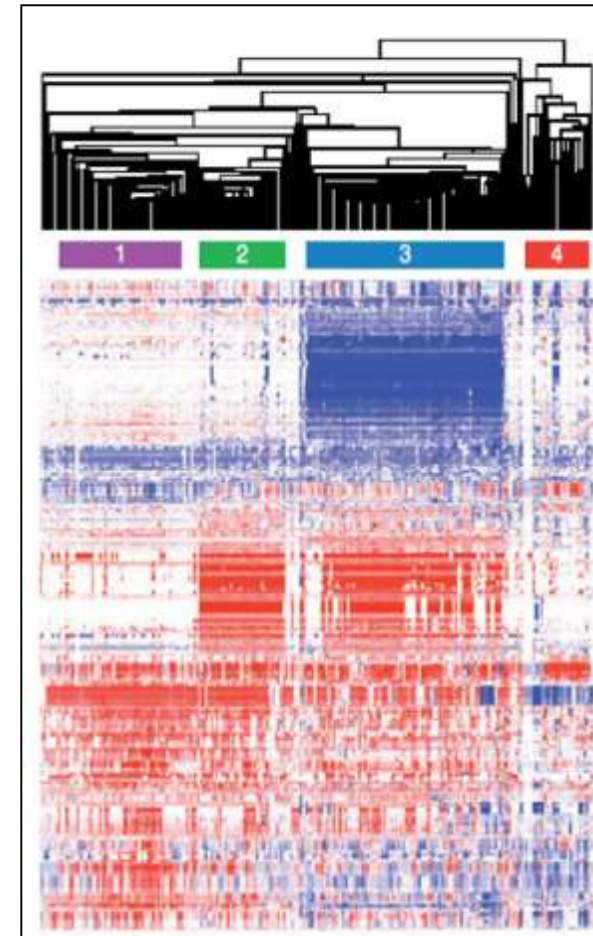
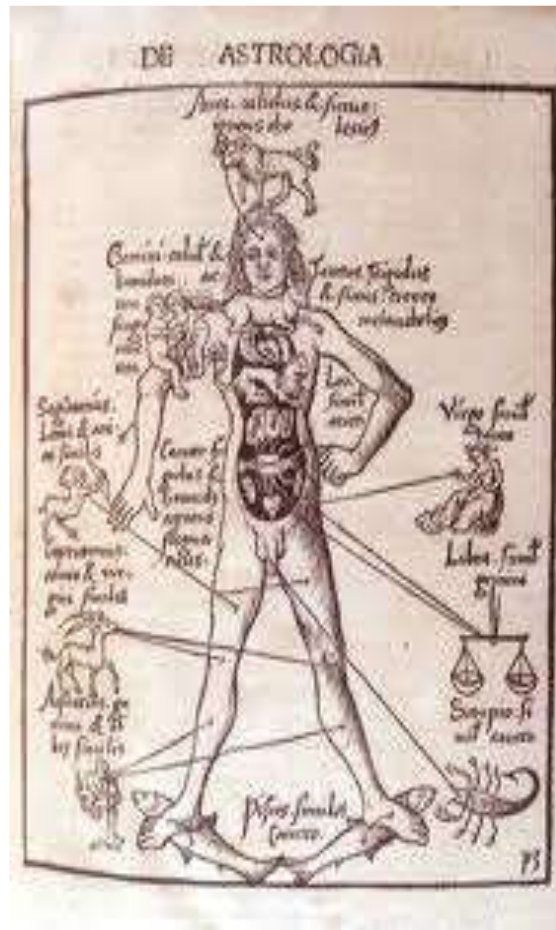


The Evolution of Precision Oncology:

**George Poste, D.V.M., Ph.D, F.R.C.Path, F.R.S.
Chief Scientist, Complex Adaptive Systems Initiative
and Del E. Webb Chair in Health Innovation
Arizona State University
(george.poste@asu.edu; Tel. 480-727-8662)
www.casi.asu.edu**

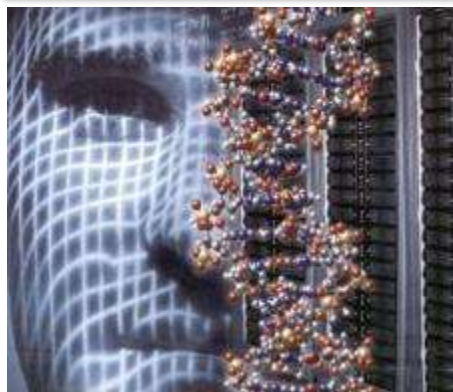
**Keynote Presentation:
2nd Annual West Cancer Center Oncology Symposium
Memphis, Tennessee. 18 November 2016**

Medical Progress: From Superstitions to Symptoms to Signatures

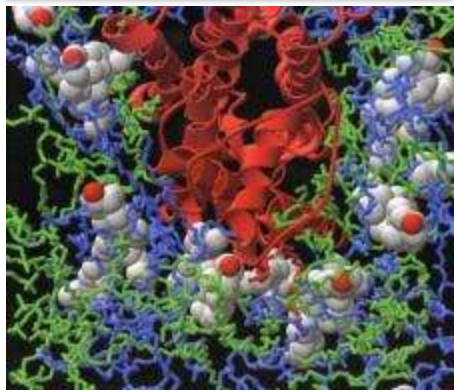


Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

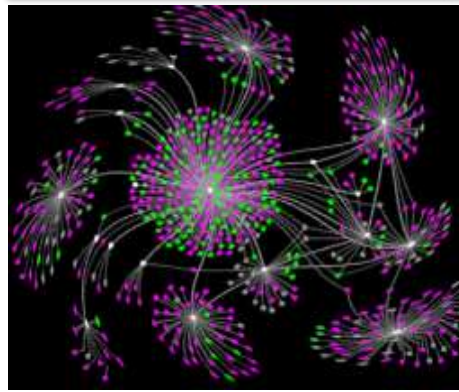
(Epi)Genomics



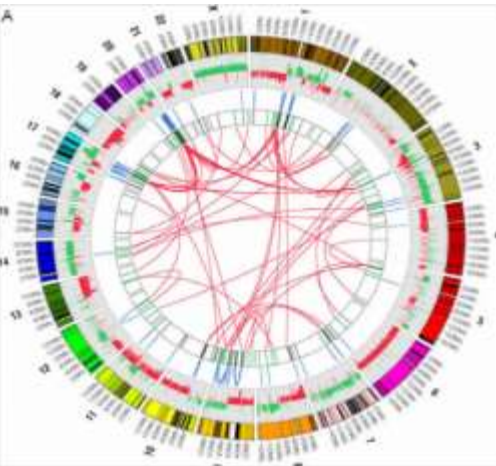
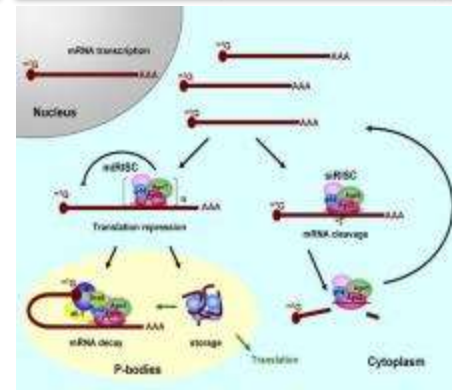
Proteomics



Molecular Pathways and Networks



Network Regulatory Mechanisms



**ID of Causal Relationships Between
Molecular Network Perturbations and Disease**



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

BIOMARKER TESTS FOR MOLECULARLY TARGETED THERAPIES

Key to Unlocking Precision Medicine



The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Policy Issues in the Development and Adoption of Biomarkers for Molecularly Targeted Cancer Therapies

WORKSHOP SUMMARY



NATIONAL CANCER POLICY FORUM

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Technology Assessment



AHRQ
Technology
Assessment Program

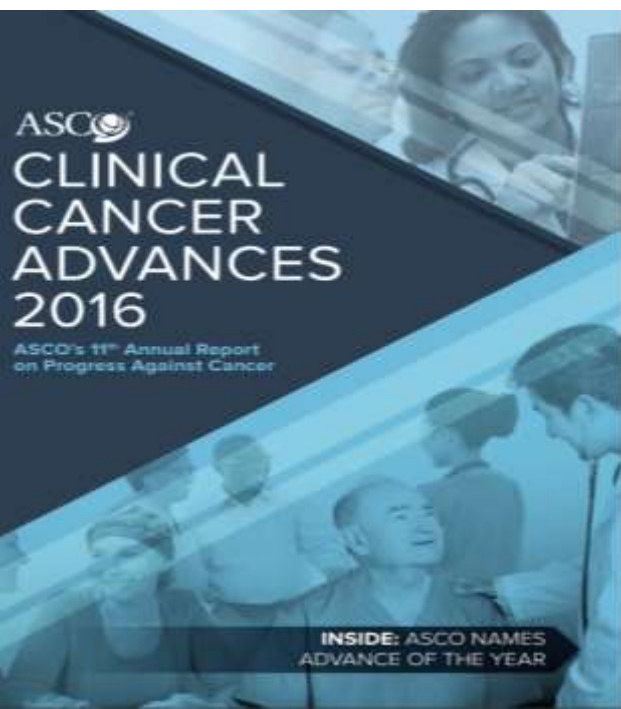
Technology Assessment of Molecular Pathology Testing for the Estimation of Prognosis for Common Cancers

Prepared for:
Agency for Healthcare
Research and Quality
540 Gaither Road
Rockville, Maryland 20850

Final
May 29, 2014

ASCO CLINICAL CANCER ADVANCES 2016

ASCO's 11th Annual Report
on Progress Against Cancer

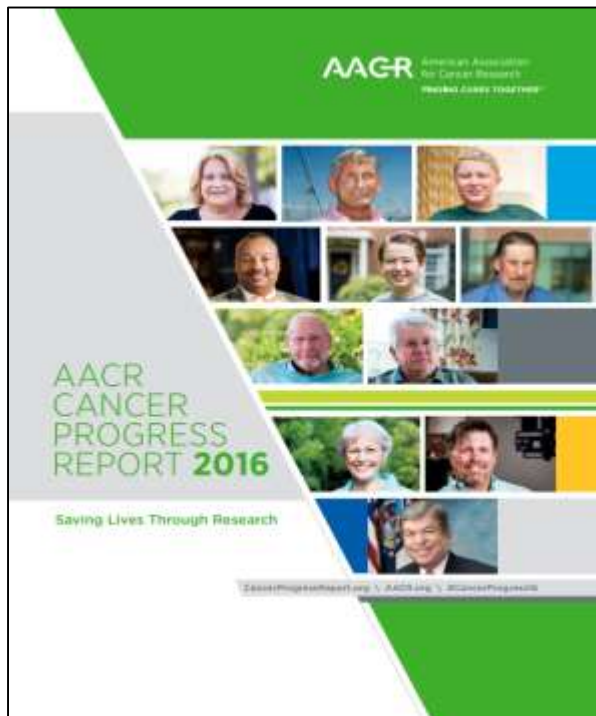


INSIDE: ASCO NAMES
ADVANCE OF THE YEAR

AAGR American Association
for Cancer Research
"WEAVING LIVES TOGETHER"

AACR CANCER PROGRESS REPORT 2016

Saving Lives Through Research



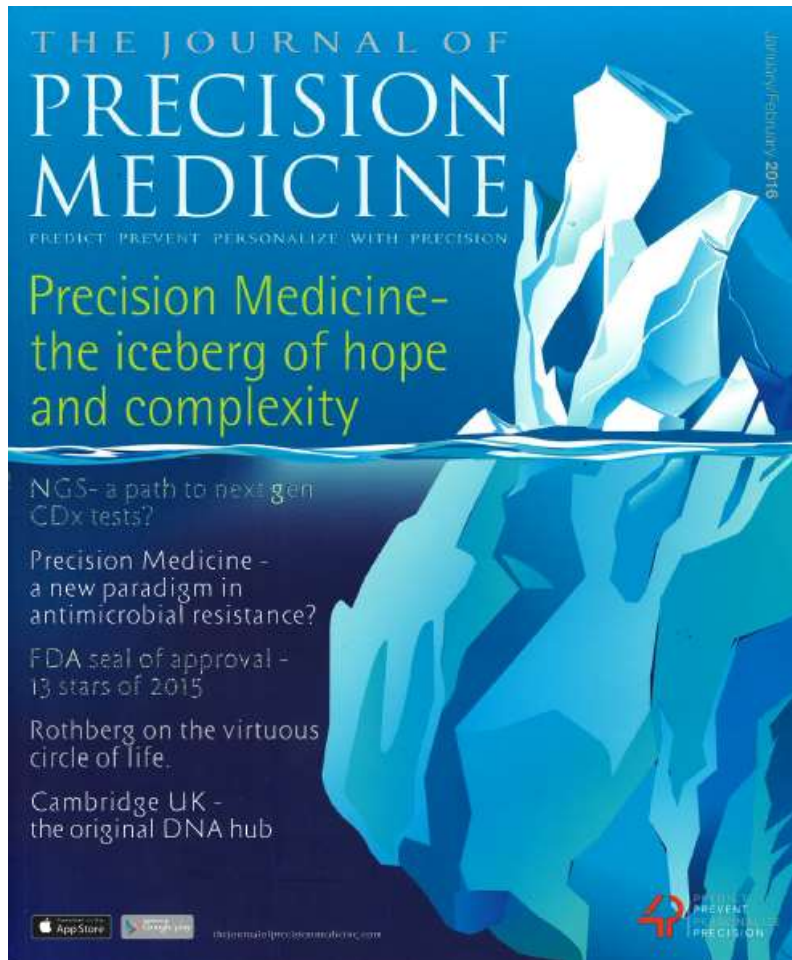
aacr.org/progressreport | aacr.org | aacr.org/progressreport

CANCER MOONSHOT BLUE RIBBON PANEL REPORT 2016 DRAFT



Presented exclusively by AACR on September 7, 2016. www.aacr.org/cancer-moonshot-blue-ribbon-panel

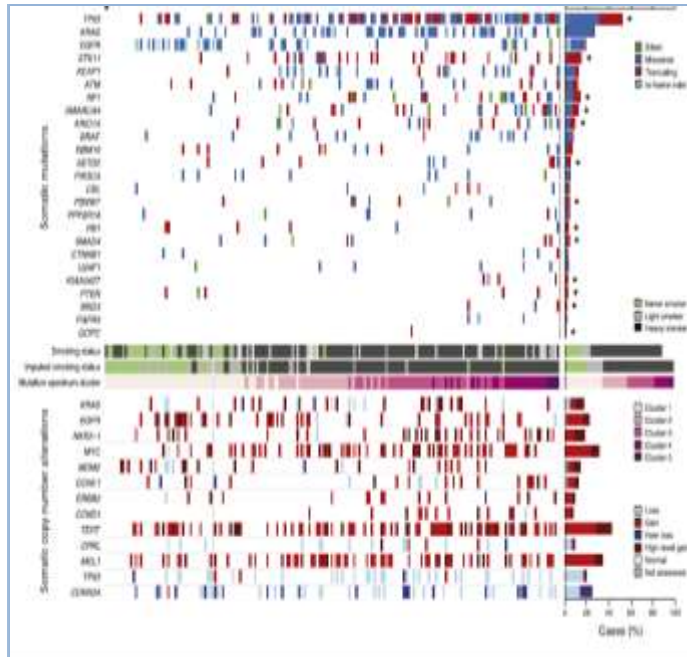
Precision Oncology: Not If, But...



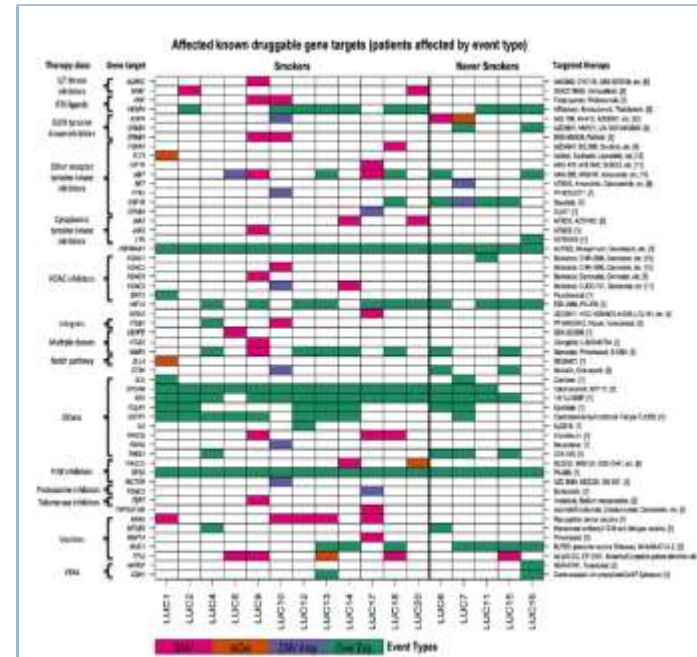
- when?
- what?
- how?
- value?

The Extravagant Landscape of Molecular Signaling Network Alterations in NSCLC

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 and variable expression of Rx targets**
- **disturbing implications for therapeutic ‘cure’ and development of new Rx**

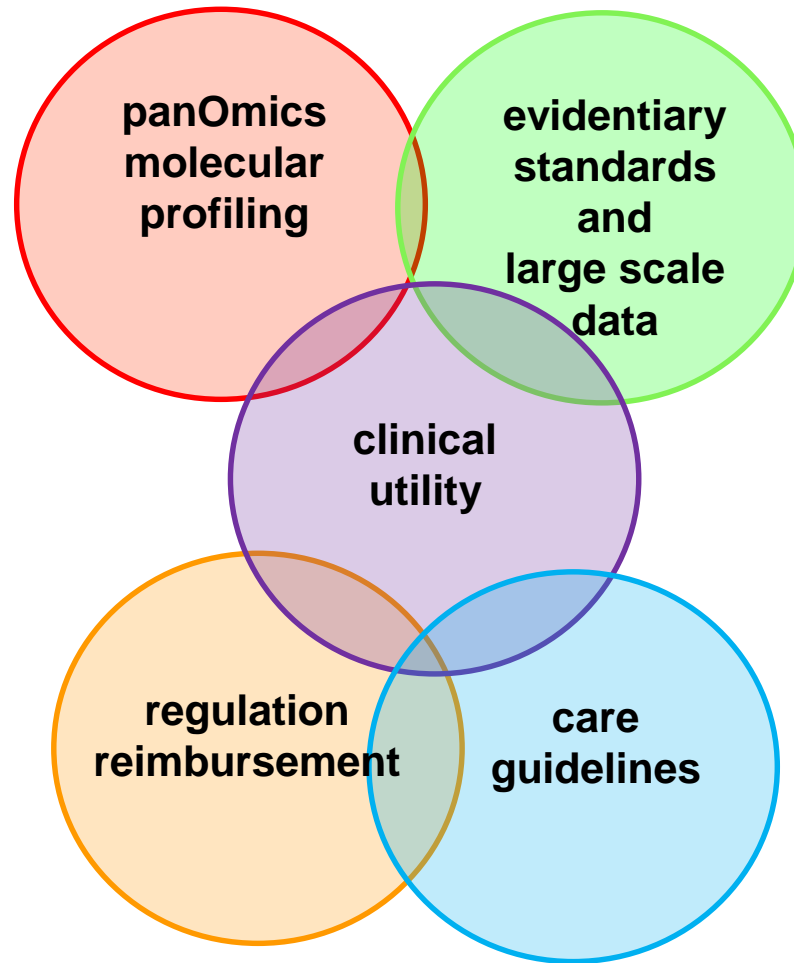
Precision Oncology

- multi-platform (“panOmics”) molecular profiling and a new taxonomy of disease classification (subtypes)
- mapping the perturbations in molecular signaling networks in disease subtypes and individual patient variation
- intellectual foundation for improved diagnostic accuracy and rational therapy selection to improve clinical outcomes and cost-of-care

Most Common Gene Mutations and CNV Alterations in Molecular Subtypes of Primary Breast Cancer

	Luminal A	Luminal B	HER2-positive	Triple negative
Gene mutations	<i>PIK3CA</i> , <i>GATA3</i> , <i>MAP3K1</i> , <i>TP53</i> , <i>CDH1</i> , <i>MLL3</i> , <i>MAP2K4</i> , <i>AKT1</i> , <i>FOXA1</i> , <i>CDH1</i> , and <i>RUNX1</i>	<i>PIK3CA</i> , <i>GATA3</i> , and <i>TP53</i>	<i>PIK3CA</i> , and <i>TP53</i>	<i>TP53</i> and <i>PIK3CA</i>
Gene gains, losses and amplifications	—	loss of <i>ATM</i> ; amplification of <i>CCND1</i> , <i>CDK4</i> , <i>CDK6</i> , and <i>MDM2</i>	Amplification of multiple genes based on the <i>HER2</i> amplicon size	loss of <i>INPP4B</i> , <i>PTEN</i> , and <i>RB1</i> ; amplification of <i>BRAF</i> , <i>CCNE1</i> , <i>EGFR</i> , and <i>KRAS</i>
Copy number alterations				
Gains	1q and 16p	1q, 8q, 17q, and 20q	1p36.33-p36.32, 4q13.3, 5p15-p12, 8q23.3-q24.21, 11q13.5-q14.1, 14q11.1-q11.2, 17q23-q24, and 19q12	1q12-q41, 3q, 6p12-p25, 7p12, 7q22-q36, 8q23.2-24.3, 10p12-p15, 12p, 17q25, and 21q22
Losses	16q	1p, 3q, 8p, 13q, 16q, 17p, and 22q	1p39, 1p36, 1p35, 1p32, 4p16.3, 7q21-q22, 7p22.3, 7q34, 7q36.1-q36.3, 8p23.3-p23.2, 8p11.23-p11.22, 9p21.3, 9q34.3, 10q26.3, 11q13.5, 11p15.5, 14q32.33, 15q11.2, 16p13.3, and 19p13.3	3p, 3q12, 4p15-p32, 4q31-q35, 5q11-q31, 8p, 12q14-23, 13q, 14q22-q23, and 15q
Amplifications	8p11-12, 8q, 11q13-14, 12q13-14, 17q11-12, 17q21-24, and 20q13	7p22, 8p11-12, 8q11-24, 11q13-14, 17q23, 19q13, and 20q13	4q13.3, 8q23.3-q24.21, 11q13.5-q14.1, 14q11.1-q11.2, 17q12-q21, and 19q12	—

Precision Oncology: The Need for Multi-Dimensional, Systems-Based Integration Across the Research to Clinical Care Continuum



The Overly-Simplistic, Reductionist Focus on Genome Sequencing



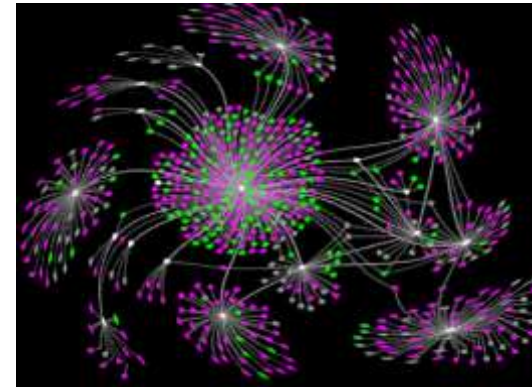
The Challenge of Genotype-Phenotype Predictions

Junk No More: Pervasive Transcription

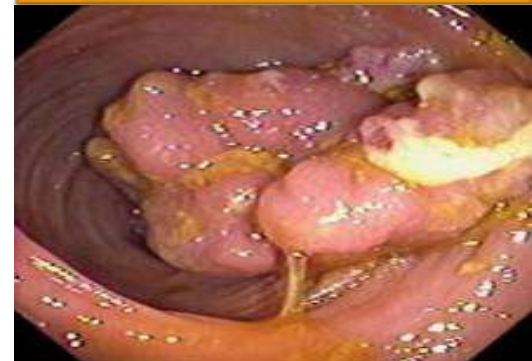
- alternate transcription /translation/ (co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing
- miRNAs/ ceRNAs/ circRNAs

recognition of genome organizational and regulatory complexity

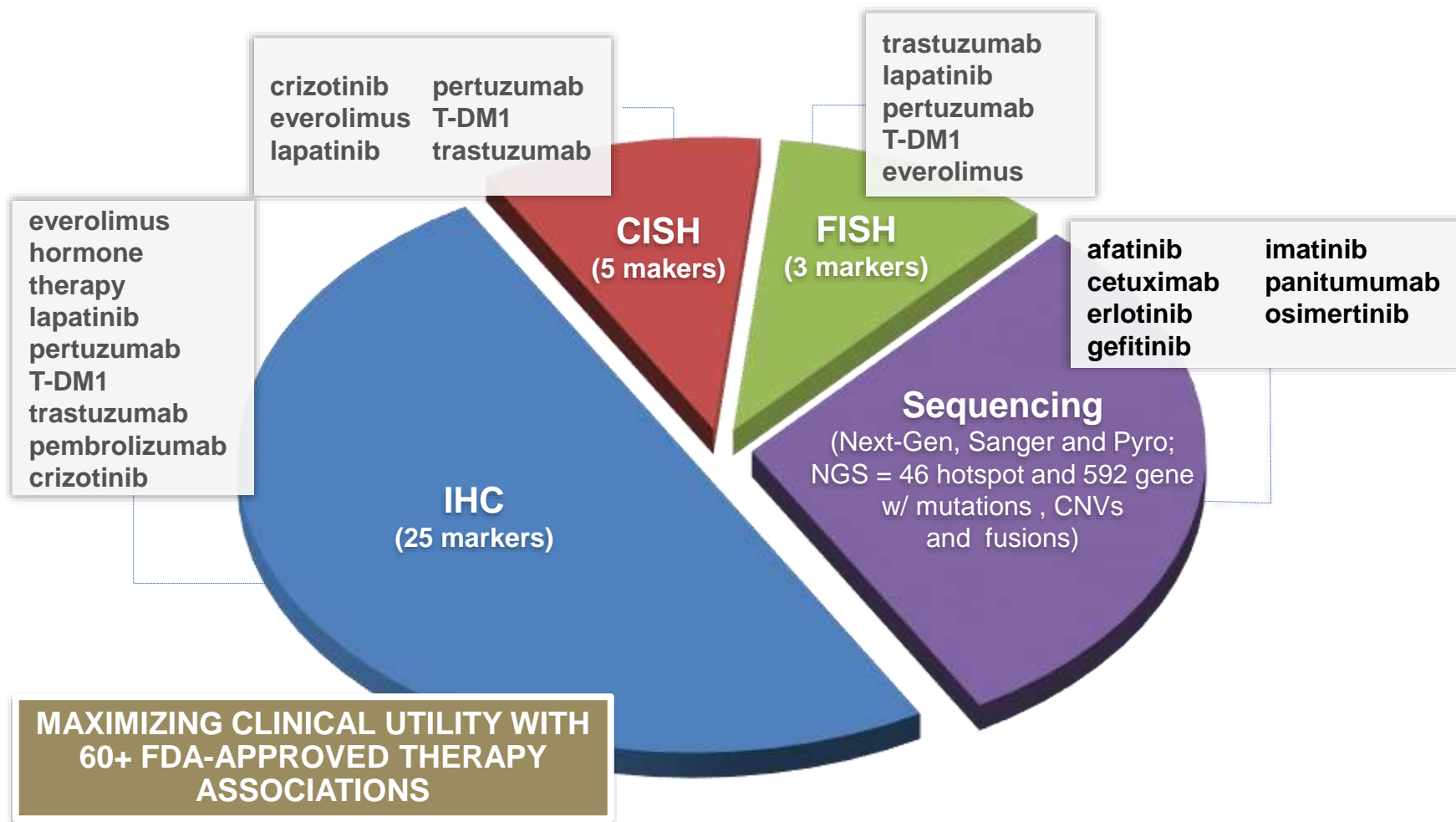
Molecular Signaling Networks



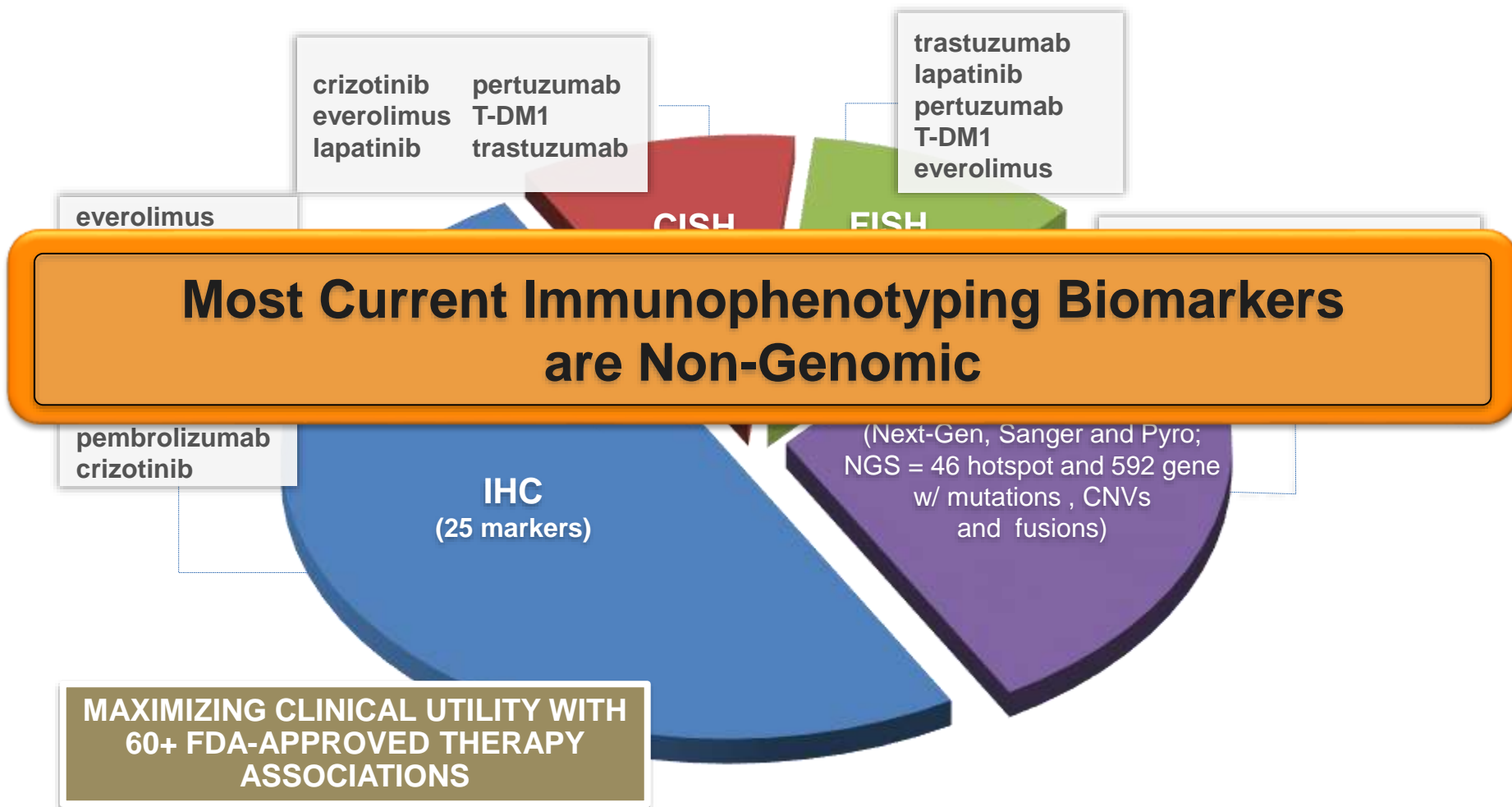
Perturbed Signaling Networks and Disease



Molecular Profiling for Comprehensive Identification of Current Target: Drug Associations in NCCN Guidelines Requires a Technology Agnostic Approach



Molecular Profiling for Comprehensive Identification of Current Target: Drug Associations Requires a Technology Agnostic Approach



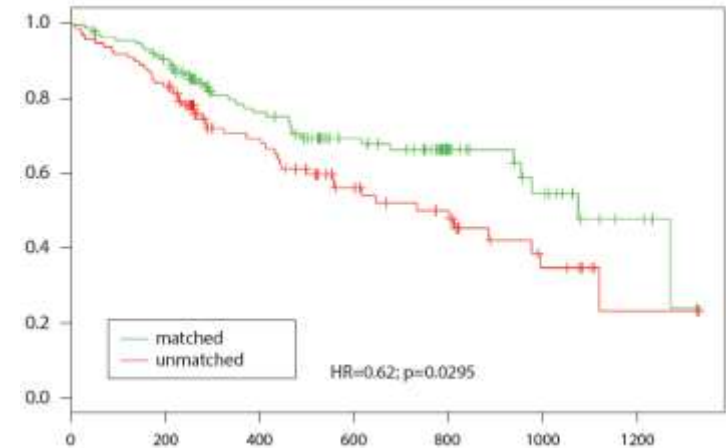
Demonstration of the Clinical Utility of Molecular Profiling in Precision Oncology

- assessment of treatment selection on clinical outcomes
- comparison of “matched” versus “unmatched” Rx regimens
 - Rx selection based on molecular profile (“matched”)
 - Rx selection by physician with inclusion of one or more Rx not recommended by the molecular profile (unmatched)

Molecular Profiling and Concordant (Matched) Rx Selection Improves Overall Survival for Ovarian Cancer Patients

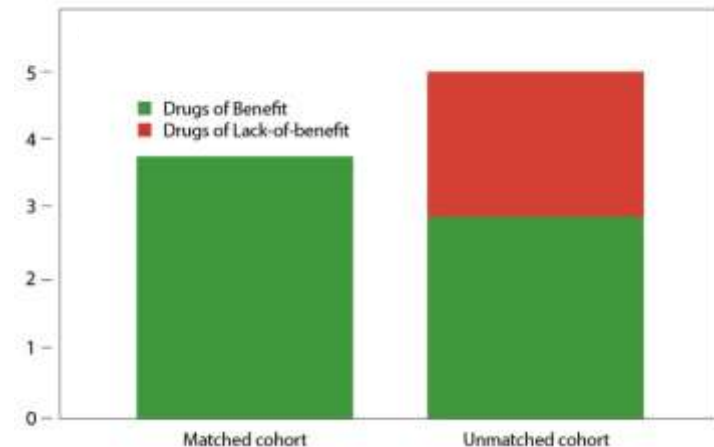


Impact of molecular profiling on overall survival of patients with advanced ovarian cancer, Thomas J. Herzog, et al. Oncotarget [Online], Volume 5 (1 March 2016).



KEY FINDINGS:

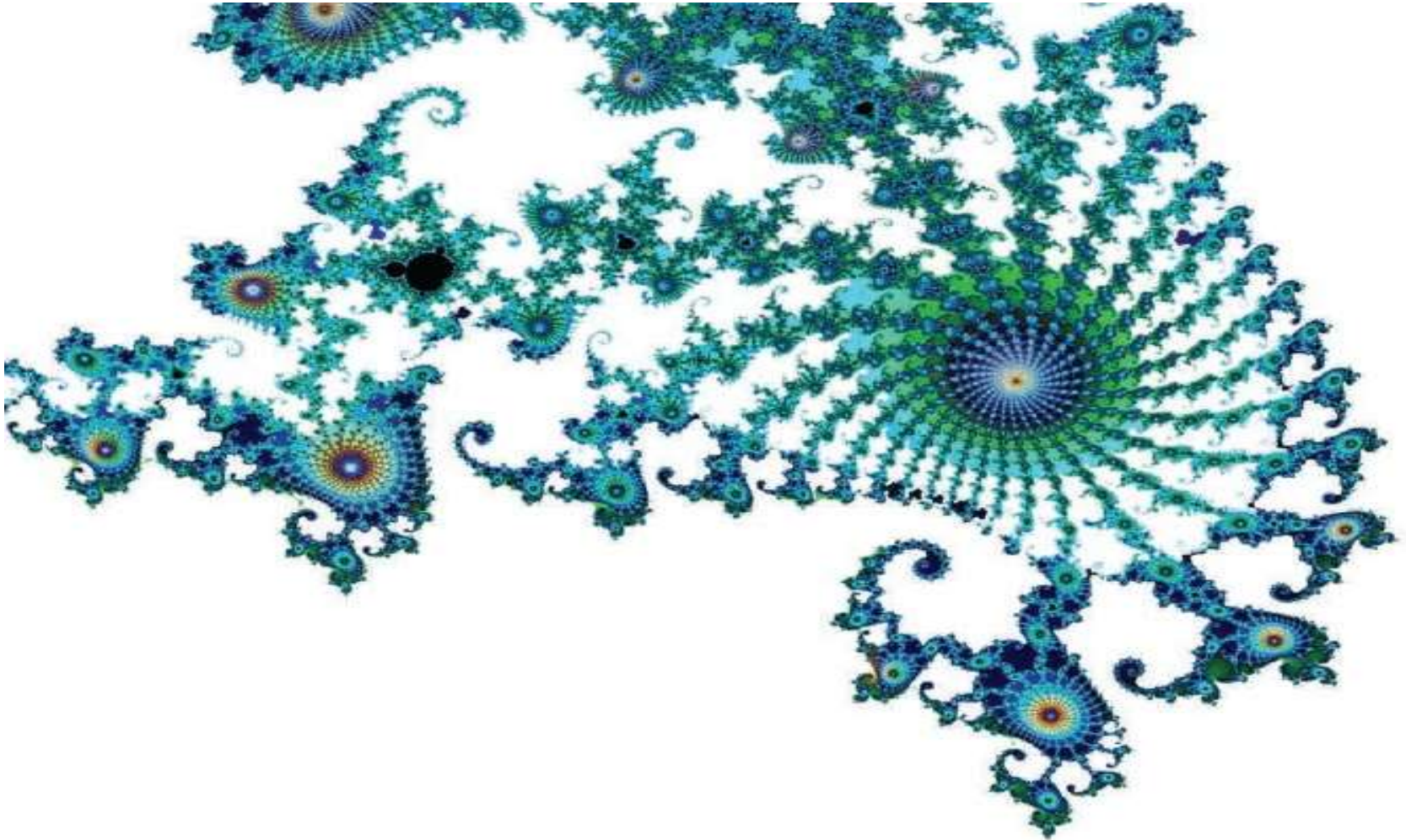
- Patients in the Matched cohort (n=121) had a **significantly higher median OS by 9 months** compared to those in the Unmatched cohort (n=103) (median OS 36 vs. 27 months, HR=0.62, $p < 0.03$).
- Matched cohort received **1.2 fewer lines of therapy** than the Unmatched cohort highlighting the benefit of avoiding potentially harmful therapies (median of 3.88 lines of therapy for Matched vs. 5.02 lines of therapy for Unmatched).



Precision Medicine Clinical Trials to Evaluate 'Match' of Rx Selection With Molecular Profiling on Clinical Outcomes

- NCI-MATCH and Pediatric-MATCH (Molecular Analysis for Therapy Choice)
- ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial)
- Lung-Map (Lung Cancer Master Protocol)
- NCI-IMPACT (Molecular Profiling-Based Assessment of Cancer Therapy)
- ASCO-TAPUR (Targeted Agent and Profiling Utilization Registry)
- NCI-Exceptional Responders Study
- Leukemia and Lymphoma Society: Beat AML Master Trial
- GBM AGILE (Adaptive Global Innovative Learning Environment)

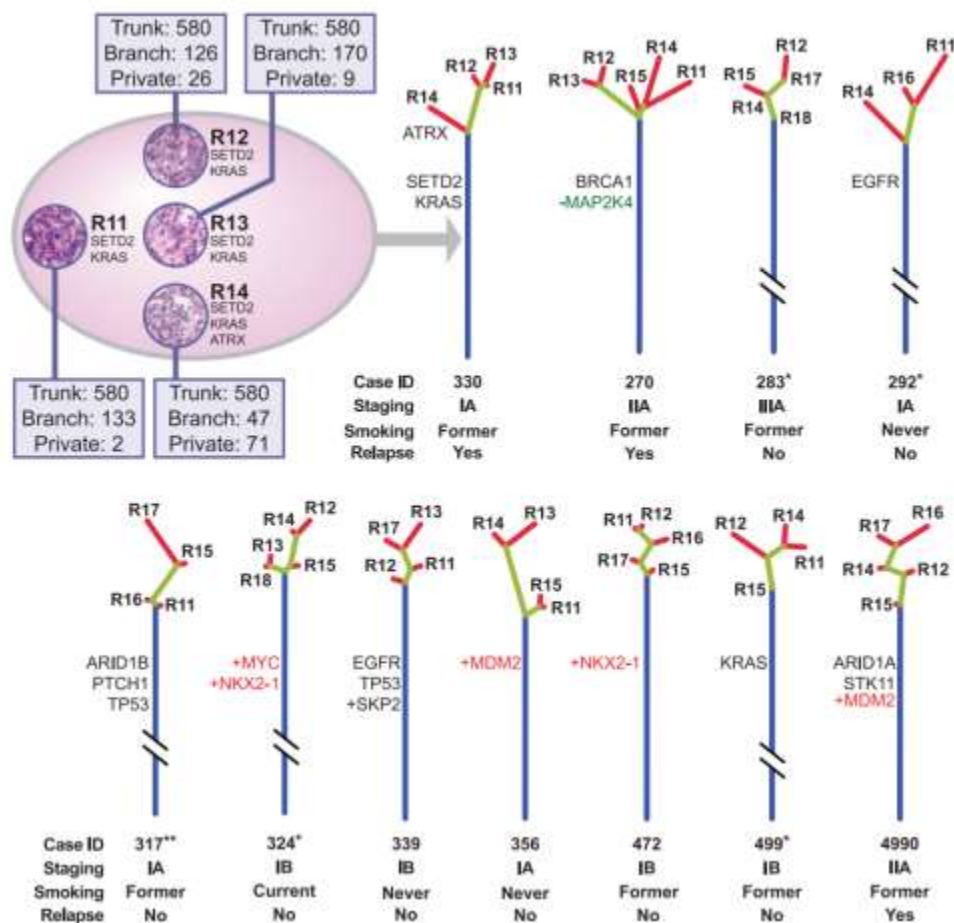
Cancer as a Complex Adaptive System: The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression and Treatment



Precision Oncology

- understanding the evolutionary dynamics of clonal diversification (heterogeneity)
- mapping the molecular pathways underlying the emergence of treatment-resistant (sub)clones
- design of new therapeutic strategies to circumvent (sub)clonal heterogeneity and treatment-resistant phenotypes

Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches



Longitudinal Tumor Profiling and Adjustment of Treatment Selection to Reflect Dynamic Changes in (Sub)Clonal Composition

- initial diagnosis ('static snapshot')
- longitudinal profiling during treatment for earlier detection of emergence of drug-resistant clones
- more agile shifts in Rx regiment to reflect changing clonal dynamics driven by Rx selection pressure(s)

Detection of Tumor-Associated Biomarkers in Blood: 'The Liquid Biopsy'

- cell-free tumor nucleic acids
 - DNA, miRNAs
- circulating tumor cells(CTC)
- exosomes

Liquid Biopsy (LB) Profiling in Monitoring of Disease Progression and Predictive Treatment Selection

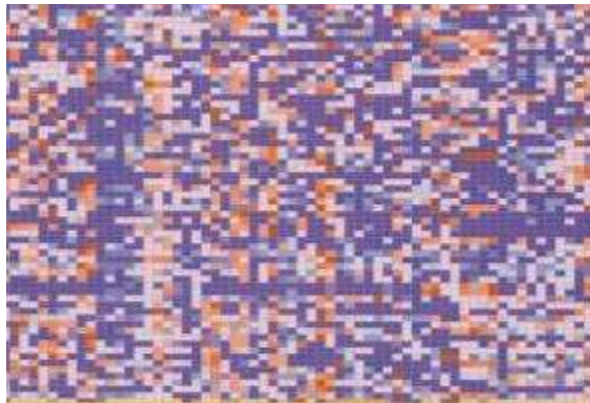
- minimal invasiveness
 - cost, clinical-patient convenience
- analytical standardization
- sensitivity and detection thresholds
- reproducibility in larger N cohorts
- concordance between LB and tissue biopsy profiles?
 - intra- and inter-lesional heterogeneity
- relationship of LB positivity to tumor burden
- variation in systemic release of CTC/ctDNA from metastases in different organs?

The Urgent Need to Improve the Effectiveness of Current Therapy and the Design of New Treatment Strategies

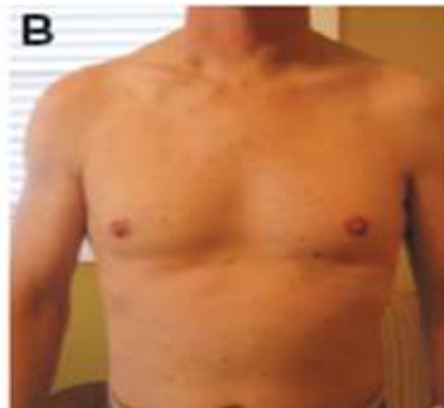
The Clinical and Economic Imperative to Reliably Identify Rx Responder (R) and Non-Responder (NR) Patients

Targeted Therapeutics and the Omnipresent Problem of Rx Failure Due to Emergence of Drug Resistance Clone

Molecular Subtyping and RX Targets



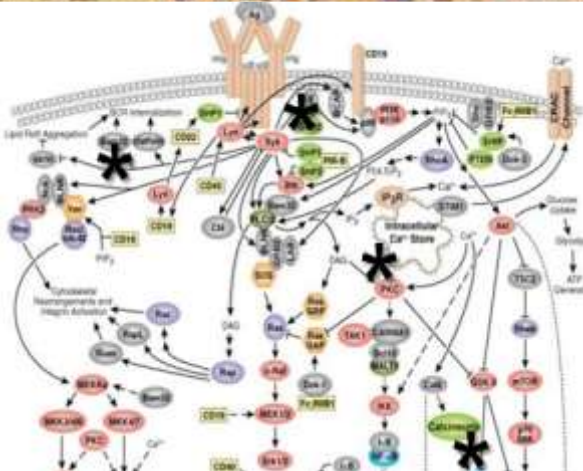
Initial Rx-Response to Targeted Rx



Rx-Resistance via Redundant Molecular Pathways



B = 15 weeks Rx (vemurafenib)
C = 23 weeks Rx and emergence of MEK1^{C121S} mutant¹



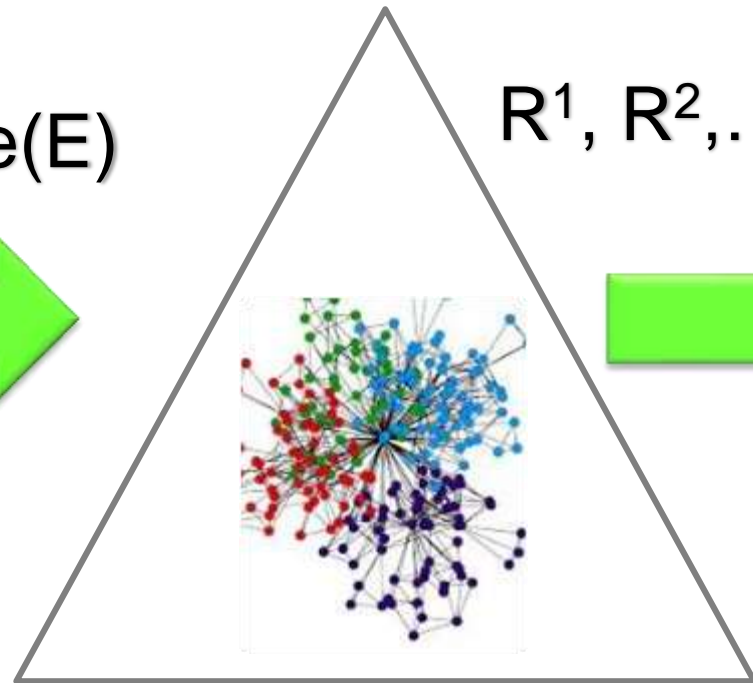
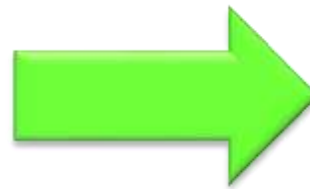
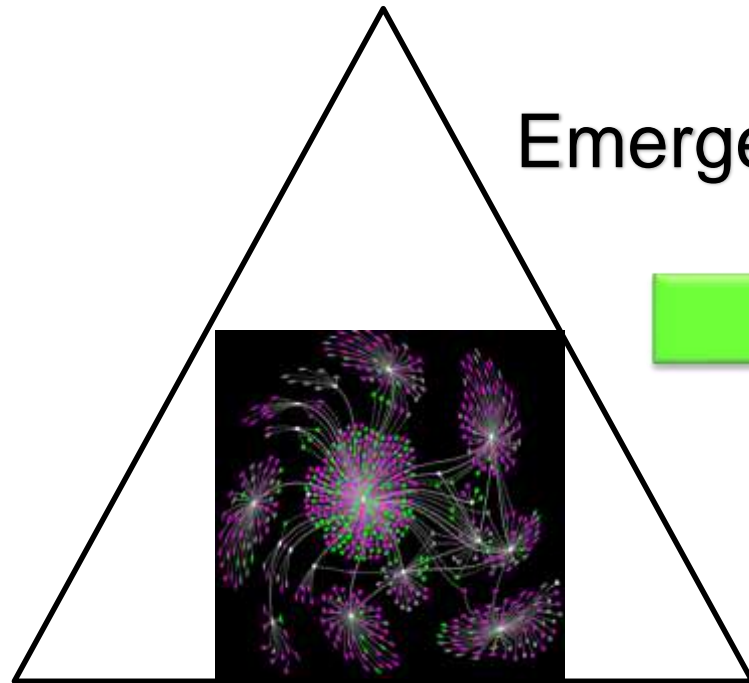
Understanding Emergent State Shifts in Molecular Signaling Networks and Identification of Triggers of Rx- Resistance (R)

dynamic molecular signaling
network topologies

new network topologies
to bypass Rx-vulnerable pathways

Emergence(E)

$R^1, R^2, \dots R^n$

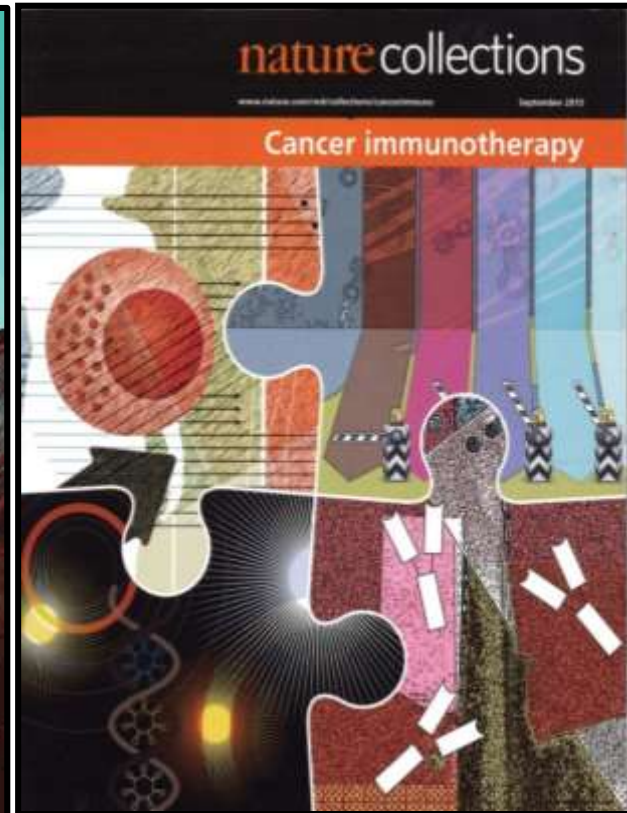


- intrinsic resistance (pre-exist prior to Rx)
- acquired resistance (Rx as selection pressure)

An Ugly But Unavoidable Question

- Is the level of network dysregulation in metastatic disease so extravagant that 'homeostatic reset' for curative therapy by current categories of chemotherapy and/or targeted agents is unlikely?
 - clinical/QOL/cost challenges of ever larger Rx combinations
 - high likelihood of molecular signaling network redundancy and selection of Rx-resistant clones
 - clinical decision points for continued multi-line intervention(s) versus palliative care

The Promise of Immunotherapy



Host Immune-Tumor Interactions

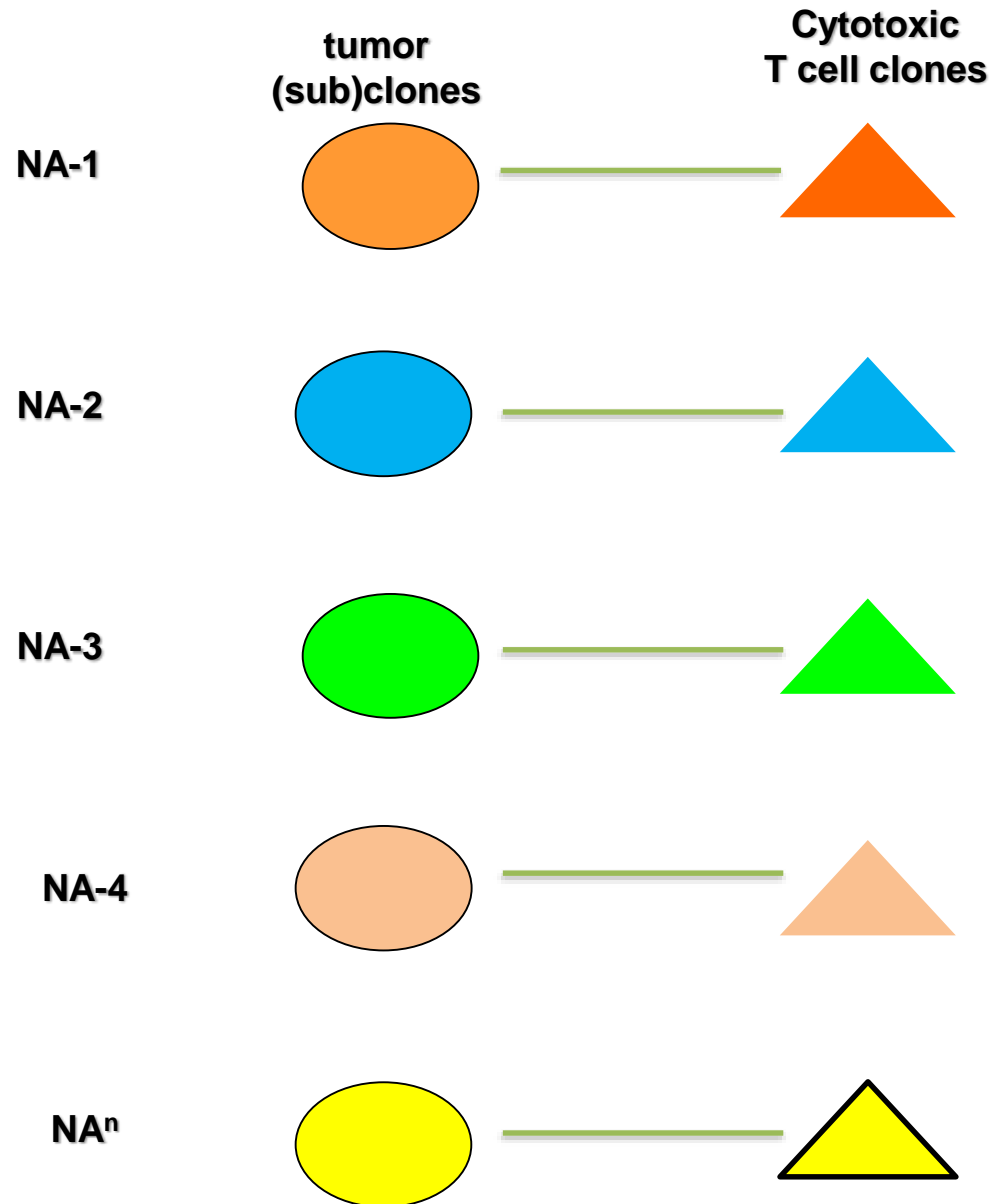
Clone Wars

**Relentless Emergence of New Tumor Cell Clones
During Tumor Progression and Immune Evasion**

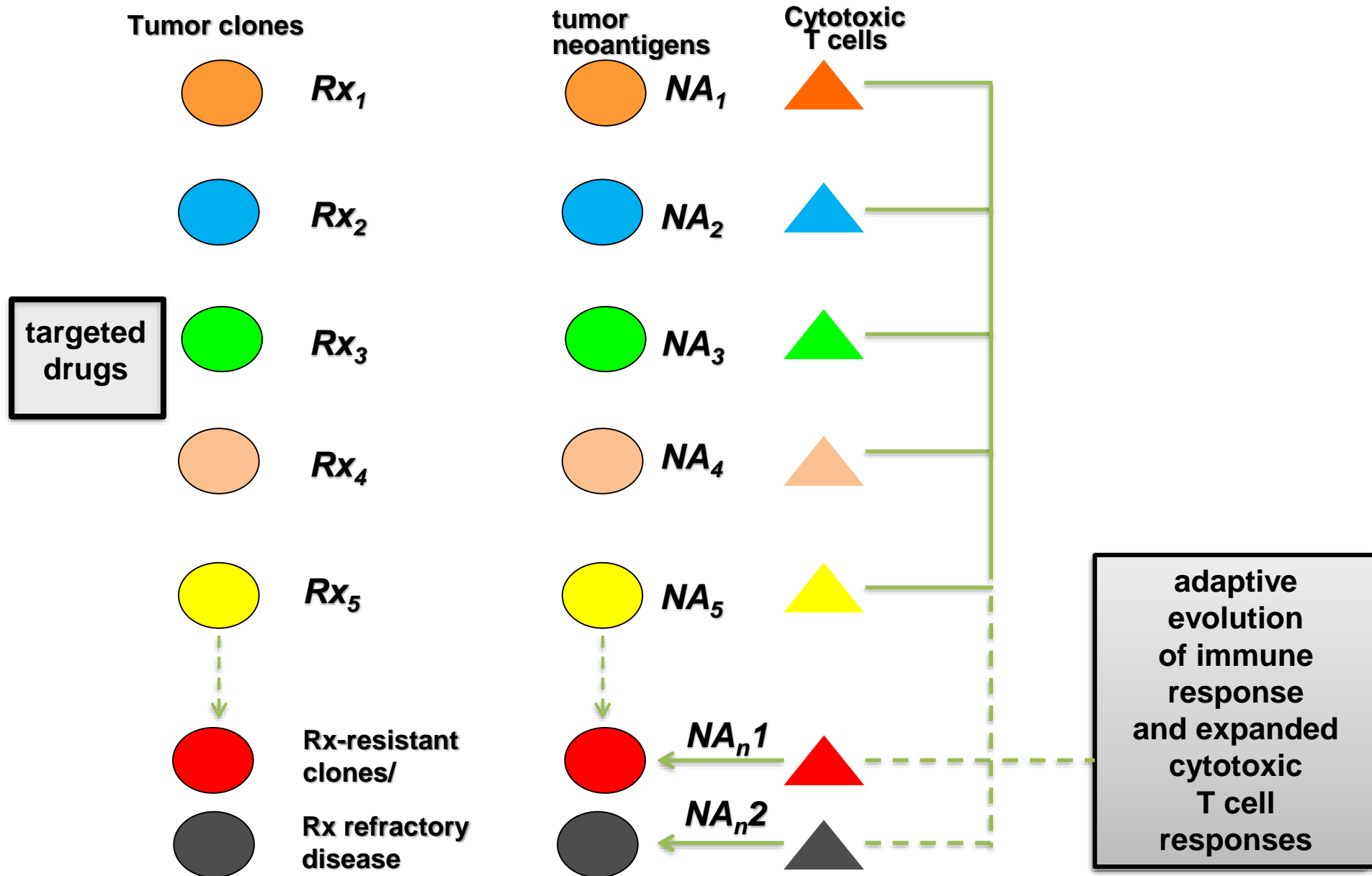
versus

**Activation of Host T Lymphocyte Clones to
Kill (Neo)Antigen-Specific Tumor Clones**

Recognition of Tumor Neoantigens (NA) by Cytotoxic (Killer) T Cells

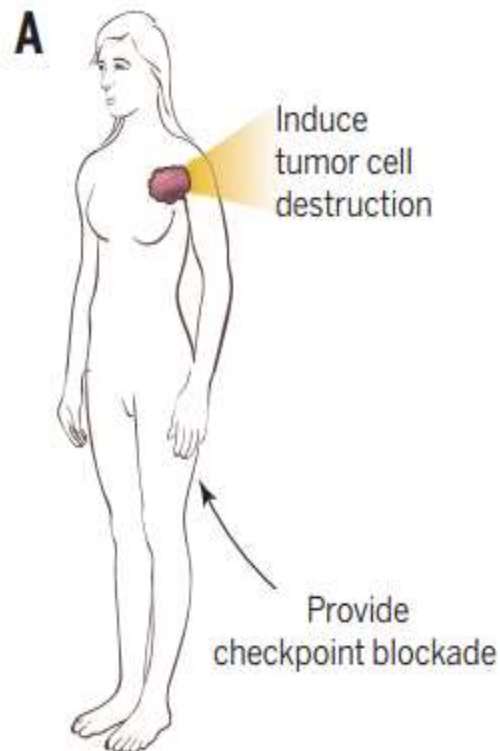


Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance

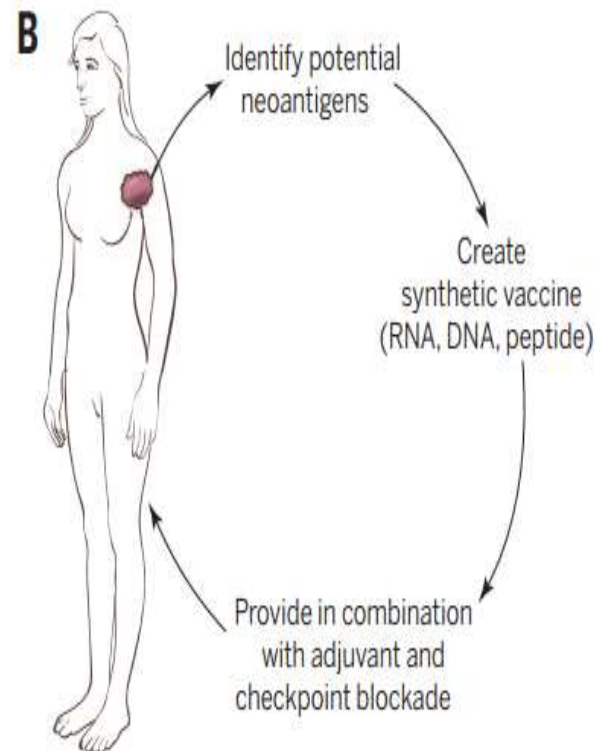


Immunotherapeutic Strategies to Enhance Immune Responses to Patient-Specific Tumor Neoantigens

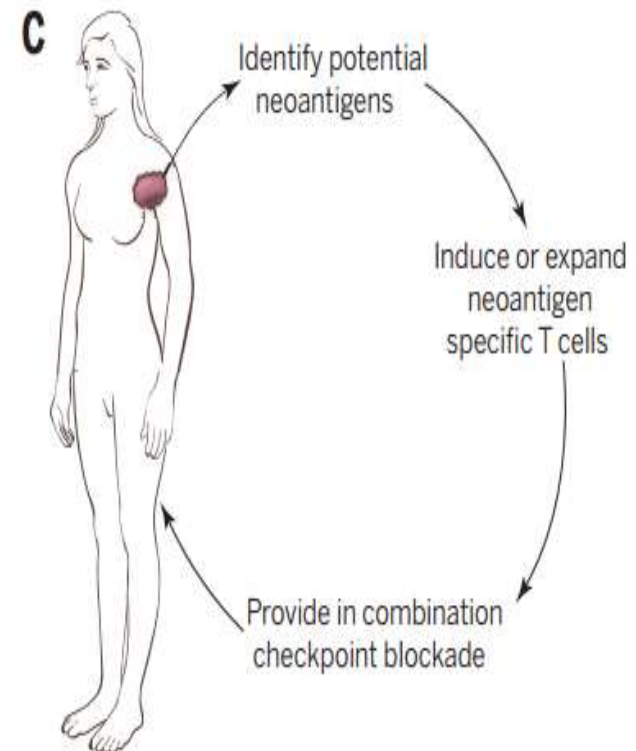
Immune Checkpoint Modulation



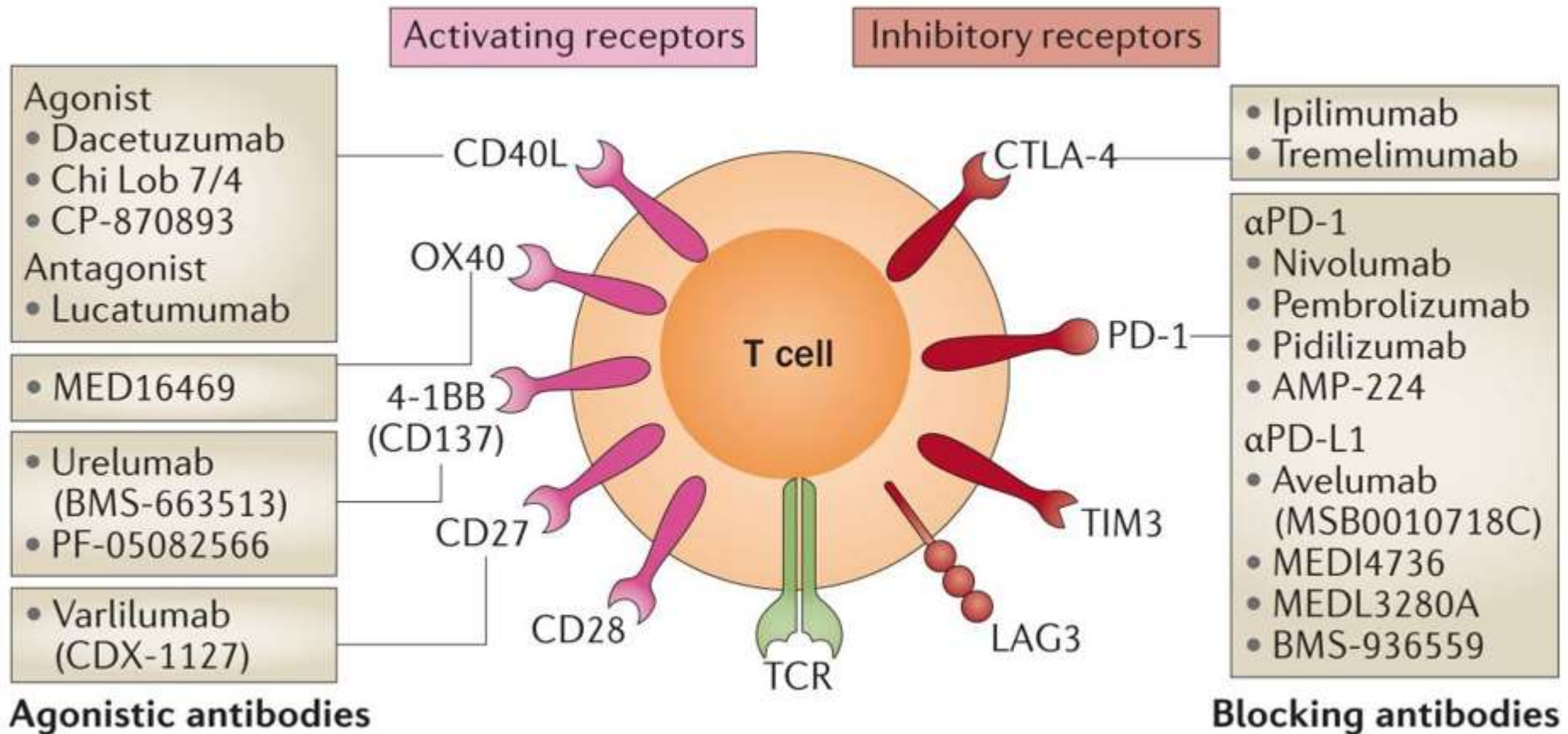
Cancer Neoantigen Vaccines



Adoptive Cell Therapy TILs, TCRs, CARs



Cancer Immunotherapy



FDA Approved Indications for PD-1, PD-L1 Immune Modulators (Nov. 2016)

Malignancy	Nivolumab	Pembrolizumab	Atezolizumab
NSCLC	●	●	● metastatic
melanoma	●	●	
RCC	●		
head and neck	●	●	
Hodgkin's lymphoma	●		
urothelial carcinoma			●

Ongoing Clinical Trials with PD-1, PD-L1 and PD-L2 Modulators (Nov. 2016)

- 803 registered trials
- 20 investigational agents
 - single agents
 - combinations with other immunotherapies, biologics, chemotherapy and vaccines
- need to recruit 166,736 patients



**“I have never seen this before,
where you have so much development activity
in the same class of drugs.**

**Should these resources,
I’m not only talking about financial resources
but also patient resources, be better off spent
into looking at more novel drugs.”**

**Dr. R. Pazdur,
Acting Director, FDA Oncology Center of Excellence
Cited in Cancer Letter 7 October 2016, p.4**

The Evolution of Cancer Immunotherapeutics (I/O)

- likely to become SOC in increasing number of indications
- need for more informed rationale for combination regimens
- new tumor cell markers for acquired immune resistance
- will new panels of immune response biomarkers be needed for each new category of I/O agents?

Why Are Some Cancer Types More Responsive to Immunotherapy?

More Responsive

- melanoma
- NSCLC
- bladder
- renal
- head and neck

Less Responsive

- pancreatic
- colorectal
- ovarian

The Tumor Mutational Landscape and Responses to Immunotherapy Agents

- hypothesis that high(er) non-synonymous mutation burden generates neoantigens recognized by the immune system
- patients with higher neoantigen burden exhibit higher durable clinical benefit
- ‘mutanome’ profiling
 - ID mutant nonamer peptides with <500nM binding affinity for patient-specific class I HLA alleles
- combination with targeted anti-cancer agents
 - increase neoantigen release?

Characterization of Tumor Classes Responsive to Immune Checkpoint Blockade

Mutational Burden	>1000 mutations/genome	10-1000 mutations/genome	<100 mutations/genome
Tumors	MSI-H tumors CRC, endometrial	NSCLC melanoma	renal cell carcinoma lymphomas head and neck cancers
Mechanism?	germline DNA MMR defects	DNA damage - smoking - UV	viral neoantigens? recurrent highly immunogenic and addicted neoantigens

Recurrent Mutations in SERPINB3 and -B4 in Melanoma Patients Responsive to anti-CTLA4 Immunotherapy

- SERPINB3 significantly mutated in melanoma (TCGA)
- mutations in SERPINB3/4 cause protein misfolding and autophagy
 - potential role of aggregates/plaques in stimulating autoimmunity (SLE, psoriasis)?
 - potential role of autophagy in enhancing autoantigen expression?

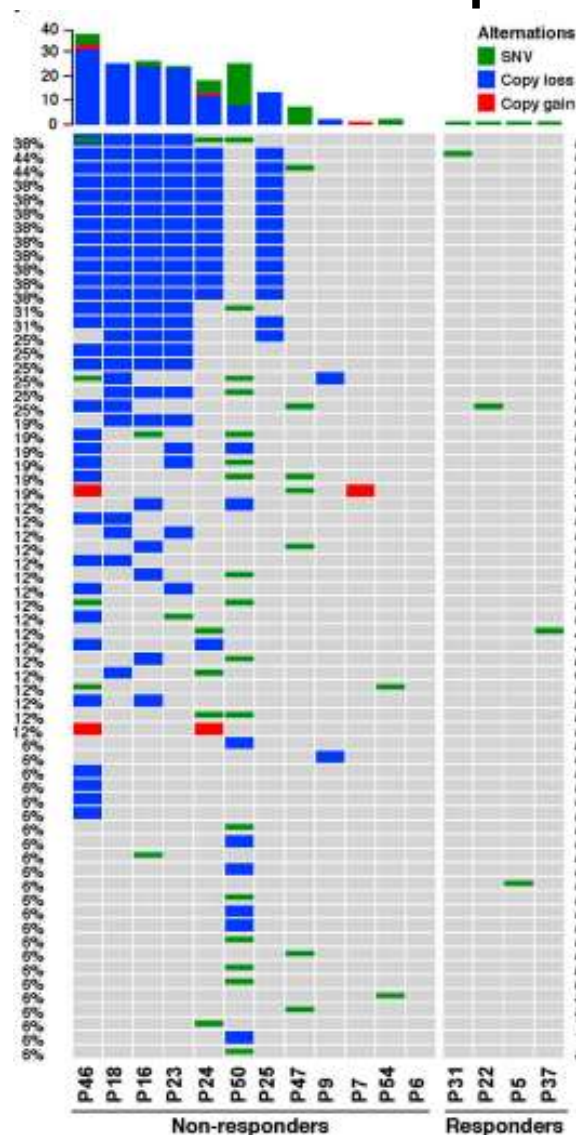
Tumor Immunophenotypes Associated With Responsiveness to Immune Checkpoint Modulators

- high tumor mutation burden
- high tumor-infiltrating CD3⁺ CD8⁺ cytotoxic lymphocytes (TIL)
- CD45RO⁺ memory T cells
- high activated Th1 helper cells density
- high expression of Th1 stimulating cytokines
 - CCL5, CXCL29, CXCL10
- higher expression of TIL checkpoint receptors
 - PD-1, PD-L1, CTLA-4, LAG3

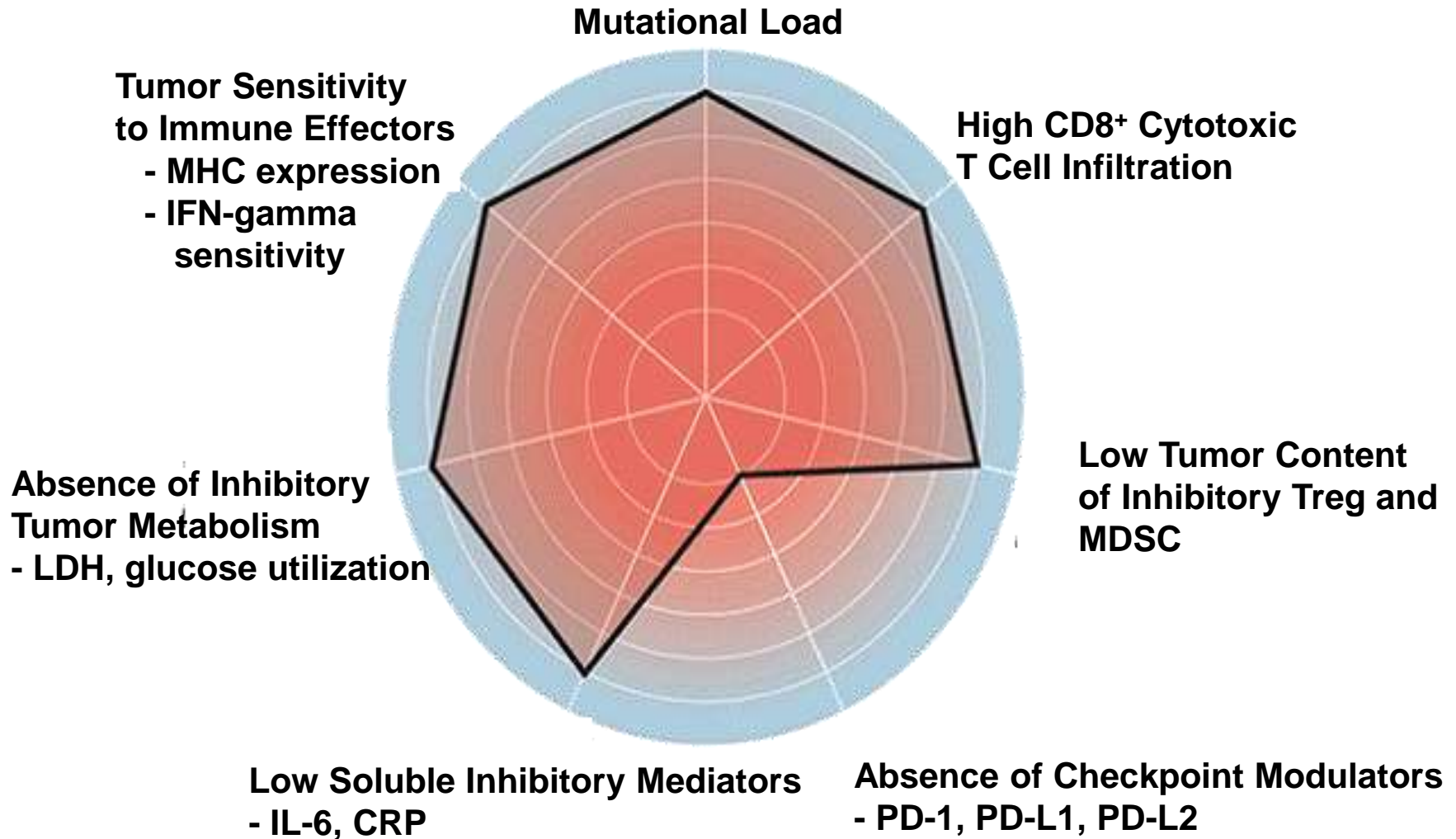
Tumor Phenotypes Associated With Low Responsiveness to Immune Checkpoint Modulators

- low mutation frequency
- high regulatory T (Treg) lymphocyte population
- high myeloid-derived suppressor cell (MDSC) population
- lower expression of TIL checkpoint receptor
 - PD-1, PD-L1, CTLA-4, LAG3
- mutations in class I/II MHC and impaired neoantigen processing
- IFN- γ receptor and intracellular signaling pathway modulation and CTL-resistance

Landscape of IFN-Gamma Pathway Copy Number Alterations in Ipilimumab Responder and Non-Responder Patients (N=16)



Cancer Immunophenotyping: Creation of an “Immunoscore or Immunogram”



Immunophenotyping: Critical Questions

- how will reagents, assays and cut-off thresholds be standardized and validated?
- if pre-I/O-Rx (baseline) tissue biopsy is not a robust prediction for R or NR status when and how should post-I/O-Rx profiling be done?
- can immunophenotyping in blood accurately mirror intratumoral events in disseminated metastases with heterogeneous neoantigen expression burdens?
- is there an 'over-arching' immunophenotype characteristic for 'R' patients that will be valid for new I/O-Rx classes with different MOAs?

Activated Cell Therapy (ACT)

“Living Drugs”

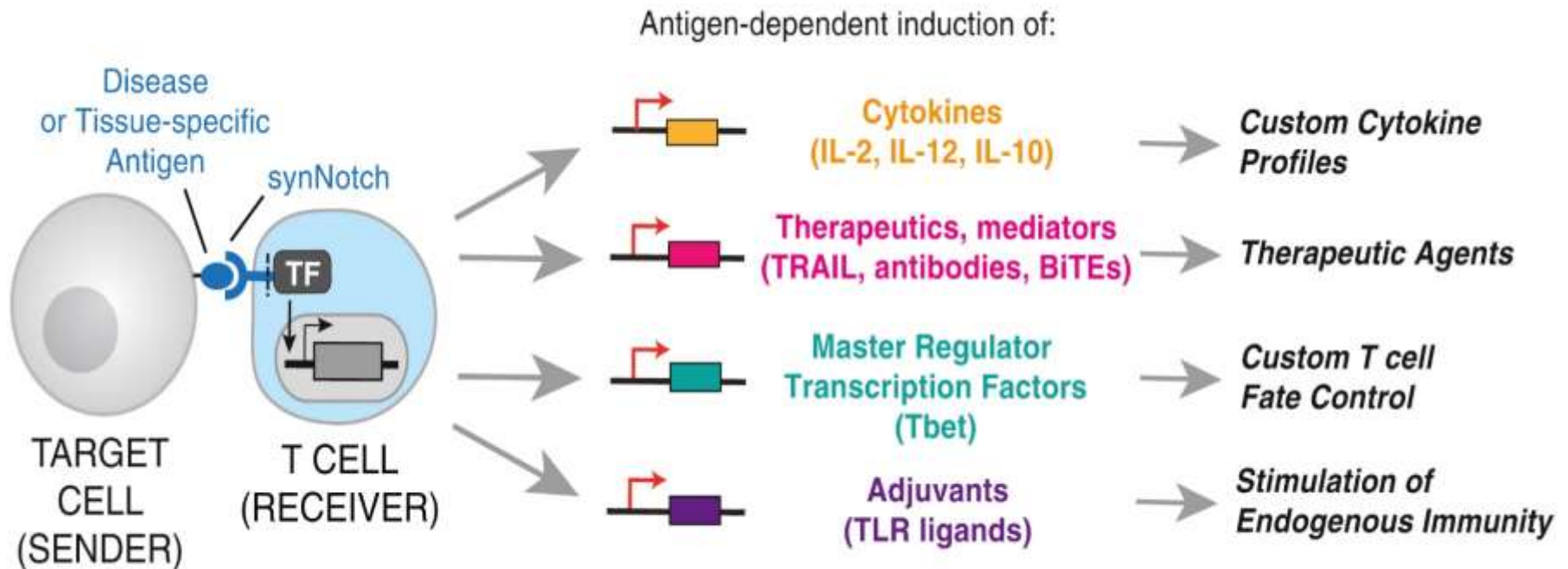
Engineering Killer T Cells for Cancer Therapy

- cytotoxic anti-tumor T cells harvested from cancer patients
- harvested cells genetically engineered and expanded ex vivo to express T cell receptor(s) (TCRs) or chimeric antigen receptors (CARs) that recognize tumor antigen(s)

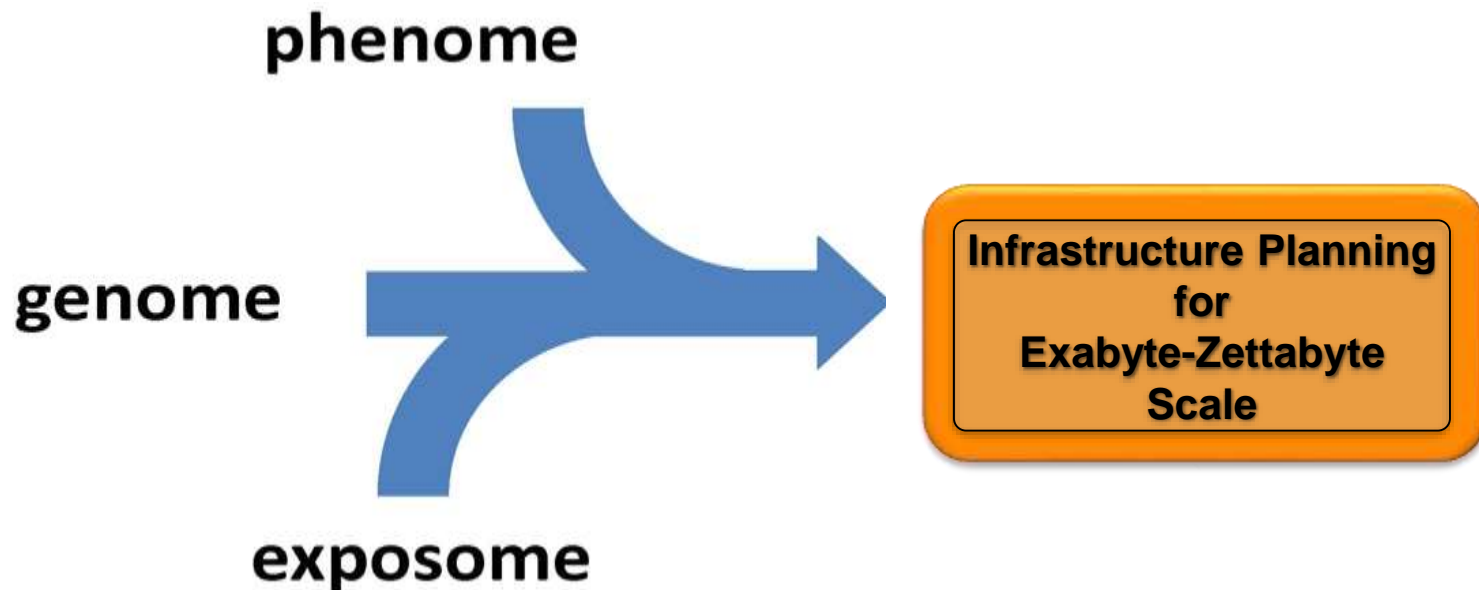
CD19 CAR-T Cell Therapy

- high remission rates and durable responses in acute lymphoblastic leukemia
- encouraging responses in NHL and chronic lymphocytic leukemia
- evolution of next-generation CAR designs to incorporate costimulatory molecules to drive/sustain in vivo expansion of CAR-T cells
- challenge of creating TCR/CARs for diverse neoantigens (hematopoietic vs. solid malignancies)
- cost and complexity of 'individualized' therapy

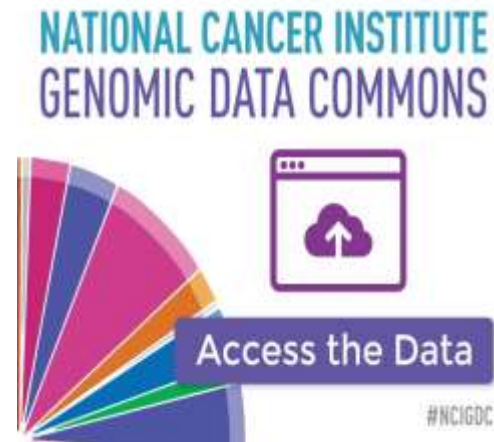
Engineering T Cells with Synthetic Notch (SynNotch) Circuits for Customizing Responsiveness to TME Signals and /or Drug Delivery



Precision Oncology: Managing the Big Data Challenge



The Quest for Democratization of Large Scale Shared Open Datasets in Precision Oncology



Obvious But Complex Issues in Data Sharing, Curation and Analysis

- scale
 - terabyte per patient and petabyte/exabyte dbases
- standards for data entry and dbase design
- depth and stringency of case documentation
 - clinical phenotyping, pathology-lab data, Rx use and outcomes
 - variation in case reporting formats
- different EMR vendors and interoperability barriers
- privacy, security and de-identification
- consent

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Data Ownership

The Future of Cancer Care

- demographics of an aging society
- new technologies and treatments
- standards and quality of care
- cost of care
- complex clinical, economic, ethical and legal landscape

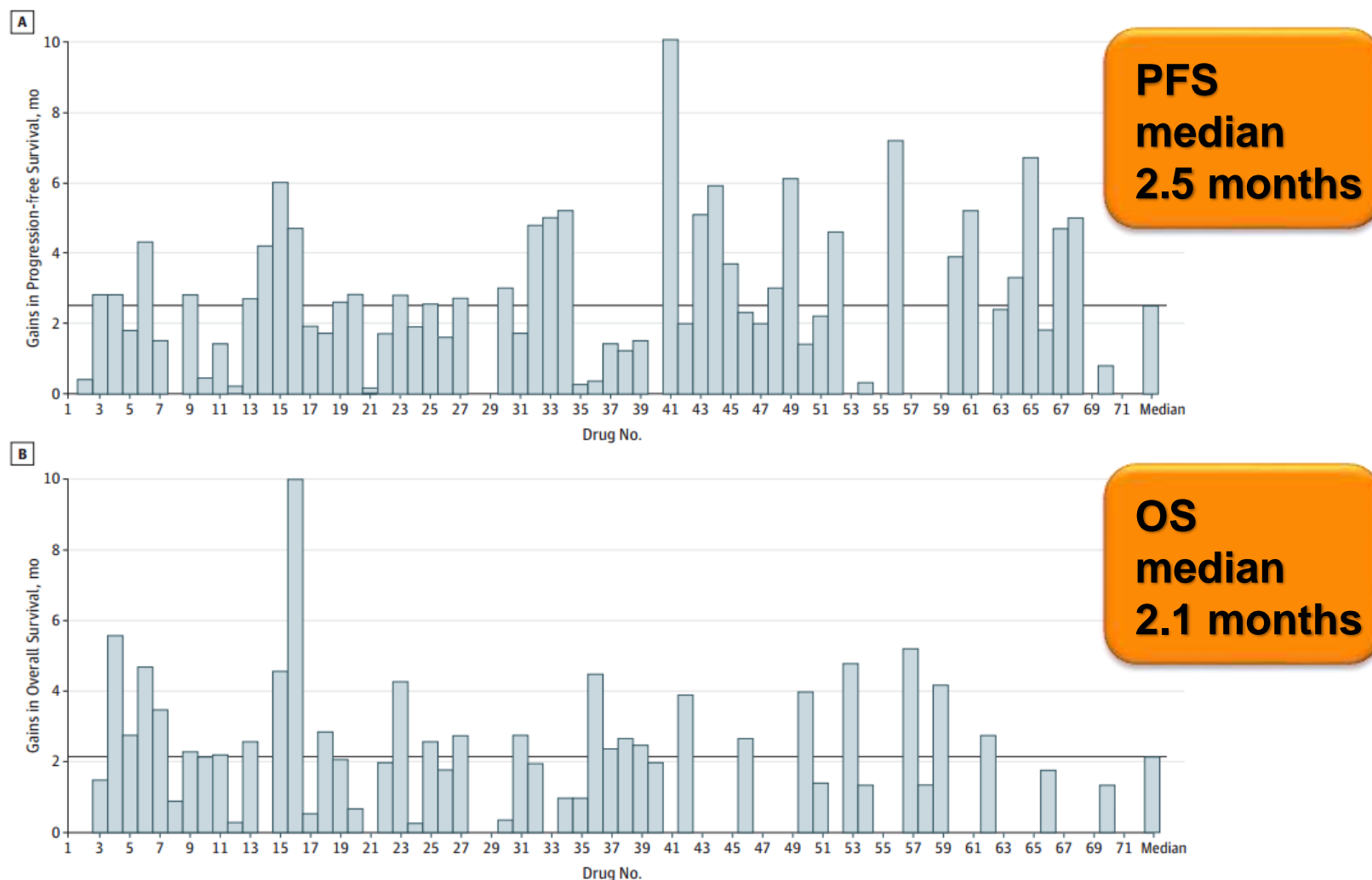
The Future of Cancer Care

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- cost of care
- complex clinical, economic, ethical and legal landscape

We Can No Longer Afford (Economically and Ethically) to Avoid Asking Tough Questions About The Adequacy of Current Approaches to Cancer Treatment and Care

Performance Comparison for New Anti-Cancer Drugs Approved 2002-2014 for Top Ten Pharmaceutical Companies

Gains in Progression-Free Survival (PFS) and Overall Survival (OS) for 71 Drugs Approved by the FDA From 2002 to 2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors



Is Widespread Adoption of Immunotherapy Economically Feasible?



- direct Rx cost
- indirect care cost
- escalating cost of combination Rx regimens (> \$200K)
- extravagant cost of cell-based therapies (\$500K - \$1.5 million)
- complex clinical management challenges and compatibility with community oncology services

The Evolving Trajectory for Payer Policy for Cancer Therapeutics

- performance – based pricing
- indication – based pricing
- reference – based pricing

The Evolving Trajectory for Payer Policy for Cancer Therapeutics

- performance – based
- indication
- value-based pricing

Robust ID of Responder and Non-Responder Patients

Key Issues in the Evolution of Precision Oncology: New Economic, Ethical and Legal Complexities

- ‘value-based’: ‘pay-for-performance’
 - ID of responder cohorts and restricted Rx use
 - indication-based pricing (industry risk)
 - clinical payment schedule linked to outcomes and Rx decisions (provider risk)
- ‘pricing life’
 - NICE comes to the USA
 - OALYs and other value-assessment metrics
- “when is enough, enough?”
 - decision criteria for balancing probability of intervention benefit versus palliative care/QOL
- ‘keeping current’
 - the data deluge and professional competency
 - new malpractice liabilities

Summary and Key Conclusions

Key Issues in the Evolution of Precision Oncology: Integration of Molecular Guidance Into Routine Care

- technology agnostic panOmics profiling
- integration of panOmics data into EMRs
- evidentiary standards for clinical utility of molecular profiling (matched vs. unmatched Rx)
- new analytical methods for monitoring tumor clonal dynamics in progression (liquid biopsy)

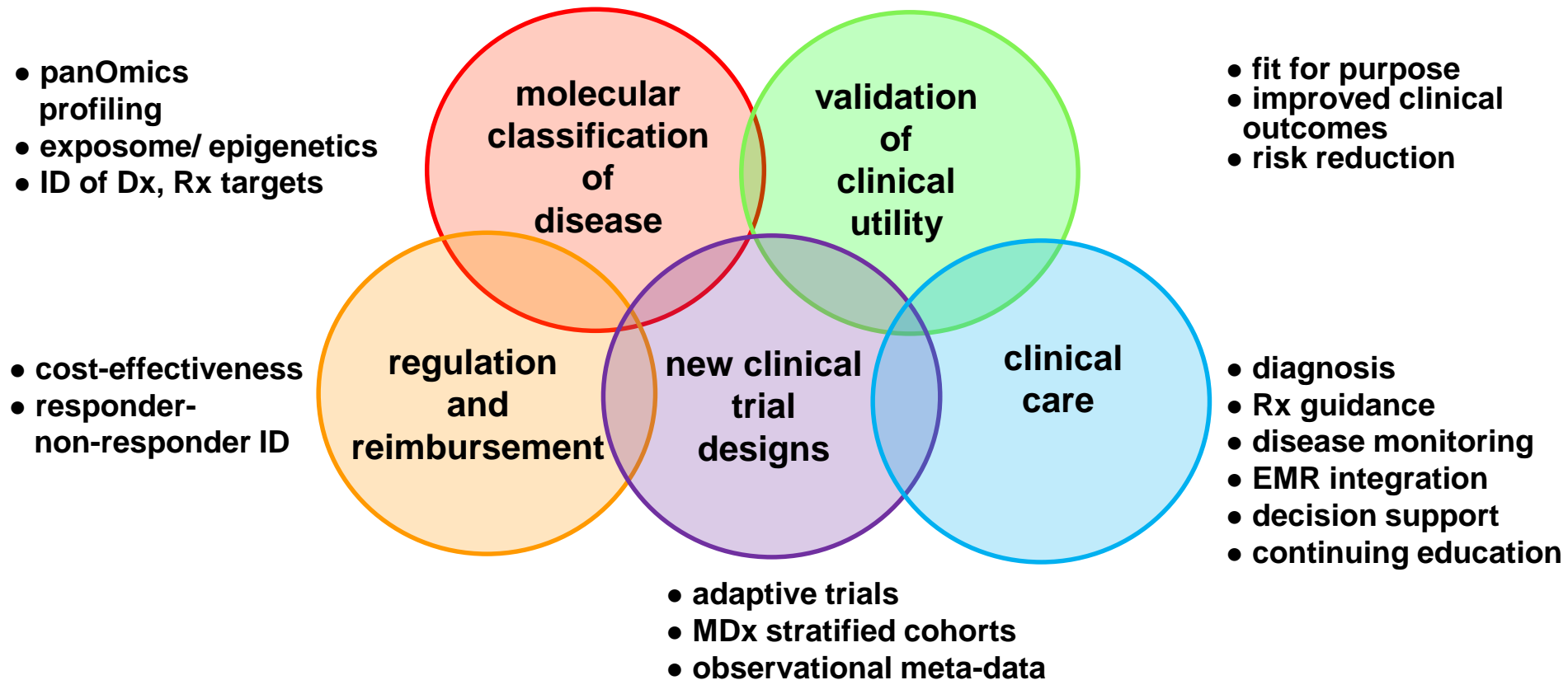
Key Issues in the Evolution of Precision Oncology: Integration of Molecular Guidance Into Routine Care

- anticipated rapid uptake of immunotherapy and new classes of I/O agents
- clinical and economic incentives for new immunophenotyping assays to identify responder and non-responder patients
- elucidation of mechanisms of acquired resistance to I/O agents

Key Issues in the Evolution of Precision Oncology: Integration of Molecular Guidance Into Routine Care

- patient profiling into ever smaller cohorts and new clinical trial designs
- agile regulatory and reimbursement policies and updating SOC guidelines to accommodate rapid changes in molecular phenotyping and therapeutic implications
- new value-based pricing and risk sharing models for pay-for-performance (outcomes)

Precision Oncology: Multi-Dimensional, Systems-based Integration Across the Research to Clinical Care Continuum



Precision Oncology: a Data-Intensive Discipline

- panOmics profiling
- exposome/ epigenetics
- ID of Dx, Rx targets

- cost-effectiveness
- responder-non-responder ID

Data Scale – the V5 Challenge:
volume, variety, velocity, veracity, value

Data Integration:
standards, interoperability, infrastructure

Data Analytics:
data science, machine learning, decision support systems

- adaptive trials
- MDx stratified cohorts
- observational meta-data

- fit for purpose
- improved clinical outcomes
- risk reduction

- Rx guidance
- disease monitoring
- EMR integration
- decision support
- continuing education