Challenges and Opportunities in Cancer Detection and Diagnosis: The Need for Systems-Based Approaches For Successful Validation of Biomarkers

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NCI Cancer Early Detection Stakeholders Meeting
Rockville, 21 May 2010

The Cancer Challenge:
The Imperative to Achieve Earlier Detection and Diagnosis

- poor short-term prospect for truncation of extended 10-15 year R&D cycle times for new drugs
- unsustainable cost of Rx therapy with current outcomes
- high failure of investigational drugs in clinical trials
- testing of investigational Rx on late-stage patients with advanced refractory disease

- clinical, economic and social value of innovation in biomarker discovery and validation will increase

Disease-Associated Biomarkers: A Key Driver in the Future Healthcare Value Chain

- detection and diagnostic classification
- staging and progression
- prognosis
- prediction of Rx response and/or adverse event(s)
- novel Rx target ID and investigational drug optimization
- profile patient populations for enrichment/adaptive clinical trial design
- surrogate markers for disease risk, disease status monitoring and Rx efficacy
- functional analysis of signaling networks

Adoption of New Technologies Demands a 'Systems' Approach to Life Cycle Analysis (LCA)

- discovery
- translation and validation
  - technical, clinical, regulatory
- demonstrating value
  - clinical, patients, payors, society
- incentives for investment/adoption
  - clinical utility
  - reimbursement
  - IP

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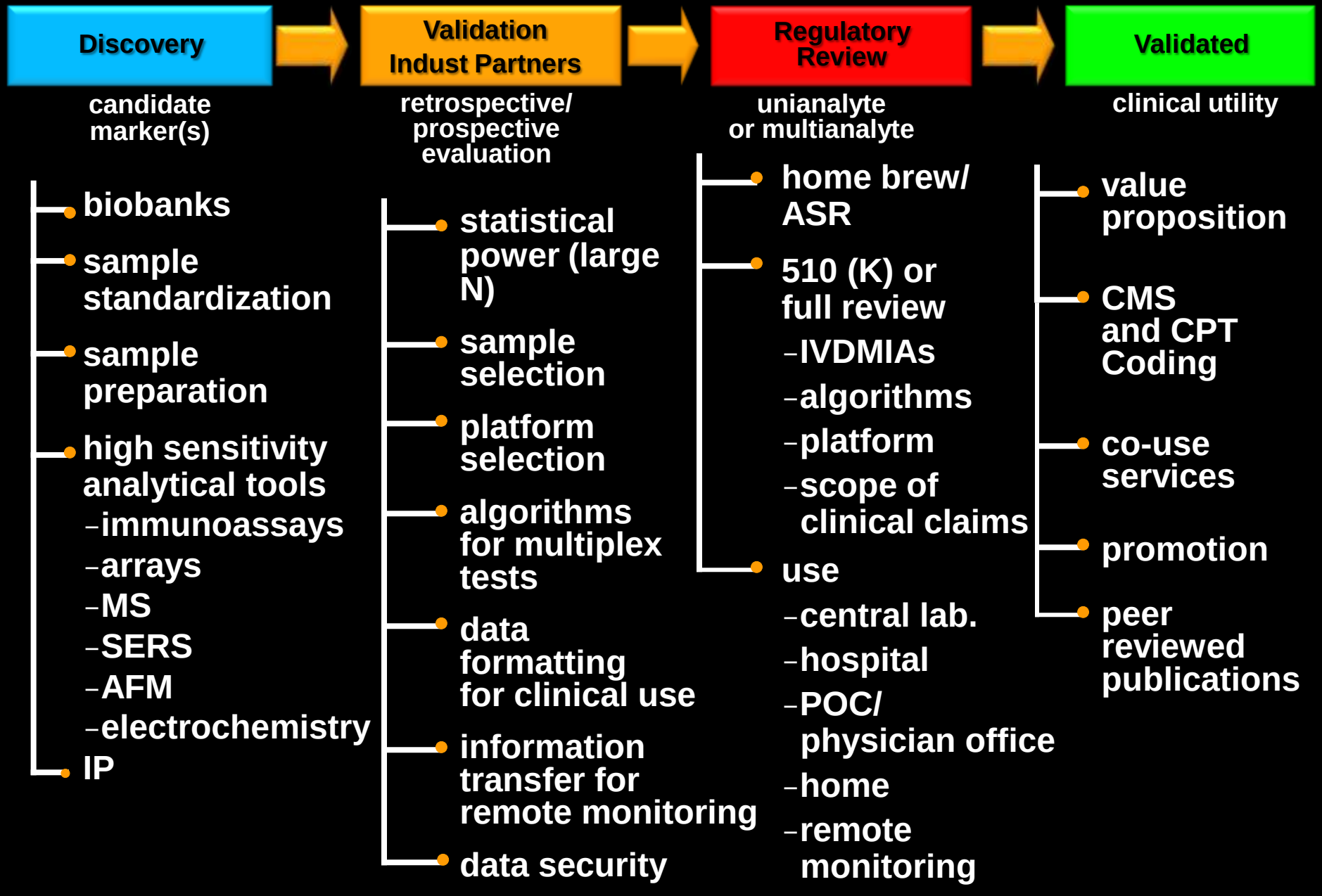
• IMPROVED CLINICAL AND PATIENT OUTCOMES

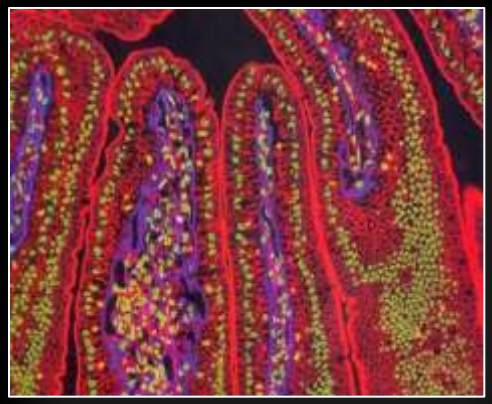
Biomarker R&D
Building An Integrated Framework

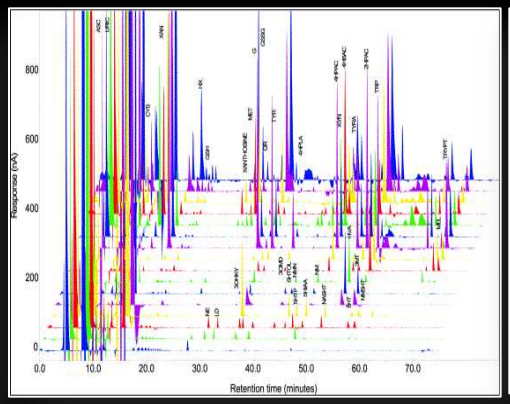


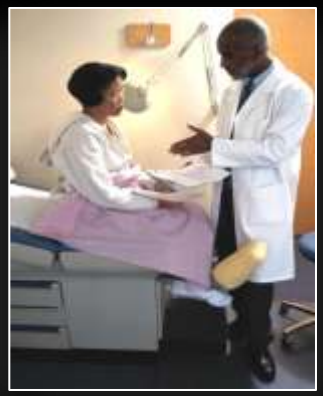
Biomarker Discovery, Validation and Adoption: The Obligate Need for 'Systems-Based' Approaches

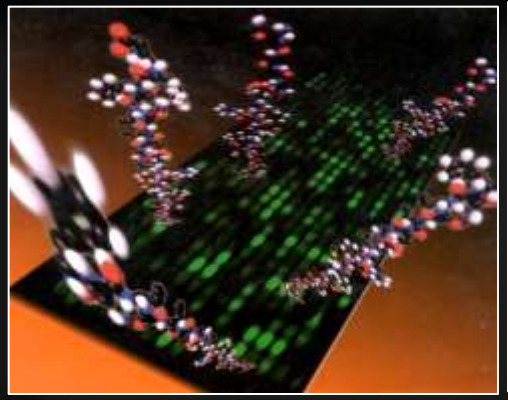
- samples
- signatures
- scale
- standards

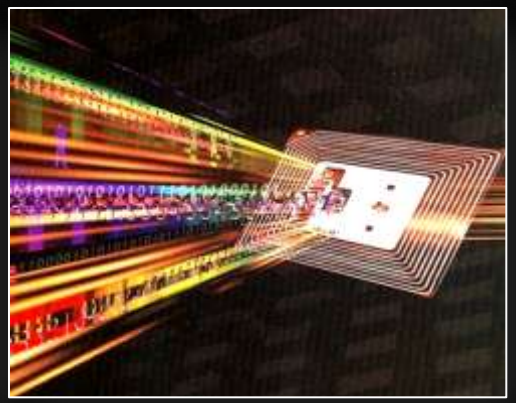
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches











Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

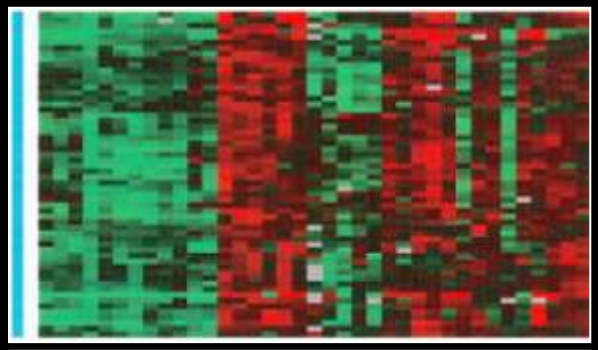
Instrumentation and Informatics

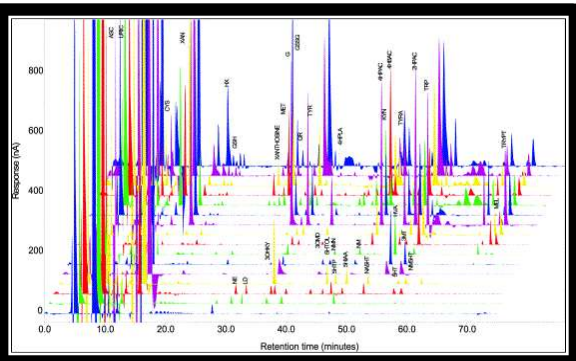
Clinical Impact and Patient Monitoring

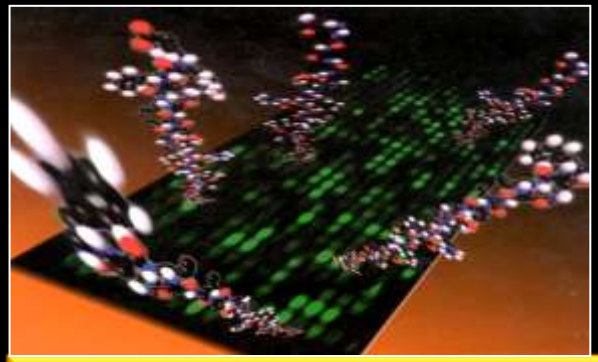
Molecular Diagnostics and Miniaturized Devices: A Key Future Driver in the Healthcare Value Chain

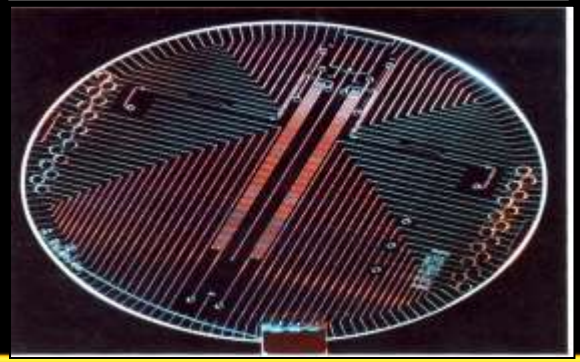
Complex Biosignature Profiling

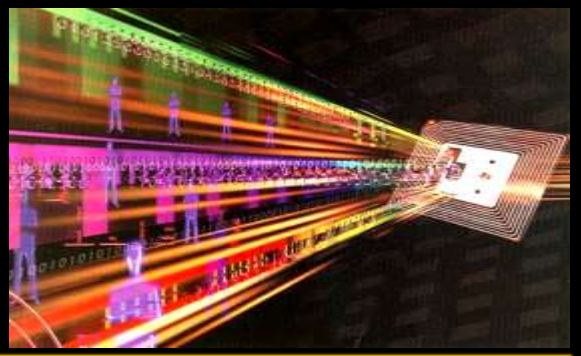
genomics	proteomics	immunosignatures











Signature Detection, Deconvolution and Multivariate Analysis

automated, high throughput multiplex assays	novel test formats and devices (POC)	new algorithms for complex signal/deconvolution

Trends in Mapping Diagnostic Signatures of Health and Disease

- unianalyte → multiplex
- simple analytical endpoint(s) → complex analytical algorithms
- technician dependent → high throughput automation; lab-on-a-chip; remote fault-diagnostics/ repair
- centralized laboratory → migration to POC; wireless remote monitoring
- population-based reference index → individualized profile and longitudinal person record as reference index

Common Problems in MS-Based Proteomics

A.W. Bell et al. (2009) Nature Methods 6, 423

- evaluation of test sample of 20 purified proteins at 5 pmole equimolar abundance
- 7/27 labs with initial correct characterization
- raw data from all sufficient to identify full 20 protein catalog and 22 derivative 1250 Da peptides
- diverse and poorly standardized databases and search engines as principal sources of erroneous reporting
  - variation in curation, annotation, comprehensiveness

- real world challenges: high complexity samples and large preanalytical (collection/storage) sample variation

- education and training to use complex technologies
- publication standards, formats and open-source dbases

Biomarkers: PubMed 2009

- 7892 citations
- 46.4% also categorized search term ‘cancer’

Disease-Associated Biomarkers and Validation of Novel Molecular Diagnostics

- literature dominated by anecdotal studies
  - academic laboratories
  - small patient cohorts
  - poor replication and confirmatory studies
- lack of standardization
- very few biomarkers subjected to rigorous validation
  - case-control studies with sufficient statistical power
  - inadequate stringency in clinical phenotyping
- lack of understanding of regulatory requirements in academic research community
  - complexities imposed by multiplex tests
  - new regulatory oversight (IVDMIAs)

Development of Companion Diagnostics and Dx Test Validation Standard

- ODAC rejection (3/2010) of *Omapro* for Gleevec-resistant CML due to T315I mutation

- failure to use single standardized assay for all patients
  - peripheral blood versus bone marrow
  - 1/3 tested locally; 2/3 tested centrally
  - centralized labs used different assays with 100 fold sensitivity difference for the mutation

Validation of Disease Associated Biomarkers

- disease related differences are small compared to biological variability
- many variables behave as QTLs with graded continuum rather than binary normal: disease separation
- 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)
- standardization and statistical powering
  - “the 20:200:2000 rule”
- new regulatory complexities for multiplex ‘signatures’ as next-generation diagnostic tests/biomarkers

“We may be lost,
but we’re having a good time”

Yogi Berra

The Cancer Biomarker Challenge

Samples

The Widespread Failure to Set Standards for Analysis and Annotation in Biomedical Research and Clinical Medicine

- predominant analysis of poorly characterized tissue samples of convenience and statistically sub-powered studies

versus

uniform QC/QA standards for sample acquisition, curation, annotation plus requisite statistical rigor

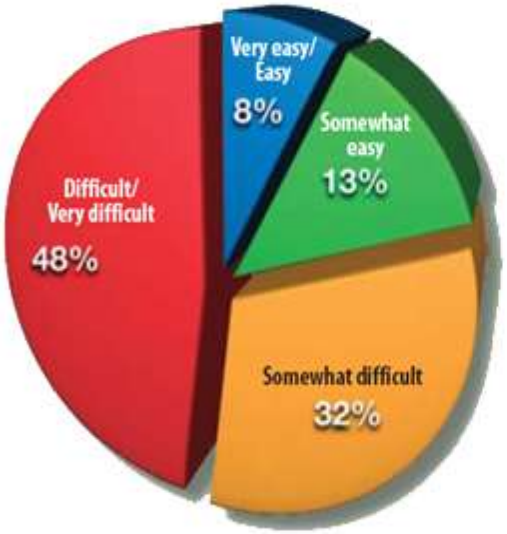
- inadequate clinical stringency in patient ‘phenotyping’ and poorly standardized criteria for patient staging, progression and outcomes

versus

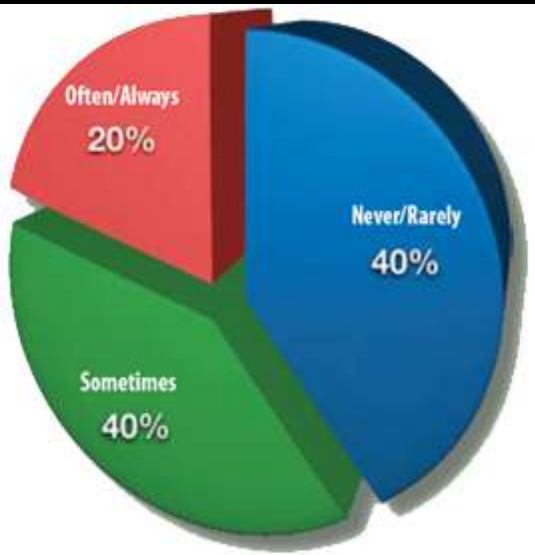
consistent protocols for patient stratification and longitudinal case records for correlation of molecular pathology with clinical outcomes

Access to Quality Biospecimens for Medical Research

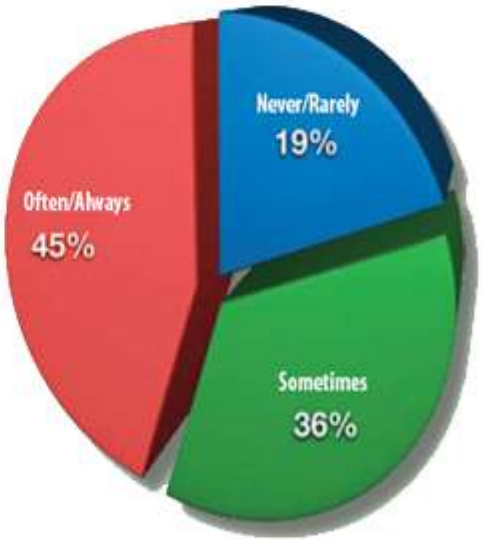
Ease of Acquiring Quality Biospecimens



Question Their Data Because of the Quality of Biospecimens

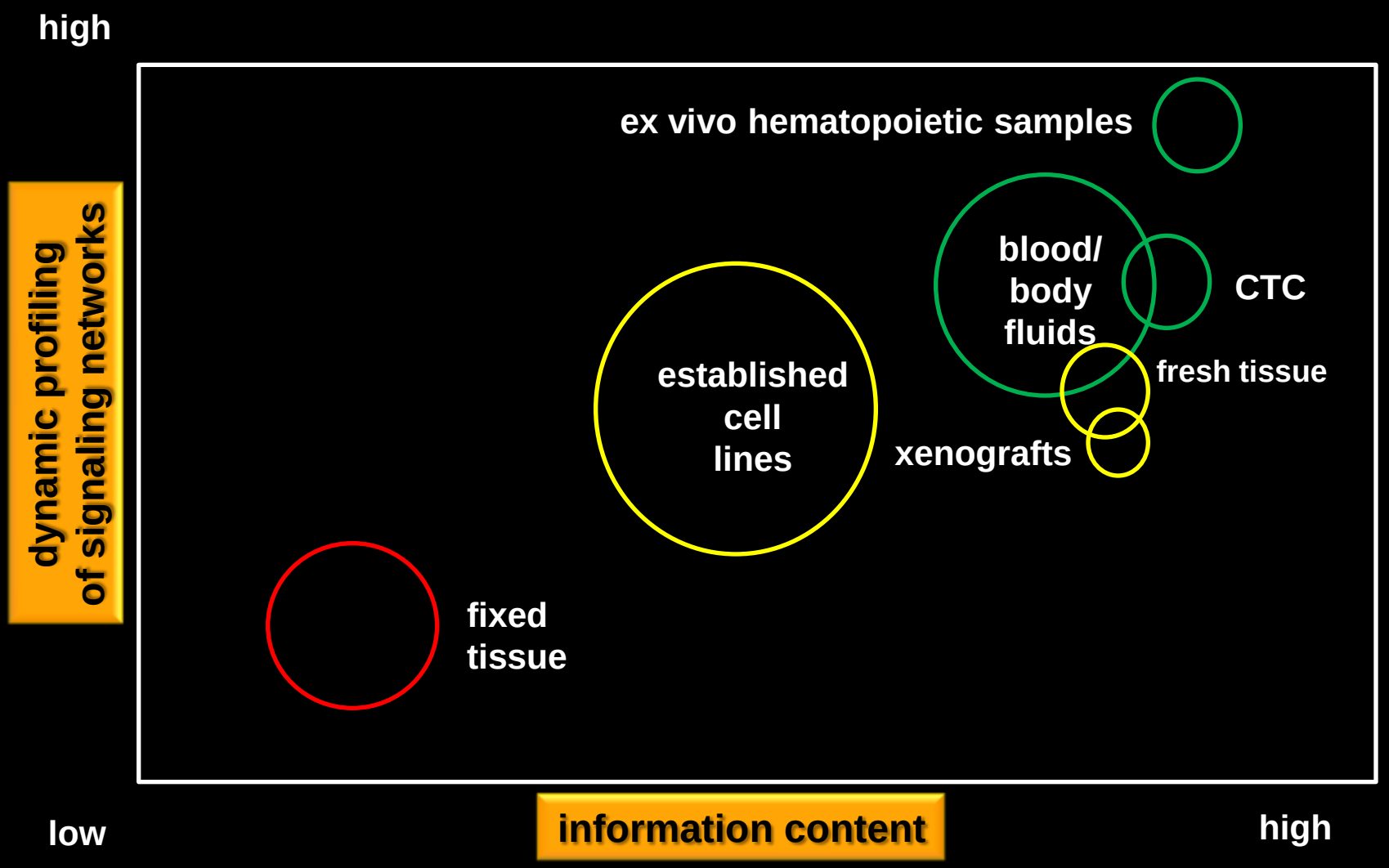


Limit Research Scope of Work Due to the Shortage of Quality Biospecimens

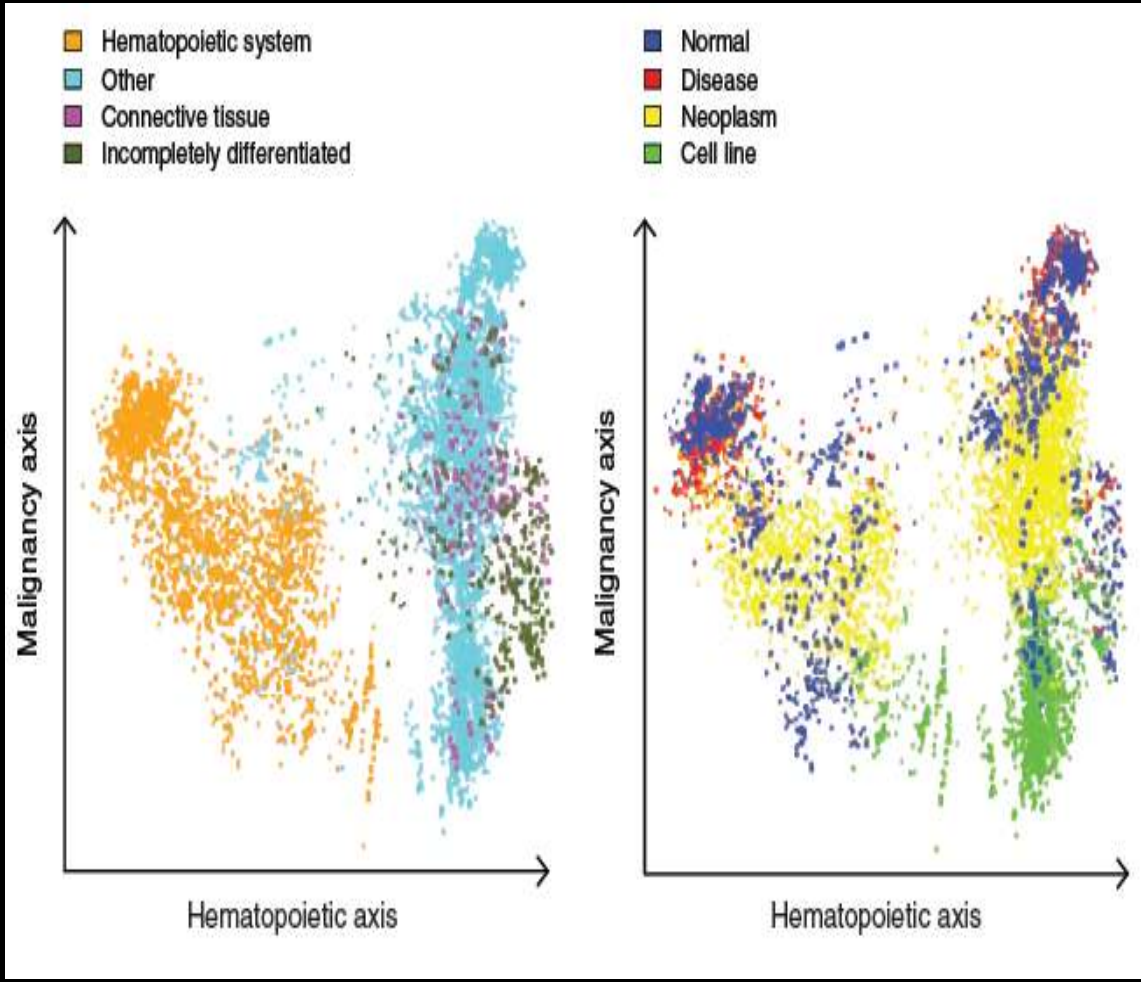


Source: Office of Biorepositories and Biospecimen Research, 2009.
http://biospecimens.cancer.gov/cahub/

Utility of Cancer Biospecimens for Biomarker Analysis



A Global Map of Human Gene Expression
M. Lukk et al. (2010) Nature Biotech. 28, 322



http://www.ebi.ac.uk/gxa/array/U133A

- 5372 microarray samples
- 206 different laboratories
- 163 different laboratories
- 369 ‘groups’
  - cell or tissues type, disease state or cell line
- gene expression matrix of 14,000 genes X5372

A Global Map of Human Gene Expression

M. Lukk et. al. (2010) nature Biotech. 28, 322

- principal component analysis of 5372 microarray datasets from 369 cell lineages/tissues/lines
- consistent segregation patterns
- solid tissue cell lines cluster together rather than with respective tissues of origin
  - 1217 genes upregulated in all cell lines
  - cell cycle, division and mitosis genes
- neoplasm samples cluster as intermediate group between homologous normal tissue and immortalized cell lines

Challenging Questions

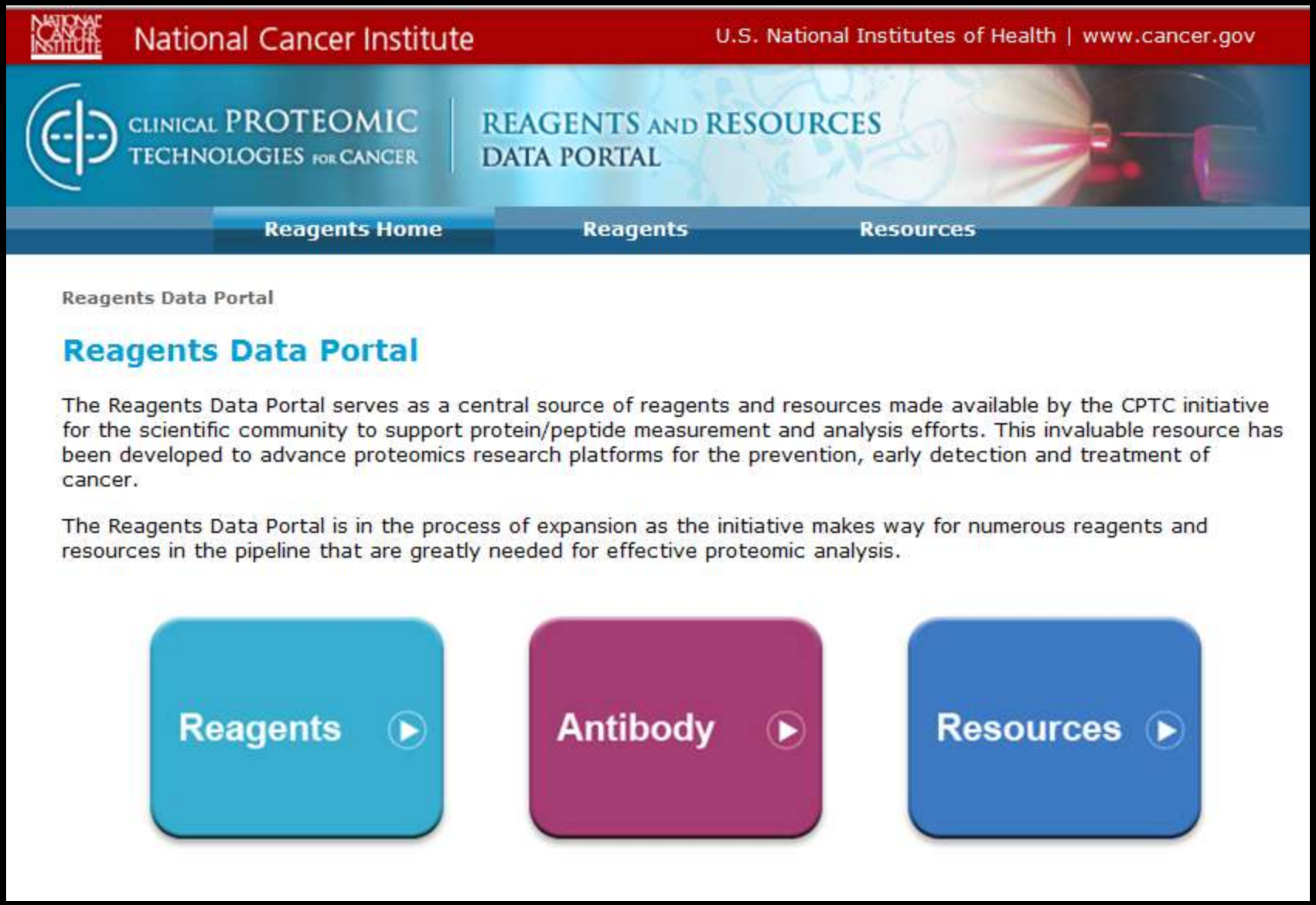
- are the phenotypes and molecular pathways of cell lines and 2D cell cultures so unrepresentative of the situation to render them irrelevant and pose blind avenues for diagnostic/therapeutic discovery?
- can the biology of metastasis be elucidated by analysis of non-metastatic cells?
- should research on biomarkers for diagnosis, staging and Rx responsiveness be funded without demonstrated access to standardized samples and disease: control cohorts and/or prospective RCT samples of requisite statistical power?

Challenges Associated With Legacy Biobanks

- highly variable storage, curation and clinical annotation
- investigator/institutional ‘terroriality’
- ambiguous and varied informed consent provisions
  - disease specific versus blanket ‘research use’
- limited longitudinal sampling and correlation with clinical outcomes
- relative absence of normal tissue cohorts

Challenges in Establishing Rigorous Correlations Between Perturbations in Molecular Pathways and Disease

- more stringent criteria for clinical phenotyping
- obtaining the right phenotypes in the right quantity
- obtaining enough investigators with the right training and right resources
- right funding mechanisms to support the right studies


National Cancer Institute
U.S. National Institutes of Health | www.cancer.gov
CLINICAL PROTEOMIC TECHNOLOGIES FOR CANCER
REAGENTS AND RESOURCES DATA PORTAL
Reagents Home
Reagents
Resources
Reagents Data Portal
Reagents Data Portal
The Reagents Data Portal serves as a central source of reagents and resources made available by the CPTC initiative for the scientific community to support protein/peptide measurement and analysis efforts. This invaluable resource has been developed to advance proteomics research platforms for the prevention, early detection and treatment of cancer.
The Reagents Data Portal is in the process of expansion as the initiative makes way for numerous reagents and resources in the pipeline that are greatly needed for effective proteomic analysis.
Reagents
Antibody
Resources

Building Large Scale, Standardized Research and Clinical Resources for Efficient Translational Research

- common multisite protocols (HIPAA, IRB)
- biorepositories
- ‘omics’ assay formats
- integrated ‘omics’ datasets
- more stringent clinical phenotyping schemes and databases
- novel algorithms
  - scale
  - non-linear dynamics
- transparent regulatory standards

Translation of the Major Potential of Molecular Medicine into Routine Clinical Practice

A Complex Multi-Dimensional Challenge

The Real World

- innovation in science and technology alone is necessary but not sufficient
- adoption requires overcoming multiple barriers
  - existing competition/standard of care
  - cultural conservatism
  - reimbursement and other financial obstacles
  - regulatory hurdles
  - threat of IP protection
- wide variation in adoption speed by different sectors
  - healthcare (10-30 years)
  - computing (1-2 years)
  - engineering (1-10 years)

Standards for ‘Omics’ Data Cross-Domain Integration, Open-Source Data Sharing and Computational Analysis

Semantics: The Need for Adoption of Standardized Taxonomies and Ontologies in Biomedical Research

- transcending the taxonomic anarchy of descriptive biology and medicine
- standardized nomenclature for biological systems
- reporting formats for quantitative data
- crucial foundation of productive assembly and analysis of large scale and open-source datasets
- facile integration of scientific and clinical data for evidence-based treatment selection/decision-analysis

OBO Foundry Ontologies
Nature Biotechnology 25, 1251 - 1255 (2009)


The Open Biomedical Ontologies

Cell Ontology (CL)

Gene Ontology (GO)

Foundational Model of Anatomy

ZFIN

Zebrafish Anatomical Ontology

Chemical Entities of Biological Interest (ChEBI)

Disease Ontology (DO)

Plant Ontology (PO)

Sequence Ontology (SO)

Ontology for Clinical Investigations (OCI)


The Open Biomedical Ontologies

Common Anatomy Reference Ontology


The Open Biomedical Ontologies

Environment Ontology

Ontology for Biomedical Investigations

Phenotypic Quality Ontology (PATO)

Protein Ontology (PRO)

OBO Relation Ontology

RNA Ontology (RnaO)

The Rise of Open-Source Networks and Consortia

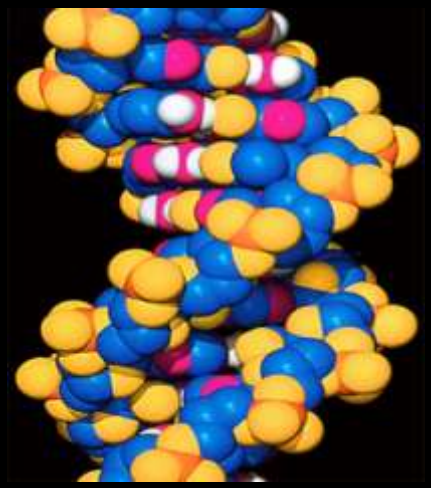
The Imperative for New Approaches: The Launch of Important New Strategic Programs

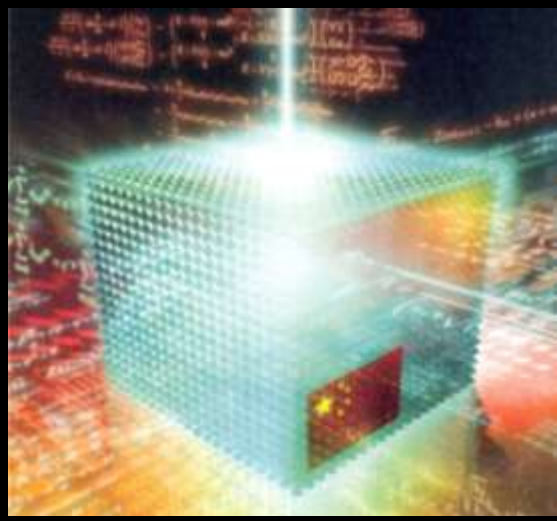
“Managing Mega-Data”

volume

scale

global networks

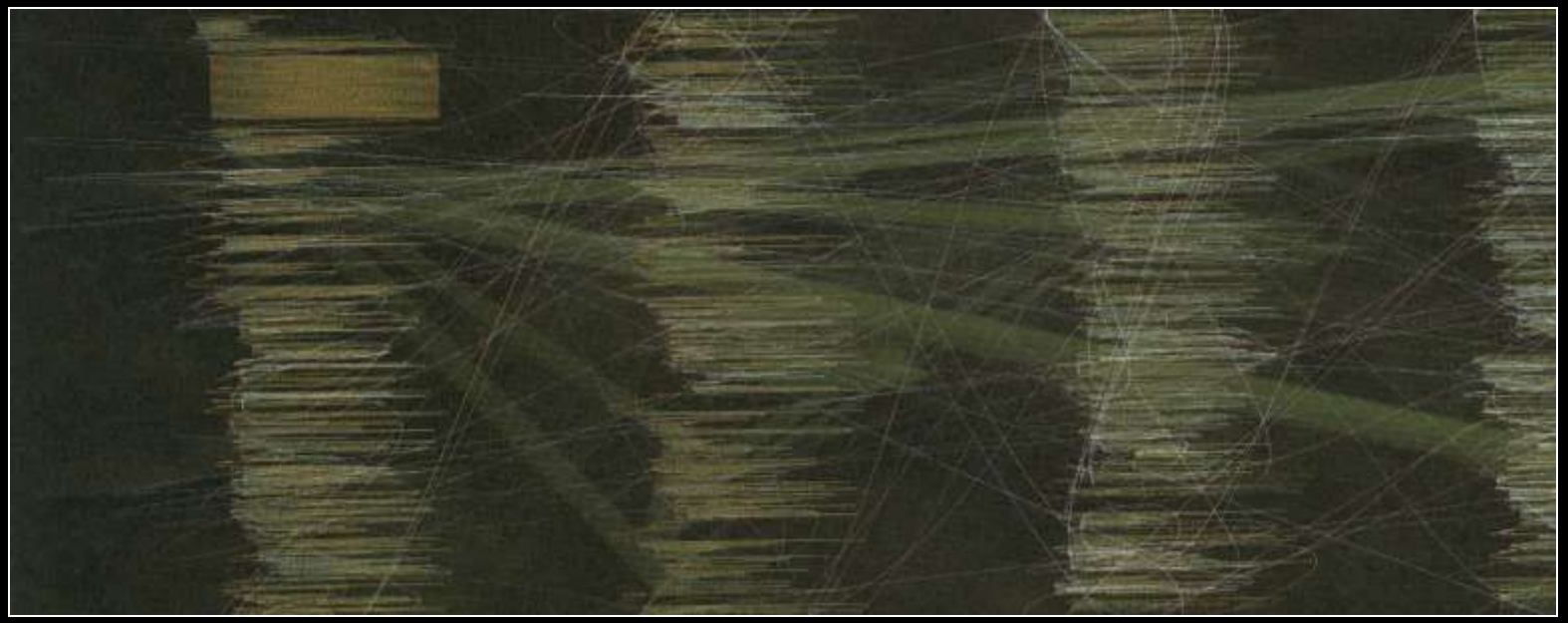




multiscale heterogeneity

integration

Mining The Data Deluge



- liberate intelligence from multiple source formats
- interoperability challenges
  - early discovery (chaos) vs. clinical trials (CDISC) vs. healthcare (HL7, SNOMED)
  - urgent imperative for methodological, ontology and data storage format standards

Setting Regulatory Standards for Multiplex IVDs

FDA

- MicroArray Quarterly Control (MAQC) Project
  - generation of RNA standards for transcriptomic assays
- Statement for Reporting Studies of Diagnostic Accuracy (STARD)
- FDA Data Template
- In Vitro Diagnostics Multivariate Index Assays (IVDMIAs)

NIST

- External RNA Controls Consortium (ERCC)
  - ‘spike’ panel of RNAs for transcriptomic assays

Regulatory Issues

- greater technical complexity of multianalyte IVD tests
  - clinical validation of claimed correlation with disease stratification/progression and/or Rx outcomes
  - stringency of sample curation and case clinical phenotyping for control cohort
  - size, cost and time of clinical validation trials
- validation of algorithms used in test interpretation/clinical decision (FDA)
  - statistical and mathematical methods “obscure to the requesting physician”
  - probabilistic versus absolute endpoints
- jurisdictional oversight authority (FDA/CMS)

Current Payor Value Propositions Do Not Align with Clinical/Economic Value of Molecular Diagnostics

The Imperative for Value-Based Pricing versus Current Cost-Based Models

- inadequate US Medicare coding and payment mechanisms
  - out moded, out-dated, lacking in transparency, inconsistently applied
- inappropriate assignment of existing CPT codes to new MDx tests
- engagement of third party payers who derive economic/clinical value from new MDx

The Perceived Value of Evidence for Coverage Determinations by Order of Significance

- BCBSA, Hayes, Kaiser Approval
- coverage in other plans
- inclusion in clinical guidelines of a major Association or College
  - discrepancy among guidelines, e.g. mammography
  - perceived rigor of the Association or College
  - agenda of Association or College
- peer review clinical journals
- FDA approval
- CLIA approval

Genes and Intellectual Property


14 March 2000

SACGHS

5 February 2010 Report

MYRIAD

ACLU

AMERICAN CIVIL LIBERTIES UNION

29 March 2010 SDNY Court Decision


16 April 2010 WSJ Editorial

Scale: Organizational and Cultural Challenges

- analytical silos: the curse of systems analysis
- entrenched historical tenets of increasingly specialized disciplines, subdisciplines and reductionism
- institutional reinforcement of fragmented approaches to complex multi-dimensional problems
  - academic departments and P&T criteria
  - funding mechanisms and study sections
- the imperative to build new capabilities in inter- and cross-disciplinary research

BIG SCIENCE

Facile Formats for Imaging Data

- samples
- signatures
- scale
- standards

- silos
- status quo
- sociology

Nature (2010) 464, 664

Point: Hypotheses first

There is little to show for all the time and money invested in genomic studies of cancer, says **Robert Weinberg** — and the approach is undermining tried-and-tested ways of doing, and of building, science.

Counterpoint: Data first

Large, unbiased genomic surveys are taking cancer therapeutics in directions that could never have been predicted by traditional molecular biology, says **Todd Golub**.

http://www.nature.com/nature/journal/v464/n7289/pdf/464678a.pdf

Standards: Relevance

- discarding biologically and/or clinically irrelevant research methods/strategies
- insidious cultural and organizational barriers to change
  - propagation of funding for historical conceptual paradigms and experimental models despite evidence of low productivity
  - inadequate mechanisms for review/funding of ambitious cross-disciplinary programs
  - abundant evidence of shortcomings in many cell/animal systems as predictive models for human cancer
  - pressure for continued publication/funding sustains irrelevant models

Translational Medicine

- inadequate feedback loops from bench to bedside
- information gap in academia on complexity and rigor of preclinical / clinical / regulatory processes
- insufficient research-oriented clinicians
- competitiveness of AMCs and logistical and financial barriers to large scale trials and uniform protocols
- cultural challenges of launching projects with directed goals in academic communities with traditionally more autonomous behaviors and dominant individual investigator mentality/reward
- escalating ‘knowledge gap’ for healthcare professionals as a barrier that threatens traditional role as informed authority and decision-maker

Changing the Sociology of Life Sciences and Clinical Research

- transcending silo mentalities, organization and funding → cross-disciplinary initiatives and new career incentives/rewards
- rebalance public funding priorities to address scale and complexity of trans-disciplinary projects → new funding vehicles with suitable scale; new review systems
- set new balance between hypothesis-driven and data-driven research → recognize importance and intellectual merits of large scale dbase assembly, curation, analysis
- poorly standardized, fragmented data → standardized ontologies, consortia, grids, open source databases for meta-analyses
- the challenge of translational research: "the valley of dearth" → stringent funding criteria for obligate assembly of full expertise spectrum; new clinical training/ medical curriculum; private: public partnerships

Forging the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

Industry

- greater recognition of value and participation in pre-competitive, open-source networks/consortia
  - drive standards
  - defray risk
  - broaden partnerships
- more proactive role in shaping new trans-disciplinary education/training/employment opportunities
  - translational medicine
  - large scale dbase analytics
  - new analytics/models for non-linear dynamics in complex systems
  - health economics outcomes/systems modeling

Forging the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

The Sociology of Biomedical Research and Clinical Medicine

- courage
  - to declare that major change is needed versus safe refuge of status quo
- disruptive change is never easy
  - active engagement will impose great demands without immediate short-term benefit(s) to individuals/institutions
- public expectancy, accountability and accomplishments

Forging the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

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Molecular Diagnostics and Imaging Technologies Can Transform Cancer Detection and Outcomes