Keynote Presentation at the Burrill & Company 2011 Annual Limited Partners and Advisory Board Meeting
Park City, UT • April 6, 2011

Promise, Peril, Productivity and Politics: The Strategic Environment for Healthcare R&D

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Sustaining Healthcare Innovation in an Era of Constraint

The Challenge of Translation of Discovery Advances to Tangible Benefits for Patients and Society

Prospect of Continuing Productivity Decline in Rx Pipelines

Molecular Diagnostics (MDx) and Data-Information Services (Ix) as Emerging Value Drivers in Improving Disease Detection and Treatment Outcome
Sustained Productivity in Healthcare R&D Will Require Systems-Based Approaches That Integrate Diagnostics, Therapeutics and Information Systems for Optimum Outcomes

Disruptive R&D Innovations Are Needed Urgently to Transcend Current Linear Incremental Strategies That Are Insufficient to Meet Future Healthcare Delivery Needs

Progress in Achieving Major Productivity Gains and Disruptive Innovations Will Require Radical Reform of the Organization and Funding of Approaches to Discovery and Proficient Translation to Products/Services
Real Healthcare Reform or Reducing Costs Without Addressing the Fundamental Problems?
The Healthcare Challenge

Outcomes
clinical, economic, quality-of-life

unmet medical needs

infinite demand versus finite resources

increasing cost of care and acceleration of new technologies

Access to Care

Innovation and Cost of Care
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
Personalized and Sustainable Healthcare

Efficient use of information and allocation of resources

Technological innovation and rigorous evaluation of effectiveness

QUALITY

ACCESS

Societal Values

COST
Disruptive Innovation in Healthcare: Redefining the Value Equation in Healthcare

Integrated AP and MDx Platforms

- Managing risk, cost, and quality
- Optimized decisions
- Health status monitoring
- Earlier disease detection and response to RX

Precision Diagnosis

Better care at lower cost

Treatment personalized to the patient
Promise
Patterns of Technology Convergence: Mapping Disease Mechanisms at the Molecular Level

Clinical Pathology and Molecular Biology

Chemistry, Engineering and Materials Science

Automated Miniaturized High Throughput Assay Systems

Information Products and Services

Evidence for Clinical Decisions and Value-Based Reimbursement

Disease Markers and Rx Targets

PROFILE

DETECT

ACT

Computing

Health Outcomes
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 K-RAS versus mutant-K-RAS
- estimated $604 million/year savings (ASCO)

clinical guidelines

- regulatory endorsement in product labeling
The Challenge Posed by Two Very Different Disease Categories

**Infectious Diseases**
- acute
- populations (public health)
- drug resistance
- tractable Rx target space
- problematic market incentives

**Cancer**
- chronic
- individuals (albeit global)
- drug resistance
- disease heterogeneity and uncertain Rx target space
- high margin markets (but sustainable?)
A Shared Global Risk: The Omnipresent Threat Posed By Microorganisms and Parasites
Infectious Diseases: A Shared Global Risk

#1
- cause of neonatal and maternal death worldwide
- economic impact of disease via premature death, disability and reduced productivity
- growing drug-resistance as most important clinical threat in both industrialized nations and DCs

#2
- cause of death worldwide

#3
- cause of death in US and Europe

The Imperative for new R&D Strategies and Investments in Diagnostics, Drugs and Vaccines
Biosecurity: Outpacing Infectious Diseases

- Bioterrorism
- Infectious Diseases of Natural Origin
- Urbanization in Developing Countries
The Global Public Health Challenge Posed by Rapid Urbanization in Developing Countries

- High Disease Transmission
- Lack of Safe Water
- Toxic Waste

- Major Deficits in Health Infrastructure
- Expanded Eco-niches and Increased Zoonotic Risks
“One Health”: The Rationale for Integration of Historically Separate Domains and Responsibilities

- Urbanization of DCs and emergence of new zoonotic threats
- Food chain as increasing source of disease risks
- Enhanced agricultural productivity to support global population growth
- Economic impact of agricultural disease on trade, development and resources/production footprints
Comfort and Complacency: The Enemies of Vigilance and Preparedness
NO ESKAPE!: Resistant Bugs and Few New Drugs

- increasing resistance in G+ and G- pathogens in hospital and community settings
- the ESKAPE pathogens
  - *Enterococcus faecium*
  - *Staphylococcus aureus*
  - *Klebsiella pneumoniae*
  - *Acinetobacter baumanii*
  - *Pseudomonas aeruginosa*
  - *Enterobacter species*
The Valley of Dearth: The Consequence of Declining R&D Investment in Antibiotic Discovery*

- 75% decrease in antibacterials approved from 1983 to 2009
- only 16 agents currently in Phase II / III clinical trials
  - only 3 as new ‘classes’ with novel mechanisms of action
  - absence of agents for therapy of AMR in G-bacilli
  - lack of systemic agents in advanced development for organisms resistant to all current antibacterials

Incentives for R&D Investment in Antibiotics

Policies and incentives for promoting innovation in antibiotic research

Equal Relevance to Stimulating R&D Innovation In Diagnostics, Anti-virals and Vaccines
“If this virus was killing more of its victims, there’d be lots of questions about whether this vaccine was produced soon enough”

Dr. Michael Osterholm
Director, CIDRAP, Univ. Minnesota
USA Today 8 Oct. 2009
Combating ‘Agent-X’
The Imperative for Innovation in Vaccine Production Technologies

- production of the relevant epitopes by chemical synthesis versus traditional ‘biological’ production methods
- dramatic reduction in vaccine production time
- rapid scaleability and production plant flexibility versus ‘biological’ methods
- compositional uniformity of chemically synthesized antigens eliminates need for regulatory approval of individual lots (unlike biological products)
Vaccine Safety: Media Sensationalism and Celebrity Quackery

TOO MANY TOO SOON

Vaccine Ingredients:
- mercury, aluminum, antifreeze, formaldehyde,
- aborted human fetus cells, chick embryos,
- monkey kidney cells, fetal bovine serum, etc.

www.safevaccines.org

CRAZY TALK

Oprah, Wacky Cures & You
The Strategic Environment for Antimicrobials and Vaccines

- Unmet Need
- Technical Feasibility
- Registration Timeline
- Investment Cost
- Competition
- Regulatory Complexity
- Value-Based Reimbursement
- Clinical Adoption
We Are Not Alone
New Perils?

New ‘Dual-Use’ Technologies
Globalization, Biosecurity, and the Future of the Life Sciences

New approaches to biological risk assessment

Strategic Plan for Outreach and Education On Dual Use Research Issues

Report of the National Science Advisory Board for Biosecurity (NSABB)

December 10, 2008

Synthetic biology

Scientific discussion meeting summary

Synthetic biology

Postnote

The Dual-use Dilemma

July 2009 Number 340
Promise or Peril?
“The War on Cancer”

National Cancer Act of 1971
December 23, 1971

Science (2011) 331, 1539

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-
How Many Americans Will Die of Cancer Today?

- 100?
- 500?
- 1000?
- 1500?
- 2000?
- 5000?
COUNTING THE COST OF CANCER

The burden of cancer, calculated as the cost of years lost from ill-health, disability or early death, outweighs all other health concerns.

- Cancer: $895.2 bn
- Heart diseases: $298.2 bn
- Cerebrovascular disease: $193.3 bn
- Lower respiratory infections (including pneumonia): $125.8 bn
- Malaria: $24.8 bn
- Cirrhosis of the liver: $92.8 bn
- Road accidents: $204.4 bn

From: T. O’Callaghan (2011) Nature 471, S4
### US Cancer Prevalence Estimates 2010 and 2020

<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>% change</th>
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<tbody>
<tr>
<td></td>
<td>2010</td>
<td>2020</td>
</tr>
<tr>
<td>Breast</td>
<td>3461</td>
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<td>812</td>
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<td>Bladder</td>
<td>514</td>
<td>629</td>
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<tr>
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<tr>
<td>Kidney</td>
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<td>426</td>
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<td>263</td>
<td>240</td>
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<tr>
<td>All Sites</td>
<td>13,772</td>
<td>18,071</td>
</tr>
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</table>

The Ethics of Hope, Hyperbole and Hubris
The Distressing State of Investigational Cancer Drug Trials in the USA

- Armitage (1997) and IOM Reports (2010)
- less than 5% cancer patients enrolled
- unacceptable inefficiencies
  - 54% of 2685 industry/NCCN trials at 14 major centers failed to accrue single patient
  - 296 to 481 steps to activate trials by NCI-STEP and/or cooperative groups
- impact of regulatory creep
  - initiation of EC/Asia trials x2 faster than in USA
- offshore migration of clinical trials
Surging Investments in Oncology R&D*

- 861 oncology/cancer drugs in clinical trials
- 147 equity offerings
- 30 debt offerings
- 117 partnerships
- 81 licensing agreements
- 4 PE deals
- 158 VC deals

*2010 data: [http://edbgroup.com-globaldatareport](http://edbgroup.com-globaldatareport)
*PhRMA: website accessed Feb.2011
“The bar for what we call ‘significant’
has fallen so low we risk tripping over it.”

Dr. Antonio Tito Fojo
Head, Experimental Therapeutics Section, NCI
2010 AACR Meeting cited in Oncology Times 25 June 2010
Tarceva (erlotinib): Genentech

- 2005 approval for use with gemcitabine for pancreatic cancer
- increased median survival by 10 days

Vectibix (panitumumab): Amgen

- 2006 approval for advanced CRC
- tumor progression slowed by 5 days
Cancer Therapeutics: Some Perplexing Questions
How Should the Value of Oncology Drugs Be Assessed?
Nice Gets Nasty (or Rational?)
What Are We Willing to Pay for Added Months of Survival in Cancer?

<table>
<thead>
<tr>
<th>Lifetime cost above standard care</th>
<th>If cancer is on par with other diseases ($150,000 per life year gained), months of added overall survival benefit needed</th>
<th>Treating cancer as worthy of much higher reimbursement ($250,000 per life year gained), months of added overall survival benefit needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>$50,000</td>
<td>4 months</td>
<td>2.4 months</td>
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<td>$100,000</td>
<td>8 months</td>
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<td>$150,000</td>
<td>12 months</td>
<td>7.2 months</td>
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<td>$200,000</td>
<td>16 months</td>
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<td>$400,000</td>
<td>32 months</td>
<td>19.2 months</td>
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<tr>
<td>$450,000</td>
<td>36 months</td>
<td>21.6 months</td>
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<tr>
<td>$500,000</td>
<td>40 months</td>
<td>24 months</td>
</tr>
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</table>

Source: Pink Sheet 13 Sept. 2010. Adapted from S. Ramsey FHCRC, ASCO 2010
Therapeutic Targeting of the Principal Phenotypic Hallmarks of Cancer

The Strategic Environment for New Oncology Therapeutics

- Unmet Need
- Clinical Adoption
- Technical Feasibility
- Registration Timeline
- Value-Based Reimbursement
- Regulatory Complexity
- Investment Cost
- Competition
Rethinking Approaches to Cancer

Is There a Fundamental Imbalance in Investment in Diagnostics Versus Therapeutics?
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 *CTNNAL1* 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: Some Perplexing Emerging Questions

- Is the multiplicity of pathways dysregulated in metastatic advanced disease an insurmountable technical barrier to design of poly-target (promiscuous) agent/combinations?
  - Highest failure rate of new Rx in any therapeutic category (8% success)

- Is the only viable strategy for mitigating the clinical, economic and emotional toll of cancer to focus on early diagnosis and removal of pre-metastatic lesions?
Successful use of MDx for Early (Pre-Metastatic) Detection in Major Cancers Will Not Eliminate Need for New Rx and Rational Rx Selection Tools

- **solid malignancies**
  - fraction of patients will still present with advanced disease due to failure to use new MDx detection platforms

- **hematopoietic malignancies**
  - distributed nature of malignant cells precludes surgical excision
  - valuable role of MDx in subtyping patients for presence/absence of Rx target(s)
A Momentous Goal:
To Dramatically Reduce The Impact of the Major Cancers

- successful early (pre-metastatic) detection/removal of cancer versus the elusive quest for a ‘cure’ for metastatic disease
  - eliminate 85% of current cancer care costs
  - dramatic reduction of the devastating physical/emotional financial toll on patients/families
Biomarkers, Biosignatures and Molecular Diagnostics: The Key Value Drivers for Personalized Medicine, Improved Healthcare and Maximizing Wellness
Cancer Diagnostics
Diagnostics M&A (2011)
Pharmaceutical-Diagnostics Partnerships

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

- BioMerieux & Merck
- BioMerieux & Ipsen SA
- Celera & Ipsen
- DxS & Amgen
- Abbott & OSI/Genetech/Roche
- Aureon Labs & Pfizer
- Celera & Abbott
- Celera & Merck
- 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
- Qiagen DxS & AstraZeneca/Teva
- Merck & Millipore
- Genzyme & CMIC
- Thermo Fisher & 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

2007 2008 2009 2010

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*List is Not Exhaustive

*Collaboration refers to partnerships biomarker discovery and assay development

**License refers to biomarker or assay licensing deals

Source: Scientia Analysis
Translation of the Major Potential of Molecular Biomarkers for Diagnosis and Treatment Selection into Routine Clinical Practice

A Complex Multi-Dimensional Challenge

Success Demands a Systems-Based Approach
Platforms for Biomarker and Biosignature Profiling

Analytes
- genomics
- proteomics (and PTMs)
- metabolomics
- toxicology

Analysis
- global analysis (non-biased)
- targeted analysis (hypothesis-driven)

Applications
- candidate ID for use with more facile platform
- routine clinical use

Alternatives
- cost
- speed
- instrumentation capital cost
- regulatory/clinical issues

Standardized Methods, Data Reporting and Database Design
- GLP/GMP; LIMS/CTMS; Regulatory Dossiers

Instrumentation: Research Use Only or Approval for Clinical Use
Disease-Associated Biomarkers and Validation of Novel Molecular Diagnostics

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

Agnostic
- analytes
- analytical platforms

Success Determinants
- systems-based strategies
- specimens
- standards/standardization
- scale/statistics
- silos and sociology
- sustainability
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
Access to High Quality Biospecimens

- #1 obstacle to ID and validation of novel biomarkers
- inappropriate ‘turf’ battles over legacy specimens
  - public versus private funding
- unknown or variable quality of legacy biorepositories and limited linkage to clinical records
- historical neglect of national-level leadership/standards for biorepository specimens and management
- poorly developed protocols for systematic classification, coordination or distribution (priorities)
“The technological capacity exists to produce low-quality data from low-quality analytes with unprecedented efficacy.”

“We now have the ability to get the wrong answers with unprecedented speed.”

Dr. Carolyn C. Compton
Director, Office of Biorepositories and Biospecimen Research
National Institutes of Health
‘10M, July 2010’
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 of validation studies
  - “the 20:200:2000 rule”
- new regulatory complexities for multiplex ‘signatures’
“We may be lost, but we’re having a good time”

Yogi Berra
The Single Most Important Leverage Point
For Rapid Mobilization of Resilient Responses
to Epi-/Pan-demics and WMD Bioterrorism

- faster Rx
- accurate Rx
- prophylactic Rx for incident personnel

- robust triage
  - rationing
  - reassurance of “worried well”
  - quarantine decisions

- real time disease surveillance data
- faster ID of incident evolution
- faster incident containment and exposure controls

New Diagnostic Technologies:
A Neglected Area of Biodefense and Biosurveillance
398 WHO-verified outbreaks 1996-2009

- 23 days for event detection
- 32 days for public communication
- 35 days for official laboratory confirmation
- 48 days for inclusion in WHO Disease Outbreak News
Global Disease Surveillance

EMERGEncy ID NET

World Health Organization

IdSA

Infectious Diseases Society of America

ProMED-mail

GPHIN

Public Health Department's Surveillance

HealthMap

Global Disease Alert Map

U.S. Influenza Sentinel Provider Surveillance Network

DoD-GEISWeb

Global Emerging Infections System

GIDEON

Quarantine Activity Reporting System (QARS).

BioPortal

biocaster

Argus Research Operations Center

GeoSentinel

The Global Surveillance Network of the ISTM and CDC

a worldwide communications & data collection network of travel/tropical medicine clinics

RABNET

Welcome to

EMPRES WATCH

Human and Animal Rabies

EUNiD

European Network of Infectious Diseases

Google.org
Geodemographic Information Systems (GIS): Real-Time, Front Line, Ground Zero Data from Field Sampling and Sentinels
Anomaly Detection and Early Alert

Disease Progression

Satellite Surveillance and Predictive Modeling of Disease Trends
<table>
<thead>
<tr>
<th>Remote Health Status Monitoring</th>
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<tbody>
<tr>
<td>Biosignature Profiling Via Sensors and Devices</td>
</tr>
</tbody>
</table>
Remote Health Monitoring and Chronic Disease Management

Lifestyle and Fitness

Information for Proactive Health Awareness (Wellness)

m.Health
Convergence

- MDx, Rx and Ix
- MDx, devices, telecommunications
  - m.Health, remote health status monitoring
- Social networks and consumer/patient empowerment
- Large scale healthcare data integration, mining and content services
- New players, new partnerships, new delivery pathways
Productivity
Yesterday,
.....it Seems So Far Away”™*
Challenges for Sustained Rx Product Flow

- Inefficient translation of academic research
  - Commercialization education (Kauffman)
- Retreat at VC from early stage discovery/pre-POC development assets
  - Valley of death
- R&D reductions in bigPharma and impact of economic downturn on biotech sector
- Complexity of chronic diseases and no prospect of enhancing asset success rate and/or truncation of R&D cycle time
- Regulatory uncertainties and increasing hurdles
  - Larger trials, risk and REMs
  - Increasing inflexibility
  - Inadequate budgets, staffing and science
Is the Productivity Decline Due to Organizational/Inefficiencies or Deeper Technological, Economic and Regulatory Challenges?

Shrink It, Cure It!

“Will fragmentation of Big Pharma R&D into multiple small units boost productivity?”

Robert Langreth
Forbes 17 January 2011

Realigning Deck Chairs Without A Map of the Icebergs!

“The core problems afflicting drug firms isn’t bureaucracy but a lack of deep understanding of disease biology. How you organize isn’t going to solve that.”

“Biotech companies are no better than Big Pharma at inventing drugs.”

The (Bio) Pharmaceutical Industry and Adapting to New Realities in Healthcare

- from proof-of-concept (POC) to proof-of-relevance (POR)
- increasing emphasis on outcomes and comparative effectiveness as core elements in reimbursement pricing
- focus on outcomes puts further strain of ROI in drug development
- selection of patient populations by MDx profiling is only avenue to address outcomes challenge
  - premium pricing for ‘guaranteed outcomes’
  - use of MDx test post-approval to identify eligibility for Rx
The Innovation Matrix

- New technologies/markets via convergence of different domains
- Emergence at margin of existing domain
- Linear innovation in existing domain/market
- Novel use of existing technologies in different domain/market

Disruption

Denial: Surprise

Funding Challenge

Low

High
(bio)pharmaceutical and traditional device companies have been slow (and most still are) to recognize the momentum of personalized medicine and the strategic disruption of new diagnostic technologies.

The key components of healthcare (physicians, providers, payors) are ill-prepared organizationally and operationally to respond to intensifying economic and social pressures for better value, improved treatment outcomes and cost control.
Disruptive Innovation in Healthcare: Redefining the Value Equation in Healthcare

- BETTER CARE AT LOWER COST
- EARLIER DISEASE DETECTION AND RESPONSE TO RX
- TREATMENT PERSONALIZED TO THE PATIENT

- PRECISION DIAGNOSIS
- molecular taxonomy of disease
- managing risk, cost and quality
- optimized decisions
- health status monitoring
- BETTER CARE AT LOWER COST
- EARLIER DISEASE DETECTION AND RESPONSE TO RX
- TREATMENT PERSONALIZED TO THE PATIENT
Integration of Previously Separate Domains: Driving Disruption

Informatics:
The Foundation for Greater Efficiency in Healthcare Delivery and
Improved Translation of Research Discoveries to Clinical Use
Five “-ics”
The Complex Inter-Relationships Shaping the Future of Healthcare

‘Omics
- mechanisms of disease
- molecular diagnostics
- rational Rx

Demographics
- aging
- remote health monitoring

Epidemics
- urbanization
- food/water resources
- instability and conflict

Economics
- cost/quality of care
- R&D investment incentives

Ethics
- access to care
- affordability
- personal accountability for risk mitigation
- privacy
- behavioral genetics
- dual-use technologies

personalized medicine
mHealth
global public health
value
values
• better diagnosis and treatment decisions (individuals)
• population data and evidence-based guidelines for best practices (health professionals)
• improved allocation of scarce/expensive resources (society)
• global health surveillance and risk reduction (global)
• acceleration of research discoveries and translation for improved care (academia, government, industry)
“Managing Mega-Data”

volume

scale

global networks

multiscale heterogeneity

integration
Big Genomics

- cost reduction and rapid acceleration of sequence datasets
- 1000 Genome Project (2010) generated more data in 6 months than GenBank accumulated in 21 years
- sequence data generation outstripping analytics
- 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 using large scale profiling studies
- current software is not scalable
- cloud computing
REPORT TO THE PRESIDENT AND CONGRESS

DESIGNING A DIGITAL FUTURE: FEDERALLY FUNDED RESEARCH AND DEVELOPMENT IN NETWORKING AND INFORMATION TECHNOLOGY

Executive Office of the President
President’s Council of Advisors on Science and Technology

DECEMBER 2010
thr mst b a futr, rt?
“We need to out-innovate, out-educate and out-build the rest of the world.”

“This is our generation’s Sputnik moment.”

“We need to celebrate not just the super bowl winners but our scientists.”

State of the Union Message
January 25, 2011
The Imaginot Line

- leadership delusion that current pre-eminence can be sustained with existing (historical) approaches
- comfort and complacency and catastrophic hubris
- the poverty of imagination and agility
  - ideas
  - incentives
  - institutions
  - ideology
The Missing Near Future: The Futurists Lament

• “why have we lost our ability to imagine the world of the near future (2020)? No version (of the near future) seems desirable and plausible.”

  Kevin Kelly

• “The now is too unstable to provide a satisfactory platform for extension into the future. There are too many wild cards too much complexity.”

  William Gibson
Protecting Turf and Sustaining the Status Quo: Silos Subvert Solutions

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
Transcending Boundaries: Emergent Domains Arising from Technology Convergence

<table>
<thead>
<tr>
<th>Systems and Synthetic Biology</th>
<th>Targeted Rx and Gene Controls</th>
<th>Regenerative Medicine</th>
<th>HPO</th>
<th>Genetic Identity</th>
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</table>

![Images corresponding to each column]
Forging a New Innovation Ecosystem for Biomedical Research and Public Health

- leverage still unique and unmatched capabilities
  - intellectual and cultural capital
  - financial and infrastructure resources

- aggressive reform of national research planning, organization and funding
  - coordinated, multidisciplinary programs with requisite scale
  - increasing standardization as foundation for proficient assembly/analysis of large scale data
  - engagement of private sector partnerships

- imperative for radical and, by definition, disruptive changes
COMMENT

Time to rethink the NIH

A radical restructure is the only way to solve the systemic problems of the world’s biggest funder of biomedical research, argues Michael M. Crow.
Adapting to the Scale and Logistical Complexity of Translational Medicine

- single investigator awards and incremental (at best) progress
- single discipline focus
- funding agencies ill-prepared to review inter/cross-disciplinary research
- ‘islands’ of individual datasets with minimal standardization
- high risk, high reward projects with prospect of radical, disruptive innovation
- obligate assembly of diverse expertise for multi-dimensional engagement
- new study sections with broader expertise, including industrial experience
- large scale, standardized, inter-operable open-source databases with professional annotation, curation and analytics
THE PROMISE OF TRANSLATIONAL MEDICINE

With Francis Collins now calling the shots at NIH, will he be able to deliver on the innovations behind the genome?
Coordination of the Complex Interactions Required to Build a Productive Translational Medical Research Capacity

- Promulgation of standards and centralized orchestration of resources (national/international)
  - Biorepositories and biospecimens
  - ‘Omics’ analytics reference standards
  - Informatics platforms (BIX, HIX) for large scale databases and analytics
  - Non-linear dynamics in complex systems
  - ID/recruitment of relevant case:control patient cohorts

- Proactive design of regulatory frameworks to address new technologies
  - Complex multivariate assays
  - Remote health monitoring
  - Review process for combination products
  - New CER tools/metrics and health economics modeling
“It’s not because things are difficult that we dare not venture. It’s because we dare not venture that they are difficult.”

Seneca
the potential economic and health benefits from biosignature diagnostic profiling transcend any other current category of healthcare innovation

realization of this potential will depend less on technological advances, albeit crucial, than the circumvention of entrenched economic, cultural and institutional interests in sustaining the status quo
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DISRUPTIVE INNOVATION DEMANDS BOLDNESS

Sustainable Health: Societal and Individual
The Complex Path to Proficient, Personalized Healthcare