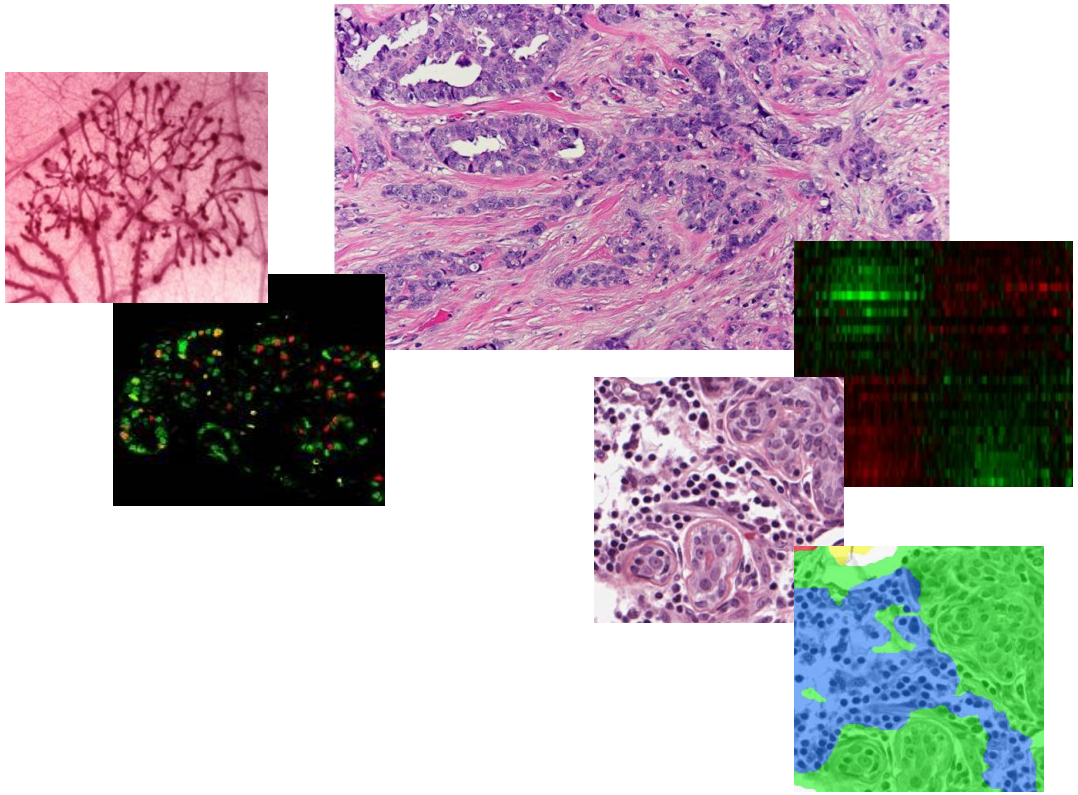

Breast Cancer

Path 17- November 2, 2021

Alina M. Hamilton, MS

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Background Information

Alina M. Hamilton

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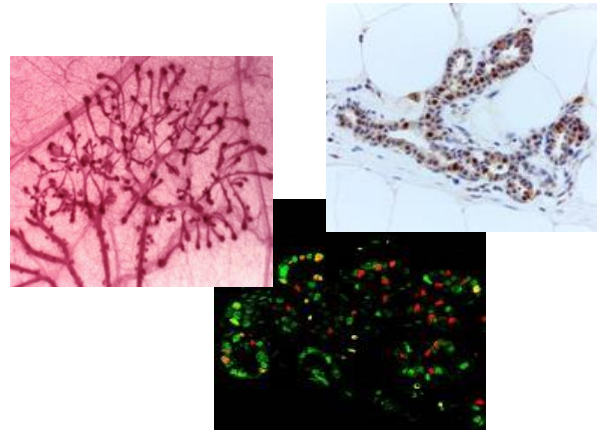
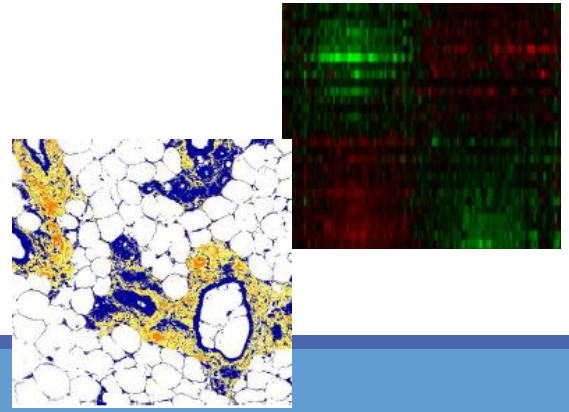


Education

- BS in Biology, Minor in Chemistry
  University of Texas Pan American, 2015

- MS in Biology
  University of Texas Rio Grande Valley, 2017

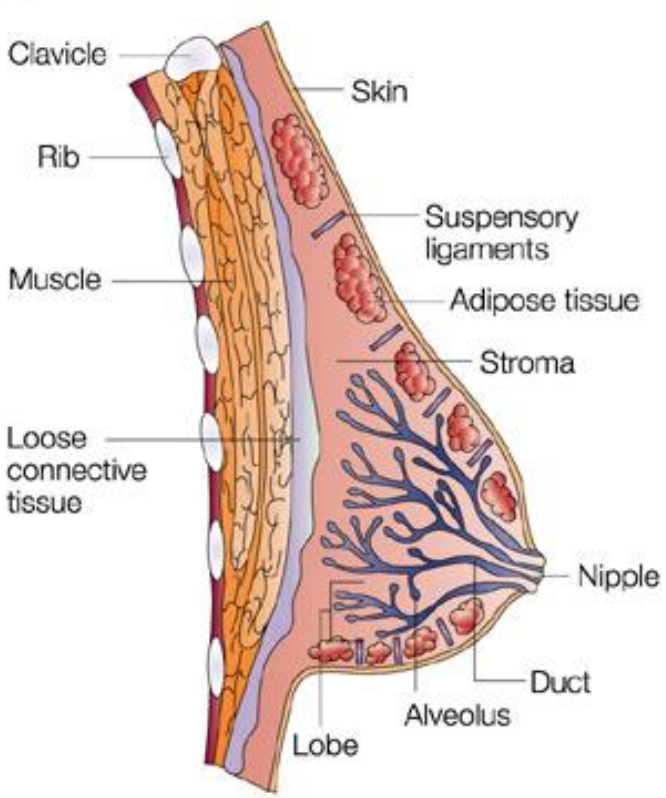
- PhD Candidate, Pathobiology and Translational Science
  UNC Chapel Hill, Anticipated 2022



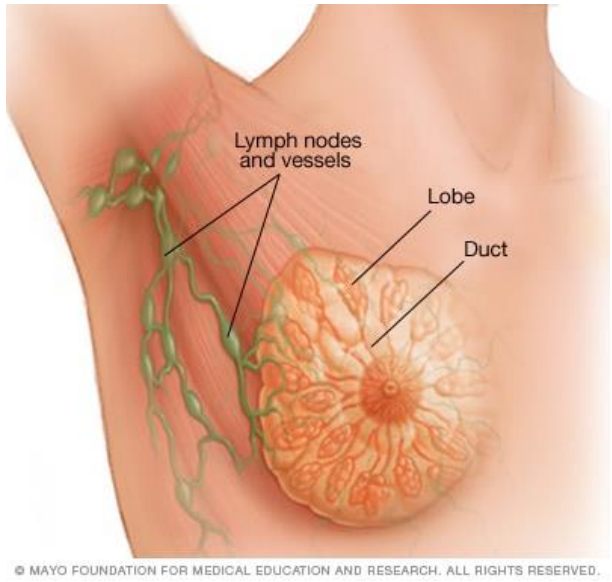
Lecture Outline

- Anatomy and Histology of Normal Breast
  - Breast Development
- Benign Breast Disease and Ductal Carcinoma *In Situ*
- Invasive Breast Cancer
  - Risk Factors
  - Staging and Grading
  - Ductal and Lobular Carcinoma
  - Clinical Breast Cancer Subtypes
  - Molecular Breast Cancer Subtypes
- Breast Cancer Disparities

Normal Breast Anatomy



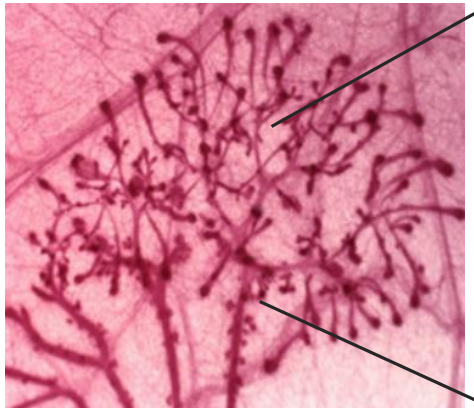
S. Ali and R.C. Coombes *Nature Reviews Cancer* 2, 101-112 (2002); doi:10.1038/nrc721



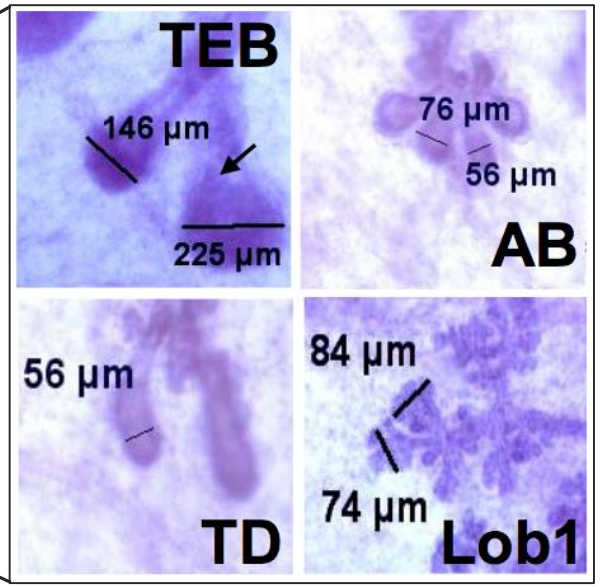
- The bulk of the breast tissue is adipose tissue interspersed with connective tissue
- Breast ducts comprise only about 10% of the breast mass
  - lobes/TDLUs
  - ducts
  - lymph nodes

Breast Anatomy- Epithelium

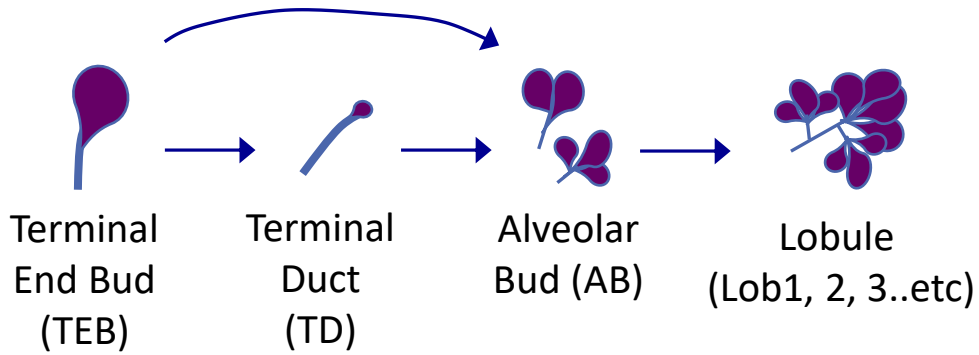
Mammary Gland Whole Mount



Pre-pubertal Sprague Dawley Rat

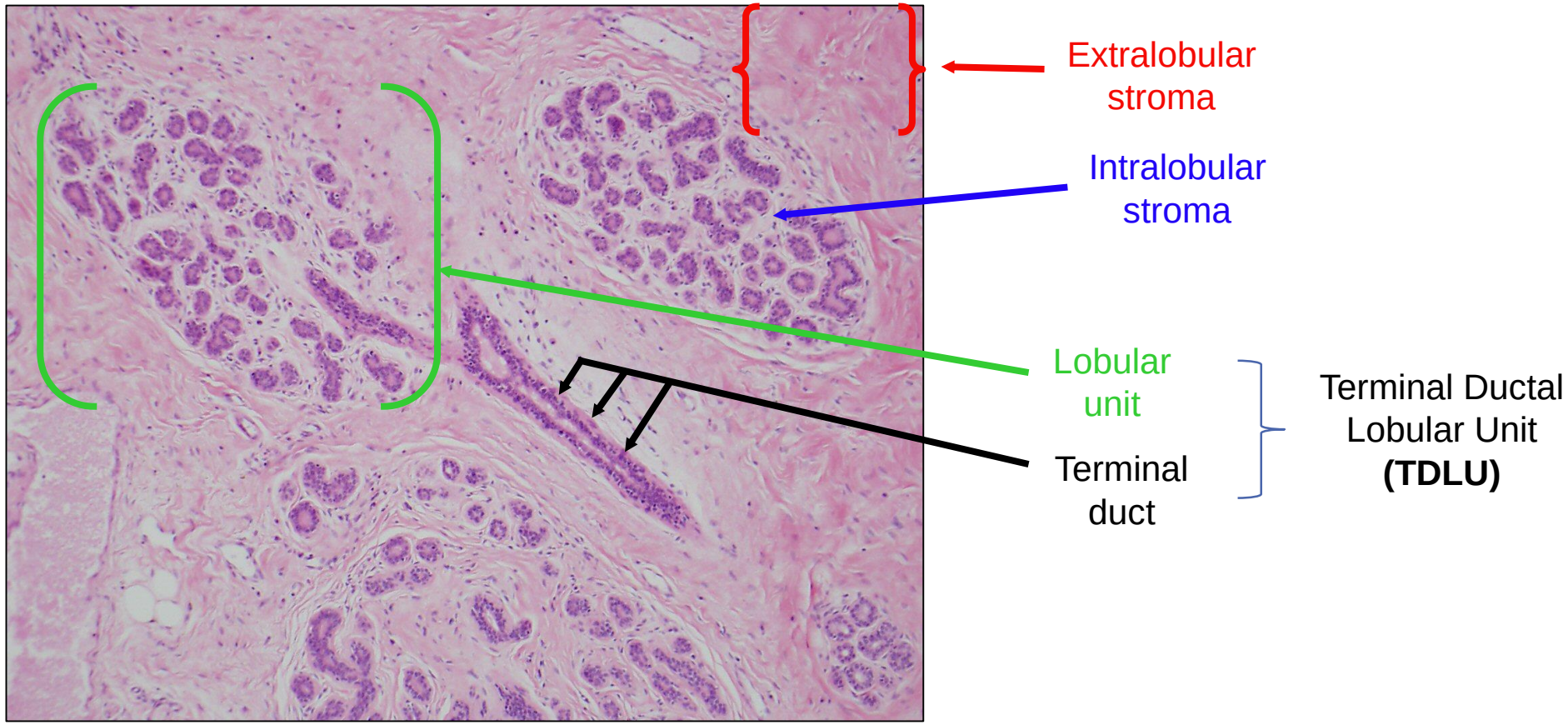


Breast Differentiation



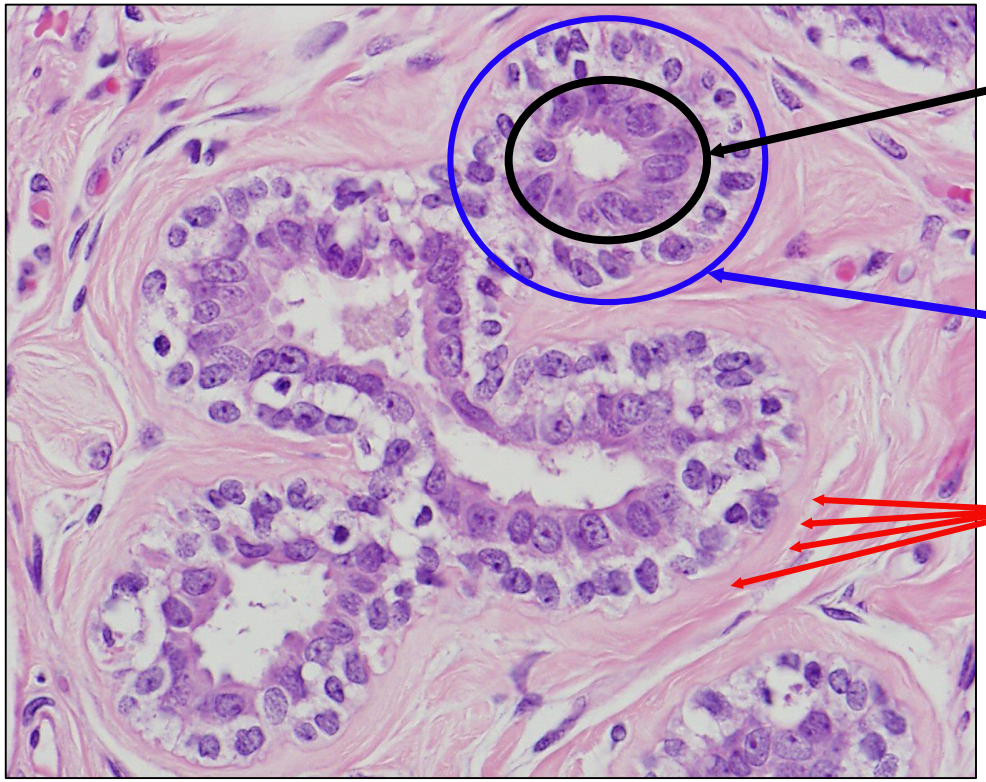
Russo *et al.*, 2005

Normal Breast Histology



Terminal Ductal Lobular Unit **(TDLU)-** Functional unit of the breast

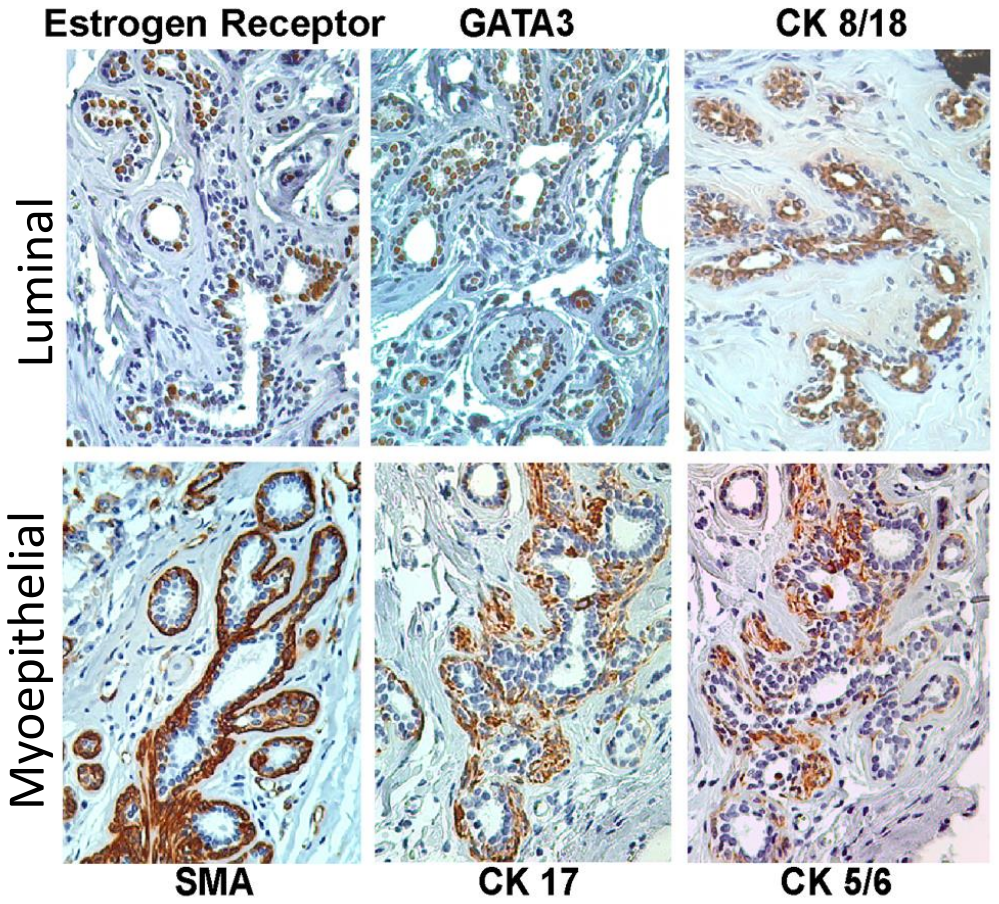
Normal Breast Histology



Luminal epithelium

Myoepithelial cells

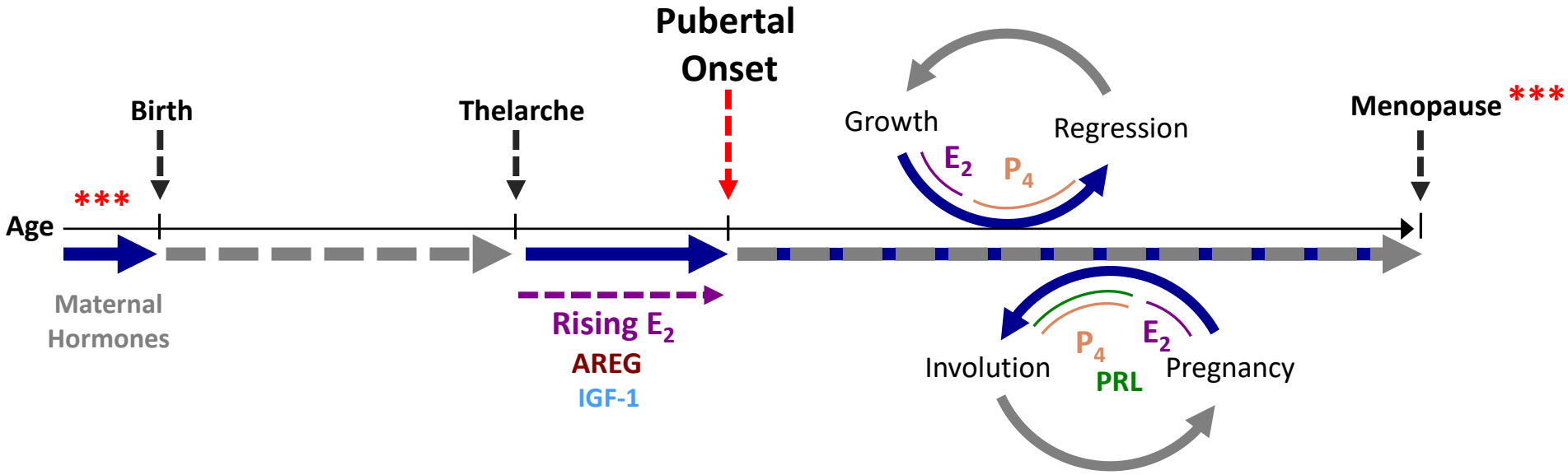
Basement membrane

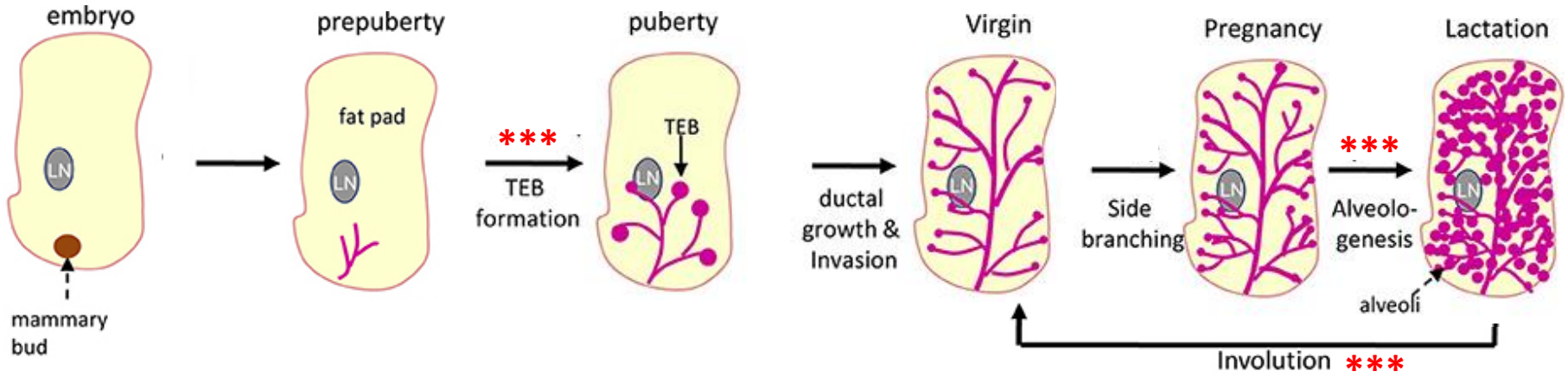


S. Ali and R.C. Coombes *Nature Reviews Cancer* 2, 101-112 (2002); doi:10.1038/nrc721

Breast Development

***Critical Developmental Window/
Window of Susceptibility = high risk!





Manavathi *et al.*, 2014

Benign Breast Disease (BBD) and Ductal Carcinoma *in Situ* (DCIS)

Benign Breast Disease (BBD)

- Benign (non-cancerous) breast conditions are unusual growths or other changes in the breast tissue that are not cancer. However, some can increase risk for breast cancer.

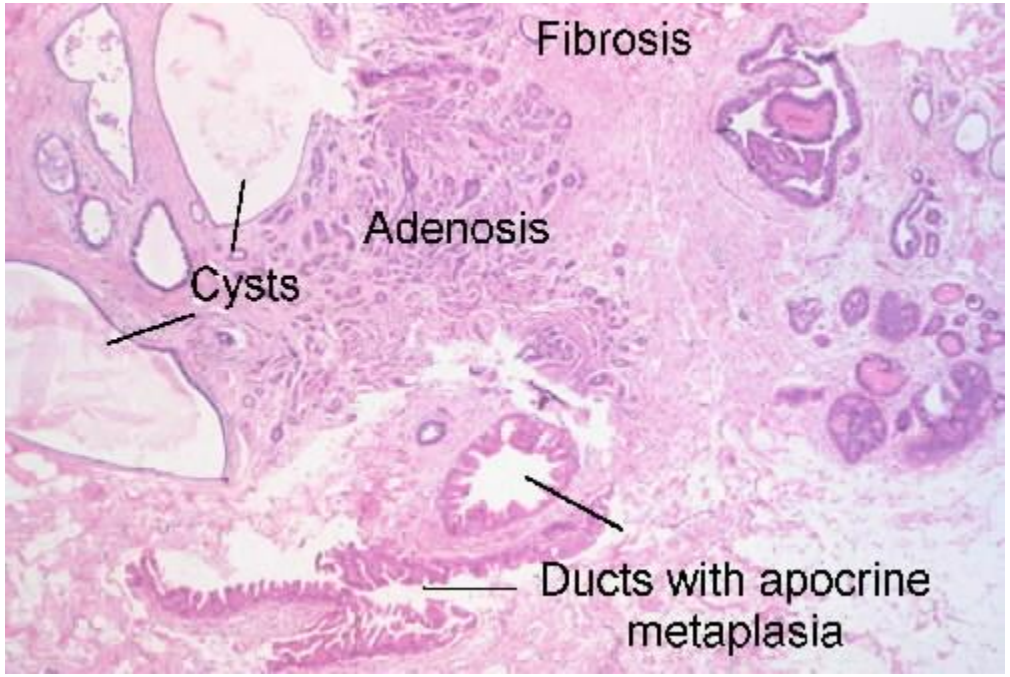
- Grouped into three risk categories:
  - No increase in risk
  - Slight increase in risk
  - Moderate increase in risk

- Symptoms can be similar to those for breast cancer (e.g., lump, pain/tenderness, skin changes, nipple discharge, local inflammation and redness)

- Diagnosis to rule out cancer and assess risk of future cancer
  - Breast physical exam and medical history
  - Imaging tests (e.g., mammography, x-ray, ultrasound, MRI)
  - Nipple discharge analysis
  - Biopsy

Examples of BBD

Fibrocystic Change — no increase in risk



Presentation: Lumpiness, thickening and swelling, often associated with the menstrual cycle

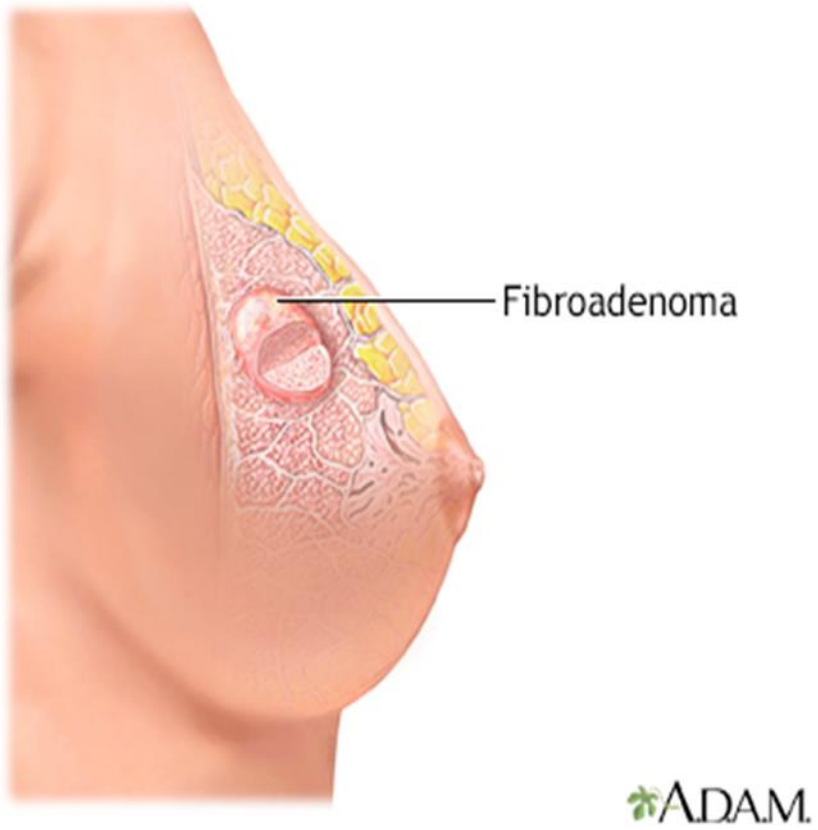
Pathogenesis: Hormonal Factors

Macroscopic Features: dense/firm breast tissue and variably sized cysts

Microscopic Features: dilated ducts/cysts, adenosis, fibrosis, apocrine metaplasia, +/- calcifications, +/- ductal hyperplasia

Examples of BBD

Fibroadenoma— no to slight increase in risk



Presentation: Usually solitary, firm, rubbery, mobile mass; slowly growing; younger pre-menopausal women

Pathogenesis: Unclear, hormone-related?

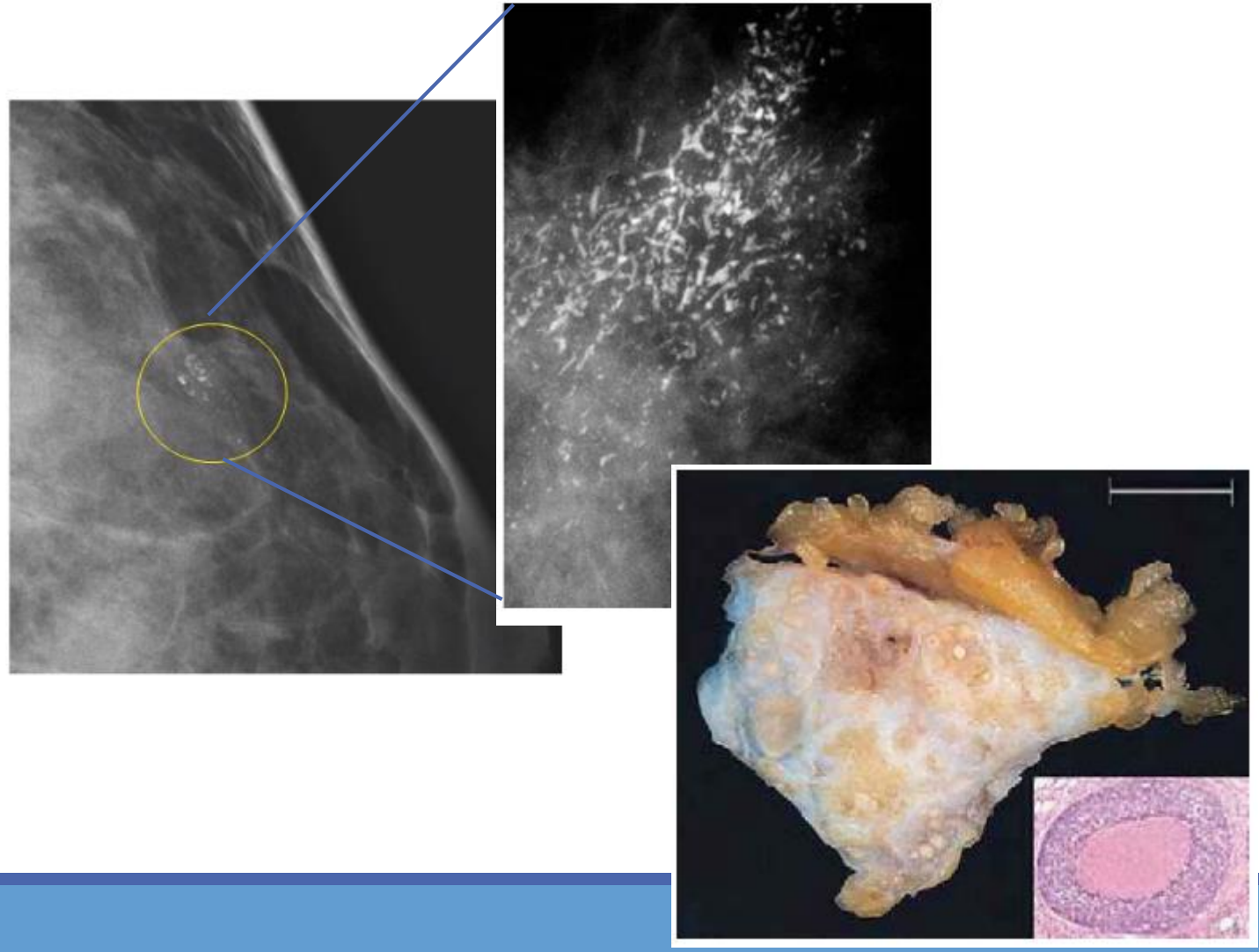
Macroscopic Appearance: Firm, circumscribed mass of variable size

Microscopic Appearance: Neoplasm comprised of benign ductal epithelium and benign stromal cells with distinct architectural pattern; very well circumscribed

Risk: no risk, unless the FA is considered “complex” and also includes large cysts (>3cm), adenosis, calcifications, apocrine metaplasia

Ductal Carcinoma *In Situ* (DCIS)

An immediate precursor to invasive breast cancer



Presentation: DCIS is usually found on a mammogram and appears as small clusters of calcifications that have irregular shapes and sizes.

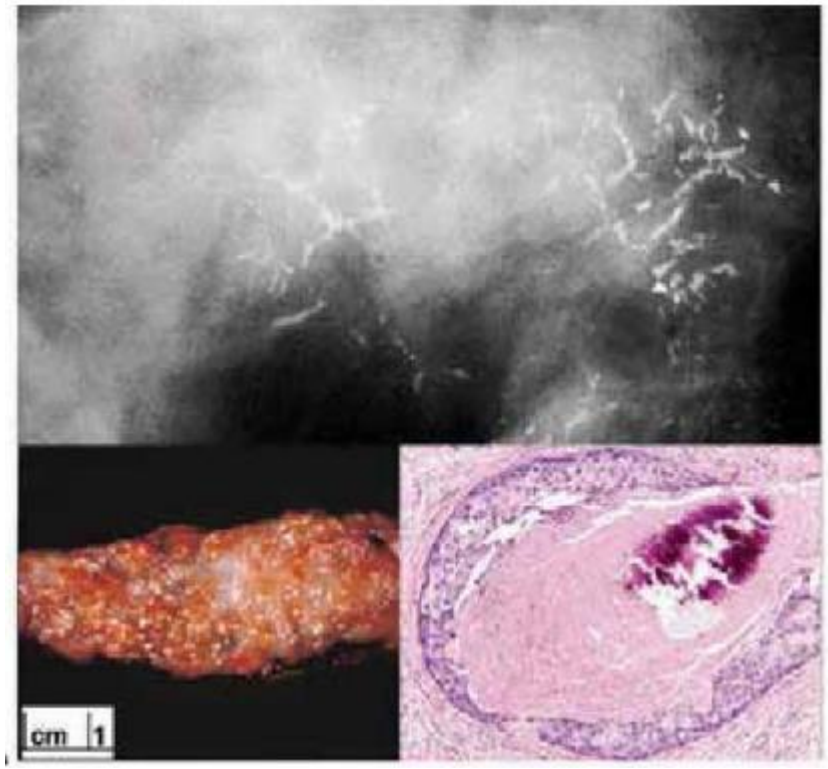
- Majority of cases are non-palpable
- >60,000 cases identified each year

Macroscopic Appearance: Usually not evident grossly, but when multifocal, tumors may be palpable and tan in color with visible white/yellow foci of comedo necrosis.

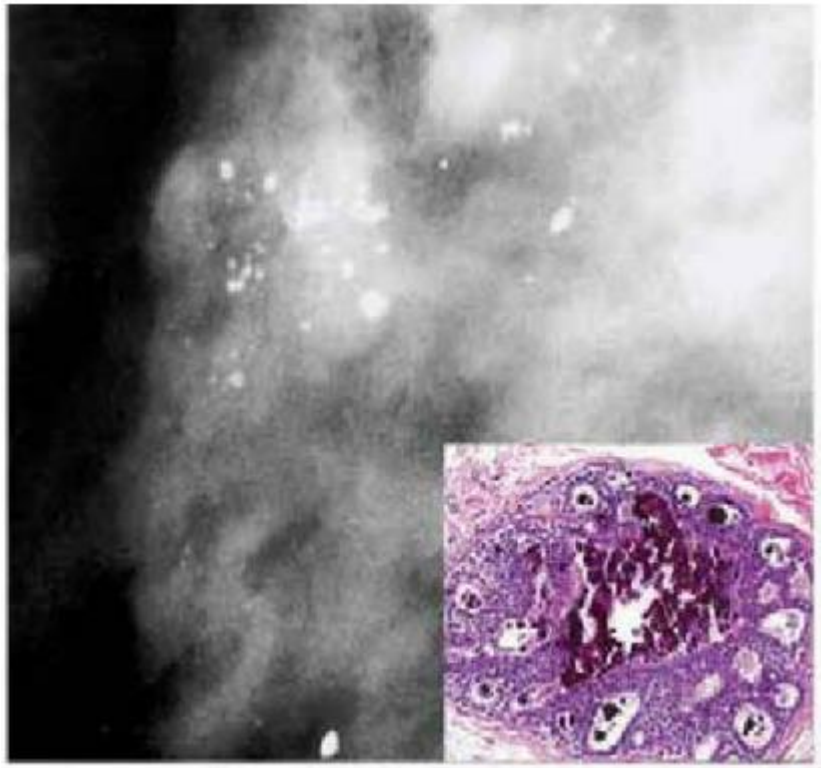
Ductal Carcinoma *In Situ* (DCIS)

An immediate precursor to invasive breast cancer

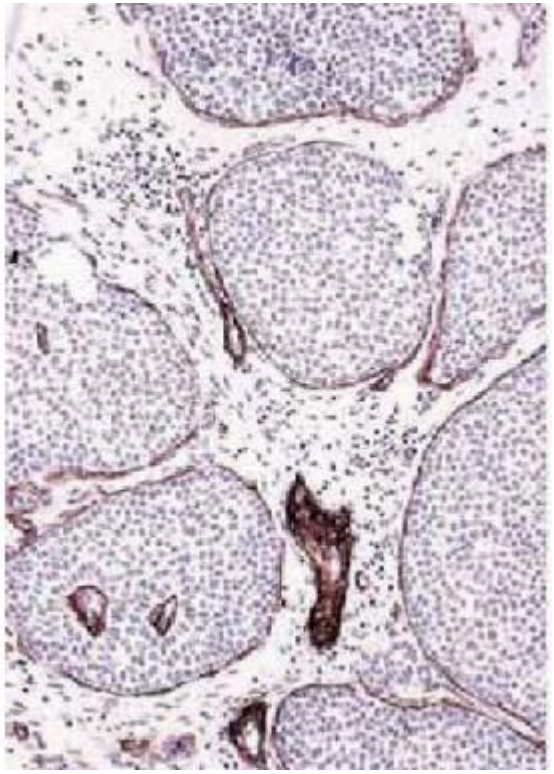
Comedo Pattern



Cribriform Pattern



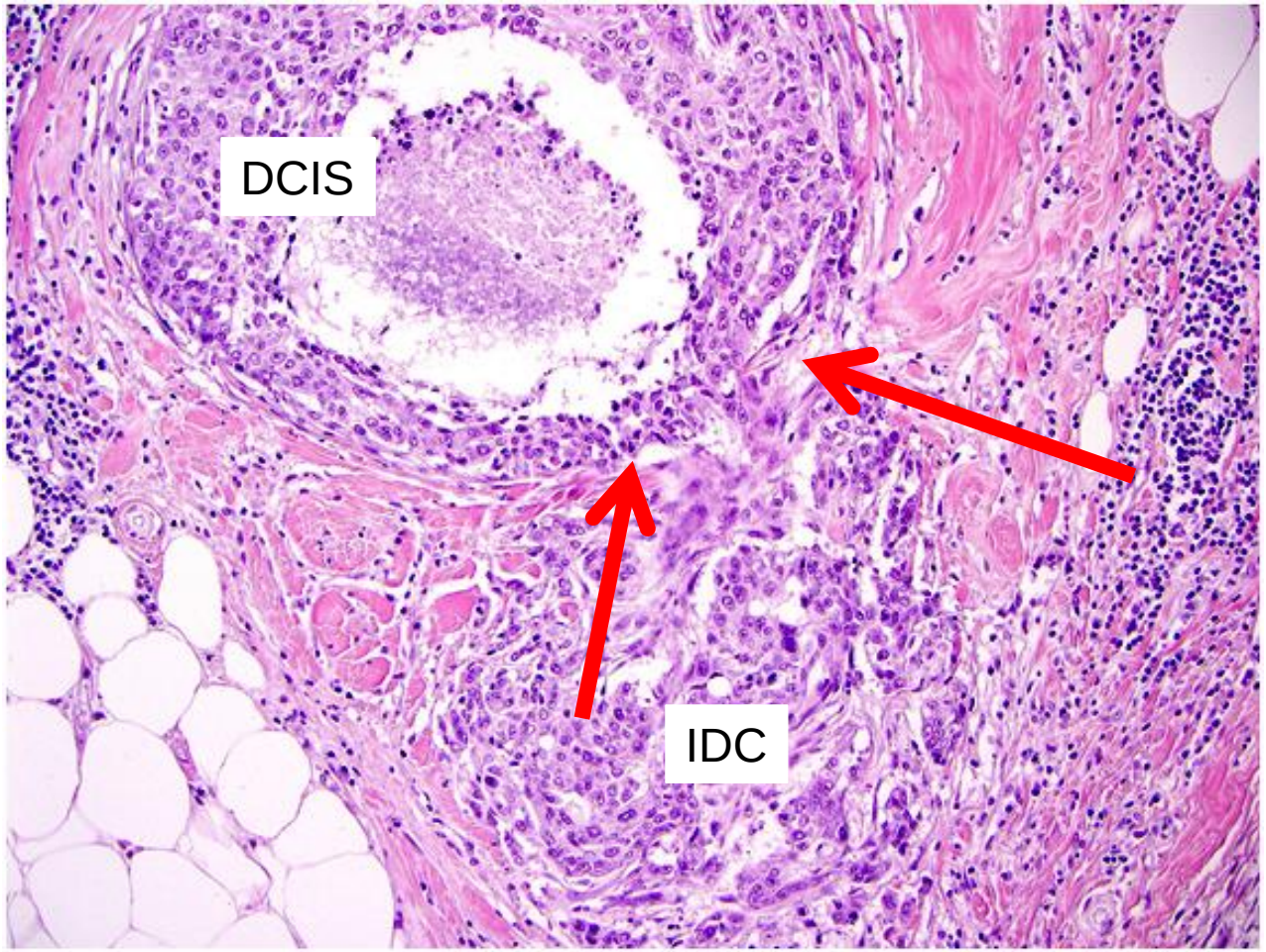
Type IV Collagen in DCIS



Intact basement membrane!

Ductal Carcinoma *In Situ* (DCIS)

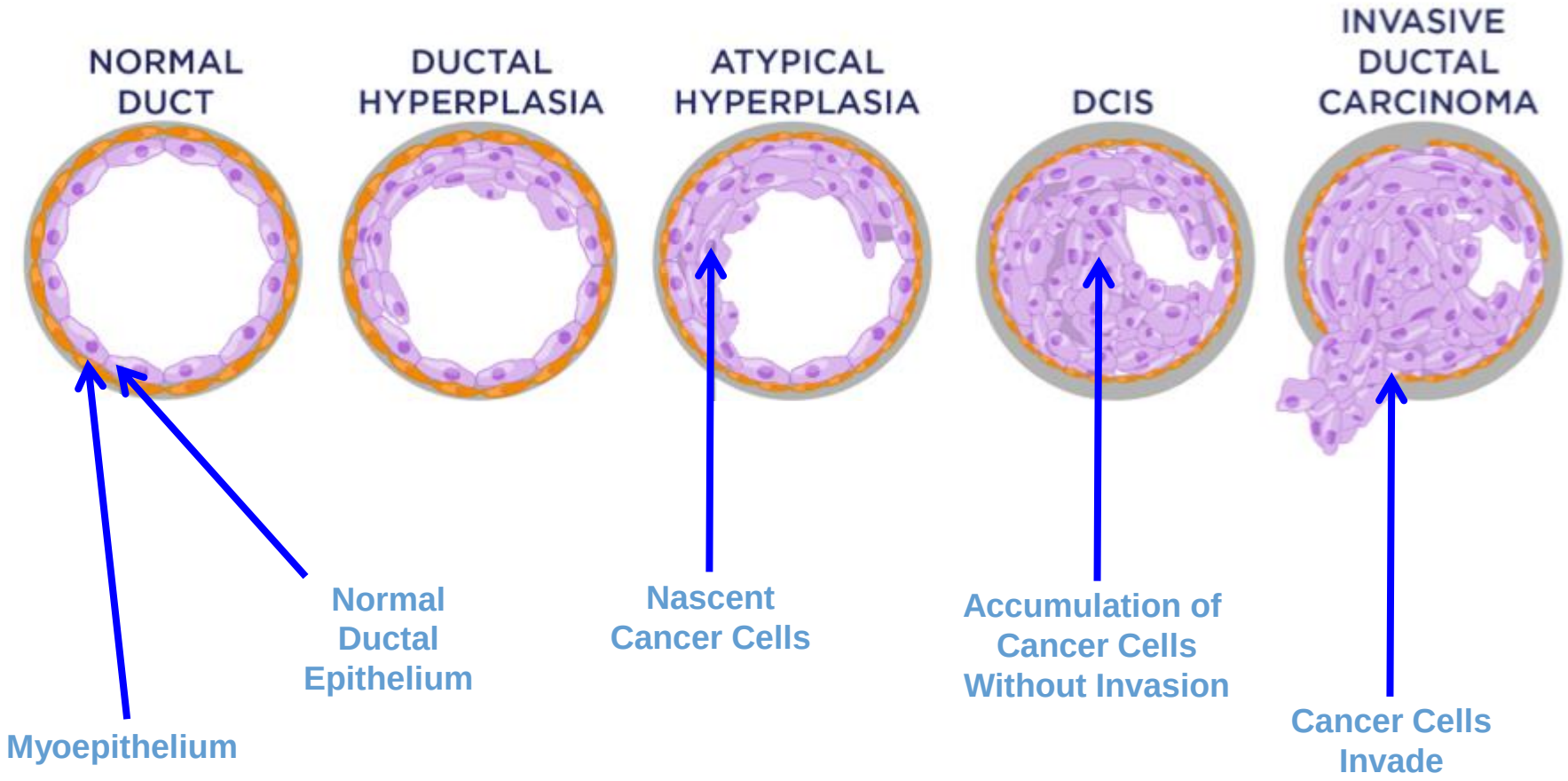
Microinvasion and Association with Invasive Ductal Carcinoma



*Red arrows indicate where cancer cells have broken out

D.C. Allred (2010) Ductal carcinoma in situ: Terminology, classification, and natural history. *J. Natl. Cancer Inst. Monographs* **41**:134-138.

Proposed Natural History of Breast Cancer Development



Ductal Carcinoma *In Situ* (DCIS)

Treatment

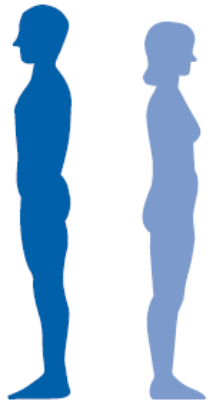
- If first mammogram is suspicious, a second higher resolution imaging may be recommended.
- If further evaluation is needed, an ultrasound-guided core needle biopsy will be performed, and sent for pathology review.
- Treatment options for DCIS include:
  - Breast-conserving surgery (lumpectomy) and radiation
  - Breast-conserving surgery (lumpectomy) and radiation plus adjuvant hormone therapy
  - Breast-removing surgery (mastectomy)
- The main goal of treatment is to *prevent* development of invasive breast cancer.

Invasive Breast Cancer

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2019 Estimates

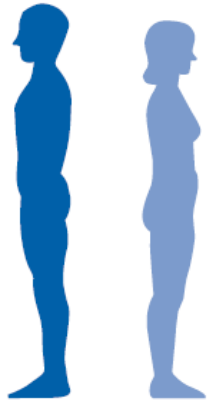
Estimated New Cases

Male			Female		
Prostate	174,650	20%	Breast	268,600	30%
Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%	Colon & rectum	67,100	7%
Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	5%
Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%	Pancreas	26,830	3%
Pancreas	29,940	3%	Leukemia	25,860	3%
All sites	**870,970**		**All sites**	**891,480**	



Estimated Deaths

Male			Female		
Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
Prostate	31,620	10%	Breast	41,760	15%
Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
Pancreas	23,800	7%	Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
Leukemia	13,150	4%	Uterine corpus	12,160	4%
Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%	Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
All sites	**321,670**		**All sites**	**285,210**	



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

Genetic Predisposition to Breast Cancer

TABLE 10.1 Genetic Predisposition to Breast Carcinoma

Gene	Syndrome	Carcinomas	Other
BRCA1	Breast Ovarian	Breast, ovary	
BRCA2	Breast Ovarian	Breast, ovary, prostate, pancreas	Fanconi anemia in homozygotes
TP53	Li-Fraumeni	Breast, brain, soft tissue, bone, etc.	
PTEN	Cowden	Breast, ovary, thyroid, colon	Adenomas of thyroid, fibroids, gastrointestinal polyps
STKII/LKB1	Peutz-Jegher	Gastrointestinal, breast	Hamartomas of bowel, buccal pigmentation
ATM	Ataxia-Telangiectasia	Breast	Homozygotes: leukemia, lymphoma, cerebellar ataxia, immune deficiency, and telangiectasia
ATM	Site-specific breast	Breast	Low penetrance
MSH2/MLH1	Muir-Torre	Colorectal, breast	

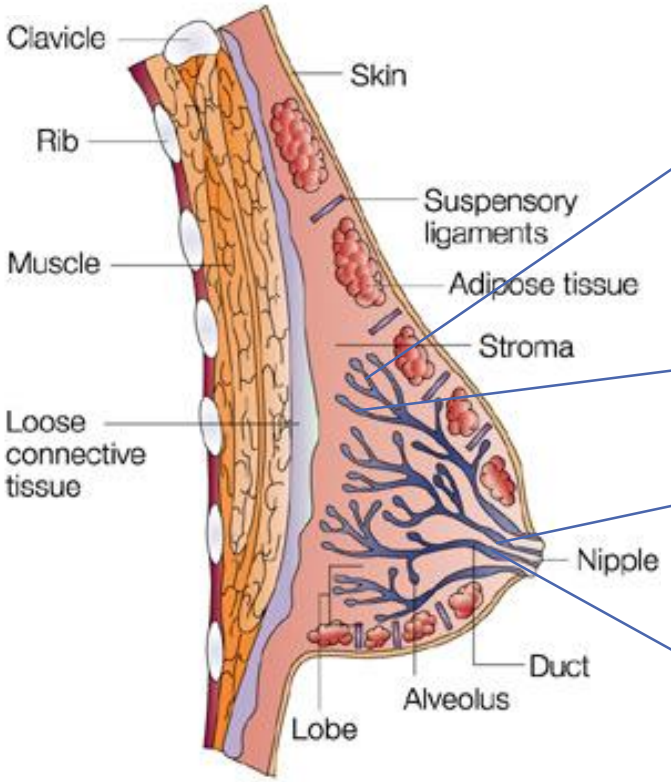
All autosomal dominant.

Adapted from Harris JR, Lippman ME, Morrow M, et al. *Diseases of the breast*. 4th ed. Philadelphia: Wolters Kluwer-Lippincott Williams and Wilkins, 2010:210.

Breast Cancer Risk Factors

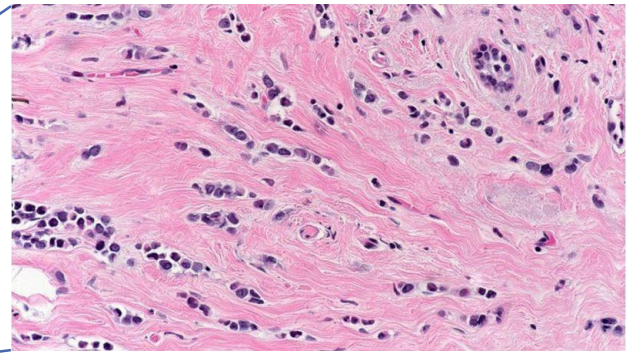
Controllable and Non-Controllable BC Risk Factors	
Age	Obesity
Genetics	Drinking Alcohol
Early menarche	Smoking
Late menopause	High Fat Diet
Nulliparity	Lack of Physical Activity
Late age at first pregnancy; not breastfeeding	Radiation Exposure, particularly to the chest
Hormone replacement therapy	Dense Breasts
Race/Ethnicity	Certain Benign Breast Diseases

Invasive Ductal and Lobular Carcinoma of the Breast



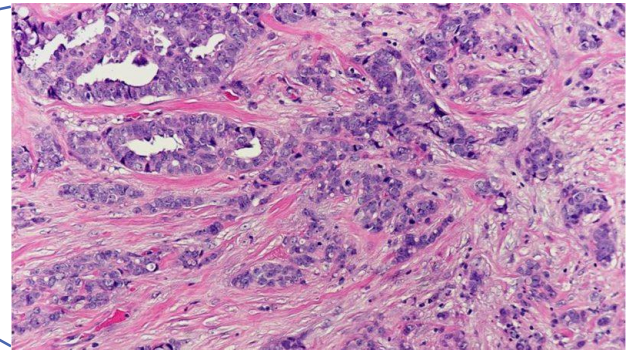
S. Ali and R.C. Coombes *Nature Reviews Cancer* 2, 101-112 (2002); doi:10.1038/nrc721

Invasive Lobular Carcinoma (ILC)



~10-15% of Cases

Invasive Ductal Carcinoma (IDC)

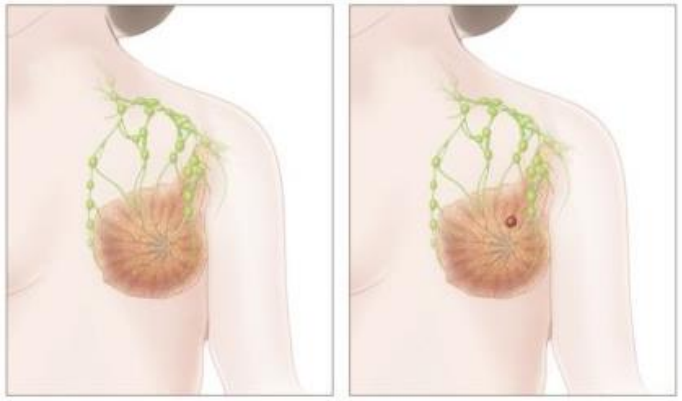


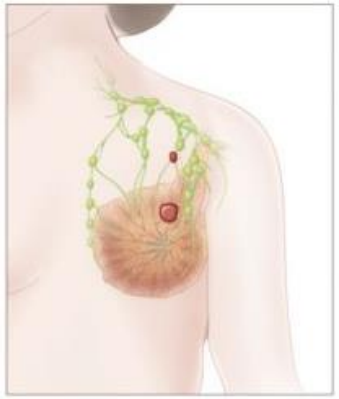
~80% of Cases

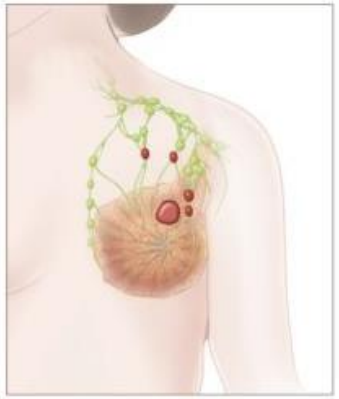
**An additional ~5% of cases are made up of rare types of breast cancer (e.g., inflammatory, mucinous, medullary, and papillary BC)

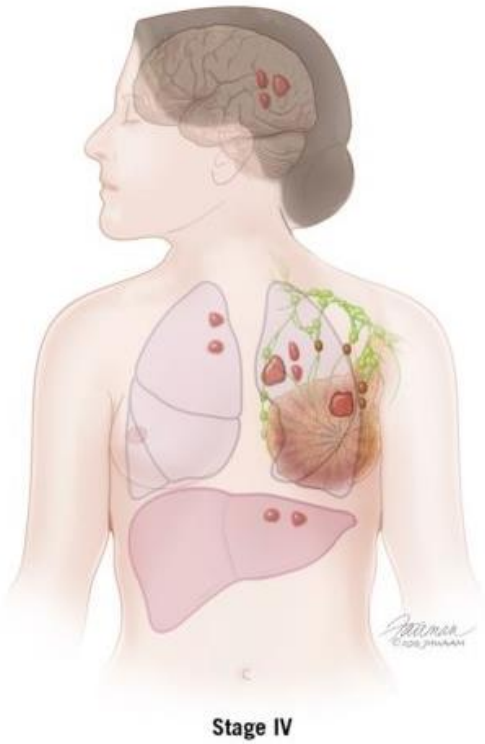
https://pathology.jhu.edu/breast/types-of-breast-cancer

Breast Cancer Staging









The pathologic stage of breast cancer is a measure of how advanced a patient's tumor is.

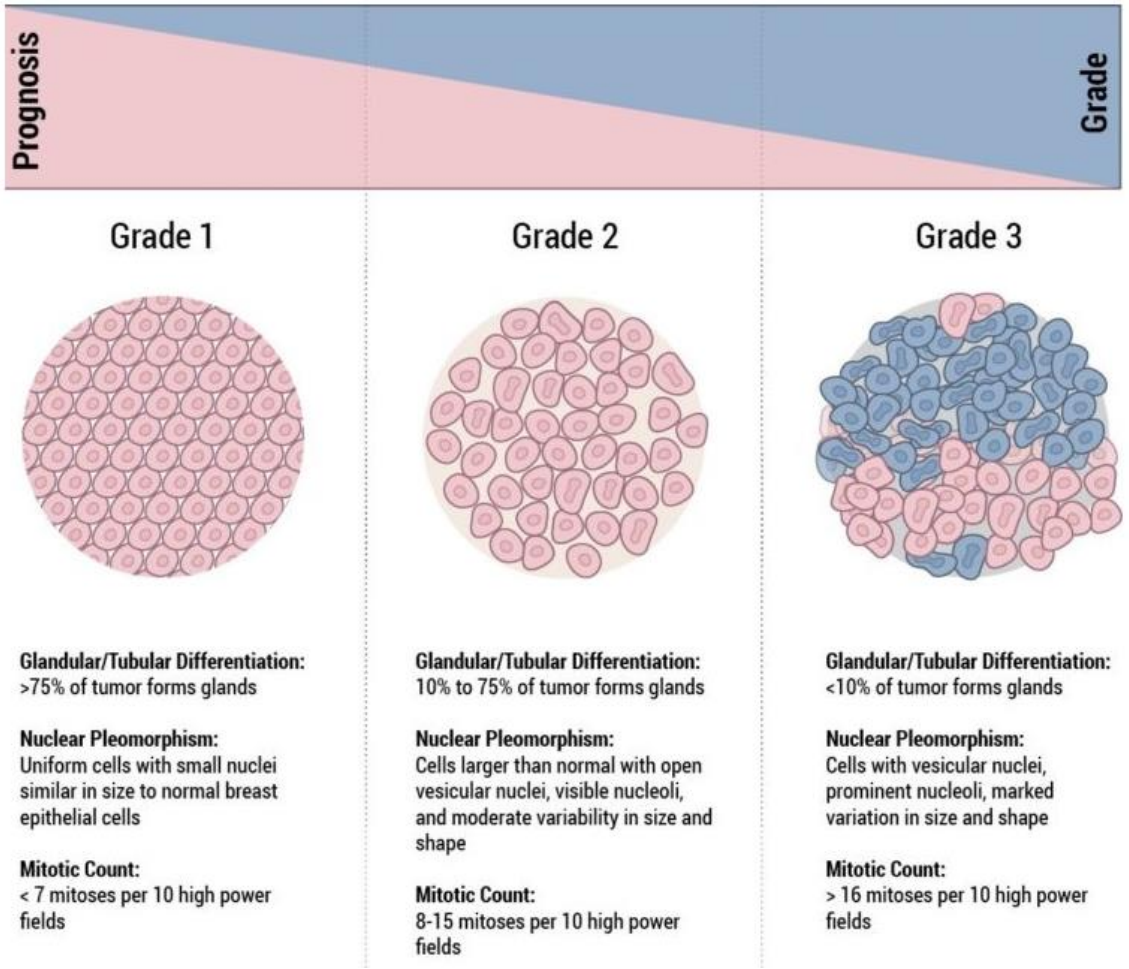
Staging takes into account:

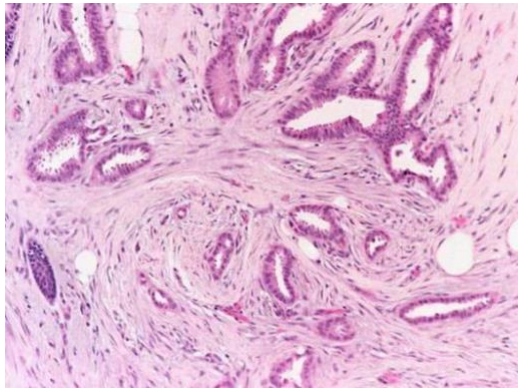
- Tumor characteristics (**T**)- DCIS, <2cm, >2 cm - ≤ 5cm, >5 cm in size
- Regional Lymph Node Metastasis (**N**)- 1-3, 4-9 and >10 axillary lymph node mets
- Distant Metastasis (**M**)

https://pathology.jhu.edu/breast/staging-grade

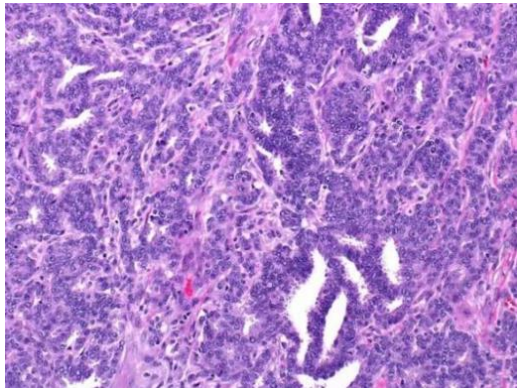
Breast Cancer Grade

The grade of a breast cancer is a prognostic representation of the "aggressive potential" of the tumor.

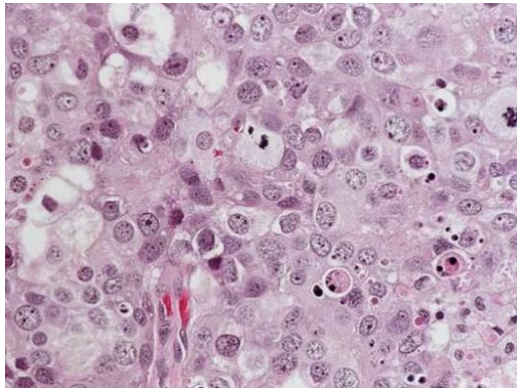




Grade 1



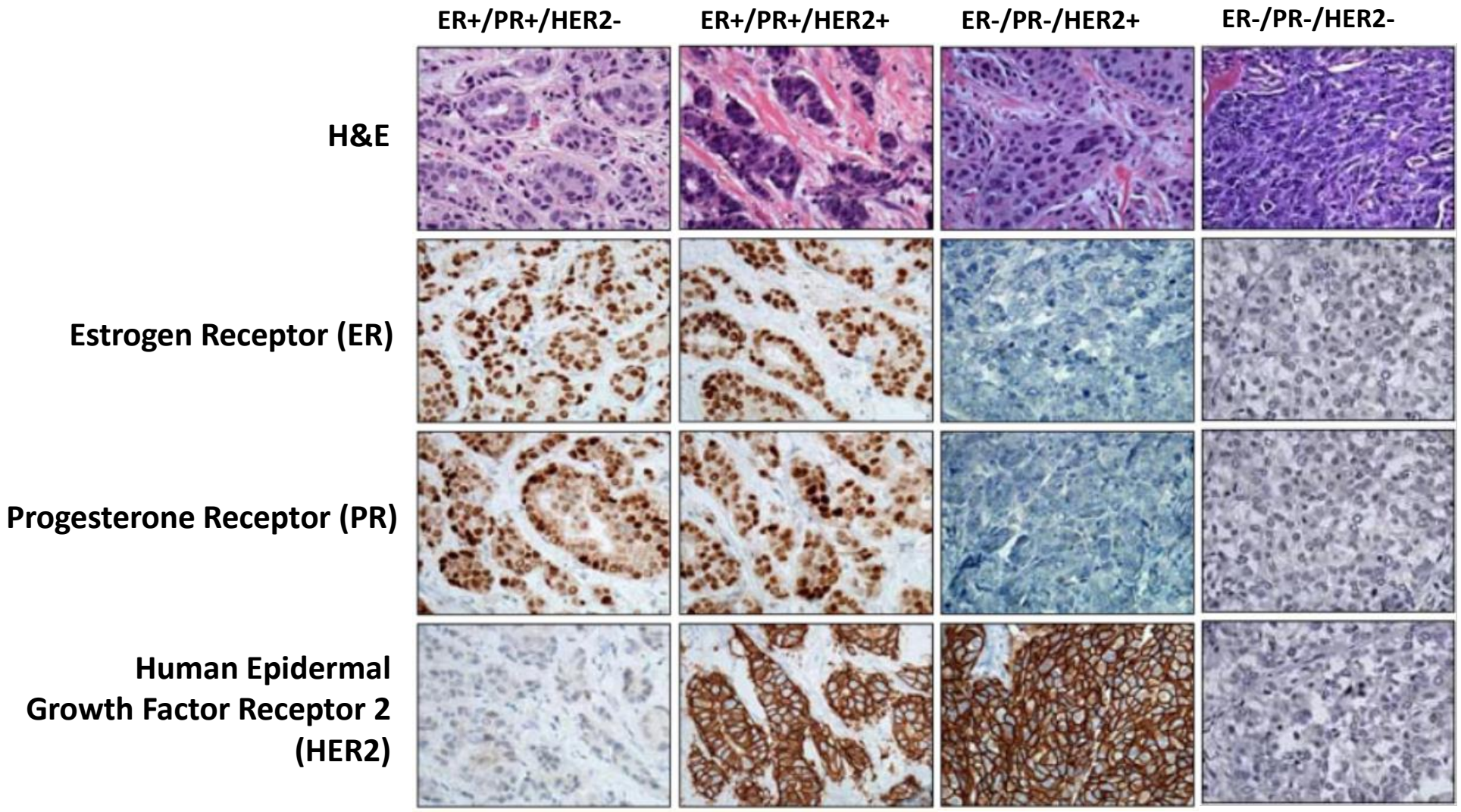
Grade 2



Grade 3

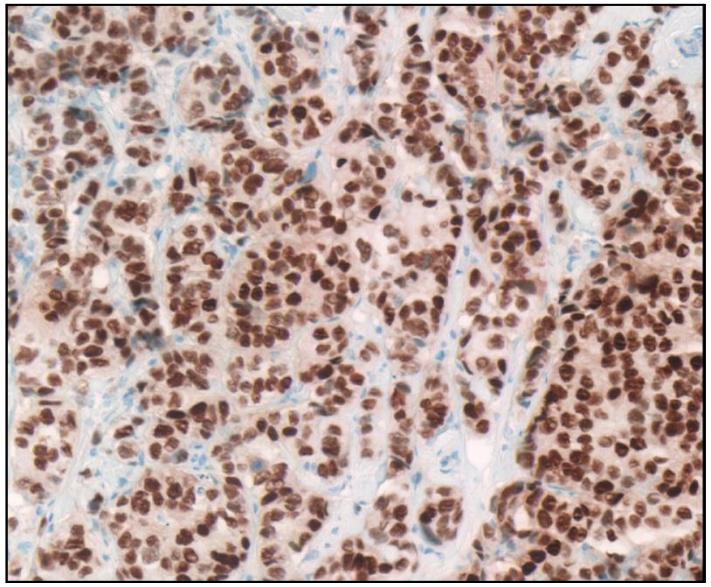
https://pathology.jhu.edu/breast/staging-grade

Clinical Breast Cancer Subtypes



Rivenbark, Am J Pathol, 2013

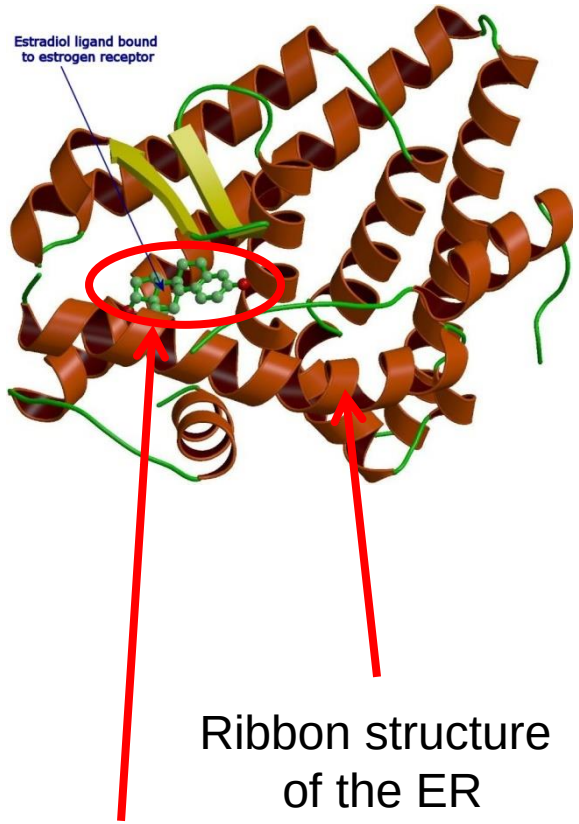
ER+ Breast Cancer



Distinct, nuclear staining for ER

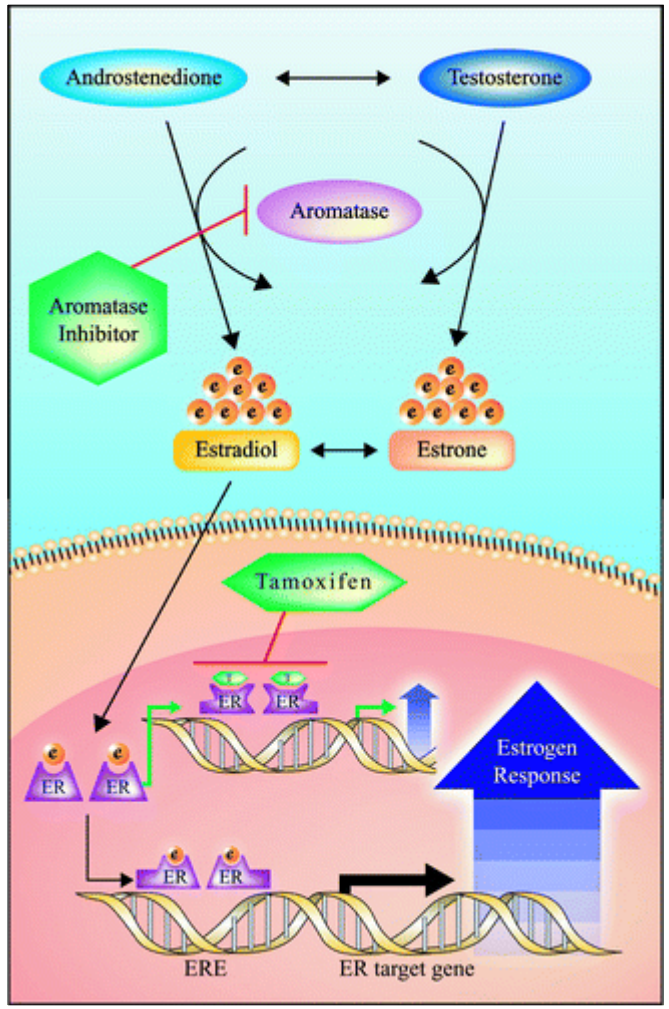
- Estrogen receptor (ER) is encoded by the ESR1 gene. The hormone estrogen binds to ER to stimulate paracrine and autocrine-mediated proliferation pathways to drive breast epithelial cell growth.
- **Approximately 70% of breast cancers are ER-positive**

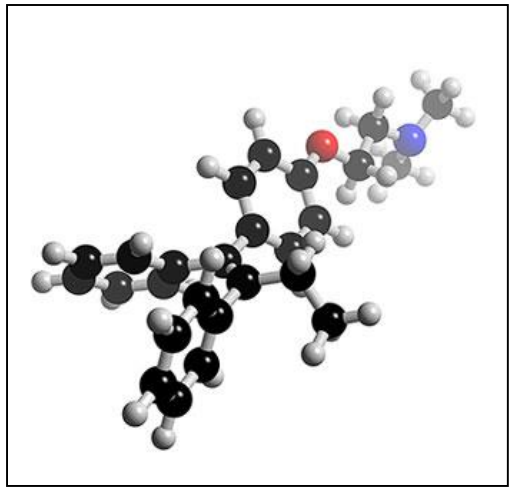
Targeted therapy for ER+ Breast Cancer



Ribbon structure of the ER

Estrogen occupying the ligand binding site of ER

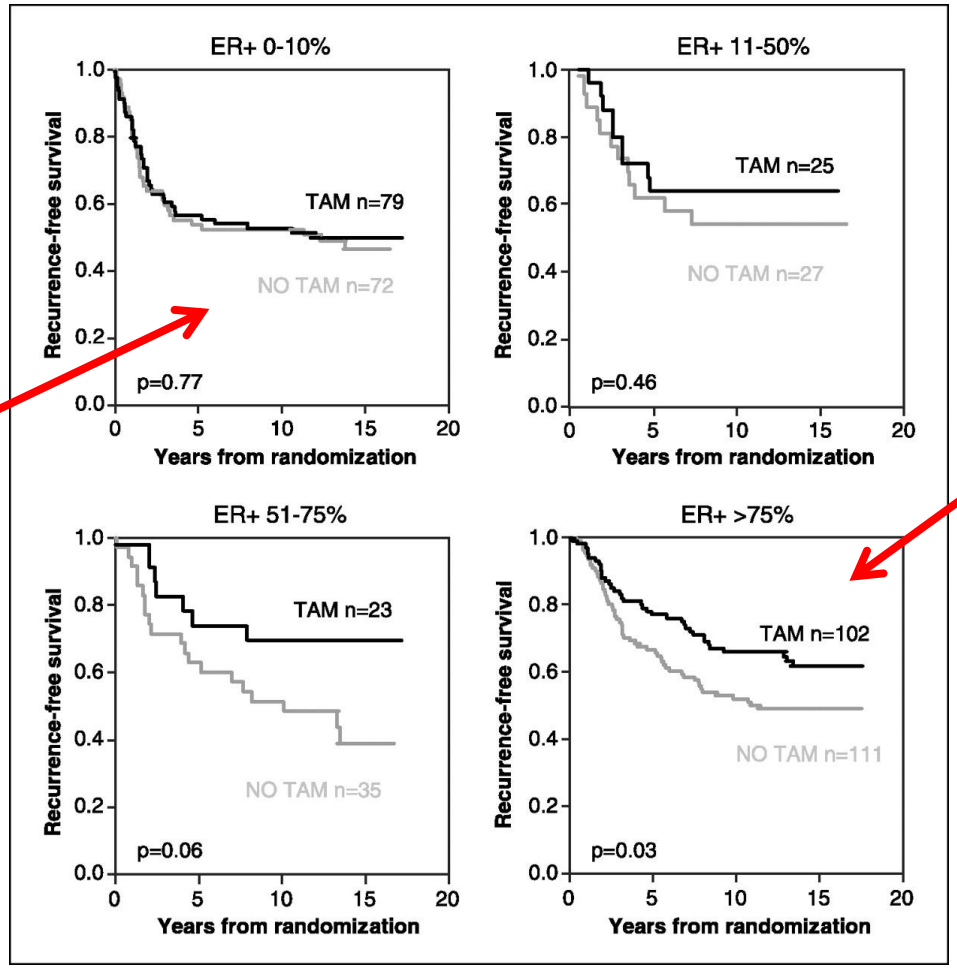




Tamoxifen mimics the structure of estrogen and can occupy the estrogen binding site of ER

Tamoxifen Treatment Improves Outcomes for ER+ Breast Cancer

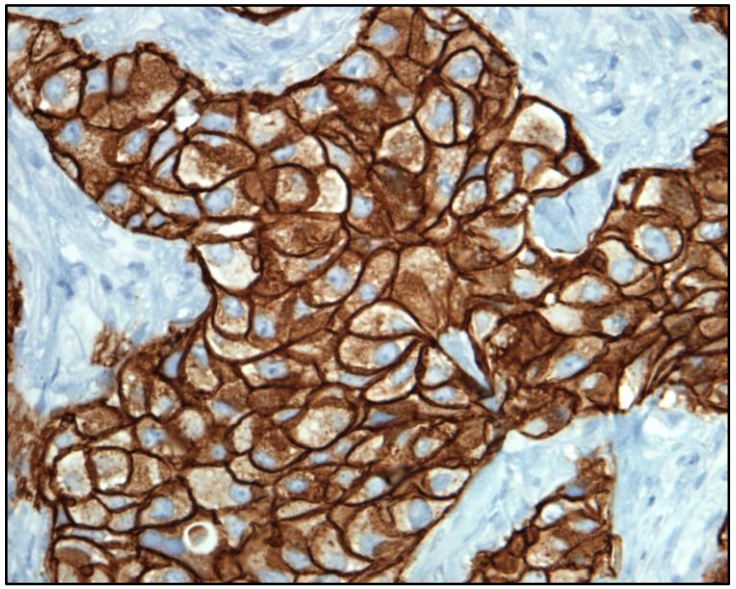
Tamoxifen produces no effect in breast cancers with low ER expression



Tamoxifen produces significant improvement in outcomes of breast cancers with high ER expression

M.Stendahl *et al*. (2006) High progesterone receptor expression correlates to the effect of adjuvant tamoxifen in premenopausal breast cancer patients. *Clin. Cancer Res*. 12:4614-4618.

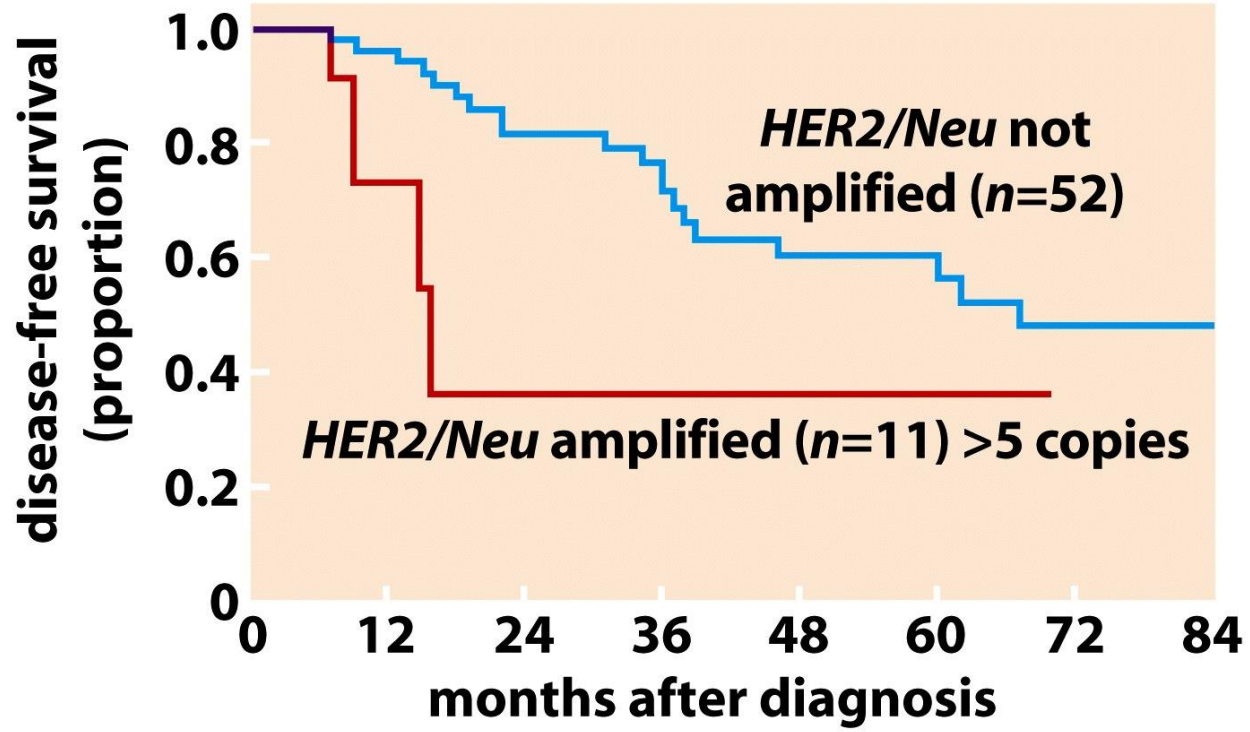
HER2+ Breast Cancer



Distinct, strong “chicken-wire” pattern of staining for HER2

- The *HER2/neu* gene encodes a member of the epidermal growth factor receptor family (*ERBB2*). Overexpression of *HER2/neu* drives cancer by virtue of hyperstimulation of growth factor receptor signaling pathways.
- **Approximately 15-20% of breast cancers are HER2-positive.**

HER2/Neu Amplification is Associated with Poor Long-term Survival Among Breast Cancer Patients

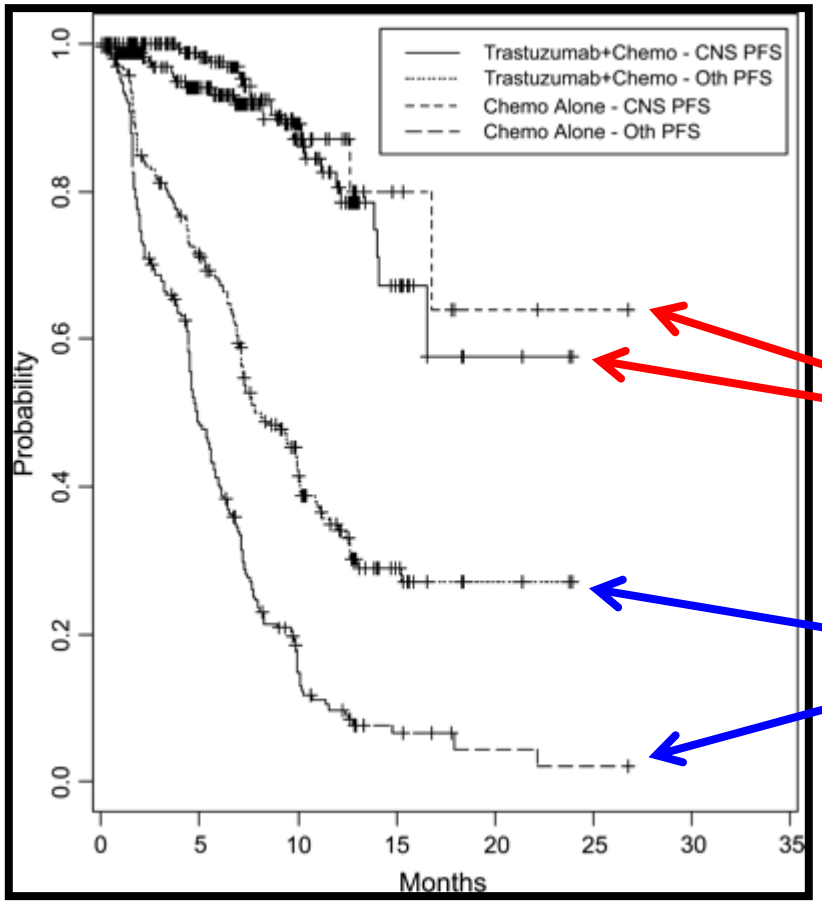


Breast cancers with amplified *HER2* are prone to relapse in the first 18 months after diagnosis and have poor overall prognosis, indicative of more aggressive disease.

From: Cellular Oncogenes (Chapter 4), pp 91-117.
R.A. Weinberg. *The Biology of Cancer*. Garland Science, 2007.

Targeted therapy for HER2+ Breast Cancer

Herceptin®
trastuzumab

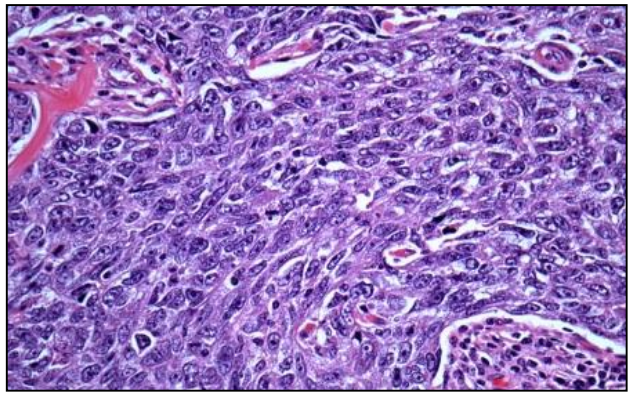


Excellent progression-free survival with Herceptin treatment

Poor progression-free survival without Herceptin treatment

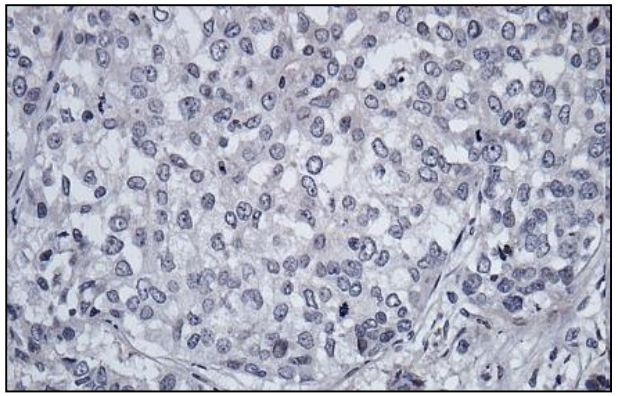
H.J.Burstein, *et al*. (2005) Isolated central nervous system metastases in patients with HER2 overexpressing advanced breast cancer treated with first-line trastuzumab-based therapy. *Annals of Oncology* 16:1772-1777.

Triple Negative Breast Cancer (TNBC)

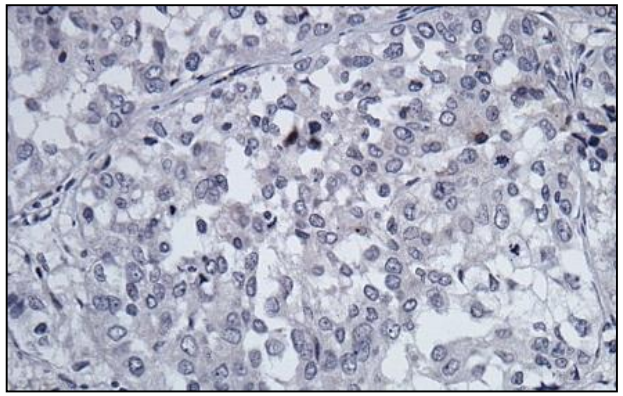


Triple-negative breast cancer

~10-15% of all BC cases are TNBC



Estrogen receptor-negative
Resistant to Tamoxifen

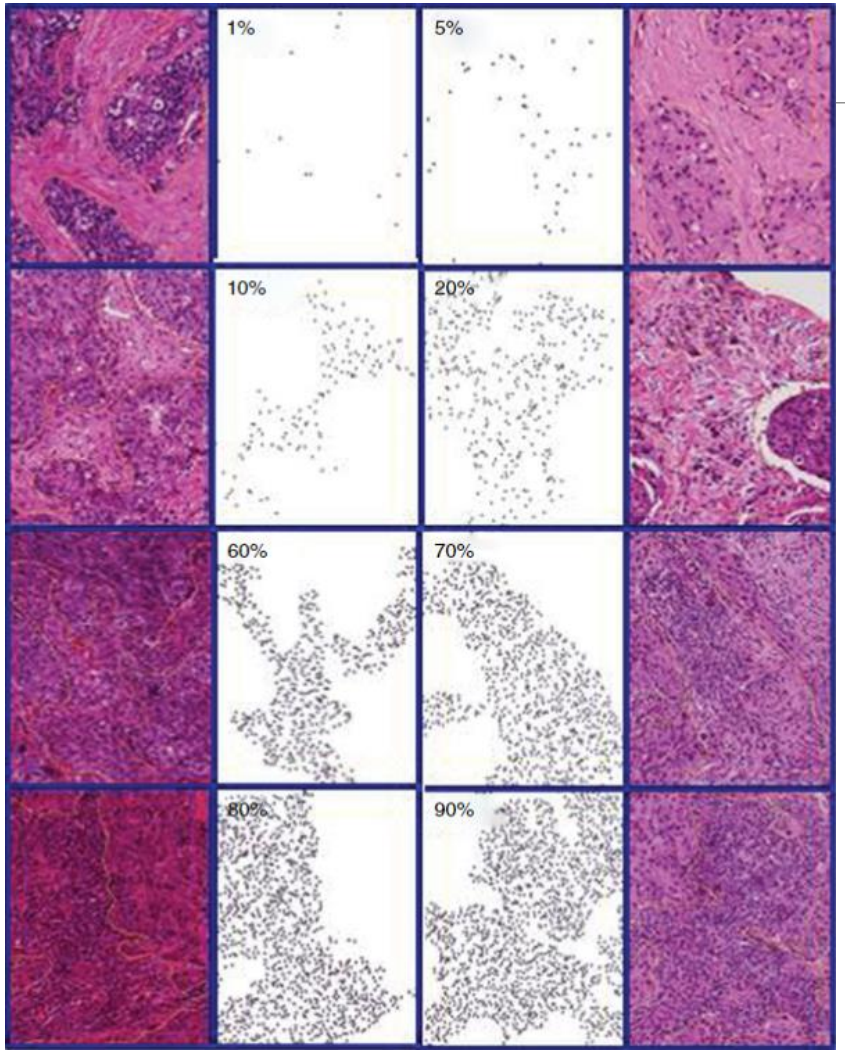


HER2-negative
Resistant to Herceptin

Standard Treatment
Cytotoxic Chemotherapy

There is a pressing need to identify targets for therapy in triple-negative breast cancer to enable molecular and personalized treatment

Tumor Infiltrating Lymphocytes Predict Outcomes in Breast Cancer



VOLUME 28 · NUMBER 1 · JANUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Tumor-Associated Lymphocytes As an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer

Carsten Denkert, Sibylle Loibl, Au
Silvia Darb-Esfahani, Ralf Kronen
Christine Solbach, Iris Schrader, M

VOLUME 32 · NUMBER 27 · SEPTEMBER 20 2014

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Prognostic Value of Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancers From Two Phase III
ed Adjuvant Breast Cancer Trials: ECOG 2197
G 1199

ert J. Gray, Sandra Demaria, Lori Goldstein, Edith A. Perez, Lawrence N. Shulman,
Molin Wang, Vicky E. Jones, Thomas J. Saphner, Antonio C. Wolff, William C. Wood,
, George W. Sledge, Joseph A. Sparano, and Sunil S. Badve

VOLUME 31 · NUMBER 7 · MARCH 1 2013

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Prognostic and Predictive Value of Tumor-Infiltrating Lymphocytes in a Phase III Randomized Adjuvant Breast Cancer Trial in Node-Positive Breast Cancer Comparing the Addition of Docetaxel to Doxorubicin With Doxorubicin-Based Chemotherapy: BIG 02-98

Sherene Loi, Nicolas Sirtaine, Fanny Piet
Ghizlane Rouas, Prudence Francis, John
Angelo Di Leo, Stefan Michiels, Martine

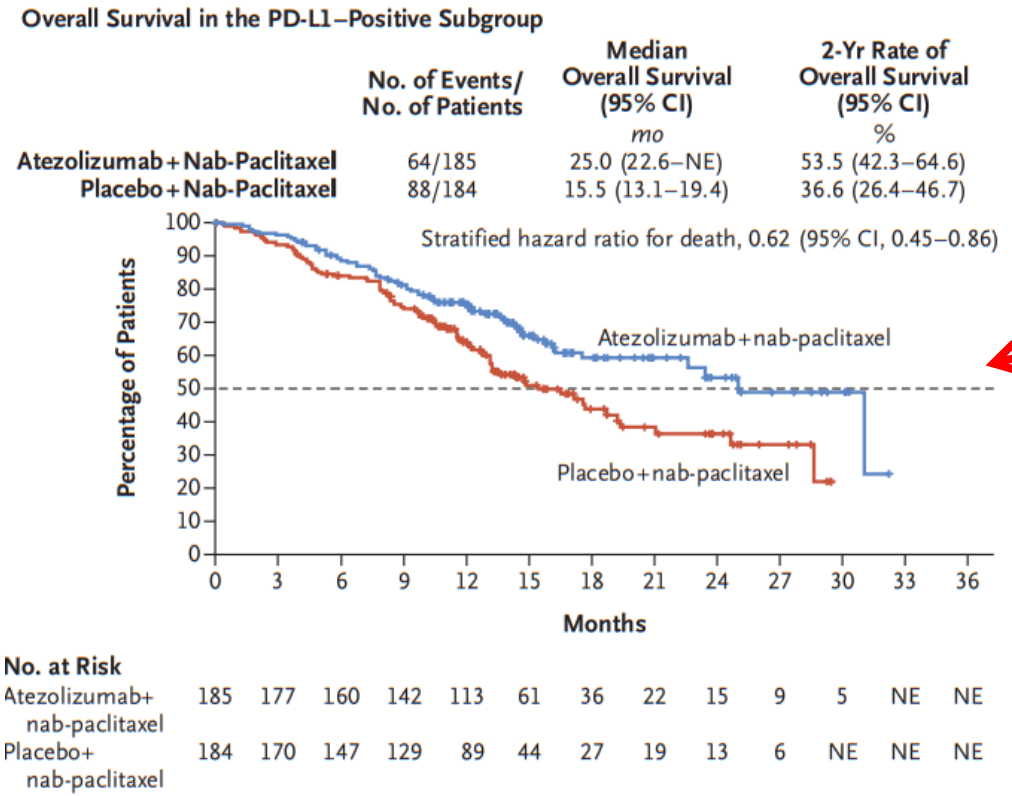
Annals of Oncology 25: 1544–1550, 2014
doi:10.1093/annonc/mdu112
Published online 7 March 2014

Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial

S. Loi[1,2*], S. Michiels[1,3], R. Salgado[4], N. Sirtaine[4], V. Jose[1], D. Fumagalli[1], P.-L. Kellokumpu-Lehtinen[5], P. Bono[6], V. Kataja[7], C. Desmedt[1], M. J. Piccart[8], S. Loibl[9], C. Denkert[10], M. J. Smyth[11], H. Joensuu[6] & C. Sotiriou[1]

Adapted from Salgado *et al*., Annals of Oncology, 2015

Immunotherapy for Metastatic Triple Negative Breast Cancer



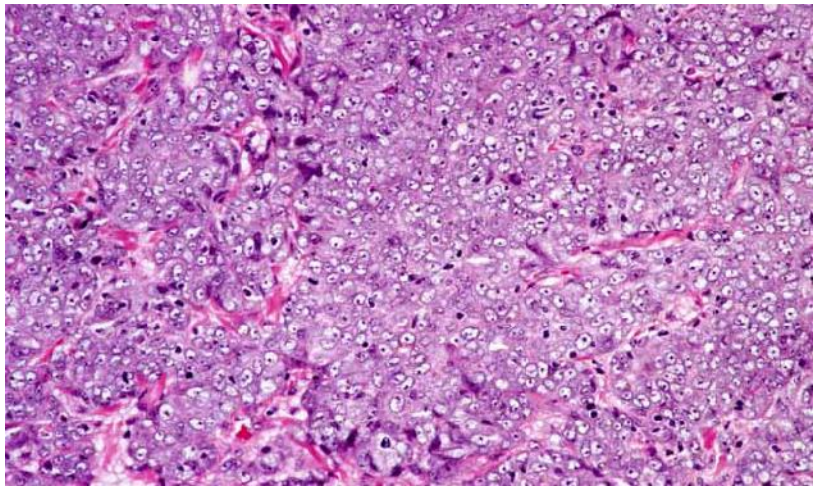
Addition of this PD-L1 inhibitor to nab-paclitaxel reduced the risk of progression or death by 40% compared with nab-paclitaxel alone!

Currently, checkpoint inhibitors (like atezolizumab and pembrolizumab) are only approved for PDL1+ metastatic TNBC. Only 30% of metastatic TNBC patients in this trial were PDL1+.

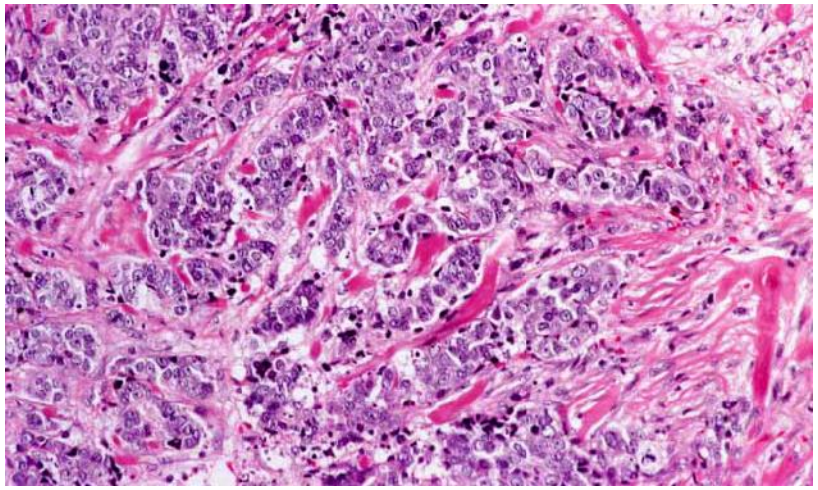
Schmid et al., N Engl J Med 2018; 379:2108-2121
DOI: 10.1056/NEJMoa1809615

Molecular Breast Cancer Subtypes: Can we improve precision medicine in breast cancer?

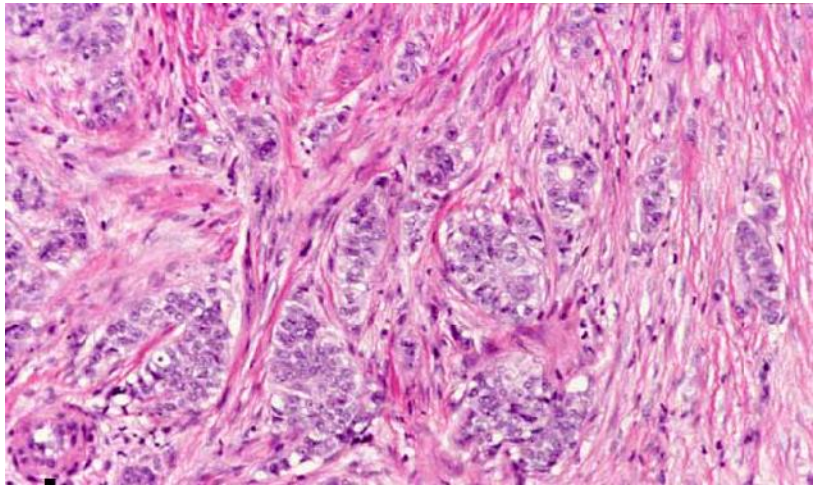
Grade III, T3 (diameter > 5cm),
Estrogen and Progesterone Receptor Positive, HER2 Negative,
3 of 4 Node Positive, all received Tamoxifen



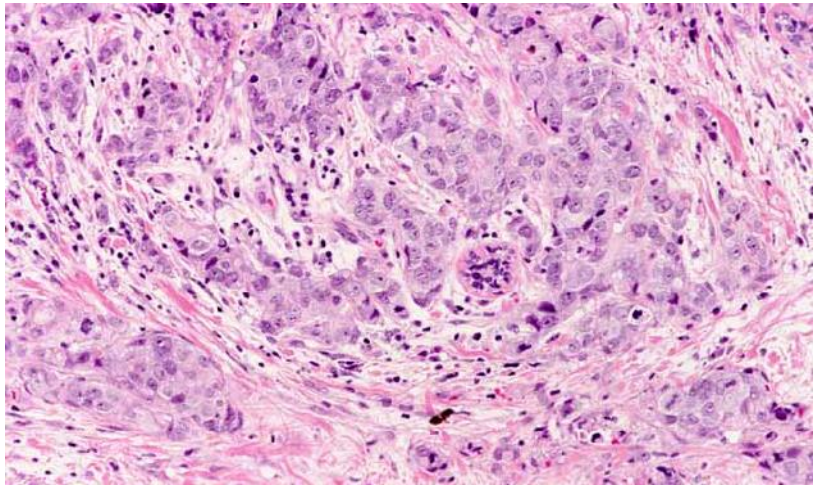
Died after 9 months



Alive for 79 months

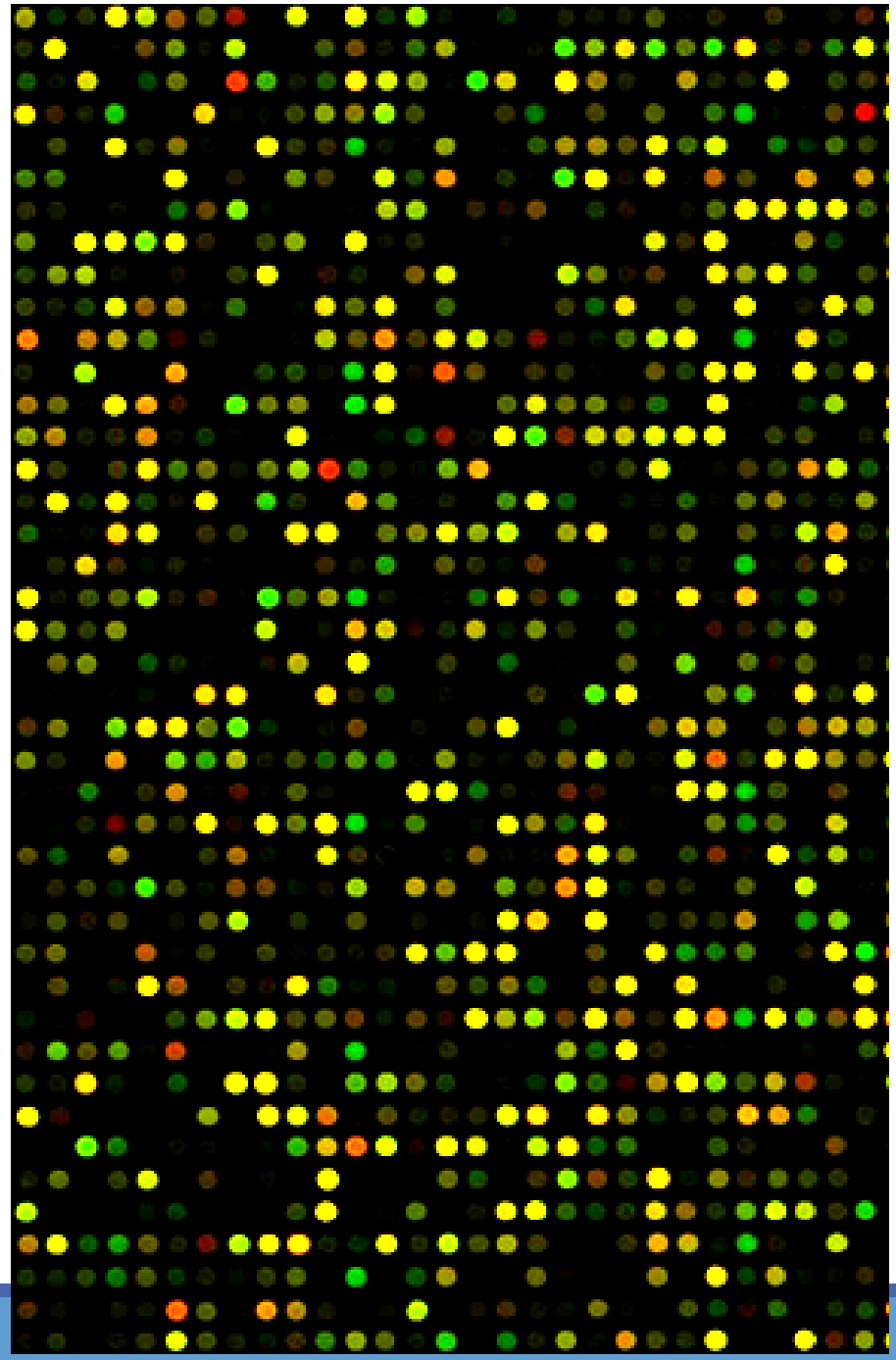


Died after 17 months



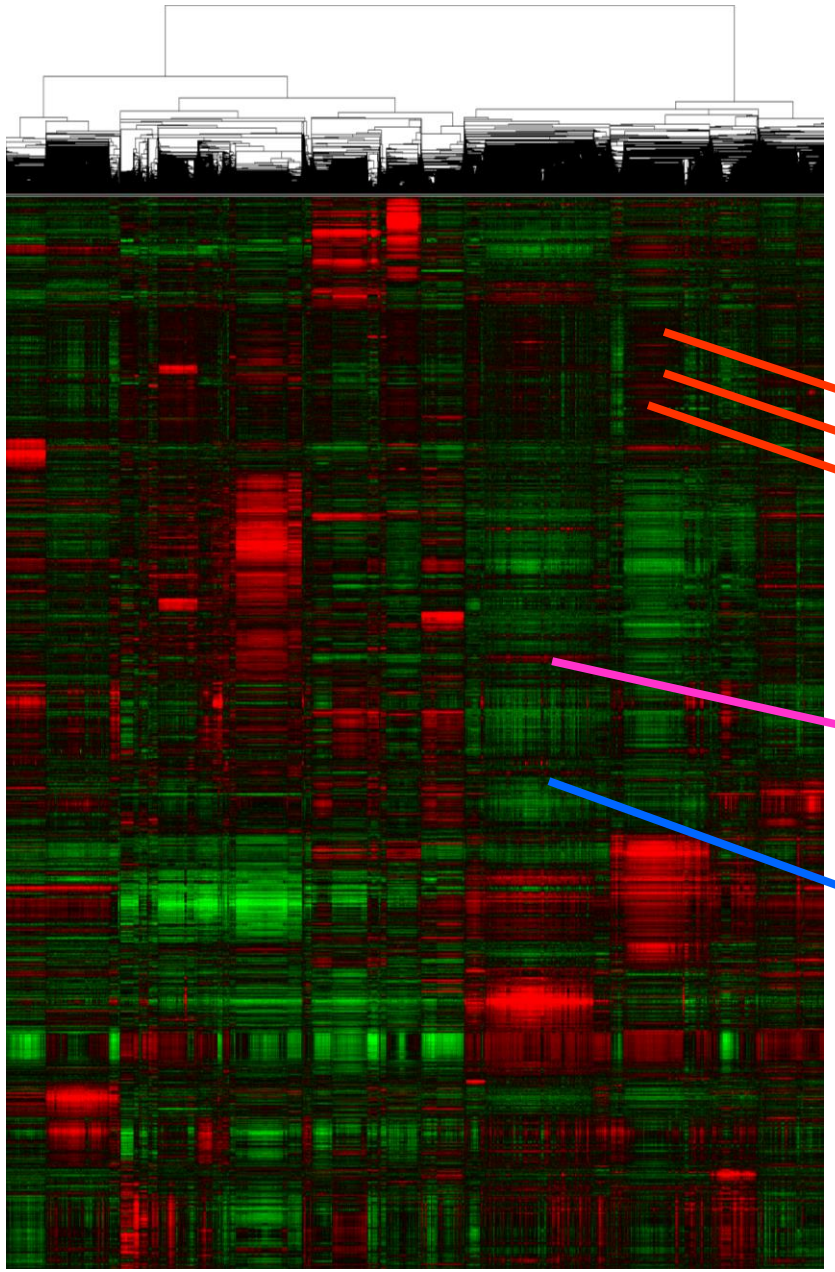
Alive for 96 months


17 August 2000
International weekly journal of science
nature
$10.00
www.nature.com
nature insight
Microbial infection
& immune defence
Microbial infection
Nature Insight
The portrait of a breast cancer
Organic superconductors Piling on the charge
Rice farming Diversity beats disease
Atmospheric CO2 The boron record
nature jobs
focus on chemistry



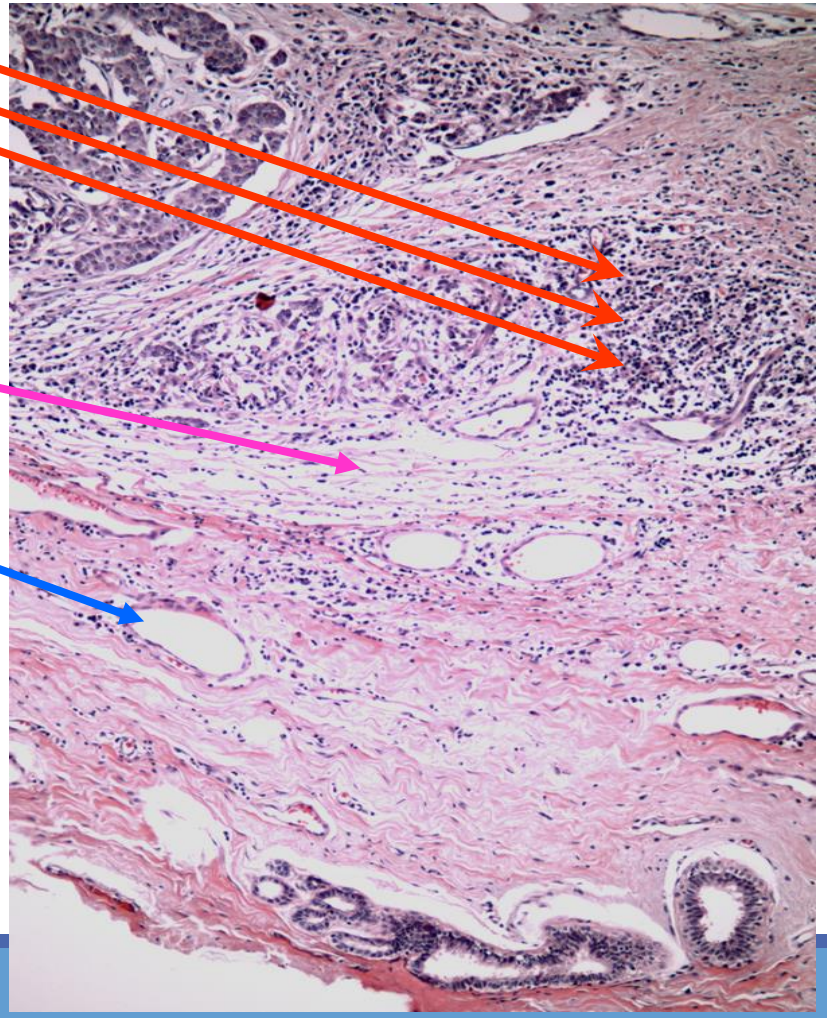
NAME	BC/FUMI0	BC/FUMI4	BC/FUMI4	BC601B-A	BC601A-B	BC/FUMI1	BC/FUMI2	BC/FUMI2	BC/FUMI1	BC/FUMI1	BC102B-E	BC/FUMI2	BC/FUMI3	BC/FUMI3	BC/FUMI1	BC/FUMI1
adipose differentiation-related prote	0.242	1.21	-0.253	-0.841	-0.423	-0.363	-0.852	-1.383		-2.642	0.501	-0.25	-0.605	-0.636	0.229	-0.626
plasminogen activator, urokinase re	0.908	0.485	-0.397	-0.767	-0.886	-0.251	-0.683	0.057	-0.317	-1.2	0.125		-0.536	-0.248		-0.365
plasminogen activator, urokinase re	0.4635	0.3545	-0.8975	-1.23	-0.8335	0.0175	-1.002	0.1555	-0.4325	-1.008	-0.1785		-0.7445	-0.1485	0.0555	0.2055
coronin, actin binding protein, 1C A	0.551	0.151	-0.422	0.007	-0.638	0.087		-0.689	-0.91	-0.853	0.052	-0.492	-0.201	-0.152	-0.368	-0.741
**coatomer protein complex, subun	-1.061	-0.8655	-0.1235	-0.9895	0.3815	-0.4955	-0.2775	-0.1465	-1.109	-0.8635	0.2615	-0.0905	-0.3225	-0.6035	0.0195	-0.9345
coactosin-like protein R78490	-0.8835	-0.4545	0.2375	-1.177	0.2155	-0.2975	-0.9385	-0.2815	-1.494	-0.5985	0.4095	-0.3465	0.2185	-0.1345	-0.2895	-0.5525
folylpolyglutamate synthase R4486	0.686	1.583	1.313	0.048	-0.272	-0.143	-0.394	0.423	-0.445	-0.854	0.322	-0.03	-0.412	0.214	-1.098	-0.175
lysozyme (renal amyloidosis) N639	-0.18	1.155	1.575	-1.635	0.355	0.295	-0.805	0.135	-2.145	-0.955	0.575	0.735	-0.435	-0.855	-0.8	-1.705
chemokine (C-C motif) receptor 1 AA036881		0.524	1.233	-1.459	-0.095	-0.122	-0.196	0.101		-0.942	-0.2	-0.133	-0.549	-0.763		-0.059
interferon, gamma-inducible protei	-0.181	-0.062	0.37	0.064	0.418	-0.33	-0.098	-0.289	-1.042	-0.332	0.907	1.056	-0.8	-0.193	-0.789	-1.25
cystatin B (stefin B) H22919	-0.188	-0.489	-0.603	0.074	-0.212	-0.295	-0.54	-0.535	-0.453	-0.479	-0.021	0.291	-0.651	-0.536	-0.401	-0.511
cathepsin S AA236164	-0.791		0.334	-0.316	0.723	-0.46	0.39	-0.452		-0.413		1.063	-0.849	-1.088	-0.94	-1.291
small inducible cytokine A2 (monoc	0.2665	0.2955	0.5315	-0.1285	0.4255	-1.099	-0.7265	-0.6035	-1.052	-1.438	0.1355	0.0365	-0.4335	0.0875	-1.218	-0.7785
natural killer cell transcript 4 AA458	0.483	0.348	0.575	-0.685	0.971	-0.335	-0.222	-0.116	-1.644	-0.66	-0.322	0.885	-0.08	-0.02	-0.441	-0.51
superoxide dismutase 2, mitochond	0.431	0.301	-0.836	0.519		-0.492	-0.834	-0.86		0.781	0.005	-1.163	-1.283	-0.969		-0.586
superoxide dismutase 2, mitochondrial AA487		0.3185	-0.6835	0.4865	0.6925	-0.7895	-0.6005	-0.5815	0.4995	0.0165	0.3755	-0.1225	-1.129	-1.137		-0.6935
transforming growth factor, beta-in	0.0235	0.6525	-0.3785	-0.5505	-0.3675	-0.4755	-0.1105	0.3435	0.0785	-0.4735	0.7925	1.532	-0.3355	-0.0885	0.2495	-0.1985
glycine dehydrogenase (decarboxy	-1.122	-1.412	-1.275	-1.764	-0.611	1.259	-1.25	-0.76	-2.159	-1.72	-1.017	-0.972	-0.715	-0.543	-0.658	-0.818
syndecan 2 (heparan sulfate protec	-1.828	-1.7	-1.409	-1.964	-0.975	1.516	-1.24	-1.75	-2.219	-2.477	-1.08	0.29	-1.641	-2.045	-0.315	-1.356
glutathione S-transferase pi R3364	-1.726	-1.892	-1.568			1.528	-1.346	-2.157	-3.114	-3.146	-0.943	0.236	-1.349	-1.674	-0.416	-1.557
chitinase 3-like 2 AA668821				-0.771	-1.436	-1.454	-0.813	-1.578	0.312	-0.167	0	-0.469	0.129	-0.566		-0.489
nuclear factor I/B W87528	0.464	-1.314	-0.187	-1.429	-0.189	0.551	-1.94	-1.372		-2.152	-1.825		-0.441	-0.928	0.316	-1.188
ras homolog gene family, member	-1.382	-0.471	-0.421	0.304	-0.448	-0.805	-0.945	-0.737	-1.222	-0.915	-0.713	-0.167	0.09	1.074		-0.393
ras homolog gene family, member	-1.311	-0.763	-0.61	0.198		-0.764	-0.391	-0.867	-1.469	-1.106	-0.486	-0.778	-0.579	0.812	0.348	-0.222
**zinc finger, DHHC domain containing 5 AA4		-0.965	-0.571	-0.304	-0.328	-0.417	-0.518	-0.473	-0.973	-0.94	-0.926	-1.153	-0.462	-0.683	0.828	0.347
keratin 5 (epidermolysis bullosa sin	-0.309	-0.485	-0.748	-0.909	-0.403	-0.127	-0.371	-0.778	-1.596	-1.787	-0.782	0.242	-0.559	-0.804	0.79	0.374
keratin 5 (epidermolysis bullosa simplex, Dowl		-0.655	-2.421	0.301	0.689	-0.38	-0.131	-1.647		-1.396	0.248	-1.118	-0.389	-1.423	1.963	-0.068
keratin 17 AA026100		-0.593	-2.294	0.181	-0.45	0.457	-1.132	-0.754		-2.708	-0.641	-0.148	-0.201	0.161	2.264	1.758
tripartite motif-containing 29 AA055	-0.523	-0.763		-0.726	-0.155	-0.401		-1.8	-1.591	-1.789	-1.076	-0.929	-1.132	-1.051		-0.24
pleiomorphic adenoma gene-like 1 AA463204		-0.7035	-0.5595	-0.7765	-0.2835		-0.1885		-1.466	-2.035	-0.1475	-0.7075	-0.4025	-1.054	0.3535	-0.5835
secreted frizzled-related protein 1 AA002080		-1.951	-2.022	-1.982	0.069	-0.117	-1.543	-2.996		-2.657	-0.275	-1.187	-0.262	-0.688	3.135	0.295
Homo sapiens cDNA FLJ11796 fis, clone HEM		-1.425		-0.74	-0.798	0.243	-0.225	-0.061		-0.957	-0.001		-0.491	-0.28	0.595	-0.721
ESTs AA074677		-0.411	-0.412	-0.879	-0.78	-0.401	-0.135	-0.508		-2.237	0.077		-0.72	-1.057		-1.301
pellino homolog 1 (Drosophila) W8	-0.3805	-1.159	-0.6945	-0.3935	-0.1785	-0.3665	-0.3835	-0.2825	0.1245	0.3185	0.2735	-1.329	-0.9455	-1.313		-0.4235
matrix metalloproteinase 7 (matrilys	-0.887			-2.32	0.16	-1.65		-1.54		-1.065	1.453		-1.55	-2.859		-0.04
moesin R22977	0.452	-0.759	-0.433	-0.691	0.148	-0.538	-0.28	-0.478	-0.477	0.019	0.062		-0.001	0.259	-0.24	-0.314
prion protein (p27-30) (Creutzfeld-J	-0.8095	-1.302	-0.5695	-1.843	-0.8355	-0.3325	-0.7305	0.2015	-0.3825	-0.2335	-0.4605	-1.181	-0.6875	-0.3315	0.2825	-0.0605
chitinase 3-like 1 (cartilage glycoprotein-39) A		1.474	1.071	0.678	0.987	-1.357		-2.185		-1.619	3.517	-0.465	-1.549	-1.699		-1.262
annexin A8 AA235002		-0.55		-0.832	0.209	0	-0.576	-0.199		-1.046	-0.454	-0.221	0.134	-0.015	0.619	0.519
hypothetical protein FLJ20481 N32	-0.078	-0.939	-1.002	0.058	-0.058	-0.158	-1.65	-0.794		-1.612	0.17	1.318	0.404	-0.312		-0.039
ADP-ribosylation factor-like 7 N353	-0.9415	-0.0585	-0.3685	-0.9365	-0.2155	0.0715	-0.2825	-0.5505		-1.107	-0.5855	0.2285	-0.2475	0.1635		-0.1405
cystatin A (stefin A) W72207		-0.532	-0.941	0.909	1.783	0.164	-0.106	-0.577		-1.496	0.588	3.351	-0.73			-0.855
inhibitor of DNA binding 3, dominar	-0.46	-0.587	-0.421	-0.358	0.326		0.638		-0.642		-0.224	-0.143	-0.445	-0.58	0.377	
complement component 1, r subcor	0.116		0.475	-1.506	0.089	-0.624	0.876	-1.115		-1.773	-0.505	-0.276	-0.204	-1.308	0.584	-0.431
nicotinamide N-methyltransferase T	0.675	-0.083	0.035	-0.244	0.053	-0.021	-0.365	-1.174	-1.235	-1.789	-0.688	0.972	-0.261	-0.532	0.606	0
myosin IE AA029956	-0.6075		-0.5465	-0.8195	-0.3755	-0.3535	-0.5545	-0.6505		-1.089	0.0005	-0.0205	0.1535	-0.1775		-0.0005
major histocompatibility complex, c	-0.494	-0.582	-1.091	-0.32	0.305	-0.098	-0.085	0.262	-1.668	-1.457	-0.039	-0.362	-0.218	-0.838	-0.197	-0.537
fatty acid binding protein 7, brain W72051			-1.595	-2.086	-1.717	-0.387	-2.433	-0.184			-1.441		-0.603	0.446		0.728
kynureninase (L-kynurenine hydrolase) H874	-0.342	-0.591	1.233	0.358	-0.954	-1.687	-1.194	-1.515	-2.291	-0.198	0.075	-0.657	-1.675	-0.58	-1.138	
cytochrome P450, subfamily I (dio	1.065	-0.579	0	-0.767	0.392	-0.386	-0.479	-0.752	-0.401	-0.549	0.165	0.11	-0.605	-0.779	0.499	-0.131
cytochrome P450, subfamily I (dio	2.202	-0.047	-0.231	-0.604	-0.234	-0.713	-0.836	-1.99	-1.558	-1.474	0.425	0.622	-0.872	-1.706		-0.579
S100 calcium binding protein A8 (c	-1.641	0.014	-1.05	4.29	-0.162	-0.899	-1.625	-1.818		-2.268	-1.165	-1.2	-1.797	-1.329		-1.087
signal transducer and activator of transcription	-0.2855	-0.6135	2.59	-0.0555	-0.4895	-0.3215	-1.224	-1.718	-1.387	-0.4765	-0.7565	-1.143	-0.8755			-0.9545
gamma-aminobutyric acid (GABA) A receptor	3.044		-1.498	0.076	0.153	-0.766	-0.789			-1.485	-0.69		-0.823	-0.104		-0.235
EphB6 AA609284			0.6365	-1.062	-0.5295	-0.1345		-0.6565				-0.0415	-0.0885	0.0535		-0.3235
secretory leukocyte protease inhibi	-2.088	-1.806	-1.596	0.434	-1.378	-1.269	-0.849	-1.961	-2.645	-3.187	-1.637		-0.996	-1.568	0.538	-1.344
aldo-keto reductase family 1, member C1 (dih	0.83	0.835	-0.435	1.743	1.173	-0.558	-1.21			-1.547		-0.834	0.712	0.104		-0.296
latrophilin W74533	-1.28	0.216	-0.322	-0.467	-0.563	0.111	0.383	-0.648	-0.95	-1.333	-0.903		0.469	0		0.274
echinoderm microtubule associated	-0.0045	-0.1755	-0.1055	0.1595	-0.2585	-0.5155	-1.05	-0.3895	-0.1395	-0.8335	-0.0445	-0.4845	0.0045	-0.7135	0.1435	-0.2125
epidermal growth factor receptor (erythroblast	-0.676	-1.527	-0.203	-1.07	-1.157	-0.979	-1.085			-2.181	-1.547	-0.782	-0.768			0.432
ERO1-like (S. cerevisiae) AA18680	0.3395	0.4075	-0.6115	-0.3415		-0.4095	-0.8285	-0.4075	-0.4405	-0.4075	-1.335	-0.2325	-0.7075	-0.7125		-0.3035
**hypothetical protein FLJ20624 R	-0.232	-0.341		-0.153	-0.446	0.838	-1.658	0.466	-0.553	-0.909	-0.199	-0.662	-0.334	0.371	-0.029	0.617
forkhead box D1 AA069132	-1.192	-0.07	-0.666	-0.596	0.02	0.388	-0.54	0.11		-1.016	-1.28	-1.077	-0.051	-0.477	-0.561	0.796
met proto-oncogene (hepatocyte growth factor receptor) AA410591		-1.151	-0.373	0.228			0.322			-0.654	-0.23	0.176	0.74	0.446		0.177
ESTs, Weakly similar to TRHY_HUMAN TRICH	-0.137	-0.378	-0.339	0.263	0.618	0.02	0.518			-1.656	1.242	0.885	0.19	0.389		-0.164
ESTs AA149250			1.847	-0.295	0.293		-0.215			-1.641	-0.868	-0.33	-0.395	0.21		-0.185
Homo sapiens mRNA; cDNA DKFZp564O2364	3.135	0.0215	0.3145	0.7915	-0.2245	1.343	-0.0505			-0.1155	1.125		-0.1125	-0.5255		-0.3445
hypothetical protein FLJ10337 AA1	-0.6325	0.8375	0.2155	-0.7935	-0.1815	-0.3315	-0.4795	-0.6435	-0.6095	-0.4435	0.2225	0.0585	-0.3355	0.2375		0.1205
integral membrane protein 3 AA034	-0.998	-0.313	0.52	-1.106	-0.005	-0.618	-0.901	-0.847	-2.533	-2.828	-1.247	-0.647	-1.005	-1.651	-0.119	-0.465

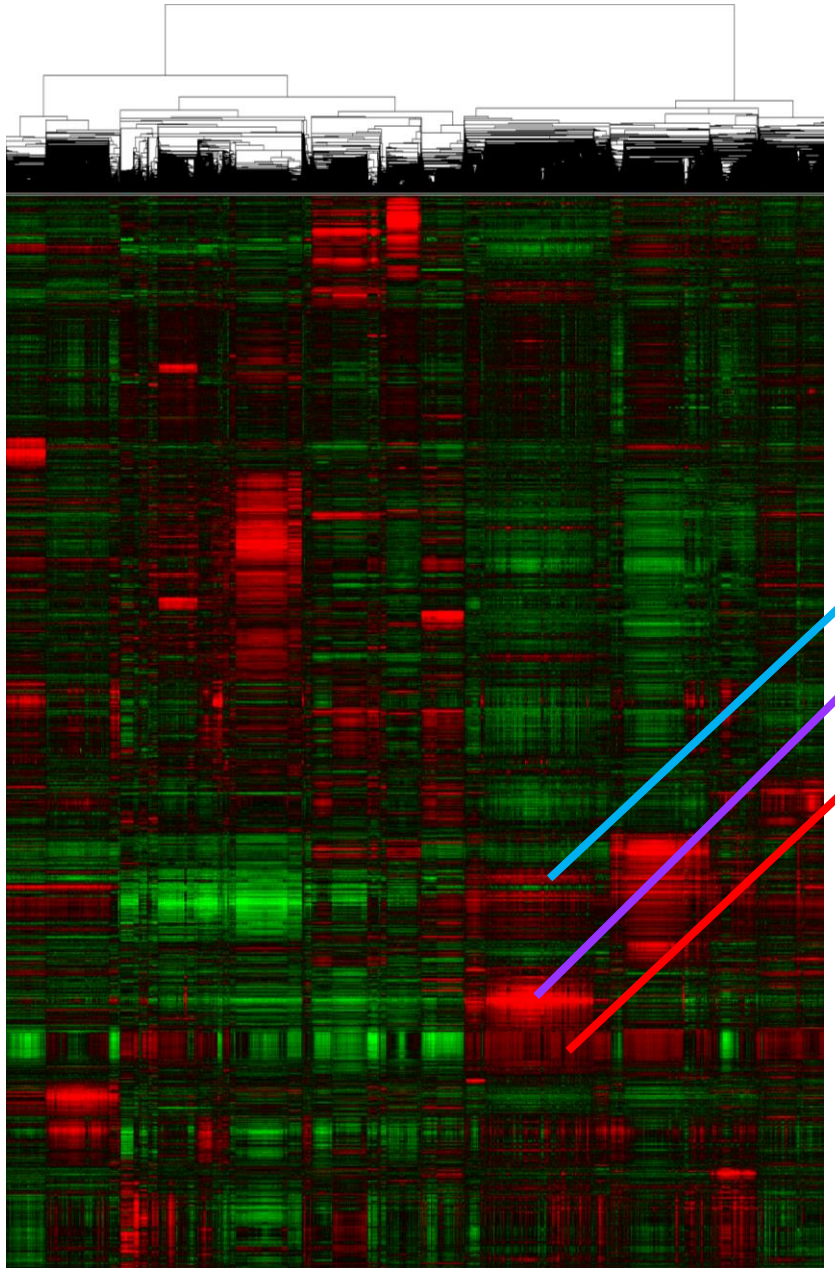
Using hierarchical clustering to decode the mess



B-cells
T-cells
Macrophages
Fibroblasts
Endothelial Cells

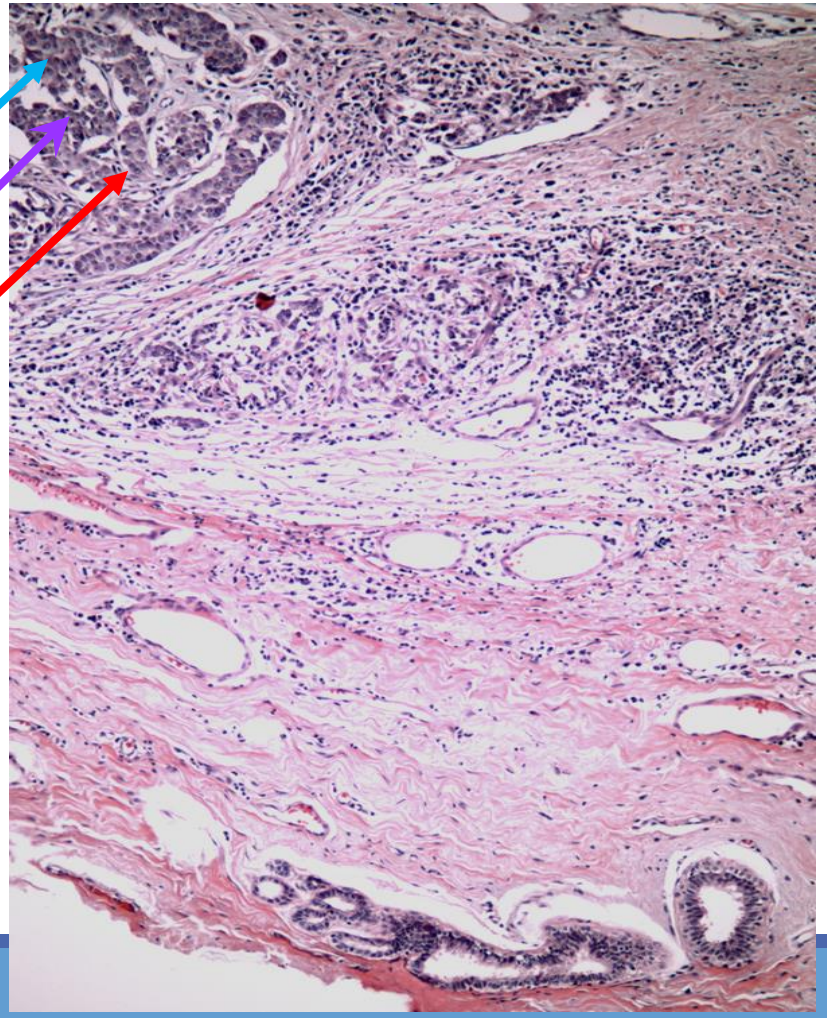
Unsupervised cluster analysis of 10,000 grossly dissected human tumors



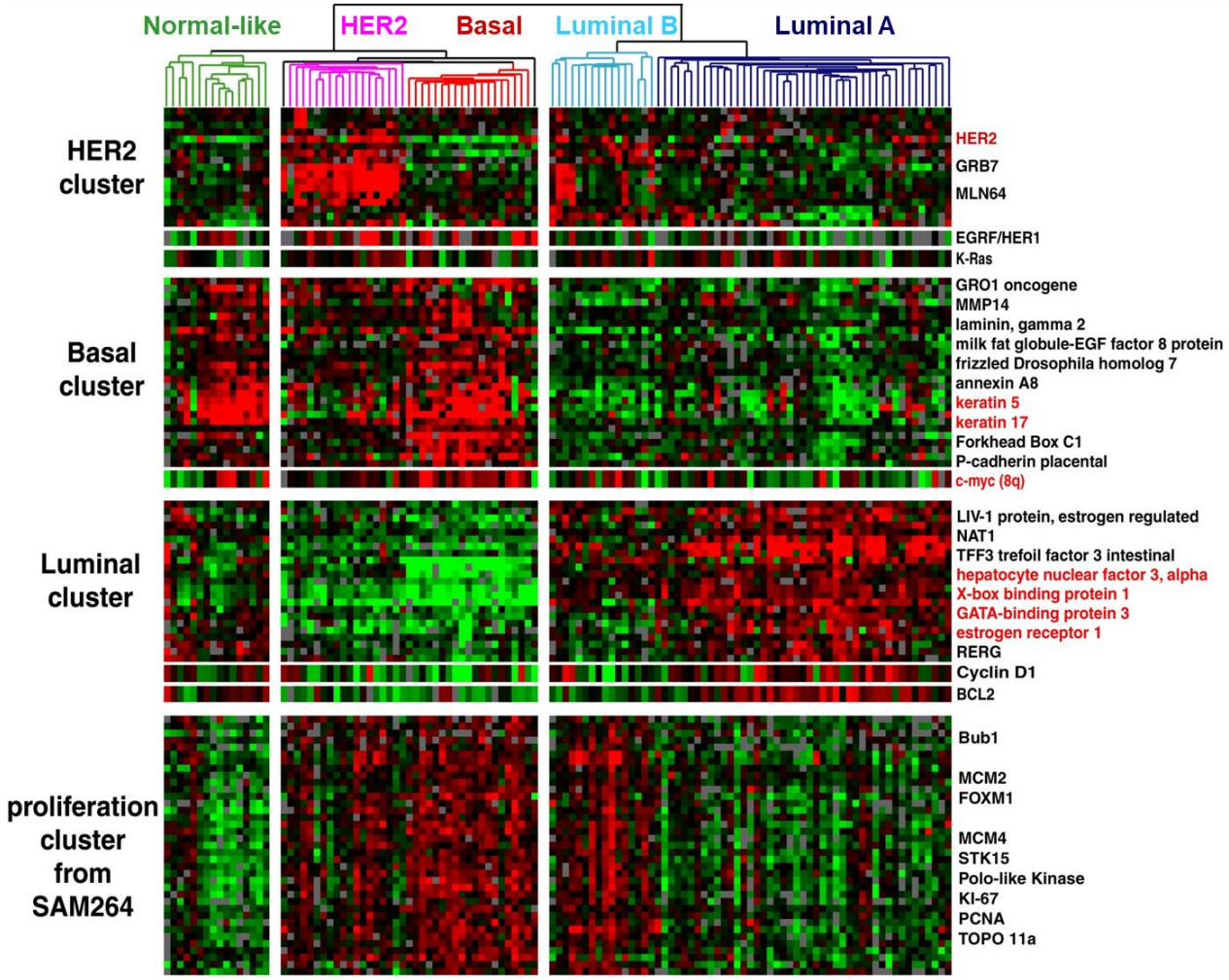


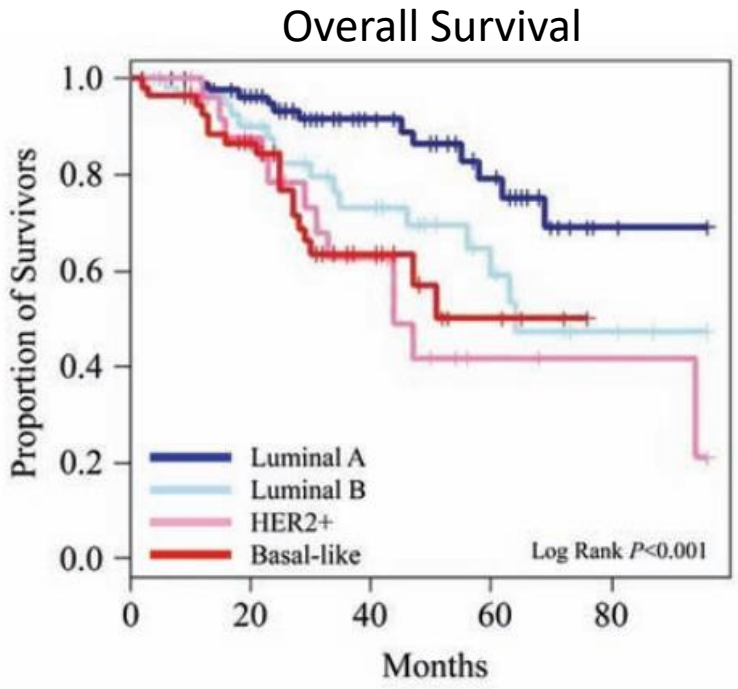
B-cells
T-cells
Macrophages
Fibroblasts
Endothelial Cells

Luminal/ER+ genes
HER2 amplicon
Proliferation



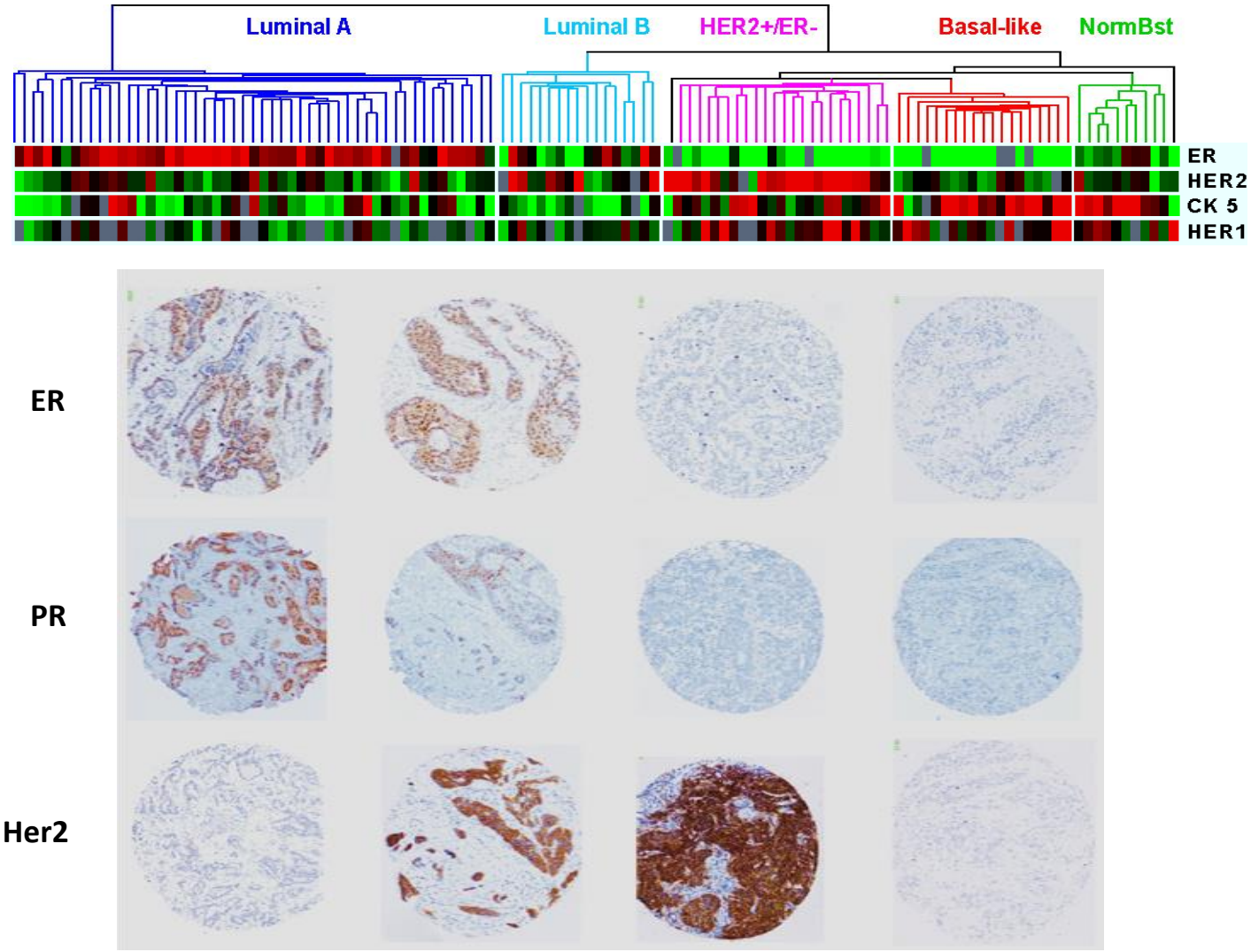
Breast Cancer “Intrinsic” Molecular Subtypes





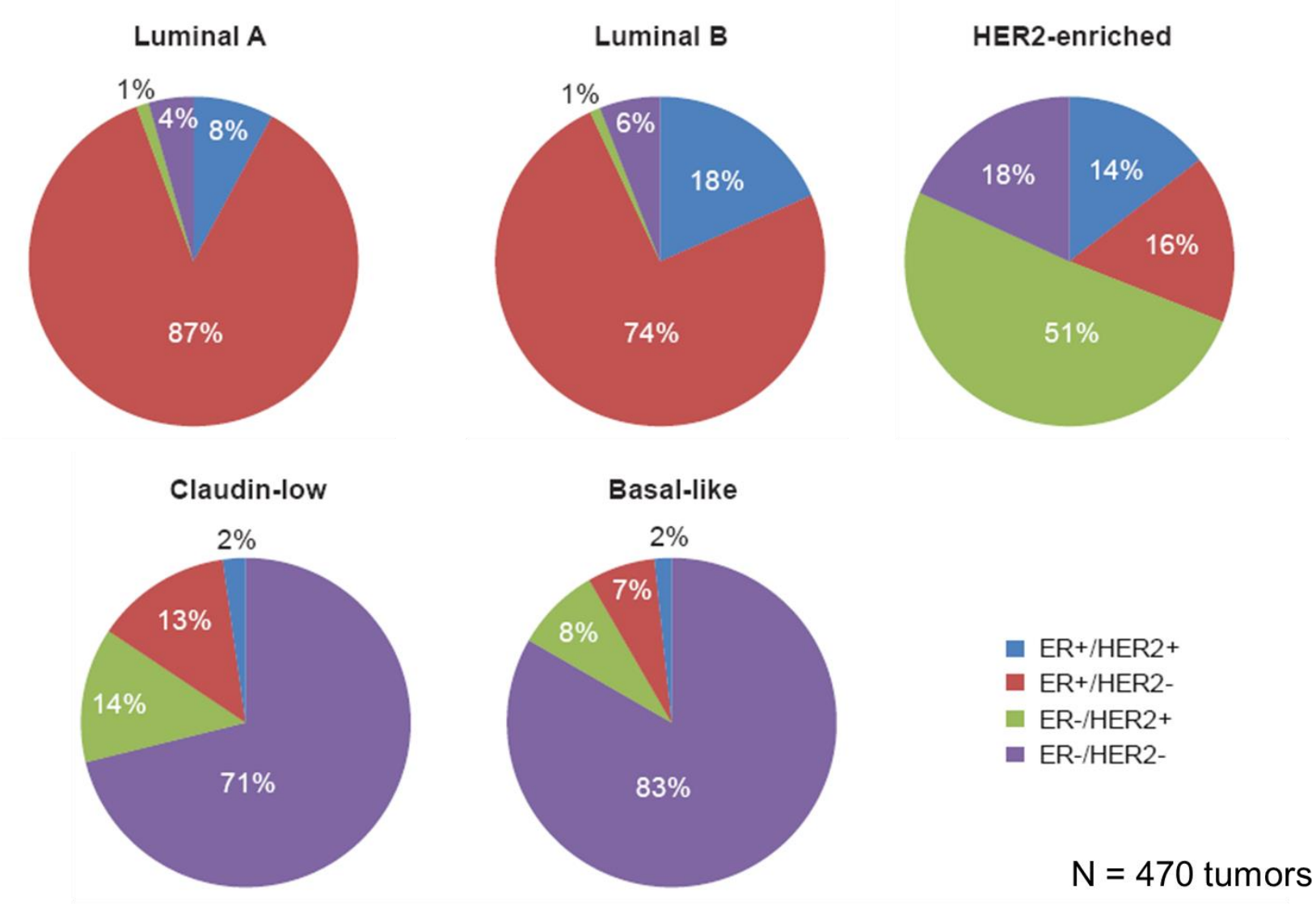
Perou et al., Nature, 2000

Similarity between Clinical and Molecular Subtypes

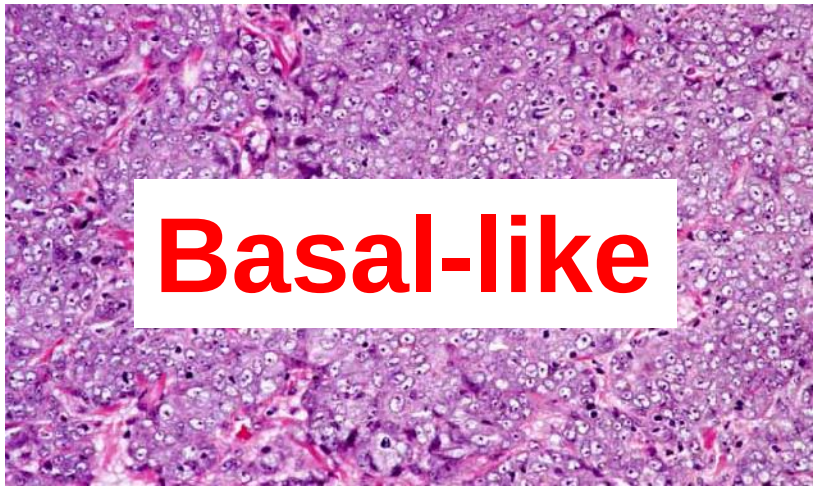


Adapted from Sandhu *et al.*, Lab Med 2009

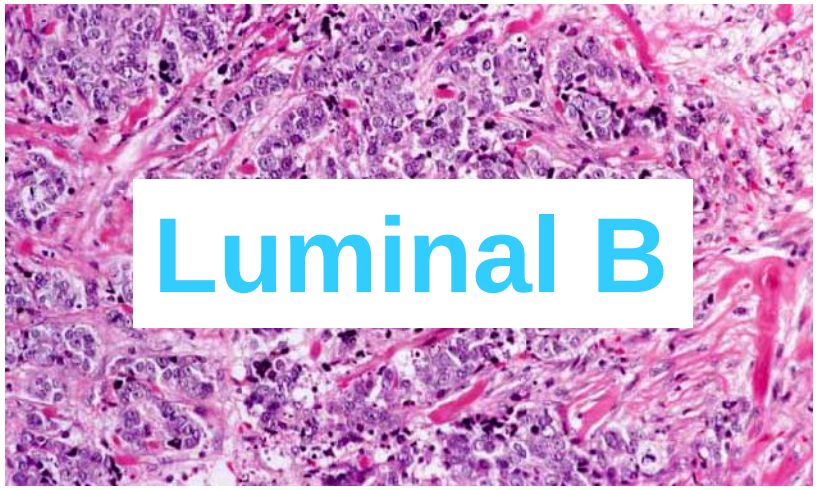
Overlap between Clinical and Molecular Subtypes



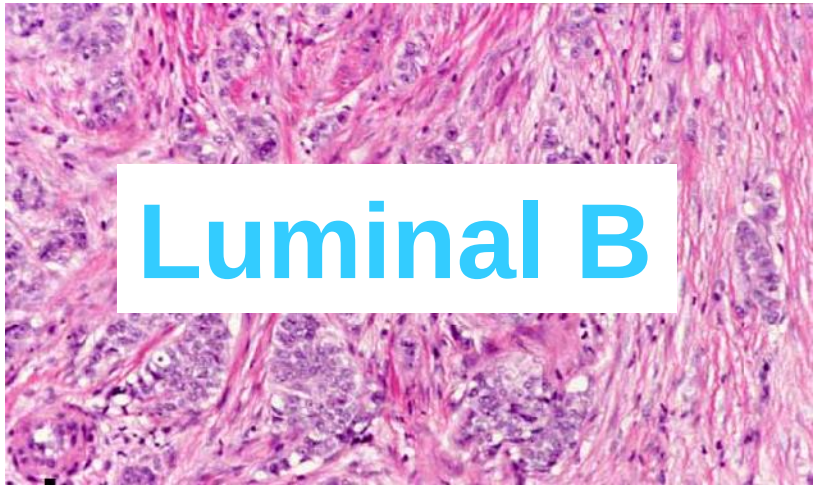
Grade III, T3 (diameter > 5cm),
Estrogen and Progesterone Receptor Positive, HER2 Negative,
3 of 4 Node Positive, all received Tamoxifen



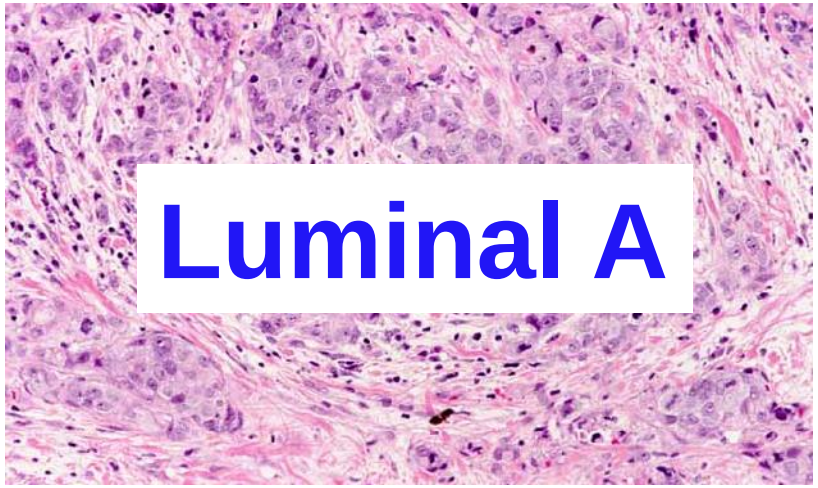
Died after 9 months



Alive for 79 months

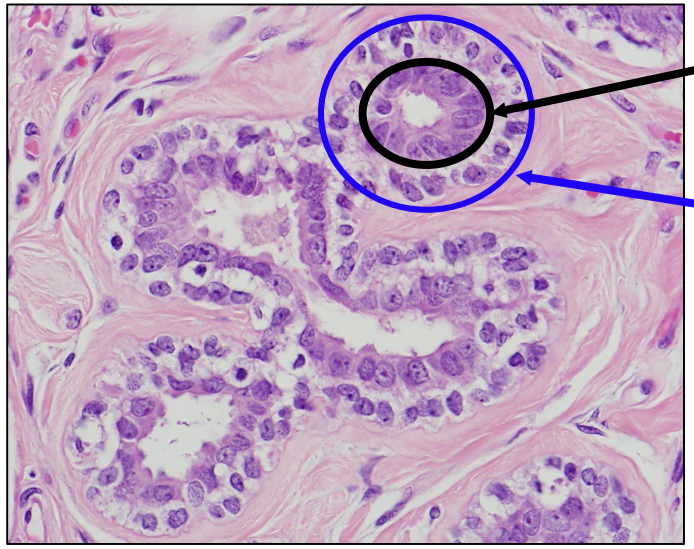


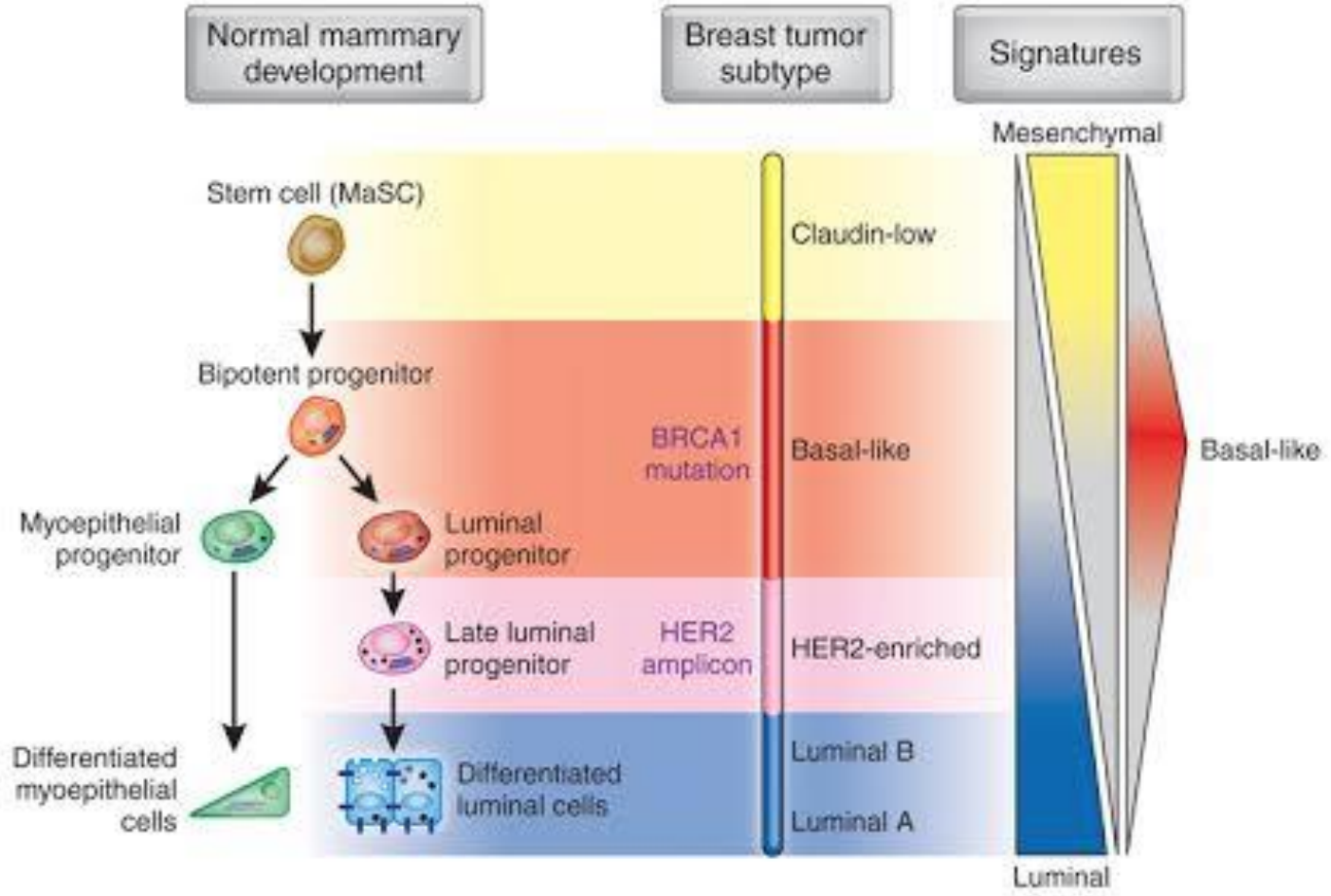
Died after 17 months



Alive for 96 months

Breast Cancer Cells of Origin?





Prat & Perou, Nature Medicine, 2009

Breast Cancer Gene Expression Assays for Risk and Therapeutic Stratification

Oncotype DX	MammaPrint	Prosigna

• Eligibility
  • Stage I, II, IIIa
  • Invasive or DCIS
  • ER positive
  • HER2 neg
  • Lymph node neg or pos
	• Eligibility
	  • Stage I or II
	  • Invasive Carcinoma
	  • Hormone receptor positive (ER or PR)
	  • Lymph node neg
	  • HER2 pos or neg
	  • Tumor size <= 5cm
		• Eligibility
		  – Stage I or II
		  – Invasive Carcinoma
		  – Hormone receptor positive (ER or PR)
		  – Lymph node neg or pos

• 21 gene signature	• 70 gene signature	• 50 gene signature
• Estimates risk of 10 year recurrence with a Recurrence Score of 0-100 and risk categories of Low, Intermediate and High.	• Estimates risk of 10 year recurrence with Low and High risk categories	• Estimates risk of 10 year recurrence with a Prosigna Score from 0-100 and risk categories of Low, Intermediate or High

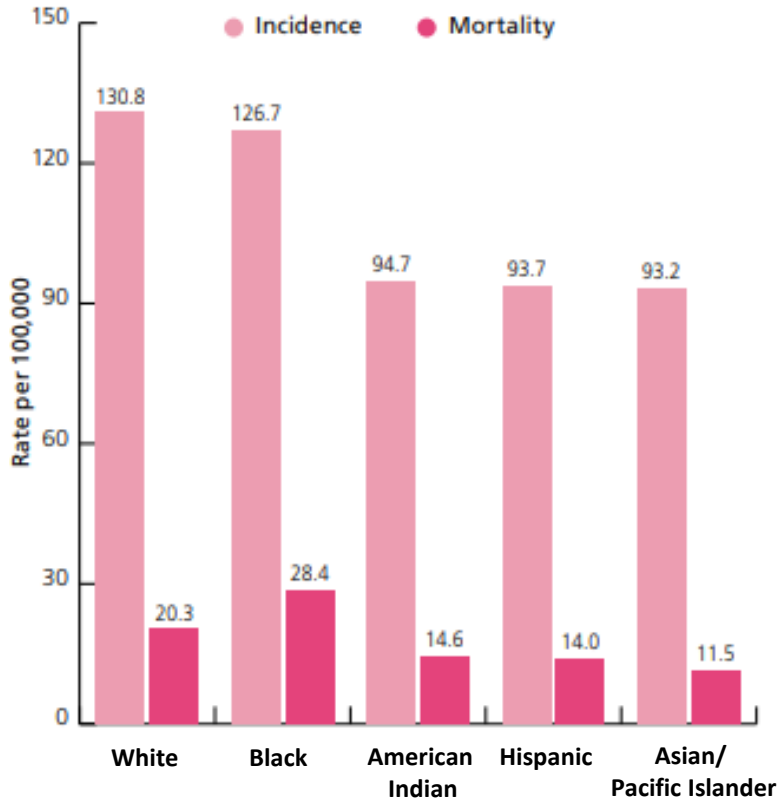
Paik et al., NEJM, 2004; van de Vijver et al., NEJM, 2002; Dowsett, JCO 2013

Breast Cancer Disparities

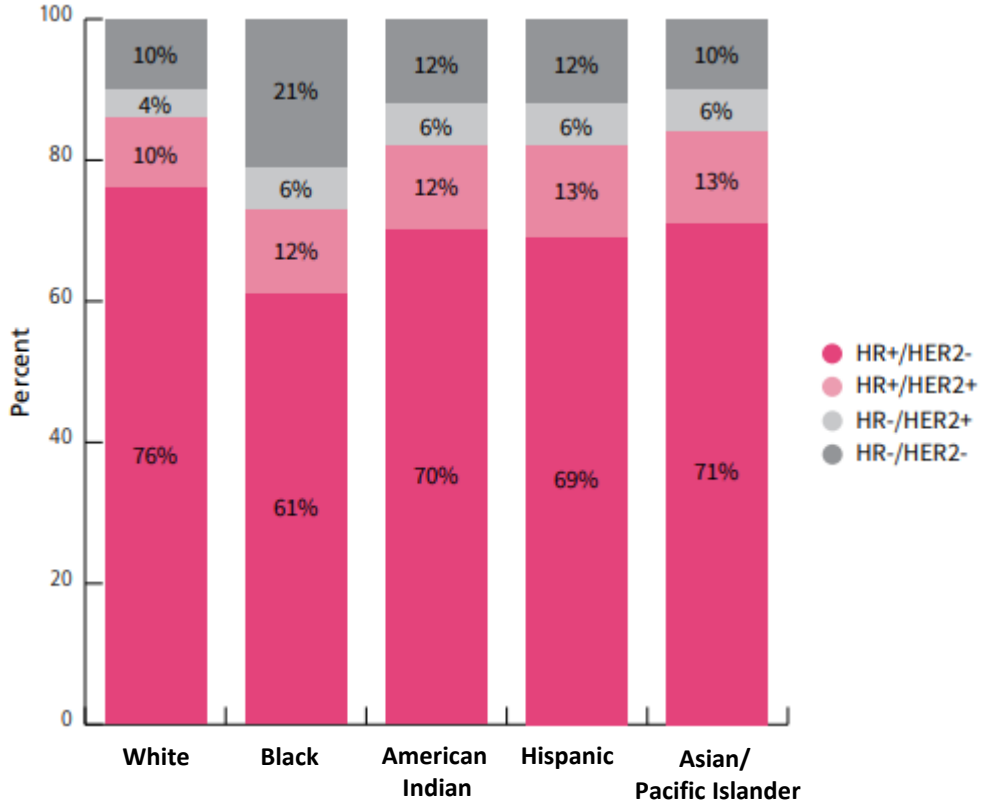
Breast Cancer Incidence and Mortality by Race

United States Cancer Statistics, 2016

Female BC Incidence and Death Rates by Race/Ethnicity, US



Distribution of BC Subtypes by Race/Ethnicity, US



Based on November 2018 submission data (1999-2016): U.S. HHS, CDC and NCI, June 2019, NAACCR, 2019
American Cancer Society, Inc., Surveillance Research, 2019

Black Women Are Often Underrepresented In Breast Cancer Clinical Trials

Study	Goal of Study	% Study Population (Black)	Reference
IMpassion130 Trial	Test Atezolizumab+ Nab-Paclitaxal for treatment of PDL1+ TNBC	4.9% - 7.6%	Schmid *et al.*, NEJM 2018
Oncotype DX Study	Development of OncotypeDX recurrence score	5%	Paik *et al.*, NEJM 2004
TAILORx Trial	Validation of OncotypeDX recurrence score	7%	Sparano *et al.*, NEJM 2018
NCI-Sponsored Randomized Phase III Chemotheray Trial	Evaluate association of race and outcomes in anthracycline- and taxane-treated ER+ breast cancer	8%	Sparano *et al.*, JNCI 2012

22.2% of the North Carolina population and

13.4 % of the United States population is Black

Women <40 and >65 are Underrepresented in Clinical Trials

Table 1. Estimated New DCIS and Invasive Breast Cancer Cases and Deaths among Women by Age, US, 2019

	DCIS cases		Invasive cases		Deaths	
Age	**Number**	**%**	**Number**	**%**	**Number**	**%**
<40	1,180	2%	11,870	4%	1,070	3%
40-49	8,130	17%	37,150	14%	3,250	8%
50-59	12,730	26%	61,560	23%	7,460	18%
60-69						
70-79	**54%**		**59%**		**72%**	
80+						
All ages	**48,100**		**268,600**		**41,760**	

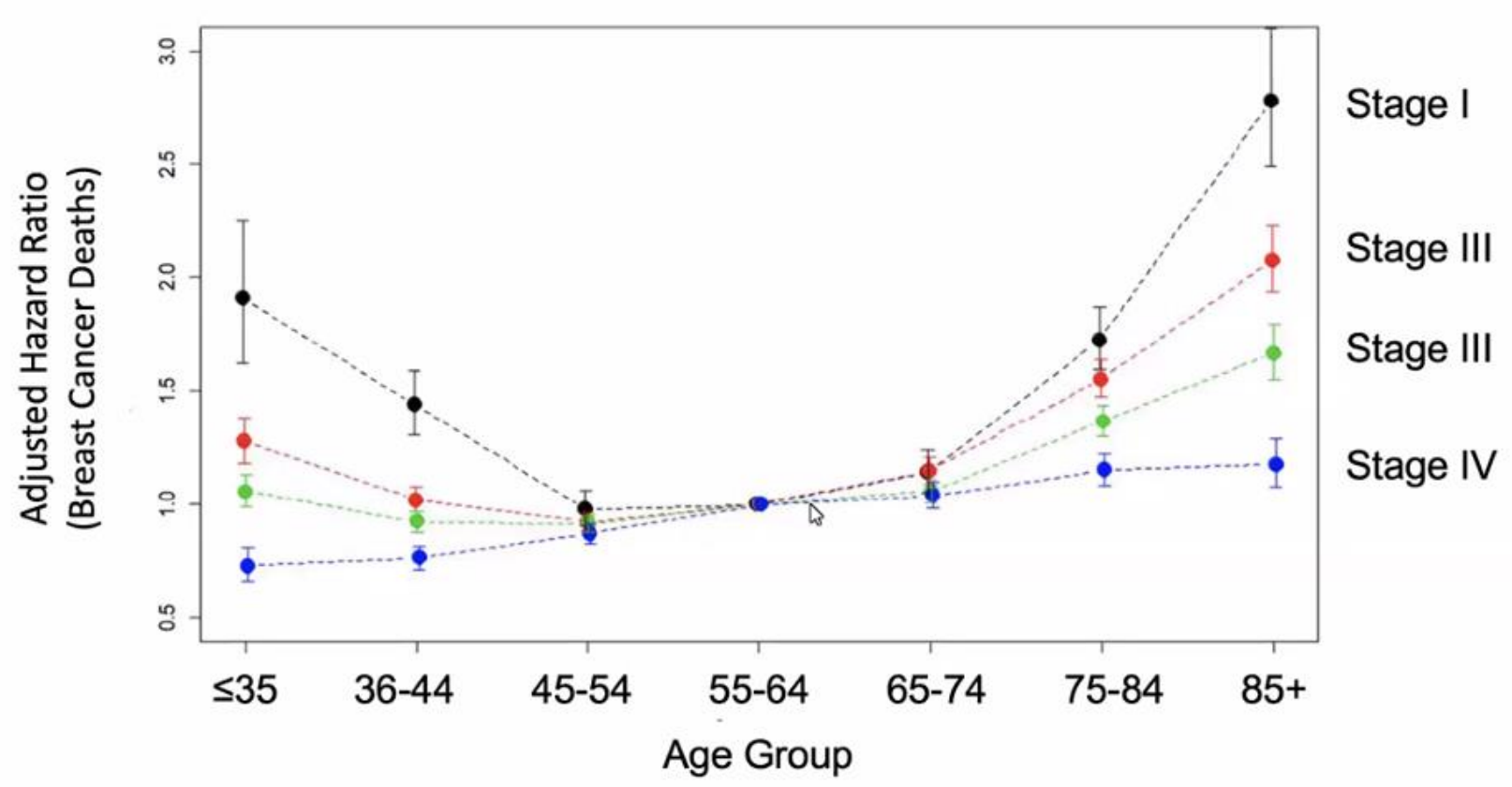
Estimates are rounded to the nearest 10. Percentages may not sum to 100 due to rounding.

Proportion (%) of Patients Accrued by Age

Age	Accrued
<40	7-10%
>65	20-24%

Freedman, et al., *J Clin Oncol*, 2016
Freedman & Partridge, *Breast*, 2013
Partridge and Rosenberg, unpublished

Younger and Older Women Have Poorer Outcomes



SEER data, 2000-2012; Freedman et al., *Cancer* 2018

Carolina Breast Cancer Study (CBCS)

- Population based study designed to study racial disparities in breast cancer.
- Enrolled approximately 5300 women with breast cancer from 44 NC counties.
- Black and young women were oversampled, so that these populations would comprise approximately 50% of the final study population.
- Rich in epidemiological, demographic and biological variables.

Carolina Breast Cancer Study 44-County Study Area