A View of the Future of Clinical Research (at Duke)

Robert M Califf MD
Vice Chancellor for Clinical and Translational Research
Duke University
November 13th, 2013

Conflicts

• All of my “industry relationships” can be found at www.dcri.org/about-us/conflict-of-interest/Califf-COI_2013
• I work as an official in an academic health and science system that depends on a margin from the current reimbursement system that rewards behaviors that may not be good for your health!

Key Points

• Health outcomes in the US are not good and increasingly poor compared with the global competition
• We lack evidence for much of what we do
• We are entering a new era in which the underlying data fabric can be transforming by the creation of a learning health system
  – Clinical trials at a pace not imaginable in the past
  – Information that directly links personalized medicine and population health in a way that demands and suggests action
• Intelligent use of these data will require successful collaboration across a spectrum of providers, clinical investigators, administrators and quantitative/information scientists
• We are continuing to work on a system that meets the needs of society for efficient, high quality research that answers important questions at a fast rate and lower cost
THE PROBLEM STATEMENT
WHAT ARE WE TRYING TO SOLVE?

Age-Standardized Years of Life Lost Relative to Comparator Countries and Ranking by Cause in 2010

<table>
<thead>
<tr>
<th>Cause</th>
<th>Sweden</th>
<th>Italy</th>
<th>Spain</th>
<th>Australia</th>
<th>Norway</th>
<th>Netherlands</th>
<th>Austria</th>
<th>Luxembourg</th>
<th>Germany</th>
<th>Canada</th>
<th>France</th>
<th>Ireland</th>
<th>Greece</th>
<th>UK</th>
<th>Finland</th>
<th>Belgium</th>
<th>Portugal</th>
<th>Denmark</th>
<th>USA</th>
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<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>10</td>
<td>53</td>
<td>67</td>
<td>4</td>
<td>13</td>
<td>8</td>
<td>15</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>61</td>
<td>91</td>
<td>41</td>
<td>7</td>
<td>9</td>
<td>2</td>
<td>11</td>
<td>18</td>
<td></td>
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<tr>
<td>COPD</td>
<td>44</td>
<td>8</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>2</td>
<td>15</td>
<td>14</td>
<td>8</td>
<td>6</td>
<td>11</td>
<td>16</td>
<td>17</td>
<td>4</td>
<td>15</td>
<td>18</td>
<td>16</td>
<td>10</td>
<td></td>
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<tr>
<td>Other cardiovascular and circulatory diseases</td>
<td>15</td>
<td>4</td>
<td>12</td>
<td>6</td>
<td>14</td>
<td>2</td>
<td>15</td>
<td>14</td>
<td>8</td>
<td>6</td>
<td>11</td>
<td>16</td>
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<td>15</td>
<td>18</td>
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<td>10</td>
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<td>Congenital anomalies</td>
<td>30</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>17</td>
<td>2</td>
<td>19</td>
<td>15</td>
<td>16</td>
<td>7</td>
<td></td>
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<tr>
<td>Aortic aneurysm</td>
<td>15</td>
<td>7</td>
<td>2</td>
<td>10</td>
<td>14</td>
<td>3</td>
<td>16</td>
<td>2</td>
<td>10</td>
<td>4</td>
<td>15</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>10</td>
<td>14</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>13</td>
<td>15</td>
<td>2</td>
<td>11</td>
<td>1</td>
<td>7</td>
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<td>18</td>
<td>16</td>
<td>19</td>
<td>11</td>
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</tr>
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</table>

6

GBD 2010 Study: Lancet 2012 December
Health Inequities - 3

Probability of survival to age 50 for females in 21 high-income countries, 1980-2006.

Red circles depict data for the United States. Grey circles depict data for the other high-income countries.

Source: National Research Council, 2011

Mortality Experiences of the 8 Americas

The Best of Times, the Worst of Times

Fundamental science unprecedentedly advanced, but:

- Poor transition of basic or clinical observations into interventions that tangibly improve human health
- Drug/device/diagnostic development system in crisis
- Clinical trials system in crisis
- Poor adoption of demonstrably useful interventions

People unhealthier and funders of biomedical research enterprise (public and private) impatient

Eroom’s Law

The number of new drugs approved by the FDA per billion US dollars (inflation-adjusted) spent on research and development (R&D) has halved roughly every 9 years since 1950.
Why do we need Systems Biology to identify and predict Biomarker Sets?

Disease and drug action originate at the cellular level but physiological effects (e.g., symptoms, drug action) are at the organismal levels. Unraveling such complexity requires systems approaches.

Iyengar, NYU 2009

The Cycle of Quality: Generating Evidence to Inform Policy

Measurement and Education

Early Translational Steps

Clinical Trials

Clinical Practice Guidelines

Performance Measures

Outcomes

Discovery Science

Evaluation of Speed and Fluency

Conflict-of-interest Management

Pay for Performance

Transparency to Consumers

Evaluation of Speed and Fluency

Drug Discovery

Clinical Care

Organ-based specialties

Pathology, Neurology, etc.

Cell Physiology

Systems Pharmacology

Transforming Medicine

6 Medical Therapies Proven to Reduce Death

<table>
<thead>
<tr>
<th>Therapy</th>
<th># pts</th>
<th>Reduction in deaths:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Relative</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>18,773</td>
<td>23%</td>
</tr>
<tr>
<td>Fibrinolitics</td>
<td>58,000</td>
<td>18%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>28,970</td>
<td>13%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>101,000</td>
<td>6.5%</td>
</tr>
<tr>
<td>2nd prev:</td>
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<td></td>
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<tr>
<td>Aspirin</td>
<td>54,903</td>
<td>15%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>20,312</td>
<td>21%</td>
</tr>
<tr>
<td>Statins</td>
<td>17,017</td>
<td>23%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>9,297</td>
<td>17%</td>
</tr>
<tr>
<td>CHF:</td>
<td></td>
<td></td>
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<tr>
<td>ACE inhibitor</td>
<td>7,105</td>
<td>23%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>12,385</td>
<td>26%</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>1,663</td>
<td>30%</td>
</tr>
</tbody>
</table>

Califf RM et al, Health Affairs, 2003
**Goals for CRUSADE Registry**

**Improve Adherence to ACC/AHA Guidelines for Patients with Unstable Angina/Non-STEMI**

**Acute Therapies**
- Aspirin
- Clopidogrel
- Beta Blocker
- Heparin (UFH or LMWH)
- Early Cath
- GP IIb-IIIa Inhibitor

**Discharge Therapies**
- Aspirin
- Clopidogrel
- Beta Blocker
- ACE Inhibitor
- Statin/Lipid Lowering
- Smoking Cessation
- Cardiac Rehabilitation

**Evaluating the Process of Care**
- An adherence score is applied to each patient, incorporating the components of process of care.
- The score from each patient then combined for all patients at each hospital.
- Typical scores ranged from 50 to 95%.
- All 400 hospital adherence scores then ranked in quartiles — best to worst.

Circulation, JACC 2002 — ACC/AHA Guidelines update

**Link Between Overall ACC/AHA Guidelines Adherence and Mortality**

- Every 10% increase in guidelines adherence
  - 11% decrease in mortality

**Which Treatment is Best for Whom? High-Quality Evidence is Scarce**

**Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines**

- Tricoci P et al. JAMA 2009;301:831-41

Data from ACC/AHA practice guidelines from 1996 to September 2004 were analyzed by personnel in the ACC for recommendatons and were the basis for guidelines or 27 topic-specific committees and 5 expert panels. A detailed description of each guideline topic is available from the ACC.

Data Sources and Study Selection: Data from ACC/AHA practice guidelines from 1996 to September 2004 were analyzed by personnel in the ACC for recommendatons and were the basis for guidelines or 27 topic-specific committees and 5 expert panels. A detailed description of each guideline topic is available from the ACC.

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Applying Classification of Recommendations and Level of Evidence

**Class I**
Benefit >> Risk
Additional studies with focused objectives needed
IT IS REASONABLE to perform procedure/administer treatment

**Class IIa**
Benefit >> Risk
Additional studies with focused objectives needed
IT IS REASONABLE to perform procedure/administer treatment

**Class IIb**
Benefit ≥ Risk
Additional studies with broad objectives needed; Additional registry data would be helpful
Procedure/Treatment may be considered

**Class III**
Risk ≥ Benefit
No additional studies needed
Procedure/Treatment should NOT be performed/administered since it is not helpful and may be harmful

Applying Classification of Recommendations and Level of Evidence

**Level A:** Recommendation based on evidence from multiple randomized trials or meta-analyses
Multiple (3-5) population risk strata evaluated; General consistency of direction and magnitude of effect

**Level B:** Recommendation based on evidence from a single randomized trial or non-randomized studies
Limited (2-3) population risk strata evaluated

**Level C:** Recommendation based on expert opinion, case studies, or standard-of-care
Very limited (1-2) population risk strata evaluated

Level of Evidence A
Current Guidelines*

*Guidelines expressing Level of Evidence

OUR ROLE ON THE NATIONAL SCENE
WHERE ARE WE HEADED?
Mechanistic Scientific Focus

- Discover pathways through probing of biological targets
- Develop novel biomarkers of disease and drug response
- Promote the early identification of safety signals as well as on-target and off-target effects
- Use a systems biology approach, advanced imaging and "omics" (genomics, proteomics and metabolomics) to measure the physiological effects of medical interventions
- Reclassify disease and develop molecular signatures to predict response, non-response, and toxicity

The Relevant Definitions

- **Phase 1 human clinical research**
  
  The first stage of testing in human subjects (often healthy volunteers). This includes trials designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of an intervention.

- **Proof of concept human research**
  
  Exploration and validation of a proposed mechanism by which a perturbation (drug, device, behavioral or environmental) has an effect based on a basic biological or observational premise.
### Re-engineering the Clinical Research Enterprise

**Plan and start a few demonstration networks**
- Simplify complex regulatory systems – demonstration projects
- Plan for networks in place for all institutes

**Funding mechanism to sustain national system through consensus of all constituents ("1% solution")**
- 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 large clinical trials; scientific information for patients, families, advocacy groups

**Establish repositories of biological specimens and standards for collection**
- Standardize nomenclature, data standards, core data, forms for most major diseases
- Start a library of these elements shared between institutes and NLM

**Develop efficient network administration infrastructure at NIH**
- ONE medical nomenclature with national data standards (agreed to by NIH, CMS, FDA, DOD, CDC)
- Data standards updated "in real time" through networks
- National repository of images and samples

**THE ESSENTIAL ISSUE**

The "Tower of Babel" of data from databases, literature, and clinical trials: without controlled vocabulary and data standards we are somewhat lost!

**THE LEARNING ISSUE**

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

#### Level of Difficulty

<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>26</td>
<td></td>
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</tbody>
</table>
The Research Treatment Distinction: A Problematic Approach for Determining which Activities should have Ethical Oversight

• In the past we’ve divided the world into clinical care vs research
• One is “acting in best interest of patient” while other treats patient as a “subject”, so requiring special ethics oversight
• This leads increasingly to a troublesome situation in which when its called “QI” or “clinical care” and doesn’t involve attempt to create generalizable knowledge (learning), no ethics oversight occurs
• As we move to a learning health system in which learning is expected, a prominent group of ethicists is coming forward this month with an argument that we should make a major change in the moral framework of healthcare

7 Proposed Moral Obligations in a Learning Health Care System

• Respect the rights and dignity of patients
• Respect clinician judgments
• Provide optimal clinical care to each patient
• Avoid imposing nonclinical risks and burdens on patients
• Address health inequalities
• Conduct continuous learning activities that improve the quality of clinical care and health care systems
• Contribute to the common purpose of improving the quality and value of clinical care and health care systems
  - Introduction and 7 commentaries
Health Care Systems Research Collaboratory

A Virtual Home for Knowledge about Pragmatic Clinical Trials using Health Systems: www.theresearchcollaboratory.org

1. Pragmatic trial design
2. Electronic health record as core data collection instrument
3. At least 2 integrated health systems collaborating to answer the question
   * Over 80 applications—7 funded to go forward with planning phase
PCORI's Mission and Vision

- The Patient-Centered Outcomes Research Institute (PCORI) is an independent, non-profit health research organization authorized by the Patient Protection and Affordable Care Act of 2010.
- PCORI funds patient-centered research to assist patients, caregivers, and other stakeholders in making informed health decisions.

Mission
PCORI helps people make informed healthcare decisions and improve healthcare delivery and outcomes by producing and promoting high-integrity, evidence-based information that informs decisions about prevention, diagnosis, treatment, and the broader healthcare community.

Vision
Patients and the public have the information they need to make decisions that reflect their desired health outcomes.

National Patient-Centered Clinical Research Network: Our Vision

Steering Committee - Awardees
- PCORI
- AHRQ, NIA, FDA, NCM, CMS

Scientific Advisory Board
- Special Expert Group

Coordinating Center Staff
Clinical Data Research Networks (CDRN)

- $56 million to support up to 8 new or existing CDRNs for 18 months

COOPERATIVE AGREEMENT AWARD 18 MONTHS LATER

- At least two health care systems engaged
- Willingness and capacity to work toward data standardization with other awardees
- Willingness to participate in collaborative studies with data sharing as part of a national research infrastructure
- > 1,000,000 patients enrolled
- Data standardized within network and with other awardee networks
- Patients, system, and clinicians engaged in governance & use
- Capable of implementing clinical trials

Patient-Powered Research Networks

- $12 million is available to support up to 18 new or existing PPRNs for 18 months.

COOPERATIVE AGREEMENT AWARD 18 MONTHS LATER

- Patients with a single condition, interested in research participation.
- Ability to increase size and diversity of patient membership
- Willingness to build standardized database of patient-reported data
- Willingness to explore collection of electronic clinical data.
- Target size of 0.5% of U.S. population with condition (≤50 patients for rare diseases; 10,000 for most common)
- Patient-reported data collected for at least 80% of cohort
- Patients involved in governance
- Standardized data suitable for sharing with other infrastructure members

Typical Trial Organization: Coordinating Center (Academic or CRO) and Enrolling Sites
Interoperable Networks
Share Sites and Data

Integration of Clinical Research Networks

- Link existing networks so clinical studies and trials can be conducted more effectively
- Ensure that patients, physicians, and scientists form true "Communities of Research"

A systems science approach to improving population health

- How do individual patients’ social and environmental contexts influence health outcomes?
- How do we best use evidence of these connections in the broader context of population health and illness?
- How do we best target effective interventions to settings where maximal impact is most likely?
- Who are the key stakeholders in the health ecosystem who must be at the table?
Embracing Complexity: Mapping the terrain of diabetes in Durham County, North Carolina

- Top layer – shows concentrations of diabetes patients.
- Next layer down - percentage single female head of household.
- Below that in purple, another indicator of economic status.
- The bottom layer maps the county boundary and streets.
- Vertical green spines – longitude ad latitude coordinates of where diabetes patients live and locations of key social or commercial institutions, that can be used to link all of these disparate data sets together based on shared geography.

Miranda, Ferranti, Strauss, Neelon, Califf. Health Affairs 2013; 32:608-1615

Mapping the terrain of diabetes for Durham County

By integrating multiple components into a comprehensive system, GHIS and associated analytical applications offer innovative strategies that can facilitate progress toward achieving the Triple Aim and, in so doing, can **fundamentally change how health systems address the health needs of their communities**

Miranda, Ferranti, Strauss, Neelon, Califf. Health Affairs 2013; 32:608-1615

WHAT CAN WE DO LOCALLY?
Duke Clinical Research

- Align our technology resources with biological, mechanistic research
- Align our clinical care and research systems (enterprise wide planning)
- Lead the way in developing functional use of electronic health records for research
- Optimize the function of DOCR/CRUs in 4 dimensions:
  - Portfolio management (are we doing the right research?)
  - Operational efficiency (are we optimizing our resources?)
  - Research productivity (are we contributing our share of knowledge?)
  - Human capital development (are we training, educating and enabling human growth of our people?)

DTMI Organizational Structure

The CTSA at Duke – The Integrated Home
Duke’s Vision of the Data Mart

Integrated Home – IT programs Timeline

Common Resources

- Pilot Funding
- Biostatistics
- Biobanking
- Regulatory Affairs
- Research Participant Recruitment Core
- Resource Navigation
- Common Services Application and Catalog
- Data Marts
Site Based Research Evolved

- **Site based research - History**
  - 1931 - 1990’s - Departmental Faculty Model
    - Investigators developed ideas and grant applications
    - Clinicians developed relationships with outside sponsors
      - Multi-center trial participation
      - Investigator-initiated industry-sponsored
    - Model: Investigator/Coordinator team
      - Surplus funds, if any, flowed to residual accounts
      - Effort not consistently applied
    - Financial process not well established
  - Monitoring of Trial activity not well established

  **CRSO Model (2006-2012)**
  - CRSO established to create consistency and compliance around research billing
    - Very regimented in operation, with limited knowledge of the clinical research engine
    - Performed bill risk determinations
    - Reviewed billing grids built by SBRs
    - Established operational policies around clinical research at Duke Medicine
  - SBRs established to provide clinical research oversight and structure within existing departments
    - Provided central points of contact for CRSO
    - Interfaced with all other central offices for support (PRMO, OCRC, DHTS, etc.)
    - SBRs built billing grids to show proper assignment of charges generated
    - Developed and negotiated budget and payment terms
    - Reviewed protocol and submitted to IRB
    - Performed QI/QA process
    - Responsible for staff oversight

  **Reassessment (2011)**
  - Clinical Research Units were autonomous
    - No standardization across CRUs
    - Led to high variability in work and performance
  - Distribution of roles and responsibilities were undefined and highly variable
    - Some individuals performed jobs they were not trained/qualified to perform
    - Variable CRU structures lead to inconsistent interactions with Central research support offices
  - Financial management practices were not consistently defined
    - Not all negotiated budgets were adequate to cover costs
    - Inconsistent charge structure, unintentionally produced competition between CRUs and departments for similar services
    - Billing/receivables processes were not uniform across the enterprise
Future DOCR Model (influenced by Maestro Care Implementation and NIH regulations)

Summary

• Our clinical research system is great except:
  – Too expensive and inefficient
  – Contributes to our low health status compared to rest of world
  – Doesn’t answer most critical questions

• The disruptive innovation is underway
  – Systems biology to understand mechanisms
  – EHR for small scale research
  – Learning health systems for large scale research

• We are well positioned to contribute
  – Portfolio
  – Efficiency
  – Knowledge generation
  – Human capital