Personal Perspective

• I have witnessed a revolution in healthcare
• During my professional career
  – Insights into public health measures like blood pressure and fundamentals of diet have advanced dramatically
  – Amazing drugs and devices have been developed and deployed
  – We have taken on the menace of tobacco and we’re winning the battle
  – Age specific mortality has been reduced by over 50% with resulting increases in American and global longevity and functional status
The Next Revolution

• **Will result from the transformation of information**
• In order to apply this fundamental revolution to improve health and quality of life, we must:
  – Learn how to share and create business models that work to improve sharing
  – Invest heavily in curating information
  – Work together to develop social and ethical constructs to deal with privacy, confidentiality and security
  – Create a workforce that can both create new methods and integrate information into practice
  – Give the workforce time to invest in knowledge generation as a routine part of practice
  – Work with the public to gain support and understanding
Mortality in the 20th Century

Better treatment of cardiovascular disease, low birth-weight infants

Reduced infectious disease mortality (clean water, sewers, antibiotics, better nutrition)
Eight Americas: Investigating Mortality Disparities across Races, Counties, and Race-Counties in the United States

Christopher J. L. Murray, Sandeep C. Kulkarni, Catherine Michaud, Niels Tomijima, Maria T. Bulzacchelli, Terrell J. Landiorio, Majid Ezzati

1 Harvard School of Public Health, Boston, Massachusetts, United States of America, 2 Harvard University Initiative for Global Health, Cambridge, Massachusetts, United States of America, 3 Center for Population and Development Studies, Harvard University, Cambridge, Massachusetts, United States of America, 4 University of California San Francisco, San Francisco, California, United States of America

Funding: This research was supported by a cooperative agreement, awarded by the Centers for Disease Control and Prevention and the Association of Schools of Public Health (grant U36/CCU300430-23) and by the National Institute on Aging (grant PO1-AG17625). The funders had no role in study design, data collection and analysis, decision to publish, or

ABSTRACT

Background

The gap between the highest and lowest life expectancies for race-county combinations in the United States is over 35 y. We divided the race-county combinations of the US population into eight distinct groups, referred to as the “eight Americas,” to explore the causes of the disparities that can inform specific public health intervention policies and programs.

Mortality Experiences of the 8 Americas

Males

Females

All-cause mortality, ages 45–54 for US White non-Hispanics (USW), US Hispanics (USH), and six comparison countries: France (FRA), Germany (GER), the United Kingdom (UK), Canada (CAN), Australia (AUS), and Sweden (SWE).
Truth and Expertise

• We are seeing an erosion in public confidence in:
  – Veracity of traditional sources of information
  – The value of credentialed expertise
  – Science itself

• The deluge of information is a key factor
Precision Medicine Initiative: Modernizing FDA Regulation of Genomic Laboratory Tests

Traditional testing

Next generation sequencing
Relative Complexity of Therapies

- One subunit of a protein: $10^2$ Atoms
  - L-tryptophan
  - Small Molecule Drug

- Protein composed of about 1100 subunits: $10^5$ Atoms
  - IgG antibody molecule
  - Protein Biologic

- Cell composed of about 3.6 x $10^6$ proteins: $10^{14}$ Atoms
  - Mesenchymal stem cell
  - Cellular Biologic
CRISPR/Cas9 Gene Editing

• Cas9 nuclease can be directed to cut at specific locations designated by guide RNAs

• Though there is some concern for off-target effects, CRISPR/Cas9 is a powerful technique for altering genes
Short Introduction to Genome Editing

Three major forms of genome editing:
- Zinc Finger Nucleases (mid-2000s)
- TALENs (Transcription activator-like effector nucleases) (late 2000s)
- CRISPR (clustered regulatory interspersed short palindromic repeats and associated enzymatic activities (e.g., Cas9) (2011-2012 depending on whom you ask)

Until these three forms of editing, alteration of genomic DNA could control the nature of the change (i.e., sequence-specific alterations), but except for the technically very difficult homologous recombination, neither:
- the specific location (i.e., site-specific alterations), nor
- the exact nature of the change
  - Deletion of specific nucleotides
  - Substitution of nucleotide/s
  - Addition of sequences by insertion at a specific site
Same microbial markers at different body sites

- Lactobacillus salivarius

Different microbial markers correlated at different body sites

- Genetic predisposition
  - HLA-DRB1
  - PADI4
  - TNFAIP3
  - PTPN22

Environmental factors
- Smoking
- Female sex
- Cold temperature
- Obesity

- Klebsiella pneumoniae
- Positively correlated

- Clostridium asparagiforme
- Negatively correlated

- Lactococcus spp.
- Prevotella intermedia

- Synovitis
- Cartilage damage and bone erosion
Drug Discovery and Development Timeline

Drug Discovery
- Pre-Discovery: 3 - 6 years
- 5,000 - 10,000 compounds

Preclinical
- 250

Clinical Trials
- Phase 1
  - Number of Volunteers: 20 - 100
  - Duration: 6 - 7 years
- Phase 2
  - Number of Volunteers: 100 - 500
  - Duration: 6 - 7 years
- Phase 3
  - Number of Volunteers: 1,000 - 5,000
  - Duration: 6 - 7 years

FDA Review
- Duration: 0.5 - 2 years

Scale-Up to Mfg.
- Duration: Indefinite

Post-Marketing Surveillance
- Duration: Indefinite
The Opportunity

• Information technology and “data science” have reached a phase of rapid acceleration
• We can sense, measure, compute, analyze and transmit in a manner that was imaginable only to a few a decade ago
• The translation of this capacity across the translational spectrum is “wide open”
• Technology advances rapidly, people change slowly
• I’ve never seen a better time to be in translational medicine
• “Luck is what happens when preparation meets opportunity.”
The Engine

• Data—abundant and overwhelming
• Information—a lot going into the computer, not much coming out
• Knowledge--< 15% of major clinical decisions informed by high quality information
• Wisdom—how often are we “the emperor with no clothes” given the paucity of evidence
• The time is right to shift the action to the right on this continuum
Precision medicine for the population, and the patient

It is more important to know what sort of person has a disease than to know what sort of disease a person has.

Hippocrates
A Critical Conceptual Issue in Precision Medicine

• Personalized medicine was sold in many quarters as an approach in which deep study of a few people could be generalized to entire populations

• Deep dives into individuals and small groups will remain important, but...

• Precision medicine is evolving with the realization that due to the multidimensional heterogeneity of the problem, in order to devise effective therapies we need deep study of the entire population to find predictive (probabalistic) relationships that can be applied to individuals based on what they have in common with others (“patients like us”)

23
Many tools to dissect individualized health

- Health records
- Poverty
- Genomics
- Metabolomics
- Proteomics
- Food deserts
- Images
- mHealth
The challenge: integrating multiple datasets for discovery and implementation
Big Challenges in Biomedicine

• Lack of significant information over the time dimension — Measurements made to assess biology and human health are made periodically in visits to healthcare or research

• Missing systems biology — When developing concepts of human biology or drug development we make limited measurements focused on specific mechanisms—we’re looking “under the lamppost”

• Missing the ability to measure the interactions of biology, sociology, environment and decision-making that could enable optimization of individualized and population health — Although we know that health and disease are the product of the interactions of genes, multiple derivative biological systems, environment, social context and personal decisions, we tend to look at one part of the time
THE PRECISION MEDICINE INITIATIVE® COHORT PROGRAM

• One million or more volunteers, reflecting the broad diversity of the U.S.

• Opportunities for volunteers to provide data on an ongoing basis

• Data shared freely and fast to inform a broad variety of research studies
Patient Partnerships

Technologies

EHRs

Genomics

Data Science
Planet of the Phones
Geographic Health Information Systems: A Platform To Support the ‘Triple Aim’

Donald Berwick and colleagues’ influential 2008 Health Affairs article, ‘The Triple Aim: Care, Health, and Cost,’ describes a conceptual framework developed by the Institute for Healthcare Improvement for improving the US health care system. In the Triple Aim, the institute has identified three aims that must be simultaneously pursued: improve the experience of care, improve the health of populations, and reduce per capita costs of health care. In this article we introduce and describe information technology designed to support health systems and communities in achieving the Triple Aim. We demonstrate how this technology can be used to assess the health of a defined population and to integrate evidence on health status and programmatic interventions.
Generating Evidence to Inform Decisions

- **1** FDA Critical Path
- **2** NIH Roadmap
- **3** Data Standards
- **4** Network Information
- **5** Empirical Ethics
- **6** Priorities and Processes
- **7** Inclusiveness
- **8** Use for Feedback on Priorities
- **9** Conflict of Interest Management
- **10** Evaluation of Speed and Fluency
- **11** Pay for Performance
- **12** Transparency to Consumers

**Measurement and Education**

**Early Translational Steps**

**Clinical Trials**

**Clinical Practice Guidelines**

**Outcomes**

**Performance Measures**

**Discovery Science**
Learning health care systems

In a learning health care system, research influences practice and practice influences research.

EVALUATE
Collect data and analyze results to show what works and what doesn’t.

ADJUST
Use evidence to influence continual improvement.

IMPLEMENT
Apply plan in pilot and control settings.

DESIGN
Design care and evaluation based on evidence generated here and elsewhere.

DISSEMINATE
Share results to improve care for everyone.

INTERNAL AND EXTERNAL SCAN
Identify problems and potentially innovative solutions.
Historical model of clinical research: Many recruitment sites and a coordinating center

- Hub & spoke model
- Top-down decision-making
- Sites operated independently

www.fda.gov
Modified Model
Data Shared, Sites owned by Health Systems
Academic medical centers in the US have become academic health and science systems (AHASs!)—they are no longer ivory towers—they are major economic engines and social forces in our society.
The “Biomedical Academic System”

Previously Independent Sites now part of large integrated health systems
increasingly sophisticated data warehouses
Nodes are Operational Clusters Using Common Data
God at His computer
Drug Surveillance and Trials

Coordinating Center

Sentinel
Sentinel Distributed Analysis

1- User creates and submits query (a computer program)

2- Data partners retrieve query

3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return results via secure network

6- Results are aggregated
Sentinel Distributed Database*

- Populations with well-defined person-time for which most medically-attended events are known
  - 193 million members**
  - 351 million person-years of observation time
  - 39 million people currently accruing new data
  - 4.8 billion dispensings
  - 5.5 billion unique encounters
    - 51 million acute inpatient stays
  - 33 million people with ≥1 laboratory test result

* As of August 2015, excludes HCA and BCBS of Massachusetts
** Double counting exists for individuals who change health plans
Device Surveillance and Trials
National System Paradigm Shift

- **Passive Surveillance**: Challenging to find right pre/post market balance without confidence in post-market data
  - Current
  - Parallel track to clinical practice
  - Inefficient one-off studies

- **Active Surveillance**:
  - Leverage RWE to support regulatory decisions throughout TPLC
  - Embedded in Health Care System (collect data during routine clinical care)
  - Shared system to inform the entire Ecosystem (patients, clinicians, providers, payers, FDA, Device Firms)
Post Market Studies, including comparative effectiveness

PCORnet

www.fda.gov
Demonstration Project Overview-NIH
Healthcare Systems Research Collaboratory

10 Demonstration Projects spanning 12 NIH institutes and centers

Major clinical outcome trials

1-year planning phase (UH2)

Implementation phase (UH3)

Using EHRs and minimal additional data collection

Log order reduction in cost

Collaboratory Coordinating Center
LIRE – Lumbar Image Reporting and Epidemiology
SPOT – Suicide Prevention Outreach Trial
TSOS – Trauma Survivors Outcomes and Support
TIME – Time to Reduce Mortality in End-Stage Renal Disease (sites to be selected from units across all 50 states)
STOP CRC – Stop Colorectal Cancer in Priority Populations
PPACT – Collaborative Care for Chronic Pain
PROVEN – Pragmatic Trial of Video Education in Nursing Homes
ABATE – Active Bathing to Eliminate Infection
ICD-Pieces – Improving Chronic Disease Management with Pieces
Additional sites to be determined
PCORnet embodies a “community of research” by uniting people, clinicians & systems

A national infrastructure for people-centered clinical research

20 Patient-Powered Research Networks (PPRNs) + 13 Clinical Data Research Networks (CDRNs) = PCORnet
PCORnet represents: ~110 million patients who have had a medical encounter in the past 5 years

*Some individuals may have visited more than one Network Partner and would be counted more than once*
### Policy efforts underpinning RWE push

#### Cures provisions (Sec. 3022)

- Requires FDA to establish a program to evaluate the potential use of real world evidence to:
  - Help support the approval of new indications for an approved drug
  - Help support or satisfy post approval study requirements

#### PDUFA RWE provisions

- Tracks with Cures Act
- Requires FDA to establish a program to evaluate the potential use of real world evidence to:
  - Help support the approval of new indications for an approved drug
  - Help support or satisfy post approval study requirements

### Reinforcing of a Learning Health Care System:

- Doesn’t change approval standards, rather it better supports and enables use of data and evidence on outcomes that are hard to get from traditional RCTs (e.g., outcomes that are too costly, too small populations with particular clinical features, too long follow-up needed, diff impact in diff clinical settings, etc.)
- Learning from real-world patient experiences can support better informed health care decision-making by a range of stakeholders
Real World Data vs Evidence

Real-World Data Sources
- Claims Data
- EMRs/EHRS
- Prospective Observational Data
- Patient Pathways
- Surveillance
- Mortality Database
- Primary and Secondary Care Data
- Administrative Data
- Disease and Device Registries
- Pharmacy Data
- Cost Studies
- Mobile Devices
- Consumer Data
- Social Media

Real-World Evidence
- Identifying Unmet Needs
  - Natural History
  - Co-morbidities
  - Burden of Illness
  - Incidence and Prevalence
  - Disease Mechanisms
  - Clinical Practice Patterns

- Informing Clinical and Policy Decisions
  - Usage Patterns
  - Outcome Predictors
  - Benefit/Risk in Subgroups
  - Pharmacovigilance
  - Population-Level Impact
  - New Indications

Prediscovery → Drug Discovery → Preclinical Development → Clinical Development (Phases I, II, III) → FDA Review and Approval → Postmarketing Evaluation (Phase IV)

Real World Data and Efficacy

Real-World Evidence — What Is It and What Can It Tell Us?

• Real-world evidence can be used across a wide spectrum of research, ranging from observational studies to studies that incorporate planned interventions, whether with or without randomization at the point of care.

• Incorrect to contrast the term “real-world evidence” with the use of randomization in a manner that implies that they are disparate or even incompatible concepts.

• Must consider the components of such trials that are critical to obtaining valid results and minimizing bias.
Laying the Foundation

Data Standards

Stakeholder Engagement

Guidances

Demonstrations

Use of Electronic Health Record Data in Clinical Investigations

Electronic Source Data in Clinical Investigations

Use of Electronic Informed Consent
Call to Action

• Organize operational systems that bring together research networks embedded in practice
  
  — to enable patients, consumers, clinicians, industry, government, and health care systems to participate in prospective trials and observational studies
  
  — Develop operational/regulatory approaches to facilitate practice-based systems for therapeutic research, safety surveillance, public health, and quality improvement.
  
  — Support adequate time commitment for clinicians to engage with patients to ensure mutual understanding and appropriate consent
  
  — Efficient systems for contracting and liability
  
  — Clinical care and research closely aligned in “learning health system” supported by education and training
  
  — **How can delivery systems with their evolving power create a system that encourages participation in an efficient system?**
Call to Action

• Establish a robust framework for privacy, confidentiality, and security
  • endorsed by patients and consumers to ensure the trust a learning health system will require,
  • Robust procedures that ensure data security and protect confidentiality
  • Efficient and thorough digital system of education and research permissions for patients
  • Balance of individual autonomy and public health needs
  • Great start: Precision Medicine Initiative: Privacy and Trust Principles
  • How can delivery systems take on a more constructive role to move the system to a participatory learning system?
Call to Action

• Adopt a common approach to configuring, storing, and re-using digital health care data to enable use in care, research, safety surveillance, and public health
  – As called for in the Nationwide Interoperability Roadmap published by the Office of the National Coordinator for Health Information Technology.
  – Common standards and terminology for prospective data collection
  – Continuous effort to curate data to produce high quality data sets for analysis using common data models
  – Leverage existing digital health/healthcare data to create efficiencies (registries, claims data, EHR data, personal devices)
  – Can delivery systems figure out how to share data at the scale needed now that we understand the needed sample sizes?
Call to Action

• Develop and test new methods to reliably answer research questions
  – more efficient RCTs,
  – Novel designs such as cluster-randomized trials, basket trials
  – And more reliable observational studies aimed at assessment of interventions
  – “Meta-knowledge” on which methods are best for which types of questions
  – By leveraging data already collected by health information technology and other electronic sources to answer research questions or facilitate the conduct of new trials.
  – Will delivery systems value clinical science enough to create the needed work force and reward scholarly activity in this arena?
Call to Action

• Ensure the development of novel approaches focusing on streamlining and harmonizing processes in ways that eliminate barriers that promote unnecessary complexity, while ensuring safeguards that are truly needed.
  – Streamlined and harmonized processes eliminate barriers to efficient research while ensuring needed safeguards
  – Systems for high quality and efficient ethics review and contracting
  – Development of approaches to assuring quality systems through better use of analytics
  – Can delivery systems regard efficiency in research with the same seriousness as they have addressed efficiency in clinical care?
Many of today’s patient groups serve as active partners in the clinical trial enterprise and invest private funding in milestone driven research with focus on leveraging their assets to de-risk research and increase return on investment.
PG Engagement Across the Research & Development Continuum

- **From Bench to Bedside and Back**
  - Input re interest of research question to patient community
  - Providing data on unmet need & therapeutic burden
  - Fundraising and direct funding for research to identify target molecules
  - Facilitating collaboration with NIH
  - Characterizing the disease & relevant mechanisms of action

- **Fundraising & direct funding for research, trial operations support**
  - Assistance in selecting & recruiting optimum clinical sites
  - Clinical infrastructure support
  - Helping educate/motivate patient community & recruit for trials
  - Providing patient feedback on participant experience
  - Serving on Data & Safety Monitoring Board
  - Input for any trial adaptations or modifications
  - Accompanying sponsor to milestone meetings, e.g., after phase 2 & 3

- **Serving on post-market surveillance initiatives**
  - Helping return study results to participants
  - Co-presenting results
  - Publications/communications re results
  - Feedback on how patient community views results
  - Natural history database & registry support
  - Working with payers re reimbursement

*Adapted from Parkinson’s Disease Foundation materials for CTTI’s Patient Groups & Clinical Trials Project*
Data Activation and Testing Outcomes
Digital Transformation

2010
Individual Productivity
IT Silos

- Data on premise, hard to access, analyze and use
- Productivity tools built for individual, local usage
- IT focusing on where it computes

2020
Collective Intelligence
Distributed Computing

- Data stored in cloud, simple to query
- Collaborative, cloud based productivity applications
- Machine learning drives deep, actionable insights
- IT changing how it computes
The New Einsteins Will Be Scientists Who Share

From cancer to cosmology, researchers could race ahead by working together—online and in the open

By MICHAEL NIELSEN

In January 2009, a mathematician at Cambridge University named Tim Gowers decided to use his blog to run an unusual social experiment. He picked out a difficult mathematical problem and tried to solve it completely in the open, using his blog to post ideas and partial progress. He issued an open invitation for others to contribute their own ideas, hoping that many minds would be more powerful than one. He dubbed the experiment the Polymath Project.

Several hours after Mr. Gowers opened up his blog for discussion, a Canadian-Hungarian mathematician posted a comment. Fifteen minutes later, an Arizona high-school math teacher chimed in. Three minutes after that, the UCLA mathematician Terence Tao commented. The discussion ignited, and in just six weeks, the mathematical problem had been solved.
Whole Genome Sequencing Program (WGS)

GenomeTrakr

- State and Federal laboratory network collecting and sharing genomic data from foodborne pathogens
- Distributed sequencing based network
- Partner with NIH
- Open-access genomic reference database
- Can be used to find the contamination sources of current and future outbreaks

http://www.fda.gov/Food/FoodScienceResearch/WholeGenomeSequencingProgramWGS/default.htm#trakr
For Big-Data Scientists, ‘Janitor Work’ Is Key Hurdle to Insights

By STEVE LOHR   AUG. 17, 2014
PATIENT LEAVES HOSPITAL ALIVE

by Dr James Leftonatrolley

THERE was widespread shock today at the news that a patient had left a hospital today without having been killed by a medical error.

A spokesman for the hospital said, “This is a very rare occurrence and there is no cause for alarm. We will be launching a full enquiry at once into what went right. We can only apologise to the undertakers.”
We Want you to be Creative Using Big Data and to be Responsible to Create High Quality Evidence to Support Intervention