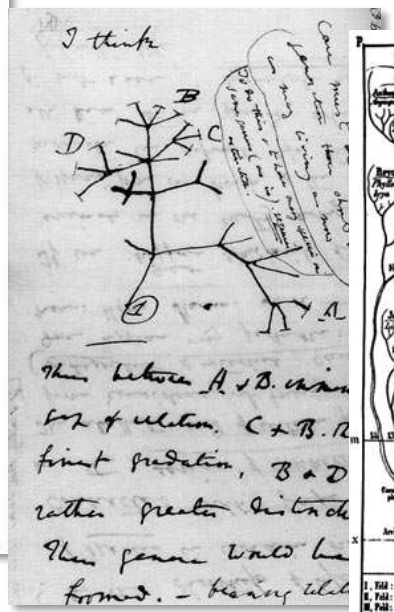
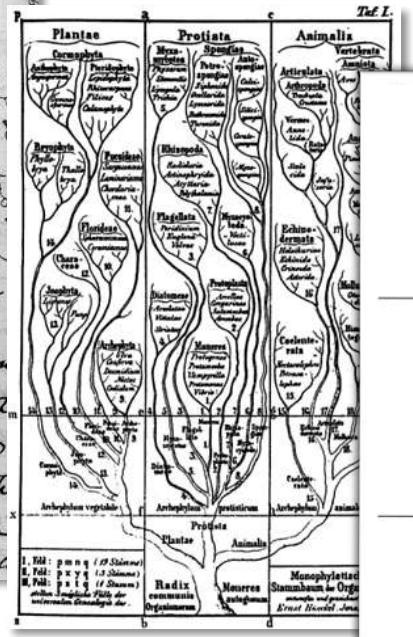
Brystkreft

– en sykdom med ulike ansikt

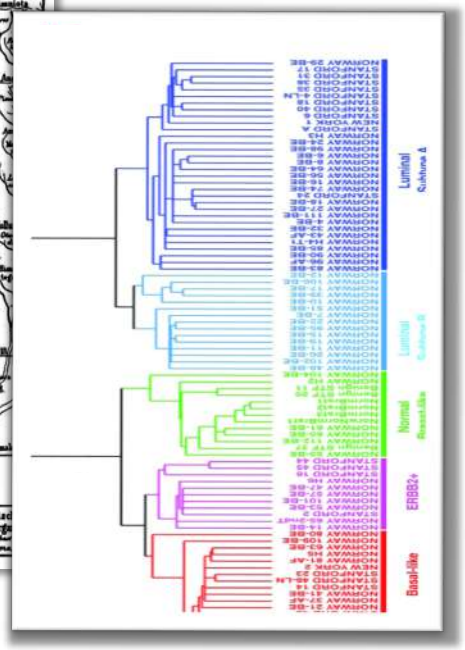
Linneus



Darwin



Haeckel



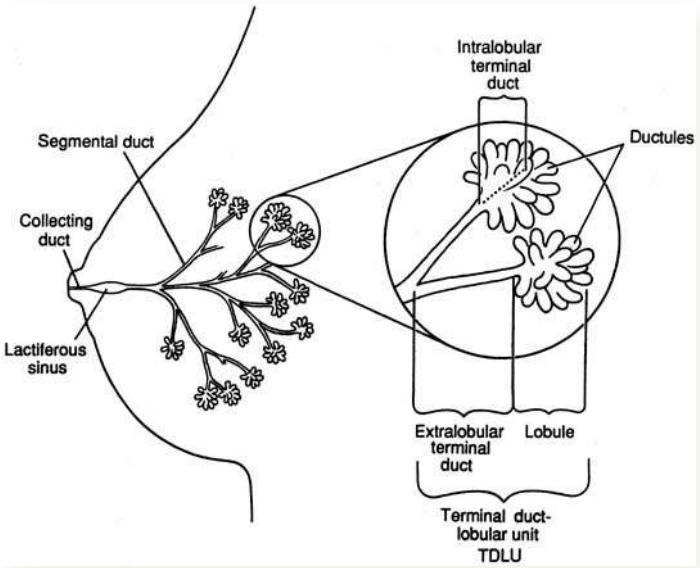
Perou

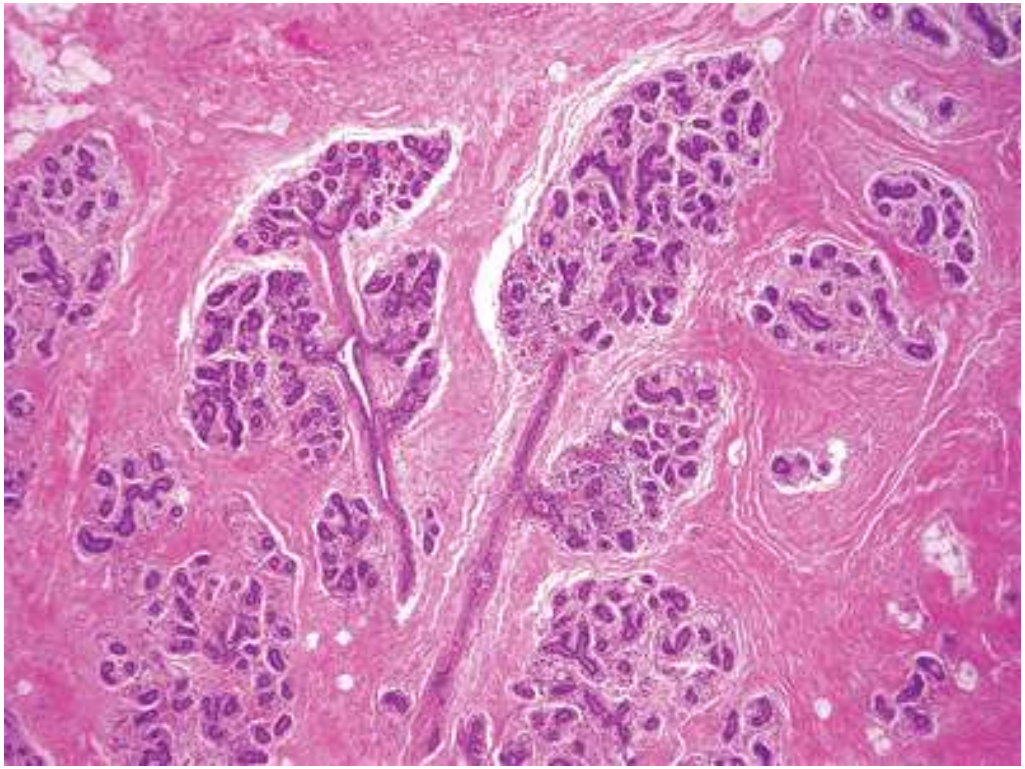
OnkoLiS 2020

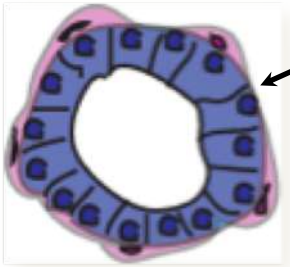
Hege E. G. Russnes, MD, PhD
Dept. of Pathology and
Dept of Cancer Genetics, Institute for Cancer Research
Oslo University Hospital

Oslo University Hospital
Norwegian Radium Hospital

The breast



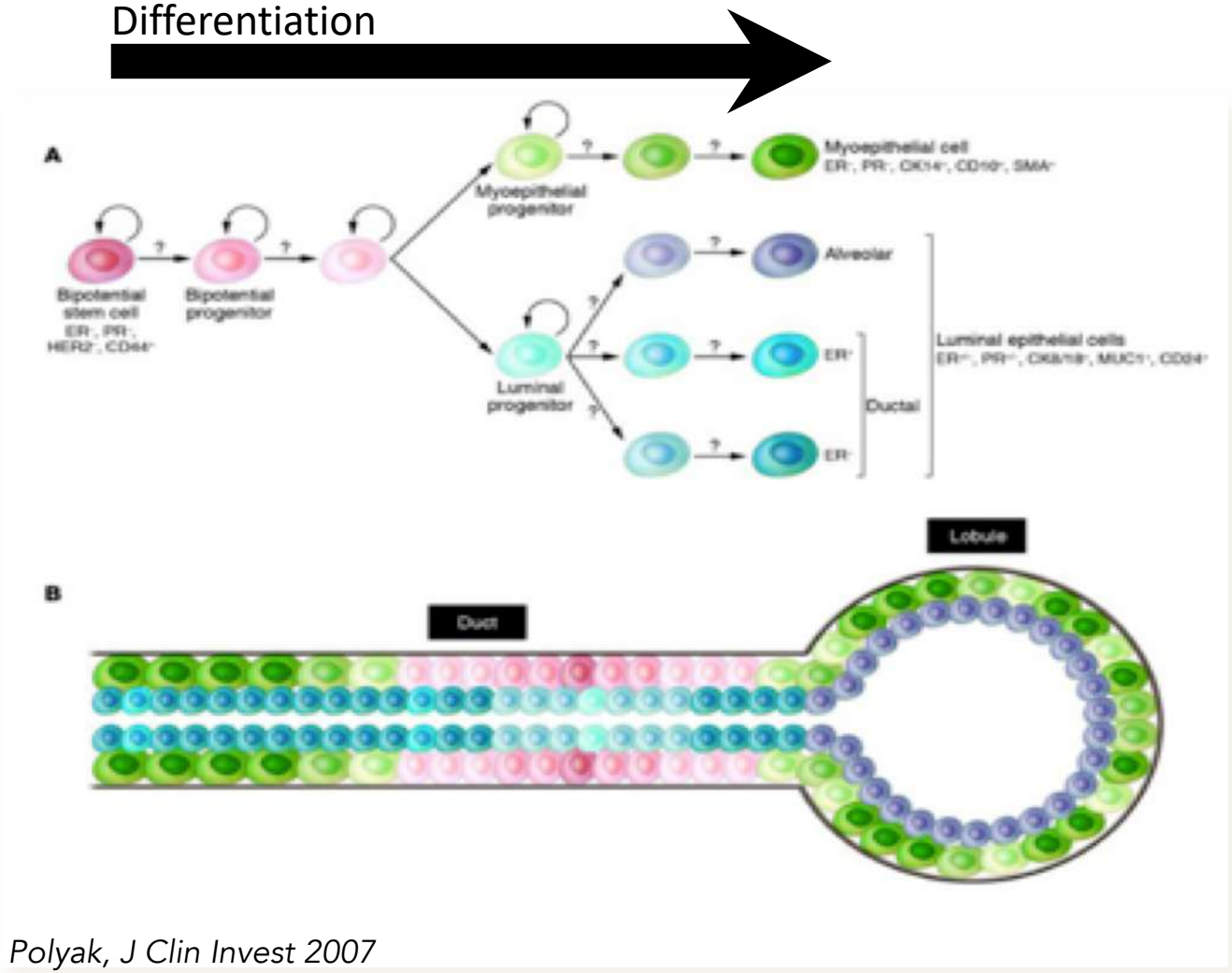




Luminal epitelial cells

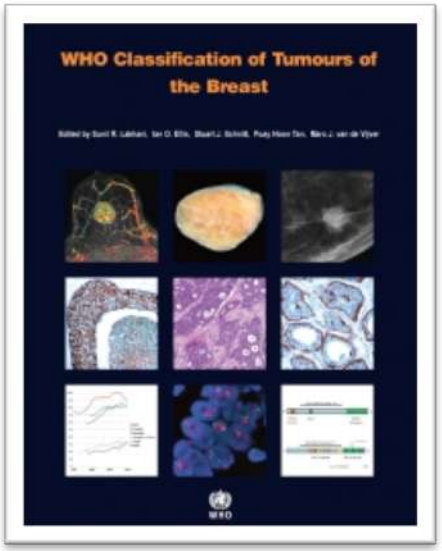
Myoepitelial/basal cells

An assumed hierarchical relationship between the cell types



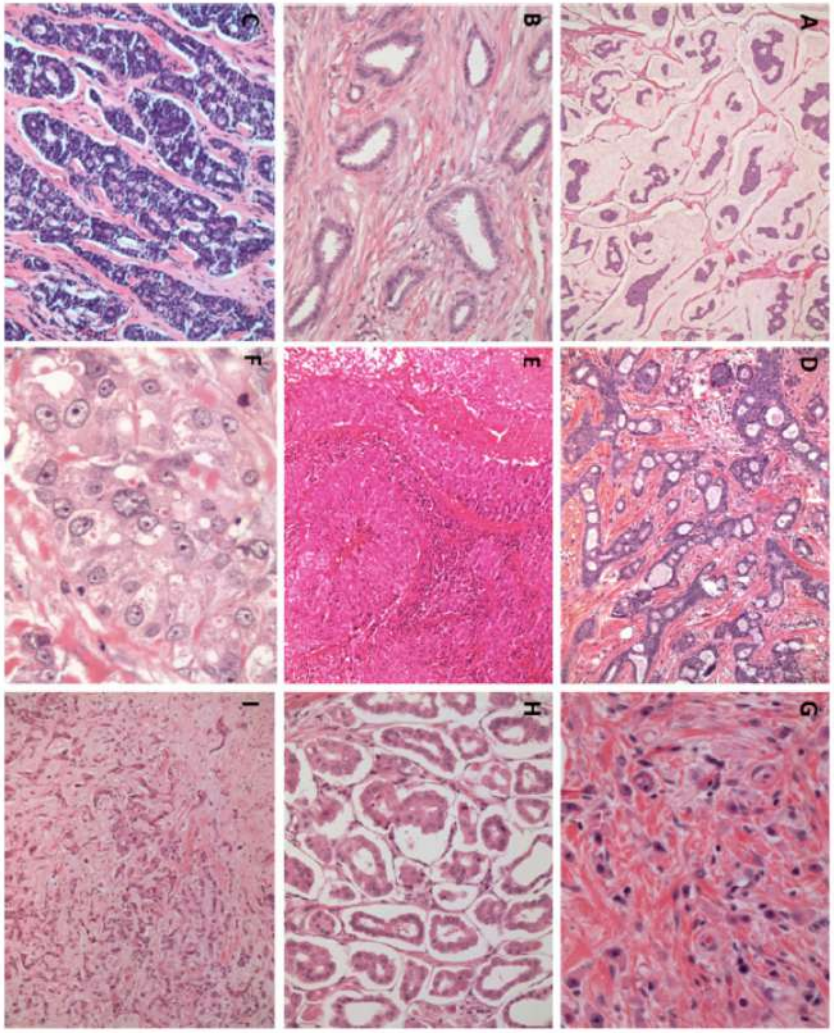
From Polyak, J Clin Invest 2007

Morphology based classification

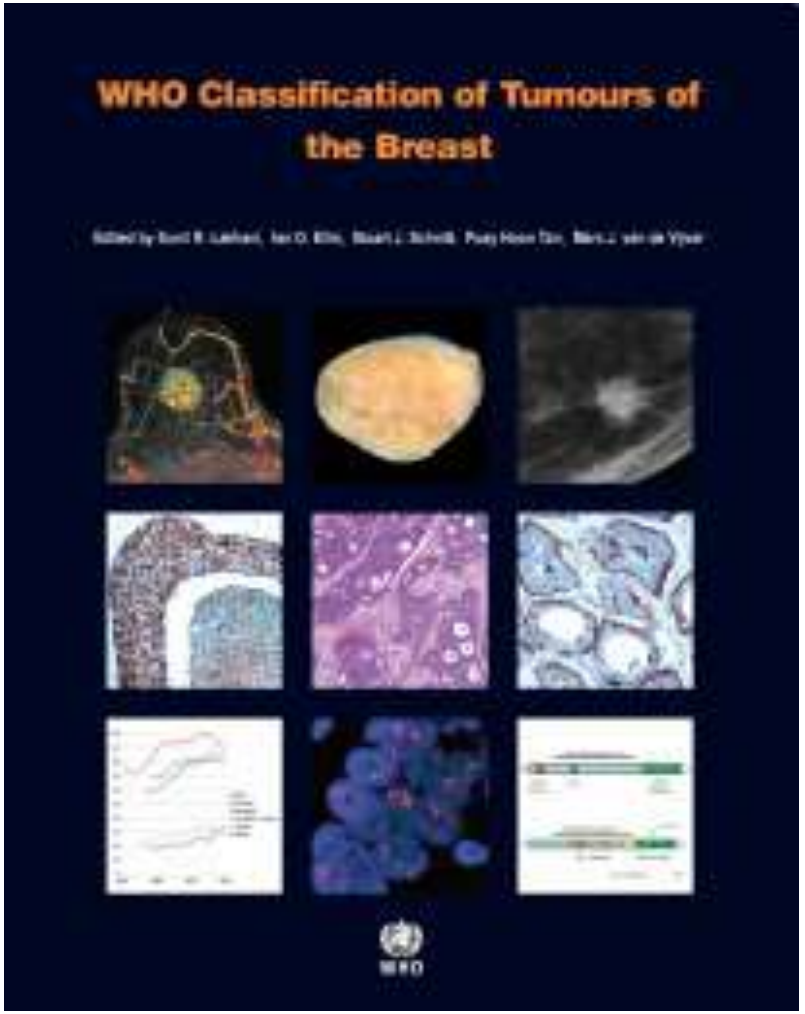


- Invasive carcinomas of no special type, NST (previously known as “ductal”) – a wide specter
- Special type carcinomas
- Mixed carcinomas

Classification by morphology



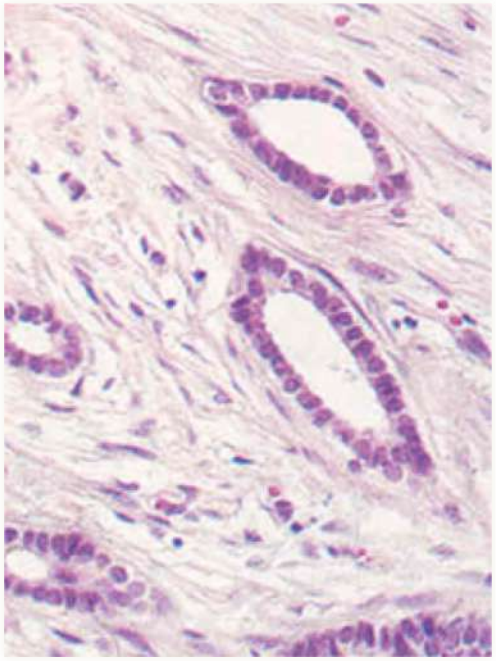
Dieci, The Oncologist 2014



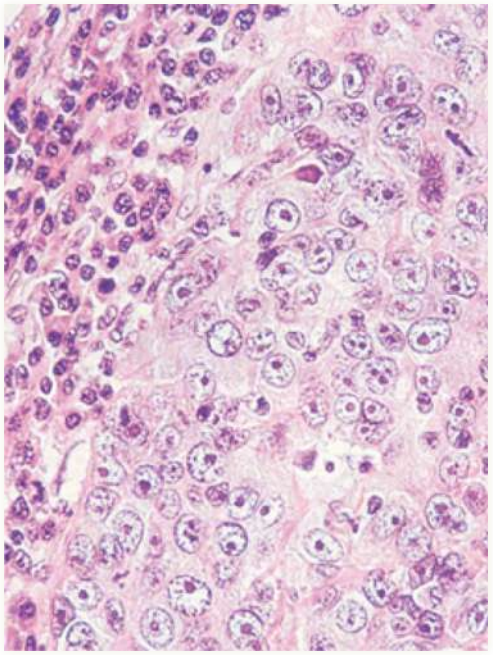
Morphology = phenotype!

"A phenotype is the ensemble of observable characteristics displayed by an organism"

Indolent behavior:



Aggressive behavior:

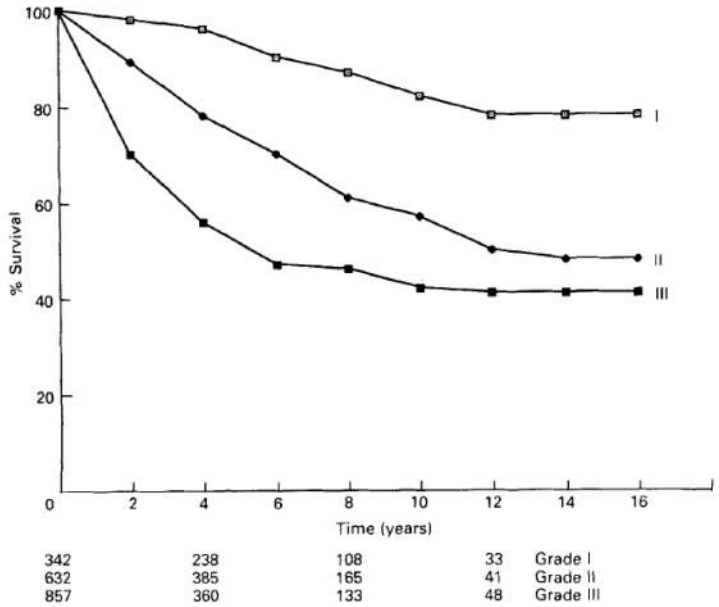


Histological grade

Table 1. Summary of semiquantitative method for assessing histological grade in breast carcinoma

Feature	Score
Tubule formation	
Majority of tumour (>75%)	1
Moderate degree (10–75%)	2
Little or none (<10%)	3
Nuclear pleomorphism	
Small, regular uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic counts	
Dependent on microscope field area (see Table 2)	1–3

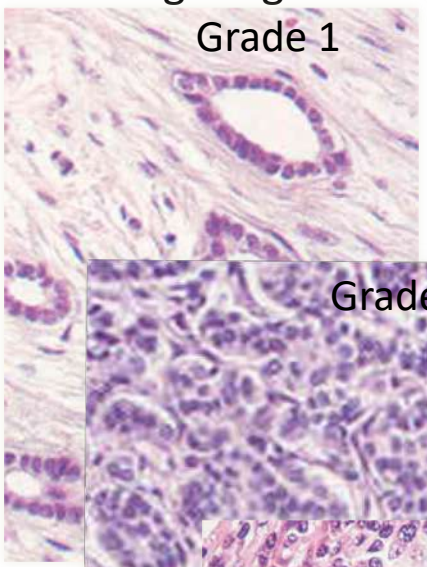
3–5 points: grade I —well-differentiated
6–7 points: grade II —moderately differentiated
8–9 points: grade III—poorly differentiated

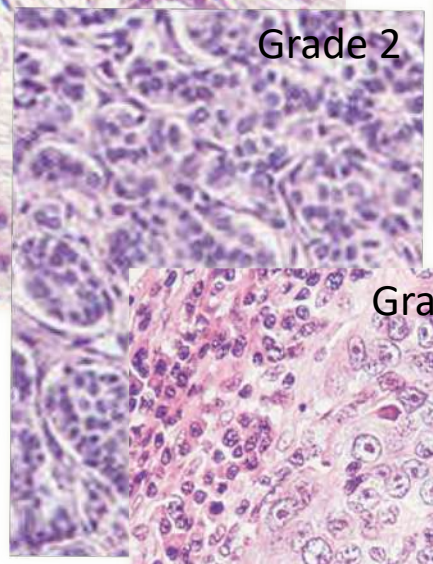


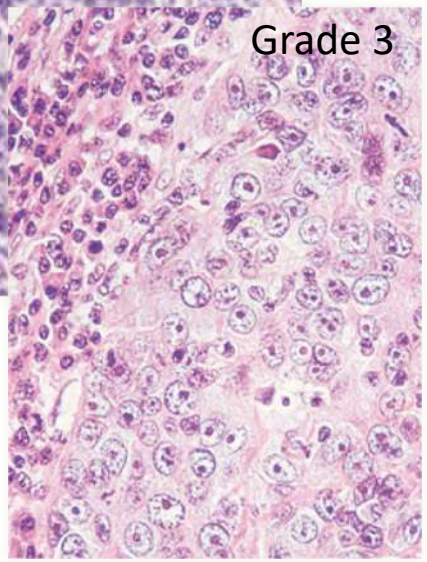
Elston and Ellis, Histopathology, 1991

Grouping of breast cancer - 2020

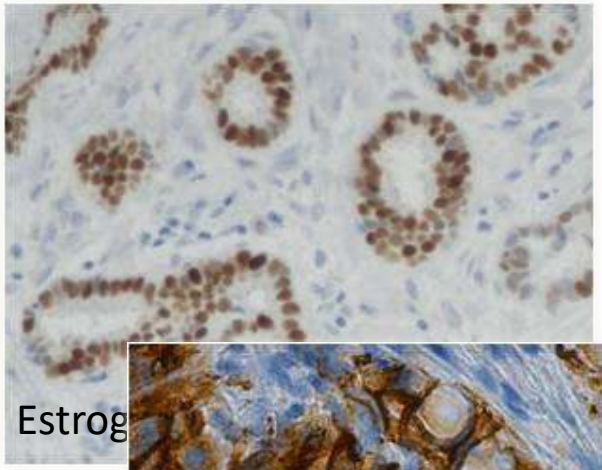
Histological grade

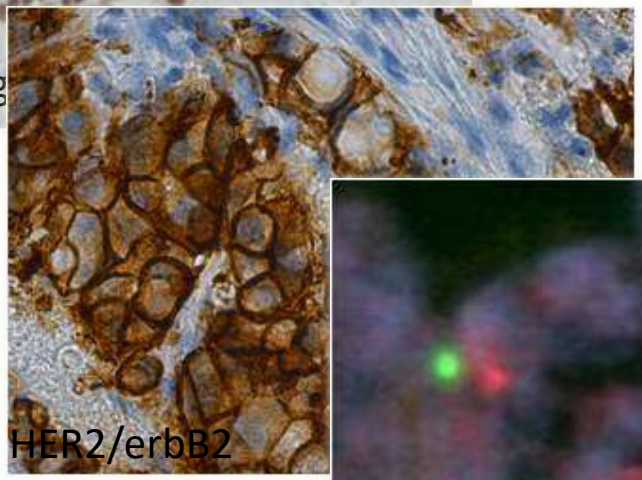


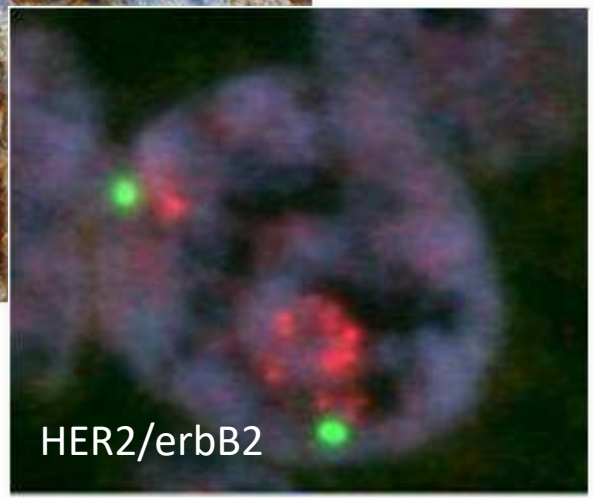




ER/PgR/Ki67/HER2

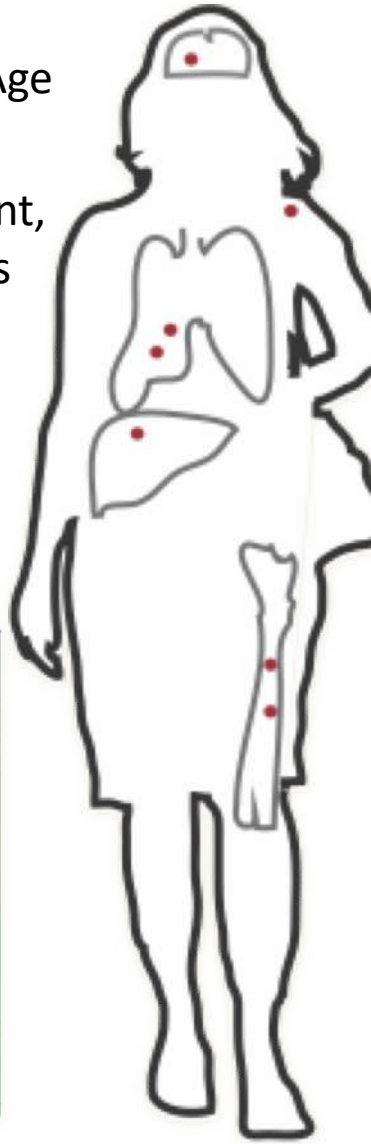






Age

Size, nodal involvement, metastases TNM



St. Gallen consensus meeting 2015

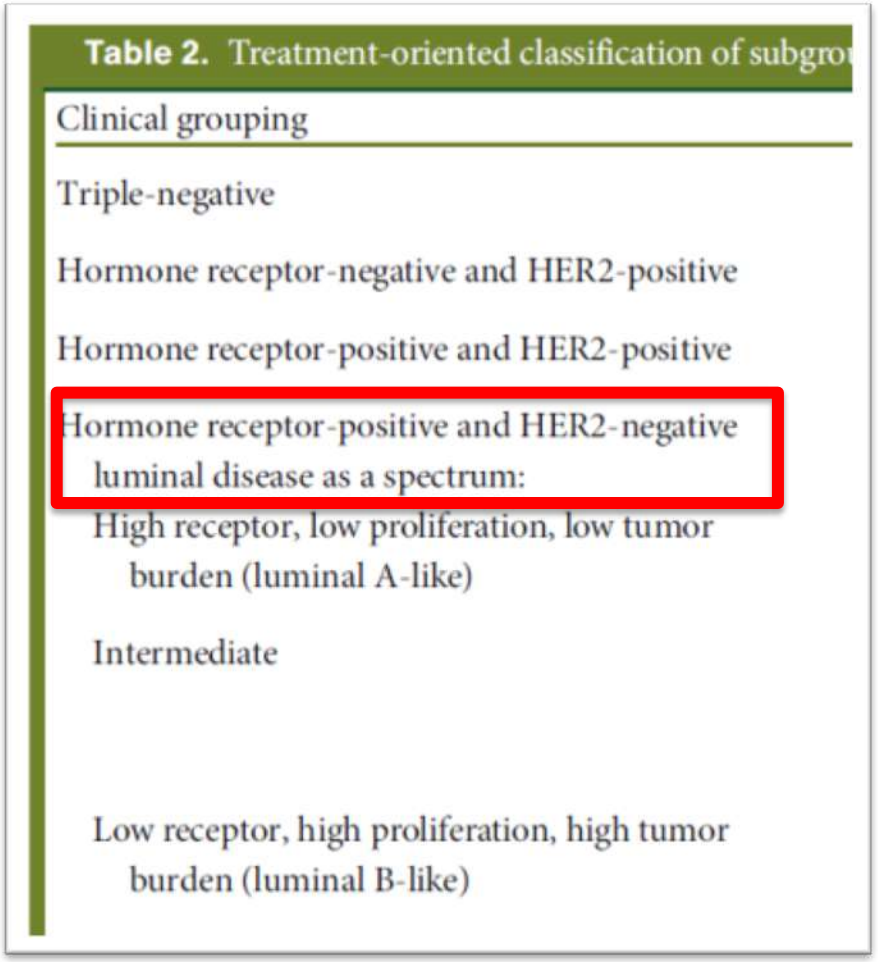


Table 2. Treatment-oriented classification of subgro

Clinical grouping
Triple-negative
Hormone receptor-negative and HER2-positive
Hormone receptor-positive and HER2-positive
Hormone receptor-positive and HER2-negative luminal disease as a spectrum:
High receptor, low proliferation, low tumor burden (luminal A-like)
Intermediate
Low receptor, high proliferation, high tumor burden (luminal B-like)

- TNBC
- ER-/HER2+
- ER+/HER2+
- ER+/HER2-
  - Low proliferation
  - Intermediate proliferation
  - High proliferation

Coates et al, Ann Oncol 2015

Revolution in technology reveals unknown biology

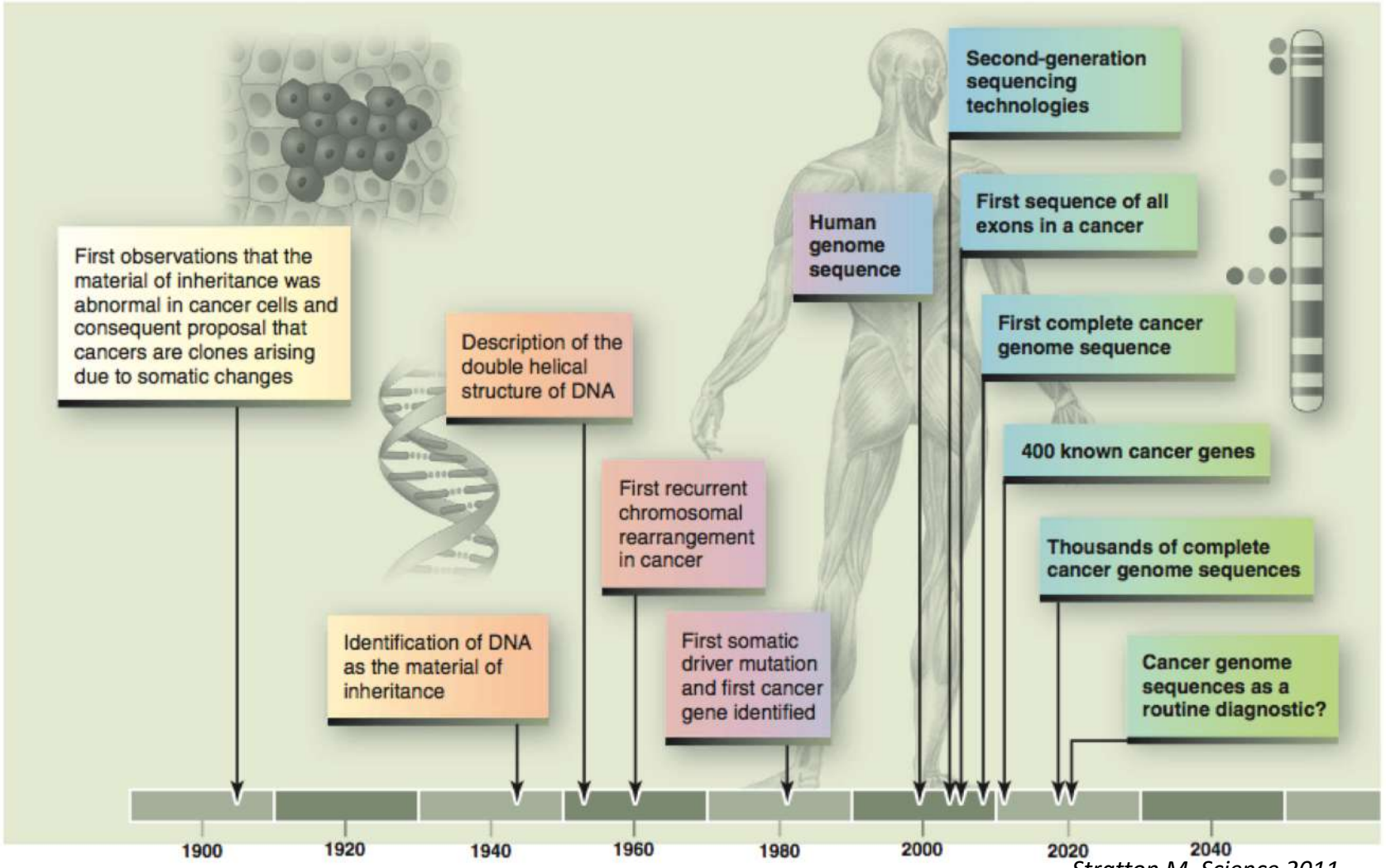


Fig. 1. Time line showing key events in the investigation of the cancer genome.

Stratton M. Science 2011

Molecular based classification

- Biomarkers/signatures for treatment prediction?
- Biomarkers/signatures recognizing biological distinct traits?
- Genomic – transcriptomic – metabolomic – proteomic features?
- Integrated approaches?
- Are they recapitulating already established classes…?
- What is the clinical implication?
- And are the designated class the same throughout the entire evolution of given cancer?

Molecular based classification

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- Biomarkers/signatures recognizing biological distinct traits?
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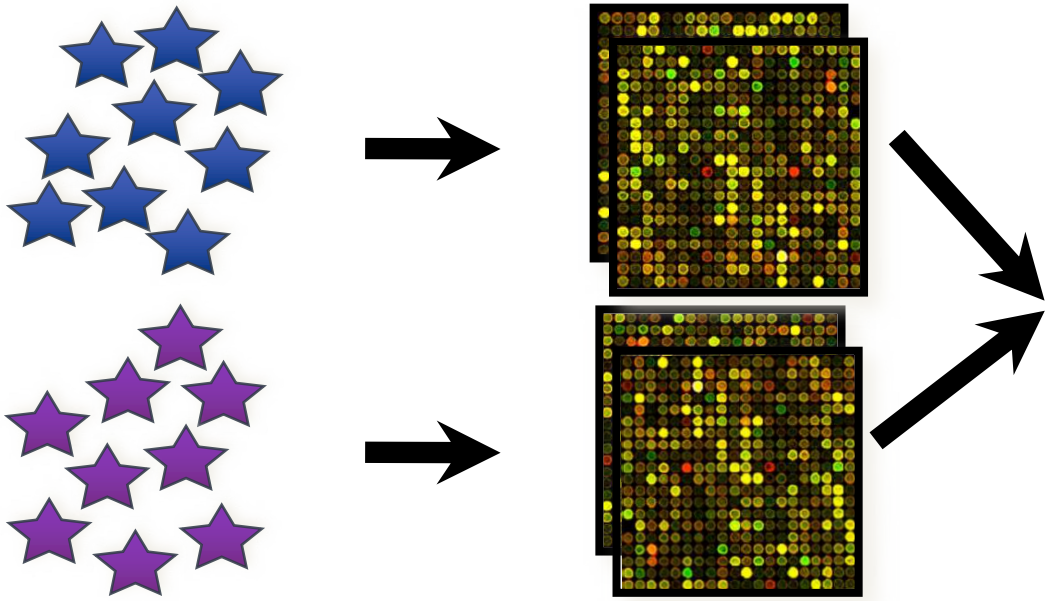
- Are they recapitulating already established classes…?
- What is the clinical implication?
- And are the designated class the same throughout the entire evolution of a given tumor?

Identification of biomarker/signatures for treatment prediction

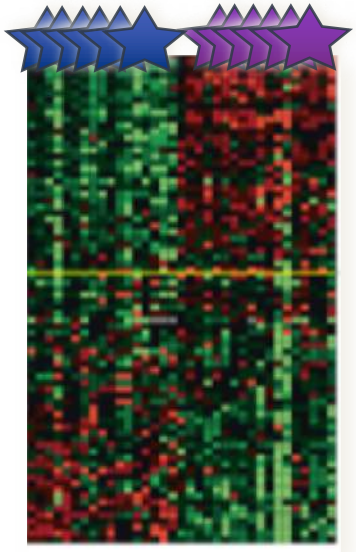
Patient samples with **same treatment**, comparison of findings in responders vs. non-responders

Supervised analyses

Selected tumor samples



Molecular markers with predictive or prognostic potential

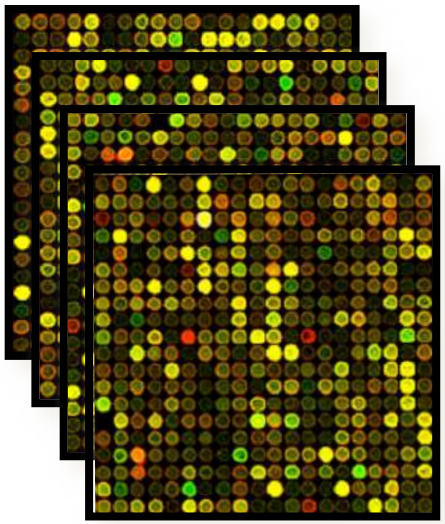


Identification of biomarker/signatures recognizing biological distinct traits

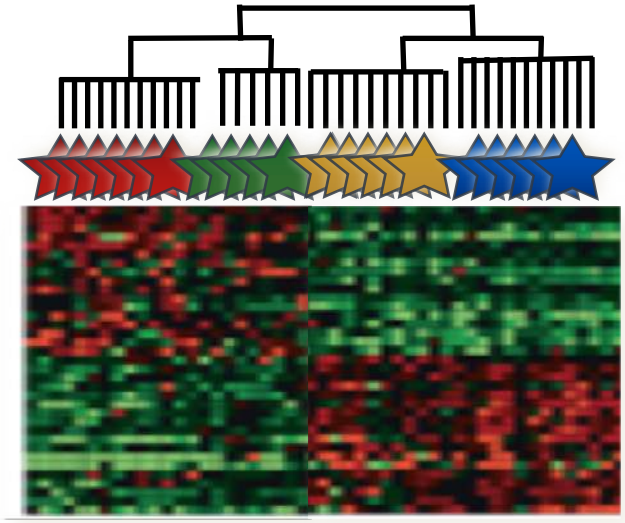
Patient samples **regardless of treatment type**, comparison of findings across all individual samples

Unsupervised analyses

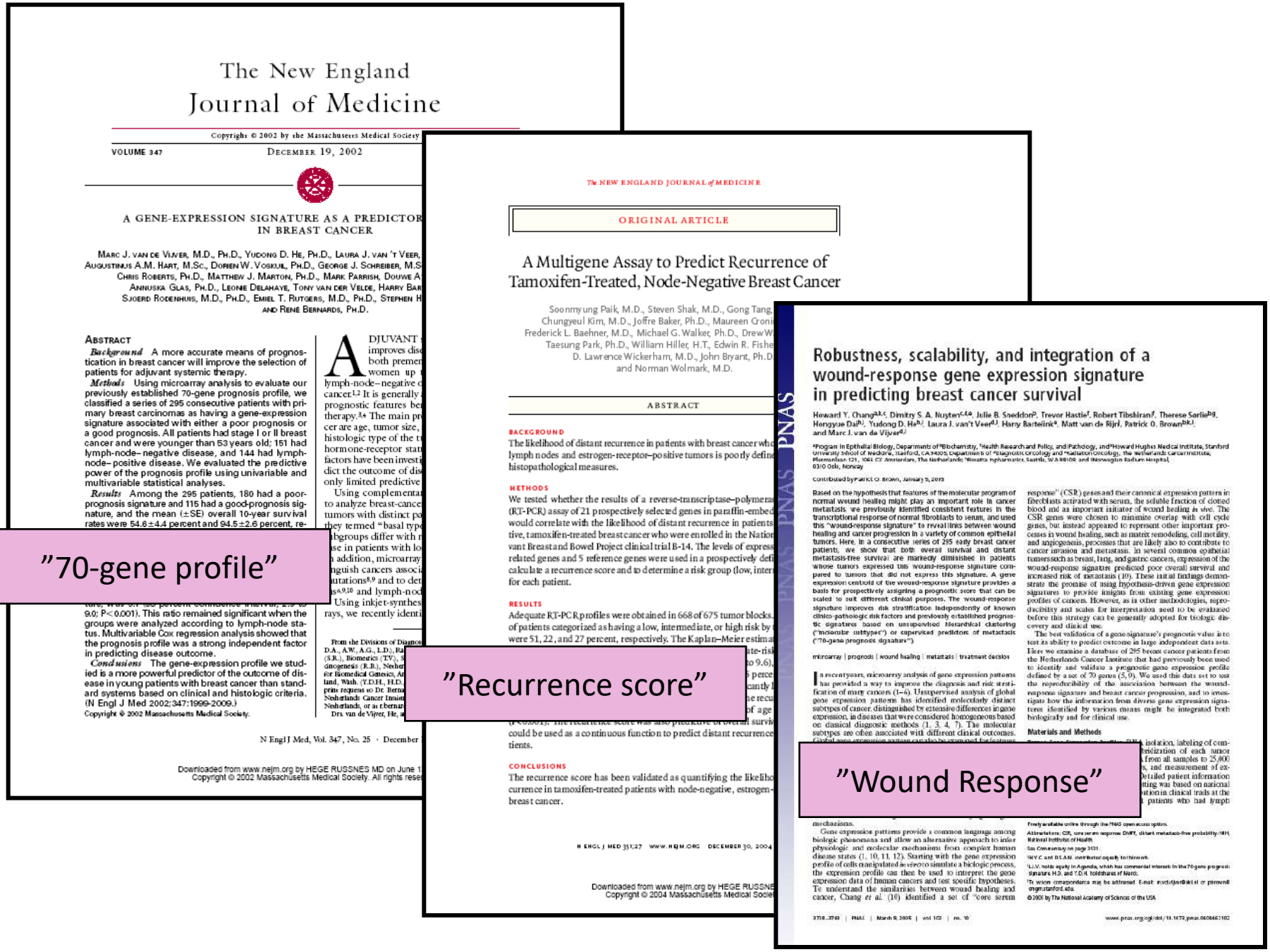
Tumor samples



Molecular markers for tumor classes



Treatment prediction	Class identification
Needs validation in clinical prospective trial	Needs validation in clinical prospective trial
Important for treatment stratification	Important for treatment stratification
Often restricted to a specific technology and specific algorithms	Often restricted to a specific technology and specific algorithms
Only valid for a given treatment regimen and a selected patient group	Independent of treatment regimen, **but needs to enter** into "treatment prediction" trials
Limited usefulness for identification of novel treatment regimens	Aims at identification of novel treatment regimens


The New England Journal of Medicine
VOLUME 347 DECEMBER 19, 2002
A GENE-EXPRESSION SIGNATURE AS A PREDICTOR IN BREAST CANCER
ABSTRACT
THE NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer
ABSTRACT
BACKGROUND
METHODS
RESULTS
CONCLUSIONS
PNAS
Robustness, scalability, and integration of a wound-response gene expression signature in predicting breast cancer survival
Materials and Methods
”70-gene profile”
”Recurrence score”
”Wound Response”

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

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

Departments of [b]Genetics and [l]Surgery, The Norwegian Radium Hospital, Montebello, N-0310 Oslo, Norway; [d]Department of Genetics and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599; Departments of [e]Health Research and Policy and Statistics, [c]Genetics, [i]Pathology, [i]Surgery, and [m]Biochemistry and Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA 94305; Departments of [g]Medicine (Section of Oncology), [f]Surgery, and [k]Biochemical Endocrinology, Haukeland University Hospital, N-5021 Bergen, Norway; and [h]Life Sciences Division, Lawrence Orlando Berkeley National Laboratories, and Department of Molecular and Cellular Biology, University of California, Berkeley, CA 94720

Contributed by David Botstein, July 17, 2001

this study was to classify breast carcinomas based n gene expression patterns derived from cDNA d to correlate tumor characteristics to clinical out- f 85 cDNA microarray experiments representing 78 broadenomas, and four normal breast tissues were erarchical clustering. As reported previously, the cancers could be classified into a basal epithelial-like group, an *ERBB2*-overexpressing group and a normal breast-like group based on variations in gene expression. A novel finding was that the previously characterized luminal epithelial/estrogen receptor-positive group could be divided into at least two subgroups, each with a distinctive expression profile. These subtypes proved to be reasonably robust by clustering using two different gene sets: first, a set of 456 cDNA clones previously selected to reflect intrinsic properties of the tumors and, second, a gene set that highly correlated with patient outcome. Survival analyses on a subcohort of patients with locally advanced breast cancer uniformly treated in a prospective study showed significantly different outcomes for the patients belonging to the various groups, including a poor prognosis for the basal-like subtype and a significant difference in outcome for the two estrogen receptor-positive groups.

The biology of breast cancer remains poorly understood. Although lymph node metastases (1), histologic grade (2), expression of steroid and growth factor receptors (3, 4), estrogen-inducible genes like cathepsin D (5), protooncogenes like *ERBB2* (6), and mutations in the *TP53* gene (7, 8) all have been correlated to prognosis, knowledge about individual prognostic factors provides limited information about the biology of the disease. Thus, because of their internal correlations in multivariate analysis, the prognostic value of many of these parameters fades away (9, 10).

The cellular and molecular heterogeneity of breast tumors and the large number of genes potentially involved in controlling cell features of phenotypic variation, might provide the basis for an improved taxonomy of cancer (11–14).

Recently, we reported that variations in gene expression patterns in 40 grossly dissected human breast tumors analyzed by cDNA microarrays and hierarchical clustering provided a distinctive "molecular portrait" of each tumor, and that the tumors could be classified into subtypes based solely on differences in these patterns (14). The present work refines our previous classifications by analyzing a larger number of tumors and explores the clinical value of the subtypes by searching for correlations between gene expression patterns and clinically relevant parameters. We found that classification of tumors based on gene expression patterns can be used as a prognostic marker with respect to overall and relapse-free survival in a subset of patients that had received uniform therapy. One finding was the separation of estrogen receptor (ER)-positive tumors into at least two distinctive groups with characteristic gene expression profiles and different prognosis.

Materials and Methods

Patients and Tumor Specimens. A total of 78 breast carcinomas (71 ductal, five lobular, and two ductal carcinomas *in situ* obtained from 77 different individuals; two independent tumors from one individual diagnosed at different times) and three fibroadenomas were analyzed in this study. These include 40 tumors that were previously analyzed and described (14). Four normal breast tissue samples from different individuals also were included, three of which were pooled normal breast samples from multiple individuals (CLONTECH). In summary, 85 tissue samples representing 84 individuals were analyzed. Tissue samples were snap-frozen in liquid N_2 and stored at −170°C or −80°C. All tumor specimens analyzed contained more than 50% tumor cells. Fifty-one of the patients were part of a prospective study on locally advanced breast cancer (T_3/T_4 and/or N_2 tumors) treated with doxorubicin monotherapy before surgery followed by adjuvant tamoxifen in the case of positive ER and/or progesterone receptor (PgR) status (15). All but three patients were treated with tamoxifen. ER and PgR status was determined by using ligand-binding assays, and mutation analysis of the *TP53* gene was performed as described (15). All common polymorphisms were recorded, but are considered wild type in this study. A detailed list of all samples and clinical data for the patients is included in Table 1, which is published as supporting information on the PNAS web site, www.pnas.org.

y Analysis. Total RNA was isolated by phenol- rm extraction (Trizol, GIBCO/BRL), and mRNA was by either magnetic separation using Dynabeads (Dy- he Invitrogen FastTrack 2.0 Kit. All experiments and the production of microarrays were performed as described (14), with detailed protocols available at http://cmgm.

Abbreviations: ER, estrogen receptor; SAM, significance analysis of microarrays.

[a]T.S. and C.M.P. contributed equally to this work.

[n]To whom reprint requests should be addressed. E-mail: alb@labmed.uio.no.

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"Intrinsic classification"

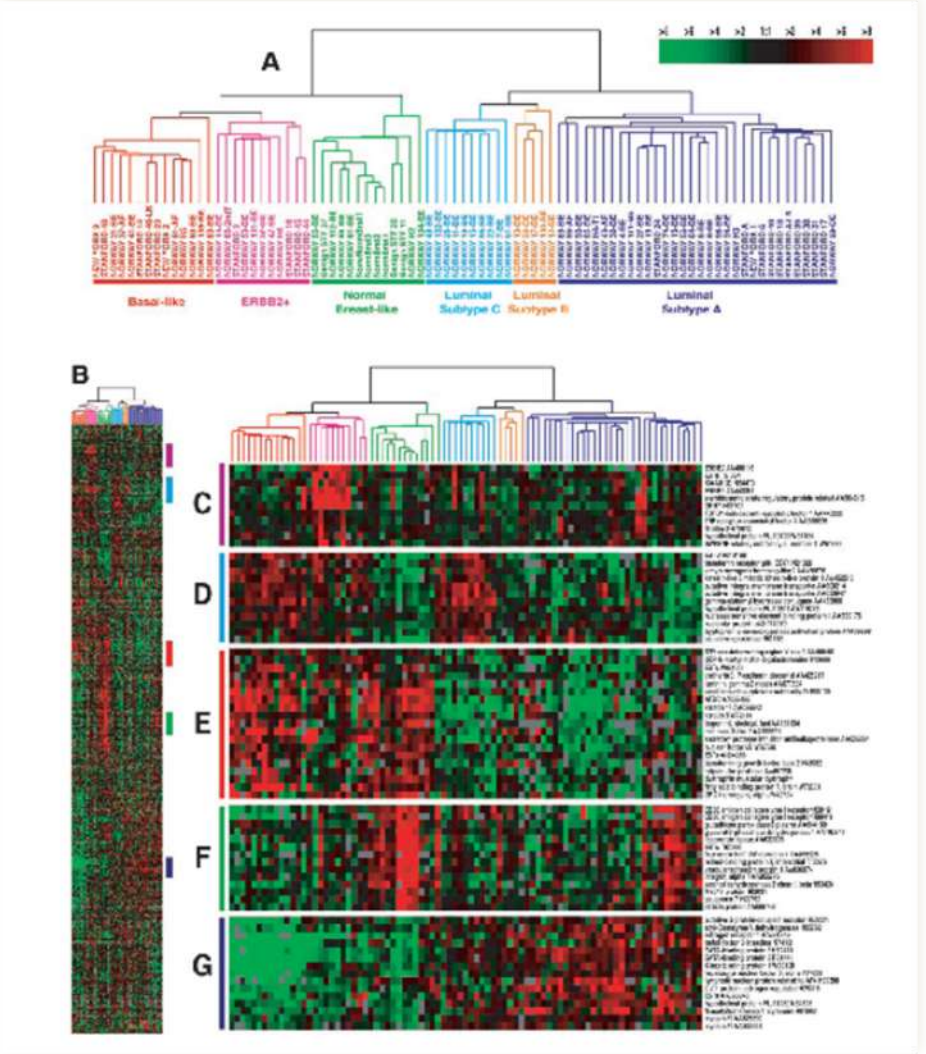
559 clones representing 494 unique genes

Perou et al. Nature 2000
Sørlie et al. PNAS 2001

Molecular subtypes by gene expression

- 561 genes selected as most “intrinsic” for individual tumors before and after treatment
- Clustering of other sets of tumors by the expression of these genes group them into five main groups

Luminal A, Luminal B, HER2-enriched, Basal-like and Normal-like.



Sørlie et al. PNAS 2001

Pathway differences - phenotypes

- Some pathways vary between subtypes
- Some pathways vary within subtypes

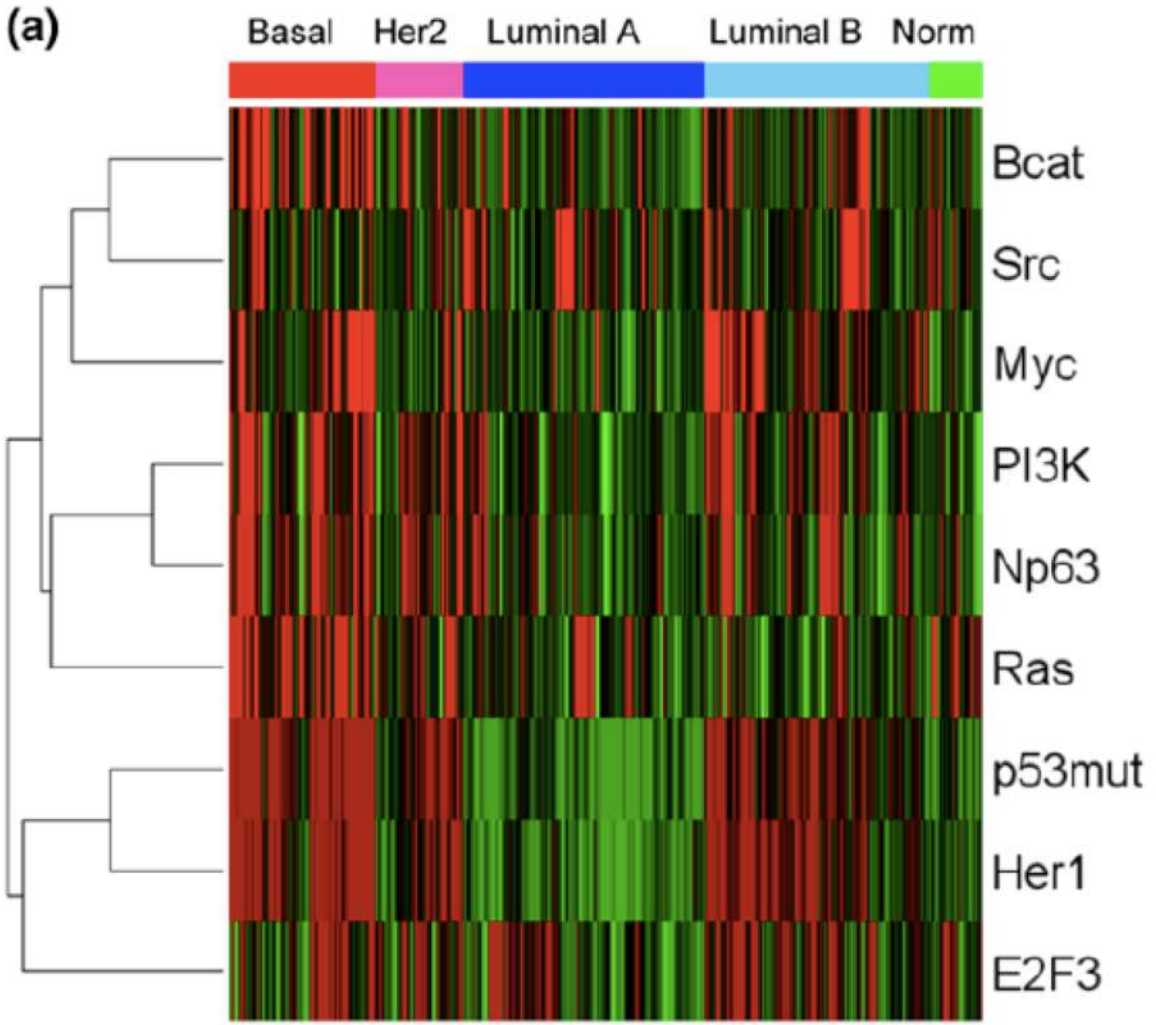


Bild et al., Breast Cancer Res 2009

Luminal breast cancer

Luminal A characteristics:

- ~60% of breast cancers
- ER and PR positive
- Tend to have low proliferation level
- Do not overexpress HER2
- Includes ER positive special type cancers (tubular, mucinous)
- High expression of hormone receptors and associated genes
- Respond to endocrine therapy
- Good prognosis, a large subset are cured by surgery alone (of post menopausal patients)

Luminal B characteristics:

- ~10% of breast cancers
- ER positive but can be PgR low
- High proliferation level
- Respond to endocrine therapy and chemotherapy
- Adverse prognosis if not treated appropriately

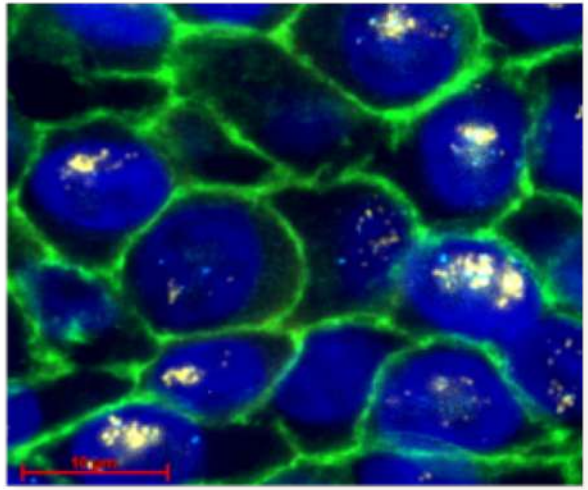
HER2-enriched and basal-like breast cancer

HER2- enriched

- Can be either ER+ or ER-
- HER2 pathway active
- Can have gain of HER2 (low level or high level)
- High proliferating
- Can have extensive immune cell infiltration
- Can respond to chemotherapy
- Very slim prognosis until HER2 target therapy was introduced (Trastuzumab)
- Dual-blockage is promising (to avoid resistance, i.e. relapse)
- NB: a HER2 enriched tumor can be clinically HER2 negative…

Basal-like:

- ER-/PgR-/HER2-
- Frequently grade 3
- Solid growth
- High proliferation
- Can have extensive immune cell infiltration
- Can be positive for CK5/6, EGFR
- Can respond to chemotherapy



ImmunoFISH:
Blue: DAPI (nuclear)
Green: HER2 protein
Yellow: HER2 gene probe
Light blue: Cent 17 probe

St. Gallen consensus meeting 2015

Table 2. Treatment-oriented classification of subgroups of breast cancer

Clinical grouping	Notes
Triple-negative	Negative ER, PgR, and HER2
Hormone receptor-negative and HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-negative luminal disease as a spectrum:	ER and/or PgR positive $\geq 1\%$[a]
High receptor, low proliferation, low tumor burden (luminal A-like)	Multiparameter molecular marker 'favorable prognosis' if available. High ER/PgR and clearly low Ki-67[b]. Low or absent nodal involvement (N 0–3), smaller T size (T1 T2).
Intermediate	Multiparameter molecular marker 'intermediate' if available[c]. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.
Low receptor, high proliferation, high tumor burden (luminal B-like)	Multiparameter molecular marker 'unfavorable prognosis' if available. Lower ER/PgR with clearly high Ki-67[b]. More extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, larger T size (T3).

[a]ER values between 1% and 9% were considered equivocal. Thus, endocrine therapy alone cannot be relied upon for patients with these values.
[b]Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.
[c]Not all multiparameter molecular marker tests report an intermediate score.

Coates et al, Ann Oncol 2015

St. Gallen consensus meeting 2015

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Intermediate	
Low receptor, high proliferation, high tumor burden (luminal B-like)	Multiparameter molecular marker 'unfavorable'. Lower ER/PgR with clearly high Ki-67[b]. More extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, larger T size (T3).

[a]ER values between 1% and 9% were considered equivocal. Thus, endocrine therapy alone cannot be relied upon for patients with these values.
[b]Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.
[c]Not all multiparameter molecular marker tests report an intermediate score.

"Basal-like"

"HER2-enriched"

"Luminal B/HER2-like"

"Luminal A-like"

"Luminal B-like"

Still IHC phenotypes for diagnosis – but luminal disease in need of more

Coates et al, Ann Oncol 2015

Molecular based classification

- Biomarkers/signatures for treatment prediction?
- Biomarkers/signatures recognizing biological distinct traits?
- Genomic – transcriptomic – metabolomic – proteomic features?
- Integrated approaches?
- Are they recapitulating already established classes…?
- What is the clinical implication?
- And are the designated class the same throughout the entire evolution of a given tumor?

Similarities in phenotype....


Cesar

...but different genotype!

DNA Translocations and copy number changes

Few alterations...

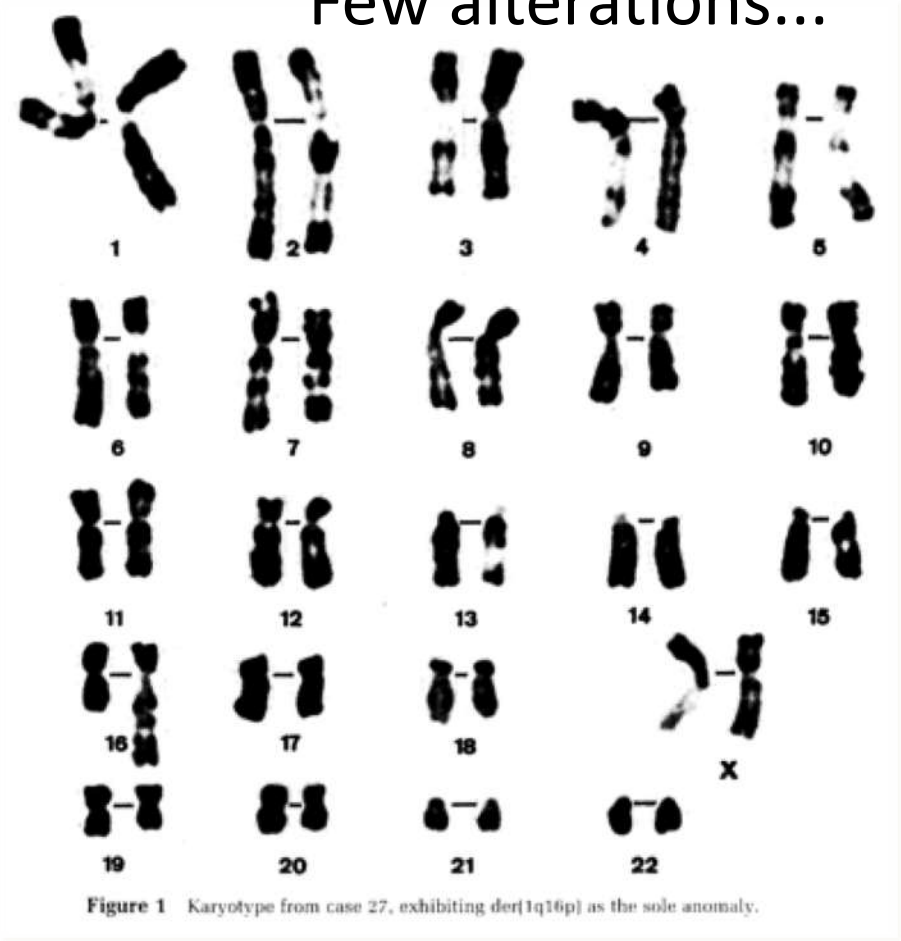
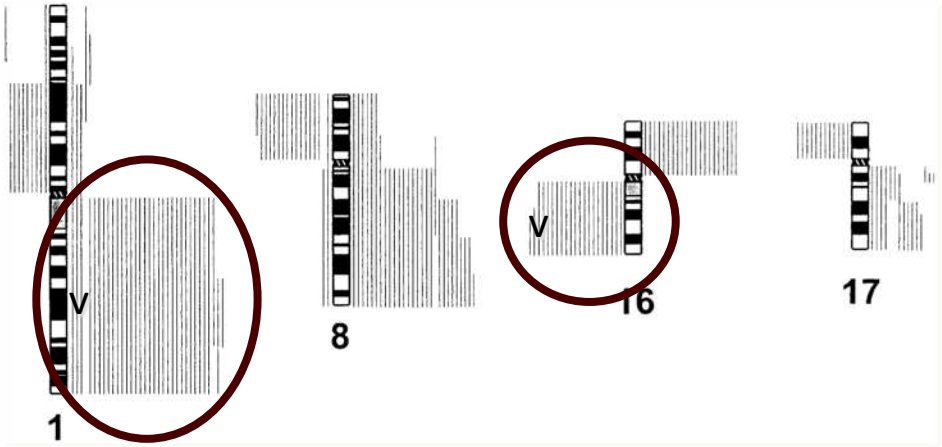
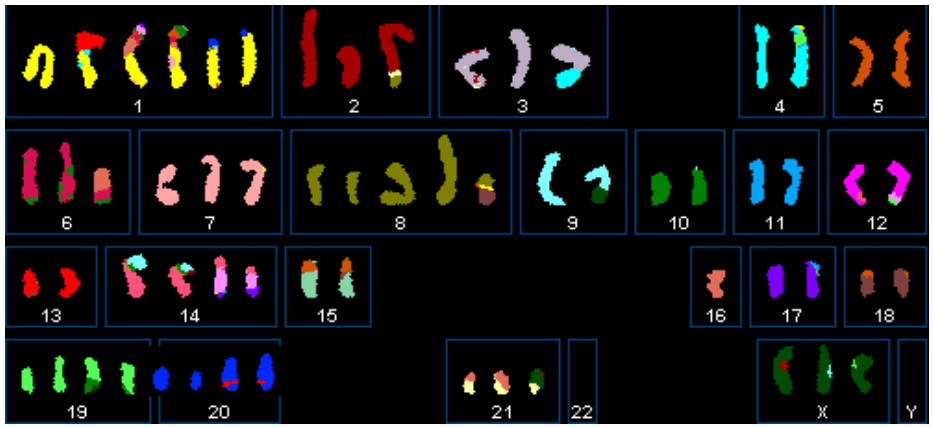


Figure 1 Karyotype from case 27, exhibiting der(1q16p) as the sole anomaly.

Dutrillaux et al. Cancer Genet Cytogenet 1990



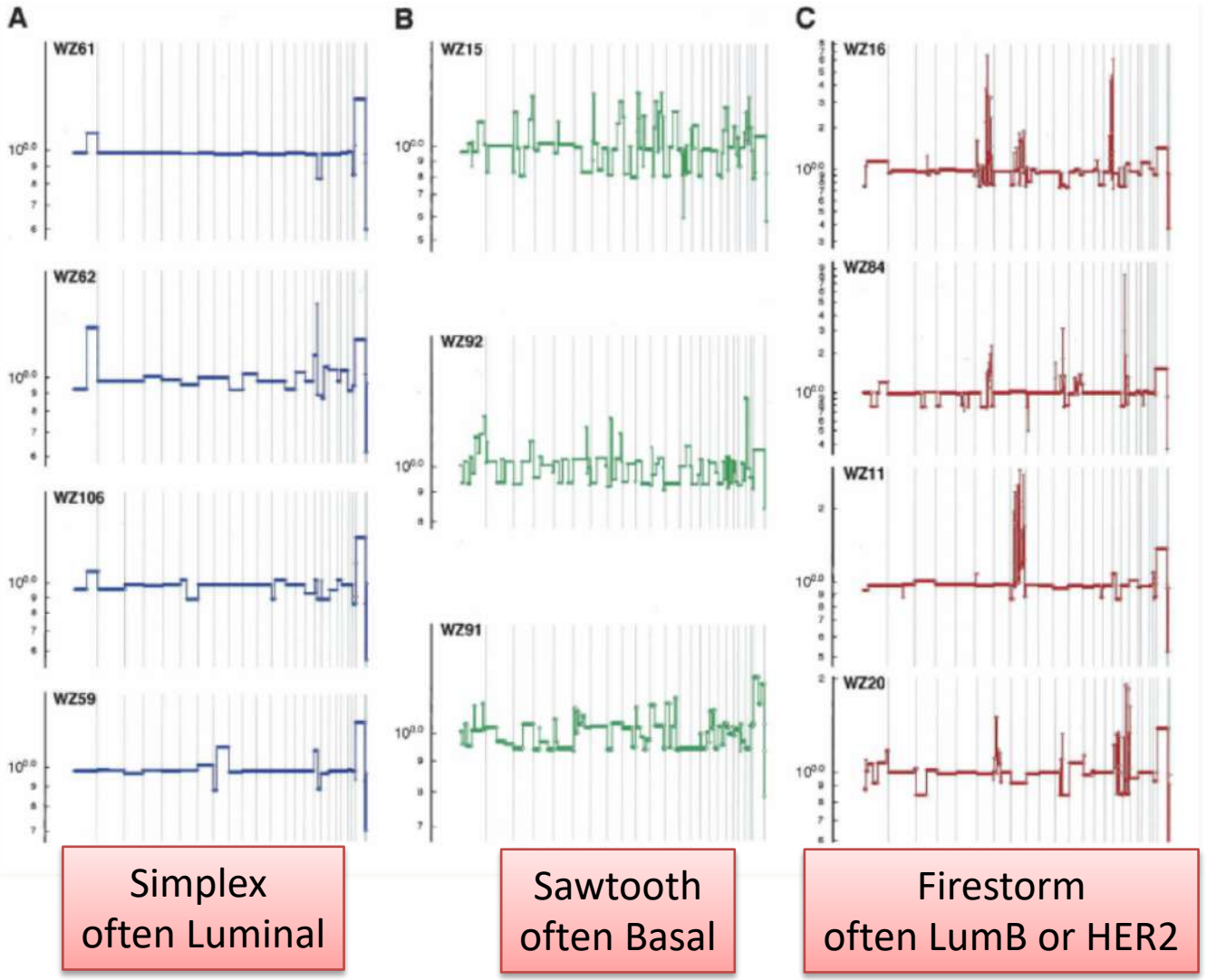


MDA-MB-157, From http://www.path.cam.ac.uk

...many alterations

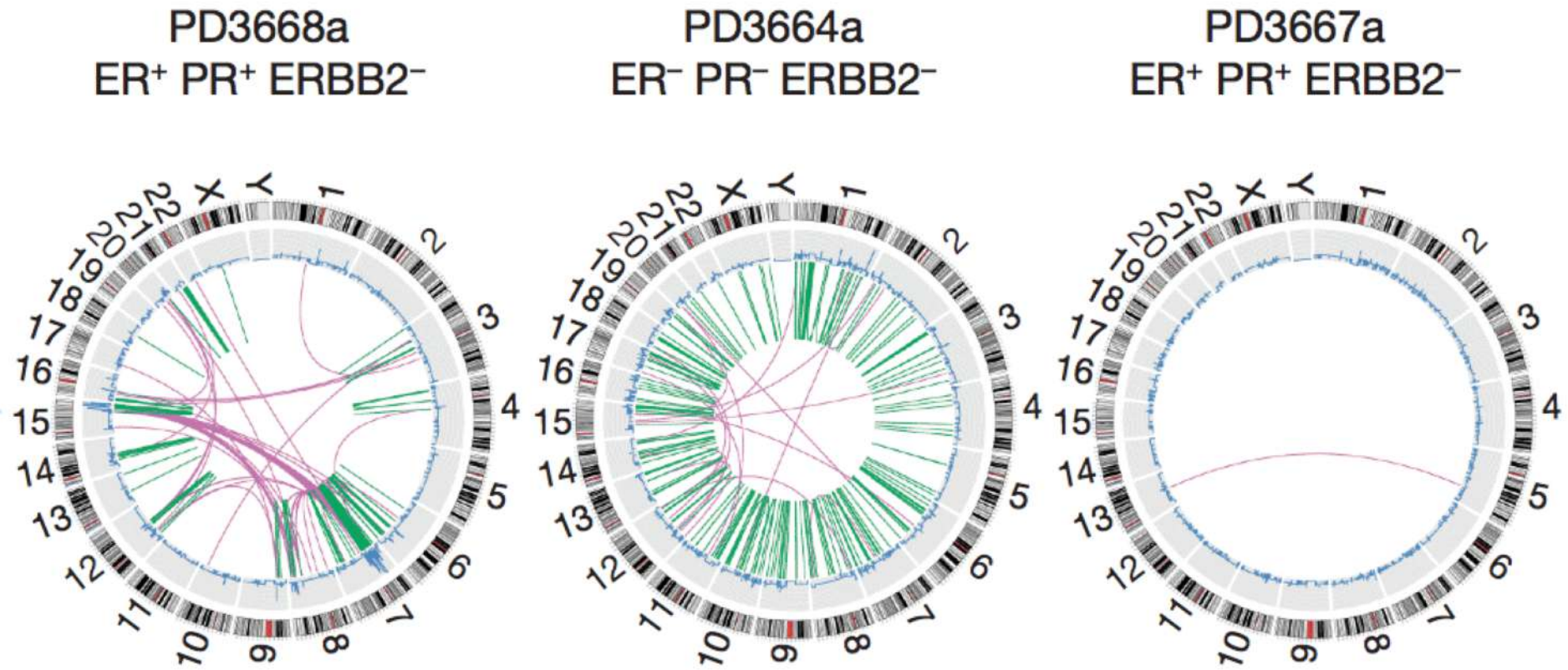
Patterns of genomic rearrangements

- Breast cancer genomes show three main patterns of alterations
  - simplex
  - complex/saw tooth
  - complex/fires torm



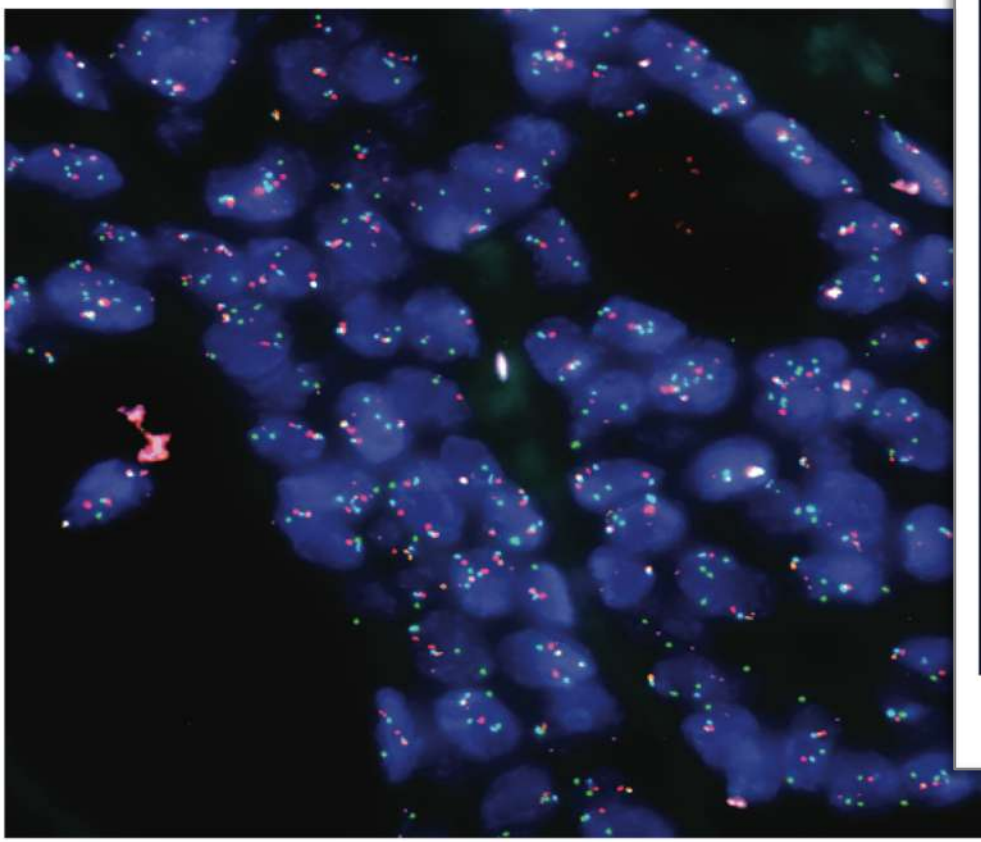
Hicks et al. Genome Res 2006

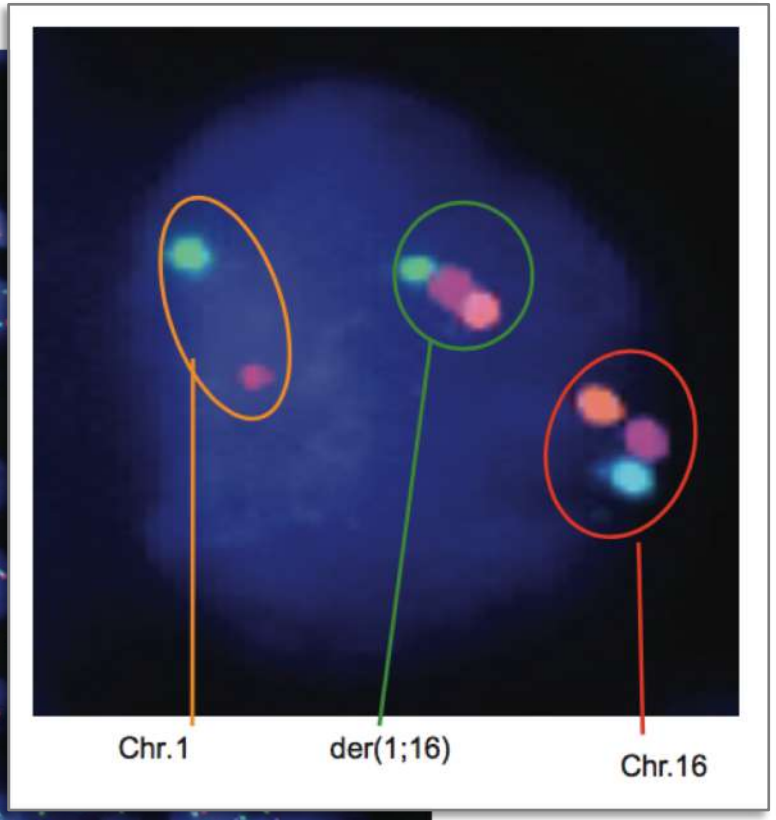
Sequenced breast cancer genomes - structural rearrangements



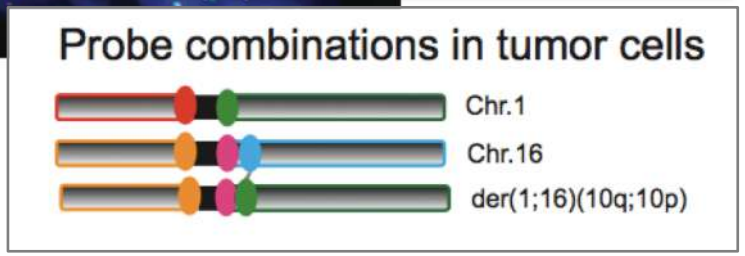
Stephens, Nature 2009

Centromere close translocations; gain and losses of whole chromosome arms





Coll. With A. Zetterberg, CCK, KI, Stockholm



Rye et al, Genes Chrom Cancer 2015

Class discovery by integrating DNA alterations and gene expression data

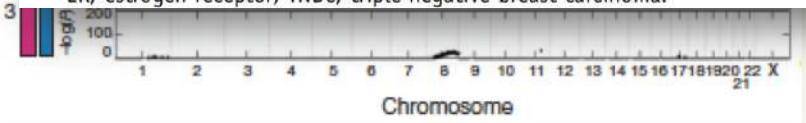
Different genomic drivers across ER+ breast cancer

Table 1 Overview of the Integrative Cluster Subtypes and the Dominating Properties with Regard to Copy Number Driving Events, Biomarkers, Type of DNA Architecture,[46] Dominant PAM50 Subtype, and Clinical Outcome

Integrative cluster group	Copy number driver	Pathology biomarker class	DNA architecture	Dominant PAM50	Clinical characteristics (survival)
1	Chromosome 17/ chromosome 20	ER^+ ($HER2^+$)	Simplex/firestorm (chromosome 17q)	Luminal B	Intermediate
2	Chromosome 11	ER^+	Firestorm (chromosome 11q)	Luminal A and B	Poor
3	Very few	ER^+	Simplex/flat	Luminal A	Good
4	Very few	ER^+/ER^-	Sawtooth/flat	Luminal A (mixed)	Good (immune cells)
5	Chromosome 17 (*HER2* gene)	$ER^-(ER^+)/HER2^+$	Firestorm (chromosome 17q)	Luminal B and HER2	Extremely poor (in pre-Herceptin cohorts)
6	8p deletion	ER^+	Simplex/firestorm (chromosome 8p/ chromosome 11q)	Luminal B	Intermediate
7	Chromosome 16	ER^+	Simplex (chromosome 8q/chromosome 16q)	Luminal A	Good
8	Chromosome 1, Chromosome 16	ER^+	Simplex (chromosome 1q/chromosome 16q)	Luminal A	Good
9	Chromosome 8/ Chromosome 20	ER^+ (ER^-)	Simplex/firestorm (chromosome 8q/ chromosome 20q)	Luminal B (mixed)	Intermediate
10	Chromosome 5, Chromosome 8, Chromosome 10, Chromosome 12	TNBC	Complex/sawtooth	Basal-like	Poor 5-year, good long-term if survival

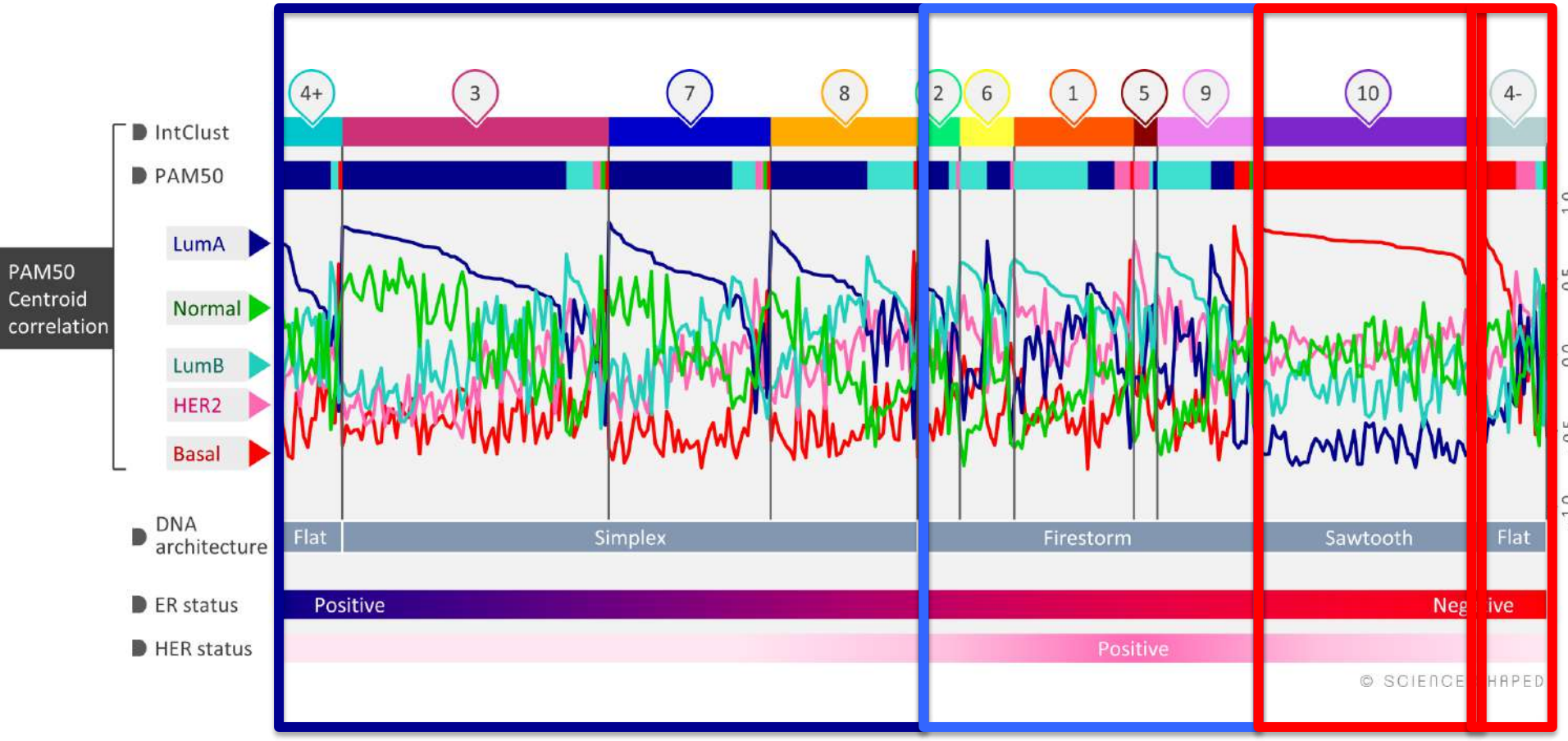
ER, estrogen receptor; TNBC, triple-negative breast carcinoma.

Russnes et al. Am J Pathology, 2017



Curtis et al. Nature, 2012

PAM50 – IntClust – DNA architecture

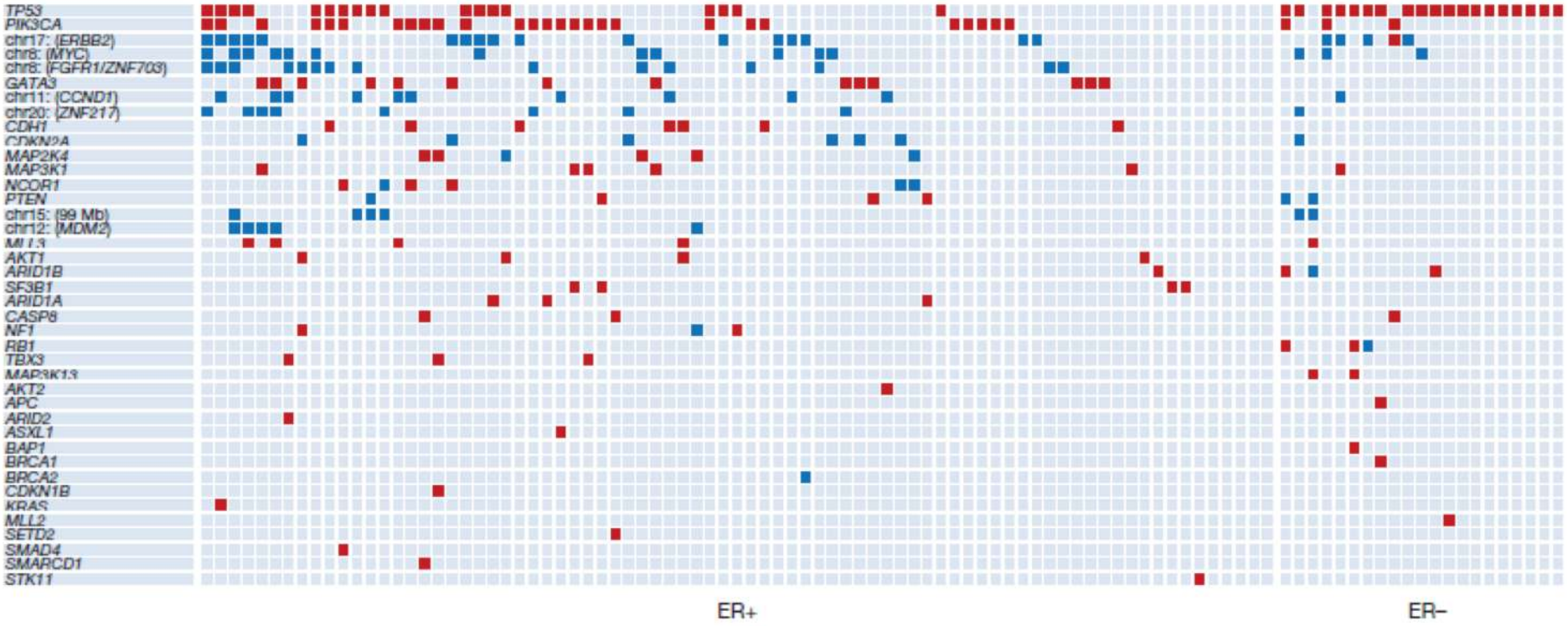


NB: centroid classification has five dimensions!

Russnes et al., Am J of Pathology, 2017

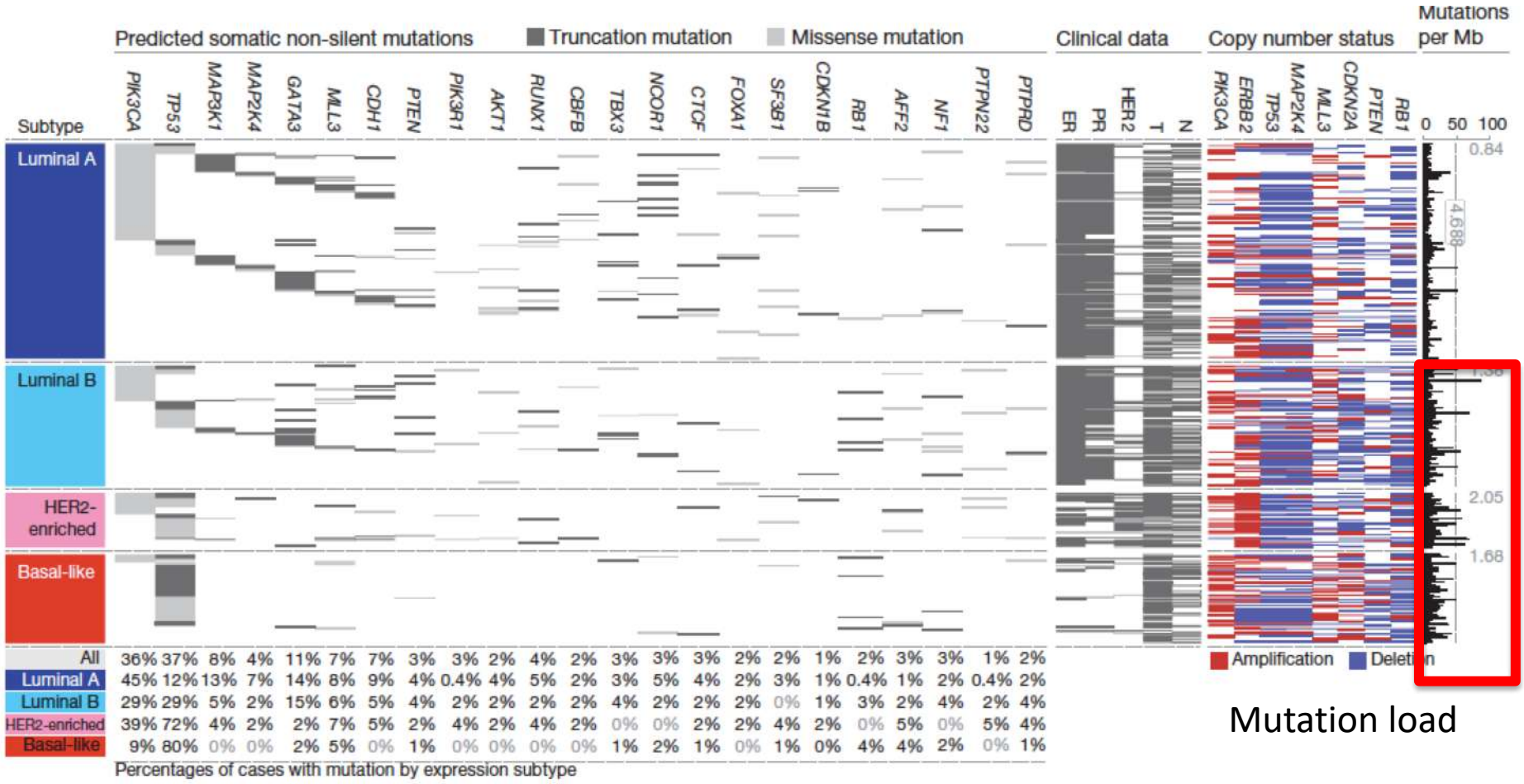
Mutations - “Personal” profiles?

100 breast cancer samples, 40 genes -> a total of 73 different combinations of mutated genes!



Stephens et al. Nature 2012

A specter of DNA mutations



Mutation load

The cancer genome atlas (TCGA) 2012

Molecular based classification

- Biomarkers/signatures for treatment prediction?
- Biomarkers/signatures recognizing biological distinct traits?
- Genomic – transcriptomic – metabolomic – proteomic features?
- Integrated approaches?
- Are they recapitulating already established classes…?
- What is the clinical implication?
- And are the designated class the same throughout the entire evolution of a given tumor?

Yes – but clearly adding more!
Luminal breast cancer

Table 2. Treatment-oriented classification of subgroups of breast cancer

Clinical grouping	Notes
Triple-negative	Negative ER, PgR, and HER2
Hormone receptor-negative and HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-negative luminal disease as a spectrum:	ER and/or PgR positive ≥1%[a]
High receptor, low proliferation, low tumor burden (luminal A-like)	Multiparameter molecular marker 'favorable prognosis' if available. High ER/PgR and clearly low Ki-67[b]. Low or absent nodal involvement (N 0–3), smaller T size (T1 T2).
Intermediate	Multiparameter molecular marker 'intermediate' if available[c]. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.
Low receptor, high proliferation, high tumor burden (luminal B-like)	Multiparameter molecular marker 'unfavorable prognosis' if available. Lower ER/PgR clearly high Ki-67[b]. More extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, larger T size (T3).

[a]ER values between 1% and 9% were considered equivocal. Thus, endocrine therapy alone cannot be relied upon for patients with these values.
[b]Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.
[c]Not all multi

"LumA-like"

"intermediate group"

"LumB-like"

Multiparameter molecular marker needed

Coates et al, Ann Oncol 2015

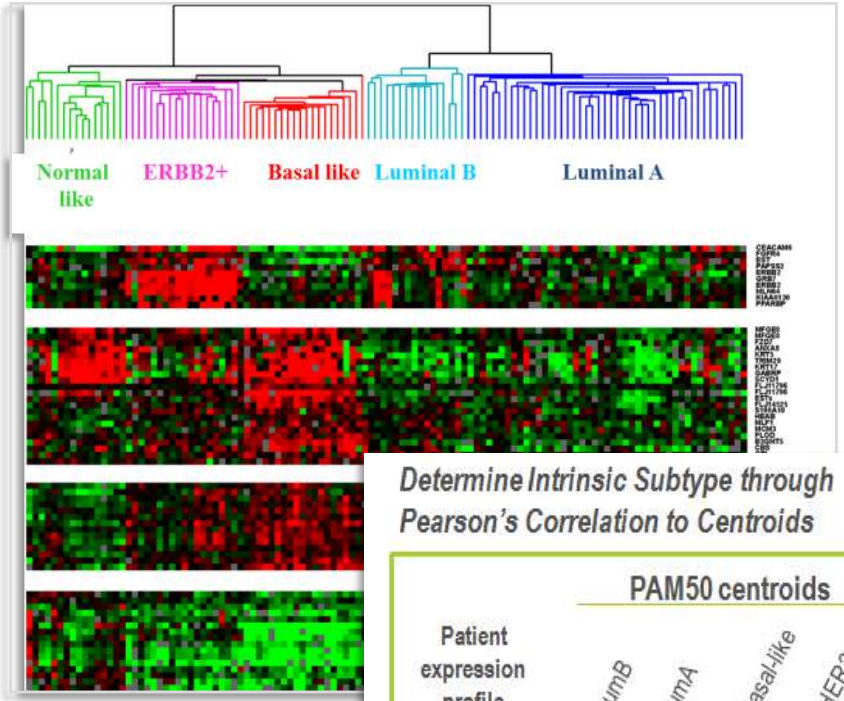
Luminal disease is defined as a spectrum

Several validated molecular multimarker tests predict prognosis and/or therapy response:

- Oncotype Dx
- Mammaprint
- BCI
- IHC4
- Rotterdam signature
- Prosigna (PAM50 ROR)
- Endopredict
- Mammostrat
- MammaTyper

- …but Ki-67 is easy and cheaper

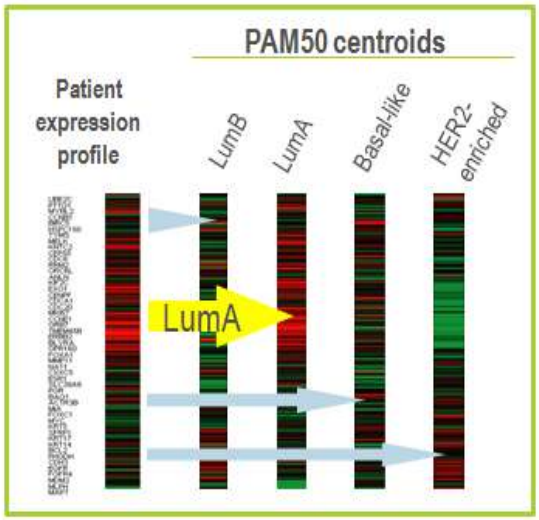
From intrinsic subtypes to PAM50 to Prosigna



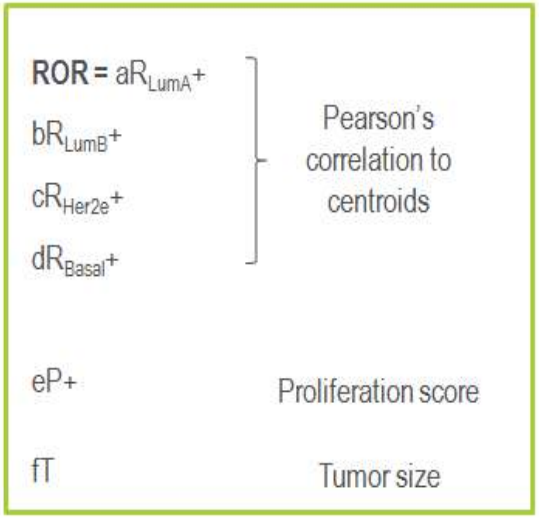
Sørlie, Perou et al PNAS, 2

- PAM50: **5 subtypes** *(Parker et al. JCO 2009)*
- Prosigna™ Breast Cancer Prognostic Gene Signature Assay on the nCounter® Dx Analysis System (Nanostring) **4 subtypes and ROR score**
- Assignment of subclass by **centroide correlation**

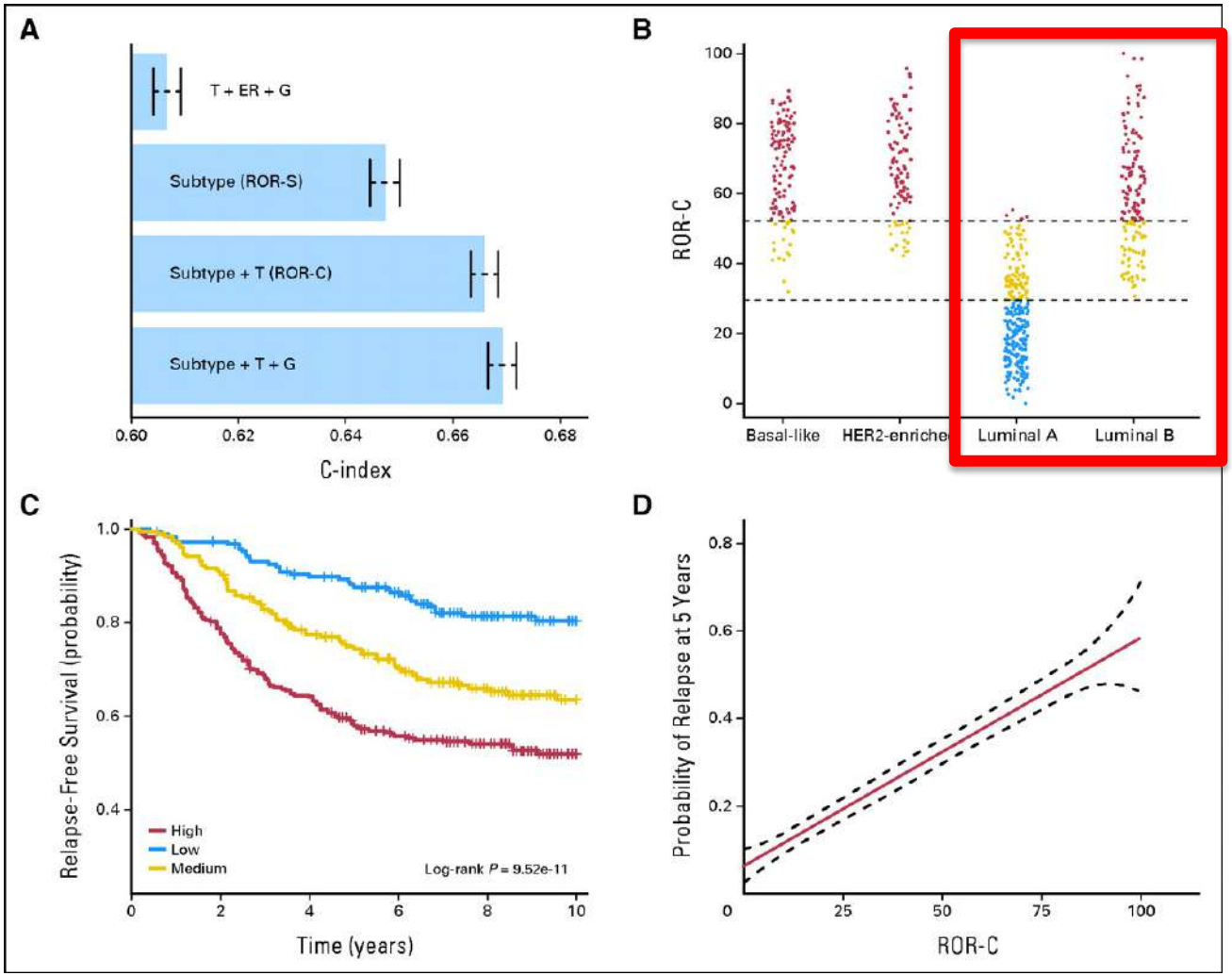
Determine Intrinsic Subtype through Pearson's Correlation to Centroids



Calculate Risk of Recurrence (ROR) Score



PAM50/Prosigna: Risk of relapse (ROR) predictions using a test set of node-negative, no systemic therapy patients.



Joel S. Parker et al. JCO 2009;27:1160-1167

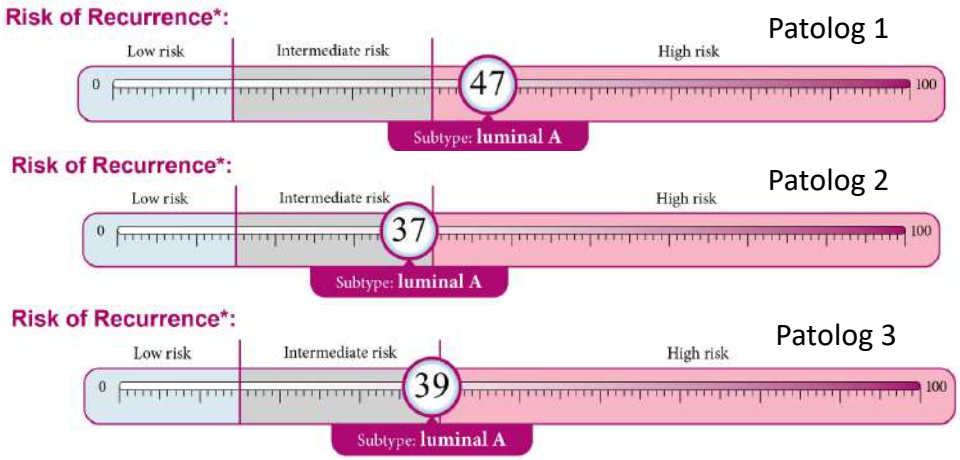
NanoString nCounter Analysis System

- Not PCR based – suited for RNA from FFPE
- Can be run as both a research instrument and a diagnostic instrument (black box)
- Up to 800 genes (can do DNA and protein as well)

Challenge: regional intra tumor heterogeneity

Tumor area selection by three pathologists:

Prosigna score:



Luminal A ROR: 47 High risk

Luminal A ROR: 37 Intermed. risk

Luminal A ROR: 39 Intermed. risk

Morphology is of importance: the selection of area can determine use of adjuvant chemotherapy or not!

The diversity of Basal-like tumors

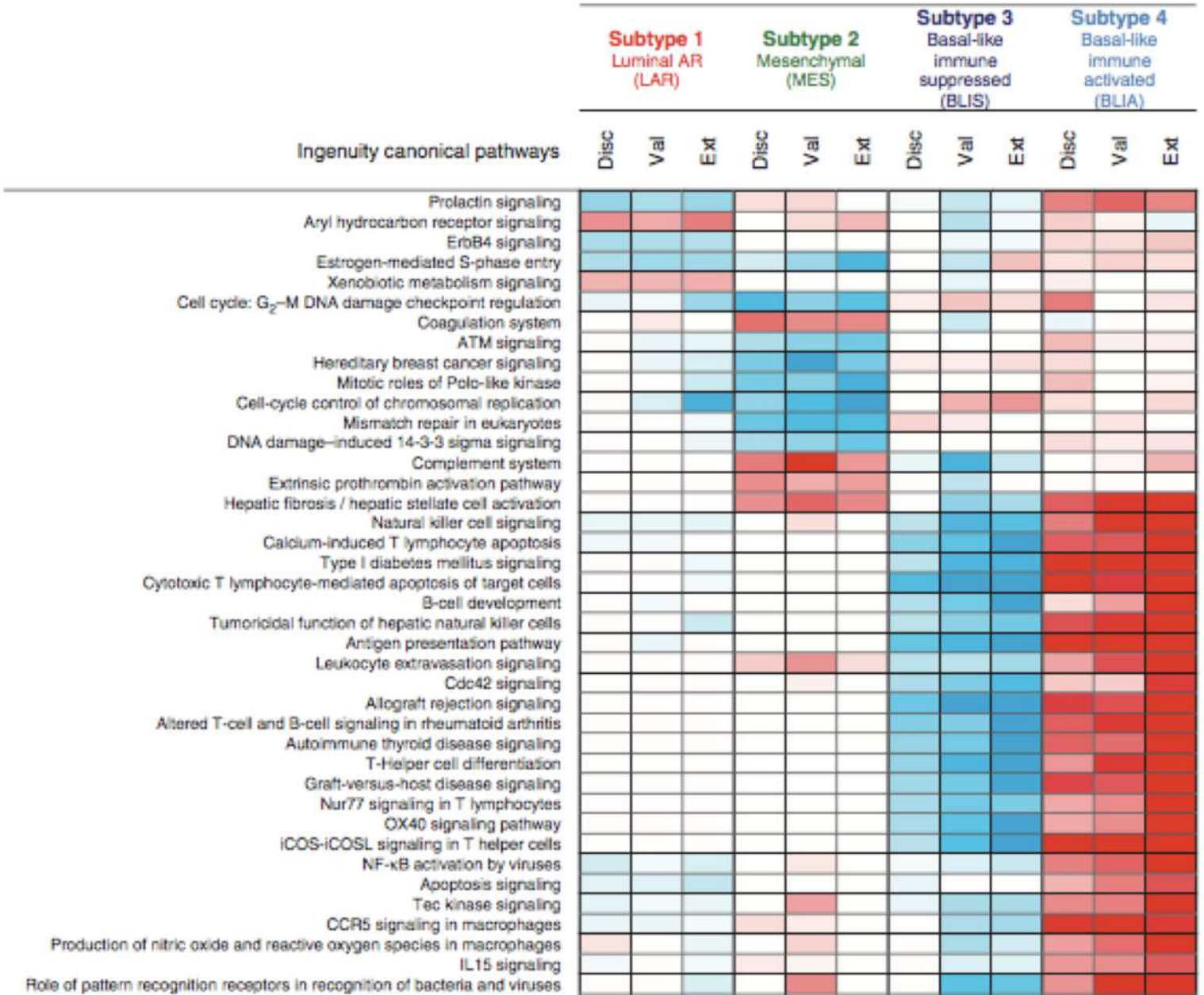
Biology of Human Tumors

Clinical Cancer Research

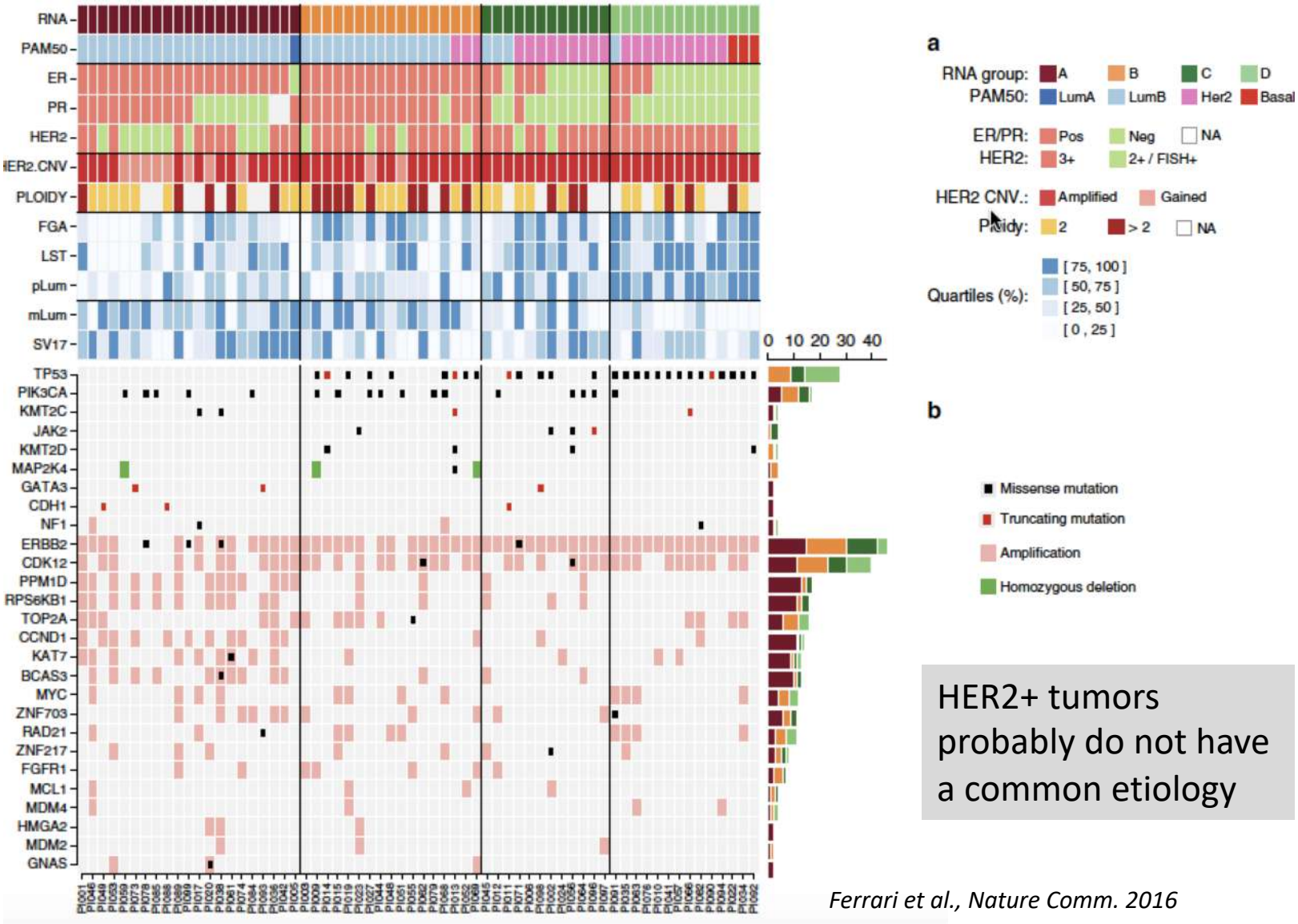
Comprehensive Genomic Analysis Identifies Novel Subtypes and Targets of Triple-Negative Breast Cancer

Matthew D. Burstein[1], Anna Tsimelzon[2], Graham M. Poage[3], Kyle R. Covington[2], Alejandro Contreras[2,4], Suzanne A.W. Fuqua[2], Michelle I Savage[3], C. Kent Osborne[2], Susan G. Hilsenbeck[2], Jenny C. Chang[5], Gordon B. Mills[6], Ching C. Lau[7], and Powel H. Brown[3]

Molecular pathways enriched in the four groups



The diversity of HER2+ tumors

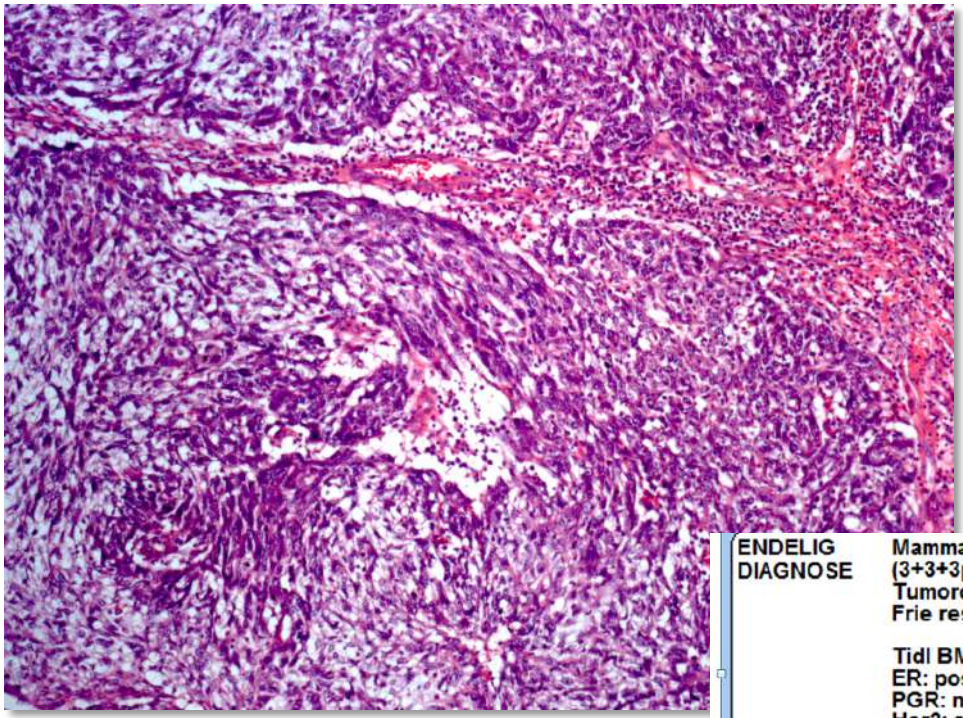


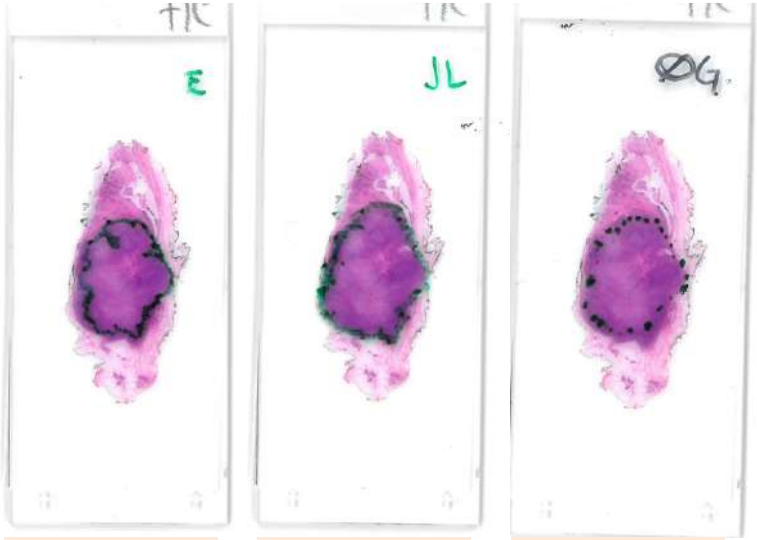
HER2+ tumors probably do not have a common etiology

Ferrari et al., Nature Comm. 2016

Diagnostic challenge: ER status by molecular multimarker test

Tumor area selection by three pathologists:





Basal-Like ROR: 62 High Risk	Basal-Like ROR: 62 High Risk	Basal-Like ROR: 61 High Risk

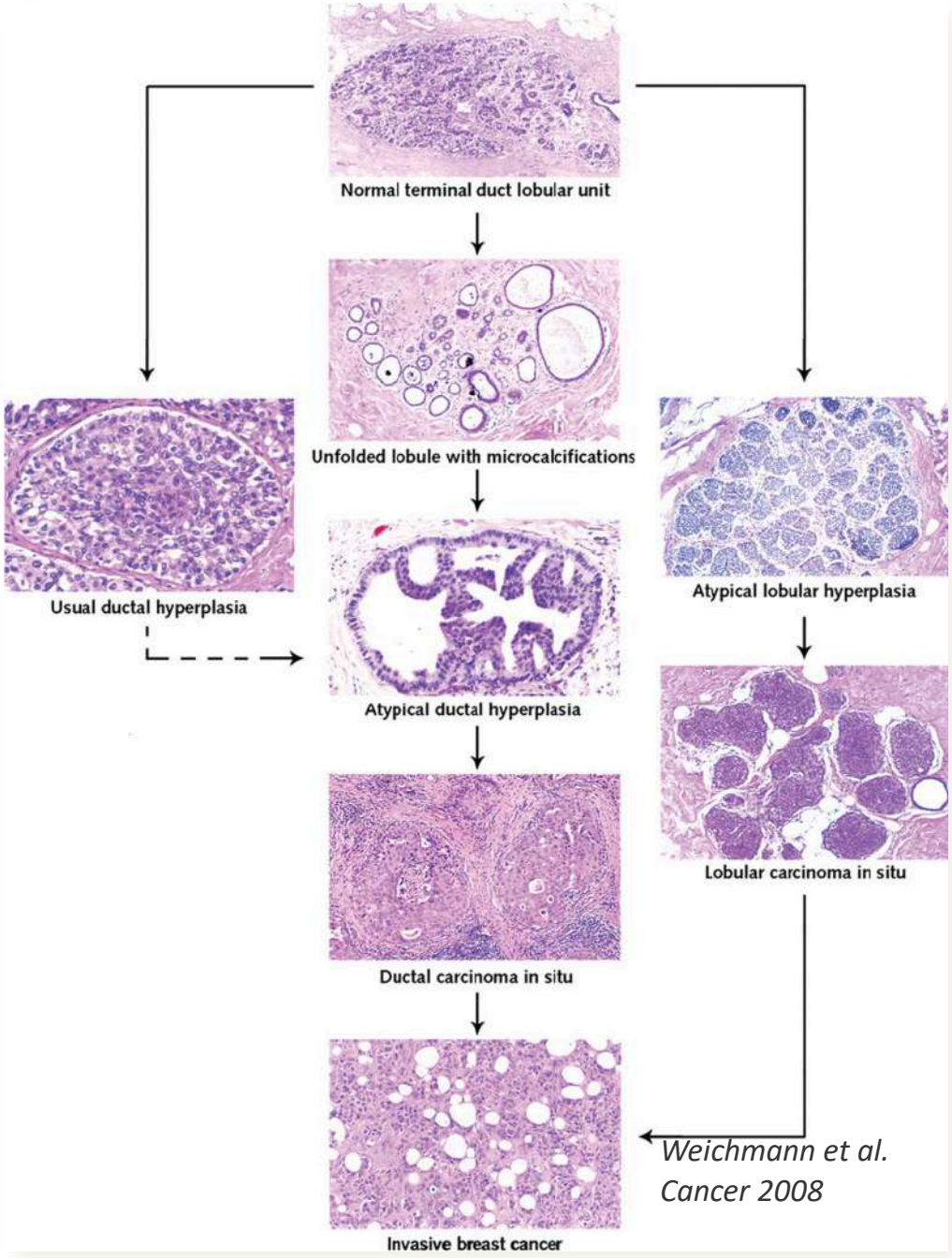
NB: Not ER+ by gene PAM50, and medullary BC is most frequently ER-

ENDELIG DIAGNOSE	Mammaresektat (ve. side) med infiltrende duktalt karsinom, histologisk grad 3 (3+3+3p) Tumordiameter 23 mm Frie reseksjonsrender, knapp ventralt (under 0,5 mm) Tidl BM15 13094: ER: positiv (ca. 20%) PGR: negativ (0%) Her2: score=0 ved immunhistokjemi (klinisk negativ) Ki-67 score: >75% gjennom hele tumor BU15 28335: En sentinel lymfeknute uten påviste patologiske forandringer
SNOMED	T 04030 M 85003 pT2 pN0 pMx G3 F 12391 F 12645 E her2N P ki763 P 11010
Vurdering	Reseptorstatus, HER-2 og Ki-67 er gjentatt i operasjonspreparatet med samme resultat som i grovnålsbiopsi. Tumor har morfologisk visse medullære trekk.

Molecular based classification

- Biomarkers/signatures for treatment prediction?
- Biomarkers/signatures recognizing biological distinct traits?
- Genomic – transcriptomic – metabolomic – proteomic features?
- Integrated approaches?
- Are they recapitulating already established classes…?
- What is the clinical implication?
- And are the designated class the same throughout the entire evolution of a given tumor?

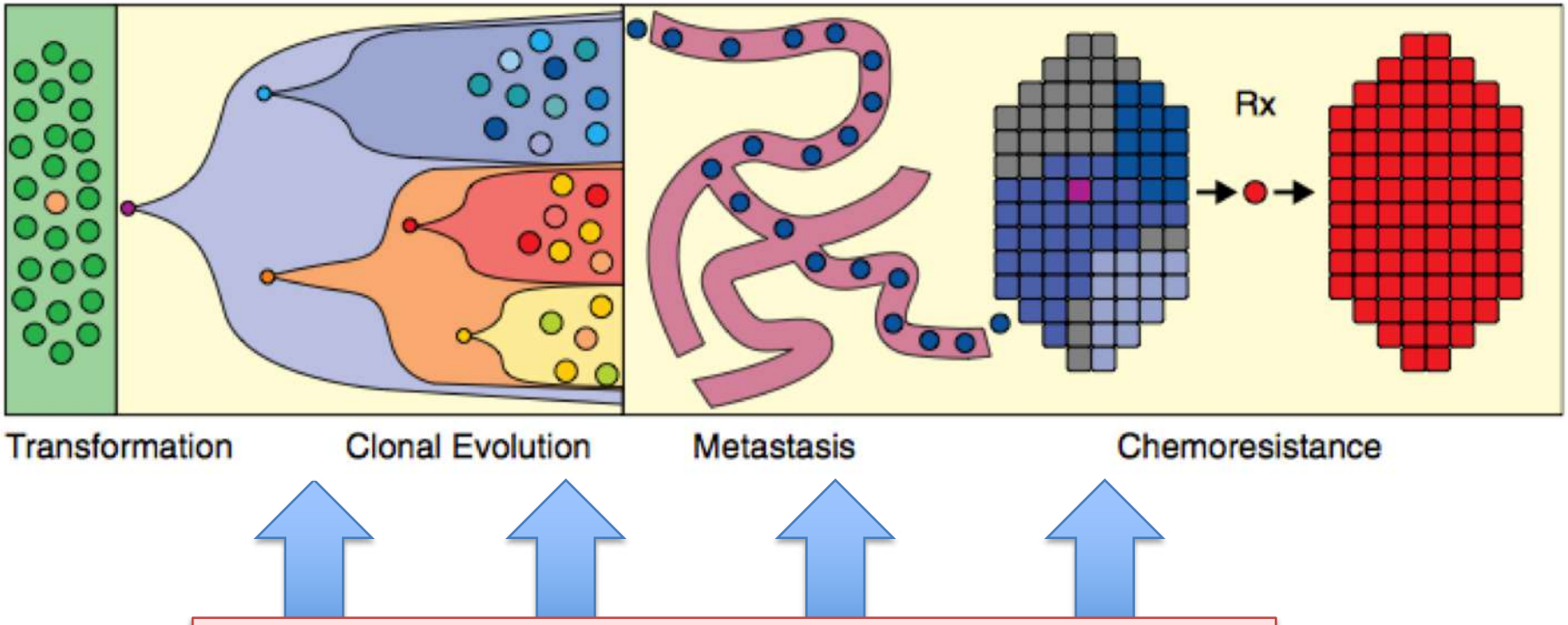
Pre-invasive disease: Many different histological appearances with uncertain relationship…



Weichmann et al. Cancer 2008

Heterogeneity and evolution - disease progression

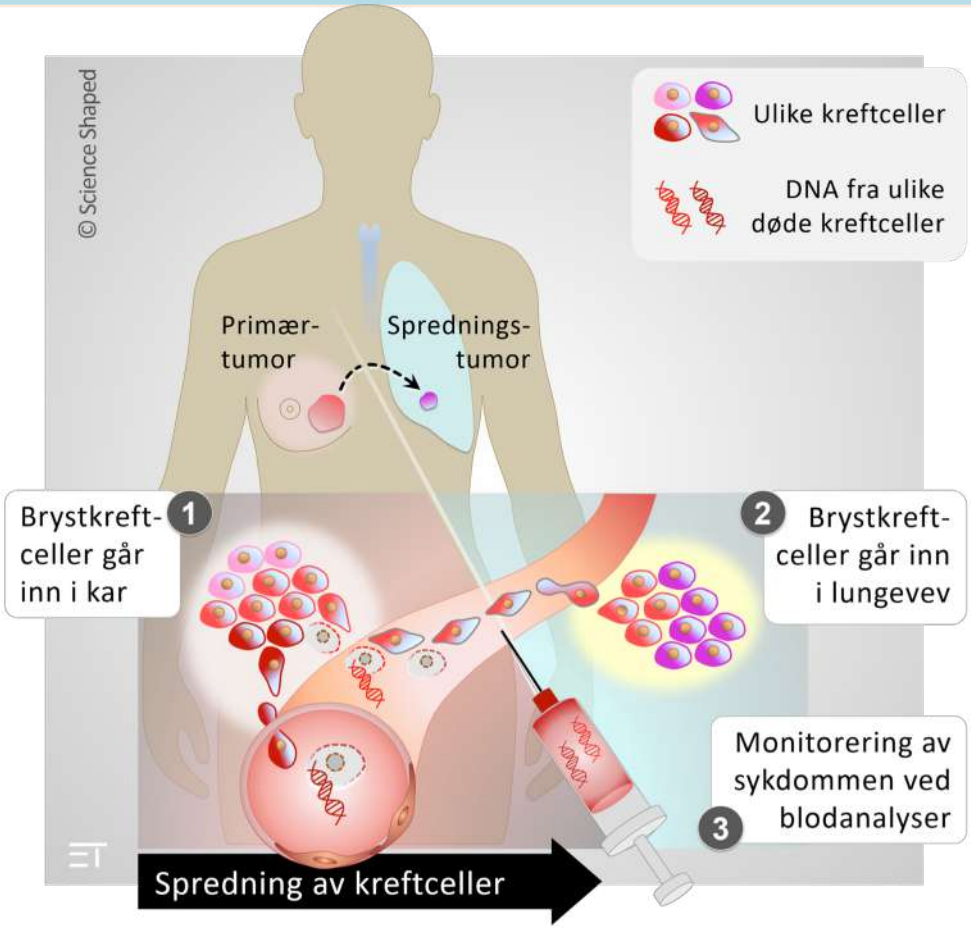
Navin, Genome Biol 2014



At what time point can metastatic potential be revealed?
Prediction of therapy response?

Liquid biopsies

Development and standardization of protocols and assays for cell-free tumor DNA detection in peripheral blood



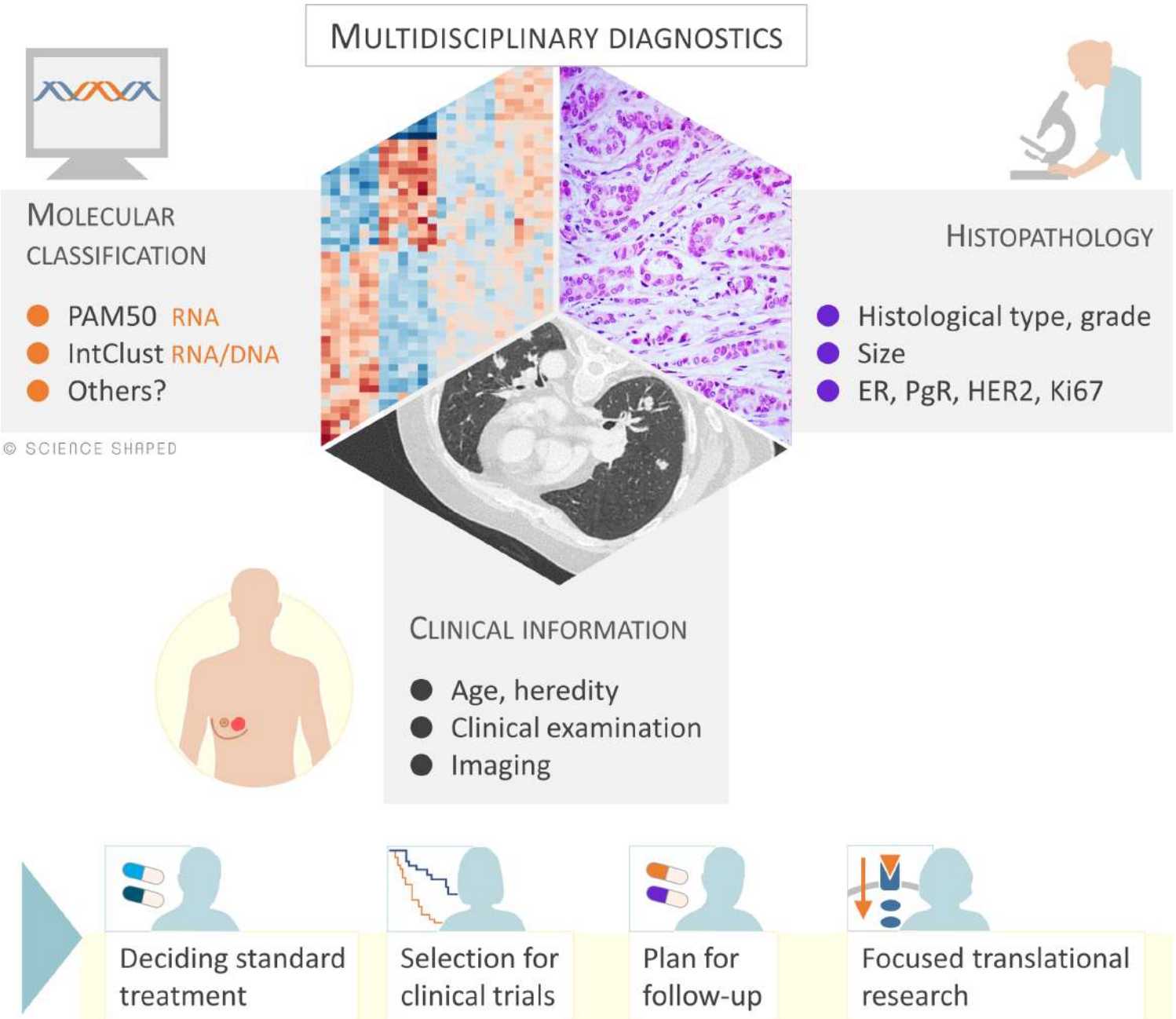
- Promising for monitoring neo-adjuvant treatment
- Promising in metastatic setting
- But need many markers or NGS based tests

- NB: value of circulating cells (CTC) or disseminated cells (DTC) needs to be considered

Molecular classification of breast cancer

2019, ASCO Educational book:

	Hereditary Cancer Risk	Tumor Gene-Expression Signatures	Tumor Genomic Mutations
Assay	Germline DNA test	Tumor RNA–expression assay	Tumor (or circulating tumor or cell-free) DNA for genomic profiling
Number of Genes Measured	Varies by assay; typically 2 to 40.	Varies by assay; typically 10-100	Varies by assay; typically > 400
Assay Readout	Mutations in germline DNA	Patterns of gene expression often weighted with proprietary score	Mutations, deletions, amplifications in tumor DNA
Clinical Role	Defining hereditary cancer syndromes (e.g., BRCA1/2); identifying patients for selected therapy in metastatic breast cancer with PARP inhibitors or platinum analogs	Prognostic markers for outcome in ER+ breast cancer; predicting benefit from adjuvant chemotherapy in ER+ breast cancer	Identifying mutations for targeted therapy in metastatic breast cancer, including dynamic evolution of mutations associated with treatment resistance; potential surrogate for cancer burden in setting of metastatic disease
Recommend for:	All patients with metastatic breast cancer; patients with early-stage breast cancer with family history or other clinical features associated with hereditary cancer syndromes	Women with early-stage ER+ breast cancer, typically stage 1 or 2, for deciding whether to recommend adjuvant chemotherapy in addition to endocrine therapy	Selection of endocrine/targeted treatments in advanced ER+ breast cancer based on PIK3CA or ESR1 mutations; experimental for other precision medicine purposes



Russnes et al., Am J of Pathology, 2017

Tusen takk!

Oslo University Hospital
Norwegian Radium Hospital