NIH Health Care Systems Research Collaboratory

Taking Stock and Moving Forward

Robert M Califf MD

May 23rd, 2017
CONFLICTS

• I start working half-time at Verily Life Sciences (member of Alphabet family) starting June 1
• I also work half-time at an academic medical center/health system that is dealing with balancing learning and margin
• And an appointment at another AMC/system with hard choices to make about technology alignment
Five Years Ago

- Idea of learning health system gaining intellectual traction
- EMR’s being introduced on a national scale
- Recognition that speed and cost of generating evidence not acceptable
- NIH takes a bold step to change paradigm for evidence generation
- Where are we today?
Today

- We all have electronic health records
- Tremendous growth of biomedical measurement capability
- Consolidation of health systems
- Cloud computing, arrays of processors
- Silicon Valley with cash and desire to invest in health issues
- Cost of generating evidence and speed still unacceptable
- Are we making progress?
“to strengthen the national capacity to implement cost-effective large-scale research studies that engage health care delivery organizations and patients as research partners”
Top 3 Things for Collaboratory (IMHO)

1) Get results and publish
2) Develop approach to broader dissemination and implementation
3) Develop “metaknowledge”
   A. What is working?
   B. What are the toughest hurdles for those hoping to do pragmatic trials?
      i. What are solutions to overcoming the hurdles?
   C. Turn metaknowledge into policy
Our National Clinical Research System is Well-intentioned But Flawed

- High percentage of decisions not supported by evidence*
- Health outcomes and disparities are not improving
- Current system is great except:
  - Too slow, too expensive, and not reliable
  - Doesn’t answer questions that matter most to patients
  - Unattractive to clinicians & administrators

We are not generating the evidence we need to support the healthcare decisions that patients and their doctors have to make every day.

* Tricoci P et al. JAMA 2009;301:831-41
Which Treatment is Best for Whom?  
High-Quality Evidence is Scarce

< 15% of Guideline Recommendations Supported by High Quality Evidence

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD  
Joseph M. Allen, MA  
Judith M. Kramer, MD, MS  
Robert M. Califf, MD  
Sidney C. Smith Jr, MD

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.
Trial Hyperinflation

Figure 3. Mean Total Grant Cost per Patient Index, Biomedical R&D Price Index, and pooled hedonic indexes, 1989–2011

Index (1989 = 1.000)

Source: Authors’ calculations based on Medidata Solutions, Inc.’s, PICAS® database.

Berndt E, Cockburn I. Monthly Labor Review, June 2014
Inequalities in Life Expectancy Among US Counties, 1980 to 2014 Temporal Trends and Key Drivers


Life Expectancy at Birth by County, 2014

Counties in South Dakota and North Dakota had the lowest life expectancy, and counties along the lower half of the Mississippi, in eastern Kentucky, and southwestern West Virginia also had very low life expectancy compared with the rest of the country. Counties in central Colorado had the highest life expectancies.

Figure Legend:
Change in Life Expectancy at Birth by County, 1980 to 2014

Compared with the national average, counties in central Colorado, Alaska, and along both coasts experienced larger increases in life expectancy between 1980 and 2014, while some southern counties in states stretching from Oklahoma to West Virginia saw little, if any, improvement over this same period.
Figure Legend:

Absolute and Relative Inequality Among Counties in Life Expectancy and Age-Specific Mortality Risks, 1980–2014

Shaded areas along the plotted data represent 95% uncertainty intervals. Absolute geographic inequality was quantified as the difference between the 99th and first percentile level, and relative geographic inequality was quantified as the ratio of the 99th to the first percentile level.
Precision Medicine Initiative: Modernizing FDA Regulation of Genomic Laboratory Tests

Traditional testing

Next generation sequencing
Relative Complexity of Therapies

One subunit of a protein

Protein composed of about 1100 subunits

Cell composed of about 3.6 x 10^6 proteins

10^2 Atoms

10^5 Atoms

10^{14} Atoms

L-tryptophan
Small Molecule Drug

IgG antibody molecule
Protein Biologic

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.
Many tools to dissect individualized health

- Health records
- Poverty
- Food deserts
- Genomics
- Metabolomics
- Proteomics
- Patient-specific iPSC-derived cells
- Images
- mHealth
The challenge: integrating multiple datasets for discovery and implementation
Smartphone

Cardiac and Activity Monitor

Sleep Sensor
Scalable & Standardized Tools

- Serum
- Whole Blood
- PBMCS
- Plasma
- Saliva
- Urine
- Stool
- Microbiome (16S rRNA)
- Proteomics
- Metabolomics
- Genomics (WGS, DNA arrays)
- Epigenomics (Methyl arrays)
- Transcriptomics (RNA-seq)
- Immunophenotyping (CyTOF)

In-house, each now applied in multiple sclerosis study
External, internalization planned

~6TB data per visit
Aggregated & Searchable Participant Data
Mapping Health

By Maria Lynn Miranda, Jeffrey Farewell, Benjamin Strauss, Brian Nowak, and Robert M. Califf

Geographic Health Information Systems: A Platform To Support The ‘Triple Aim’

ABSTRACT Despite the rapid growth of electronic health data, most data systems do not connect individual patient records to data sets from outside the health care delivery system. These isolated data systems cannot support efforts to recognize or address how the physical and environmental context of each patient influences health choices and health outcomes. In this article we describe how a geographic health information system in Durham, North Carolina, links health system and social and environmental data via shared geography to provide a multidimensional understanding of individual and community health status and vulnerabilities. Geographic health information systems can be useful in supporting the Institute for Healthcare Improvement’s Triple Aim Initiative to improve the experience of care, improve the health of populations, and reduce per capita costs of health care. A geographic health information system can also provide a comprehensive information base for community health assessment and intervention for accountable care that includes the entire population of a geographic area.

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...
Data Activation and Testing Outcomes

What Impacts Behavior?

A
CONTROL

B
VARIATION

37%
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

Verily
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

Early Translational Steps

Discovery Science

Outcomes

Performance Measures

Clinical Trials

Clinical Practice Guidelines

Measurement and Education
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.

**IMPLEMENT**
Apply plan in pilot and control settings.

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

**ADJUST**
Use evidence to influence continual improvement.

**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
Modified Model
Data Shared, Sites owned by Health Systems
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
Device Surveillance and Trials

NEST

Coordinating Center
Post Market Studies, including comparative effectiveness
Integration of Clinical Research Networks

? CTSA Trial Innovation Network

• Link existing networks so clinical studies and trials can be conducted more effectively

• Ensure that patients, physicians, and scientists form true “Communities of Research”
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

![Map showing the distribution of demonstration projects across the United States]
PCORnet embodies a “community of research” by uniting people, clinicians & systems

20 Patient-Powered Research Networks (PPRNs) + 13 Clinical Data Research Networks (CDRNs) = PCORnet
A national infrastructure for people-centered clinical research
Resulting in a national evidence system with unparalleled research readiness

PCORnet represents:

- 110 million patients who have had a medical encounter in the last 5 years
  - *some individuals may have visited more than one Network Partner and would be counted more than once

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<td>22–64</td>
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Pool of patients:

- For clinical trials: 42,545,341
- For observational studies: 83,131,450
People-Centered Research Foundation

• Launched March 21st

Mission to engage patients, families, research participants, clinicians, scientists, and health system leaders in the design, conduct, dissemination, and implementation of research and analysis that leads to improvements in the health and well-being of individuals and populations and the performance of health care delivery systems
Inaugural Board

• Chair – Robert Califf, MD, former FDA Commissioner and Professor of Medicine, Duke University

• Board –
  • Richard Bankowitz, MD, MBA, FACP, Executive Vice President, Clinical Affairs, America’s Health Insurance Plans (AHIP)
  • Josephine P. Briggs, MD, Director, National Center for Complementary and Integrative Health (NCCIH)
  • Marc M. Boutin, JD, Chief Executive Officer, National Health Council (NHC)
  • Donna Cryer, President & CEO of the Global Liver Institute
  • Craig Lipset, MPH, Head of Clinical Innovation, Global Product Development, Pfizer
  • Joanne Waldstreicher, MD, Chief Medical Officer, Johnson & Johnson
  • Reed Tuckson, MD, Managing Director of Tuckson Health Connections
New entity for continued operations: NewCo.

A non-profit corporation to be established to facilitate transition of current operations and to execute mission-aligned strategy toward sustainability.
### 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

Real-World Evidence: 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?

Rachel E. Shée
Gerald J. Dal Pan, M. Nina L. Hunter, Ph
Peter W. Marks, M.D.
Robert Temple, M.D., J

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

Demonstration

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?
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.
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?
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

### Pre-Discovery
- 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

### Pre-Clinical
- 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

### Phase 1/2/3
- FDA review & approval
- 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

### PAS/Outcomes
- Providing public testimony at the FDA Advisory Committee & other FDA hearings
- Preparing submission for newborn screening when appropriate
- 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*
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?
Integrated at “enterprise level”

Disease Registries—Granular, Detailed

Electronic Health Records

Claims data

Health System A

Health System B

Etc…

Fundamental Informatics Infrastructure—Matrix
Organizational Structure
For Big-Data Scientists, ‘Janitor Work’ Is Key Hurdle to Insights

By STEVE LOHR  AUG. 17, 2014
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?
Top 3 Things for Collaboratory (IMHO)

1) Get results and publish
2) Develop approach to broader dissemination and implementation
3) Develop “metaknowledge”
   A. What is working?
   B. What are the toughest hurdles for those hoping to do pragmatic trials?
      i. What are solutions to overcoming the hurdles?
   C. Turn metaknowledge into policy
Summary

• We have become complacent with lack of knowledge about best course of action for individuals and populations

• Consequences are substantial
  – Individual health
  – Population health

• Collaboratory is at the leading edge of a new way of learning in health care

• How do we move this along?