Translation of Innovations: A Broad Perspective

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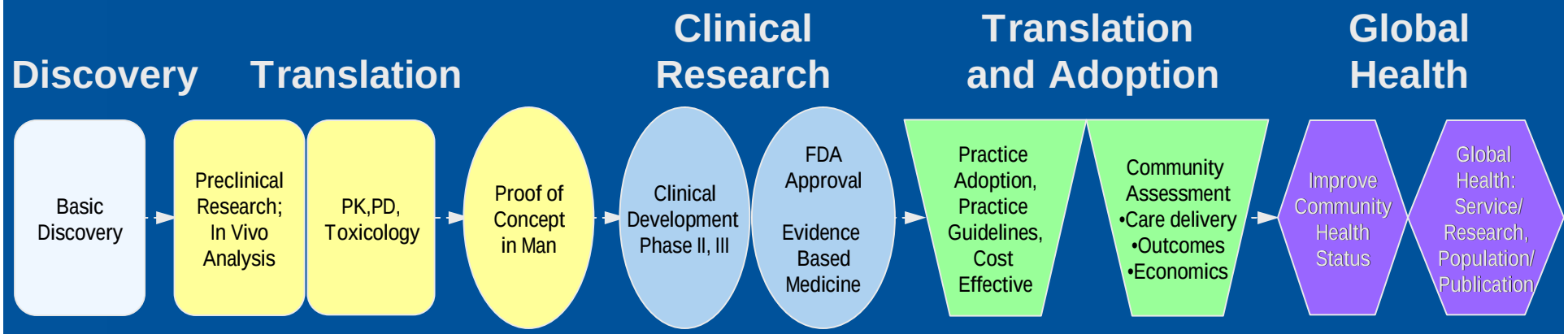
Concepts

- **Biological science is advancing at an amazing rate**
- **Translation is lagging behind; the issues are not technological**
- **Translation of medical innovation inevitably must deal with the intersection of:**
  - Financing
  - Regulation
  - Culture
- **There is reason to be concerned that all 3 areas have gotten out of step with the current state of scientific knowledge**
- **Most disturbingly, it can be argued that the reward for taking risk to promote innovation is often inversely related to societal need**

Translation of Innovations



Current State Entities

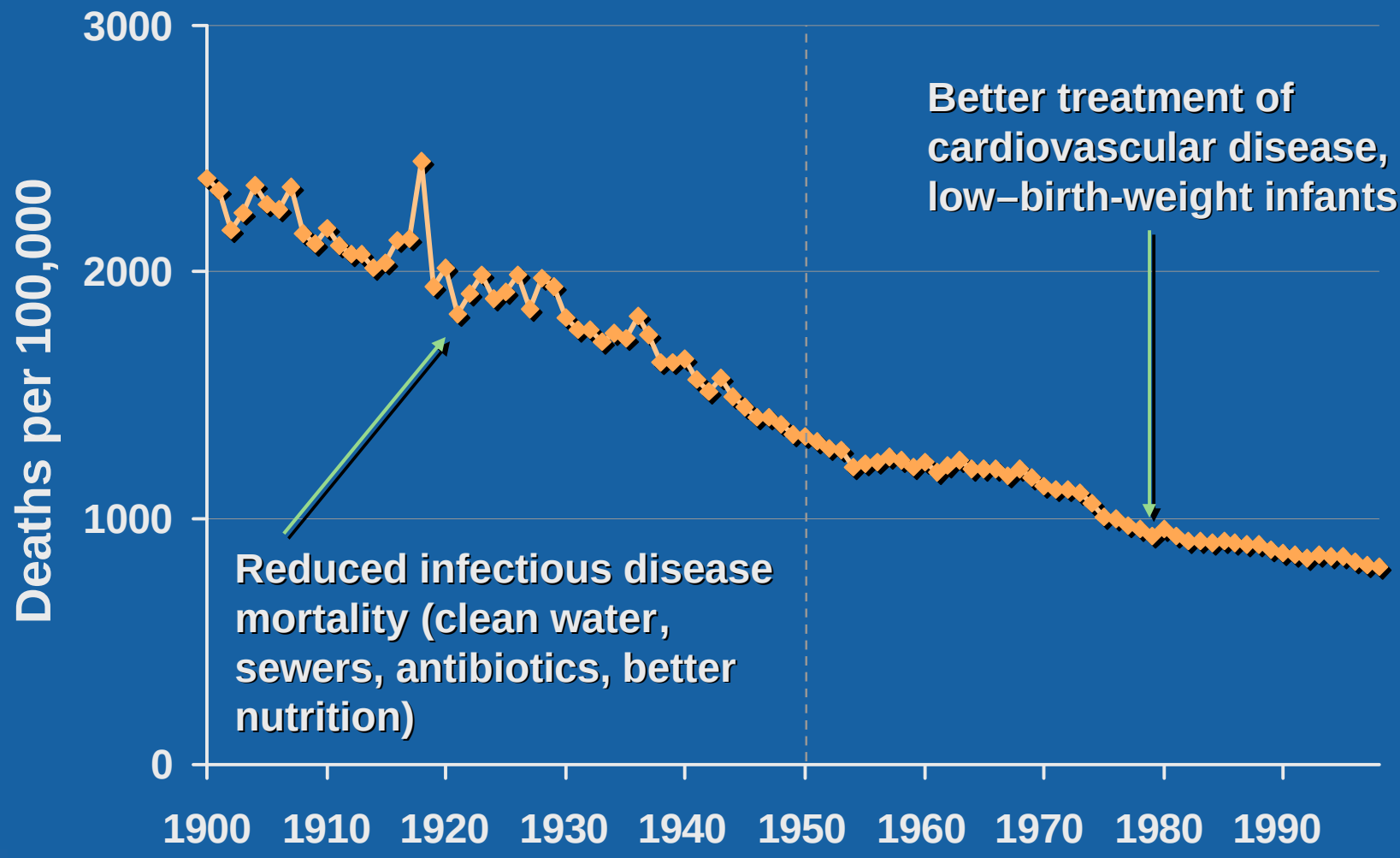
AHS/Industry/ Biotech	Industry/Biotech	Clinical Research Organizations/AHS	HCS/Hospitals/ Practices/FQHC/AHS	Government NGOs

Fragmented/Disorganized

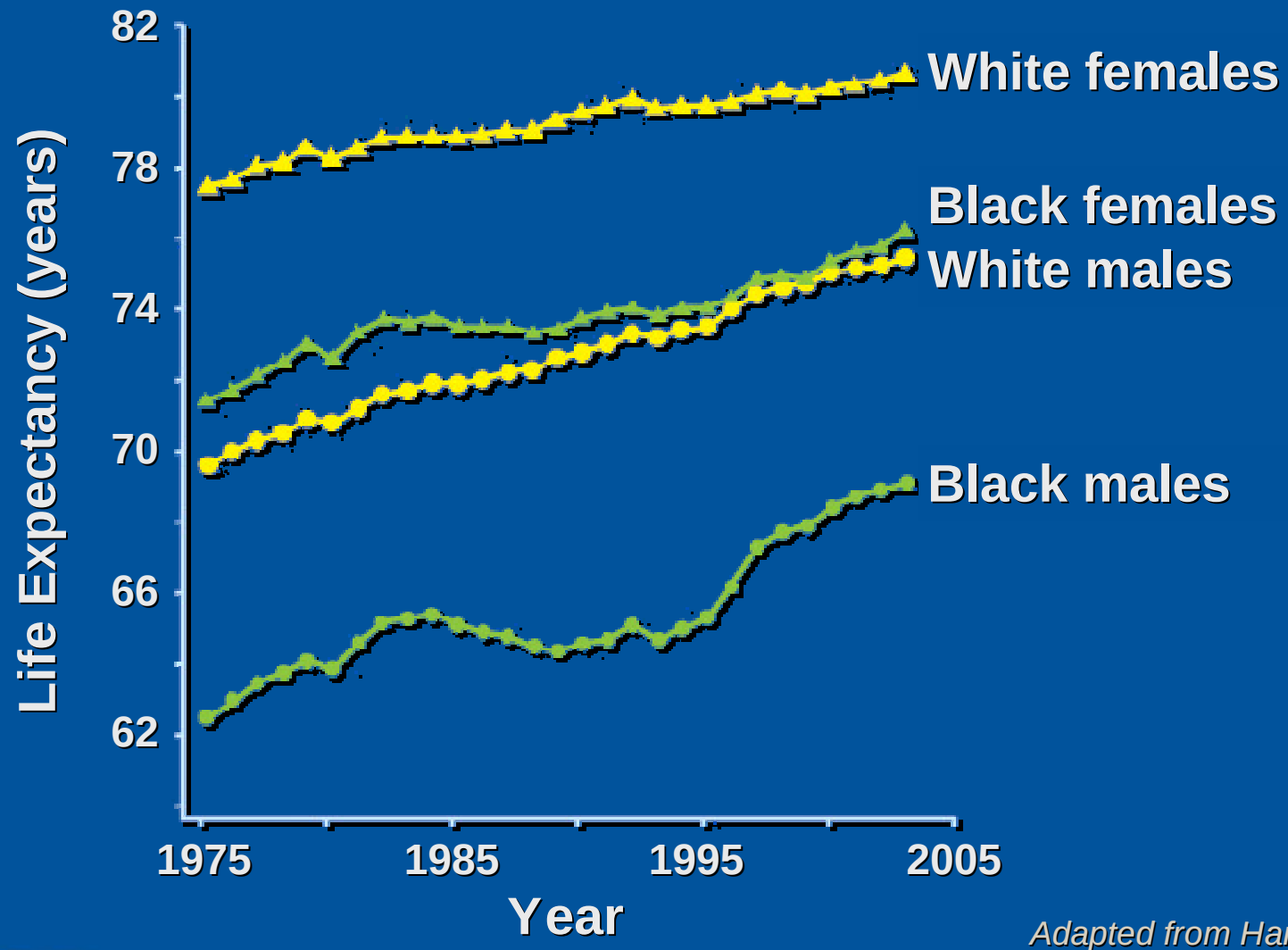
Basic Discovery → Preclinical Research → PD/PK/ Toxicology → Proof of Concept In Man → Phase II, III and IV → Health Service and Outcomes Research → Guidelines And Adoption → Community Health Trends → Global Health Research and Service

Current Timeline 25-30 Years

Mortality in the 20th Century

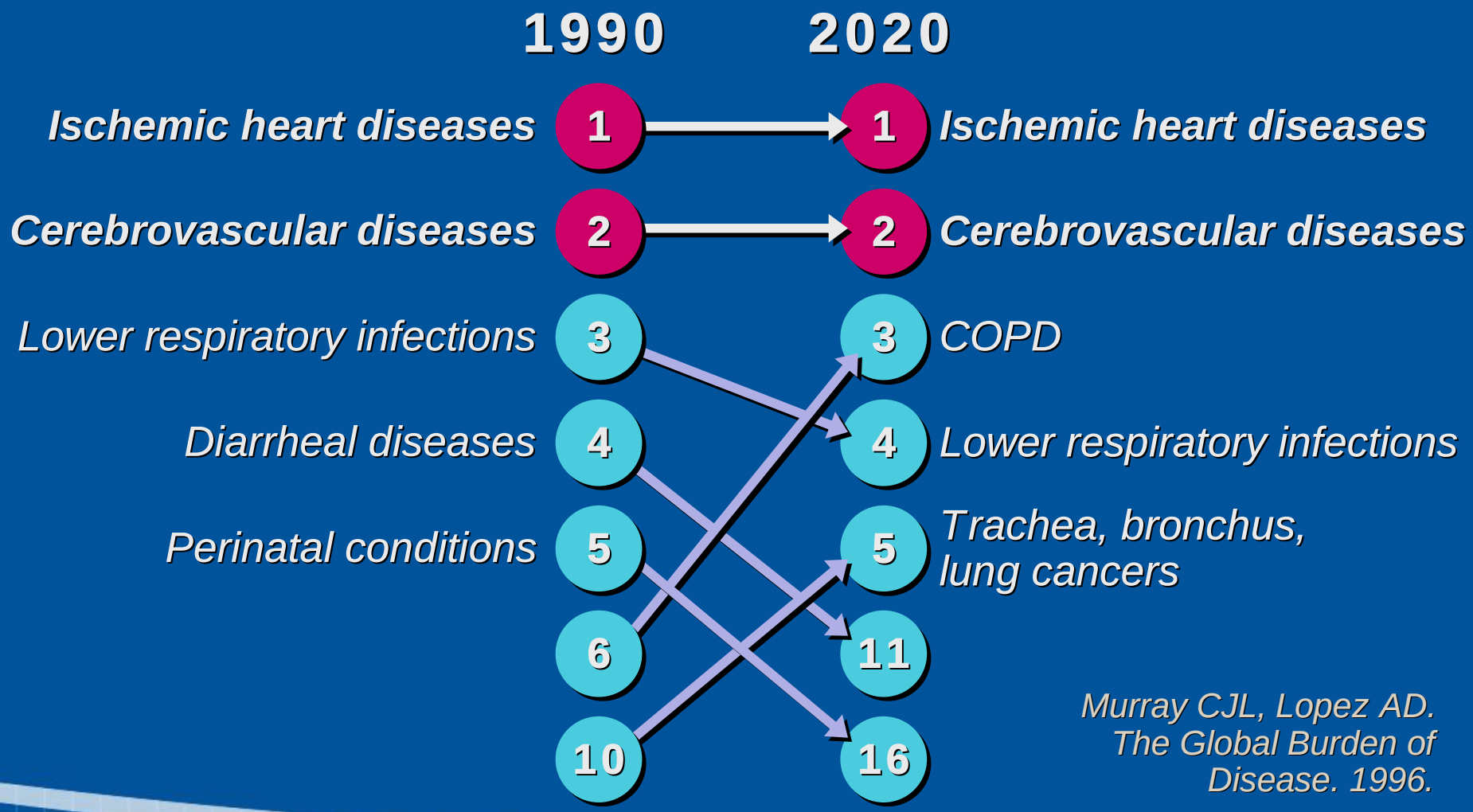


Life Expectancy at Birth



Adapted from Harper et al, JAMA 2007;297:1224–1232

Leading Causes of Death



Murray CJL, Lopez AD. The Global Burden of Disease. 1996.

The Fundamental Nature of the Problem

- **Drugs and biologics**
  - Going after a new target gives a bigger potential payout to investors
  - Going after a previously proven target gives a much higher probability of success
  - The net effect is that “follow-ons” are a better bet on average
- **Health services**
  - The investment needed to change current practice is enormous
- **The intersection of diagnostic testing and therapeutics has uncertain regulatory status with poor reimbursement prospects**

Changing the Health Care System

Internet

Consumerism

IT

"-omics"

Medical technology

Congress

Pressures *for* change

Regulation

Financing

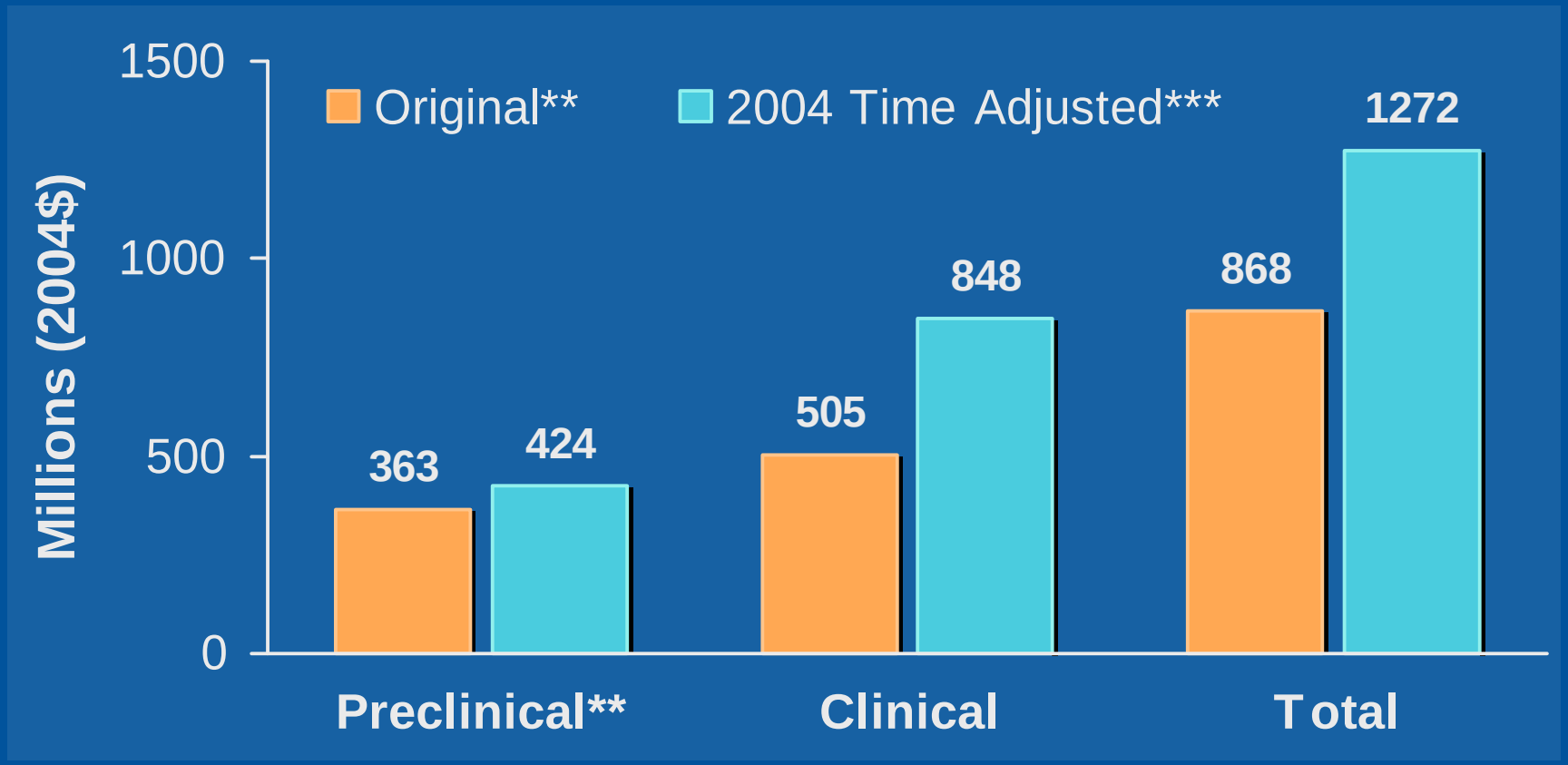
Fragmented marketplace

Professional autonomy

Congress

Pressures *against* change

Comparative Pre-Approval Capitalized Costs per Approved New Molecule

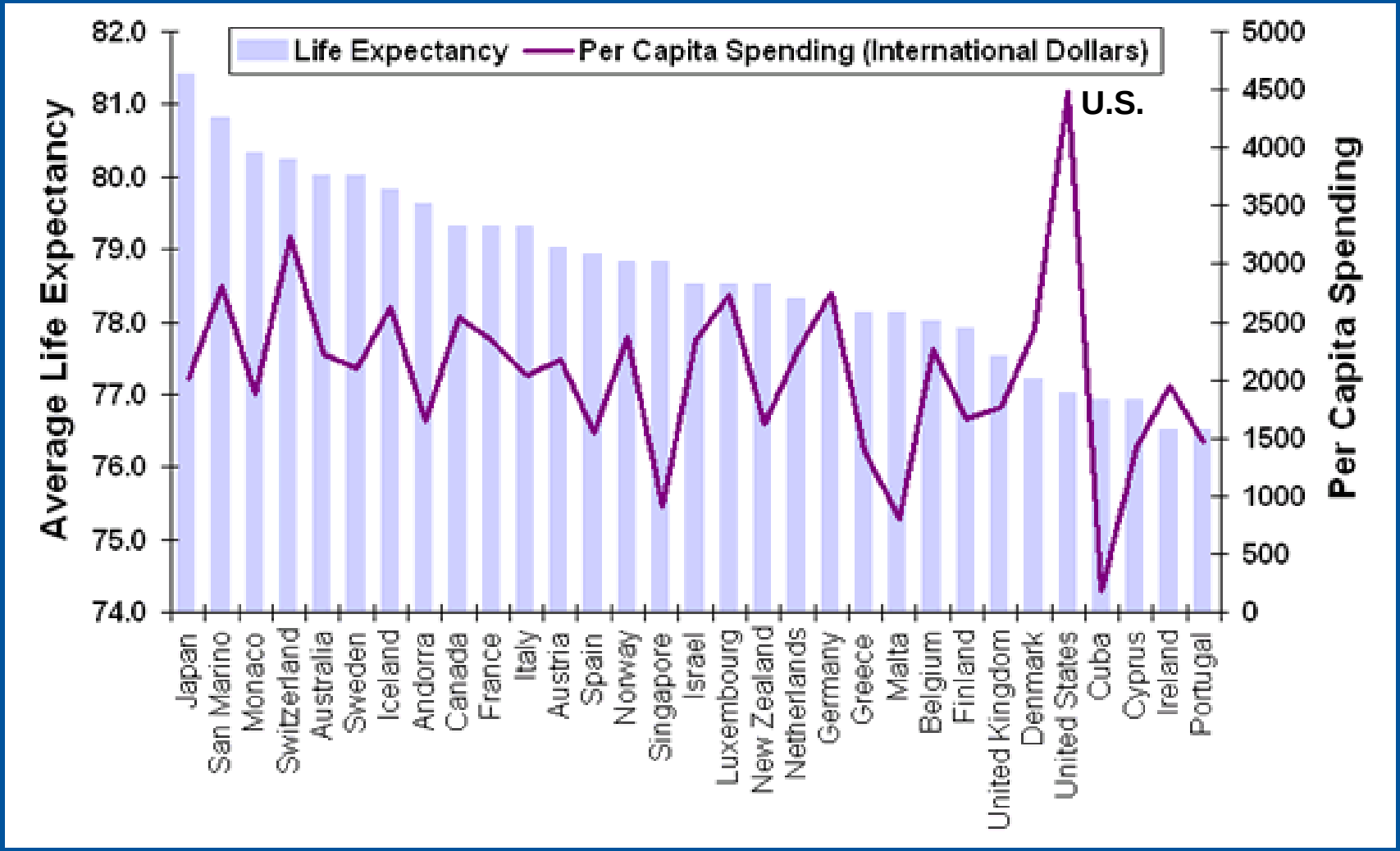


*** All R&D costs (basic research and preclinical development) prior to initiation of clinical testing*

**** Based on a 5-year shift and prior growth rates for the preclinical and clinical periods*

DiMasi et al. 2003

The Cost of a Long Life



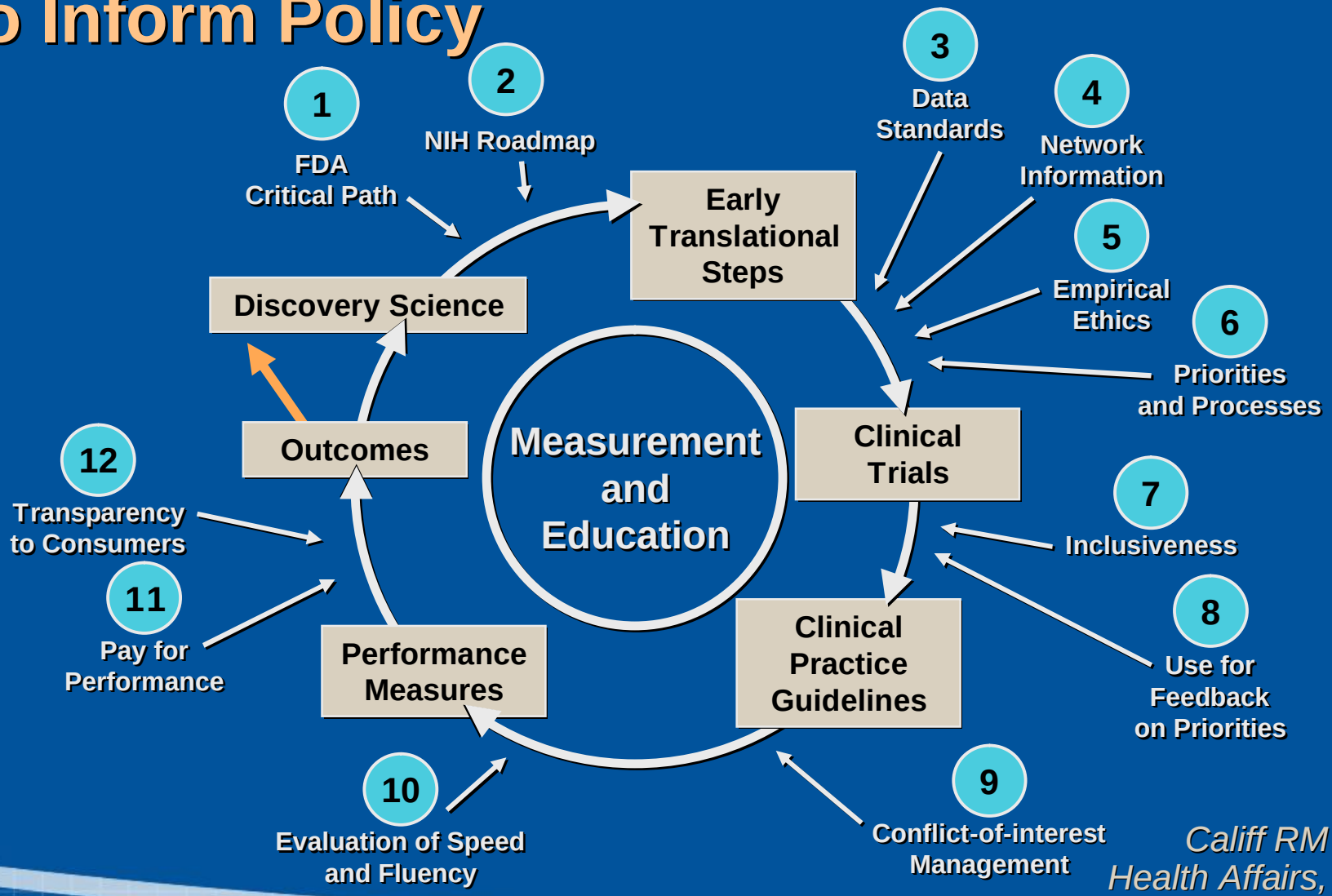
UC Project for Global Inequality

DTMI

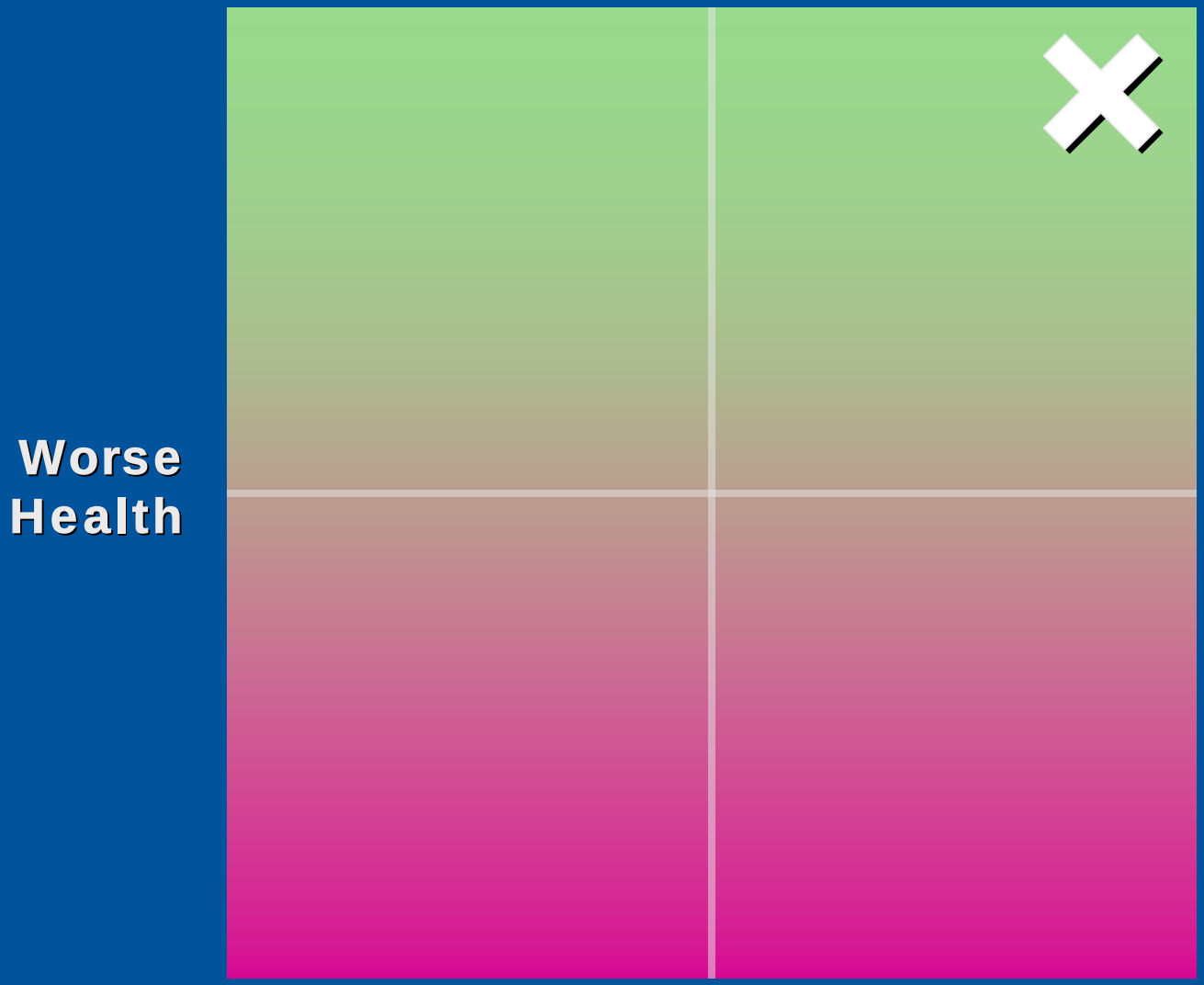
Transforming Medicine


WE
WANT
YOU...
To practice evidence-based medicine

The Cycle of Quality: Generating Evidence to Inform Policy

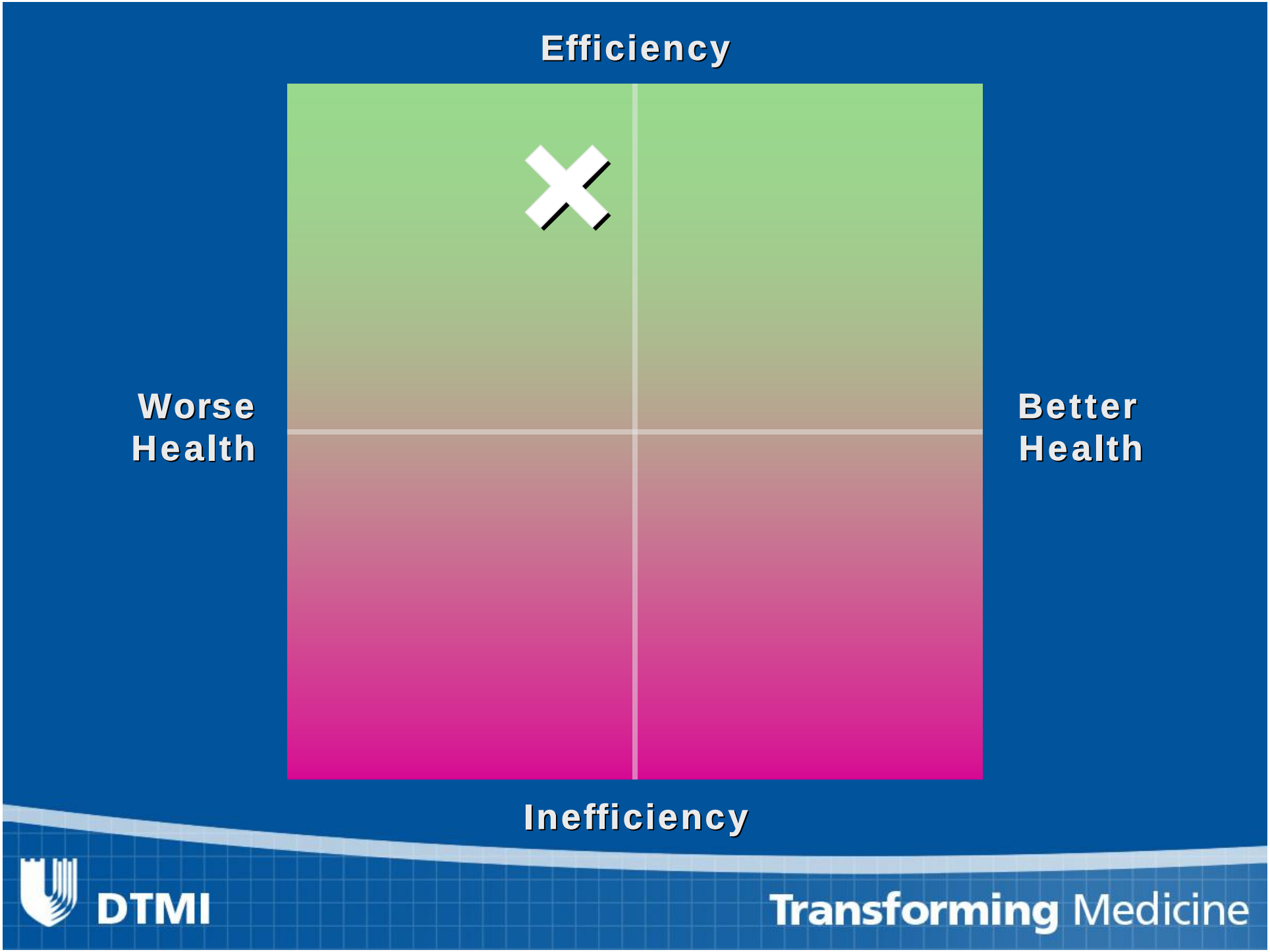


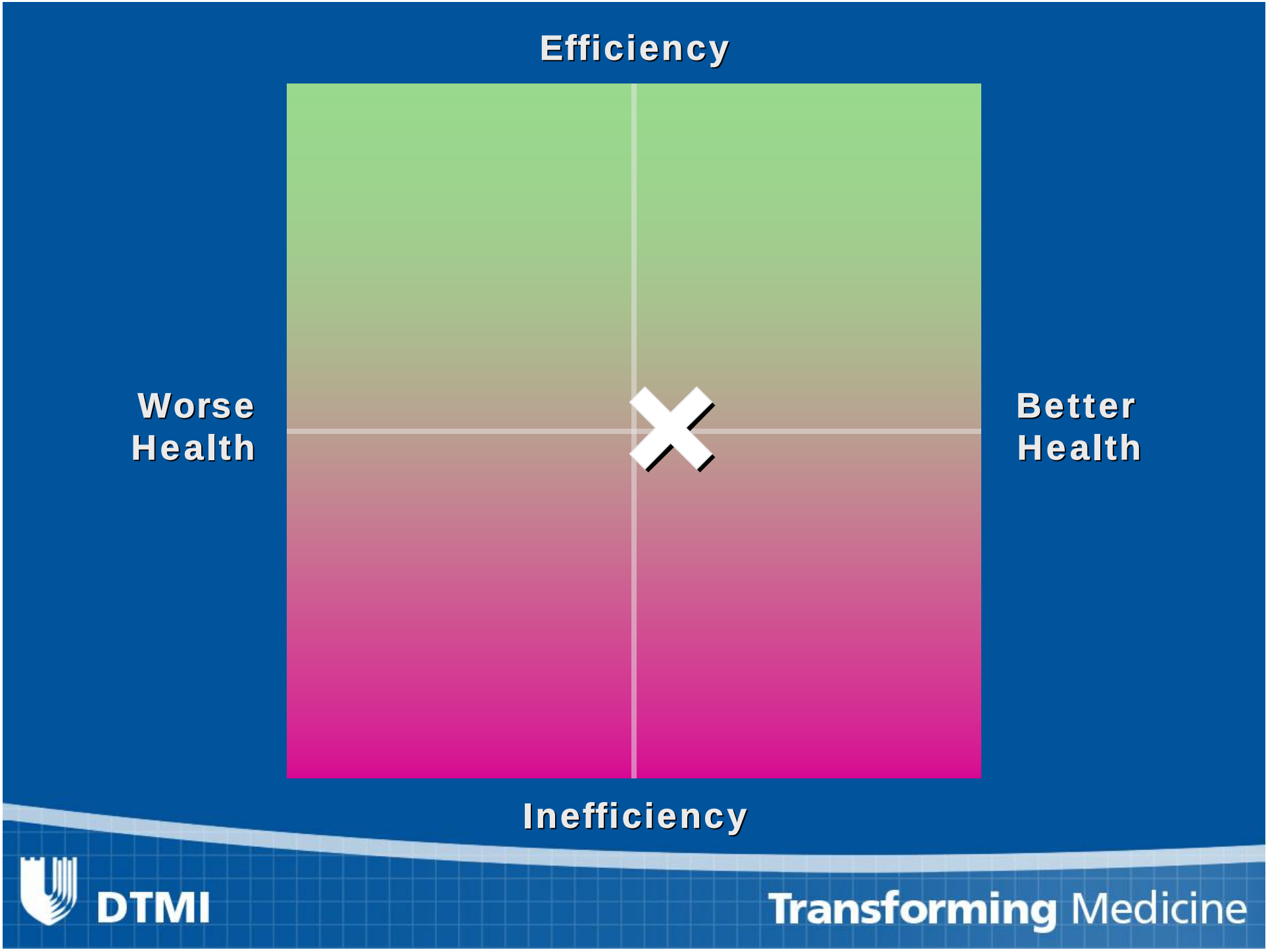
Califf RM et al, Health Affairs, 2007



DTMI

Transforming Medicine


Efficiency
Worse Health
Better Health
Inefficiency



DTMI

Transforming Medicine

First block:

Translation from concept into first human studies

Second block:

Translation from clinical trials into practice

"The Valley of Death"

- **Space between target discovery and first evidence of proof of concept in humans**
- **Investment interest low**
- **Large gap between scientific advance and predictive regulatory science**
- **Decision making dominated by anecdote and intuition**

  Predictive models impossible without sharing of knowledge about failures

- **Need to define the "precompetitive" and "procompetitive" spaces**

Shared Knowledge and Competition

- **Precompetitive**

  Knowledge that advances a field before the point at which competition based on proprietary knowledge is in play

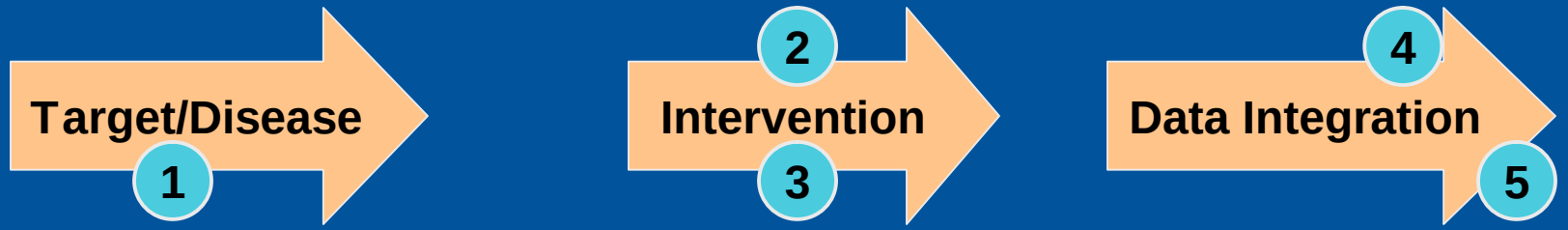
- **Procompetitive**

  Knowledge that “levels the playing field” by causing “a rising tide for all ships” in the midst of other proprietary knowledge that provides a competitive advantage

Early Phase Human Studies

- **Many discoveries fail because of unanticipated off-target effects that are only detected in later phase testing**
- **Traditional pK/pD will not solve this problem**
  - But of course pK/pD is a basal necessity
- **We need new approach involving experimental medicine units that enable systems measurement in humans**
  - Integrated physiology—more extensive monitoring
  - Genomic profiling—requires sharing of data
  - Functional imaging—very big technology

How will DCRU Enhance Early Phase Clinical Trials and Patient Care? Or What Do We Really Want to Do?

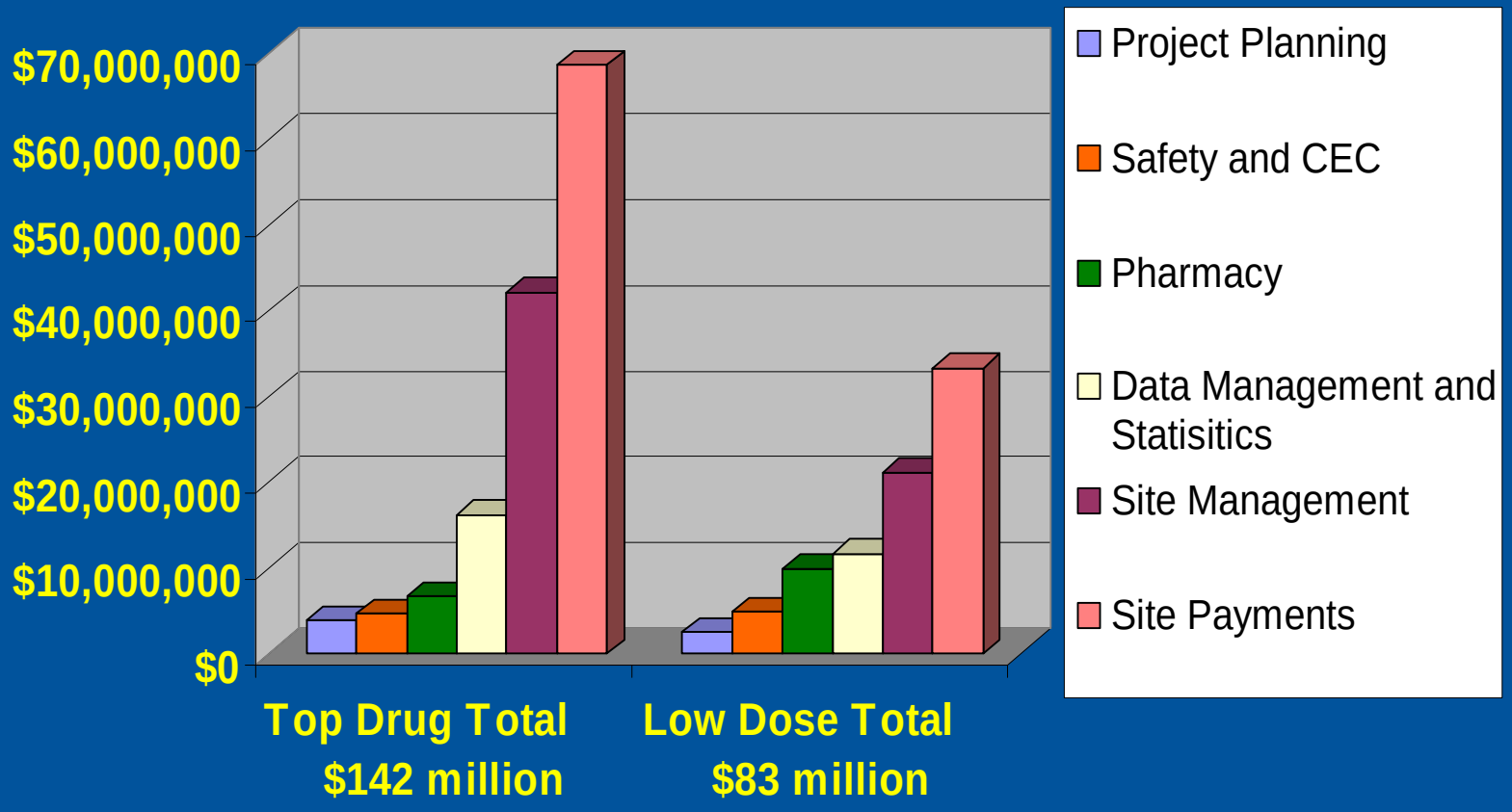


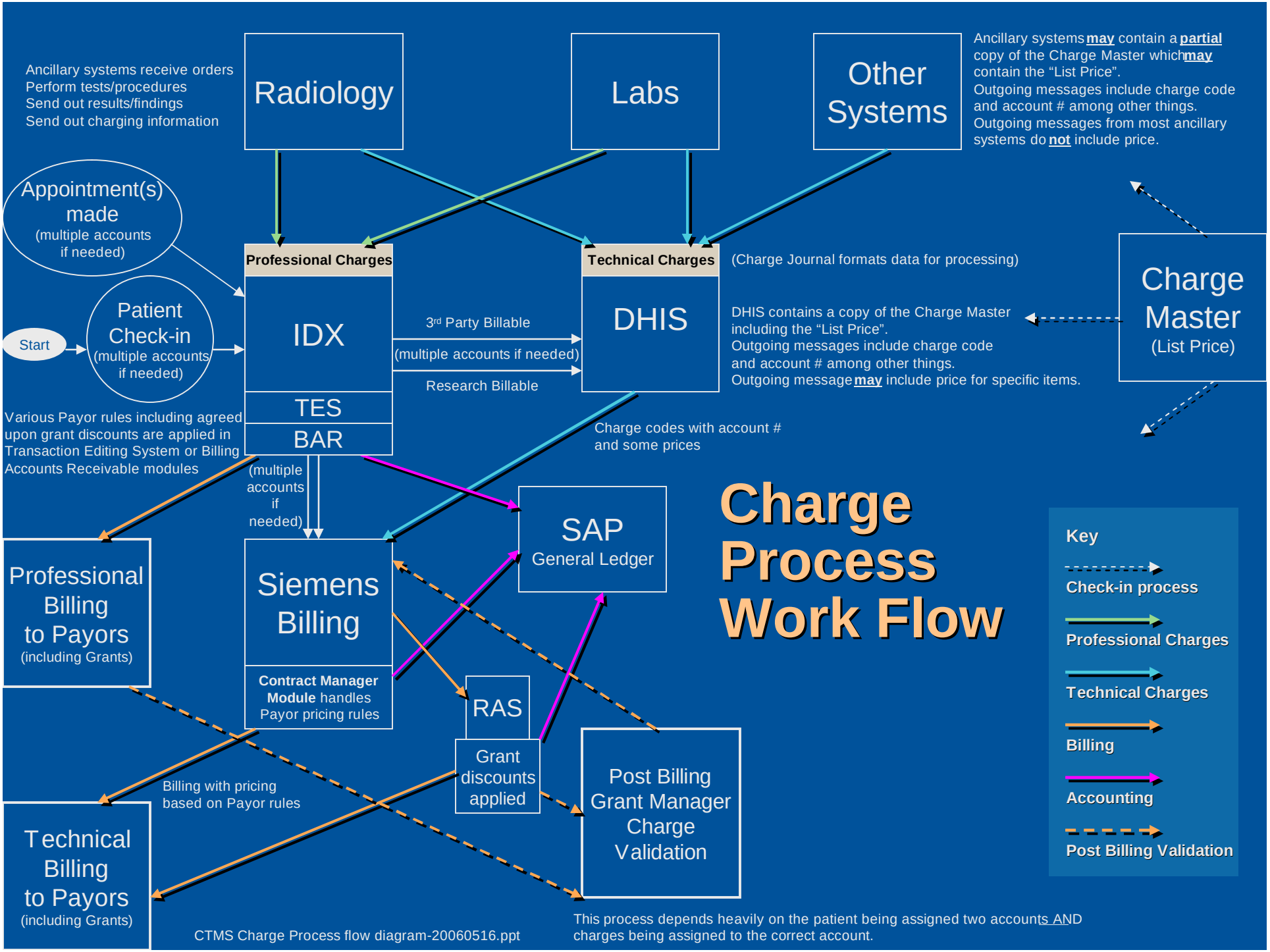
- Research Tool Box
- Patient populations highly characterized
- IT & Bioinformatics deployed to collate and organize the array of results so they can be interpreted through statistical advice and analysis of what can be done
- Better biological understanding of response
- Define novel biological targets
- Early response
- New Research Methodologies
- Toxicity

Clinical Trials

- Way too expensive (especially in US)
- Way too slow (especially in US)
- ? Quality without standard definitions for quality
- Results: high cost of Phase 3a/b clinical trials becomes inhibiting factor for areas requiring definitive data prior to marketing

Estimated Trial Costs




Ancillary systems receive orders
Perform tests/procedures
Send out results/findings
Send out charging information
Radiology
Labs
Other Systems
Ancillary systems may contain a partial copy of the Charge Master which may contain the "List Price".
Outgoing messages include charge code and account # among other things.
Outgoing messages from most ancillary systems do not include price.
Appointment(s) made
(multiple accounts if needed)
Professional Charges
Technical Charges
(Charge Journal formats data for processing)
Charge Master
(List Price)
Patient Check-in
(multiple accounts if needed)
Start
IDX
3rd Party Billable
(multiple accounts if needed)
Research Billable
DHIS
DHIS contains a copy of the Charge Master including the "List Price".
Outgoing messages include charge code and account # among other things.
Outgoing message may include price for specific items.
TES
BAR
Various Payor rules including agreed upon grant discounts are applied in Transaction Editing System or Billing Accounts Receivable modules
Charge codes with account # and some prices
(multiple accounts if needed)
SAP
General Ledger
Professional Billing to Payors
(including Grants)
Siemens Billing
Contract Manager Module handles Payor pricing rules
RAS
Grant discounts applied
Billing with pricing based on Payor rules
Post Billing Grant Manager Charge Validation
Technical Billing to Payors
(including Grants)
Charge Process Work Flow
Key
Check-in process
Professional Charges
Technical Charges
Billing
Accounting
Post Billing Validation
CTMS Charge Process flow diagram-20060516.ppt
This process depends heavily on the patient being assigned two accounts AND charges being assigned to the correct account.

FDA Critical Path PPP: Clinical Trials Transformation Initiative (CTTI)

- **First meeting on October 11th**
- **Develop FDA white papers to inform policies**
- **Goals**
  - Enhance regulations that improve the quality of clinical trials
  - Eliminate guidances and practices that increase costs but provide no value
  - Empirical study of the value of guidances and practices
- **Key players**
  - FDA, industry, academia, patient advocates, non-academic clinical research professionals

Post-Marketing Translation

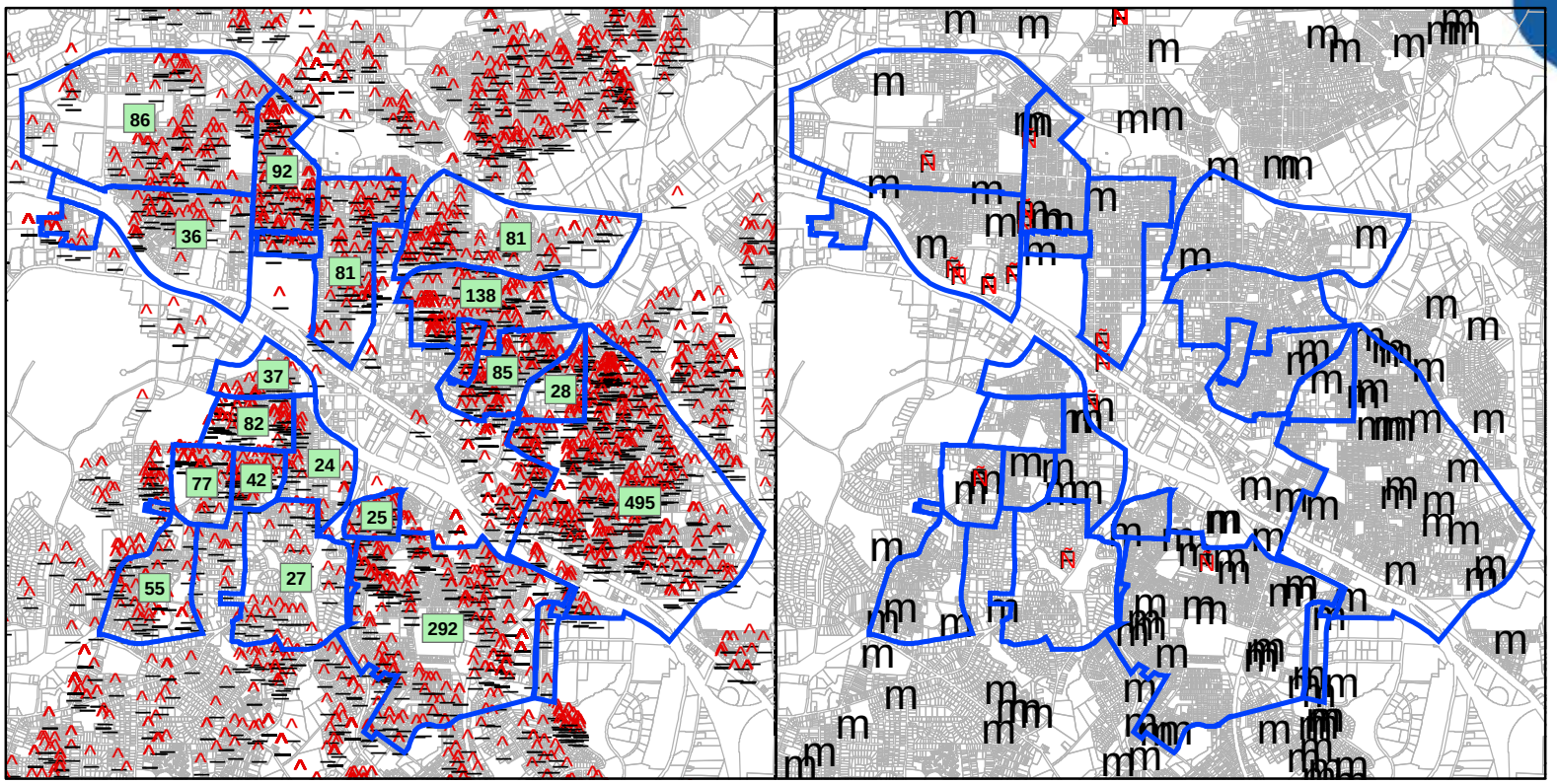
- **Dearth of funding except for industry funded trials**
- **Most of these trials are attempting to expand market with NPV metric using current reimbursement system (trial won't be done unless the pre-test probability of a positive result for the sponsor is very good)**
- **Little public funding for creation of novel (disruptive) systems**

  Reagan-Udall Center at FDA

  ? CTSA/strengthening AHRQ

Public and Global Health

- **Increasing similarities notable between US issues and global issues**
- **Financial rewards detract from providing needed health services**
- **Health systems heavily and increasingly incentivized to cater to the expensive technology needs of paying customers**
  - Out of pocket diagnostic testing and prevention
  - Procedures and pictures for insured



Legend

2001 Births

Number of Neighborhood Births in 2001

Central Durham Neighborhoods

Doctors Offices

Day Care

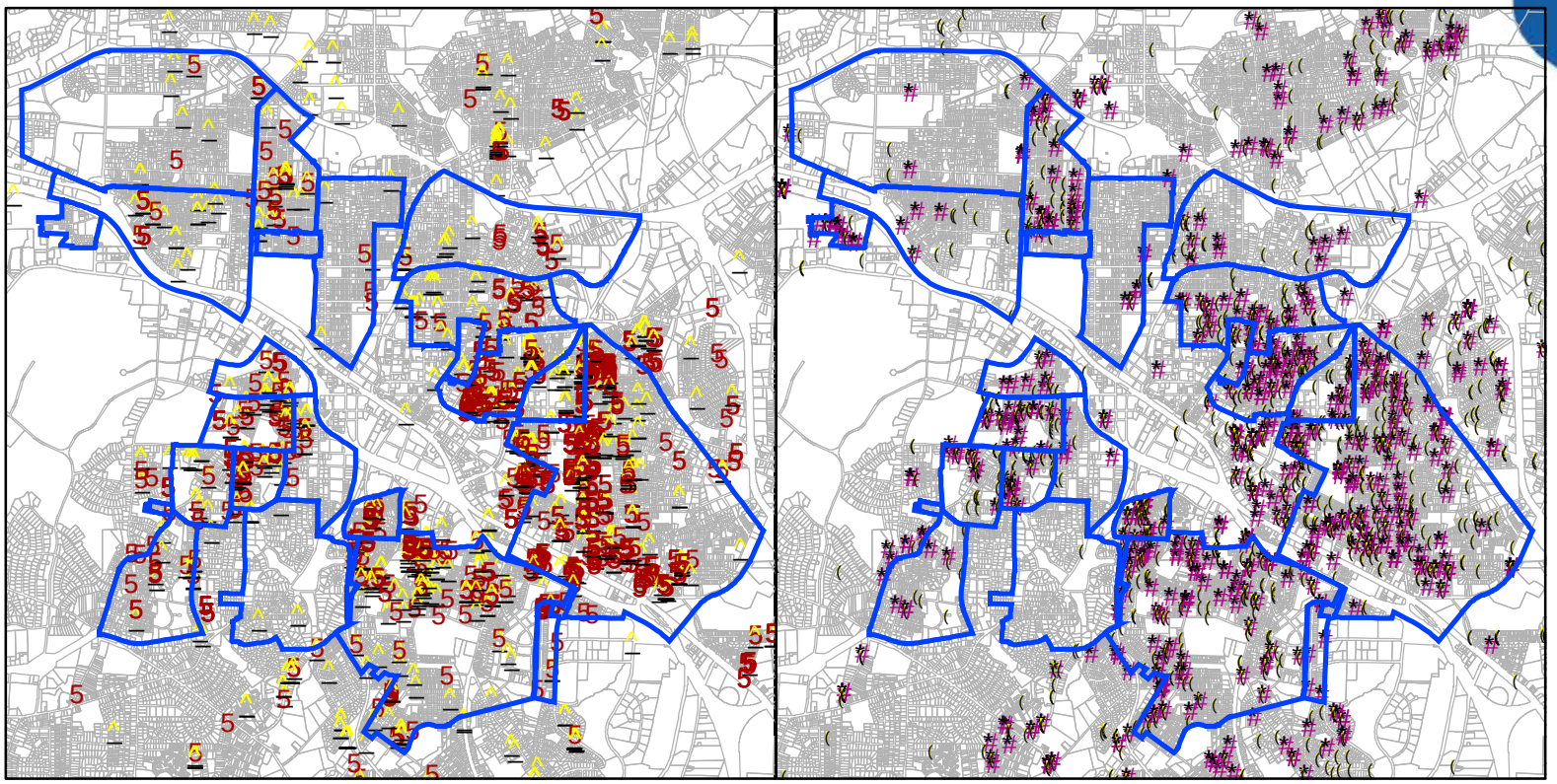
N

W

S

CEHI

Children's Environmental Health Initiative



Legend

2002 Housing Code Enforcements

- Complaint Initiated
- 5 Inspector Initiated

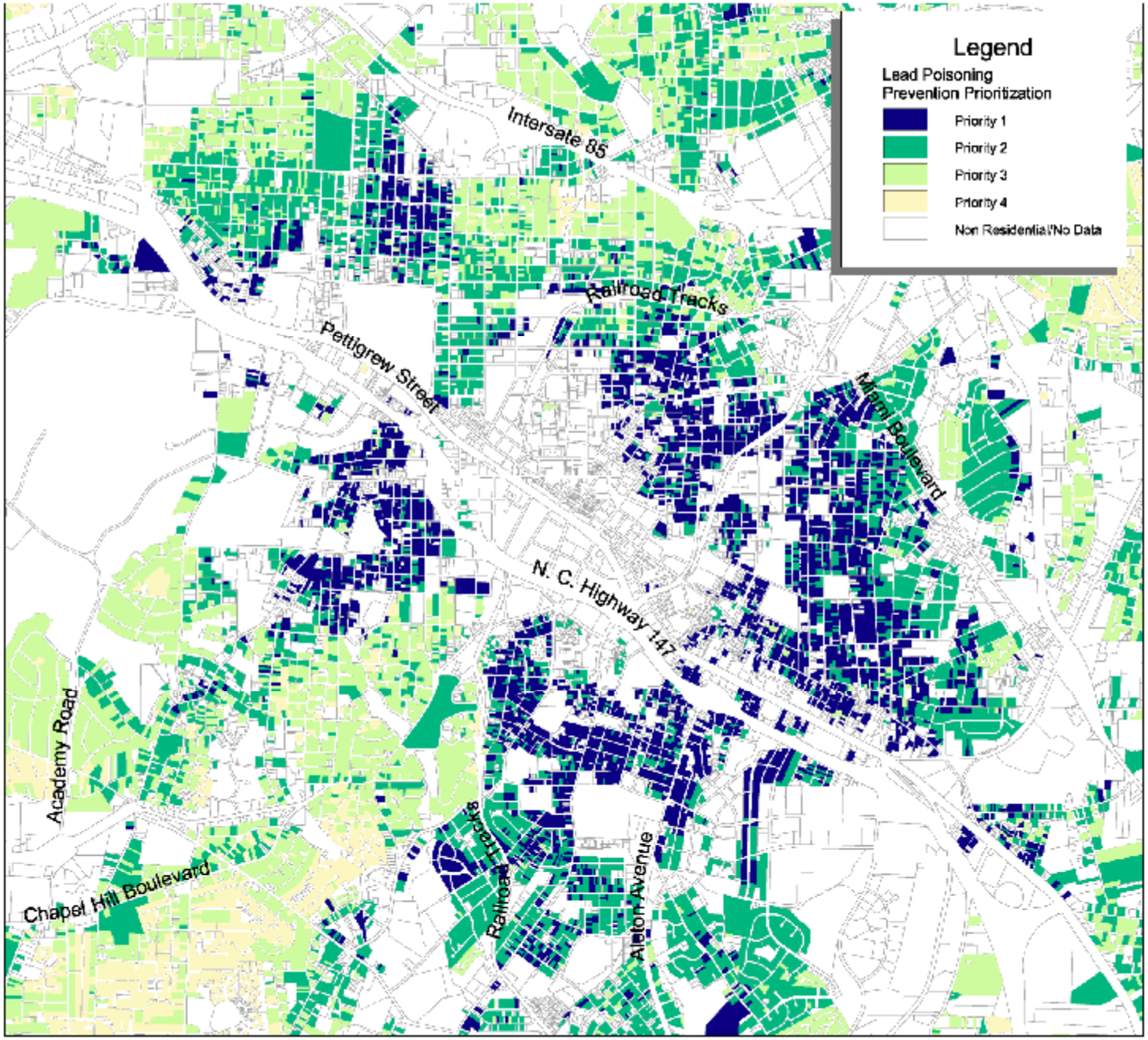
2002 Arrestee Addresses

- (Assault Arrests
- # Drug Related Arrests

Central Durham Neighborhoods

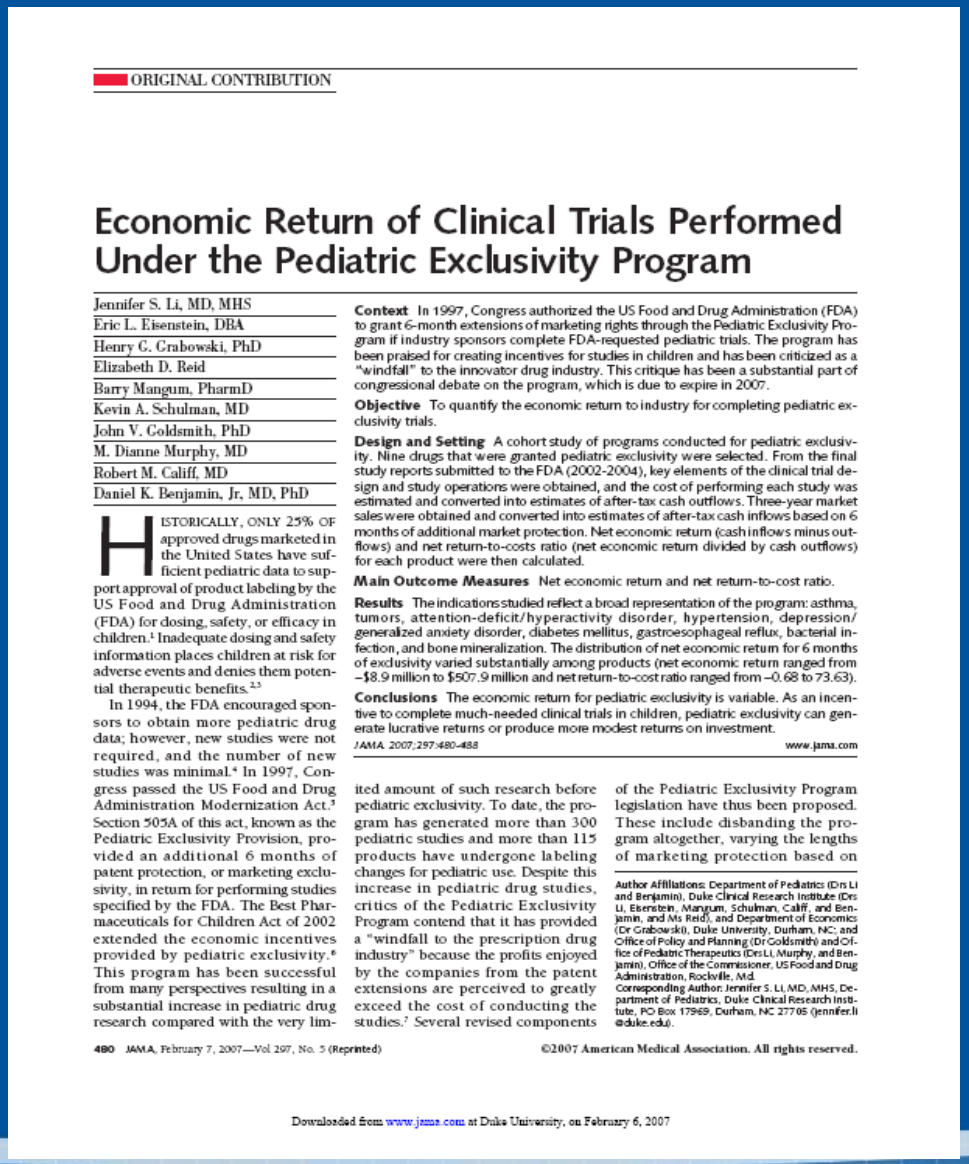
N W CEHI S

Children's Environmental Health Initiative


Legend
Lead Poisoning
Prevention Prioritization
Priority 1
Priority 2
Priority 3
Priority 4
Non Residential/No Data
Intersate 85
Railroad Tracks
Pettigrew Street
Main Boulevard
N. C. Highway 147
Academy Road
Chapel Hill Boulevard
Railroad Tracks
Alston Avenue

Pediatric FDA meta-research

- Pediatric exclusivity has stimulated an unprecedented number of drug studies in children (138 labeling changes to date)
- Objective: To quantify economic return to industry for 6 mos of pediatric exclusivity
- 9 drugs studied; net economic return and net return to cost ratios evaluated
- Median cost per written request $12.34 million
- Large variability in net economic return (-$8.9 million to $507.9 million) and net return to cost ratio (-0.68 to 73.63)



ORIGINAL CONTRIBUTION

Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program

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Elizabeth D. Reid
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Daniel K. Benjamin, Jr, MD, PhD

Context In 1997, Congress authorized the US Food and Drug Administration (FDA) to grant 6-month extensions of marketing rights through the Pediatric Exclusivity Program if industry sponsors complete FDA-requested pediatric trials. The program has been praised for creating incentives for studies in children and has been criticized as a "windfall" to the innovator drug industry. This critique has been a substantial part of congressional debate on the program, which is due to expire in 2007.

Objective To quantify the economic return to industry for completing pediatric exclusivity trials.

Design and Setting A cohort study of programs conducted for pediatric exclusivity. Nine drugs that were granted pediatric exclusivity were selected. From the final study reports submitted to the FDA (2002-2004), key elements of the clinical trial design and study operations were obtained, and the cost of performing each study was estimated and converted into estimates of after-tax cash outflows. Three-year market sales were obtained and converted into estimates of after-tax cash inflows based on 6 months of additional market protection. Net economic return (cash inflows minus outflows) and net return-to-costs ratio (net economic return divided by cash outflows) for each product were then calculated.

Main Outcome Measures Net economic return and net return-to-cost ratio.

Results The indications studied reflect a broad representation of the program: asthma, tumors, attention-deficit/hyperactivity disorder, hypertension, depression/generalized anxiety disorder, diabetes mellitus, gastroesophageal reflux, bacterial infection, and bone mineralization. The distribution of net economic return for 6 months of exclusivity varied substantially among products (net economic return ranged from −$8.9 million to $507.9 million and net return-to-cost ratio ranged from −0.68 to 73.63).

Conclusions The economic return for pediatric exclusivity is variable. As an incentive to complete much-needed clinical trials in children, pediatric exclusivity can generate lucrative returns or produce more modest returns on investment.

JAMA. 2007;297:480-488 www.jama.com

HISTORICALLY, ONLY 25% OF approved drugs marketed in the United States have sufficient pediatric data to support approval of product labeling by the US Food and Drug Administration (FDA) for dosing, safety, or efficacy in children.[1] Inadequate dosing and safety information places children at risk for adverse events and denies them potential therapeutic benefits.[2,3]

In 1994, the FDA encouraged sponsors to obtain more pediatric drug data; however, new studies were not required, and the number of new studies was minimal.[4] In 1997, Congress passed the US Food and Drug Administration Modernization Act.[5] Section 505A of this act, known as the Pediatric Exclusivity Provision, provided an additional 6 months of patent protection, or marketing exclusivity, in return for performing studies specified by the FDA. The Best Pharmaceuticals for Children Act of 2002 extended the economic incentives provided by pediatric exclusivity.[6] This program has been successful from many perspectives resulting in a substantial increase in pediatric drug research compared with the very limited amount of such research before pediatric exclusivity. To date, the program has generated more than 300 pediatric studies and more than 115 products have undergone labeling changes for pediatric use. Despite this increase in pediatric drug studies, critics of the Pediatric Exclusivity Program contend that it has provided a "windfall to the prescription drug industry" because the profits enjoyed by the companies from the patent extensions are perceived to greatly exceed the cost of conducting the studies.[7] Several revised components of the Pediatric Exclusivity Program legislation have thus been proposed. These include disbanding the program altogether, varying the lengths of marketing protection based on

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Corresponding Author: Jennifer S. Li, MD, MHS, Department of Pediatrics, Duke Clinical Research Institute, PO Box 17969, Durham, NC 27705 (jennifer.li@duke.edu).

Pediatric FDA meta-research

- Objective: To quantify the dissemination of results of studies conducted for pediatric exclusivity
- Evaluated 253 studies submitted to FDA from 1998-2004
- Labeling changes positive for 127/253(50%)
- Only 113/253 published
- Efficacy studies and positive labeling change more likely to be published

ORIGINAL CONTRIBUTION

Peer-Reviewed Publication of Clinical Trials Completed for Pediatric Exclusivity

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Lisa Mathis, MD
Debbie Avant, RPh
Robert M. Califf, MD
Jennifer S. Li, MD, MHS

Context Much of pediatric drug use is off-label because appropriate pediatric studies have not been conducted and the drugs have not been labeled by the US Food and Drug Administration (FDA) for use in children. In 1997, Congress authorized the FDA to grant extensions of marketing rights known as "pediatric exclusivity" if FDA-requested pediatric trials were conducted. As a result, there have been over 100 product labeling changes. The publication status of studies completed for pediatric exclusivity has not been evaluated.

Objective To quantify the dissemination of results of studies conducted for pediatric exclusivity into the peer-review literature.

Design Cohort study of all trials conducted for pediatric exclusivity between 1998 and 2004 as determined by MEDLINE and EMBASE searches through 2005, the subsequent labeling changes, and the publication of those studies in peer-reviewed journals. We categorized any labeling changes resulting from the studies as positive or negative for the drug under study. We then evaluated aspects of the studies and product label changes that were associated with subsequent publication in peer-reviewed medical journals.

Main Outcome Measures Publication of the trial data in peer-reviewed journals.

Results Between 1998 and 2004, 253 studies were submitted to the FDA for pediatric exclusivity: 125 (50%) evaluated efficacy, 51 (20%) were multi-dose pharmacokinetic, 34 (13%) were single-dose pharmacokinetic, and 43 (17%) were safety studies. Labeling changes were positive for 127/253 (50%) of studies; only 113/253 (45%) were published. Efficacy studies and those with a positive labeling change were more likely to be published.

Conclusions The pediatric exclusivity program has been successful in encouraging drug studies in children. However, the dissemination of these results in the peer-reviewed literature is limited. Mechanisms to more widely disperse this information through publication warrant further evaluation.

JAMA. 2006;296:1266-1273 www.jama.com

FOR A PRODUCT TO BE MARKETED in the United States, the sponsor must submit adequate and well-controlled trials that demonstrate the efficacy and safety of the product when used as intended to the US Food and Drug Administration (FDA). These trials are the basis of the labeling or package insert instructions that are provided for each product that is approved by the FDA. Children are usually not included in most product submission studies and therefore, the data on dosing, efficacy, and safety that are available for adults are not usually available for pediatric patients. Other data may be available but are often not from the same type of rigorous clinical trials. Historically, 75% of drug products have insufficient labeling information for pediatric dosing, safety, or efficacy.

Inadequate dosing and safety information places children at risk for adverse events and denies them potential therapeutic benefits. Physicians who care for children have therefore, been forced to either withhold treatment shown to be effective in older patients or provide drugs to children in whom the dose, efficacy, and safety have not been studied. This prescription practice is known as off label use because there is not adequate pediatric information in the labeling. This off-label use may result in benefit, no effect, or harm, depending on how much other information about use of the product in the pediatric population is available. The lack of information has had a negative impact on pediatric therapeutics, including reliance on anecdotal practice patterns and adaptation of data from adult trials that may not be applicable to children.

Congress passed the Food and Drug Administration Modernization Act in 1997. One component of this act is the authorization of a pediatric exclusivity process, whereby the study of therapies used in children, and potentially of use in pediatrics, is encouraged via

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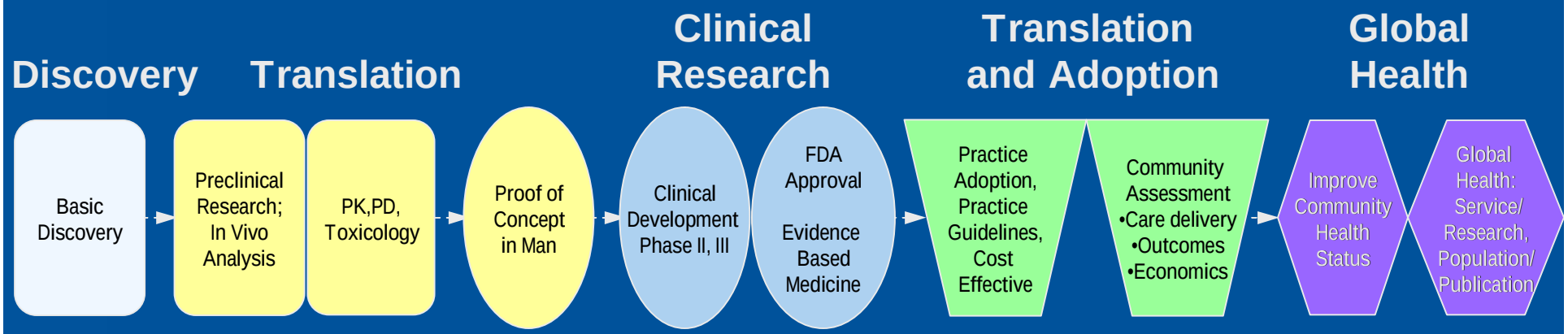
Translation of Innovations



Current State Entities

AHS/Industry/ Biotech	Industry/Biotech	Clinical Research Organizations/AHS	HCS/Hospitals/ Practices/FQHC/AHS	Government NGOs

Fragmented/Disorganized

Basic Discovery → Preclinical Research → PD/PK/ Toxicology → Proof of Concept In Man → Phase II, III and IV → Health Service and Outcomes Research → Guidelines And Adoption → Community Health Trends → Global Health Research and Service

Current Timeline 25-30 Years