Challenges and Opportunities in Precision (Personalized) Medicine

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April 12, 2014



FULFILLING THE PROMISE OF PERSONALIZED MEDICINE

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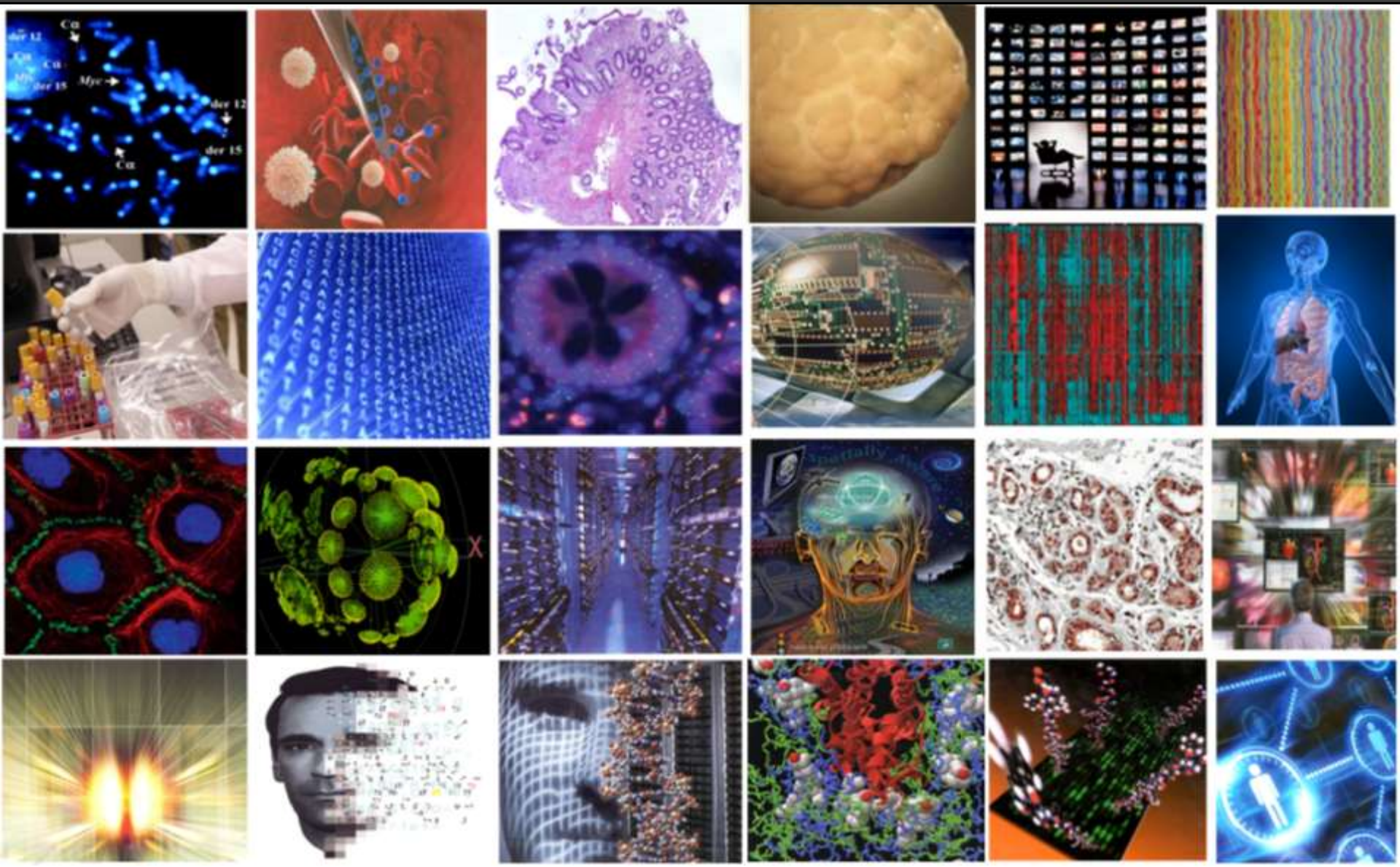
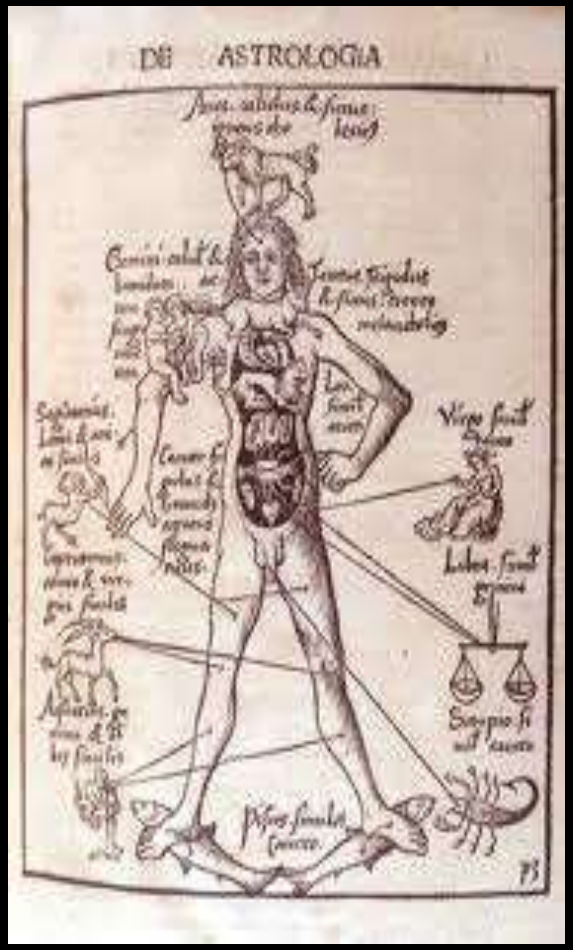
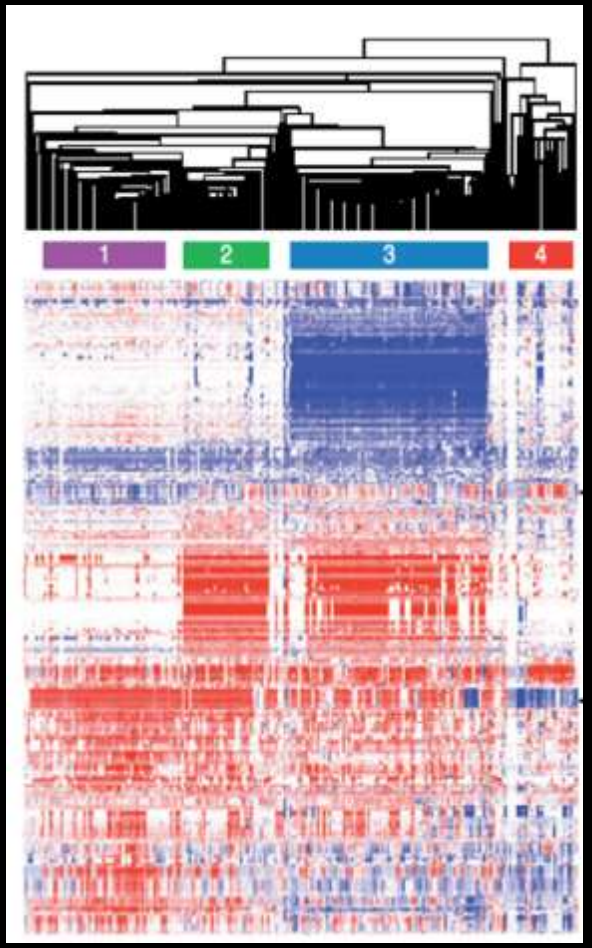


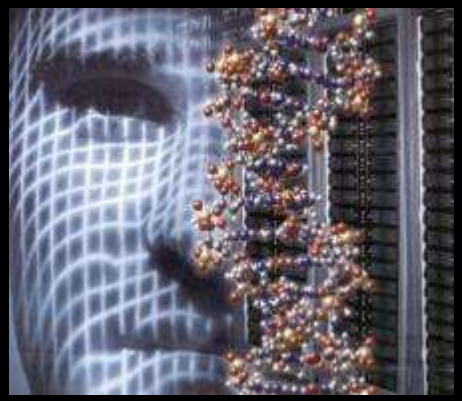
Medical Progress:
From Superstitions to Symptoms to Signatures



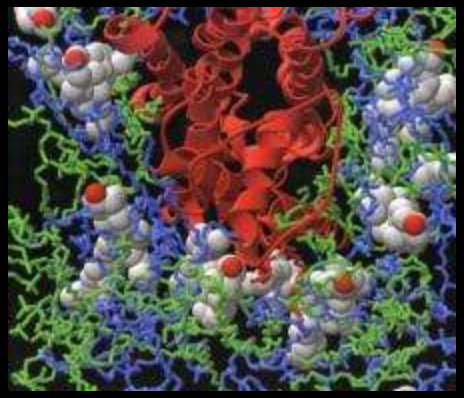


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

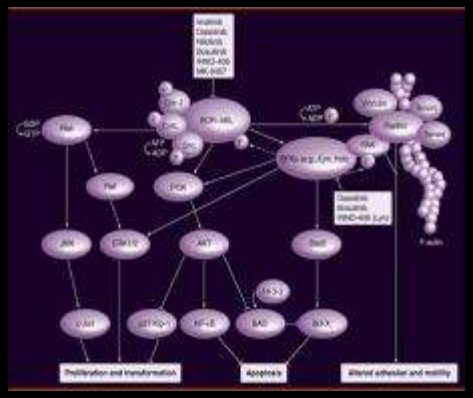
Genomics



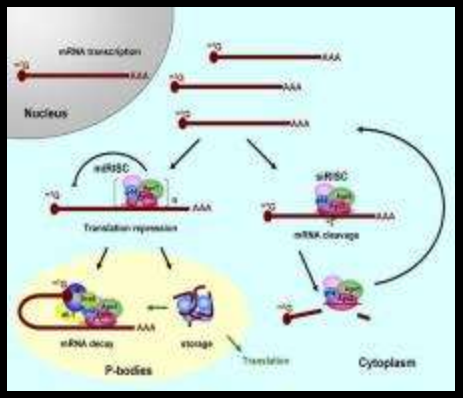
Proteomics

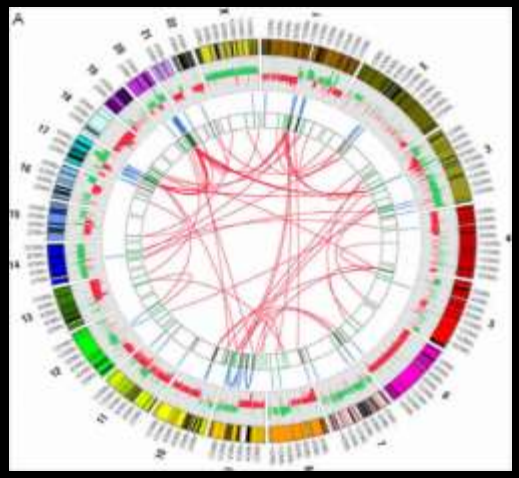


Molecular Pathways and Networks



Network Regulatory Mechanisms

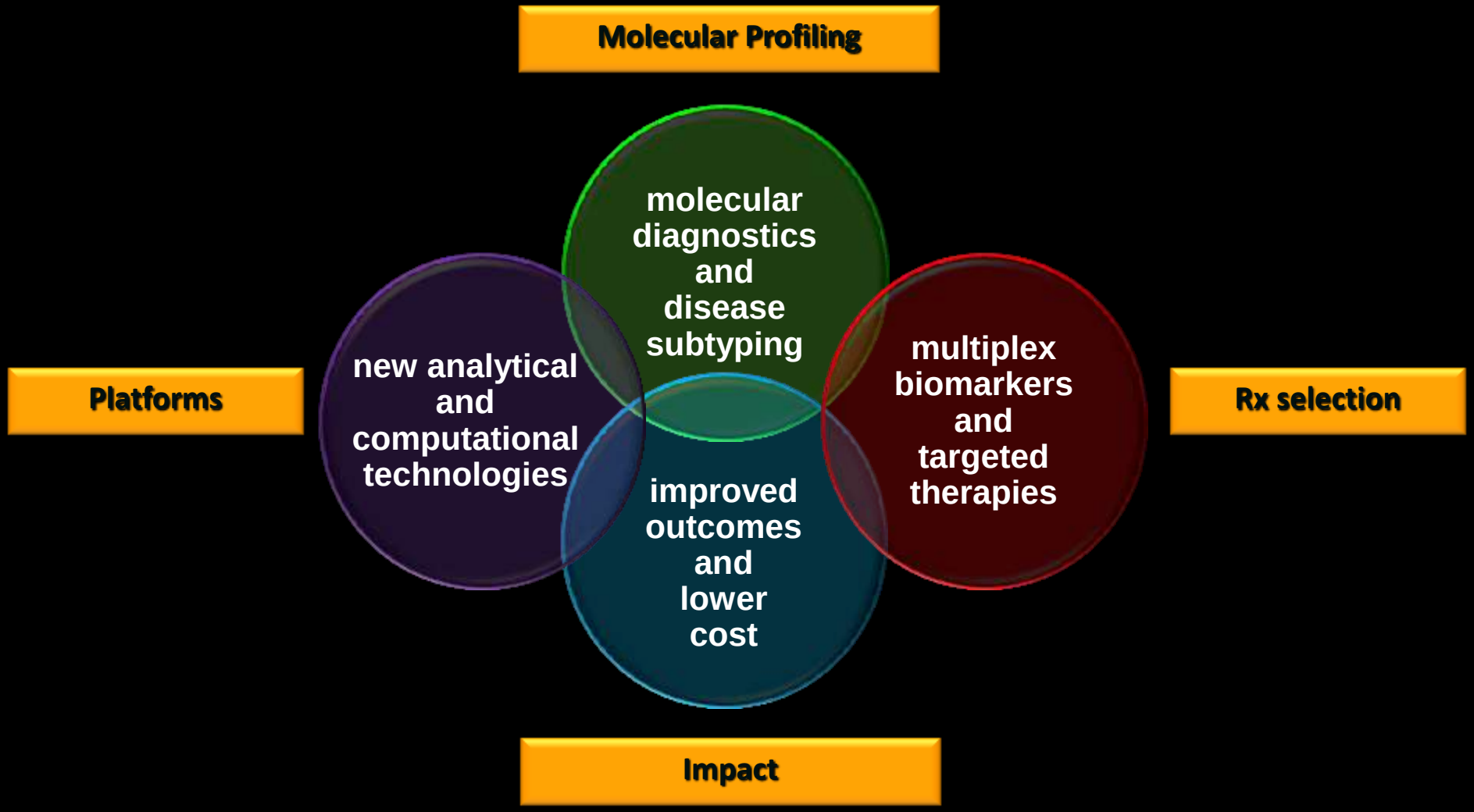




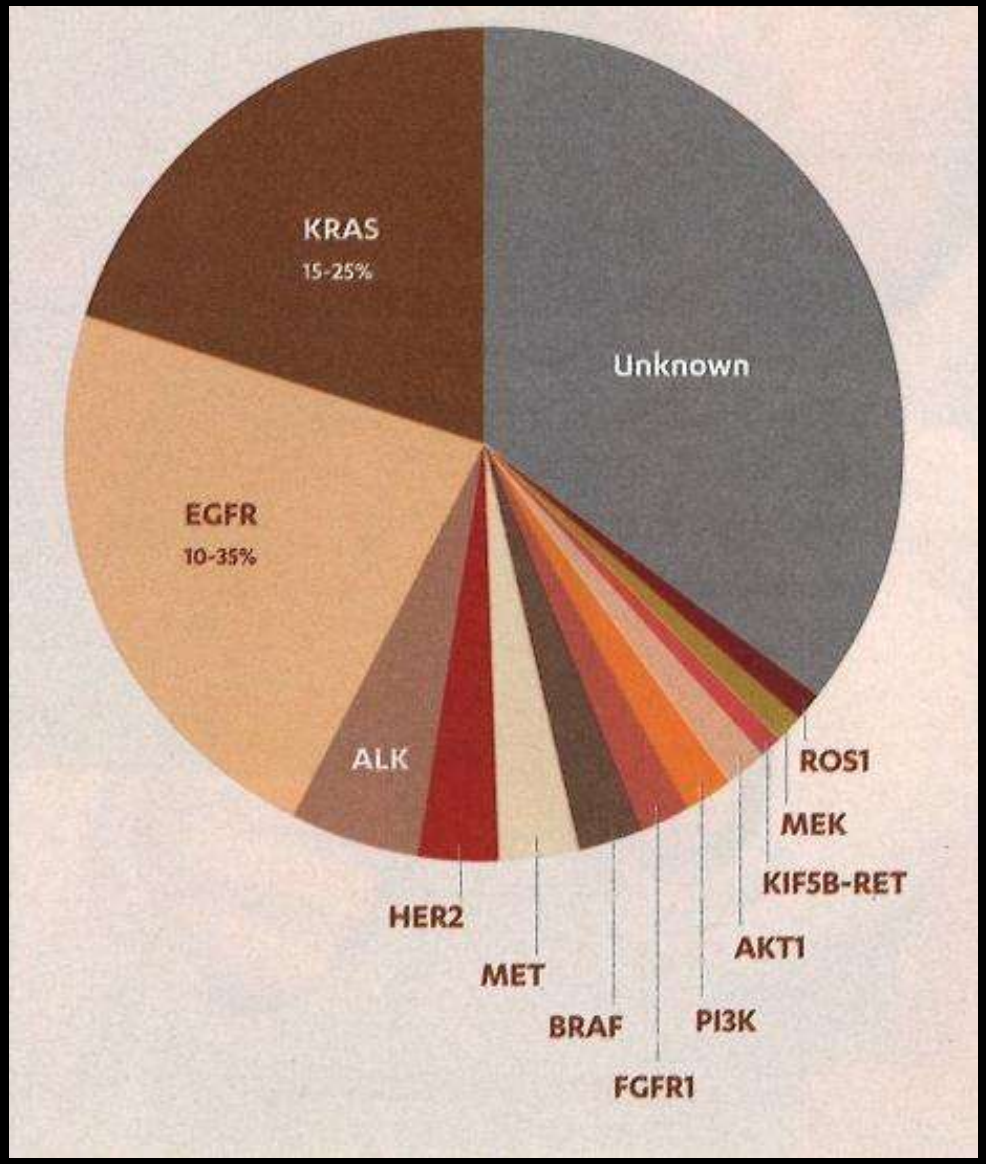
ID of Causal Relationships Between Network Perturbations and Disease

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

Precision (Personalized) Medicine

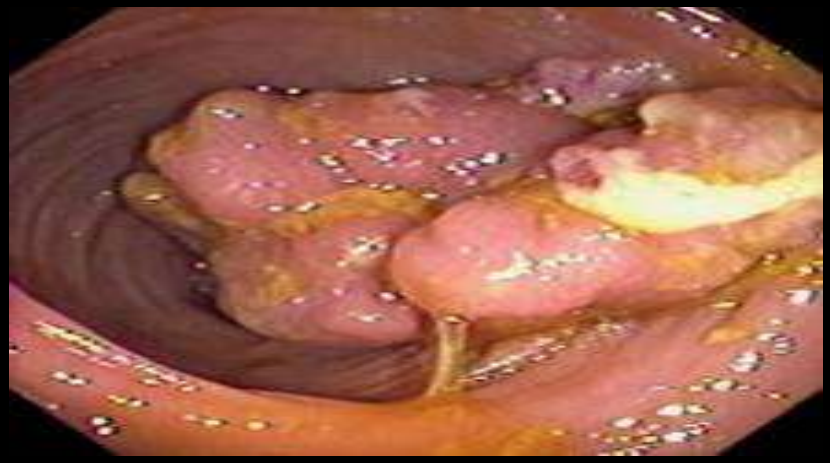


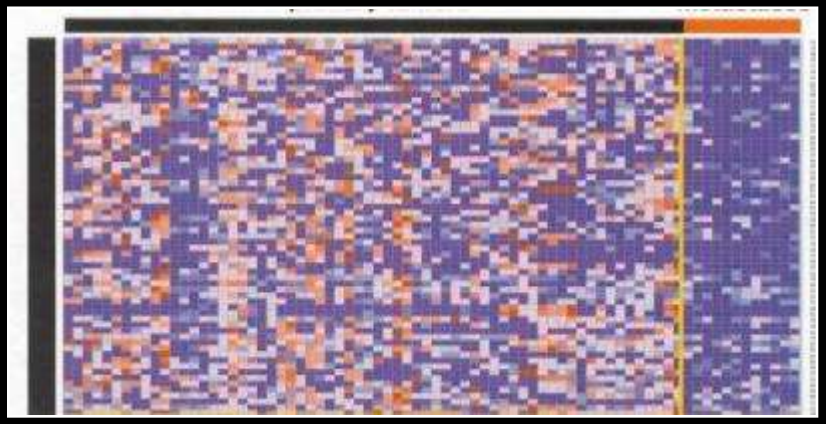
Molecular Biomarkers in NSCLC (2013)



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

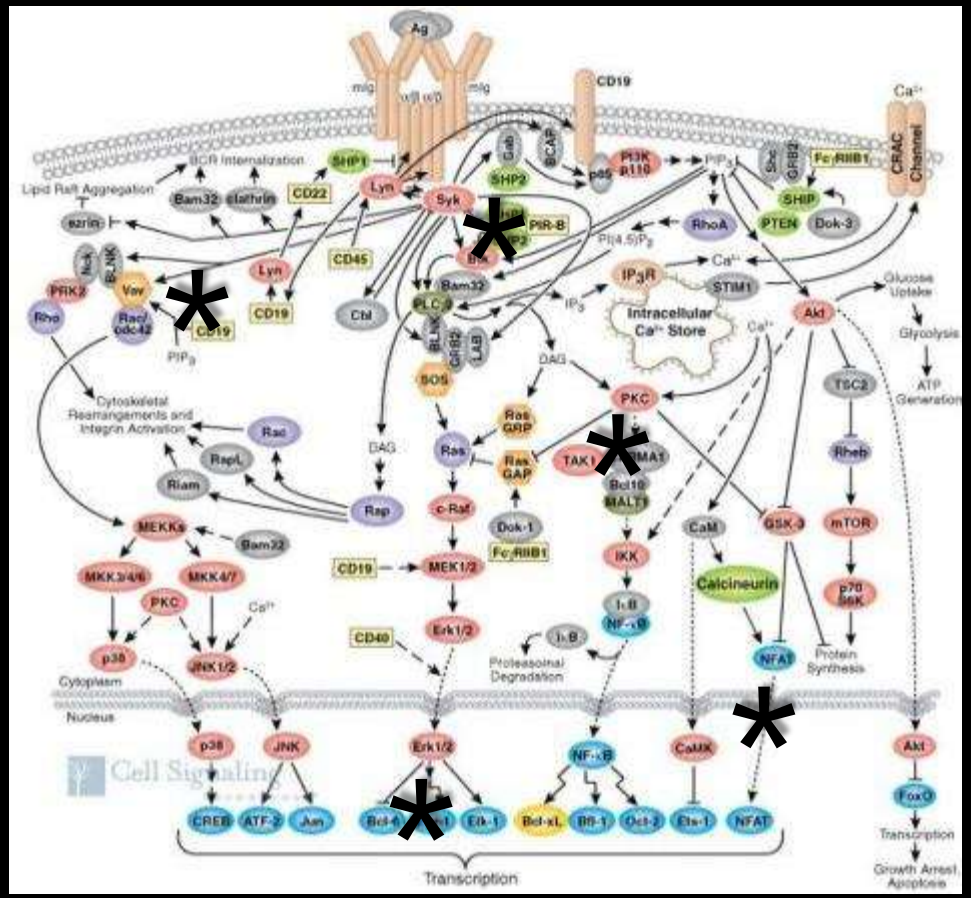
"Omics" Profiling to Identify Disease Subtypes (+ or - Rx Target)





Multiplex Profiling

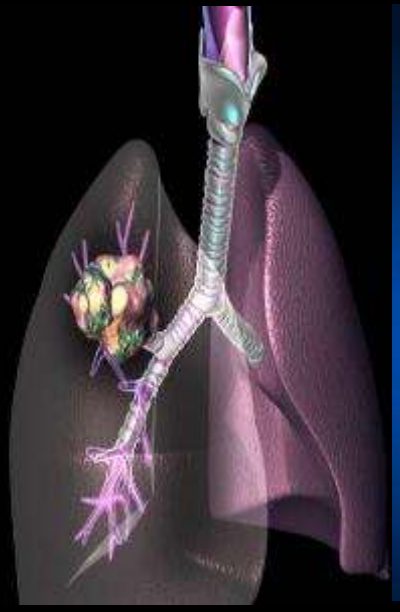
Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action



Right Rx for Right Disease Subtype

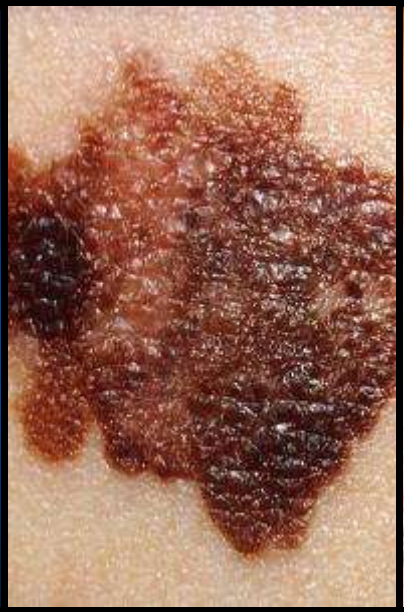
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics - the Right Rx for the Right Disease (Subtype)

Her-2+
(Herceptin)
(Perjeta)



EML4-ALK
(Xalkori)

K-ras
(Erbitux)
(Vectibix)



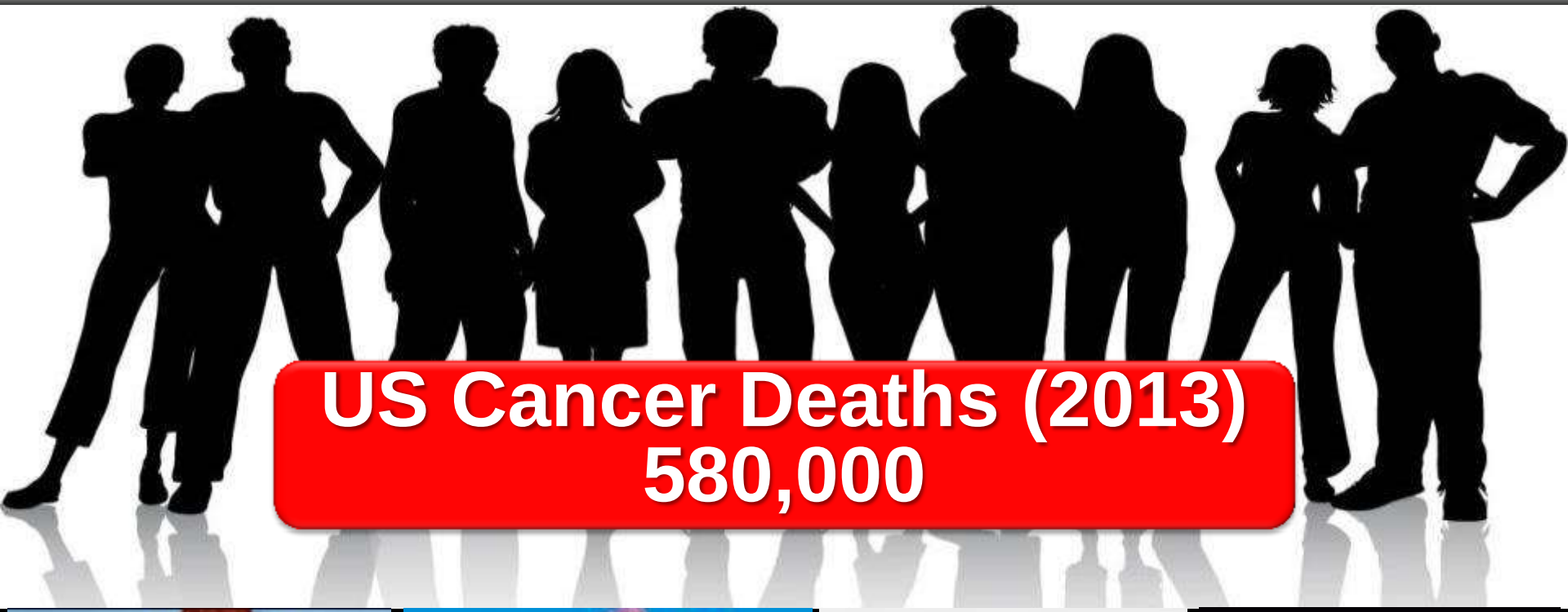
BRAF-V600
(Zelboraf)

CFTR-G551
(Kalydeco)

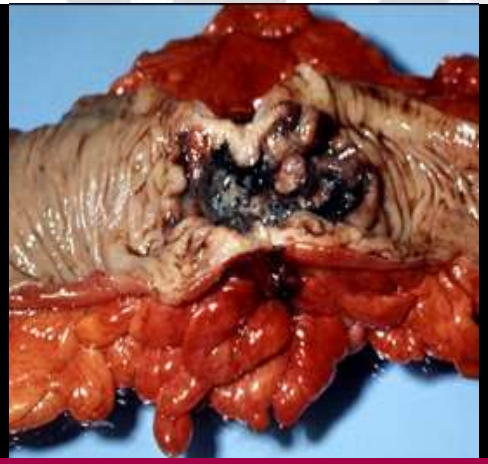
Targeted Oncology Therapies in Molecularly Stratified Populations

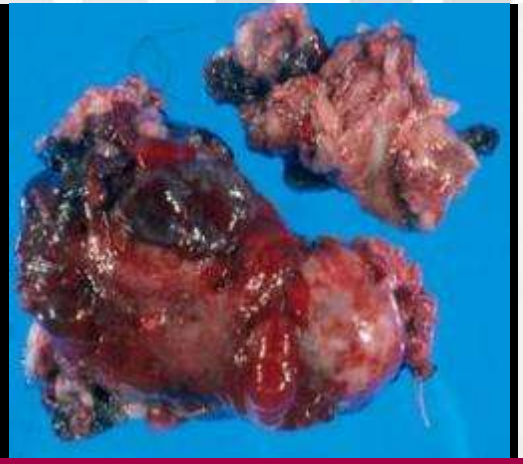
Cancer	Target	Agent
Breast carcinoma	HER2 amplification	Trastuzumab, Lapatinib
NSCLC	EGFR mutations	EGFR TKIs (erlotinib, gefitinib)
NSCLC	EML-ALK	ALK inhibitors (crizotinib)
GIST	KIT and PDGFRA mutations	Imatinib
Melanoma	BRAF-V600 mutation	BRAF inhibitor (vemurafenib)
Ewing's sarcoma	EWS-FLI translocation	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)

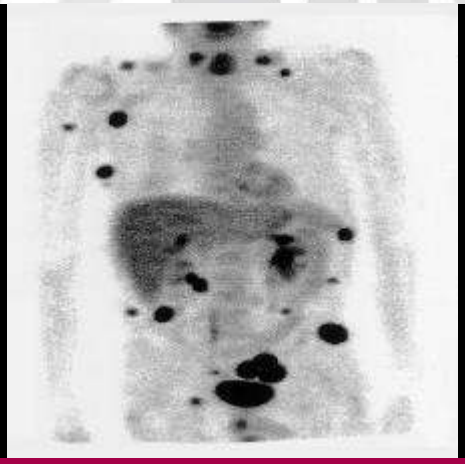
Confronting the Clinical, Economic and Human Toll of Cancer

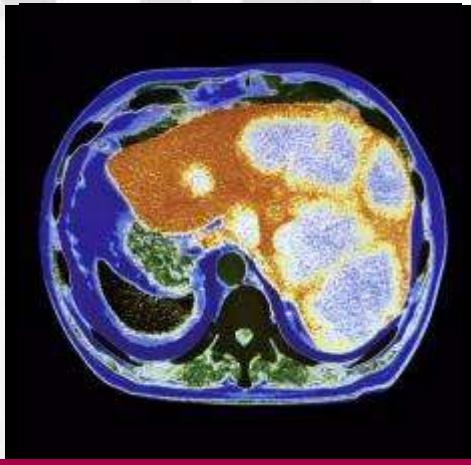


US Cancer Deaths (2013)
580,000







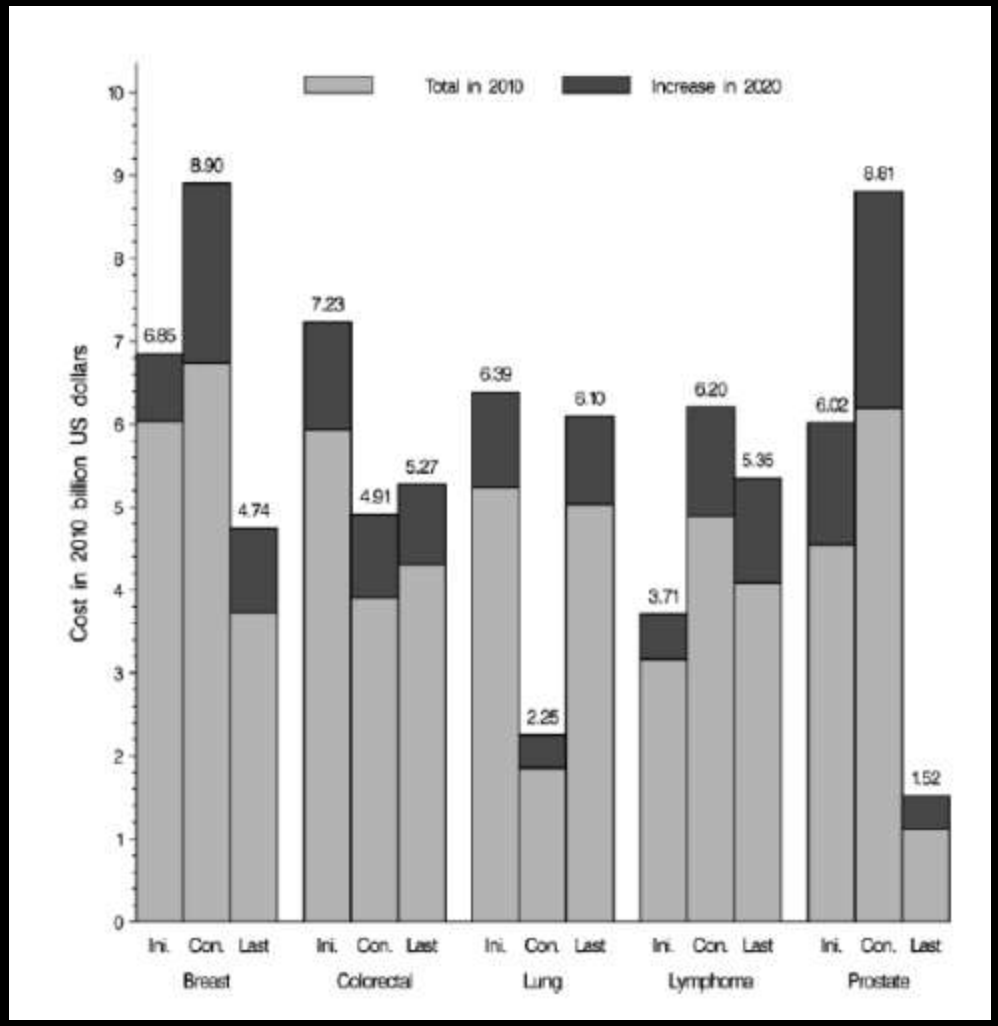


US Cancer Prevalence Estimates 2010 and 2020

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

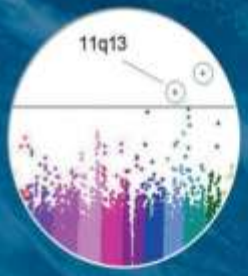
Estimates of U.S. National Expenditures for Cancer Care 2010-2020

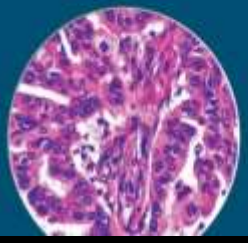


$124 billion and projected to rise to $207 billion (66% increase) by 2020

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

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





World Cancer Report 2014

Edited by BERNARD W. STEWART and CHRISTOPHER P. WILD

International Agency for Research on Cancer

World Health Organization

The State of

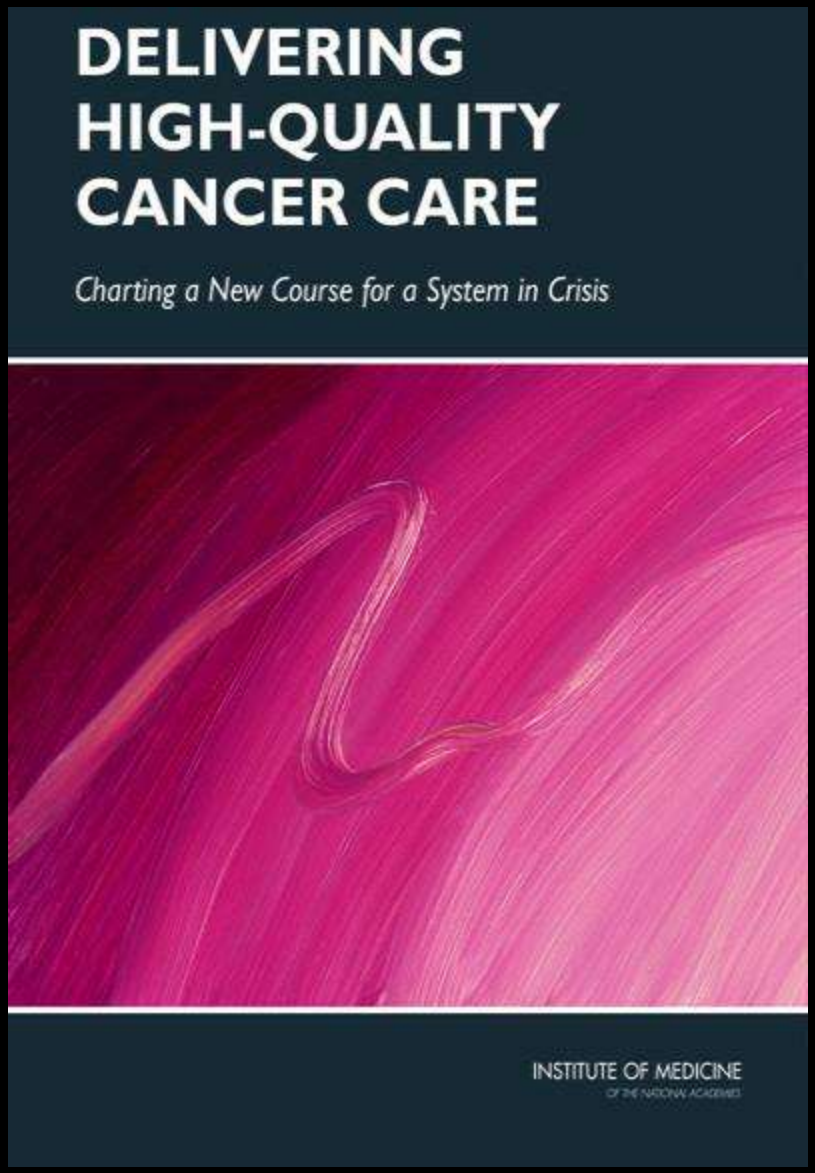
Cancer Care in America™: 2014

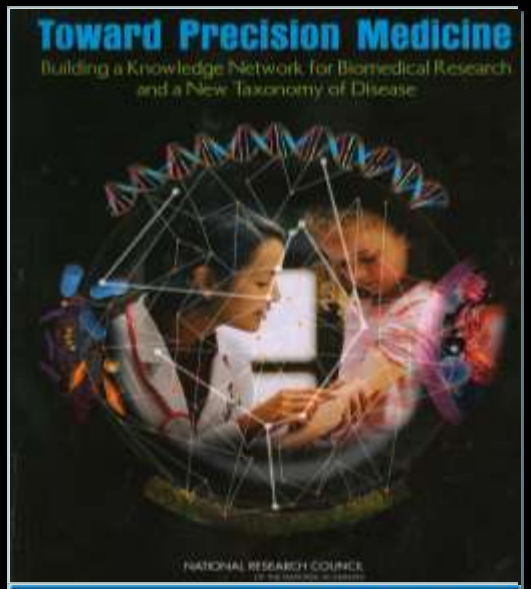
ASCO

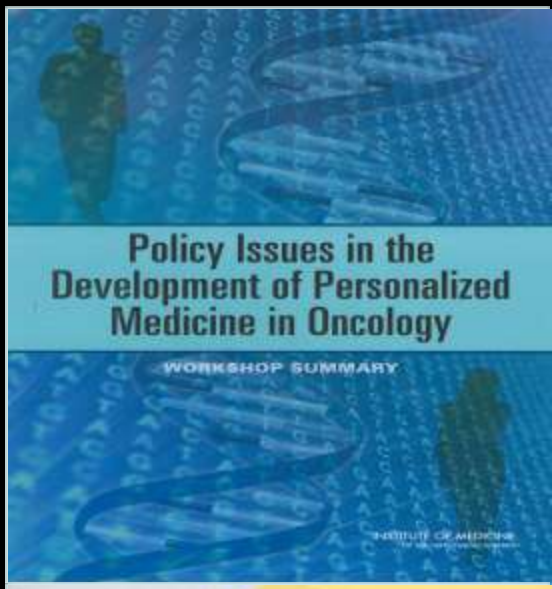
American Society of Clinical Oncology

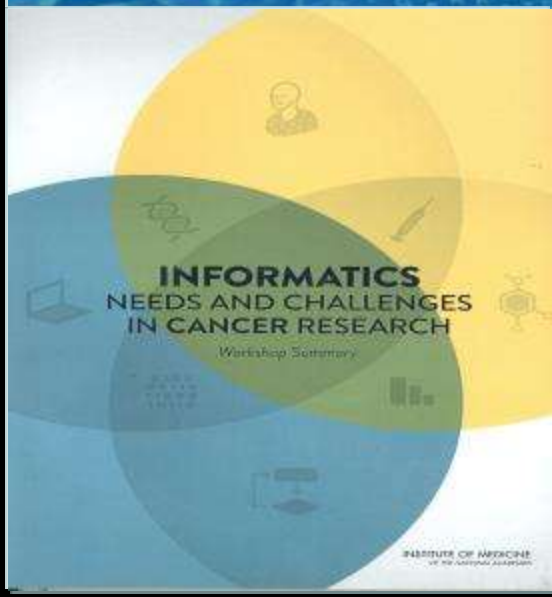
Making a world of difference in cancer care

The Current Status of Cancer Care

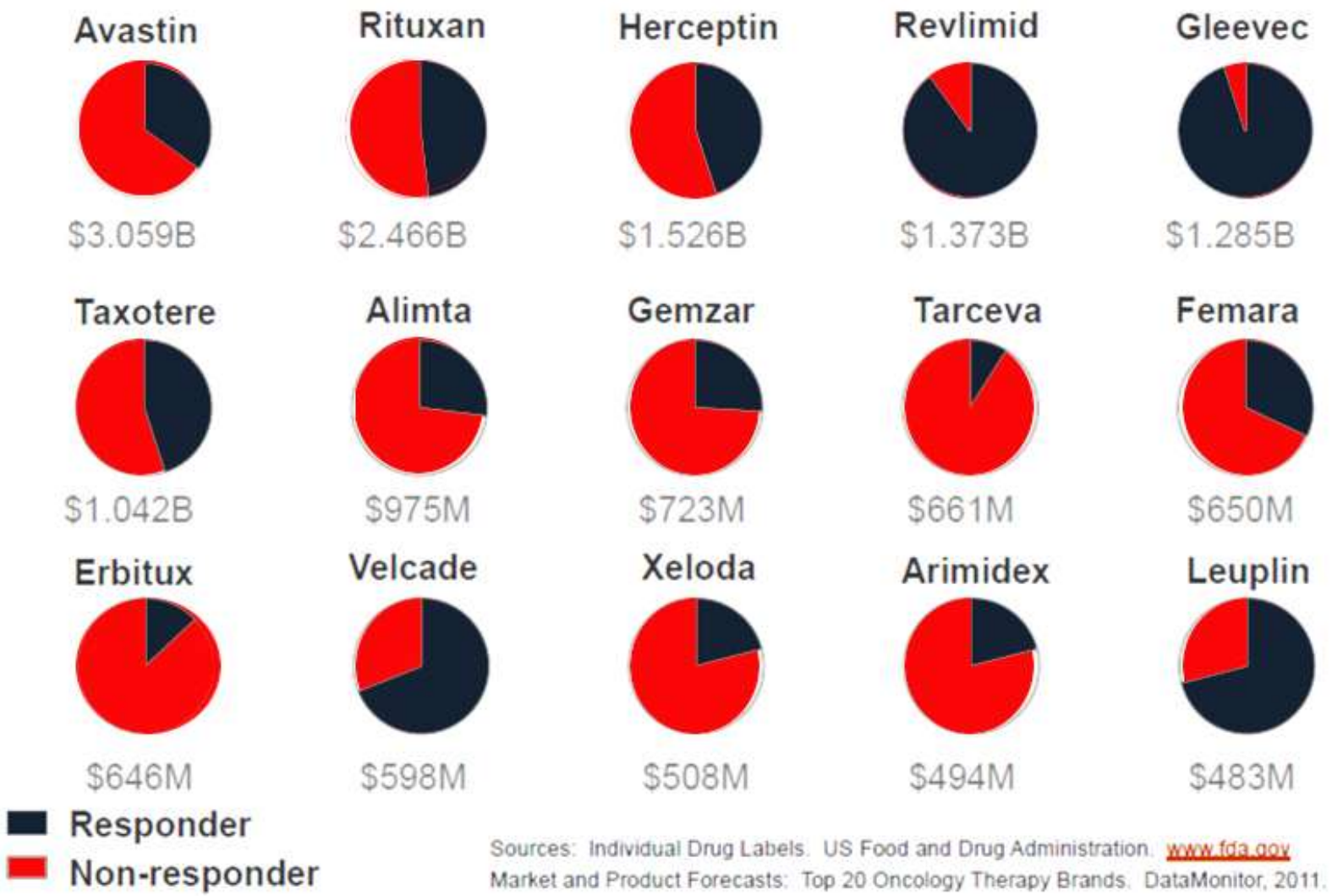








Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly



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

Beyond SOC Guidelines: Patient Care Challenges in Oncology

Clinical Scenario	Clinical Challenge	Selection of Treatment Option
Rare	Undefined standard of care ***(How do I treat?)***	Limited published evidence to guide treatment decisions
Aggressive	Limited standard treatment options ***(How do I optimize any future treatment strategy?)***	Limited time in face of poor prognosis
Metastatic and refractory diseases	Difficult to treat cancers ***(What's next; Am I beyond standard of care?)***	Emerging data on novel drug: target associations revealed by molecular profiling

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Molecular profiling identifies potential therapies not otherwise considered

Drug	Associated Biomarker	On Compendium Tumor Types	Off Compendium Tumor Types	% Positive
trastuzumab (Herceptin)	HER2	Breast Gastric	Ovarian Gastroesophageal Colorectal	30% 14% 30%
nab-paclitaxel (Abraxane)	SPARC	Breast NSCHC	Gastroesophageal Pancreatic Melanoma	37% 36% 41%

Caris Life Sciences data. 60,000+ tumors profiled data set. Information on file.

Evidence

“There is a lack of evidence showing the impact of guidelines on clinical practice and patient outcomes.”

Dr. G. H. Lyman
University of Washington School of Medicine
Medscape 11 April 2014

- **response to McKesson Speciality Health press release that CMS is considering proposal from NCCN, US Oncology and McKesson to use NCCN guidelines to control cost and promote more uniform medical practice**

Evidence

"Even within NCCN,
certainly the majority of decision nodes
that are enshrined in NCCN
are not supported by high level evidence."

Dr. Clifford Hudis
President, ASCO
Interview in Cancer Letter 22 Nov. 2013, 39

Molecular Profiling and Rx Selection in Cancer Treatment

- should molecular profiling be conducted on all patients as SOC?
- should patients receive SOC if profiling indicates absence of molecular targets for the SOC regimen?

WILL

- **Whole Genome Sequencing (WGS) Change Everything?**

WHEN

- **Will WGS Become Just Another Laboratory Test Value?**

HOW

- **Will WGS Affect Patient Care?**


Radical Reinvention
Introducing NextSeq™
A Whole Human Genome on Your Desktop
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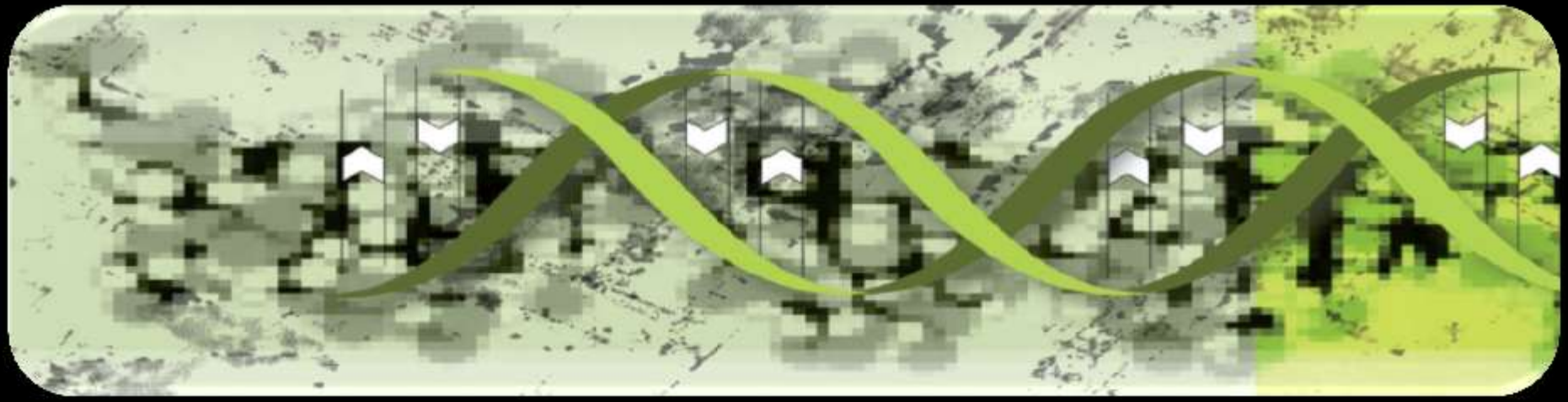
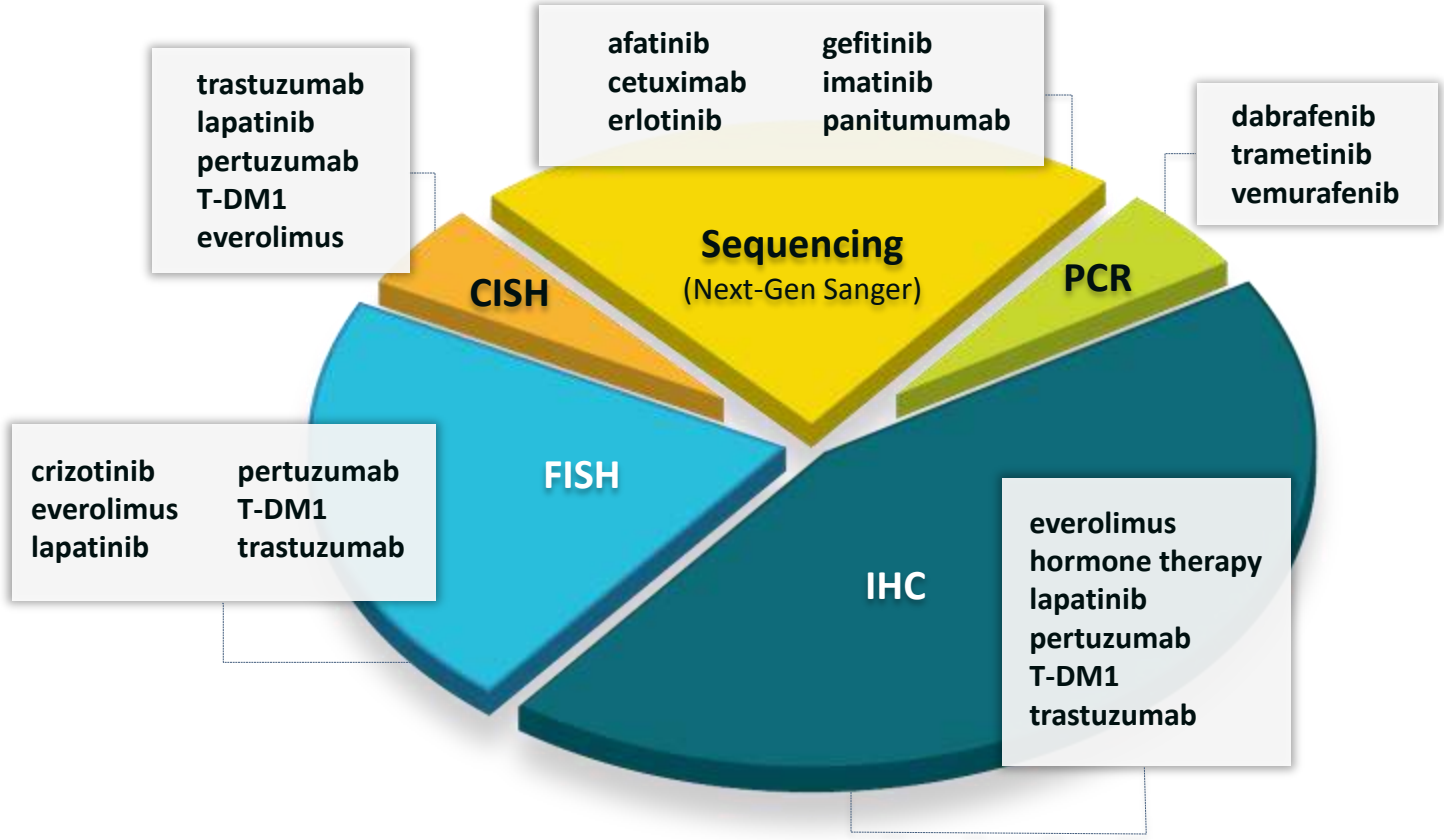
- The $1000 (or less) Whole Genome Sequence (WGS)
- The $? Interpreted WGS
- The $? Reimbursed WGS for Clinical Use

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 and Transform Treatment Options

The Need for Multiple Molecular Diagnostic Platforms to Maximize the Number of Actionable Drug: Target Associations to Guide Therapeutic Decisions



FISH = fluorescent in situ hybridizaiton

CISH = chronogenic in situ hybrization

IHC = immunohistochemistry

The Anticipated Need to Expand the 'panOmics' Analyte Repertoire for Comprehensive Diagnostic Profiling

Mapping Non-coding Regulatory Systems for Genes and Coupled Gene Networks

The Increasing Complexity of the RNA Universe

- m(messenger)RNA
- t(transfer)RNA
- r(ribosomal)RNA

- microRNAs (miRs,miRNAs)
- long non-coding RNAs (lncRNAs)
- competing endogenous RNAs (ceRNAs)
- circular RNAs (circRNAs)
- small nucleolar RNAs (snoRNAs)
- PIWI-interacting RNAs

- 3'-UTR RNA-binding proteins and mRNA stability

miRNA Network Dynamics in Cancer

- 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 CXC L-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
- see Snood et al. (2013) Nat. Commun.

The Complex Regulation of the PTEN Tumor Suppressor Gene by Modulation of MicroRNAs (miRs) and Competing Endogenous RNAs (ceRNAs)

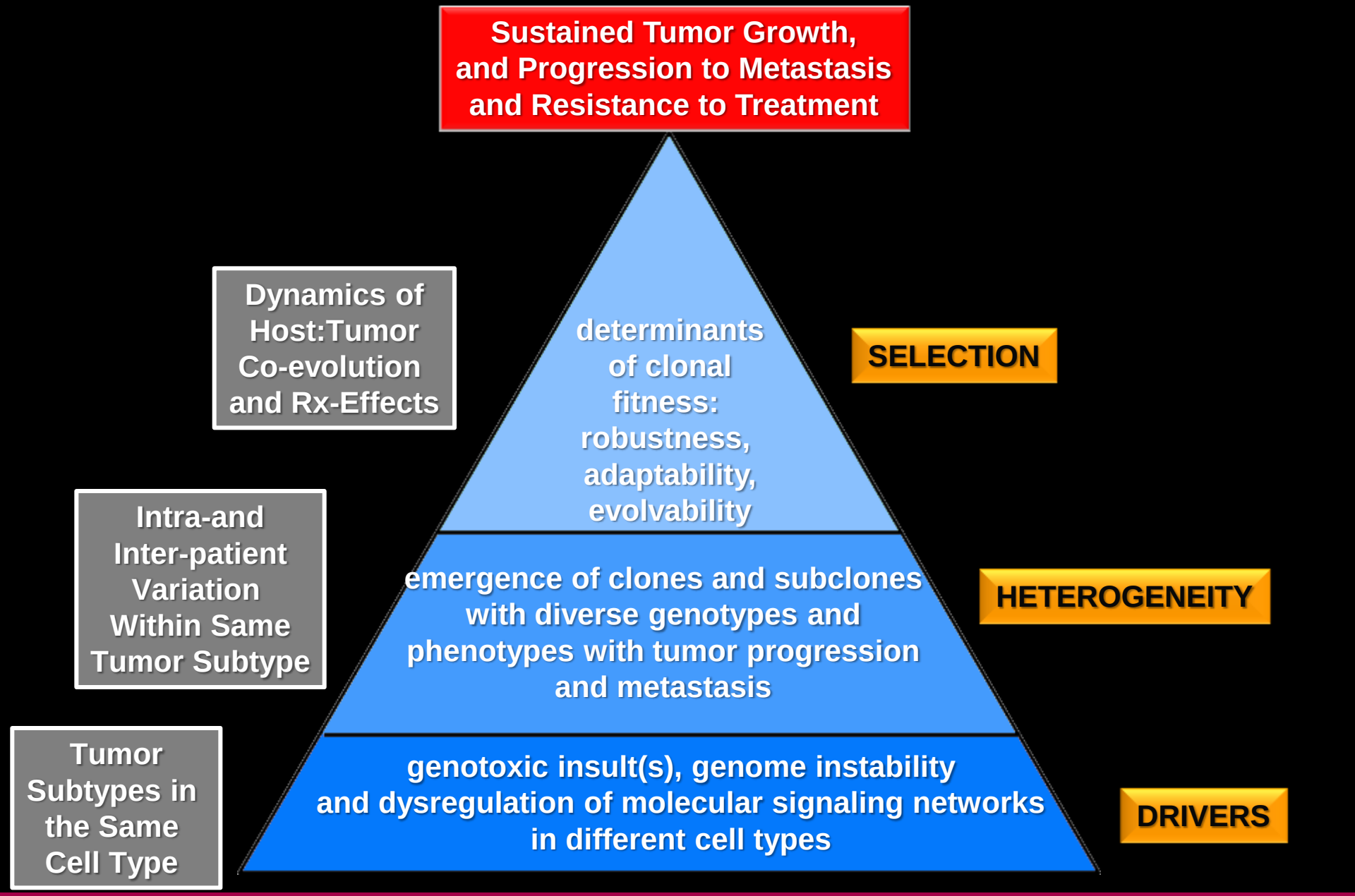
- CNOT6L
- VAPA
- ZeB2
- VCAN

- miR17 and 19 families
- miR17, 19, 26 families
- miR25, 92a, 181 and 200
- miR 136 and 144

- pseudogene PTENP1 miR 17, 19, 21, 26 and 214 families

Challenging Questions Regarding Future Directions in Cancer Research and Clinical Oncology

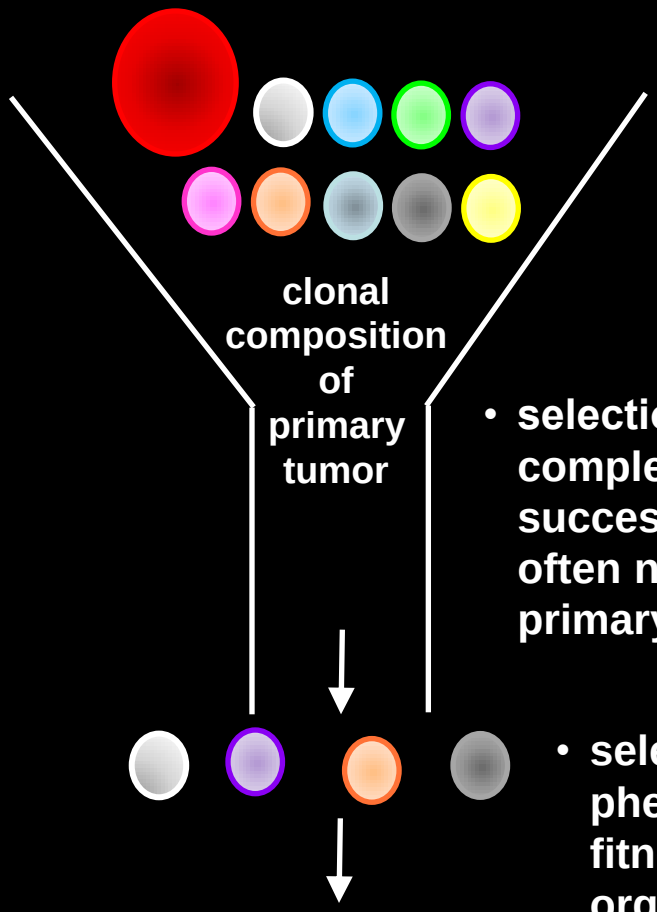
Cancer as a Complex Adaptive System



Major Knowledge Gaps in Understanding Clonal Dynamics and Fitness Landscapes in the Progression of Malignant Tumors

- mutation rates in different clones
- nature and frequency of selection pressures affecting clonal fitness
- fitness effects of different mutations and combinations
- fitness requirements for survival in different tissue microenvironments for metastatic success
- nature of competition and mutualism between co-evolving clones in same tumor or metastasis
- role of different therapeutic modalities and dosing regimens as selection pressures

The Selection Bottleneck (Selection Sweep) in Metastatic Dissemination



- dominant clone and spectrum of lower frequency clones
- zonal localization of individual clones

- selection bottleneck for 'fitness' to complete multiple steps needed to successfully metastasize (note: often not the dominant clone the primary tumor)

- selection for clonal phenotypes with preferred fitness for growth in specific organs?

- further clonal diversification within individual metastases

Nature (3 April 2014) Vol. 508, 7494

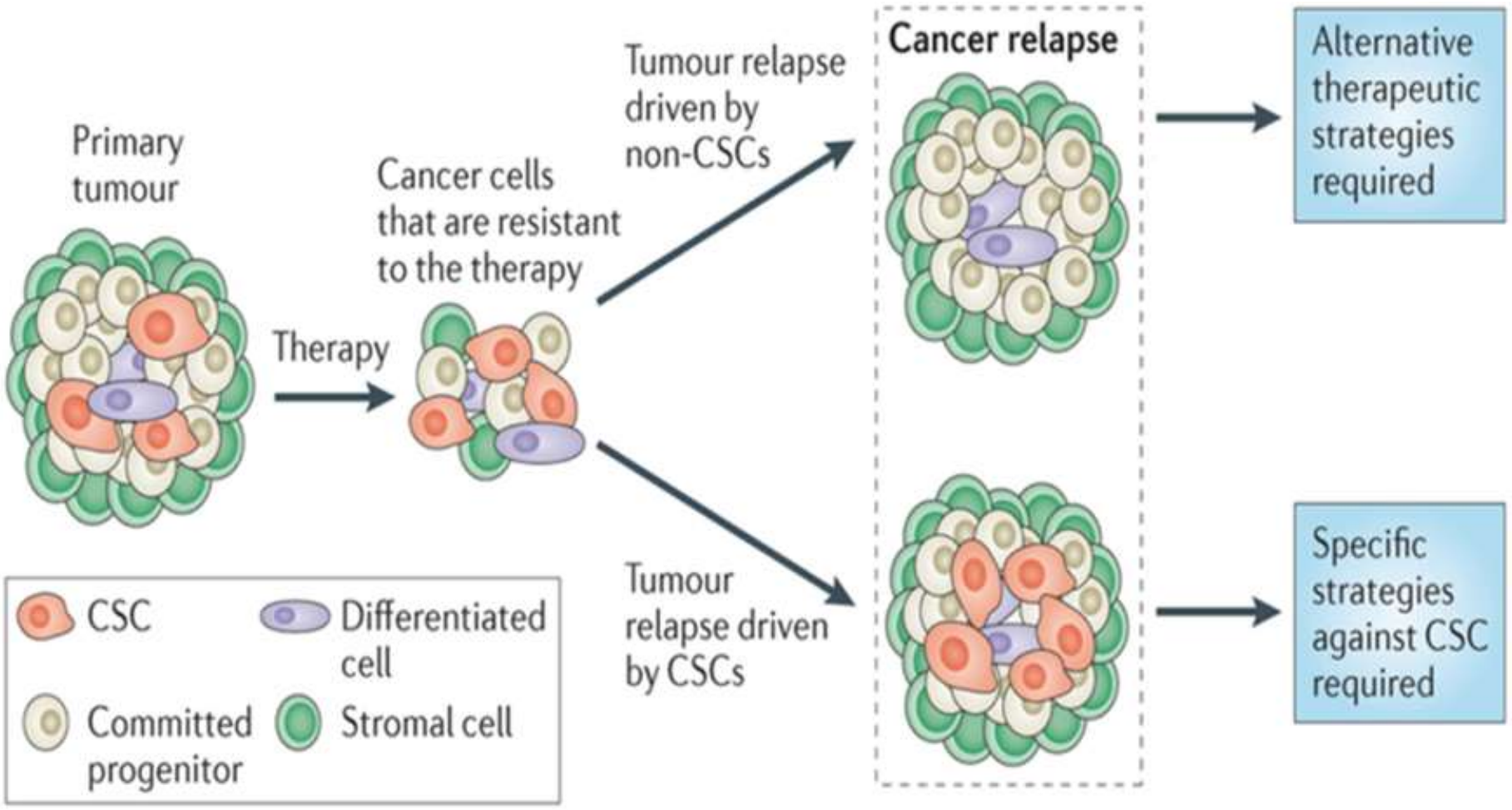
Cancer Stem Cells

- 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?

Are Current Targeted Treatments Attacking Both Stem Cells and Progenitor/Differentiated Cells or Largely Only the Latter?

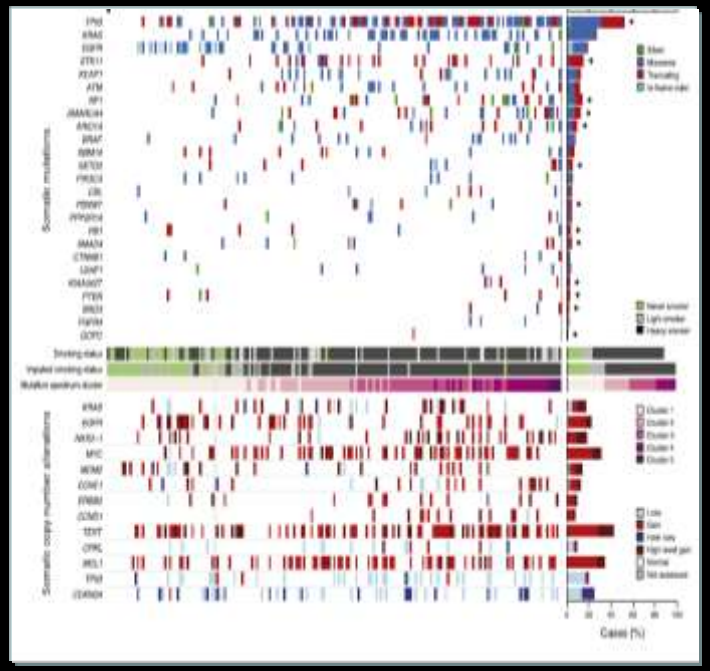
If Stem Cells Are Surviving Unscathed then Therapeutic Failure is Inevitable and New Therapeutic Approaches to Selectively Attack Stem Cells Are Required

Implications of Different Cell-of-Origin Models for Cancer on Therapeutic Strategies

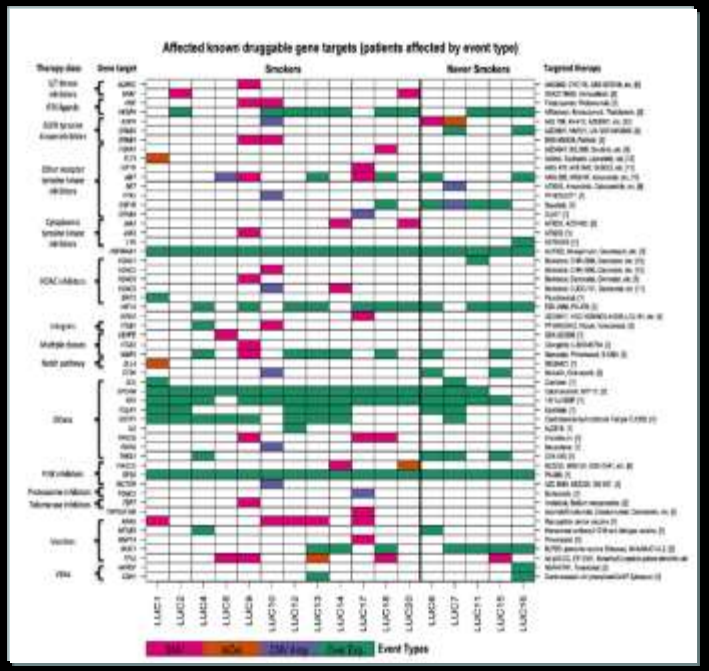


Adapted From: B. Beck and C. Blanpain (2013) Nature Rev. Cancer 13, 734

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



Mutations in Individual Non-small Cell Lung Cancer



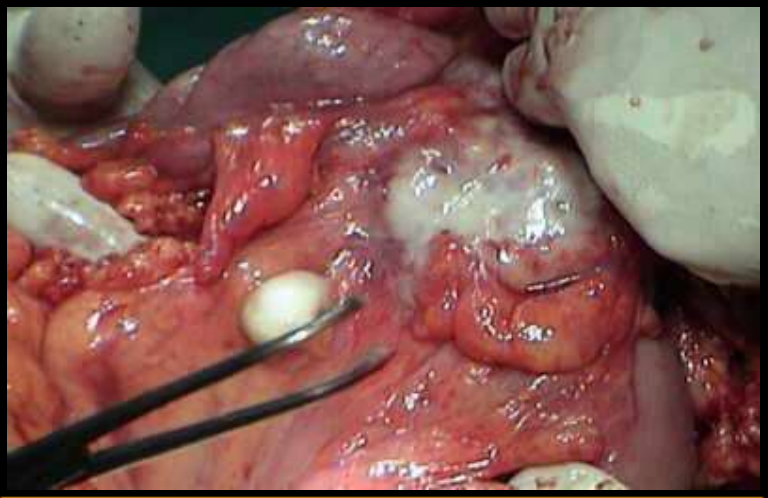
Drug Targets in Individual Non-Small Cell Lung Cancers

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

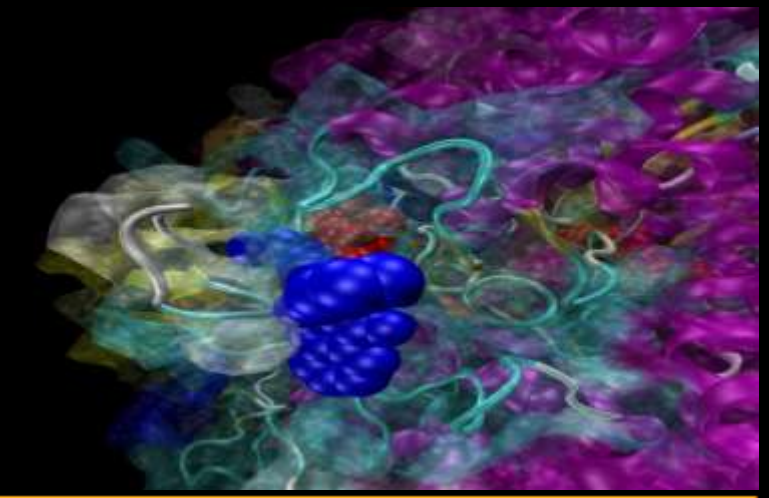
Dynamic Clonal Heterogeneity in Tumor Progression: The Most Clinically Dangerous Phenotypes

Evasion of Detection/Destruction by Host Immune System

Use of Host Systems to Promote Progression



Invasion and Metastasis



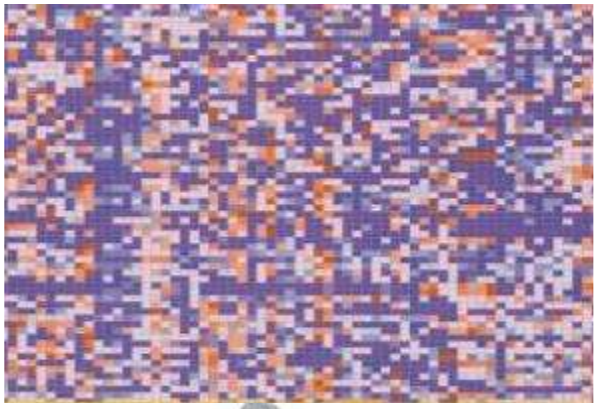
Emergence of Drug-Resistant Clones

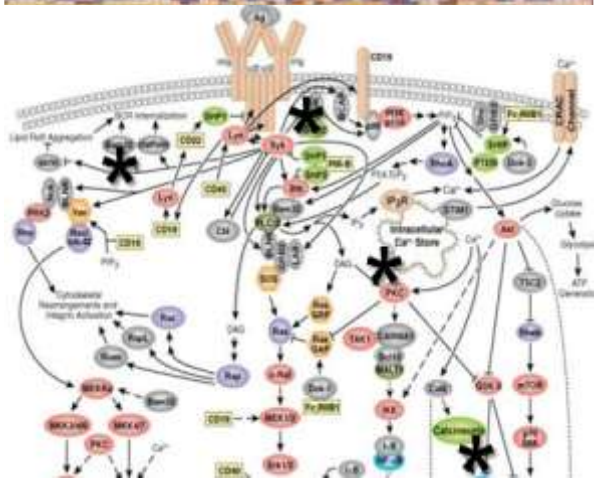
The Problem and The Challenge

- how to hit multiple tumor clones?
- how to hit multiple tumor clones at multiple sites of metastatic disease?
- how to hit each new variant clone that may emerge as an escape variant driven by intrinsic genomic instability and/or by the selection pressure of treatment?

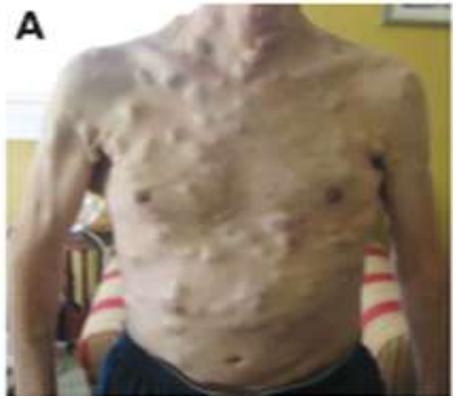
Clonal Heterogeneity and the Relentless Emergence of Drug-Resistant Clones (Intrinsic and/or Acquired Resistance)

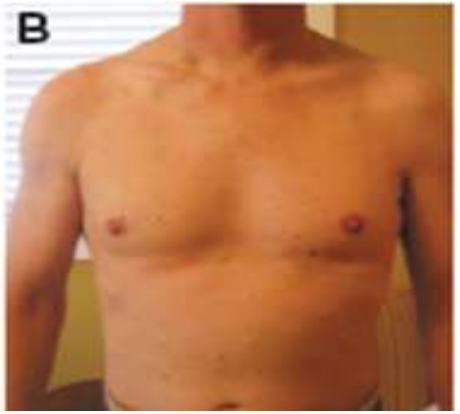
Molecular Subtyping and RX Targets



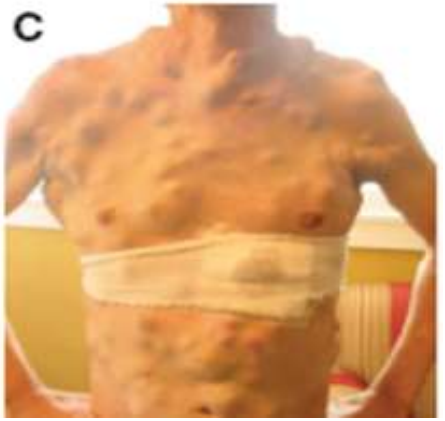


Initial Rx-Response to Targeted Rx





Rx-Resistance via Redundant Molecular Pathways

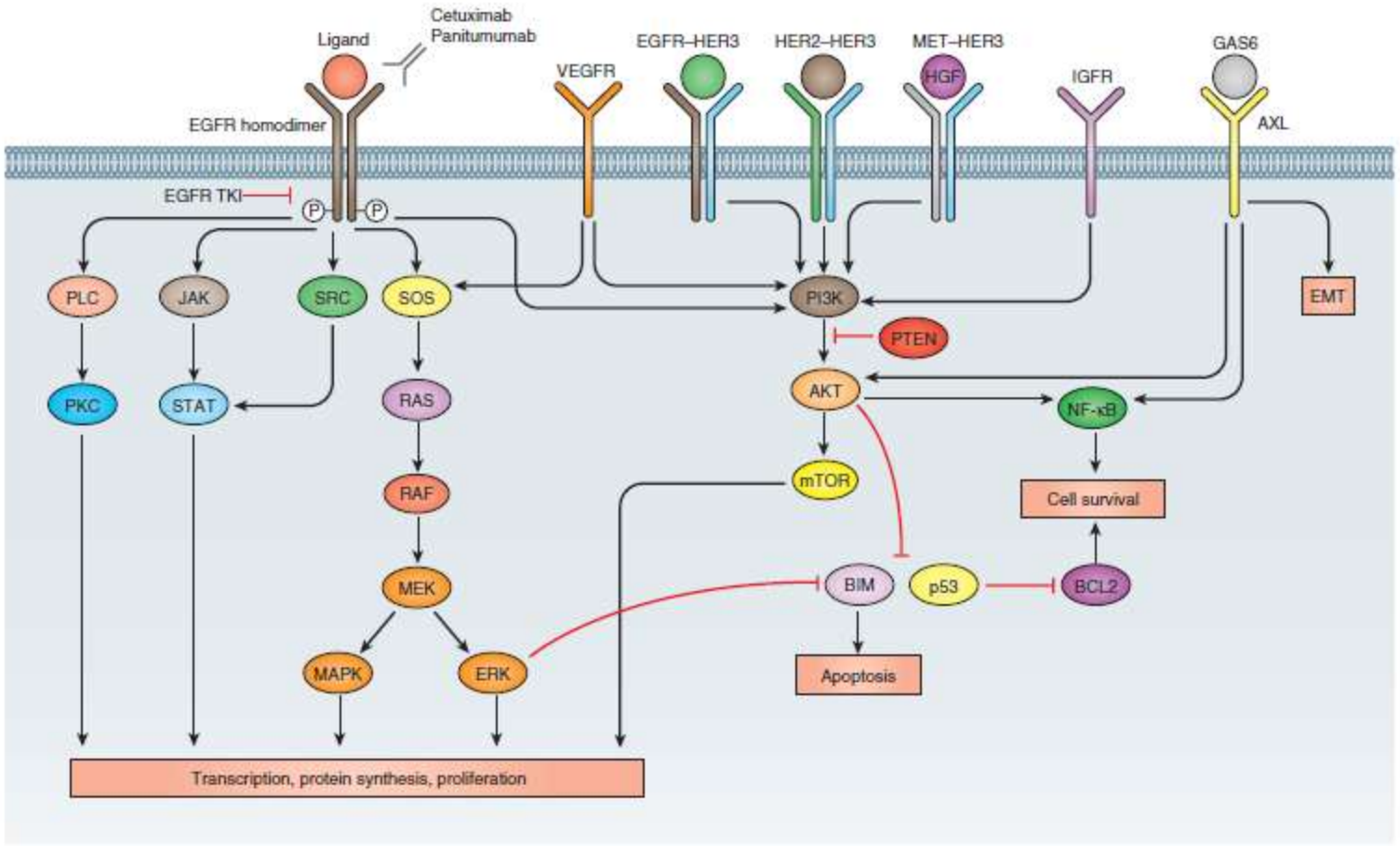


B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

Mutations Responsible for Acquired Resistance to Targeted Therapies

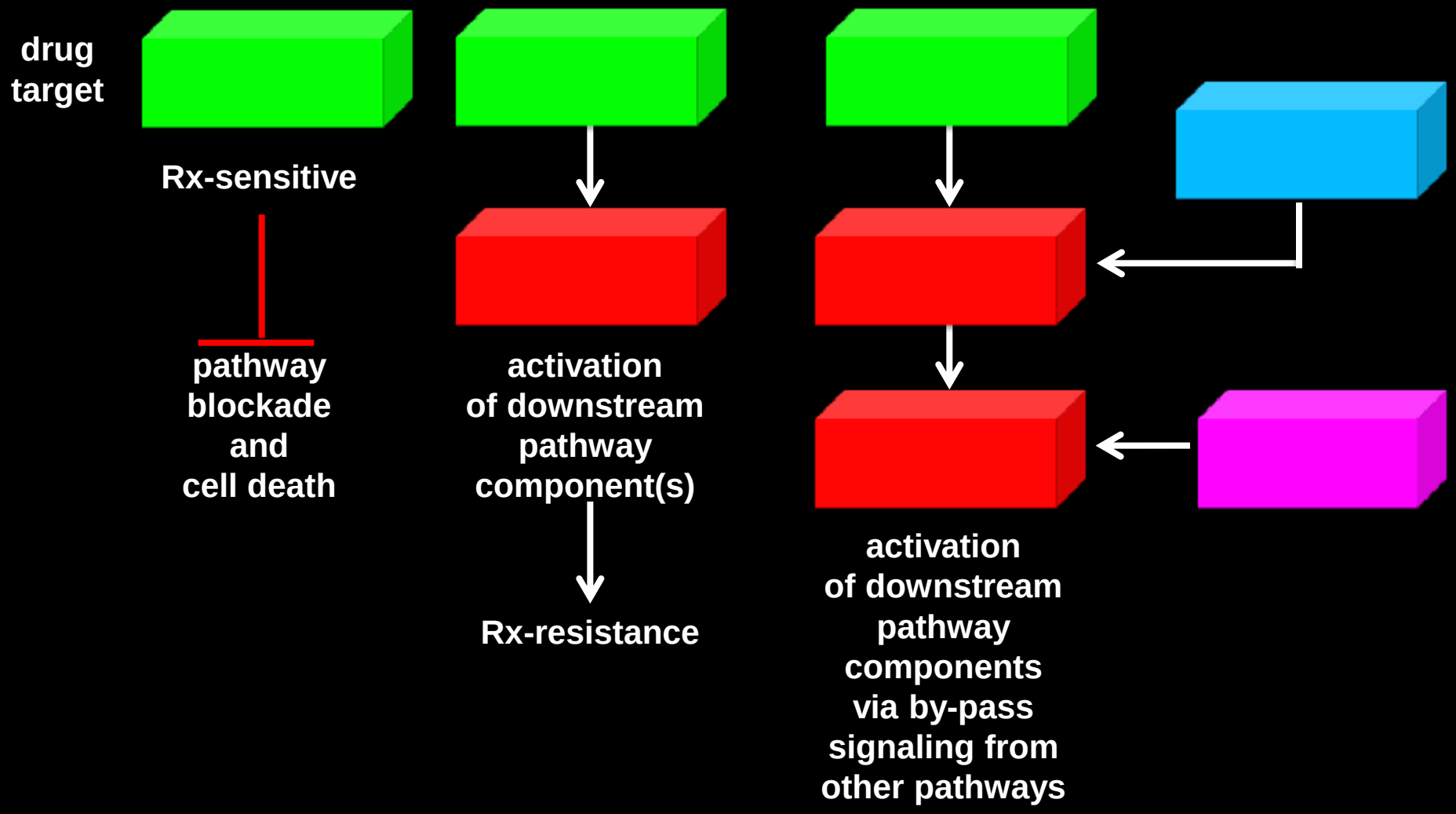
Gene	Genetic mutation	Tumor type	Acquired drug resistance
EGFR	T790M	Advanced NSCLC	Gefitinib Erlotinib
KRAS	Codon 12, 13 and 61	Colorectal cancer	Cetuximab
KIT	T670I	GIST	Imatinib
PIK3CA	NS	NSCLC	Erlotinib Gefitinib
ALK	C1156Y L1196M	NSCLC	Crizotinib
MEK1	C121S	Melanoma	Vemurafenib
BRAF	Amplification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

EGFR Signaling Pathways in Cancer: Targeted Therapies and By-Pass Pathways for Drug-Resistance



From: C. R. Chong and P. A. Jänne (2013) Nat Med.;19(11):1389

Network Pharmacology and Emergence of Drug-Resistant Cells



Resistance to TKIs in EGFR-Mutant Lung Adenocarcinomas* Development of Resistance to Gefitinib or Erlotinib in c.40% Patients After One Year

additional mutations in Rx target

- second-site resistance EGFR mutations (>50%)

mutations/activation of downstream and/coupled pathways

- amplification of MET receptor gene (5-10%)
- mutations in PIK3CA encoding P110α subunit of downstream lipid kinase PI3K (<5%)
- BRAF mutations (<1%)

trans-differentiation

- histologic transformation: EMT or small lung cancer (<5%)

* K. Ohashi et al. (2012) PNAS 109, 12282

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

- multisite action by single Rx in the same pathway
  - blockade of most likely predicted “escape” domains involved in D^r
- multi-target promiscuity by single Dx in different pathways
  - control of off-target AEs
- Rx combinations with multisite (single pathway) and/or multitarget actions (different pathways)
  - 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

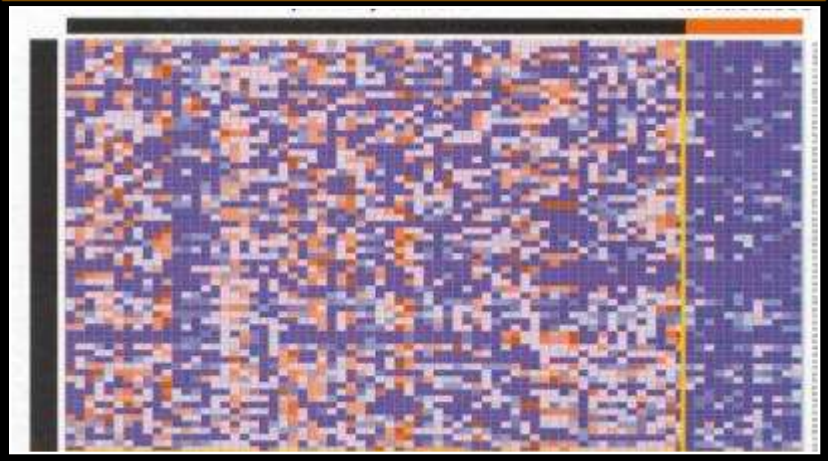
Adapted from: S. Tanaka et al. (2013) Nature Rev. Clin. Oncol. 10,14

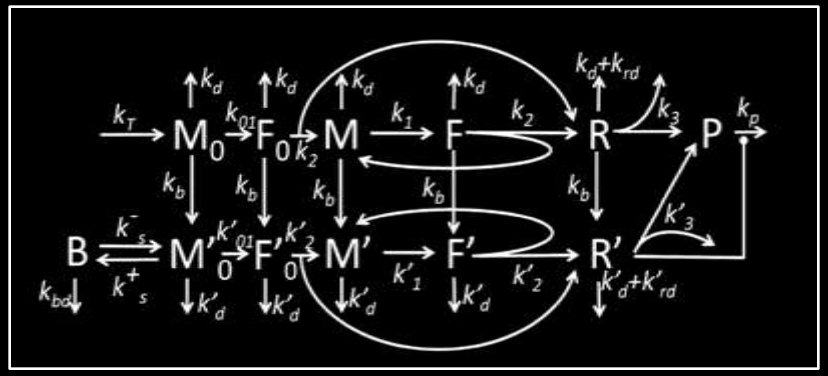
Irreversible Kinase Inhibitors and Cancer

- less potential for drug resistance phenotypes than reversible inhibitors?
- Afatinib (B-Ingelheim)
  - EGFR kinase inhibitor NSCLC (EMA and FDA approval)
- Ibrutinib (Janssen:Pharmacyclics)
  - FDA accelerated approval
  - Bruton's TK (BTK) inhibitor
- Dacomitinib (Pfizer)
  - EGFR inhibitor NSCLC (III), brain, head and neck (II)
- Neratinib (Puma)
  - EGFR inhibitor, breast (III), NSCLC, Gastric (II)

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

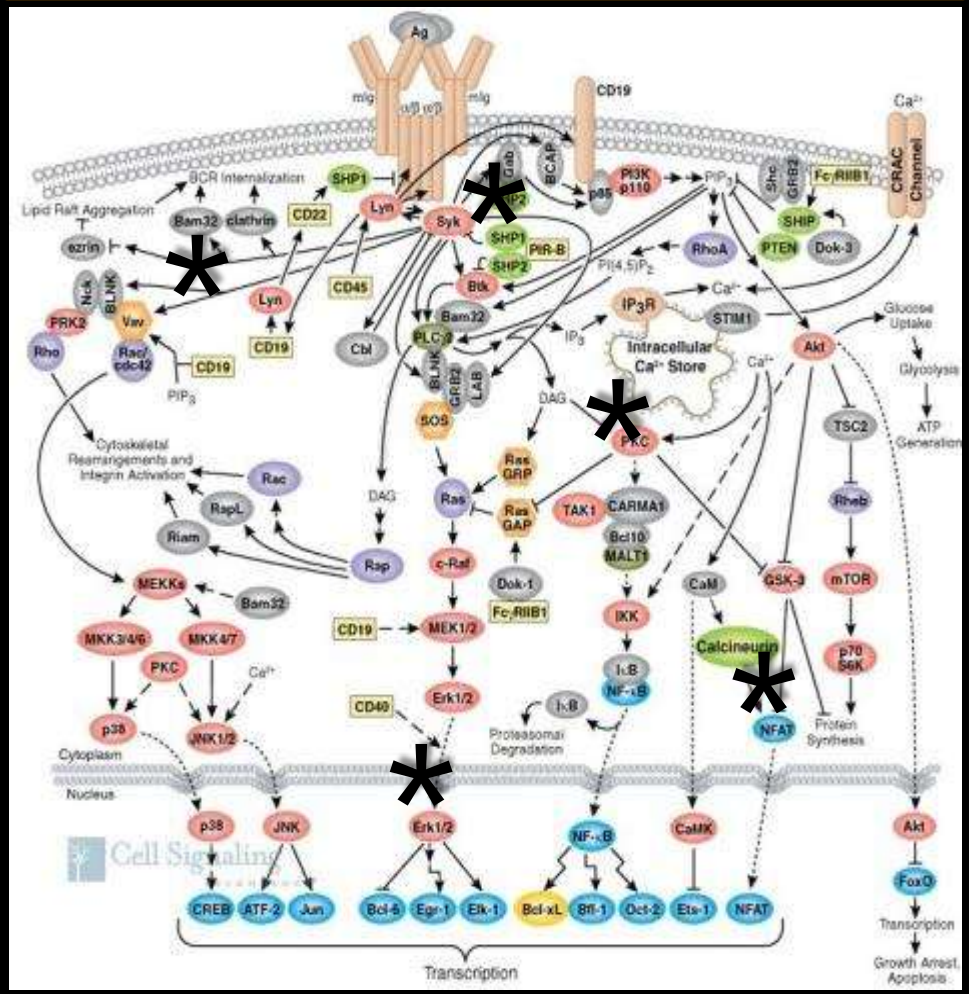
panOmics Profiling to Identify Disease Subtypes (+ or - Rx Target)





The Challenge of Non-Linear Information Flow in Biological Networks

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

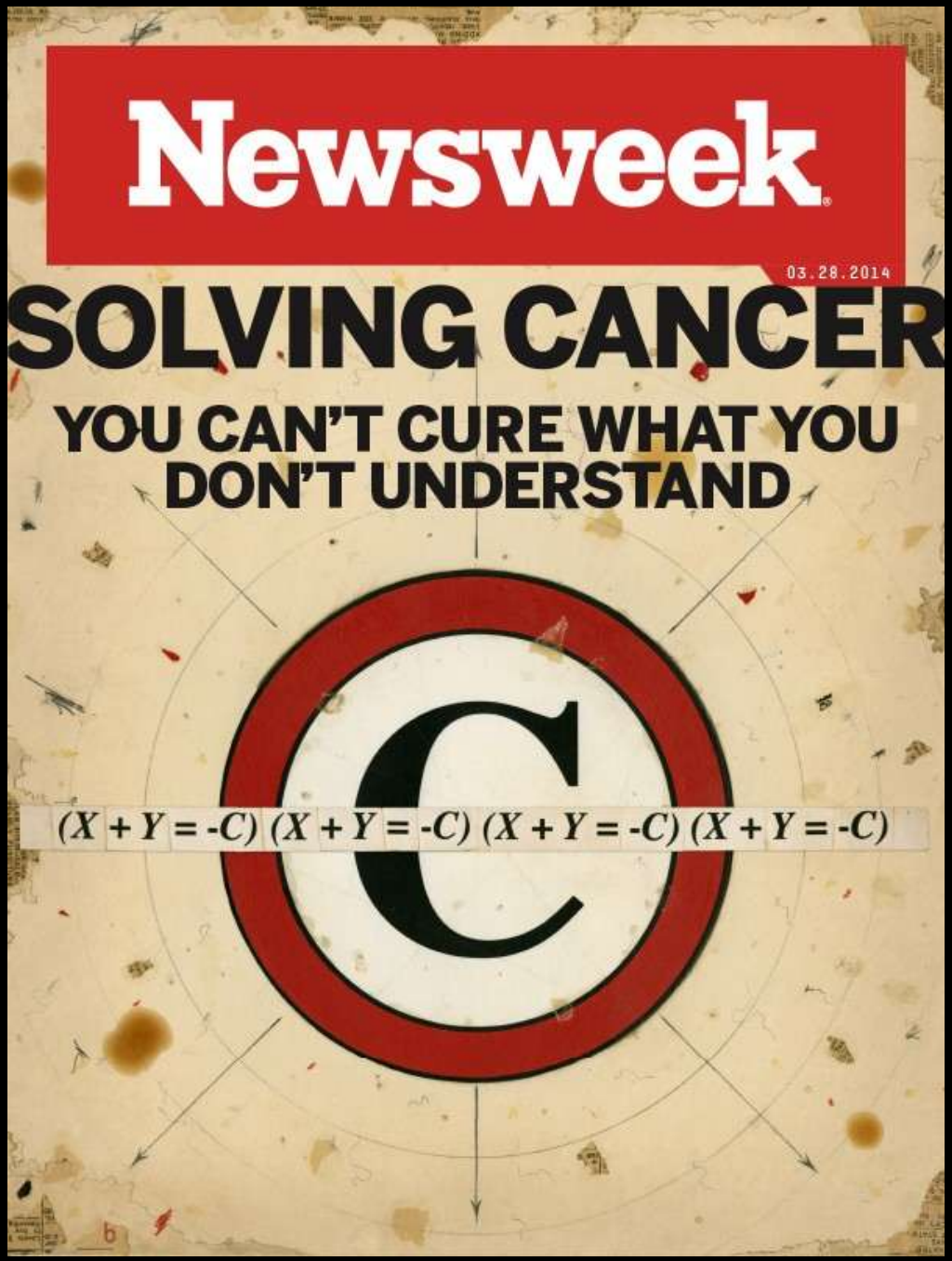


"Omics" Technologies and the Elucidation of Perturbations in Molecular Network 'Wiring' in Complex Diseases

- 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?

An Ugly (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?

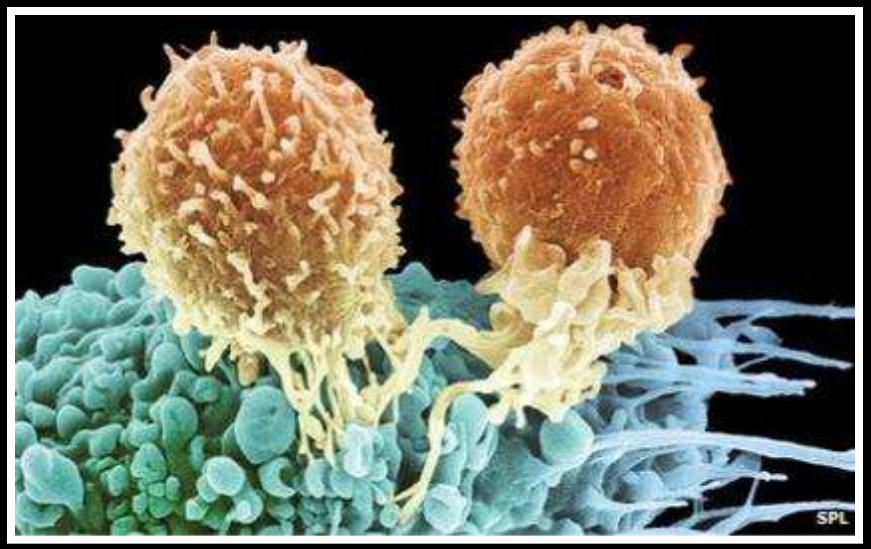


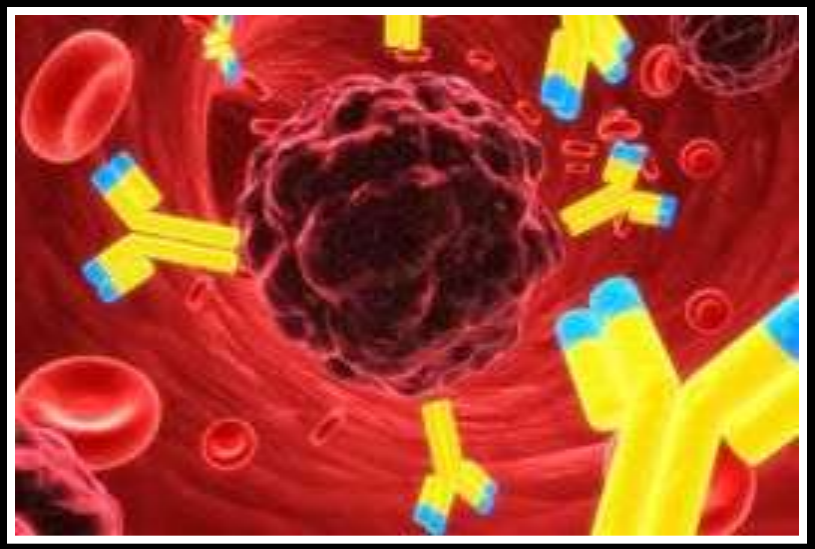
- cancer as a complex adaptive system
- dynamics of clonal evolution during tumor progression and treatment
- clonal evolutionary dynamics as a complex interplay between tumor (evasion) and host (detection/ destruction) activities
- the evolution of clonal heterogeneity is the core problem in effective therapy


Science
20 December 2013 | $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS

Immunoevasion by Tumor Cells

- "stealthy" tumor cell strategies that reduce detection and/or killing by body's immune defenses, therapeutic monoclonals and anti-cancer vaccines



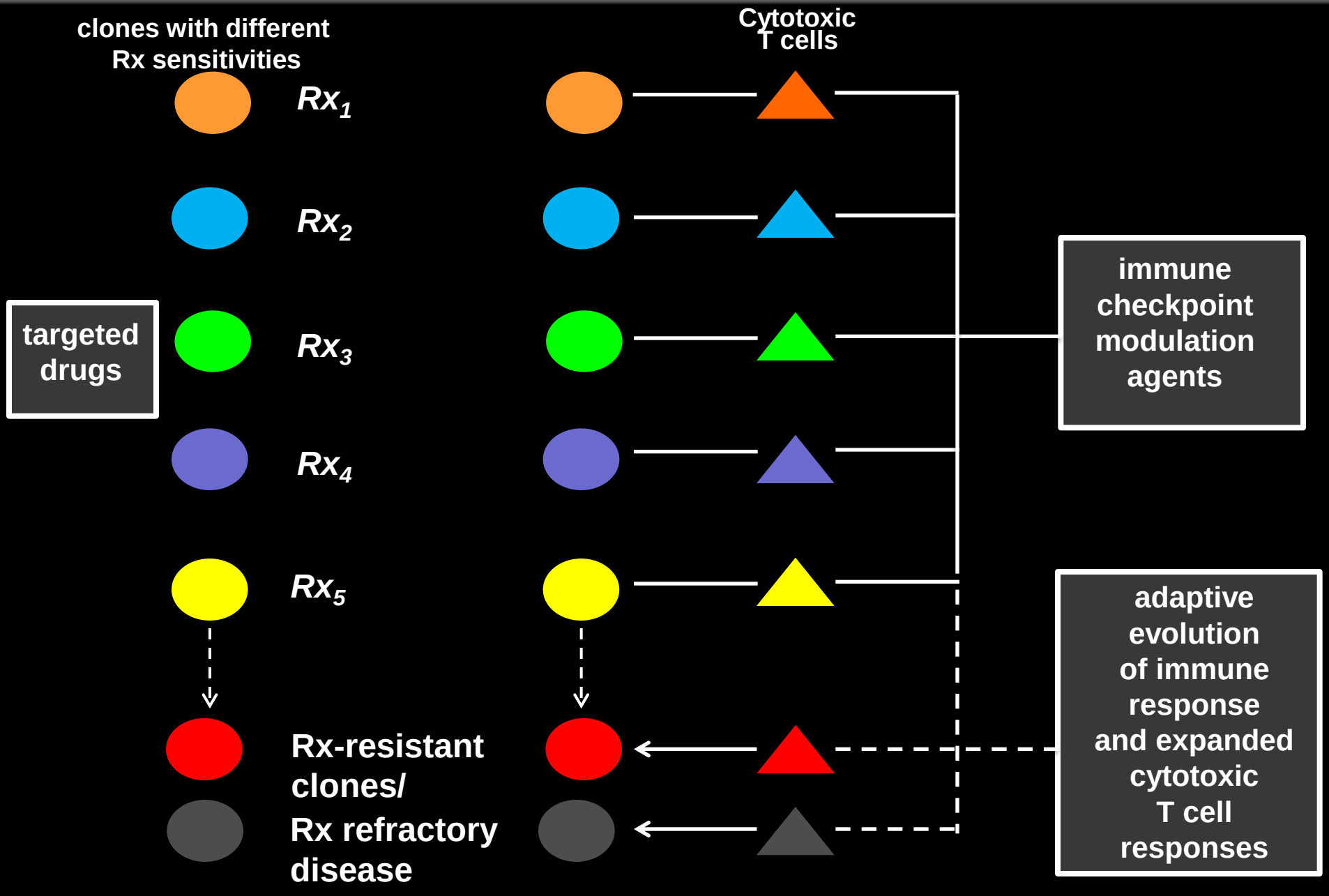


New Therapeutic Strategies to Circumvent Tumor-Mediated Suppression of Anti-Tumor Immune Responses

- circumventing tumor-mediated activation of T regulatory (Treg) cells to limit activity of anti-tumor killer T cells

- immune checkpoint modulation
  - "releasing the brakes" on the immune system
  - "removing the blindfold"
  - "unleashing the killer instinct"

The Promise of Immune Checkpoint Modulation Versus The Drug Resistance Problem in Targeted Therapy



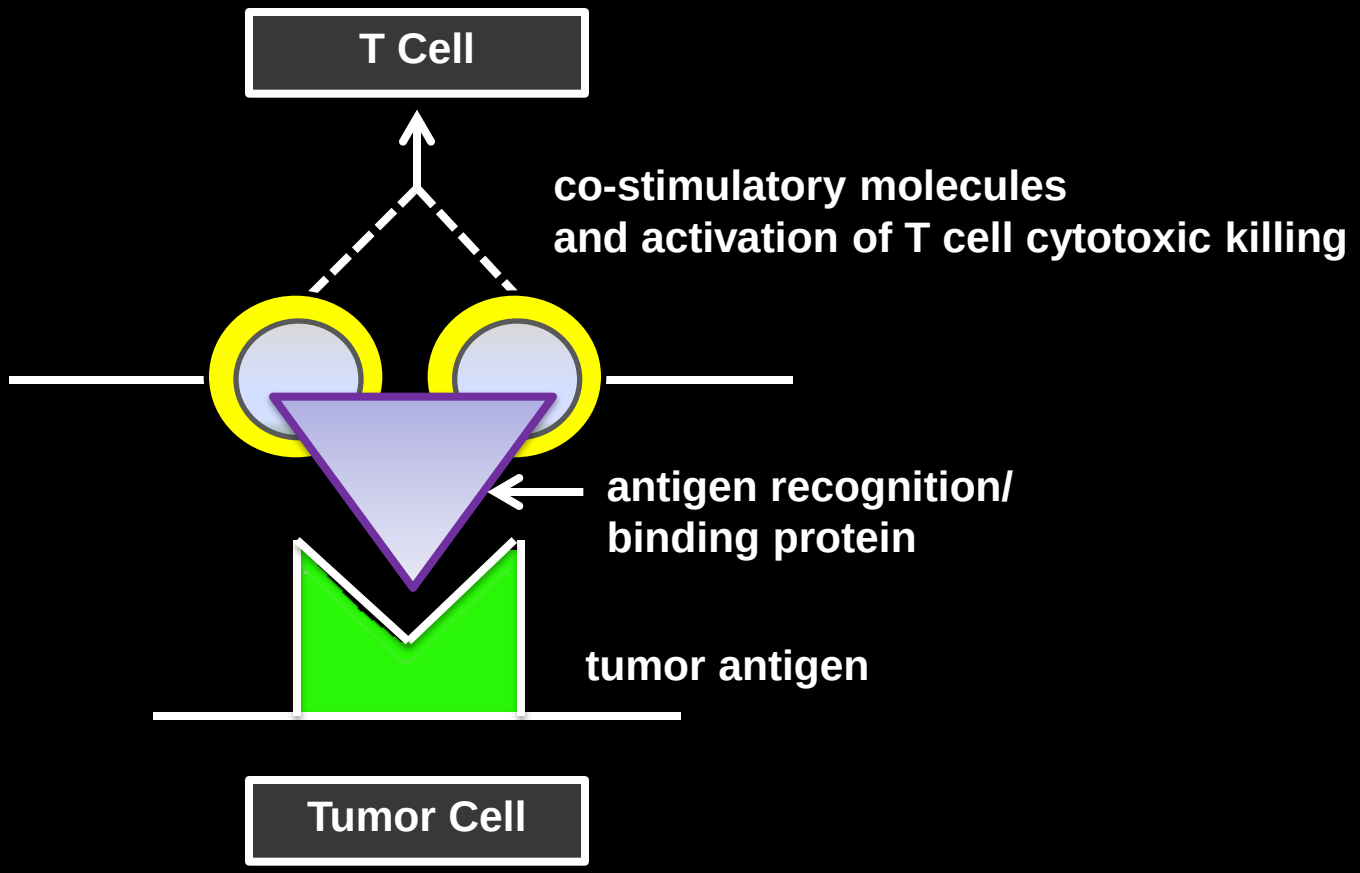
Immune Checkpoint Modulation

- CTLA-4; iplimumab (BMS approved)
- PD-1 antibodies and PD-1 ligands (Phase I/II/III)
- OX4; nivolumab (Phase III)

Engineering Killer T Cells for Cancer Therapy

- killer T cells harvested from cancer patients
- harvested cells genetically engineered in vitro to express T cell receptor(s) (TCRs) or chimeric antigen receptors (CARs) that recognize tumor antigen(s)
  - TCR/CAR genes delivered by viral vectors
  - TCRs must be genetically matched to the patients immune type

Three Component Chimeric Antigen Receptors (CARs)



Immunotherapy and Cancer
The Limitations of Personalized Treatments Versus Broad-Use Immunotherapeutics

- production cost and technical complexity of individualized treatment
  - local versus centralized production
  - facilities and expertise
  - regulatory review

Major Conceptual and Technical Barriers in Understanding the Role of Immunity in Protection and Disease

- limited metrics for multiplex functional monitoring of status of the immune system
  - poor predictive potential of animal models for humans
  - diverse cell classes
  - complex repertoire of cell-cell and cell-mediator interactions
  - monitoring of antigen expression dynamics in tumor clones
  - anatomic compartmentalization and lack of sampling tools
  - evolution of immune-escape variants

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

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

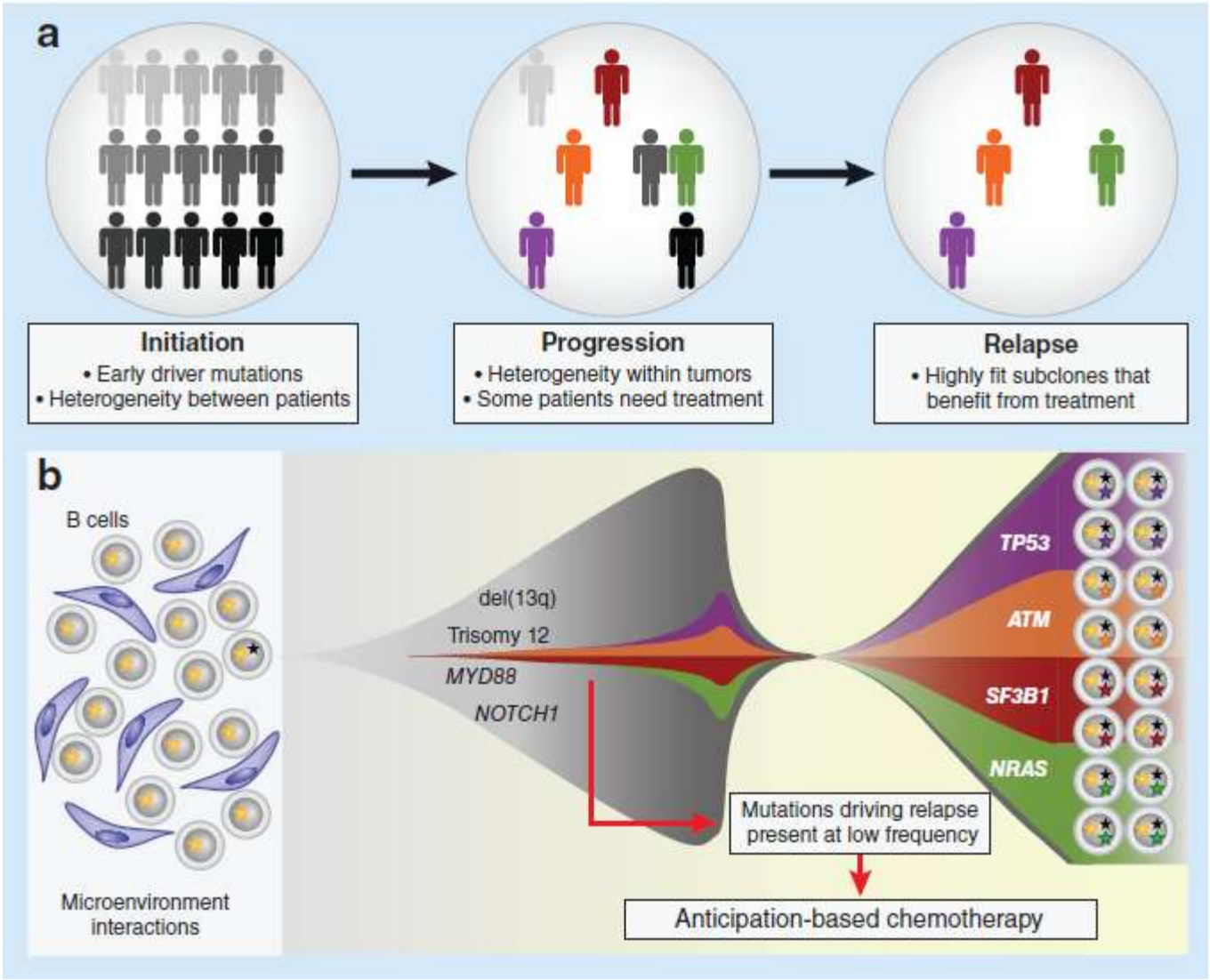
The Liquid Biopsy: The Need for New Diagnostic Tools for More Sensitive Longitudinal Monitoring of Tumor Progression

- 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

Monitoring The Evolution of Rx Resistance With Tumor Progression

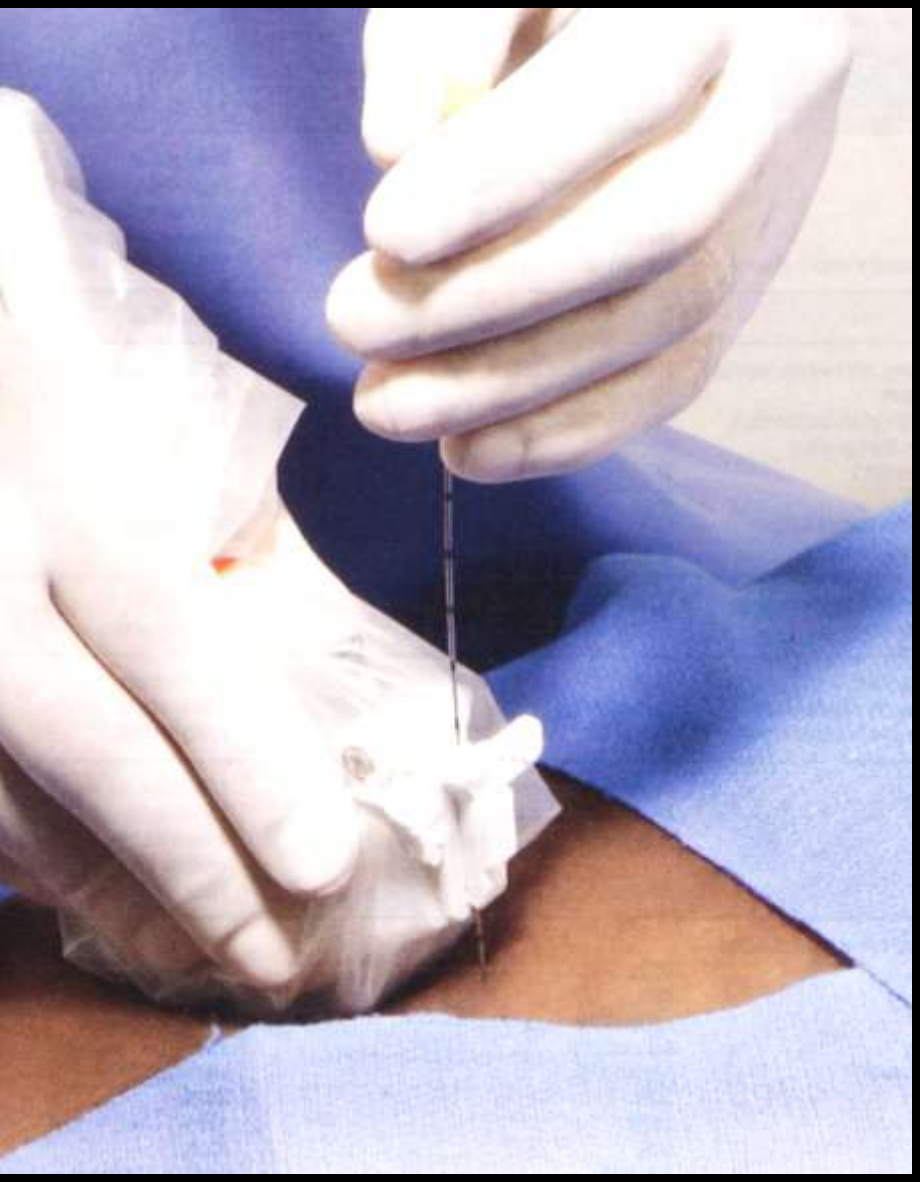
- emergence of new KRAS mutations in CRC patients treated with cetuximab (Misale et al. 2012. Nature 486, 532)
- pre-existing ‘minor’ clones with KRAS mutations identified in metastases
- new clones sensitive to investigational Rx targeting MEK
- mutant clones detected in blood as early as 10 months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

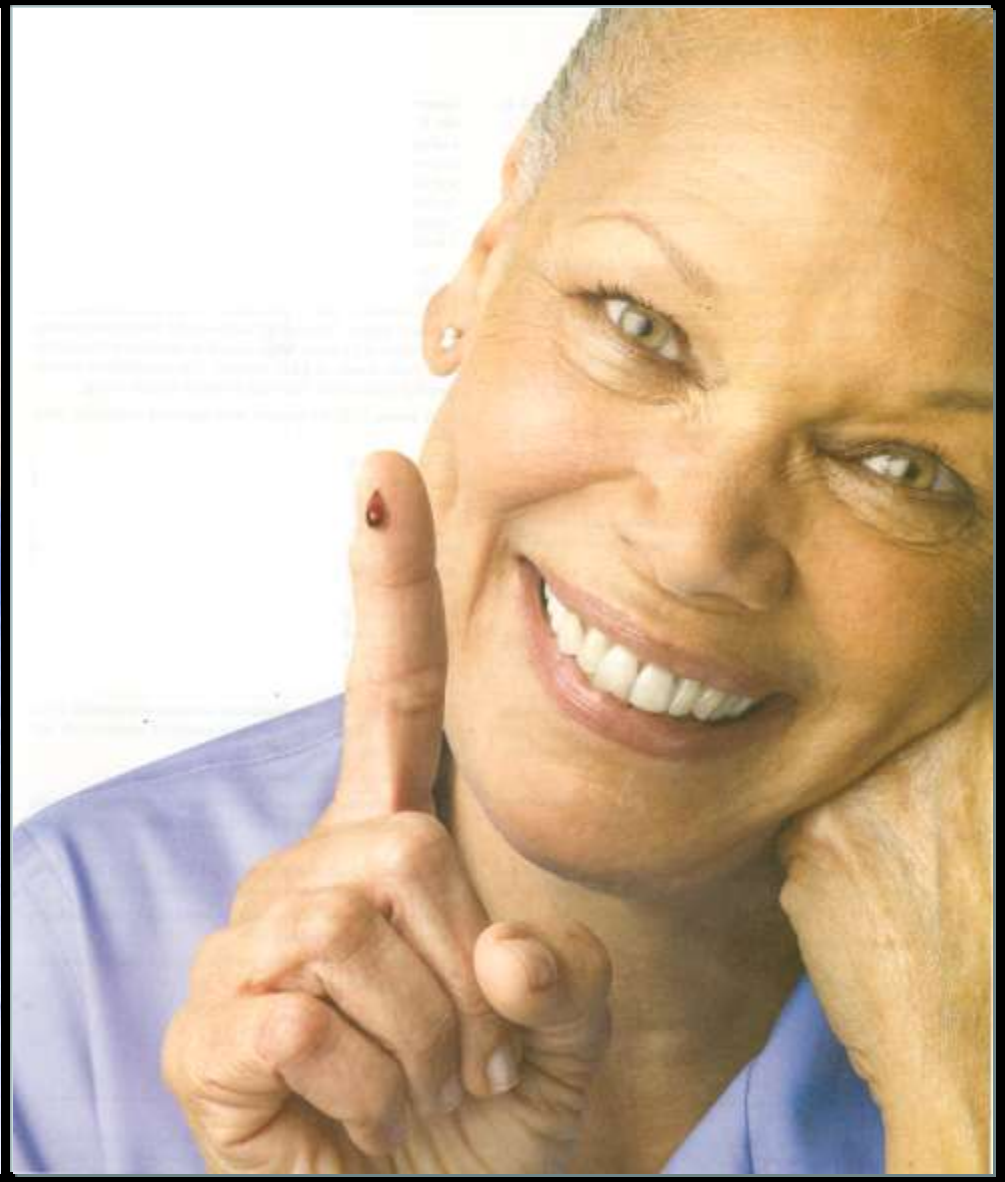
Anticipation-Based Chemotherapy in CLL



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

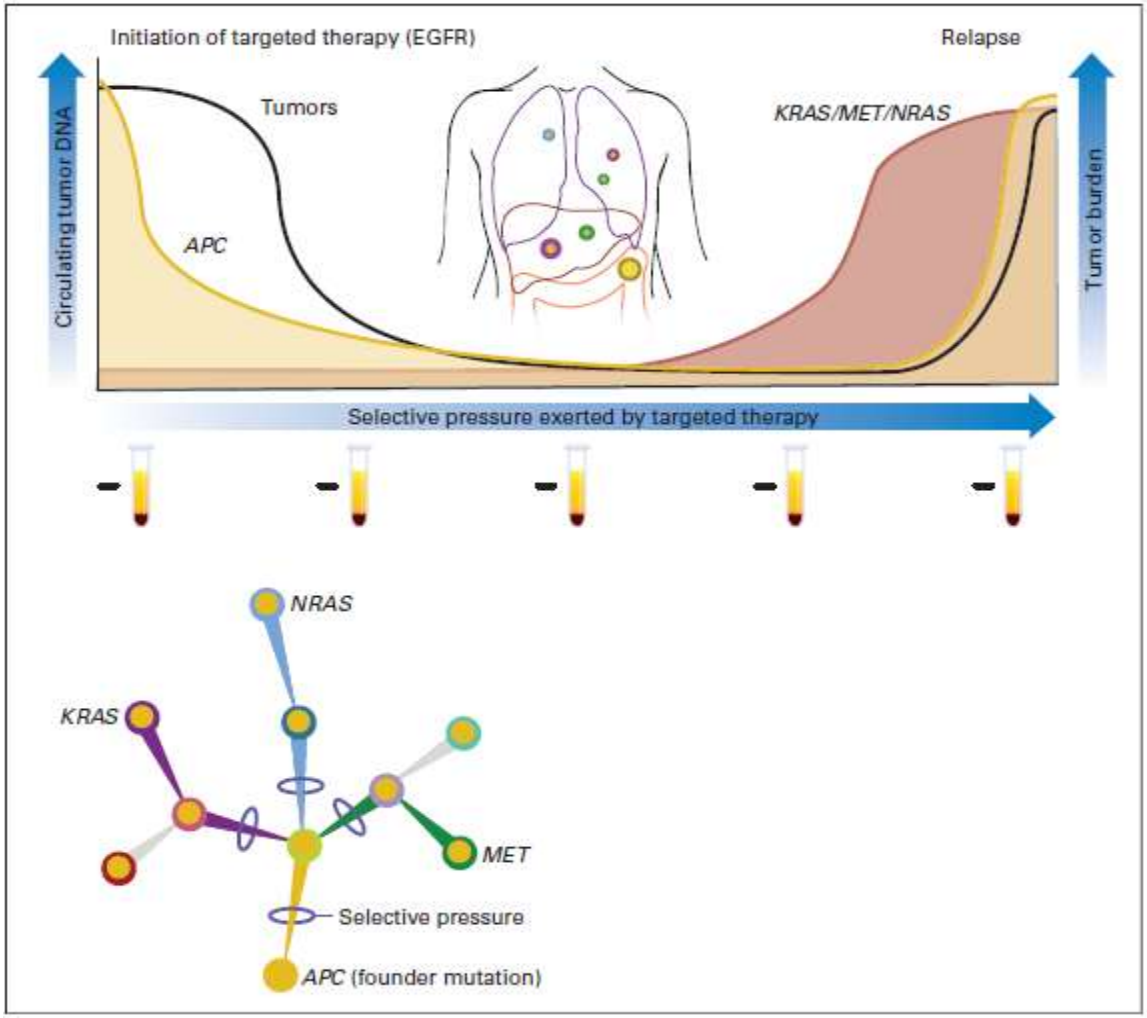




The Liquid Biopsy:
The Urgent Need for New Minimally Invasive Diagnostic Tools for More Sensitive Longitudinal Monitoring of Tumor Progression

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

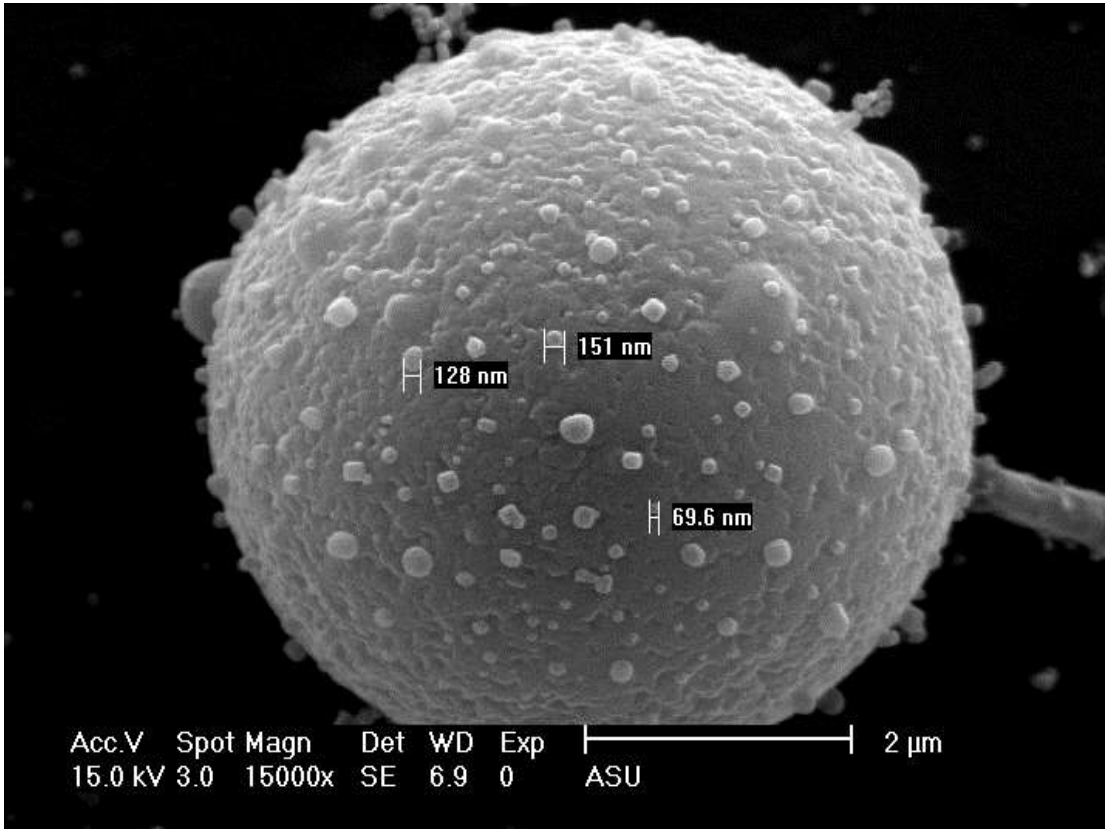
"Liquid Biopsy"
Monitoring of Changing Clonal Dynamics by Monitoring Tumor Specific Biomarkers in CRC



At diagnosis = APC and KRAS (Wild Type)
emergence = KRAS and NRAS mutations and MET amplification clones
From: L. A. Diaz Jr and A. Bardelli (2014) J Clin Oncol 32, 579

CARISOME™

CIRCULATING MICROVESICLE (cMV) TECHNOLOGY



Exploration of the Role of Exosomes in Tumor Progression

- cancer-specific signatures
  - miRNA, mRNA, proteins
  - identify tissue of origin
  - 'cargo' changes with progression
- role in modulating host immune defenses?
- role in epithelial-mesenchymal transition?
- role in 'preconditioning' of organs for metastatic seeding?
- potential value in Dx?
  - minimally invasive versus biopsy
  - longitudinal disease monitoring in patients
- potential value as markers of Rx response/resistance/ relapse?

CARIS LIFE SCIENCES

Carisome™

- a blood-based technology to detect and profile tumor-derived biomarkers
- proprietary microvesicle isolation technology
- minimally invasive method to detect and monitor cancer progression and changing clonal dynamics on therapy
- potential in diagnosis and therapeutic response monitoring
- more than $100 million R&D investment to date

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

Oncology Therapeutics: An Unsustainable Enterprise Using Current Approaches?

- highest failure rate in clinical trials of any therapeutic class (8% success)
- slow adoption of new clinical trial designs using stratified patient subpopulations
- testing of new investigational drugs on late-stage patients with advanced and/or refractory disease
  - cellular composition likely unrepresentative of tumors at intitial presentation
  - effect of repeated Rx cycles on clonal phenotypes and immune system damage

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; S-1400)
- 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

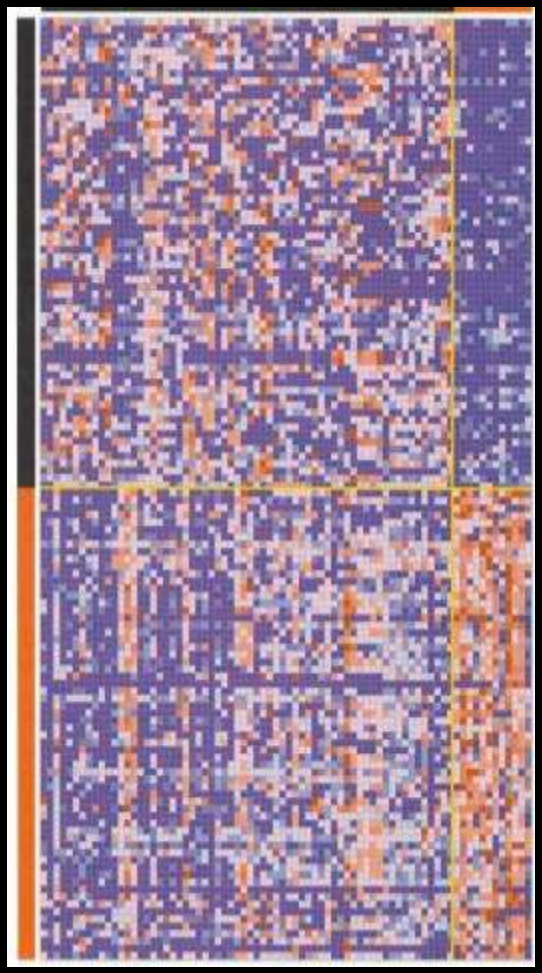
Enrichment and Adaptive Trials Using MDx-Stratified Patients: Consequences of Foregoing Phase III RCTs

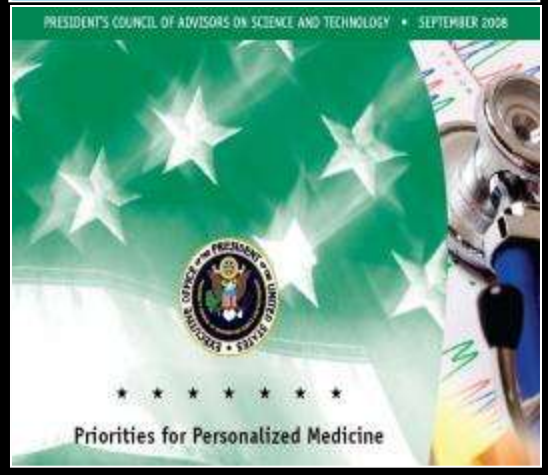
- appeal of faster trials and patient access to promising Rx (terminal diseases)
- less definitive evidence regarding safety and efficacy (smaller ‘N’)
- more complex regulatory filings for ‘combination’ protocols (Rx^n, MDx^n)
- accelerated approval should require reciprocal agreement for market withdrawal if confirmatory trials are negative
  - “fast on, fast off”
  - lessons from Avastin

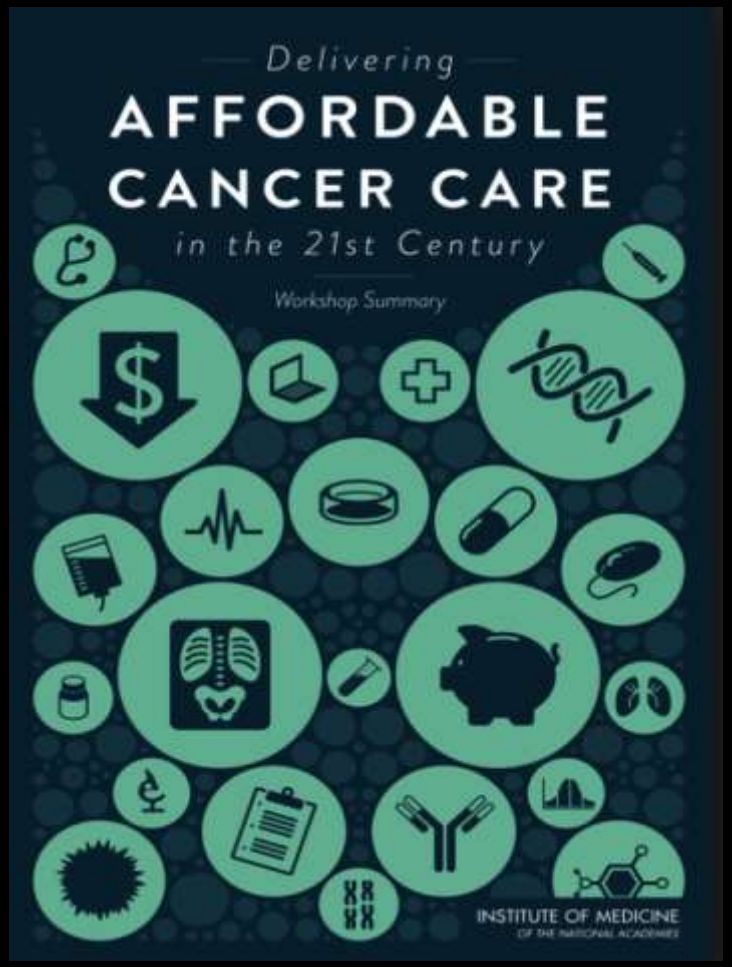
Precision Medicine and
Escalating Technical Complexities

The Need for Agile, Adaptive Regulatory and Reimbursement Policies

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?

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)

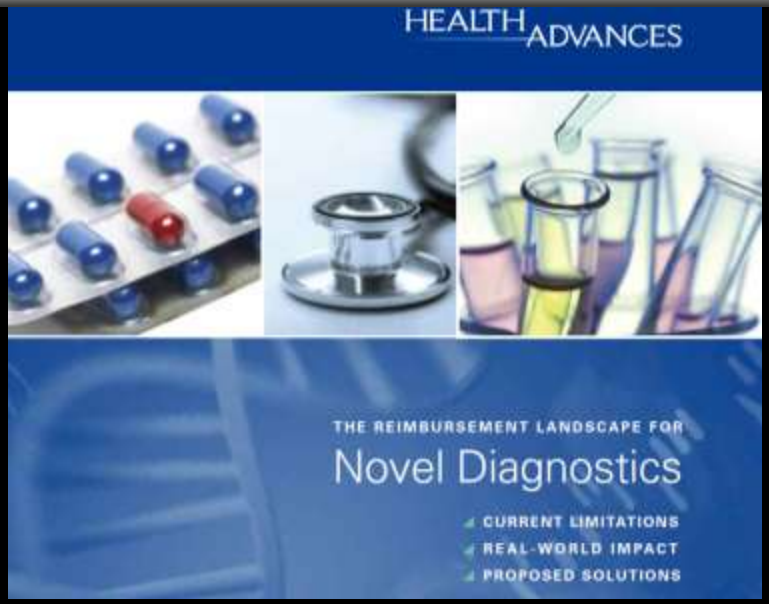
*No citation available. ‡Trial size not reported. Abbreviations: +, improved; –, not improved; AGC, advanced gastric cancer; CRC, colorectal cancer; FOLFIRI, 5-fluorouracil, leucovorin and irinotecan; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; GBM, glioblastoma multiforme; HCC, hepatocellular 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).

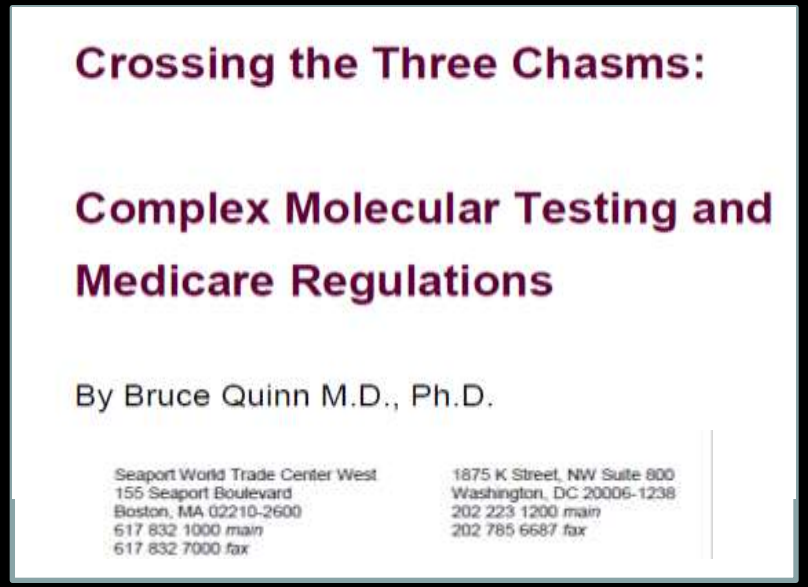
From: A. Rapisarda and G. Melillo (2012) Nat. Rev. Clin. Oncol. 9, 378

Cost of Recently Approved Anti-Cancer Drugs

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

Educating Payors on the Value of Molecular Profiling in Healthcare: Shift from Cost-Based Pricing to Value-Based Reimbursement to Incentivize Biomarker R&D





Regulatory Considerations for Molecular Diagnostic Tests

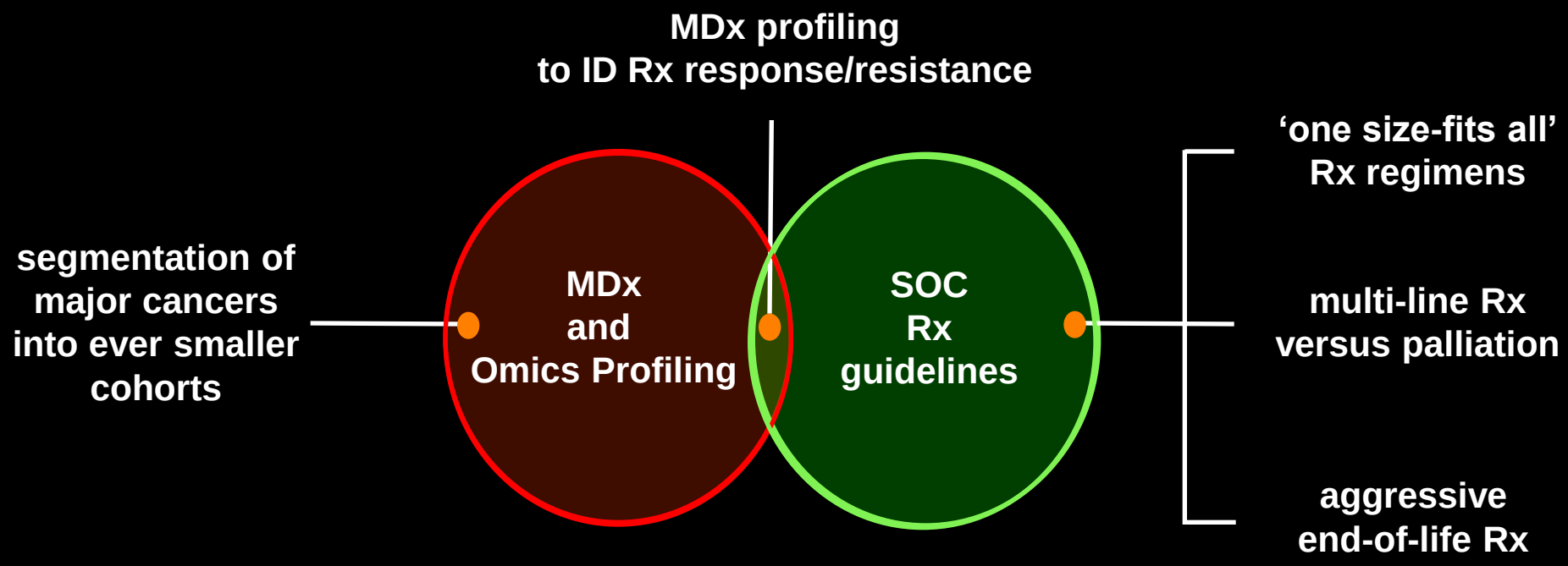
- increasing R&D cost complexity of new molecular diagnostic tests versus LDTs
- need for greater FDA oversight based on technical complexity
  - 510(k) and pre-market approval (PMA)

Cancer: A Case Study in Technology Assessment

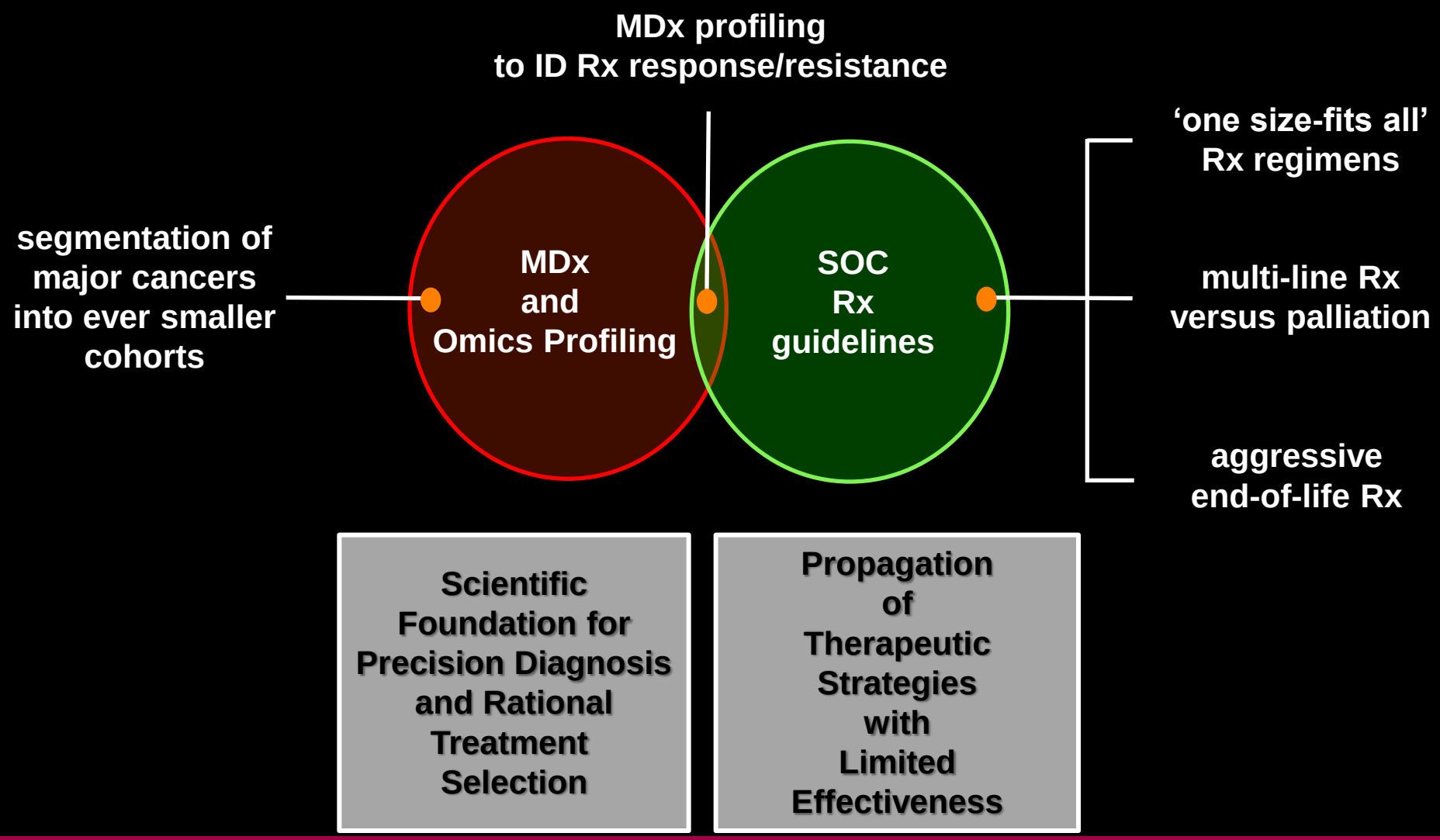
A Study in Reimbursement Policy Contrasts:

Targeted Therapeutics (Rx) Versus Molecular Diagnostics (MDx) in Oncology

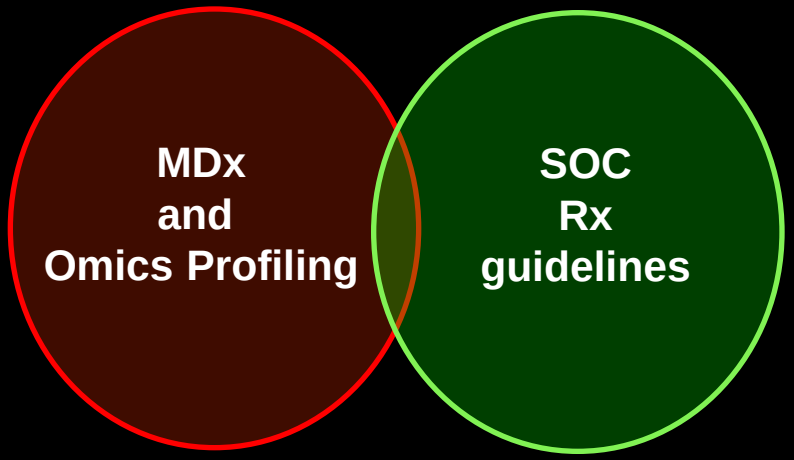
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology



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

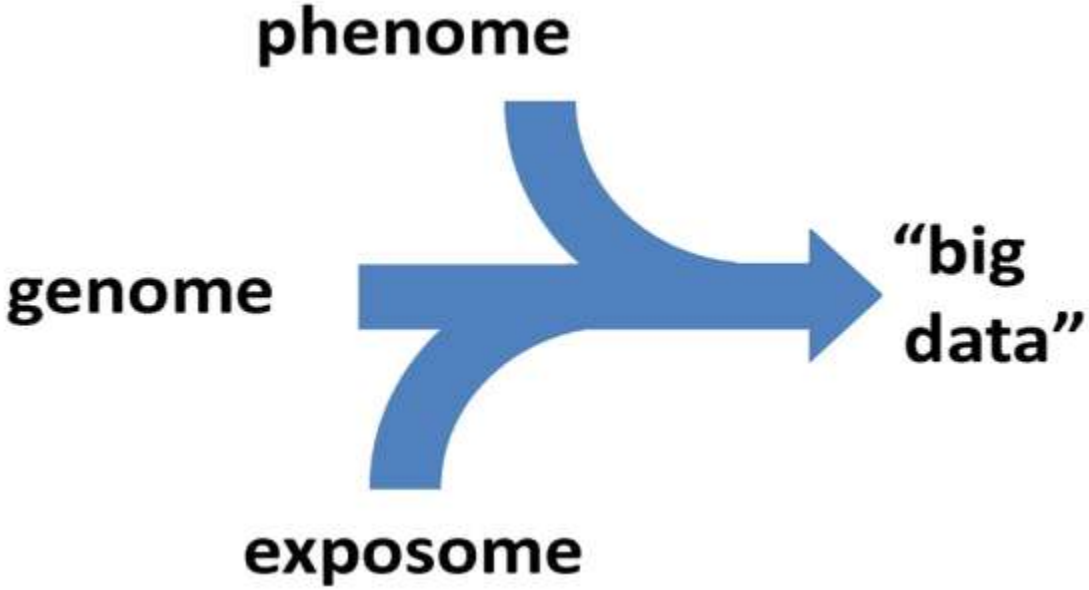


The Need for Value-Based Reimbursement of New Molecular Profiling Services: A Market Failure that Threatens Innovation in Precision Medicine



- 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

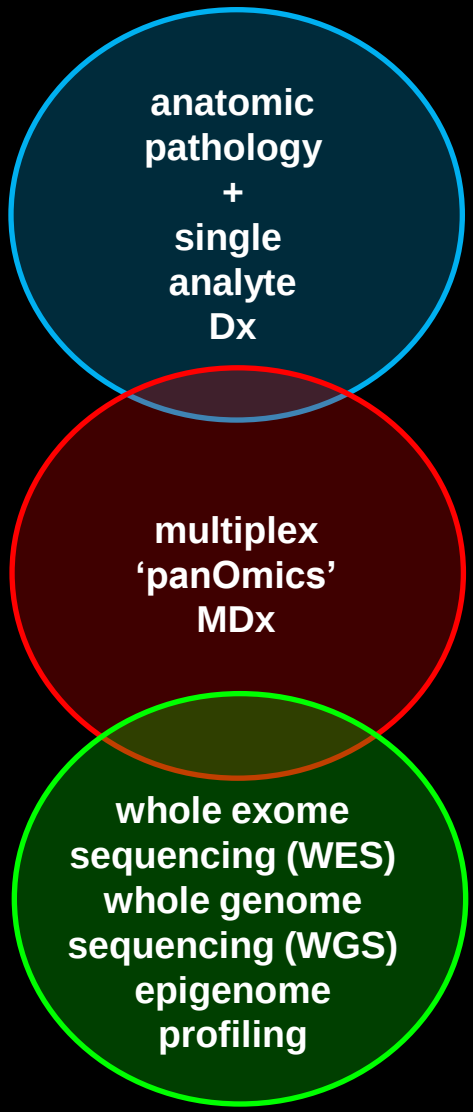
The Imminent Arrival of the Zettabyte (10^{21}) Era



The Omics Data Storage Challenge
(J. Starren et al. 2013 JAMA 309, 1237)

- typical EHR
  - 375 KB/patient
- radiologic picture archiving and communication system (PACS)
  - 104 MB/patient
  - x277 > EHR
- WGS
  - 3-10 million variants/individual
  - 5-10 GB/individual
  - x50 > imaging

PanOmics Profiling and the Data Deluge



- volume
- velocity
- variety
- veracity
- value

V5 data

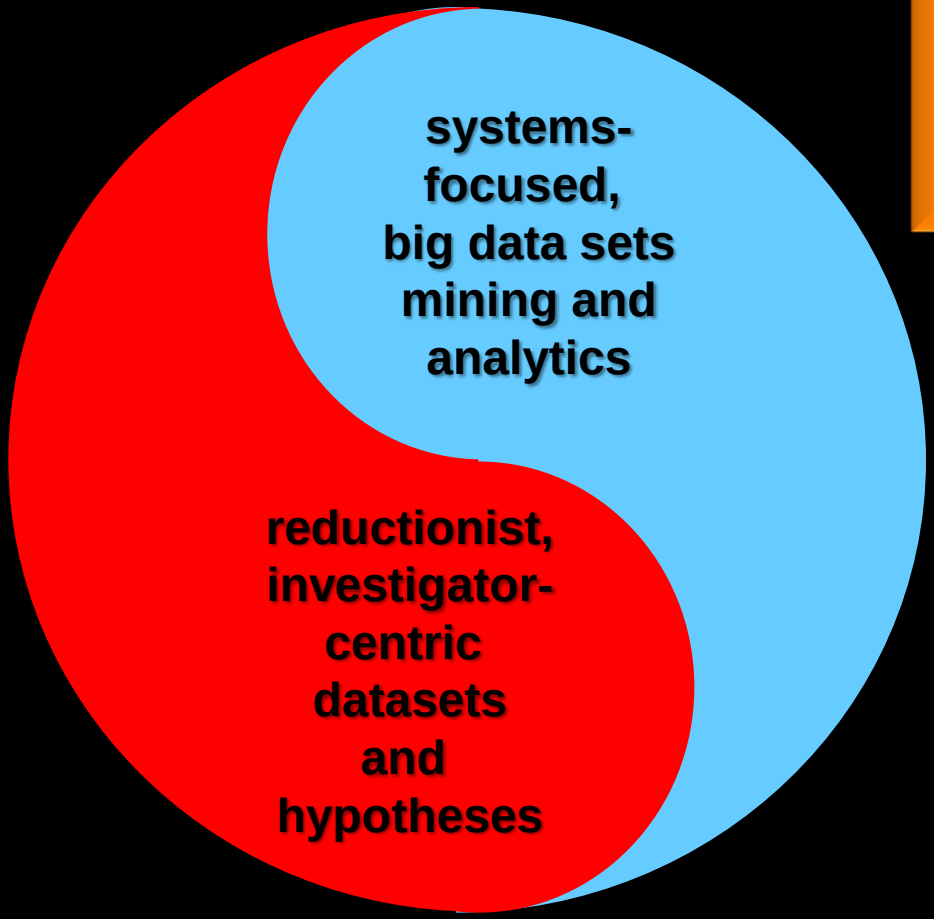
infrastructure

integration

intelligence at ingestion

education/ training of HCPs

Cross-Domain Convergence, Complexity and Increasing Dependency on Data-Intensive Methods and New Knowledge Networks

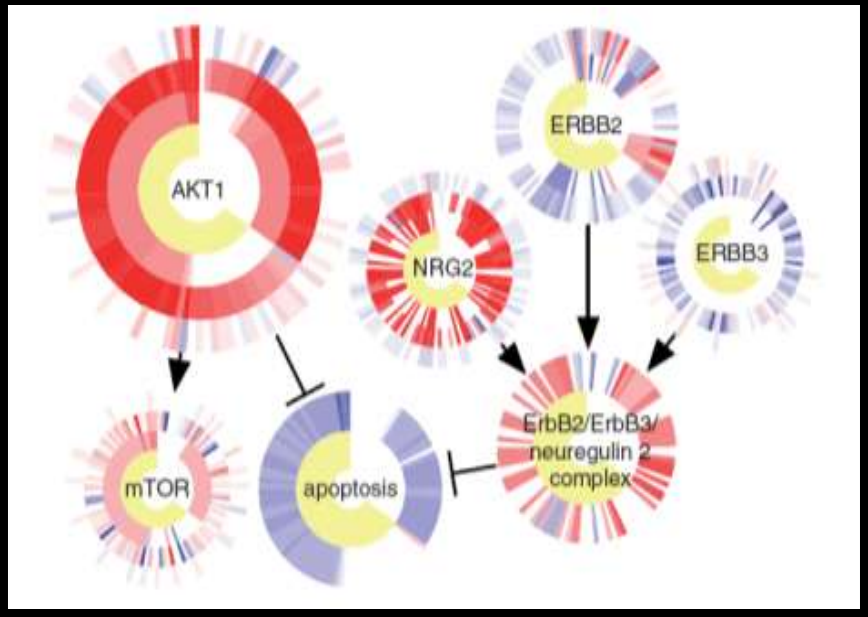


unbiased datasets and pattern mining

hypothesis driven

Assimilation of Concepts of Molecular Medicine into Routine Practice and Health Records

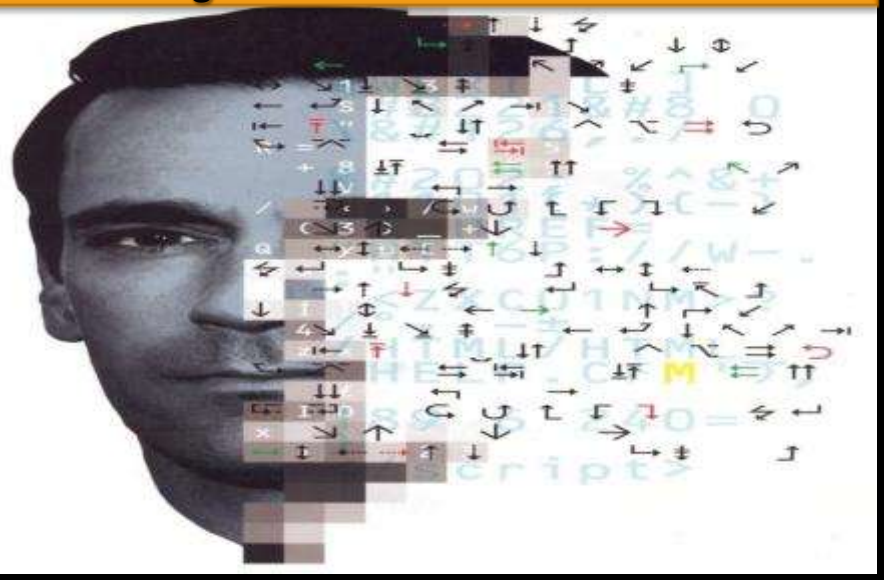
ASCO CANCER·LINQ™
Learning Intelligence Network for Quality

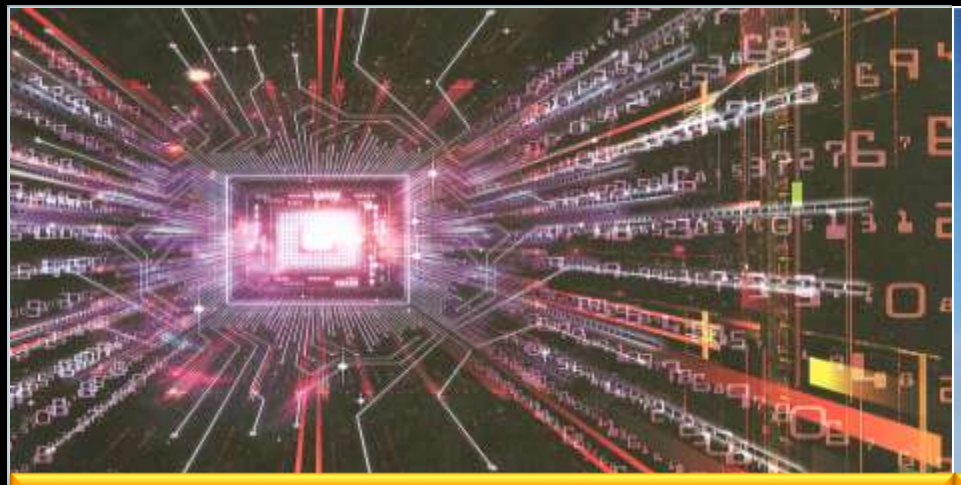


Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

Data Deluge

Cognitive Bandwidth Limits

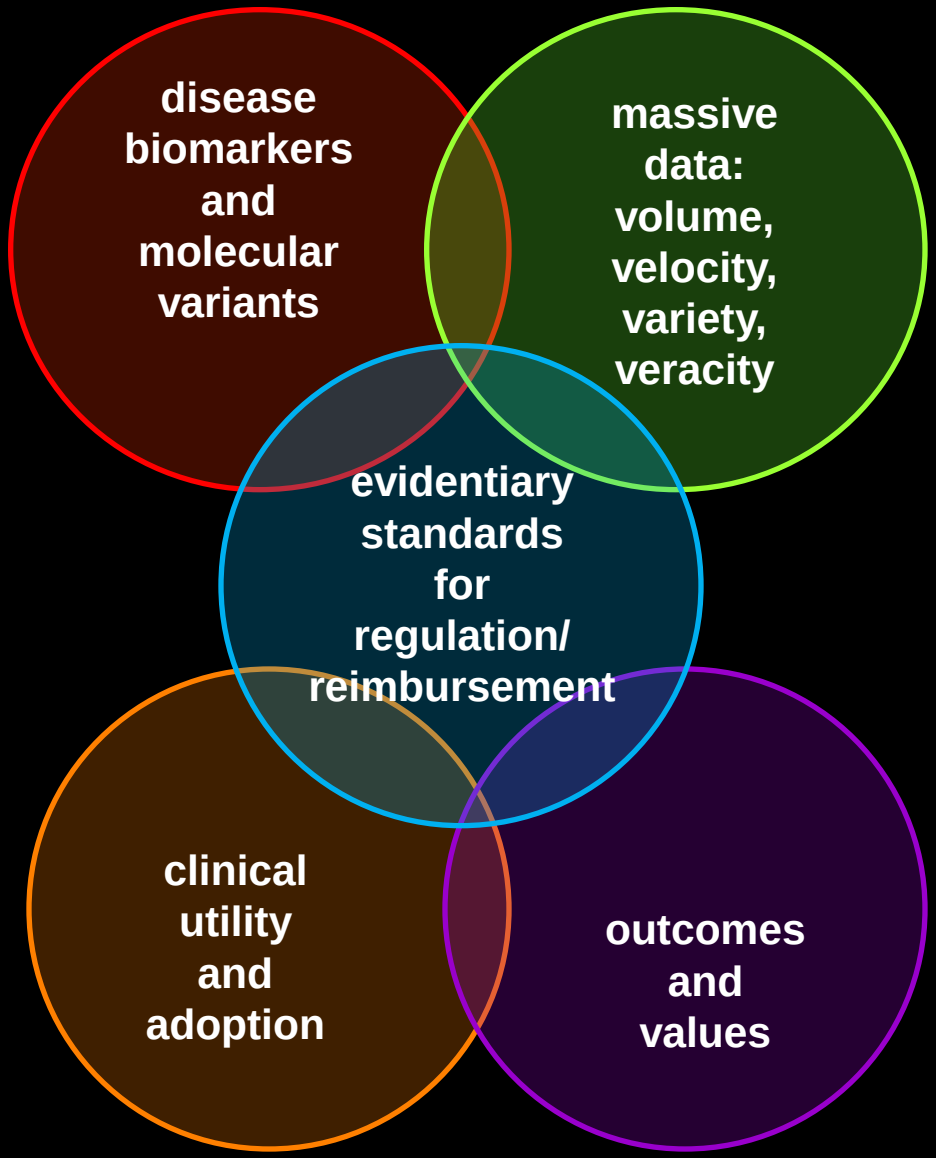




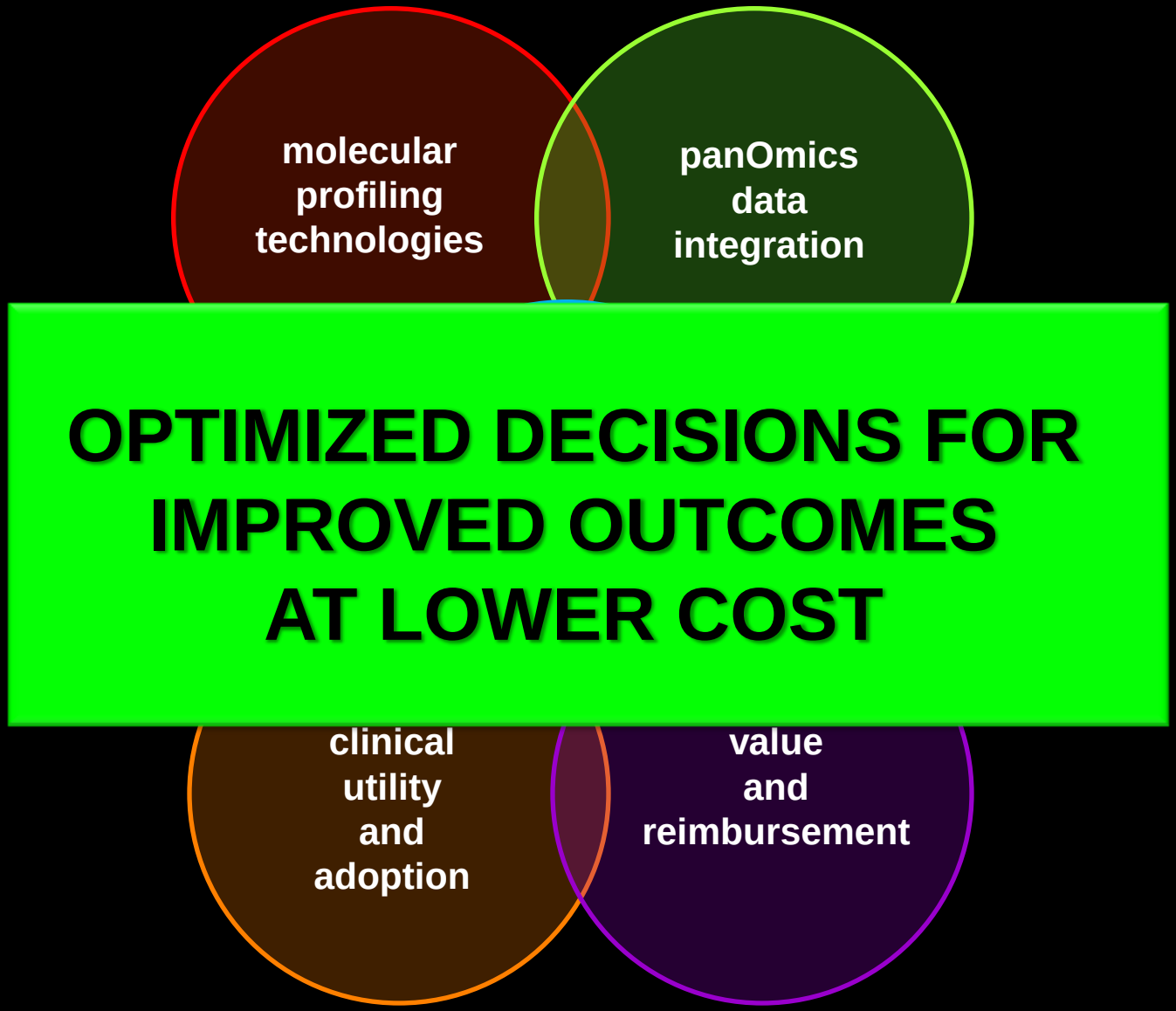
Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

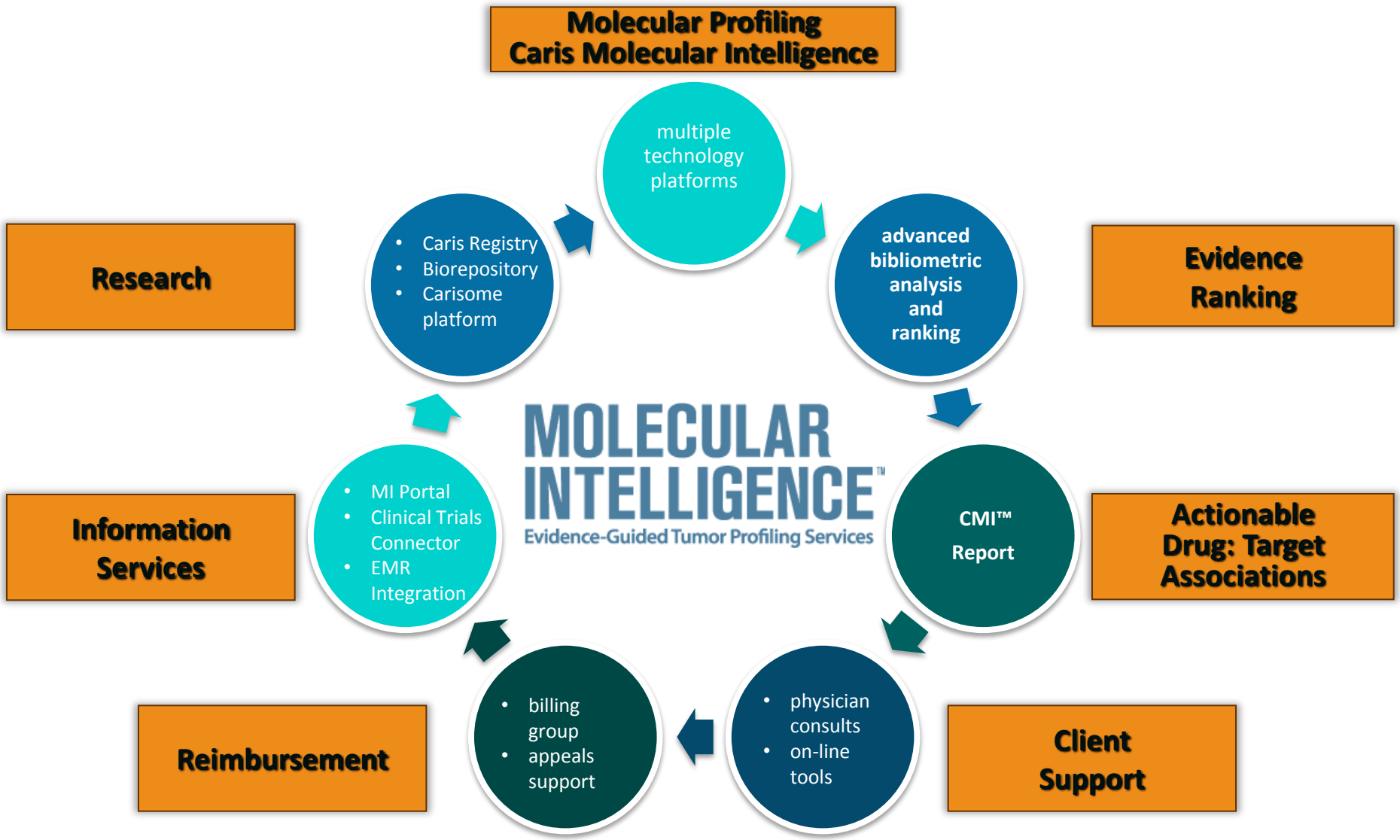
Analytical and Clinical Validation of Molecular Determinants of Disease (Subtypes) and Treatment Options



Identification and Validation Biomarkers: A Complex, Multi-Dimensional Challenge



The Caris Approach to Precision Oncology and Clinical Oncology Information Services



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