The Evolution of Precision Oncology: Biological Complexity, Big Data and Big Price Tag

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Keynote Presentation:
The Cancer Prevention and Research Institute of Texas
Innovations in Cancer Prevention and Research Conference
Austin, Texas • 10 November 2015
Confronting the Clinical, Economic and Human Toll of Cancer

US Cancer Deaths (2014)
580,000
# US Cancer Prevalence 2010 and Estimated for 2020

<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>% change</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2020</td>
</tr>
<tr>
<td>Breast</td>
<td>3461</td>
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<tr>
<td>Lung</td>
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<tr>
<td>Kidney</td>
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<td>426</td>
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<tr>
<td>Leukemia</td>
<td>263</td>
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<tr>
<td>All Sites</td>
<td>13,772</td>
<td>18,071</td>
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</table>

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

Avastin: $3.059B  
Rituxan: $2.466B  
Herceptin: $1.526B  
Revlimid: $1.373B  
Gleevec: $1.285B

Taxotere: $1.042B  
Alimta: $975M  
Gemzar: $723M  
Tarceva: $661M  
Femara: $650M

Erbitux: $646M  
Velcade: $598M  
Xeloda: $508M  
Arimidex: $494M  
Leuplin: $483M

Responders vs. Non-responders

Medical Progress:
From Superstitions to Symptoms to Signatures
ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease
Cancer as a Complex Adaptive System: Emergent Phenomena and Tumor Progression (System State Shifts)

- Escape From Controls of Normal Tissue Architecture
- Genome Instability and Emergence of Heterogeneous Clones/Subclones
- Evasion of Detection/Destruction by Host Immune System
- Use of Host Tissue Microenvironments to Promote Progression
- Invasion and Metastasis
- Emergence of Drug-Resistant Clones
Extravagant Cellular and Molecular Heterogeneity

The Omnipresent Hallmark of Malignancy

A Formidable Barrier to Effective (Curative) Therapy
“malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations

- disturbing implications for therapeutic ‘cure’ and development of new Rx
Intratumor Genetic Heterogeneity in Multiple Regions of Primary Tumor and Three Metastases (Perinephric and Chest Wall) in RCC

From: M. Gerlinger et al. (2012) NEJM 366, 883
The Long Tail of Disease

- Cancer as the extreme outlier in disease complexity?
  - Disease subtypes plus the heterogeneity of clonal diversification within individuals
  - Large dynamic range of clinical phenotypes and variable patterns of disease progression
  - Highly variable Rx responses
  - Intrinsic and acquired Rx resistant clones/subclones

- Cancer as the ultimate orphan disease?
  - Every cancer is unique: the N of 1 challenge!
Cancer Genomes: A Formidably Complex Catalog of Genomic Instabilities and Molecular Network Disruptions
Spectrum of Somatic Mutations in Cancer Genomes

The Cancer Gene Catalog: Close to Completion or Continued Expansion and Escalating Interpretation Ambiguities?

<table>
<thead>
<tr>
<th>Mutational Frequency</th>
<th>Detection Status</th>
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<tr>
<td>&gt;20%</td>
<td>reaching saturation</td>
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<tr>
<td>10-20%</td>
<td>increasing but at lower rate</td>
</tr>
<tr>
<td>5-10%</td>
<td>increasing linearly</td>
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<tr>
<td>&lt;5%</td>
<td>accelerating</td>
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</table>

Adapted from M.S. Lawrence et al (2014) Nature 505, 495

Projected Requirement for Analysis of 100,000 Samples Across 50 Different Tumor Types for Comprehensive Inventory
Making Sense of Cancer Genomic Data

**driver mutations**
- oncogenes (activation)
- suppressor genes (inactivation)

**passenger mutations**
- multiple genetic changes caused by genome instability that are not fundamental to cancer initiation and progression
- accumulate with increasing genome instability
- may still confer adaptive survival advantage to cancer cells and may become drivers in late stage cancer
Will whole Genome Sequencing Be the Panacea for Making Precision Oncology a Reality?

- Clinical Utility: Not If, but When, What and How
- Hype Is Always Followed by the Hard Work of Demonstrating Value
- The Latest Example of Overly Simplistic Reductionism in Biomedicine
Deep Phenotyping: 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

Cell-specific Molecular Interaction Networks

Perturbed Networks and Disease Pathogenesis

recognition of (epi)genome organizational and regulatory complexity
Cancer as a Complex Adaptive System

The Complex Evolutionary Ecology of Malignant Neoplasms
Cancer as a Complex Adaptive System: The Relentless Emergence of New Clones and Subclones in Tumor Progression
Metastasis Results from Preexisting Variant Cells Within a Malignant Tumor
I. J. Fidler and M. Kripke (1977) Science 197, 893-5
Clonal Expansion and Phenotypic Diversification (Heterogeneity) with Tumor Progression

- **Initiating Mutation**: The first event in the clonal expansion process.
- **First Clonal Expansion**: Expansion of cells after the initiating mutation.
- **Second Mutation**: A mutation that occurs after the first clonal expansion.
- **Second Clonal Expansion**: Expansion of cells after the second mutation.
- **Increased Mutation Rate**: The rate at which mutations occur increases with each expansion.
- **Multiple Independent Mutations**: Each expanded clone can accumulate additional mutations.
- **Multiple Parallel Clonal Expansions**: The process can lead to the emergence of multiple distinct clones.
Mapping the Dynamics of Clonal Evolution in Progression of Malignant Tumors: Clonal Branching and Subclone Formation

- timing of mutational events
  - ‘early events’ present in clones in both primary tumor and metastases
  - private mutations (unique to individual patients or individual metastatic lesions in same patient) likely occurred late(r) in progression
Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches

From: J. Zhang et al. (2014) Science 346, 256
Clonal Diversification via Linear, Branched and Punctuated Evolution

- common (shared) set of foundation mutations in clones and subclones suggest origin from a single somatic cell
- complex aneuploid copy number variations (CNVs) occur early in punctuated bursts
  - profiles similar in primary, metastases and CTCs
- point mutations evolve gradually over time
  - high frequency of rare subclonal (<1%) mutations
The Selection Bottleneck (Selection Sweep) in Metastatic Dissemination

- Clonal composition of primary tumor
- 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
Paget’s Seed and Soil Hypothesis (1889)
Heterogeneity Between Matched Primary and Metastatic Sites in Pancreatic Ductal Adenocarcinoma and Site Specific Gene Expression

The Tumor Microenvironment

From: Ray-Coquard Future Oncol. (2013) 9, 12 Suppl. 1, 11
Interactions between Tumor Clones and Subclones in Modulation of Growth Rates and Metastatic Potential

Interactions among clonal subpopulations affect stability of the metastatic phenotype in polyclonal populations of B16 melanoma cells

George Poste*, John Doll*, and Isaiah J. Fidler*

*Department of Tumor Biology, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101; †Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104; and ‡Cancer Metastasis and Treatment Laboratory, National Cancer Institute-Frederick Cancer Research Center, Frederick, Maryland 21701

Communicated by Peter C. Nowell, May 4, 1981

Evolution of tumor cell heterogeneity during progressive growth of individual lung metastases

George Poste*, James Tzeng†, John Doll*, Russell Greig*, David Rieman*, and Irving Zeidman†

*Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101; †Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Communicated by Sidney Weinhouse, August 4, 1982
Cancer Research is Approaching An Inflection Point

Continued Accumulation of Observational Data
Or
Identification of Predictive Rule Sets for Trajectories of Tumor Cell Heterogeneity and Clonal Evolution?
“The cancer biology community 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

“The coupling between observational data and biological insight is frayed, if not broken.”

Cancer has the Largest Dataset in Biomedical Research but has no unifying theory beyond evolution.

The urgent need for predictive rule sets to understand the organization of molecular signaling networks and disease-associated disruptions.

Mapping concurrent, non-linear events in signaling networks will require new technologies, new analytics and new computational algorithms.
encoded information and expression as cell-specific signaling networks

topology of signaling networks and information flow

stable networks and information fidelity (health)

dysregulated networks and altered information flow (disease)
Network Structure and Cell ‘State Spaces’ in Complex Systems

- Network topology
- Fragility/resilience, adaptation/evolution
- Network dynamics and system states
- Connectivity
- Composability
Understanding State Shifts in Complex Adaptive Systems and Identification of Triggers of Emergence in Clonal Diversification

- network topology
- state shifts

Emergence (E)

- black swans
- dislocations
- tipping points
- irreversible cascades

- phase shifts
- perturbations
- inflection points
- unintended consequences

- critical thresholds
- bifurcations
- trigger points

$E_1, E_2, \ldots, E_n$
what are the features/distributions/correlations of molecular network perturbations in different malignancies?

how can insights into network/subnetwork perturbations improve therapeutic target selection and new strategies for restoration of homeostasis?

how can computationally-intensive analytics for profiling network perturbations be accelerated to improve diagnosis and ID of new therapeutic targets?
Dynamic Modeling of Complex Signaling Pathways and Networks

- what parts of the network are the most/least sensitive to perturbation?
- what parts of the network are most/least influential on the rest of the network when perturbed?
- how can these foci of network robustness/vulnerability be exploited to improve therapy?
Defining Cell ‘States’, ‘Fates’ and ‘Trajectories’

Where Will A Cell End Up?
Excursional Landscapes (Trajectories) for ‘State Spaces’ in Specific Cell Lineages (Canalization: after C. H. Waddington 1937)

- landscape of possible states
- concept of “attractor” landscapes
  - transition between states (attractors) with many intermediate distributions along a trajectory between them
- new technologies for high resolution panOmics of single cells
The Discovery and Validation of New Diagnostic Biomarkers and Rx Targets Will Require Major Changes in Current Research Approaches

Standards, Standards, Standards!

Scale: Collaborations and Consortia
Lost in Translation:
The Poor Performance Record of Biomarker Discovery and Validation

  - over 120,000 claimed biomarkers or biomarker combinations (biosignatures)
  - less than 100 molecular diagnostics in clinical use or advanced validation trials

- widespread lack of understanding of regulatory requirements in academic research community
  - GLP, GMP, Records, RUO instruments versus Clinical Use
  - technical and regulatory complexities of multiplex assays (IVDMIAs)
The Unsatisfactory State of Discovery Research for Biomarkers and New Drug Targets

Error(s) in the Most Proximal Activities Will Cascade and Contaminate Downstream Efforts

Inadequate and Erratic Clinical Phenotyping

Specimens of Convenience: Poor Annotation and Uncertain Provenance

Statistically Underpowered Sample Sets

$n \ll p$

Sampling Bias: Intra- and Inter-lesional Heterogeneity (Oncology)
Sloppy and Unstandardized Science: The Growing Problem of Poor Reproducibility in Biomedical Publications


Nat. Rev. Drug Disc. 2011 10, 63

Reliability of ‘new drug target’ claims called into question
Building Large Scale, Standardized Resources for Biomedical Research: New Collaboration Networks and Consortia

- rigorously phenotyped/matched/consented disease and normal specimens
- biobanking and reagents: leadership and national policies to create standardized resources for the research community
- standardization of pre-analytical and analytical methods
- standardized data ontologies and formats for large scale datasets/federated databanks
Genetically Engineered Mouse (GEM) Tumor-Derived Allografts for Improved (GDA) for Preclinical Assessment of Potential Drug Candidates

From: C-P Day et al. (2015) Cell 163, 47

Genetically-Engineered Mouse Models (GEMMs) and GEMM-derived Allografts (GDAs)

Use of Gene Editing Tools (CRISPR-Cas) to Expand Diversity of Genomic Perturbations in GEMMs
Improving the Success Rate for New Oncology Therapeutics

- high R&D costs (>$1 billion)
- protracted development time (5-12 years)
- high failure rates in clinical trials (75-95%)
- unsustainable business model in an era of economic constraint and concern over high cost agents conferring only limited gains in PFS/OS
The Problem and The Challenge

- how to hit multiple tumor clones?
- how to hit multiple tumor clones at multiple anatomic sites of metastatic disease?
- how to hit emergent drug-resistant clones (intrinsic and acquired resistance)?
- how to design multi-target combinatorial Rx regimens compatible with patient tolerability and cost-effectiveness?
Targeted Therapeutics and Cancer

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)
current Rx discovery strategies still dominated by targeting single or small number of aberrant molecular targets

- omnipresent problem of inevitable Rx failure due to emergence of Rx-resistant clone(s)

- highly targeted Rx (or limited combinations) cannot achieve the multi-target interactive ‘promiscuity’ needed to block escape mechanisms via pathway redundancies in resistant clone(s)
Redundancy and Robustness in Molecular Signaling Networks: The Biological Foundation of Rx Resistance
Are Cancer Stem Cells (CSCs) the Optimum Target for New Rx Agents?

- ongoing debate on existence/role of CSCs
- important priority for resolution
- cellular plasticity and inter-conversion of stem and non-stem cell populations?
- do Rx-resistant clones/subclones arise only from CSCs?
- need for robust CSC markers in different malignancies
Rethinking Clinical Trial Design In An Era of Molecular Subtyping of Cancer
Can Large Scale, “All Comers”, Randomized Clinical Trials Be Justified in an Era of Molecular Profiling?

Segmentation (Stratification) of Patient Cohorts by Molecular Profiling and Clinical Trials

New Regulatory Issues
Stratified Trials

- molecular profiling of patients to ID drug target positive (T+) versus T-negative (T-) cohorts
- enroll only T+ patients into the trials
- regulatory Rx approval and labeling only for use in T+ patients
- obligate need for “companion diagnostic” test to profile patients before Rx can be prescribed
New Clinical Trial Designs

- adaptive (Bayesian) platform trials
- basket trials (TAPUR, NCI-MATCH)
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

The Quest for the ‘Liquid Biopsy’
The Search for ‘Liquid Biopsy’ Methods for Dynamic Monitoring of Tumor Progression and Faster Assessment of Treatment Responses

Fine Needle Aspiration (FNA) Biopsy

Minimally-Invasive Profiling (Blood/Other Body Fluids)
Anticipation-Based Chemotherapy in CLL

Liquid Biopsy: CTCs and/or ctDNA/RNA
Liquid Biopsy: Exosomes
Validation of Liquid Biopsy Platforms

- profiled analytes should reflect the full heterogeneity spectrum exhibited by metastases
- proactive identification of new clones and D' clones ahead of evident clinical progression
  - guide agile, anticipatory Rx regimen change(s)
- detection of minimal residual disease and relapse risk
- value as rapid read-out of efficacy of investigational Rx (vs RECIST, other clinical criteria)
Knowing When to Stop!

“Insanity is doing the same thing over and over again and expecting a different result.”

Albert Einstein
Challenging Questions

- has the gap between basic science and realizable therapeutic applications widened?
- is the level of network dysregulation in metastatic disease so extravagant that ‘homeostatic (curative) reset’ by current categories of targeted drugs is unlikely?
  - technical challenges of design of multi-target promiscuity in a single Rx
  - clinical/QOL impact/cost of ever larger Rx combinations in face of high likelihood of network redundancy and selection of Rx-resistant clones
The Promise of Immunotherapy Versus The Drug Resistance Neoantigens Problem in Targeted Therapy

**targeted drugs**

- $Rx_1$
- $Rx_2$
- $Rx_3$
- $Rx_4$
- $Rx_5$

**clones**

- $NA_1$
- $NA_2$
- $NA_3$
- $NA_4$
- $NA_5$

**Cytotoxic T cells**

- $NA_{n1}$
- $NA_{n2}$

**immuno-therapeutic regimens**

- Adaptive evolution of immune response and expanded cytotoxic T cell responses

- Rx-resistant clones/
- Rx refractory disease
Immunotherapeutic Strategies to Target Patient-Specific Tumor Neoantigens

A. Immune Checkpoint Modulation
   - Induce tumor cell destruction
   - Provide checkpoint blockade

B. Cancer Neoantigen Vaccines
   - Identify potential neoantigens
   - Create synthetic vaccine (RNA, DNA, peptide)
   - Provide in combination with adjuvant and checkpoint blockade

C. TILs, TCRs, CARs
   - Identify potential neoantigens
   - Induce or expand neoantigen specific T cells
   - Provide in combination checkpoint blockade

Current Challenges in Immuno-oncology

- profiling the molecular immunophenotypes of responder and non-responder patients
  - different immune response biomarkers for each class of immunomodulatory regimen?

- inadequate knowledge of tumor neoantigen expression repertoire
  - tumor subtypes in specific cell lineages
  - intra-patient and inter-patient heterogeneity

- complexity and cost of ‘customized’ bioprocess development for adoptive cell therapy
  - expansion of autologous TILS
  - genetically engineered multiplex TCRs and CARs
Precision Medicine Will Only Be As Precise As The Available Data Allows

Large Scale PanOmics and a Pending Data Deluge

End-to-End Interoperability of Data Formats and Databases From Discovery to Clinical Care Decisions
Data Access Will Become a Critical Factor in the Accuracy and Safety of Clinical Decisions Using NGS and panOmics Patient Profiling Platforms

- anticipated expansion of molecular data profiles on millions of individuals
- value will reside in defining robust correlations with clinical outcomes and demonstration of clinical utility
- transitioning from the current black box of panOmics signatures of unknown significance to increasingly accurate causal associations and clinically actionable information
Big Data: the V6 – D3 Challenge
V6: volume, variety, velocity, veracity, visualization, value
D3: dynamics, dimensionality, decisions

Managing Big Data is Not a Simple Extrapolation from Current Informatics Approaches

Current Institutional Structures and Competencies and Public Research Funding Policies Are Ill-Prepared for Pending Disruptive Change
WELCOME TO BIOMEDICAL RESEARCH AND PATIENT MEDICAL RECORDS
The Unavoidable Data-Intensive Evolution of Healthcare: Major Challenges Ahead

PB and TB Data Streams

Ontologies and Formats for Data Integration

Longitudinal Data Migration and Inter-operable Databases

New Data Analytics, Machine Learning, NLP Methods

Infrastructure, Storage and Privacy

Data Science and Data Scientists
The Pending Era of Cognitive Systems: Overcoming the “Bandwidth” Limits of Human Individuals

- limits to individual expertise
- limits to our multi-dimensionality
- limits to our sensory systems
- limits to our experiences and perceptions
- limits to our objective decision-making
The Extended Cognosphere:

- massive computing power
- mega-metadata
- automated analytics
- intelligence at ingestion
- new clinical decision algorithms
Vanguard R&D Meets the Real World: The Future Debate on Cancer Care

- Demographics of an Aging Society and Increased Cancer Incidence
- Cost-Effectiveness of Care
- Complex Clinical, Scientific, Economic, Ethical and Legal Issues
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?
Can we continue to afford the high cost of anti-cancer drugs for modest gains in PFS/OS and limited QOL?

- cost-effectiveness analysis metrics
- QALY: Quality Adjusted Life Year
What Are We Willing to Pay for Added Months of Survival in Cancer?

<table>
<thead>
<tr>
<th>Lifetime cost above standard care</th>
<th>If cancer is on par with other diseases ($150,000 per life year gained), months of added overall survival benefit needed</th>
<th>Treating cancer as worthy of much higher reimbursement ($250,000 per life year gained), months of added overall survival benefit needed</th>
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<tbody>
<tr>
<td>$50,000</td>
<td>4 months</td>
<td>2.4 months</td>
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<td>8 months</td>
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<td>$150,000</td>
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<td>$200,000</td>
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<td>12 months</td>
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<td>$400,000</td>
<td>32 months</td>
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<td>$450,000</td>
<td>36 months</td>
<td>21.6 months</td>
</tr>
<tr>
<td>$500,000</td>
<td>40 months</td>
<td>24 months</td>
</tr>
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</table>

Source: Pink Sheet 13 Sept. 2010. Adapted from S. Ramsey FHCRC, ASCO 2010
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

From: T. Fojo et al. (2014) JAMA Otolaryngology–Head & Neck Surgery 140, 1225
# Hypothetical Scenarios for Indication-Based Drug Pricing

<table>
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<tr>
<th>Drug and Indication</th>
<th>Median Survival Gain In Years</th>
<th>Current Monthly Price</th>
<th>Price Based On Indication With Most Value</th>
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<tbody>
<tr>
<td><strong>Abraxane (Celgene)</strong></td>
<td></td>
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<tr>
<td>Metastatic breast cancer</td>
<td>0.18</td>
<td>$6,255</td>
<td>$6,255</td>
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<tr>
<td>Non-small cell lung cancer</td>
<td>0.08</td>
<td>$7,217</td>
<td>$2,622</td>
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<tr>
<td>Pancreatic cancer</td>
<td>0.15</td>
<td>$6,766</td>
<td>$448</td>
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<td><strong>Tarceva (Roche/Astellas)</strong></td>
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<tr>
<td>First-line treatment metastatic non-small cell lung cancer</td>
<td>0.28</td>
<td>$6,292</td>
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<tr>
<td>Pancreatic cancer</td>
<td>0.03</td>
<td>$5,563</td>
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<tr>
<td><strong>Erbitux (BMS/Lilly)</strong></td>
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<td>Locally advanced squamous cell carcinoma of head/neck</td>
<td>1.64</td>
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<td>First-line treatment recurrent or metastatic squamous cell carcinoma of head/neck</td>
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<td><strong>Herceptin (Roche)</strong></td>
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<td>Adjuvant treatment breast cancer</td>
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<td>Metastatic breast cancer</td>
<td>0.40</td>
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*Source: JAMA article by Peter Bach, Oct. 3, 2014*
A Pricing and Reimbursement Dichotomy

Dx

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

MDx and PanOmics Profiling

MDx profiling to ID Rx response/resistance

SOC Rx guidelines

‘one size-fits all’ Rx regimens and slow adoption of subtyping
multi-line Rx versus palliation
aggressive end-of-life Rx

Foundation for Precision Diagnosis and Rational Treatment Selection

Propagation of Therapeutic Strategies With Uncertain Outcomes

segmentation of major cancers into ever smaller cohorts
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology

MDx and PanOmics Profiling

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

SOC Rx guidelines
Cancer as a Complex Adaptive System

Confronting the Tumor Cell Heterogeneity Problem
Making Precision Oncology a Reality Will Require New Insights Into Clonal/Subclonal Diversification and the Causal Underlying Perturbations in Molecular (Informational) Networks.

Achievement of this Objective Will Require Profound Changes in Current Conceptual, Analytical, Organizational and Funding Frameworks to Adopt New Multi-disciplinary, Integrated Systems-Based Approaches.
Silos Subvert Solutions

**Bold National Leadership is Needed to:**
- promote large scale, multidisciplinary cross-domain collaborations
- drive standards for biospecimens and panOmics profiling
- fund infrastructure/data science competencies for a looming big data world
The Need for Systems-Based Planning to Integrate New Competencies Across the Entire Continuum from Discovery to Clinical Care
Slides available @ http://casi.asu.edu/