ASU Complex Adaptive Systems Initiative
Arizona State University

10th Institute for Systems Biology International Symposium

The Evolution of Personalized Medicine: Opportunities and Challenges

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

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

Slides available @ www.casi.asu.edu

Declared Interests:

- Board of Directors: Monsanto, Exelixis, Caris Life Sciences
- Scientific Advisory Board: Synthetic Genomics, Anacor
- I0M Forum on Global Infectious Diseases
- USG Activities: DoD, DHS

ASU Complex Adaptive Systems Initiative
Arizona State University

The Environment for Biomedical R&D and Healthcare Delivery

Sustaining Innovation in an Era of Economic Constraint

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

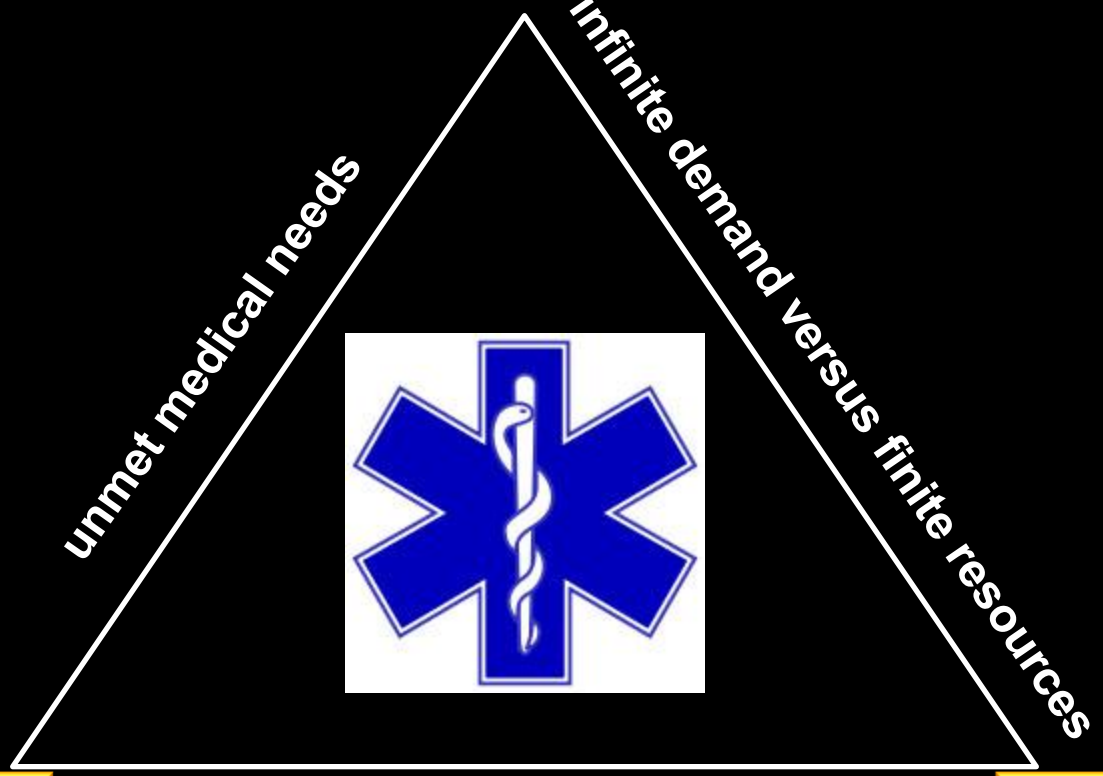
**Silos Subvert Solutions:
The Imperative for Systems-Based Approaches to Integrate Diagnostics, Therapeutics and Informatics to Improve Health Outcomes and Control Costs**

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

The Healthcare Challenge

Outcomes

clinical, economic, quality-of-life

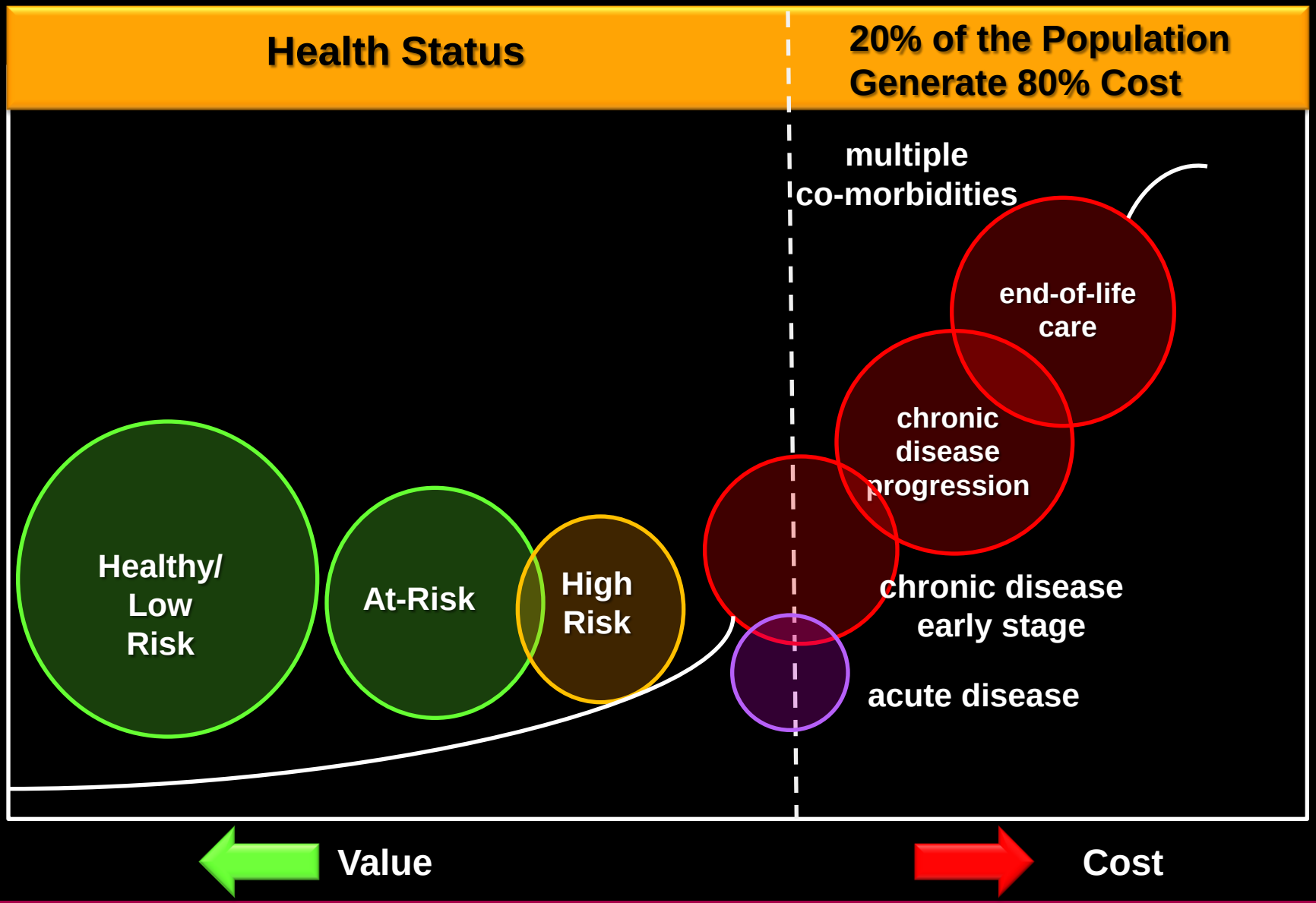


Innovation and Cost of Care

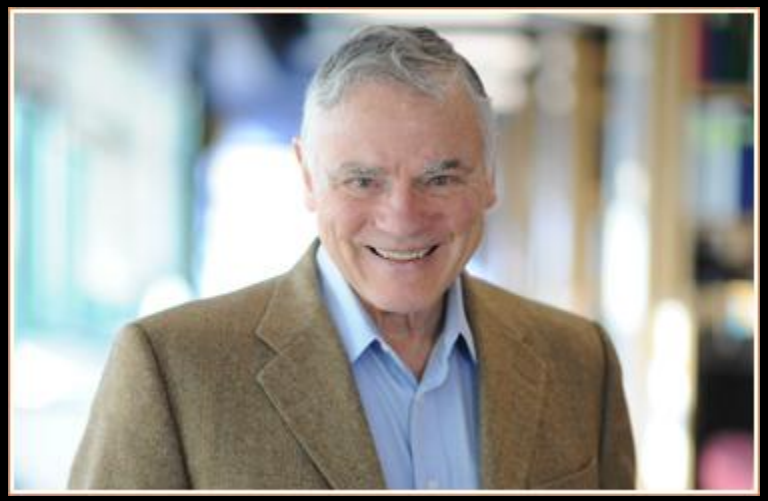
increasing cost of care
and acceleration of new technologies

Access to Care

The Economic, Social and Clinical Benefits of Proactive Mitigation of Disease Risk and Chronic Disease Co-Morbidities



P4 Medicine



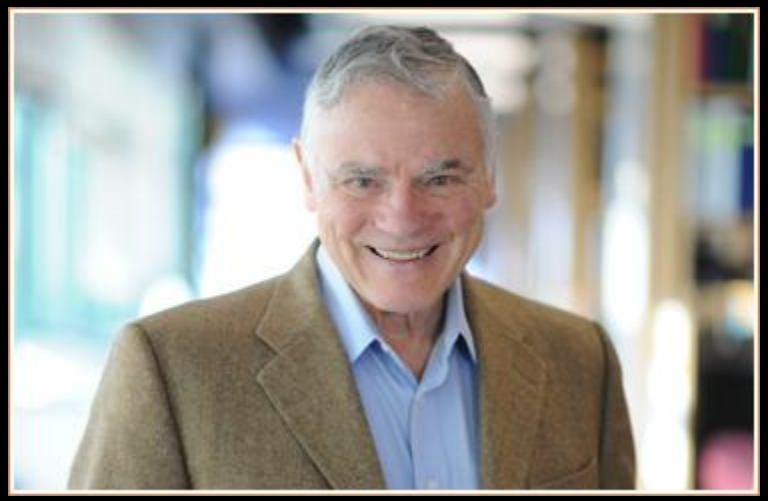
Dr. Leroy Hood
Institute for Systems Biology,
Seattle, Washington

- **predictive**
- **preventive**
- **personalized**
- **participatory**

Dr. Leroy Hood, Institute for Systems Biology, Seattle. Lecture on P4 Medicine (posted online at http://www.slideshare.net/osumedicalcenter/dr-leroy-hood-lecuture-on-p4-medicine)

P4 Medicine + Two More ‘P’s’

P4 Medicine



Dr. Leroy Hood
Institute for Systems Biology,
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- predictive
- preventive
- personalized
- participatory

Price

- research innovation
- products
- delivery of care

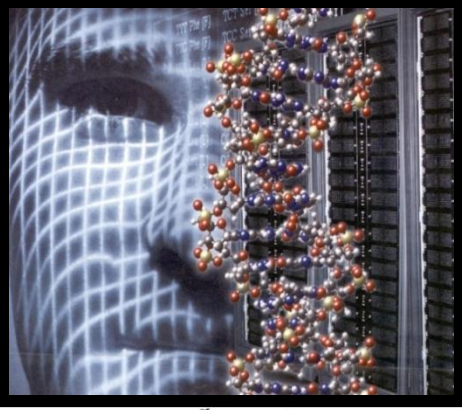
Policy

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

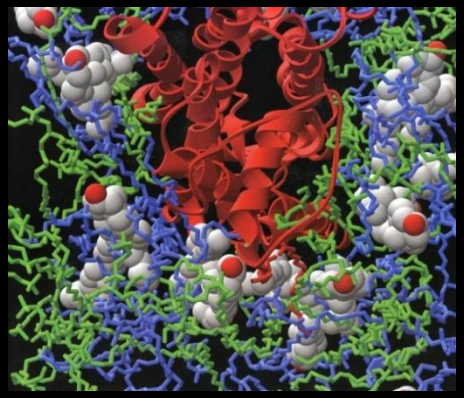
Dr. Leroy Hood, Institute for Systems Biology, Seattle. Lecture on P4 Medicine (posted online at http://www.slideshare.net/osumedicalcenter/dr-leroy-hood-lecuture-on-p4-medicine)

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

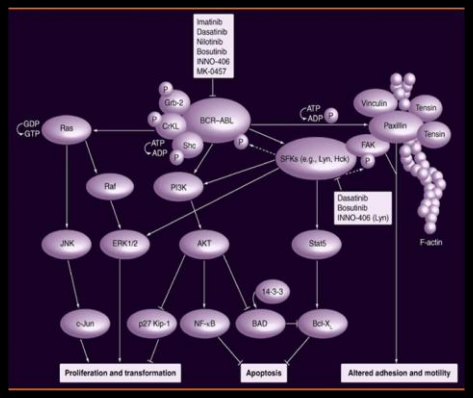
Genomics



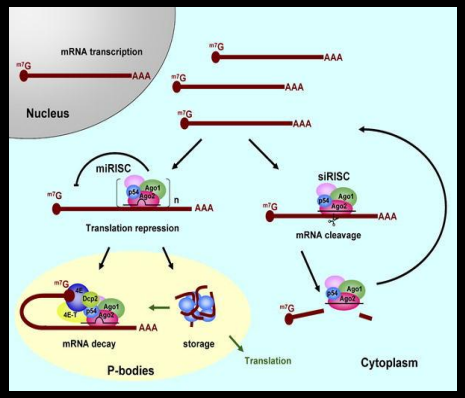
Proteomics

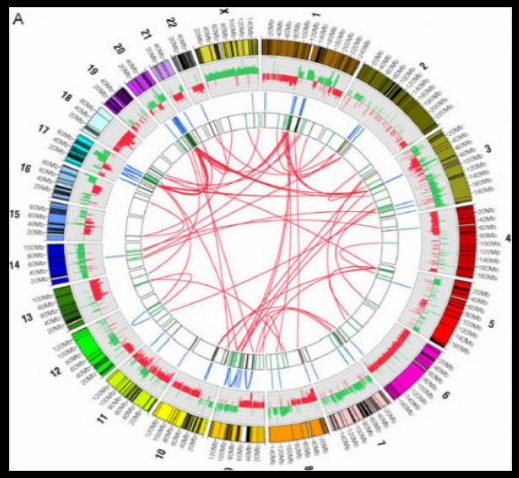


Molecular Pathways and Networks



Network Regulatory Mechanisms

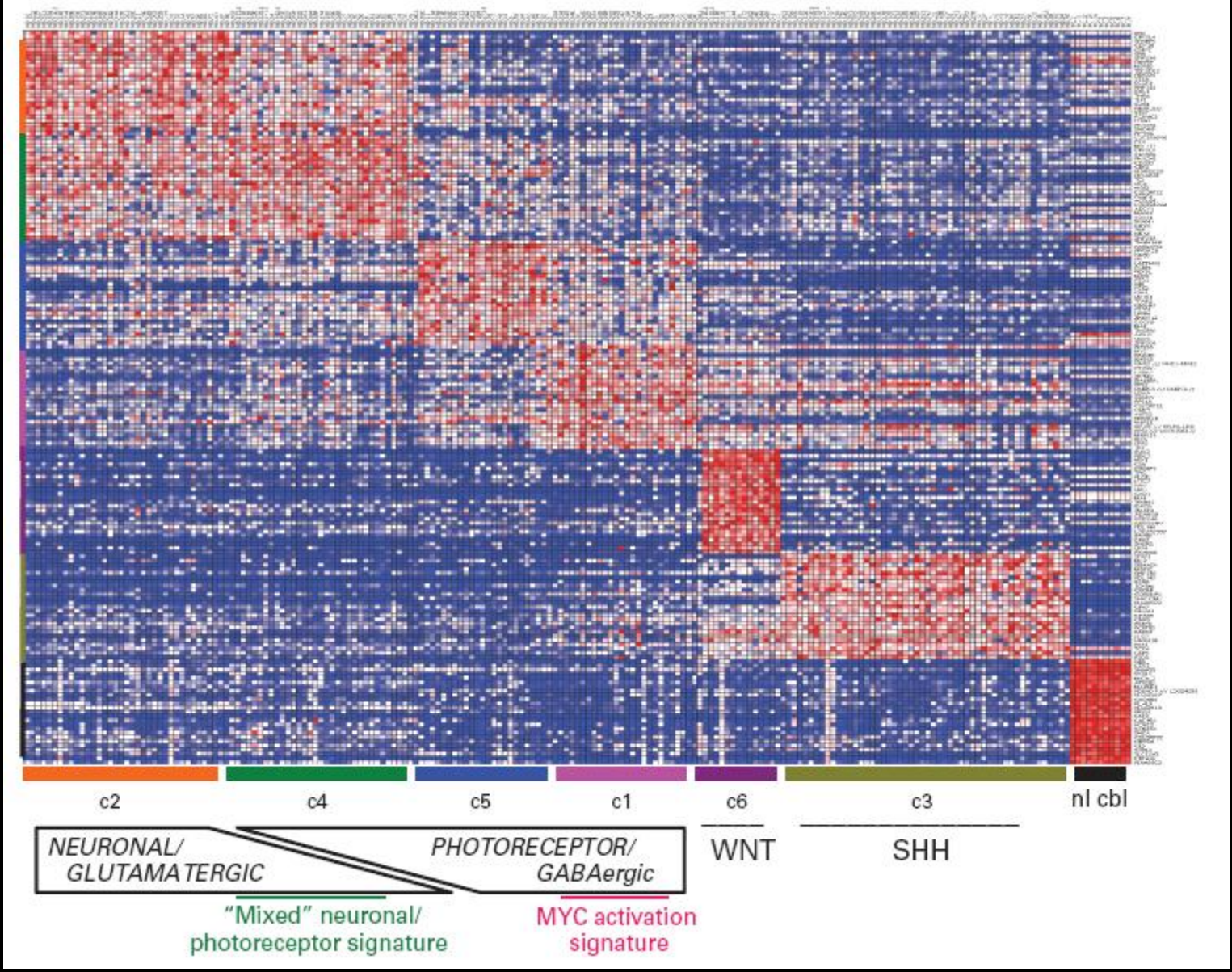




ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signatures of Disease or Predisposition to Disease

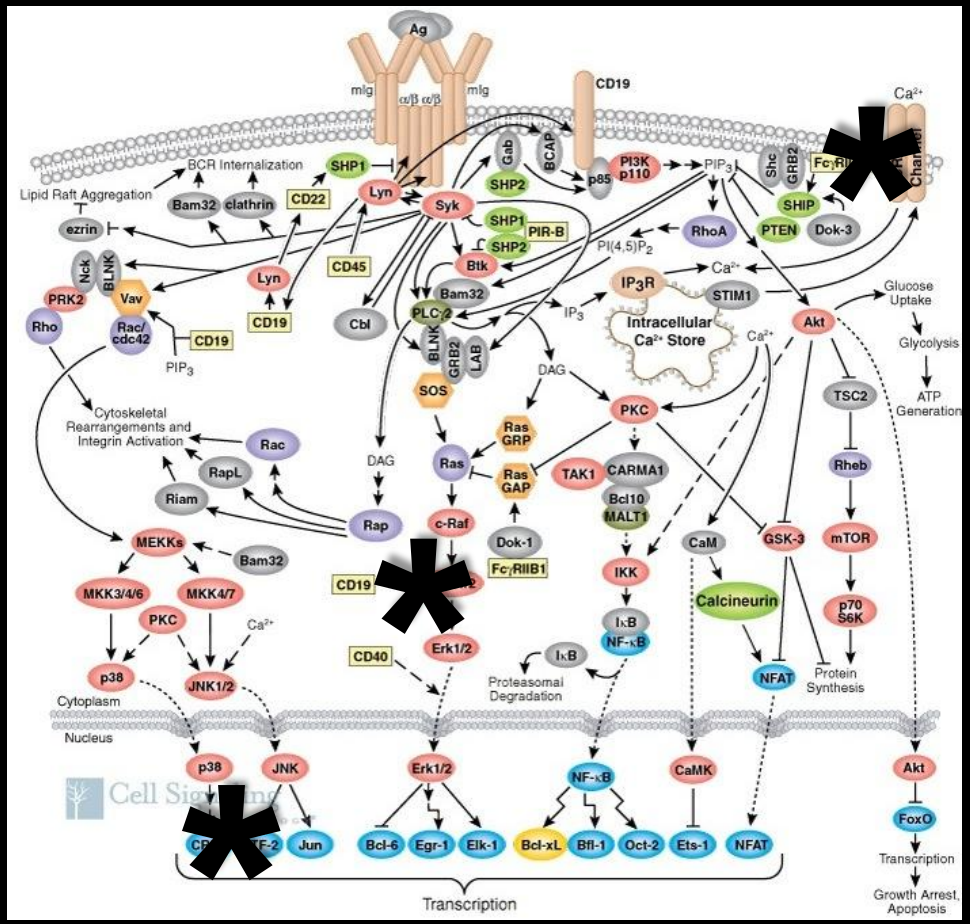
Classification of Six Subgroups of Medulloblastoma



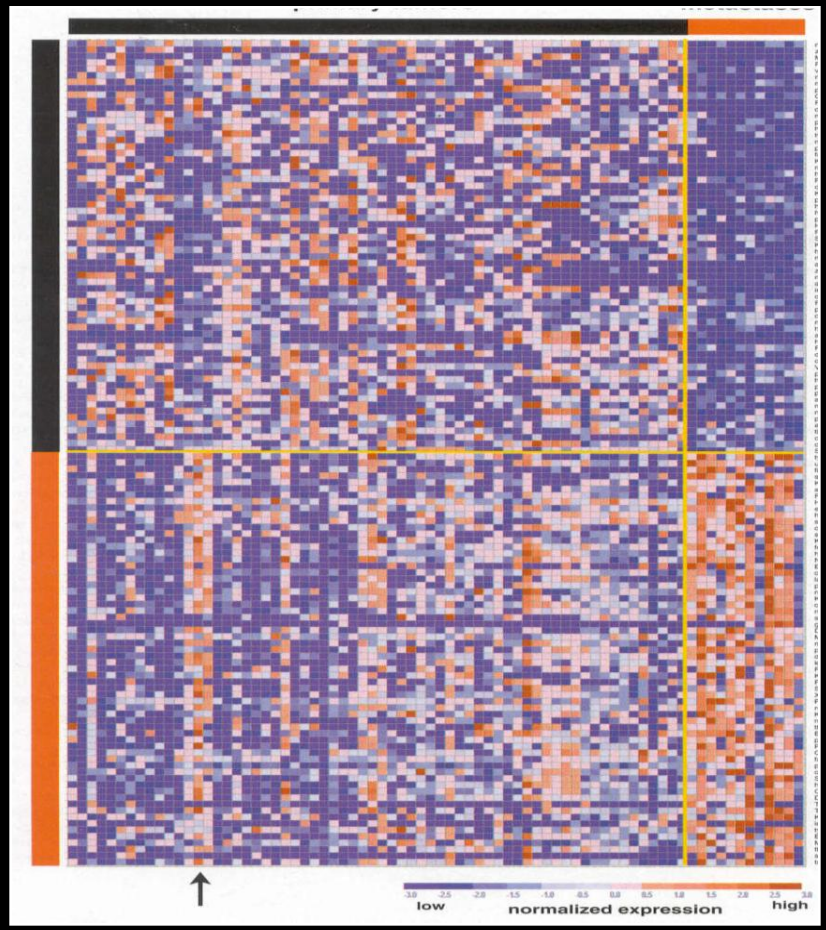
From: Y-J Cho 2010 J. Clin. Oncol. 29, 1424

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

Vectibix® (panitumumab)

AMGEN

ERBITUX® CETUXIMAB

ImClone Systems Incorporated

- higher response in patients with wt K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)

clinical guidelines

NCCN

ASCO®

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

- regulatory endorsement in product labeling

CMS

BlueCross BlueShield

UnitedHealthcare®
Healing health care. Together.®

- payor adoption

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

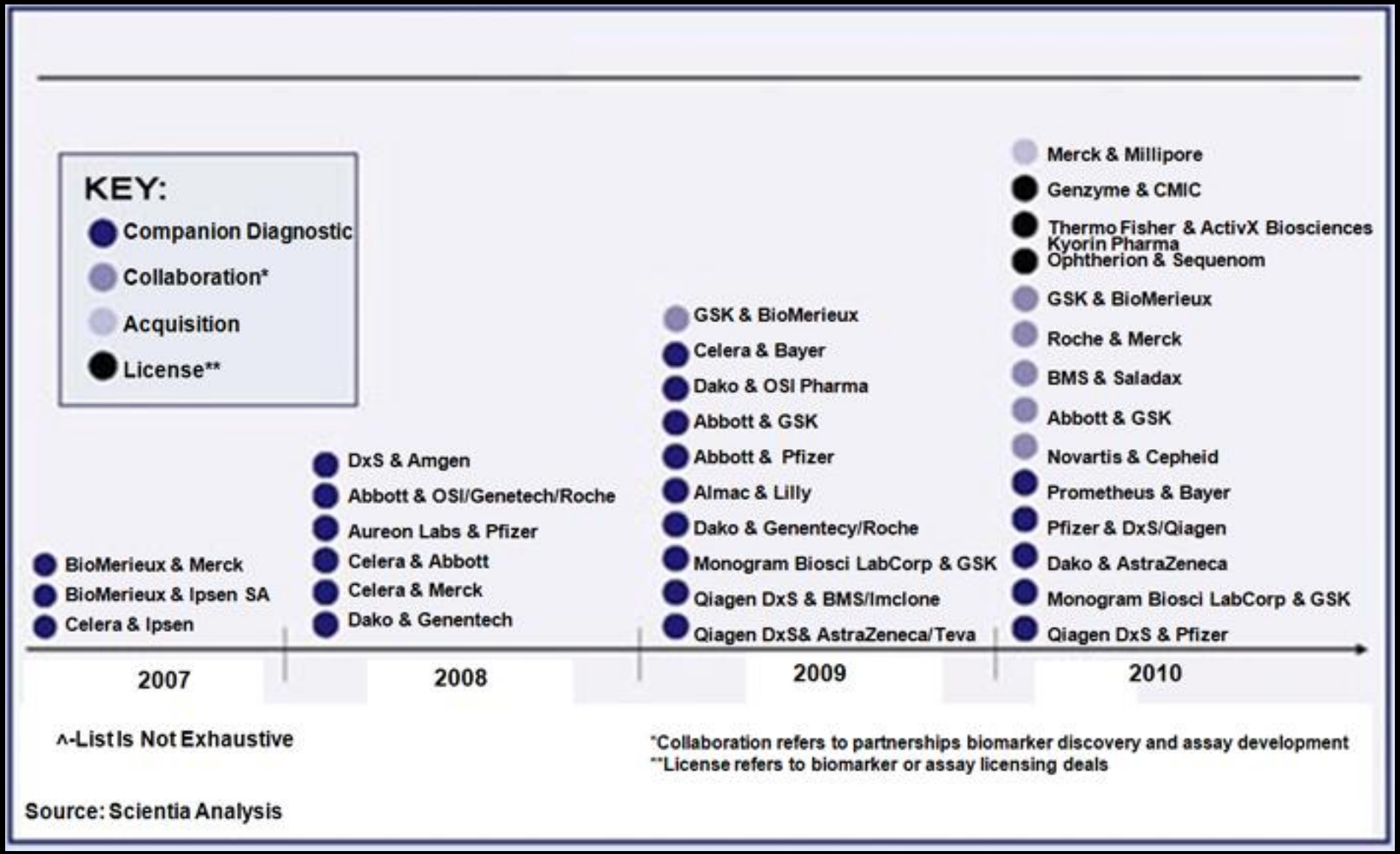
Mechanism	Marker	Drug
Somatic Mutations	KRAS	cetuximab; panitumumab; gefitinib; erlotinib
	BRAF	cetuximab; panitumumab; gefitinib; erlotinib
	PI3K	cetuximab; panitumumab; lapatinib; trastuzumab
	EGFR	gefitinib; erlotinib
Germ Line Mutations	BRCA1/2	olaparib
SNPs	UGT1A1	irinotecan
	CYP450	tamoxifen
	Fc RII/III	trastuzumab; rituximab; erbitux
Gene Amplification or Copy Number Variant	HER2	trastuzumab
	EGFR	gefitinib; erlotinib
	Top2A	anthracyclines
Protein Over-Expression	EGFR	cetuximab
	HER2	trastuzumab
	ERCCI	platinum compounds
	B-tubulin	taxanes
Protein Loss; Mutations, Copy Number Variant	PTEN	trastuzumab

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



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)

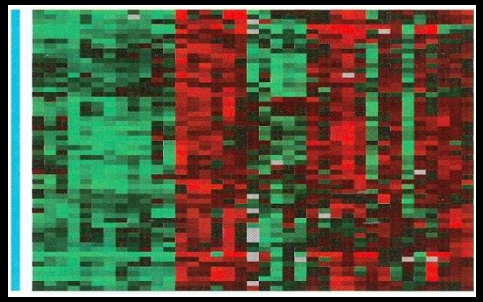
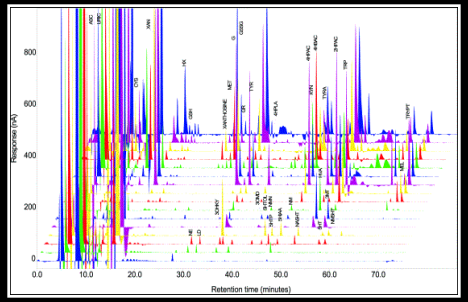
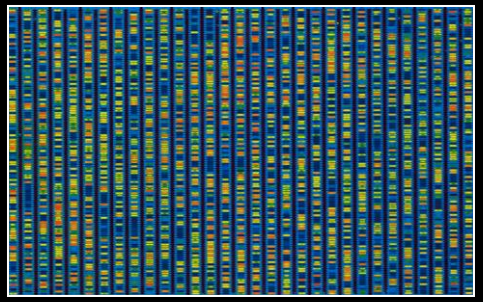
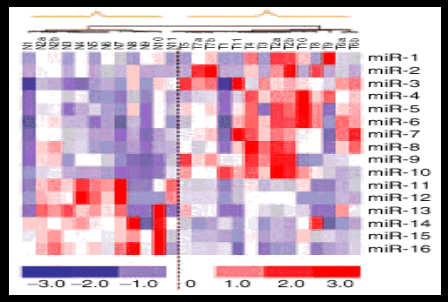
Large Scale Profiling of Cancer Patients to Identify Cohorts Expressing Rx Target(s) for Phase II Trials

Target	# Patients Screened	# Eligible Patients	# Centers	# Countries
EML4 ALK^{+}: lung cancer*	1500	82	9	1
HER2^{+}: gastric cancer**	3803	549	122	24

* 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

life technologies™ ion torrent

illumina

454 SEQUENCING Roche

IBM

Oxford NANOPORE Technologies®

Electronic Bio Sciences

华大基因 BGI

Complete genomics

BioNanomatrix

PACIFIC BIOSCIENCES

imagination at work

Helicos BioSciences Corporation

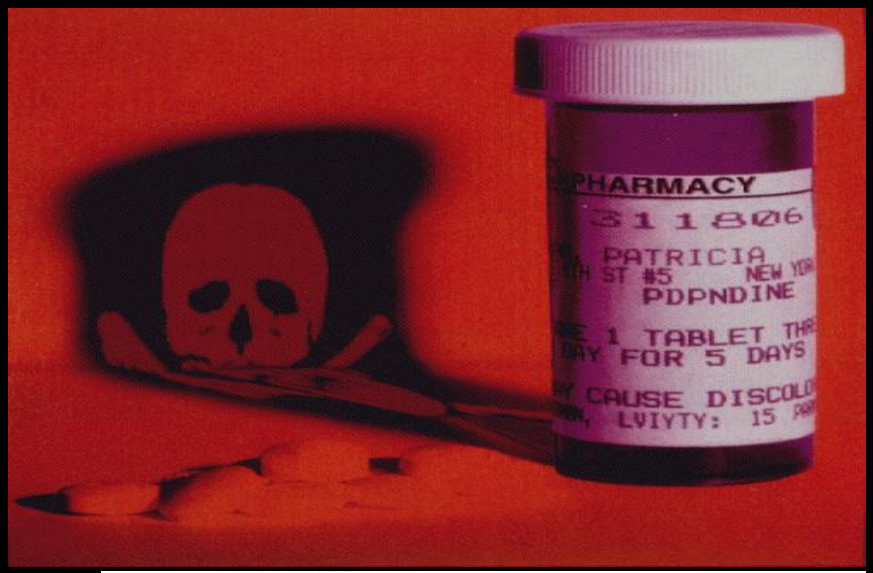
Whole Genome Sequencing (WGS)

- 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

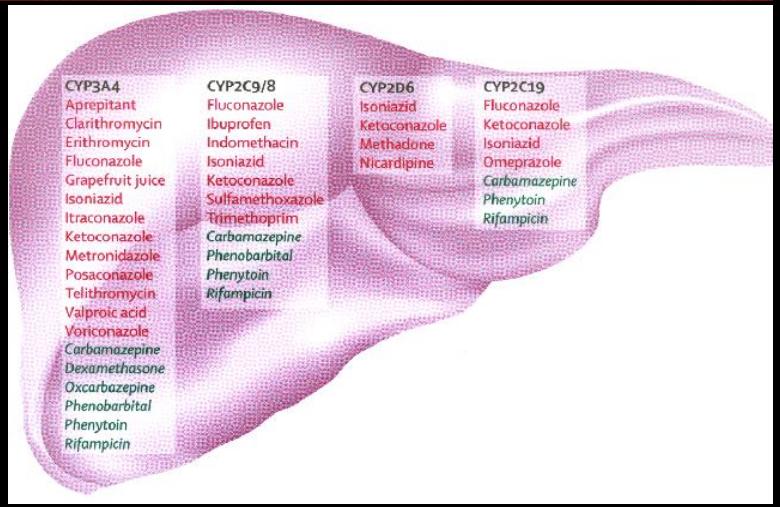
Big Genomics and Managing Massive Data

- 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

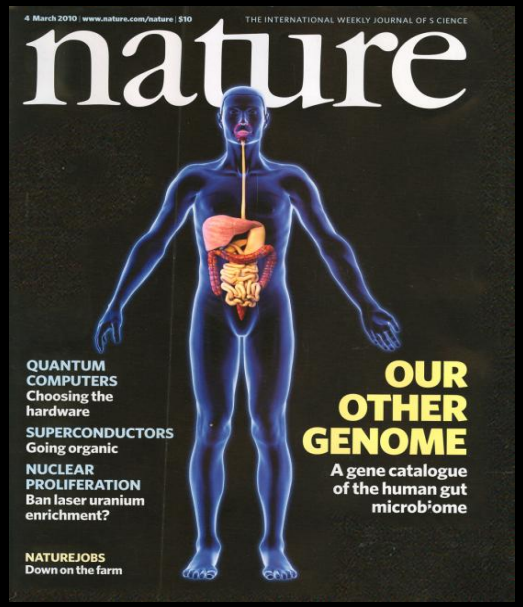


The Application Gap in the Clinical Use of Pharmacogenomic (PG) Information Relevant to Patient Safety

- 121 drug labels contain PG information

- F. Freuh et al. Pharmacotherapy (2008) 28 (8)
- 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

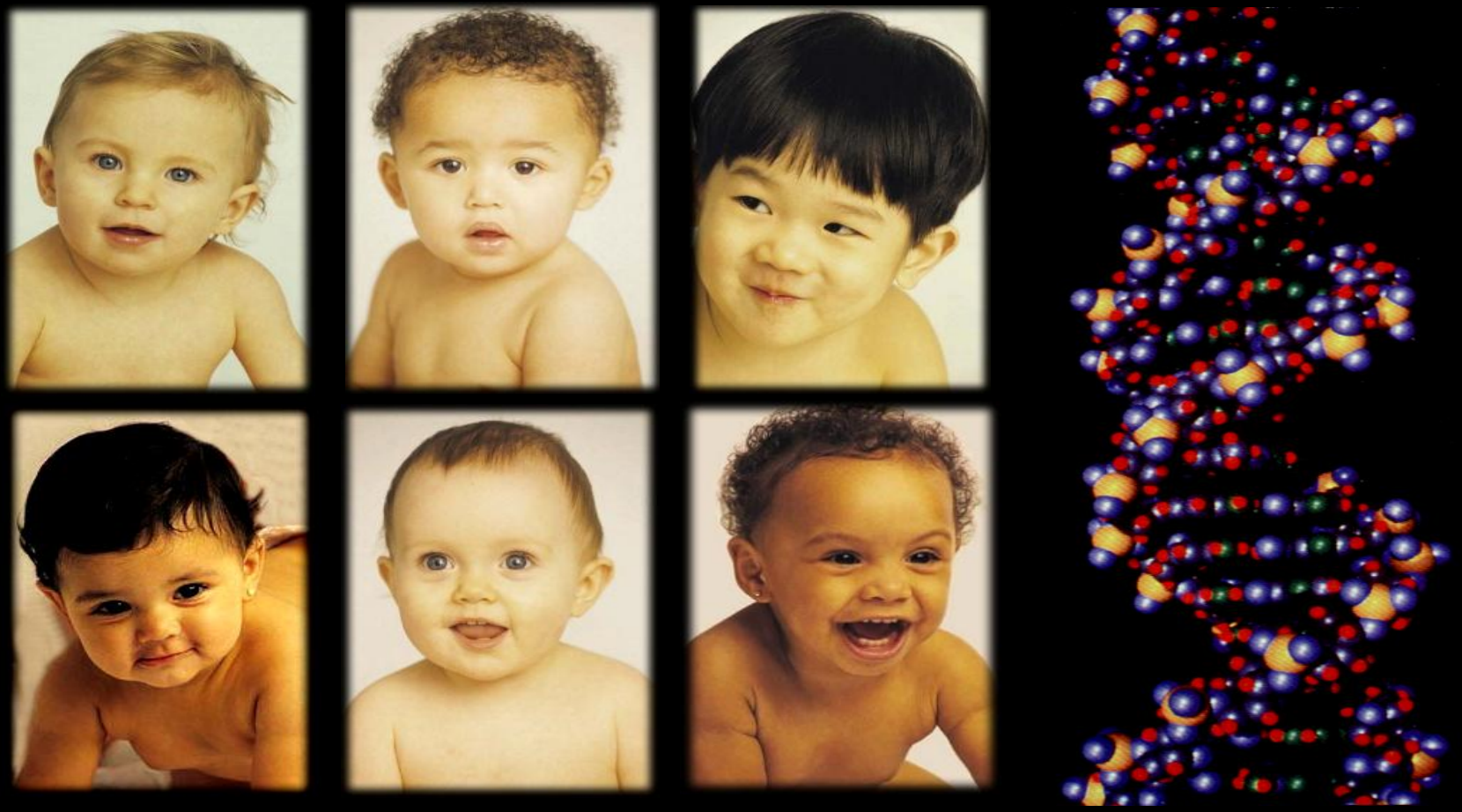
We Are Not Alone: Variation in the Human Microbiome as a Potential Factor in Health and Disease



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

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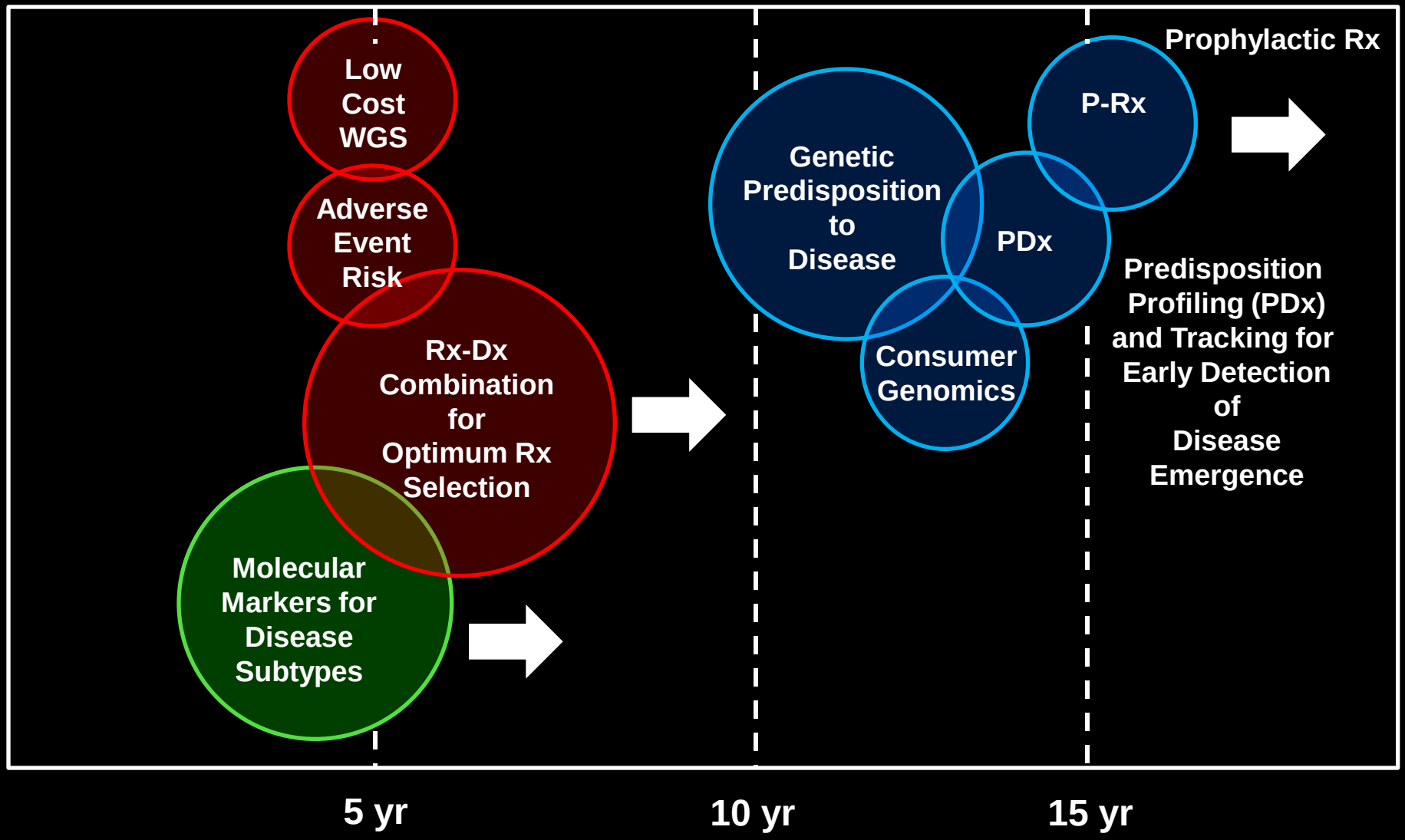
  - epistasis
  - epigenetics

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



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

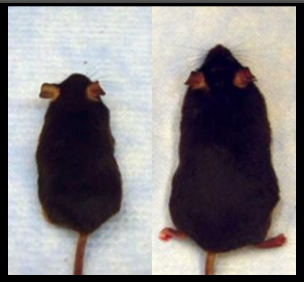
- recognition of increasing organizational and regulatory complexity
  - SNPs, haplotypes, CNVs, indels
  - non-coding RNA regulatory networks
  - epistasis
  - epigenetics and imprinting
  - nuclear compartmentalization and *trans*-expression
  - environmental interactions (exposome)
  - effects of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

Genomic Complexity, Individual Variation and the Challenge of Genotype-Phenotype Prediction

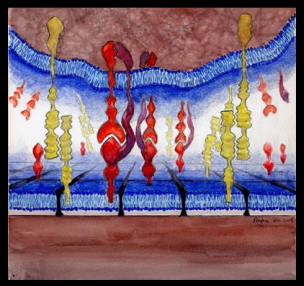
- recognition of genome organizational and regulatory complexity
- non-linear relationship between genotype and phenotype
- formidable analytical challenges for biomedical and mathematical sciences

- 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?

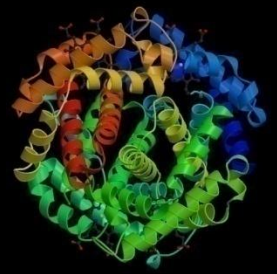
The Evolution of Drug Discovery



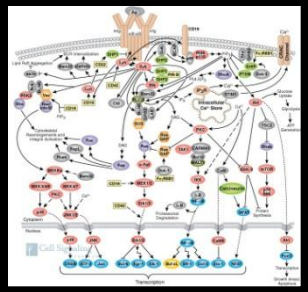
- empirical screening



- 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

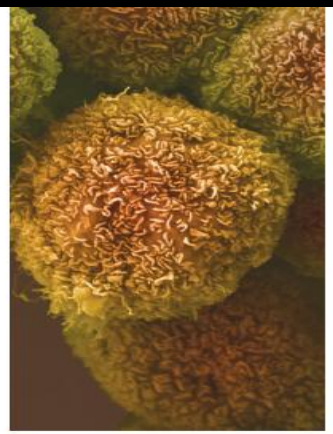
The Challenge of Drug Discovery for Late-Onset, Chronic, Multigenic Diseases

- 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



Science (2011) 331, 1539

SPECIAL SECTION

INTRODUCTION

Celebrating an Anniversary

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-

Cancer Crusade at 40

US Cancer Prevalence Estimates 2010 and 2020

Site	# People (thousands) 2010	2020	% change
Breast	3461	4538	31
Prostate	2311	3265	41
Colorectal	1216	1517	25
Melanoma	1225	1714	40
Lymphoma	639	812	27
Uterus	588	672	15
Bladder	514	629	22
Lung	374	457	22
Kidney	308	426	38
Leukemia	263	240	29
All Sites	13,772	18,071	32

From: A.B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

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 intitial 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

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

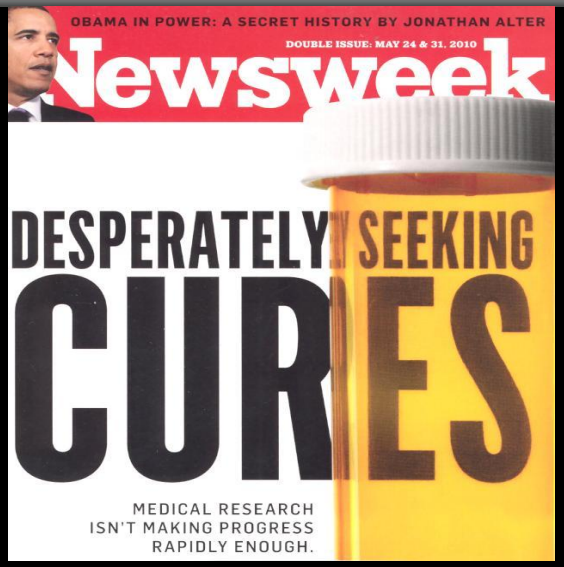
How Many Drugs Acting on the Same Target Can The Market Support? PI3K Inhibitors in Cancer Clinical Trials

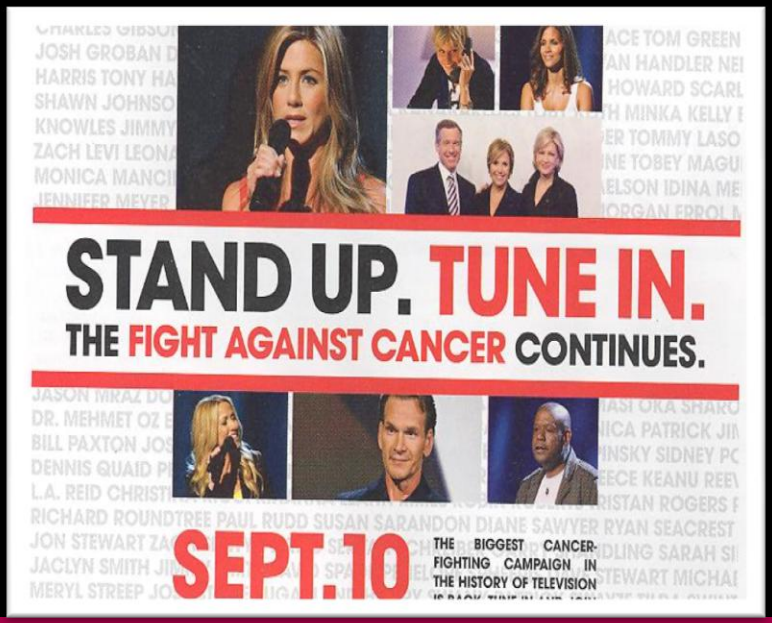
Drug		Status	Mechanism
Bayer	BAY806946	Phase I	Dual mTOR/PI3K
Exelixis/Sanofi	XL765	Phase I	Dual mTOR/PI3K
Genentech/Roche	GDC0980	Phase I	Dual mTOR/PI3K
GlaxoSmithKline	GSK2126458	Phase I	Dual mTOR/PI3K
Novartis	BEZ235	Phase I/II	Dual mTOR/PI3K
Novartis	BGT226	Phase I/II	Dual mTOR/PI3K
Pfizer	PF04691502	Phase I	Dual mTOR/PI3K
Pfizer	PK1587	Phase I	Dual mTOR/PI3K
Semafore	SF1126	Phase I	Dual mTOR/PI3K
Exelixis/Sanofi	XL147	Phase I/II	PI3K
Genentech/Roche	GDC0941	Phase I	PI3K
Novartis	BKM120	Phase I/II	PI3K
Oncothyreon	PX866	Phase I/II	PI3K
Zenyaku Kogyo	ZSTK474	Phase I	PI3K
Novartis	BYL719	Phase I	PI3Kα
Amgen	AMG319	Phase I	PI3Kδ
Calistoga Pharma	CAL101	Phase I/II	PI3Kδ
Genentech/Roche	GDC0032	Phase I	PI3K [a]

SOURCES: Semafore, ClinicalTrials.gov

April 18 — April 24, 2011
Bloomberg Businessweek


YOU'RE NOT JUST
STRENGTHENING MUSCLES.
YOU'RE STRENGTHENING
A MOVEMENT.


OBAMA IN POWER: A SECRET HISTORY BY JONATHAN ALTER
DOUBLE ISSUE: MAY 24 & 31, 2010
Newsweek
DESPERATELY SEEKING
CURES
MEDICAL RESEARCH
ISN'T MAKING PROGRESS
RAPIDLY ENOUGH.


STAND UP. TUNE IN.
THE FIGHT AGAINST CANCER CONTINUES.
SEPT.10
THE BIGGEST CANCER-FIGHTING CAMPAIGN IN THE HISTORY OF TELEVISION


National Breast Cancer Coalition
The
Breast
Cancer
Deadline
2020
Breast Cancer Deadline
Why Now?
September 20, 2010
BreastCancerDeadline2020.org

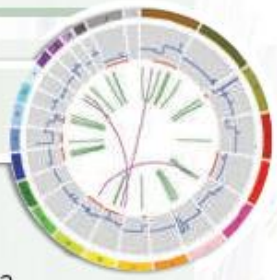
The Complexity of Cancer Genomes

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.

Source: E. D. Pleasance *et al. Nature* **463,** 184–190 (2010).



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.

Source: E. D. Pleasance *et al. Nature* **463,** 191–196 (2010).

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.

Source: L. Ding *et al. Nature* **464,** 999–1005 (2010).

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.

Source: E. R. Mardis *et al. N. Engl. J. Med.* **361,** 1058–1066 (2009).

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

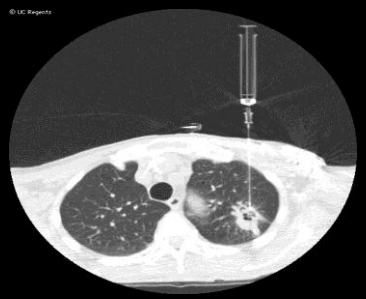
Access to High Quality Biospecimens, Biobanks and DNA Repositories: A Major Obstacle for Biomarker Discovery

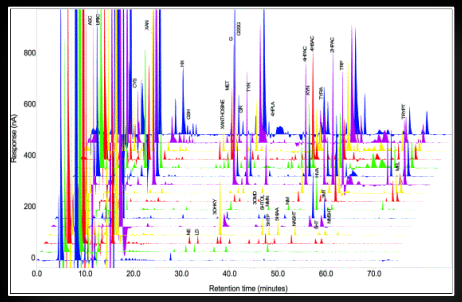
scale
and
standards

or

academic
anecdotes

Building Large Scale, Standardized Resources for Biomedical Research



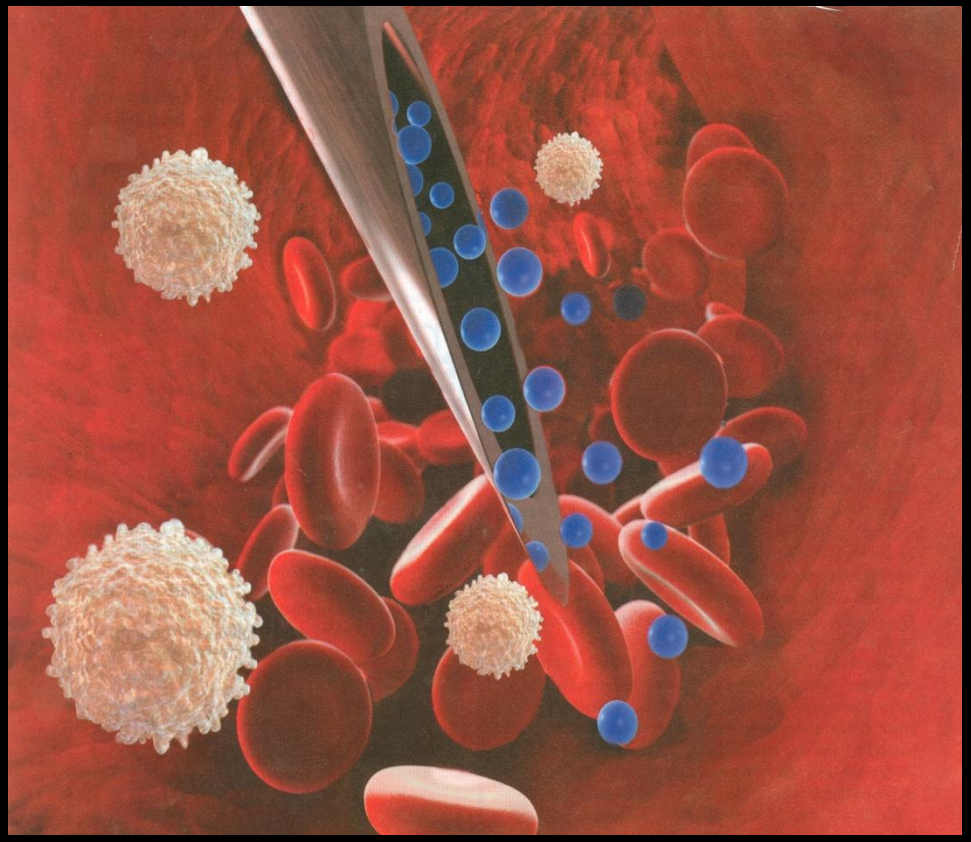


- rigorously phenotyped/matched/consented disease and normal specimens
- biobanking: leadership and national policies to create a vital research resource
- standardization of pre-analytical and analytical methods
- standardized data ontologies and formats for large scale datasets/federated databanks

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



Source: For the Record 12-6-10

- 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

STRATEGIC PRIORITIES 2011 – 2015

Responding to the Public Health Challenges of the 21st Century

Department of Health and Human Services
United States Food and Drug Administration

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:

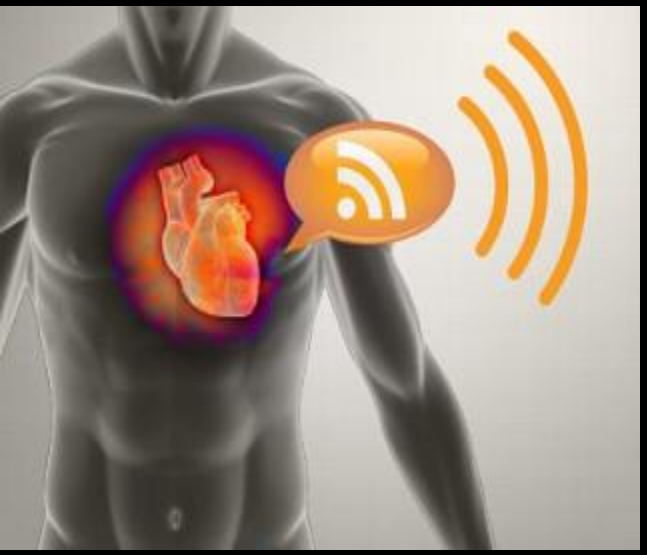
The Most Broad and The Most Valuable Definition of Personalized Healthcare

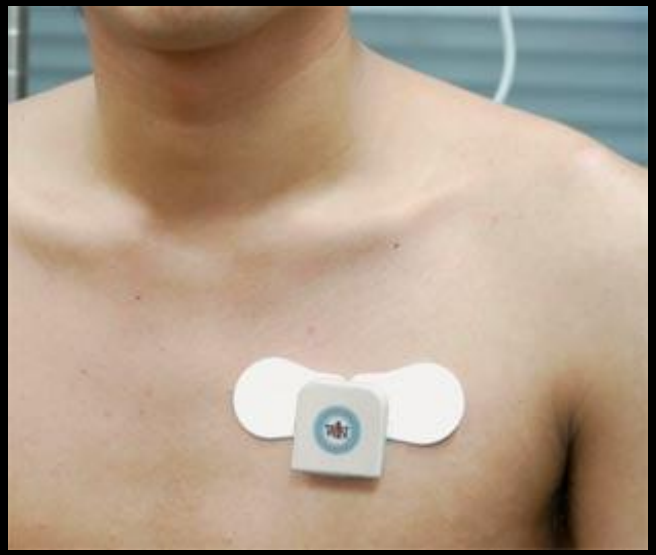
The Convergence of Telecommunications, Digital Media and Healthcare: The Rise of m.Health and e.Health

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





m.Health

Remote Health Monitoring and Management of Chronic Diseases

Lifestyle and Fitness Tracking

Information for Proactive Health Awareness (Wellness)

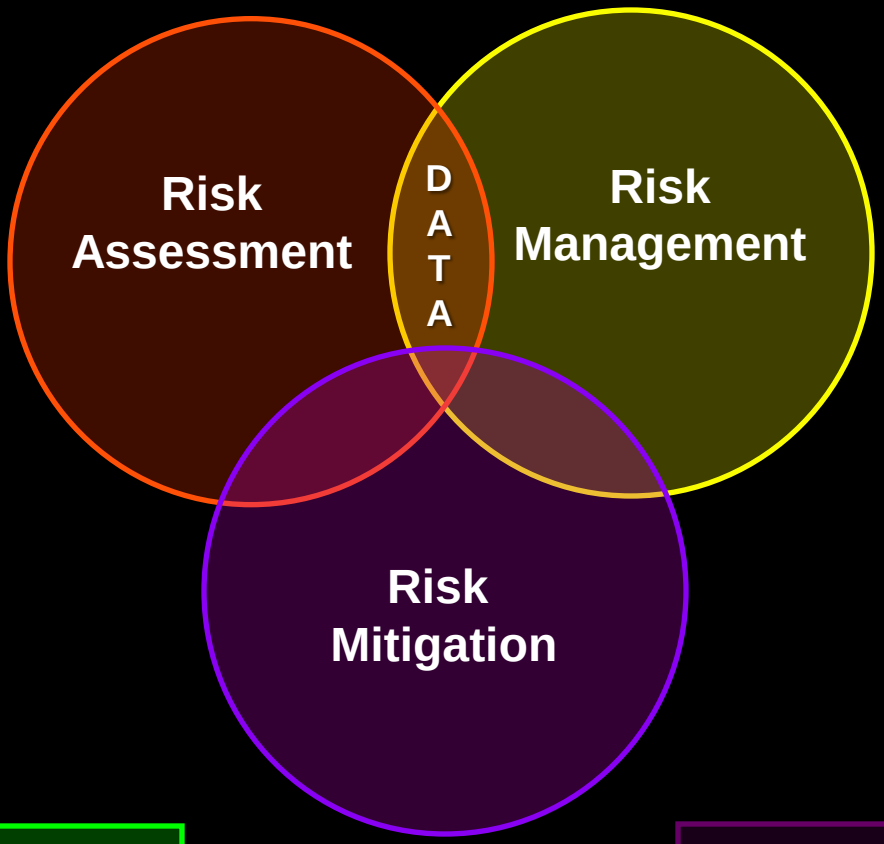
Wireless Devices for Health Status Monitoring

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

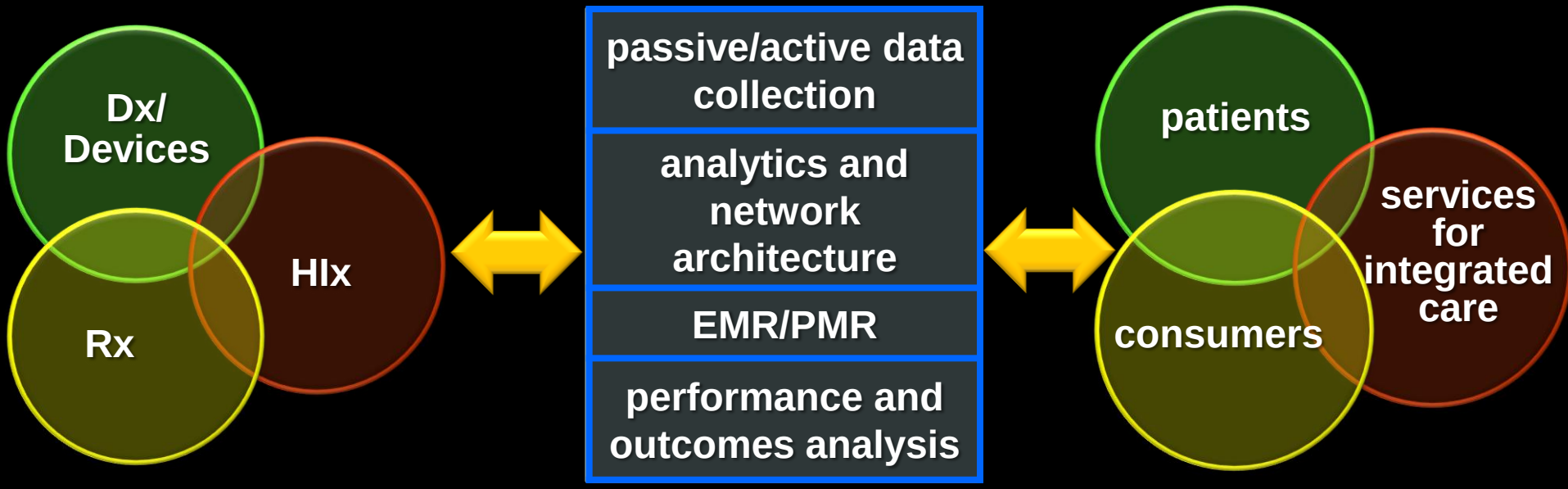
From
Fragmented Healthcare Delivery
To
Integrated Health Systems and Services

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

*From: C.A. Sinsky (2011) Ann. Int. Med. 154, 61

A New Healthcare Ecosystem Arising From Convergence of Technologies and Markets



Integrated Technology Platforms

Data Mining and Integration Services

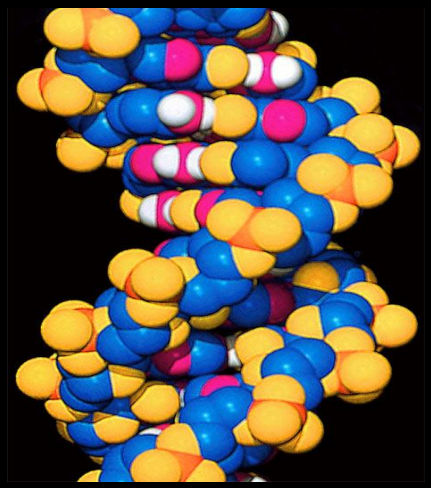
Increasingly Targeted Care and Efficient Use of Finite Resources

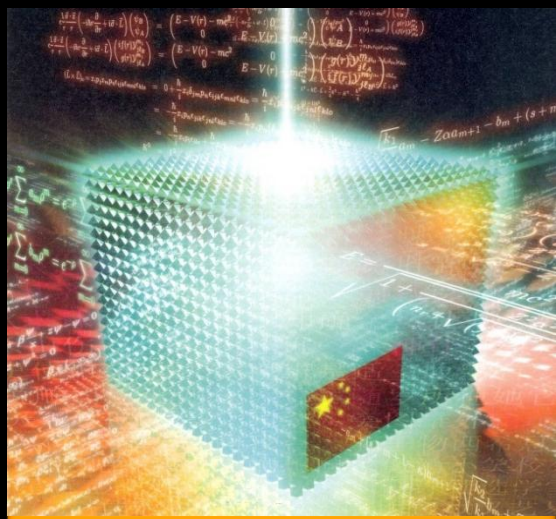
“Managing Mega-Data”

volume

scale

global networks





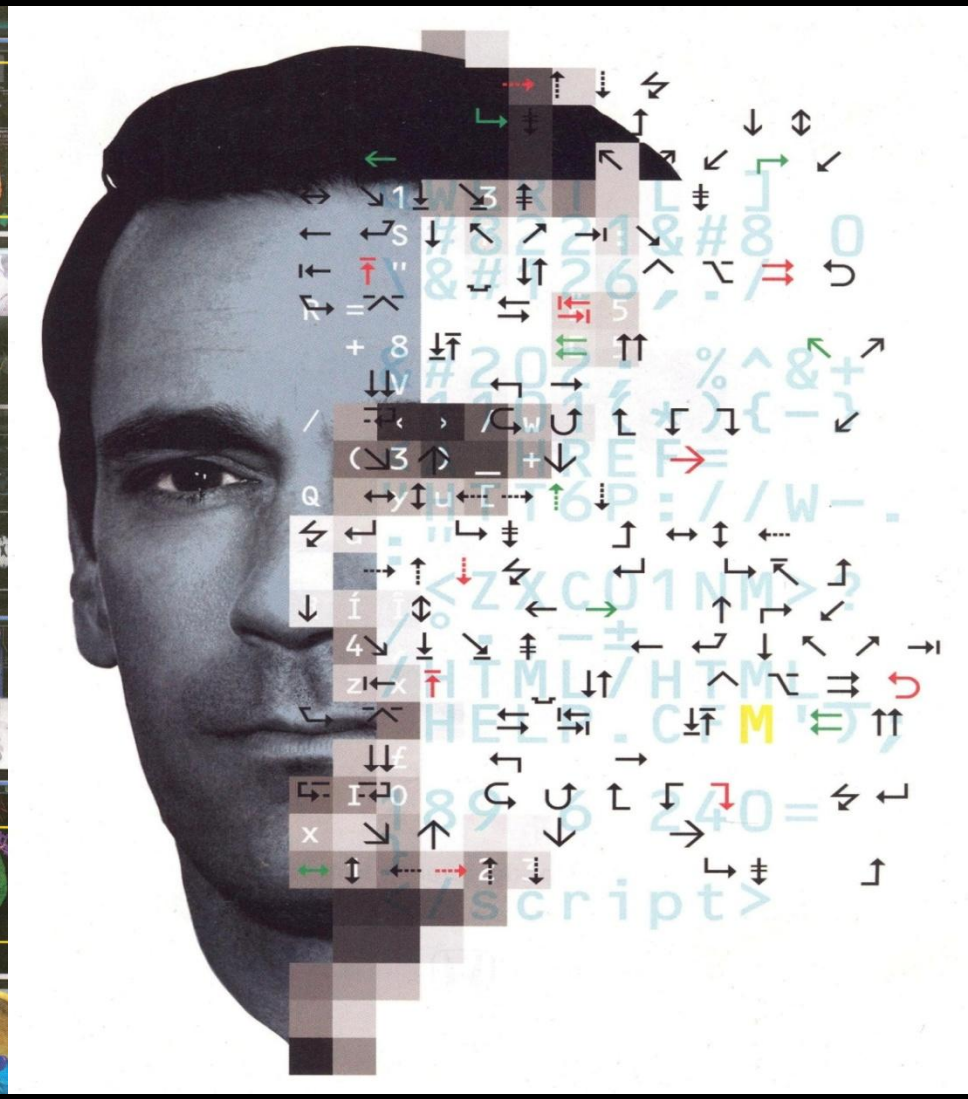
multiscale heterogeneity

integration

Social Networks and Consumer: Patient Empowerment

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

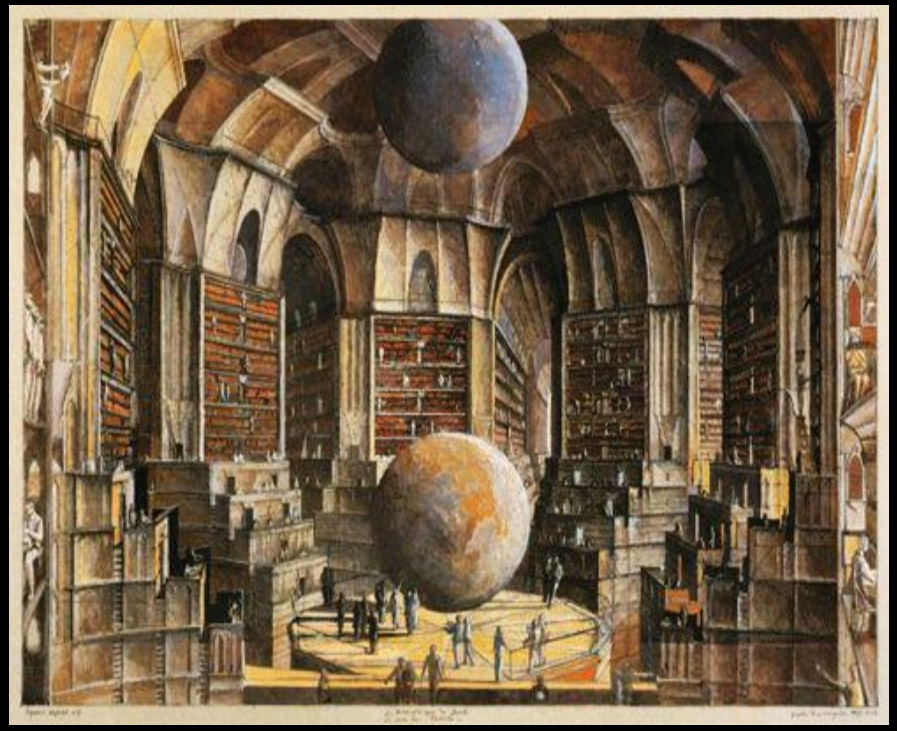
Massive Data

Data Standards and Inter-operable Federated Databanks

Increasing Importance of Open Source Systems

New Organizational Networks
Funding Policies and Infrastructure Investment

The Inadequate Adoption of Standardized Ontologies for Biomedical Data and Inter-Operable Formats for Data Annotation, Curation and Mining



Erik Desmazières: La salle des planètes
Illustration for Jorge Luis Borge's:
"The Library of Babel"

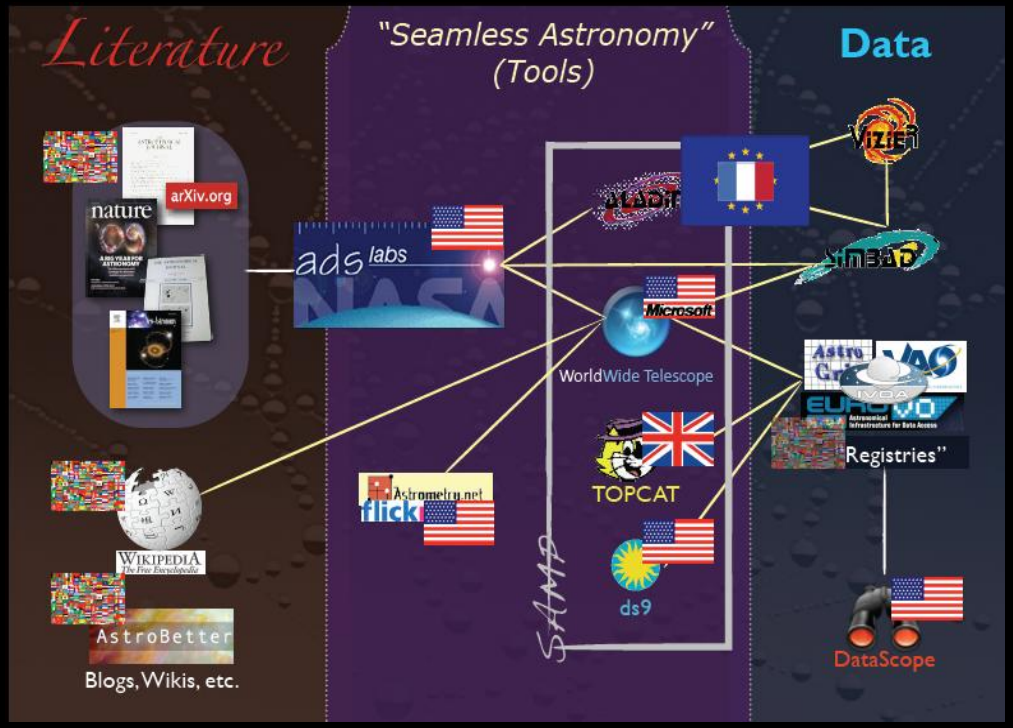
"We walk the corridors,
searching the shelves and
rearranging them looking for lines of
meaning amid leagues of cacophony
and incoherence"

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

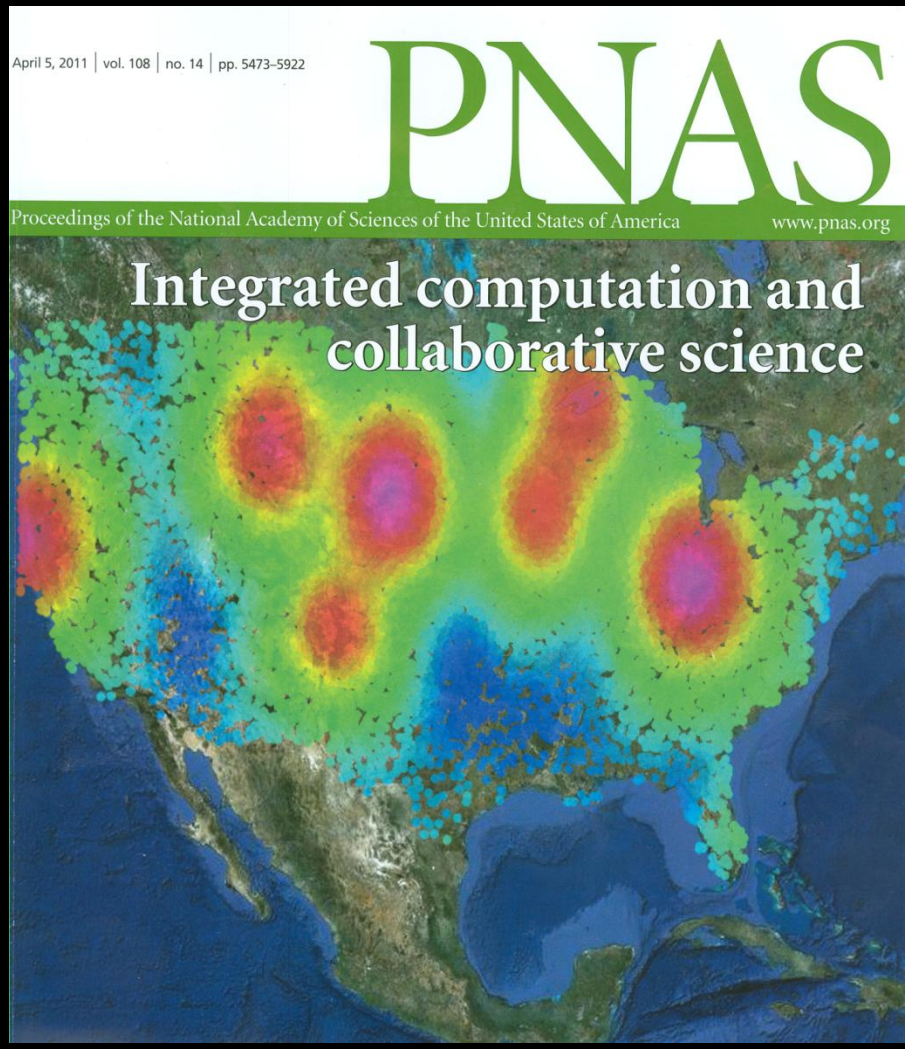
The Urgent Need for Standards and Infrastructure Scale for Data-Intensive Scientific Discovery

- 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



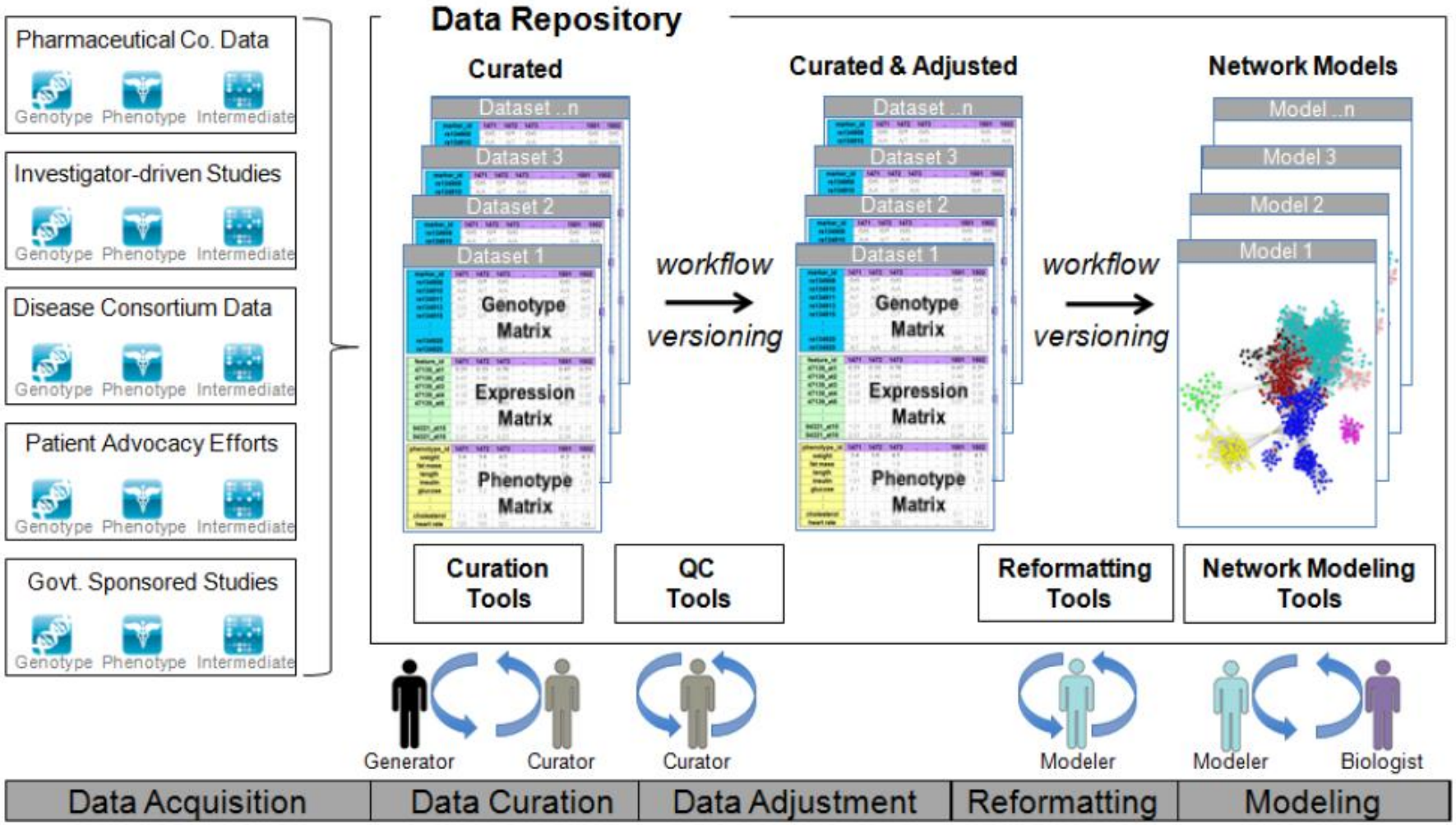
Keynote: Alyssa Goodman, Harvard – Robertson Auditorium
"Seamless Astronomy: How astronomers share, explore and discover"



Open Data Systems and Crowd Sourcing in Biomedical R&D

Building Large Scale Datasets of Human Disease Using 'Open-Commons' Community-Based Inputs and Modeling

Sage Bionetworks Commons and Platform



From: J. M. J. Derry et al. (2011) NaturePrecedings doi:10.1038/npre.2011.5883.1

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

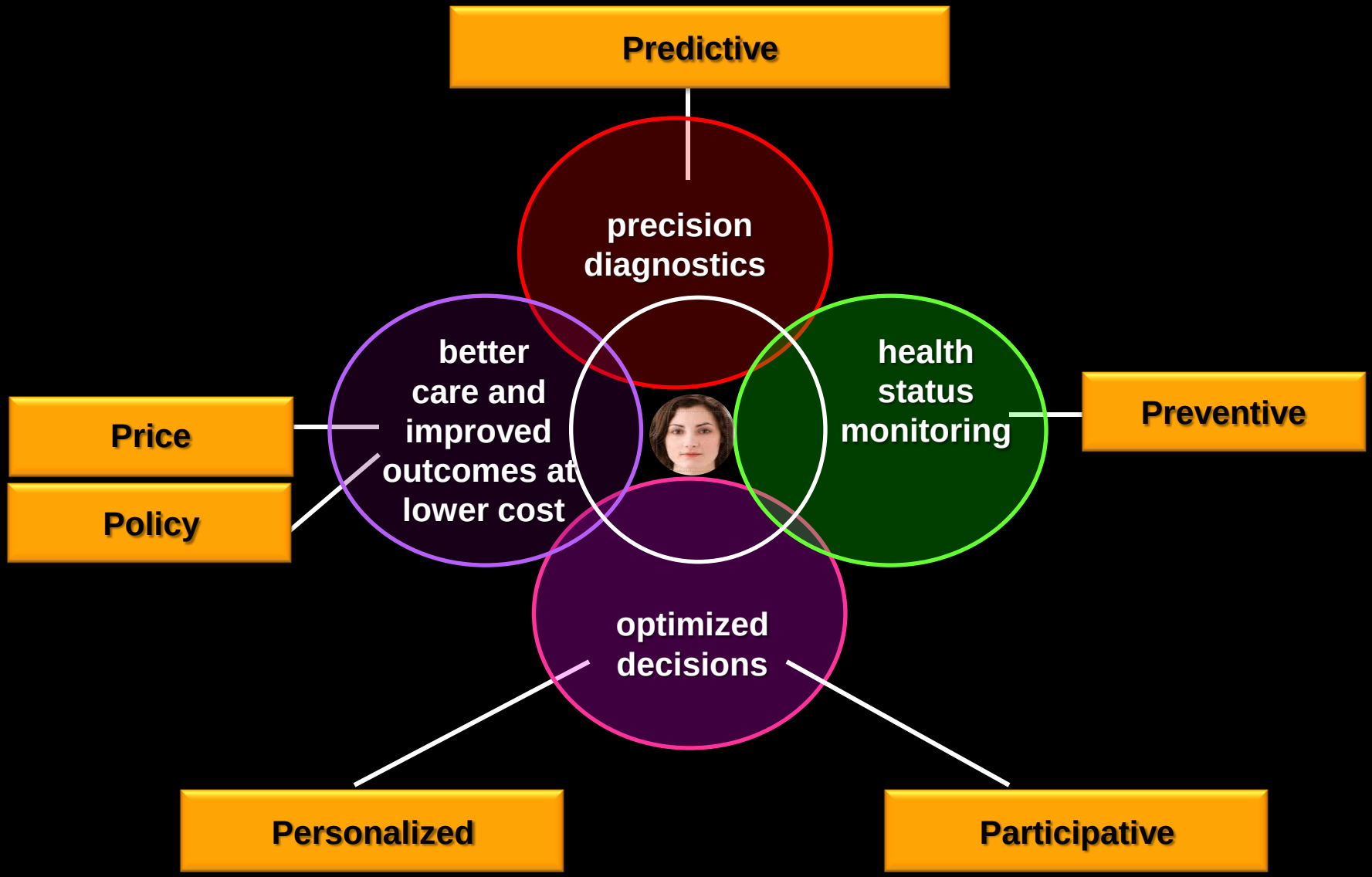
- cultural
  - silos subvert solutions
  - protection of the status quo
  - reward structures
- funding
  - not just dollars
  - imperative for new systems-based organizational and operational approaches to address complex multidimensional problems
- education and training
  - single discipline focus 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

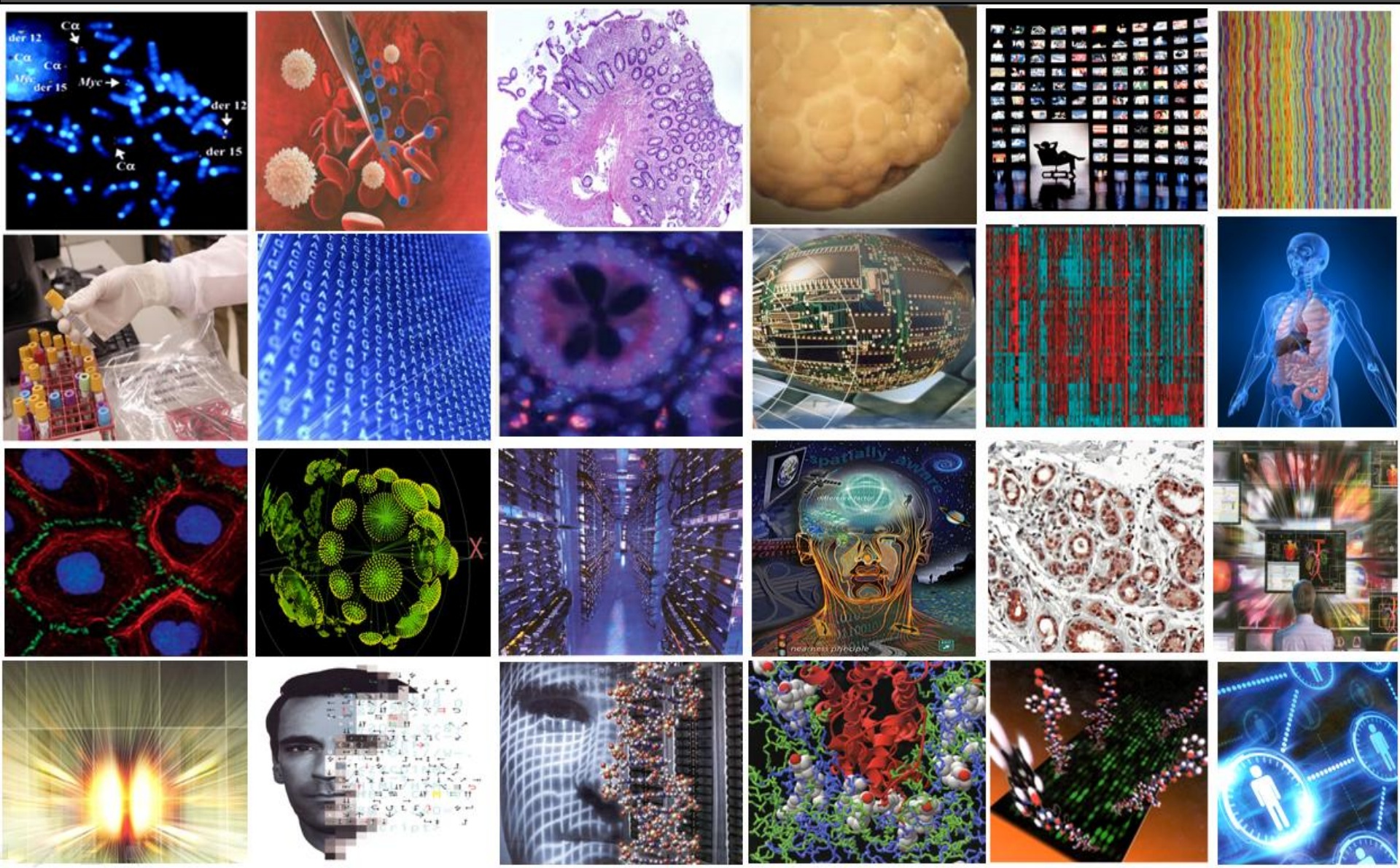
Government Policies

- 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)



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



Reference List Citations:

Image / Diagram / Table / Article / Website

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- Slide No. 8, Fig. 1 (C), Y-J Cho 2010 JCO Apr 10, 2011:1424-1430; published online on November 22, 2010 (http://jco.ascopubs.org/content/29/11/1424.full.pdf)
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- Slide No. 16, from paper E.L. Kwak et al. (2010) NEJM 363, 1693 and ** Y. Bang et al. (2010) Lancet 376, 687
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- Slides No. 36, quote adapted from National Cancer Act of 1971 (December 23, 1971) and **Science (2011) 331, 1539**
- Slide No. 37, Figure From: A.B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117
- Slide No. 40, Table Adapted from: Semafore, ClinicalTrials.gov latest update can be found online at C&EN April 11, 2011 Volume 89, Number 15 pp. 15 – 19
- Slide No. 43, Tables from Source: E. D. Pleasance et al. Nature 463, 191-196 (2010)
- Slide No. 51, Left Image Source: For the Record 12-6-10
- Slide No. 52, Cover of FDA Report (Dec 22, 2010) A Call for Clarity: Open Questions on the Scope of FDA Regulation of mHealth. A whitepaper prepared by the mHealth Regulatory Coalition (http://mhealthregulatorycoalition.org/wp-content/uploads/2010/12/mrcwhitefinal122210.pdf)
- Slide No. 61, *From: C.A. Sinsky (2011) Ann. Int. Med. 154, 61
- 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 Borge's: "The Library of Babel" can be found online (http://booklover.tumblr.com/post/3957813775/speciesbarocus-erik-desmazieres-la-salle-des)
- Slide No. 69, Keynote: Alyssa Goodman, Harvard – Robertson Auditorium "Seamless Astronomy: How astronomers share, explore and discover" (http://sagecongress.org/2011/Goodman.pdf)
- Slide No. 71, Image From: J. M. J. Derry et al. (2011) NaturePrecedings doi:10.1038/npre.2011.5883.1