The CER Vision of Tomorrow: Tailoring Medicine to the Individual
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Comparative Effectiveness and Personalized Medicine
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Challenge of Rising U.S. Health Expenditures

*Biomedical Research Must Deliver*

National Health Expenditures as a Percent of GDP

- **Actual**
- **Projected**

$4.35$ trillion
NIH: Steward of Medical and Behavioral Research for the Nation

“Science in pursuit of fundamental knowledge about the nature and behavior of living systems ... and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability.”
Opportunities for Research and NIH

Francis S. Collins

The mission of the National Institutes of Health (NIH) is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and to reduce the burdens of illness and disability. The power of the molecular approach to health and disease has steadily gained momentum over the past several decades and is now poised to catalyze a revolution in medicine. The foundation of success in biomedical research has always been, and no doubt will continue to be, the creative insights of individual investigators. But increasingly those investigators are working in teams, accelerated by interdisciplinary approaches and empowered by open access to tools, databases, and technologies, so a careful balance is needed between investigator-initiated projects and large-scale community resource programs. For both individual and large-scale efforts, it is appropriate to identify areas of particular promise. Here are five such areas that are ripe for major advances that could reap substantial downstream benefits.

High-Throughput Technologies

In the past, most biomedical basic science projects required investigators to limit their scope to a single aspect of cell biology or physiology. The revolution now sweeping the field is the ability to be comprehensive—for example, to define all of the genes of the human or a model organism, all of the human proteins and their structures, all of the common variations in the genome, all of the major pathways for signal transduction in the cell, all of the patterns of gene expression in

Translational Medicine

Critics have complained in the past that NIH is too slow to translate basic discoveries into new diagnostic and treatment advances in the clinic. Some of that criticism may have been deserved, but often the pathway from molecular insight to therapeutic benefit was just not bring them to clinical trials and U.S. Food and Drug Administration (FDA) approval.

As one example, the NIH Therapeutics for Rare and Neglected Diseases (TRND) (3) program will allow certain promising compounds to be taken through the preclinical phase by NIH, in an open environment where the world’s experts on the disease can be involved. Furthermore, as information about common diseases increases, many are being resolved into distinct molecular subsets, and so the TRND model will be even more widely applicable.

The first human protocol (for spinal cord injury) involving human embryonic stem cells (hESCs) was approved by the FDA in 2009, and the opening up of federal support for hESC research will bring many investigators into this field. The ability of transforming human skin fibroblasts and other cells into induced pluripotent stem...
Personalized Medicine, Defined

- Personalized medicine uses an individual's genetic profile and individual information about environmental exposures to guide decisions made in regard to the prevention, diagnosis, and treatment of disease.
- Knowledge of a patient's genetic profile can help health care providers select the proper medication or therapy and administer it using the proper dose or regimen.
- Personalized medicine is being advanced through data and technologies from the Human Genome Project:
  - Genome wide association studies (GWAS)
  - DNA sequencing
Diagnosis and Risk Prediction

- Identify rare variant responsible for childhood illness
- Begin colonoscopy at age 40
Diagnosis and Risk Prediction

Pharmacogenomics

- Identify rare variant responsible for childhood illness
- Begin colonoscopy at age 40

- Drug dose of antidepressant determined by drug metabolism genetic profile
Diagnosis and Risk Prediction

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- Drug dose of antidepressant determined by drug metabolism genetic profile

New Therapies

- Gene-based drug therapy for cancer
- Gene therapy for blindness
Comparative Effectiveness Research at NIH

NIH conducts research in 88 of 100 IOM CER priority areas

Since Barack Obama became the 44th President of the United States in January 2009, nearly all sectors of society have engaged in intense discussions about the best ways to stimulate the nation’s economy and reform the US health care system. The National Institutes of Health (NIH) has been—and will continue to be—in the middle of such conversations, emphasizing the power of biomedical research to show what health interventions yield the greatest benefits.

Health reform and economic concerns may have moved comparative effectiveness research (CER) from relative obscurity into the public policy spotlight. However, CER is not a new concept to NIH, which has long recognized and supported the value of CER for providing evidence-based, well-validated approaches to medical care.

For instance, nearly 2 decades ago, NIH-supported researchers published results of the Cardiac Arrhythmia Suppression Treatment (CAST) study. CAST was the first randomized, placebo-controlled clinical trial to show that some drugs can increase the risk of sudden cardiac death in patients with certain heart conditions. The results led to changes in national clinical practice guidelines and in the marketing of antiarrhythmic drugs. The study is considered one of the first examples of CER and paved the way for NIH to become an active participant in CER research.

Since then, NIH has pursued multiple initiatives to improve comparative effectiveness research. One example is the National Health Expenditure Accounts, which track the allocation of resources across different health care sectors. This initiative helps NIH understand how funds are being used and identify areas where additional research is needed.

NIH has also worked to improve the transparency and accessibility of its research, making it easier for other researchers, clinicians, and policymakers to access and use the findings. This includes developing standards for reporting the results of clinical trials and ensuring that NIH-funded research is conducted in line with ethical guidelines.

NIH has made significant investments in CER, including the Common Data Elements (CDE) initiative, which aims to standardize data collection across different health care settings. This allows researchers to pool data from multiple studies, increasing the power of their analyses.

In summary, NIH’s commitment to comparative effectiveness research is evident in its support of a wide range of projects and initiatives that aim to improve the quality and efficiency of health care. The agency’s research has already had a significant impact, and it continues to play a leading role in advancing the field of CER.
CER: Diabetes Prevention Program (DPP) Trial

- 57 million Americans at high risk for developing type 2 diabetes (pre-diabetes)
- DPP trial: NIH-funded study of 3,000+ high-risk adults
  - Metformin reduces risk by 31%
  - Modest lifestyle changes reduce risk by 58%
    - 5-7% lower body weight; exercise 30 minutes/5x per week
    - Recent follow-up: protective effects persist for at least a decade
Figure 1. Incidence of Diabetes According to Treatment Group and Genotype at Variant rs7903146. The P values were determined by the log-rank test.
Common Variants in 40 Genes Assessed for Diabetes Incidence and Response to Metformin and Lifestyle Intervention in the Diabetes Prevention Program

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FIG. 1. Diabetes incidence in the DPP, by genotype at rs8065082 in the SLC47A1 gene. This SNP is in tight LD with rs2289669 (r² ~ 0.8), whose major allele predicts a poorer response to metformin (5). In the DPP, major allele homozygotes at rs8065082 did not benefit from metformin with regard to diabetes prevention, whereas minor allele carriers did (P < 0.001).
**Iressa™ (gefitinib)**

- New genome-based drug for lung cancer that blocks the EGF receptor kinase
- Many lung cancer patients failed to respond
- But some subjects got a dramatic response
- Why?

CT scans showing response of liver metastases to Iressa
Gefitinib (Iressa): A Timeline

- **1994**: New class of epidermal growth factor receptor (EGFR) inhibitors discovered
- **1998**: Phase I trials show favorable tolerability and unprecedented responses
- **2003**: FDA approves Iressa for non-small cell lung cancer (NSCLC) patients previously treated with standard chemotherapy
- **2004**: Phase III ISEL study finds Iressa confers no significant survival advantage in overall NSCLC population
  - However, patients of Asian origin and never-smokers benefit
  - Harvard studies suggest EGFR mutations underlie some of the exceptional responses
Gefitinib (Iressa): A Timeline

- **2005**: FDA considers withdrawing Iressa, but instead decides to restrict use to patients who
  - are in clinical trials
  - benefitted from the drug
- **2008**: IPASS9 study finds Iressa more effective than doublet chemotherapy in EGFR mutation positive patients
- **2009**: European Union approves Iressa as a first-line treatment for adults with locally advanced or metastatic NSCLC with EGFR mutations
Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

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A Progression-free–Survival Population

P<0.001

Progression-free Survival (%)

Standard chemotherapy (N=110)
Gefitinib (N=114)

Months since Randomization

0 3 6 9 12 15 18 21 24 27
Clopidogrel (Plavix): Responses

- 1996: CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial results – Found clopidogrel more effective in reducing combined risk of ischaemic stroke, myocardial infarction, vascular death in patients with atherosclerotic vascular disease.
- Noted “lack of observed benefit of clopidogrel over aspirin” in certain subgroups.
- 1997: Plavix receives FDA approval.
- 2006: CYP2C19*2 and *3 identified as modifiers of clopidogrel metabolism.
- 2009: Retrospective analysis of effect of CYP2C19 genotypes on clopidogrel metabolism.
- 2010: FDA adds black box warning to Plavix.
CER at NIH: Treatment of Childhood Absence Epilepsy

- **Childhood Absence Epilepsy**
  - The most common pediatric epilepsy
  - Treated with one of 3 drugs: ethosuximide, valproic acid, or lamotrigine
  - Which is the most efficacious and tolerable initial treatment?

- **Clinical trial: >450 newly-diagnosed children randomly assigned a treatment**

- **Results:**
  - Ethosuximide and valproic acid: more effective than lamotrigine
  - Ethosuximide: associated with fewer adverse attentional effects

[Image: ClinicalTrials.gov, NCT00088452]
CER and Personalized Medicine

- CER should be guided by the emerging science of genomics and personalized medicine
- CER studies should include participant genomic and environmental exposure data, in order to understand why some individuals benefit from a treatment while others do not
- CER will generate research hypotheses relevant to personalized medicine by exploring why certain groups may or may not respond to an intervention
- NIH is well positioned to evaluate the comparative outcomes related to various genotypes and environmental exposures
HMO Research Network Collaboratory

A New Opportunity to Advance the Science of Health Care Decision-making

A consortium of 16 integrated health systems covering more than 13 million people

- Increase accessibility of existing HMO research resources
- Scale up scientific, data, and operational infrastructure
- Accelerate large epidemiology studies, clinical trials, and health care services research
- Focus on risk factors, rare diseases, CER, patient accrual, and reimbursement models

http://www.hmoresearchnetwork.org/about.htm
Health Care Legislation and CER: Patient-Centered Outcomes Research Institute (PCORI)

- Non-profit corporation to organize, fund CER
  - Board of Directors announced on September 23, 2010
    - A. Eugene Washington, MD, MSc is Chairman
    - Includes Directors of NIH, AHRQ
    - Standing methodology committee will include NIH, AHRQ

Subtitle D—Patient-Centered Outcomes Research

SEC. 6301. PATIENT-CENTERED OUTCOMES RESEARCH.

(a) In General.—Title XI of the Social Security Act (42 U.S.C. 1301 et seq.) is amended by adding at the end the following new part:

*PART D—COMPARATIVE CLINICAL EFFECTIVENESS RESEARCH*

Patient-Centered Outcomes Research Institute: The Intersection of Science and Health Care

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The Patient Protection and Affordable Care Act created the Patient-Centered Outcomes Research Institute (PCORI), a nonprofit corporation that is neither an agency nor an
NIH...
Turning Discovery Into Health

U.S. Department of Health & Human Services
National Institutes of Health