Human Adaptation to Information: A Challenge for the Next Decade

Robert M Califf MD
Vice Chancellor for Health Data Science
Duke University
Advisor, Verily Life Sciences
June 15th, 2017
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
“Chronic, multifactorial disease problems can be studied, but not by the methods of the present or past. If one wishes to create useful information... computer technology must be exploited.”

—Eugene Stead, MD

1960s

• Dr. Eugene Stead developed concept of “computerized textbook of medicine”
• Formation of the Duke Databank for Cardiovascular Diseases
<table>
<thead>
<tr>
<th>Date</th>
<th>Name of Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-1-47</td>
<td>John Doe</td>
<td>25</td>
<td>Acute Appendicitis</td>
<td>10-1-47</td>
</tr>
<tr>
<td>9-4-47</td>
<td>Jane Smith</td>
<td>30</td>
<td>Appendicitis</td>
<td>10-6-47</td>
</tr>
<tr>
<td>9-5-47</td>
<td>Robert Johnson</td>
<td>35</td>
<td>Appendicitis</td>
<td>10-7-47</td>
</tr>
<tr>
<td>9-6-47</td>
<td>Mary Brown</td>
<td>20</td>
<td>Appendicitis</td>
<td>10-8-47</td>
</tr>
<tr>
<td>9-7-47</td>
<td>William Davis</td>
<td>40</td>
<td>Appendicitis</td>
<td>10-9-47</td>
</tr>
<tr>
<td>9-8-47</td>
<td>Elizabeth White</td>
<td>22</td>
<td>Appendicitis</td>
<td>10-10-47</td>
</tr>
<tr>
<td>9-9-47</td>
<td>James Green</td>
<td>33</td>
<td>Appendicitis</td>
<td>10-11-47</td>
</tr>
</tbody>
</table>

Note: The dates and names are examples and do not reflect real patient information.
Mortality in the 20th Century

Better treatment of cardiovascular disease, low birth-weight infants

Reduced infectious disease mortality (clean water, sewers, antibiotics, better nutrition)
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).

Anne Case, and Angus Deaton PNAS 2015;112:15078-15083
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.
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:
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.
Figure 3. Mean Total Grant Cost per Patient Index, Biomedical R&D Price Index, and pooled hedonic indexes, 1989–2011

Index (1989 = 1.000)

Pooled hedonic index with trial phase, therapeutic area, and year as indicator variables

Biomedical R&D Price Index

Pooled hedonic index with trial phase, therapeutic area, and year as indicator variables and with SWE and LPATIENTS added to base model as regressors

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

Berndt E, Cockburn I. Monthly Labor Review, June 2014
Generating Evidence to Inform Decisions

Early Translational Steps

Measurement and Education

Clinical Practice Guidelines

Clinical Trials

Data Standards

Network Information

Empirical Ethics

Priorities and Processes

Inclusiveness

Use for Feedback on Priorities

Performance Measures

Outcomes

Discovery Science

1. FDA Critical Path

2. NIH Roadmap

3. Measurement and Education

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
Burning Platform: Overwhelming Complexity

Many tools to dissect individualized health

Health records

Poverty

Genomics

Proteomics

Metabolomics

Patient-specific iPSC-derived cells

Images

mHealth
The challenge: integrating multiple datasets for discovery and implementation
Google’s mission is to organize the world’s information and make it universally accessible and useful.
Baseline Study

10,000 participants

All-Comers:
Healthy → Disease(s)
- Coronary Calcium
- Echo
- Electrocardiogram
- OCT
- Chest X-Ray
- Stress Echo

- Study Watch
- Sleep Sensor
- Study Hub

- Clinical Labs
- Clinical Assessments

- Baseline Visit
- Year 1 Visit
- Year 2 Visit
- Year 3 Visit
- Year 4 Visit

(Yearly Onsite Visits)
(Quarterly Onsite, Online, Phone)
Scalable & Standardized Tools

- Samples:
  - Serum
  - Whole Blood
  - PBMCS
  - Plasma
  - Stool
  - Saliva
  - Urine

- Assays:
  - Clinical Labs
    - Genomics (WGS, DNA arrays)
    - Epigenomics (Methyl arrays)
    - Transcriptomics (RNA-seq)
    - Immunophenotyping (CyTOF)
    - Microbiome (16S rRNA)
    - Proteomics
    - Metabolomics

- Data per visit: ~6TB

- Tools:
  - Consent Widget
  - Survey Widget
  - Administrator Portal
  - Mobile App
  - Sensors
  - Molecular Platforms
  - Data Analytics
  - Etc.

- External/at clinic site
- In-house, each now applied in multiple sclerosis study
- External, internalization planned
Smartphone

Cardiac and Activity Monitor

Sleep Sensor
We want to create an experience people can get excited about.
We want to create an experience people can get excited about.
Aggregated & Searchable Participant Data
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
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 and Efficacy

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

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P.,
Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H.,
Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D.,
Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D.,
Robert Temple, M.D., Jai

• 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.
For Big-Data Scientists, ‘Janitor Work’ Is Key Hurdle to Insights

By STEVE LOHR  AUG. 17, 2014
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.