Confronting the Cancer Challenge: The Need for New Diagnostic and Treatment Strategies

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Declared Interests

Board of Directors
- Monsanto
- Exelixis
- Caris Life Sciences
- Bulletin Atomic Scientists

Scientific Advisory Boards
- Synthetic Genomics
- Burrill and Co.
- Pfizer
- University of Michigan, Alfred Taubman Medical Research Institute

Advisory/Consultancy
- USG Depts. of Defense and Homeland Security
- Institute of Medicine Global Forum

Slides available @ http://casi.asu.edu/
Medical Progress:
From Superstitions to Symptoms to Signatures
Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

Genomics

Proteomics

Molecular Pathways and Networks

Network Regulatory Mechanisms

ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

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

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

Multiplex Profiling

Right Rx for Right Disease Subtype
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics (CoDx) - 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)
The Evolution of the Classification of NSCLC

From: T. Li et al. (2013) JCO 31, 1039
Molecular Profiling in Cancer and Identification of Actionable Rx Targets

**Mutational Analysis (NGS)**
- ABL
- AKT1
- ALK
- APC
- ATM
- CDH1
- CDKN2A
- c-KIT
- HRAS
- CSF1R
- ERBB2
- ERBB4
- BXWZ
- FGFR1
- FGFR2
- FGFR3
- FLT3
- GNAS
- HNF1A
- IDH1
- JAK2
- JAK3
- KDR
- KRAS
- MLH1
- MPL
- NOTCH1
- NPM1
- NRAS
- BRAF
- PDGFRα
- PTEN
- PTPN11
- RET
- SMAD4
- SMARCB1
- SMO
- SRC
- STK11
- TP52
- VHL

**Protein Expression (IHC)**
- AR
- ER
- HER2
- MGMT
- PR
- PTEN
- SPARCM
- SPARCP
- TLE3
- ERCC1
- PGP
- RRM1
- TOPO1
- TS

**FISH/CISH**
- HER2
- ALK
- ROS1

**Gene Symbols**
- GNAQ
- GNA11
- PIK3CA
- ABL
- AKT1
- ALK
- APC
- ATM
- CDH1
- CDKN2A
- c-KIT
- HRAS
- CSF1R
- ERBB2
- ERBB4
- BXWZ
- FGFR1
- FGFR2
- FGFR3
- FLT3
- GNAS
- HNF1A
- IDH1
- JAK2
- JAK3
- KDR
- KRAS
- MLH1
- MPL
- NOTCH1
- NPM1
- NRAS
- BRAF
- PDGFRα
- PTEN
- PTPN11
- RET
- SMAD4
- SMARCB1
- SMO
- SRC
- STK11
- TP52
- VHL
- EGFR
- TOP2A
- cMET
- AR
- ER
- HER2
- MGMT
- PR
- PTEN
- SPARCM
- SPARCP
- TLE3
- ERCC1
- PGP
- RRM1
- TOPO1
- TS
Molecular Diagnostics (MDx) and Tumor Profiling as the Intellectual Foundation of Rational Care

- subtyping of cancers based on molecular profile(s)
- from one-size-fits-all treatment to targeted Rx
- rational selection of Rx based on presence or absence of Rx ‘target’ in a patient’s tumor
- monitoring of Rx response for early detection of Rx resistance and more agile, adaptive change in Rx (or palliation recommendation)
- elimination of futile therapy (cost, QOL)
- shift focus to optimum therapy plus ethical shift to increase use of palliative care
US Cancer Deaths (2012)

577,000
## US Cancer Prevalence Estimates 2010 and 2020

<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>3461</td>
<td>4538</td>
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<tr>
<td>Prostate</td>
<td>2311</td>
<td>3265</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1216</td>
<td>1517</td>
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<tr>
<td>Melanoma</td>
<td>1225</td>
<td>1714</td>
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<tr>
<td>Lymphoma</td>
<td>639</td>
<td>812</td>
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<tr>
<td>Uterus</td>
<td>588</td>
<td>672</td>
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<tr>
<td>Bladder</td>
<td>514</td>
<td>629</td>
</tr>
<tr>
<td>Lung</td>
<td>374</td>
<td>457</td>
</tr>
<tr>
<td>Kidney</td>
<td>308</td>
<td>426</td>
</tr>
<tr>
<td>Leukemia</td>
<td>263</td>
<td>240</td>
</tr>
<tr>
<td>All Sites</td>
<td>13,772</td>
<td>18,071</td>
</tr>
</tbody>
</table>

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

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

Ini. = within 1 year of Dx; Con = continuing; Last = last year
The Need for New Conceptual Strategies to Improve the Detection and Therapy of Metastatic Disease

- too many drugs fail!
- too many biomarkers fail!
- clinical trials are too expensive and too long!
Cancer: A Formidably Complex Catalog of Genomic Changes and Disruptions in Cellular Molecular Signaling Networks
Copy Number Alteration in 5135 Tumors from 14 Solid Tumor Types

From: G. Iyer et al. (2013) JCO 31, 3133
Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC

From: M. Gerlinger et al. (2012) NEJM 366, 883
EVERY WOMAN IS UNIQUE, SO IS HER CANCER

REGISTER FOR WHEEL TO SURVIVE SAN DIEGO
REGISTER FOR WHEEL TO SURVIVE SAN FRANCISCO
VIEW THE 2012 ANNUAL REPORT

About Clearity
The Clearity Foundation was launched in 2008 to help ovarian cancer patients and their physicians make better-informed treatment decisions based on the molecular profile of the tumor (the “tumor blueprint”). Our goal is to help women with recurrent ovarian cancer live longer, healthier lives by enabling a more individualized approach to therapy selection.

What Are Tumor Blueprints?
A tumor blueprint provides information about tumor characteristics at the molecular level. This genomic analysis can help prioritize drugs that are more likely to be effective for an individual patient.

Patient Stories
Since inception, Clearity has helped to empower hundreds of women with information to individualize treatment based on their unique tumor blueprints.

WATCH OUR VIDEO!
LEARN MORE

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

Genes For ....
The 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
Pervasive Transcription

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

Cell-specific Molecular Interaction Networks

recognition of genome organizational and regulatory complexity

Perturbed Networks and Disease
Whole Genome Sequencing and Characterization of Dysregulation of Molecular Signaling Pathways in Disease

- need for obligate profiling of epigenetic modifications
- limits of current knowledge of function(s) and dynamics of non-coding regions
  - miRNAs, long range promoters/enhancers
- alterations in coding genes are not necessarily reflected in mRNA/protein expression
“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
● urgent need for new conceptual approaches to understand the evolutionary dynamics and dysregulation of molecular signaling networks in tumor progression

● cancer as a complex adaptive system (CAS)
Multi-scale (Spatio-Temporal) Co-Evolution of Cancer Cells and Host Responses as Complex Ecological and Information Networks

- chemical
- viral
- hormonal
- nutritional

initiation/promotion

base state

tumor progression and clonal diversification

Adapted from A. Barker and K. Buetow
Failure Rates for 105 Investigational Drugs 2011-2012*

Adapted from: Nature Reviews Drug Discovery (2013) 12, 569

*148 failures but reason(s) reported only for 105
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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genetic mutation</th>
<th>Tumor type</th>
<th>Acquired drug resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>T790M</td>
<td>Advanced NSCLC</td>
<td>Gefitinib, Erlotinib</td>
</tr>
<tr>
<td>KRAS</td>
<td>Codon 12, 13 and 61</td>
<td>Colorectal cancer</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>KIT</td>
<td>T670I</td>
<td>GIST</td>
<td>Imatinib</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>NS</td>
<td>NSCLC</td>
<td>Erlotinib, Gefitinib</td>
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<tr>
<td>ALK</td>
<td>C1156Y, L1196M</td>
<td>NSCLC</td>
<td>Crizotinib</td>
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<td>MEK1</td>
<td>C121S</td>
<td>Melanoma</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>BRAF</td>
<td>Amplification</td>
<td>Melanoma</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>NRAS</td>
<td>Q61K</td>
<td>Melanoma</td>
<td>Vemurafenib</td>
</tr>
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</table>
Redundancy and Robustness in Molecular Signaling Networks: The Biological Mechanism(s) of Rx Resistance
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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Tumor type and setting</th>
<th>PFS</th>
<th>OS</th>
<th>Trial</th>
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<tbody>
<tr>
<td>Bevacizumab plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XELOK and cetuximab</td>
<td>CRC (2nd line)</td>
<td>-</td>
<td>NR</td>
<td>CAIRO2* (n = 765)</td>
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<tr>
<td>Oxaliplatin-based or irinotecan-based chemotherapy and panitumab</td>
<td>CRC (2nd line)</td>
<td>-</td>
<td>NR</td>
<td>DACCEC14 (n = 1,063)</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>CRC (adjunct)</td>
<td>-</td>
<td>NR</td>
<td>NASSPC0806 (n = 2,672)</td>
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<tr>
<td>Ocepataxol</td>
<td>MBC (2nd line)</td>
<td>-</td>
<td>-</td>
<td>AVADO1101 (n = 426)</td>
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<tr>
<td>Eribulin</td>
<td>NSCLC (2nd line)</td>
<td>+</td>
<td>-</td>
<td>BOLERO1 (n = 636)</td>
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<tr>
<td>Caperepaxol and docetaxel</td>
<td>LGCC (3rd line)</td>
<td>+</td>
<td>-</td>
<td>SUMAST11 (n = 774)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>PC (1st line)</td>
<td>-</td>
<td>-</td>
<td>CALGB10303 (n = 535)</td>
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<tr>
<td>Gemcitabine and eribulin</td>
<td>PC (1st line)</td>
<td>+</td>
<td>-</td>
<td>AVERA16 (n = 351)</td>
</tr>
<tr>
<td>Docetaxel and prednisone</td>
<td>PR (1st line)</td>
<td>+</td>
<td>-</td>
<td>CALGB10401 (n = 1,050)</td>
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<tr>
<td>FOLFOX or XELOX</td>
<td>CRC (adjunct)</td>
<td>-</td>
<td>NR</td>
<td>AVANT22 (n = 3,460)</td>
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<tr>
<td>Axitinib plus</td>
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<tr>
<td>Gemcitabine</td>
<td>PC (1st line)</td>
<td>NR</td>
<td>-</td>
<td>VANILLA* (n = 2,052)</td>
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<tr>
<td>Sunitinib plus</td>
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<tr>
<td>Monotherapy</td>
<td>MBC (2nd line)</td>
<td>-</td>
<td>-</td>
<td>SUN1102013 (n = 700)</td>
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<tr>
<td>Monotherapy</td>
<td>HCC (2nd line)</td>
<td>NR</td>
<td>-</td>
<td>SUN11170*</td>
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<td>Paclitaxel</td>
<td>MBC (2nd line)</td>
<td>NR</td>
<td>NR</td>
<td>SUN10534*</td>
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<tr>
<td>Caperepaxol</td>
<td>MBC (2nd line)</td>
<td>-</td>
<td>-</td>
<td>SUN10L099* (n = 442)</td>
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<tr>
<td>Docetaxel</td>
<td>MBC (2nd line)</td>
<td>-</td>
<td>NR</td>
<td>SUN10L054* (n = 694)</td>
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<td>-</td>
<td>SUN1122Z*</td>
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<tr>
<td>Eribulin</td>
<td>NSCLC (2nd line)</td>
<td>+</td>
<td>-</td>
<td>SUN10679*</td>
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<td>Pemetrexed +</td>
<td>PR (2nd line)</td>
<td>NR</td>
<td>-</td>
<td>SUN11L20* (n = 873)</td>
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<tr>
<td>Sorafenib plus</td>
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<tr>
<td>Carboptaxol and paclitaxel</td>
<td>MM (2nd line)</td>
<td>-</td>
<td>NR</td>
<td>PRIEMA* (n = 270)</td>
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<tr>
<td>Carboptaxol and paclitaxel</td>
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<td>PTK787 plus</td>
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<tr>
<td>FOLFOX</td>
<td>CRC (2nd line)</td>
<td>+</td>
<td>-</td>
<td>CONFIRM2* (n = 655)</td>
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<tr>
<td>FOLFOX</td>
<td>CRC (1st line)</td>
<td>-</td>
<td>-</td>
<td>CONFIRM1 (n = 1,068)</td>
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<tr>
<td>Suvorexant plus</td>
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<tr>
<td>FOLFOX</td>
<td>CRC (3rd line)</td>
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<td>NCT00211281*</td>
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<td>LUXCORN and other agents</td>
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<td>NR</td>
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<td>NCT00204252*</td>
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<td>NR</td>
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<td>-</td>
<td>-</td>
<td>TEST14* (n = 1,141)</td>
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<td>-</td>
<td>ZD451* (n = 534)</td>
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<td>Dentican plus</td>
<td></td>
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<tr>
<td>FOLFOX</td>
<td>CRC (3rd line)</td>
<td>-</td>
<td>NR</td>
<td>HORIZON III* (n = 1,076)</td>
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<tr>
<td>Monotherapy or Inotuzumab</td>
<td>GEM (2nd line)</td>
<td>-</td>
<td>-</td>
<td>INOZIL* (n = 323)</td>
</tr>
</tbody>
</table>

Expression of Same Mutation in Cancers Arising in Different Cell Lineages but with Different Response to Same Targeted Therapy

Melanoma  
BRAF-V600

positive response to vemurafenib

CRC  
BRAF-V600

10% patients carry mutation but unresponsive to vemurafenib due to compensatory activation of EGFR
Molecular Signaling (Information) Network Dysregulation and the Challenge of Network Pharmacology
Network Pharmacology and Drug Discovery: Key Principles

- there are few single molecular targets for Rx action
- effective Rx requires modulation of multiple targets in multiple pathways
- there are no linear pathways, only networks and subnetworks
- there are also highly interconnected networks/subnetworks between tissues
  - e.g. modulation of liver network induces changes in pancreatic islet network
“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
Tumor Cell Heterogeneity and Core Challenges in Cancer Diagnosis and Treatment

- Improved prediction of network dysregulation patterns and most likely drug resistance/immune evasion “escape pathways”
- New minimally invasive methods for longitudinal monitoring of clonal dynamics with tumor progression
- More agile therapeutic regimens to reflect changing clonal dynamics and earlier detection of emergence of drug-resistant clones

Confronting the complexity of clonal heterogeneity and metastatic disease
The Dynamic Evolution of Niche Microenvironments in Metastatic Cancer Via Local and Systemically Recruited Host Cells and Cytokine Production

Immunology-Oncology: An Emerging Therapeutic Strategy

YERVOY 2-year overall survival:

24%*

(95% CI: 16.0, 31.5) vs 14% for gp100 (95% CI: 8.0, 20.0)*

*Estimated overall survival rate with YERVOY alone in the pivotal phase 3 study publication.

Amgen is researching ways to help T cells target cancer.

Find it

Fight it

Oncolytic immunotherapy

ONCOLYTIC IMMUNOTHERAPY

Oncolytic immunotherapy involves a modified virus to help T cells find and fight cancer cells as part of a systemic, tumor-specific immune response.

Learn more at: www.oncolyticimmunotherapy.com

Genentech

In advanced prostate cancer

PROVENGE

ACTIVATE THE POWER OF THE IMMUNE SYSTEM.
EXTEND SURVIVAL.

PROVENGE activated T cell

What if you could help the immune system respond to cancer cells?
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
Monitoring The Evolution of Rx Resistance With Tumor Progression

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

From: Zong et al. (2012) Science 338, 1622-26
viSNE (Visualized Nearest Neighbor Embedding)
Analysis of Mass Cytometry Data at Single Cell Resolution in AML at Initial Diagnosis and Relapse

From: E-a David et al. (2013) Nature Biotechnol. 31, 545
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

- faster detection of emergence of Rx-resistant/immune evasion clones
  - pre-exist prior to Rx
  - acquired resistance driven by relapse risk
  - minimal residual disease and relapse risk
- scientific foundation for more agile shifts in treatment regimens
  - clinical care
  - new clinical trial designs
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
Antibody-Mediated Capture of Tumor-Derived Exosomes from Human Prostate Cancer Cells

From: Caris Life Sciences
The Isolation and Profiling of Circulating Tumor Cells (CTCs) and Identification of Cancer Stem Cells (CSCs)

From: V. Plaks et al. (2013) Science 341, 1186
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?
Molecular Profiling and Redesigning Cancer Clinical Trials
Molecular Profiling and Stratification of Patient Populations and Improved Clinical Trials of Investigational Drugs

- MDx stratification of patients for ‘enrichment’ trials using only target-positive cohorts
- reduce attrition and candidate failure rate, particularly in high cost Phase III studies
- reduce clinical development costs (and time?)
- streamline regulatory review and approval
<table>
<thead>
<tr>
<th>Target</th>
<th># Patients Screened</th>
<th># Eligible Patients</th>
<th># Centers</th>
<th># Countries</th>
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</thead>
<tbody>
<tr>
<td>EML4 ALK⁺: lung cancer*</td>
<td>1500</td>
<td>82</td>
<td>9</td>
<td>1</td>
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<tr>
<td>HER2⁺: gastric cancer**</td>
<td>3803</td>
<td>549</td>
<td>122</td>
<td>24</td>
</tr>
</tbody>
</table>

* 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)
- 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
Cancer Clinical Trials
Defining Priorities for Phase I Studies in Increasingly Small Subsets of Target-Positive Patients

- burgeoning portfolio of investigational agents
- increasing number directed to identical molecular targets
- transcending the constraints of initial evaluation in treatment failure/refractory patients
  - prior Rx failure typically without evidence that patient exhibited relevant Rx target for the failed agent
  - Rx selection of cellular phenotypes that may be unrepresentative of tumor at initial presentation
  - impact of prior Rx cycles on host defense and clonal dynamics
Selection of Drug Candidates for Phase I Trials

- validate presumed MOA in Phase I with target-enriched patients
- greater use of neo-adjuvant (pre-surgery) Rx and assessment of pathologic complete response (PCR)
  - threshold PCR response level to proceed?
  - assumes optimum dosing and availability of predictive biomarkers
Consequences of Foregoing Phase III RCTs and Granting of Accelerated Regulatory Approval

- faster trials and patient access to promising Rx (terminal diseases)
- less definitive evidence regarding safety and efficacy
- possibility that post-marketing studies will not be confirmatory and product withdrawal
- accelerated regulatory approval pathway should provide facile reciprocal withdrawal provisions
- need for enforcement of sponsors to launch/complete post-approval studies with reasonable speed
Defining What Works and Defining Value
The Need for a Better Conceptual Framework for Understanding the Biology of Different Patterns of Progression and Risk in Different Tumor Types

- cancer still perceived (and treated) as a diagnosis with lethal consequences if left untreated
- clear evidence of indolent tumors and screening programs result in increased incidence
  - breast, prostate, lung and thyroid
  - ‘IDLE’ lesions
- ‘cancer’ should be reserved for lesions with reasonable likelihood of lethal progression if untreated (“consequential lesions”)
  - mitigate the “over diagnosis-over treatment” dilemma
### Change in Incidence and Mortality 1975-2010 Per 100,000 Individuals

**Surveillance, Epidemiology and End Results Data**

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>% Change</th>
<th>Mortality</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
<td>105.07</td>
<td>126.02</td>
<td>31.45</td>
<td>21.92</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td>94</td>
<td>145.12</td>
<td>30.97</td>
<td>21.81</td>
</tr>
<tr>
<td><strong>Lung and bronchus</strong></td>
<td>52.26</td>
<td>56.68</td>
<td>42.56</td>
<td>47.42</td>
</tr>
<tr>
<td><strong>Colon</strong></td>
<td>41.35</td>
<td>28.72</td>
<td>28.09</td>
<td>15.51</td>
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<tr>
<td><strong>Cervical</strong></td>
<td>14.79</td>
<td>6.71</td>
<td>5.55</td>
<td>2.26</td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td>4.85</td>
<td>13.83</td>
<td>0.55</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Melanoma</strong></td>
<td>7.89</td>
<td>23.57</td>
<td>2.07</td>
<td>2.74</td>
</tr>
</tbody>
</table>

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

- **Over-diagnosis/over treatment of indolent lesions**
- **Slow growing consequential tumors/screening reduces morbidity/mortality via removal of precursor lesions**
- **Screening expands indolent incidence but limited impact on aggressive subtypes**
The Imminent Arrival of the Zettabyte \((10^{21})\) Era
The Growing Education and Knowledge Gaps in Comprehension of Molecular Medicine Concepts Among Healthcare Professionals
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
The Wellness Premium

Greater Engagement and Incentivization of Consumers/Patients in Care Decisions and Sustaining Wellness

Social Media, Patient Advocacy Groups and New Opportunities for Observational Studies on Population Health and Outcomes
Interactive Patient-Centered Initiatives (PCIs)

- social media, patient advocacy and consumer/care-giver engagement
- new opportunities to capture, share, mine and integrate data
  - both research and clinical studies
- matchmaking for more proficient research studies/clinical trial recruitment
Physician (HCP): Patient Communications in Chronic and/or Terminal Illness

- clinical challenge of balance between ethical transparency and empathy
- the vulnerability of patients: “Trust and surrender” to presumed “authoritative knowledge”
- physicians/HCPs are rushed and stressed
- oncologists know but often deny the limited efficacy of many interventions
  - when to move from continued aggressive intervention to palliative care?
  - why do so many physicians chose to go gently into the night? (WSJ)
- the syntax of survival (JAMA 2013 310, 1027)
  - complex interplay between fear, hope, optimism and reality
  - verbal content, tone, facial expression and body language
patient autonomy is valued by easily relinquished

transparency and the paradox of choice (B. Schwartz)
  - the more choices offered the less patients want to choose

powerful predispositions to elect aggressive therapy
  - avoid anticipated regret: “I know I did everything I could”
  - economic/legal advantages for physician to defer to SOC/consumer guidelines

increasing shortcomings in clinical guidelines/compendia
  - protracted updating
  - patient-stratification based on molecular profiling
Challenging Questions Regarding Future Directions in Cancer Research and Clinical Oncology
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?
Cost of Recently Approved Anti-Cancer Drugs

- brenfuximab (Adcetris) $216,000/course
- ipilimab (Yervoy) $123,000/year
- crizotinib (Xalkori) $115,000/year
- vismodegib (Erivedge) $75,000/course
- sipuleucel-t (Provenge) $93,000/year
- petuzumab (Perjeta) $70,800/year
- cabazitaxel (Jevtana) $96,000/year
- vemurafenib (Zelboraf) $61,000/year
- abiraterone (Zytiga) $60,000/year
- premetrexed (Alimta) $30,000/course
Doing More, But Not Necessarily Doing Better

Buy and Bill: Oncologists’ Financial Incentives Are Not Aligned With Rational Therapy and Quality of Care
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology

MDx profiling to ID Rx response/resistance

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

segmentation of major cancers into ever smaller cohorts

MDx and Omics Profiling

Scientific Foundation for Precision Diagnosis and Rational Treatment Selection

Propagation of Irrational Therapeutic Strategies With Limited Effectiveness
The Need for Value-Based Reimbursement of New Molecular Profiling Services: A Market Failure that Threatens Innovation in Precision Medicine

- MDx and Omics Profiling
- SOC Rx guidelines

- 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 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
The Thin Line Between Hype and Hope
Choices

• celebrity populism and belief that more money will solve everything

  versus

• fundamental reassessment of why therapeutic success for metastatic solid tumors remains so elusive

  plus

• recognition that cancer is a complex adaptive system demands major changes in current approaches to cancer research and clinical oncology
Molecular Profiling is a Disruptive Technology

Molecular Profiling Will Drive Major Shifts in Cancer Diagnosis, Clinical Care, Business Models and Markets
is the massive public and private sector R&D investment in new anticancer Rx directed to **single** targets/single pathways intellectually flawed based on current knowledge that **multiple** pathways/modules/and subnetworks are dysregulated?
Is Rx Therapy of Advanced Metastatic Disease a Desired but Unattainable Goal?
A Nasty (But Largely Ignored) Question

- is the scale of molecular network dysregulation and relentless ‘state shifts’ (clonal dynamics) in advanced metastatic disease so extreme that Rx-circumvention or reset of network stability (homeostasis) via Rx action at multiple sites in multiple pathways are not feasible with current approaches?
Challenging Questions

- would returns from current multi-billion investments in cancer research and drug discovery be improved by realignment of the funding balance to accord higher priority to biomarker-based tumor profiling services?
  - earlier (pre-metastatic) detection of ‘consequential’ tumors (=cure)
  - robust separation of indolent and consequential tumors (reduce overtreatment of low risk disease)
  - dynamic monitoring of tumor progression and more agile Rx shifts to reflect emergence of Rx-resistant clones
  - establish comprehensive inventory of Rx-escape pathways to better guide new Rx discovery
Silos Subvert Solutions: Organizational and Cultural Challenges

- the need for integrated end-to-end solutions
  - building new organizational and operational competencies and infrastructure
- the imperative to build new capabilities in inter- and cross-disciplinary research
  - big science and big data
  - clinical medicine and regulatory science
  - public: private partnerships
  - clinical education
Silos Subvert Solutions: The Slow Response of Academic Biomedicine to Technology Convergence and Cross-Disciplinary Requirements

- Predominance of investigator-centric, reductionist approaches
- Fragmented data and poor inter-operability of databases
- Anachronistic curricula
- Institutional sclerosis and career barriers
- Inadequate cyberinfrastructure
- Specialty silos reinforced by funding policies and promotion
- Poor standardization and reproducibility of publications
New Conceptual, Methodological and Organizational Frameworks for Data-Intensive Biomedical R&D

- Increasing dependency on systems-based, data-intensive analytics and new knowledge networks
- Agile knowledge networks
- New curricula and career rewards
- Intelligent systems
- Integration and analytics for large scale datasets
- Ontologies, semantics, facile data sharing and interoperabilities
- Increased automation
- Quantitative data open data
- Technology and cross-domain convergence
- Large scale team-based projects
CHANCE
is good
you go first
Overcoming Resistance to Change

“Even the Gods cannot strive against necessity.”

Ancient Greek Proverb