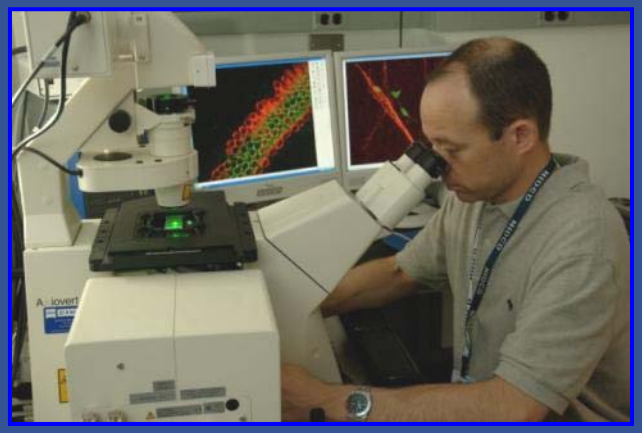
The Role of NIH in CER

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

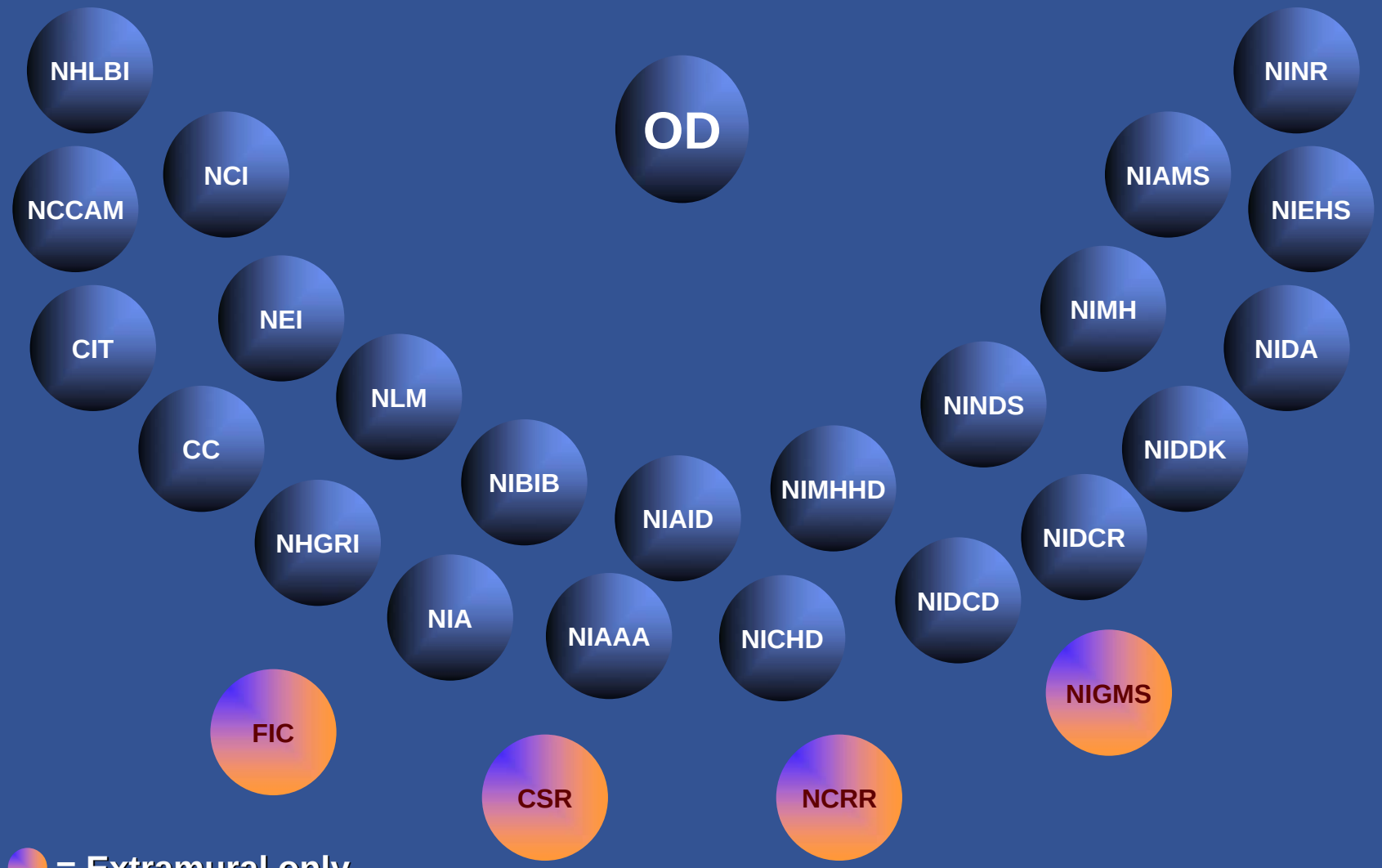
The Second National Comparative Effectiveness Summit
September 13, 2010

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."

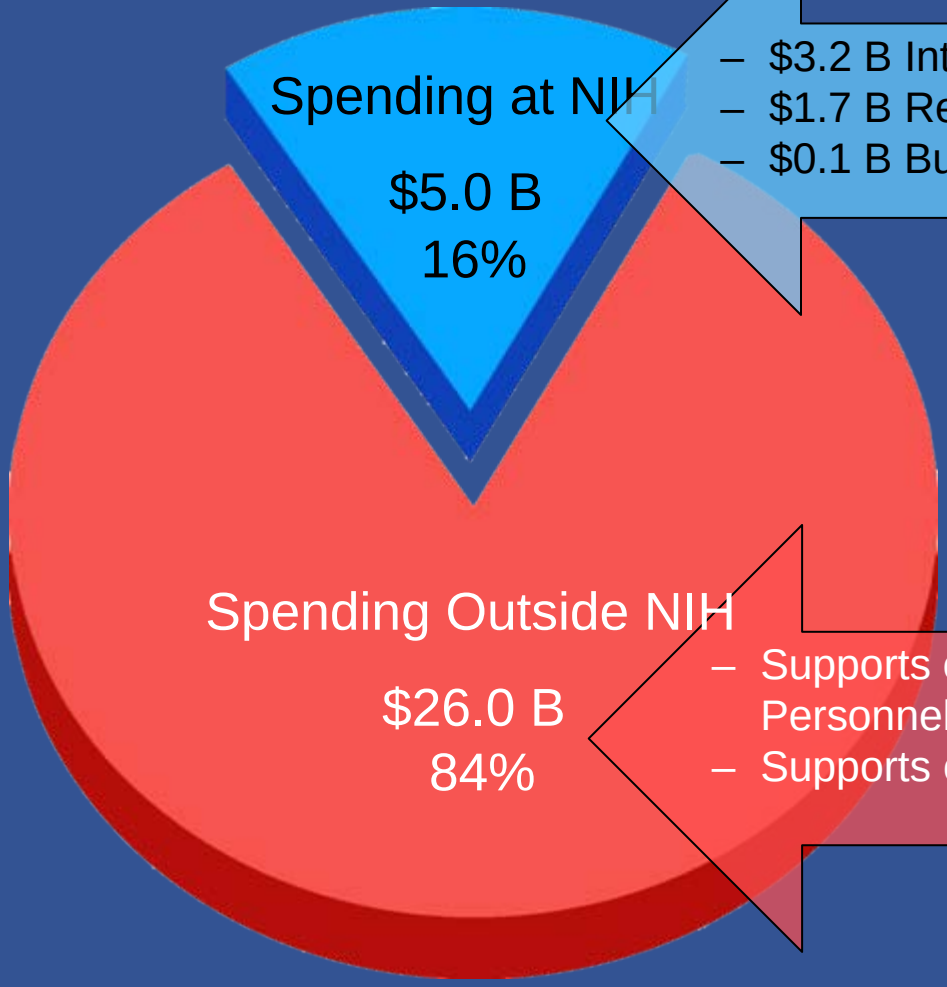


NIH Consists of 27 Institutes and Centers



NIH Extramural & Intramural Funding

FY 2010 Presidents Budget: $30.988 Billion*



- $3.2 B Intramural Research
- $1.7 B Research Management & Support
- $0.1 B Buildings and Facilities

- Supports over 325,000 Scientists & Research Personnel
- Supports over 3,000 Institutions

* Includes $150 million from the Special type 1 Diabetes appropriation.

POLICYFORUM

RESEARCH AGENDA

Opportunities for Research and NIH

Francis S. Collins

The promise of fundamental advances in diagnosis, prevention, and treatment of disease has never been greater.

1 JANUARY 2010 VOL 327 SCIENCE

Published by AAAS

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

sive information about the genetic underpinnings of 20 major tumor types. This information will likely force a complete revision of diagnostic categories in cancer and will usher in an era where abnormal pathways in specific tumors will be matched with the known targets of existing therapeutics. Another example is the opportunity to understand how interactions between ourselves and the microbes that live on us and in us (the "microbiome") can influence health and disease (*2*).

Translational Medicine

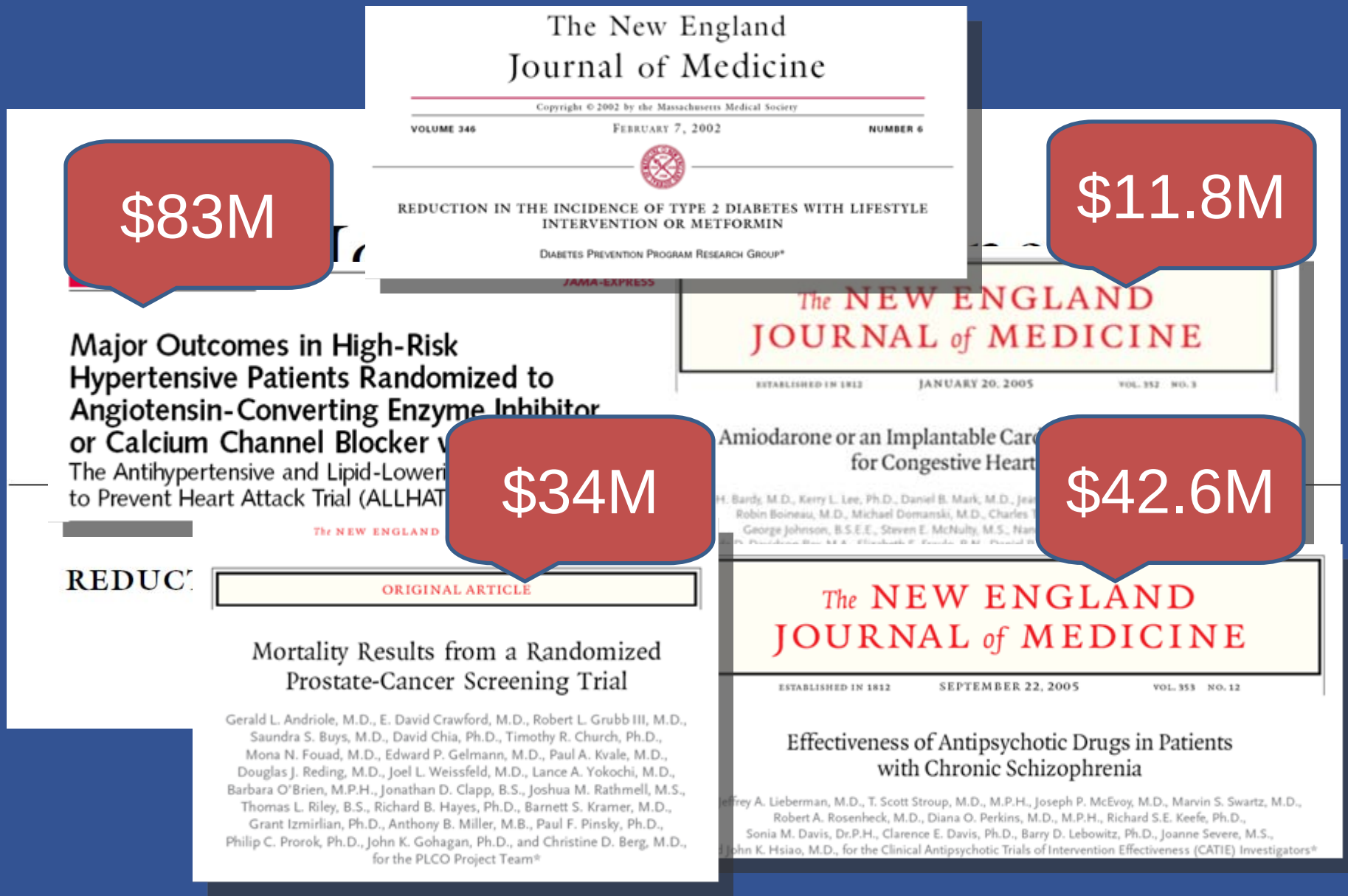
Critics have complained in the past that NIH is too slow to translate basic discoveries into new diagnostic and treatment advances in the clinic. Some of that criticism may have been deserved, but often the pathway from molecular insight to therapeutic benefit was just not

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.

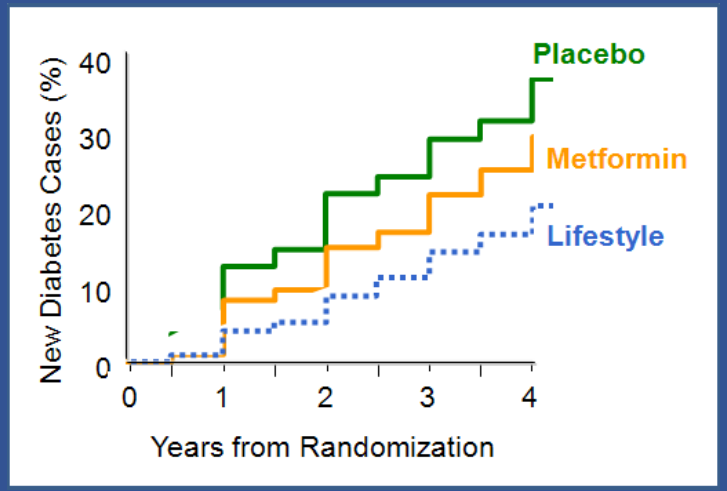
The first human protocol (for spinal cord injury) involving human embryonic stem cells (hESCs) was approved by the FDA in 2009, and the opening up of federal support for hESC research will bring many investigators into this field. The capability of transforming human skin fibroblasts

CER at NIH: Type 2 Diabetes



Delivery: 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



DPP Trial: Taking research results to the public

- "Small Steps, Big Rewards" – NIH campaign (with CDC; 200+ private partners)

Total NIH Support for the DPP, 1994–2010

$267,589,000

small steps
big rewards
Prevent type 2 Diabetes

Comparative Effectiveness Research at NIH

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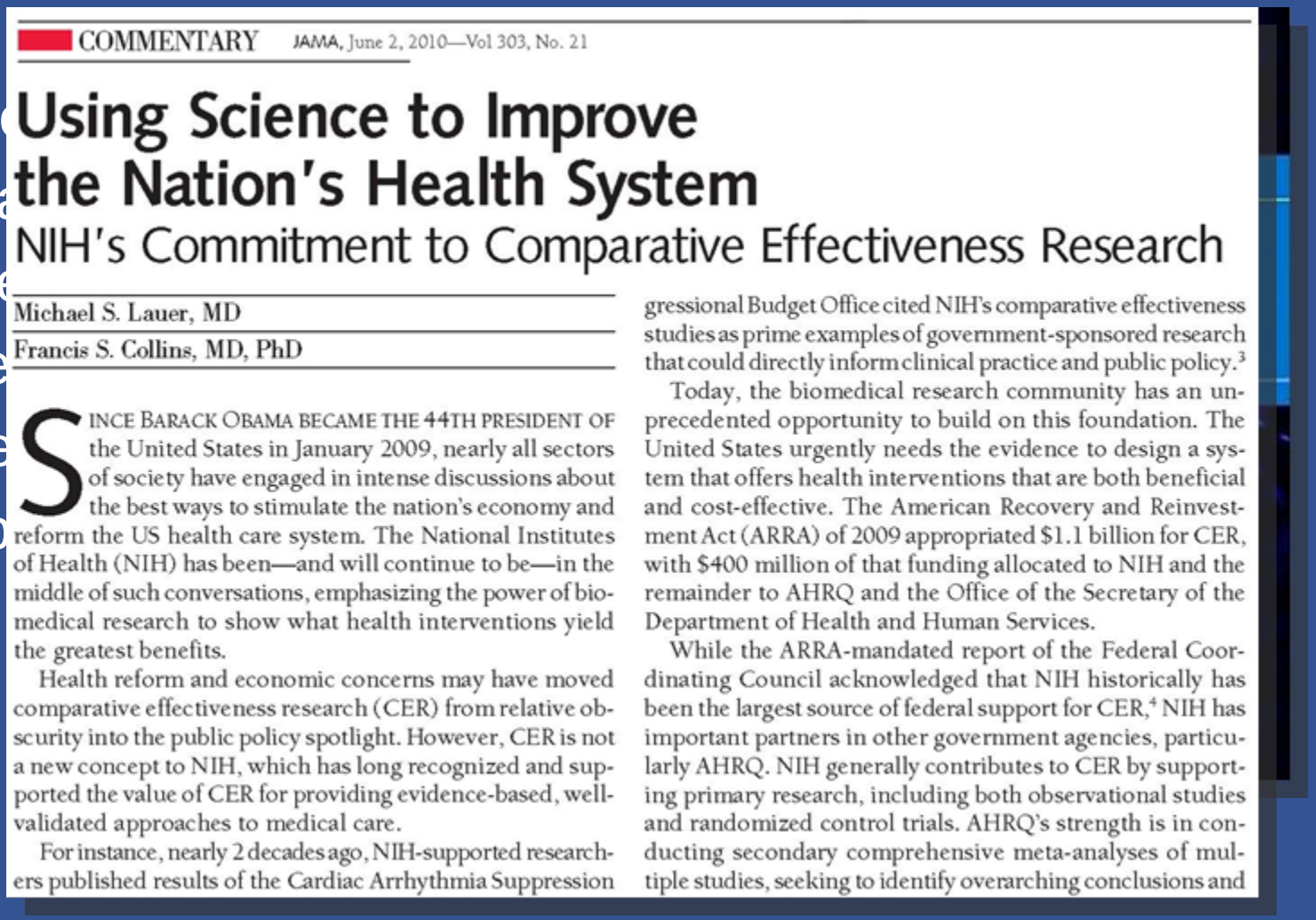


COMMENTARY JAMA, June 2, 2010—Vol 303, No. 21

Using Science to Improve the Nation's Health System

NIH's Commitment to Comparative Effectiveness Research

Michael S. Lauer, MD
Francis S. Collins, MD, PhD

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

gressional Budget Office cited NIH's comparative effectiveness studies as prime examples of government-sponsored research that could directly inform clinical practice and public policy.[3]

Today, the biomedical research community has an unprecedented opportunity to build on this foundation. The United States urgently needs the evidence to design a system that offers health interventions that are both beneficial and cost-effective. The American Recovery and Reinvestment Act (ARRA) of 2009 appropriated $1.1 billion for CER, with $400 million of that funding allocated to NIH and the remainder to AHRQ and the Office of the Secretary of the Department of Health and Human Services.

While the ARRA-mandated report of the Federal Coordinating Council acknowledged that NIH historically has been the largest source of federal support for CER,[4] NIH has important partners in other government agencies, particularly AHRQ. NIH generally contributes to CER by supporting primary research, including both observational studies and randomized control trials. AHRQ's strength is in conducting secondary comprehensive meta-analyses of multiple studies, seeking to identify overarching conclusions and

NIH conducts research in 88 of 100 IOM CER priority areas

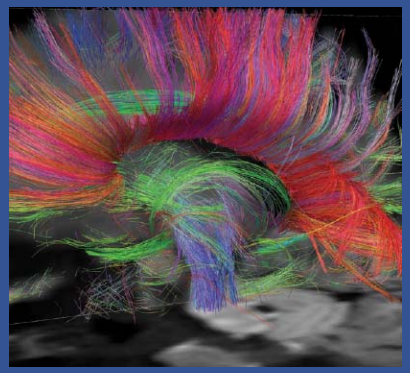
The Recovery Act and CER at NIH

As of July, 2010, NIH has

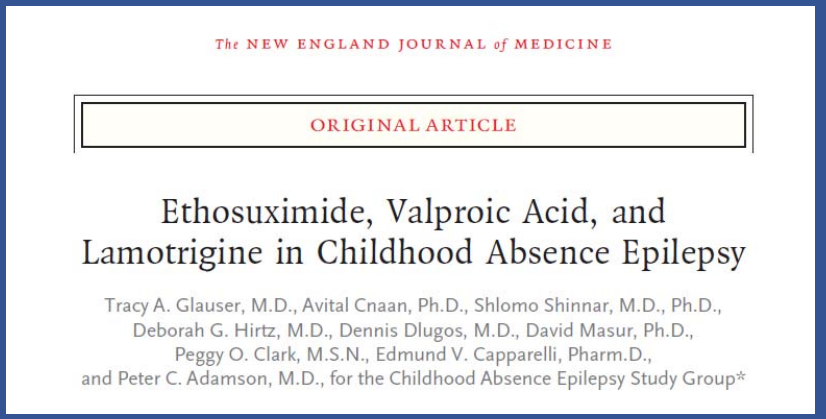
- Obligated all $400M toward 214 CER projects, including:
  - Treatment and Outcomes for Atrial Fibrillation in Clinical Practice
  - Comparative Effectiveness of Breast Imaging Strategies in Community Practice
  - Conservative Versus Dialytic Management in Stage V Chronic Kidney Disease
- Identified gaps; developed RFAs to address
  - Methodology in CER ($21M)
  - Research Gaps ($4.5M)
  - CER Training and Career Development ($25.5M)
  - Behavioral Economics ($29.5M*)

*Funded through the Office of the Secretary, HHS

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



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

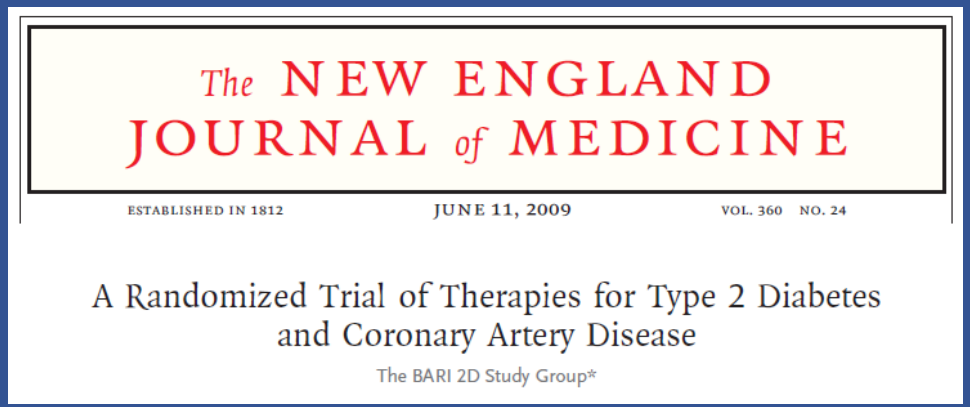
Ethosuximide, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy

Tracy A. Glauser, M.D., Avital Cnaan, Ph.D., Shlomo Shinnar, M.D., Ph.D., Deborah G. Hirtz, M.D., Dennis Dlugos, M.D., David Masur, Ph.D., Peggy O. Clark, M.S.N., Edmund V. Capparelli, Pharm.D., and Peter C. Adamson, M.D., for the Childhood Absence Epilepsy Study Group*

ClinicalTrials.gov, NCT00088452

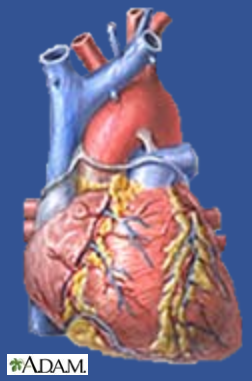
BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) **Trial***

- Study Design
  - Patients had type 2 diabetes, stable CVD, and documented ischemia
  - All received state-of-the-art medical therapy
- Trial: prompt revascularization percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) **vs.** delayed or no revascularization
- Conclusions
  - Revascularization can be delayed in many patients receiving optimal medical therapy
  - Patients with extensive coronary disease do better with prompt CABG than with medical therapy alone



*Funded by NHLBI, NIDDK, and industry

Bypass Surgery (CABG) vs. Angioplasty (PCI)



- Problem: doctors lack data to decide between procedures for coronary artery disease
- CER Response: database of ~80K patients to assess long-term clinical and cost outcomes of CABG vs. PCI based on:
  - Hospitalizations
  - Subsequent heart attacks
  - Need to repeat revascularization procedures
  - Patient survival
- Subsets of data will be used to analyze interactions with age; gender; other medical conditions (e.g., stroke and kidney failure)

FY 2009 GO grant funding, NHLBI, $2,655,996, PI: William S. Weintraub, M.D., Christiana Care Health Services, Delaware

Systolic Blood Pressure (SBP) Intervention Trial (SPRINT)

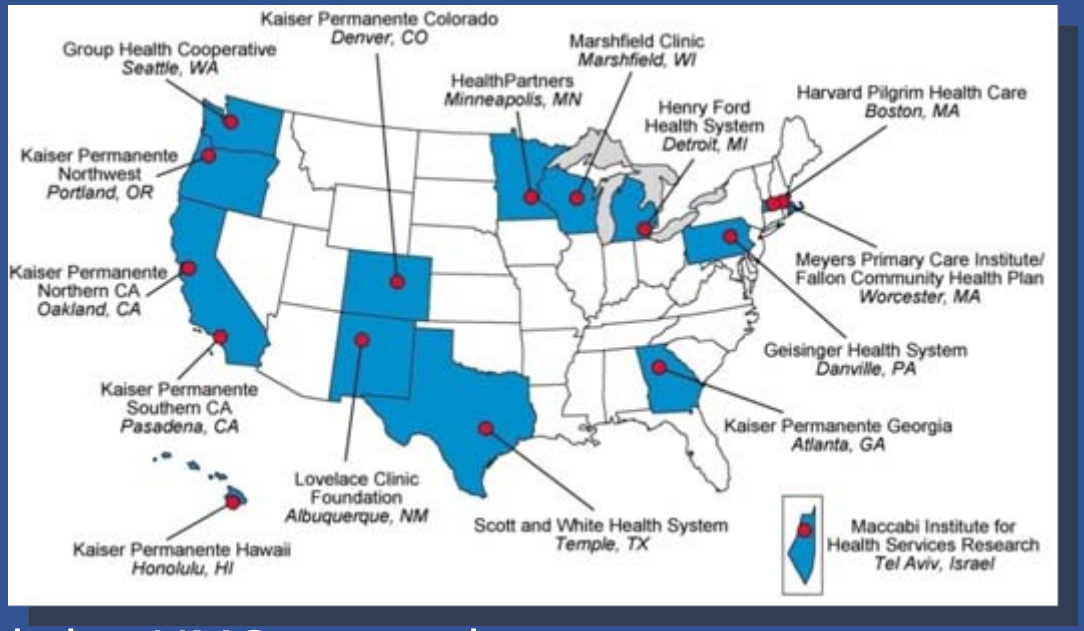
- SPRINT:
  - Does treating SBP to a lower goal compared to the standard (<120 vs. <140mmHg) reduce morbidity and mortality from cardiovascular or kidney diseases, or dementia?
  - 7,500 participants across the U.S.
- SPRINT-SENIOR:
  - Additional cohort of 1,750 participants aged 75+ (ARRA funding)
  - Does SPRINT treatment reduce cardiovascular or kidney diseases, or dementia, in senior participants?

- Sub-study, SPRINT-MIND: does treatment reduce age-related decline in brain volume and cognitive function?

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

COMMENTARY Science Translational Medicine

HEALTH REFORM

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

Carolyn Clancy[1] and Francis S. Collins[2]*

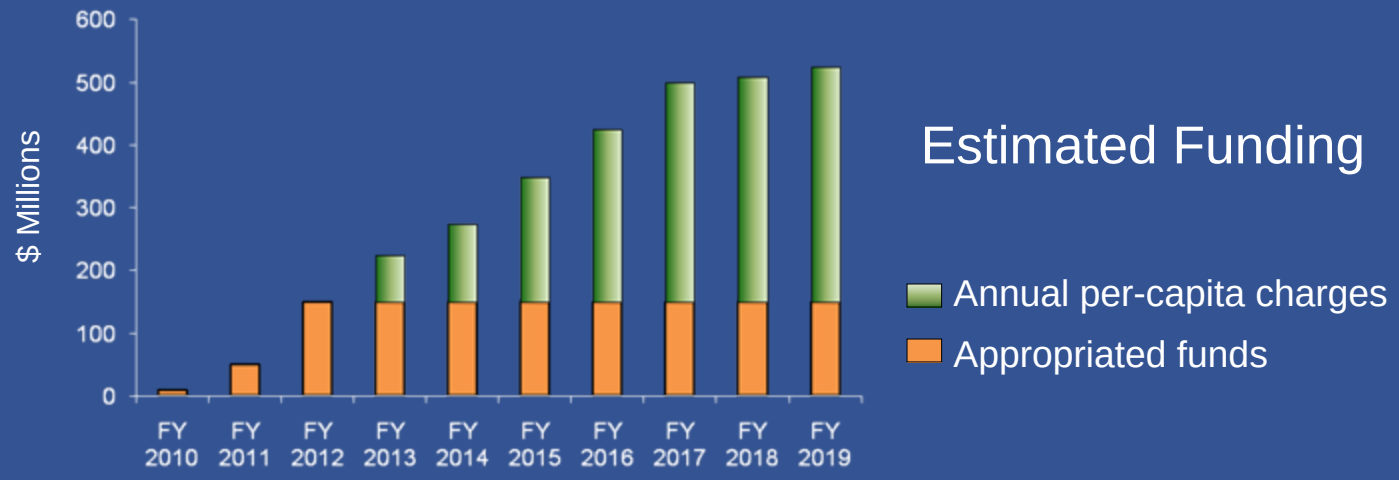
Published 23 June 2010; Volume 2 Issue 37 37cm18

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 establishment of the U.S. government. PCORI's mission is to support the production of well-validated scientific evidence to assist the nation in making informed decisions about a broad range of health care–related issues. In this Commentary, the directors of the Agency for Healthcare Research and Quality and the National Institutes of Health discuss PCORI's opportunities to contribute to a robust portfolio of scientific inquiry that builds on their agencies' investment in comparative effectiveness research.

IMPROVING PATIENT OUTCOMES

The Agency for Healthcare Research and Quality (AHRQ) and the National Institutes of Health (NIH) embrace the establishment of PCORI, which will build on our agencies' longstanding investment in comparative effectiveness research (CER) to provide well-validated evidence-based approaches to medical care that can improve patient outcomes (3). CER is designed to inform health care decisions by providing evidence related to the effectiveness, benefits, and harms of different treatment options for a given condition, including subgroups within that condition. The evidence is generated through research that compares drugs, medical devices, tests, surgeries, or methods to deliver health care.

Historically, NIH and AHRQ have



CER and Personalized Medicine

- CER should be guided by the emerging science of genomic and personalized medicine
- CER will generate research hypotheses relevant to personalized medicine by exploring why certain groups may or may not respond to an intervention
- 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
- NIH is uniquely positioned to evaluate the comparative outcomes related to various genotypes and environmental exposures

Clopidogrel (Plavix)

- Drug Functions:
  - Works by preventing platelets from forming clots
  - Must be activated by specific enzymes (P450)
- Clinical Observations:
  - Commonly used in patients at risk for heart attacks and strokes
  - *However,* it does **not** work for about **30%** of the U.S. population
- Research Question: *why is this drug ineffective in nearly 1/3 of the population?*

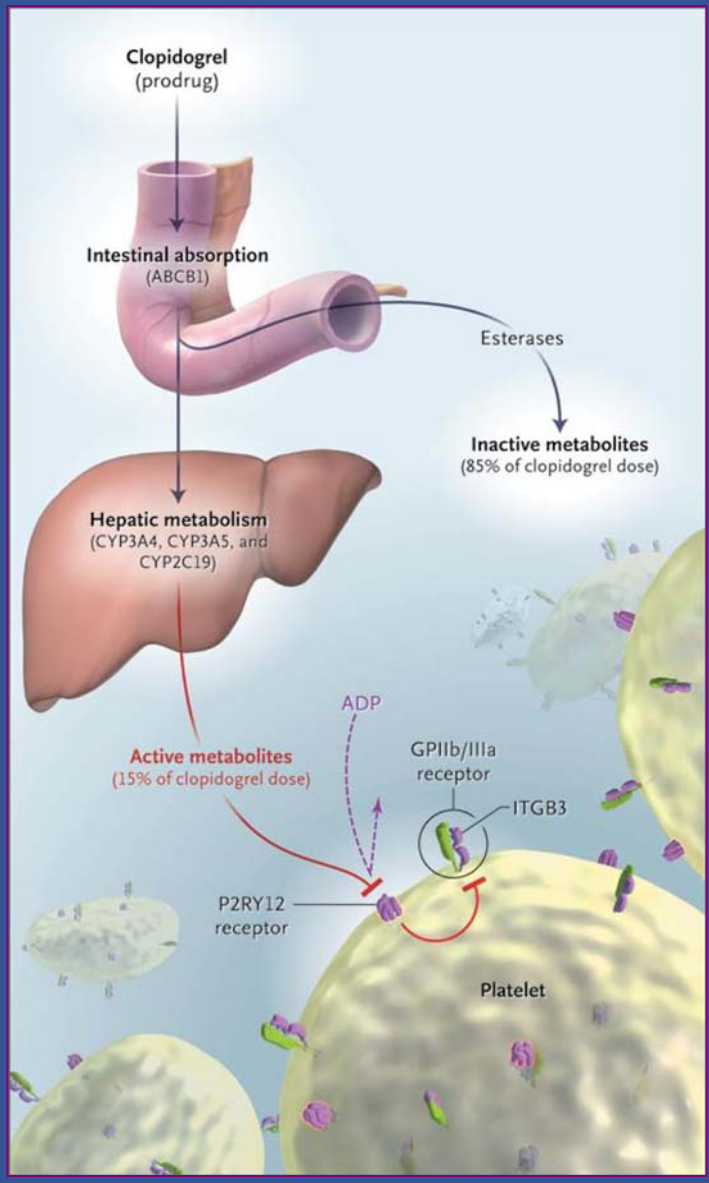


Image: T. Simon, C. Verstufyt, et. al, NEJM

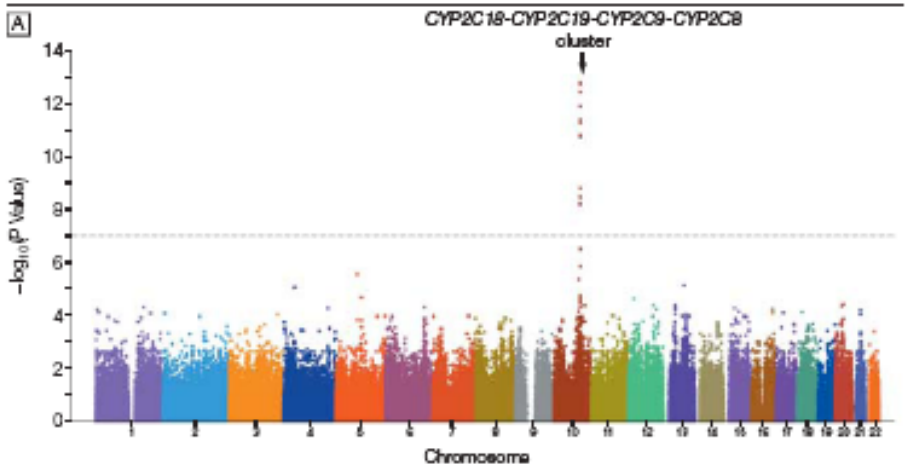
Clopidogrel (Plavix): The Evidence

JAMA®

ORIGINAL CONTRIBUTION

Association of Cytochrome P450 2C19 Genotype With the Antiplatelet Effect and Clinical Efficacy of Clopidogrel Therapy

Figure 2. Genome-Wide Association Study of Adenosine Diphosphate–Stimulated Platelet Aggregation in Response to Clopidogrel



From Shuldiner et al., JAMA, 8/26/09, vol 302

Comparative Effectiveness and Personalized Medicine: An Essential Interface

A national conference on the status of comparative effectiveness research and its use in policy and practice

October 19-20, 2010
Masur Auditorium
Building 10 (Clinical Center)
National Institutes of Health
Bethesda, Maryland

Registration **required – There is no registration fee**

ECRI Institute
The Discipline of Science. The Integrity of Independence.

AHRQ

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NIH…
Turning Discovery Into Health

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