Molecular Assessment of Risk: my world turned upside down

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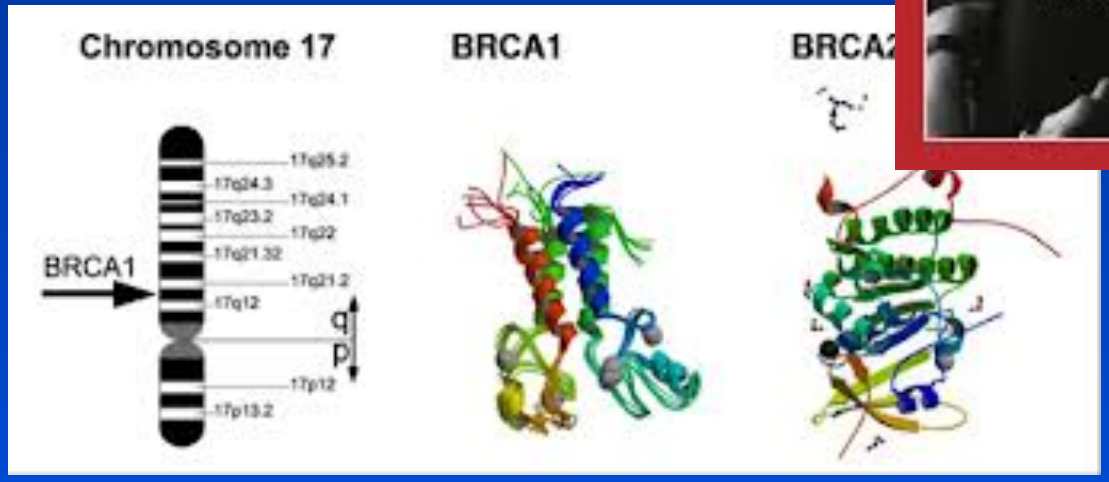
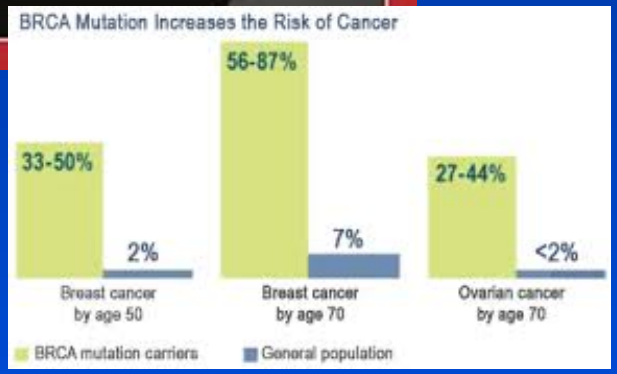
BRCA 1 and 2 are Tumor Suppressor Genes

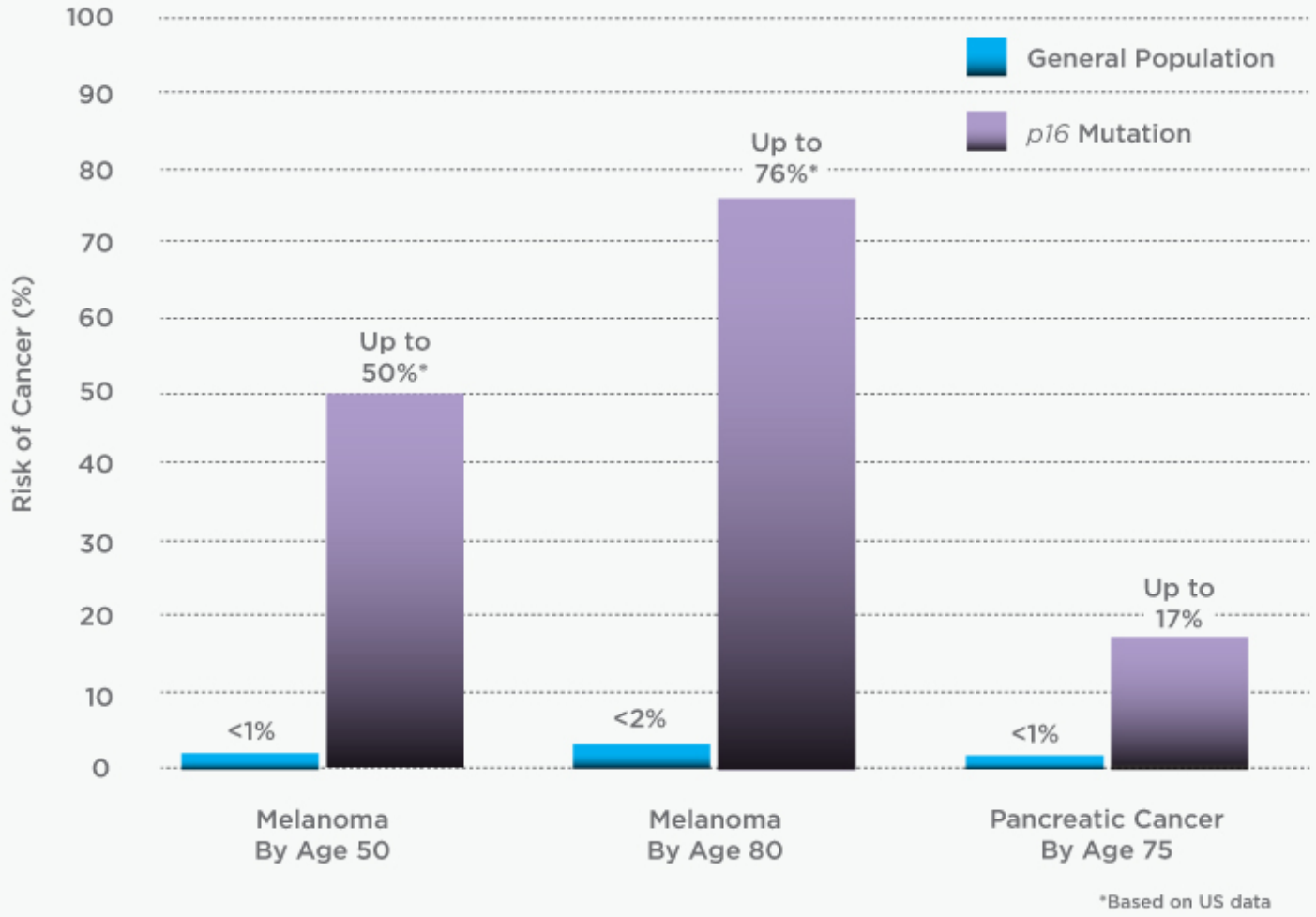
- BRCA 1 cloned in 1994; BRCA 2 in 1995
- BRCA 1 on 17q12-21; BRCA 2 on 13q12-13
- Both genes are very large
- Most known mutations lead to premature termination of protein
- Therefore, loss of tumor suppression



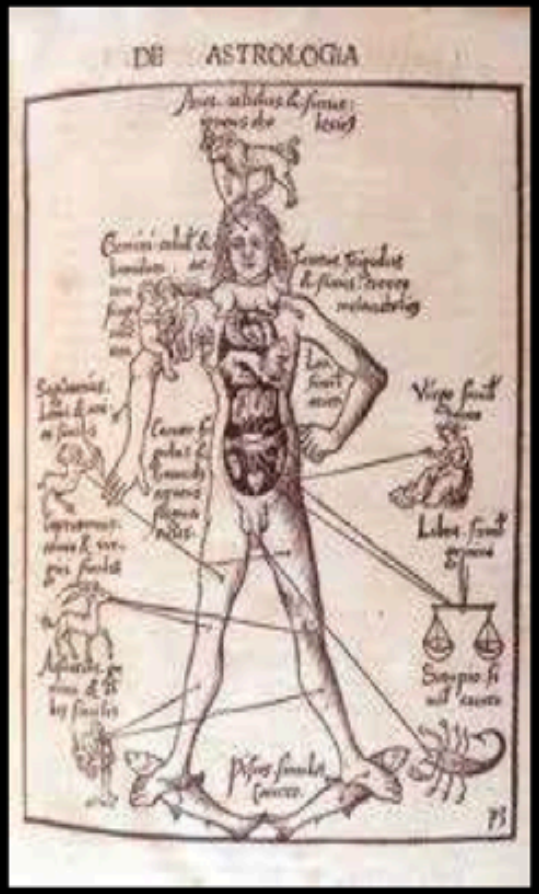


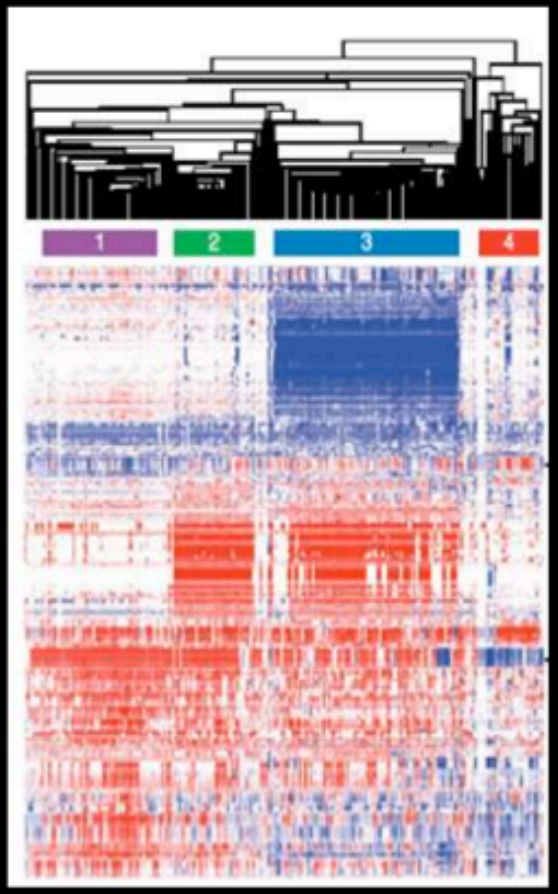
- **Risk is the potential of losing something of value, weighed against the potential to gain something of value. Values (such as physical health, emotional well being or financial wealth) can be gained or lost when taking risk resulting from a given action, activity and/or inaction, foreseen or unforeseen.**

- **Risk can also be defined as the intentional interaction with uncertainty.**

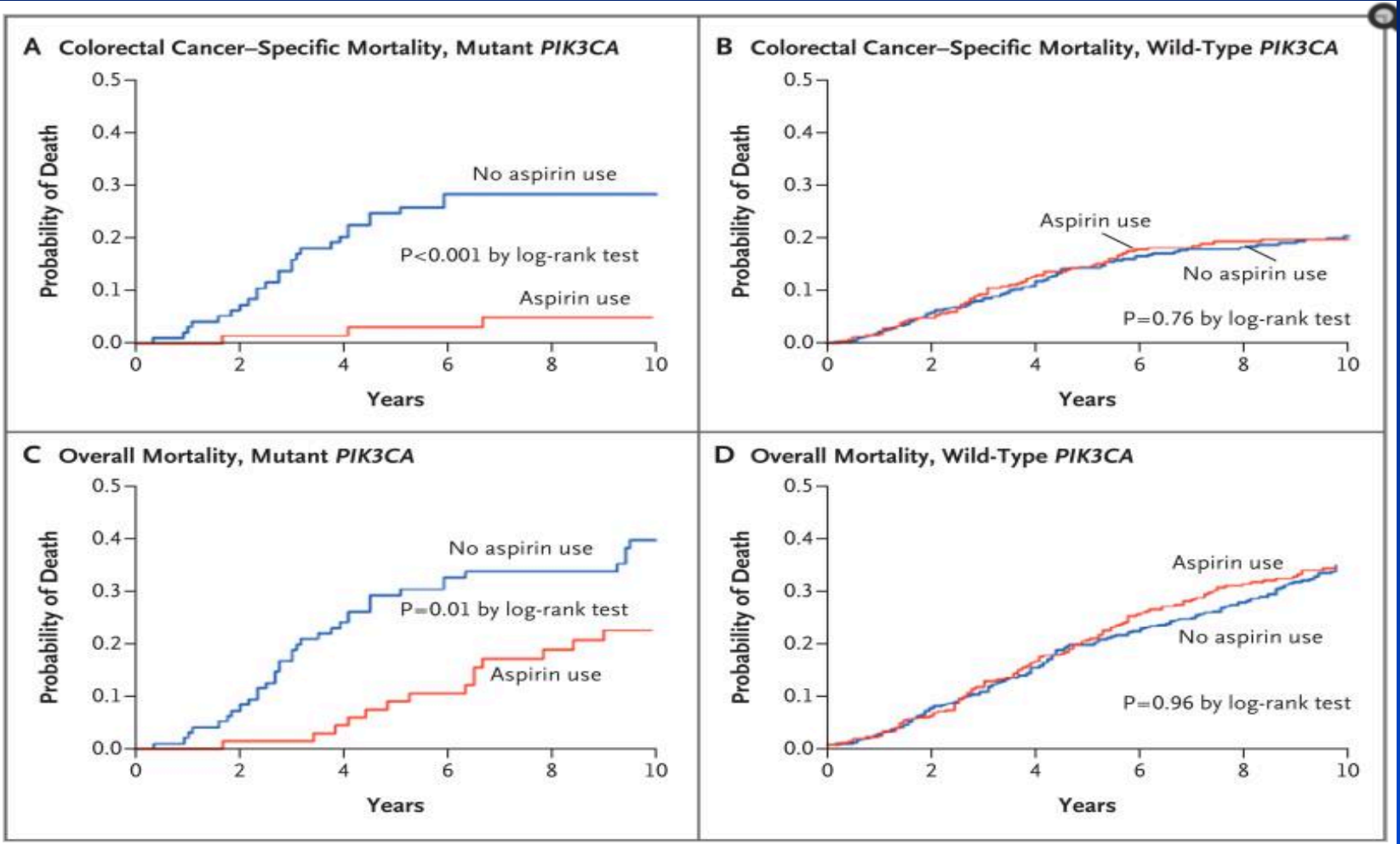

100
90
80
70
60
50
40
30
20
10
0
Risk of Cancer (%)
General Population
p16 Mutation
Up to 50%*
Up to 76%*
Up to 17%
<1%
<2%
<1%
Melanoma By Age 50
Melanoma By Age 80
Pancreatic Cancer By Age 75
*Based on US data

Medical Progress:
From Superstitions to Symptoms to Signatures





ASA reduces mortality



N Engl J Med. 2012 October 25; 367(17): 1596–1606.

RISK ASSESSMENT

- Experience-based (limited knowledge)
- Shared experience model (expert opinion)
- Evidence-based model (statistical data)
- Individual patient data (-omics-based)

Healthcare: An Expensive Menu Without Prices

Managing the Demands of an Aging Society and Chronic Disease Burden in an Era of Economic Constraint

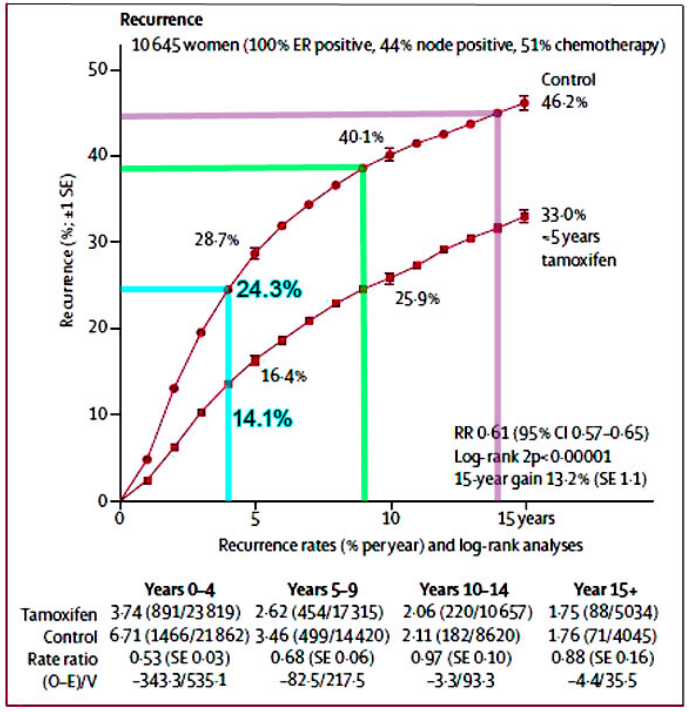
Shift From a "Do More, Bill More" Healthcare System to Managing Individual Risk for Improved Health Outcomes and Cost Control

Sustainable Health: Societal (Economic) and Individual (Wellness)

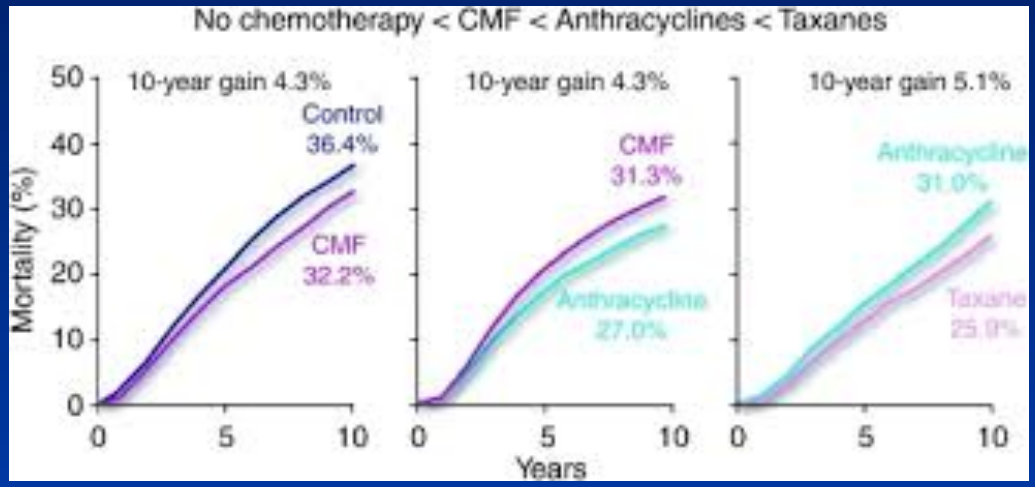
Evidence-Based Approach

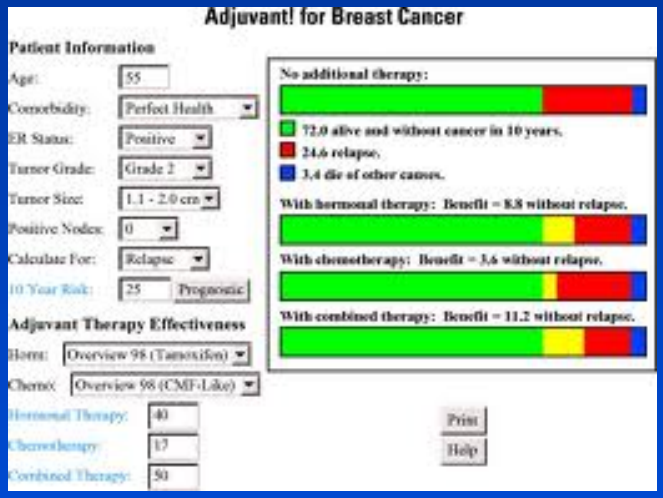
Recurrence Rate Calculation:

Recurrence rate here means the proportion of recurrences occurring in the total population of ER+ women over time, and is therefore a rate of the cumulative incidence of recurence. The rates outlined in aqua are the cumulative recurrence incidents occurring by year 4.



	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5





SYMPHONY™ Summary

Personalized Breast Cancer Genomic Profile

For Patients

PATIENT/ID		SPECIMEN		PHYSICIAN	
Patient:	Jane Doe	Requisition:	DP 90022403	Ordering Physician:	James Edney, MD
DOB:	31-Oct-1963	Collection Date:	25-Mar-2012	Account:	Univ. of Nebraska Med. Ctr
Patient #:	024836267	Date Received:	25-Mar-2012	Address:	42nd and Emile
Gender:	Female	Report Date:	29-Mar-2012	City, St., Zip:	Omaha, NE 68198
		Specimen Type:	Surgical		

1 Your SYMPHONY® Results

MammaPrint® Results

Your Tumor is Low Risk

High Risk of Recurrence | Low Risk of Recurrence

TargetPrint® Results
quantitative mRNA gene expression

	-1.0	0	1.0
ER Positive			▲
PR Positive			▲
HER2 Negative	▲		

BluePrint™ Subtype when combined with MammaPrint: **Low Risk Luminal**

2 Probability of Distant Recurrence WITHOUT SYSTEMIC TREATMENT

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

10% MammaPrint Low Risk Within 10 Years

A MammaPrint Low Risk result means that a patient with early stage breast cancer has a good baseline prognosis and an excellent prognosis for survival without adjuvant systemic therapy. For Low Risk patients, there is a 10% probability of distant recurrence within 10 years. See report for details.[1,2] In the RASTER Trial MammaPrint Low Risk patients who did not receive any systemic treatment had 100% Distant Recurrence Free Interval at 5 years.[5]

3 Probability of Distant Recurrence WITH SYSTEMIC TREATMENT

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

5% ER Positive With Endocrine Therapy Within 10 Years

For ER positive patients in general, endocrine therapy can reduce the risk of recurrence up to 50%.[3,4]

Agendia Inc. | 22 Morgan | Irvine | CA | 92618 | Ph. 888.321.2732 | Fax 866.756.7548
customercare@agendia.com | www.agendia.com

agendia® decoding cancer

M-USA-001-

Sample Patient Report Form

genomic health™ | oncotype DX™ Breast Cancer Assay

Genomic Health, Inc.
301 Penobscot Drive
Redwood City, CA 94063
Tel (866) ONCOTYPE (866-662-6897)

PATIENT REPORT

Patient: Doe, Jane
Sex: Female
DOB: 01/01/1950
Medical Record/Patient #: 556677771
Date of Surgery: 11/23/2004
Specimen ID: SURG-0001

Requisition: R00003G
Date Received: 12/01/2004
Date Reported: 12/13/2004
Client: Community Medical Center
Treating Physician: Dr. Harry D Smith
Submitting Pathologist: Dr. John P Williams
Additional Physician: Dr. Sally M Jones

ASSAY DESCRIPTION

Oncotype DX™ Breast Cancer Assay uses RT-PCR to determine the expression of a panel of 21 genes in tumor tissue. The Recurrence Score™ is calculated from the gene expression results. The Recurrence Score range is from 0-100.

RESULTS

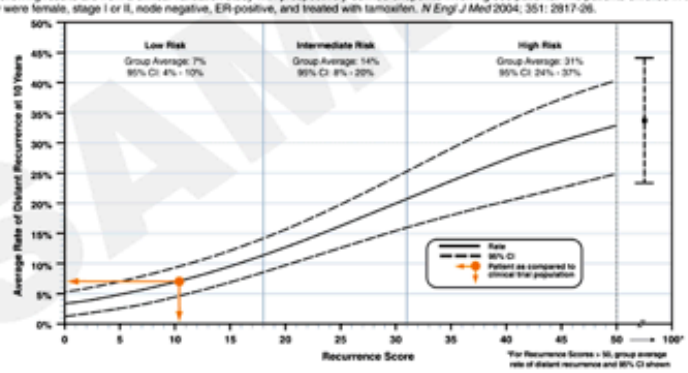
Recurrence Score = 10

Test results should be interpreted using the information in the Clinical Experience section below, which applies only to patients consistent with this clinical experience.

CLINICAL EXPERIENCE

Patients with a Recurrence Score of 10 in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of 7% (95% CI: 5%-9%)

The following results are from a clinical validation study with prospectively-defined endpoints involving 668 patients. The patients enrolled in the study were female, stage I or II, node negative, ER-positive, and treated with tamoxifen. *N Engl J Med* 2004; 351: 2817-26.



Laboratory Director: Patrick Joseph, MD

CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. These results are adjunctive to the ordering physician's workup.

301 Penobscot Drive Redwood City, CA 94063 (866) ONCOTYPE (866-662-6897)

GH004 Rev007 06/29/2005

A Cardinal Principle in Healthcare: If It Isn't Billable, It Won't Happen

Ambiguities and Lack of Transparency in Reimbursement Policies for MDx and Genome Sequencing

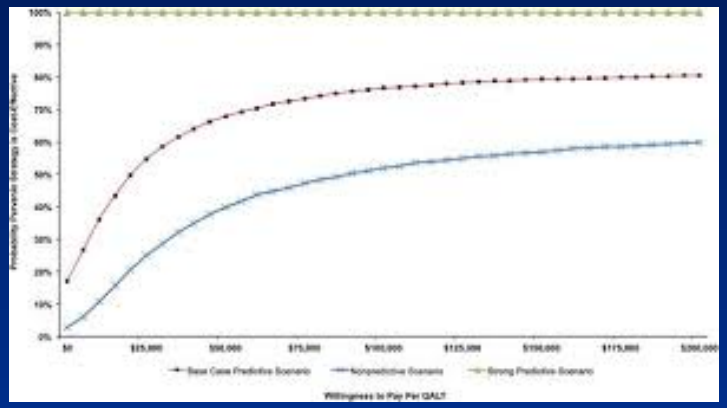
The Urgent Need for Streamlining Coding, Coverage and Payment Policies

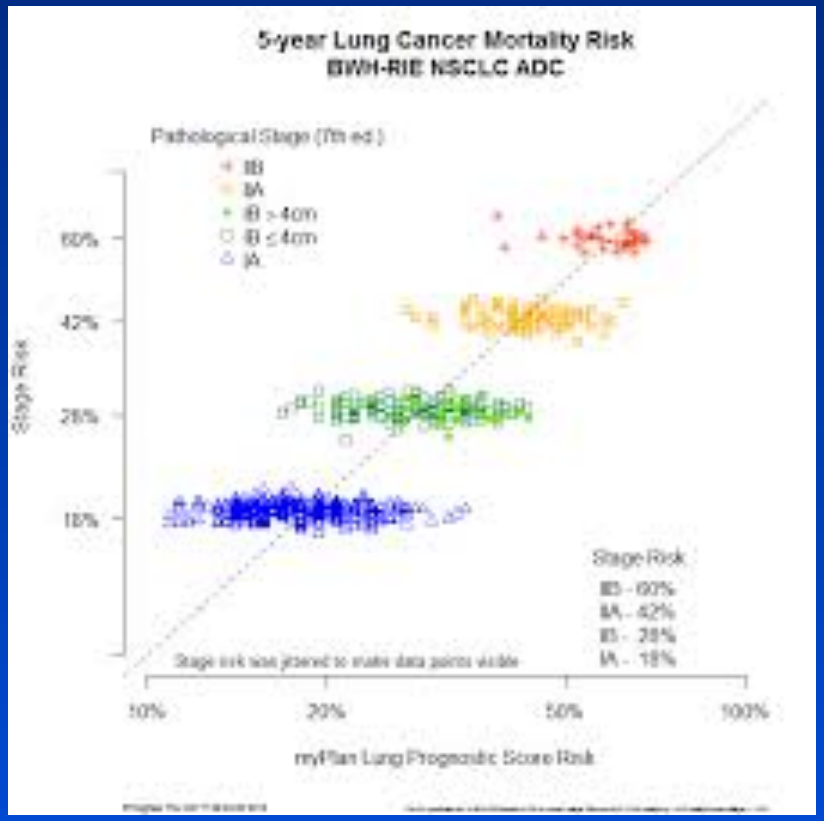
Value-Based Reimbursement Policies to Reward Dx Innovation and Recover Escalating R&D Costs

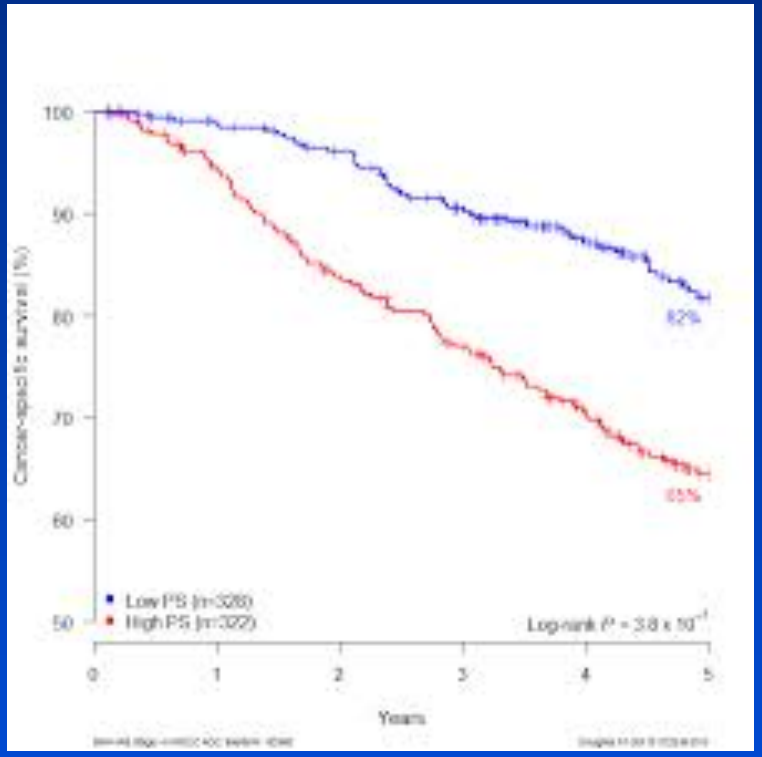
Citation		Country	Results
First author	Year		
Klang[10]	2010	Israel	Cost-effective (ICER $10 770 per QALY gained)
Kondo[11]	2010	Japan	Cost-effective (ICER $3 848 in LN- population; ICER $5 685 in LN+)
O'Leary[12]	2010	Australia	Cost-effective (ICER $9 986 per QALY gained)
Tsoi[13]	2010	Ontario, Canada	Cost-effective (ICER< $65 000 per QALY gained in 2008 CAD)
Hassan[14]	2011	Ontario, Canada	Cost-saving
de Lima Lopes[16]	2012	Singapore	Cost-saving (SGD $2 344 in net direct and indirect costs)
Liaropoulos[17]	2011	Greece	Cost-saving
Madaras[18]	2011	Hungary	Cost-effective (ICER €12 600 to €25 300 per QALY gained)
Paulden[19]	2011	Ontario, Canada	Cost-effective (ICER $29 000 per QALY in AO low risk); cost-saving in AO high risk

Abbreviations: AO, Adjuvant! Online; LN-, lymph node negative; LN+, lymph node positive; ICER, incremental cost-effectiveness ratio; NCCN, National Comprehensive Cancer Network; QALY, quality adjusted life year; CAD, Canadian dollars; SGD, Singapore dollars.

Early Stage Lung CA

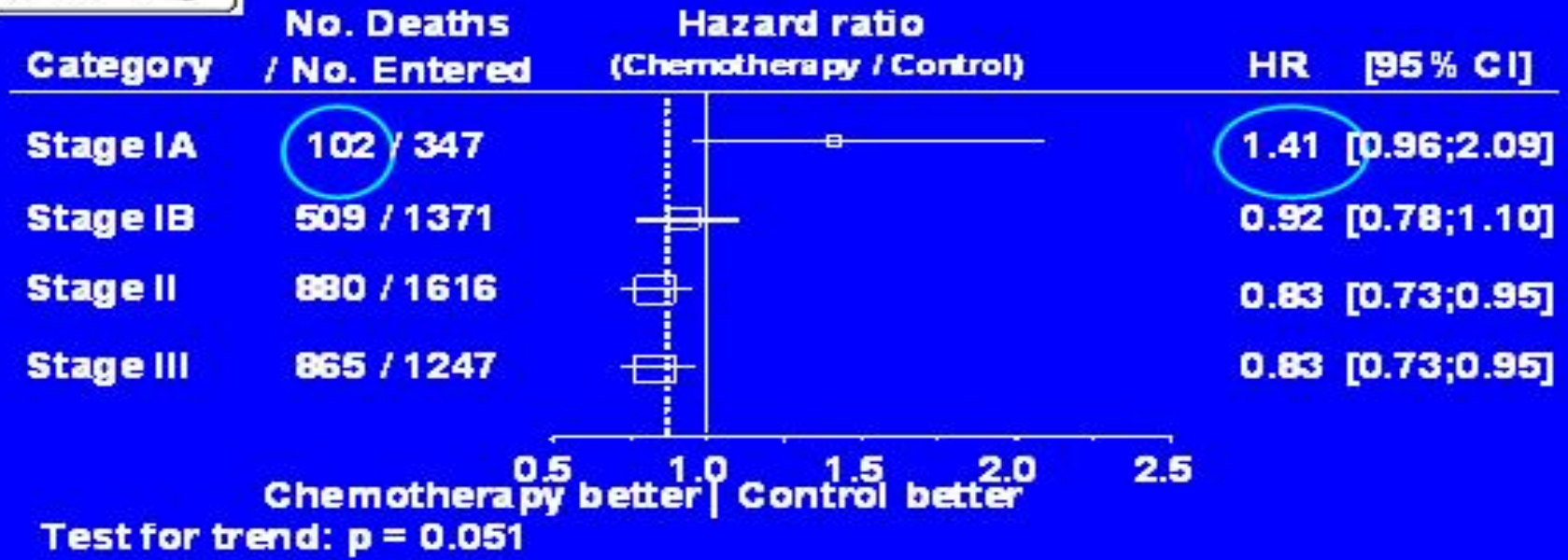






CT effect & stage

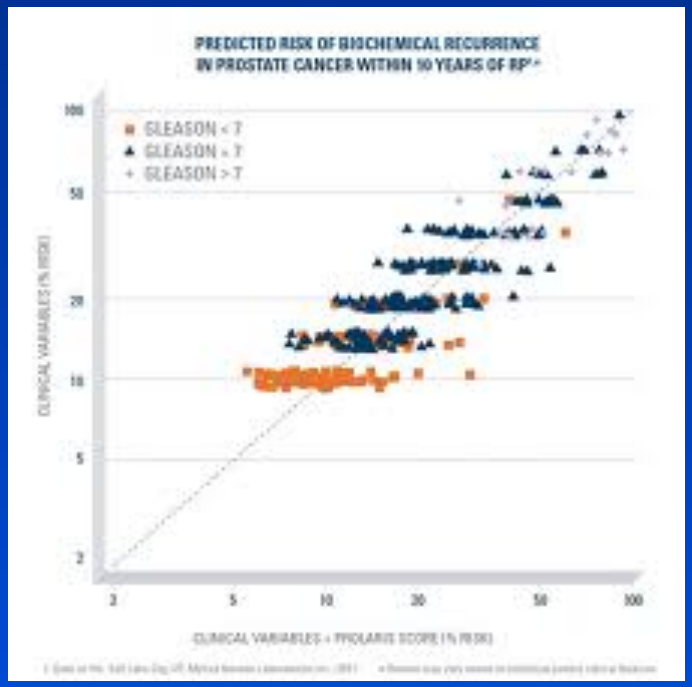
Institut de cancérologie GUSTAVE ROUSSY

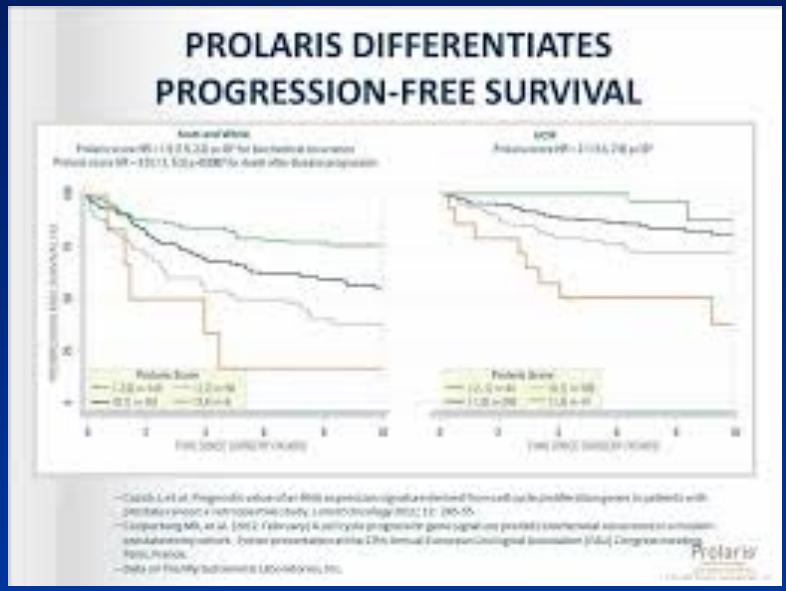


CT may be detrimental for stage IA, but stage IA patients were generally not given the potentially best combination cisplatin+vinorelbine (13% of stage IA patients versus ~43% for other stages) 11/15

ASCO 2006 A#7008 Pignon JP, et al.

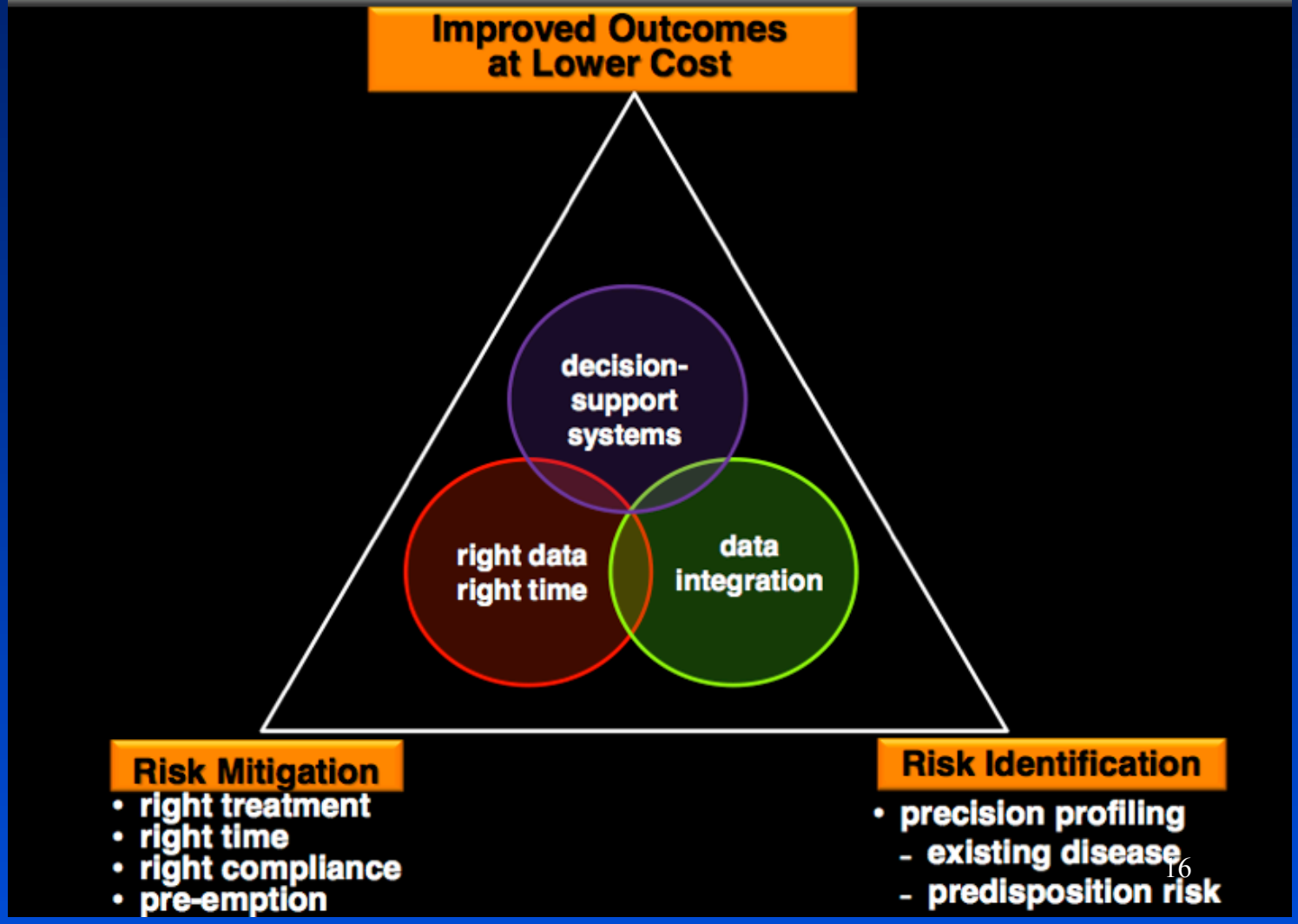
Prostate CA





Active surveillance versus aggressive therapy (surgery or XRT)

Information and Evidence
The Core Elements of Proficient Healthcare

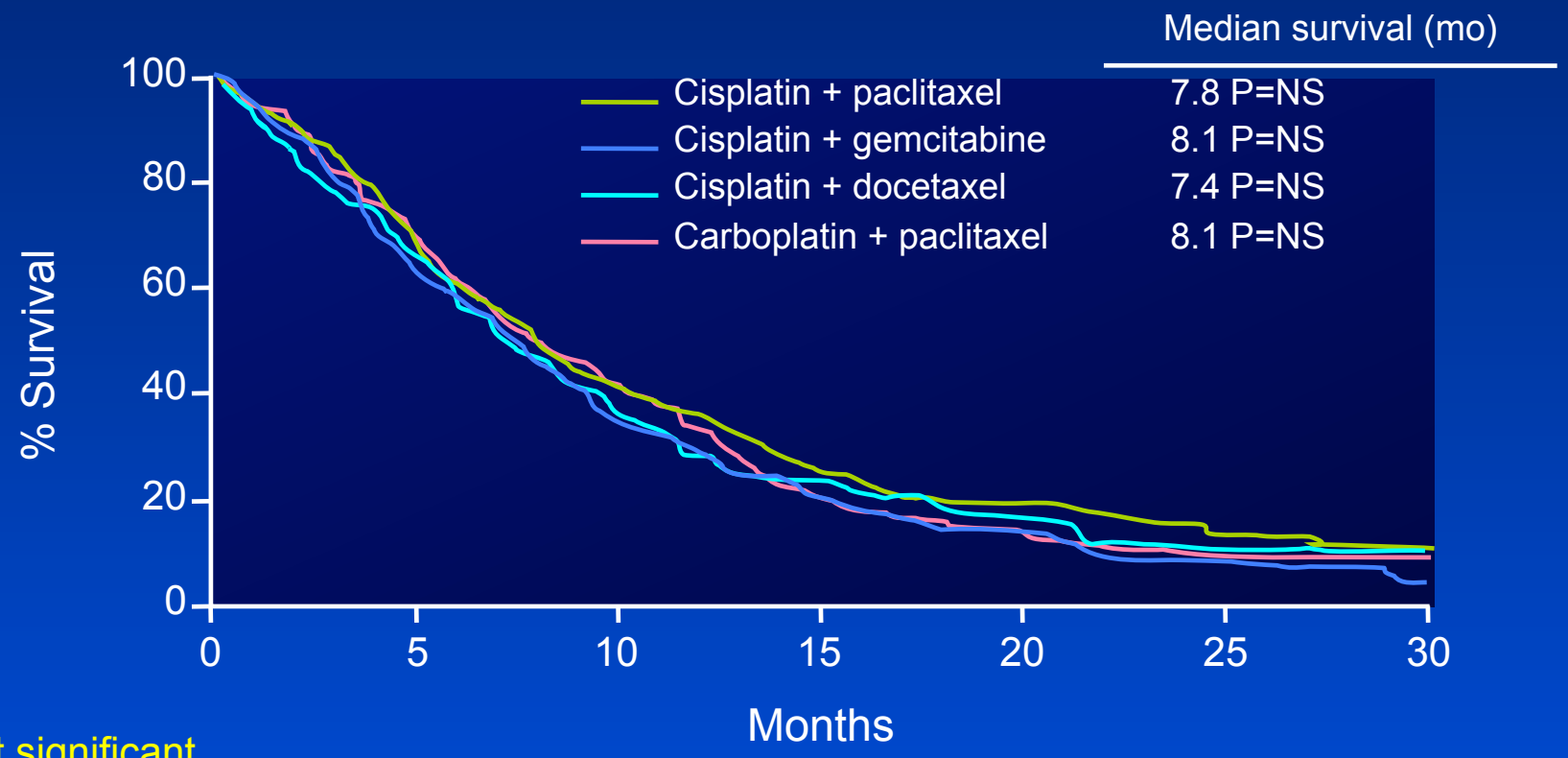


1990's Case Study

- 65 yo male with NSCLCA
- 39 yo female with NSCLCA

Would your treatment plan be the same for these 2 patients?

Advanced Stage NSCLC: Platinum-based doublet chemotherapy (ECOG 1594)



NS = not significant.

Schiller et al. N Engl J Med. 2002;346:92.

2008 Case Study

- 65 yo male who smokes, has a squamous histology
- 39 yo female who is a non-smoker with a adenocarcinoma

Would your treatment plan be the same for these 2 patients?

PEMETREXED AND HISTOLOGY

1st-line NSCLC (N=1725)
PEM/cisplatin
vs gemcitabine HCl/cisplatin

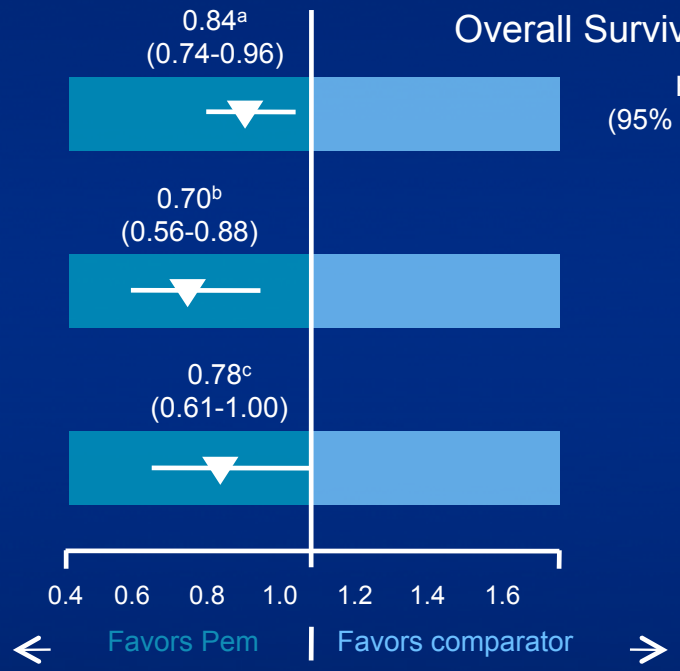
Nonsquamous
(N=1252)

Maintenance NSCLC (N=663)
PEM + BSC vs placebo + BSC

Nonsquamous
(N=481)

2nd-line NSCLC (N=571)
PEM vs docetaxel

Nonsquamous
(N=399)



a Adjusted for gender, stage, basis of diagnosis, and performance status.

b Unadjusted hazard ratios are provided.

c Adjusted for ECOG PS, time since prior chemotherapy, disease stage, and gender.

31.Scagliotti G, et al. Oncologist. 2009;14:253-263.
32.Ciuleanu T, et al. Lancet. 2009;374:1432-1440.

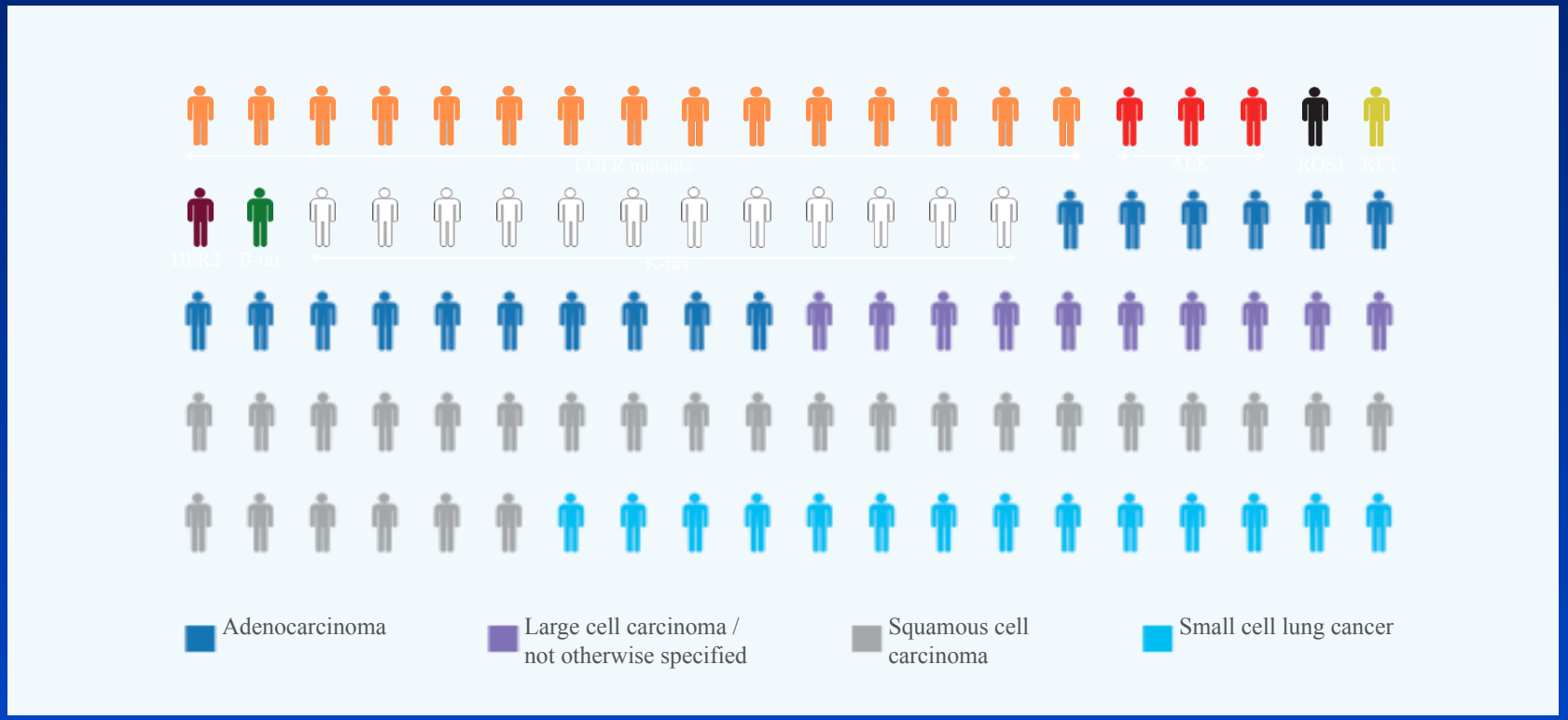
Today: Case Study

- 65 yo male who smokes, has a squamous histology, low ERCC1 and low RRM1, ALK-, EGFR wt, cMET+

- 39 yo female who is a non-smoker with a adenocarcinoma, EGFR mutation +, and high ERCC1 and high RRM1

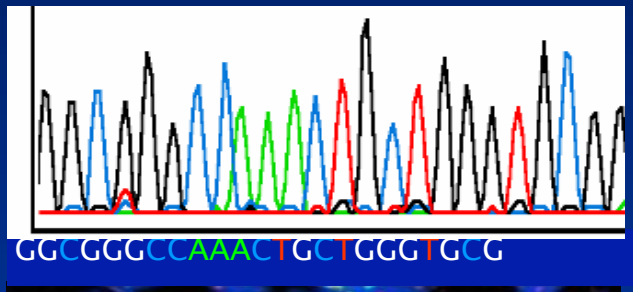
Would your treatment plan be the same for these 2 patients?

Where We Have Evolved – Molecular Subtypes

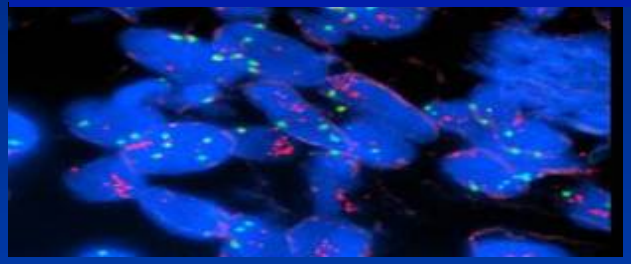


Adapted from Scagliotti, GV. Individualized therapy in lung cancer: where are we in 2012? 13th International Lung Cancer Congress; July 19-22, 2012; Huntington Beach, CA. - See more at: http://www.onclive.com/publications/obtn/2012/september-2012/molecular-discoveries-pave-way-for-rapid-advances-in-lung-cancer/2#sthash.0tvpHdzu.dpuf

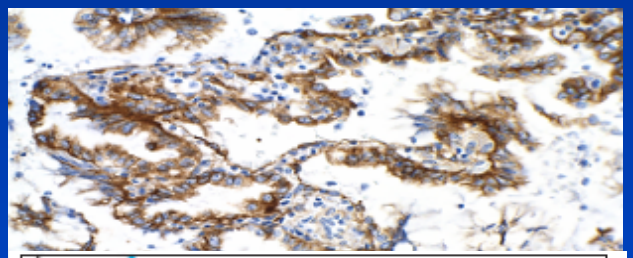
Potential Predictive Biomarkers of EGFR Pathway Activation



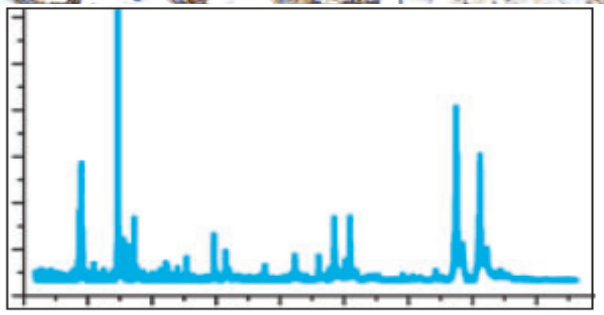
- EGFR mutation status by gene sequencing



- EGFR gene copy number by fluorescence in situ hybridization (FISH)

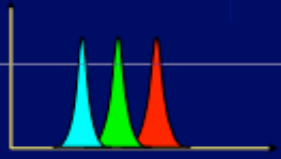


- EGFR protein expression by immunohistochemistry (IHC)

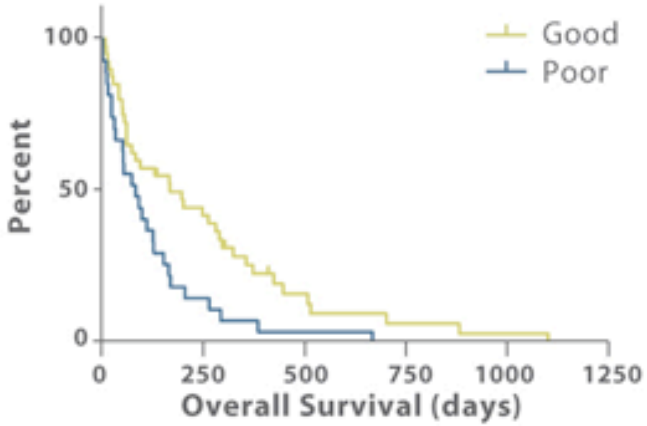


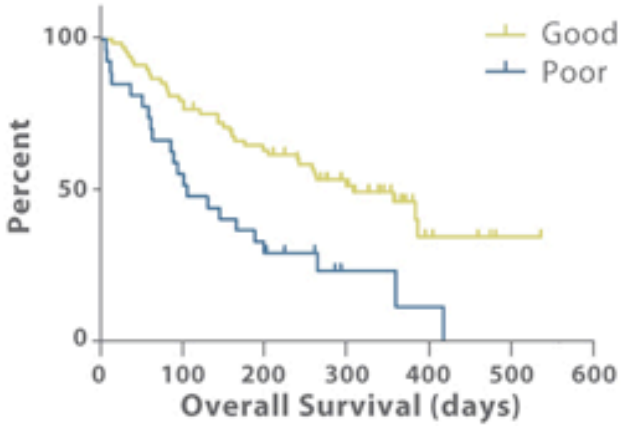
- Serum Proteomics by MALDI MS

Serum MALDI-TOF-MS to predict sensitivity to gefitinib



Survival Analysis of VeriStrat Validation Sets*



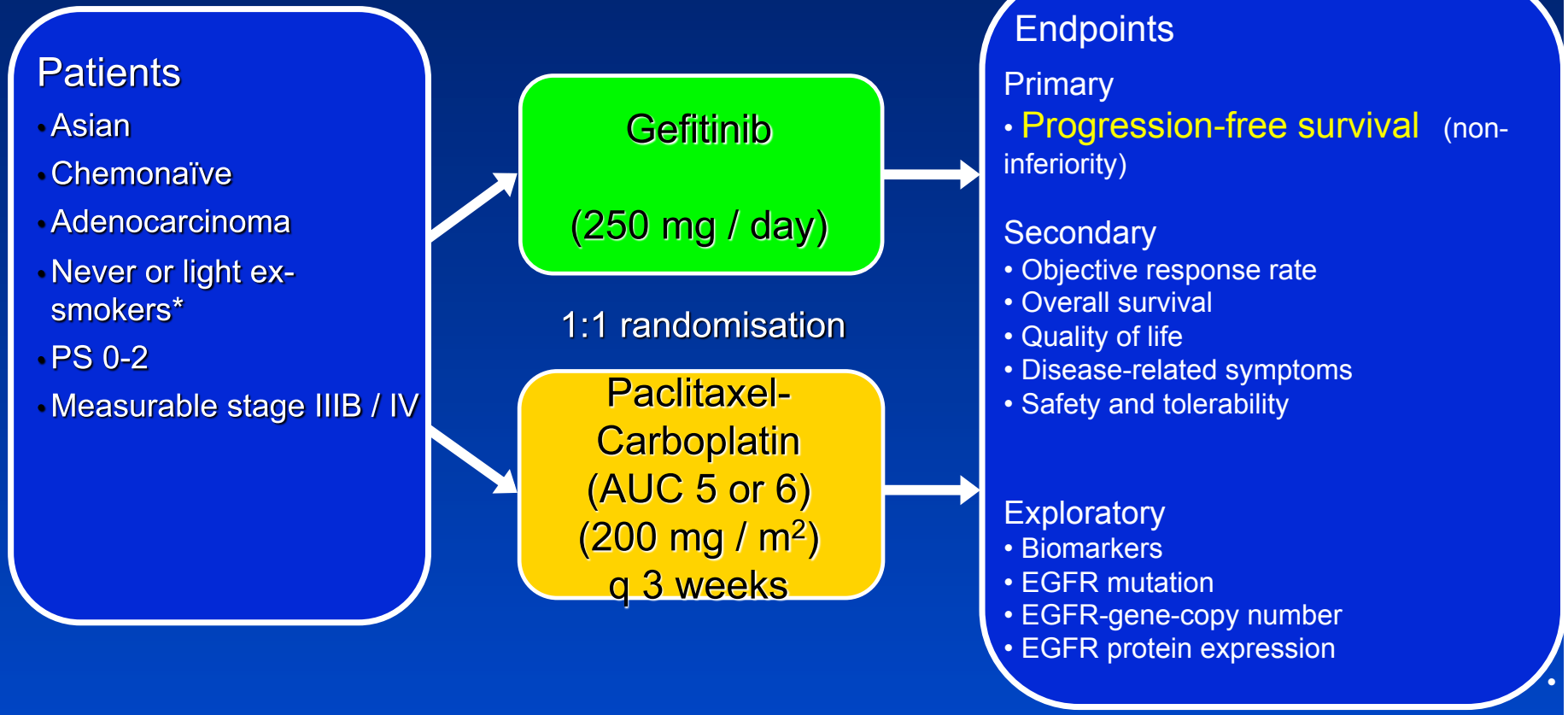


Italian B
N=67 (39 Good, 27 Poor)
Events: 35 Good, 27 Poor
Median survival: 207 days (Good), 92 days (Poor)
***p*=0.0062, HR=0.45**

ECOG 3503
N=96 (69 Good, 27 Poor)
Events: 36 Good, 25 Poor
Median survival: 306 days (Good), 107 days (Poor)
***p*=0.0007, HR=0.33**

*Data and figures have been updated since publication in Taguchi et al.[1]

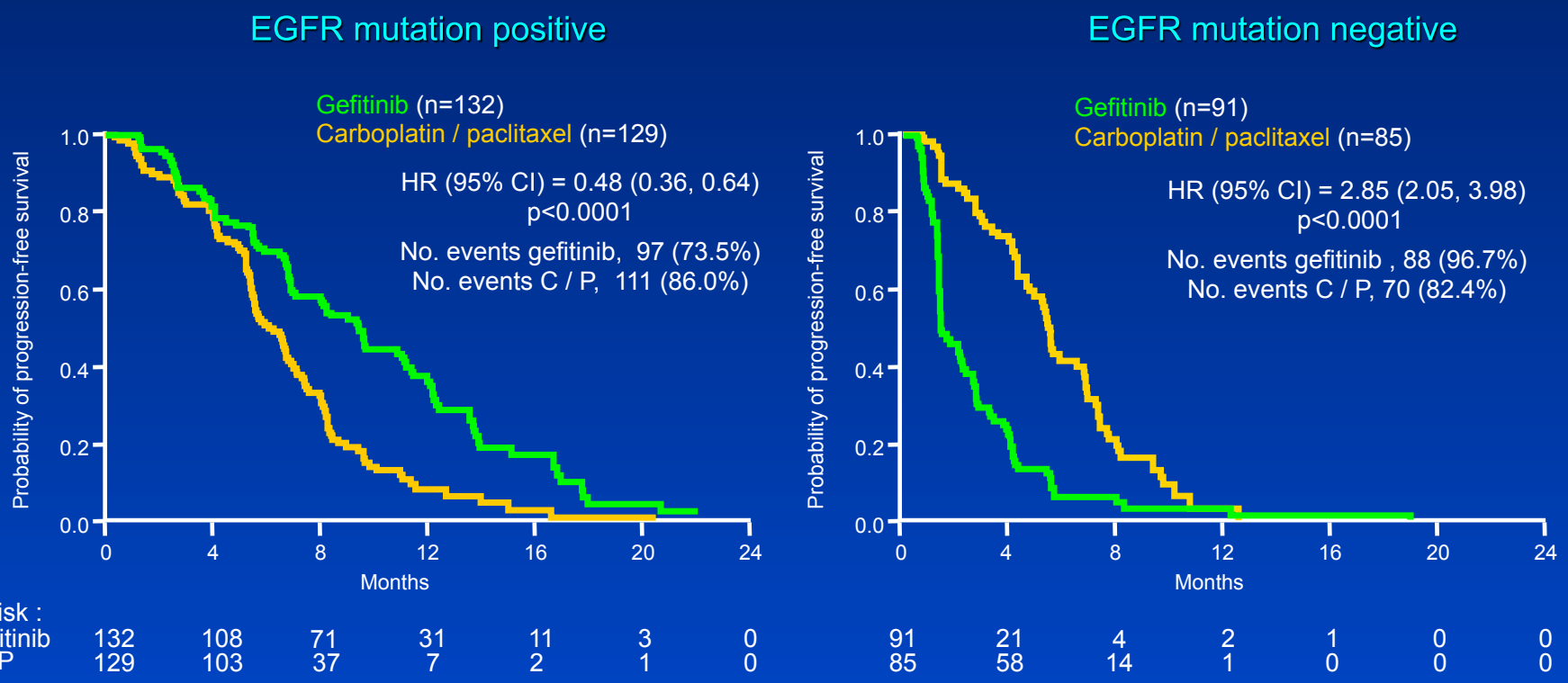
IPASS: Gefitinib vs Chemotherapy in Asia



At ESMO Sept 15 2008 reported to be Positive for PFS: Gefitinib

Mok: ESMO, 2008

IPASS: Progression-free survival in EGFR mutation positive & negative patients



Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

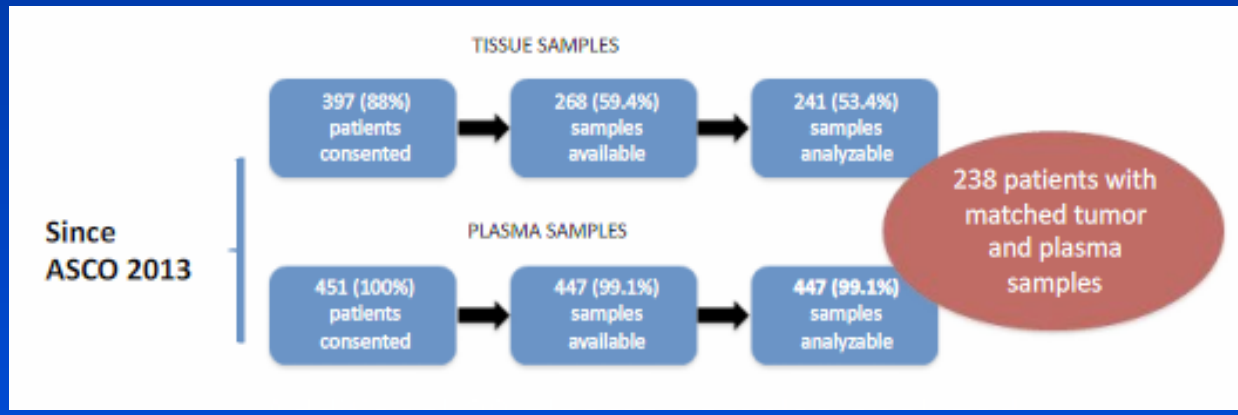
Mok: ESMO, 2008

IASLC 15th World Conference on Lung Cancer
October 27 – October 30, 2013
Sydney, Australia
WCLC.IASLC.ORG

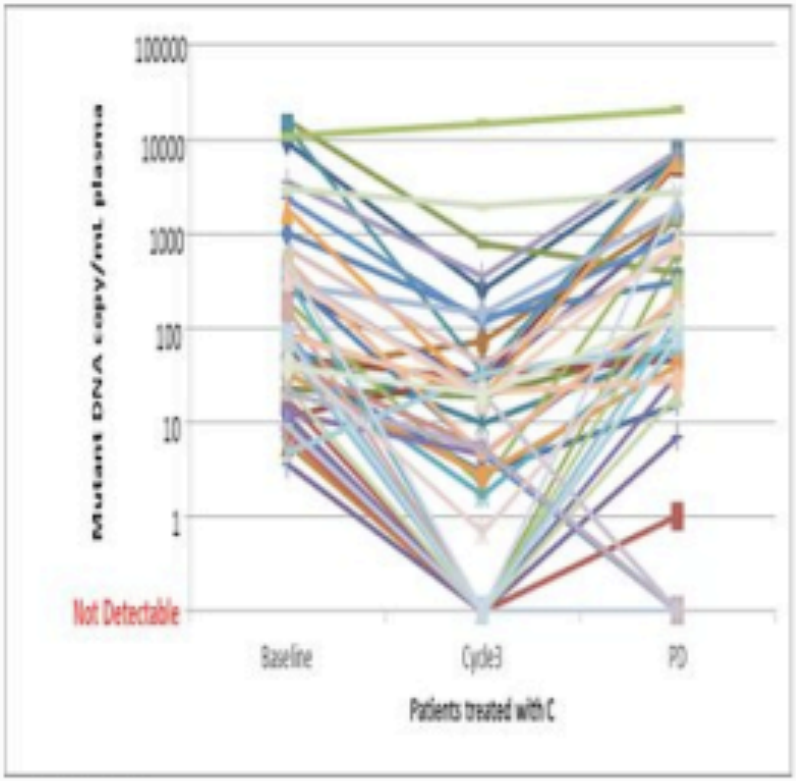
Dynamic Change in Plasma DNA EGFR Mutation (pEGFR Mut) in FASTACT-2

Tony Mok, Yi Long Wu, Matt Truman, Lin Wu, et al.

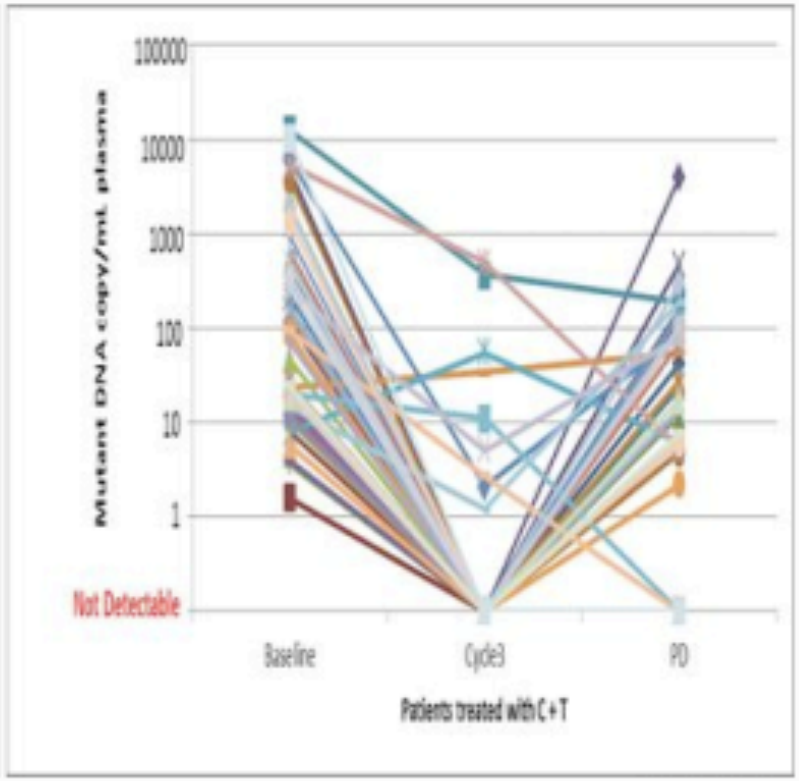
The Chinese University of Hong Kong, Department of Clinical Oncology, Prince of Wales Hospital, Shatin, NT, Hong Kong



Dynamic Mutant DNA change during therapy



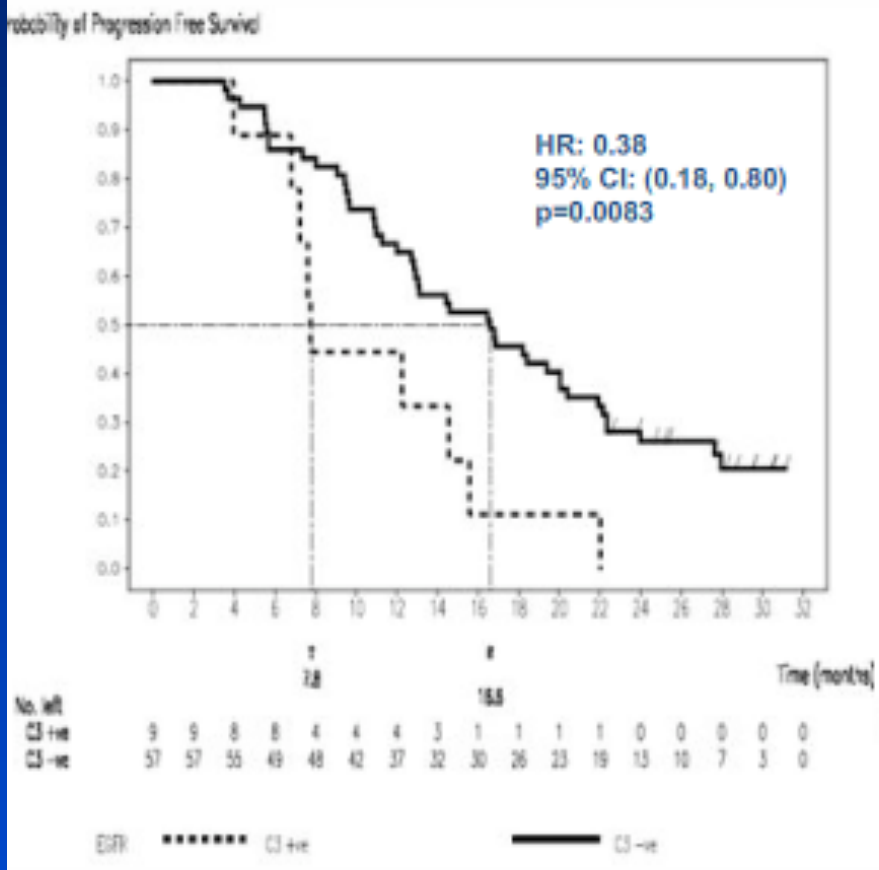
Chemo + Placebo



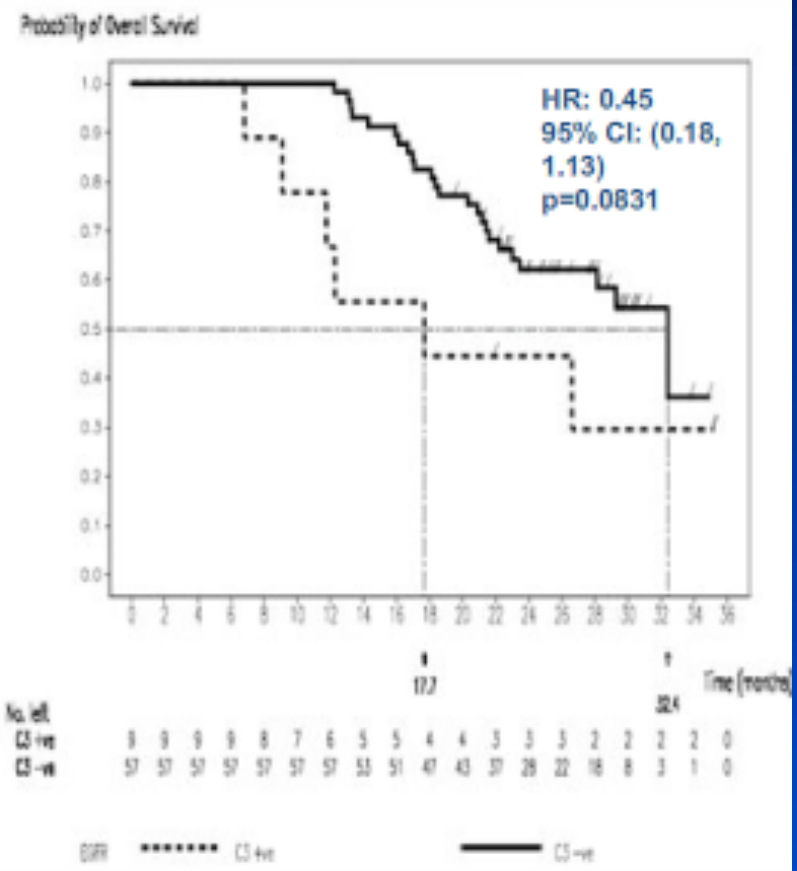
Chemo + erlotinib

Positive plasma DNA for EGFR at Cycle 3 predicts PFS and OS (Chemo + Erlotinib arm only)

PFS

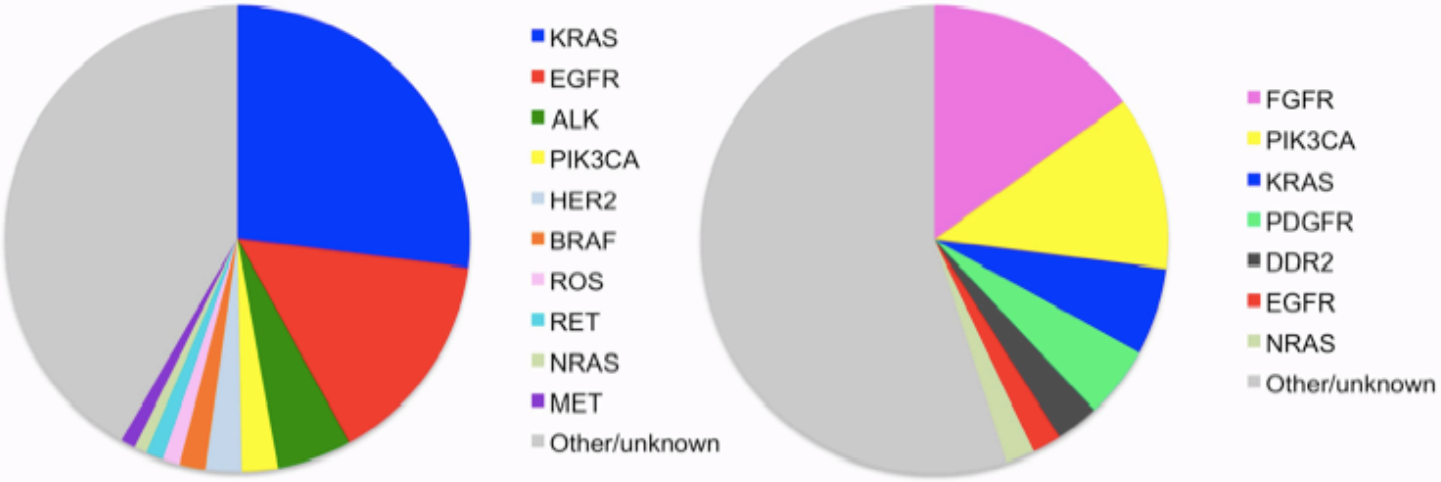


OS



Genetic Profiles by Histologic Subtype

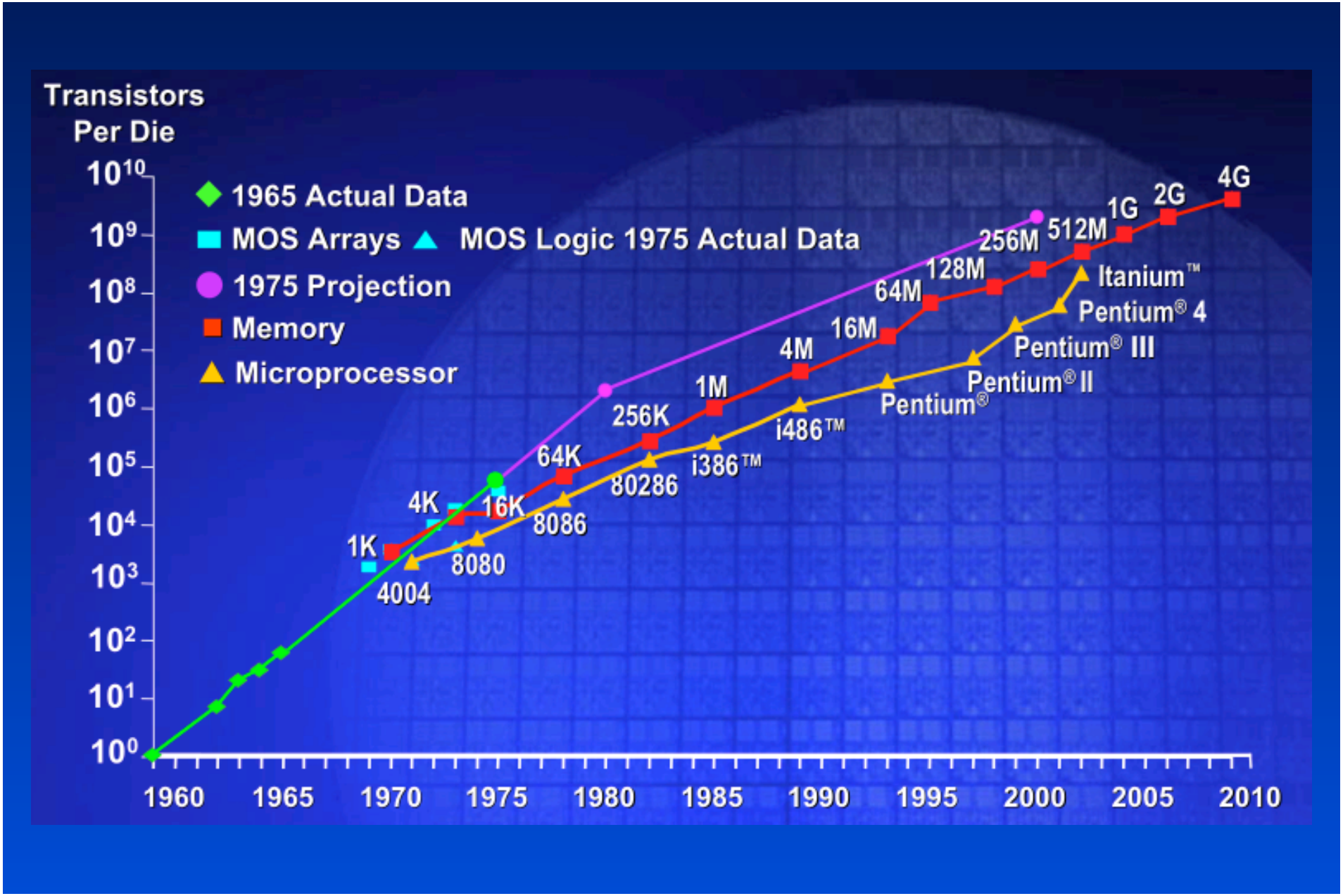
Oncogenic drivers differ between adenocarcinomas and squamous cell carcinomas

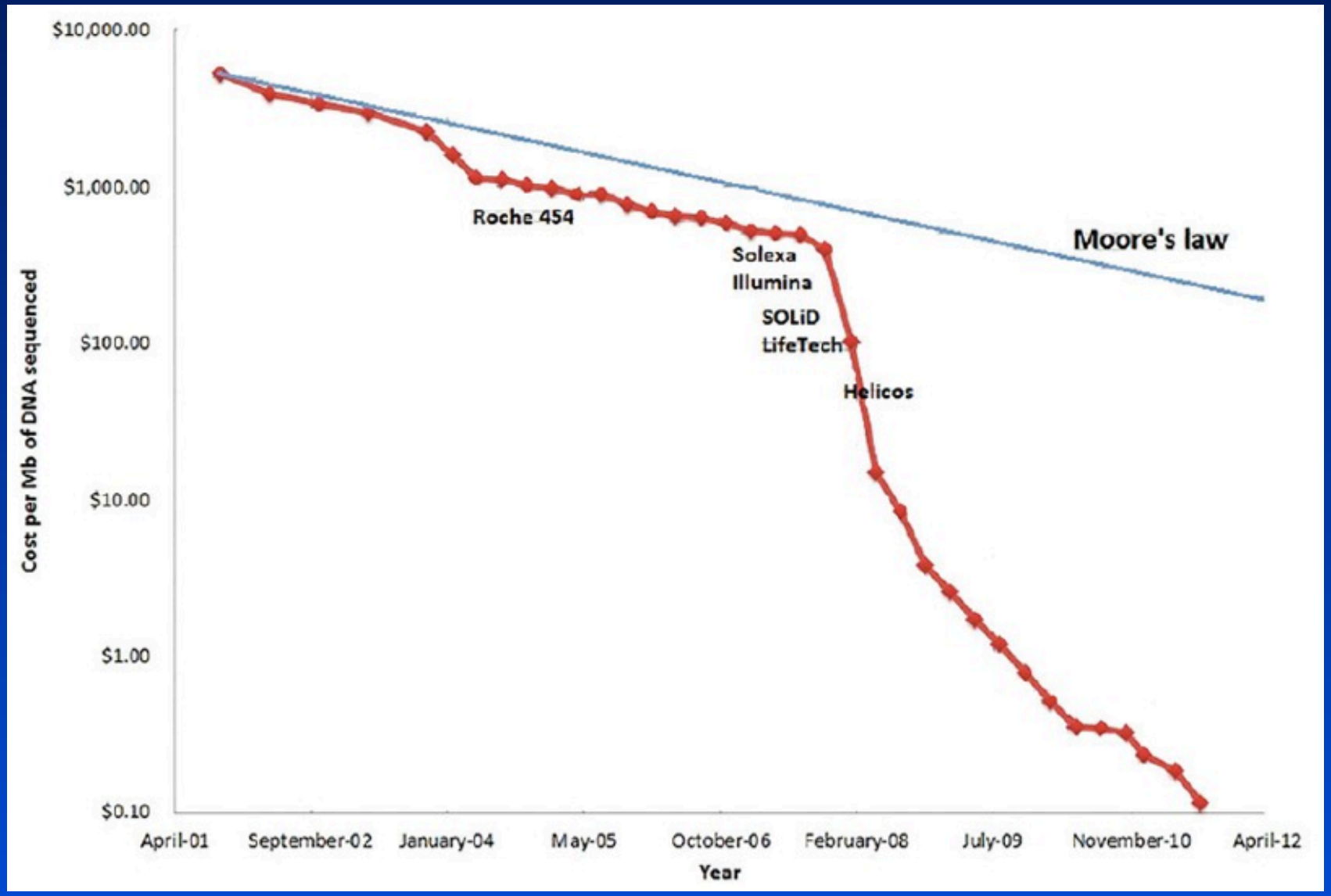


Adenocarcinoma

Squamous cell carcinoma

Sequist et al., Ann Oncol 22:2616, 2011; Bergethon et al., JCO Jan 3, 2012; Weiss et al., Sci Transl Med 2:62ra93. 2010; Kris et al., WCLC 2011; Hammerman et al., Cancer Discovery 1:78, 2011; AJ Iafrate, personal communication


Transistors
Per Die
10^{10}
10^{9}
10^{8}
10^{7}
10^{6}
10^{5}
10^{4}
10^{3}
10^{2}
10^{1}
10^{0}
1965 Actual Data
MOS Arrays
MOS Logic 1975 Actual Data
1975 Projection
Memory
Microprocessor
1K
4K
16K
64K
256K
1M
4M
16M
64M
128M
256M
512M
1G
2G
4G
4004
8080
8086
80286
i386™
i486™
Pentium®
Pentium® II
Pentium® III
Pentium® 4
Itanium™
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010


$10,000.00
$1,000.00
$100.00
$10.00
$1.00
$0.10
Cost per Mb of DNA sequenced
Roche 454
Solexa
Illumina
SOLiD
LifeTech
Helicos
Moore's law
April-01
September-02
January-04
May-05
October-06
February-08
July-09
November-10
April-12
Year

Drug Development Risk v Reward

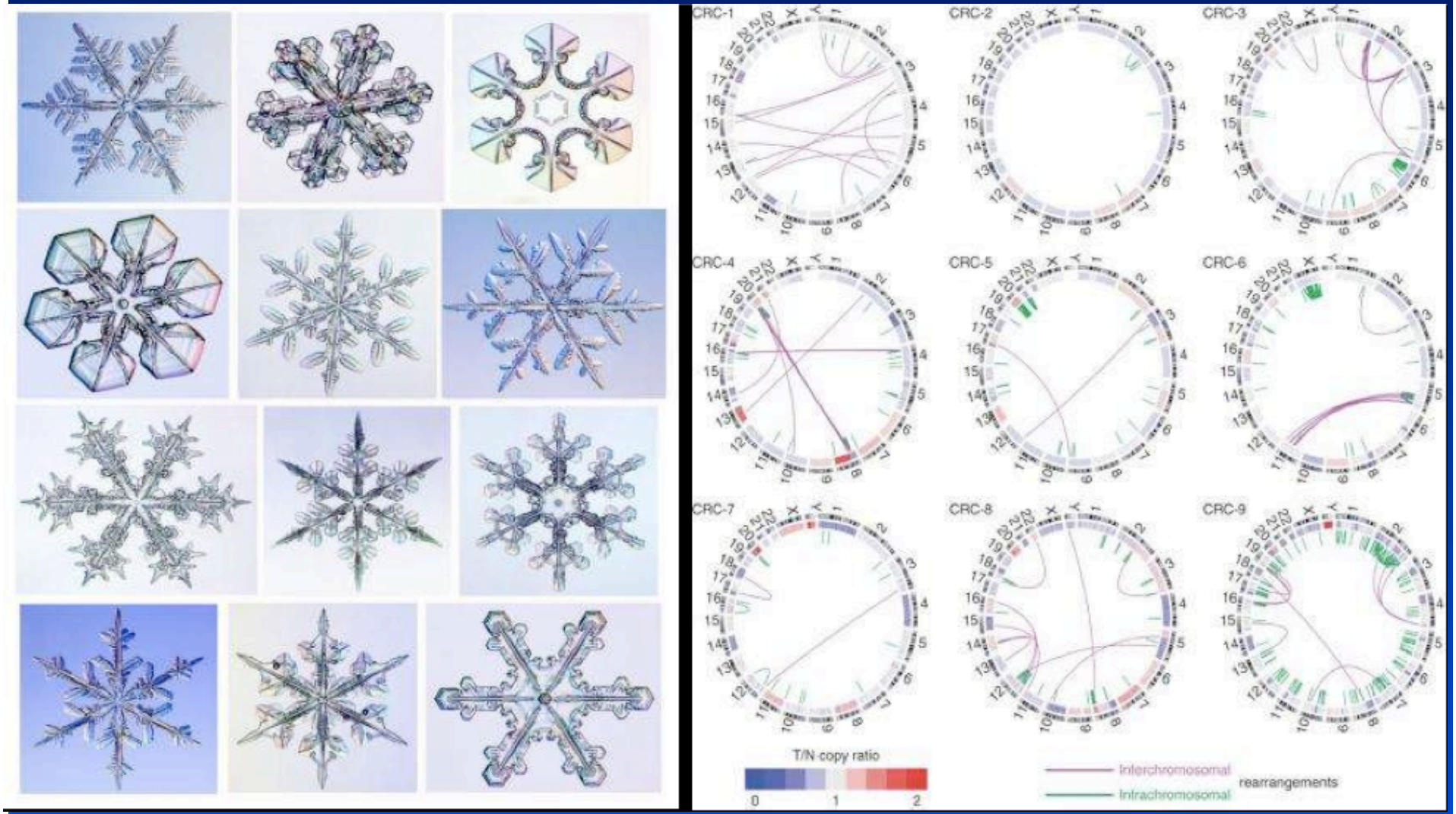
Average oncology drug development cost: $802 million.

- Some drugs over $1.5 billion (Iressa)
- Only 8 percent of oncology new molecular entities (NMEs) reach the market
- 6 out of 10 candidates fail in Phase III testing (Iressa)
  - Iressa is now approved in Europe for use in treating adults with locally advanced or metastatic non-small cell lung cancer, **whose tumors have an EGFR mutation**.

PLX4032 Approach

- Start with mutation (BRAFV600E)
- Search for compounds active against specific mutation
- Development cost about **$40 million**
- **70% response rate**
- **Plexxikon sells to Diichi Sankyo in 2011 for $935 million**

Drug target focus critical to controlling costs of future drug development


CRC-1
CRC-2
CRC-3
CRC-4
CRC-5
CRC-6
CRC-7
CRC-8
CRC-9
T/N copy ratio
0
1
2
Interchromosomal
Intrachromosomal
rearrangements

"Malignant Snowflakes"
The Extravagant Genetic and Phenotypic Diversity of Solid Malignancies

- inter-patient heterogeneity
- intra-patient heterogeneity
  - zonal within a lesion (primary and metastases)
  - dormant micrometastases versus metastases
  - different metastases
- new patterns of temporal variability with tumor progression
- selection effects of Rx regimen and emergence of clones with pre-existing or acquired Rx resistance

Disruptive Technologies

• sailing ships	versus	steam ships
• horses	versus	automobiles
• trains	versus	aeroplanes
• large mainframe computers	versus	personal devices
• valve-based electronics	versus	transistor devices
• labor-intensive agriculture and manufacturing	versus	mechanization, automation, robotics
• bricks and mortar 'bigbox' stores	versus	web-based suppliers

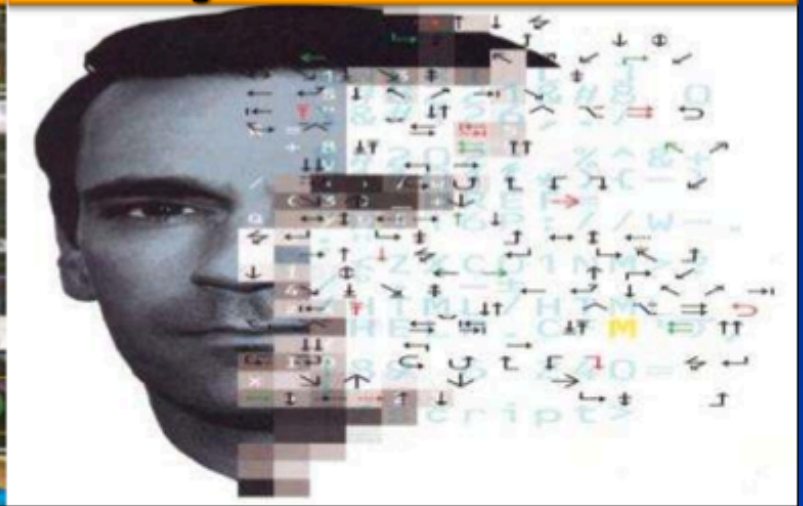
Disruptive Technologies

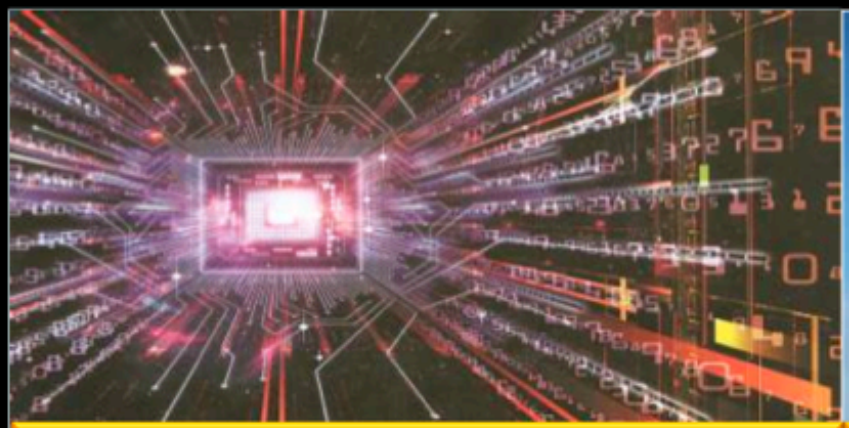
- major shifts in business models and markets
- typically unanticipated/denied by market leaders/KOLs
- emerge at margins of existing fields
- emerge at points of convergence (fusion) between previously different fields (science/markets)
- typically driven by newcomers or sudden, radically different events (existential threats)

Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

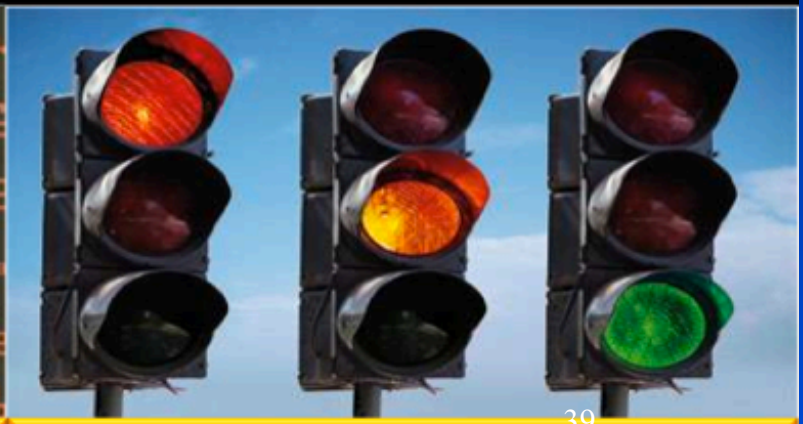
Data Deluge

Cognitive Bandwidth Limits





Automated Analytics and Decision Support



Facile Formats for Actionable Decisions

Discovery consists of seeing what everbody else has seen and thinking what no one else has thought…

-Albert Szent-Gyorgi 1962