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Centre for Medical Ethics and Law

Precision Medicine: Legal & Ethical Challenges

Precision Medicine for Cancer Care -Prime Time versus Provocation Treat ?

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Disclosures

- Janice Tsang

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

Cancer is an aging disease...

- CANCER is an aging disease, though the shared mechanisms underpinning the two processes remain unclear.
- *Genomic instability* is a hallmark of both aging and carcinogenesis
- The incidence of cancer increases with age:
  - exploitation of large-scale population screening programs
  - the improvement of diagnostic capacities worldwide

Agostar B et al. The management of cancer in the elderly: targeted therapies in oncology. Immunity & Aging. 2008 Dec 30;5:16. doi: 10.1186/1742-4933-5-16.

Conventional Cancer Treatment

- The MAINSTAY of treatment for cancer in the old days:
  - Surgery
  - Radiotherapy
  - Chemotherapy

Not curative for metastatic disease

Locoregional side effects,
Palliative for advanced disease

Systemic side effects,
Only adjunct in most cases

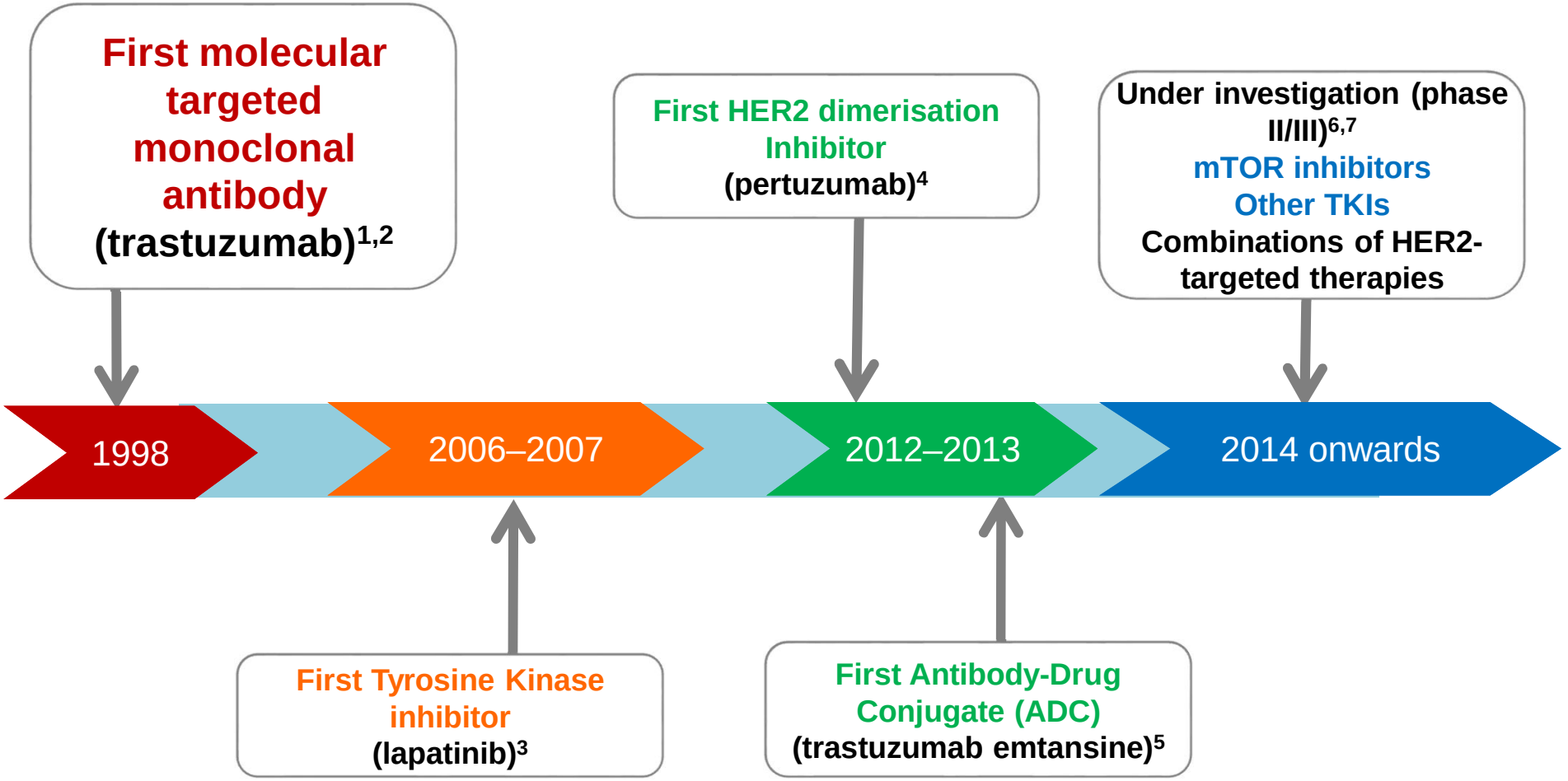
Summary of Molecular Targeted Therapy -over the last 2 decades...

Cancer Type	Targeted Therapies
CML	Imatinib, Sunitinib, Dasatinib, Nilotinib...
Other Haemic Malignancies	Rituximab, Alemtuzumab, Bortezomib...
Breast Cancer	Trastuzumab, Lapatinib, Pertuzumab, TDM-1, Everolimus, Palbociclib (anti-CDK 4/6)
Colorectal Cancer	Bevacizumab, Cetuximab, Panitumumab...
Hepatocellular Carcinoma	Sorafenib, Bevacizumab...
Lung Cancer (NSCLC)	Gefitinib, Erlotinib, Bevacizumab,Crizotinib, PDL-1 immunotherapy..
Pancreatic Carcinoma/ CholangioCa	Erlotinib, Bevacizumab...
Renal Cell Carcinoma	Bevacizumab, Sunitinib, Sorafenib, Temsirolimus, Everolimus, Pazopanib, Axitinib...
Gastrointestinal Stromal Tumour	Imatinib, Sunitinib...

Agostar B et al. The management of cancer in the elderly: targeted therapies in oncology. Immunity & Aging. 2008 Dec 30;5:16. doi: 10.1186/1742-4933-5-16.

Where we are today and where we hope to be tomorrow…

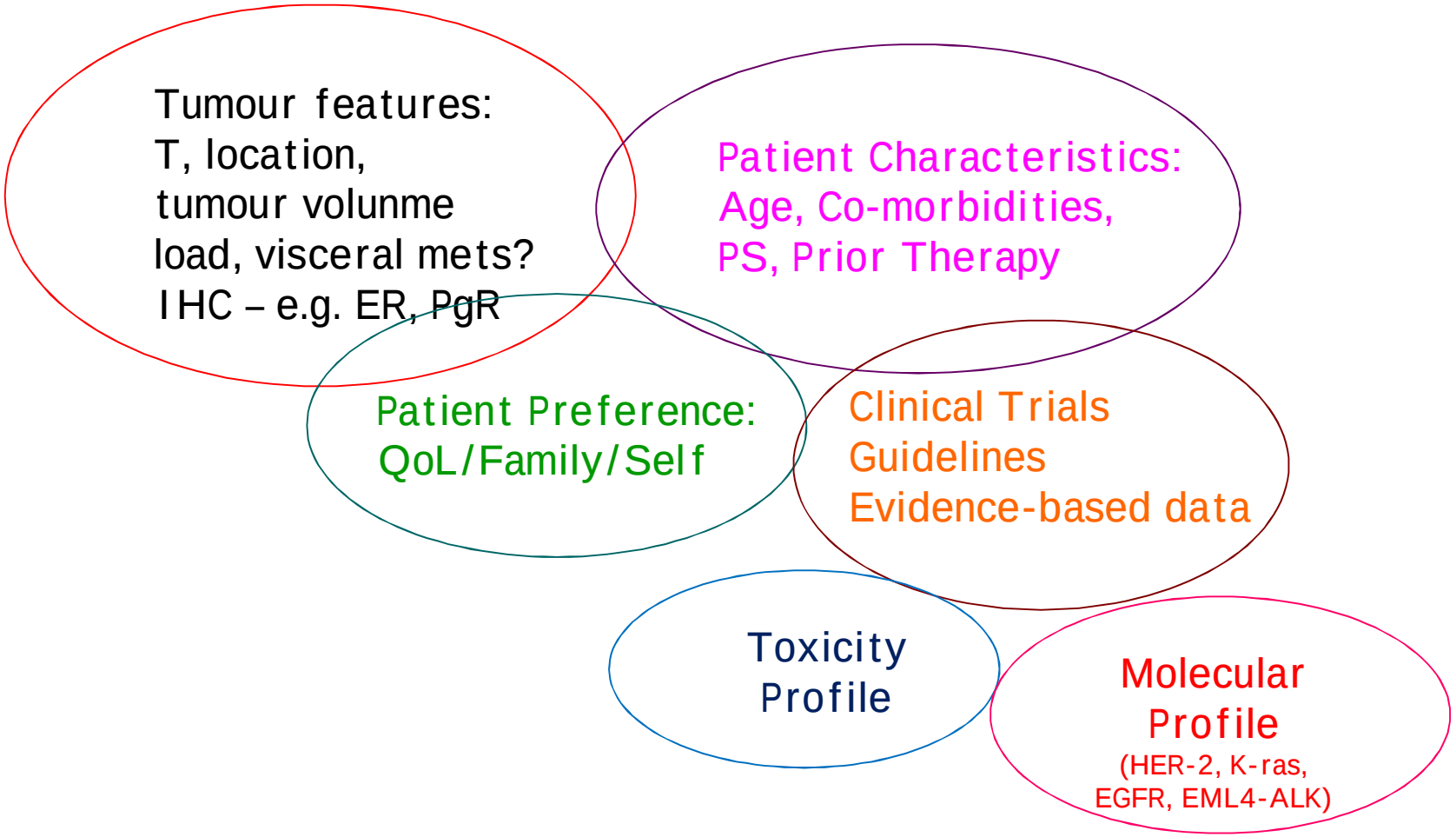
– using Breast Cancer as an illustration

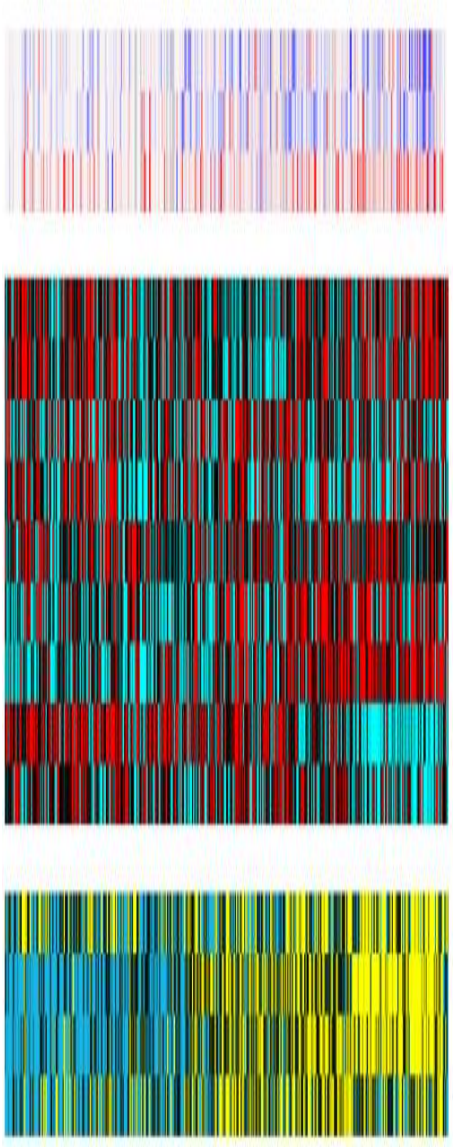


* Only first approved indications in mBC are shown here.

1. Slamon DJ, *et al. N Engl J Med* 2001; 344:783- 792; 2. Marty M *et al. J Clin Oncol 2005*; 23:4265- 4274;
3. Geyer C *et al*. *N Engl J Med* 2006; 355:2733-43; 4. Baselga J *et al*. *N Engl J Med* 2012;366:109-19;
5. Verma et al. N Engl J Med. 2012 Nov 8;367:1783–1791. Erratum in: N Engl J Med. 2013 ;368:2442; 6.Gradishar. Ann Oncol. 2013;24:2492–2500; 7. Perez EA& Spano JP. Cancer. 2012;118:3014–3025

Decision Making in Cancer Treatment



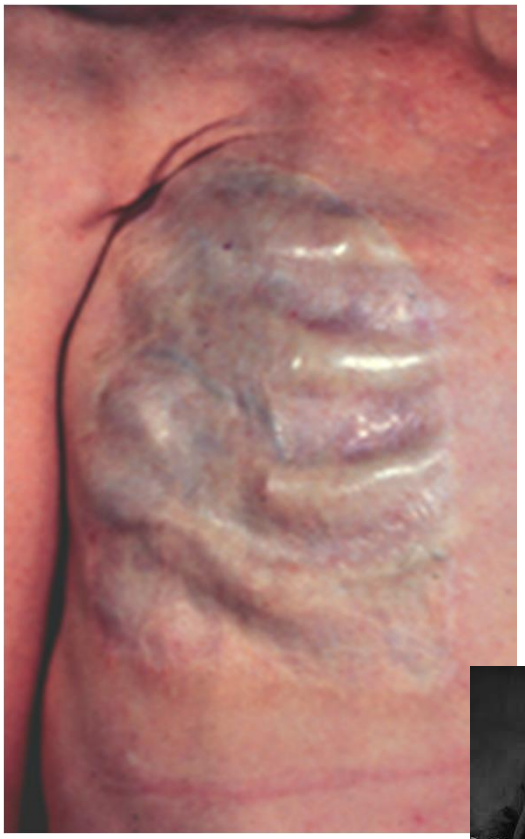


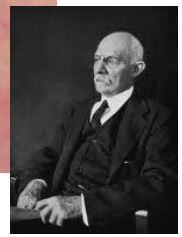
Background

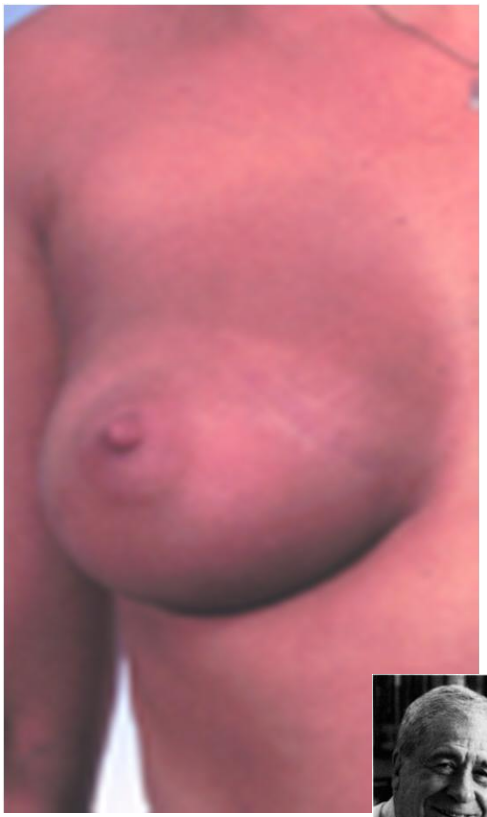
- Results of our translational research in the last decade, have revolutionized our understanding of breast cancer as a heterogeneous disease:
- Genomics and transcriptomics have been helping to narrow down the number of candidate oncogenes -“One-size-fits-all” approach becomes less relevant

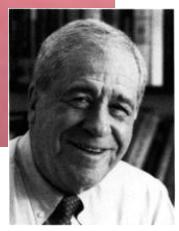
HKBOG
Hong Kong
Breast
Oncology Group

Changing Portraits of Breast Cancer



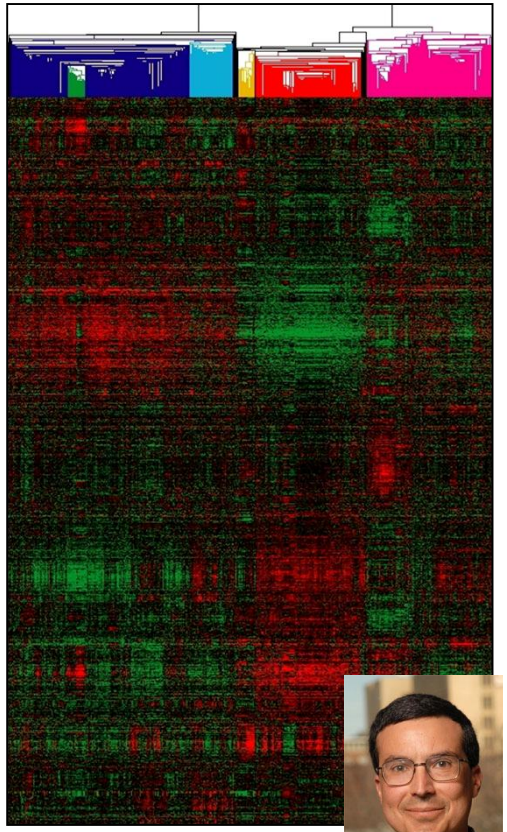


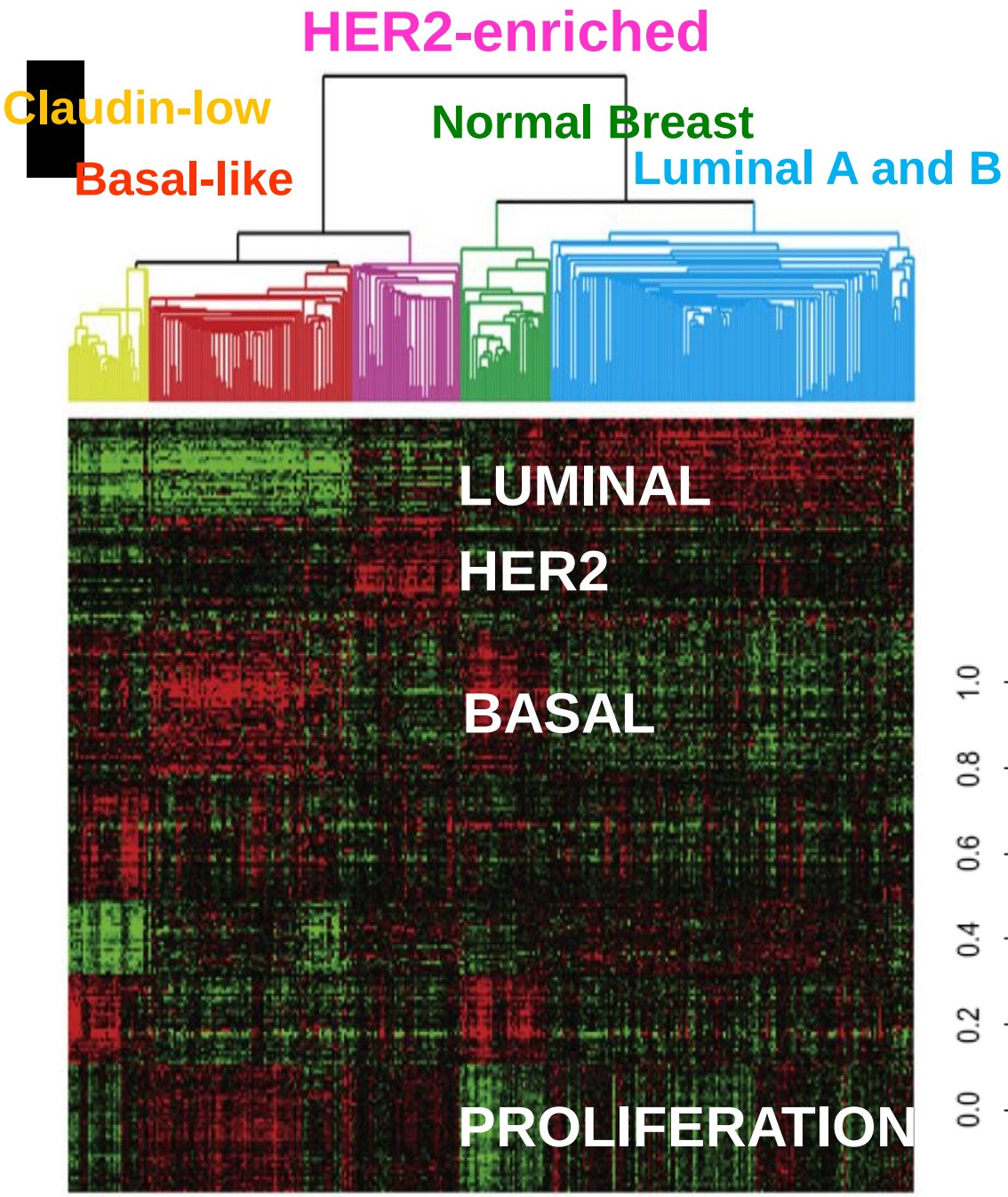




claudin low

Lum A Lum B Basal Her2

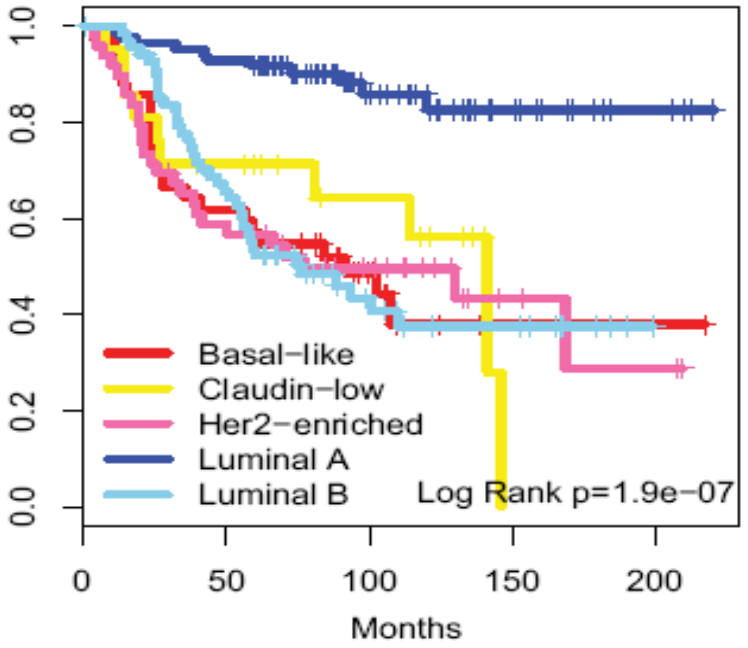




Intrinsic Subtypes

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



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
    - HER2 amplified/overexpressed breast cancer

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

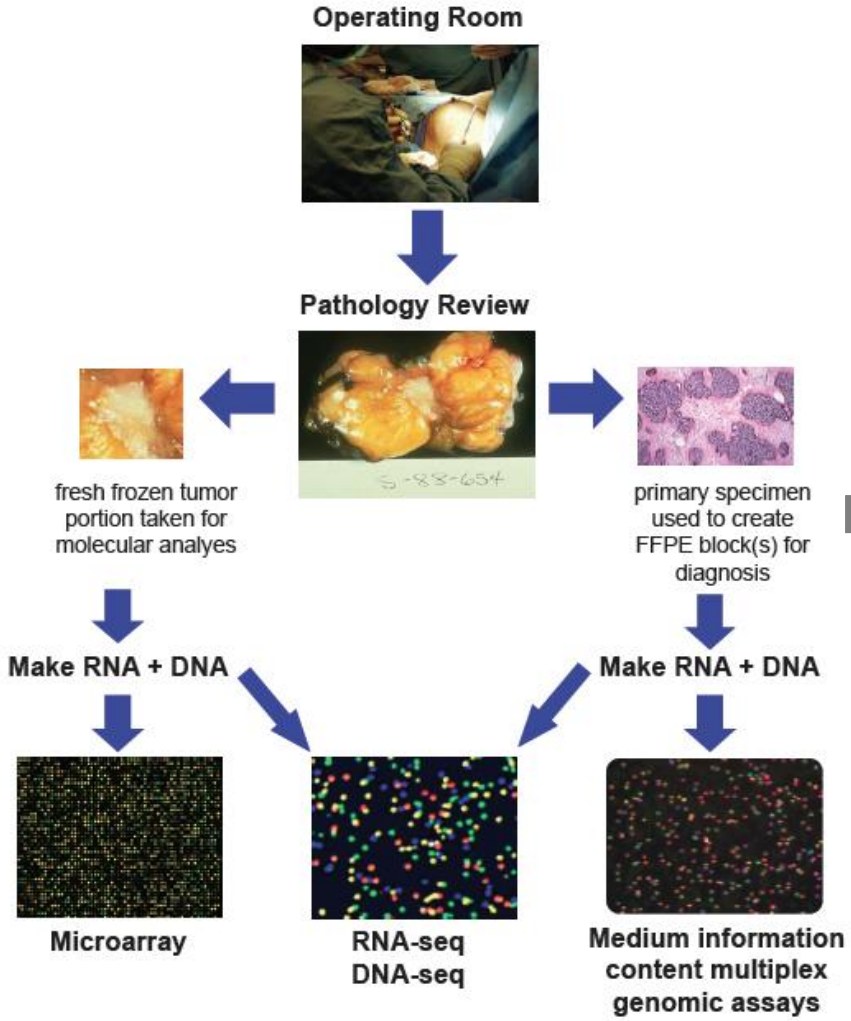
FDA Definition of “Biomarker”

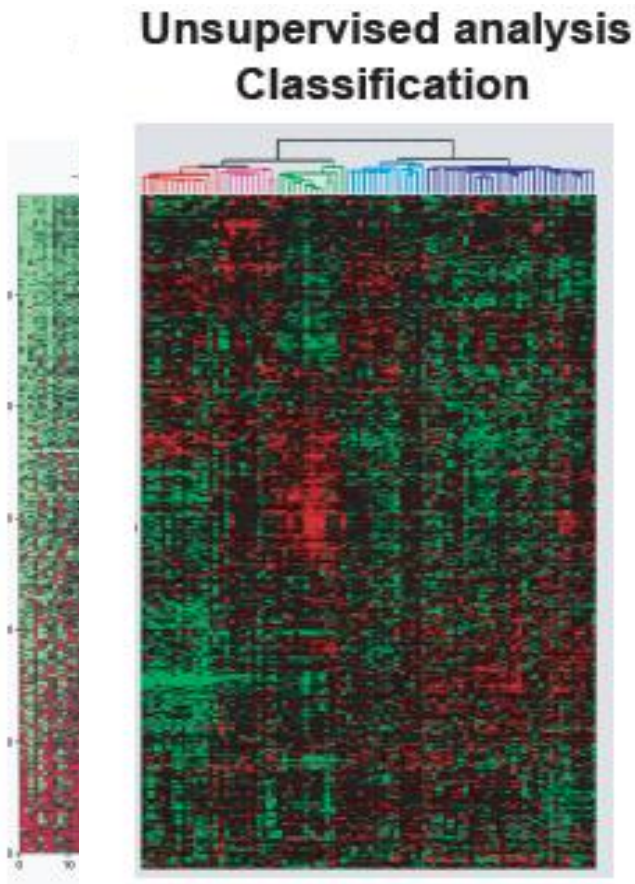
- A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

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 tumours





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

Intrinsic subtypes classifier

Examples:

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

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

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

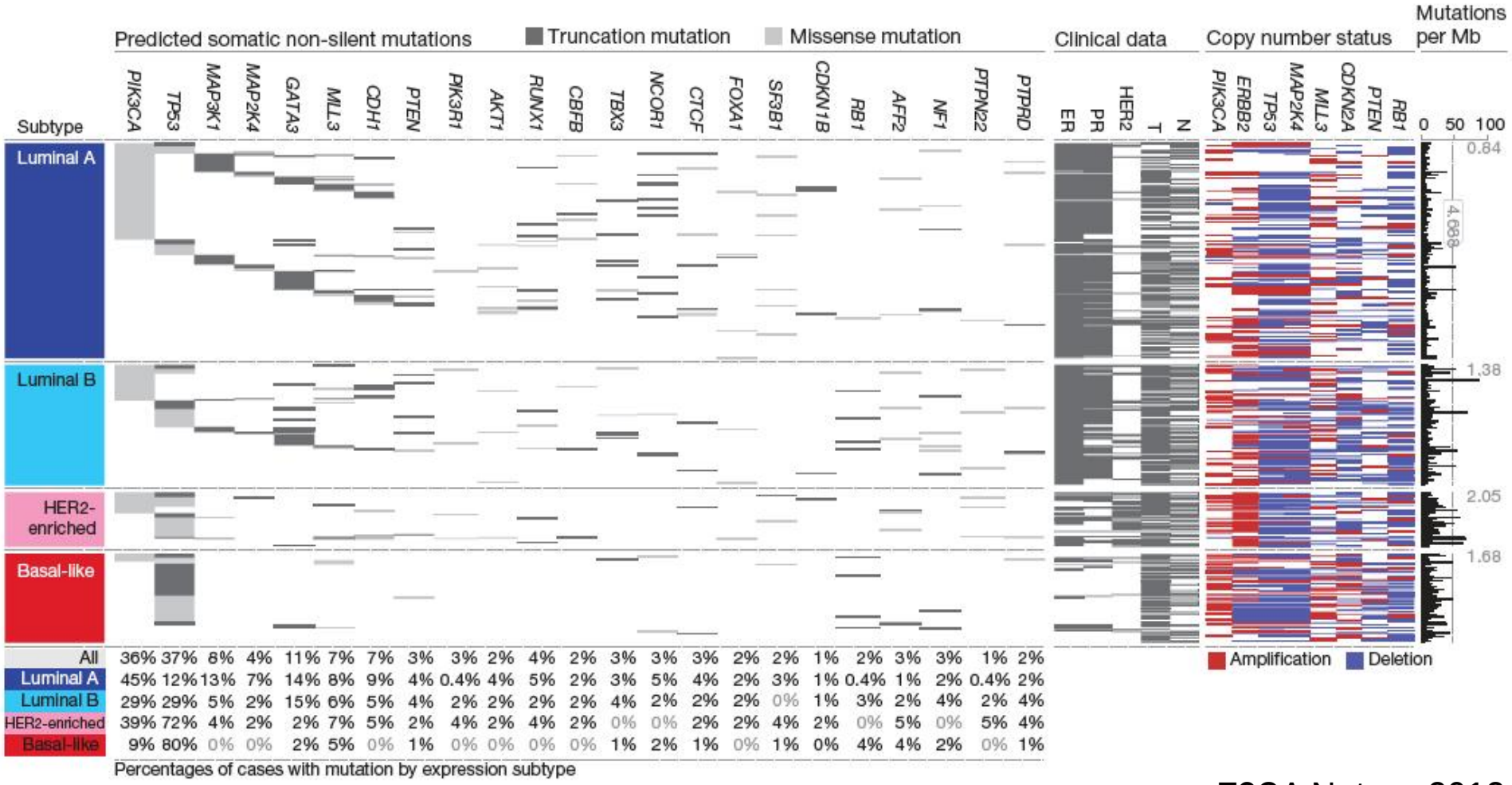
ARTICLE

doi:10.1038/nature11412

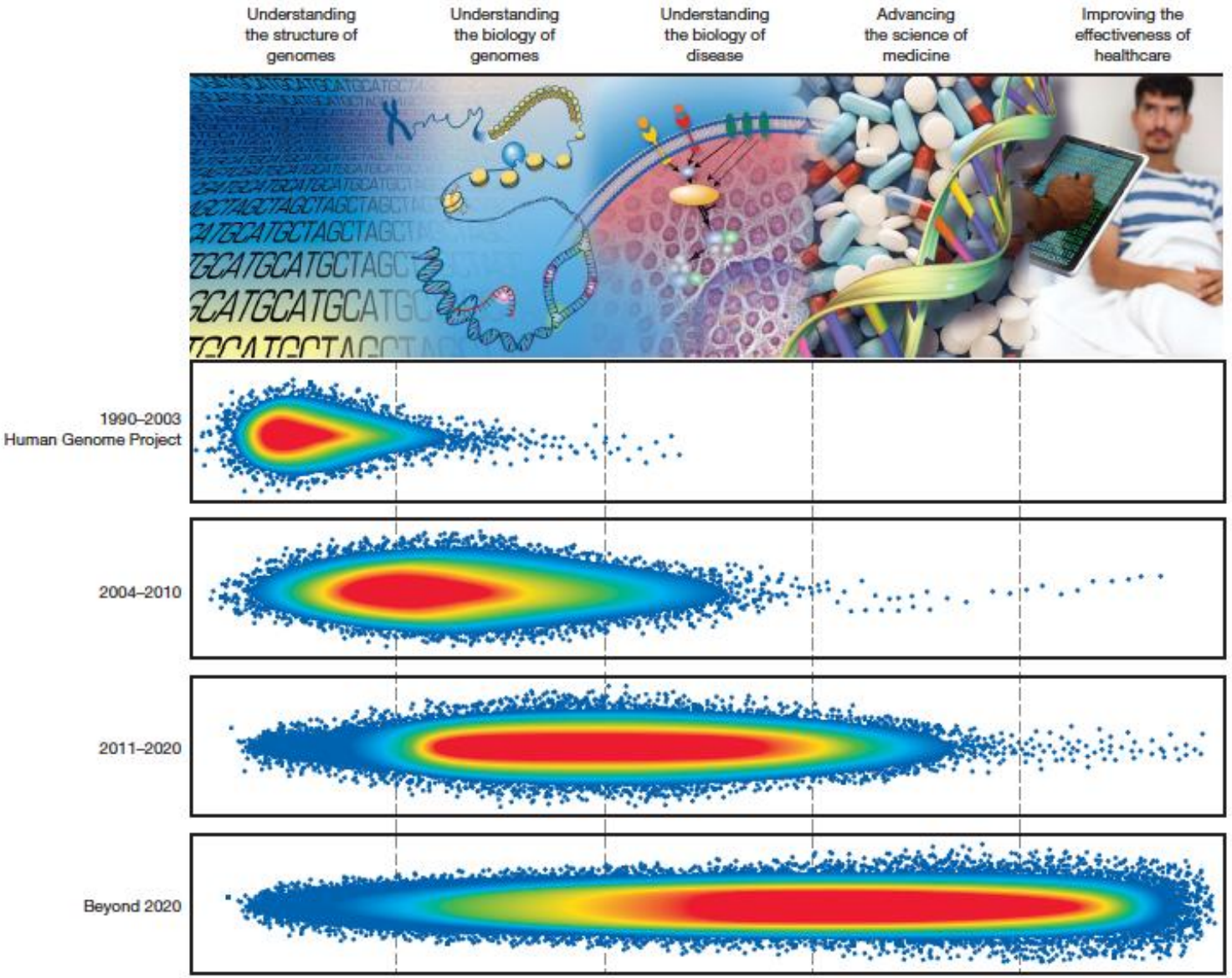
Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

Diverse mutations of breast cancer subtypes



TCGA Nature 2012



Green et al. Nature 2011 470: 204: 213

Evolution of Prediction Tools in breast cancer clinics...

- We know chemotherapy reduces **relative risk** of death by 30 – 40%
- In ER +ve disease endocrine therapy can have at least as great an effect as chemotherapy
- Can we identify groups where a reduction of a small **absolute risk** is not worth the risks / side effects of treatment?

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age: 50

Comorbidity: Perfect Health

ER Status: Negative

Tumor Grade: Grade 3

Tumor Size: > 5.0 cm

Positive Nodes: 4 - 9

Calculate For: Mortality

10 Year Risk: 79 Prognostic

Adjuvant Therapy Effectiveness

Horm: Tamoxifen (Overview 2000)

Chemo: CA*4 then T*4

Hormonal Therapy: 0

Chemotherapy: 38

Combined Therapy: 38

No additional therapy:

20.3 alive in 10 years.

78.6 die of cancer.

1.1 die of other causes.

With hormonal therapy: Benefit = 0.0 alive.

With chemotherapy: Benefit = 17.3 alive.

With combined therapy: Benefit = 17.3 alive.

Print Results PDF | Access Help and Clinical Evidence

Images for Consultations

How should you advise this patient?

Adjuvant! for Breast Cancer (Version 8.0)

Patient Information

Age: 60

Comorbidity: Perfect Health

ER Status: Positive

Tumor Grade: Grade 2

Tumor Size: 2.1 - 3.0 cm

Positive Nodes: 0

Calculate For: Mortality

10 Year Risk: 17 Prognostic

Adjuvant Therapy Effectiveness

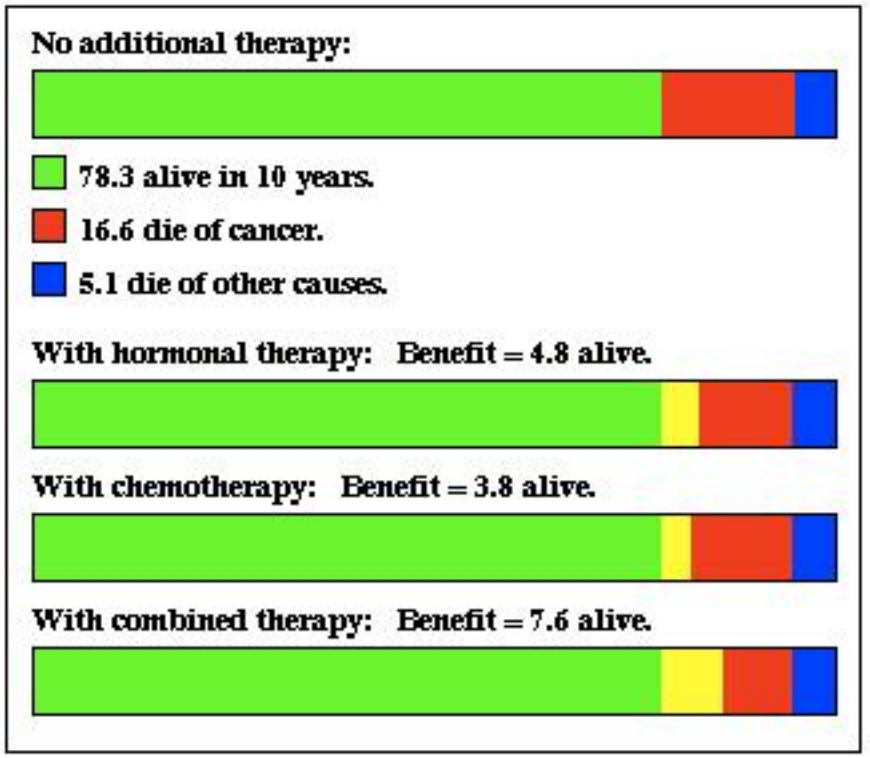
Horm: Tamoxifen (Overview 2000)

Chemo: CA*4 then T*4

Hormonal Therapy: 32

Chemotherapy: 26

Combined Therapy: 50



Print Results PDF | Access Help and Clinical Evidence

Images for Consultations

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)

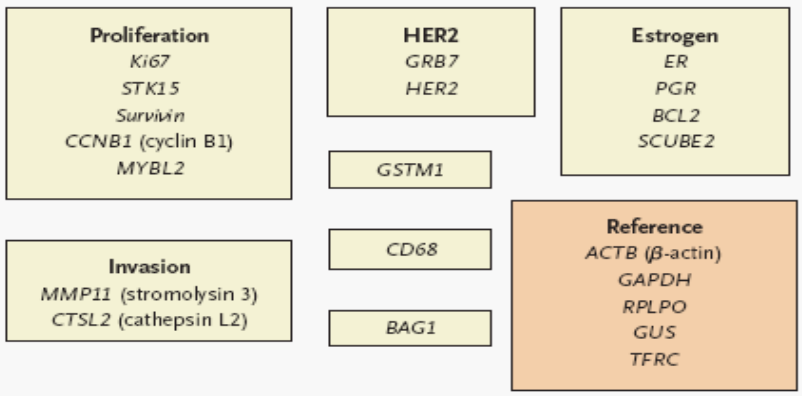
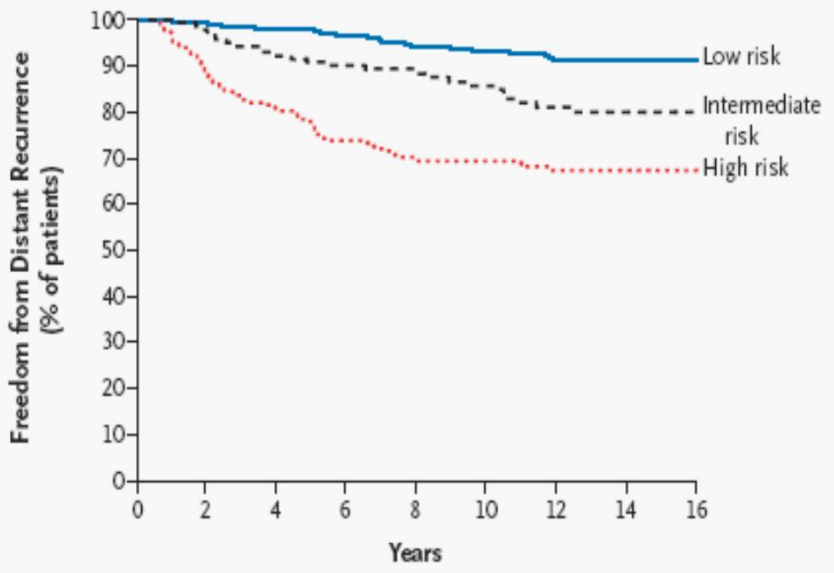


Figure 1. Panel of 21 Genes and the Recurrence-Score Algorithm.

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)

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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.

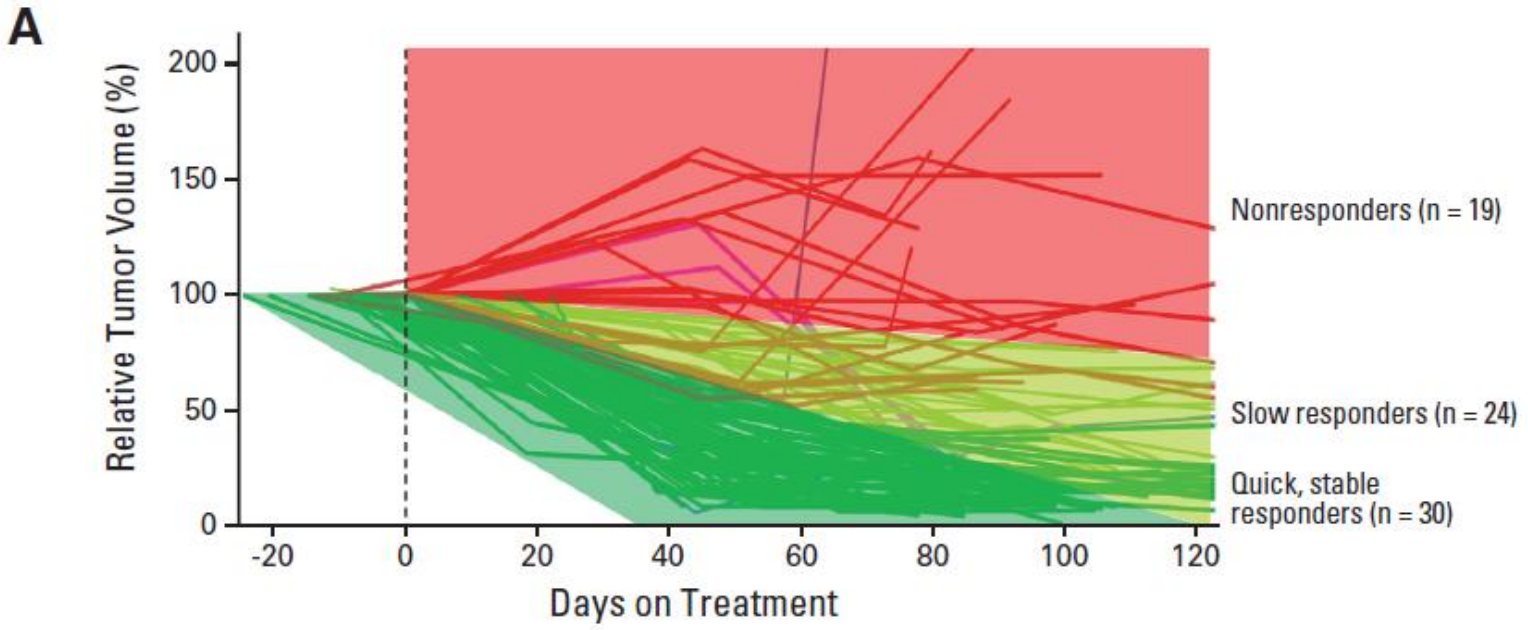
Supported by Breakthrough Breast

A B S T R A C T

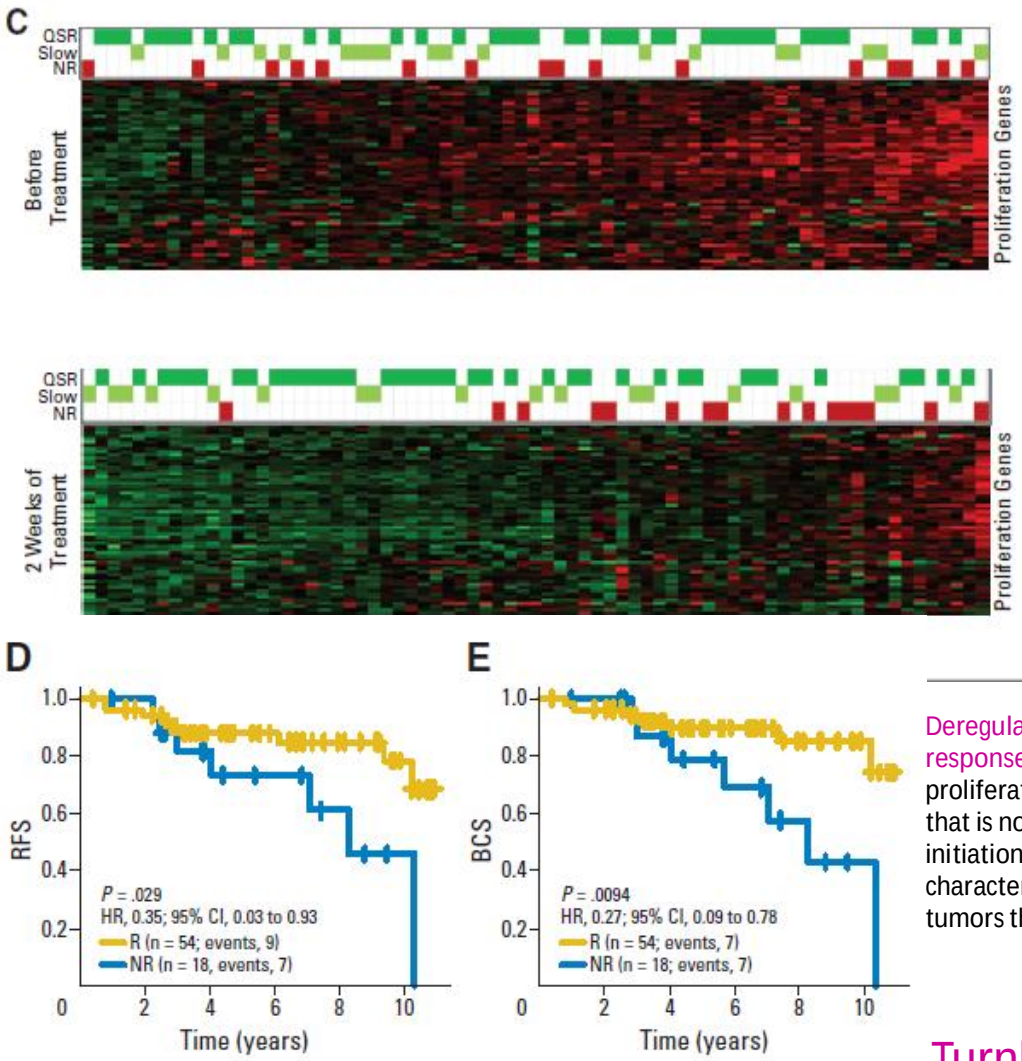
Purpose
Aromatase inhibitors (AIs) have an established role in the treatment of breast cancer. Response rates are only 50% to 70% in the neoadjuvant setting and lower in advanced disease. Accurate biomarkers are urgently needed to predict response in these settings and to determine which individuals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

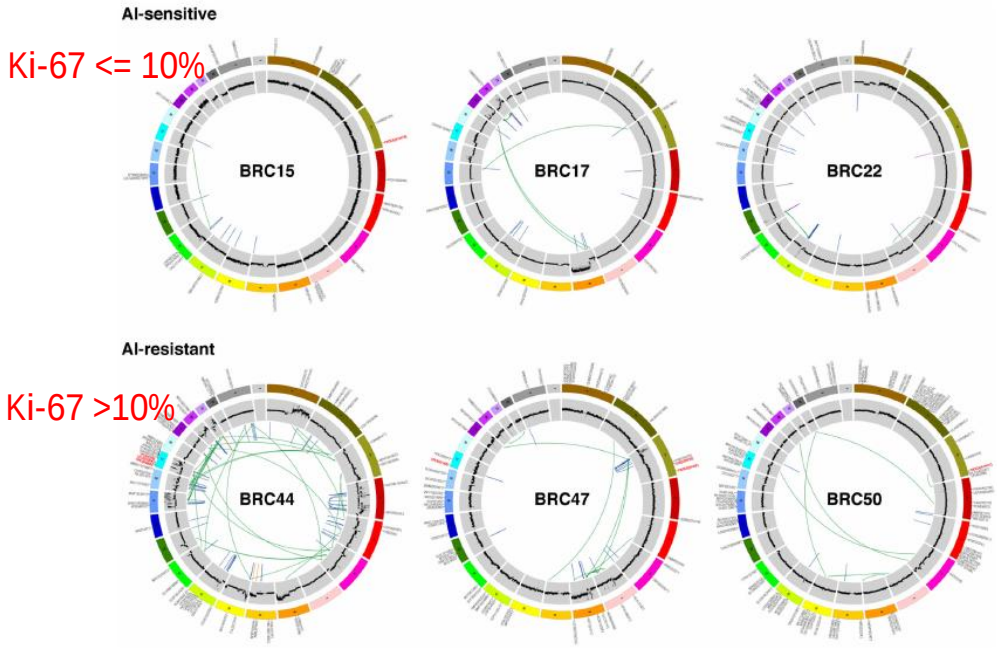
Published in final edited form as:
Nature. ; 486(7403): 353–360. doi:10.1038/nature11143.

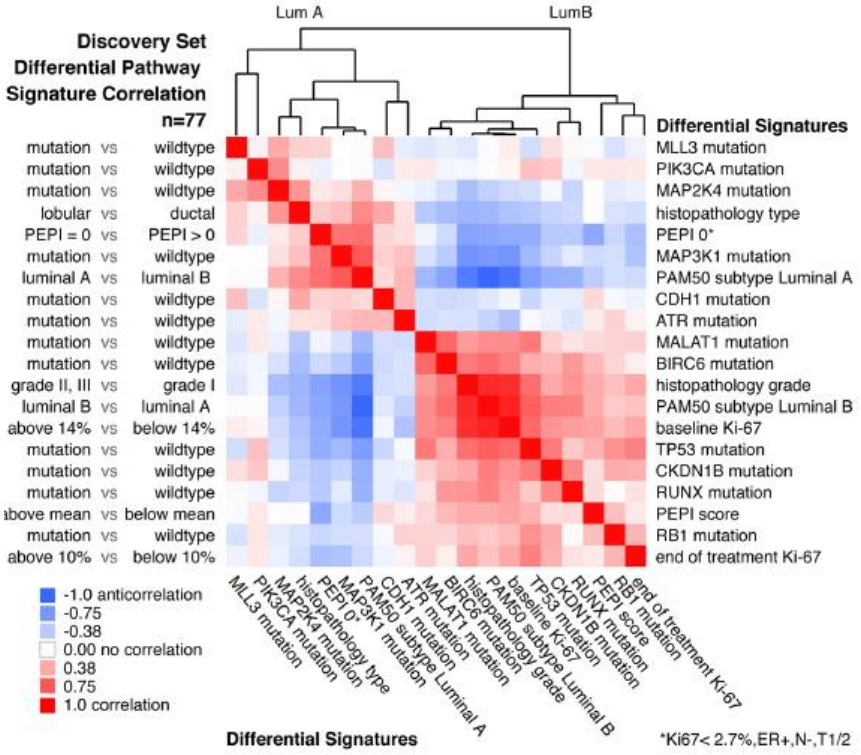
Whole Genome Analysis Informs Breast Cancer Response to Aromatase Inhibition

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], **Cyr Schierding**[3,4], **Joshua F. McMichael**[3,4], **Christopher A. M**

Neoadjuvant Setting…

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

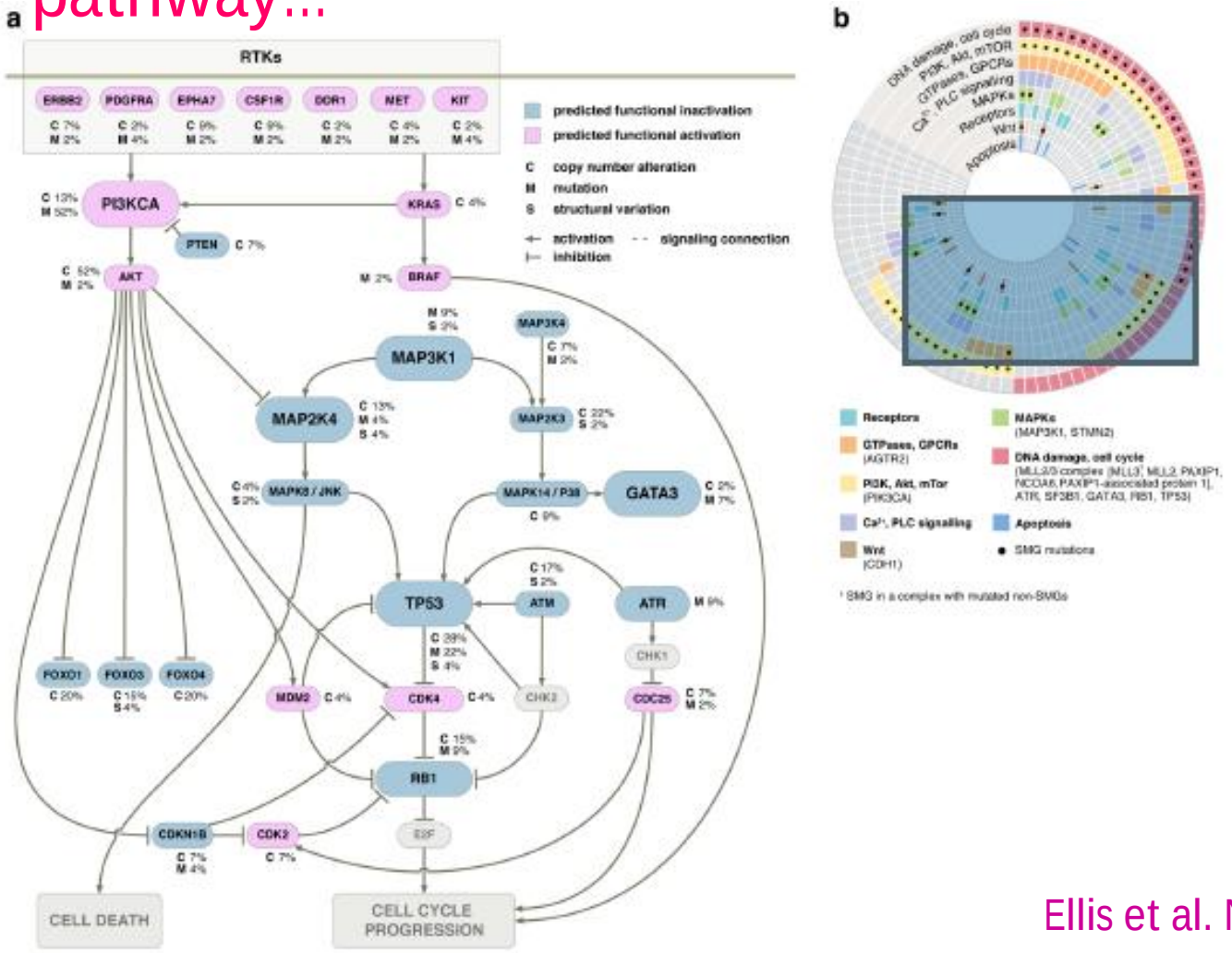




Genomic wide somatic mutations (WGA) and response to neoadj AI

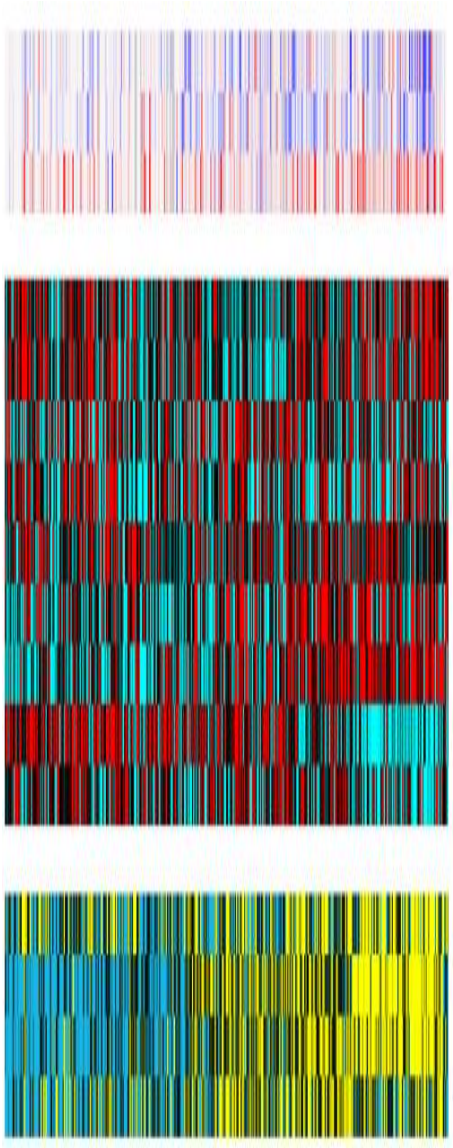
Figure 5. Pathway signatures reveal connections between mutations and clinical outcomes

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…



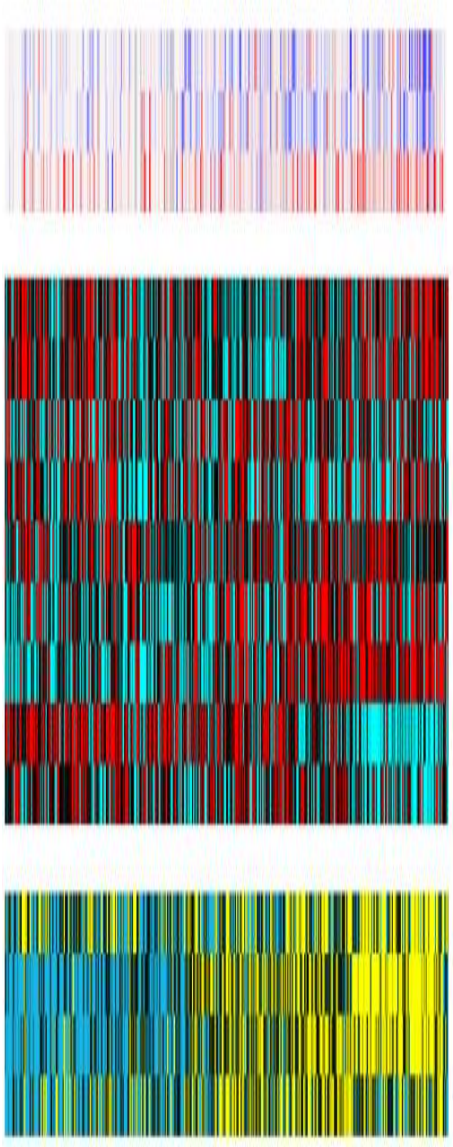
Ellis et al. Nature 486:353-60, 2012

Added Value of Precision Medicine in the Genomic Era



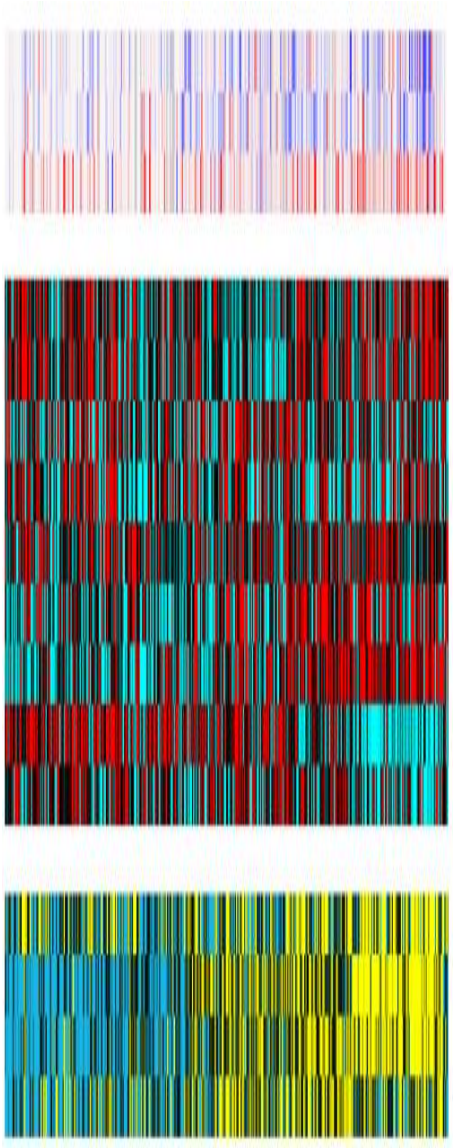
- "One-size" does not fit all
- Identifying the right therapy or the right patient
  - Enhance clinical outcomes
  - Increase benefit : risk ratio
  - Accelerate new therapeutic development for breast cancer

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

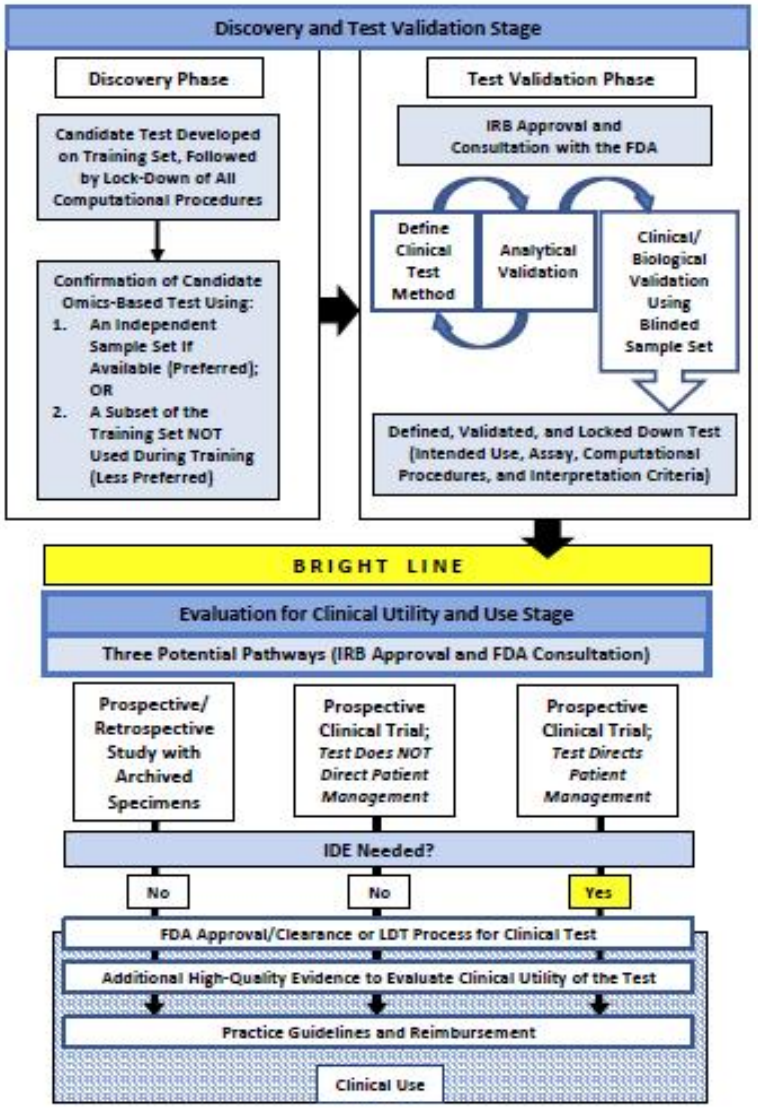
Development of Genomic Signatures…



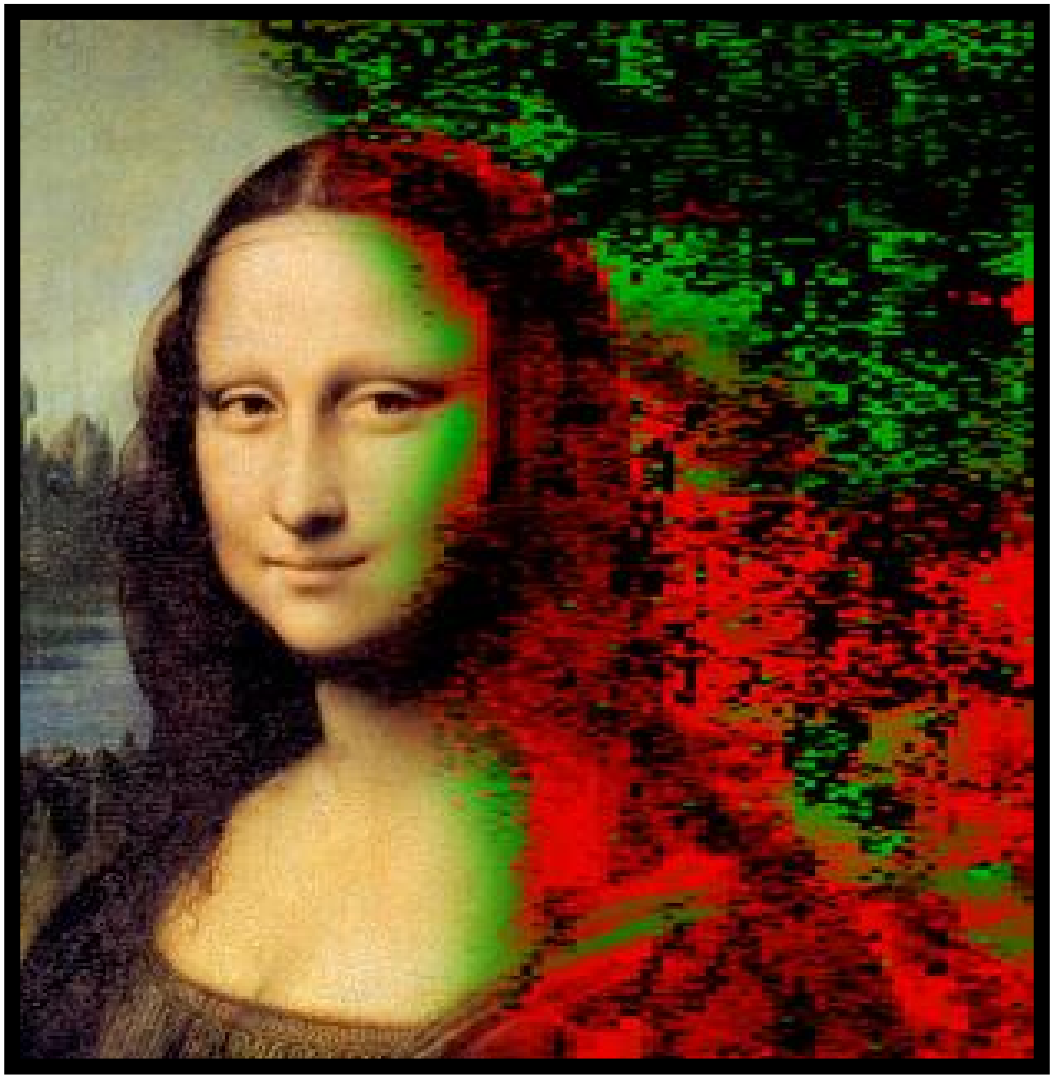
- Discovery
  - NGS, RNA seq, proteomics
  - Analytical validation
  - Training sets and validation sets
- Clinical Validation
  - Prognostic & Predictive value
  - Retrospective vs Prospective L-T FU
  - Compared with old therapies
- Clinical Utility

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

FIGURE: Omics-Based Test Development Process

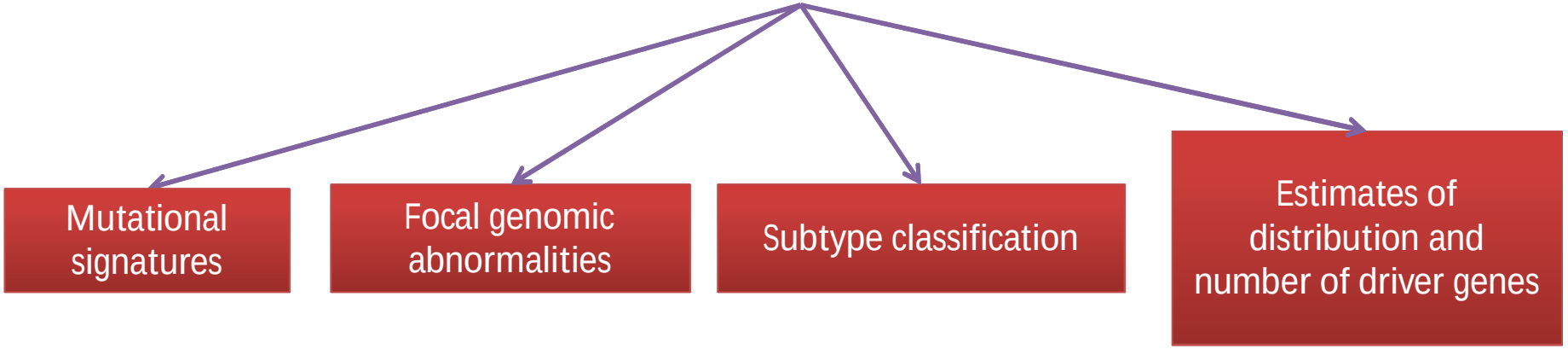


Emerging Treatment Options vs Challenges…



Potential of clinical cancer genomics – *Scientists' viewpoint*

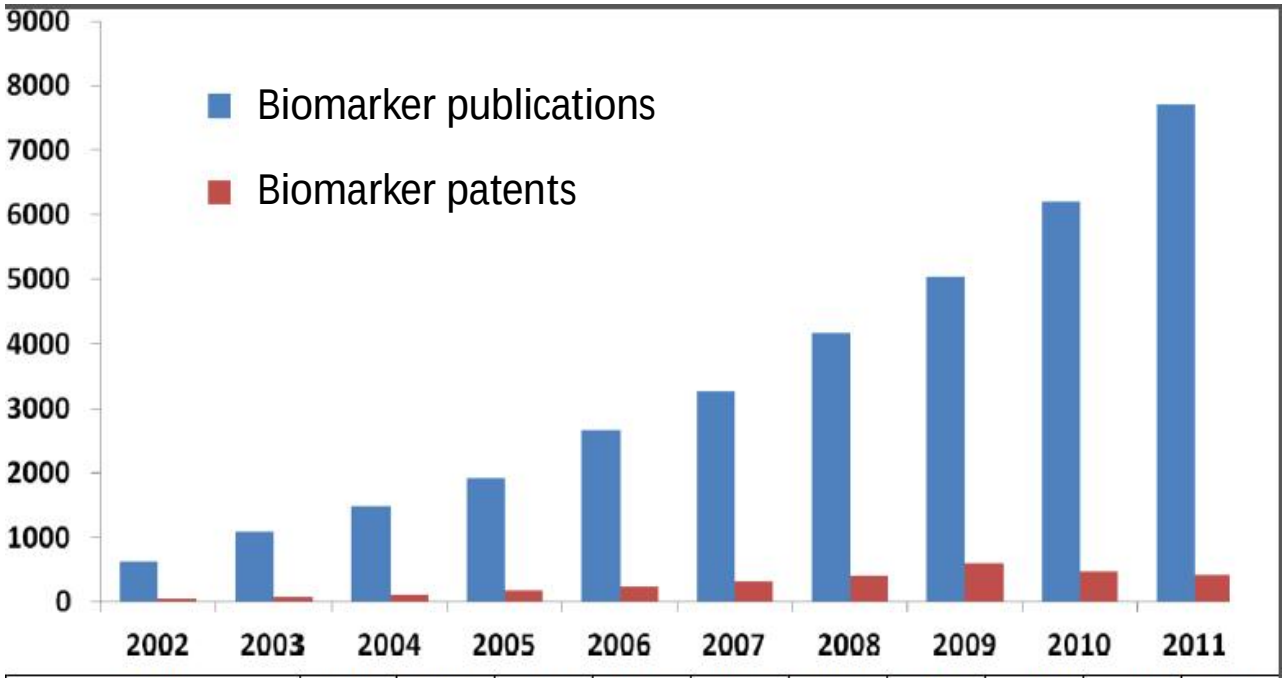
Large-scale sequencing projects like the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA).



There is no shortage of new biomarkers available for clinical translation.....an era of "cancer biomarker discovery"

Clinical Translation....??

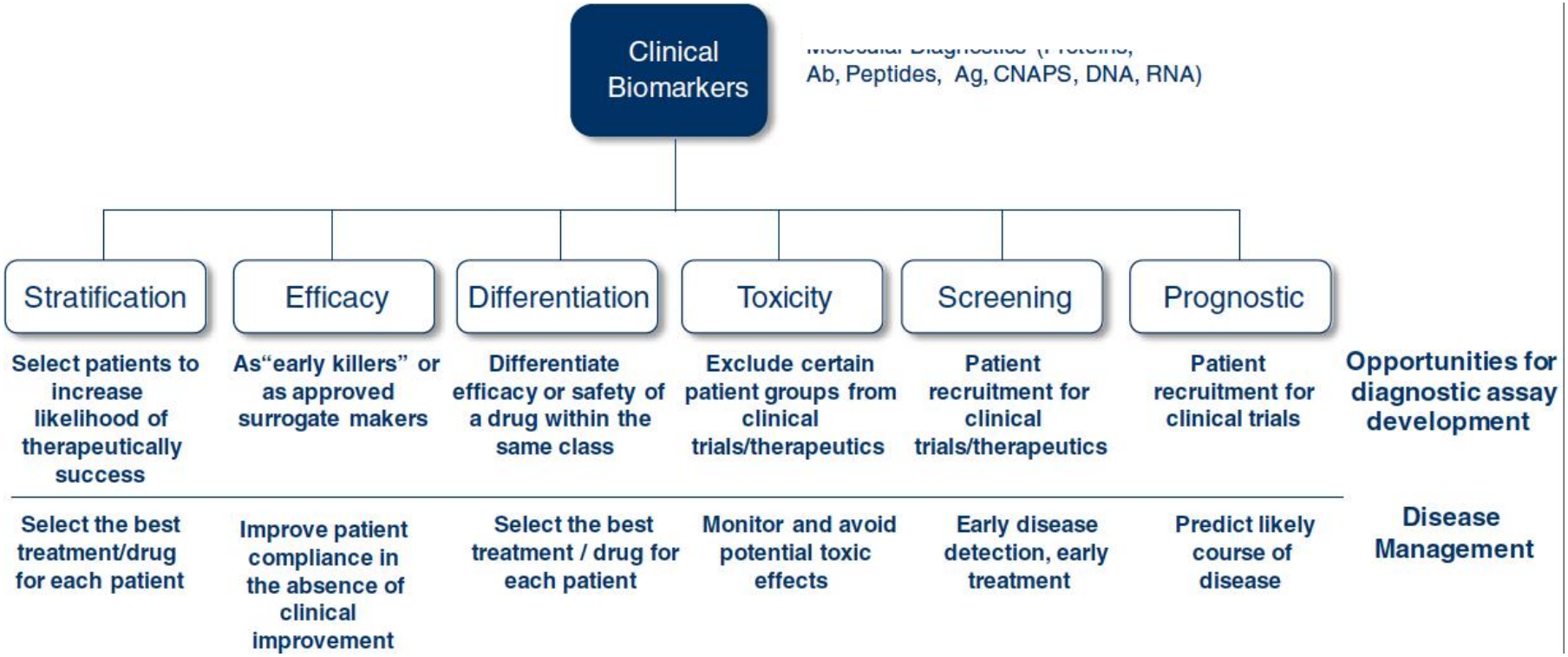
- Clinical biomarkers need to be highly specific and sensitive
- Majority of the biomarker discoveries do not meet the criteria of high sensitivity and specificity.



Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Biomarkers Publikation	625	1087	1478	1920	2661	3270	4168	5033	6208	7720
Biomarker Patents	50	74	95	180	238	320	396	593	471	407

The lack of sensitivity and/or specificity leads to a low number of patent application and, in addition to this, to a low number of successful market applications.

Potential of clinical cancer genomics – *Clinicians'* viewpoint



Challenges to clinical-translational application

- Source: Convenience sampling
- Reproducibility
  - Biology
  - Assay
  - Analysis
- Pharmaco-economics of genomic tests
- End-user of the test: Physicians and patients

Convenience sampling

- Discovery-based genomic studies rely on “convenience samples”
- All of the serous ovarian cancer samples analyzed in TCGA were harvested from women with advanced (Stages III and IV) tumor – making it difficult to identify critical early changes
- To be meaningful in a screened population, diagnostic biomarkers must be discovered in early-stage, non-metastatic cancers since biomarker expression can change over the course of a disease.

Reproducibility - *assays*

- Clinical application - tests need to be highly accurate & reproducible.

- Very little research available into quality control of genomic studies

  – A recent study extracted DNA once from each part of a tumor/normal pair and shipped aliquots of this sample to five large international sequencing centers (*Buchhalter et al. 2014*)

  – Each center sequenced and analyzed the same sample using their own protocols.

  – Only ~ 20% of mutations were common to all five centers, while one third were predicted by only a single center.

Reproducibility – *inherent biology*

- Intra-tumoural heterogeneity
  - Studies universally show that individual tumors are comprised of myriad cell types present at different frequencies in different spatial sites.
  - Small populations of cancer stem cells that might be the source of metastatic cells and therefore represent most important information
  - Multiple core biopsies ? How many is enough, ? Feasibility in a patient population
- Stromal interactions
  - Interactions of the malignant cells with the surrounding stroma, or stochastic factors that are not captured by any biomarker, are important in the progression of early lesions

Reproducibility - *analysis*

- Significant diversity in the analysis of cancer genomic data.

- Even small differences in the way a data set is preprocessed and analyzed can yield massive differences in the predictions of a final biomarker
  - appears that the more complex the biomarker, the more sensitive it is to processing differences, both in terms of computational methodologies and sample fixation processes.

- However, analysis methods cannot yet be standardized because there is very little consensus in the field about the best methods for different problems.

Pharmaco-economic of genomic tests

- $$$$$$$$$$$$$$$$$$$$

- Limited number of pharmaco-economic studies for genomic biomarkers to date.

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.

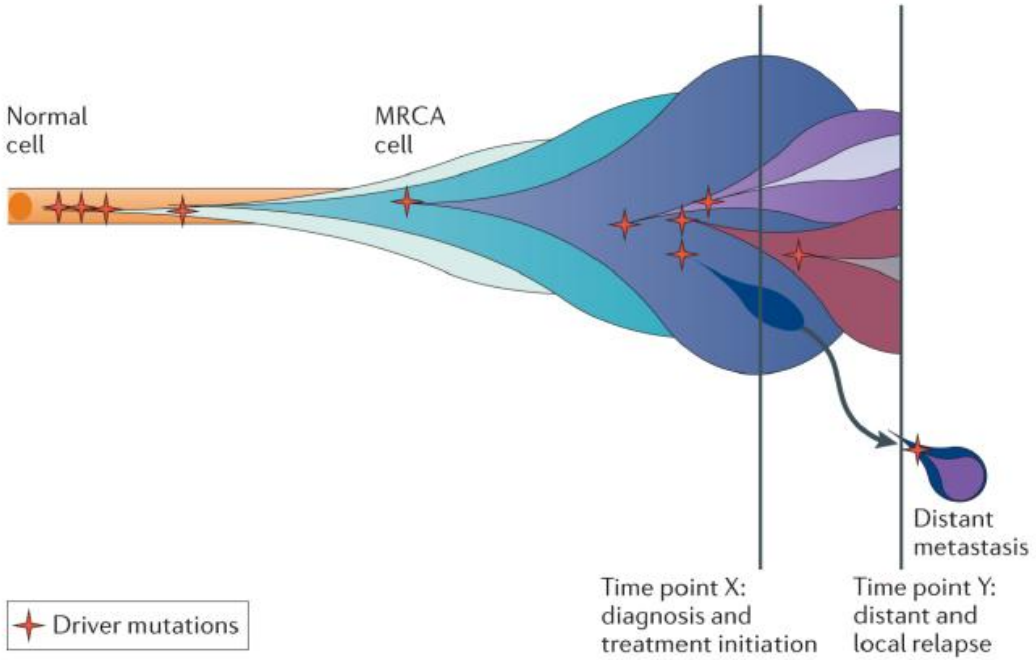


Figure 1. The evolution of clonal populations

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

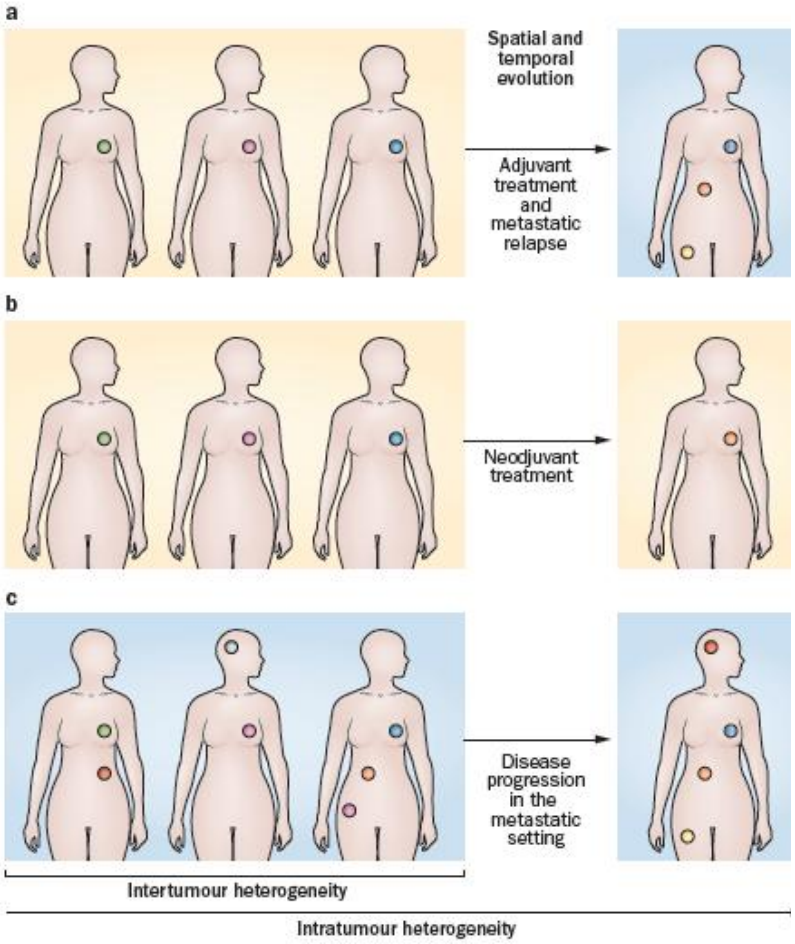


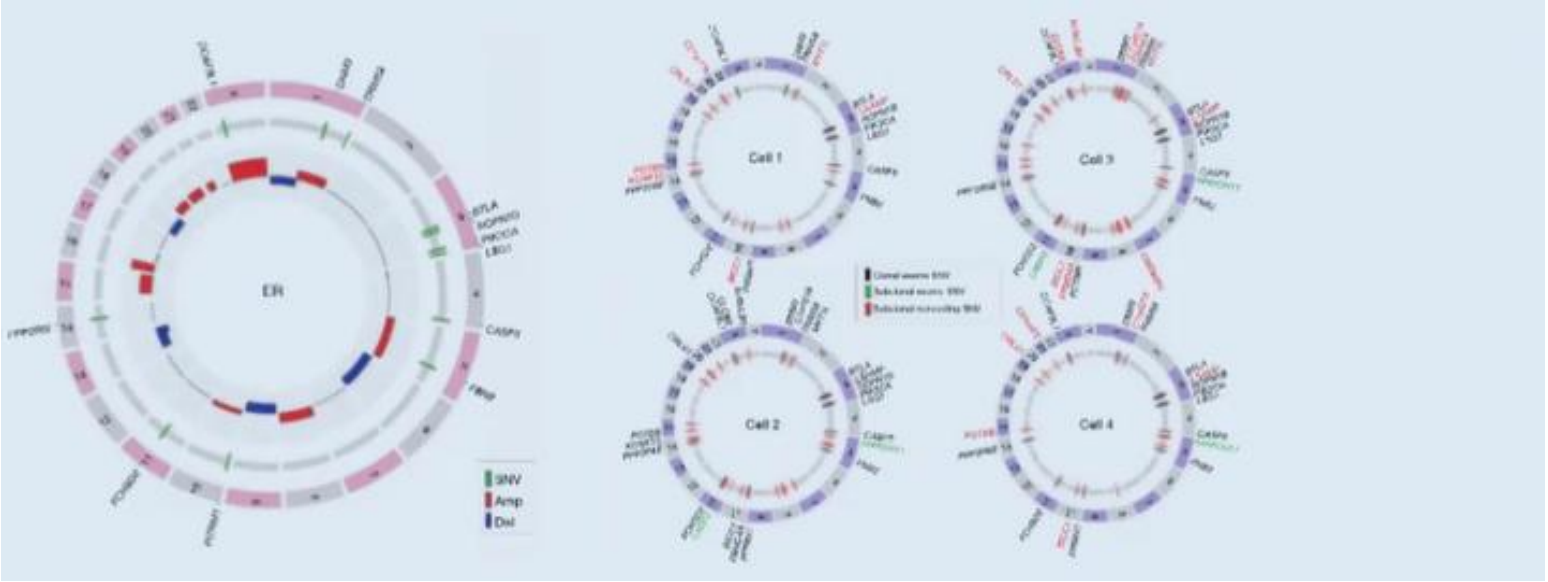
Table 4 | Clinical implications of tumour heterogeneity in breast cancer

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

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)

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

San Antonio Breast Cancer Symposium, December 8-12, 2015

Subclonal diversification of primary breast cancer revealed by multiregion sequencing

Lucy R Yates[1,2], Moritz Gerstung[1], Stian Knappskog[3,4], Christine Desmedt[5], Gunes Gundem[1], Peter Van Loo[1,6], Turid Aas[7], Ludmil B Alexandrov[1,8], Denis Larsimont[5], Helen Davies[1], Yilong Li[1], Young Seok Ju[1], Manasa Ramakrishna[1], Hans Kristian Haugland[9], Peer Kaare Lilleng[9,10], Serena Nik-Zainal[1], Stuart McLaren[1], Adam Butler[1], Sancha Martin[1], Dominic Glodzik[1], Andrew Menzies[1], Keiran Raine[1], Jonathan Hinton[1], David Jones[1], Laura J Mudie[1], Bing Jiang[11], Delphine Vincent[5], April Greene-Colozzi[11], Pierre-Yves Adnet[5], Aquila Fatima[11], Marion Maetens[5], Michail Ignatiadis[5], Michael R Stratton[1], Christos Sotiriou[5], Andrea L Richardson[11,12], Per Eystein Lønning[3,4], David C Wedge[1] & Peter J Campbell[1]

The sequencing of cancer genomes may enable tailoring of therapeutics to the underlying biological abnormalities driving a particular patient's tumor. However, sequencing-based strategies rely heavily on representative sampling of tumors. To understand the subclonal structure of primary breast cancer, we applied whole-genome and targeted sequencing to multiple samples from each of 50 patients' tumors (303 samples in total). The extent of subclonal diversification varied among cases and followed spatial patterns. No strict temporal order was evident, with point mutations and rearrangements affecting the most common breast cancer genes, including *PIK3CA*, *TP53*, *PTEN*, *BRCA2* and *MYC*, occurring early in some tumors and late in others. In 13 out of 50 cancers, potentially targetable mutations were subclonal. Landmarks of disease progression, such as resistance to chemotherapy and the acquisition of invasive or metastatic potential, arose within detectable subclones of antecedent lesions. These findings highlight the importance of including analyses of subclonal structure and tumor evolution in clinical trials of primary breast cancer.

Yates et al, Nature Medicine Vol 21: 751-763, 2015

Take Home

- Breast cancer genomic evolution is chaotic i.e. there is no fixed temporal order
- Multifocal disease is clonally related but can exhibit “clonal sweep” with dominant mutations in one focus and another set in another focus
- Post-treatment samples exhibit new driver mutations, i.e. a single look for a therapeutic driver makes little sense – we need continuous genomic monitoring
- Precision medicine driven by DNA sequencing of a single pretreatment sample is a naïve proposition

San Antonio Breast Cancer Symposium, December 8-12, 2015

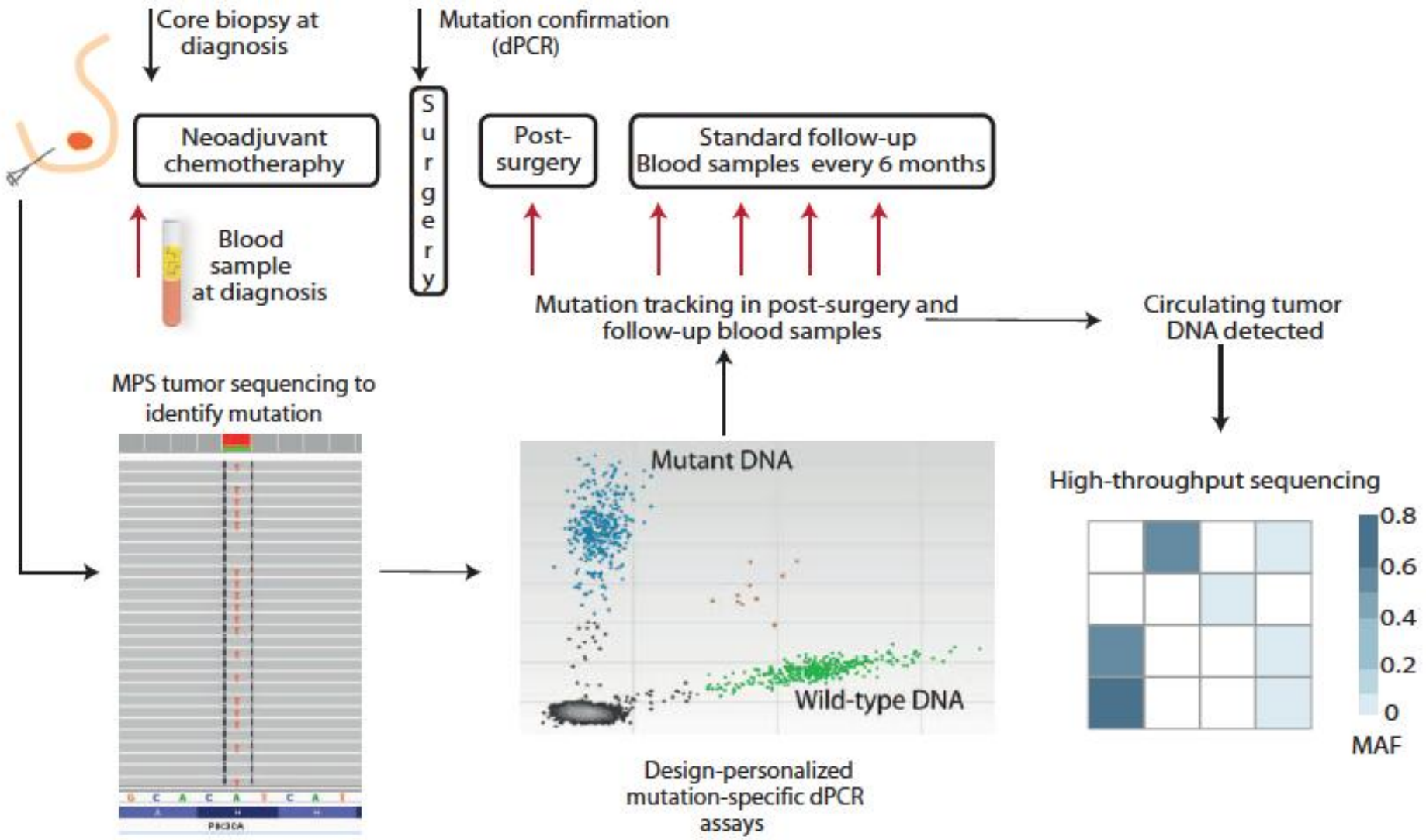
CANCER

Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer

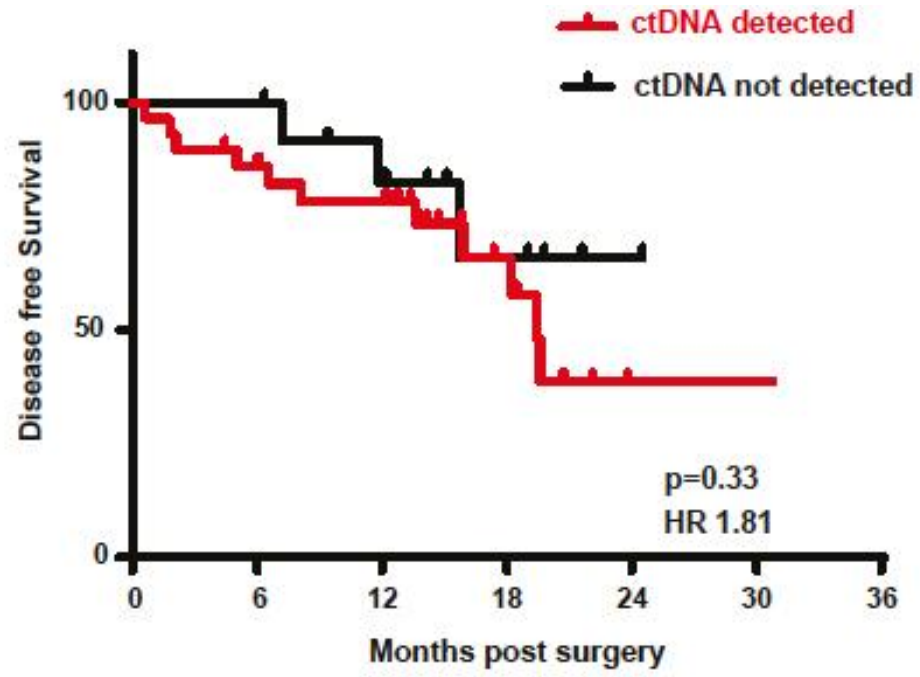
Isaac Garcia-Murillas,[1]* Gaia Schiavon,[1,2]*† Britta Weigelt,[3] Charlotte Ng,[3] Sarah Hrebien,[1] Rosalind J. Cutts,[1] Maggie Cheang,[4] Peter Osin,[2] Ashutosh Nerurkar,[2] Iwanka Kozarewa,[1] Javier Armisen Garrido,[1] Mitch Dowsett,[1,2] Jorge S. Reis-Filho,[3] Ian E. Smith,[2] Nicholas C. Turner[1,2‡]

The identification of early-stage breast cancer patients at high risk of relapse would allow tailoring of adjuvant therapy approaches. We assessed whether analysis of circulating tumor DNA (ctDNA) in plasma can be used to monitor for minimal residual disease (MRD) in breast cancer. In a prospective cohort of 55 early breast cancer patients receiving neoadjuvant chemotherapy, detection of ctDNA in plasma after completion of apparently curative treatment—either at a single postsurgical time point or with serial follow-up plasma samples—predicted metastatic relapse with high accuracy [hazard ratio, 25.1 (confidence interval, 4.08 to 130.5; log-rank $P < 0.0001$) or 12.0 (confidence interval, 3.36 to 43.07; log-rank $P < 0.0001$), respectively]. Mutation tracking in serial samples increased sensitivity for the prediction of relapse, with a median lead time of 7.9 months over clinical relapse. We further demonstrated that targeted capture sequencing analysis of ctDNA could define the genetic events of MRD, and that MRD sequencing predicted the genetic events of the subsequent metastatic relapse more accurately than sequencing of the primary cancer. Mutation tracking can therefore identify early breast cancer patients at high risk of relapse. Subsequent adjuvant therapeutic interventions could be tailored to the genetic events present in the MRD, a therapeutic approach that could in part combat the challenge posed by intratumor genetic heterogeneity.

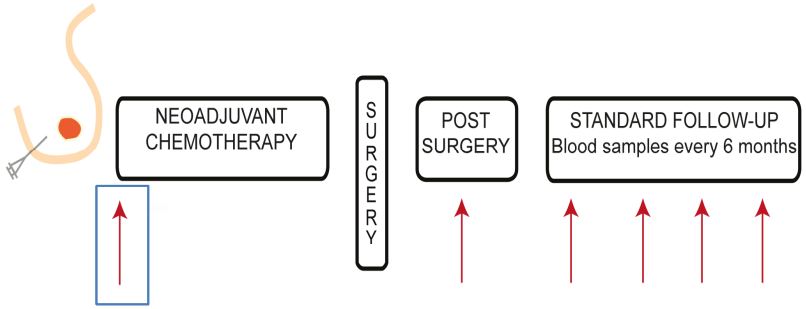
Science Translational Medicine 26 Aug 2015: Vol. 7, Issue 302, pp. 302ra133



Predicting early relapse – baseline plasma

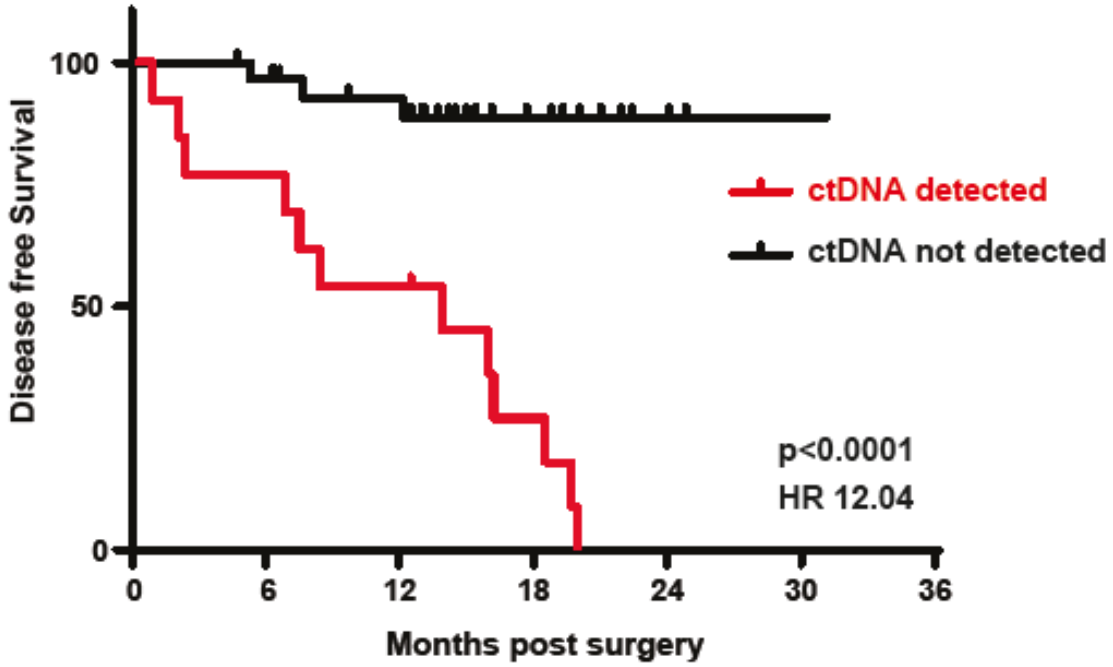


69% (29/42) mutation detected in baseline plasma

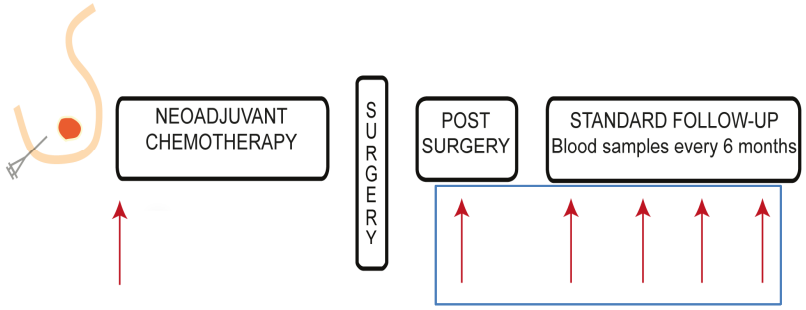


San Antonio Breast Cancer Symposium, December 8-12, 2015

Predicting early relapse – mutation tracking



Improved sensitivity with dynamic mutation tracking that is highly accurate in predicting relapse



2015 and beyond...

Trends in Translational Breast Cancer Research

- How will documentation of complex somatic mutation patterns help breast cancer clinical care?
- Is circulating Tumor DNA analysis clinically valuable?

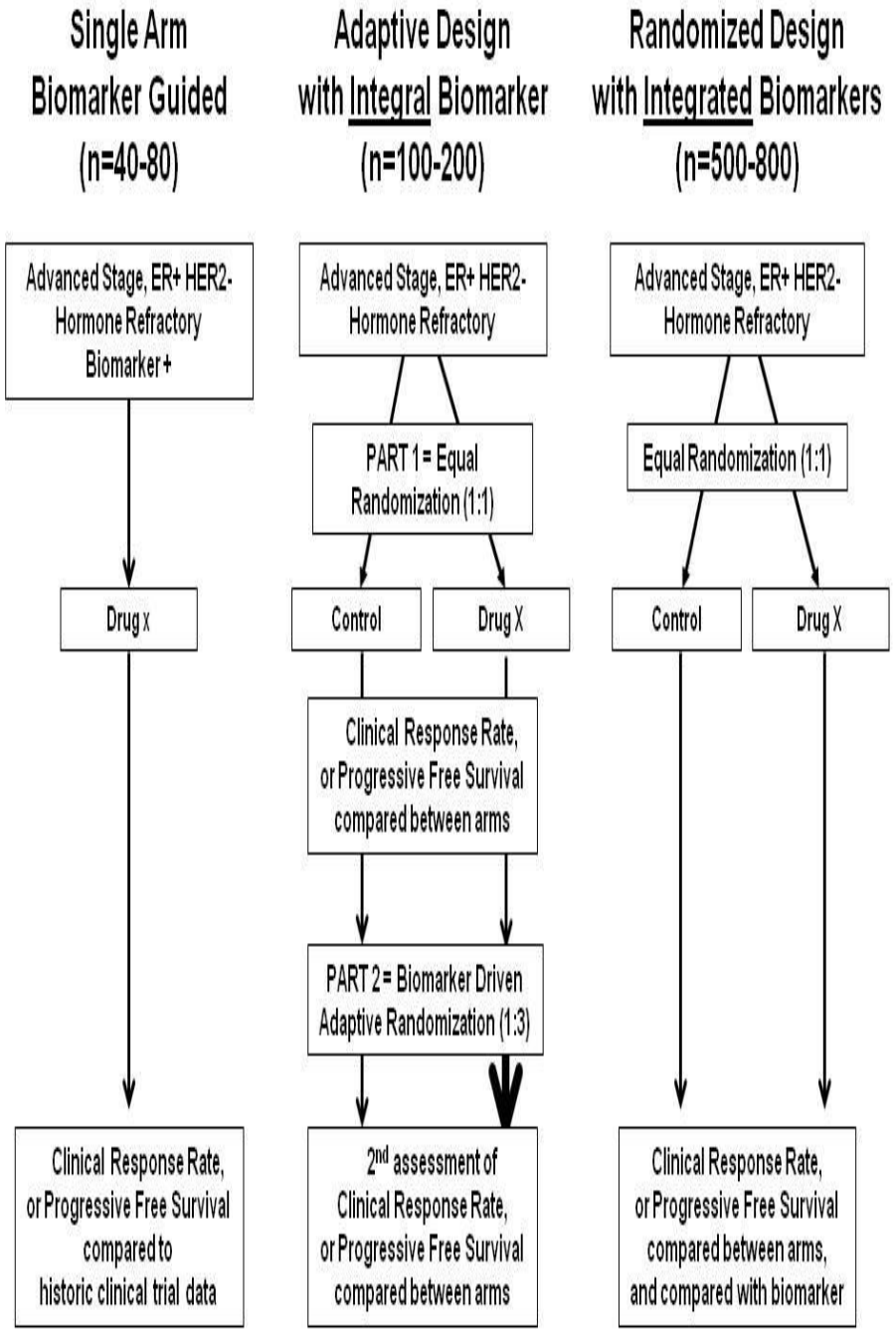
The Way Forward – Companion Diagnostics (CDx)

- HER-2 and Herceptin - now been on the market for more than a decade. However, the number of drugs marketed alongside CDx remains small

- Pharmaceutical companies are increasingly looking to develop a drug and diagnostic test simultaneously, in a process referred to as drug-diagnostic-co-development so-called companion diagnostic (CDx), to better define the appropriate patient population for treatment.

- CDx are increasingly important tools:

    1. Reduced costs through pre-selected (smaller) patient population;
    2. Improved chances of approval;
    3. Significantly increased market uptake;
    4. Added value for core business (late phase);
    5. Regulatory trend to have CDx mandatory.



Choices for Clinical Trial Design

1. There is no one “right trial design” as multiple features must be taken into consideration

2. if the preliminary drug and biomarker data are very strong, then single arm Phase II studies may be enough

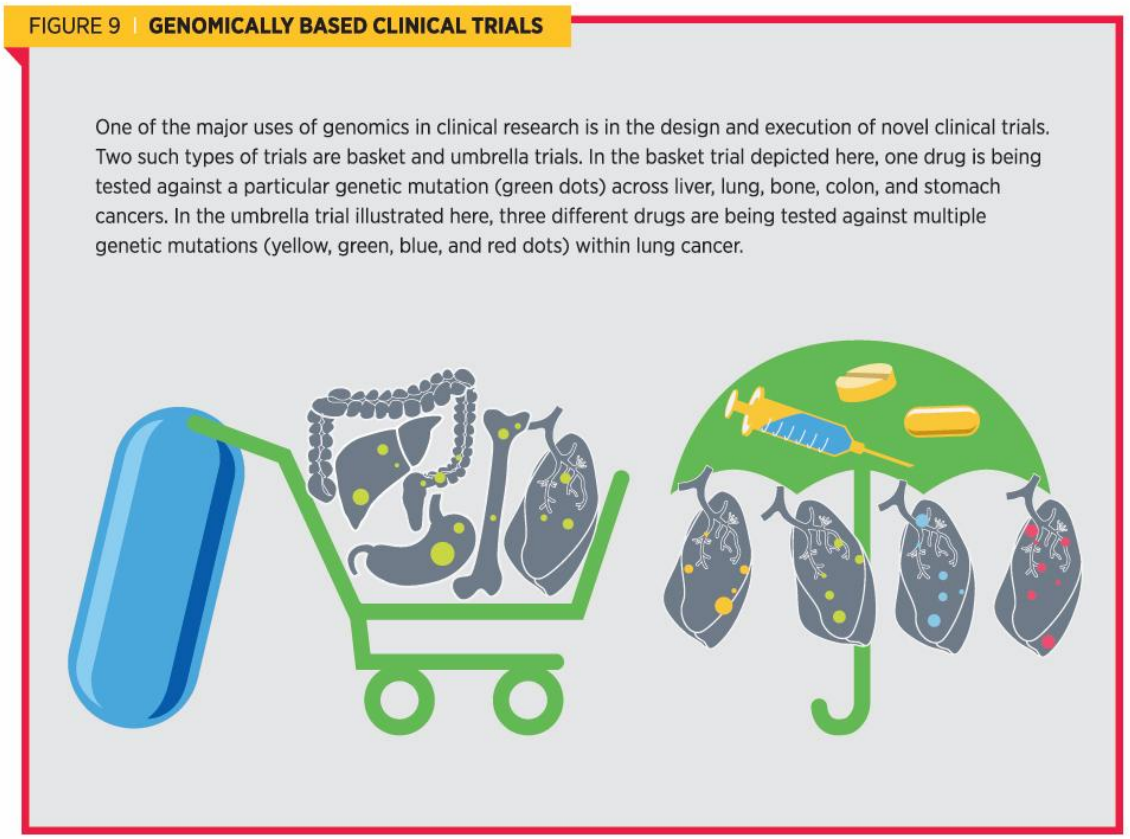
1. if possible, an “adaptive step” is desirable for promising drugs/biomarkers, but this adds cost and the need for real time trial monitoring of response rates

2. if there is a question as to the efficacy of the drug, or the clinical validity of the biomarker, or multiple biomarkers, then a randomized design may be best. This design also provides maximal opportunities for discovery

Courtesy slide of Charles Perou

Proteomics in Clinical Trials

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



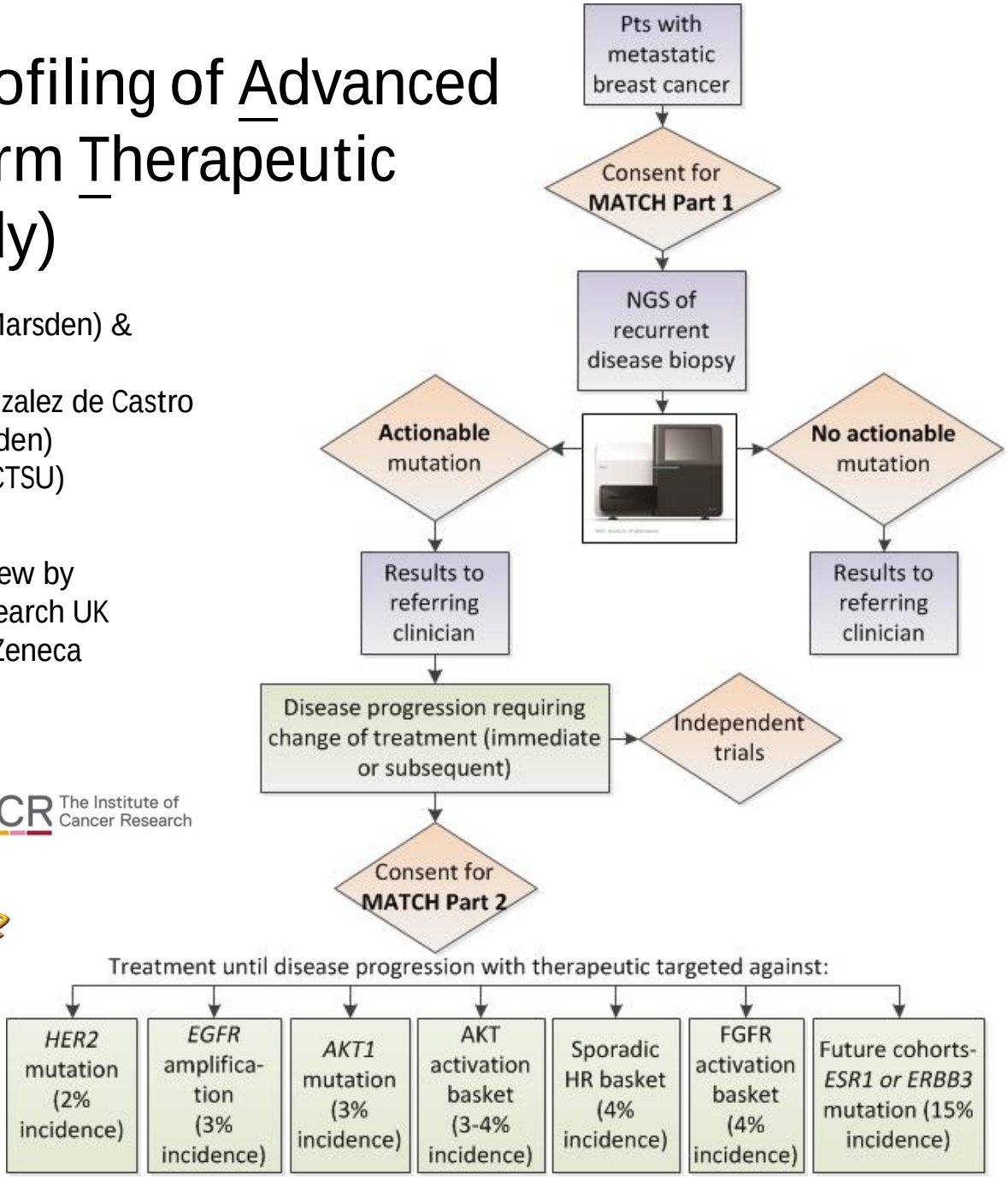
Umbrella Trials
-seek to test a drug or drugs across multiple genetic mutations within a particular type of cancer. For example, the I SPY-2 umbrella trial in breast cancer.

"Transforming lives through research", AACR (2014)

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

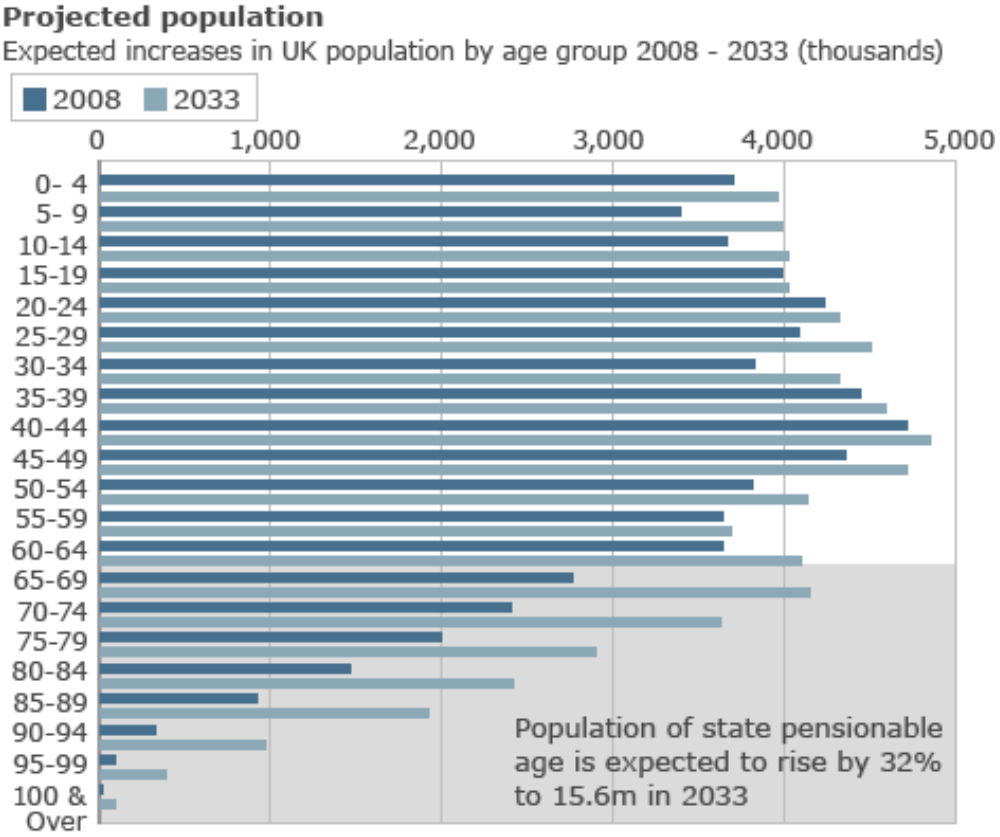


Courtesy of Stephen Johnston

Challege of Aging Society & Aging Cancer Patients

By 2030, there could be 50% more people greater than 65 years old, and 100% more people greater than 80 years old

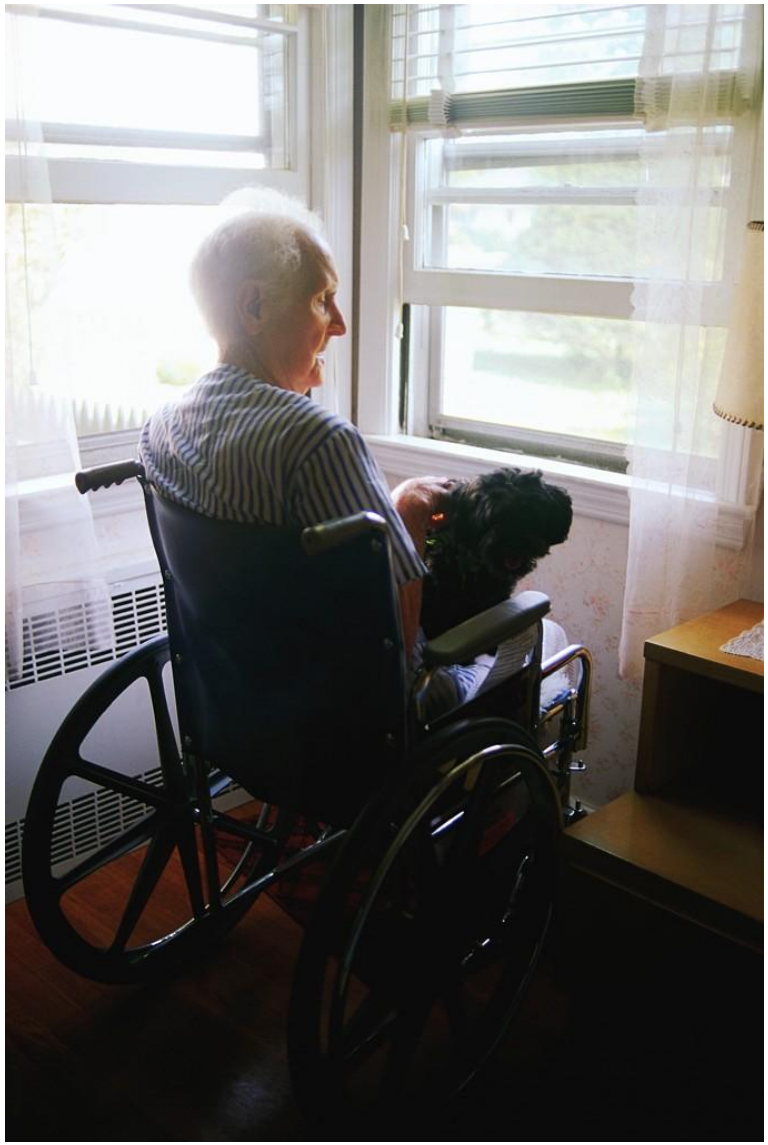
By the year 2030, most patients with cancer will be aged over 65 years and many will be frail.



Agostar B et al. The management of cancer in the elderly: targeted therapies in oncology. Immunity & Aging. 2008 Dec 30;5:16. doi: 10.1186/1742-4933-5-16.

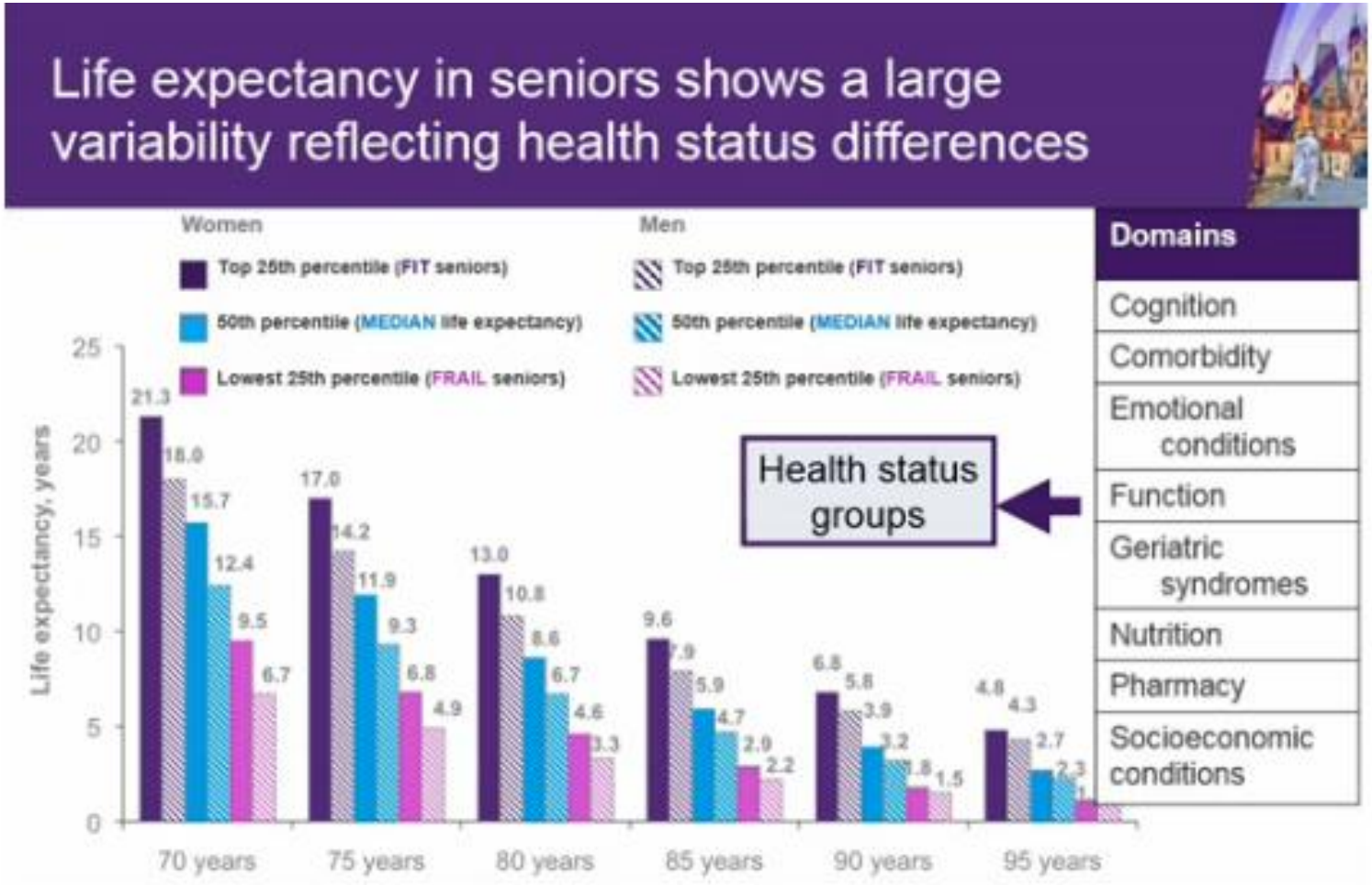
Courtesy of Dr. Joseph Kwan

Elderly People – Same age otherwise…

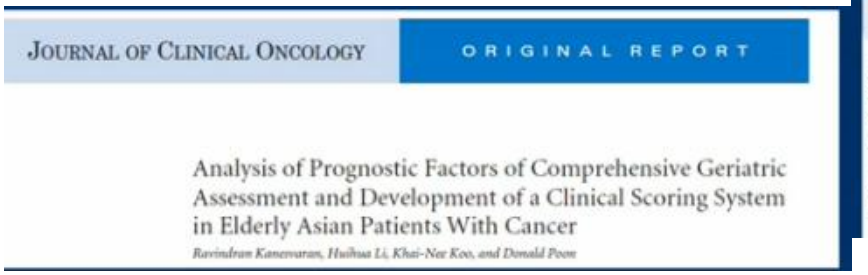


Both are 80+ year-old...
Will you treat them for cancer?

Same age yet having different life expectancies

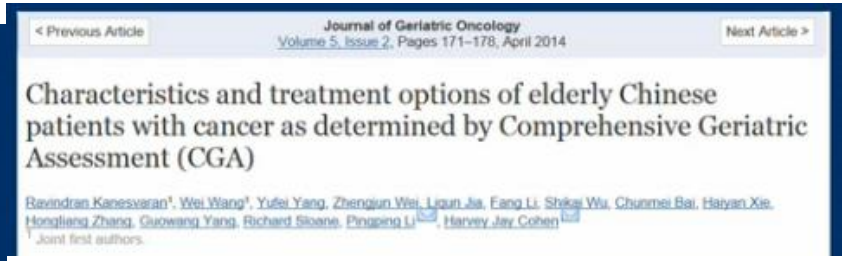


Water LC et al , JAMA 2001


JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Analysis of Prognostic Factors of Comprehensive Geriatric Assessment and Development of a Clinical Scoring System in Elderly Asian Patients With Cancer

Ravindran Kanesvaran, Huihua Li, Khai-Nee Koo, and Donald Poon


< Previous Article Journal of Geriatric Oncology Volume 5, Issue 2, Pages 171–178, April 2014 Next Article >

Characteristics and treatment options of elderly Chinese patients with cancer as determined by Comprehensive Geriatric Assessment (CGA)

Ravindran Kanesvaran[1], Wei Wang[1], Yufei Yang, Zhengjun Wei, Liqun Jia, Fang Li, Shikai Wu, Chunmei Bai, Haiyan Xie, Hongliang Zhang, Guowang Yang, Richard Sloane, Pingping Li, Harvey Jay Cohen

[1] Joint first authors.

- The first prognostic scoring system for elderly cancer patients to date develop based on the CGA.
- Important descriptive information on elderly Asian cancer patients gleaned.
- A nomogram able to predict an individual patient's 1, 2 and 3 year survival with reasonably good accuracy.

Karnesvaran et al, JCO 2011

- The largest prospective study of CGA done on elderly cancer patients in Asia with 803 patients from 9 hospitals in Beijing who were 65 y.o. or above with a diagnosis of cancer at any stage.
- Using CGA questionnaire with Chinese translation of the Gero-Oncology Health & Quality of Life Assessment Tool –demonstrated CGA appropriate for Chinese cancer patients
- Mean age of 72, 59.8% being male, 45% had concurrent TCM, 70% ADL-I

Karnesvaran et al, JGO 2014

SIOG on Geriatric Assessment in Elderly Cancer Patients


VOLUME 32 · NUMBER 24 · AUGUST 20 2014

JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

International Society of Geriatric Oncology Consensus on Geriatric Assessment in Older Patients With Cancer

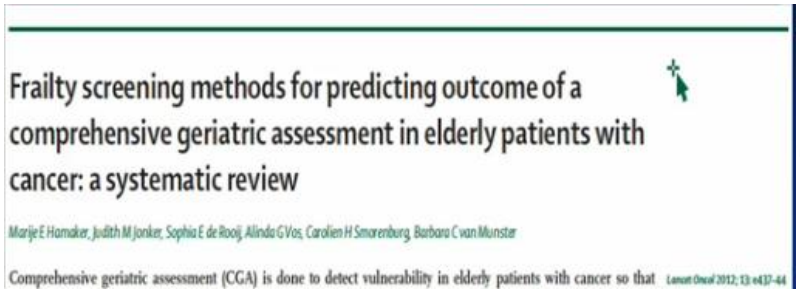
Hans Wildiers, Pieter Heeren, Martine Puts, Eva Topinkova, Maryska L.G. Janssen-Heijnen, Martine Extermann, Claire Falandry, Andrew Artz, Etienne Brain, Giuseppe Colloca, Johan Flamaing, Theodora Karnakis, Cindy Kenis, Riccardo A. Audisio, Supriya Mohile, Lazzaro Repetto, Barbara Van Leeuwen, Koen Milisen, and Arti Hurria


Geriatric Assessment Tools and Recommendations

Annals of Oncology | Published online 16 June 2014

Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations

L. Decoster, K. Van Puyvelde, S. Mohile, U. Wedding, U. Basso, G. Colloca, S. Rostoft, J. Overcash, H. Wildiers, C. Steer, G. Kimmick, R. Kanesvaran, A. Luciani, C. Terret, A. Hurria, C. Kenis, R. Audisio, and M. Extermann


Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review

Marije E Hamaker, Judith M Jonker, Sophia E de Rooij, Alinda G Vos, Carolien H Smorenburg, Barbara C van Munster

Comprehensive geriatric assessment (CGA) is done to detect vulnerability in elderly patients with cancer so that

- Adjuvant chemotherapy for breast cancer:
  - Reduces relative death risk by 15.3%
- Beta-blockers for myocardial infarction:
  - Reduces MI relative mortality by 22%
- CGA might reduce mortality by 14% for elderly cancer patients
  - M. Etermann , H. Cohen 2000

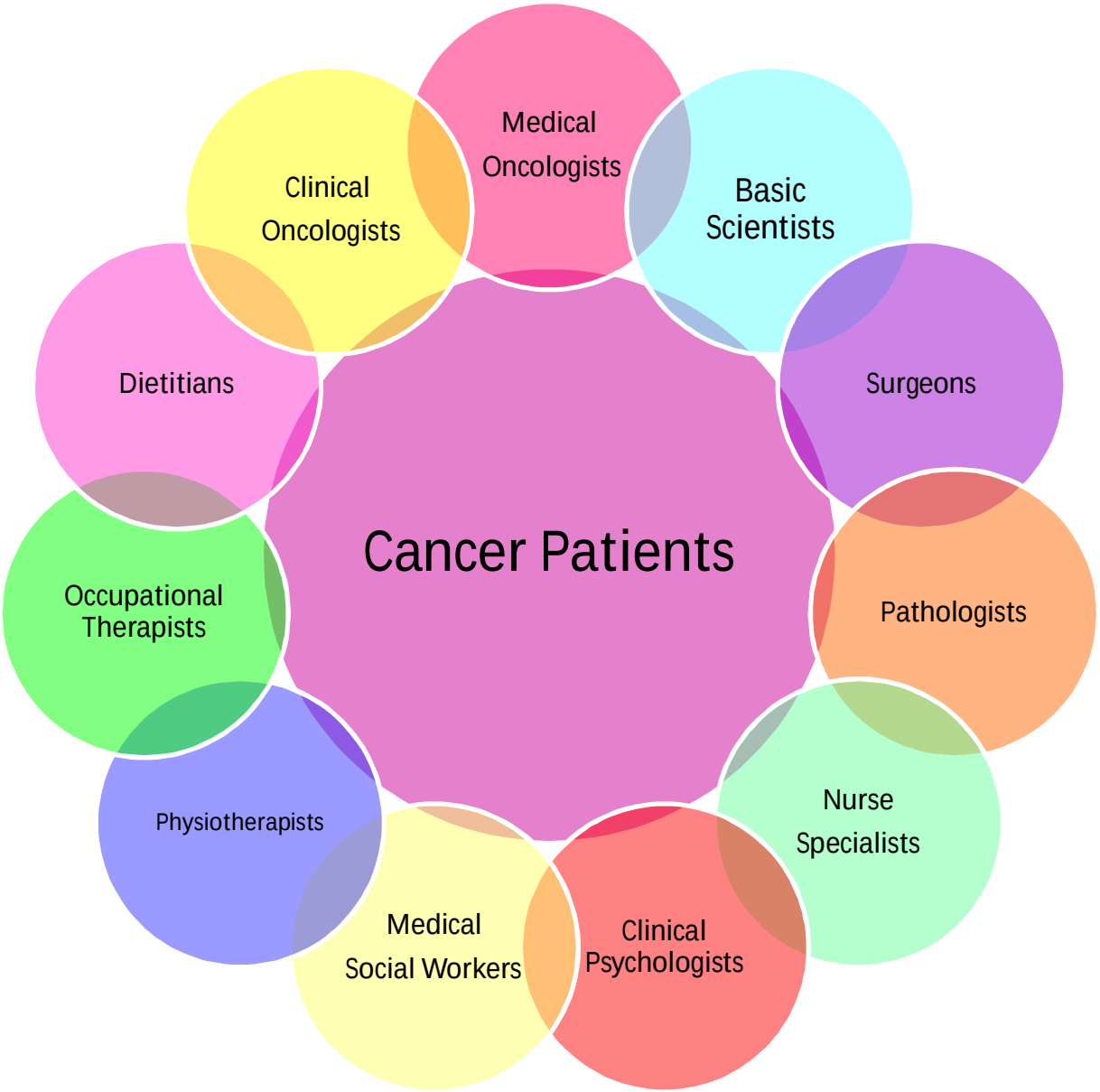
Conclusion

- 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 PRECISION MEDICINE for breast cancer (or other cancers) will include drug development and intelligent design of clinical trials for increasingly small subgroup of patients with specific host and disease characteristics through a multidisciplinary platform.

The Multidisciplinary Team Model for Cancer Care (MDT Model)



Thank You!

Acknowledgements

The Centre for Law, Medicine & Life Sciences of the University of Cambridge
The Centre for Medical Ethics & Law, The University of Hong Kong (HKU)
Dr. Philip Beh, CMEL & MEHU, LKS Faculty of Medicine, HKU
Dr. Anthony Ng, Wyng Foundation
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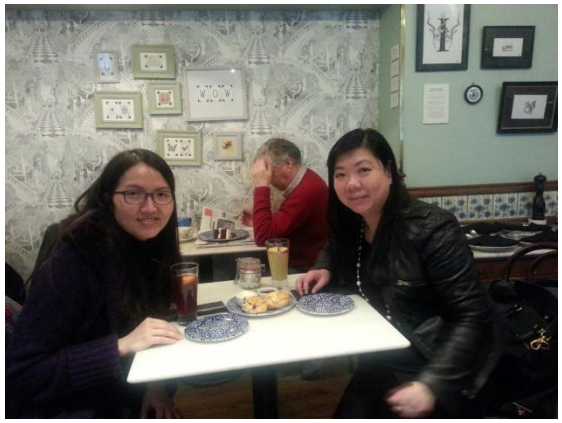
All the breast and non-breast cancer patients and collaborators



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Precision Medicine: Legal & Ethical Challenges

Precision Medicine for Cancer Care -Prime Time versus Provocation Treat ?

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