Special Symposium: Clinical Relevance of Genotyping ER Positive Breast Cancer

Emerging Treatment Options in the Genomic Era

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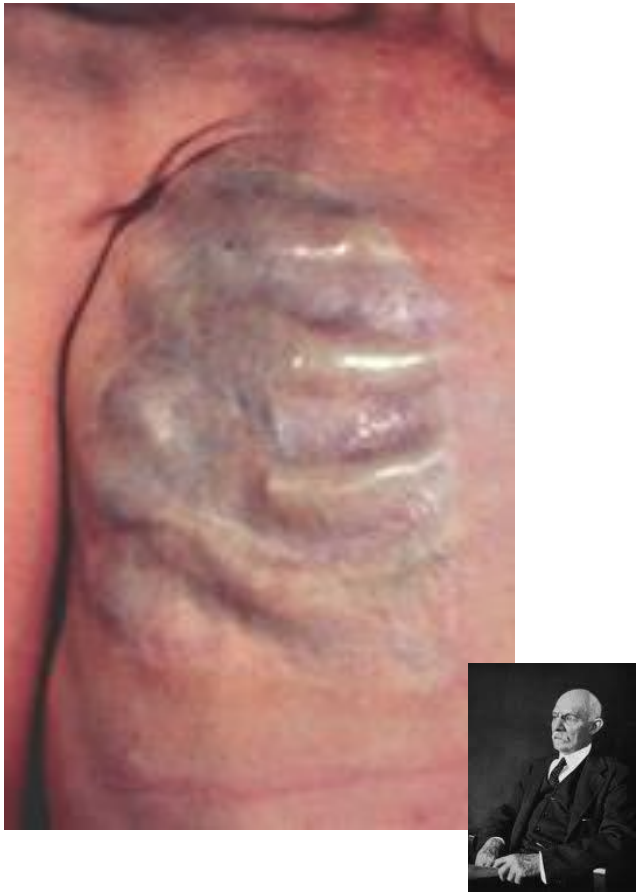
Suntec City, Singapore
19th December, 2015

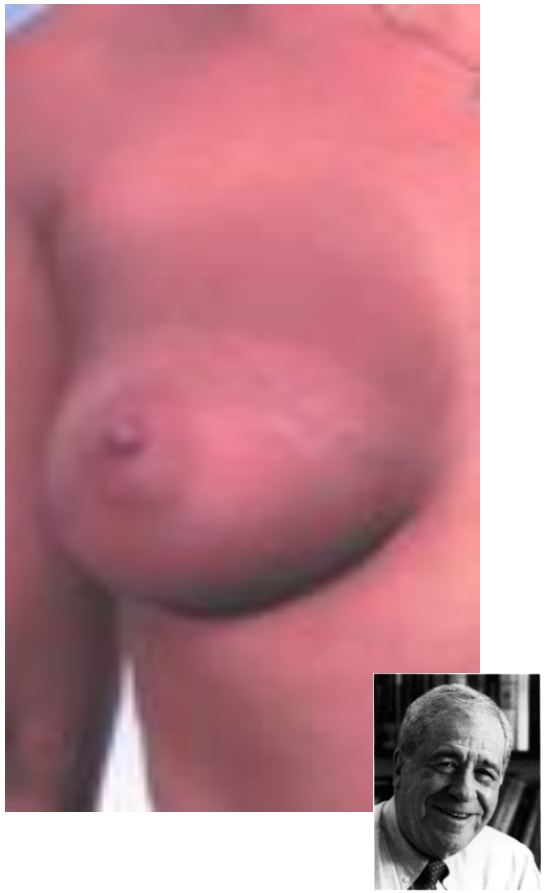
Disclosures

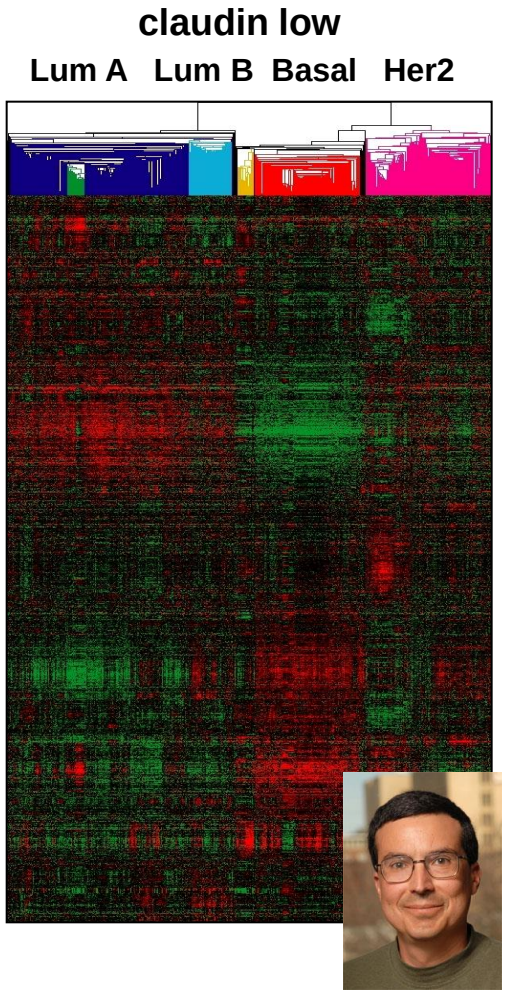
- Janice Tsang

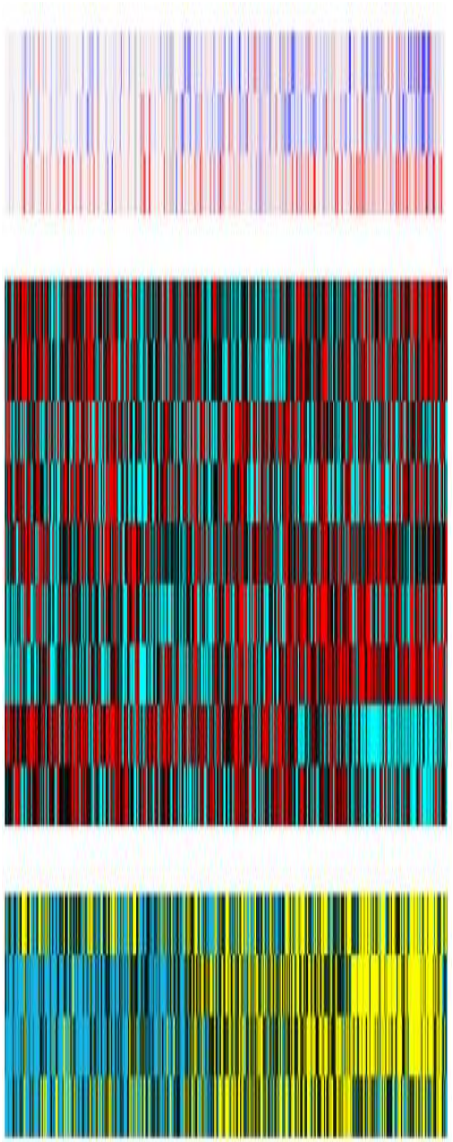
- Consultant or Advisory Role:
  AstraZeneca, Eisai, GlaxoSmithKline,
  Novartis & Pfizer

Changing Portraits of Breast Cancer









Background

- Results of our translational research in the last decade, have revolutionized our understanding of **breast cancer** as a **heterogeneous disease**:
- **Genomics** and transcriptomics have been helping to narrow down the number of candidate oncogenes -“One-size-fits-all” approach becomes less relevant

Genomic Medicine for Breast Cancer Patients

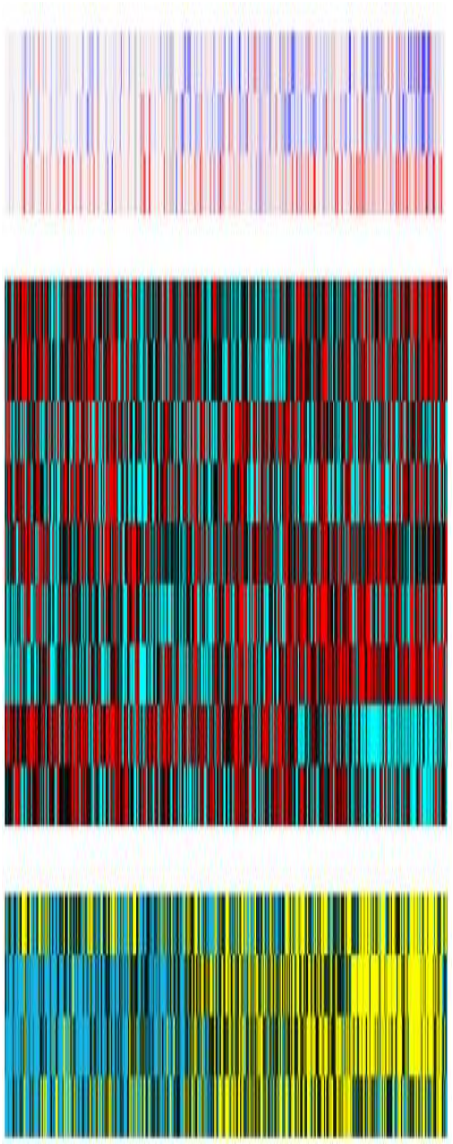
(beyond ER, PR, HER2, and chemotherapy)

Altered genes with predictive biomarker potential	Treatment approach	Strength of hypothesis for somatic alteration–targeted drug match (reference)
PIK3CA mutation	PIK3CA-selective inhibitors	2 Phase I BYL719 (18)
FGFR1 amplification, *FGF3* amplification, other FGF ligands and receptors, and rare receptor mutations	FGFR small-molecule inhibitors and antibodies	2 Phase I BGJ398 (48) and phase I E3800 (47)
Inherited and somatic *BRCA1* and *BRCA2* mutation	PARP inhibitors	2 Olaparib (49) and veliparib: NCT01506609[a]
Cyclin D1/CDK4/CDK6 amplification or deletion of *CDKN1B*, CDKN2A, and CDKN2B	CDK4/6 inhibitors	2 PD0332991 (40)
AKT1–3 gain-of-function mutation/gene fusion via translocation/amplification	AKT inhibitors	3 MK-2206: NCT01277757[a]
GATA3 mutation	Aromatase inhibition	3 Retrospective analysis of Z1031 (4)
PTEN/INPP4B loss-of-function mutation/deletion/loss of expression in TNBC	Broad-spectrum PI3K pathway inhibitors	3 BKM120: NCT01629615[a]
MDM2 amplification in *TP53* wild-type tumors	MDM2 inhibitors	3 RO5503781: NCT01462175[a]
HER2 mutation	Small-molecule *HER2* kinase inhibitors	3 Neratinib: (NCT01670877)[a] (50)
PIK3R1 loss-of-function mutation	PI3K pathway inhibitors?	4
MLL family member mutation	HDAC inhibition?	4
Rare RTK mutations	Various matched inhibitors?	4

NOTE: Number 1 indicates approved therapy; 2, early evidence of efficacy; 3, clinical investigations under way; and 4, clinical investigations not yet activated.

Ellis and Perou, Cancer Discovery, 2013 (PMID 23319768)

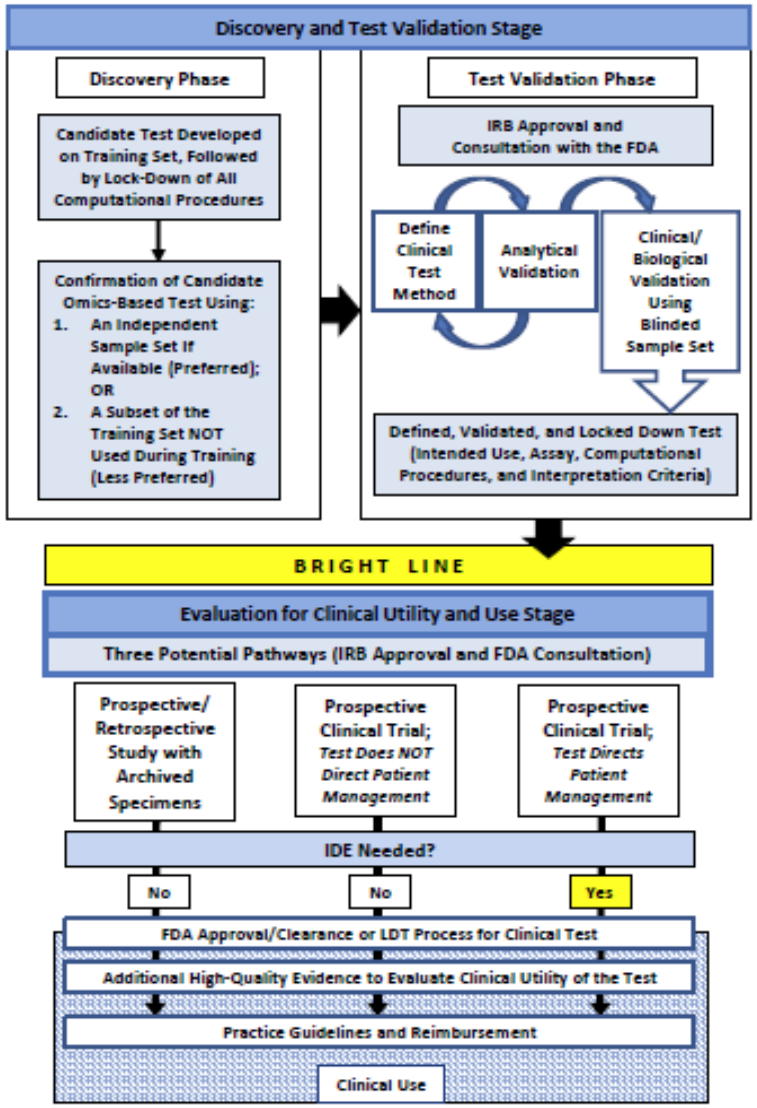
Development of Genomic Signatures…

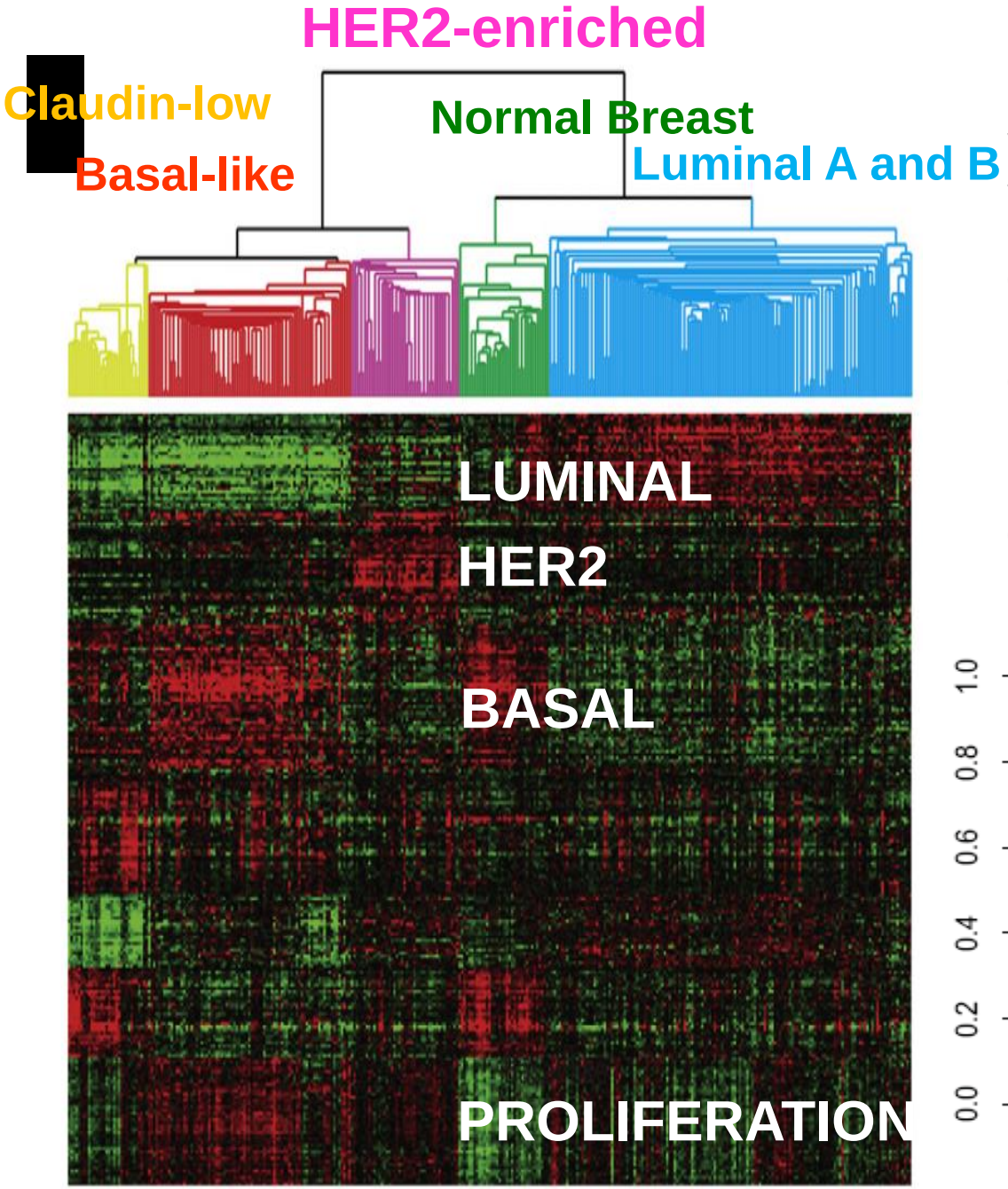


- Discovery
  - NGS, RNA seq, proteomics
  - Analytical validation
  - Training sets and validation sets
- Clinical Validation
  - Prognostic & Predictive value
  - Retrospective vs Prospective L-T FU
  - Compared with old therapies
- Clinical Utility

Best practices for translational omics studies Institute of Medicine (www.iom.edu/translationalomics)

FIGURE: Omics-Based Test Development Process

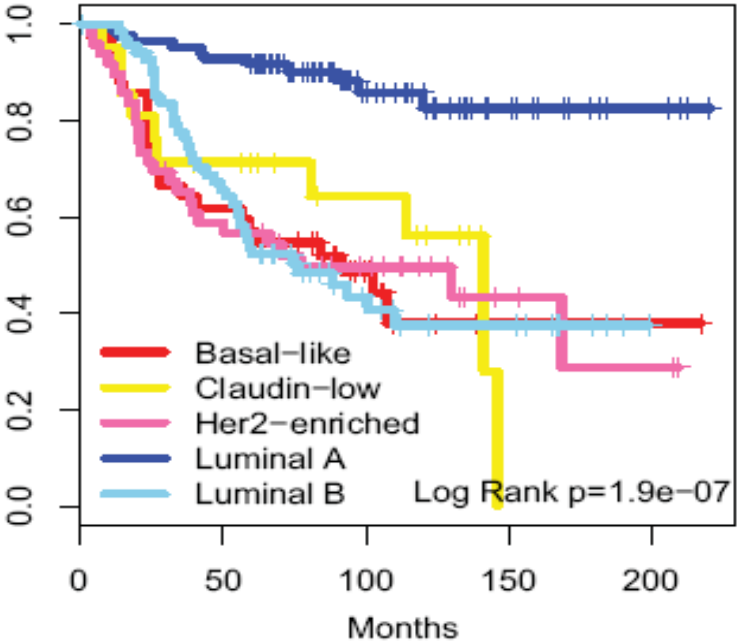




Intrinsic Subtypes

Perou et al., Nature 2000
Sorlie et al., PNAS 2001
Sorlie et al., PNAS 2003
Nielsen et al., CCR 2004
Cheang et al., CCR 2008
Parker et al., JCO, Feb 2009
Cheang et al., JNCI 2009
Prat et al., BCR 2010
Nielsen et al., CCR 2010
Cheang et al., CCR 2012

Relapse-free survival



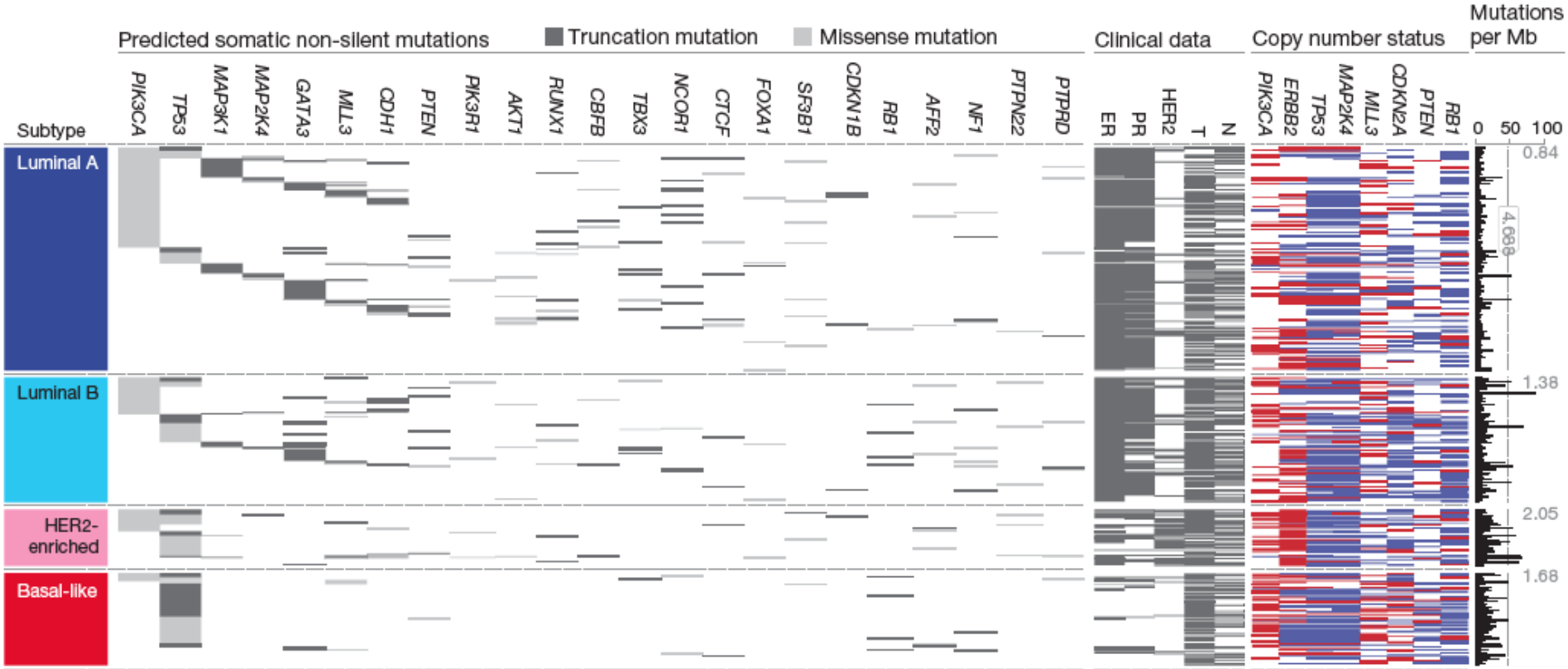
ARTICLE

doi:10.1038/nature11412

Diverse mutations of breast cancer subtypes

Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*



Subtype	PIK3CA	TP53	MAP3K1	MAP2K4	GATA3	MLL3	CDH1	PTEN	PIK3R1	AKT1	RUNX1	CBFB	TBX3	NCOR1	CTCF	FOXA1	SF3B1	CDKN1B	RB1	AFF2	NF1	PTPN22	PTPRD
All	36%	37%	8%	4%	11%	7%	7%	3%	3%	2%	4%	2%	3%	3%	3%	2%	2%	1%	2%	3%	3%	1%	2%
Luminal A	45%	12%	13%	7%	14%	8%	9%	4%	0.4%	4%	5%	2%	3%	5%	4%	2%	3%	1%	0.4%	1%	2%	0.4%	2%
Luminal B	29%	29%	5%	2%	15%	6%	5%	4%	2%	2%	2%	2%	4%	2%	2%	2%	0%	1%	3%	2%	4%	2%	4%
HER2-enriched	39%	72%	4%	2%	2%	7%	5%	2%	4%	2%	4%	2%	0%	0%	2%	2%	4%	2%	0%	5%	0%	5%	4%
Basal-like	9%	80%	0%	0%	2%	5%	0%	1%	0%	0%	0%	0%	1%	2%	1%	0%	1%	0%	4%	4%	2%	0%	1%

Percentages of cases with mutation by expression subtype

TCGA Nature 2012

Prognostic Marker

- valuable if provides extra information beyond that provided by clinicopathological features

- A prognostic marker
  - associated with clinical outcome irrespective of treatment given
    - tumour size, tumour grade, no. of positive lymph nodes

Sparano JA et al. Sur Oncol Clin N Am. 2010;19:581-606

Predictive Marker

- Predicts clinical benefit from a specific therapy
  - ER – endocrine therapy
  - HER2/neu over-expression –anti-HER2 directed therapies
- KRAS mutation for EGFR therapy
- Pathological complete response (pCR) to predict long-term survival – FDA program
- Some predictive markers also prognostic

Sparano JA et al. Sur Oncol Clin N Am. 2010;19:581-606

BIOMARKERS

Predictive factors to select patients for specific therapies

Prognostic factors to segregate patients into risk groups

Surrogate endpoints as measurements before, during and after treatment, used as a measure of disease activity to determine whether the treatment is working

Usual steps

1. Develop a "locked down" version of genomic classifier to identify patients likely to benefit
2. Determine the reproducibility/robust of measurement of the classifier/biomarker
3. With a pre-defined analysis plan using the completely specified classifier/ biomarker to design and/or analyze a new clinical trial to test the effectiveness

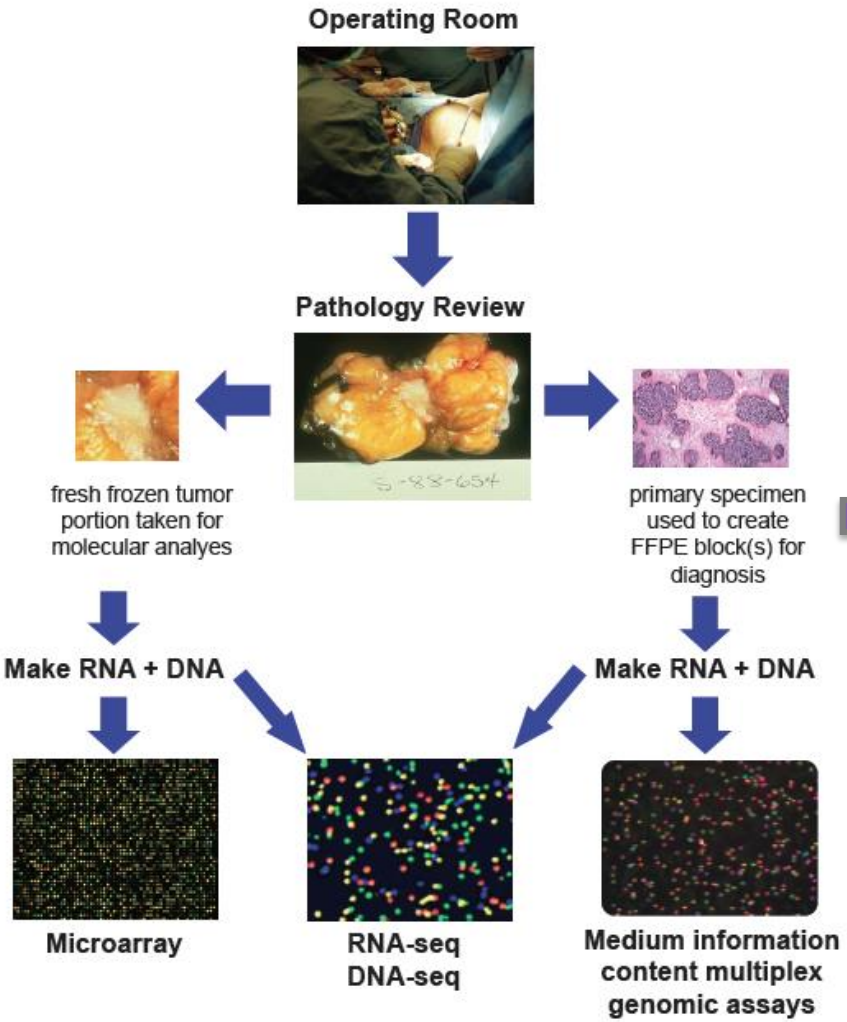
FDA Definition of "Biomarker"

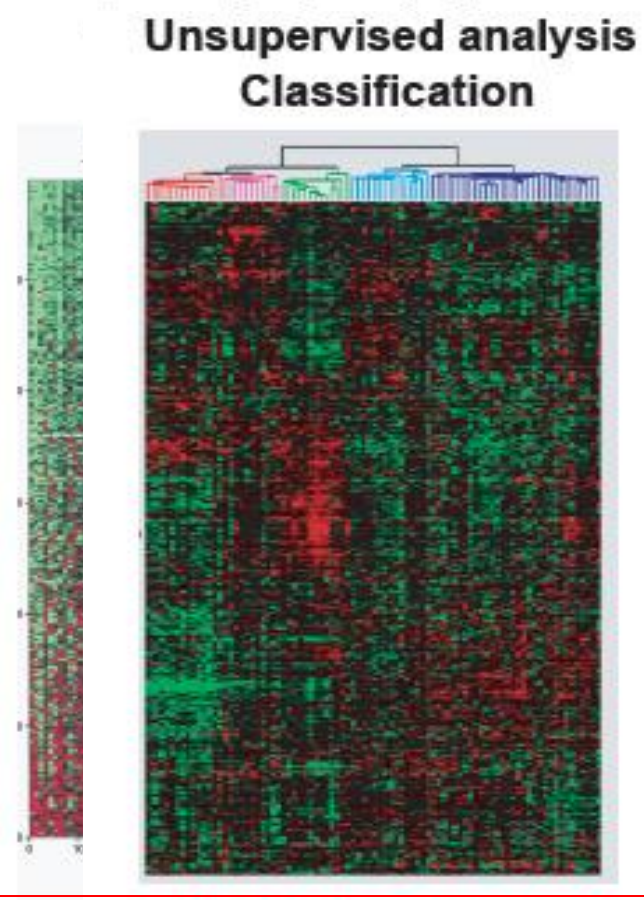
- A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Use of biomarkers

- Diagnosis
- Tool for staging disease
- Indicator of disease status
- Predict and/or monitor clinical response to an intervention

Overview of gene expression analysis of human breast tumors





Intrinsic subtypes classifier (Perou et al. *Nature* 2000; 406:747-752; Sorlie et al. *PNAS* 2001; 98:10869-10874)

1. OncotypeDX® recurrence score (Paik et al. *N Engl J Med* 2004)
2. MammaPrint® (Van't Veer et al. *Nature* 2002; 415:530-536)

Carey L, Cheang M and Perou C. Chapter 29 "Genomics, Prognosis and Therapeutic Interventions" of Diseases of the Breast, 5th edition, *In Press*

Courtesy of Maggie Cheang

Various Genomic Platforms

1)Immunohistochemical staining (IHC4)

2)Molecular Classification

3)Genomic Expression Profiligng Prognostic platform

4) Genomic Expression Profiling Immunomodulatory

5) Targeted sequencing

6) Whole exome (genome) sequencing

7) Big Data

-The Cancer Genome Atlas (TCGA)

Gene expression, Exome Sequencing, DNA copy number, miRNA expression, DNA methylation etc.

-Molecular Taxonomy of Breast Cancer International Consortium (METABRIC)

Cuzick et al. J Clin Oncol 2011

A Multi-gene Assay to Predict Recurrence of Tamoxifen-Treated Node-Negative Breast Cancer.
Paik et al., The New England Journal of Medicine, 351:2817-26 (2004)

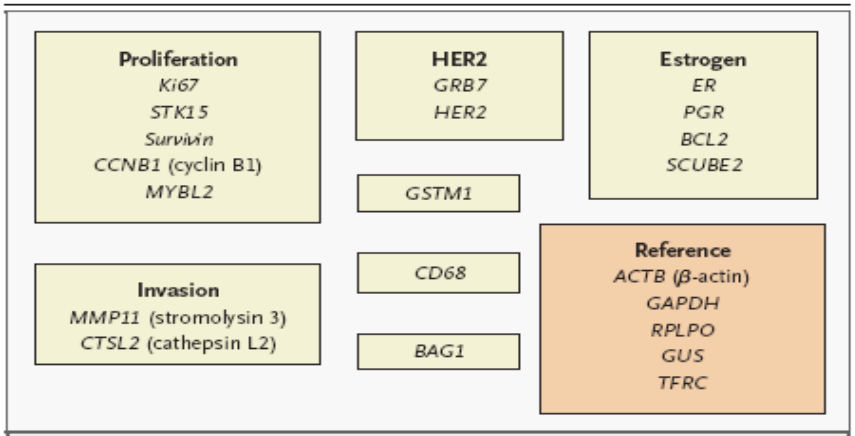
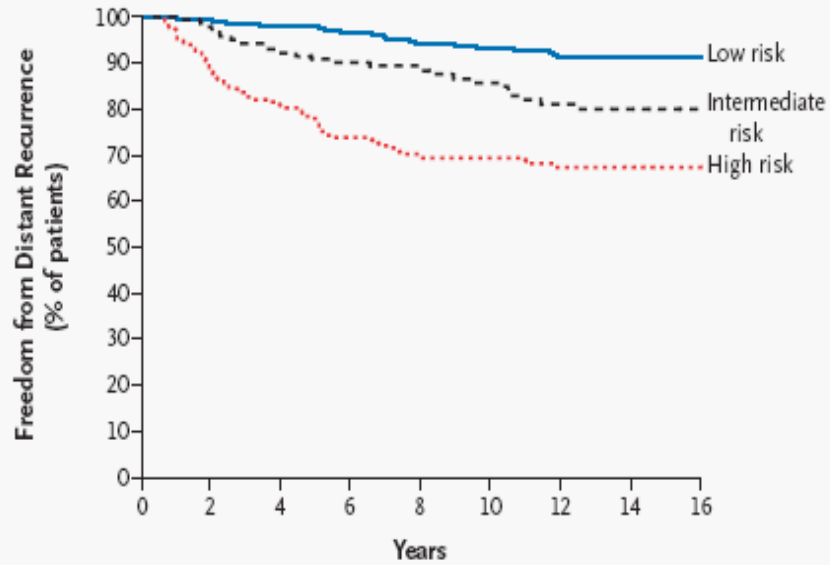


Figure 1. Panel of 21 Genes and the Recurrence-Score Algorithm.

The recurrence score on a scale from 0 to 100 is derived from the reference-normalized expression measurements in four steps. First, expression for each gene is normalized relative to the expression of the five reference genes (*ACTB* [the gene encoding β-actin], *GAPDH*, *GUS*, *RPLPO*, and *TFRC*). Reference-normalized expression measurements range from 0 to 15, with a 1-unit increase reflecting approximately a doubling of RNA. Genes are grouped on the basis of function, correlated expression, or both. Second, the *GRB7*, *ER*, proliferation, and invasion group scores are calculated from individual gene-expression measurements, as follows: *GRB7* group score = 0.9 × *GRB7* + 0.1 × *HER2* (if the result is less than 8, then the *GRB7* group score is considered 8); *ER* group score = (0.8 × *ER* + 1.2 × *PGR* + *BCL2* + *SCUBE2*) ÷ 4; proliferation group score = *Survivin* + *KI67* + *MYBL2* + *CCNB1* [the gene encoding cyclin B1] + *STK15*) ÷ 5 (if the result is less than 6.5, then the proliferation group score is considered 6.5); and invasion group score = (*CTSL2* [the gene encoding cathepsin L2] + *MMP11* [the gene encoding stromolysin 3]) ÷ 2. The unscaled recurrence score (RS_U) is calculated with the use of coefficients that are predefined on the basis of regression analysis of gene expression and recurrence in the three training studies[24-26]: RS_U = +0.47 × *GRB7* group score − 0.34 × *ER* group score + 1.04 × proliferation group score + 0.10 × invasion group score + 0.05 × *CD68* − 0.08 × *GSTM1* − 0.07 × *BAG1*. A plus sign indicates that increased expression is associated with an increased risk of recurrence, and a minus sign indicates that increased expression is associated with a decreased risk of recurrence. Fourth, the recurrence score (RS) is rescaled from the unscaled recurrence score, as follows: RS = 0 if $RS_U < 0$; RS = 20 × (RS_U − 6.7) if $0 \le RS_U \le 100$; and RS = 100 if $RS_U > 100$.



No. at Risk

Low risk	338	328	313	298	276	258	231	170	38
Intermediate risk	149	139	128	116	104	96	80	66	16
High risk	181	154	137	119	105	91	83	63	13

Figure 2. Likelihood of Distant Recurrence, According to Recurrence-Score Categories.

A low risk was defined as a recurrence score of less than 18, an intermediate risk as a score of 18 or higher but less than 31, and a high risk as a score of 31 or higher. There were 28 recurrences in the low-risk group, 25 in the intermediate-risk group, and 56 in the high-risk group. The difference among the groups is significant (P<0.001).

Gene Expression-based Clinical Assays 2013

Test	Approval or Endorsement	Predicting Prognosis	Predicting Treatment Benefit using Randomized Clinical Trials					Randomized Prospective Study
			General Chemo	Endocrine	Taxane	Anthrac.	Herceptin	
OncotypeDX® RT-PCR, FFPE	NCCN: Prediction of chemotherapy benefit	NSABP-B14	NSABP-B20 (+/- CMF) SWOG8814 (+/- CAF)	NSABP-B14	NSABP B28 (failed to predict a benefit)	NO	NO	TAILORx (node- to report 2014-15) RxPONDER (1-3 nodes, recruiting)
Prosigna® nCounter, FFPE	CE Mark, FDA: Prediction of 10-year DRFS in ER+, node 0-3, postmenop. treated with endocrine therapy	ATAC, ABCSG08	NO	NO	NO	NO	NO	NO
PAM50 research-based assay RT-PCR and microarray, FFPE and fresh	NA	NCIC-MA5, NCIC-MA12, GEICAM/9906, multiple non-randomized trial cohorts	NO	NCIC-MA12	GEICAM9906, CALGB 9342-9840 (low proliferation predicts weekly paclitaxel benefit)	NCIC-MA5 (CMF vs. CEF; epirubicin benefit in HER2E subtype only)	NOAH (HER2E benefits the most)	NO
Mammaprint® microarray, fresh and FFPE	FDA (fresh): risk for distant mets, <61 years, Stage I-II, tumor ≤5cm and node-negative	multiple non-randomized trial cohorts including RASTER	NO	NO	NO	NO	NO	MINDACT Prognosis validation (to report 2014-15)
EndoPredict® RT-PCR, FFPE	CE Mark	ABCSG06, ABCSG08, GEICAM9906	NO	NO	GEICAM9906 (failed to predict a benefit)	NO	NO	NO
Breast Cancer Index SM RT-PCR, FFPE	NO	ATAC, Stockholm, multiple non-randomized trial cohorts	NO	NO	NO	NO	NO	NO

Slide courtesy of C Perou (UNC)

Courtesy of Chuck Perou & Maggie Cheang

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Neoadjuvant Setting…

Accurate Prediction and Validation of Response to Endocrine Therapy in Breast Cancer

Arran K. Turnbull, Laura M. Arthur, Lorna Renshaw, Alexey A. Larionov, Charlene Kay, Anita K. Dunbier, Jeremy S. Thomas, Mitch Dowsett, Andrew H. Sims , and J. Michael Dixon

Arran K. Turnbull, Laura M. Arthur, Lorna Renshaw, Alexey A. Larionov, Charlene Kay, Jeremy S. Thomas, Andrew H. Sims, J. Michael Dixon, University of Edinburgh Cancer Research UK Centre, Edinburgh; Anita K. Dunbier, Mitch Dowsett, Institute of Cancer Research, London, United Kingdom; and Anita K. Dunbier, University of Otago, Dunedin, New Zealand.

Published online ahead of print at www.jco.org on June 1, 2015.

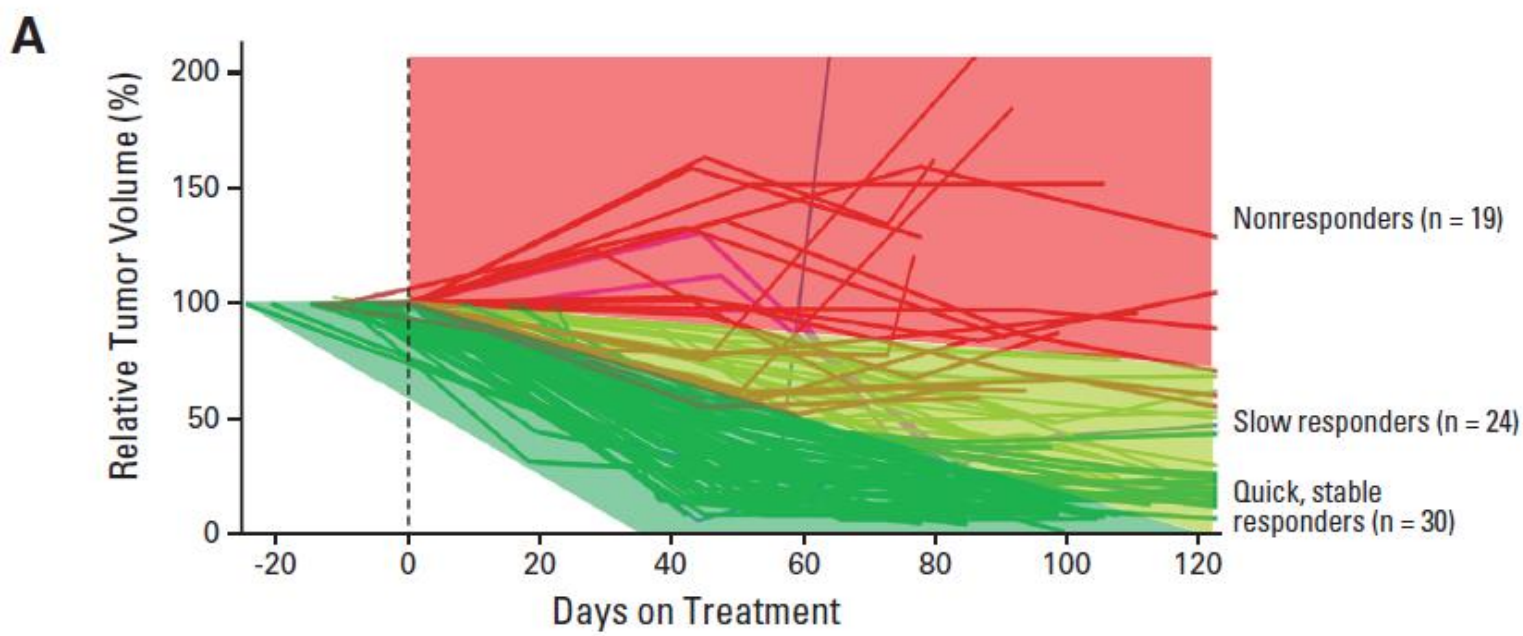
Supported by Breakthrough Breast

A B S T R A C T

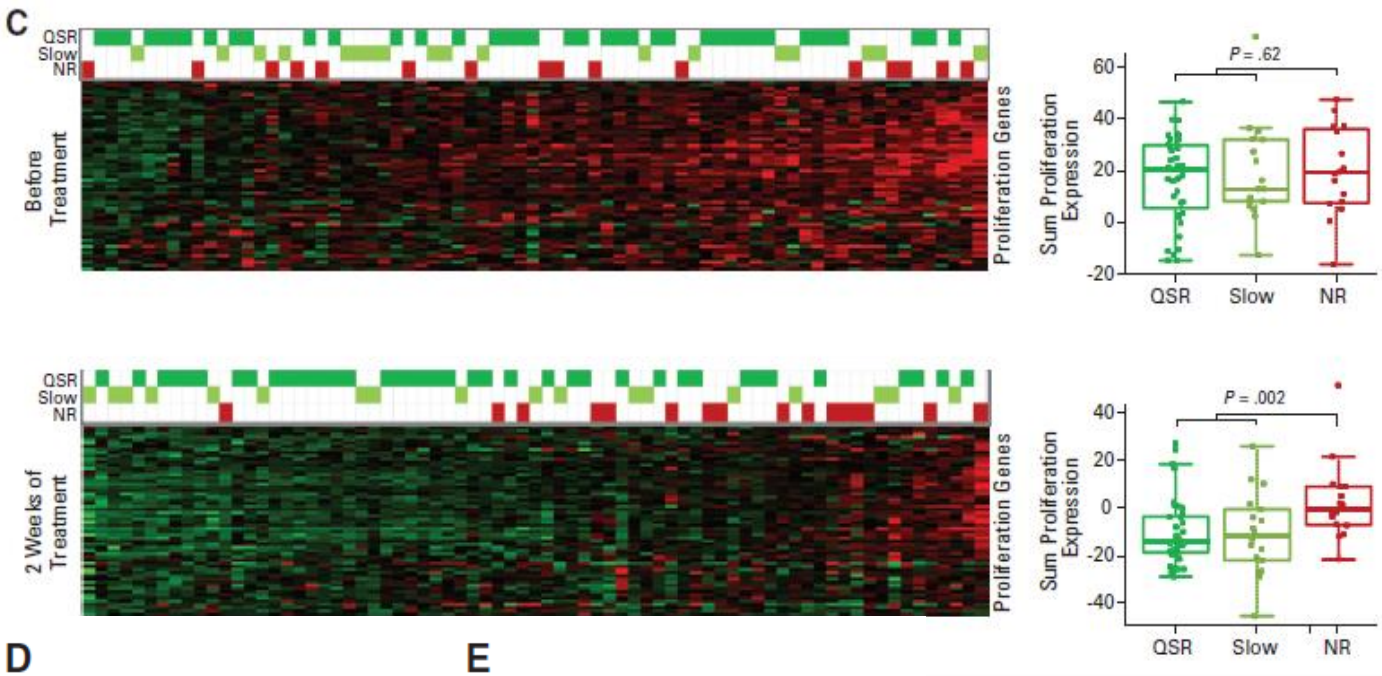
Purpose
Aromatase inhibitors (AIs) have an established role in the treatment of breast cancer. Response rates are only 50% to 70% in the neoadjuvant setting and lower in advanced disease. Accurate biomarkers are urgently needed to predict response in these settings and to determine which individuals will benefit from adjuvant AI therapy.

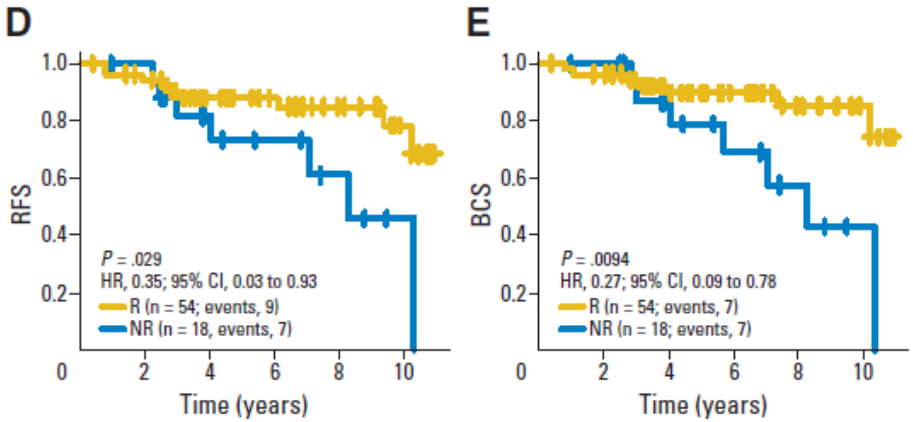
Patients and Methods
Pretreatment and on-treatment (after 2 weeks and 3 months) biopsies were obtained from 89 postmenopausal women who had estrogen receptor–alpha positive breast cancer and were receiving neoadjuvant letrozole for transcript profiling. Dynamic clinical response was assessed

Relative changes in breast tumour size measured by 3-dimensional ultrasound in BC patients receiving neoadjuvant letrozole...



A 4-gene predictive model to clinical response to AI by 2 wks is associated with clinical response





Deregulated immune and **apoptotic responses** before treatment and cell proliferation
that is not reduced 2 weeks after initiation of treatment are functional characteristics of breast tumors that do not respond to AIs

The molecular response to letrozole was characterized and a four-gene classifier of clinical response was established (accuracy of 96%) on the basis of the level of two genes before treatment (**one gene [*IL6ST*] was associated with immune signaling, and the other [*NGFRAP1*] was associated with apoptosis**) and the level of two proliferation genes (*ASPM*, *MCM4*) after 2 weeks of therapy. The four-gene signature was found to be 91% accurate in a blinded, completely independent validation data set of patients treated with anastrozole

Turnbull et al. J Clin Oncol 33:3370-2278, 2015

NIH Public Access
Author Manuscript
Nature. Author manuscript; available in PMC 2012 December 21.

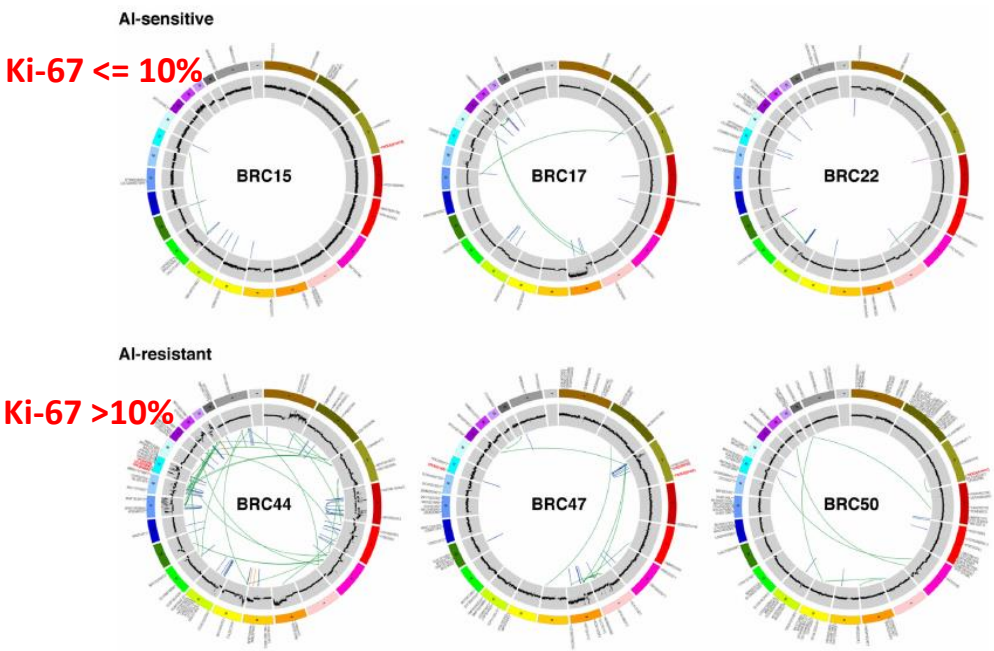
Published in final edited form as:
Nature. ; 486(7403): 353–360. doi:10.1038/nature11143.

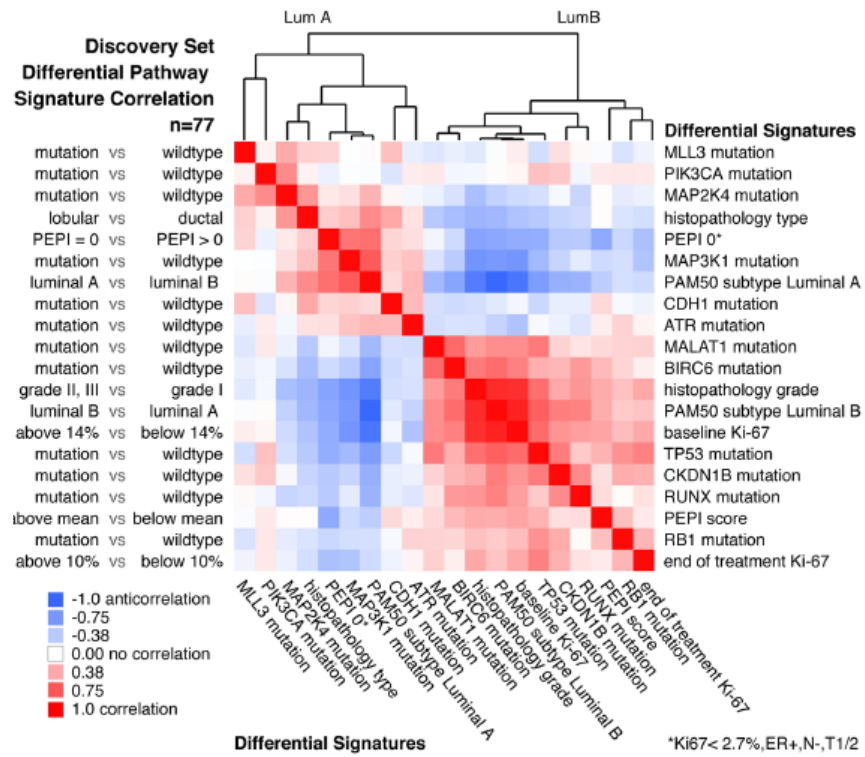
Neoadjuvant Setting…

Pathway signatures connections between mutations and clinical outcomes…low risk PEPI score cluster with luminal A subtype…

Whole Genome Analysis Informs Breast Cancer Response to Aromatase Inhibition

Matthew J. Ellis[1,2,5,*], Li Ding[3,4,*], Dong Shen[3,4,*], Jingqin Luo[5,6], Vera J. Suman[7], John W. Wallis[3,4], Brian A. Van Tine[1], Jeremy Hoog[1], Reece J. Goiffon[9,17,18], Theodore C. Goldstein[24], Sam Ng[24], Li Lin[1], Robert Crowder[1], Jacqueline Snider[1]. Karla Ballman[7]. Jason Weber[1,8,9], Ken Chen[3,4], Daniel C. Koboldt[3,4], Cyı
Schierding[3,4], Joshua F. McMichael[3,4], Christopher A. M

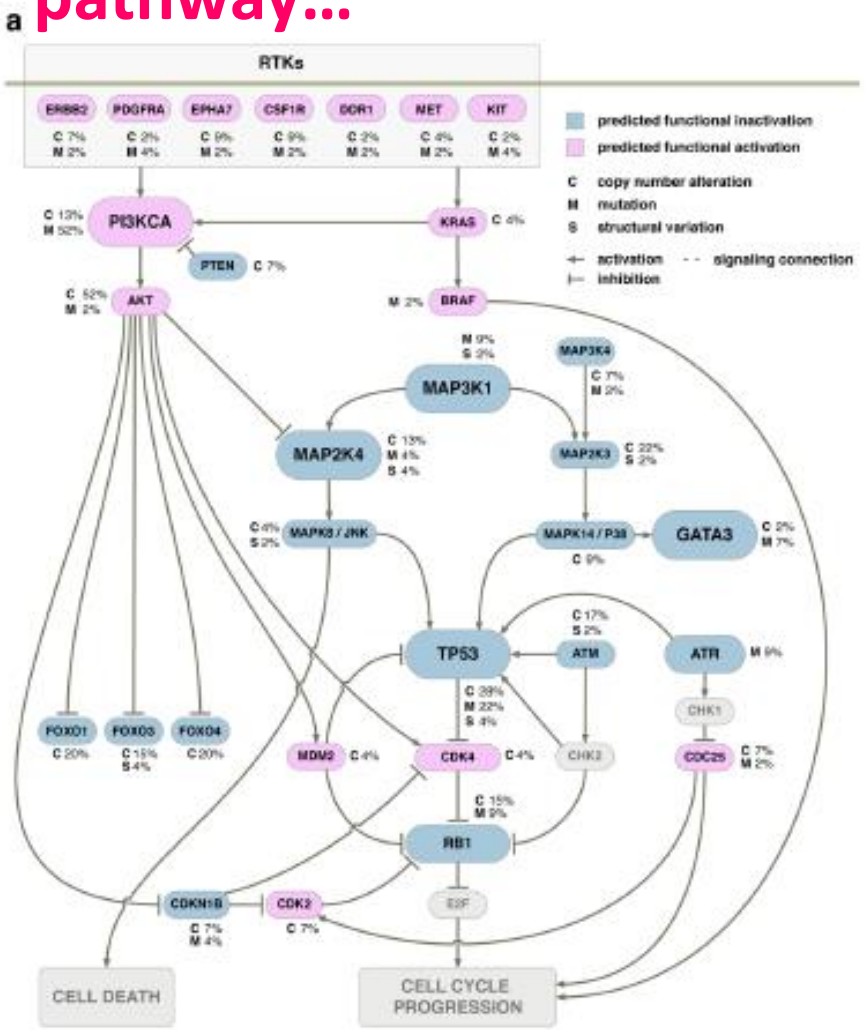


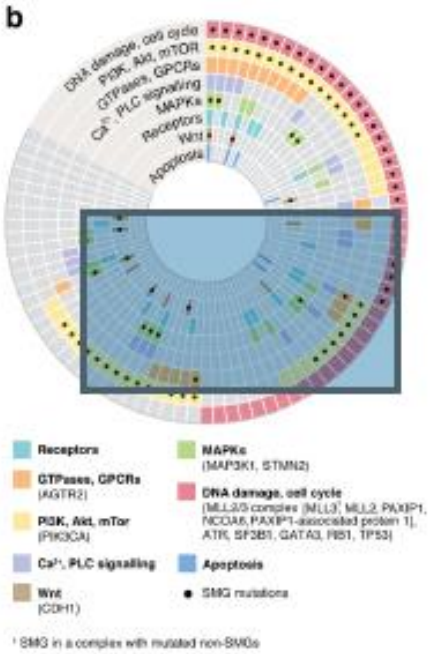


Genomic wide somatic mutations (WGA) and response to neoadj AI

Figure 5. Pathway signatures reveal connections between mutations and clinical outcomes

Difficult to identify the key mutation pathway in luminal BC– due to the inter-connectedness of the complicated network with too many ways to perturb a pathway…





Ellis et al. Nature 486:353-60, 2012

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Adjuvant Setting…

Genomic Index of Sensitivity to Endocrine Therapy for Breast Cancer

W. Fraser Symmans, Christos Hatzis, Christos Sotiriou, Fabrice Andre, Florentia Peintinger, Peter Regitnig, Guenter Daxenbichler, Christine Desmedt, Julien Domont, Christian Marth, Suzette Delaloge, Thomas Bauernhofer, Vicente Valero, Daniel J. Booser, Gabriel N. Hortobagyi, and Lajos Pusztai

From The University of Texas M. D. Anderson Cancer Center, Houston TX; Nuvera Biosciences, Woburn, MA; Institut Jules Bordet, Brussels, Belgium; Institut Gustave Roussy, Villejuif, France; General Hospital Leoben, Loeben; Medical University of Graz, Graz; and Medical University of Innsbruck, Austria.

Submitted January 28, 2010; accepted May 26, 2010; published online ahead of print at www.jco.org on August 9, 2010.

Supported by grants from the Commonwealth Foundation for Cancer Research to W.F.S., the National Cancer Institute (Grant No. 1-R21 CA118156-01A1) to W.F.S., the Breast Cancer Research Foundation to L.P. and W.F.S., the "Fonds National de la Recherche Scientifique" to C.S., the Ameri-

See accompanying editorial on page 4101

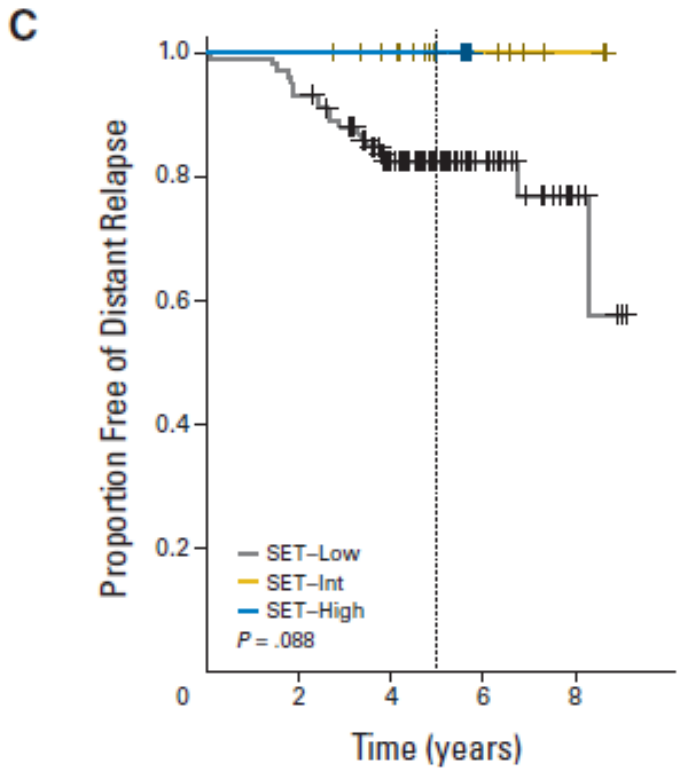
A B S T R A C T

Purpose
We hypothesize that measurement of gene expression related to estrogen receptor α (ER; gene name *ESR1*) within a breast cancer sample represents intrinsic tumoral sensitivity to adjuvant endocrine therapy.

Methods
A genomic index for sensitivity to endocrine therapy (SET) index was defined from genes coexpressed with *ESR1* in 437 microarray profiles from newly diagnosed breast cancer, unrelated to treatment or outcome. The association of SET index and *ESR1* levels with distant relapse risk was evaluated from microarrays of ER-positive breast cancer in two cohorts who received 5 years of tamoxifen alone as adjuvant endocrine therapy (n = 225 and 298, respectively), a cohort who received neoadjuvant chemotherapy followed by tamoxifen and/or aromatase inhibition (n = 122), and two cohorts who received no adjuvant systemic therapy

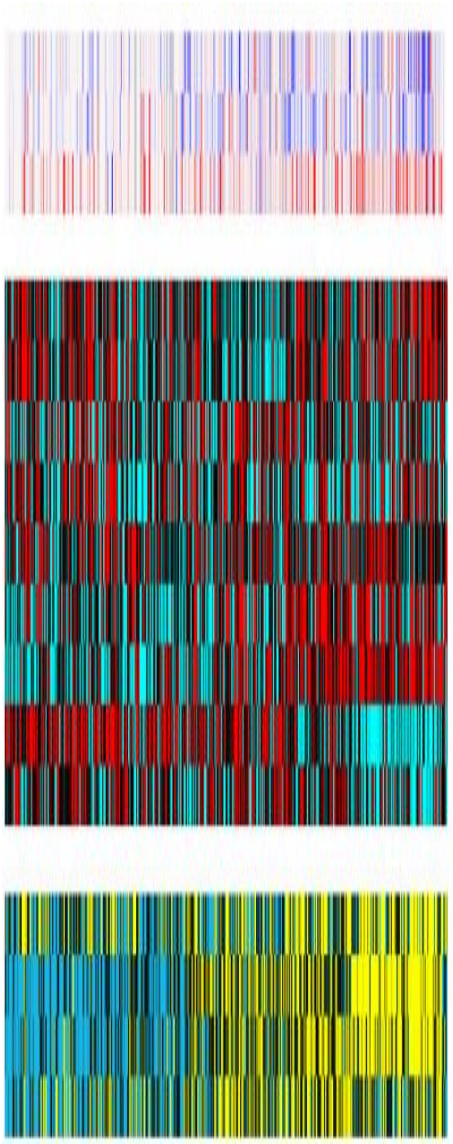
A genomic index for **sensitivity to endocrine therapy (SET) index** was defined from genes coexpressed with *ESR1* in 437 microarray profiles from newly diagnosed breast cancer, unrelated to treatment or outcome. The association of SET index and *ESR1* levels with distant relapse risk was evaluated from microarrays of ER-positive breast cancer in two cohorts who received 5 years of tamoxifen alone as adjuvant endocrine therapy (n 225 and 298, respectively.

The SET index of ER-related transcription predicted survival benefit from adjuvant endocrine therapy, not inherent prognosis. Prior chemotherapy seemed to enhance the efficacy of adjuvant endocrine therapy related to SET index



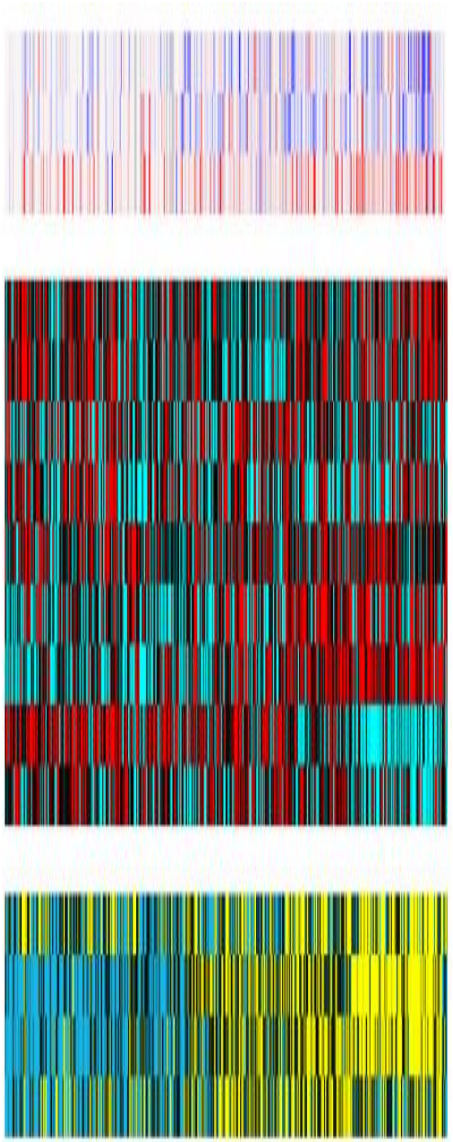
No. at risk					
SET–Low	100	94	65	29	7
SET–Int	16	16	14	7	3
SET–High	6	6	6	1	1

Added Value of Precision Medicine in the Genomic Era



- **"One-size"** does not fit all
- Identifying the right therapy or the right patient
  - Enhance clinical outcomes
  - Increase benefit : risk ratio
  - Accelerate new therapeutic development for breast cancer

Added Value of Precision Medicine in the Genomic Era



- New targets = new biomarkers
  - Efficient development of validated companion diagnostic markers essential
- Translational studies important to better understand reasons for success and failure, and to gain new insights in breast cancer biology that may provide new therapeutic opportunities

Emerging Treatment Options vs Challenges…

Cancers not limited to BC are highly dynamic evolutionary…

Ongoing linear and branching evolution results in **multiple simultaneous subclones** that may individually be capable of giving rise to episodes of disease relapse and metastasis. The dynamic clonal architecture is shaped by **mutation and competition between subclones in light of environmental selection pressures**, including those that are exerted by cancer treatments.

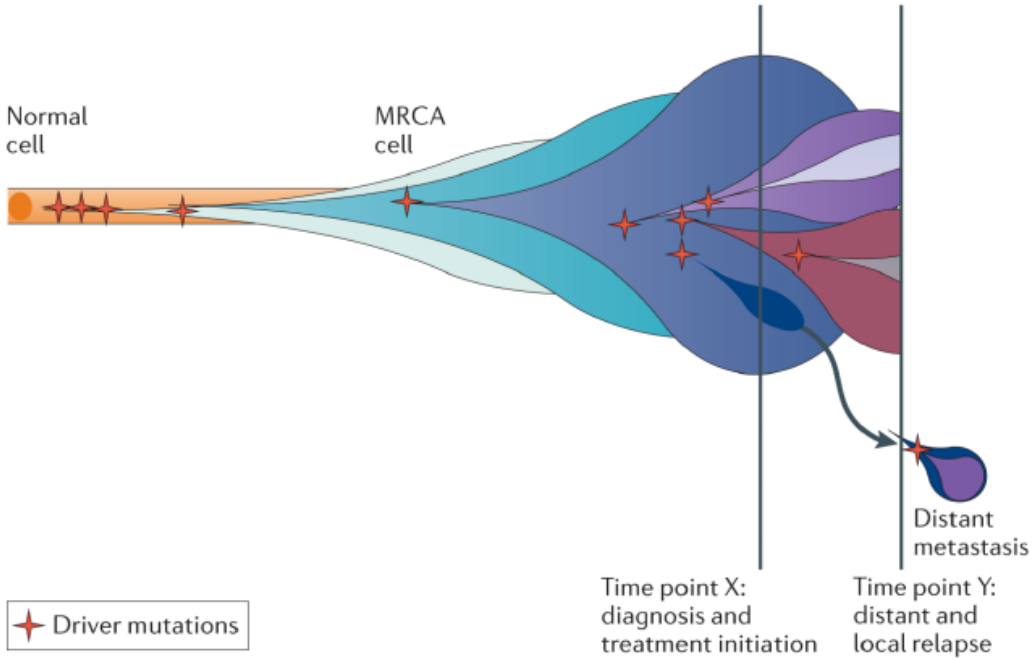


Figure 1. The evolution of clonal populations

Heterogeneity of Breast Cancer

- From a single common disease to many rare diseases
  - Intratumoral heterogeneity
    - How many populations? Hierarchy?
    - Primary vs relapsed/metastatic tumour samples
    - Solid biopsy vs liquid biopsy (CTCs, plasma DNA)
  - Intertumoral heterogeneity
    - How many tumours?
    - Molecular segmentation or granularity?
  - Heterogeneity of the host
    - immunity

Heterogeneity of Breast Cancer

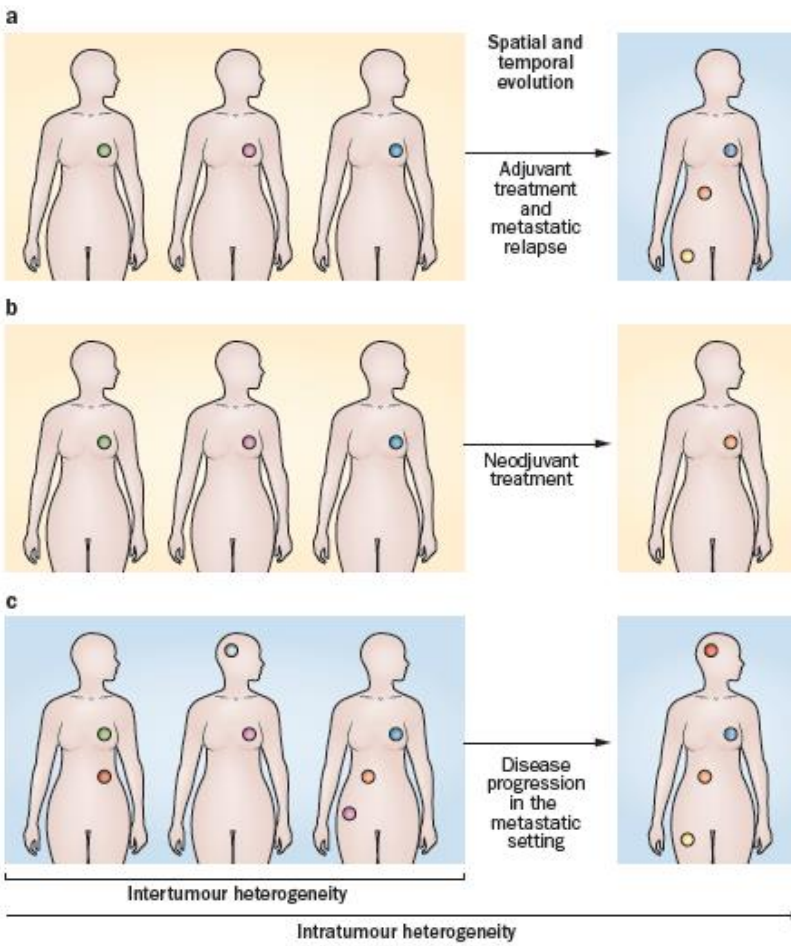


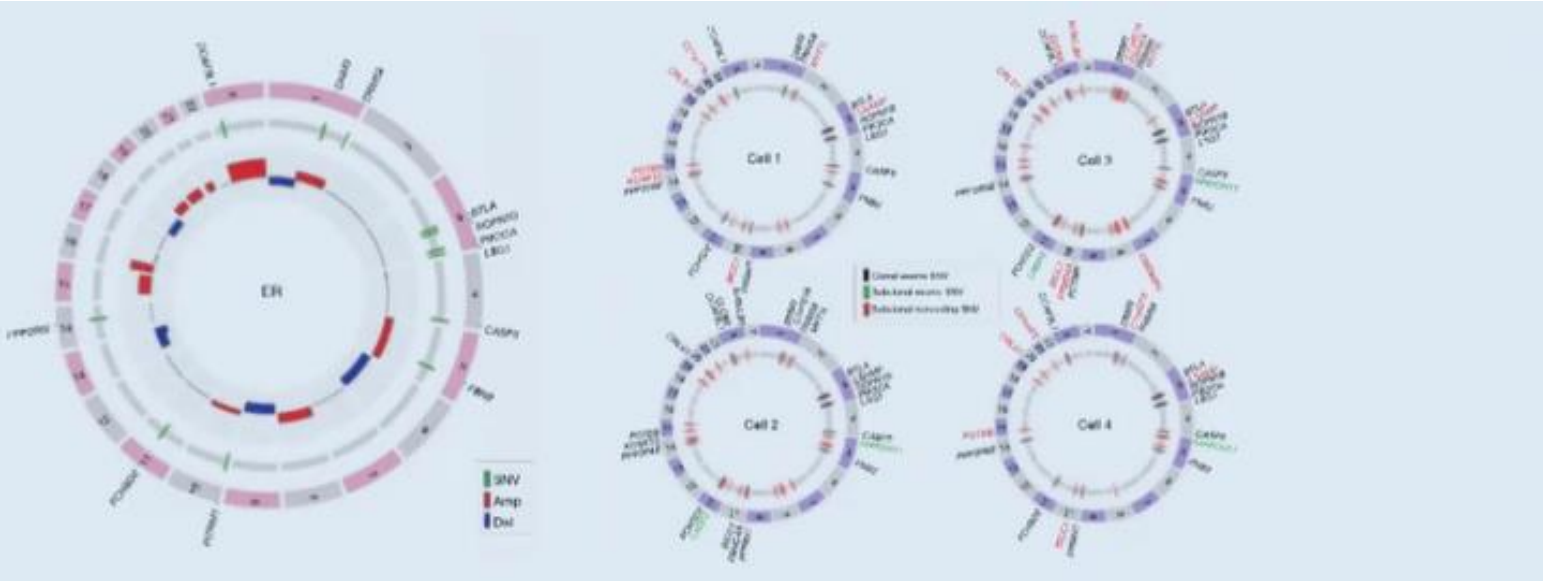
Table 4 | Clinical implications of tumour heterogeneity in breast cancer

Type of heterogeneity	Clinical implications	Potential solution
Intertumour	Need for patient stratification	High-throughput molecular profiling technique Molecular classifiers
	Need for therapy selection/clinical development of targeted agents	Innovative trial designs: Master protocols Basket trials Adaptive trial design N-of-1 studies
Intratumour	Need to define the phenotype of the recurrent disease	Metastatic biopsy
	Molecular evolution of the disease	Repeated tumour biopsies Geographically separated biopsies Liquid biopsies
	Identification of driver events	Next-generation sequencing Bioinformatic tools and algorithms Systems biology Animal models/functional validation
	Identification of predictive biomarkers	Deep sequencing Single-cell sequencing
	Emergence of treatment resistance	Combination of targeted agents Exploiting passenger events Eradicating the 'lethal close' Adaptive therapy Targeting the tumour microenvironment Cancer immunotherapy

Zardavas, Irrthum, Swanton & Picaart. Nat Rev Clin Oncol 12:381-394, 2015

Heterogeneity of Breast Cancer

- Tumour heterogeneity in breast cancer even occurs at single cell level



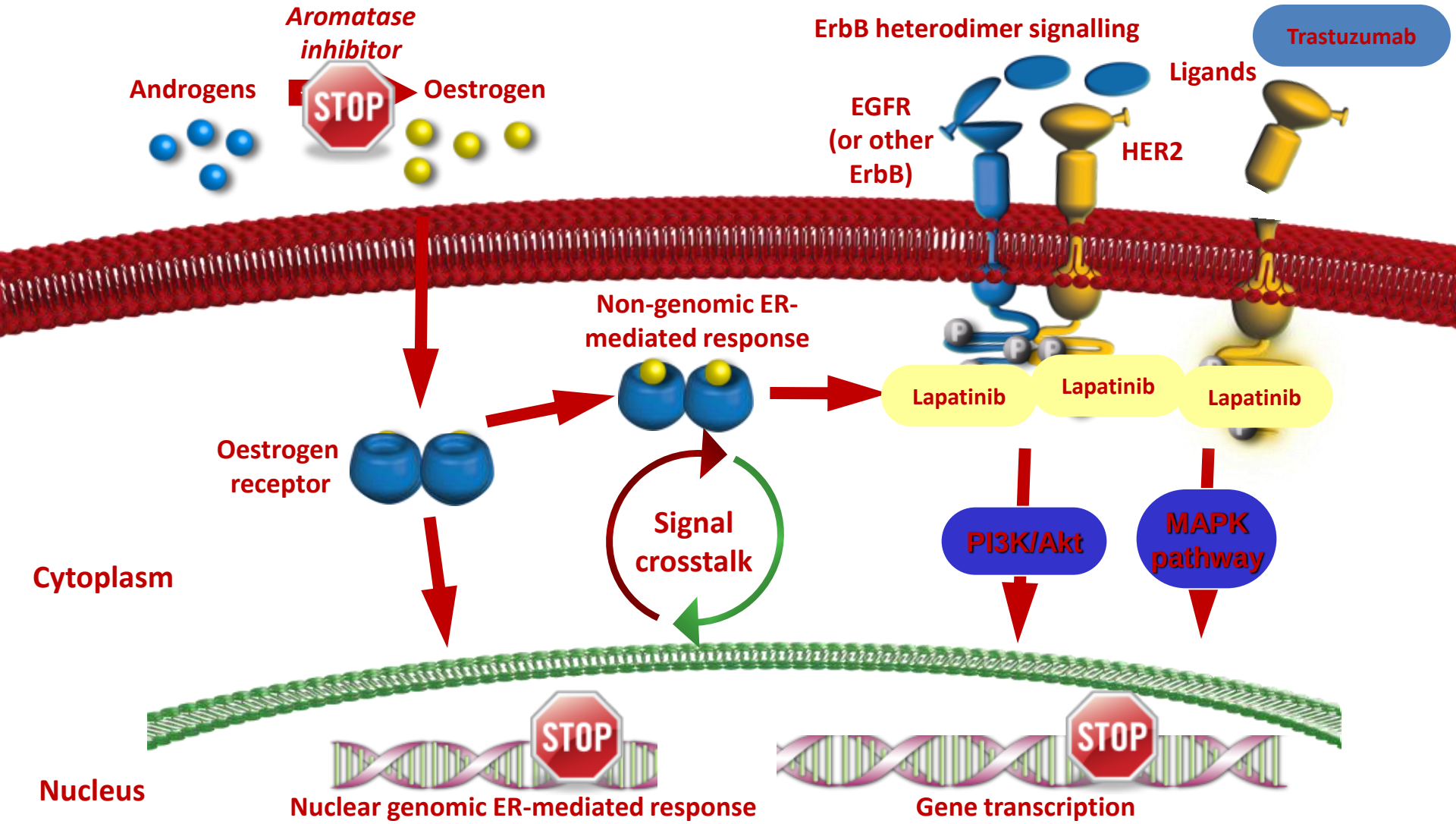
Nature 512:155-160, 2014

Change of ER/PgR & HER2 status

- 3-28% of all metastatic lesions will either loose or acquire ER expression.
- 3-25% of the patients will loose or acquire the HER2 overexpression or amplification.

J Natl Cancer Inst 93: 1441-6, 2001
Ann Oncol 13: 1036-43, 2002
Br J Cancer 93:552-6, 2005
Cancer 103: 1763-9, 2005

Overcoming Endocrine Resistance: Mode of Action in HER2+/HR+ Breast Cancer – Cross-talk between the ER and HER-2 pathways…



Adapted from Prat, Baselga. *Nat Clin Pract Oncol* 2008; **5**: 531-542.

Further New Challenges…

- The incidence of breast cancer is increasing
- The breast cancer patients are living longer
- Our research and clinical trials have proven success…
- ***Matching science with the affordability…***

  …the high expectation of the patient and the general public…

  patient classification, and selection for specific therapies

Proteomics in Clinical Trials

Basket Trials
-aim to test one drug or one particular genetic mutation across multiple organs.

FIGURE 9 | **GENOMICALLY BASED CLINICAL TRIALS**

One of the major uses of genomics in clinical research is in the design and execution of novel clinical trials. Two such types of trials are basket and umbrella trials. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, bone, colon, and stomach cancers. In the umbrella trial illustrated here, three different drugs are being tested against multiple genetic mutations (yellow, green, blue, and red dots) within lung cancer.

Umbrella Trials
-seek to test a drug or drugs across multiple genetic mutations within a particular type of cancer. For example, the I SPY-2 umbrella trial in breast cancer.

"Transforming lives through research", AACR (2014)

Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER)

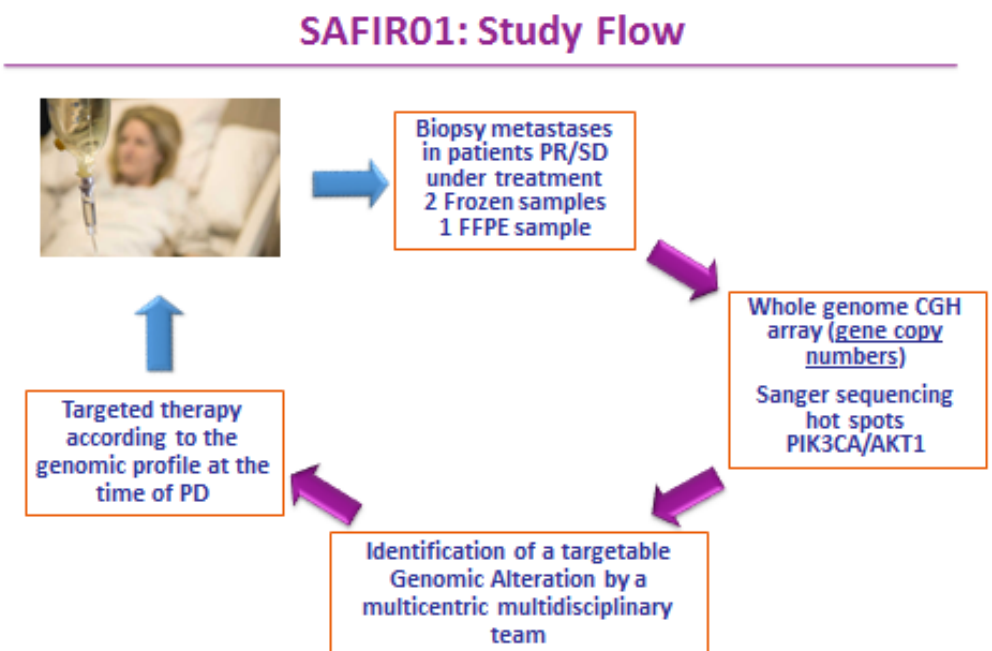
Fabrice André, Thomas Bachelot, Frederic Commo, Mario Campone, Monica Arnedos, Véronique Dieras, Magali Lacroix-Triki, Ludovic Lacroix, Pascale Cohen, David Gentien, Jose Adélaide, Florence Dalenc, Anthony Goncalves, Christelle Levy, Jean-Marc Ferrero, Jacques Bonneterre, Claudia Lefeuvre, Marta Jimenez, Thomas Filleron, Hervé Bonnefoi

Lancet Oncol 2014; 15: 267–74

Summary

Background Breast cancer is characterised by genomic alterations. We did a multicentre molecular screening study to identify abnormalities in individual patients with the aim of pro genomic alterations.

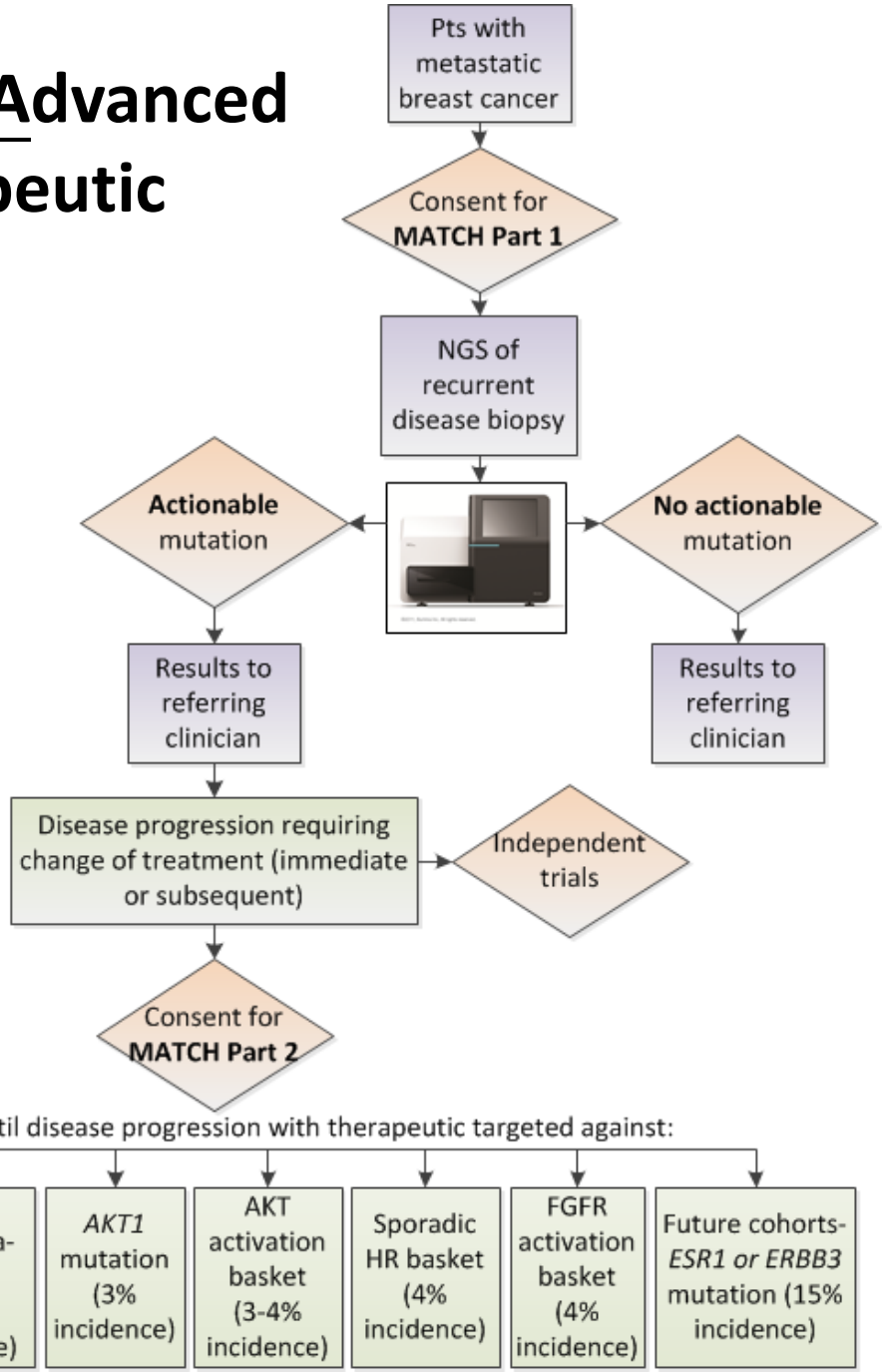
Methods From June 16, 2011, to July 30, 2012, we recruited patients w for biopsy in 18 centres in France. Comparative genomic hybridi *PIK3CA* (exon 10 and 21) and *AKT1* (exon 4) were used to assess met targets were decided on the basis of identified genomic alteration



The UK Molecular profiling of Advanced breast cancer to inform Therapeutic Choices (MATCH study)

Clinical Leads: Dr Nicholas Turner (Royal Marsden) & Dr Alistair Ring (Brighton and Sussex)
Molecular Sequencing Lead: Dr David Gonzalez de Castro (Institute of Cancer Research / Royal Marsden)
Methodology Lead: Prof Judith Bliss (ICR-CTSU)

Proposed funders: applications under review by Breakthrough Breast Cancer & Cancer Research UK
Proposed pharmaceutical partners: AstraZeneca



NHS National Institute for Health Research Clinical Research Network
The ROYAL MARSDEN
ICR The Institute of Cancer Research
CANCER RESEARCH UK
BREAKTHROUGH BREAST CANCER
AstraZeneca

Courtesy of Stephen Johnston

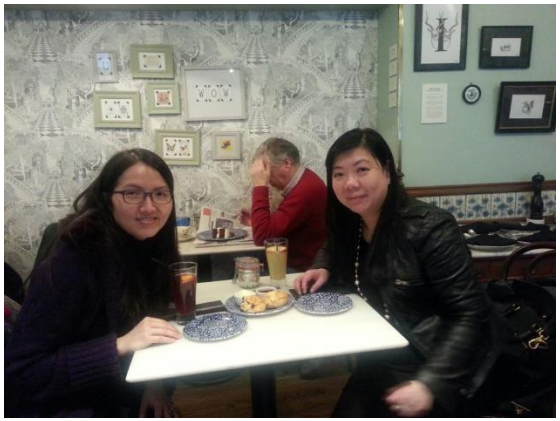
Conclusion

- We have entered the genomic era where we are one step forward to further enhancement of personalized medicine and precision medicine.
- Clinical validity is demonstrated yet awaiting the prime time for clinical utility with demonstration of clinically meaningful benefit.
- Basket trial or umbrella trial should be the - trend with prospective L-T FU with mutational analysis.

Conclusion

- There are emerging new technologies with liquid biopsy (CTCs, ctDNA), leading to potential serial and non-invasive mutational analyses, likely to become available in the near future.
- Efforts to realize the dream **of personalized treatment for breast cancer** will include drug development and intelligent design of clinical trials for increasingly small subgroup of patients with specific host and disease characteristics.

Acknowledgements



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Emerging Treatment Options in the Genomic Era

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