





# Technology and Molecular Medicine: A Developer's Perspective

Dr. George Poste
Chief Scientist, Complex Adaptive Systems
and Del E. Webb Chair in Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

Presentation at ASU:University of Chicago Public Health Law Conference: Technology and the Rising Cost of Health Care - A Paradigm Shift

Sandra Day O'Connor College of Law, Arizona State University, Tempe, AZ 2 March 2013 **Healthcare: An Expensive Menu Without Prices** 

Managing the Demands of an Aging Society and Chronic Disease Burden in an Era of Economic Constraint

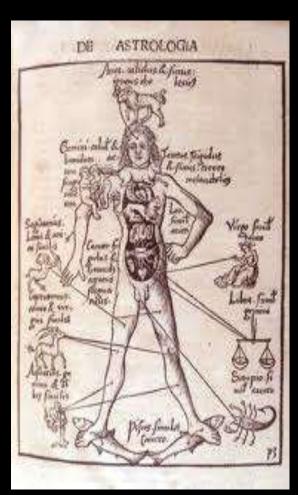
Shift From a "Do More, Bill More" Healthcare System to Managing Individual Risk for Improved Health Outcomes and Cost Control

Sustainable Health: Societal (Economic) and Individual (Wellness)

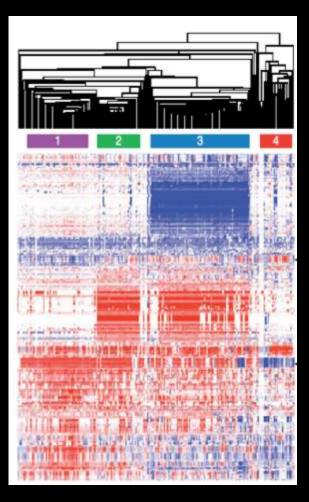
### **New Technologies and Healthcare Cost**

- merely additive cost or superior outcomes and cost-effectiveness?
  - direct plus indirect costs
- technology acceleration and cross-sector convergence
  - medicine, engineering, computing, m.health, social media
- asynchrony between pace of technology and slow refinement of regulatory/reimbursement policies and translation into routine clinical practice

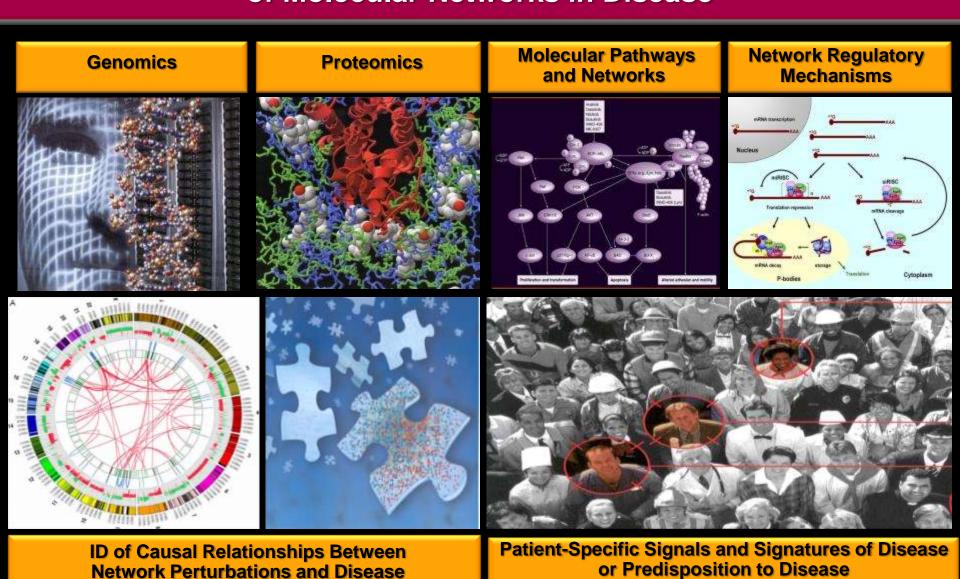
# Medical Progress: From Superstitions to Symptoms to Signatures



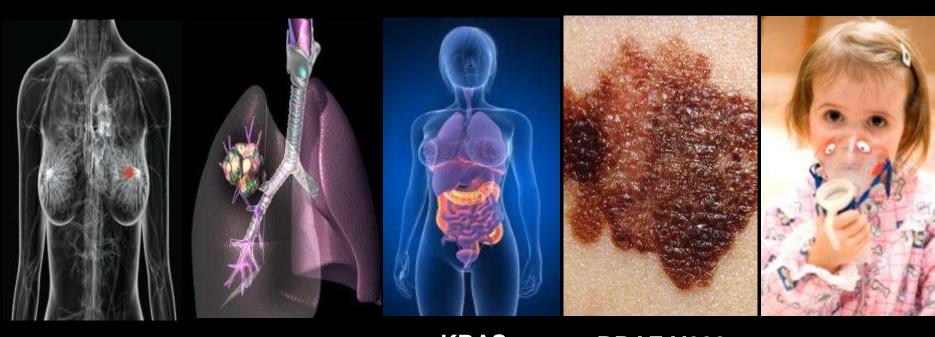




# Precision (Personalized) Medicine: Integrated "Omics" Profiling and Mapping Disruption of Molecular Networks in Disease



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



Her-2+ (Herceptin) (Perjeta)

EML4-ALK (Xalkori)

KRAS (Erbitux) (Vectibix)

BRAF-V600 (Zelboraf)

CFTR-G551 (Kalydeco)

### New Technologies and Healthcare Cost

**Precision Medicine: Mapping the Molecular Basis of Disease** 

Precision Medicine: A New Era in Diagnostic Accuracy, Rational Treatment Selection and Risk Mitigation

A Study in Reimbursement Policy Contrasts:

Targeted Therapeutics (Rx) Versus Molecular Diagnostics (MDx)

in Cancer Care

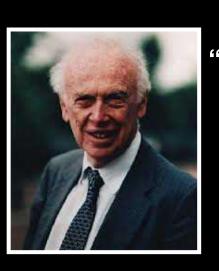
### The Projected Increase in US Cancer Cases (2010 to 2020) J. Nat. Cancer Inst. (2011) 103, 117

- projected 20-40% increase in cases
  - demographics
- limited anticipated Rx improvements
- \$124 billion rising to \$158 billion (27% increase)
  - constant costs/survival
- \$124 billion rising to \$207 billion (66% increase)
  - 5% increase in care costs
- opportunity to blunt cost escalation via use of MDx and molecular profiling for rational Rx selection

#### The Price 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 (Zytiga) \$60,000/year
- premetrexed (Alimta) \$30,000/course

### **A Welcome Perspective**



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

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

#### The Unacceptable Status of Current Cancer Care Delivery

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

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



Non-responder

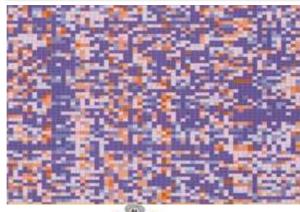
Sources: Individual Drug Labels. US Food and Drug Administration. <a href="www.fda.gov">www.fda.gov</a>
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

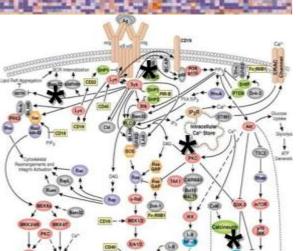
### **Targeted Therapeutics and Cancer**

Molecular Subtyping and RX Targets

Initial Rx-Response to Targeted Rx

Rx-Resistance via Redundant Molecular Pathways





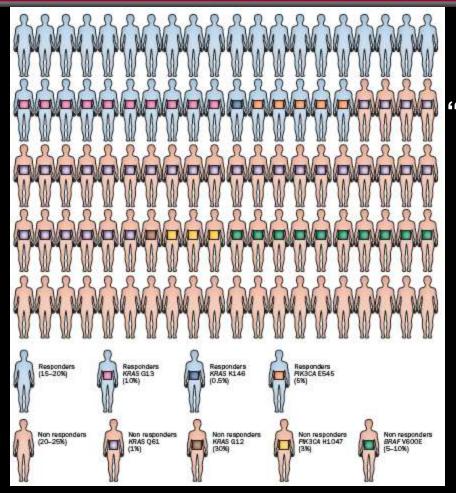






B = 15 weeks Rx (Zelboraf®) C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

## Molecular Diagnostics and Identification of Responder/Non-Responder Patients for Rational Rx



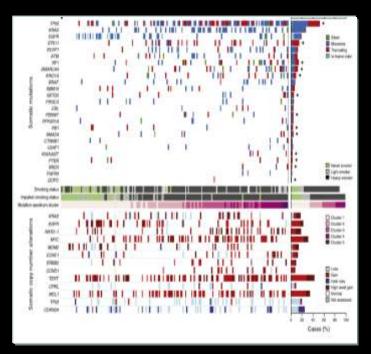
"The problem with all these tests, soon I'll have nothing (treatments) I can offer my patients"

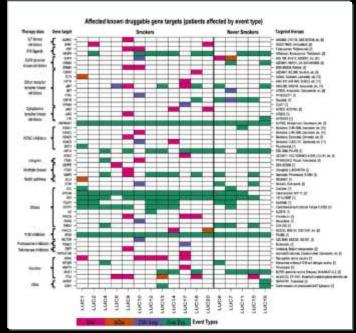
"Eminent Oncologist" (journal's designation) Drug Discovery World. Spring 2011, p. 61.

Frequencies of Molecular Alterations in CRC and Responsiveness to Cetuximab or Panitumumab

From: M. Martini et al. (2012) Nature Rev. Clin. Oncol.

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

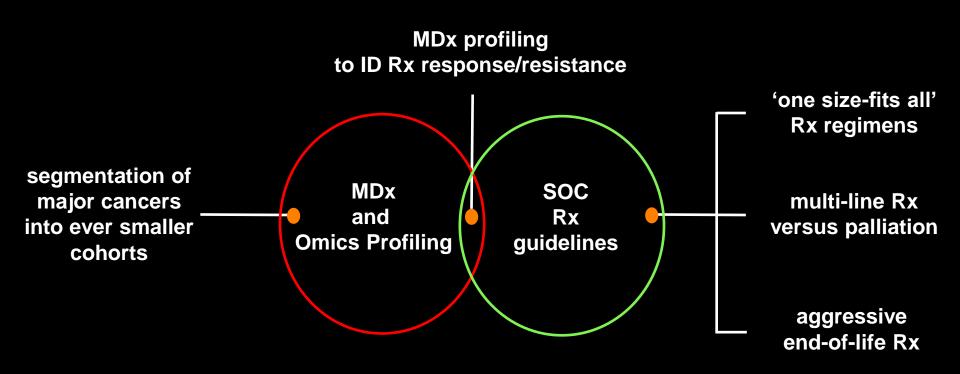




Mutations in Individual Non-small Cell Lung Cancer Drug Targets in Individual Non-Small Cell Lung Cancers

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

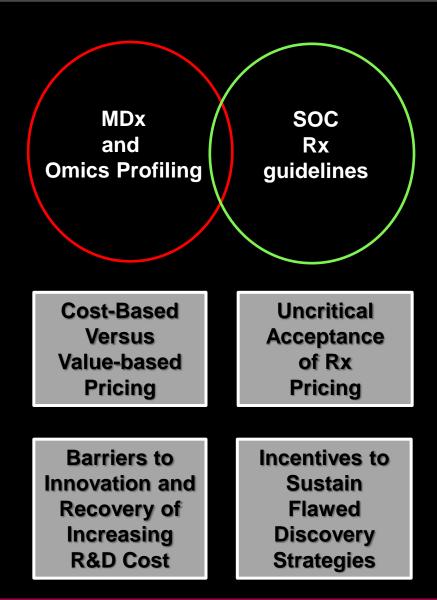
### Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology



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

- molecular diagnostics as the intellectual foundation of rational care
  - subtyping of cancers based on molecular profile(s)
  - rational selection of Rx based on presence or absence of Rx 'target' in a patient's tumor
  - monitoring of Rx response for early detection of Rx resistance and adaptive change in Rx (or palliation recommendation)
  - elimination of futile therapy (cost, QOL)
  - shift focus to optimum therapy plus increase use of palliative care

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



#### The Evolution of Clinical Laboratory Diagnostic Tests

#### unianalyte

- low technical complexity and development cost (<\$1M)</li>
- CLIA certification and validation with small sample set
- clear, typically binary, endpoint
- low inter-patient variation and reference ranges









## multianalyte "signatures" (Omics)

- high complexity and cost (>\$10-100M)
- CLIA plus 510(k)/PMA? plus validation on large sample set(s)
- probabilistic endpoints and computational algorithms
- substantial inter-patient variation (genetics) and dynamic range of analytes

#### The Evolution of Clinical Laboratory Diagnostic Tests

#### unianalyte

transparent regulatory policies/oversight



 low test price based on cost of materials/labor for assay



- tardy development of guidelines/policies
  - IVDMIAS, MAAAS
  - genome sequencing
- lack of HCP familiarity with molecular medicine and multiplex profiling
- new pricing to reflect increased R&D cost, time and risk
- value-based pricing for clinical utility





### The Two Most Feared Phrases in Industry



"did not meet the Street's expectations"



"investigational and not medically necessary"

## The Reimbursement Environment for Genetic Tests in 2013\*

- new CPT coding (AMA) to replace 'stacking'
- Tier I: c.100 codes, cover estimated 90% of current testing
  - analyte-specific but platform and testing lab agnostic
- Tier II: 9 'buckets'
  - not analyte-specific but graded by complexity
- no distinction between LDTs and FDA approved tests
- lack of CMS direction on pricing: use of 'gap fill' model for formulaic price in 2013
- no pricing proposals for tests using 'algorithms' (IVDMIAs/MAAAs)

## MDx Pricing Proposals for CMS



- significant industry concern over pricing mechanism
- BRAF-V600E mutation analysis for Zelboraf
  - proposed \$58 price = 78% reduction versus \$259code stacked test
- KRAS codon 12 and 13 mutations for EGFR-Mabs in CRC
  - proposed \$226 = 75% reduction versus \$911 stacked pricing (versus \$116 for EGFR mutation analysis in NSCLC)

#### Medicare Coverage with Evidence Development (CED)

- reimbursement with sponsor commitment to clinical study(ies) to produce evidence of clinical utility/effectiveness
- industry concern over cost and potential duplicative studies for products where FDA has mandated Phase IV studies or REMS
- CED study protocols in CMS draft guidance (11/29/12) stipulate how study results are applicable to subsections of the Medicare population
  - older patients with high rates of comorbidities
- need for fixed duration of CED study
- ethics of patient enrollment
  - coercive in order to receive Rx?

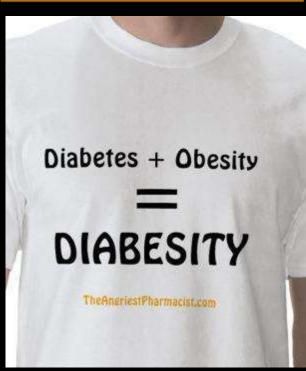
# Three Different Scenarios for the Use (Value) of New Diagnostic Technologies for Early Detection of Disease and/or Disease Predisposition

**Cancer Detection Before Metastasis** 

Cardiovascular/
Metabolic Diseases

Neurodegenerative Diseases





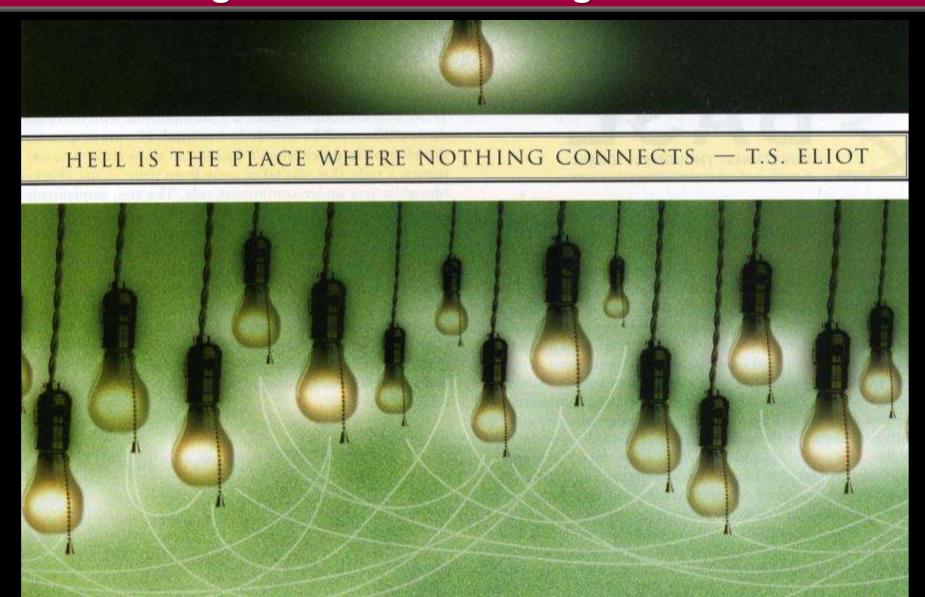


Early Diagnosis and Curative Surgery

Lifestyle Changes and/or Rx to Limit Risk

The Dilemma of Early Diagnosis Without Rx

# Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo



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

- HITECH funding for health IT does not promote innovation
  - e.replication of paper records
  - limited ability to assimilate new data categories (genomics)
  - the interoperability 'iceberg'

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





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

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

### Disruptive Technologies and the Need to Redress Wasted Billions in Flawed Clinical and Delivery Systems for Cancer Care

- incorporation of new technologies into old business models typically drives cost up without productivity gain(s)
- disruptive technologies drive new business models, products, services and processes
- the disruptive technologies needed to redress the massive inefficiencies in healthcare services will need to emerge from the outside

#### Molecular Omics Profiling as a Disruptive Technology

#### **Feature**

- emergence typically unanticipated by market leaders/KOLS
- emergence at margins of existing fields
- emergence via convergence of previously separate fields

#### Indicator(s)

- led by molecular biologists not pathologists/lab test industry
- physician refuge in anachronistic SOC guidelines
- MDx/sequencing invading anatomic pathology, microbiology and pharmacy science
- MDx/genseq/sensors involve mol. biol., engineering computing
- mobile devices and remote monitoring
- precision medicine meets big data and digital medicine

### Molecular Profiling and Diagnostics as Disruptive Technologies

#### **Feature**

 emergence driven by new value-propositions/ existential threats

#### Indicator(s)

- unsustainable healthcare costs
- cost and low efficacy of oncology Rx without patient stratification
- payors/patients demand greater value= improved efficacy and outcomes

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

