Generating Evidence to Inform Decisions in the Era of Precision Medicine

Robert M Califf MD

September 19th, 2016

HL 7 30th Plenary

Baltimore, MD
Generating Evidence to Inform Decisions

- FDA Mission
- The promise of biological, engineering and information revolutions
- Current deficiencies in the system
- Outline of a future system
- What we need from you!
FDA Regulates a Spectrum of Health Products: 20-25 cents of every GDP dollar
FDA Mission

FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation.
FDA Mission

• FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health. FDA also has responsibility for regulating the manufacturing, marketing and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.
FDA Mission

Finally, FDA plays a significant role in the Nation’s counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.
AMAZING OPPORTUNITIES
“And that’s why we’re here today. Because something called precision medicine … gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen.”

President Barack Obama
January 30, 2015
The U.S. Precision Medicine Initiative
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
The Precision Medicine Initiative® Cohort Program

Sign up for updates at: https://www.nih.gov/precisionmedicine
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.
Planet of the Phones

Cost of data per mb, $

Mobile-broadband connections, bn
- Developing
- Developed

Mobile data transmitted
Exabytes* per month
- N America
- W Europe
- Asia Pacific
- Rest of world

F’CAST

Jon Berkeley
Precision Medicine Initiative: Modernizing FDA Regulation of Genomic Laboratory Tests

Traditional testing

Next generation
Modernizing FDA Regulation of Genomics

– Develop and implement **standards** to assure quality
– Develop **open-source tools** to help test developers meet standards (*precisionFDA*)
– Support the development of a **data commons** for evidence on the clinical relevance of genetic variation

Develop and implement an adaptive standards-based regulatory approach
A community platform for NGS assay evaluation and regulatory science exploration.

precisionFDA demonstrates FDA’s commitment to innovating the regulatory science needed to advance the growing era of precision medicine

ROBERT CALIFF
FDA
Genome Editing:
Technical Background

https://biobeat.nigms.nih.gov/
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
Time Line: Altering Genomes for Desired Traits

• **Irradiation** → random breakage, mutagenesis, selection for desired phenotype (from age of agriculture to present)

• **Exposure to chemical mutagens** → random mutagenesis, selection for desired phenotype (~150 years)

• **Genetic Engineering** → introduction of recombinant DNA constructs at random locations in the genome (~1973), or using homologous recombination

• **Genome Editing** → *ex ante* selection of location of genetic alteration (~2008)
Three Things Can Happen with Sequence-Specific Nuclease Systems

Site-specific

1. Insertion of nucleotide/s (genes)
2. Exchange of nucleotide/s (substitution)
3. Deletion of nucleotide/s (genes)

Genotypic change may not dictate phenotype

• Functional knock-outs can occur using any of the 3 approaches
• “Added” traits may result from attenuation of repressor
“THE SYSTEM”
1962 (Kefauver-Harris) Drug Amendments

• Significant portion of drugs on the market were not effective for all labeled indications
• Legislation to make changes in drug testing met with resistance
• Then came Thalidomide
  • Greatest impact not in U.S., but led to passage of ‘62 law
1,200 U.S. DOCTORS GOT BANNED PILL FOR TESTS

Thalidomide, the sleeping pill that has caused thousands of infant malformations in Europe had been distributed to 1,200 physicians in the United States for investigational use since 1959, before it was banned in the United States.

This figure has been supplied by the William S. Merrell Co. of Cincinnati, manufacturer of the drug, to the Food and Drug Administration here. FDA inspectors are now checking the physicians to make sure they have returned or destroyed their supplies of the drug, as requested by the Merrell Company in March.

The investigational use of the drug in the United States dates to 1959. It is not known by FDA if the drug was used experimentally during early pregnancy, the critical period in which the malformations are caused.

Several malformed infants in the United States have been linked to their mothers' use of the drug. In none of these publicly-reported cases, however, was the drug given by a licensed physician in the United States.
Kefauver-Harris Amendment

• 1962 law led to much greater control of clinical investigation by FDA
  – to ensure veracity of clinical trial data
  – provided basis for setting clinical trial standards
• Mandated informed consent for participation in trials, the first time such a provision was required in the U.S.
• Standard for pre-market approval based on “adequate and well-controlled studies”
Legislation can be Effective!

• Drug and device legislation created a revolution in evidence generation
  – Required the industry to fund and find means to conduct adequate and well-controlled studies of drugs and many high risk devices
  – Prompted the clinical community to focus on a serious examination of the quality of clinical evidence
• Created modern clinical trials industry
  – Infrastructure and regulatory oversight
But the World has Changed!

• System has served society well
  – Therapeutic armamentarium was limited
  – Understanding of therapeutics and evidence was rudimentary

• Changes now call for upgrading system
  – Scientific, technological, methodological

• Transform the evidence generation system enterprise into a system capable of meeting societal needs in an efficient, sustainable fashion
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

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

Berndt E, Cockburn I. Monthly Labor Review, June 2014
THE OPPORTUNITY: EVIDENCE GENERATION ON A DIFFERENT SCALE
How do we Optimize the Evidence Part of the Equation?
## Re-engineering the Clinical Research Enterprise

<table>
<thead>
<tr>
<th>Time</th>
<th>1-3 years</th>
<th>4-7 years</th>
<th>8-10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increasing Level of Difficulty</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Demonstration networks</strong></td>
<td>Funding mechanism to sustain national system through consensus of all constituents (&quot;1% solution&quot;)</td>
<td>National Clinical Research System creates effectiveness data that moves rapidly into the community AND data on outcomes and quality of care; sustained efficient infrastructure to rapidly initiate clinical trials; scientific information for patients, families, advocacy groups</td>
<td></td>
</tr>
<tr>
<td>Simplify complex regulatory systems</td>
<td>Simplified regulatory system in place for networks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Networks in place for all institutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Establish repositories of biological specimens and standards for collection</strong></td>
<td>Data standards shared across NIH institutes</td>
<td>ONE medical nomenclature with national data standards (agreed to by NIH, CMS, FDA, DOD, CDC)</td>
<td></td>
</tr>
<tr>
<td>Standardize nomenclature, data standards, core data, forms</td>
<td>Funding mechanisms evaluated to determine which are most efficient</td>
<td>Data standards updated ‘in real time’ through networks</td>
<td></td>
</tr>
<tr>
<td>Library of elements shared between institutes and NLM</td>
<td></td>
<td>National repository of images and samples</td>
<td></td>
</tr>
<tr>
<td>Efficient network administration infrastructure at NIH</td>
<td></td>
<td>Critical national “problem list”</td>
<td></td>
</tr>
<tr>
<td>Standards for capturing images for research</td>
<td></td>
<td>Most efficient network funding mechanisms in place across NIH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Create NIH standards to provide “safe haven” for clinical research</strong></td>
<td>Standards for safe haven in place</td>
<td>Participation in research is a professional standard</td>
<td></td>
</tr>
<tr>
<td>Inventory and evaluate existing public-private partnerships, networks, CR institutions, and regulatory systems</td>
<td>Regulations and ethics harmonized with FDA, CMS</td>
<td>Study, evaluation and training regarding clinical research a part of every medical, nursing, pharmacy school</td>
<td></td>
</tr>
<tr>
<td>Establish FORUM(S) of all stakeholders</td>
<td>Public private partnership mechanisms in place</td>
<td>Clinical research practices documented and updated regularly to maintain safe haven</td>
<td></td>
</tr>
<tr>
<td>Standards and pilot creation of a National Clinical Research Corps</td>
<td>100,000 members of certified “Clinical Research Corps”</td>
<td>Networks provide detailed training about network specific issues</td>
<td></td>
</tr>
<tr>
<td>Demonstration/planning grants to enhance/evaluate/develop model networks</td>
<td>Standards shared across NIH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.

**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.

Internal

External
Sentinel: Distributed Data Networks
(Over 190,000,000 people included)
PCORnet embodies a “community of research” by uniting people, clinicians & systems

Patient-Powered Research Networks (PPRNs) + Clinical Data Research Networks (CDRNs) = PCORnet

A national infrastructure for people-centered clinical research
Underpinned by a Common Data Model

- Vital Status
- Demographic
- Condition
- Procedures
- Encounters
- Lab Results
- Claims
- Biospecimen & Genomic Data
- Prescribing
- Patient Satisfaction
Here’s how PCORnet’s distributed research network works

The Researcher sends a question to the PCORnet Coordinating Center through the Front Door

The Coordinating Center converts the question into a query with an underlying executable code, and sends it to PCORnet partners

PCORnet partners review the query and provide a response, which is sent back through the Front Door to the Researcher
Resulting in a national evidence system with unparalleled research readiness

Number of people with data available in PCORnet to date:

~145 Million

*Based on data from 57 DataMarts as of July 15, 2016
Demonstration Project Overview-NIH Healthcare Systems Research Collaboratory

10 Demonstration Projects spanning 12 NIH institutes and centers

1-year planning phase (UH2)

Implementation phase (UH3)
ACA Mandate

Requirement for “the coordination of relevant Federal health programs to build data capacity for comparative clinical effectiveness research in order to develop and maintain a comprehensive interoperable data network to collect, link and analyze data on outcomes and effectiveness from multipole sources, including electronic health records”

PPACA, Title VI. Transparency and Program Integrity. Subtitle D Section 6301
Multiple Developing Efforts

• FDA
  – Sentinel, National Evaluation System for health Technology (NEST), MDUFA data standardization

• NIH
  – CTSA, HCS Collaboratory, Multiple institute/Center Networks

• CDC Vaccine Surveillance Network

• ASPE—PCOR-Trust Fund

• PCORI-PCORnet

• CMS
  – Enclave, Coverage with Evidence Development

• Million Veterans’ Program (MVP)

• Precision Medicine Initiative (PMI)
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
  - generate high-quality evidence for purposes including therapeutic research, safety surveillance, public health, and quality improvement.
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,
  • Great start: Precision Medicine Initiative: Privacy and Trust Principles
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.

• Importantly, this approach involves leveraging existing data collection methods while facilitating interoperability among different data sources and supporting their use for other applications.
Call to Action

• Develop and test new methods to reliably answer research questions, thereby making possible
  – more efficient RCTs,
  – Novel designs such as cluster-randomized trials, basket trials
  – And more reliable observational studies

• By leveraging data already collected by health information technology and other electronic sources to answer research questions or facilitate the conduct of new trials.
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.
WE NEED YOUR HELP IN THIS NEW ERA
OF BIG BIOLOGY, BIG DATA AND
PRECISION MEDICINE
How can you help us?

• Train the workforce for the future
• Help us curate data
• Help us develop standards and terminology that work in an evolving system
• Develop effective interface with clinicians so that the work becomes more efficient and clinicians have time to spend with patients
• Regulatory science!
  – Methods to develop effective standards and terminology
  – Defining quality in data for learning
For Big-Data Scientists, ‘Janitor Work’ Is Key Hurdle to Insights

By STEVE LOHR   AUG. 17, 2014
“My hope is that this becomes the foundation, the architecture, whereby in 10 years from now we can look back and say that we have revolutionized medicine.”

- PRESIDENT BARACK OBAMA
If We Had An Efficient Evidence Generation System....

• Much more of clinical practice could be guided by high quality evidence
• Clinicians and their practice organizations could focus on interpreting the evidence and applying it
• The role of opinion and expertise would be at least as important, but it would be put to a much higher purpose—providing precision healthcare