

What is Translational Research: A Review of the Clinical and Translational Research Continuum

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Richard Sean Stack MD Distinguished Professor
Director, Duke Clinical Research Institute
Duke University Medical Center





Conflict of Interest Reporting: Relationships with Industry

- I direct a large clinical research group at Duke (> 220 faculty and > 1200 staff). The DCRI is an Institute within the Duke School of Medicine; I report to the Dean of the Medical School and the Vice Chancellor for Clinical Research.
- DCRI receives funding from multiple sources: government, professional societies, foundations and private industry.
- Industry funding accounts for approximately 60% of annual research funding through the DCRI.
- Full details on my relationships with industry are available on the DCRI public website:
 - ***<http://www.dcri.duke.edu/research/coi.jsp>***



Translational Research: Topics to Cover

- Definitions
- Key societal issues and themes
- Role of Academic Health Systems
- A few examples

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Translational research

From Wikipedia, the free encyclopedia

Translational research is another term for translative research and [translational science](#), although it fails to disambiguate itself from forms of research that are not scientific (e.g., market research), which are currently considered outside its scope. Translational research is a way of thinking about and conducting scientific research to make the results of research applicable to the population under study and is practised in the natural and biological, behavioural, and social sciences. In the field of medicine, for example, it is used to translate the findings in basic research more quickly and efficiently into medical practice and, thus, meaningful health outcomes, whether those are physical, mental, or social outcomes. In medicine in particular, governmental funders of research and [pharmaceutical](#) companies have spent vast amounts internationally on basic research and have seen that the [return on investment](#) is significantly less than anticipated. Translational research has come to be seen as the key, missing component.

With its focus on removing barriers to multi-disciplinary collaboration, translational research has the potential to drive the advancement of applied science. An attempt to bridge these barriers has been undertaken particularly in the medical domain where the term [translational medicine](#) has been applied to a research approach that seeks to move "from bench to bedside" or from laboratory experiments through clinical trials to actual point-of-care patient applications. However, the term [translational medicine](#) is a misnomer, as medicine is not a science: it is the clinical practice of healing the given individual whereas science addresses principles and populations. This distinction is the primary reason that science needs to be translated at all. "Translational medicine" would best be termed "Translational medical science".



Report of the Translational Research Working
Group of the National Cancer Advisory Board

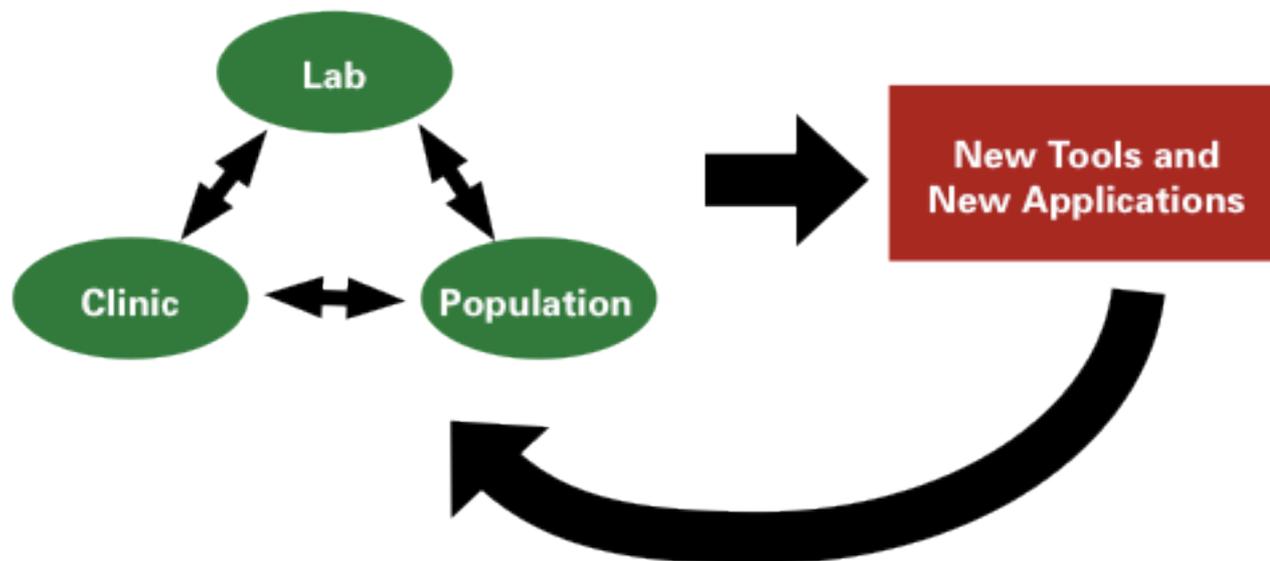
**Transforming Translation—
Harnessing Discovery
for Patient and Public Benefit**





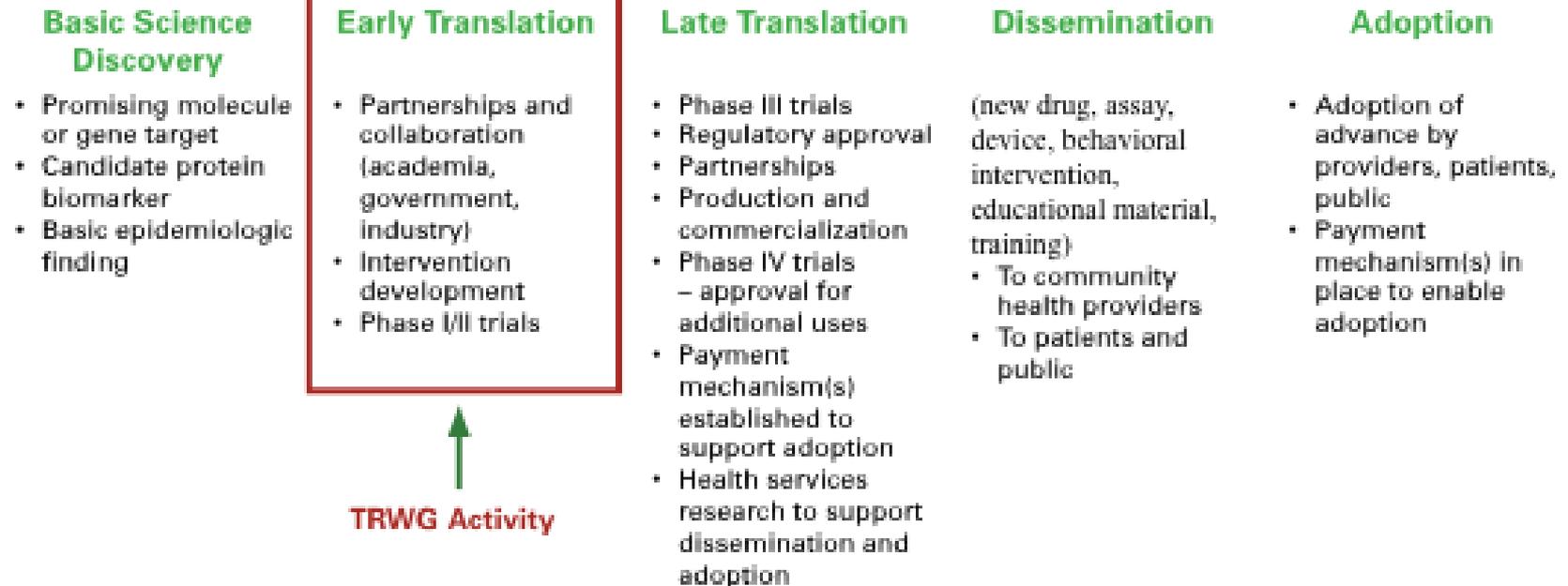
Appendix B: TRWG Translational Research Definition and Scope of Activity

“Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality.”

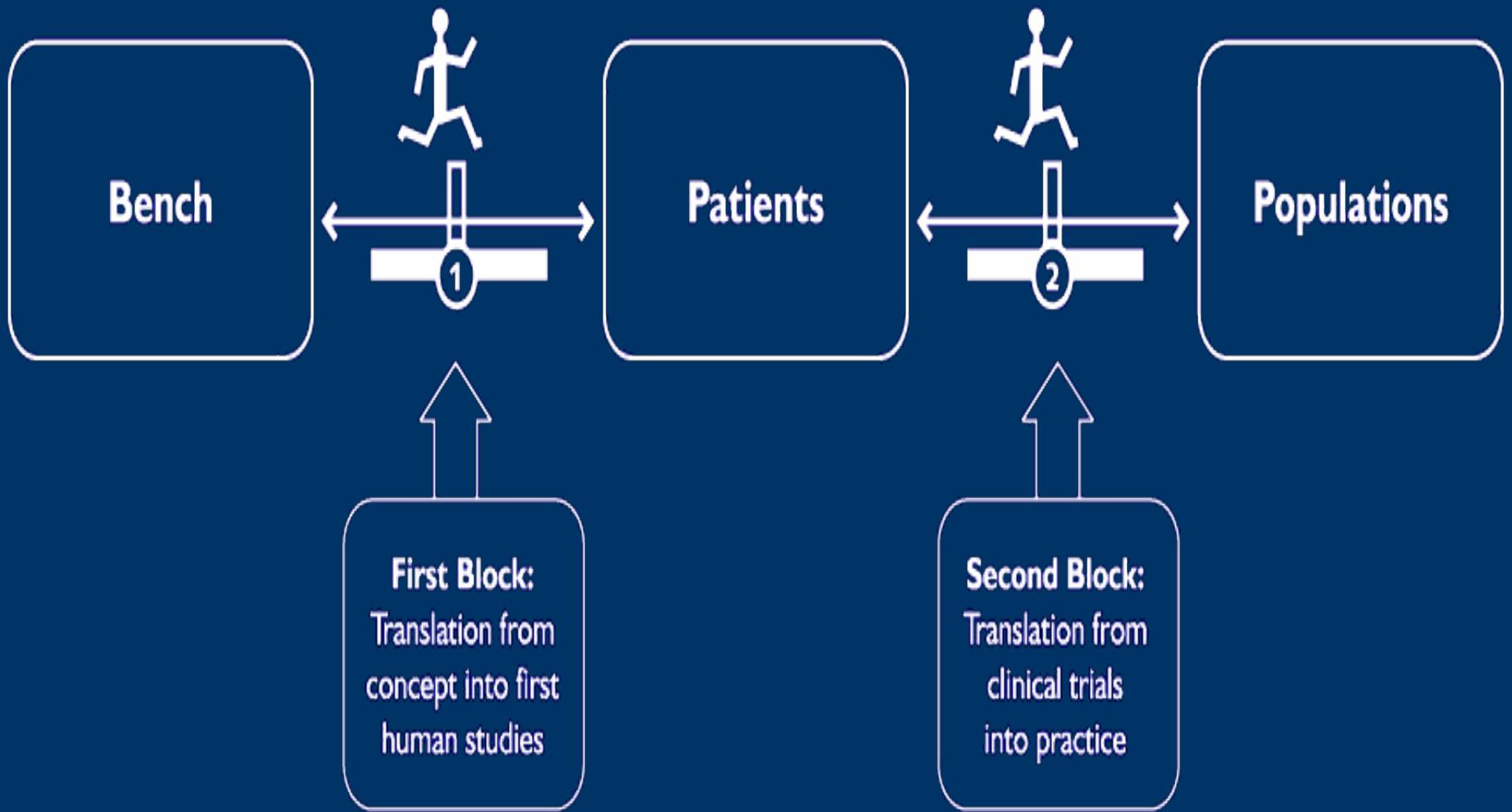


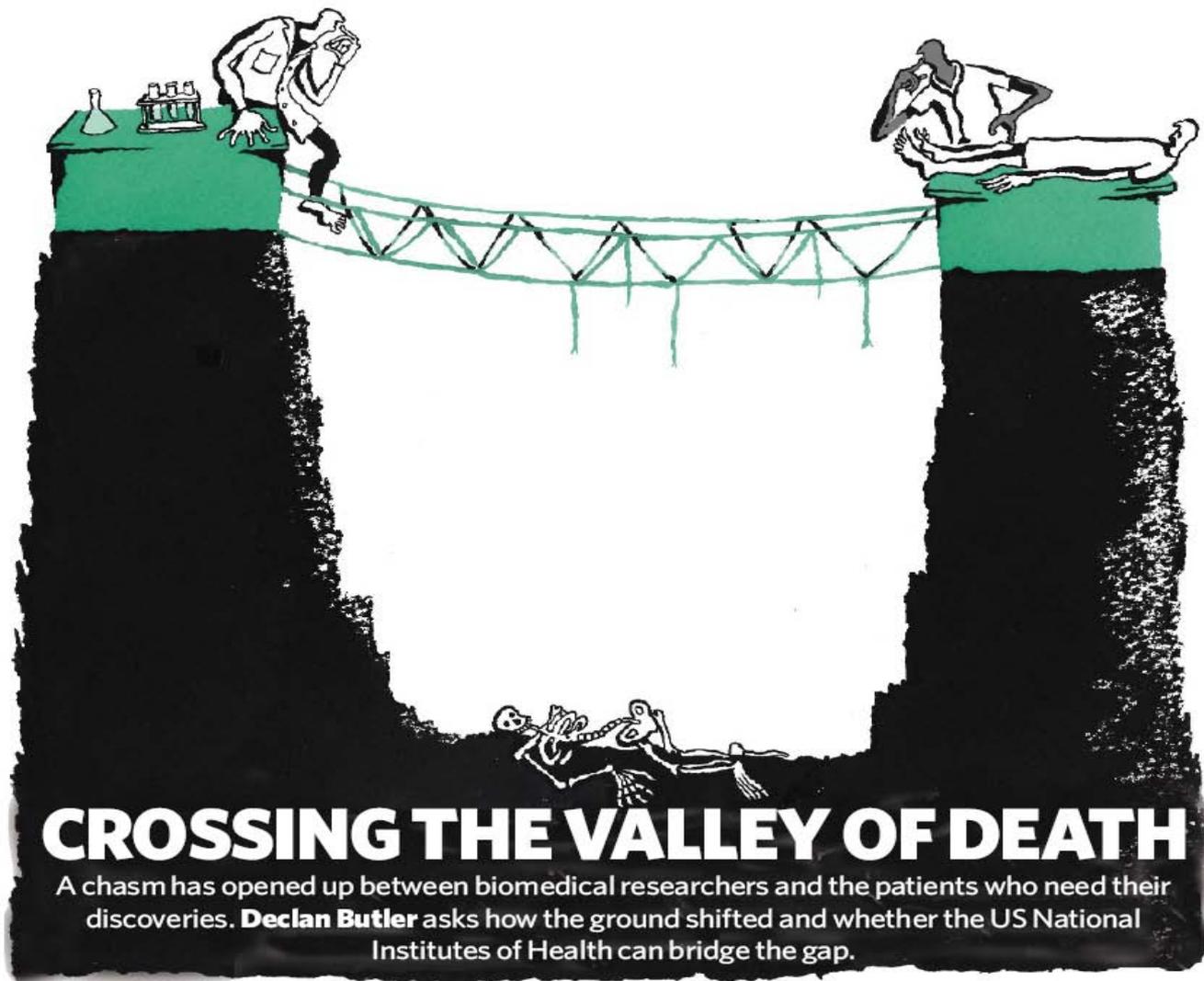


The Translational Continuum*

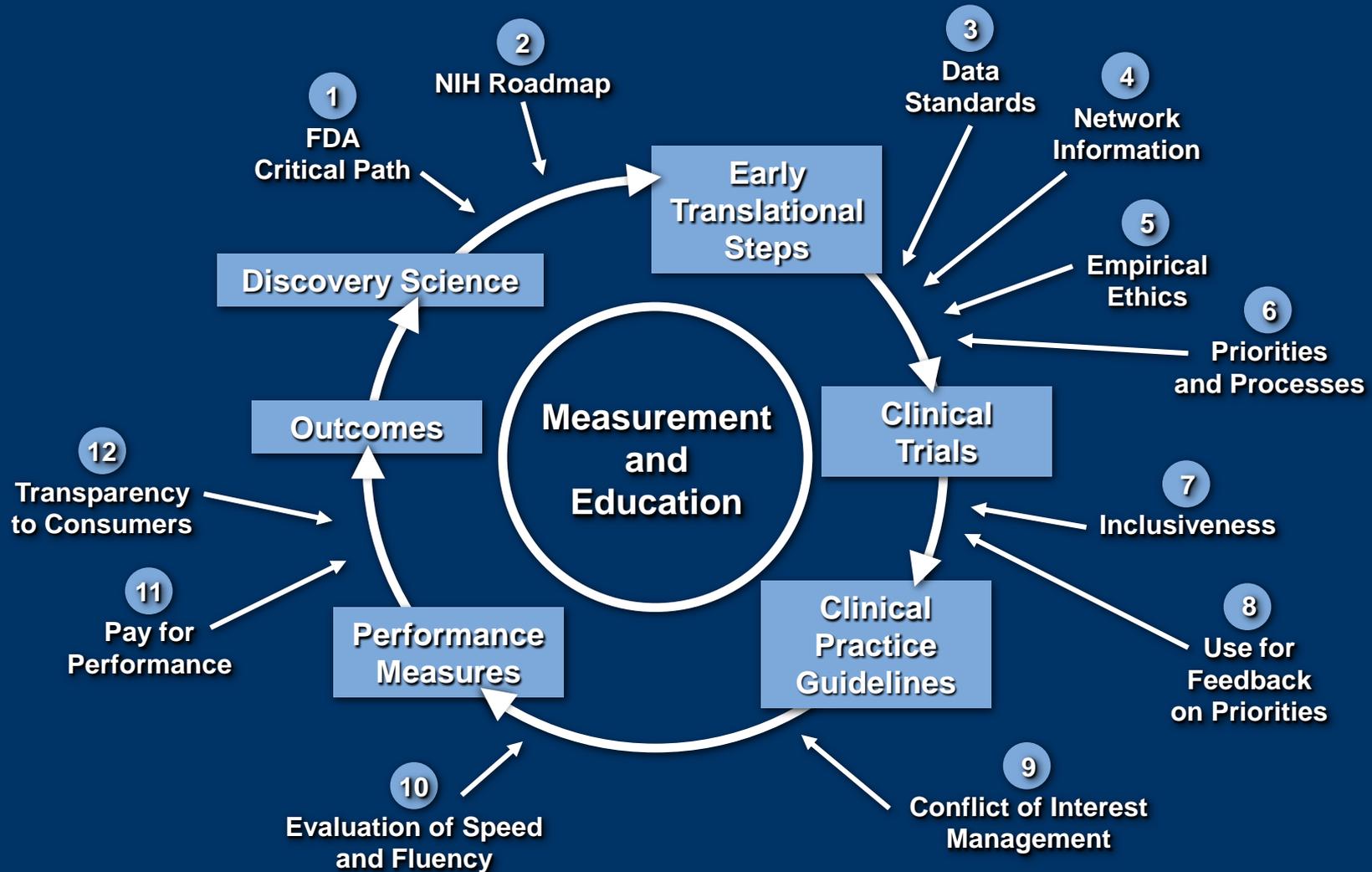


* From the President's Cancer Panel's 2004-2005 report Translating Research Into Cancer Care: Delivering on the Promise.





Cycle of Quality: Generating Evidence to Inform Policy



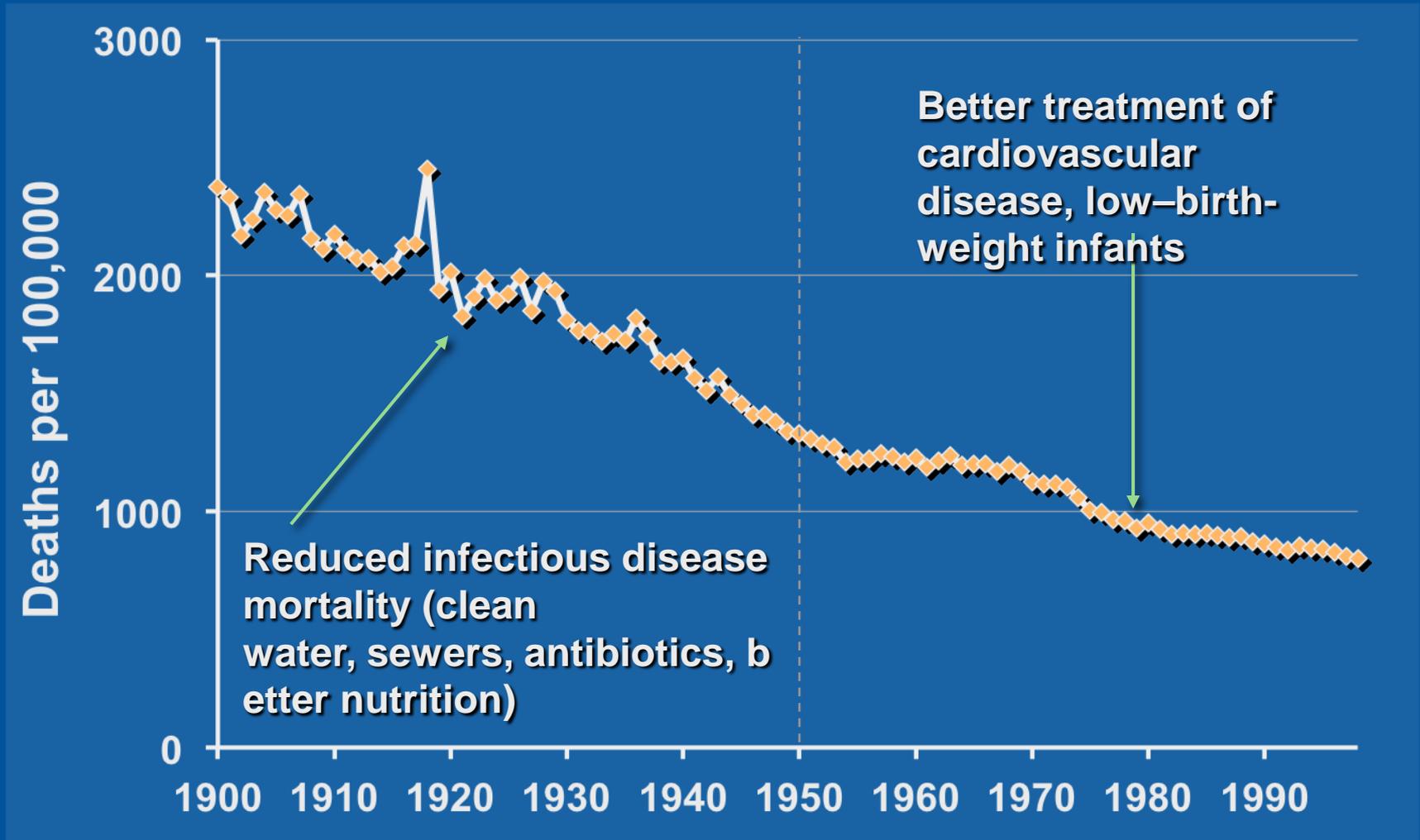
*-Califf RM, Harrington RA, Madre L, et al,
Health Affairs, 2007*



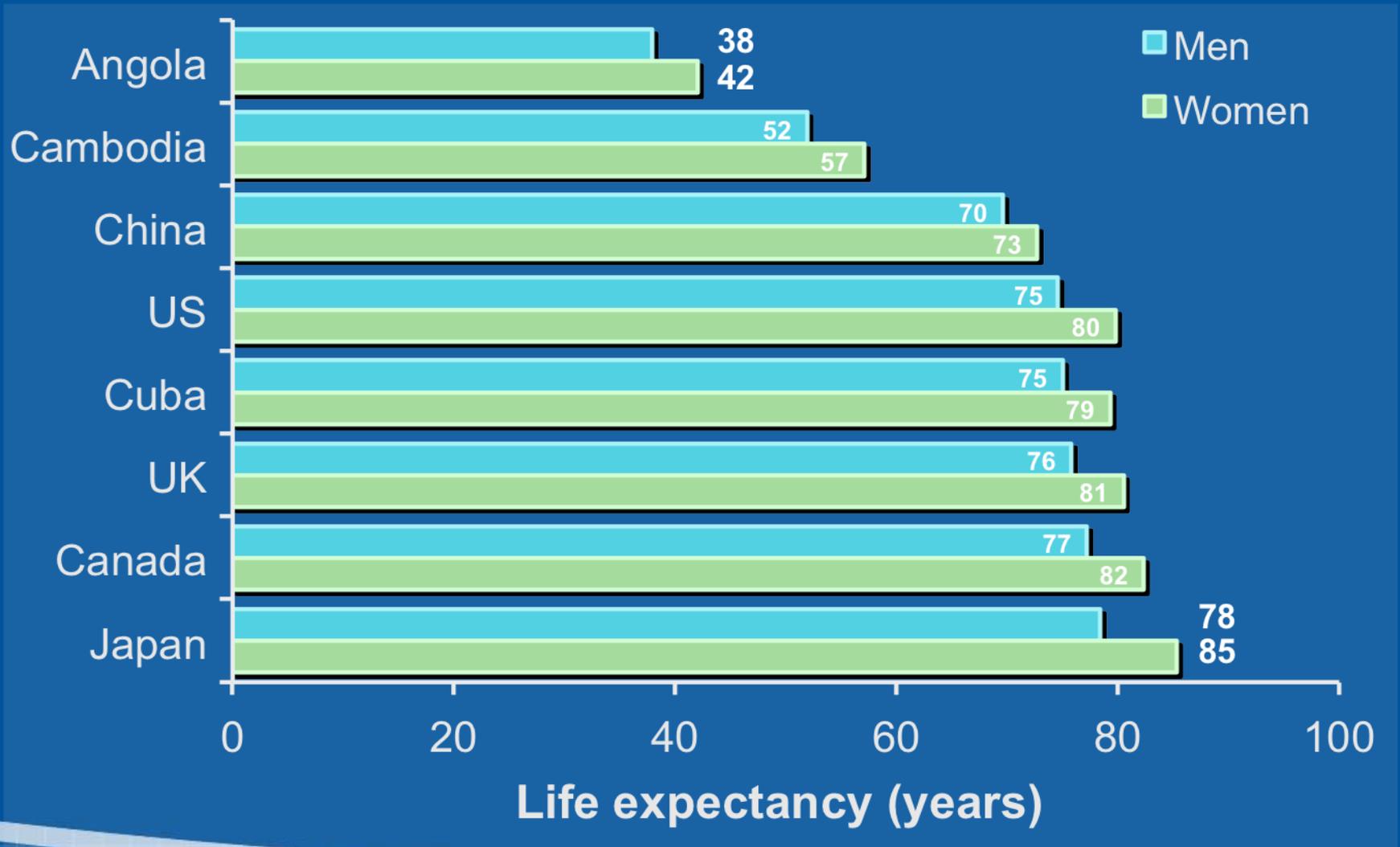
Key Trends in Translational and Clinical Research

- Dominance of communication/management of information
- Globalization—need international connections to be on cutting edge
- NIH—need to demonstrate translation to health benefit/funding constraints
- Pharma/devices—no longer focused on acquiring molecules and targets—surplus in hand; focused on better ability to develop products with value (value means improvement in health)
- Comparative effectiveness research (CER) mandate
- Healthcare reform pressing on accountability

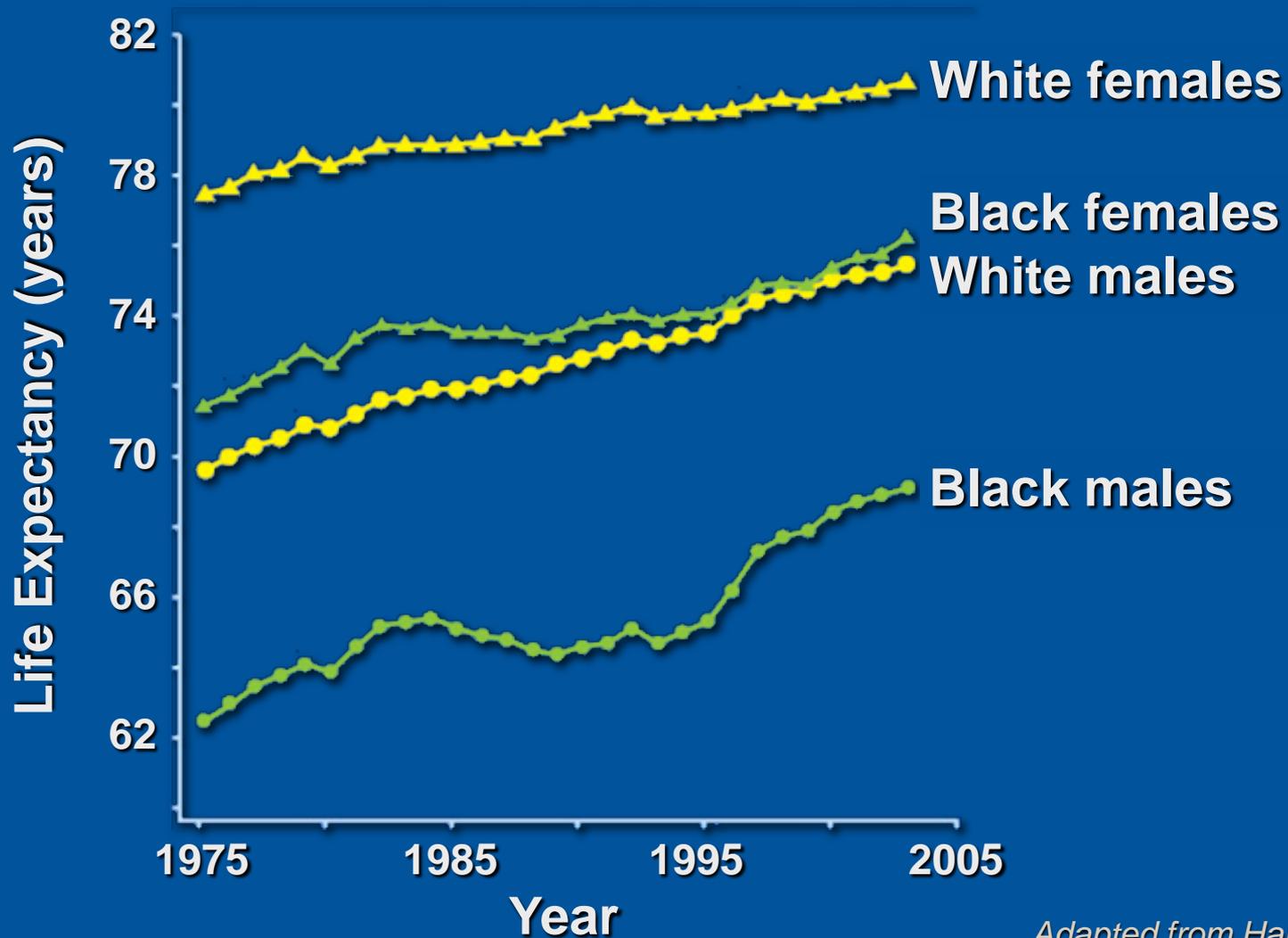
Mortality in the 20th Century



Life Expectancy Around the World



Life Expectancy at Birth



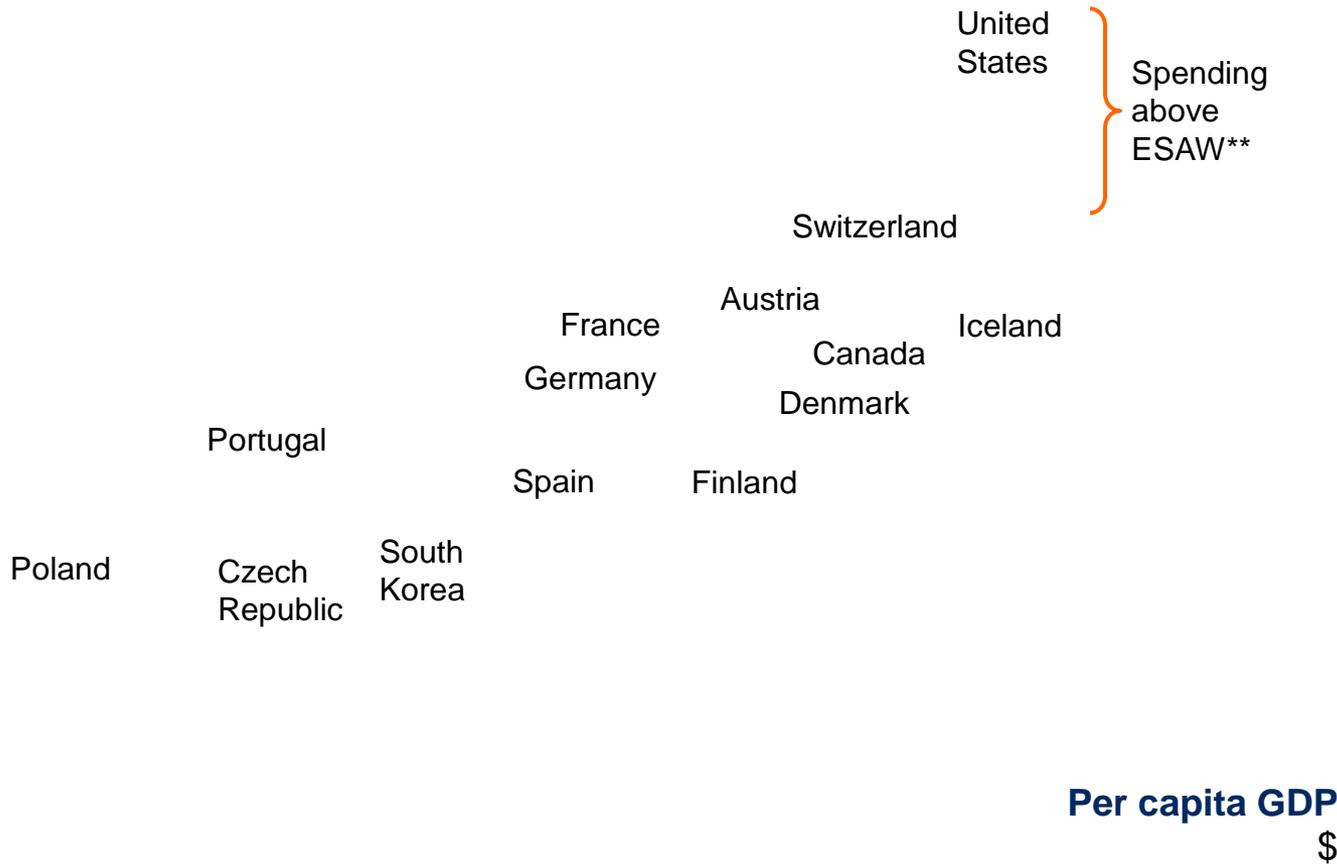
*Adapted from Harper et al,
JAMA 2007;297:1224–1232*



The United States spends far more on health care than expected even when adjusting for relative wealth

Per capita health care spending, 2006
\$ at PPP*

2006 R²=0.88



* Purchasing power parity.

** Estimated Spending According to Wealth.

Funding of US Biomedical Research, 2003-2008

E. Ray Dorsey, MD, MBA

Jason de Roulet, MD

Joel P. Thompson, MPH

Jason I. Reminick, MS

Ashley Thai, BS

Zachary White-Stellato

Christopher A. Beck, PhD

Benjamin P. George, BS

Hamilton Moses III, MD

BIOMEDICAL RESEARCH IS VALUED highly by individuals, governments, foundations, and corporations. Research is seen as a source of more effective treatments and preventive measures and as a route to political policy, economic development, and new commercial products.

In 2005, we reported that total public and private financial support of US biomedical research increased substantially during the preceding decade, with a tripling in nominal amount and doubling after adjustment for inflation be-

Context With the exception of the American Recovery and Reinvestment Act, funding support for biomedical research in the United States has slowed after a decade of doubling. However, the extent and scope of slowing are largely unknown.

Objective To quantify funding of biomedical research in the United States from 2003 to 2008.

Design Publicly available data were used to quantify funding from government (federal, state, and local), private, and industry sources. Regression models were used to compare financial trends between 1994-2003 and 2003-2007. The numbers of new drug and device approvals by the US Food and Drug Administration over the same period were also evaluated.

Main Outcome Measures Funding and growth rates by source; numbers of US Food and Drug Administration approvals.

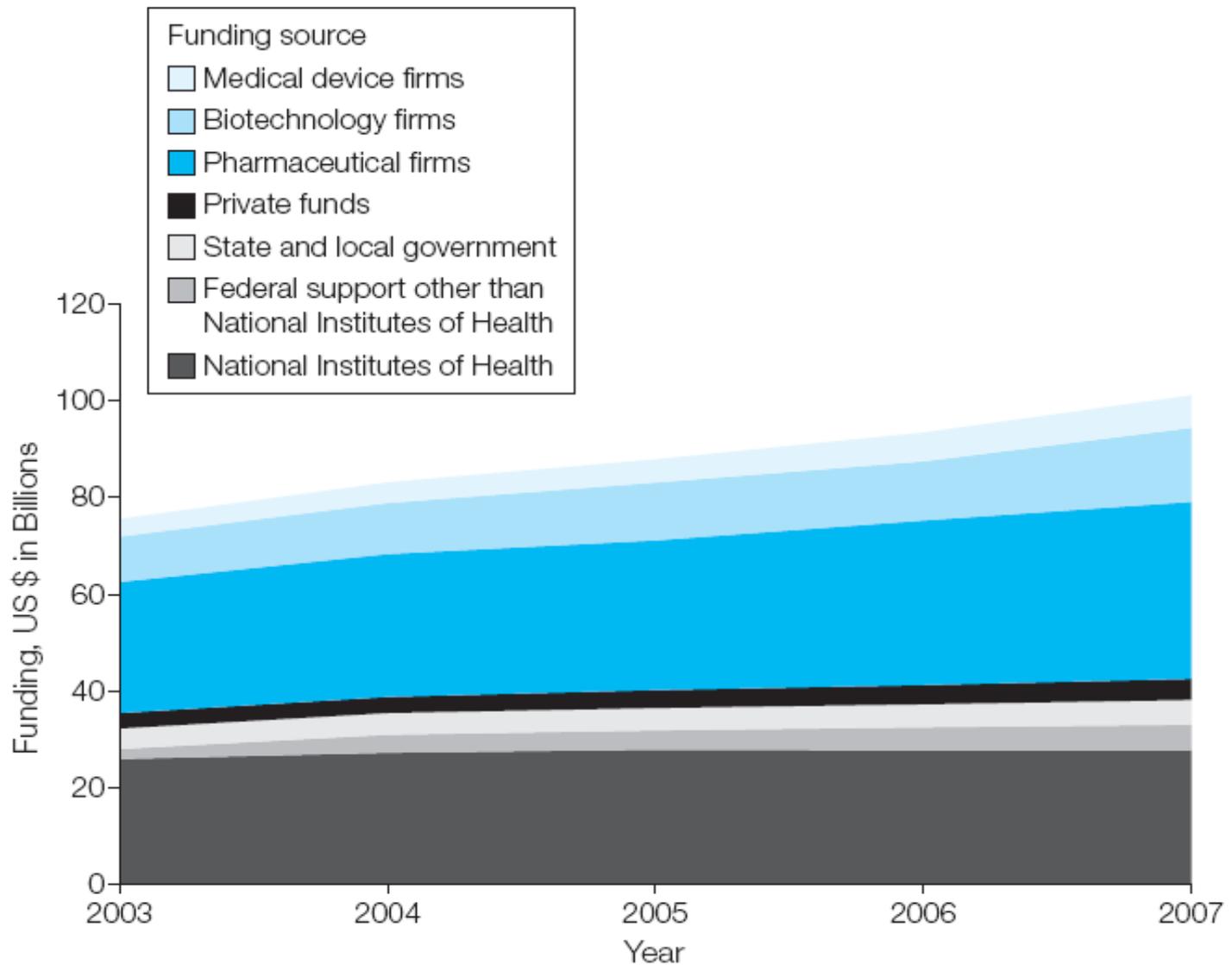
Results Biomedical research funding increased from \$75.5 billion in 2003 to \$101.1 billion in 2007. In 2008, funding from the National Institutes of Health and industry totaled \$88.8 billion. In 2007, funding from these sources, adjusted for inflation, was \$90.2 billion. Adjusted for inflation, funding from 2003 to 2007 increased by 14%, for a compound annual growth rate of 3.4%. By comparison, funding from 1994 to 2003 increased at an annual rate of 7.8% ($P < .001$). In 2007, industry (58%) was the largest funder, followed by the federal government (33%). Modest increase in funding was not accompanied by an increase in approvals for drugs or devices. In 2007, the United States spent an estimated 4.5% of its total health expenditures on biomedical research and 0.1% on health services research.

Conclusion After a decade of doubling, the rate of increase in biomedical research funding slowed from 2003 to 2007, and after adjustment for inflation, the absolute level of funding from the National Institutes of Health and industry appears to have decreased by 2% in 2008.

JAMA. 2010;303(2):137-143

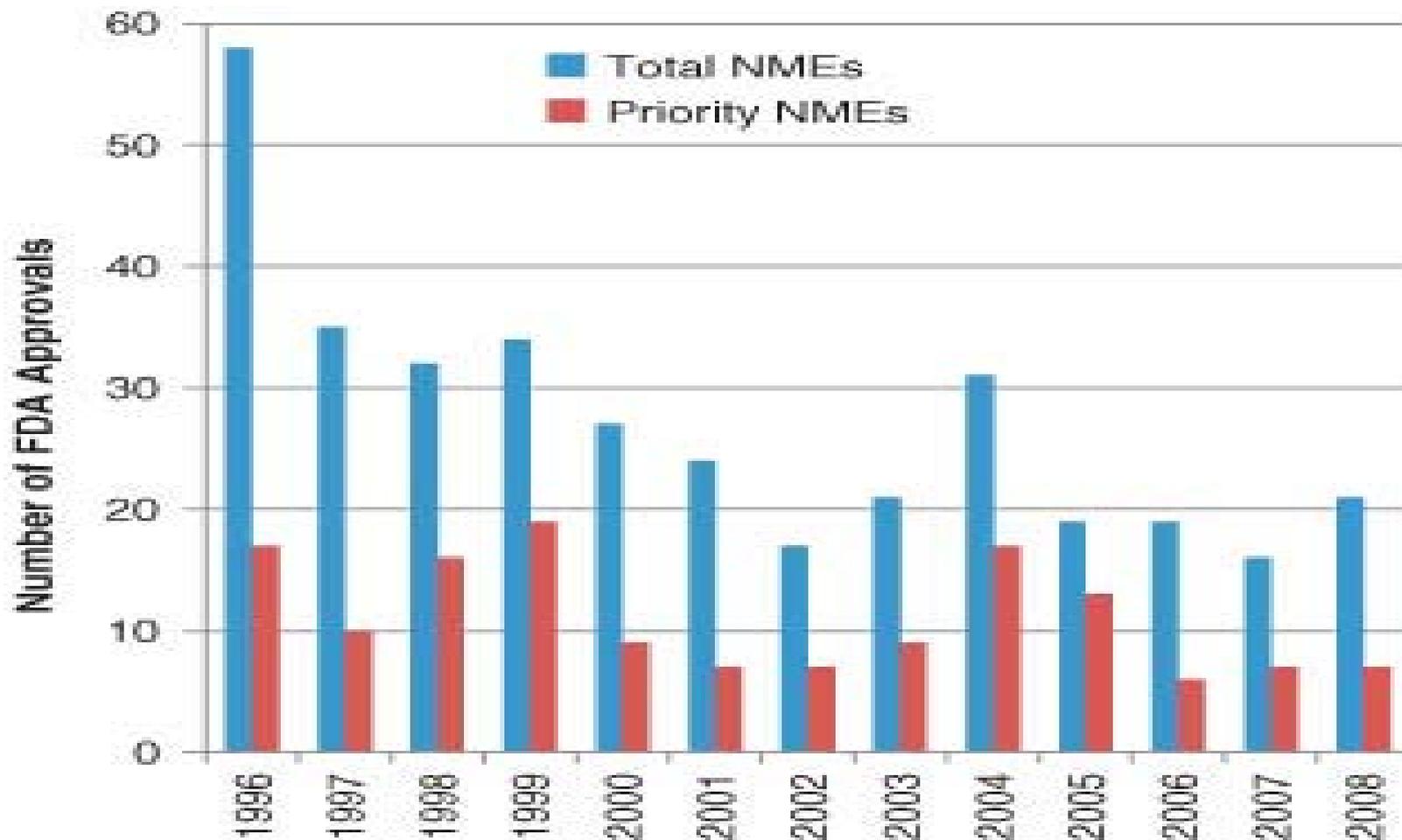
www.jama.com

Figure 1. Funding for Biomedical Research by Source, 2003-2007





FDA New Drug Approvals (NME)





Conflict of Interest in Medical Research, Education, and Practice

Bernard Lo and Marilyn J. Field, *Editors*

Committee on Conflict of Interest in Medical
Research, Education and Practice

Board on Health Sciences Policy

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OF THE NATIONAL ACADEMIES

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www.nap.edu

N Engl J Med 2011;364:535-41.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

The Role
in the Di

Ashley J. Stevens,
Patrick C

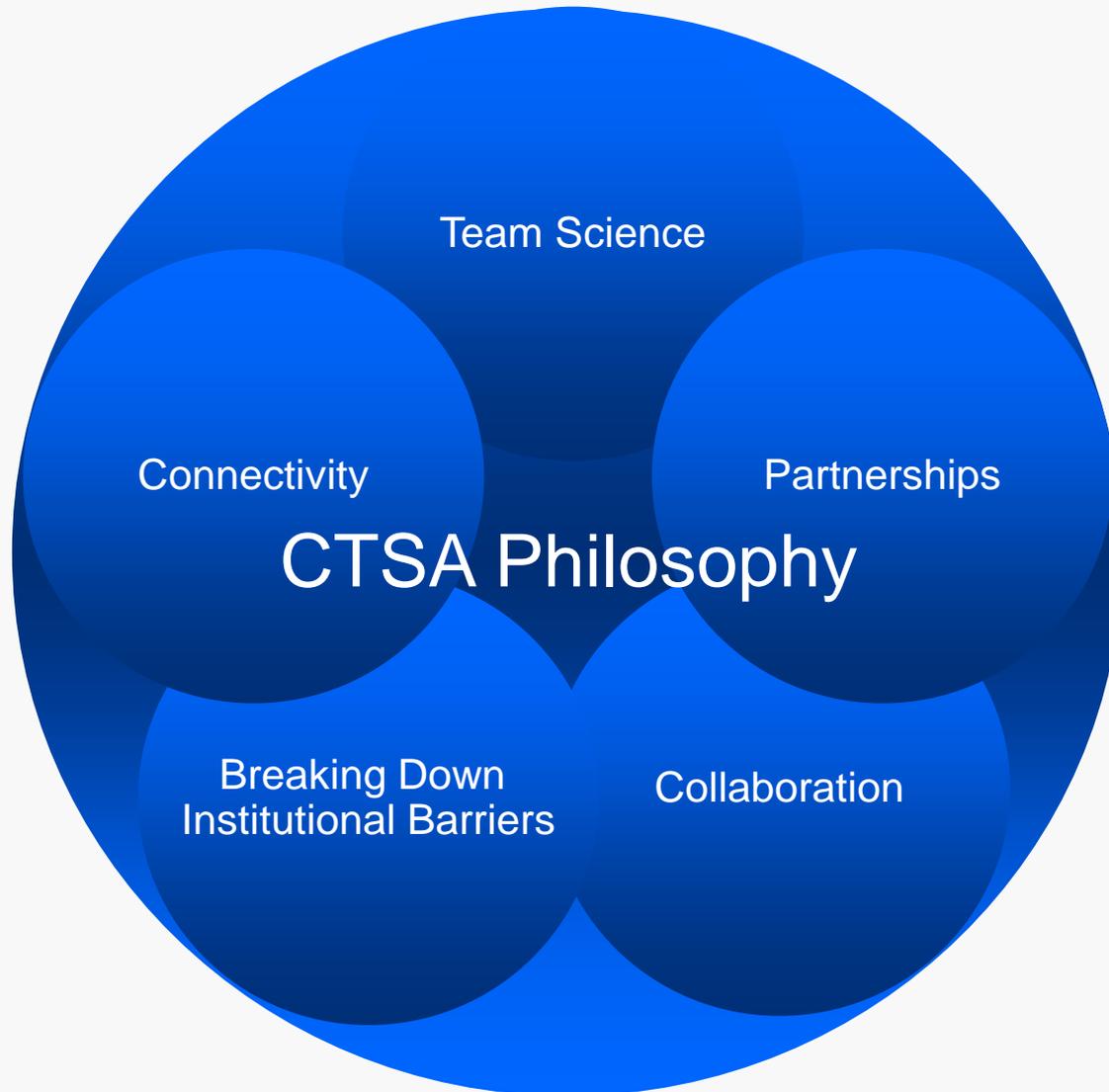
Drugs include:

- Lovastatin (Mevacor)
- Imatinib (Gleevec)
- Paclitaxel (Taxol)
- Sunitib (Sutent)
- Abciximab (ReoPro)
- Filgrastim (Neupogen)
- HPV vaccine (Gardasil)
- Ganciclovir (Vitrasert)
- Ketoconazole (Nizoral)

Research
and Vaccines

A., Katrine Wyller, M.B.E.,
e, M.B.A., Ph.D.,
, J.D.

Guiding Principles of the CTSA Consortium



Scientific Management Review Board (SMRB) Recommendations to NIH



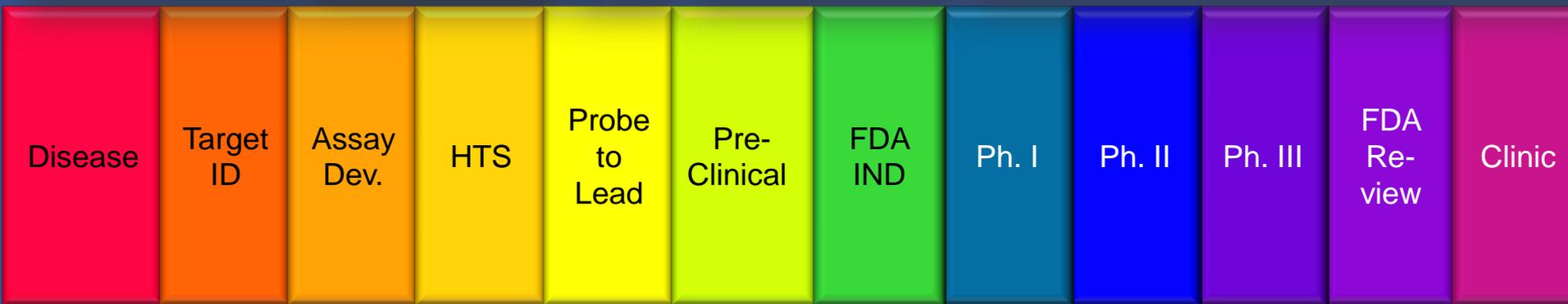
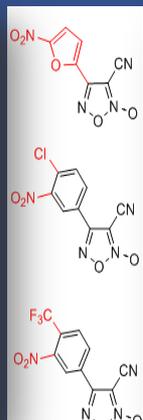
- May 2010
 - NIH Director Francis Collins asks SMRB to determine how NIH could better support translational and therapeutic sciences
- December 2010
 - SMRB recommends (12 to 1) that a new translational medicine and therapeutics center be created
 - SMRB also recommends NIH undertake a more extensive and detailed analysis through a transparent process to evaluate the new center's impact

Creation of the National Center for Advancing Translational Sciences (NCATS)

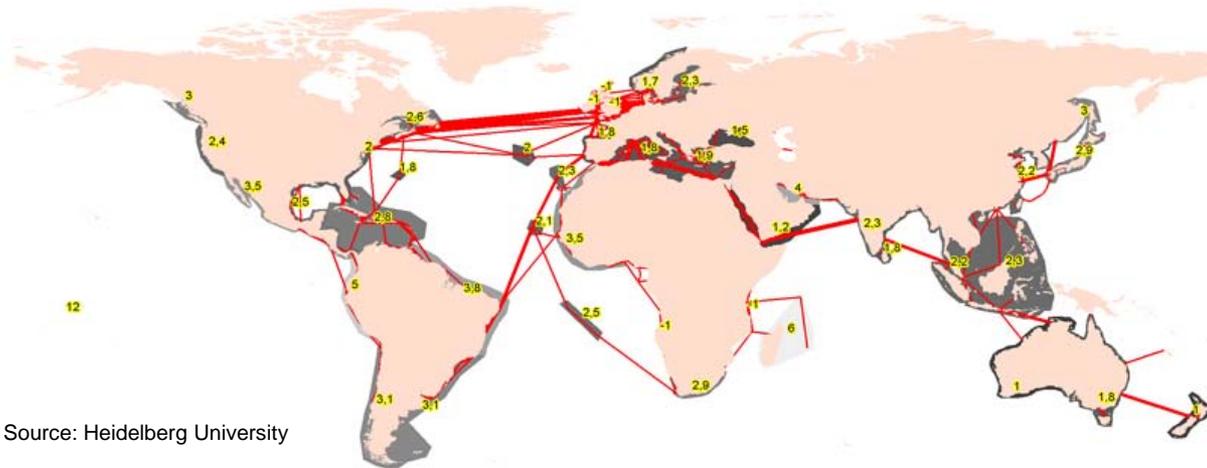
To advance the discipline of translational science and catalyze the development and testing of novel diagnostics and therapeutics across a wide range of human diseases and conditions



National Center for Advancing Translational Sciences



Global Information Networks are Driving Knowledge Creation and Collaboration...



Source: Heidelberg University

Global Telegraph Network, 1900



Global Internet Traffic Flow, 2008

Source: PriMetrica, Inc.

SOUNDING BOARD

**Ethical and Scientific Implications of the Globalization
of Clinical Research**

Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H.,
Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D.,
and Kevin A. Schulman, M.D.

- Since 2002, the number of FDA investigators outside the US has grown by 15% annually, while the number inside the US has declined by 5.5%.
- One-third of phase 3 trials of the 20 largest US pharmaceutical companies are being conducted solely outside the US.
- For those same firms and studies, a majority of study sites (13,521 of 24,206) are outside the US.



The role of academic health science systems in the transformation of medicine



Victor J Dzau, D Clay Ackerly, Pamela Sutton-Wallace, Michael H Merson, R Sanders Williams, K Ranga Krishnan, Robert C Taber, Robert M Califf

The challenges facing the health of communities around the world are unprecedented, and the data are all too familiar. For 5 billion people living in developing countries, environmental factors and inadequacies in hygiene, economic development, and health-care access are the main causes of shortened life expectancies. Improvements in health status, including reductions in infant mortality and declining incidence of infectious diseases, are being met by the new epidemics of obesity, diabetes mellitus, and cardiovascular disease.¹

Developed countries are beset by disparities in access to care and health outcomes,^{2,3} unreliable quality, and high costs.⁴ Increased demand for services, ageing populations, inadequate evidence to guide practice, and a misdirected emphasis on research and treatment in late-stage disease contribute to the high cost of health care.⁵ In many countries, these difficulties are exacerbated by fragmented health-care delivery systems, resulting in inadequate continuity of care across community, primary-care, and tertiary-care settings. The creation of novel treatments remains protracted and expensive,⁶ new discoveries are not delivered swiftly to patients,^{7,8} and population-wide strategies using cheap, simple, and efficient interventions are not effectively implemented.⁹

Many countries, including the USA, the UK, Singapore,

In order to achieve transformation, two distinct translational blocks or gaps in the discovery-care continuum must be overcome.^{10,11} The first is the gap between a scientific discovery and its clinical translation (ie, from bench to bedside); the second is the gap between expert acceptance of the application and its broad adoption in practice by local and global communities (ie, from bedside to population). AHSCs traditionally give their discoveries to industry at the first gap and to practising physicians at the second gap, thereby creating barriers and inefficiencies. We believe that AHSCs are ideally poised to become system integrators that are capable of bridging these translational gaps, thereby greatly reducing delays and inefficiencies between discovery and global adoption. These system integrators do not replace industry or non-academic providers, rather, they improve the capacity to develop and deliver new treatments by filling the spaces between academic discovery, science, industry, and the general health-care delivery system. In the USA, the Roadmap Initiative of the National Institutes of Health (Bethesda, MD),¹²⁻¹⁵ and resulting Clinical and Translational Science Awards¹⁶ have shown this perspective. Examples of US institutions that have begun to develop models of integrated translational research and care-delivery systems include the University of Pennsylvania (Philadelphia, PA), Johns

Lancet 2010; 375: 949-53

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See Online/Comment

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R C Taber PhD,

Prof R M Califf MD); and

Duke-National University of

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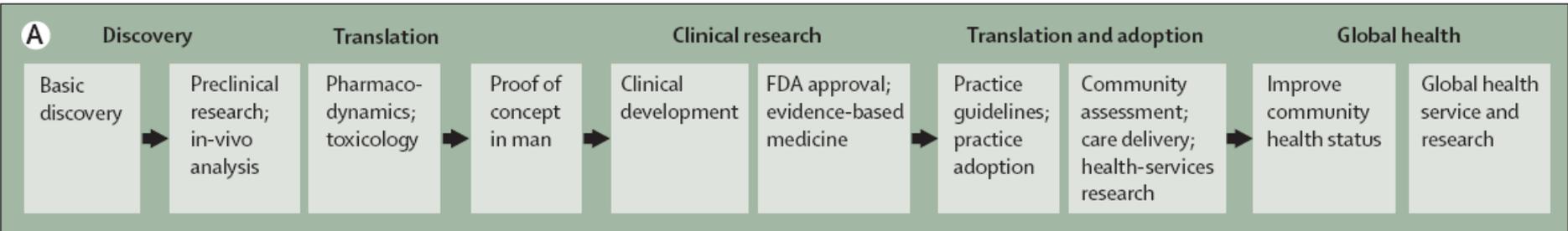
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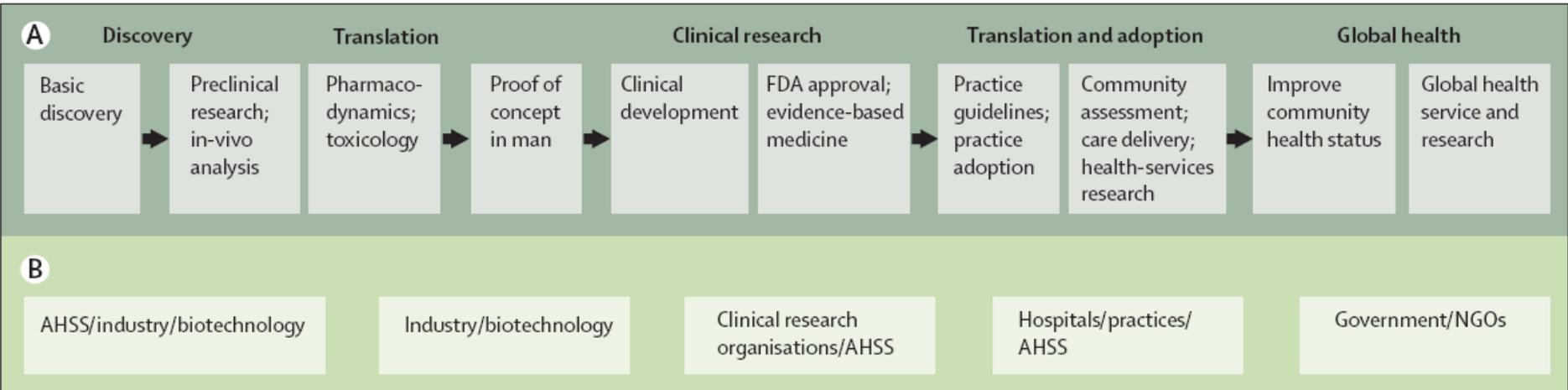


Discovery to Care Continuum





Current Fragmented Approach





Duke Medicine Model for Translation

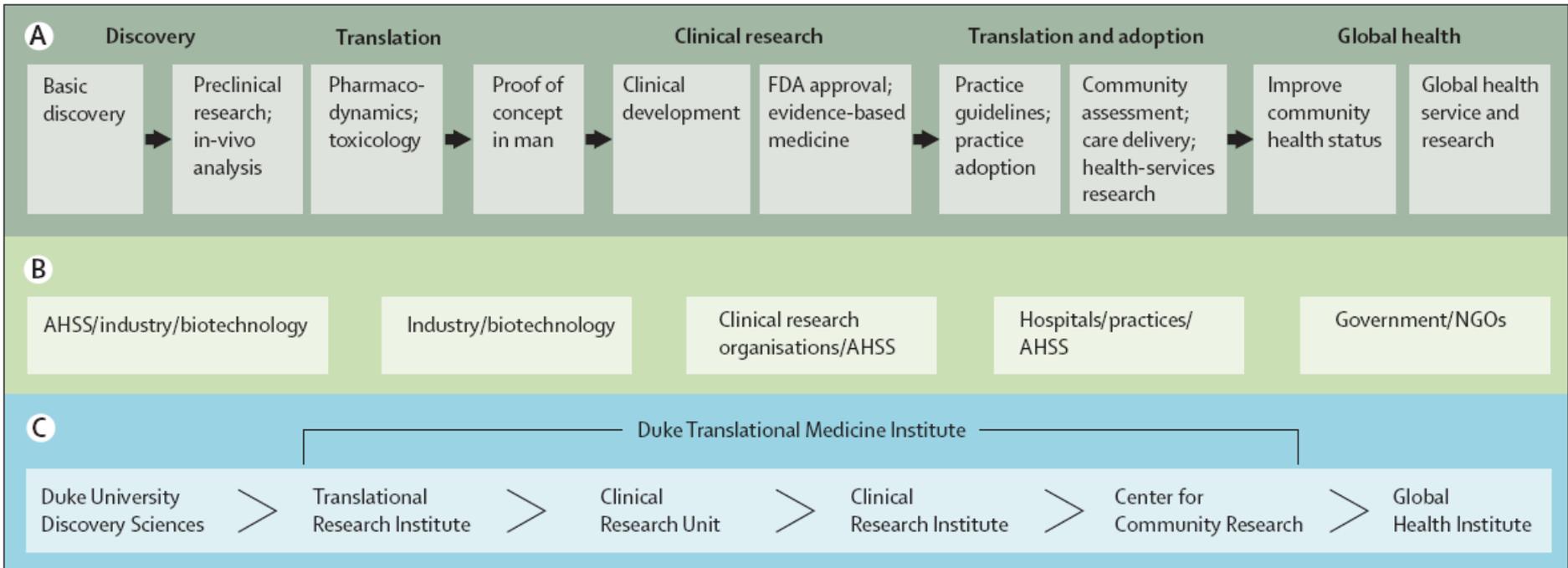
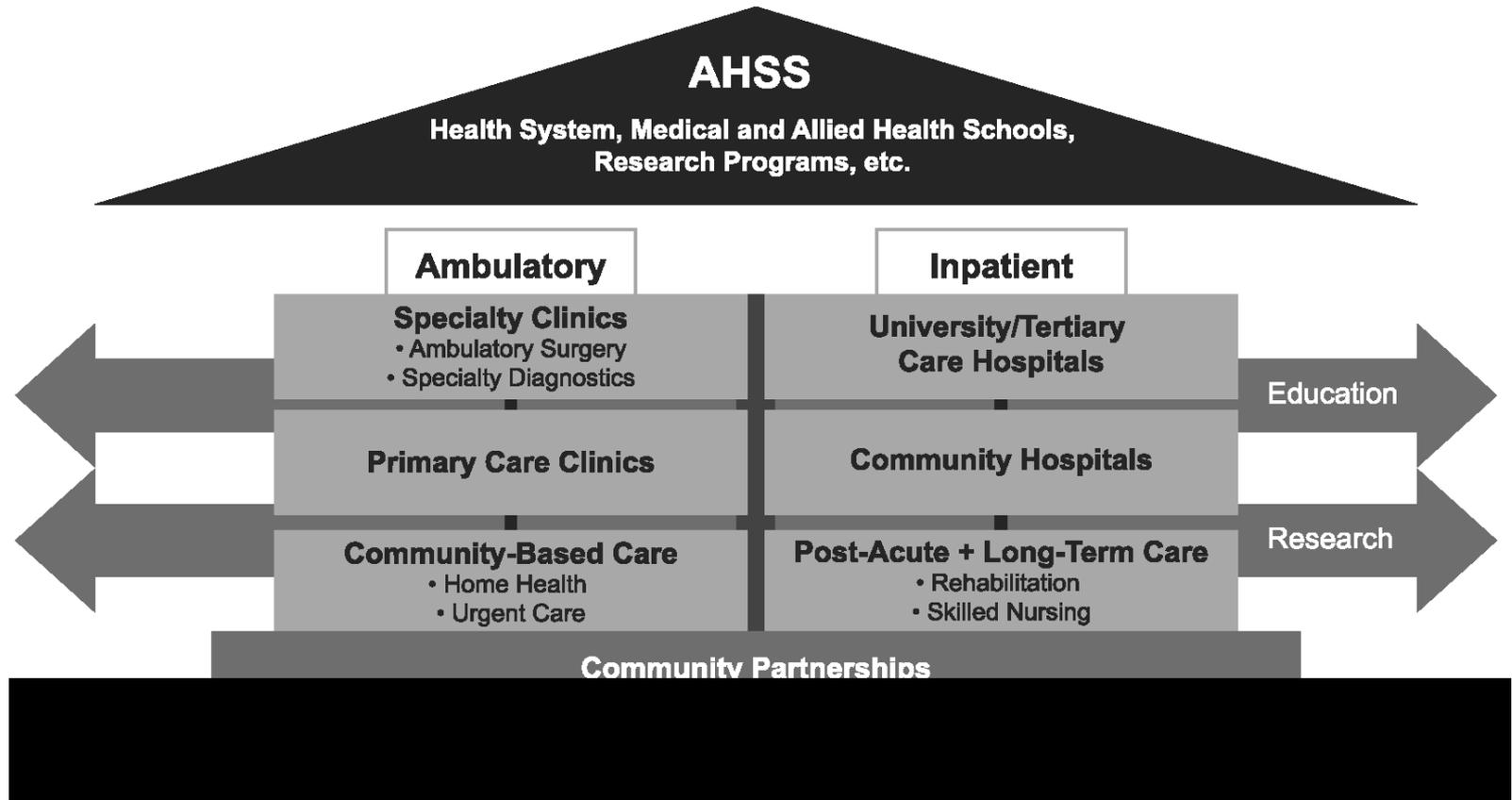


Figure 1: Academic health science systems as integrators
 (A) The discovery-care continuum, including discovery science, preclinical and clinical research, adoption in practice, and global uptake; (B) current fragmented organisational structure of the clinical research enterprise; (C) Duke Medicine model: a continuous, intercommunicated discovery-care model. FDA=US Food and Drug Administration. AHSS=Academic health science systems. NGOs=non-governmental organisations.

Academic Health Science Systems



Schematic of AHSS as a Vertically Integrated Care Delivery System



Duke Translational Medicine Institute Mission

*To catalyze translation across the
continuum of scientific
discovery, clinical research, care
delivery, and global health*

DTMI
Duke Translational Medicine Institute

DTRI
Duke
Translational
Research Institute

DCRU
Duke
Clinical
Research Unit

DCRI
Duke
Clinical
Research Institute

DTNI
Duke
Translational
Nursing Institute

DCCR
Duke
Center for
Community Research

Discovery Science

Duke Global Health Institute

Biomedical Informatics

Biostatistics

Core Laboratories

Education and Training

Ethics

Child Health

Project Leadership

Regulatory Affairs

Site-based Research

First-in-human

Application at the point of care

Preclinical research

Proof of Concept

Phase II-IV

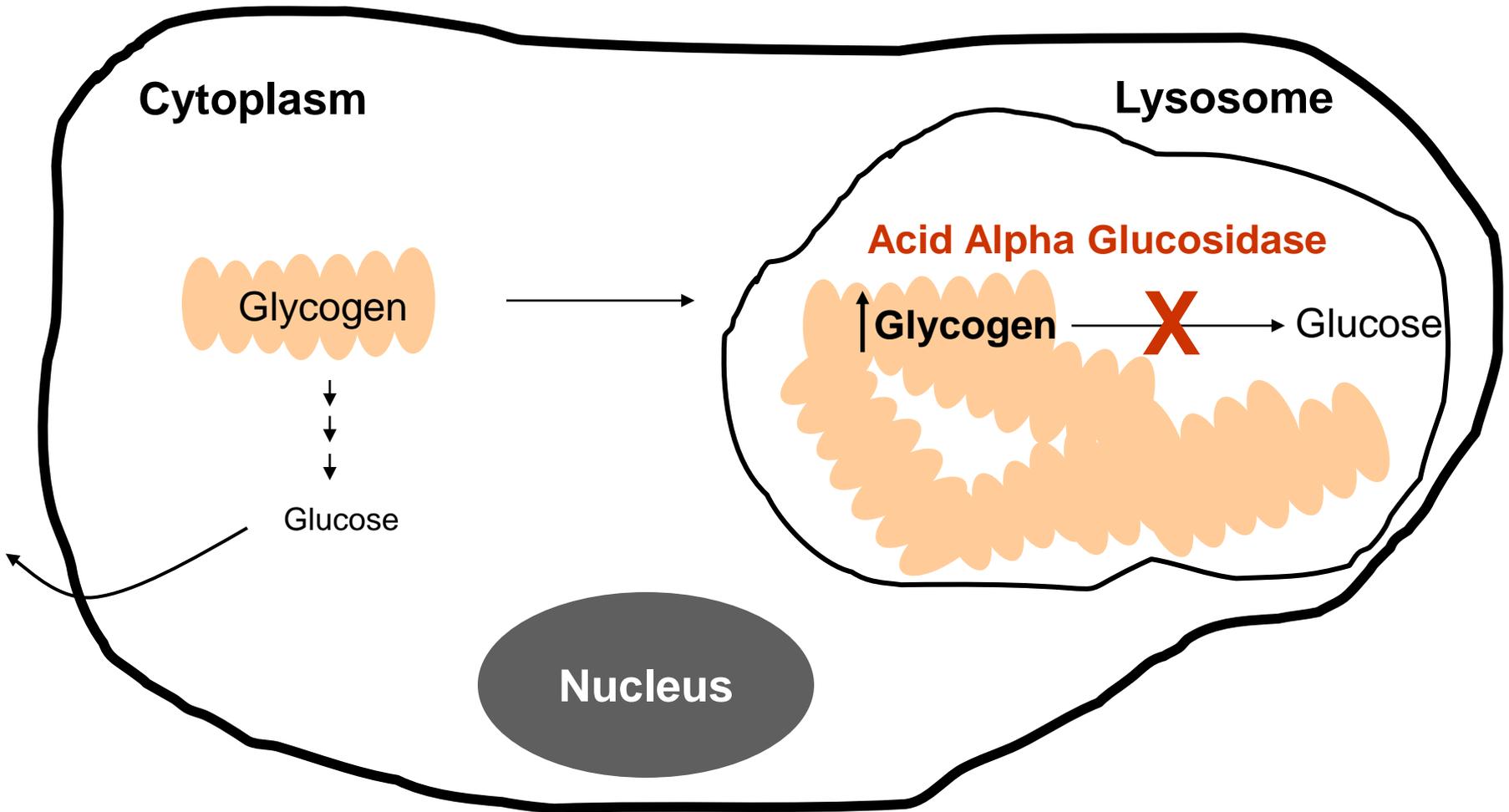
Application in the community

Pompe Disease Overview

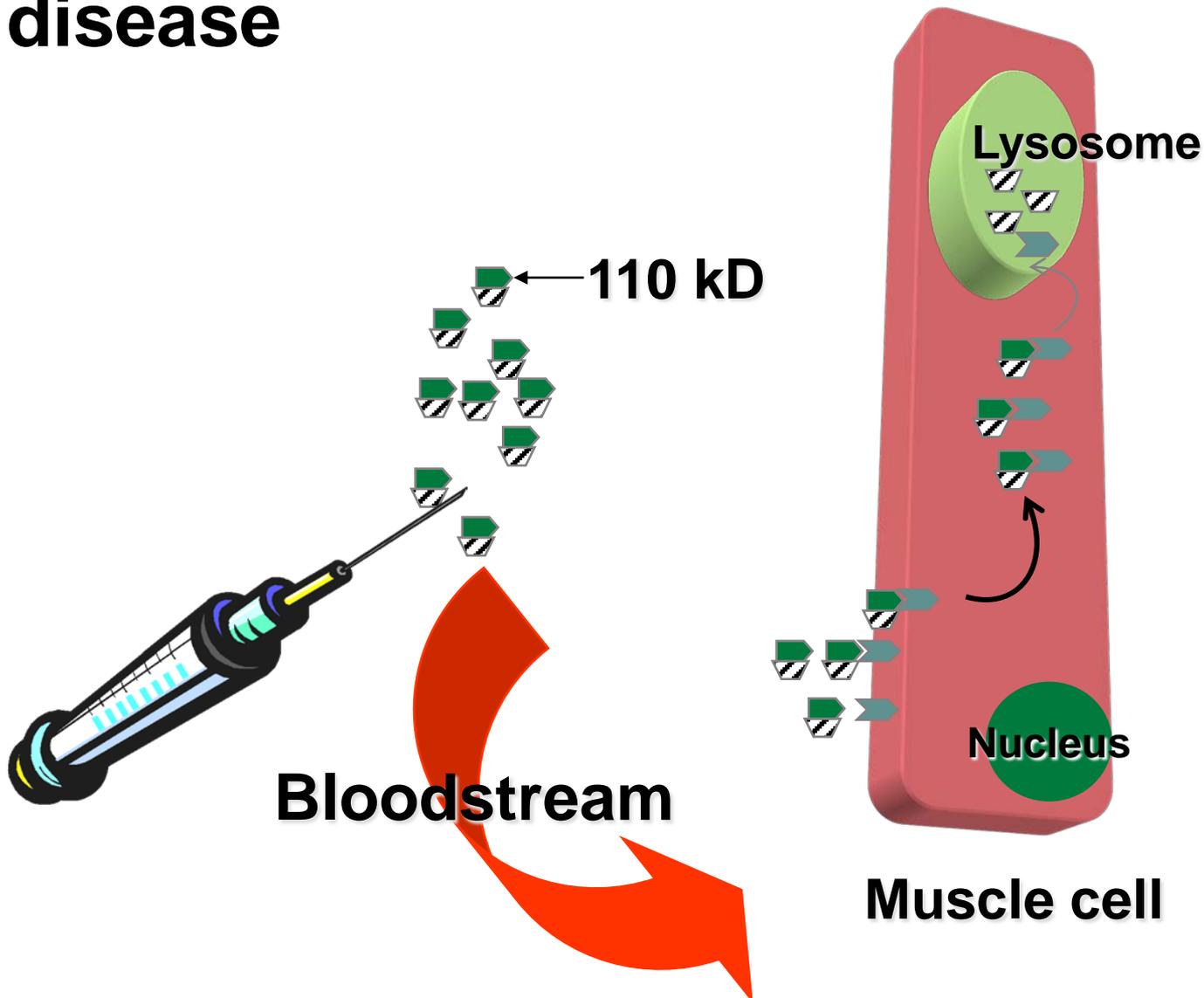
- A metabolic myopathy (cardiac, skeletal & smooth muscle) caused by deficiency of lysosomal enzyme acid alpha glucosidase (GAA)
 - From early onset + rapid progression to death
 - To later onset + slower progression (longer survival, marked morbidity)
- Pan-ethnic, 1:40,000 frequency (thus an ultra orphan disease)
- Clinical spectrum determined by:
 - GAA mutations: fully deleterious → partially deleterious
 - GAA activity: total deficiency → partial deficiency
 - Glycogen accumulation and tissue damage in muscle: rapid → slower

Pompe is Caused by a Deficiency of GAA

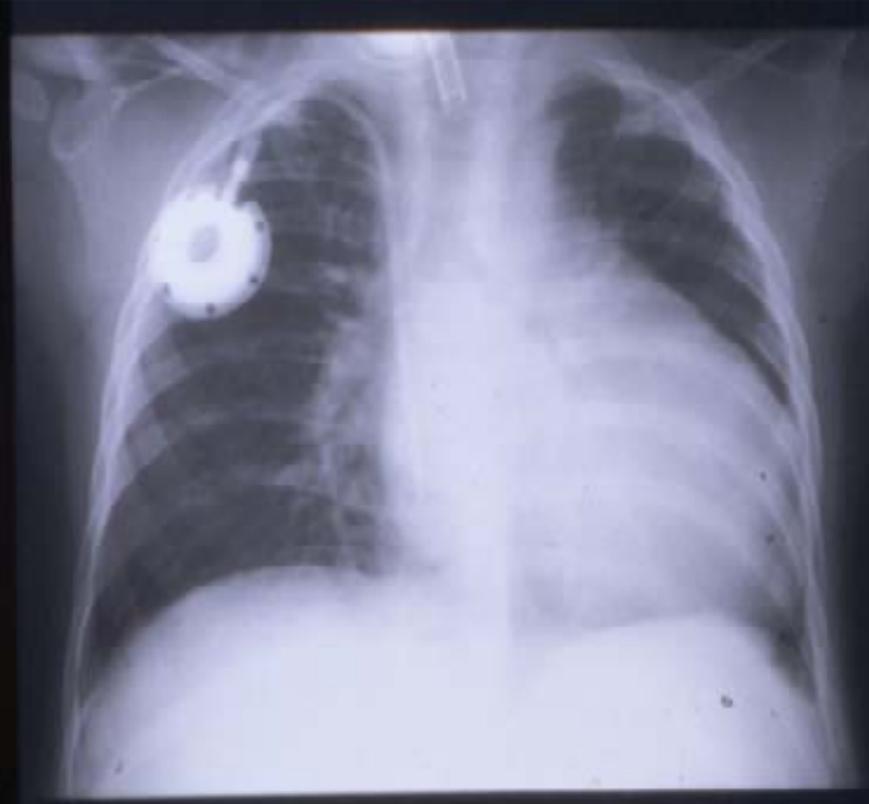
Work of YT Chen and PriyaKishnani & Team



Hypothesis: IV injection of enzyme corrects muscle disease



Pompe Heart Before and 12 Weeks After ERT



LETTERS

Genetic variation in *IL28B* and spontaneous clearance of hepatitis C virus

David L. Thomas^{1*}, Chloe L. Thio^{1*}, Maureen P. Martin^{2*}, Ying Qi², Dongliang Ge³, Colm O'hUigin², Judith Kidd⁴, Kenneth Kidd⁴, Salim I. Khakoo⁵, Graeme Alexander⁶, James J. Goedert⁷, Gregory D. Kirk⁸, Sharyne M. Donfield⁹, Hugo R. Rosen¹⁰, Leslie H. Tobler¹¹, Michael P. Busch¹¹, John G. McHutchison¹², David B. Goldstein³ & Mary Carrington^{2,13}

with treatment response

LETTERS

Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance

Dongliang Ge¹, Jacques Fellay¹, Alexander J. Thompson², Jason S. Simon³, Kevin V. Shianna¹, Thomas J. Urban¹, Erin L. Heinzen¹, Ping Qiu³, Arthur H. Bertelsen³, Andrew J. Muir², Mark Sulkowski⁴, John G. McHutchison² & David B. Goldstein¹

A look at Durham...

*** Population = 246,896**

Children = 24.3 %

>65 = 9.5%

African American = 38%

Latino / Hispanic = 11%

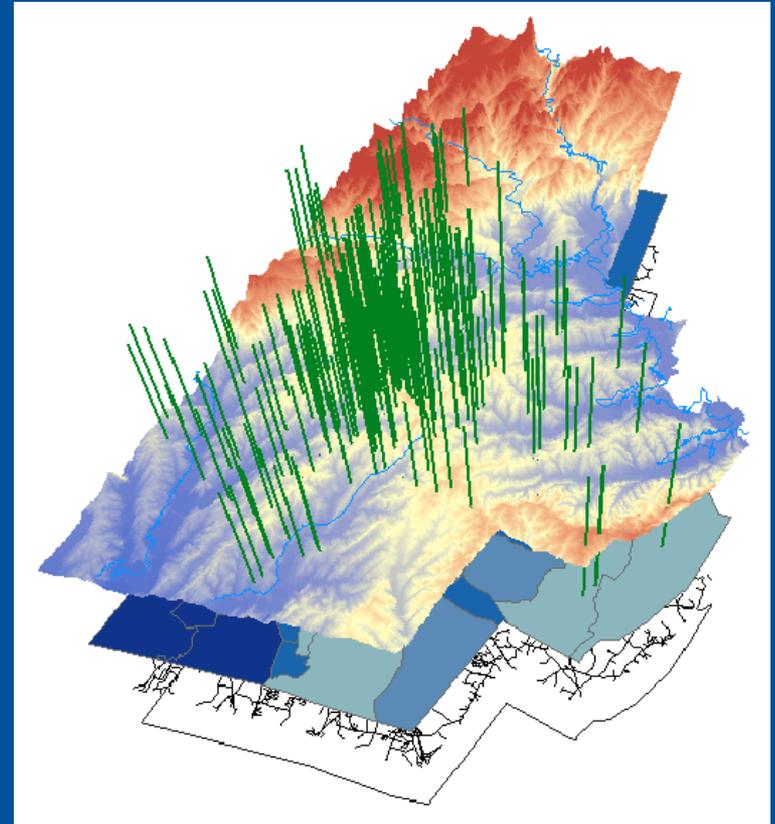
*** Median household income = \$44,048**

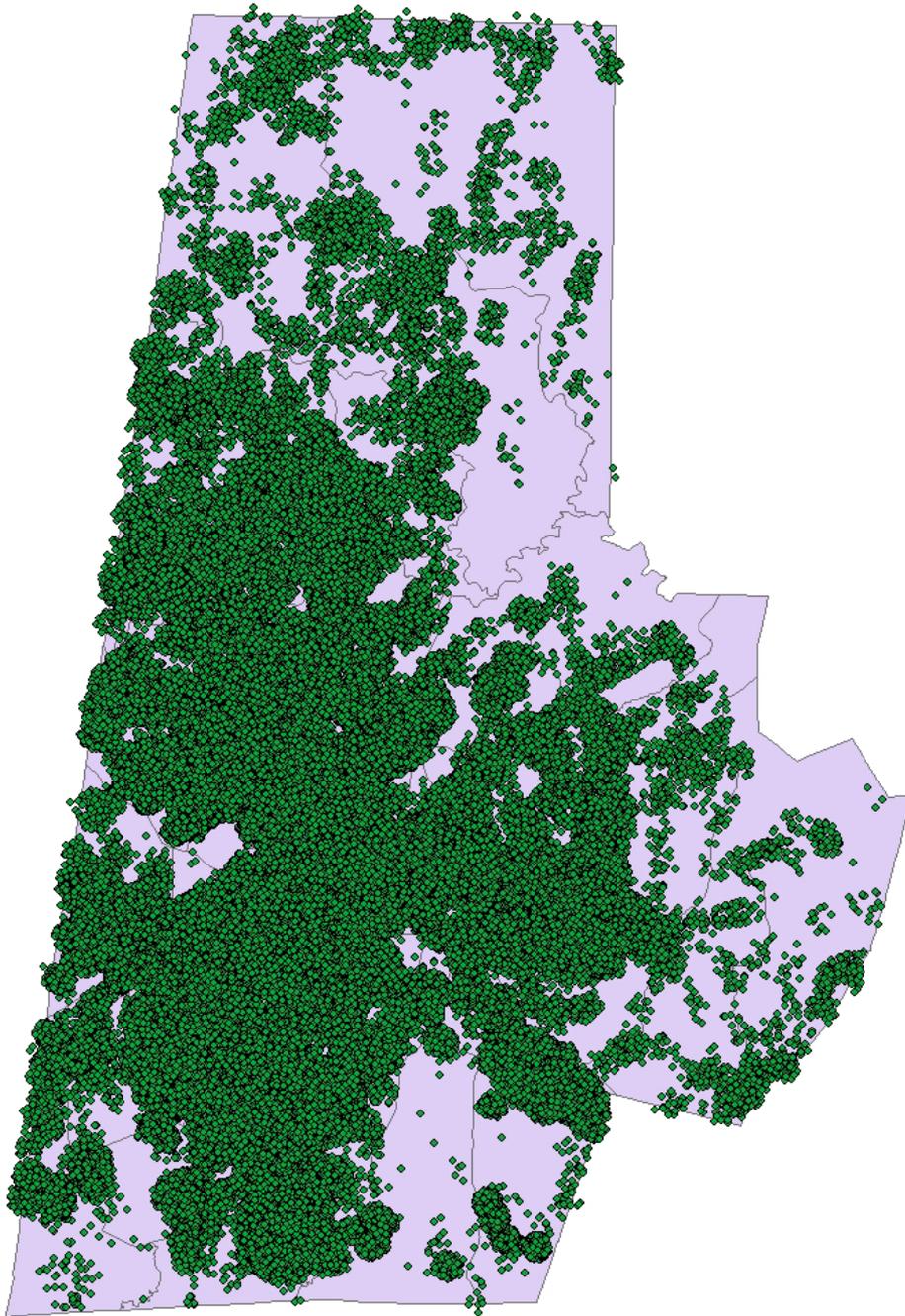
*** % living in poverty = 14.9%**

*** Homeownership rates = 54.3%**

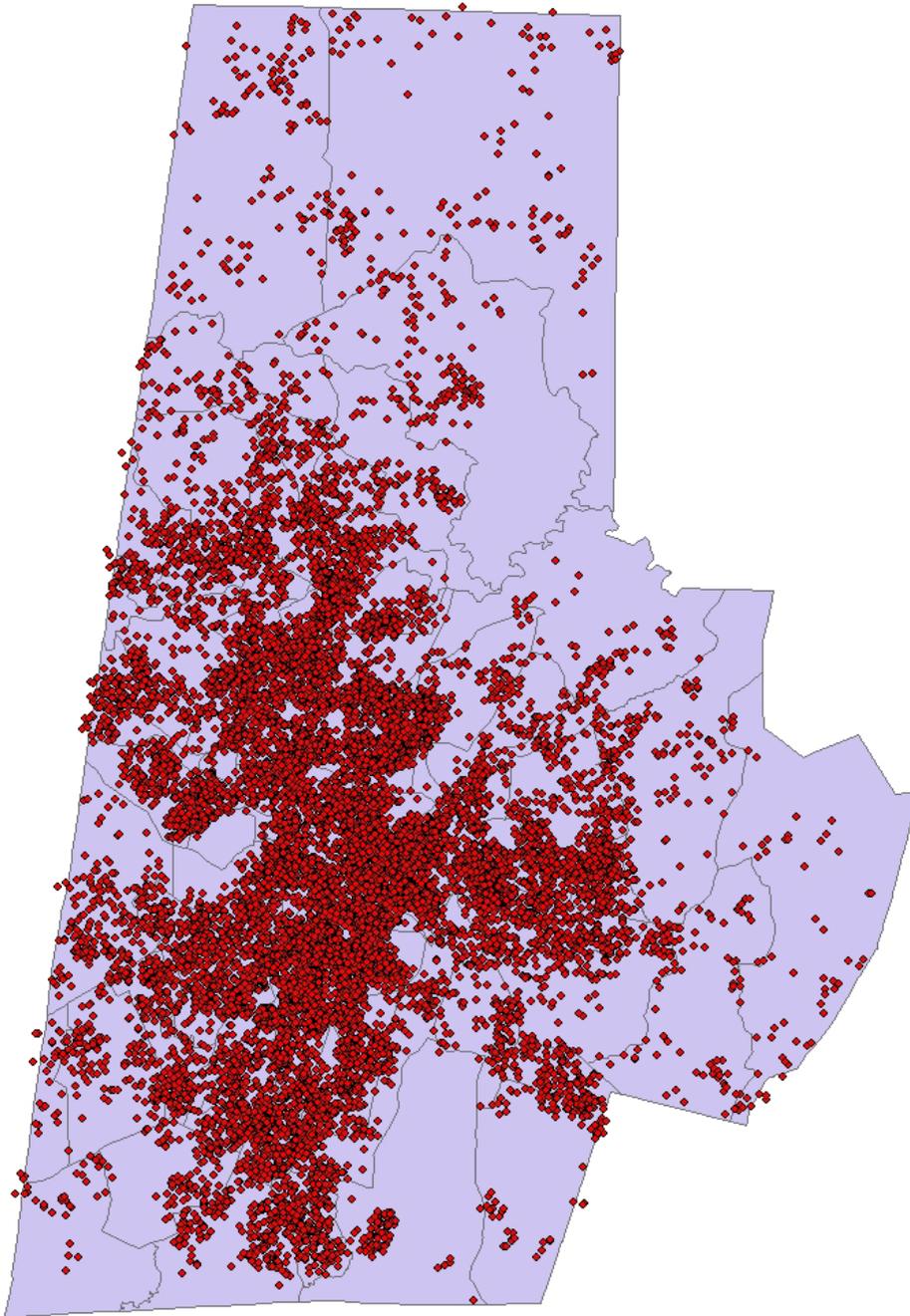
Geographic Information Systems (GIS)

- ✦ A set of tools for managing, visualizing, exploring, querying, editing, and analyzing information linked to geographic locations
- ✦ Displays data as maps, tables, and charts





- All patients seen at Duke, 2007-2009
- 215,731 unique patients
- ~80% of Durham County population



- DM patients seen at Duke, 2007-2009
- 14,345 unique patients (8.7% of all patients >20 yo, 14.3% of all patients >40 yo)

Durham County Stats (per CDC):

In 2008, ~ 10% of adults diagnosed with diabetes

North Carolina (CDC):

In 2008, ~ 9% of adults diagnosed with diabetes;

By Race: 8.4% White, 15.6% AA, 12.4% NA, 4.5% Hispanic, 4.3% Other

US Stats (National Diabetes Fact Sheet):

5.8 million children and adults in the US; or 8.3% of the population have diabetes.

Age 65 years or older: 10.9 million, or 26.9% of all people in this age group have diabetes;

By Race: 7.1% of non-Hispanic whites, 8.4% of Asian Americans, 12.6% of non-Hispanic blacks, 11.8% of Hispanics

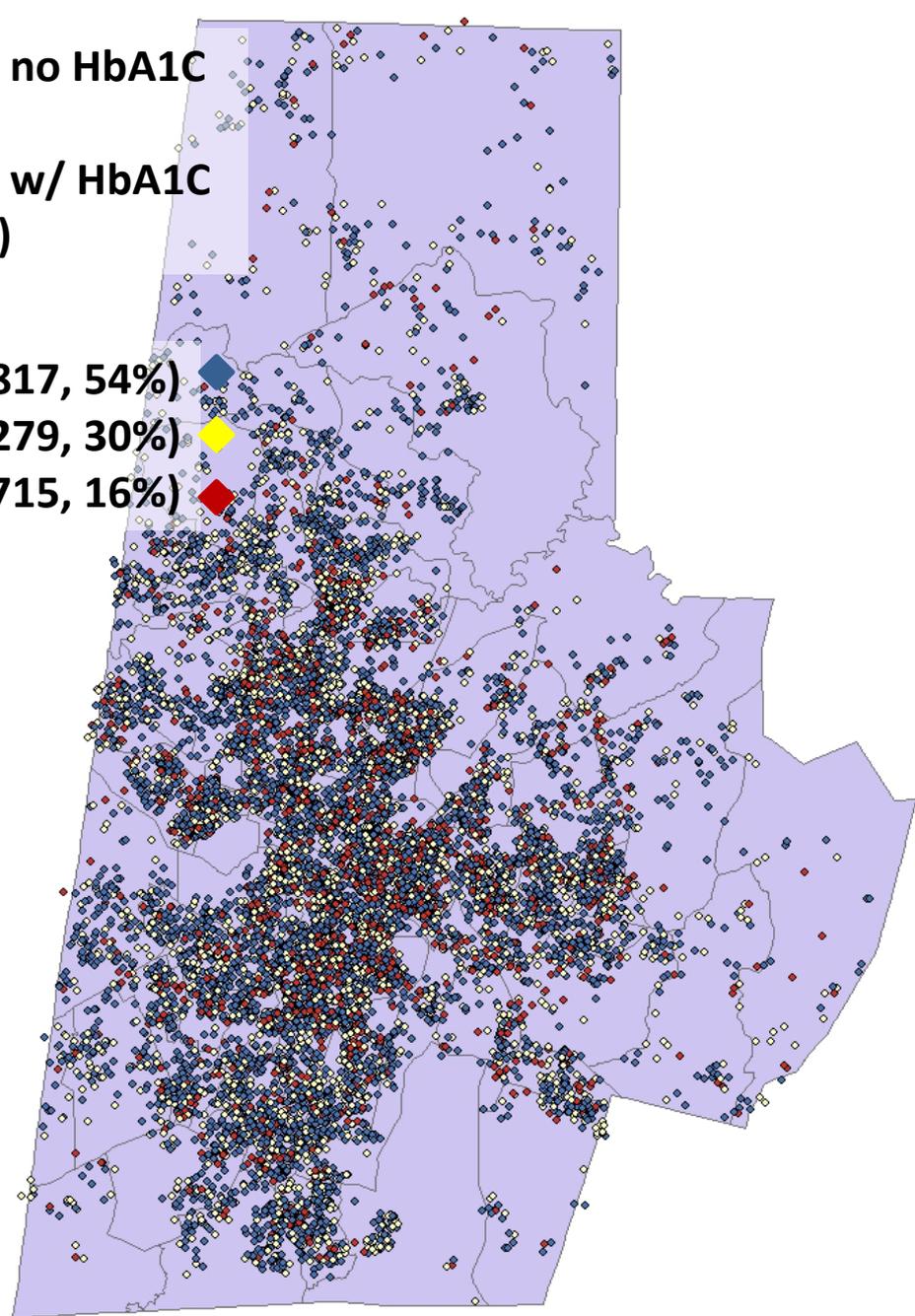
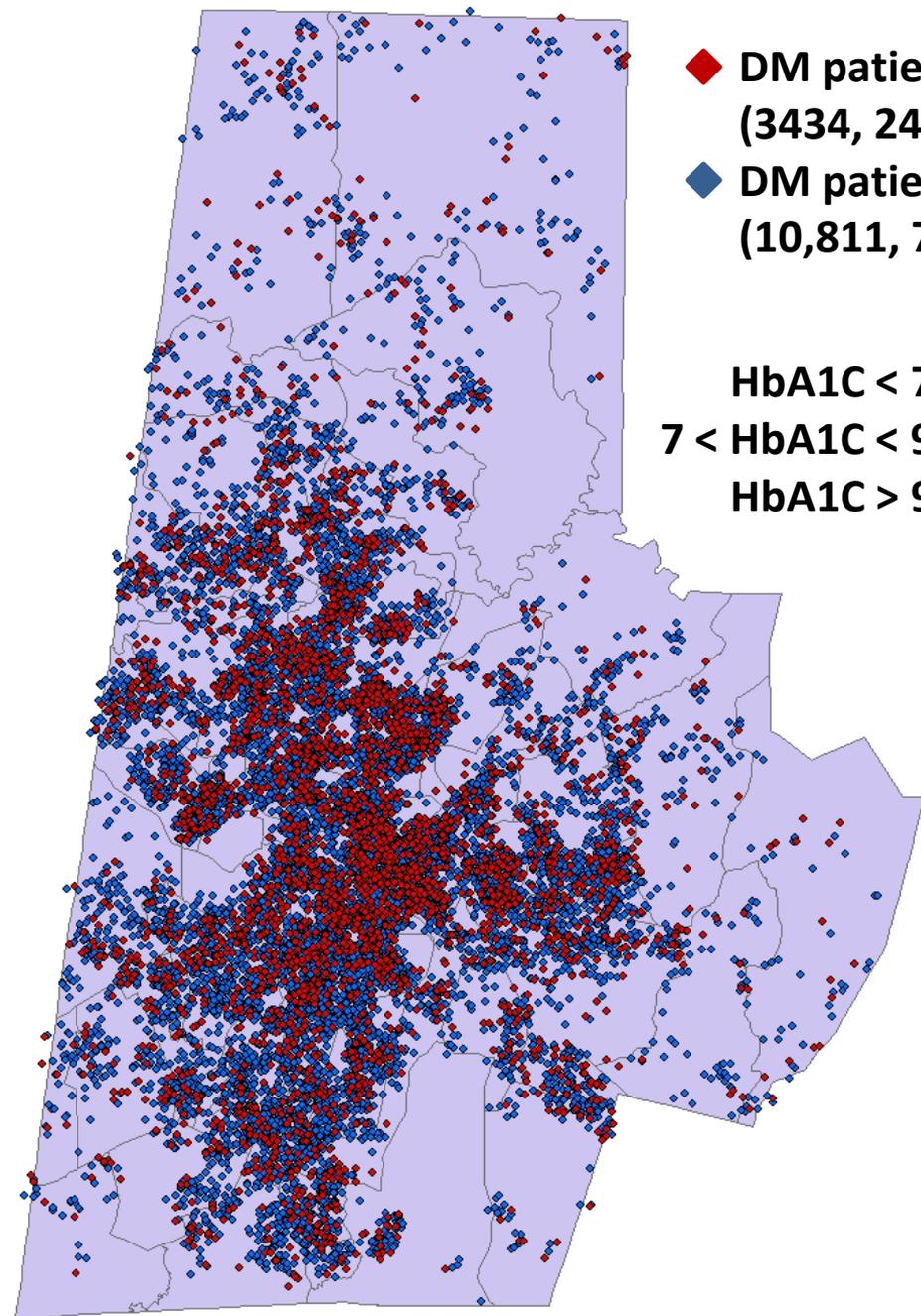
◆ DM patients, no HbA1C
(3434, 24%)

◆ DM patients, w/ HbA1C
(10,811, 76%)

HbA1C < 7 (5817, 54%) ◆

7 < HbA1C < 9 (3279, 30%) ◆

HbA1C > 9 (1715, 16%) ◆





Translational Research: Topics Covered

- Definitions
- Key societal issues and themes
- Role of Academic Health Systems
- A few examples