ASU COMPLEX ADAPTIVE SYSTEMS
ARIZONA STATE UNIVERSITY

BioConference LIVE

The Need for Critical Reassessment of Current Strategies for Cancer Therapy

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Virtual Presentation at the BioConference Live on Cancer: Research, Discovery and Therapeutics

October 16-17, 2013

Q&A Session at the End

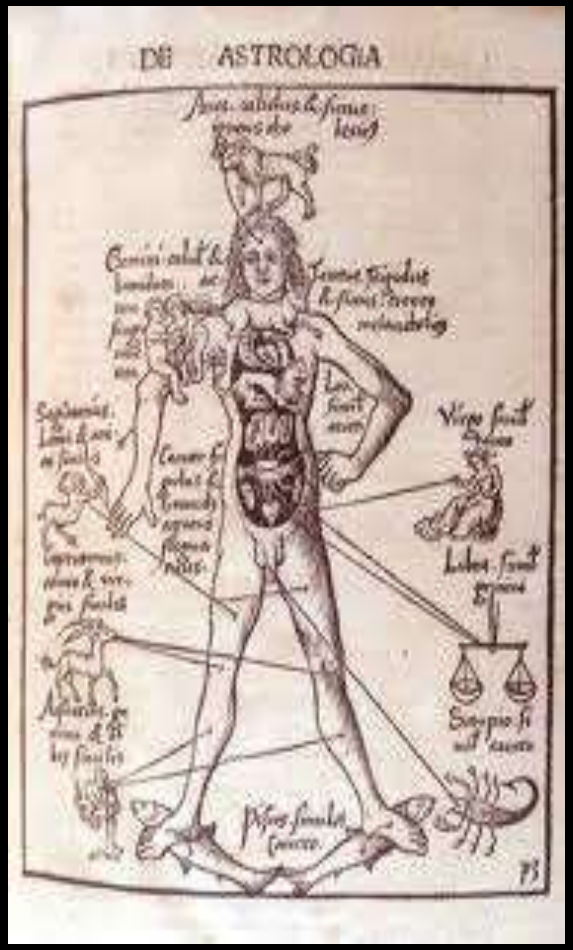
- there will be a Q&A session at the end of the presentation, please hold all questions or use the chat function, and your questions will be addressed at the end

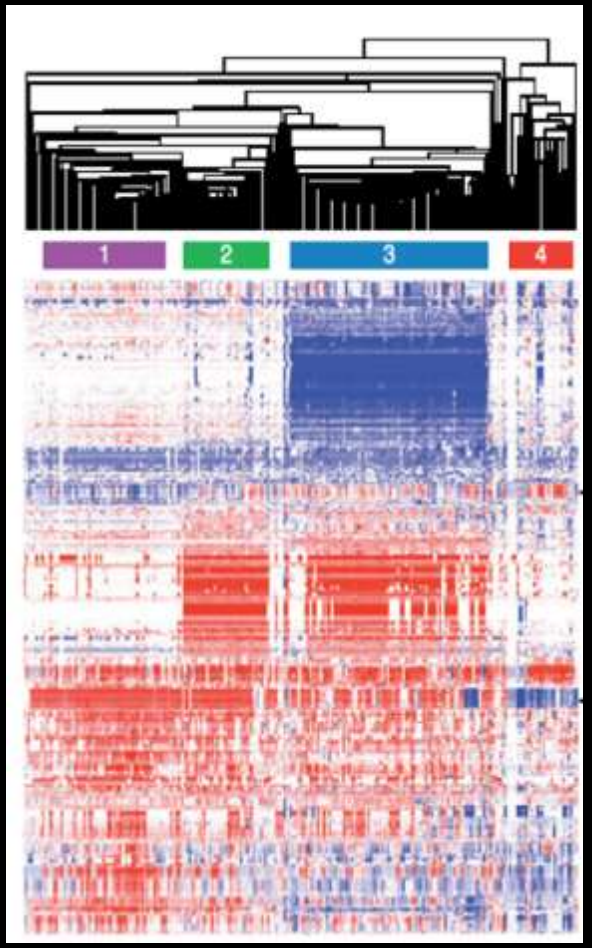
Declared Interests

Board of Directors	Scientific Advisory Boards	Advisory/Consultancy
–Monsanto –Exelixis –Caris Life Sciences –Bulletin Atomic Scientists	–Synthetic Genomics –Burrill and Co. –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/

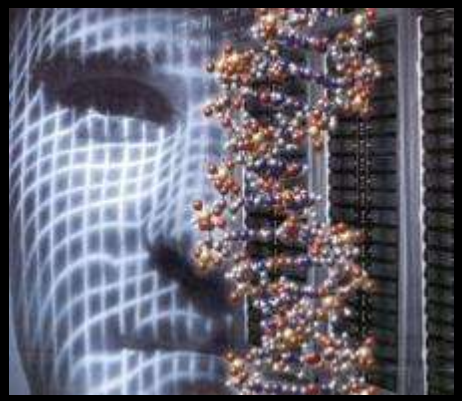
Medical Progress:
From Superstitions to Symptoms to Signatures



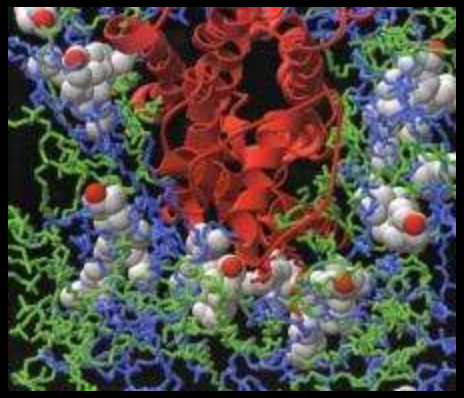


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

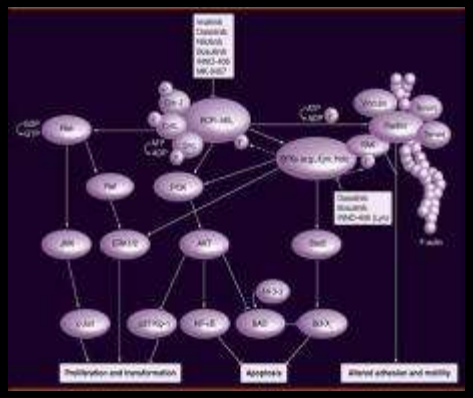
Genomics



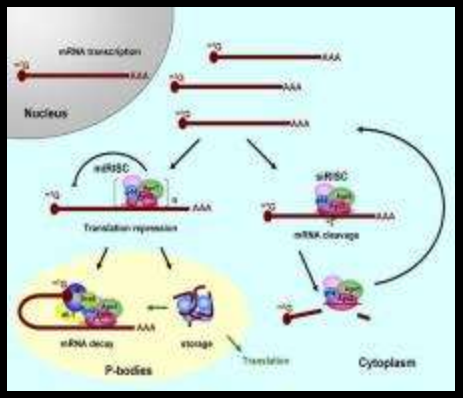
Proteomics

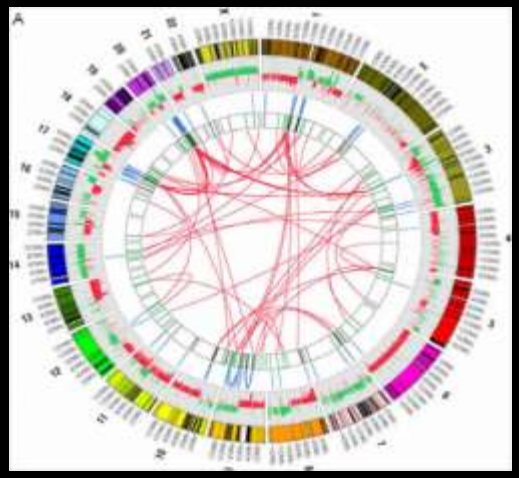


Molecular Pathways and Networks



Network Regulatory Mechanisms



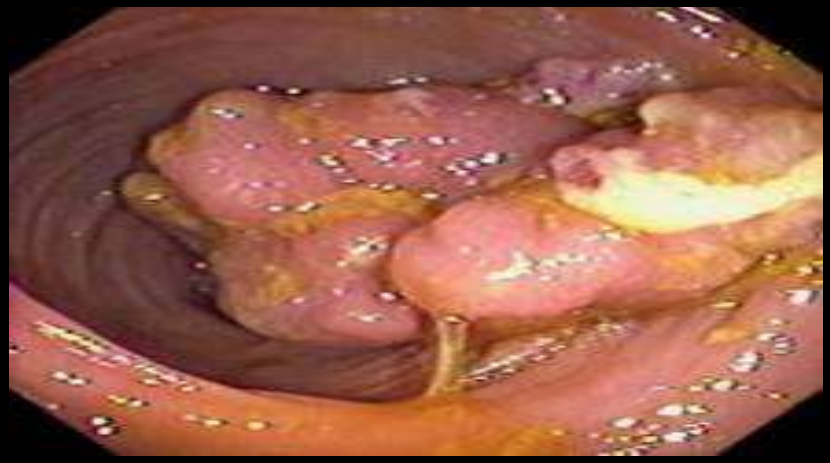


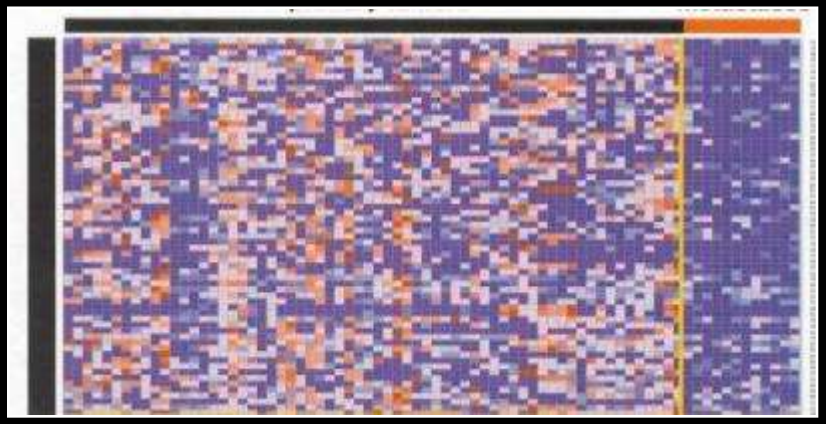
ID of Causal Relationships Between Network Perturbations and Disease

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

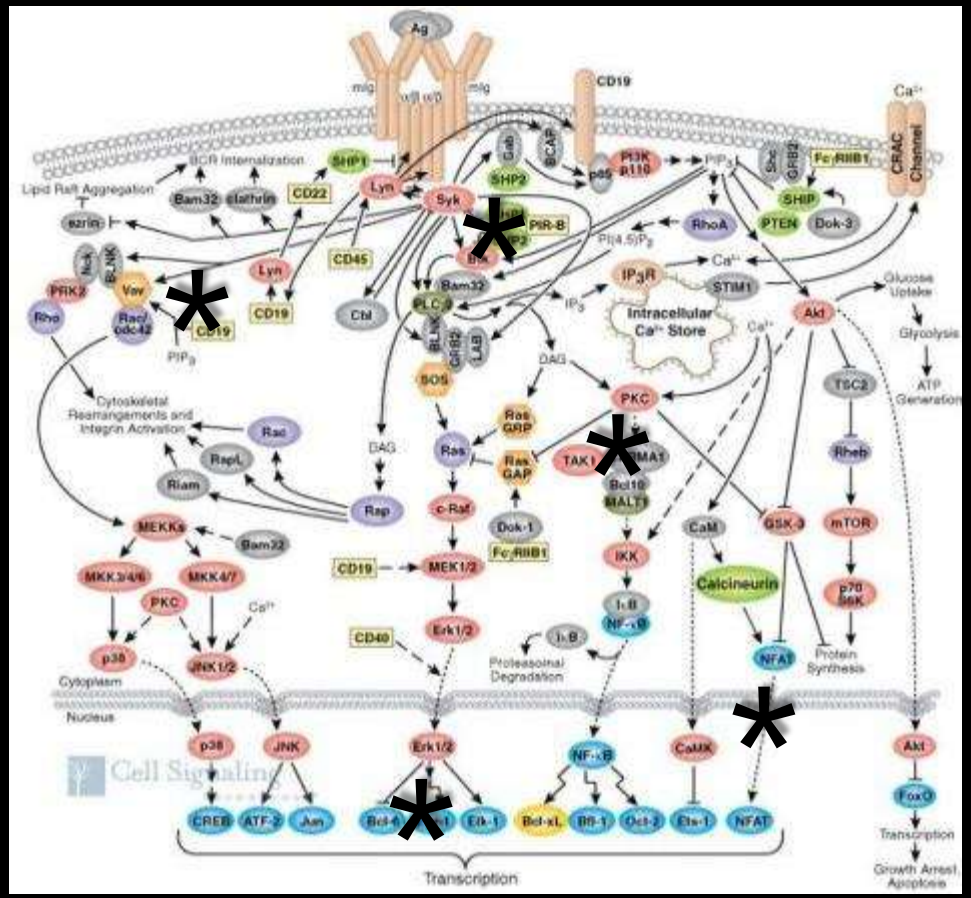
"Omics" Profiling to Identify Disease Subtypes (+ or - Rx Target)





Multiplex Profiling

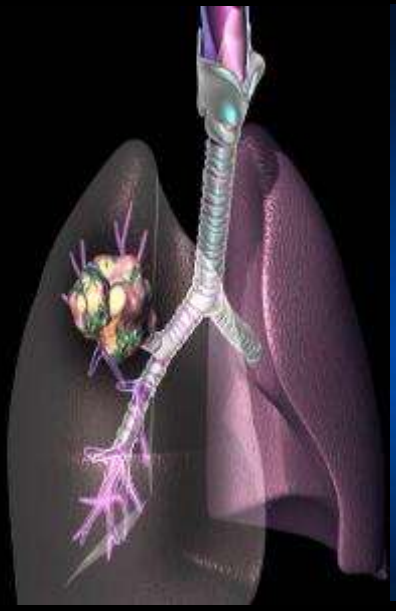
Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action



Right Rx for Right Disease Subtype

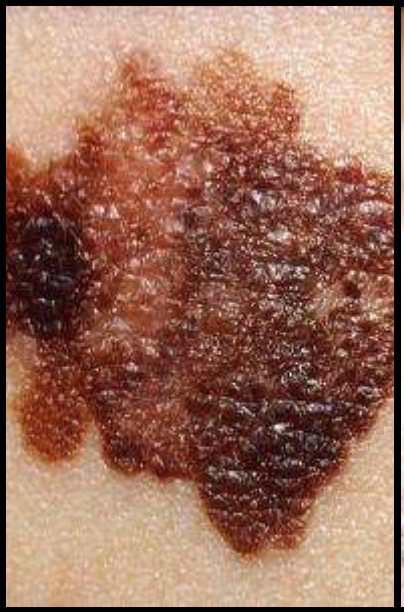
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics – the Right Rx for the Right Disease (Subtype)

Her-2+
(Herceptin)
(Perjeta)



EML4-ALK
(Xalkori)

K-ras
(Erbitux)
(Vectibix)



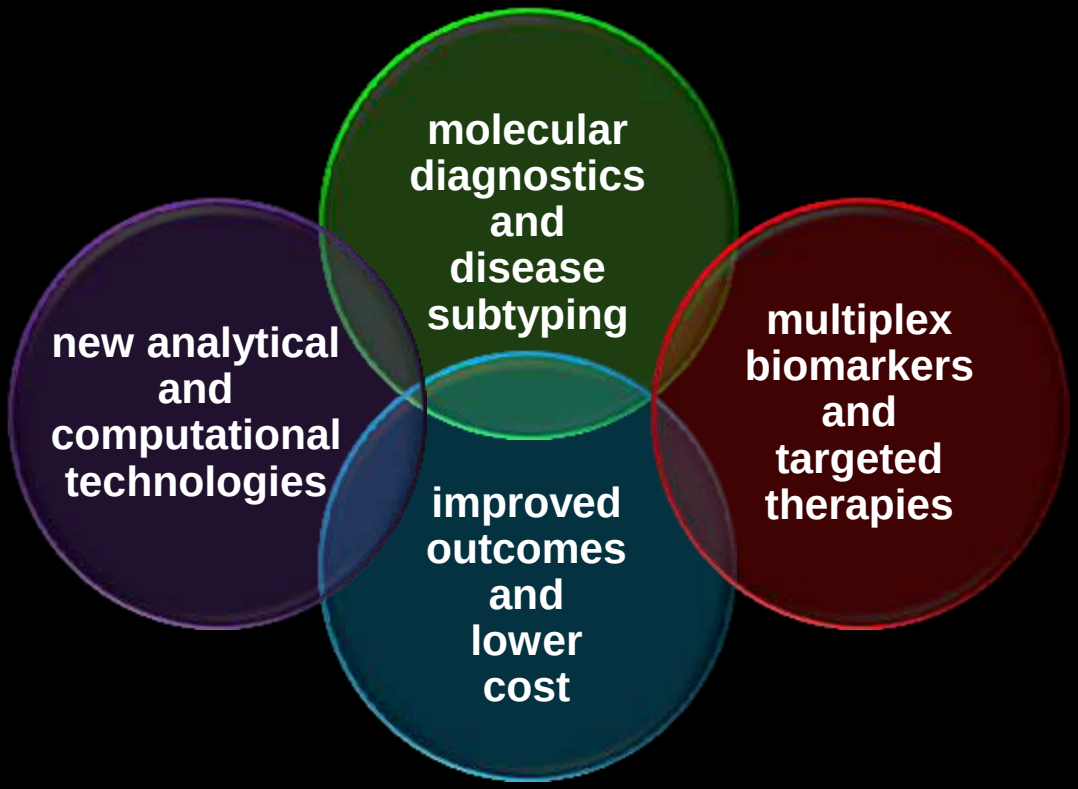
BRAF-V600
(Zelboraf)

CFTR-G551
(Kalydeco)

Targeted Oncology Therapies in Molecularly Stratified Populations

Cancer	Target	Agent
Breast carcinoma	HER2 amplification	Krastuzumab, lapatinib
NSCLC (adenoCA)	EGFR mutations	EGFR TKIs (erlotinib, gefitinib)
NSCLC	EML-ALK	ALK inhibitors (crizotinib)
GIST	KIT and PDGFRA mutations	Imatinib
Melanoma	BRAF-V600 mutation	BRAF inhibitor (vemurafenib)
Ewing's sarcoma	EWS-FLI translocation	anti-IGF1R ab (figitumumab)
Medulloblastoma BCC	PTCH1 or SMO mutations	SMO inhibitors (vismodegib)
Ovarian/ breast CA	BRCA1/BRCA2 mutations	PARP inhibitors (olaparib)
PRCC	MET mutations	MET TKIs (ARQ197. XL880)

Precision (Personalized) Medicine



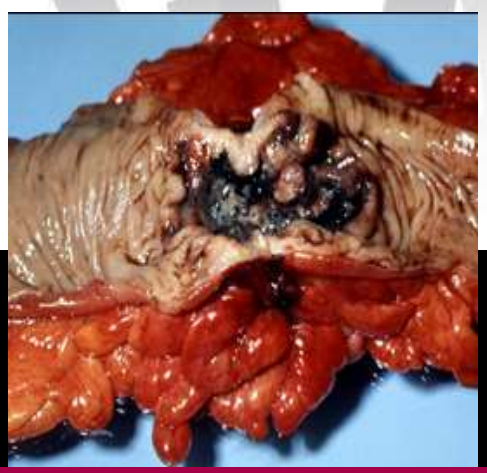
Molecular Diagnostics (MDx) and Tumor Profiling as the Intellectual Foundation of Rational Care

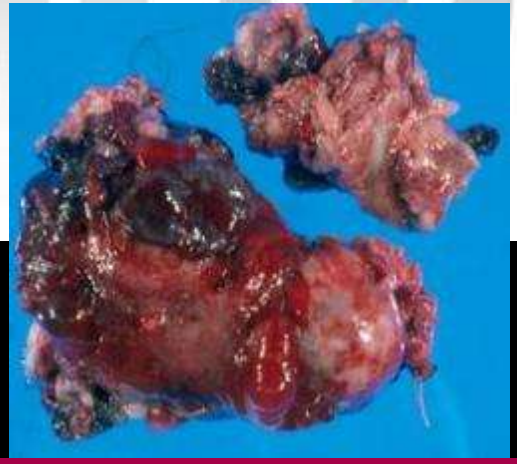
- subtyping of cancers based on molecular profile(s)
- from one-size-fits-all treatment to targeted Rx
- rational selection of Rx based on presence or absence of Rx ‘target’ in a patient’s tumor
- elimination of futile therapy (cost, QOL)
- shift focus to optimum therapy plus ethical shift to increased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

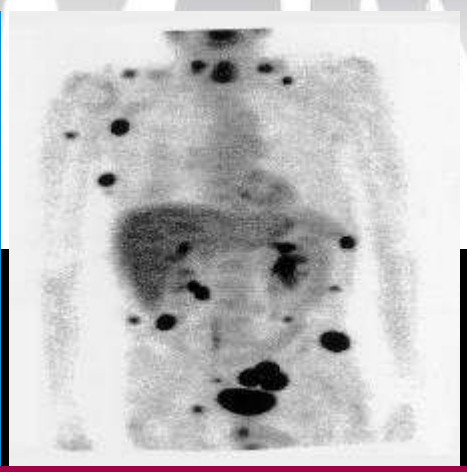
Disease Subtyping and Targeted Therapy: The Right Rx for the Right Disease Subtype

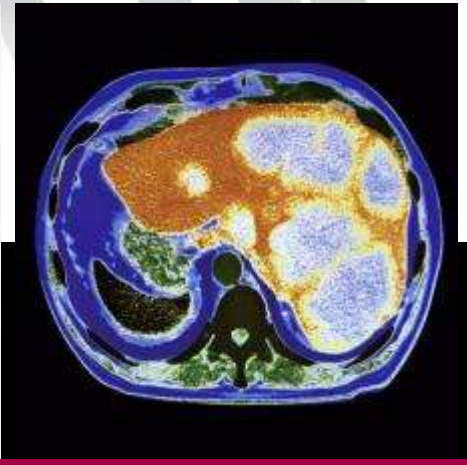
- improved clinical outcomes
- cost-effectiveness in eliminating futile Rx
- reducing high failure rate of investigational drugs in clinical trials by testing only on relevant patients
  - faster and cheaper trials
  - new trial designs (adaptive; basket)
  - greater regulatory clarity
  - premium pricing for guaranteed outcomes (P4P)?

US Cancer Deaths 2012







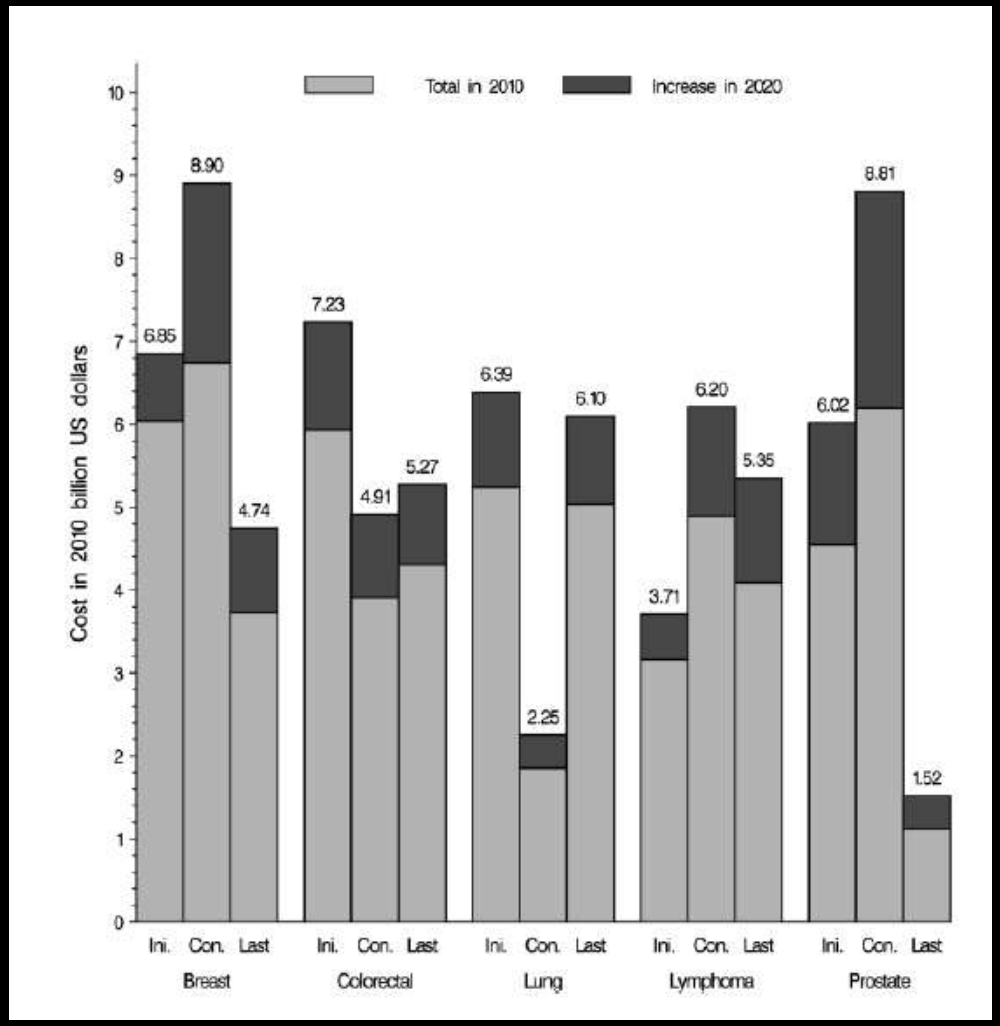


US Cancer Prevalence Estimates 2010 and 2020

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

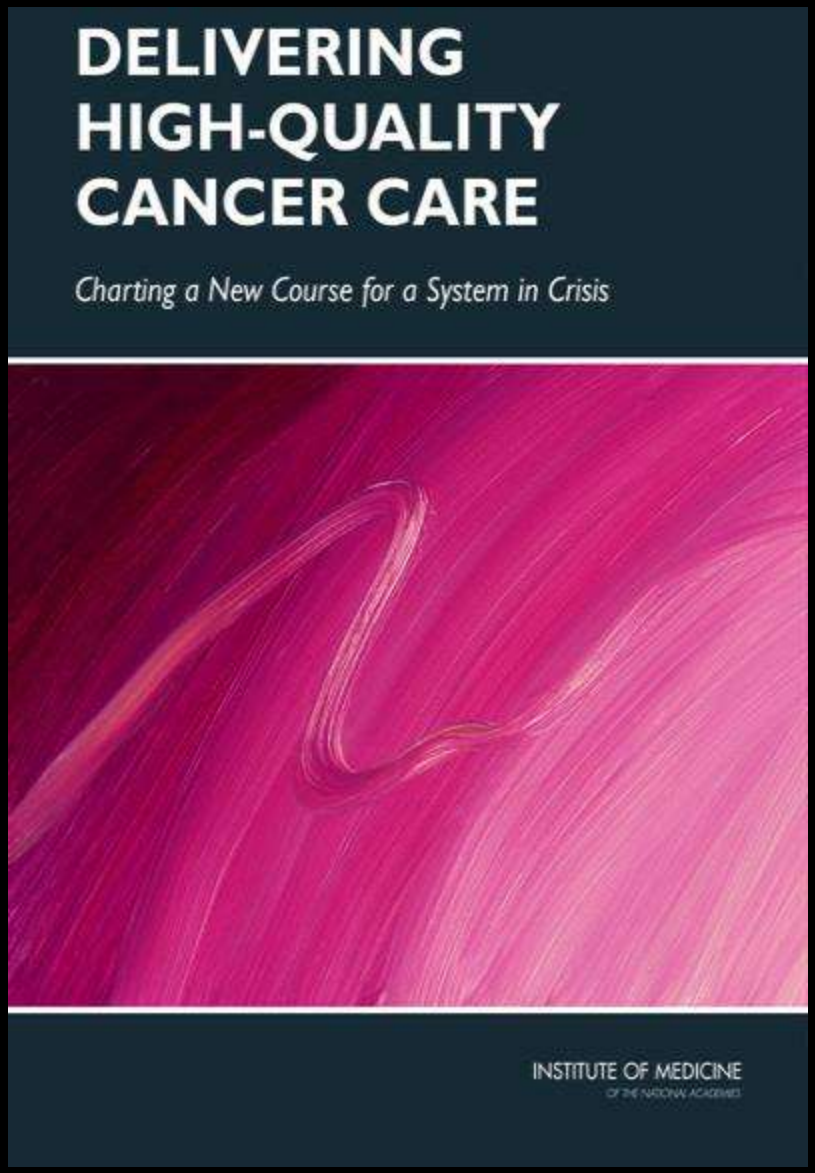


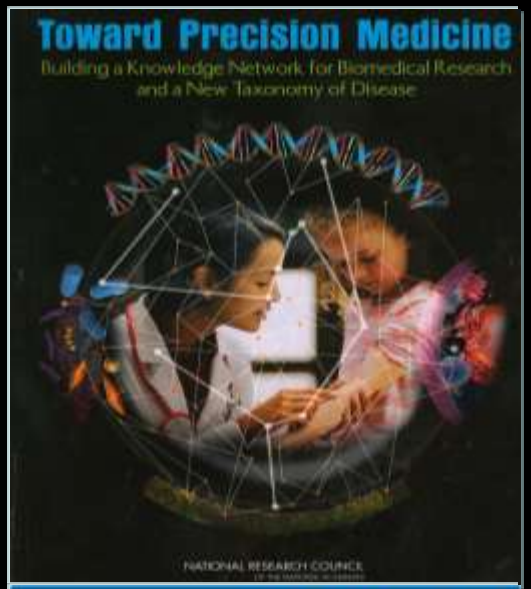
$124 billion and projected to rise to $207 billion (66% increase) by 2020

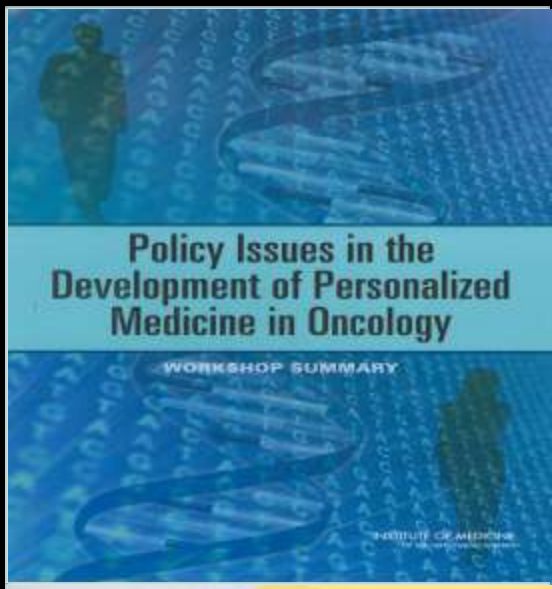
Ini. = within 1 year of Dx; Con = continuing; Last = last year

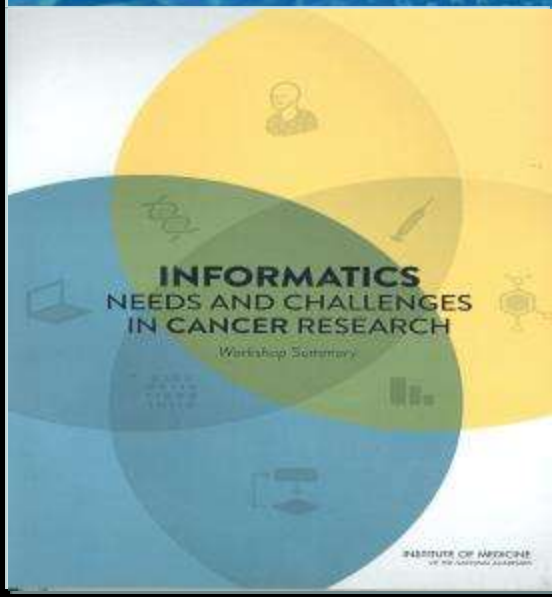
From: A. B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

The Current Status of Cancer Care









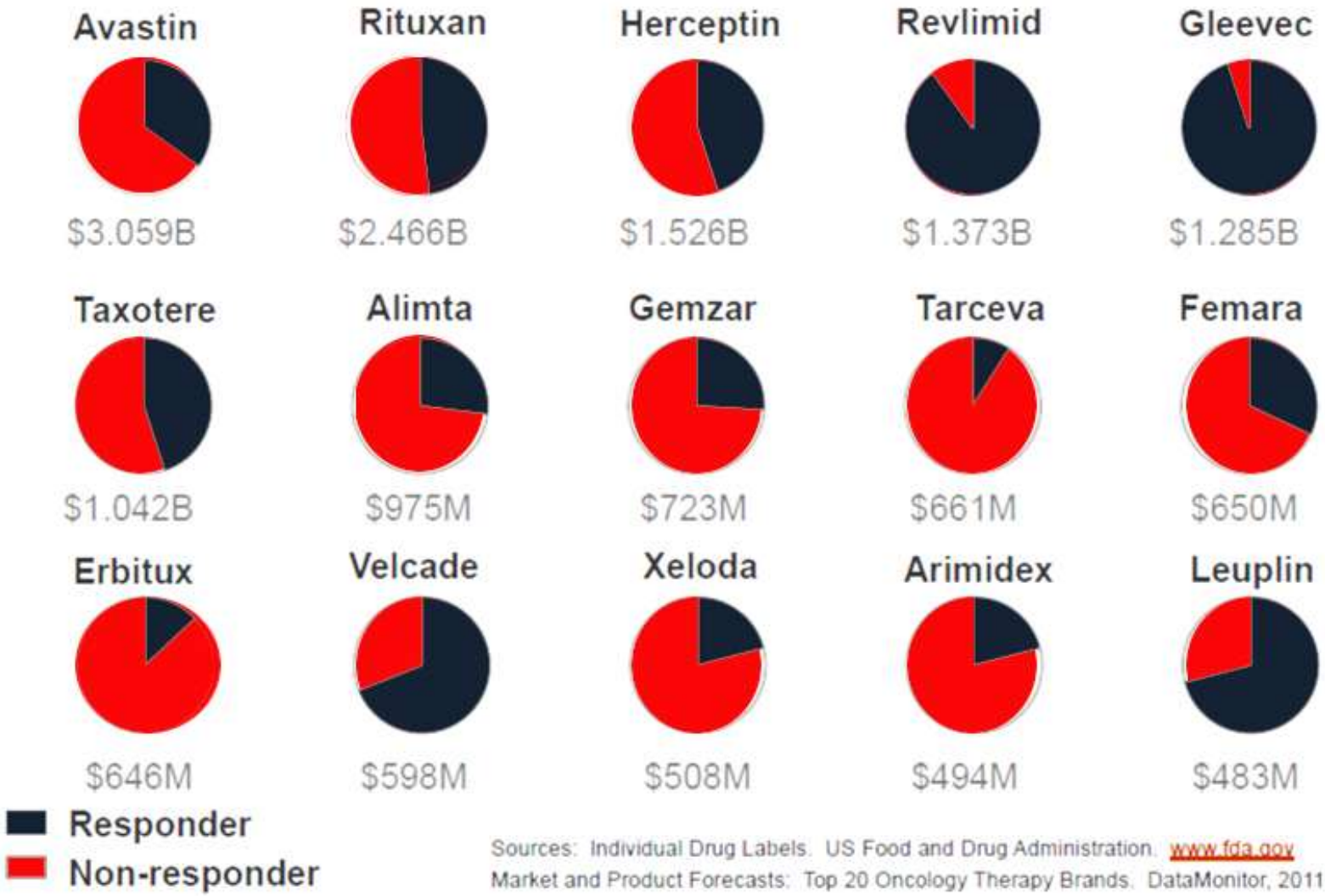
The Need for New Conceptual Strategies to Improve the Detection and Therapy of Metastatic Disease

too many drugs fail!

too many biomarkers fail!

clinical trials are too expensive and too long!

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



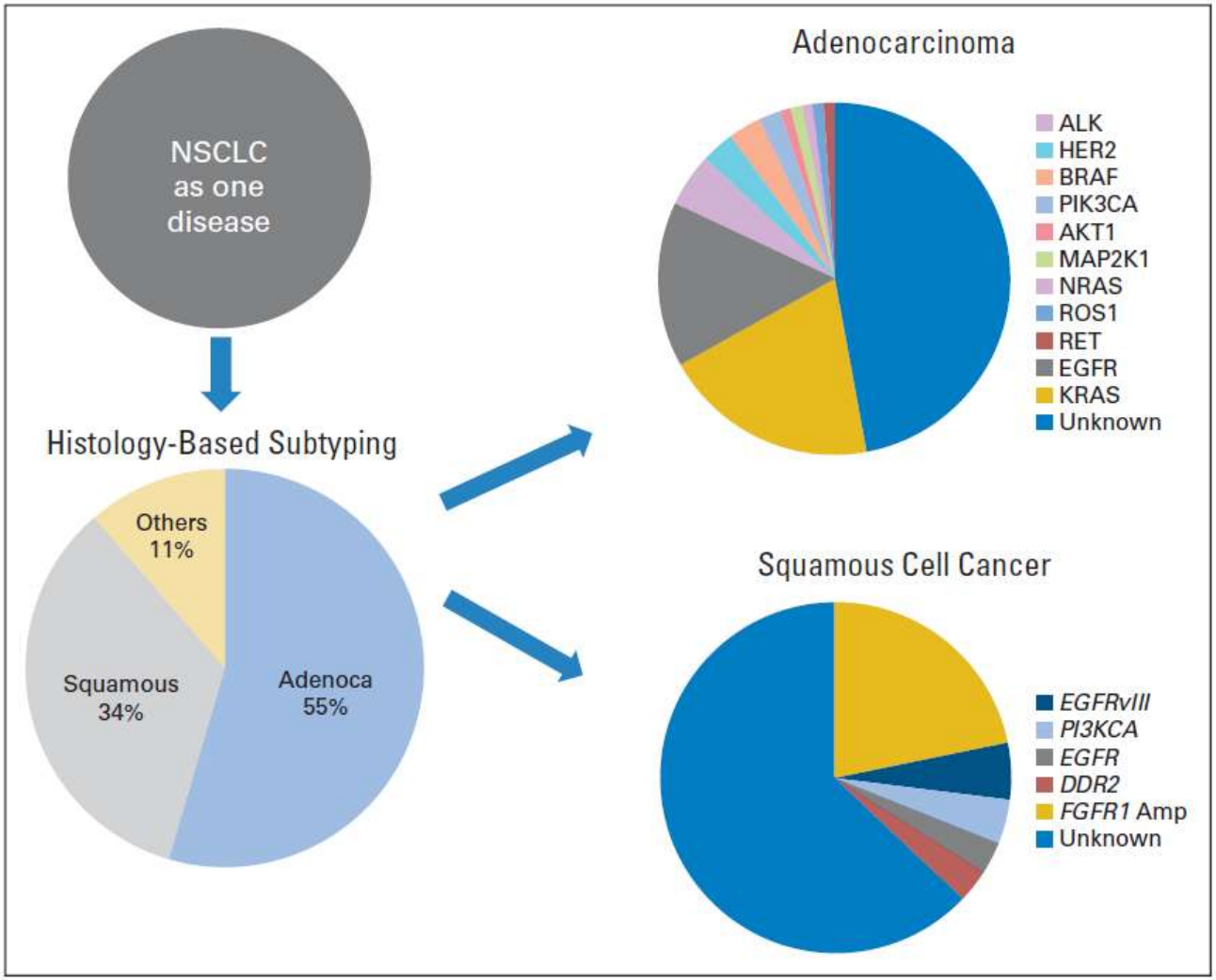
Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

Re-Thinking the Cancer Problem

- conceptual
- technical (research, translation and clinical oncology)
- organizational
- cultural
- public policy (regulation and reimbursement)

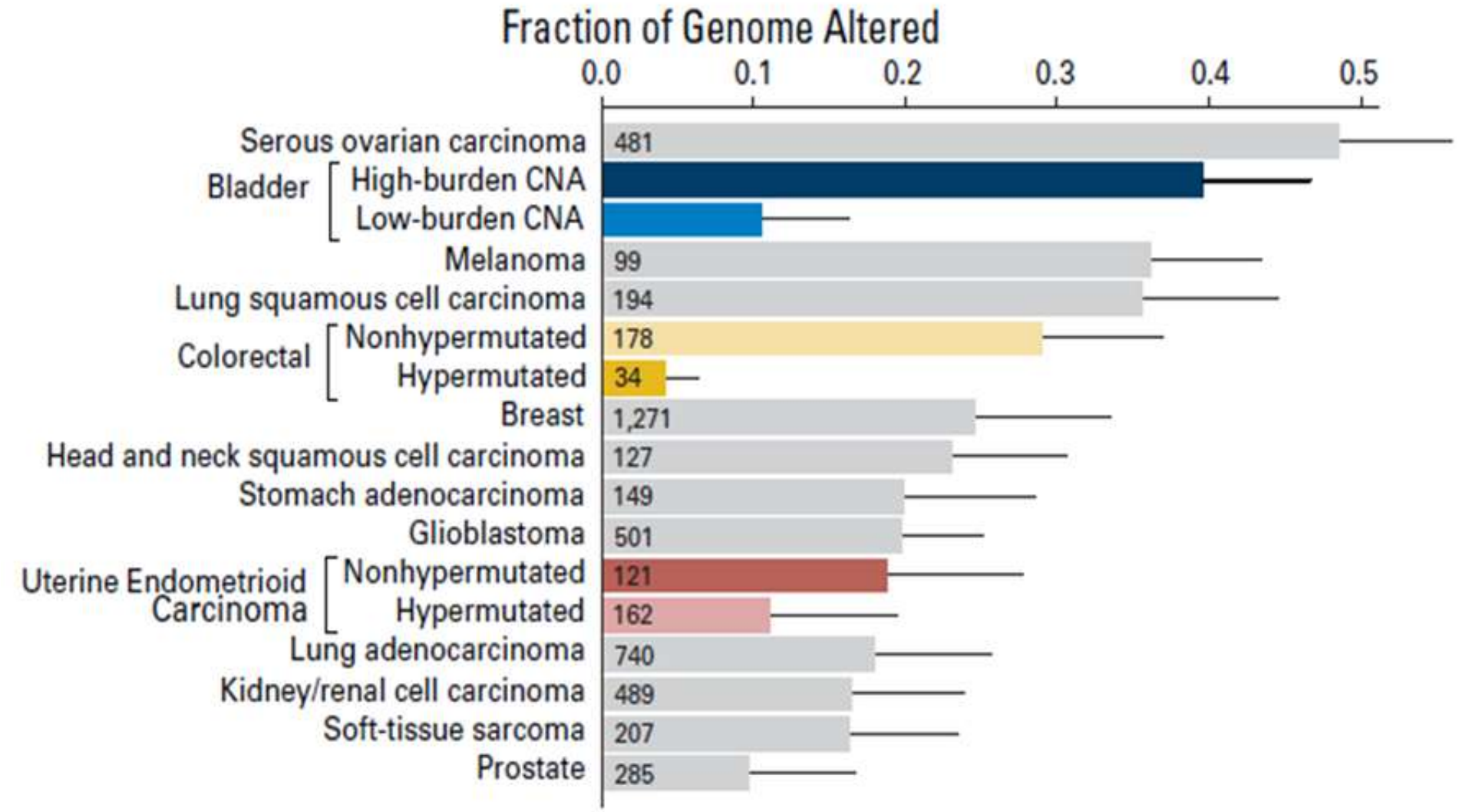
Cancer: A Formidably Complex Catalog of Genomic Changes and Disruptions in Cellular Molecular Signaling Networks

The Evolution of the Classification of NSCLC



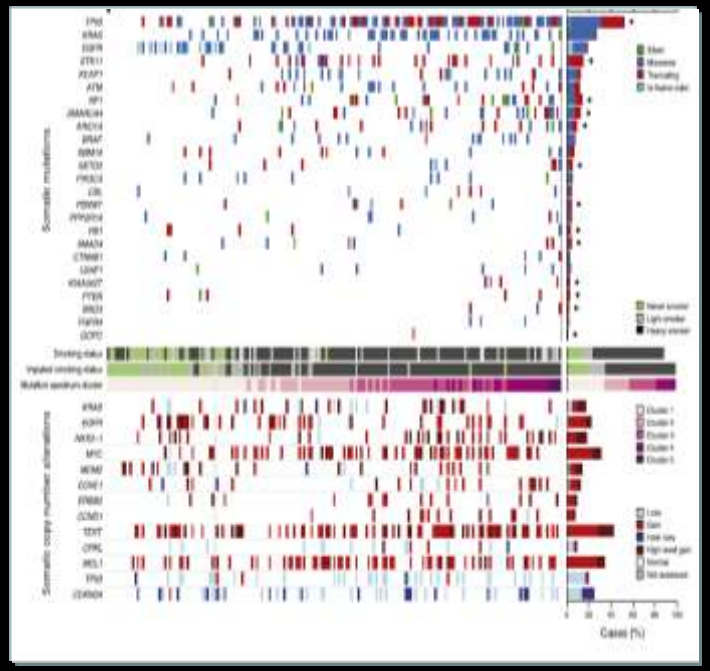
From: T. Li et al. (2013) JCO 31, 1039

Copy Number Alteration in 5135 Tumors from 14 Solid Tumor Types

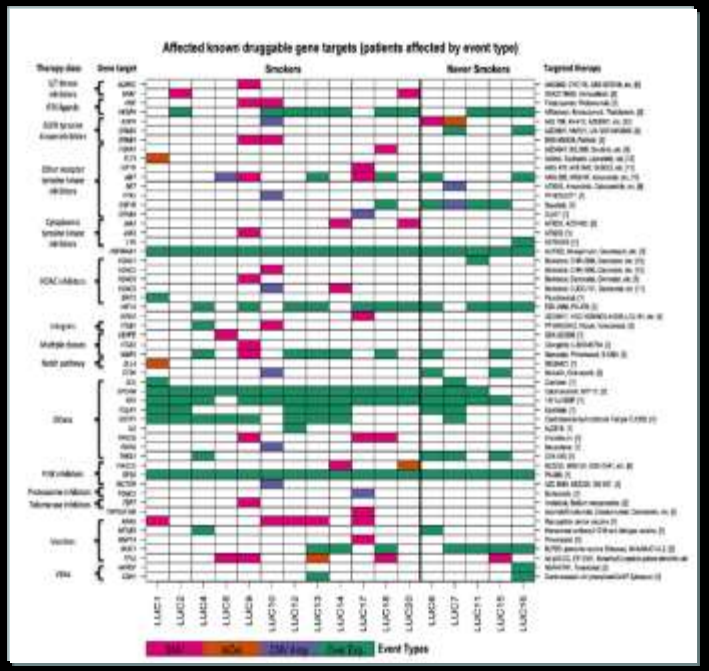


From: G. Iyer et al. (2013) JCO 31, 3133

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



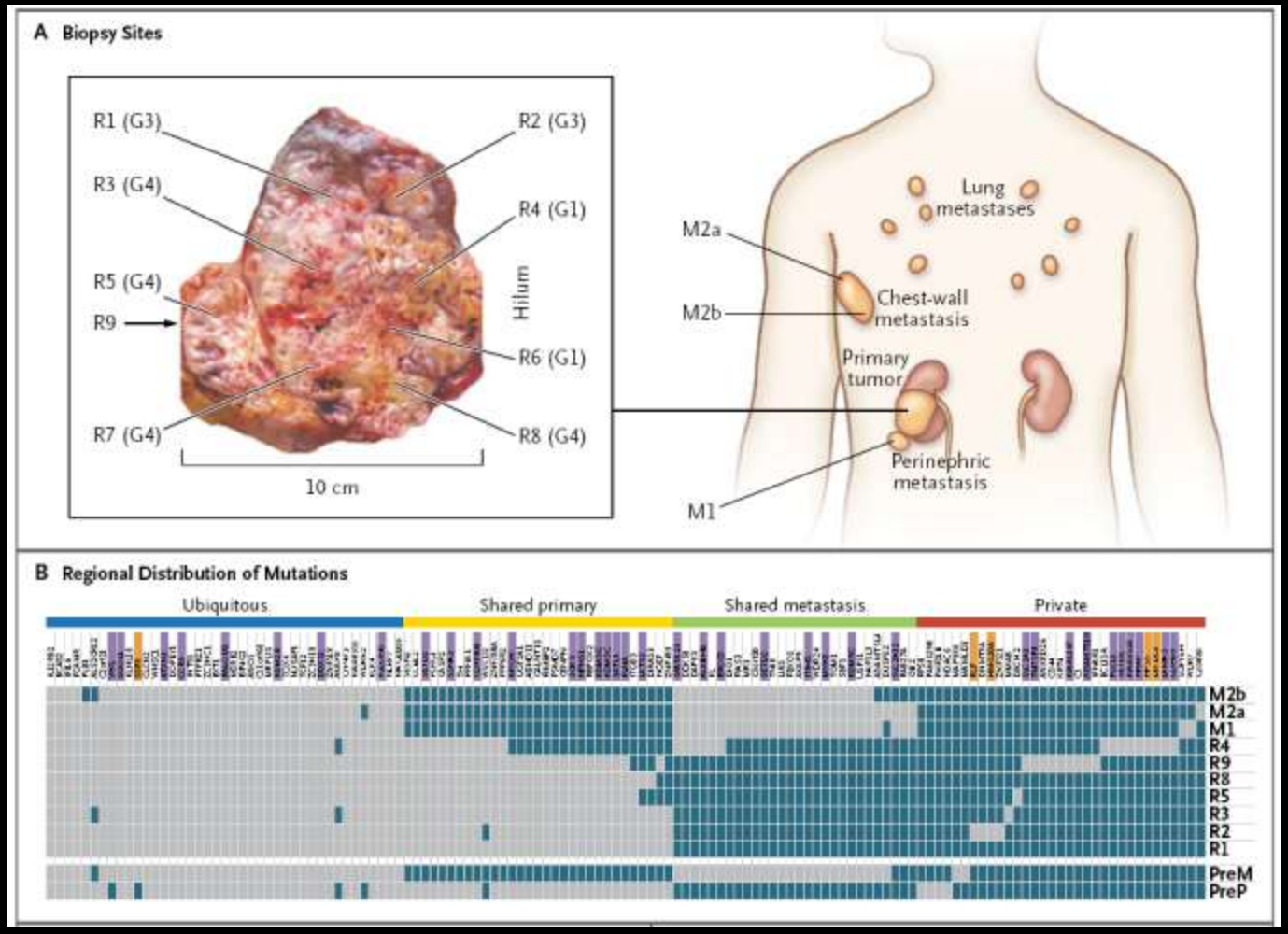
Mutations in Individual Non-small Cell Lung Cancer



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

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



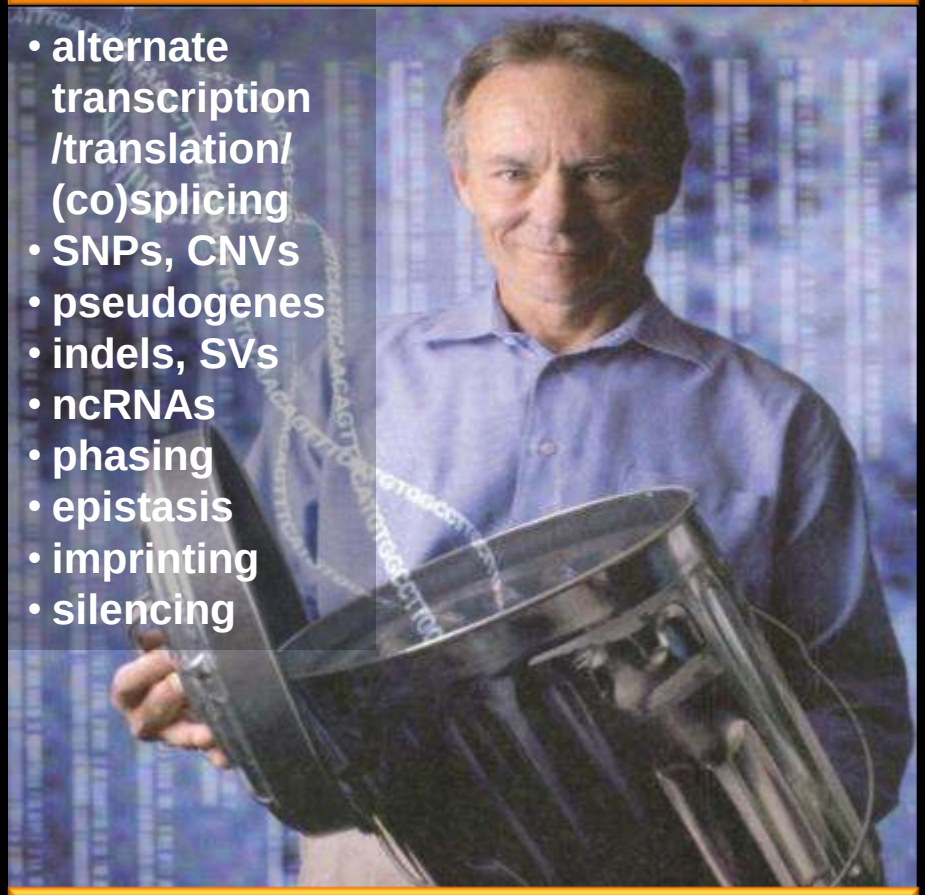
From: M. Gerlinger et al. (2012) NEJM 366, 883

Genes For ….
The Overly Simplistic and 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

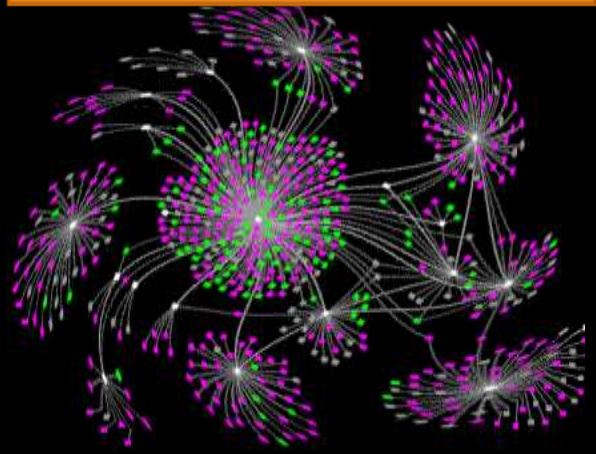
Junk No More: Pervasive Transcription



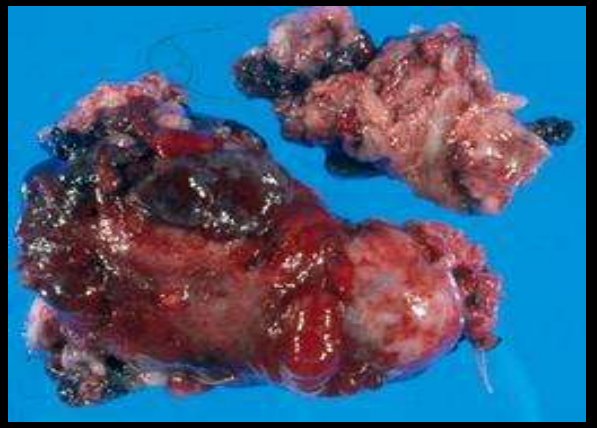
- alternate transcription /translation/ (co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing

recognition of genome organizational and regulatory complexity

Cell-specific Molecular Interaction Networks



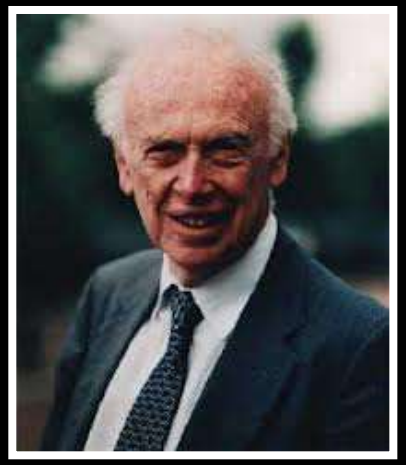
Perturbed Networks and Disease



Molecular Profiling and Disease Classification

- network inference methods based on expression data alone are at best incomplete
  - fail to separate direct and indirect regulatory events
- integration of different datatypes perform better than individual datatypes in prediction of regulatory networks
  - sequence
  - expression
  - protein-DNA interactions (ChIP-chip/ChIP-seq)
  - miRNAs and ncRNAs
  - protein-protein interactions
  - chromatin profiling (epigenomics)

Redefining Approaches to Cancer Drug Discovery, Clinical Trials and Regulatory Approval



“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

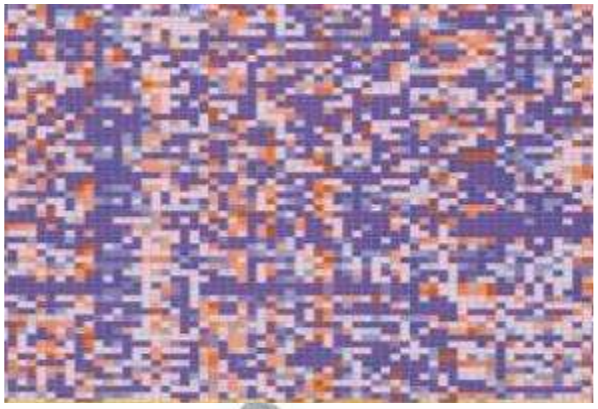
Confronting the Biological Complexity of Multigenic, Late-Onset Chronic Diseases

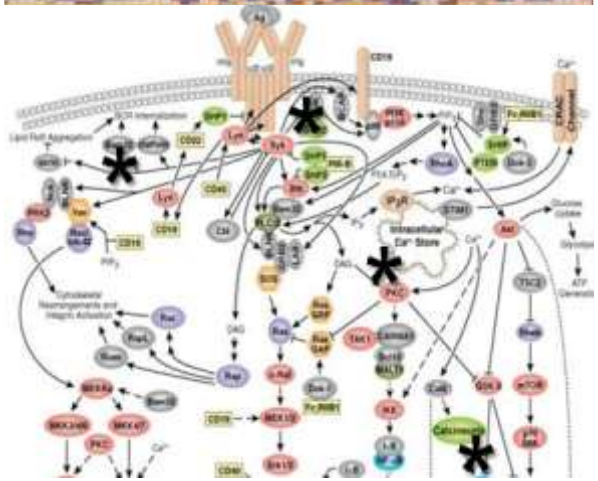
Understanding the Perturbation and Dysregulation of Complex Biological Network Architectures in Disease

Mapping Clonal Population Dynamics in Tumor Progression and Emergence of Drug Resistant Clones

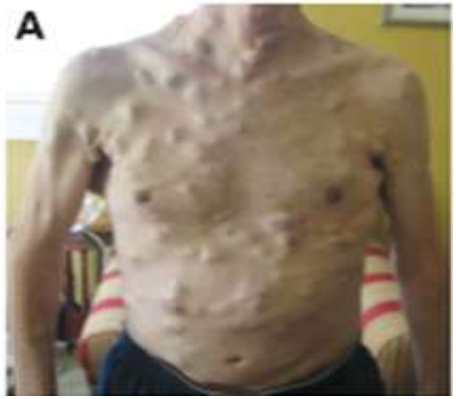
Clonal Heterogeneity and the Relentless Emergence of Drug-Resistant Clones (Intrinsic and/or Acquired Resistance)

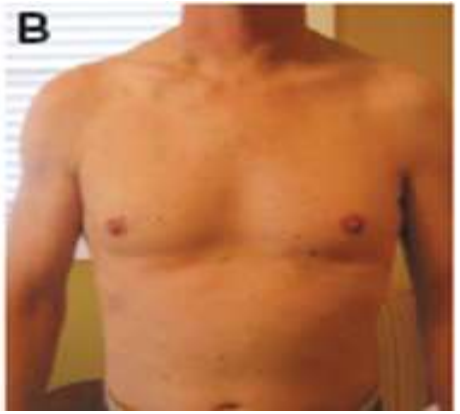
Molecular Subtyping and RX Targets



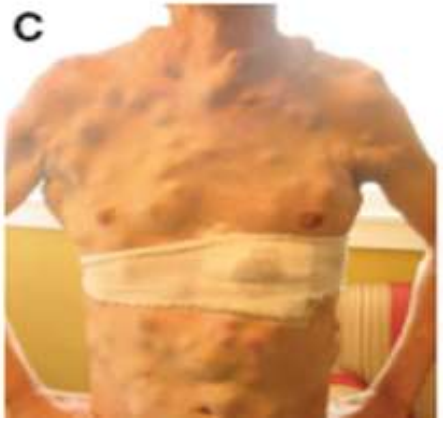


Initial Rx-Response to Targeted Rx





Rx-Resistance via Redundant Molecular Pathways



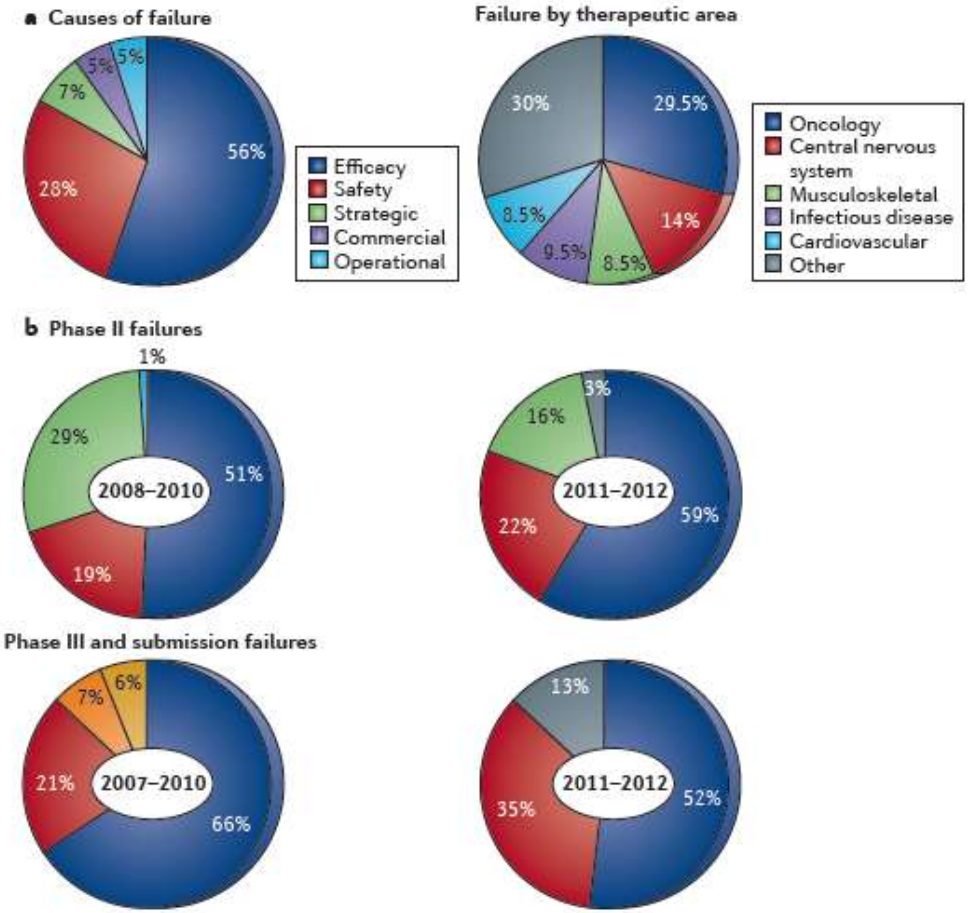
B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

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

Reducing the Failure Rate of Investigational Drugs in Clinical Trials

Failure Rates for 105 Investigational Drugs 2011-2012*



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

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

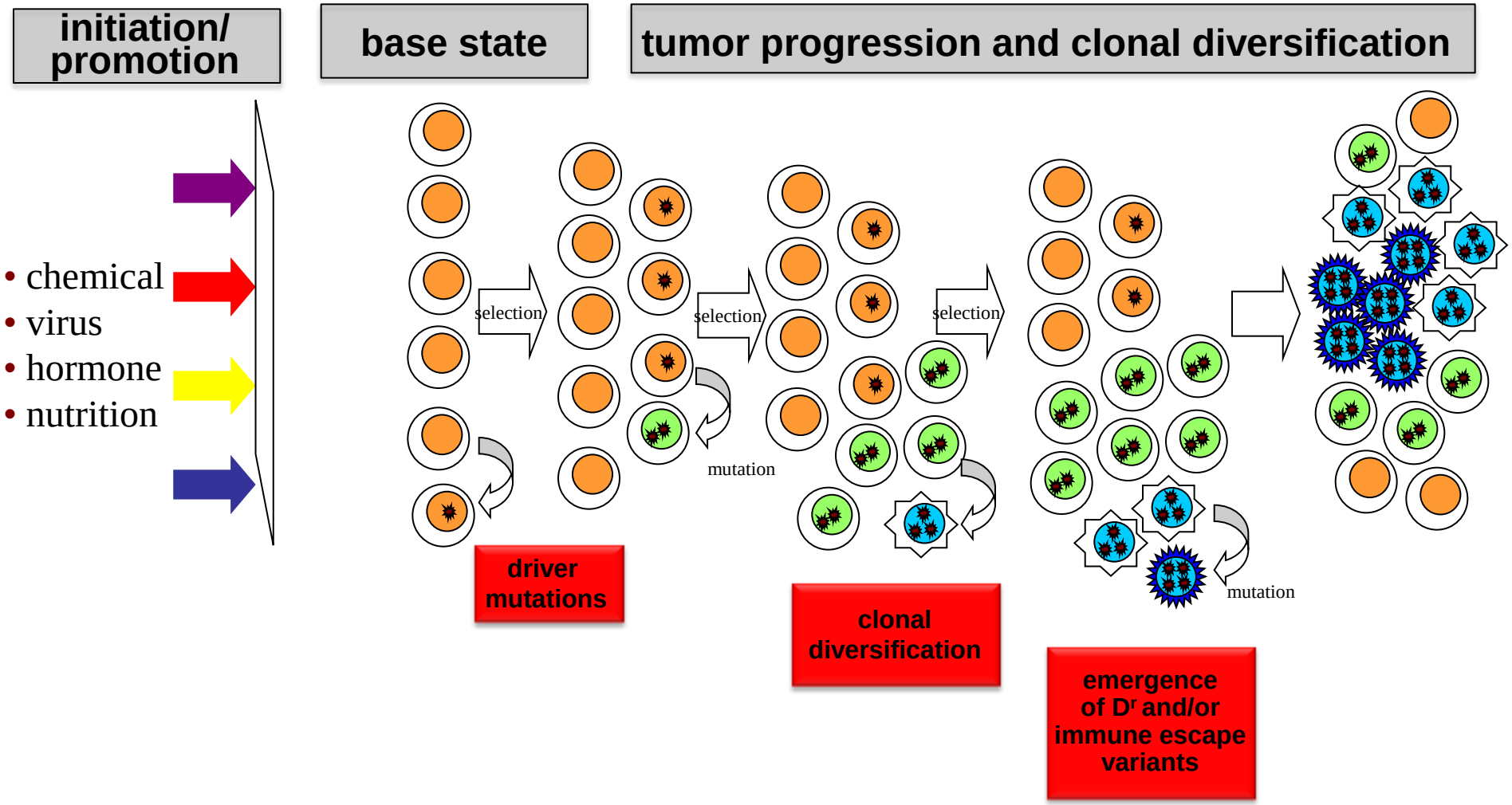
Failed Phase III Clinical Trials of anti-VEGF Agents

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 5fluorouacil	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).

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

The Complex Evolutionary Ecology of Malignant Neoplasms

- are there discernible consistent patterns (signatures) of pathway dysregulation in neoplams arising in specific cell types/tissues?
- what determines the kinetics of clonal diversification and emergence of metastatic clones in tumor progression?
- what is the balance between stochastic and deterministic events in the genesis of clonal heterogeneity?
  - driver versus passenger mutations
  - non-random pathways and ‘fitness islands’
- how does the tumor microenvironment(s) attenuate or promote trajectories and kinetics of clonal heterogeneity, metastatic emergence and drug responses?

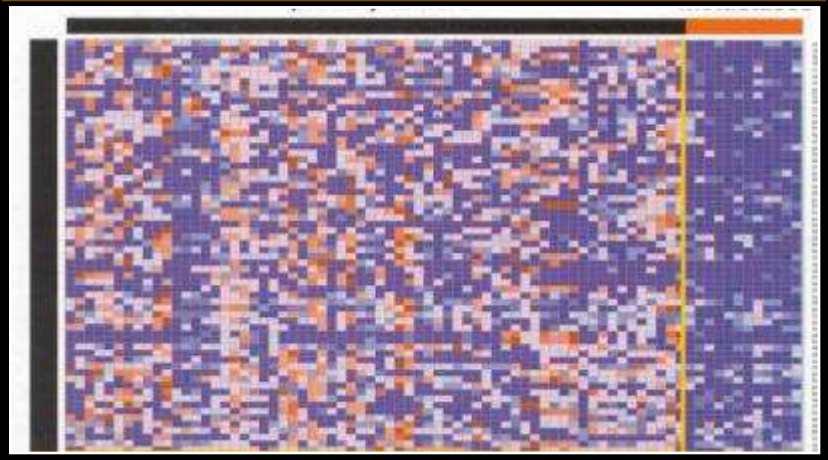
Tumor Cell Heterogeneity and Core Challenges in Cancer Diagnosis and Treatment

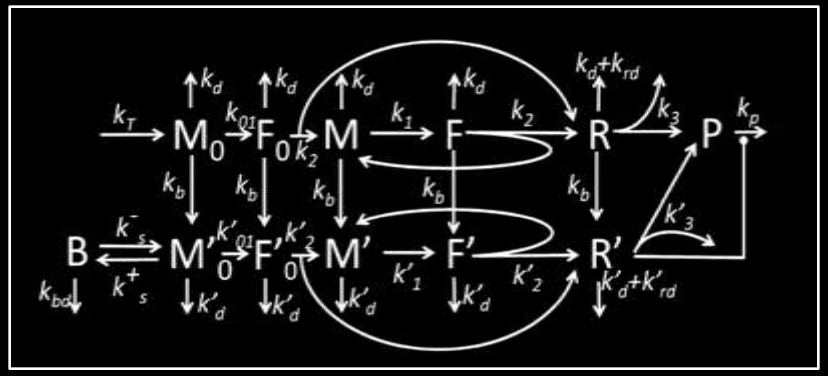
confronting the complexity of clonal heterogeneity and metastatic disease

- 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

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

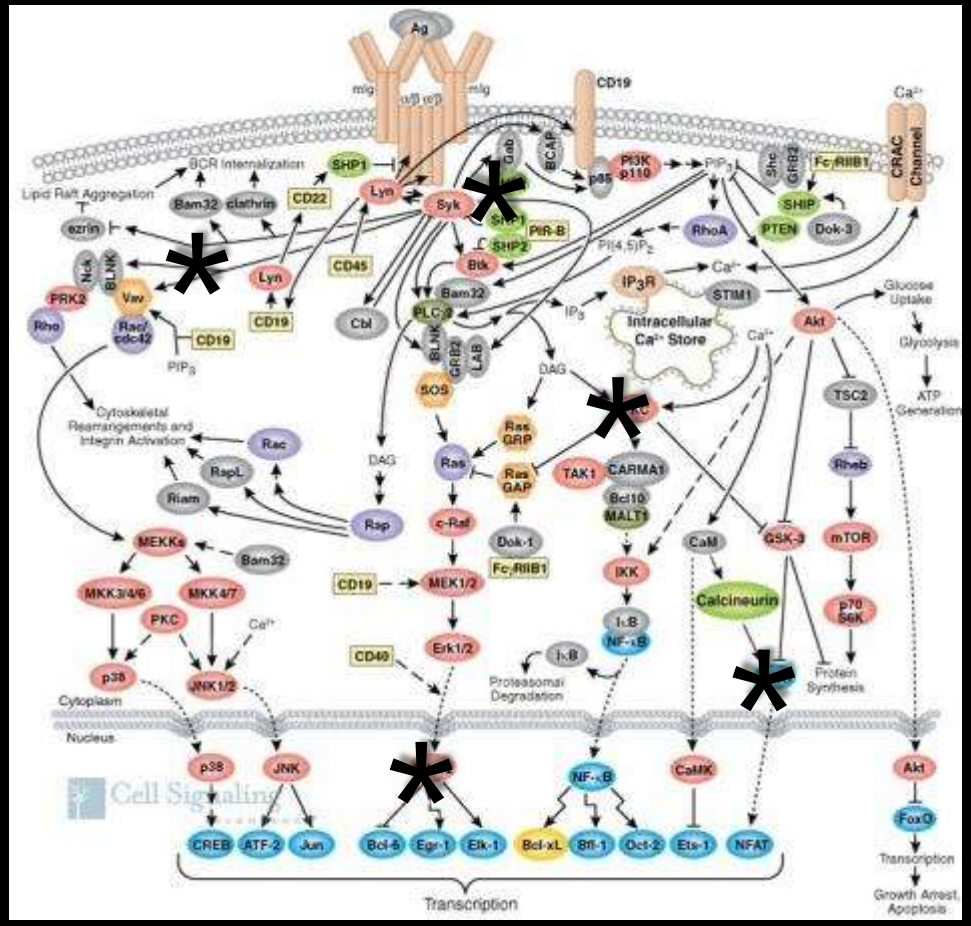
iOmics Profiling to Identify Disease Subtypes (+ or - Rx Target)





Modeling of Information Flow in Biological Networks

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



Context

anti-EGFR antibody therapy and K-ras

- CRC codon 12 mutations resistant
- CRC pG13D mutations sensitive

Vemurafenib and BRAFv600 mutations

- melanoma:sensitive
- CRC: resistant due to EGFR amplification

Imatinib and KIT mutations in GIST

- exon 11 sensitive @ 400mg does
- exon 9 sensitive @ 800mg doses

Differential Sensitivity of Glioma-Versus Lung Cancer-Specific EGFR Mutations to EGFR Kinase Inhibitors

- EGFR mutations in lung cancer reside in the intracellular kinase domain
- EGFR mutations in GBM cluster in the extracellular domain and include in-frame detections (variant III) and missense mutations
  - poor clinical results in GBM with erlotinib, gefitinib
  - sensitivity of EGFR ectodomain mutants to lapatinib but Phase I studies in GBM failed to extend PFS
- I. Vivanco et al. (2012) Cancer Disc. 2, 458

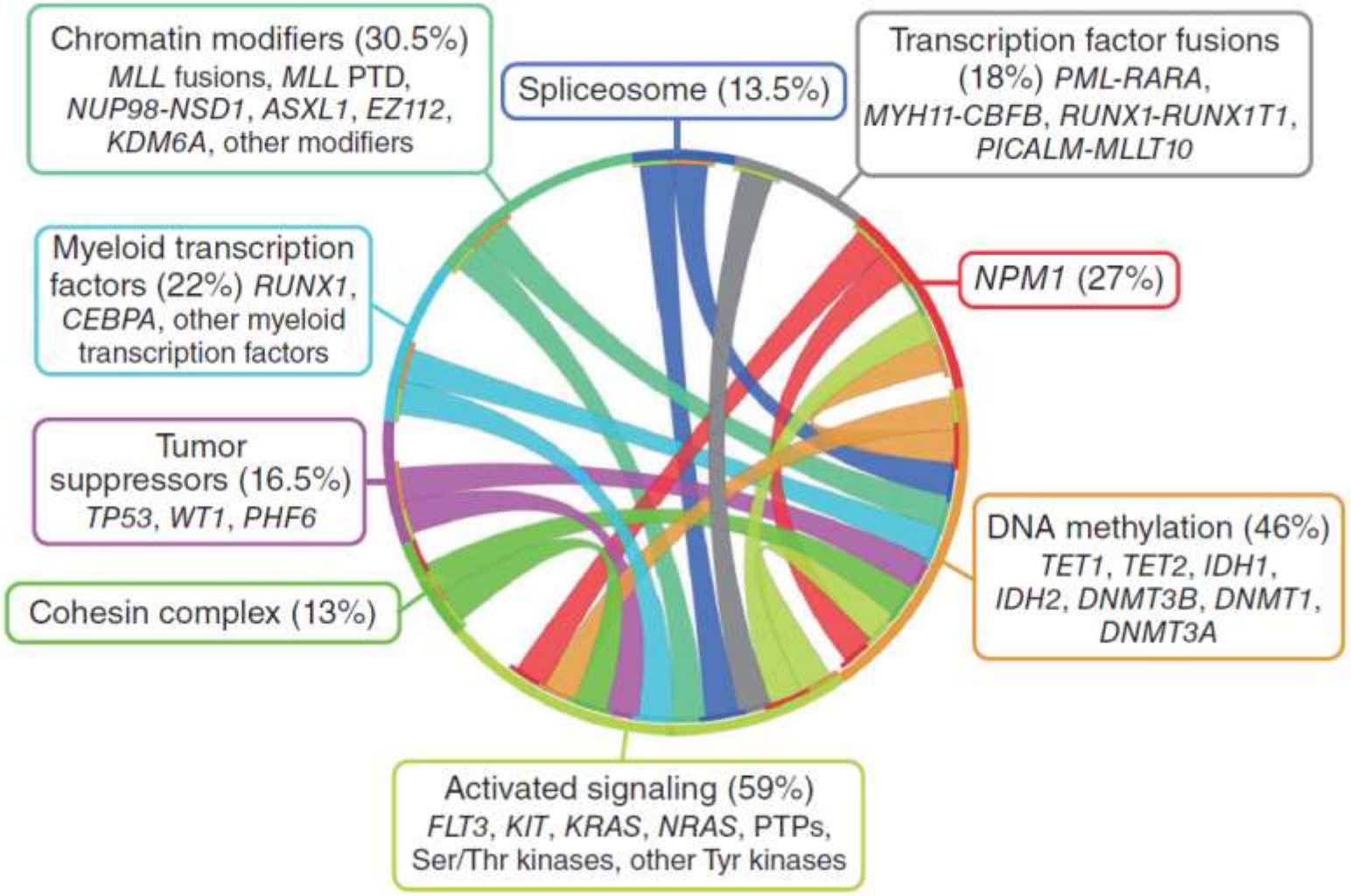
"Omics" Technologies and the Elucidation of Perturbations in Molecular Network 'Wiring' in Complex Diseases

- 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

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

Circos Plot of Diverse Genetic Alterations in AML: Ribbons Indicate Associations Between Pathways



From: S-J. Chen et al. (2013) Nature Genetics 45, 586

Modeling and Simulation of Biological Pathways and Networks

- intrinsic constraints of representational denotations (ODE) and sequential I/0 models
- classical mathematical models suffer from generalization of abstraction of population of heterogenous agents into single continuous variable versus multiple interacting state spaces
- need for new computational and mathematical tools to address concurrency as the key design feature in network organization (complexity) and properties (regulation)
  - algorithmic systems biology
  - prediction of behavior, including emergence

Therapeutic Options for Multi-target Modulation of Dysregulation in Complex Biological Networks

- multisite action on a single target by single Rx
  - blockade of most likely predicted “escape” domains involved in D^r
- multi-target promiscuity in a single Rx
  - control of off-target AEs
- Rx combinations with multisite and and/or multitarget actions
  - patient tolerance, cost,
  - clinical trial design for large Rx combinations
- new regulatory paradigms

Limited Efficacy of Multi-Target Rx in Glioblastoma

Agent	Target
sorafenib	PDGFR-α,β, VEGFR-2,3, BRAF, c-Kit, Ras
imatinib	PDGFR-α,β, c-Kit, Bcr–Abl
tandutinib	PDGFR-α,β, c-Kit, Flt3 (Phase II)
dasatinib	PDGFR-α,β, Src, Bcr–Abl, c-Kit, EphA2 (Phase II)
aflibercept	VEGF-A, VEGF-B, PlGF
cediranib	VEGFR-1,2,3, PDGFR-α,β, FGFR-1, c-Kit
sunitinib	VEGFR-2, PDGFR-β, c-Kit, RET, Flt3
vandetanib	VEGFR-2, EGFR, RET
cabozantinib	VEGFR-2, Met, RET, c-Kit, Flt3, Tie-2

Adapted from: S. Tanaka et al. (2013) Nature Rev. Clin. Oncol. 10,14

Irreversible Kinase Inhibitors and Cancer*

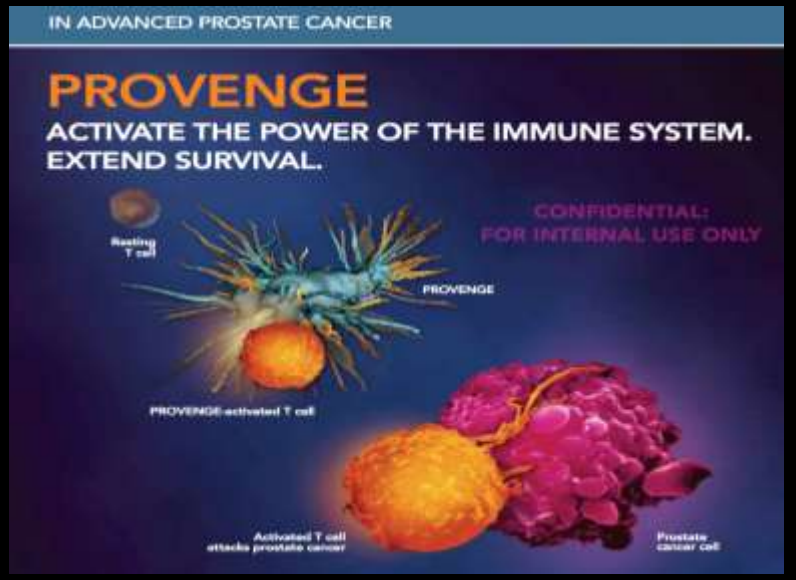
- prospect of circumventing D^r phenotypes seen with reversible inhibitors
- resistance mutations do not block inhibition
- per se but modulate rate of binding
  - relatively slow binder mutations will eventually become saturated
- more sustained duration of inhibition
  - reduce incidence of repeated intervals of incomplete target coverage
- but discrepancy between lab and clinical data
  - afatinib active in vitro against T790M EGFR resistance mutation but ineffective in NSCLC trials
  - neratinib no benefit in pts with resistance to reversible inhibitors

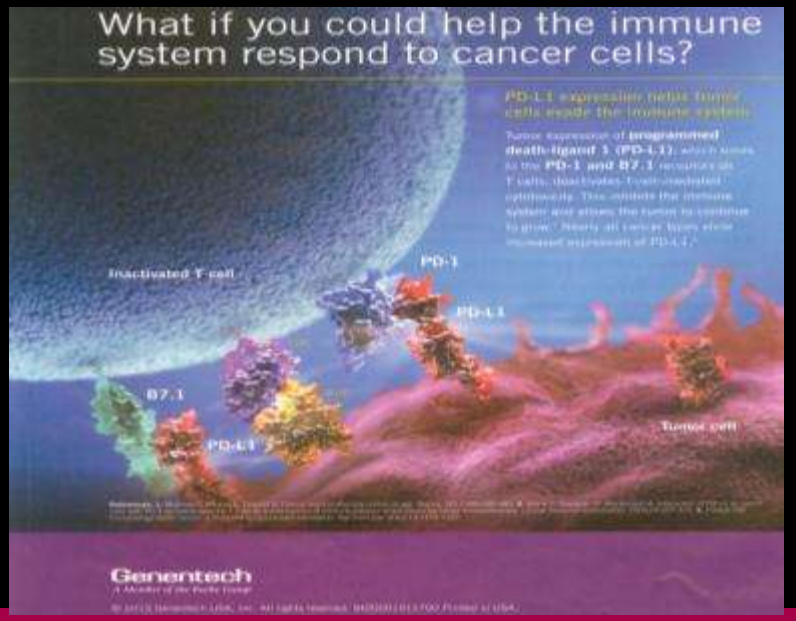
*K. Sanderson (2013) Nat. Rev. Drug Disc. 12, 649

Genome Editing to Reproduce Tumor-Related Variations in Human Cells for Improved Rx Discovery

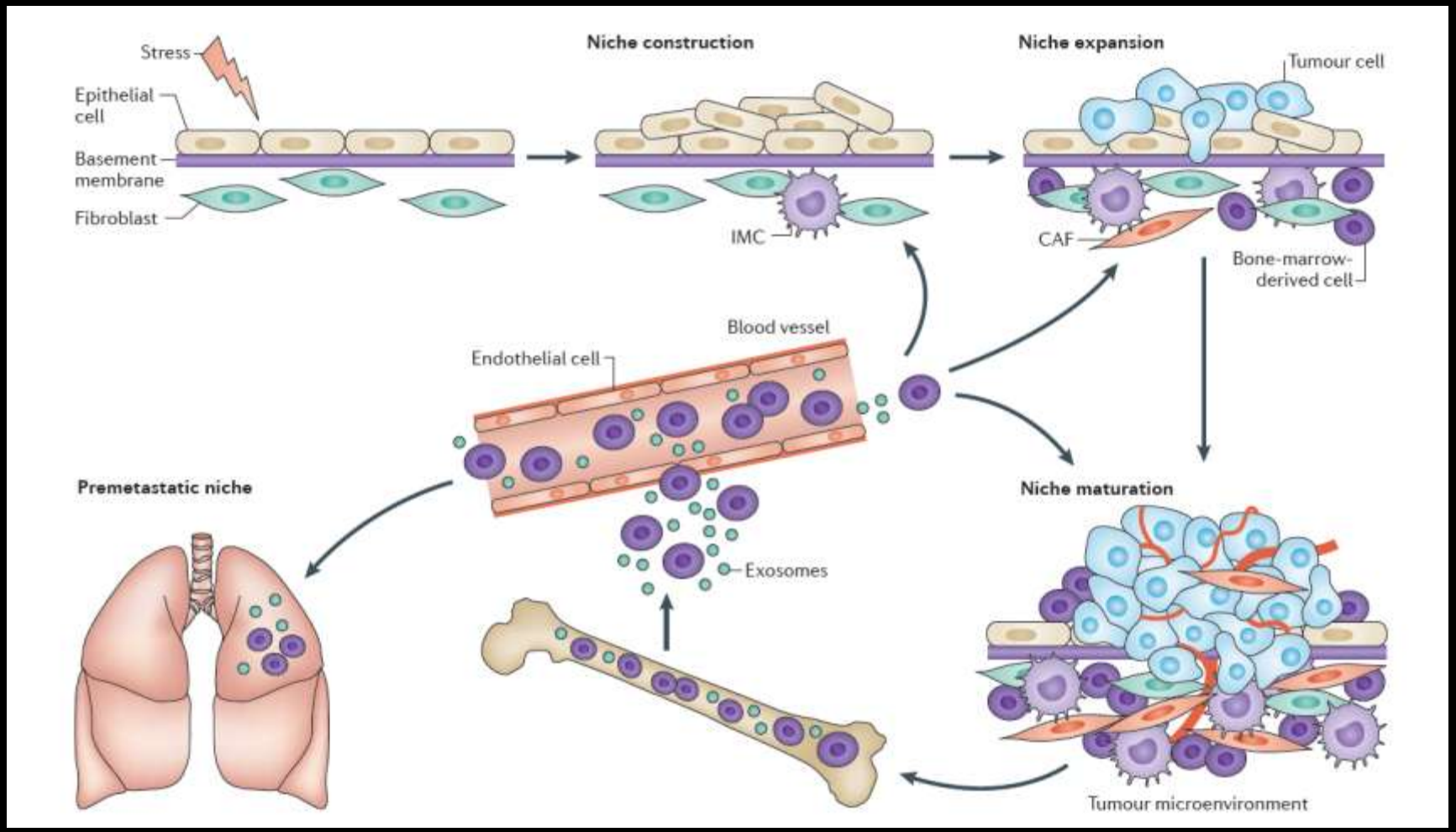
- use of tailored nucleases (TALENs)
- create double-strand breaks (DSBs) at any locus of interest for gene disruption/correction
- use of ZFNs to induce translocations at model loci
- fusion genes created during translocation formation expressed from their endogenous promoters
- more accurate models than ectopic expression of fusion proteins
- see M. Piganeau et al. (2013) Genome Res. 23, 1182

Immuno-Oncology: An Emerging Therapeutic Strategy





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

Tumor-Stroma Interactions in Cancer Progression

- growing recognition as factor in tumor aggressiveness and Rx responsiveness
- genetic analysis of micro-dissected tumor-associated stroma
- poor prognosis associated with high expression of hypoxia and angiogenesis genes
- low expression of type 1 immune response genes
- release of paracrine survival (anti-apoptosis) factors by stromal cells
- elevated stromal ‘metagene’ expression profile correlates with poor response to anthracycline-based neoadjuvant therapy in human breast cancer
- role of tumor cell epithelial-to-mesenchymal transition (EMT) and exosomes in modulating stromal response?

Context

- down regulation of miR-200 family
  - associated with worse overall survival in ovarian, renal and lung cancers
  - improved clinical outcome in breast cancer except luminal subtypes in which low expression linked to worse survival
- IL-8 and CXCL-1 are targets for miR-200 family
  - elevated levels of IL-8 associated with poor survival in ovarian, renal and lung carcinomas
- inverse correlation of IL-8 expression and number of miR-200 family members

From: Sood et al. (2013) Nature Commun. 4, 2427
doi:10.1038/ncomms3427

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?

Redesigning Traditional Clinical Trial Paradigms in an Era of Molecular Profiling and Disease Subtyping

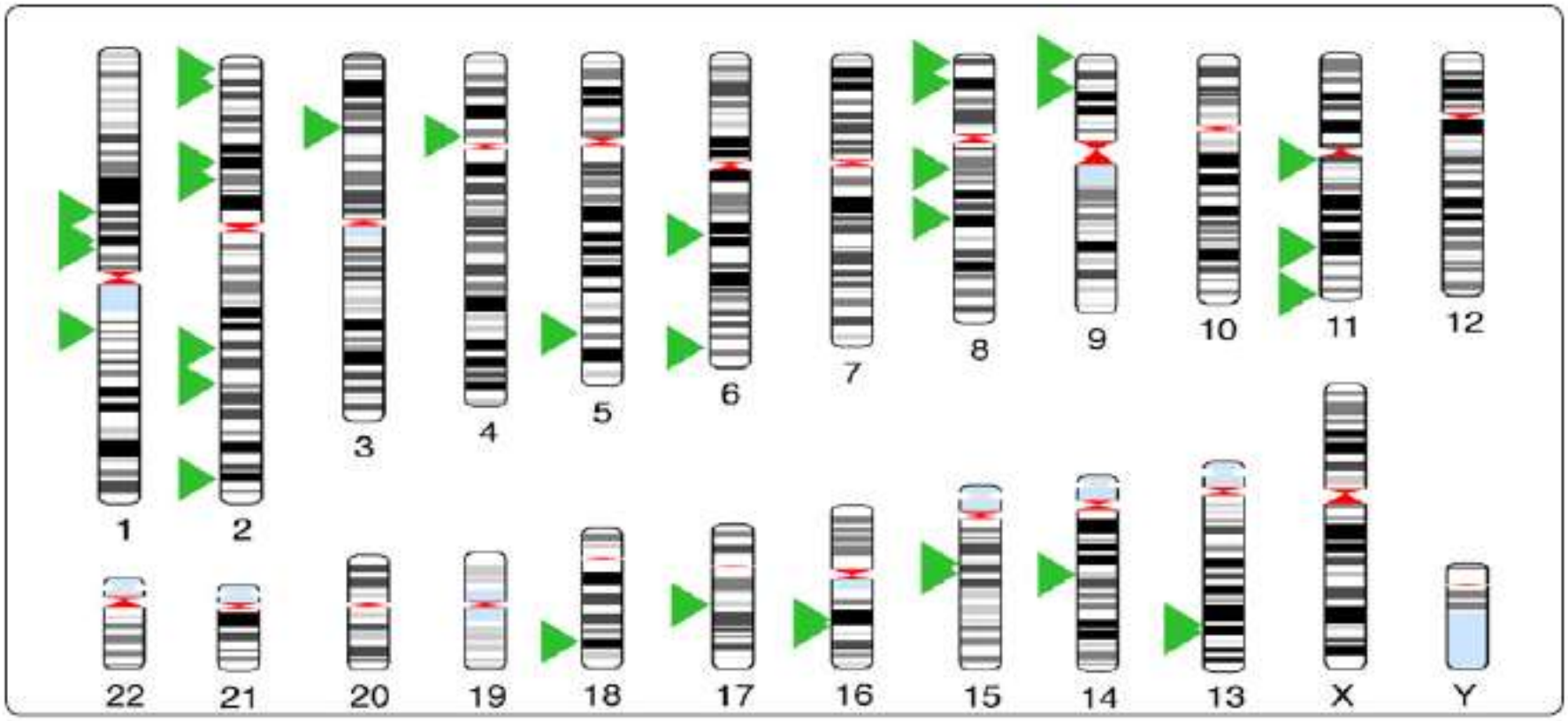
Imaging Informatics for Oncology

- RECIST (Response Evaluation Criteria in Solid Tumors) as sanctioned regulatory evaluation criteria for clinical trials
  - significant inter-reader variation in tumor lesion feature extraction
  - estimates of tumor burden and treatment response do not always correlate with time-to-progression and OS (particularly for non-cytotoxic Rx)
- methods of recording both qualitative and quantitative features in free text reports handicaps automated data analysis

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

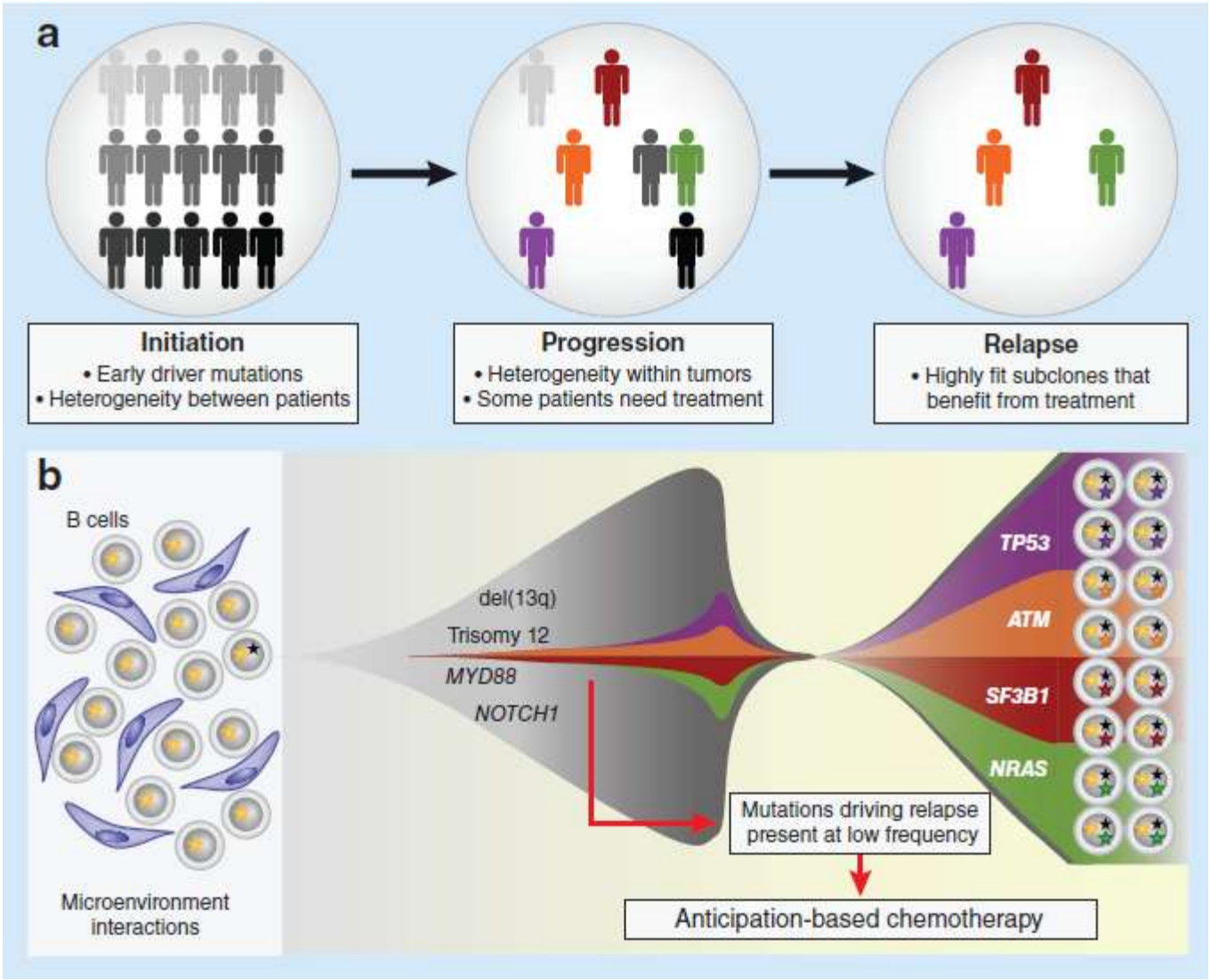
- faster detection of emergence of Rx-resistant/immune evasion clones
  - pre-exist prior to Rx
  - acquired resistance driven by Rx regimen(s)
  - minimal residual disease and relapse risk
- scientific foundation for more agile shifts in treatment regimens
  - clinical care
  - new clinical trial designs

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



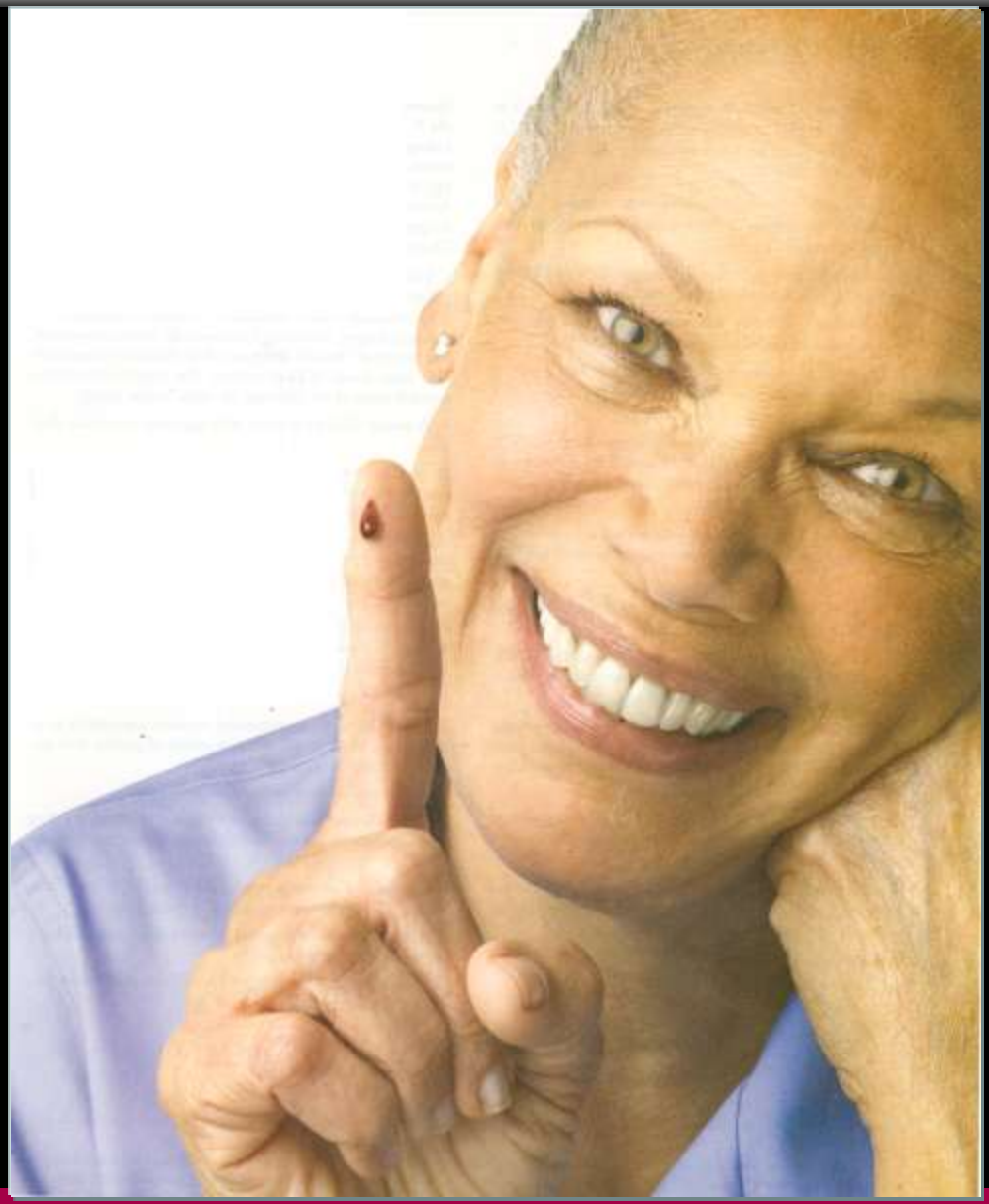
From: Zong et al. (2012) Science 338, 1622-26

Anticipation-Based Chemotherapy in CLL



From: X. S. Puente and C. López-Otín (2013) Nature Genetics 45, 230

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

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

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

The Case for Access to Expanded Treatment Options for Cancer Patients

- most SOC Rx still compromised by significant refractory disease
  - intrinsic and acquired resistance
- SOC as majority obstacle to evaluation of new investigational agents/novel combinations
- is evaluation of new agents/combinations on treatment failure populations conceptually flawed?
  - tumor cell phenotypes in refractory and ‘last resort’ patients may have little or no resemblance of tumor cell populations at initial detection

Neoadjuvant Therapy

- new opportunities for streamlined trials and accelerated approval
- Rx prior to surgery and assessment of pCR
- broader use in oncology trial based on pertuzumab (Perjeta) precedent in breast cancer
- validation of Rx action on claimed target
- earlier abandonment at lower cost for agents with limited efficacy and/or AE liabilities
- larger confirmatory trial(s) for PFS and/or OS for full approval

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

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

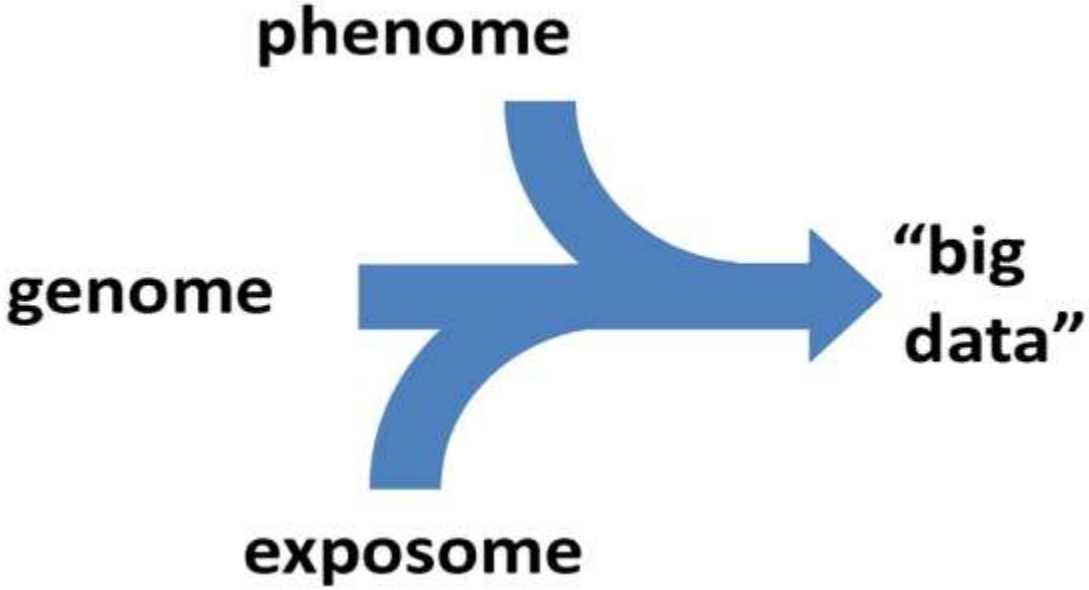
over-diagnosis/ over treatment of indolent lesions

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

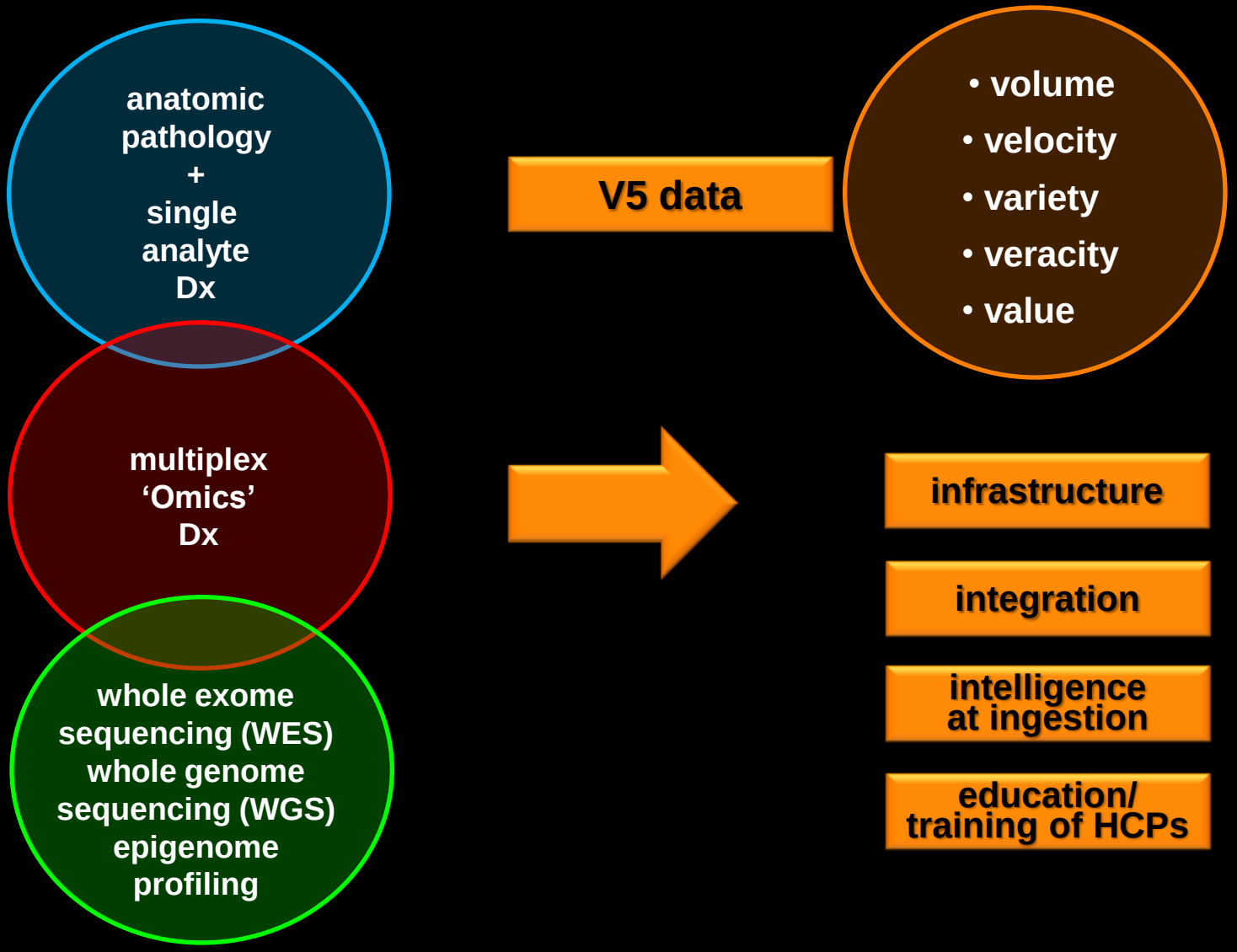
screening expands indolent incidence but limited impact on aggressive subset

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

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



Now Comes the Hard Part: The Evolution of Diagnostic Technologies for Precision (Personalized) Medicine



EECS ELECTRICAL ENGINEERING AND COMPUTER SCIENCES
COLLEGE OF ENGINEERING
UC Berkeley

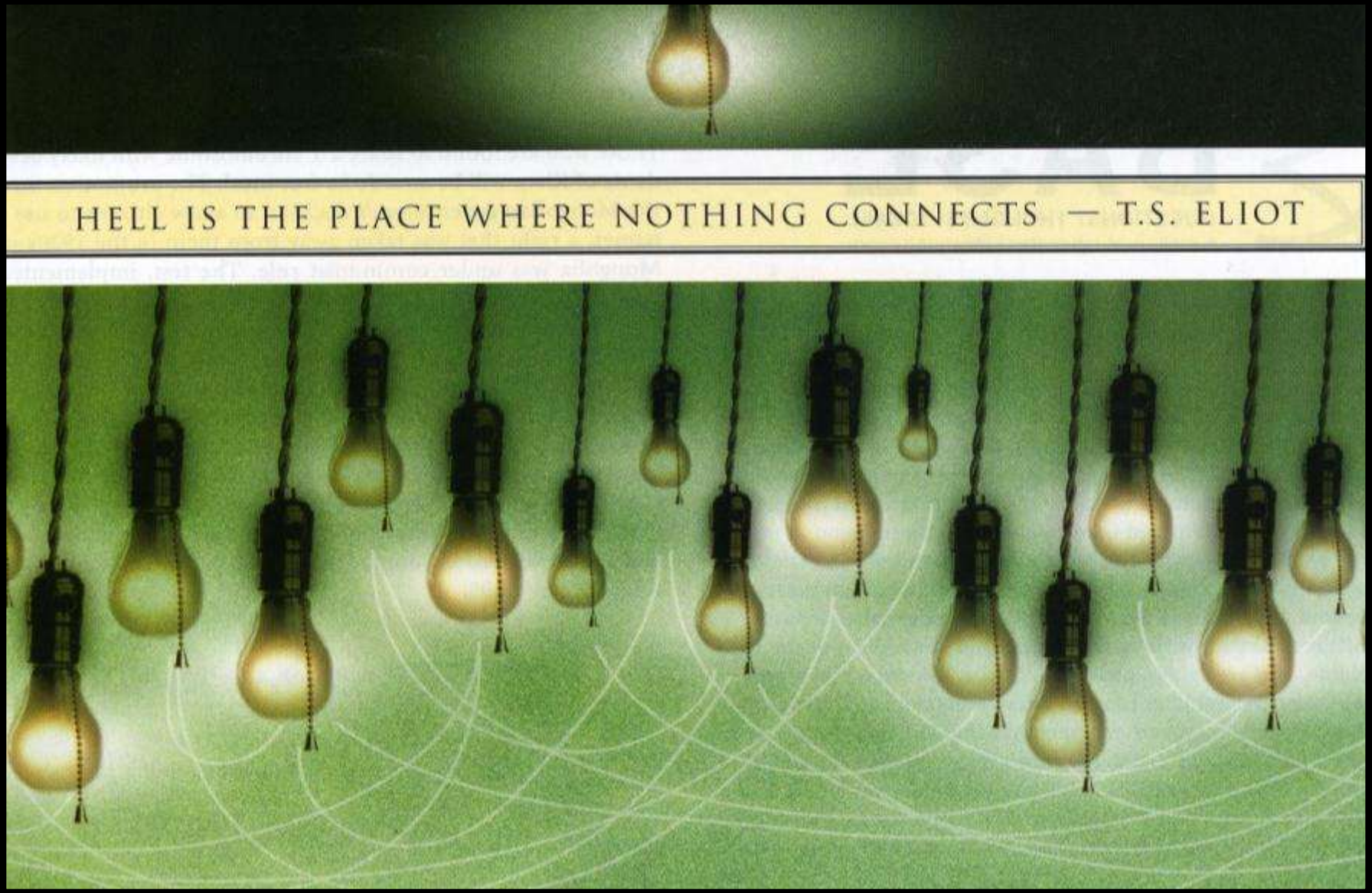
A Million Cancer Genome Warehouse

David Haussler, David A. Patterson, Mark Diekhans, Armando Fox, Michael Jordan, Anthony D. Joseph, Singer Ma, Benedict Paten, Scott Shenker, Taylor Sittler and Ion Stoica

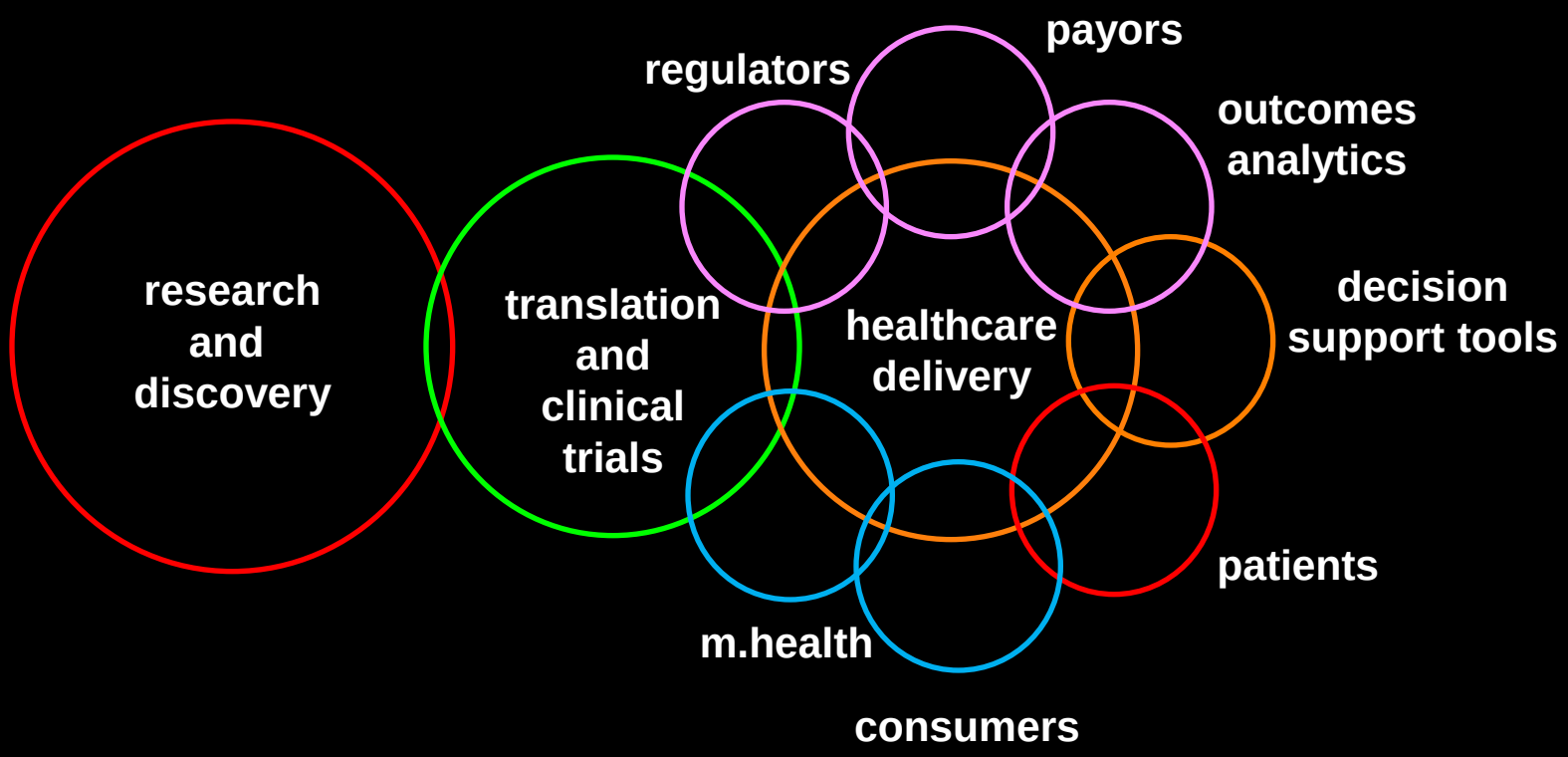
EECS Department
University of California, Berkeley
Technical Report No. UCB/EECS-2012-211
November 20, 2012

http://www.eecs.berkeley.edu/Pubs/TechRpts/2012/EECS-2012-211.pdf

Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo



The Need for Facile, Seamless Data Exchange Formats for Large Scale Biomedical Data Systems



HER/EMR Formats Must Accommodate Comprehensive Data Feeds and Promote Continuity of Care

- HITECH funding for health IT does not promote innovation
- e.replication of paper records
- limited ability to assimilate new data categories
  - "omics", social media
- the interoperability 'iceberg'
- privacy and security protections as barriers to data sharing and large scale analytics
  - observational data
  - patient reported data

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

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

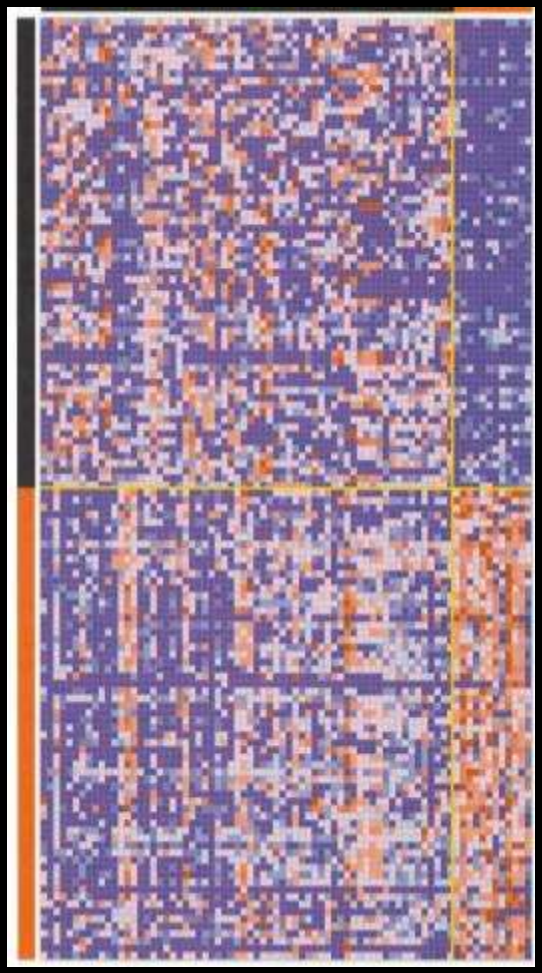
Challenging Questions Regarding Future Directions in Cancer Research and Clinical Oncology

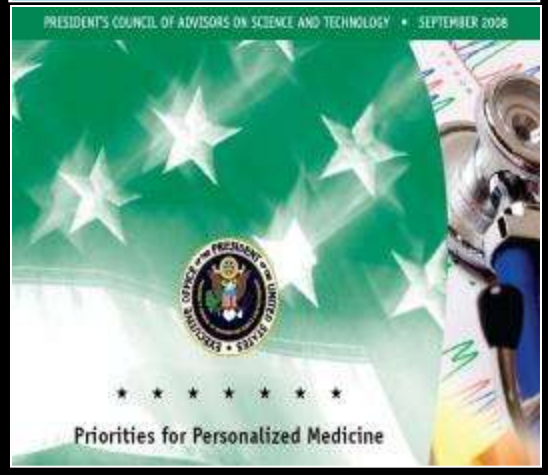
The Difficult but Largely Ignored Central Questions in Oncology and Cancer Care Delivery

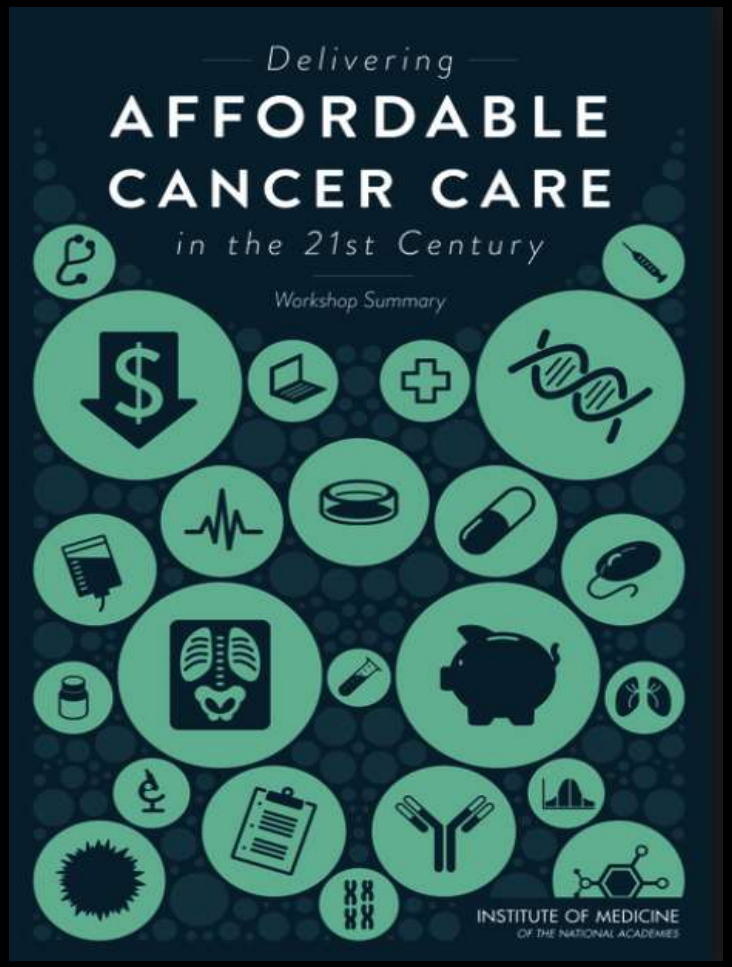
What is a meaningful advance in Rx effectiveness?

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

Precision Medicine: Key Drivers







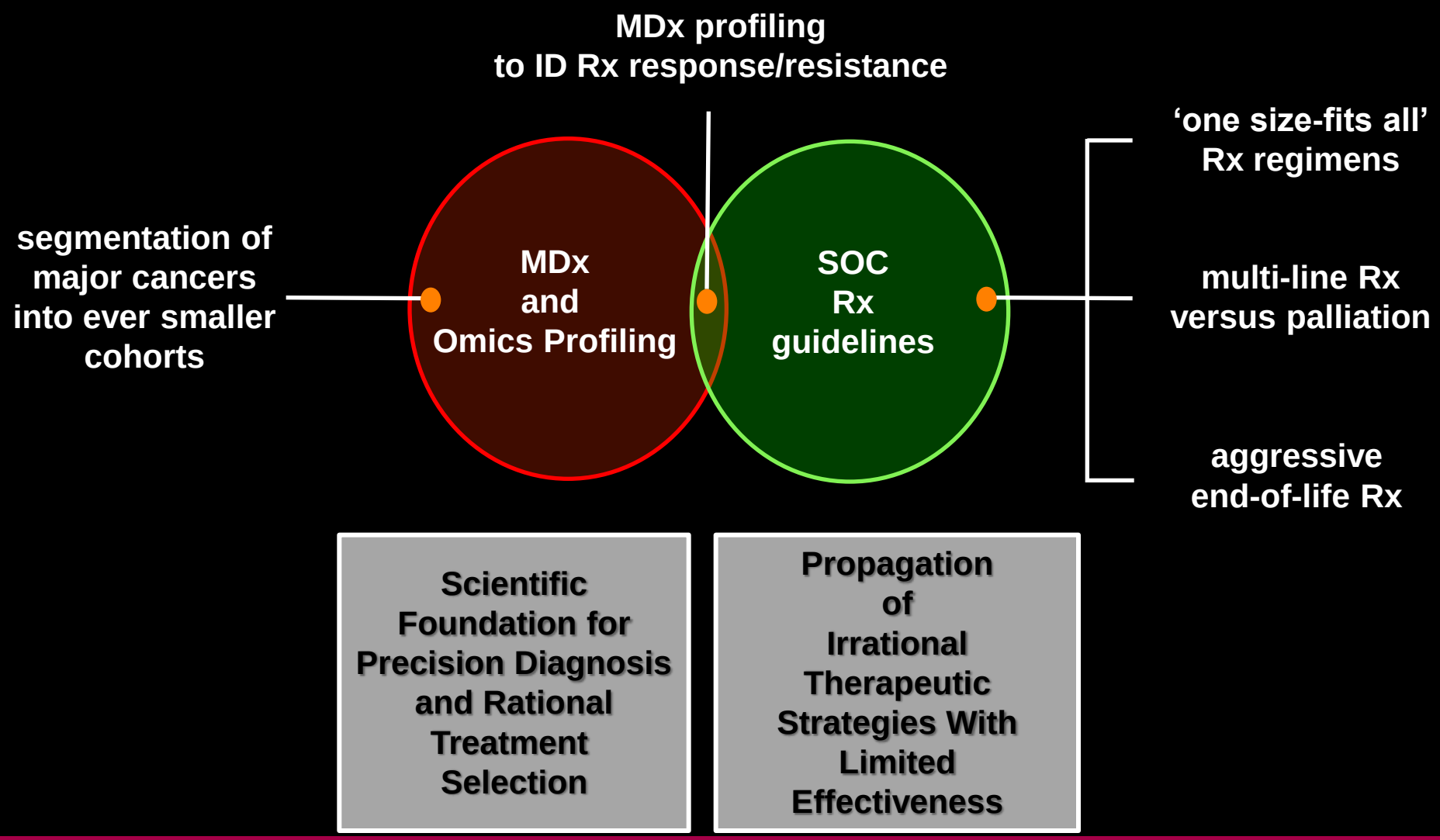
Science | **Policy** | **Cost and Outcomes**

The Unacceptable Status of Cancer Care Delivery

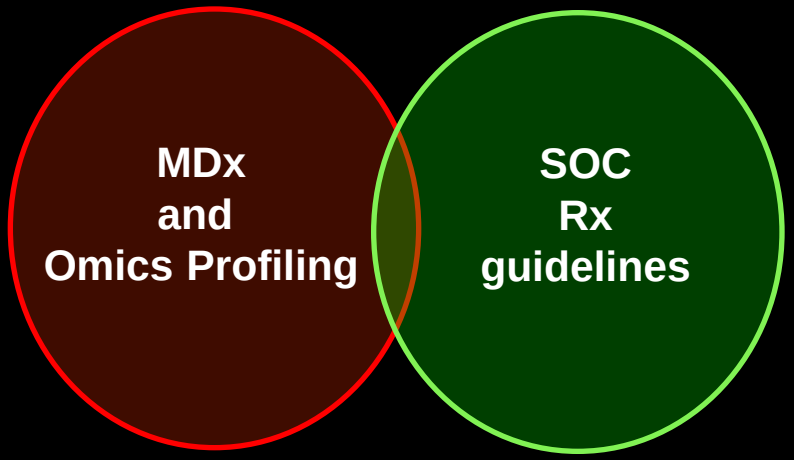
Doing More, But Not Necessarily Doing Better

Buy and Bill: Oncologists' Financial Incentives Are Not Aligned With 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

Molecular Diagnostics and Targeted Therapeutics in Oncology: Policy Contrasts in Pricing and Evaluation of Effectiveness

- uncritical acceptance of very high price of new therapeutics with marginal gains in PFS/OS
- slow adoption of molecular diagnostics to identify Rx responder/resistant patients
- economic disincentives for oncologists to profile patients due to perverse coupling of income to use of high drug costs
- current regulatory and reimbursement policies do not address the increased technical complexity, risk, time and cost to develop next-generation molecular ("omics") tests (MDx) versus traditional laboratory-developed tests (LDTs)

The Unacceptable Status of Current Cancer Care Delivery

- 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

“Integrate to Innovate”

Innovation Demands Boldness!

Standards: Relevance of Models

- discarding biologically and/or clinically irrelevant research methods/strategies
- insidious cultural and organizational barriers to change
  - propagation of funding for historical conceptual paradigms and experimental models despite evidence of low productivity
  - inadequate mechanisms for review/funding of ambitious cross-disciplinary programs
  - abundant evidence of shortcomings in many cell/animal systems as predictive models for human cancer
  - pressure for continued publication/funding sustains irrelevant models

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?

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 is not attainable?

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

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

Cancer as a Complex Adaptive System

Deconvoluting the Complexity of Cancer

Multi-dimensional Problems Will Not Be Solved by Uni-dimensional Concepts or Technologies

Engaging Complexity:

“The cancer biology community by itself is unprepared to solve the difficult transdisciplinary problems such as biological complexity, information transfer and tumor cell evolution.”

Summary Remarks Meeting Report
National Cancer Institute Meeting:
Integrating and Leveraging the Physical Sciences to Open a New frontier in Oncology
February, 2008, p. 34

Are We Yet Sufficiently Engaged?

Silos: 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
  - new paradigms for clinical trials and regulatory review
  - team-discovery vs. individual investigators
  - clinical education

Technology Acceleration and Convergence

- new organizational structures and infrastructure to support large scale end-to-end approaches
- new patterns of disruptive collaboration and intellectual fusion
- profound implications for education, research, business models, national security and public policy
- the siloed structure of current academic, industrial and governmental institutions is a major obstacle to assessment of the implications of the increased importance of new trans-disciplinary, cross-sector networks and their accompanying complexity

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

The Resistance to Change

“Even the Gods cannot strive against necessity.”

Ancient Greek Proverb

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