The Evolution of Personalized Medicine: Opportunities and Challenges

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Keynote Presentation:
The Institute for Systems Biology International Symposium:
Systems Biology and P4 Medicine.
The Institute for Systems Biology, Seattle, WA • May 15-16, 2011
Declared Interests:

- Board of Directors: Monsanto, Exelixis, Caris Life Sciences
- Scientific Advisory Board: Synthetic Genomics, Anacor
- IOM Forum on Global Infectious Diseases
- USG Activities: DoD, DHS
Sustaining Innovation in an Era of Economic Constraint

Molecular Medicine and Personalized Medicine: Key Drivers of Improved Diagnosis and Rational Therapeutics

Silos Subvert Solutions: The Imperative for Systems-Based Approaches to Integrate Diagnostics, Therapeutics and Informatics to Improve Health Outcomes and Control Costs

Managing Massive Data: Radical Reform of the Organization and Funding of Research, Healthcare Delivery and Industry Engagement
The Healthcare Challenge

- Increasing cost of care and acceleration of new technologies
- Innovation and Cost of Care
- Access to Care

Outcomes
- Clinical, economic, quality-of-life

Unmet medical needs

Infinite demand versus finite resources

Increasing cost of care and acceleration of new technologies
The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities

Health Status

Healthy/Low Risk
At-Risk
High Risk

20% of the Population Generate 80% Cost

multiple co-morbidities
end-of-life care
chronic disease progression
chronic disease early stage
acute disease

Value
Cost

20% of the Population
Generate 80% Cost
P4 Medicine

- predictive
- preventive
- personalized
- participatory

Dr. Leroy Hood
Institute for Systems Biology,
Seattle, Washington
P4 Medicine + Two More ‘P’s’

**P4 Medicine**

- predictive
- preventive
- personalized
- participatory

**Price**

- research innovation
- products
- delivery of care

**Policy**

- organization of biomedical research
- healthcare delivery
- large scale information infrastructure

Dr. Leroy Hood, Institute for Systems Biology, Seattle, Washington

Dr. Leroy Hood, Institute for Systems Biology, Seattle. Lecture on P4 Medicine (posted online at http://www.slideshare.net/osumedicalcenter/dr-leroy-hood-lecture-on-p4-medicine)
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 Signatures of Disease or Predisposition to Disease
Classification of Six Subgroups of Medulloblastoma

From Pharmaceuticals to Pharmasuitables: Right Rx for the Right Disease (Subtype)

ID Molecular Targets for Rx Action

Disease Profiling to Identify Subtypes (+ or - Rx Target)
K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

- higher response in patients with wt K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)
- regulatory endorsement in product labeling
- payor adoption

clinical guidelines
# Use of Tumor-Associated Biomarkers as Potential Rx-Response Prediction Assays

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Marker</th>
<th>Drug</th>
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<tbody>
<tr>
<td>Somatic Mutations</td>
<td>KRAS</td>
<td>cetuximab; panitumumab; gefitinib; erlotinib</td>
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<tr>
<td></td>
<td>BRAF</td>
<td>cetuximab; panitumumab; gefitinib; erlotinib</td>
</tr>
<tr>
<td></td>
<td>PI3K</td>
<td>cetuximab; panitumumab; lapatinib; trastuzumab</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>gefitinib; erlotinib</td>
</tr>
<tr>
<td>Germ Line Mutations</td>
<td>BRCA1/2</td>
<td>olaparib</td>
</tr>
<tr>
<td>SNPs</td>
<td>UGT1A1</td>
<td>irinotecan</td>
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<tr>
<td></td>
<td>CYP450</td>
<td>tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Fc RII/III</td>
<td>trastuzumab; rituximab; erbitux</td>
</tr>
<tr>
<td>Gene Amplification or Copy Number Variant</td>
<td>HER2</td>
<td>trastuzumab</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>gefitinib; erlotinib</td>
</tr>
<tr>
<td></td>
<td>Top2A</td>
<td>anthracyclines</td>
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<tr>
<td>Protein Over-Expression</td>
<td>EGFR</td>
<td>cetuximab</td>
</tr>
<tr>
<td></td>
<td>HER2</td>
<td>trastuzumab</td>
</tr>
<tr>
<td></td>
<td>ERCC1</td>
<td>platinum compounds</td>
</tr>
<tr>
<td></td>
<td>B-tubulin</td>
<td>taxanes</td>
</tr>
<tr>
<td>Protein Loss; Mutations, Copy Number Variant</td>
<td>PTEN</td>
<td>trastuzumab</td>
</tr>
</tbody>
</table>
Molecular Medicine and Rational Therapeutics: Molecular Diagnostics and Targeted Rx

- opening era in linking disease molecular pathology to rational Rx
- increasing payor, regulatory and public pressures for reliable ID of Rx-responsive patients
- demand for Dx-Rx combinations will intensify
- Dx-Rx combination will become an obligate element of NDA/BLA submission and product labeling
- development of Dx-Rx combinations as intrinsic components of R&D programs for investigational Rx

Companion Therapeutics Selected by Precision Diagnostics
Pharmaceutical-Diagnostic Partnerships

**KEY:**
- Companion Diagnostic
- Collaboration*
- Acquisition
- License**

**2007**
- BioMerieux & Merck
- BioMerieux & Ipsen SA
- Celera & Ipsen
- DxS & Amgen
- Abbott & OSI/Genetech/Roche
- Aureon Labs & Pfizer
- Celera & Abbott
- Celera & Merck
- Dako & Genentech

**2008**
- BioMerieux & Merck
- BioMerieux & Ipsen SA
- Celera & Abbott
- Dako & Genentech
- GSK & BioMerieux
- Celera & Bayer
- Dako & OSI Pharma
- Abbott & GSK
- Abbott & Pfizer
- Almac & Lilly
- Dako & Genentecy/Roche
- Monogram Biosci LabCorp & GSK
- Qiagen DxS & BMS/Imclone

**2009**
- GSK & BioMerieux
- Celera & Bayer
- Dako & OSI Pharma
- Abbott & GSK
- Abbott & Pfizer
- Almac & Lilly
- Dako & Genentecy/Roche
- Monogram Biosci LabCorp & GSK
- Qiagen DxS & AstraZeneca/Teva

**2010**
- Merck & Millipore
- Genzyme & CMIC
- ThermoFisher & ActivX Biosciences
- Kyorin Pharma
- Ophtherion & Sequenom
- GSK & BioMerieux
- Roche & Merck
- BMS & Saladax
- Abbott & GSK
- Novartis & Cepheid
- Prometheus & Bayer
- Pfizer & DxS/Qiagen
- Dako & AstraZeneca
- Monogram Biosci LabCorp & GSK
- Qiagen DxS & Pfizer

*List is Not Exhaustive

*Collaboration refers to partnerships biomarker discovery and assay development
**License refers to biomarker or assay licensing deals

Source: Scientia Analysis
Molecular Profiling and Segmentation of Patient Populations and New Clinical Trial Designs

- Rationale that only patients with the relevant Rx molecular target(s) will respond
  - Streamline drug development via enrichment trials in target-positive patient subsets

- Key assumptions
  - Molecular target(s) chosen accurately predict/correlate with Rx efficacy
  - Robust assay available (regulatory complexities of validation/qualification)

- Logistical and economic issues in ID of small/rare target-positive patient subsets
  - Size of initial screening cohort
  - Need for multi-center consortia (national/international)
Large Scale Profiling of Cancer Patients to Identify Cohorts Expressing Rx Target(s) for Phase II Trials

<table>
<thead>
<tr>
<th>Target</th>
<th># Patients Screened</th>
<th># Eligible Patients</th>
<th># Centers</th>
<th># Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML4 ALK⁺: lung cancer*</td>
<td>1500</td>
<td>82</td>
<td>9</td>
<td>1</td>
</tr>
<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
Multiplex Profiling Platforms for Molecular Diagnostics

Transcriptomics

Proteomics

Immunosignatures

miRNAs

Low Cost Whole Exome- and/or Whole Genome Sequencing
Whole Genome Sequencing (WGS)

- rapid improvements in instrumentation, cost and speed
- higher information content than exome profiling
- combination with transcriptome profiling to ID chimeric fusion transcripts
- cost:performance trajectory for WGS may soon be cheaper than cumulative cost from expanding panels of individual MDx tests
- eliminates IP challenge/royalty mountain issue with multiplex MDx panels
Big Genomics and Managing Massive Data

- sequence data generation outstripping analytics
- 1000 Genomes Project (2010) generated more data in 6 months than GenBank accumulated in 21 years
- NGS storage as high-resolution images imposes disproportionate archiving burden
  - shift to discard raw data and easier to resequence samples (assumes availability)
- data analytics and bioinformatics personnel as major choke points for large scale population profiling studies
- customized data conversion for different decision categories and decision-makers
- causal correlations with disease and Rx responsiveness established by metanalysis of large WGS datasets will shift many clinical sequencing needs back to specific genomic regions
Pharmacogenetic Predisposition to Adverse Drug Reactions

- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- est. cost of $30-50 billion
The Application Gap in the Clinical Use of Pharmacogenomic (PG) Information Relevant to Patient Safety

- 121 drug labels contain PG information
- 24.3% of 36.1 million patients took one or more drugs with PG information labels
- less than 0.1% patients tested for PG risk for Rx
- 68% US adults taking Rx drug also taking OTC product or dietary supplements
- 80,000 Rx X 300,000 OTC X 75,000 supplements = > 30 billion theoretical combinations
We Are Not Alone: Variation in the Human Microbiome as a Potential Factor in Health and Disease
The Human Microbiome: A Complex Meta-System

- host, bacteria, viruses, other organisms, metabolites, xenobiotics
- is there a core microbiome?
- how do perturbations affect disease risk/disease progression and vice-versa?
- what are the effects of microbiome metabolism of drugs and environmental xenobiotics and the resulting metabolite spectrum on health and/or treatment outcomes?
The Hunt for Gene Loci Associated with Predisposition and/or Progression of Complex, Multigenic Human Diseases
Disease Predisposition Risk Profiling for Multigenic Late-Onset Disorders

- slower evolution than many predict
- Genome-Wide Association Studies (GWAS)
  - high cost and low yield to date in terms of clinically exploitable markers
  - diseases arise from combinations of low penetrance alleles versus small sets of high penetrance alleles
- substantial ambiguities regarding probabilistic risk of developing overt disease
  - epistasis
  - epigenetics
  - environmental confounders, including Rx
Disease Predisposition Risk Profiling for Multigenic Late-Onset Disorders

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- Genome-Wide Association Studies (GWAS)
  - high cost and to date low yield in terms of clinically exploitable markers
  - disease origins from low penetrance alleles versus small combinations of sets of high penetrance alleles
- substantial ambiguities regarding probabilistic risk of developing overt disease
  - epistasis
  - epigenetics

Regulatory oversight of consumer genomic testing (CGx) for future risk of major diseases
Evolution of Molecular Profiling and Diagnostics for Improved Disease Detection, Classification and Risk Evaluation

- Low Cost WGS
- Adverse Event Risk
- Rx-Dx Combination for Optimum Rx Selection
- Molecular Markers for Disease Subtypes
- 5 yr

- P-Rx
- Prophylactic Rx
- Predisposition Profiling (PDx) and Tracking for Early Detection of Disease Emergence
- Consumer Genomics
- Genetic Predisposition to Disease
- PDx
- 10 yr

- 15 yr

Low Cost WGS and Adverse Event Risk lead to Rx-Dx Combination for Optimum Rx Selection, which in turn reveals Molecular Markers for Disease Subtypes. This process continues over 5, 10, and 15 years, with each stage leading to Prophylactic Rx and Predisposition Profiling (PDx) for early detection of disease emergence.
Translation of the Full Potential of Molecular Medicine into Routine Clinical Practice

A Complex Multi-Dimensional Challenge
Individual Variation, Genomic Complexity and the Challenge of Genotype-Phenotype Prediction

- recognition of increasing organizational and regulatory complexity
  - SNPs, haplotypes, CNVs, indels
  - non-coding RNA regulatory networks
  - epistasis
  - epigenetics and imprinting
  - nuclear compartmentalization and *trans*-expression
  - environmental interactions (exposome)
  - effects of Rx and other xenobiotics

- non-linear relationship between genotype and phenotype
Genomic Complexity, Individual Variation and the Challenge of Genotype-Phenotype Prediction

- Recognition of genome organizational and regulatory complexity
- Non-linear relationship between genotype and phenotype
- Formidable analytical challenges for biomedical and mathematical sciences

- Has the gap between basic science and realizable therapeutic applications widened?
- How can systems complexity be deconvoluted to identify tractable approaches for diagnosis, therapy selection and disease risk predisposition assessment?
The Evolution of Drug Discovery

- empirical screening

- cellular and molecular pharmacology but continued reliance on whole cell assays retains a significant level of ‘systems-complexity’

- genomics and HTS of isolated molecular targets: reductionism and elimination of systems complexity/context

- mapping molecular pathways and networks and a return to systems pharmacology
Network Pharmacology and Drug Discovery: Key Principles

- there are few single molecular targets for Rx action
- effective Rx requires modulation of pathways and networks
- there are no linear pathways, only subnetworks and networks
- there are also highly interconnected networks between tissues
  - e.g. modulation of liver network induces changes in pancreatic islet network (E. Schadt et al. (2008) PLoS 6, 1020)
Systems Pharmacology

- Elucidation of Rx action across multiple spatio-temporal scales
- Analysis of Rx action in context of network topology
  - edges, nodes and hubs
- Same drug: interaction with multiple targets
- Same target: interaction with multiple drugs
- Mapping chemotypes to pathways and subnetworks for targeted (poly)pharmacology
The Challenge of Drug Discovery in Late-Onset, Chronic, Multigenic Diseases

- mapping complex alterations in multiple molecular pathways and subnetworks, particularly in chronic, progressive disease

- ID of pathway/subnetwork connectivities, cross-talk and redundancies and implications for Rx strategies for “homeostatic reset”
  - multi-target Rx action

- designing suitable polypharmacology for multiple Rx targets
  - SAR promiscuity in a single molecule
  - Rx combinations
  - limit adverse off-target effects and/or on-target binding in non-target tissues
The Challenge of Drug Discovery for Late-Onset, Chronic, Multigenic Diseases

- complexity and multiplicity of pathway/network perturbations increases the probability of Rx refractoriness/resistance via compensatory pathways
- amplified pathway and subnetwork perturbations with disease progression?
  - significant inter-patient and intra-patient heterogeneity
  - cancer as the most extreme example?
“The War on Cancer”

National Cancer Act of 1971

December 23, 1971

In this issue of *Science*, we commemorate the 40th anniversary of the U.S. National Cancer Act, which provided a massive stimulus for cancer research. At the start of this “Cancer Crusade,” researchers were already tackling some tough questions, as reflected in papers published by *Science* in 1971. Among them: How do abnormalities in chromosome number arise in tumor cells? Can tissue-specific markers be used to determine the epithelial versus mesenchymal origin of a solid tumor? Can the immune system be manipulated so that it recog-
### 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>
</tr>
<tr>
<td>Prostate</td>
<td>2311</td>
<td>3265</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1216</td>
<td>1517</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1225</td>
<td>1714</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>639</td>
<td>812</td>
</tr>
<tr>
<td>Uterus</td>
<td>588</td>
<td>672</td>
</tr>
<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>

Oncology Therapeutics: An Unsustainable Enterprise Using Current Approaches?

- highest failure rate in clinical trials of any therapeutic class
- unchecked Rx cost for increasingly questionable clinical outcomes and QOL
- anachronistic SOC guidelines that have largely failed to incorporate the rapid momentum of new insights in causal molecular pathologies and tumor subtyping
- slow adoption of new clinical trial designs using stratified patient subpopulations
- testing of new investigational drugs on late-stage patients with advanced and/or refractory disease
  - cellular composition likely unrepresentative of tumors at initial presentation
  - effect of repeated Rx cycles on clonal phenotypes and immune system damage
The Cost of Cancer Care: The Example of Addition of Bevacizumab to Standard Therapy

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**ovarian**

- GOG Study 218 (J. Clin. Oncol. 2011 29, 1247)
  - $401,088/progression-free life year saved

**breast**

- ECOG E2100 (Eur. J. Cancer 2009 45, 1397)
  - over $200,000/QALY

- AVADO, RIBBON1 and ATHENA studies (J. Clin. Oncol. 2011 29, 1222)
  - no cost estimate but median PFS lower than in ECOG E2100

- NICE (UK) estimated QALY of $170,000 to $400,000
### How Many Drugs Acting on the Same Target Can The Market Support? PI3K Inhibitors in Cancer Clinical Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayer</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Exelixis/Sanofi</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Genentech/Roche</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Novartis</td>
<td>Phase I/II</td>
<td>Dual mTOR/PI3K</td>
</tr>
<tr>
<td>Novartis</td>
<td>Phase I/II</td>
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<tr>
<td>Pfizer</td>
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<td>Pfizer</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
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<tr>
<td>Semafore</td>
<td>Phase I</td>
<td>Dual mTOR/PI3K</td>
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<tr>
<td>Exelixis/Sanofi</td>
<td>Phase I/II</td>
<td>PI3K</td>
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<td>Genentech/Roche</td>
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<td>Oncothyreon</td>
<td>Phase I/II</td>
<td>PI3K</td>
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<tr>
<td>Zenyaku Kogyo</td>
<td>Phase I</td>
<td>PI3K</td>
</tr>
<tr>
<td>Novartis</td>
<td>Phase I</td>
<td>PI3Kα</td>
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<td>Amgen</td>
<td>Phase I</td>
<td>PI3Kδ</td>
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<tr>
<td>Calistoga Pharma</td>
<td>Phase I/II</td>
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</tr>
<tr>
<td>Genentech/Roche</td>
<td>Phase I</td>
<td>PI3K δ</td>
</tr>
</tbody>
</table>

SOURCES: Semafore, ClinicalTrials.gov
YOU'RE NOT JUST
STRENGTHENING MUSCLES.
YOU'RE STRENGTHENING
A MOVEMENT.

STAND UP. TUNE IN.
The Fight Against Cancer Continues.

OBAMA IN POWER: A SECRET HISTORY
BY JONATHAN ALTER
DOUBLE ISSUE: MAY 24 & 31, 2010

DESPERATELY SEEKING CURES
MEDICAL RESEARCH ISN'T MAKING PROGRESS RAPIDLY ENOUGH.

National Breast Cancer Coalition
The Breast Cancer Deadline
2020

Breast Cancer Deadline
Why Now?
September 20, 2010
BreastCancerDeadline2020.org
The Complexity of Cancer Genomes

**LUNG CANCER**
Cancer: small-cell lung carcinoma

- Sequenced: full genome
- Source: NCI-H209 cell line
- Point mutations: 22,910
- Point mutations in gene regions: 134
- Genomic rearrangements: 58
- Copy-number changes: 334

**Highlights:**
Duplication of the CHD7 gene confirmed in two other small-cell lung carcinoma cell lines.


**SKIN CANCER**
Cancer: metastatic melanoma

- Sequenced: full genome
- Source: COLO-829 cell line
- Point mutations: 33,345
- Point mutations in gene regions: 292
- Genomic rearrangements: 51
- Copy-number changes: 41

**Highlights:**
Patterns of mutation reflect damage by ultraviolet light.


**BREAST CANCER**
Cancer: basal-like breast cancer

- Sequenced: full genome
- Source: primary tumour, brain metastasis, and tumours transplanted into mice
- Point mutations: 27,173 in primary, 51,710 in metastasis and 109,078 in transplant
- Point mutations in gene regions: 200 in primary, 225 in metastasis, 328 in transplant
- Genomic rearrangements: 34
- Copy-number changes: 155 in primary, 101 in metastasis, 97 in transplant

**Highlights:**
The CTNNA1 gene encodes a putative suppressor of metastasis that is deleted in all tumour samples.


**BRAIN CANCER**
Cancer: glioblastoma multiforme

- Sequenced: exome (no complete Circos plot)
- Source: 7 patient tumours, 15 tumours transplanted into mice (follow-up sequencing on 21 genes for 83 additional samples)
- Genes containing at least one protein-altering mutation: 685
- Genes containing at least one protein-altering point mutation: 644
- Copy-number changes: 281

**Highlights:**
Mutations in the active site of IDH1 have been found in 12% of patients.

Cancer Therapeutics: The Most Perplexing Question of All

- does the scale of pathway/subnetwork perturbations in metastatic, advanced disease in the solid malignancies pose an insurmountable technical barrier to design of poly-target (promiscuous) agents and/or Rx combinations required to achieve curative or even effective therapy?

- is the only viable strategy for major progress in reducing the clinical, economic and emotional toll of cancer to focus on improved detection of early pre-metastatic disease?
Rethinking Approaches to Cancer
And Other Chronic Diseases

Reversing The Imbalance
in Current Research Investments in
Diagnostics Versus Therapeutics:
A Better Return on Investment?

Biomarkers, Biosignatures and Molecular Diagnostics:
The Key Value Drivers for Predictive
and Preventive Healthcare
The Poor Performance Record of Biomarker Discovery and Validation

- ‘publish and vanish’
  - over 120,000 claimed biomarkers or biomarker combinations (biosignatures)
  - less than 100 molecular diagnostics in clinical use or advanced validation trials
- literature dominated by anecdotal studies
  - academic laboratories
  - lack of standardization: biospecimens to analytical platforms
  - small patient cohorts and insufficient statistical power
  - poor replication and confirmatory studies
- widespread lack of understanding of regulatory requirements in academic research community
  - GLP, GMP, Records, RUO instruments versus Clinical Use
  - technical complexities of multiplex assays
  - new regulatory oversight (IVDMIAs)
Identification and Qualification of Biomarkers for Improved Disease Diagnosis and Treatment Selection

Success Demands a Systems-Based Approach
Access to High Quality Biospecimens, Biobanks and DNA Repositories: A Major Obstacle for Biomarker Discovery
Building Large Scale, Standardized Resources for Biomedical Research

- rigorously phenotyped/matched/consented disease and normal specimens
- biobanking: leadership and national policies to create a vital research resource
- standardization of pre-analytical and analytical methods
- standardized data ontologies and formats for large scale datasets/federated databanks
Validation of Disease Associated Biomarkers: Scale and Statistical Power

- the high dimensionality small sample size (HDSS) problem
  - high number of variables (2000-10000) and low sample size (10-100)
  - increased risk of selection of variables due to chance (overfitting)
- disease related differences are small compared to biological variability
- many variables behave as QTLs with graded continuum rather than binary normal: disease separation
- statistical powering of validation studies
  - “the 20:200:2000 rule”
Blood-Based Multiplex Diagnostics

- Blood as highly informative biospecimen for Dx profiling
- Bathes all organs
- Many ‘biosignatures’ from diseased tissues expressed in blood
- Minimally invasive, low cost acquisition and ease of repeated sampling versus tissue biopsy
- Each patient acts as their own control for longitudinal monitoring

Source: For the Record 12-6-10
If You Build It, Will They Pay?
Adoption of Disruptive Innovation

“If it isn’t billable – it isn’t going to happen”

• new technology/service that simplifies a complex/costly problem
• business model that allows market adoption of the simplified solution at low(er) cost
• value-based versus cost-based reimbursement
• new billing codes
• reimbursement for professional analysis of remote patient monitoring data streams
Wellness:

The Most Broad and The Most Valuable Definition of Personalized Healthcare

Sensor Networks for Remote Health Status Monitoring: Wireless Integrated Data Systems

- geolocation data (where)
- temporal information (when)
- contextual information (what)
- improved decision support (action)
Wireless Devices and Health Status Monitoring
Remote Health Monitoring and Management of Chronic Diseases

Lifestyle and Fitness Tracking

Information for Proactive Health Awareness (Wellness)
Wireless Devices for Health Status Monitoring

Zio™ Patch
Molecular Diagnostics and Health Information Systems as Key Elements in the Evolution of Integrated Healthcare Delivery

- Molecular Profiling: Dx/PDx
- Earlier Disease Detection and Rx Guidance
- Remote Status Monitoring
- Proactive versus Reactive Intervention
- Compliance Monitoring
- Health Data for Optimized Decisions and Outcomes
- Increased Personal Responsibility for Wellness

Risk Assessment
Risk Management
Risk Mitigation

DATA
From Fragmented Healthcare Delivery To Integrated Health Systems and Services
Health Care is Not a Solo Act
The Return of the ‘Medical Home’ Concept

- sickest one third Medicare patients*
  - has more than 7 chronic conditions
  - is receiving 7 or more Rx
  - sees 11 different MDs in 7 practices
- average primary care physician shares patients with more than 100 colleagues
- ACP endorsement of Patient-Centered Medical Home (PCMH) and Neighborhood (PCMH-N)
- improved care coordination, quality improvement via personal physician directing an extended team of healthcare professionals

A New Healthcare Ecosystem Arising From Convergence of Technologies and Markets

- passive/active data collection
- analytics and network architecture
- EMR/PMR
- performance and outcomes analysis

Integrated Technology Platforms

Data Mining and Integration Services

Increasingly Targeted Care and Efficient Use of Finite Resources

patients

services for integrated care

consumers

Dx/Devices

Rx

Hlx

Integrated Technology Platforms
“Managing Mega-Data”

- Volume
- Scale
- Global networks

- Multiscale heterogeneity
- Integration
Social Networks and Consumer: Patient Empowerment

POWER TO
THE PATIENT

Source: R&D Directions May 2010
Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency and Future Education Curricula
The Production, Diffusion and Consumption of Information and Knowledge: An Increasingly Complex Ecosystem

- Massive Data
- Data Standards and Inter-operable Federated Databanks
- Increasing Importance of Open Source Systems
- New Organizational Networks, Funding Policies and Infrastructure Investment
“We walk the corridors, searching the shelves and rearranging them looking for lines of meaning amid leagues of cacophony and incoherence”

The Library of Babel
Jorge Luis Borges (1941)
In: Labyrinths: Selected Stories and Other Writings,
New Directions, 1962 p.54

Erik Desmazières: La salle des planètes
Illustration for Jorge Luis Borge’s:
“The Library of Babel”
The Urgent Need for Standards and Infrastructure Scale for Data-Intensive Scientific Discovery

- most data is created in a form and organization that facilitates its generation rather than critical consideration of its eventual use(s)
- formidable inter-operability and scaling problems in linkage and integration of data from multiple sources and fields
- increasing importance of large datasets in generating new hypotheses and convergent loops between theory, modeling and experiment
- from local production to publically accessible (open) massive, integrated, curated depositories
- major implications for the organization and funding of research and future education/training curricula
Big Data, Big Science and Big Change Needed

Keynote: Alyssa Goodman, Harvard – Robertson Auditorium
“Seamless Astronomy: How astronomers share, explore and discover”
Open Data Systems and Crowd Sourcing in Biomedical R&D

- Sage Bionetworks
- CANCER COMMONS
- CLOUD COMMONS
- IMI - Innovative Medicines Initiative
- inspire2live
- Open PHACTS - The Open Pharmacological Concepts Triple Store
- SGC
- Ushahidi
- my experiment
- Cytoscape
- Taverna
- WIN - Worldwide Innovative Networking in personalized cancer medicine
- patientslikeme
- Open Network Biology
- ChEMBL
- creative commons
- CROWDMAP
- Ashoka
- ELIXIR
- PARTNERS FOR A CURE FOUNDATION, INC.
Building Large Scale Datasets of Human Disease Using ‘Open-Commons’ Community-Based Inputs and Modeling

The Complex Path to P4 Medicine

- the integration of biomarker diagnostic technologies, m.health and e.health
  - intellectual foundation for predictive and preventive medicine and rational treatment
  - empowering consumers and patients in treatment decision
- realization of this potential lies not just in technological innovation
- productive adoption will require circumvention of entrenched economic, cultural and institutional interests in sustaining the status quo
The Most Important Barriers to Change in Biomedical Research

- **cultural**
  - silos subvert solutions
  - protection of the status quo
  - reward structures
- **funding**
  - not just dollars
  - imperative for new systems-based organizational and operational approaches to address complex multidimensional problems
- **education and training**
  - single discipline focus and perceived career path rewards
  - anachronistic P&T criteria
- **leadership gaps in defining coherent national policies for research and healthcare delivery**
Coordination of the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

Government Policies

- Reform current CTSA funding to require systems-based assembly of full expertise spectrum and obligate industry participation.
- Promulgation of standards and centralized orchestration of resources (national/international):
  - Biorepositories and biospecimens
  - ‘omics’ analytics reference standards
  - Informatics standards and infrastructure support (BIX, HIX)
- Incentives:
  - Public:private partnerships and consortia
  - Value-based reimbursement
- Proactive regulatory science:
  - Advanced diagnostics
  - Remote health monitoring (m.Health)
  - Metadata and outcomes research
P4 Medicine (Lee Hood) + Price and Policy (George Poste)

- Precision diagnostics
- Better care and improved outcomes at lower cost
- Optimized decisions
- Health status monitoring
- Preventive
- Personalized
- Participative
- Price
- Policy
Slides available @ http://casi.asu.edu/
Reference List Citations:

- Slide No. 6-7, Dr. Leroy Hood, Institute for Systems Biology, Seattle. Lecture on P4 Medicine (posted online at http://www.slideshare.net/osumedicalcenter/dr-leroy-hood-lecture-on-p4-medicine)
- Slide No. 8, Fig. 1 (C), Y-J Cho 2010 JCO Apr 10, 2011:1424-1430; published online on November 22, 2010 (http://ico.ascopubs.org/content/29/11/1424.full.pdf)
- Slide No. 14, Figure 1: Deals between pharmaceuticals and diagnostics companies. Euro|Biotech|News (2011) Vol. 10 pg. 36. Latest image can be found online at Scientia Adv. (http://www.scientiaadv.com/pdf/EBN2011_01_special_PermStorm.pdf)
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- Slide No. 64, Images Left Source: R&D Directions May 2010 and Right Image Inf. Week 4-11
- Slide No. 67 Illustration for Jorge Luis Borges’s: “The Library of Babel” can be found online (http://booklover.tumblr.com/post/3957813775/speciesbarocus-erik-desmazieres-la-salle-des)