ASU COMPLEX ADAPTIVE SYSTEMS
ARIZONA STATE UNIVERSITY

THE CLEARITY FOUNDATION
IMPROVING TREATMENT OPTIONS FOR OVARIAN CANCER PATIENTS

Confronting the Cancer Challenge: The Need for New Diagnostic and Treatment Strategies

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Presentation at Clearity Foundation's Personalized Medicine in Oncology Series
Moores Cancer Center, La Jolla, CA

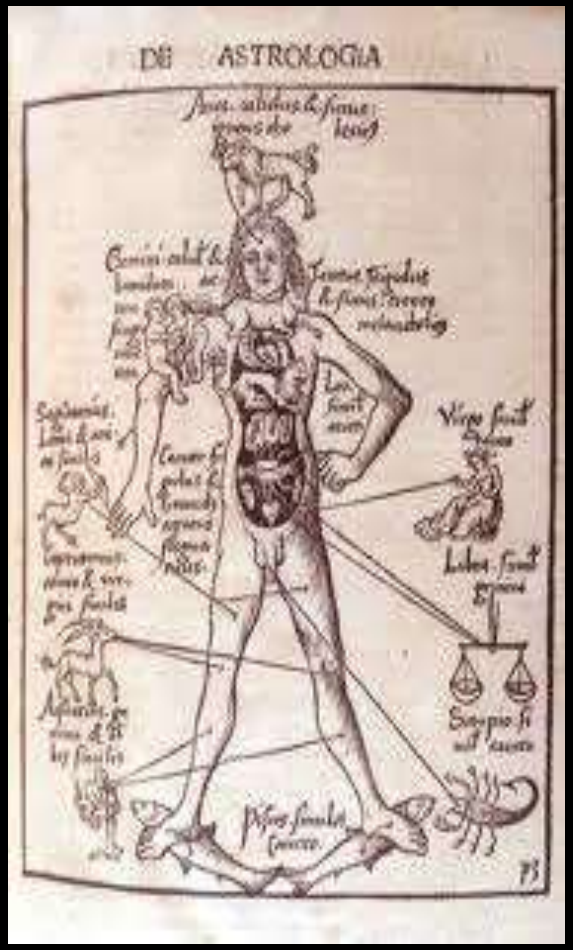
October 8, 2013

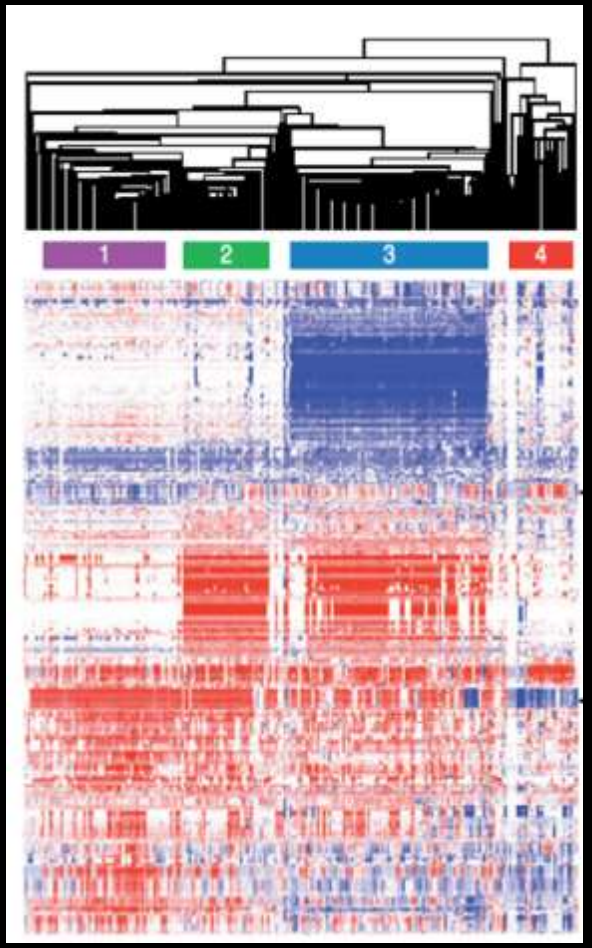
Declared Interests

Board of Directors	Scientific Advisory Boards	Advisory/Consultancy
–Monsanto –Exelixis –Caris Life Sciences –Bulletin Atomic Scientists	–Synthetic Genomics –Burrill and Co. –Pfizer –University of Michigan, Alfred Taubman Medical Research Institute	- USG Depts. of Defense and Homeland Security - Institute of Medicine Global Forum

Slides available @ http://casi.asu.edu/

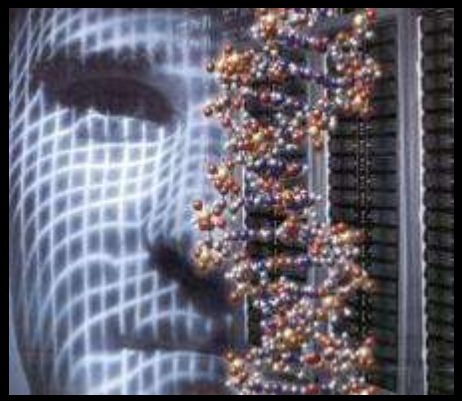
Medical Progress:
From Superstitions to Symptoms to Signatures



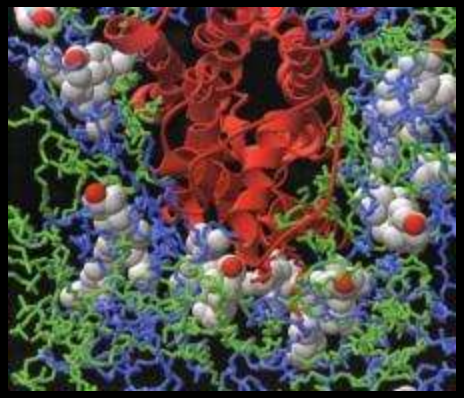


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

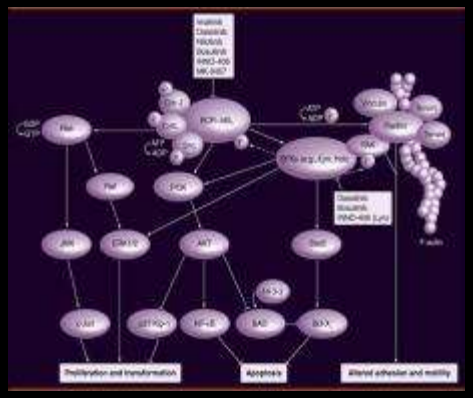
Genomics



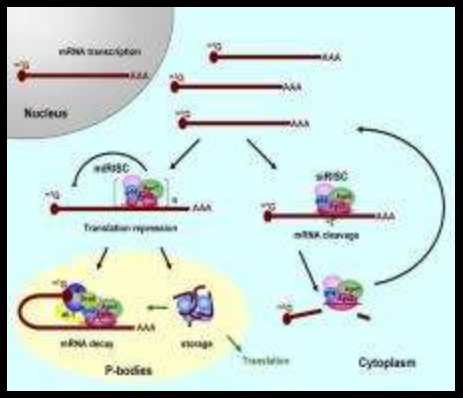
Proteomics

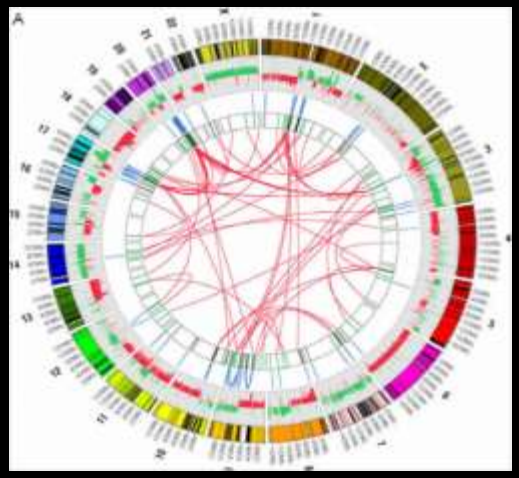


Molecular Pathways and Networks



Network Regulatory Mechanisms



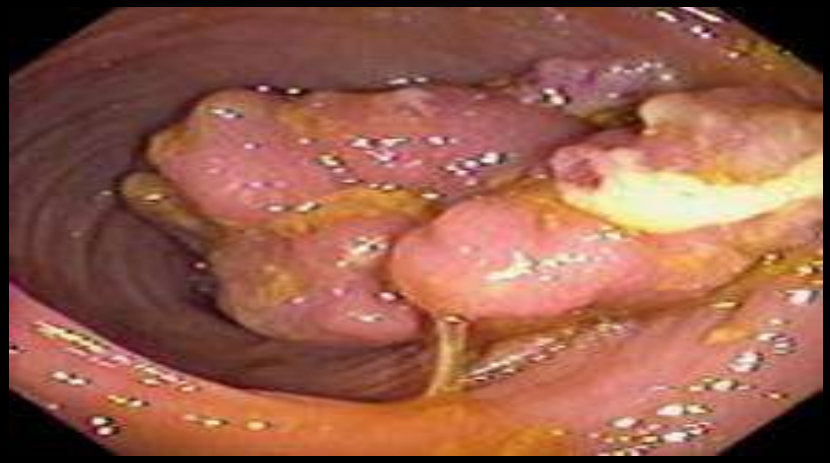


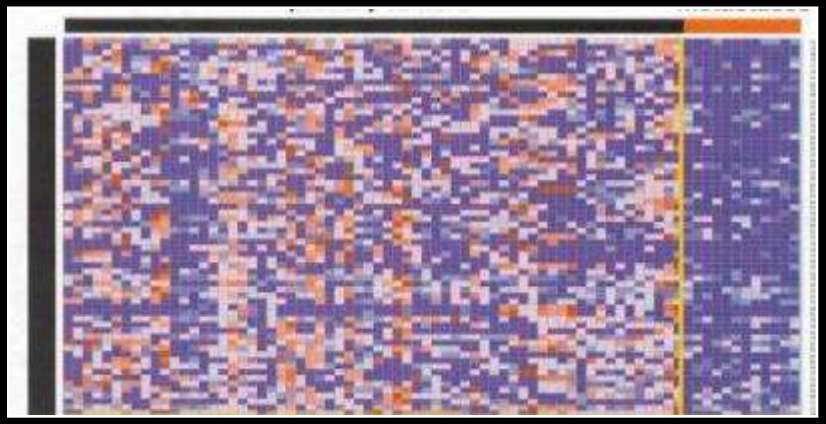
ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

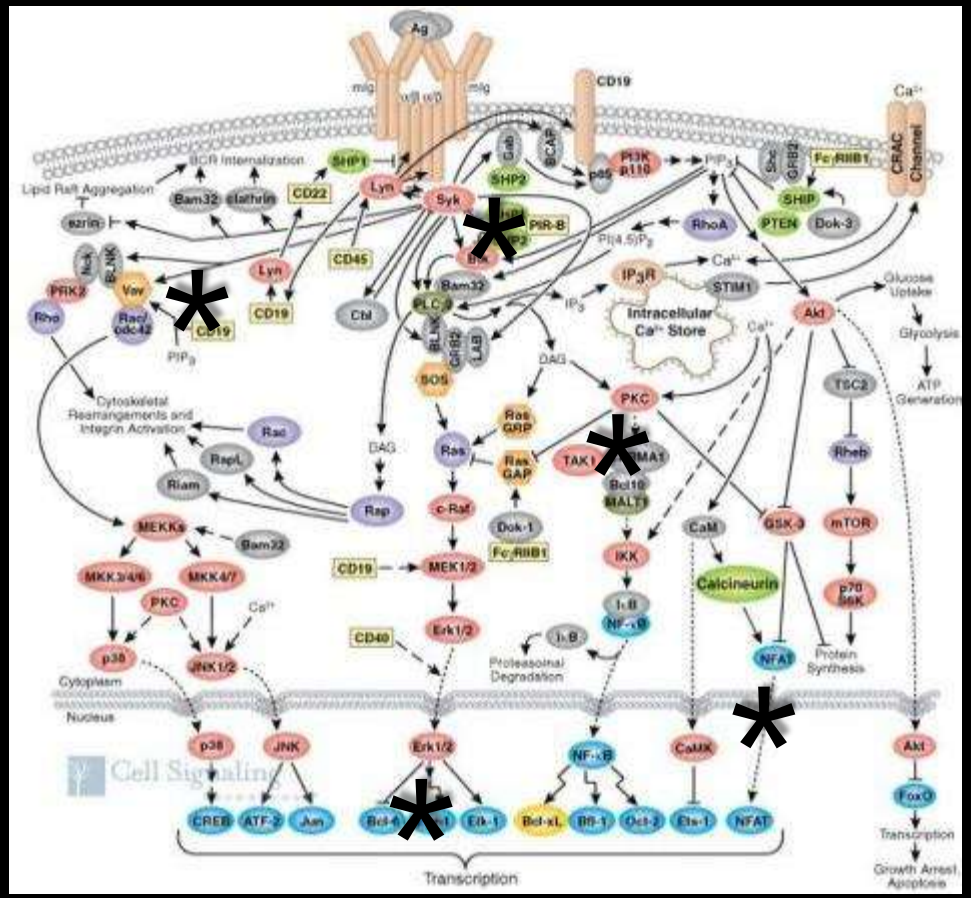
"Omics" Profiling to Identify Disease Subtypes (+ or - Rx Target)





Multiplex Profiling

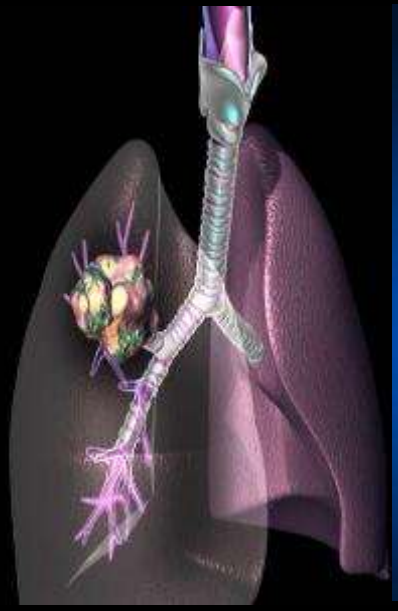
Altered Signaling Network Structure and ID of Molecular Targets for MDx and/or Rx Action



Right Rx for Right Disease Subtype

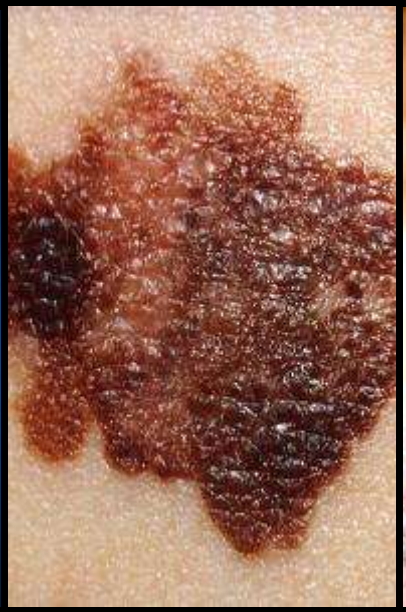
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics (CoDx)– the Right Rx for the Right Disease (Subtype)

Her-2+
(Herceptin)
(Perjeta)



EML4-ALK
(Xalkori)

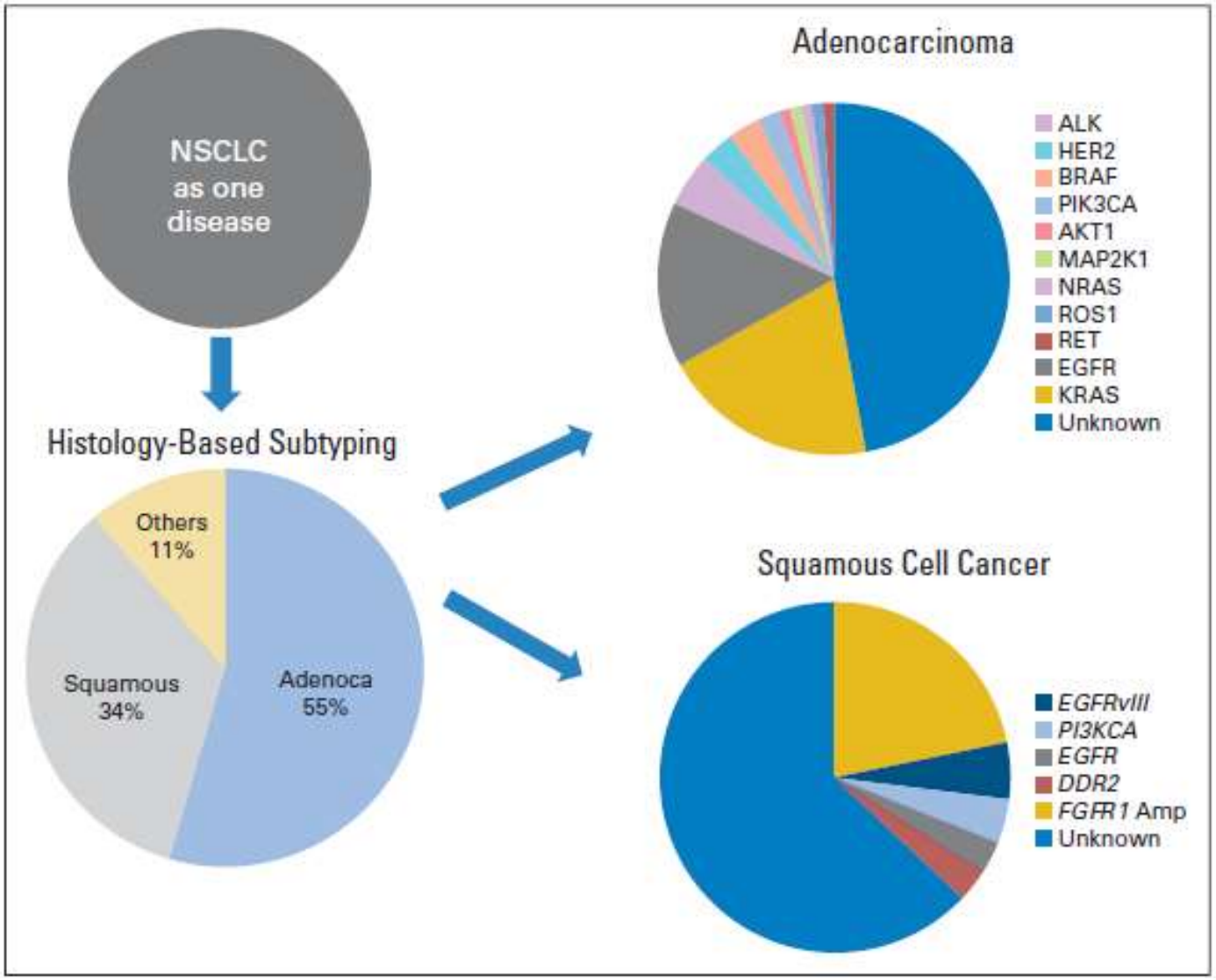
K-ras
(Erbitux)
(Vectibix)



BRAF-V600
(Zelboraf)

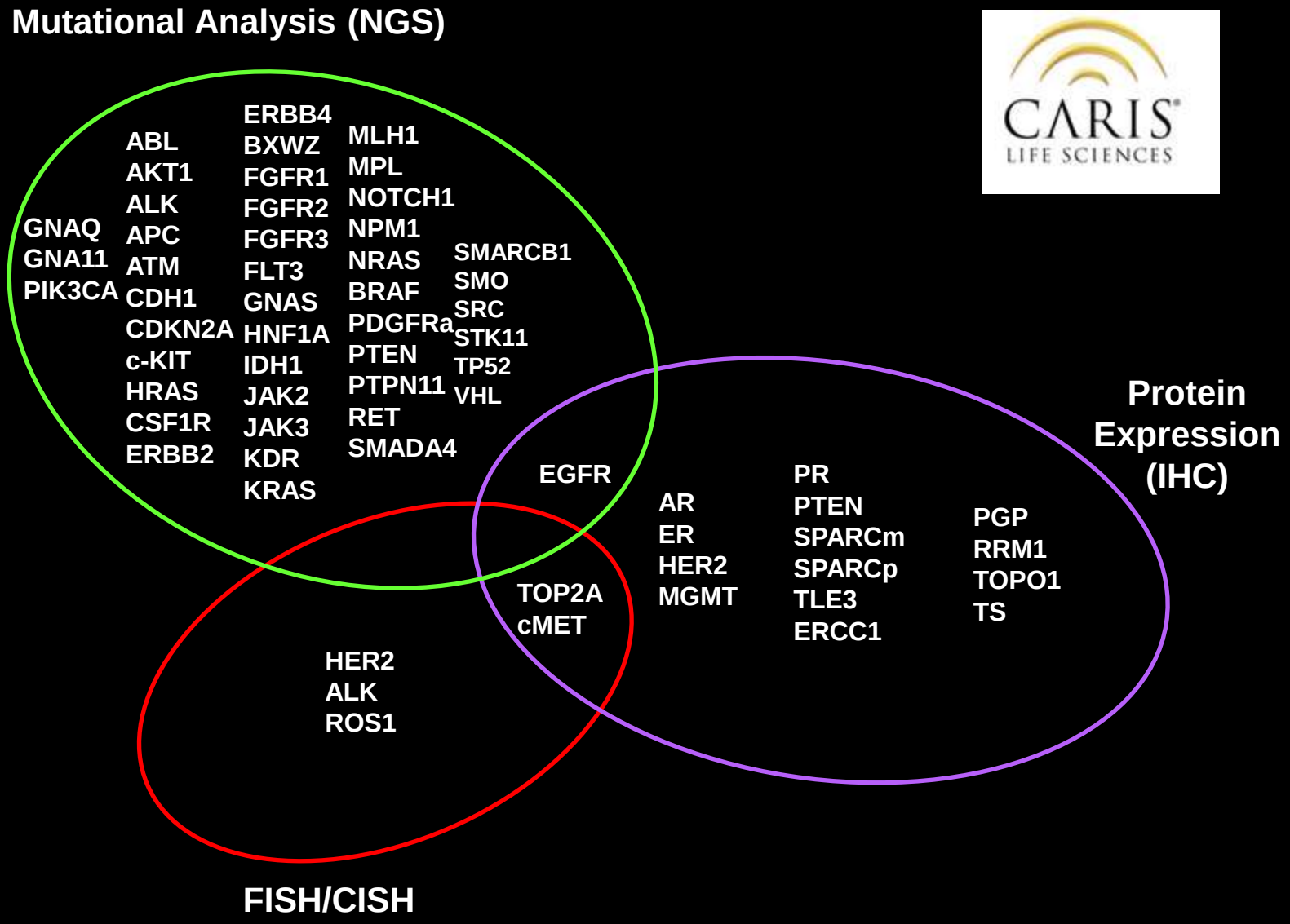
CFTR-G551
(Kalydeco)

The Evolution of the Classification of NSCLC



From: T. Li et al. (2013) JCO 31, 1039

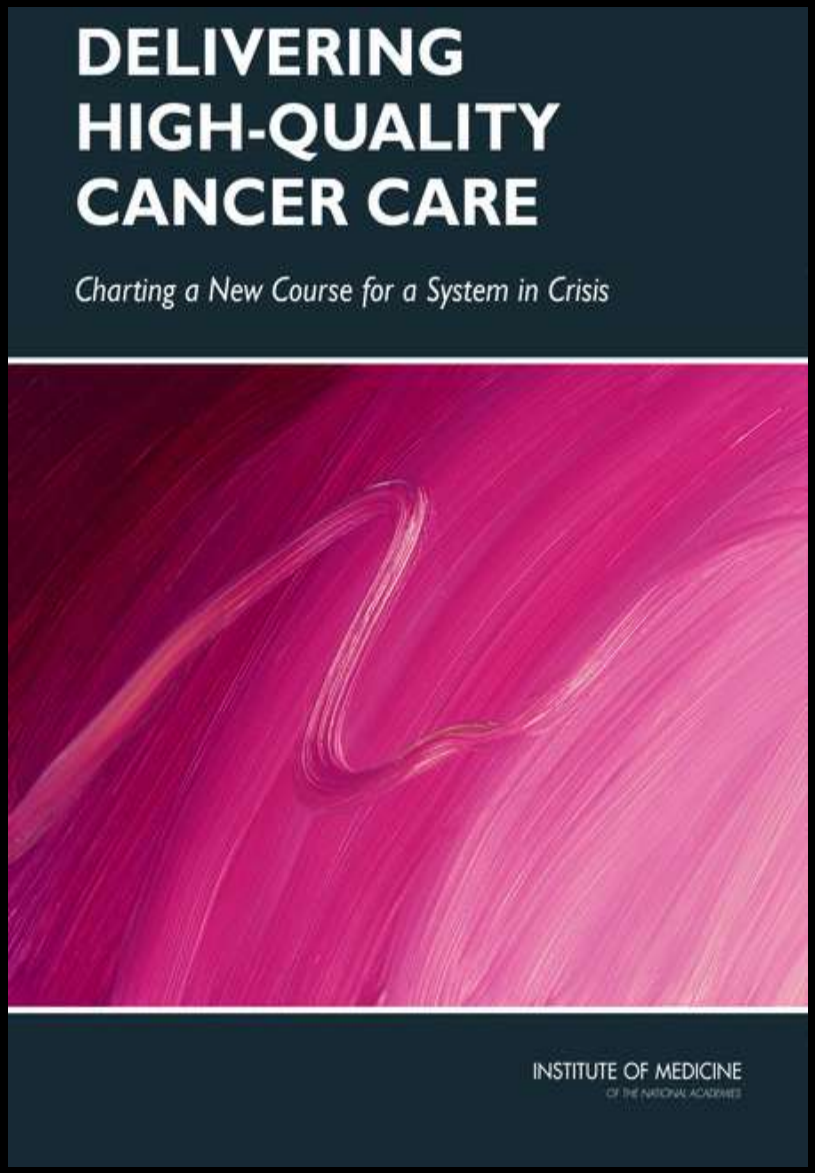
Molecular Profiling in Cancer and Identification of Actionable Rx Targets

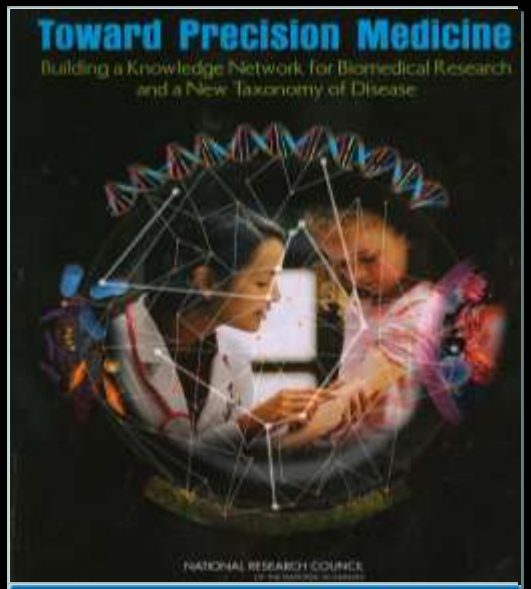


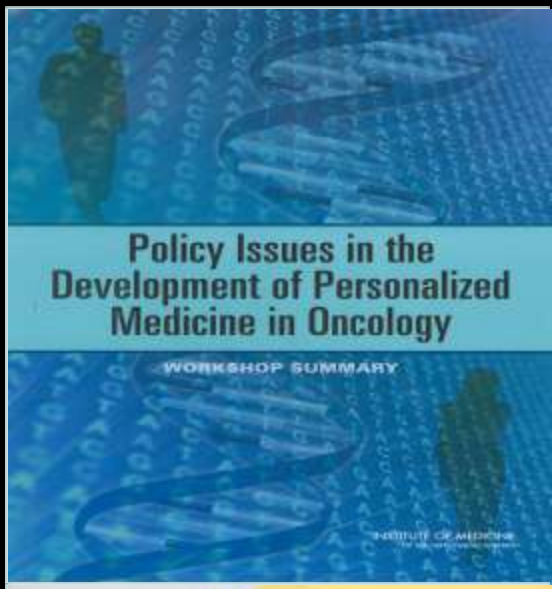
Molecular Diagnostics (MDx) and Tumor Profiling as the Intellectual Foundation of Rational Care

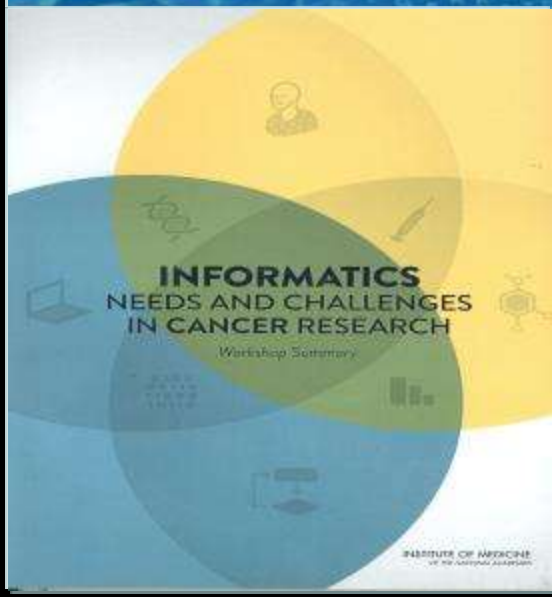
- subtyping of cancers based on molecular profile(s)
- from one-size-fits-all treatment to targeted Rx
- rational selection of Rx based on presence or absence of Rx ‘target’ in a patient’s tumor
- monitoring of Rx response for early detection of Rx resistance and more agile, adaptive change in Rx (or palliation recommendation)
- elimination of futile therapy (cost, QOL)
- shift focus to optimum therapy plus ethical shift to increase use of palliative care

The Current Status of Cancer Care

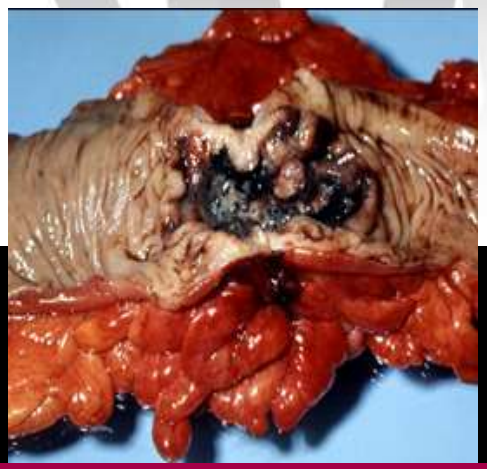


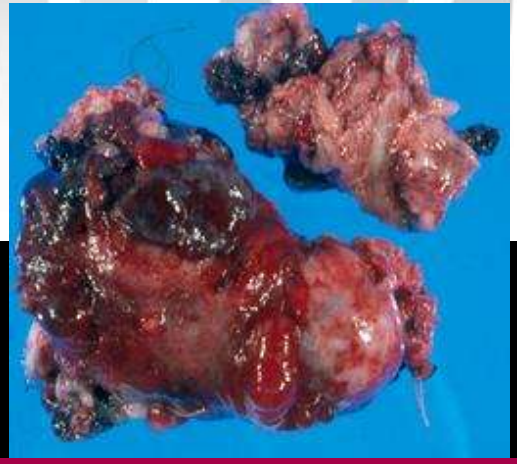


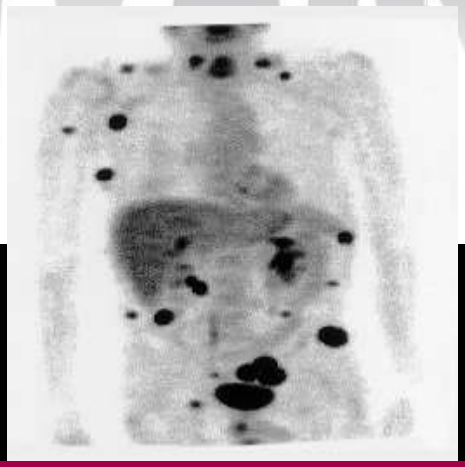


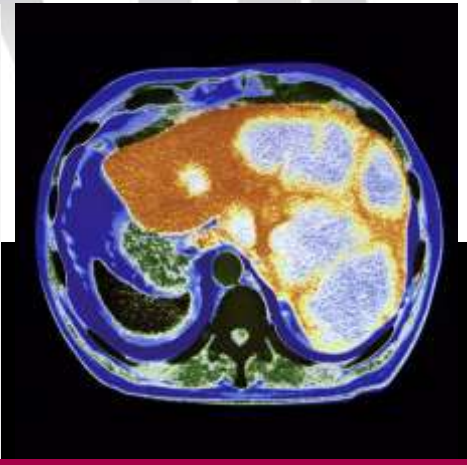


US Cancer Deaths (2012)







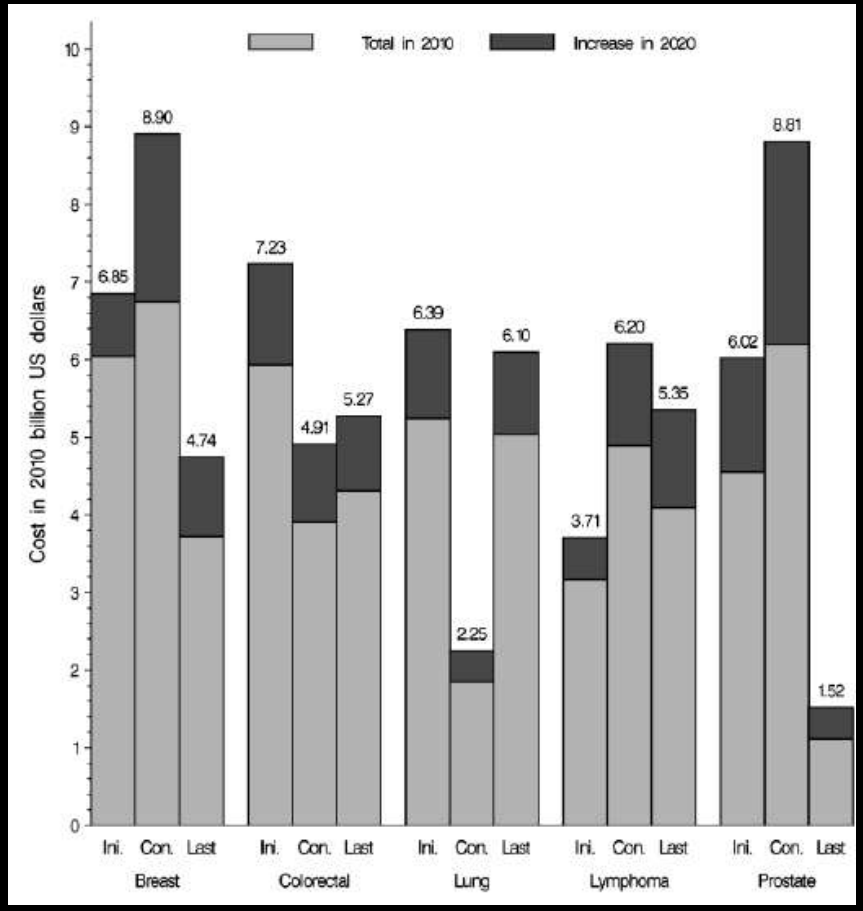


US Cancer Prevalence Estimates 2010 and 2020

Site	# People (thousands) 2010	2020	% change
Breast	3461	4538	31
Prostate	2311	3265	41
Colorectal	1216	1517	25
Melanoma	1225	1714	40
Lymphoma	639	812	27
Uterus	588	672	15
Bladder	514	629	22
Lung	374	457	22
Kidney	308	426	38
Leukemia	263	240	29
All Sites	13,772	18,071	32

From: A.B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

Estimates of U.S. National Expenditures for Cancer Care 2010



$124 billion and projected to rise to $207 billion (66% increase) by 2020

Ini. = within 1 year of Dx; Con = continuing; Last = last year

From: A. B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

The Need for New Conceptual Strategies to Improve the Detection and Therapy of Metastatic Disease

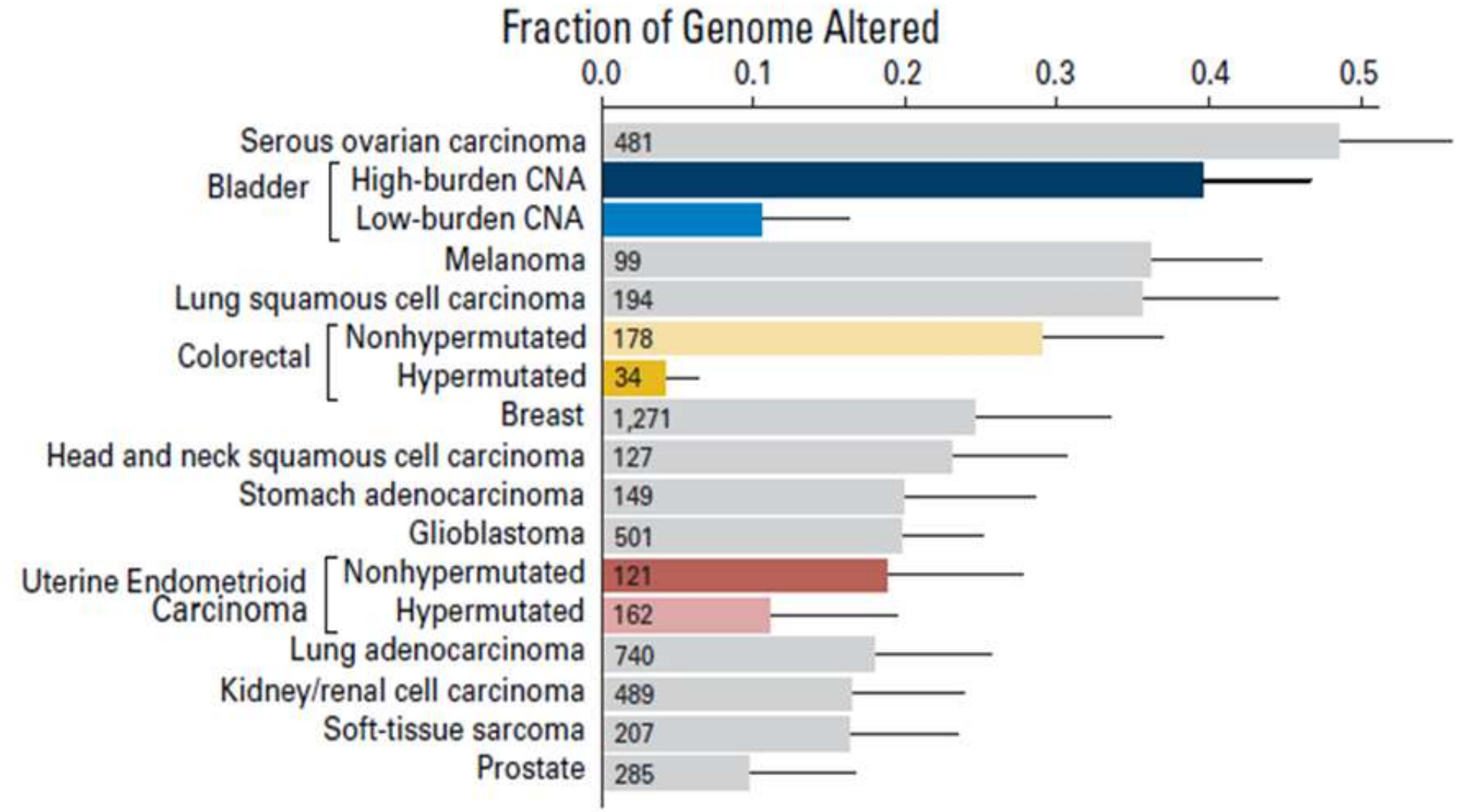
too many drugs fail!

too many biomarkers fail!

clinical trials are too expensive and too long!

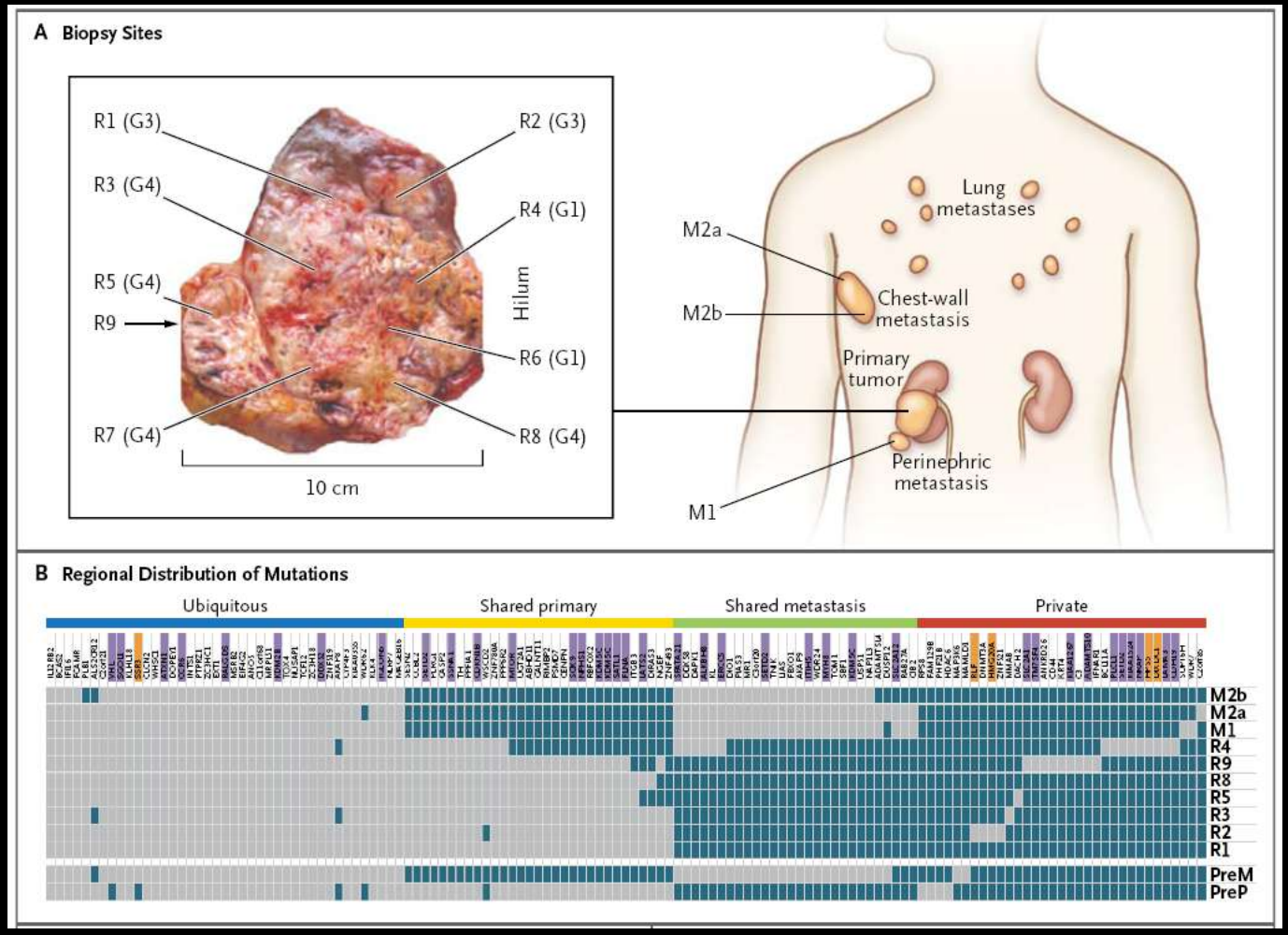
Cancer: A Formidably Complex Catalog of Genomic Changes and Disruptions in Cellular Molecular Signaling Networks

Copy Number Alteration in 5135 Tumors from 14 Solid Tumor Types



From: G. Iyer et al. (2013) JCO 31, 3133

Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC



From: M. Gerlinger et al. (2012) NEJM 366, 883

THE CLEARITY FOUNDATION

IMPROVING TREATMENT OPTIONS FOR OVARIAN CANCER PATIENTS

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DONATE NOW

EVERY WOMAN IS UNIQUE, SO IS HER CANCER

REGISTER FOR WHEEL TO SURVIVE SAN DIEGO

REGISTER FOR WHEEL TO SURVIVE SAN FRANCISCO

VIEW THE 2012 ANNUAL REPORT

About Clearity

The Clearity Foundation was launched in 2008 to help ovarian cancer patients and their physicians make better-informed treatment decisions based on the molecular profile of the tumor (the "tumor blueprint"). Our goal is to help women with recurrent ovarian cancer live longer, healthier lives by enabling a more individualized approach to therapy selection.

WATCH OUR VIDEO!

LEARN MORE

What Are Tumor Blueprints?

A tumor blueprint provides information about tumor characteristics at the molecular level. This genomic analysis can help prioritize drugs that are more likely to be effective for an individual patient.

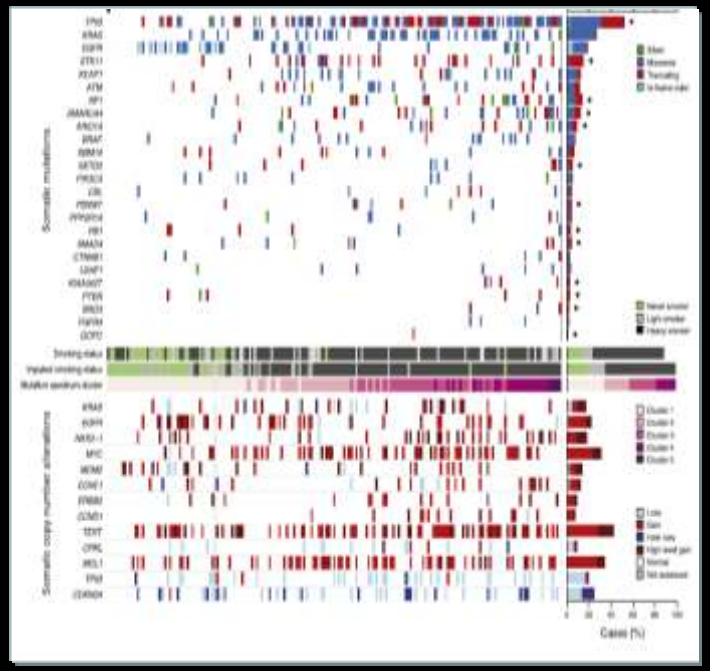
LEARN MORE

Patient Stories

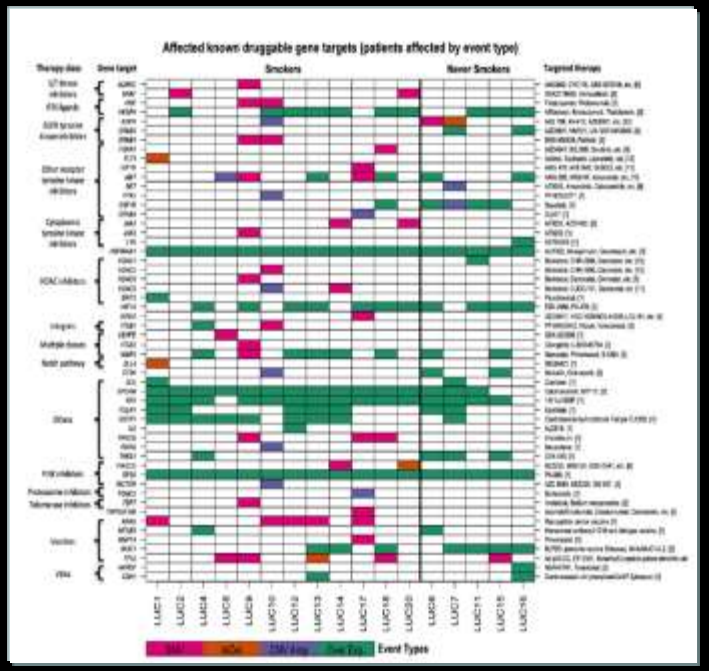
Since inception, Clearity has helped to empower hundreds of women with information to individualize treatment based on their unique tumor blueprints.

LEARN MORE

The Extravagant Landscape of Genomic Alterations in Cancer (Cell 2012, 150, 1107 and 1121)



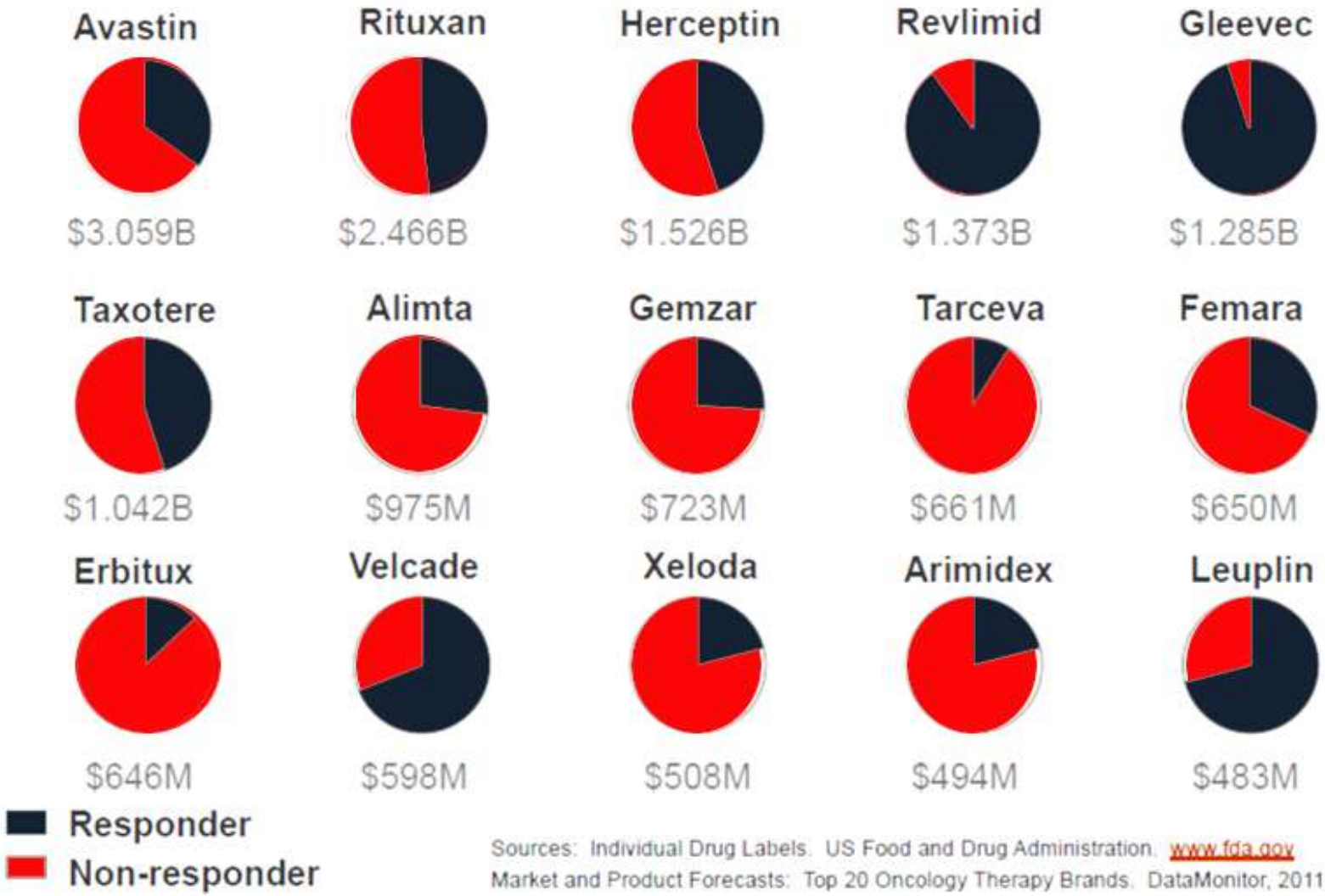
Mutations in Individual Non-small Cell Lung Cancer



Drug Targets in Individual Non-Small Cell Lung Cancers

- “malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for development of new Rx

Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly



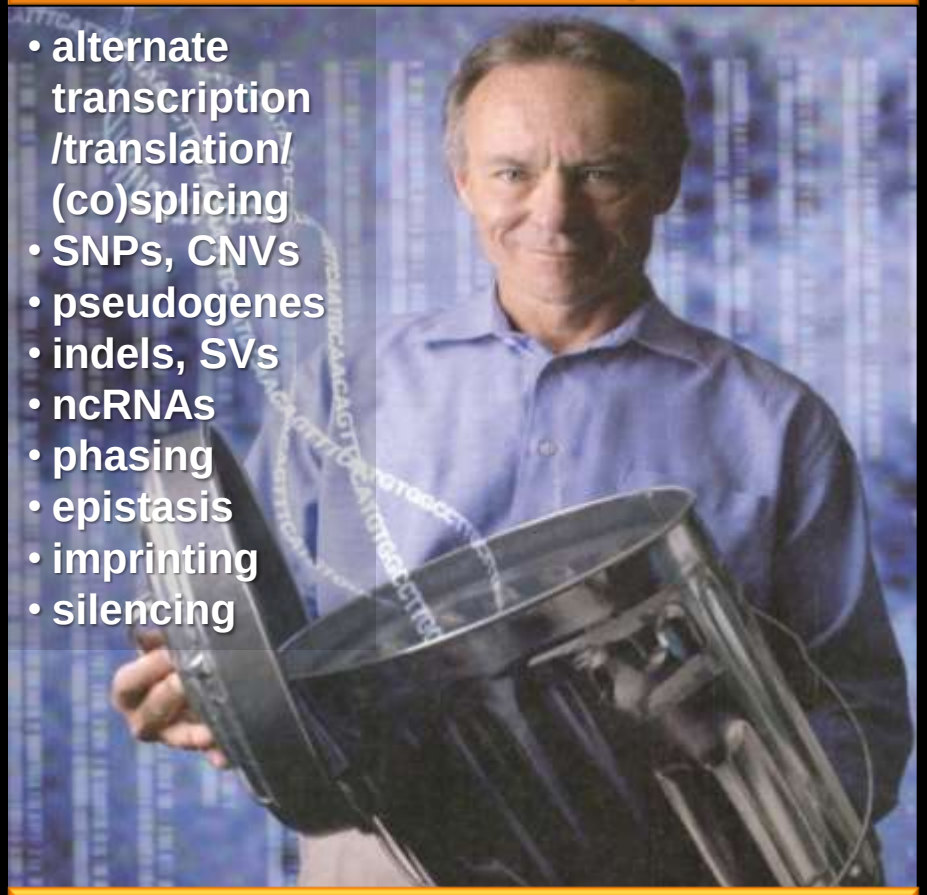
Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

Genes For ….
The Deterministic Dangers of a Genome-Sequence Centric Perspective

The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis

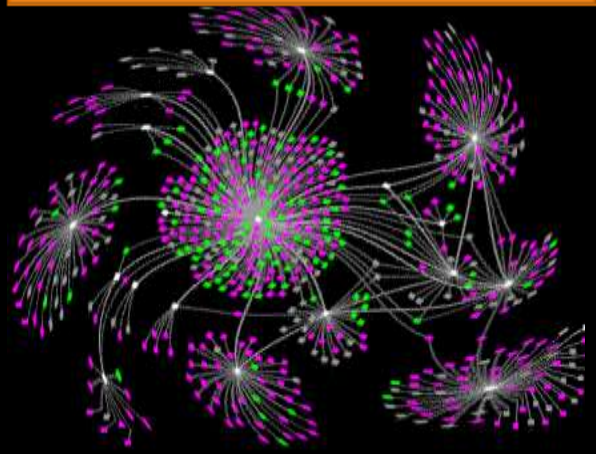
Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Predictions

Pervasive Transcription

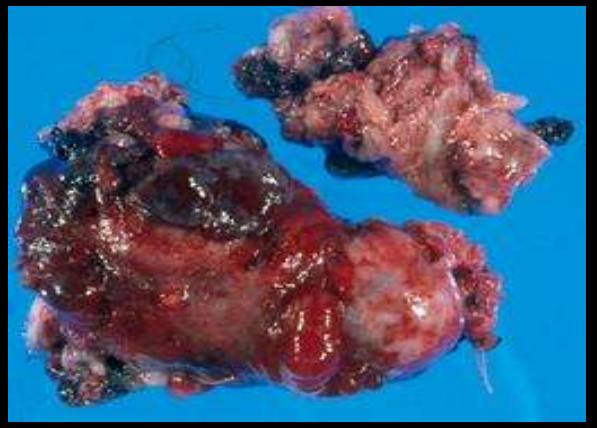


recognition of genome organizational and regulatory complexity

Cell-specific Molecular Interaction Networks

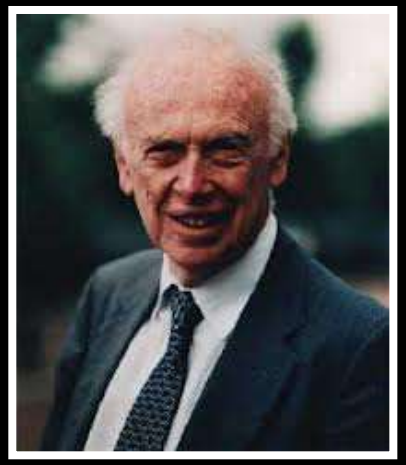


Perturbed Networks and Disease



Whole Genome Sequencing and Characterization of Dysregulation of Molecular Signaling Pathways in Disease

- need for obligate profiling of epigenetic modifications
- limits of current knowledge of function(s) and dynamics of non-coding regions
  - miRNAs, long range promoters/enhancers
- alterations in coding genes are not necessarily reflected in mRNA/protein expression



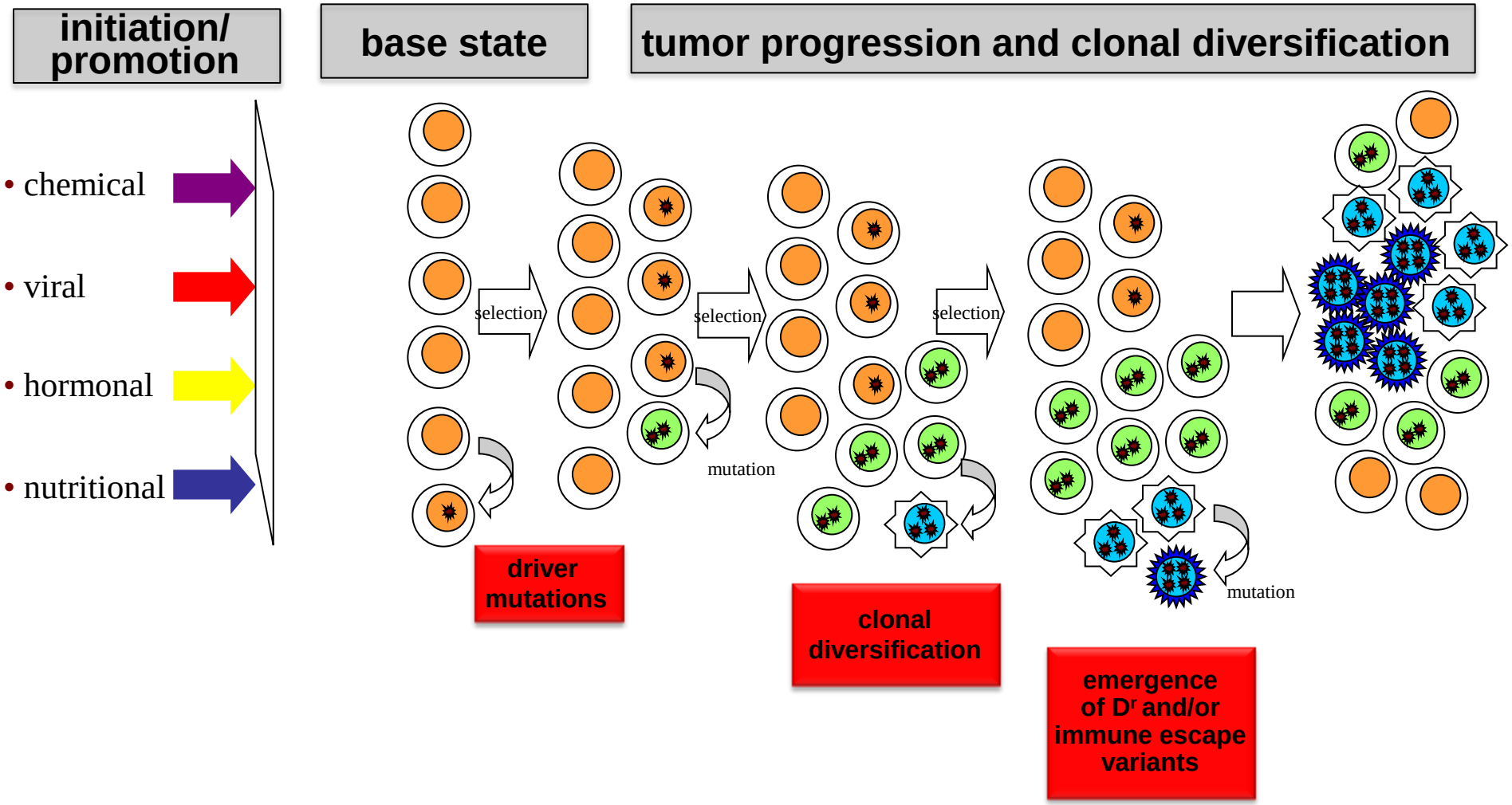
“I would like someone to declare war on cancer.
The NCI is an agency that is perpetuating
the old cancer establishment.
The FDA should not be approving drugs
that have only shown a three month survival benefit.”

Dr. James D. Watson
Nobel Laureate
2012 Celebration of Science
Washington, DC 7-9 Sept. 2012
cited in Scrip Intelligence 10 Sept. 2012

Confronting the Biological Complexity of Cancer

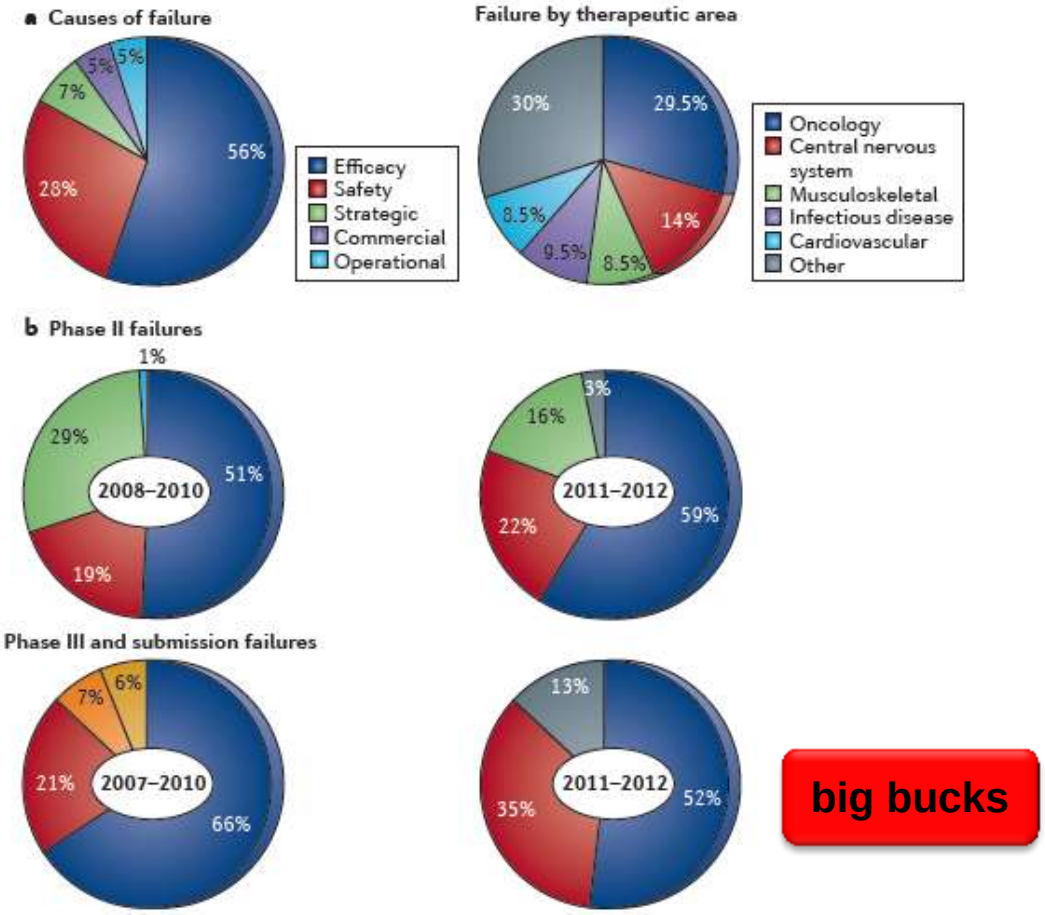
- urgent need for new conceptual approaches to understand the evolutionary dynamics and dysregulation of molecular signaling networks in tumor progression
- cancer as a complex adaptive system (CAS)

Multi-scale (Spatio-Temporal) Co-Evolution of Cancer Cells and Host Responses as Complex Ecological and Information Networks



Adapted from A. Barker and K. Buetow

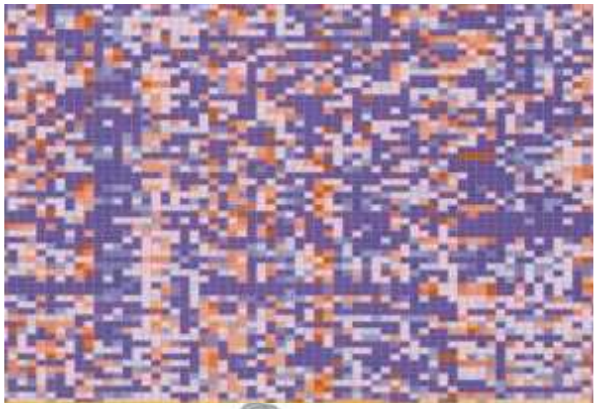
Failure Rates for 105 Investigational Drugs 2011-2012*

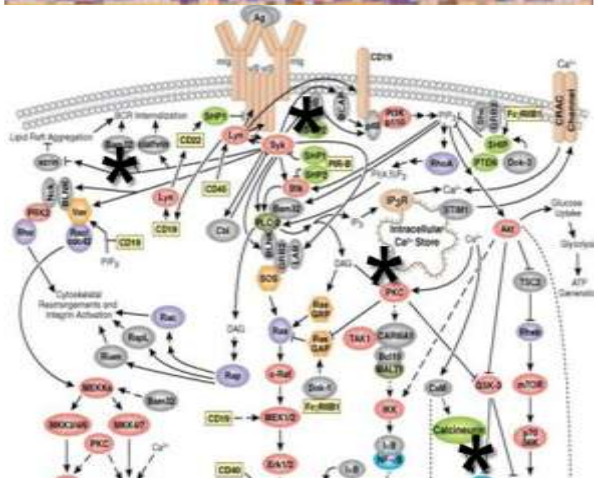


Adapted from: Nature Reviews Drug Discovery (2013) 12, 569
***148 failures but reason(s) reported only for 105**

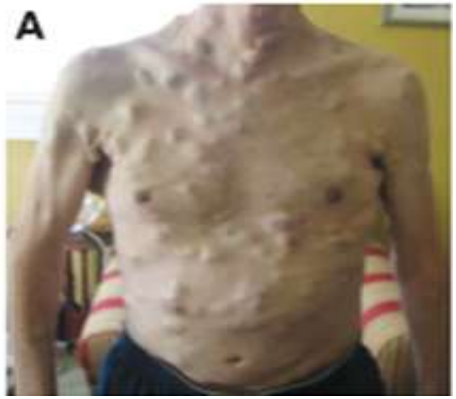
Clonal Heterogeneity and the Relentless Emergence of Drug-Resistant Clones (Intrinsic and/or Acquired Resistance)

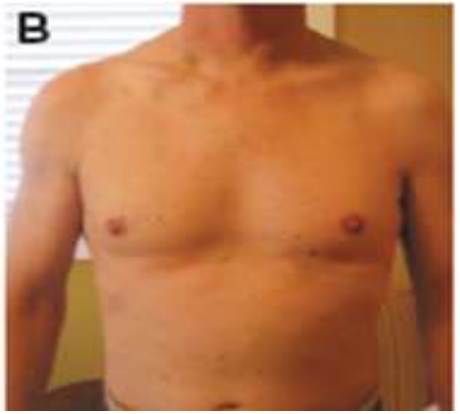
Molecular Subtyping and RX Targets



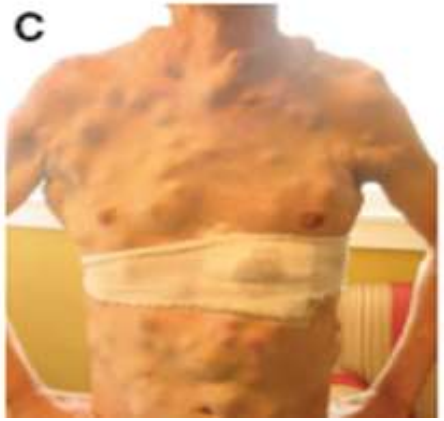


Initial Rx-Response to Targeted Rx





Rx-Resistance via Redundant Molecular Pathways

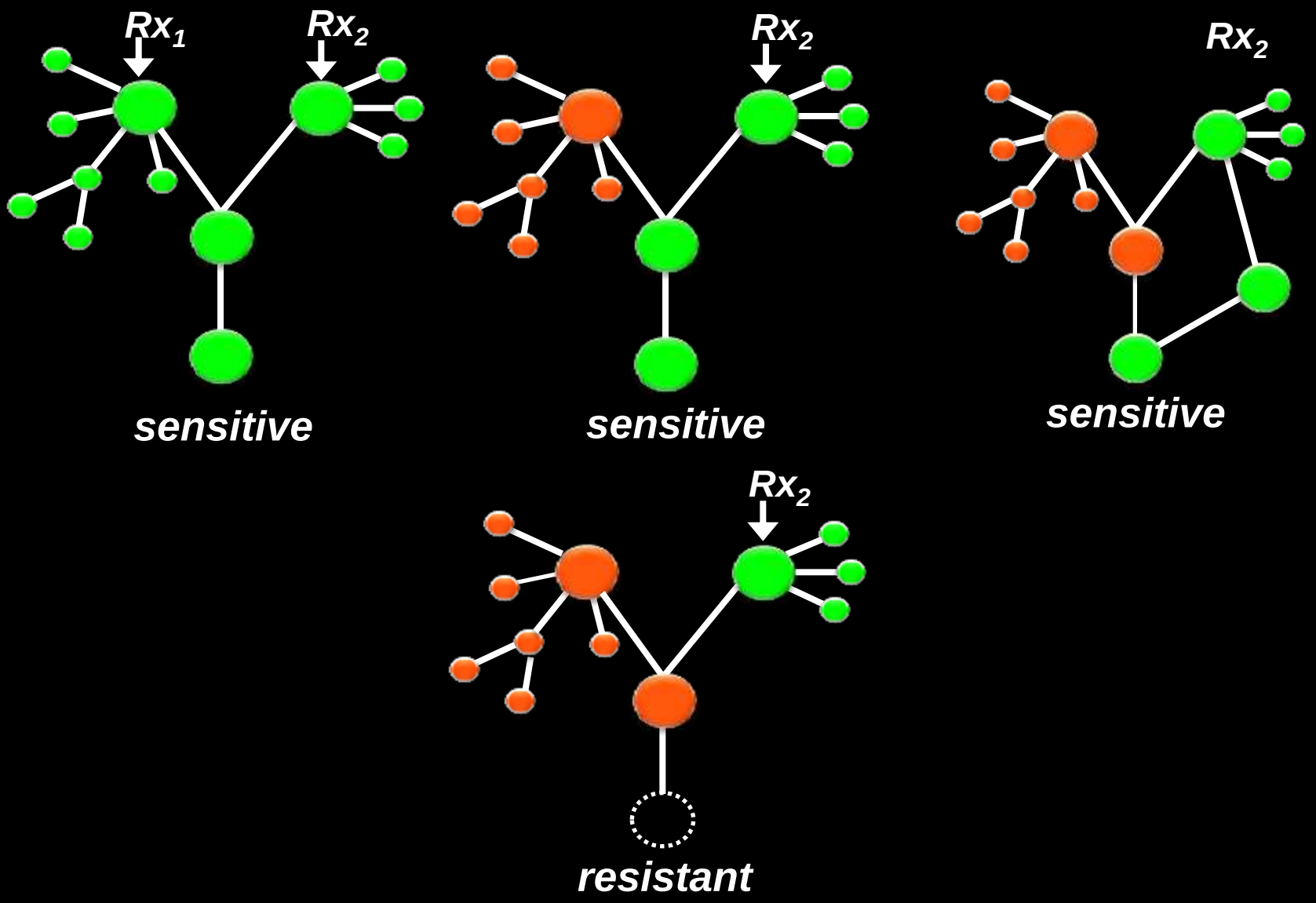


B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

Mutations Responsible for Acquired Resistance to Targeted Therapies

Gene	Genetic mutation	Tumor type	Acquired drug resistance
EGFR	T790M	Advanced NSCLC	Gefitinib Erlotinib
KRAS	Codon 12, 13 and 61	Colorectal cancer	Cetuximab
KIT	T670I	GIST	Imatinib
PIK3CA	NS	NSCLC	Erlotinib Gefitinib
ALK	C1156Y L1196M	NSCLC	Crizotinib
MEK1	C121S	Melanoma	Vemurafenib
BRAF	Amplification	Melanoma	Vemurafenib
NRAS	Q61K	Melanoma	Vemurafenib

Redundancy and Robustness in Molecular Signaling Networks: The Biological Mechanism(s) of Rx Resistance



How Many Drugs Acting on the Same Target Can The Market Support?

Failed Phase III Clinical Trials of anti-VEGF Agents

Table 1 | Failed phase III clinical trials of anti-VEGF agents

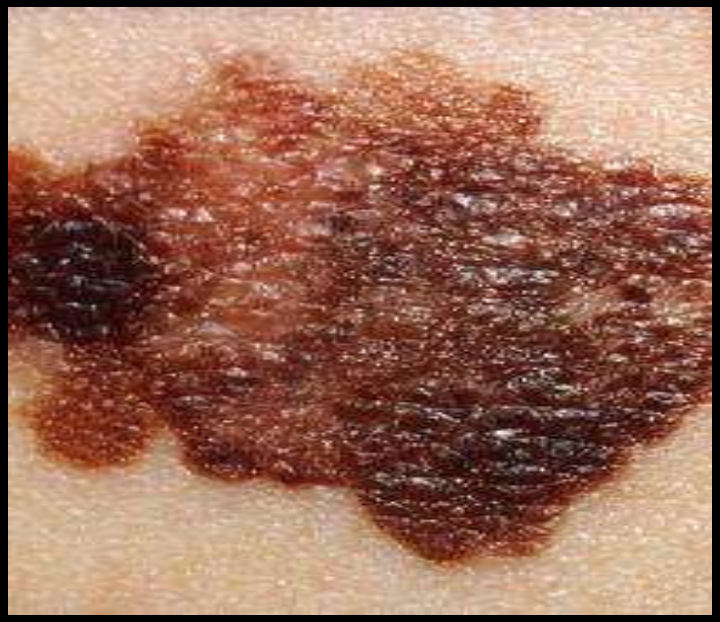
Regimen	Tumour type and setting	PFS	OS	Trial
Bevacizumab plus				
XELOX and cetuximab	CRC (1st line)	–	NR	CAIRO2[113] (*n*=755)
Oxaliplatin-based or irinotecan-based chemotherapy and panitumumab	CRC (1st line)	–	NR	PACCE[114] (*n*=1,053)
FOLFOX	CRC (adjuvant)	–	NR	NSABPC-08[115] (*n*=2,672)
Capecitabine	MBC (2nd line)	–	–	AVF2119[116] (*n*=426)
Erlotinib	NSCLC (2nd line)	+	–	BeTa[117] (*n*=636)
Capecitabine or 5-fluorouracil and cisplatin	AGC (1st line)	+	–	AVAGAST[118] (*n*=774)
Gemcitabine	PC (1st line)	–	–	CALGB80303[119] (*n*=535)
Gemcitabine and erlotinib	PC (1st line)	+	–	AViTA[120] (*n*=301)
Docetaxel and prednisone	PR (1st line)	+	–	CALGB90401[121] (*n*=1,050)
FOLFOX or XELOX	CRC (adjuvant)	–	NR	AVANT[122] (*n*=3,450)
Aflibercept plus				
Gemcitabine	PC (1st line)	NR	–	VANILLA* (*n*=2,662)
Sunitinib plus				
Monotherapy	MBC (2nd line)	–	–	SUN1107[123] (*n*=700)
Monotherapy	HCC (2nd line)	NR	–	SUN1170*‡
Paclitaxel	MBC (1st line)	–	NR	SUN1094*‡
Capecitabine	MBC (2nd line)	–	–	SUN1099* (*n*=442)
Docetaxel	MBC (1st line)	–	NR	SUN1064* (*n*=594)
FOLFIRI	CRC (1st line)	–	NR	SUN1122*‡
Erlotinib	NSCLC (2nd line)	+	–	SUN1087*‡
Prednisone	PR (2nd line)	NR	–	SUN1120* (*n*=873)
Sorafenib plus				
Carboplatin and paclitaxel	MM (2nd line)	–	NR	PRISM* (*n*=270)
Carboplatin and paclitaxel	NSCLC (1st line)	–	–	ESCAPE[124] (*n*=926)
PTK787 plus				
FOLFOX	CRC (2nd line)	+	–	CONFIRM2* (*n*=855)
FOLFOX	CRC (1st line)	–	–	CONFIRM1* (*n*=1,168)
Semaxanib plus				
FOLFIRI	CRC (1st line)	NR	–	NCT00021281*‡
Leucovorin and 5fluorouracil	CRC (1st line)	NR	–	NCT00004252*‡
Axitinib plus				
Gemcitabine	PC (1st line)	NR	–	A4061028* (*n*=630)
Vandetanib plus				
Monotherapy	NSCLC (2nd line)	–	–	ZEST[125] (*n*=1,140)
Pemetrexed	NSCLC (2nd line)	–	–	ZEAL[126] (*n*=534)
Cediranib plus				
FOLFOX	CRC (1st line)	–	NR	HORIZON III* (*n*=1,076)
Monotherapy or lomustine	GBM (2nd line)	–	–	REGAL* (*n*=325)

*No citation available. ‡Trial size not reported. Abbreviations: +, improved; –, not improved; AGC, advanced gastric cancer; CRC, colorectal cancer; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; GBM, glioblastoma multiforme; HCC, hepatocellular carcinoma; MBC, metastatic breast cancer; MM, metastatic melanoma; NSCLC, non-small-cell lung cancer; NR, not reported; OS, overall survival; PC, pancreatic cancer; PFS, progression-free survival; PR, prostate cancer; XELOX, capecitabine and oxaliplatin. Permission obtained from Nature Publishing Group © Ebos, J. M. L. & Kerbel, R. S. *Nat. Rev Clin. Oncol.* 8, 210–221 (2011).

From: A. Rapisarda and G. Melillo (2012) Nat. Rev. Clin. Oncol. 9, 378

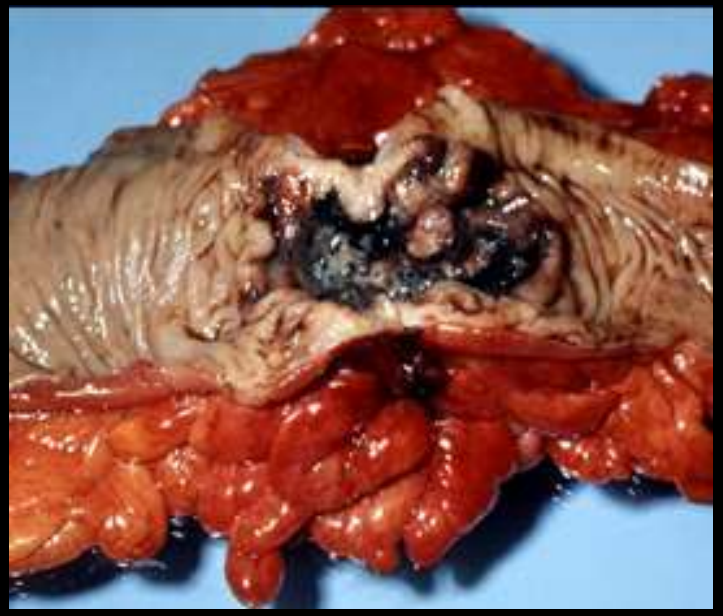
Expression of Same Mutation in Cancers Arising in Different Cell Lineages but with Different Response to Same Targeted Therapy

Melanoma
BRAF-V600



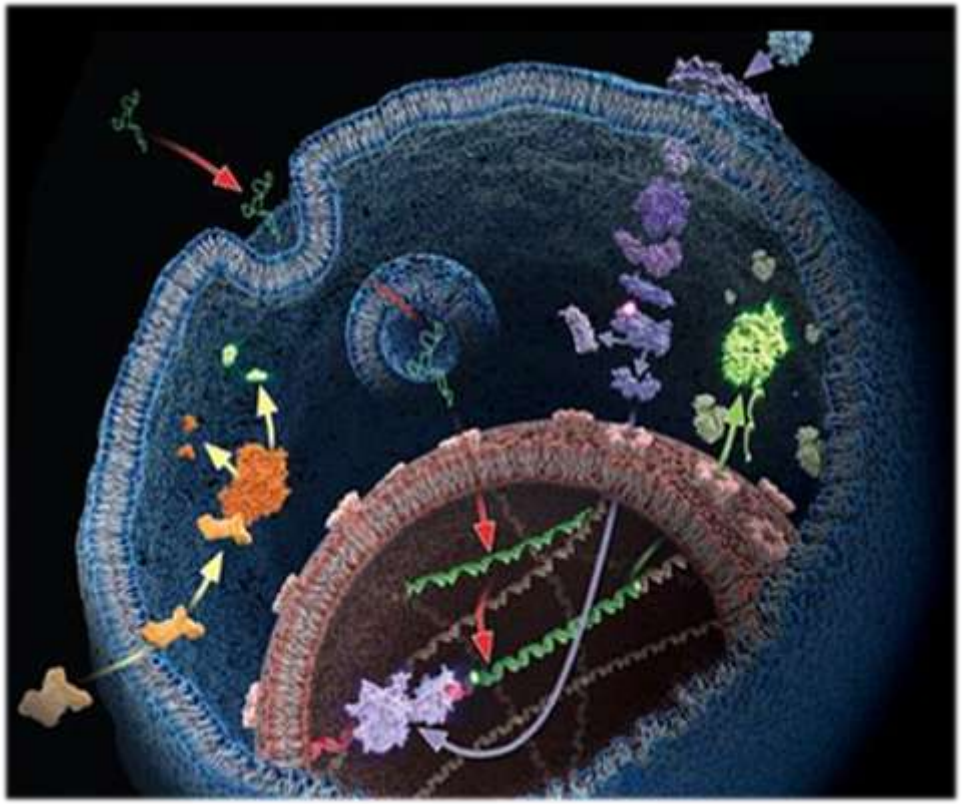
positive response
to
vemurafenib

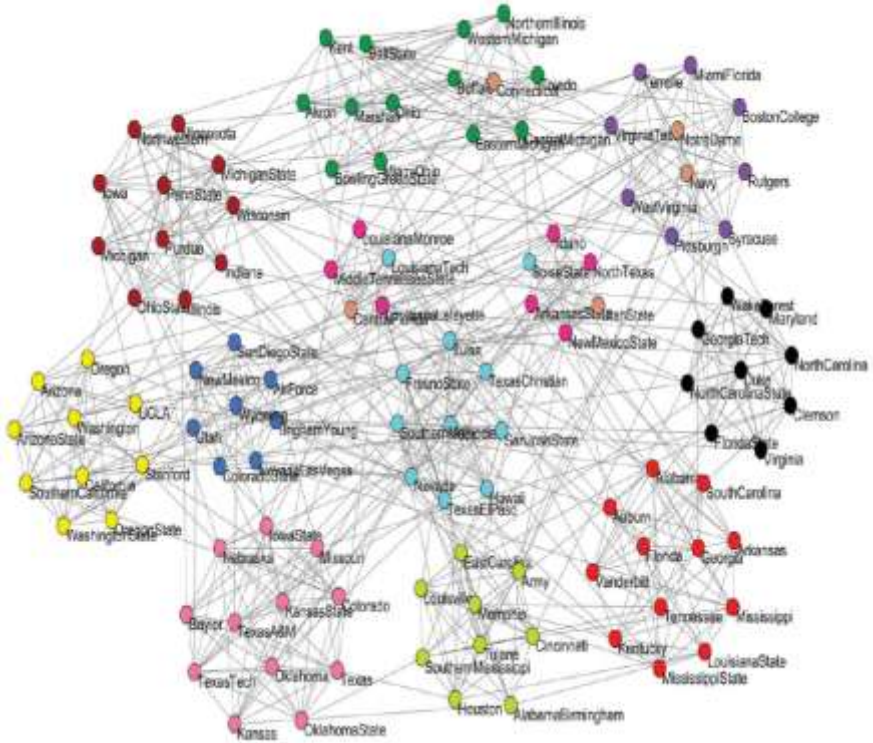
CRC
BRAF-V600



10% patients carry mutation
but unresponsive to vemurafenib
due to compensatory activation
of EGFR

Molecular Signaling (Information) Network Dysregulation and the Challenge of Network Pharmacology





Network Pharmacology and Drug Discovery: Key Principles

- there are few single molecular targets for Rx action
- effective Rx requires modulation of multiple targets in multiple pathways
- there are no linear pathways, only networks and subnetworks
- there are also highly interconnected networks/subnetworks between tissues
  - e.g. modulation of liver network induces changes in pancreatic islet network

"Omics" Technologies and the Elucidation of Perturbations in Molecular Network 'Wiring' in Complex Diseases

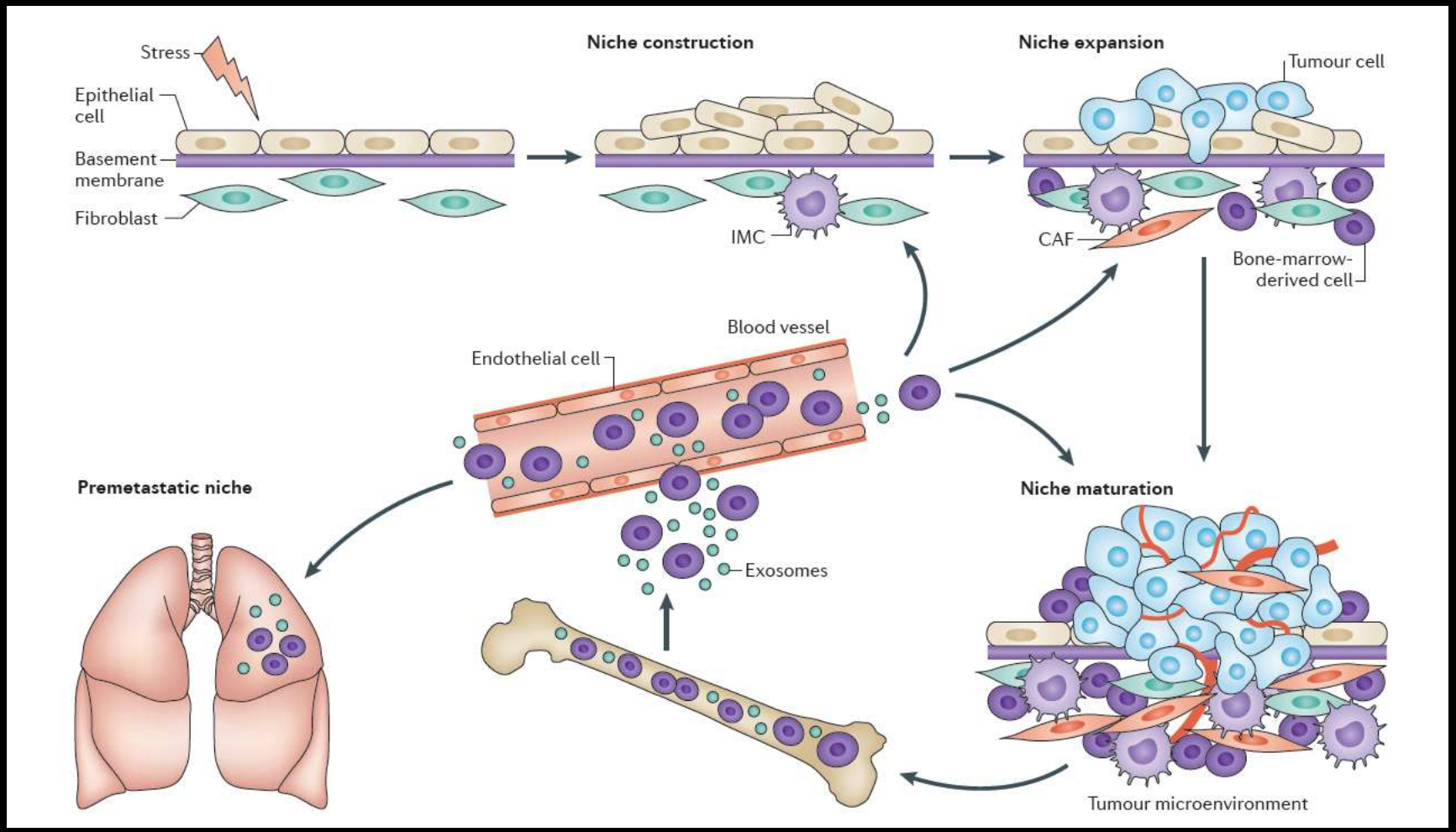
- the "dead hand" of reductionism and "the trap of linearity" as barriers to progress
- delusional pursuit of individual Rx 'targets' in face of known, extravagant network-wide perturbations
  - extensive network redundancy via pathway coupling and resulting rapid shifts to compensatory "wiring circuit" options to circumvent Rx efficacy
  - redundancy = Rx resistance
- time for a serious re-assessment of current Rx target discovery strategies

Tumor Cell Heterogeneity and Core Challenges in Cancer Diagnosis and Treatment

confronting the complexity of clonal heterogeneity and metastatic disease

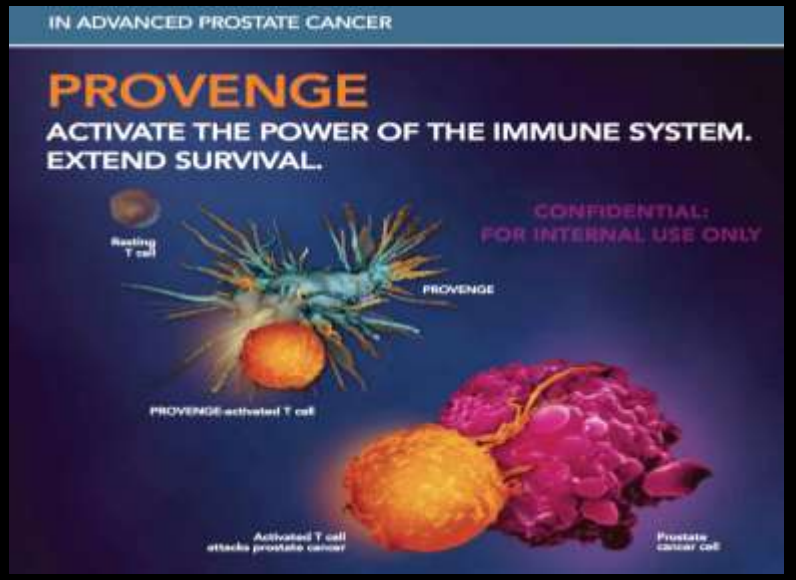
- improved prediction of network dysregulation patterns and most likely drug resistance/immune evasion “escape pathways”
- new minimally invasive methods for longitudinal monitoring of clonal dynamics with tumor progression
- more agile therapeutic regimens to reflect changing clonal dynamics and earlier dtection of emergence of drug-resistant clones

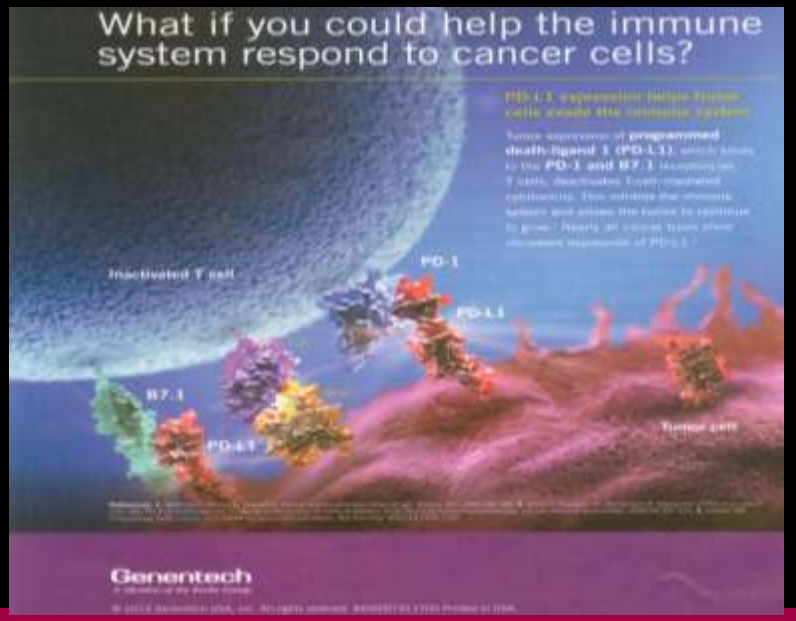
The Dynamic Evolution of Niche Microenvironments in Metastatic Cancer Via Local and Systemically Recruited Host Cells and Cytokine Production



From: M. H. Barcellos-Hoff et al. (2013) Nature Rev. Cancer 13, 511

Immuno-Oncology: An Emerging Therapeutic Strategy





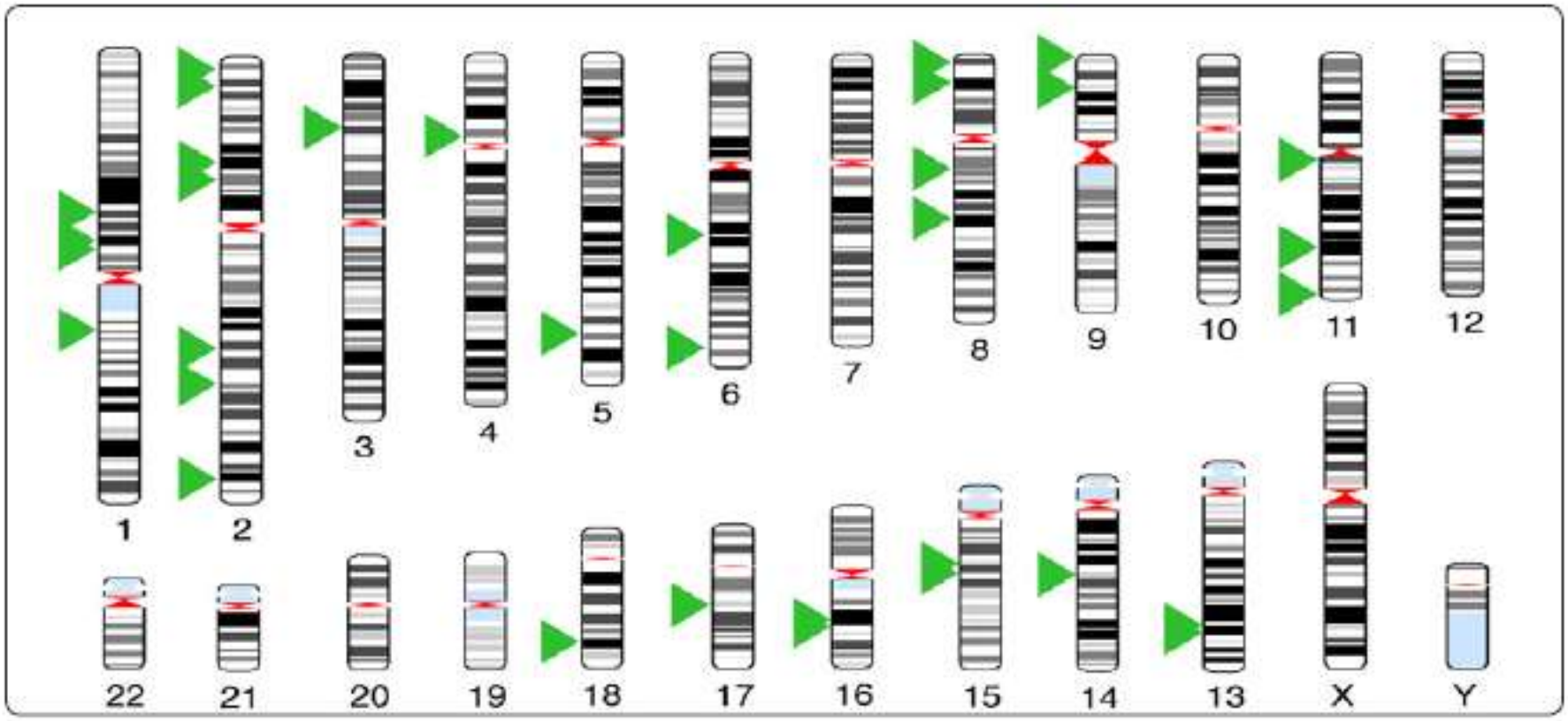
The Urgent Need for New Diagnostics and Molecular Profiling Tools for Improved Monitoring of Tumor Progression

From ‘Static Snap Shot’ at Initial Diagnosis to Dynamic Monitoring of Clonal Population Dynamics

Monitoring The Evolution of Rx Resistance With Tumor Progression

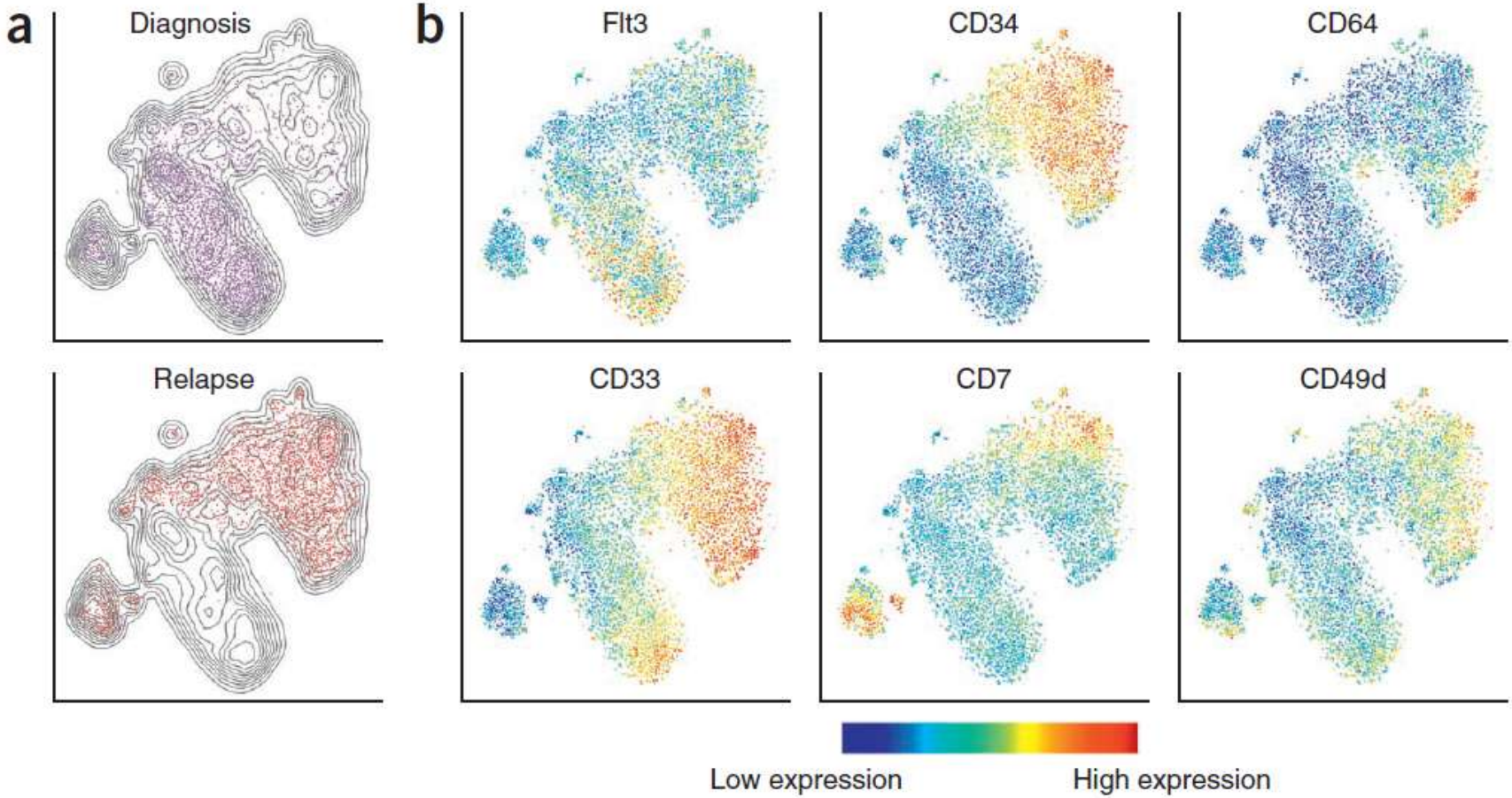
- emergence of new KRAS mutations in CRC patients treated with cetuximab (Misale et al. 2012. Nature 486, 532)
- pre-existing ‘minor’ clones with KRAS mutations identified in metastases
- new clones sensitive to investigational Rx targeting MEK
- mutant clones detected in blood as early as 10 months before cetuximab resistance and disease progression documented

MALBAC Identification of 35 SNPs in a Single Cancer Cell That Were Not Detected in Analysis of the Bulk Population



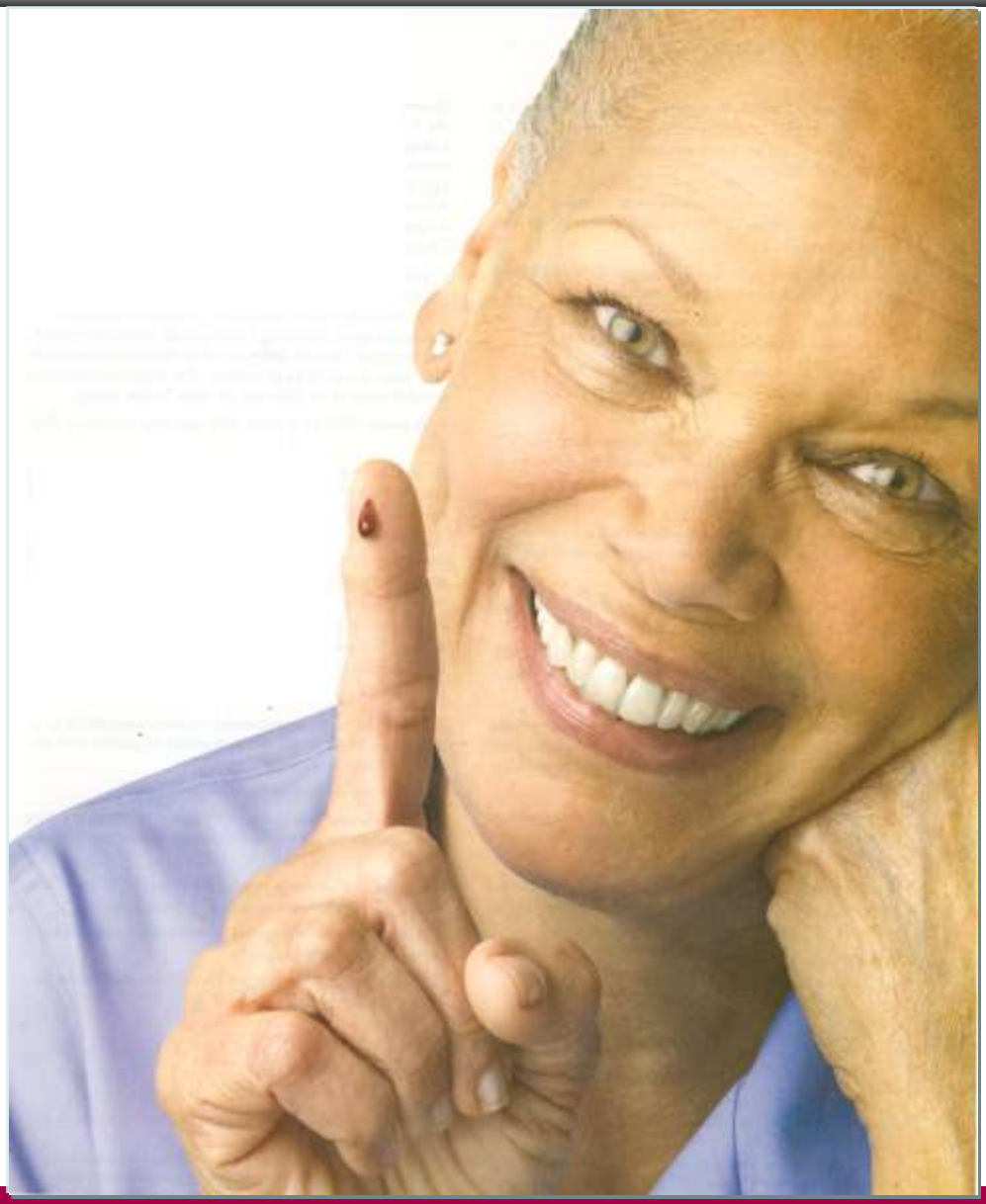
From: Zong et al. (2012) Science 338, 1622-26

viSNE (Visualized Nearest Neighbor Embedding) Analysis of Mass Cytometry Data at Single Cell Resolution in AML at Initial Diagnosis and Relapse



From: E-a David et al. (2013) Nature Biotechnol. 31, 545

The Liquid Biopsy: The Urgent Need for New Minimally Invasive Diagnostic Tools for More Sensitive Longitudinal Monitoring of Tumor Progression



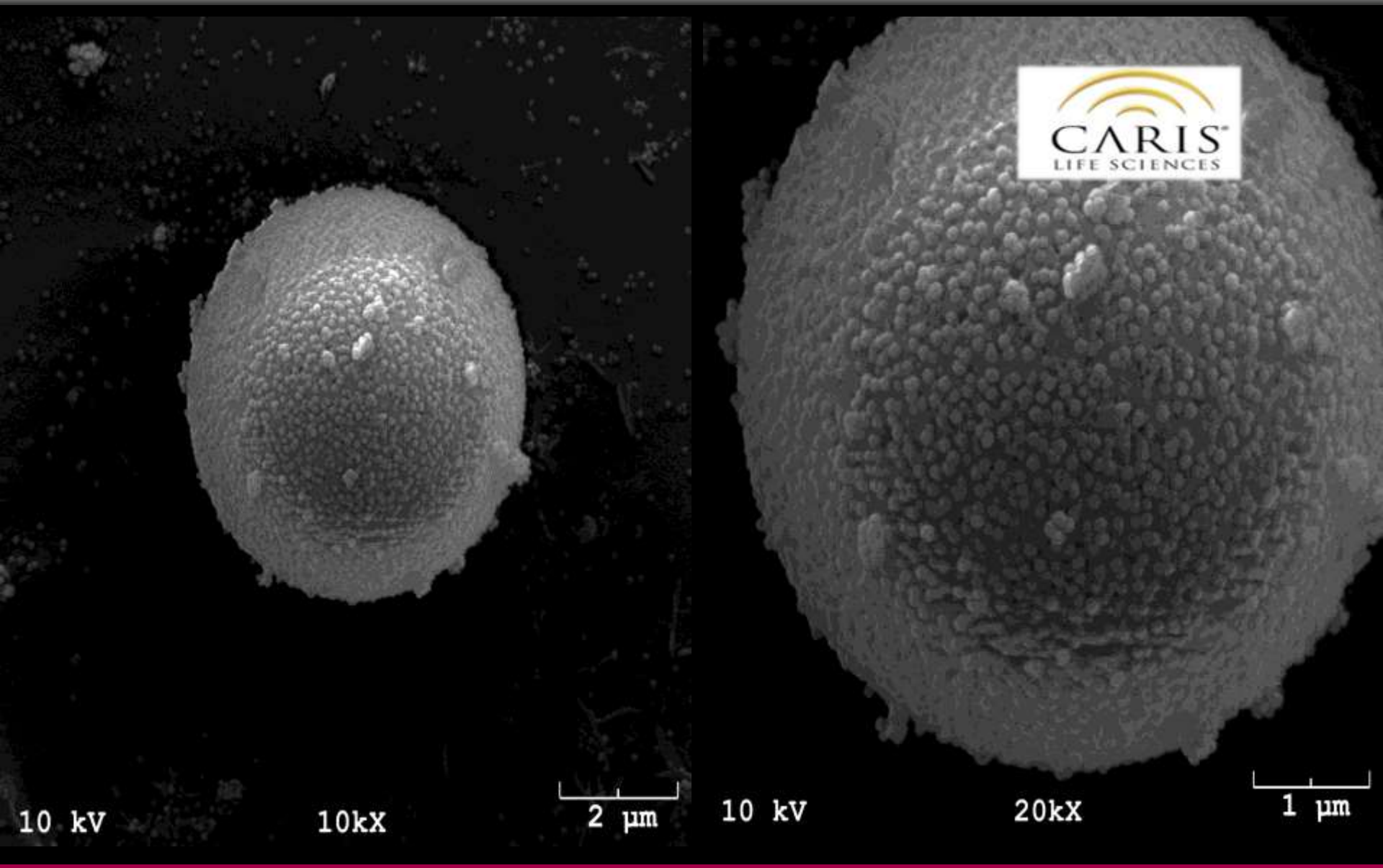
The Liquid Biopsy: The Urgent Need for New Minimally Invasive Diagnostic Tools for More Sensitive Longitudinal Monitoring of Tumor Progression

- faster detection of emergence of Rx-resistant/immune evasion clones
  - pre-exist prior to Rx
  - acquired resistance driven by relapse risk
  - minimal residual disease and relapse risk
- scientific foundation for more agile shifts in treatment regimens
  - clinical care
  - new clinical trial designs

The Liquid Biopsy:
The Urgent Need for New Minimally Invasive Diagnostic Tools for More Sensitive Longitudinal Monitoring of Tumor Progression

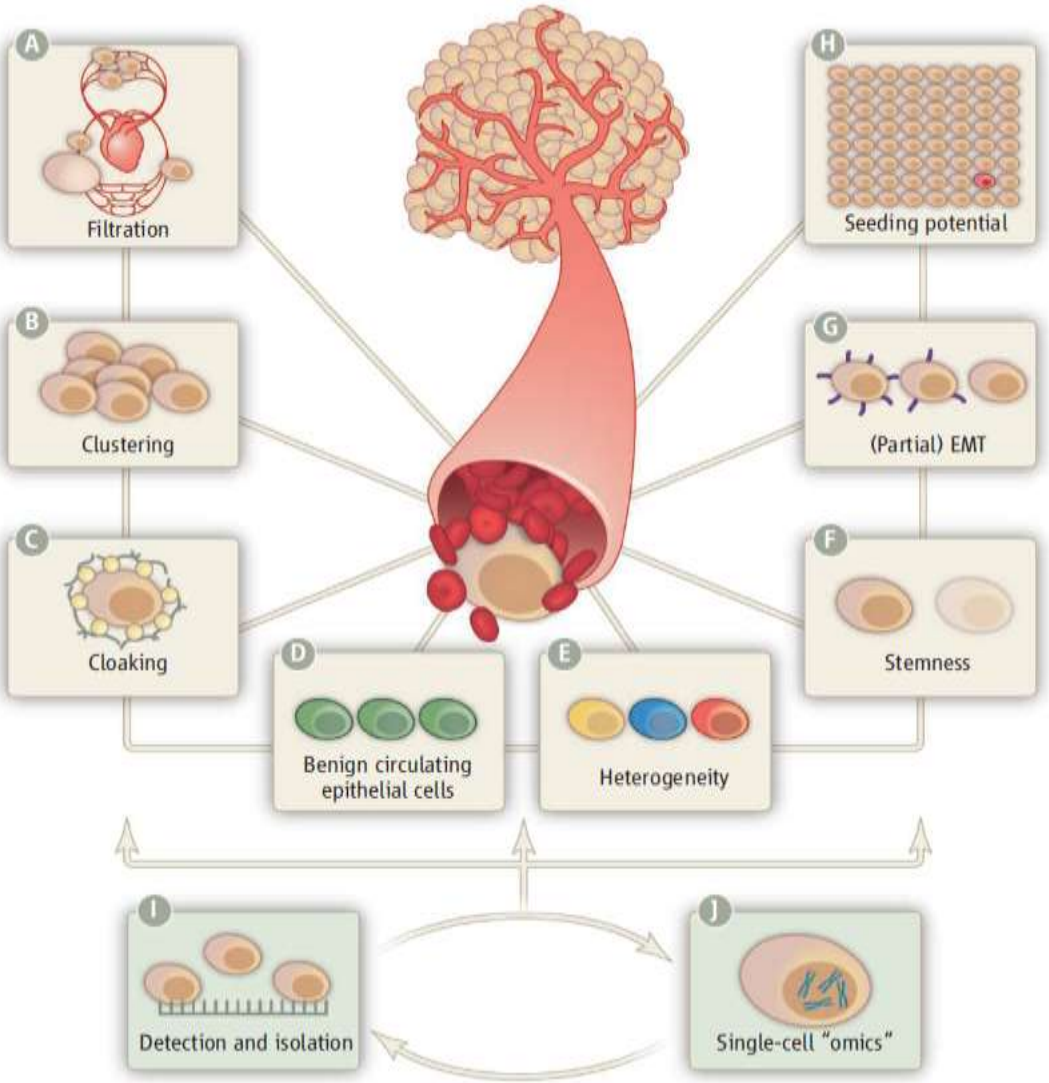
- circulating tumor cells
- circulating tumor-derived DNA/miRNA
- tumor-associated proteins (?)
- exosomes

Antibody-Mediated Capture of Tumor-Derived Exosomes from Human Prostate Cancer Cells



From: Caris Life Sciences

The Isolation and Profiling of Circulating Tumor Cells (CTCs) and Identification of Cancer Stem Cells (CSCs)



From: V. Plaks et al. (2013) Science 341, 1186

Cancer Stem Cells

- divided opinions about their existence
- accumulating evidence to support their existence
- more purposeful efforts to resolve the issue
- if they exist they represent an obvious target for Rx/immune assault
  - more limited heterogeneity?
  - genomic canalization and constrained phenotypic diversity?

Molecular Profiling and Redesigning Cancer Clinical Trials

Molecular Profiling and Stratification of Patient Populations and Improved Clinical Trials of Investigational Drugs

- MDx stratification of patients for ‘enrichment’ trials using only target-positive cohorts
- reduce attrition and candidate failure rate, particularly in high cost Phase III studies
- reduce clinical development costs (and time?)
- streamline regulatory review and approval

Large Scale Profiling of Cancer Patients to Identify Cohorts Expressing Low Frequency Rx Target(s) for Phase II Trials

Target	# Patients Screened	# Eligible Patients	# Centers	# Countries
EML4 ALK^{+}: lung cancer*	1500	82	9	1
HER2^{+}: gastric cancer**	3803	549	122	24

* E.L. Kwak et al. (2010) NEJM 363, 1693

** Y. Bang et al. (2010) Lancet 376, 687

Adaptive Trials

- use accumulating data during the trial
- add or drop agents in complex multi-arm trials (e.g. I-SPY)
- critical need for robust validated biomarkers to assess Rx response and more agile changes in regimen
- more complex statistical designs
- uncertainty in planning drug supply
- cooperation between Rx sponsors for use of multiple investigational agents

Cancer Clinical Trials
Defining Priorities for Phase I Studies in Increasingly Small Subsets of Target-Positive Patients

- burgeoning portfolio of investigational agents
- increasing number directed to identical molecular targets
- transcending the constraints of initial evaluation in treatment failure/refractory patients
  - prior Rx failure typically without evidence that patient exhibited relevant Rx target for the failed agent
  - Rx selection of cellular phenotypes that may be unrepresentative of tumor at initial presentation
  - impact of prior Rx cycles on host defense and clonal dynamics

Selection of Drug Candidates for Phase I Trials

- validate presumed MOA in Phase I with target-enriched patients
- greater use of neo-adjuvant (pre-surgery) Rx and assessment of pathologic complete response (PCR)
  - threshold PCR response level to proceed?
  - assumes optimum dosing and availability of predictive biomarkers

Consequences of Foregoing Phase III RCTs and Granting of Accelerated Regulatory Approval

- faster trials and patient access to promising Rx (terminal diseases)
- less definitive evidence regarding safety and efficacy
- possibility that post-marketing studies will not be confirmatory and product withdrawal
- accelerated regulatory approval pathway should provide facile reciprocal withdrawal provisions
- need for enforcement of sponsors to launch/complete post-approval studies with reasonable speed

Defining What Works
and
Defining Value

The Need for a Better Conceptual Framework for Understanding the Biology of Different Patterns of Progression and Risk in Different Tumor Types

- cancer still perceived (and treated) as a diagnosis with lethal consequences if left untreated
- clear evidence of indolent tumors and screening programs result in increased incidence
  - breast, prostate, lung and thyroid
  - 'IDLE' lesions
- 'cancer' should be reserved for lesions with reasonable likelihood of lethal progression if untreated ("consequential lesions")
  - mitigate the "over diagnosis-over treatment" dilemma

Change in Incidence and Mortality 1975-2010 Per 100,000 Individuals (Surveillance, Epidemiology and End Results Data)

	Incidence		% Change	Mortality		% Change
Breast[c]	105.07	126.02	20	31.45	21.92	−30
Prostate	94	145.12	54	30.97	21.81	−30
Lung and bronchus[d]	52.26	56.68	8	42.56	47.42	11
Colon	41.35	28.72	−31	28.09	15.51	−45
Cervical	14.79	6.71	−55	5.55	2.26	−59
Thyroid	4.85	13.83	185	0.55	0.51	−7
Melanoma	7.89	23.57	199	2.07	2.74	32

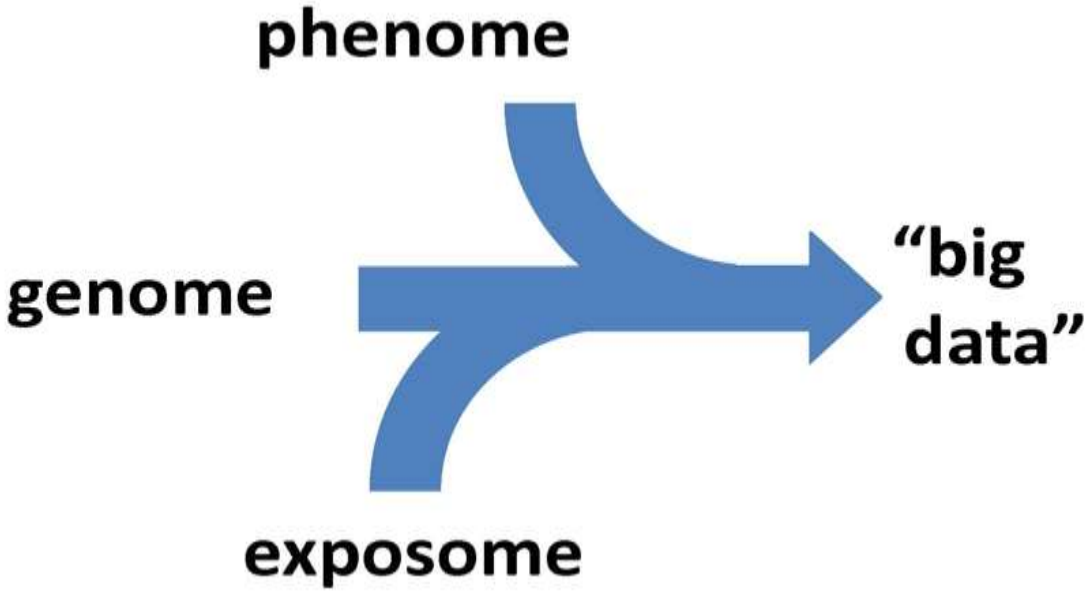
over-diagnosis/ over treatment of indolent lesions

slow growing consequential tumors/ screening reduces morbidity/mortality via removal of precursor lesions

screening expands indolent incidence but limited impact on aggressive subtypes

Adapted From: L. Esserman et a. (2013) JAMA 310, 798

The Imminent Arrival of the Zettabyte (10^{21}) Era

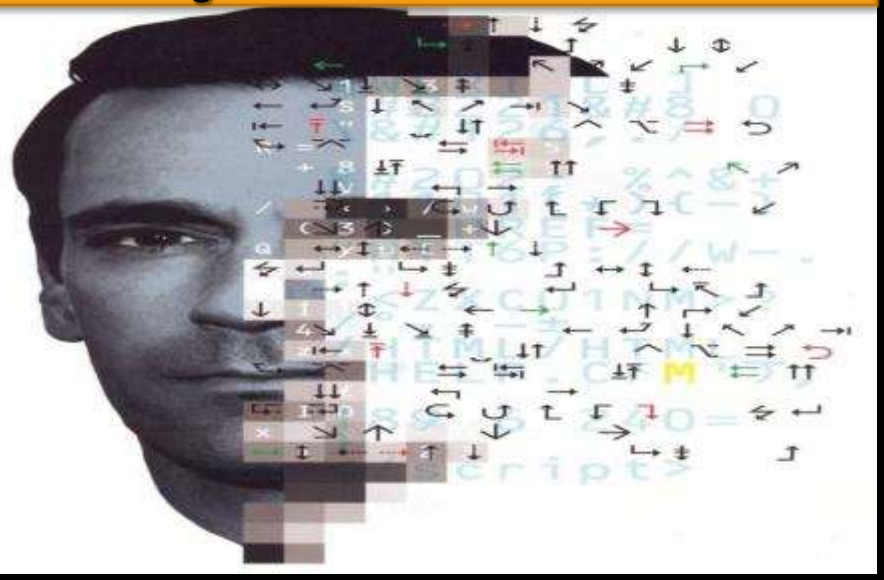


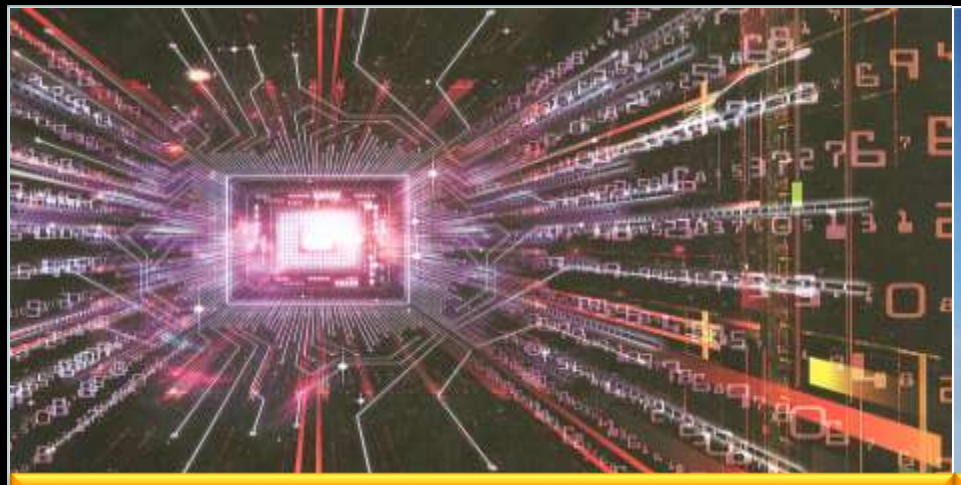
The Growing Education and Knowledge Gaps in Comprehension of Molecular Medicine Concepts Among Healthcare Professionals

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

GeneticsLaw.com

The Wellness Premium

Greater Engagement and Incentivization of Consumers/Patients in Care Decisions and Sustaining Wellness

Social Media, Patient Advocacy Groups and New Opportunities for Observational Studies on Population Health and Outcomes

Interactive Patient-Centered Initiatives (PCIs)

- social media, patient advocacy and consumer/care- giver engagement
- new opportunities to capture, share, mine and integrate data
  - both research and clinical studies
- matchmaking for more proficient research studies/clinical trial recruitment

Physician (HCP): Patient Communications in Chronic and/or Terminal Illness

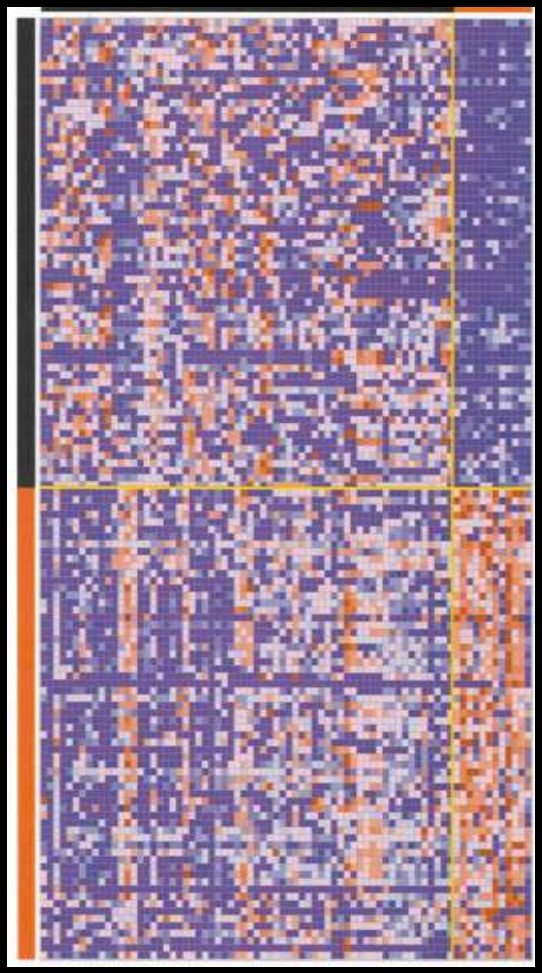
- clinical challenge of balance between ethical transparency and empathy
- the vulnerability of patients: "Trust and surrender" to presumed "authoritative knowledge"
- physicians/HCPs are rushed and stressed
- oncologists know but often deny the limited efficacy of many interventions
  - when to move from continued aggressive intervention to palliative care?
  - why do so many physicians chose to go gently into the night? (WSJ)
- the syntax of survival (JAMA 2013 310, 1027)
  - complex interplay between fear, hope, optimism and reality
  - verbal content, tone, facial expression and body language

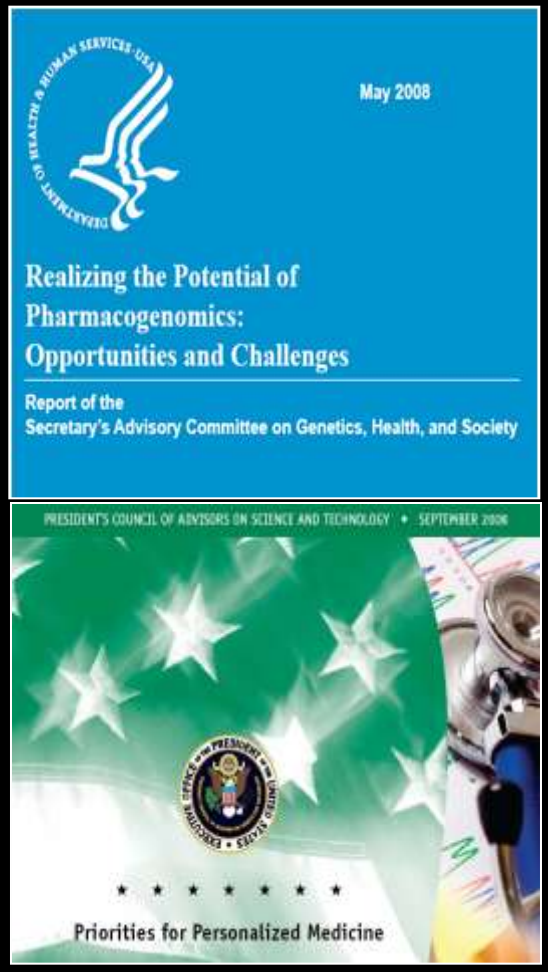
The Heuristics of Treatment Decisions by Cancer Patients

- patient autonomy is valued by easily relinquished
- transparency and the paradox of choice (B. Schwartz)
  - the more choices offered the less patients want to choose
- powerful predispositions to elect aggressive therapy
  - avoid anticipated regret: “I know I did everything I could”
  - economic/legal advantages for physician to defer to SOC/consumer guidelines
- increasing shortcomings in clinical guidelines/compendia
  - protracted updating
  - patient-stratification based on molecular profiling

Challenging Questions Regarding Future Directions in Cancer Research and Clinical Oncology

Precision Medicine: Key Drivers





Science | **Policy** | **Cost and Outcomes**

The Difficult but Largely Ignored Central Questions in Oncology and Cancer Care Delivery

What is a meaningful advance in Rx effectiveness?

Can we continue to afford the high cost of anti-cancer drugs for modest gains in PFS/OS and limited QOL?

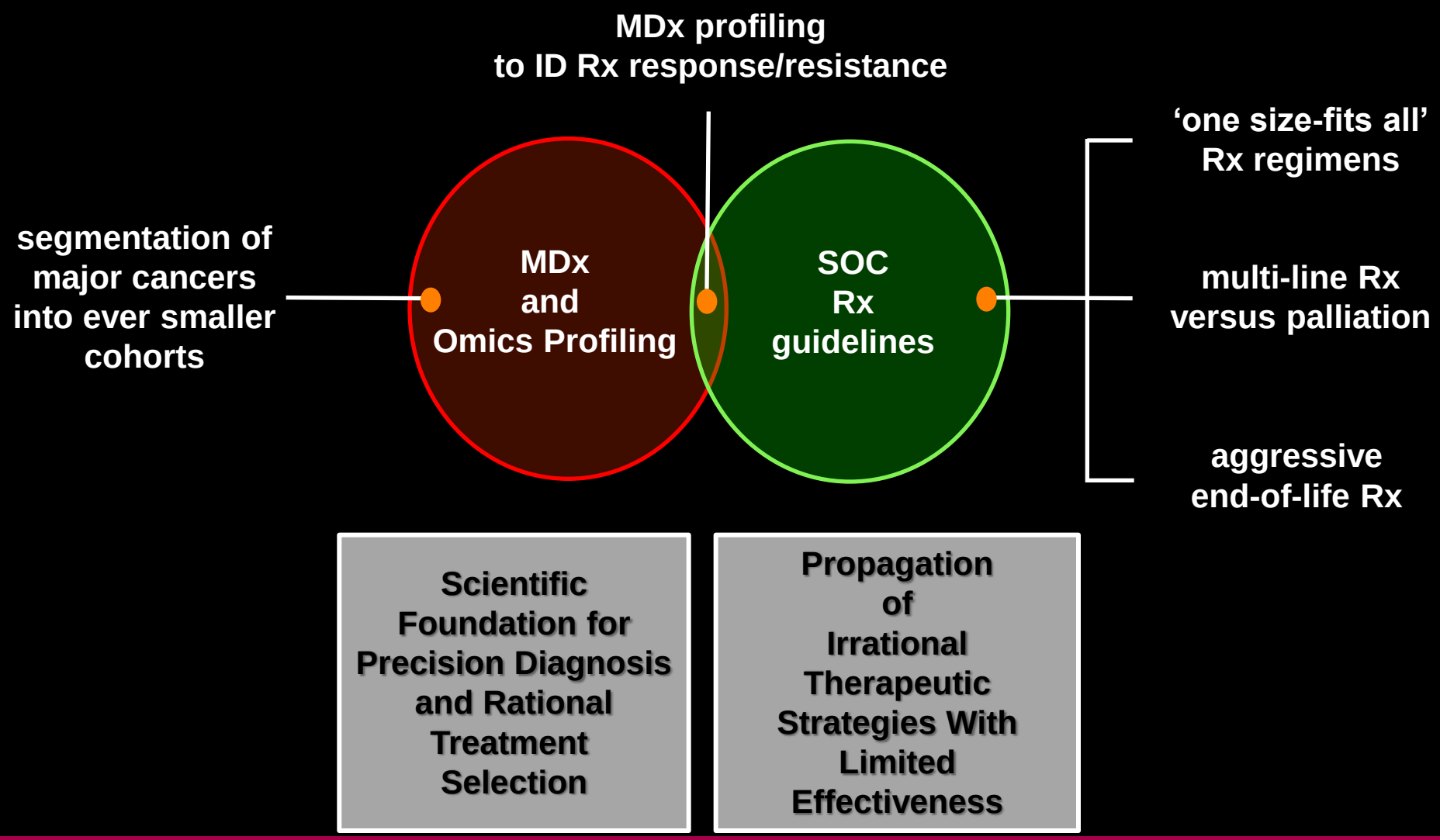
Cost of Recently Approved Anti-Cancer Drugs

- brenfuximab (Adcetris) $216,000/course
- ipilimab (Yervoy) $123,000/year
- crizotinib (Xalkori) $115,000/year
- vismodegib (Erivedge) $75,000/course
- sipuleucel-t (Provenge) $93,000/year
- petuzumab (Perjeta) $70,800/year
- cabazitaxel (Jevtana) $96,000/year
- vemurafenib (Zelboraf) $61,000/year
- abiraterone (Zytiga) $60,000/year
- premetrexed (Alimta) $30,000/course

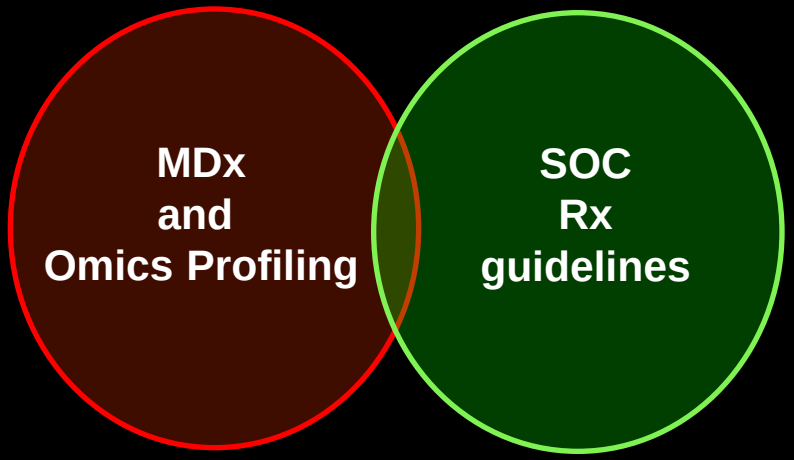
Doing More, But Not Necessarily Doing Better

Buy and Bill: Oncologists' Financial Incentives Are Not Aligned With Rational Therapy and Quality of Care

Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology



The Need for Value-Based Reimbursement of New Molecular Profiling Services: A Market Failure that Threatens Innovation in Precision Medicine



- Cost-Based Versus Value-based Pricing
- Uncritical Acceptance of Rx Pricing
- Barriers to Innovation and Recovery of Increasing R&D Cost
- Incentives to Sustain Flawed Discovery Strategies and Clinical Care

The Unacceptable Status of Current Cancer Care Delivery

- increasing cost of new Rx ($60-120K per agent)
- 60-80% oncologists' income tied to reimbursement from Rx
- reimbursement incentives misaligned with quality care and predispose to selection of high cost Rx
- slow updating of SOC guidelines to change from 'one-size-fits all' to MDx profiling
- lack of adherence to SOC and National Quality Forum guidelines and unwarranted variation in care/outcomes
- over-aggressive use of new Rx regimens in last two weeks of life

The Thin Line Between Hype and Hope

Choices

- celebrity populism and belief that more money will solve everything

versus

- fundamental reassessment of why therapeutic success for metastatic solid tumors remains so elusive

plus

- recognition that cancer is a complex adaptive system demands major changes in current approaches to cancer research and clinical oncology

Molecular Profiling is a Disruptive Technology

Molecular Profiling Will Drive Major Shifts in Cancer Diagnosis, Clinical Care, Business Models and Markets

Challenging Questions

- is the massive public and private sector R&D investment in new anticancer Rx directed to ***single*** targets/single pathways intellectually flawed based on current knowledge that ***multiple*** pathways/modules/ and subnetworks are dysregulated?

Is Rx Therapy of Advanced Metastatic Disease a Desired but Unattainable Goal?

A Nasty (But Largely Ignored) Question

- is the scale of molecular network dysregulation and relentless ‘state shifts’ (clonal dynamics) in advanced metastatic disease so extreme that Rx-circumvention or reset of network stability (homeostasis) via Rx action at multiple sites in multiple pathways are not feasible with current approaches?

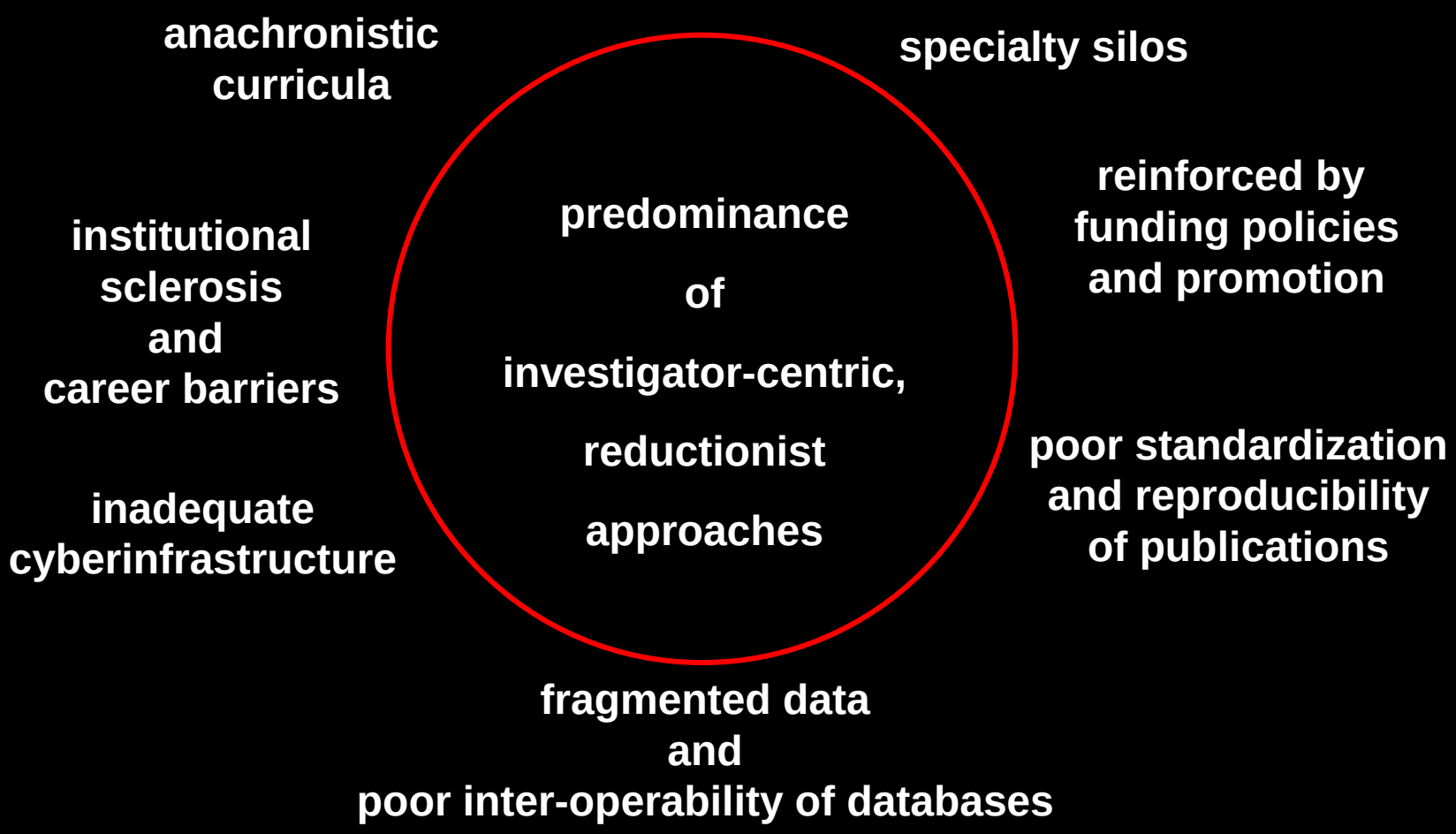
Challenging Questions

- would returns from current multi-billion investments in cancer research and drug discovery be improved by realignment of the funding balance to accord higher priority to biomarker-based tumor profiling services?
  - earlier (pre-metastatic) detection of 'consequential' tumors (=cure)
  - robust separation of indolent and consequential tumors (reduce overtreatment of low risk disease)
  - dynamic monitoring of tumor progression and more agile Rx shifts to reflect emergence of Rx-resistant clones
  - establish comprehensive inventory of Rx-escape pathways to better guide new Rx discovery

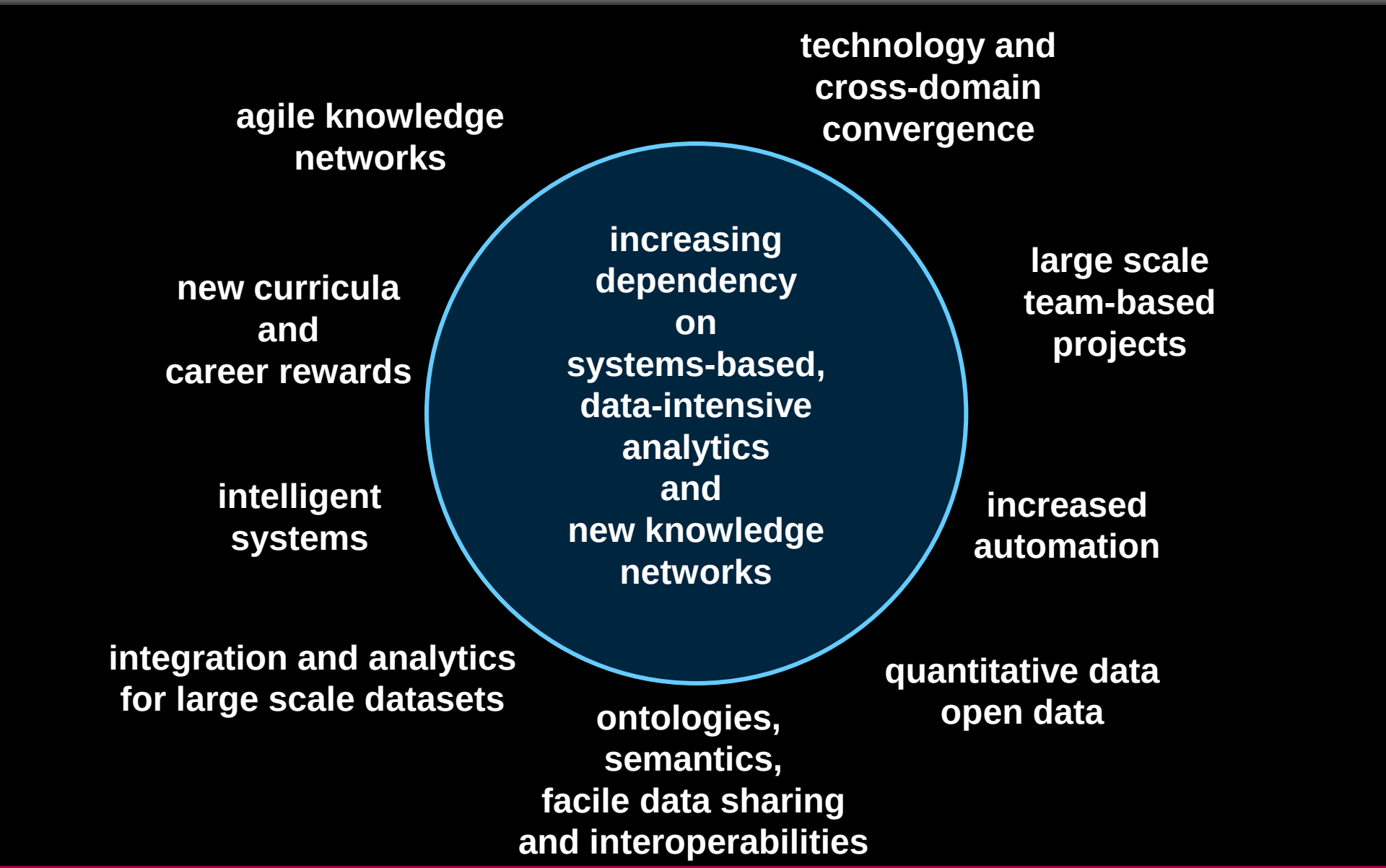
Silos Subvert Solutions: Organizational and Cultural Challenges

- the need for integrated end-to-end solutions
  - building new organizational and operational competencies and infrastructure
- the imperative to build new capabilities in inter- and cross-disciplinary research
  - big science and big data
  - clinical medicine and regulatory science
  - public: private partnerships
  - clinical education

Silos Subvert Solutions: The Slow Response of Academic Biomedicine to Technology Convergence and Cross-Disciplinary Requirements



New Conceptual, Methodological and Organizational Frameworks for Data-Intensive Biomedical R&D



BioIT World 2011 - by **Sorena Nadaf, M.S. M.MI**
Director - Translational Informatics, CIO

Overcoming Resistance to Change

“Even the Gods cannot strive against necessity.”

Ancient Greek Proverb