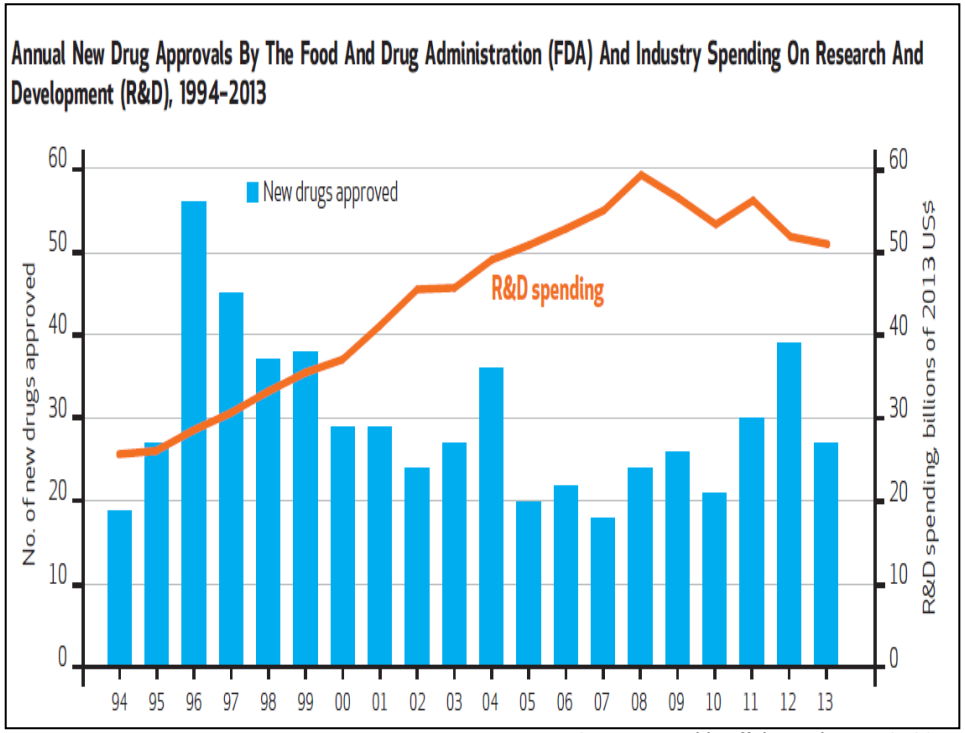
DEERFIELD®
Advancing Healthcare™

Improving Pharmaceutical Innovation By Building A More Comprehensive Database On Drug Development and Use

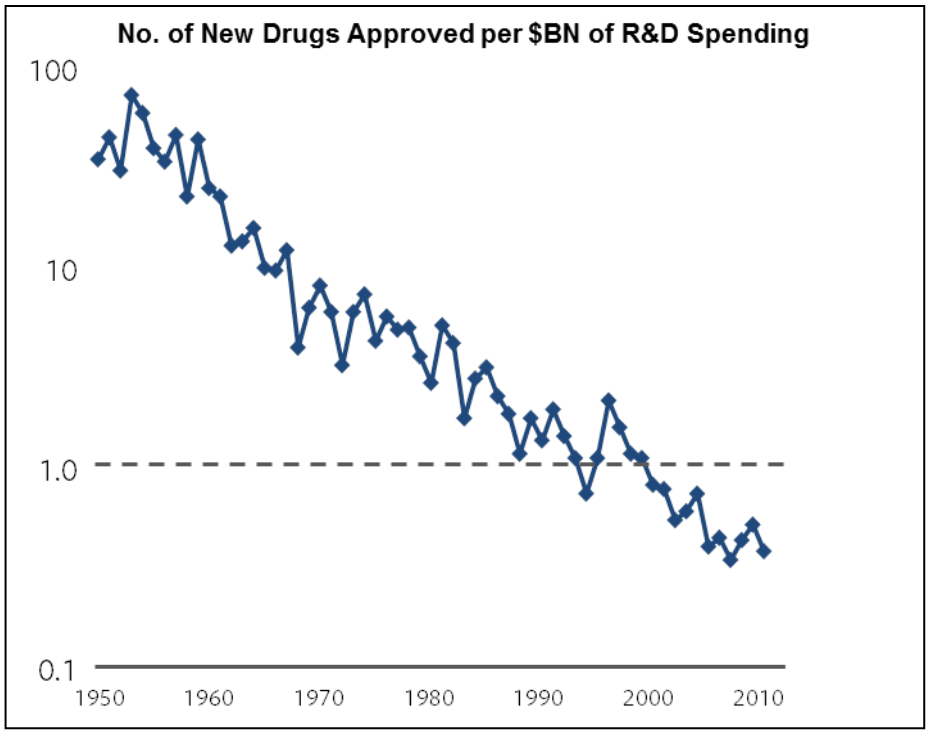
Jonathan S Leff

March 13, 2015

Available Metrics Point to Long-Term Decline in BioPharma R&D Productivity



Source: *Health Affairs*, February 3, 2015



Source: Scannell et. al, *Nature Reviews Drug Discovery*, March 2012.

Policy Makers Are Looking For Solutions

Public Law 112–144
112th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and medical devices, to establish user-fee programs for generic drugs and biosimilars, and for other purposes.

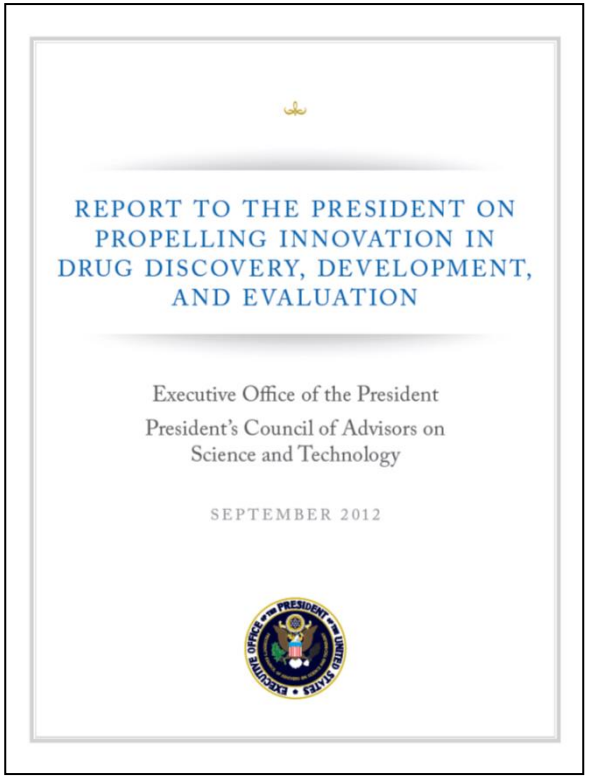
July 9, 2012
[S. 3187]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food and Drug Administration Safety and Innovation Act".

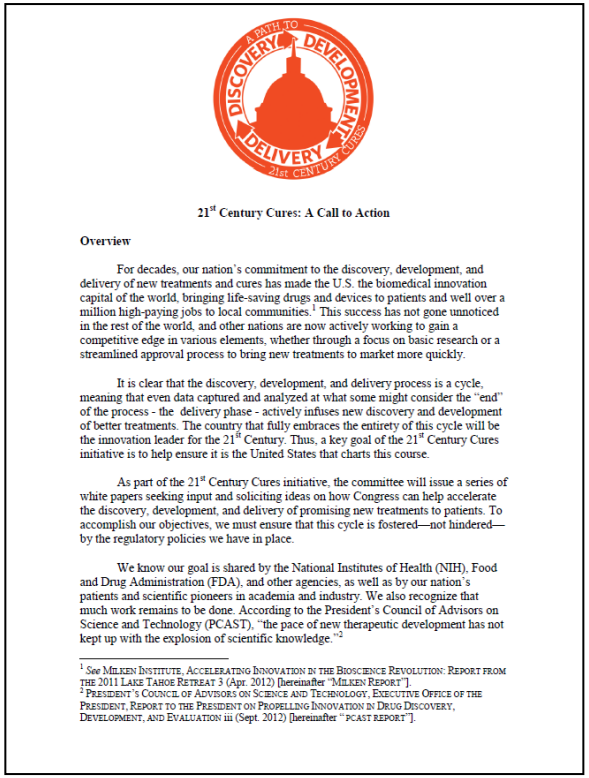
Food and Drug Administration Safety and Innovation Act.
21 USC 301 note.



REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION

Executive Office of the President
President's Council of Advisors on Science and Technology

SEPTEMBER 2012



A PATH TO DISCOVERY DEVELOPMENT DELIVERY 21st CENTURY CURES

21st Century Cures: A Call to Action

Overview

For decades, our nation's commitment to the discovery, development, and delivery of new treatments and cures has made the U.S. the biomedical innovation capital of the world, bringing life-saving drugs and devices to patients and well over a million high-paying jobs to local communities.[1] This success has not gone unnoticed in the rest of the world, and other nations are now actively working to gain a competitive edge in various elements, whether through a focus on basic research or a streamlined approval process to bring new treatments to market more quickly.

It is clear that the discovery, development, and delivery process is a cycle, meaning that even data captured and analyzed at what some might consider the "end" of the process - the delivery phase - actively infuses new discovery and development of better treatments. The country that fully embraces the entirety of this cycle will be the innovation leader for the 21st Century. Thus, a key goal of the 21st Century Cures initiative is to help ensure it is the United States that charts this course.

As part of the 21st Century Cures initiative, the committee will issue a series of white papers seeking input and soliciting ideas on how Congress can help accelerate the discovery, development, and delivery of promising new treatments to patients. To accomplish our objectives, we must ensure that this cycle is fostered—not hindered—by the regulatory policies we have in place.

We know our goal is shared by the National Institutes of Health (NIH), Food and Drug Administration (FDA), and other agencies, as well as by our nation's patients and scientific pioneers in academia and industry. We also recognize that much work remains to be done. According to the President's Council of Advisors on Science and Technology (PCAST), "the pace of new therapeutic development has not kept up with the explosion of scientific knowledge."[2]

[1] *See* MILKEN INSTITUTE, ACCELERATING INNOVATION IN THE BIOSCIENCE REVOLUTION: REPORT FROM THE 2011 LAKE TAHOE RETREAT 3 (Apr. 2012) [hereinafter "MILKEN REPORT"].
[2] PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY, EXECUTIVE OFFICE OF THE PRESIDENT, REPORT TO THE PRESIDENT ON PROPELLING INNOVATION IN DRUG DISCOVERY, DEVELOPMENT, AND EVALUATION iii (Sept. 2012) [hereinafter "PCAST REPORT"].

How Can We Fix It If We Can't Measure It?

Commonly Cited Metrics

- NME approvals per year
- R&D spending
- Venture capital investment
- New company formation
- FDA performance metrics
- Cost of drug development
- Success rates in development

Limitations

- Incomplete picture of innovation process
- Inconsistent or incomplete data sources
- Survey-based as opposed to comprehensive
- Metrics not routinely collected and updated
- Lack of broad access to underlying data

Brookings-Deerfield Innovation Database

Primary objective: develop, populate, maintain and make publicly available a comprehensive repository containing key metrics of new drug development, utilization and impact

TRACKING INNOVATION

By Gregory W. Daniel, Alexis Cazé, Morgan H. Romine, Céline Audibert, Jonathan S. Leff, and Mark B. McClellan

DOI: 10.1377/hlthaff.2014.1019
HEALTH AFFAIRS 34,
NO. 2 (2015): 319–327

Improving Pharmaceutical Innovation By Building A More Comprehensive Database On Drug Development And Use

ABSTRACT New drugs and biologics have had a tremendous impact on the treatment of many diseases. However, available measures suggest that pharmaceutical innovation has remained relatively flat, despite substantial growth in research and development spending. We review recent literature on pharmaceutical innovation to identify limitations in measuring and assessing innovation, and we describe the framework and collaborative approach we are using to develop more comprehensive, publicly available metrics for innovation. Our research teams at the Brookings Institution and Deerfield Institute are collaborating with experts from multiple areas of drug development and regulatory review to identify and collect comprehensive data elements related to key development and regulatory characteristics for each new molecular entity approved over the past several decades in the United States and the European Union. Subsequent phases of our effort will add data on downstream product use and patient outcomes and will also include drugs that have failed or been abandoned in development. Such a database will enable researchers to better analyze the drivers of drug innovation, trends in the output of new medicines, and the effect of policy efforts designed to improve innovation.

Gregory W. Daniel (GDaniel@brookings.edu) is a fellow and managing director for evidence development and innovation at the Engelberg Center for Health Care Reform at Brookings, in Washington, D.C.

Alexis Cazé is managing director of the Deerfield Institute, in Epalinges, Switzerland.

Morgan H. Romine is a research associate at the Engelberg Center for Health Care Reform at Brookings.

Céline Audibert is director of European market research at the Deerfield Institute.

Jonathan S. Leff is chairman of the Deerfield Institute, and a partner with Deerfield Management, in New York City.

Mark B. McClellan is a senior fellow and director of the Health Care Innovation and Value Initiative at the Engelberg Center for Health Care Reform at Brookings.

Over the past several decades new drugs and biologics have had a tremendous impact on the treatment of a wide range of diseases. Better scientific understanding of diseases and their progression, as well as advancements in drug development and regulation, have led to increasingly targeted and sometimes breakthrough treatments.

Despite this progress, however, the innovation ecosystem appears to be falling short of its full potential to improve health. Major advancements seen in some therapeutic areas, such as hepatitis C, melanoma, and cystic fibrosis, are not occurring for many other diseases, such as Alzheimer's disease and drug-resistant Gram-negative bacterial infections, for which treatment options remain limited despite promising basic research discoveries.

In addition, substantial growth in research and development (R&D) spending by the pharmaceutical industry has not had comparable effects on industry output, which has been relatively flat as assessed by the conventional measure of annual new molecular entities (NMEs) approved by the Food and Drug Administration (FDA)[1] (Exhibit 1). The apparent declining productivity implied by such measures (Exhibit 2) may have contributed to the decline in real R&D spending observed in recent years (Exhibit 1).

Many recent policy reform efforts have tried to address this productivity decline and improve

Proposed Research Categories and Initial Data Elements

Research category	Example questions	Data sets
Measuring characteristics of approved drugs	What is the impact of X policy on successfully marketed drugs? How are trends in development time lines and costs different by therapeutic area?	Public data on approved NMEs
Measuring impact of new drugs on health outcomes	How does the postmarket/clinical use environment change the way we view innovation? How can we better define *innovative* by including more patient-centric parameters?	Public data on approved NMEs + Clinical outcomes data
Measuring drivers of development success	What are the drivers of success overall and at each stage of development? What are the commonalities between drugs that are not approved, and how do these trends differ from those drugs that complete regulatory review?	Public data on approved NMEs + Data on non-approved products
Measuring "macro" influences on innovation	What are the broader underlying characteristics of therapeutic areas that enable innovative drug development? How does the number or output of PPPs dedicated to a specific therapeutic area affect downstream innovation?	Data on therapeutic areawide characteristics + Public data on approved NMEs + Clinical outcomes data; + Public data on approved NMEs + Data on non-approved products

EXHIBIT 4

Initial Data Elements For The Proposed First Phase Of A Database On Approved New Molecular Entities

Category of information	Data elements
Background	Unique drug identification number Trade name Active ingredient Drug class Therapeutic area Innovation category[a] Sponsor company size
Patent and early-stage development	Inventor name Country of origin Initial patent approval date Patent sponsor Country of origin for mechanism of action Companies that played a role in development Funding sources
Clinical trial	Date first used in humans Number of healthy trial volunteers Number of enrolled patients Number of trials sites in the US, EU, Japan, and rest of world Number of centers enrolling patients
Regulatory review	Company filing in the US or EU Primary filing day Primary FDA or EMA approval day FDA review tools used (such as Priority Review) EMA priority review status Primary indication in US or EU Additional indications in US or EU
Academic publication	Number of articles Average impact factor First appearance in literature
Price and uptake	Type of uptake curve Initial price Current price Peak year for sales Blockbuster status[b]
Competitors and generic products	Date of market entry Pricing Uptake Development characteristics

Path To Success

- Commitment: Brookings and Deerfield have developed the database concept with input from a variety of stakeholders, and are now committing substantial resources to support database development and data collection
- Collaboration: create a consortium of healthcare stakeholders who share the vision of providing broad access to new drug innovation metrics
- Expertise: Build consensus around key metrics and methodology
- Accuracy: Efficient sourcing of the data is a top priority

Next Steps

- Engage with key stakeholders who can contribute thought-leadership and data sources
- Develop expert groups to build consensus on research questions of interest, database design and definitions of data elements

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Thank you

IMS INSTITUTE FOR HEALTHCARE INFORMATICS

Tracking Innovation: Recent Research

Brookings Institution

March 13, 2015

Decline In Economic Returns From New Drugs Raises Questions About Sustaining Innovations

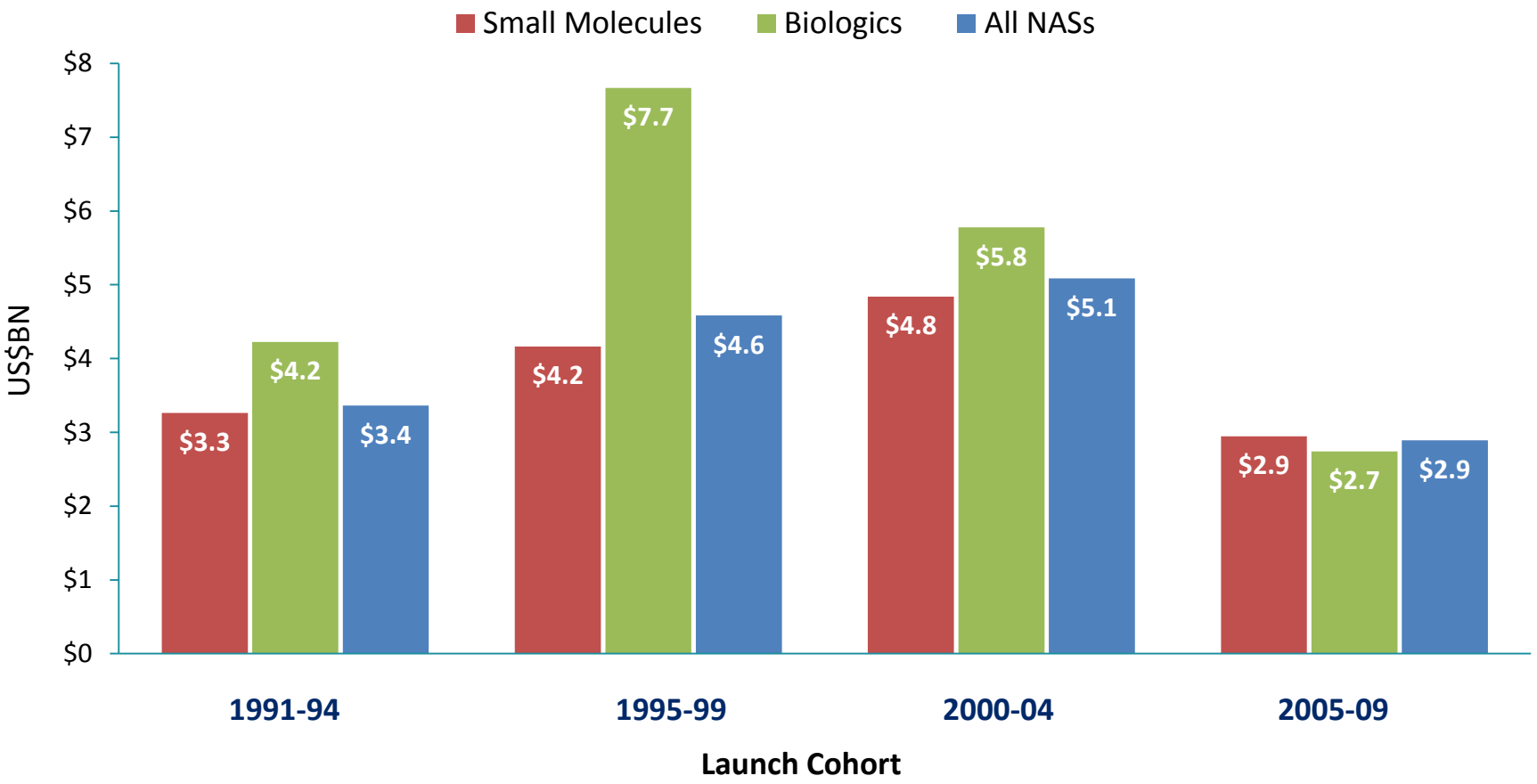
Ernst R. Berndt, Louis E. Seley Professor in Applied Economics, Alfred P. Sloan School of Management, MIT

Deanna Nass, Michael Kleinrock, Murray Aitken, IMS Institute for Healthcare Informatics

Research supported in part by the Pharmaceutical Research and Manufacturers of America, who provided funding for the data analysis undertaken by the IMS Institute for Healthcare Informatics.

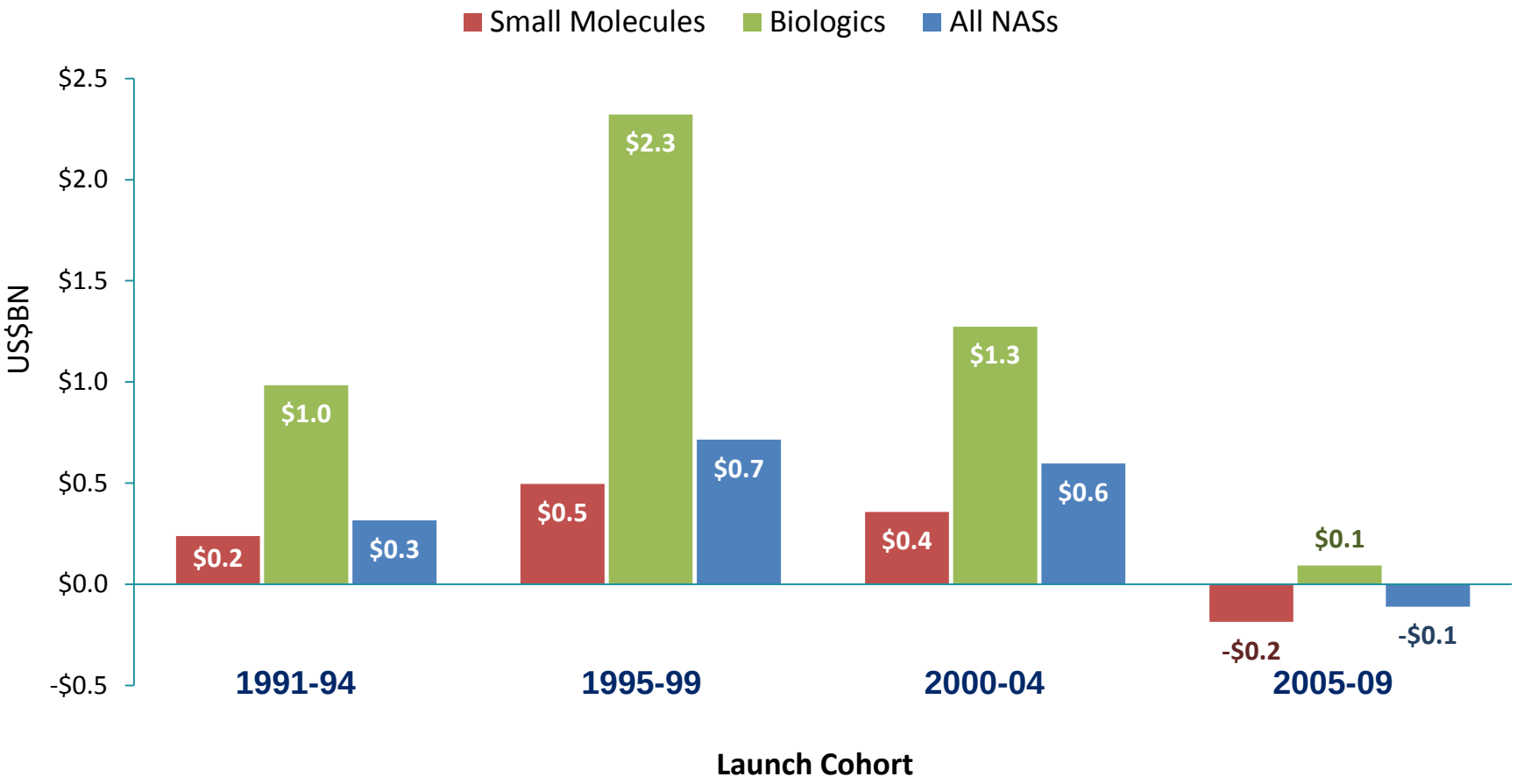
HealthAffairs

Average Present Value Of Lifetime Global Net Sales Of Novel Active Substances (NASs) By Launch Cohort



SOURCE: Authors' analysis of 1991-2012 data from IMS Health Inc.'s MIDAS database. NOTE: Average present value is the value discounted for the cost of capital, reflecting the time value of money.

Average Lifetime After-tax Net Economic Returns Of Novel Active Substances (NASs), By Launch Cohort



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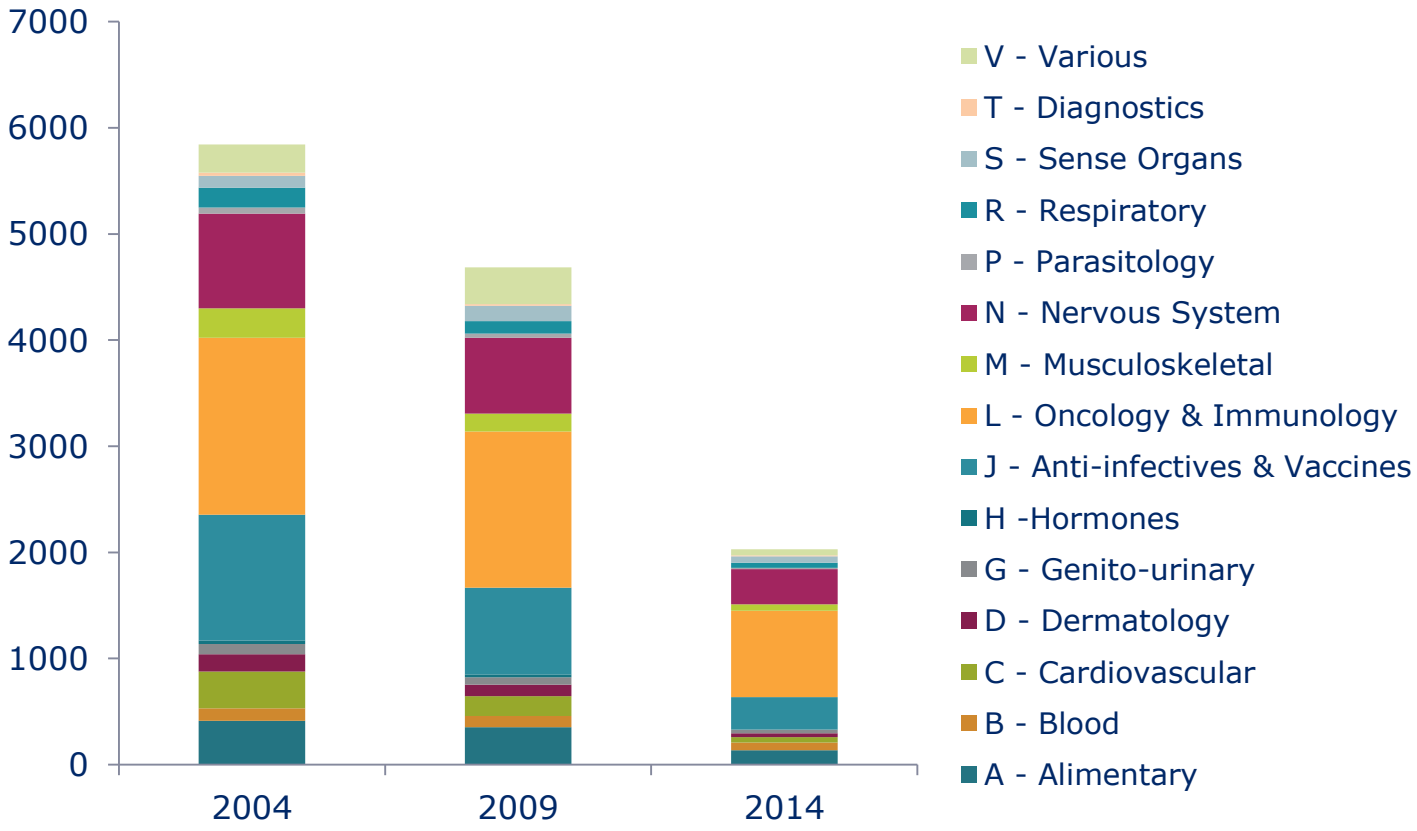
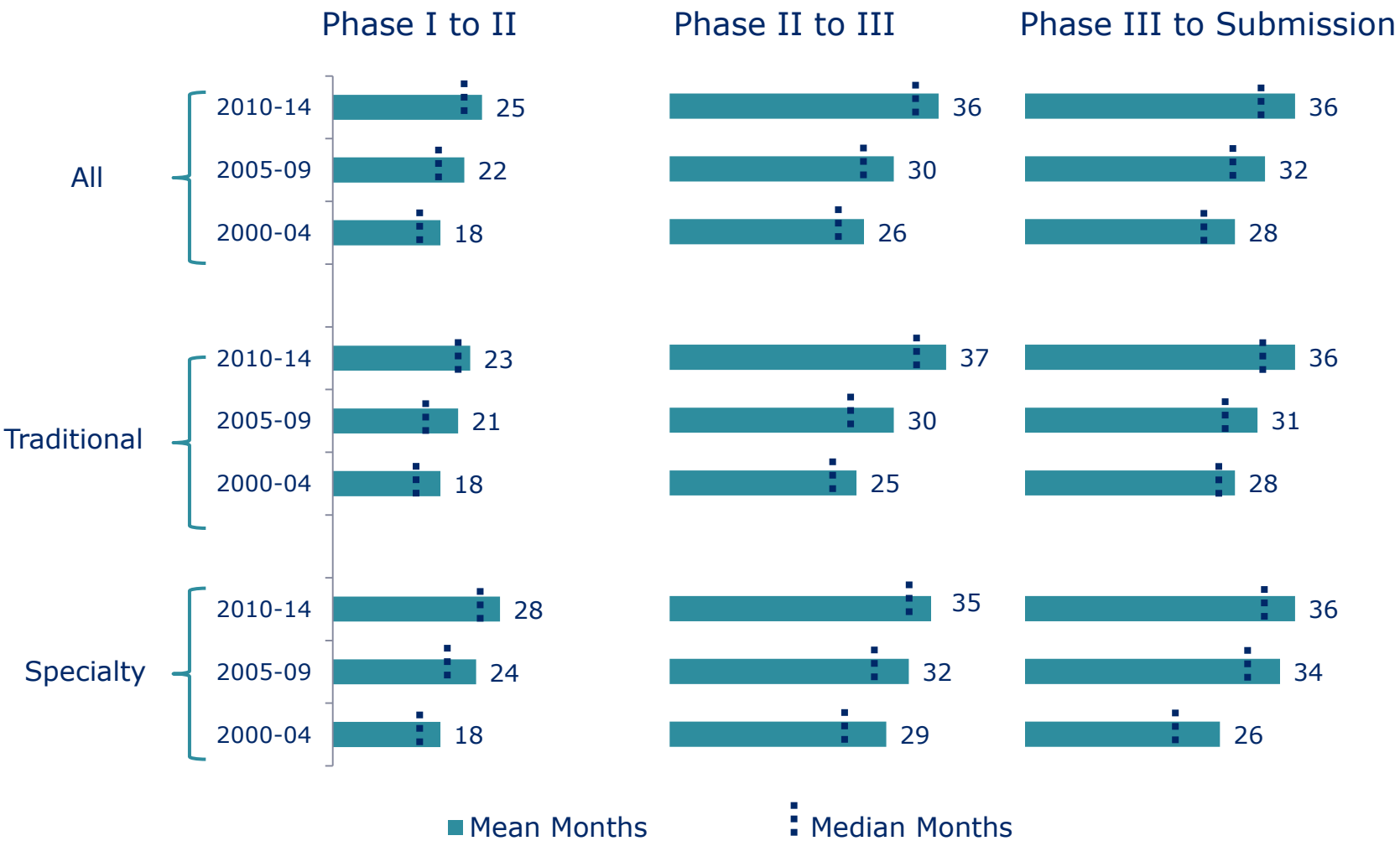
PRECLINICAL PIPELINE BY ATC LEVEL



Source: IMS R&D Focus; IMS Institute analysis

AVERAGE AND TIME FOR R&D PROJECTS TO PROGRESS TO NEXT PHASE OF RESEARCH



Source: IMS R&D Focus; IMS Institute analysis

State of Biomedical Innovation CER

Presentation at Brookings

March 13, 2015

Peter J. Neumann, Sc.D.

Tufts Medical Center

Tufts Medical Center
Institute for Clinical Research and Health Policy Studies

CEVR
Center for the Evaluation of Value and Risk in Health

Measuring innovation

1. Tufts Cost-Effectiveness Analysis Registry

2. QALY gains

3. Predicting coverage/reimbursement

1. Tufts Cost-Effectiveness Analysis Registry

www.cearegistry.org

Tufts Medical Center
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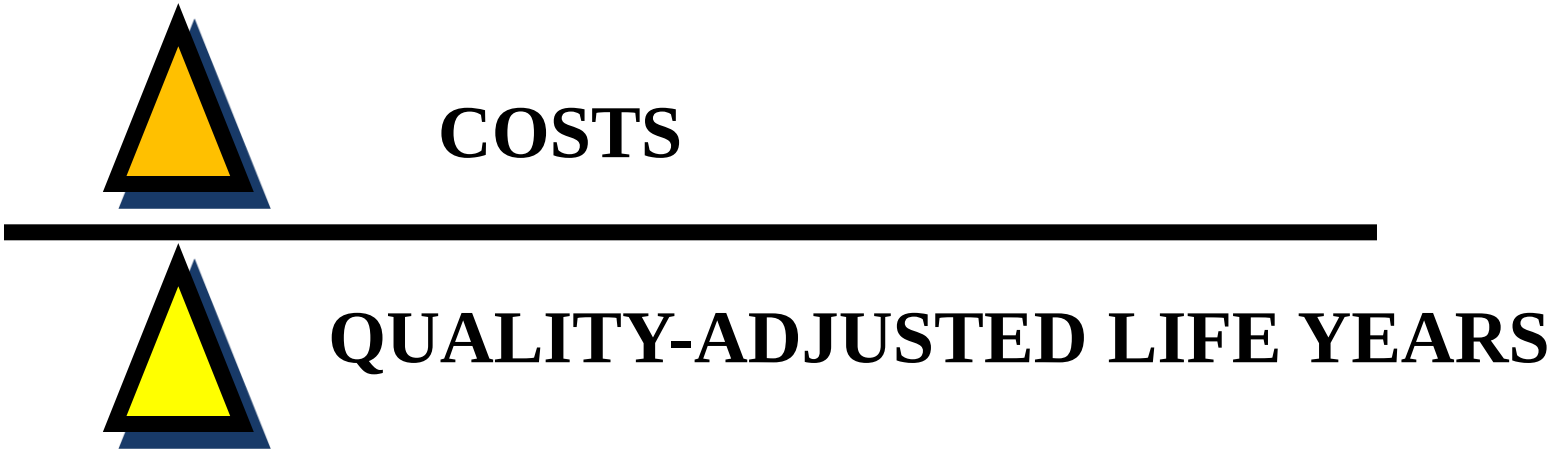
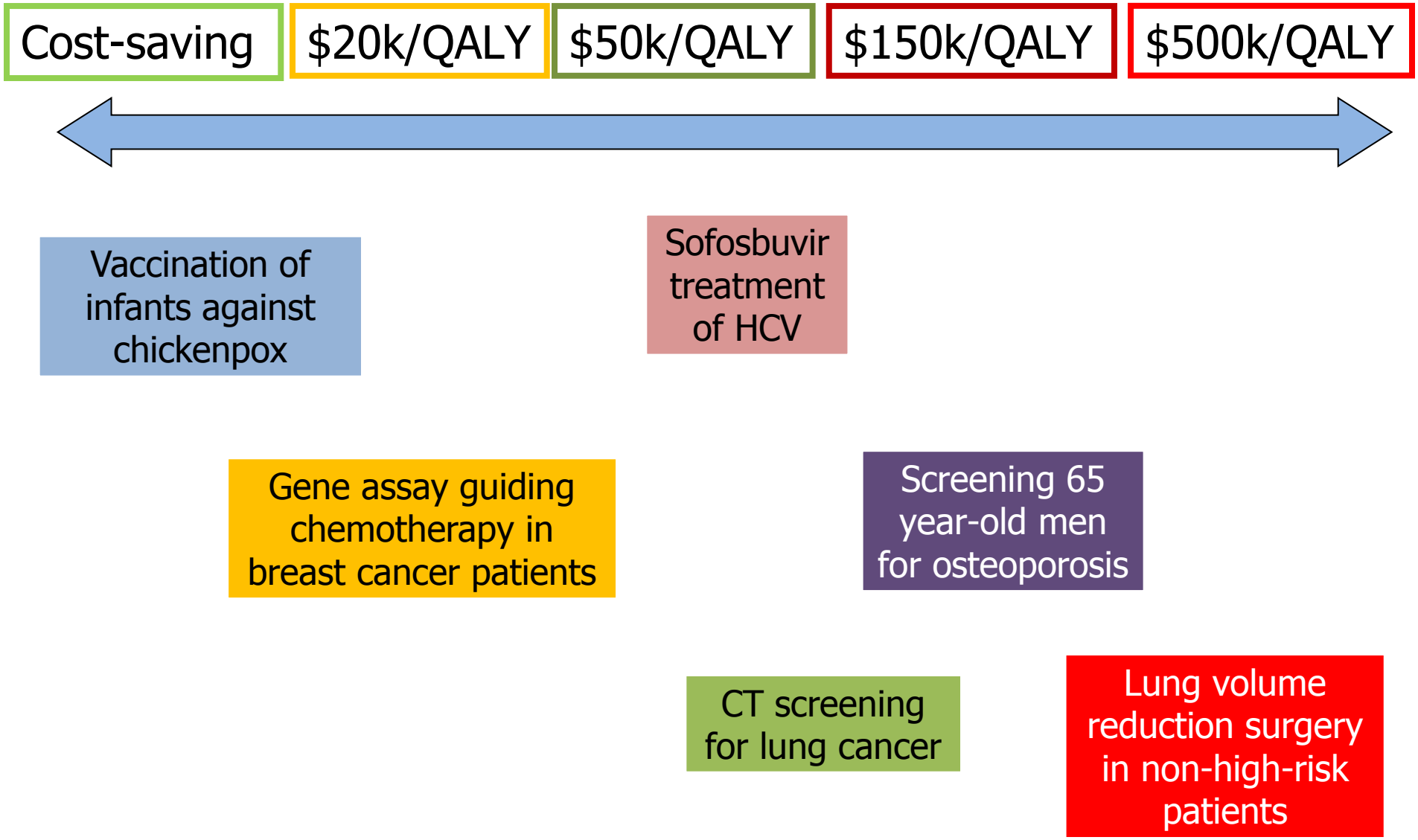
Cost/QALY Ratios



Cost Effectiveness of Selected Interventions



2. QALY GAINS

By James D. Chambers, Teja Thorat, Junhee Pyo, Matthew Chenoweth, and Peter J. Neumann

Despite High Costs, Specialty Drugs May Offer Value For Money Comparable To That Of Traditional Drugs

DOI: 10.1377/hlthaff.2014.0574
HEALTH AFFAIRS 33,
NO. 10 (2014): 1751–1760

ABSTRACT **Specialty drugs are often many times more expensive than traditional drugs, which raises questions of affordability and value. We compared the value of specialty and traditional drugs approved by the Food and Drug Administration (FDA) in the period 1999–2011. To do this, we identified published estimates of additional health gains (measured in quality-adjusted life-years, or QALYs) and increased costs of drug and health care resource use that were associated with fifty-eight specialty drugs and forty-four traditional drugs, compared to preexisting care. We found that specialty drugs offered greater QALY gains (0.183 versus 0.002 QALYs) but were associated with greater additional costs ($12,238 versus $784), compared to traditional drugs. The two types of drugs had comparable cost-effectiveness. However, the distributions across the two**

James D. Chambers (jchambers@tuftsmedicalcenter.org) is an investigator at the Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, and an assistant professor of medicine in the School of Medicine, Tufts University, in Boston, Massachusetts.

Teja Thorat is a research associate at the Center for the Evaluation of Value and Risk in Health, Tufts Medical Center.

QALY gains by FDA designation

FDA designation	Mean QALY Gains of Drugs	
	Rapid review	Regular review
Fast-track (24 of 102 drugs)	0.34	0.12**
Accelerated approval (15 of 102 drugs)	0.43	0.13**
Priority reviewer (54 of 102 drugs)	0.35	-0.02**

** $p < 0.05$

Chambers et al., 2015. Preliminary data. ** > 0.05

3. Predicting coverage

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Medicare's Enduring Struggle to Define "Reasonable and Necessary" Care

Peter J. Neumann, Sc.D., and James D. Chambers, Ph.D.

Policy implications

- Focus on value not cost
- Quantify innovation/value
- The information can inform decisions
- But combine with changed incentives

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Therapeutic Context and the Cost of Drug Development

Marta E. Wosińska, PhD

Director, Economics Staff
Office of Program and Strategic Analysis (OPSA)
Center for Drug Evaluation and Research (CDER)

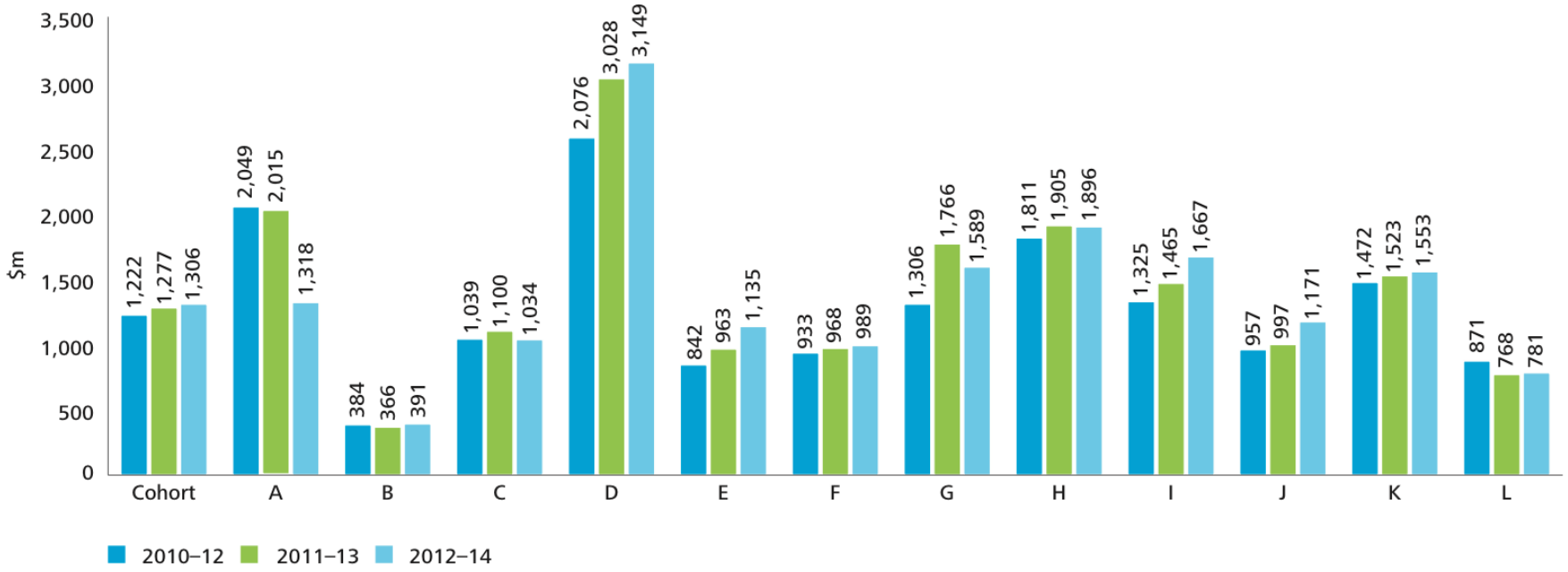
March 13, 2015

Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

Q: How much does it cost to develop a drug? A: It varies greatly.

Three-Year Rolling Average Cash Costs to Develop an Asset from Discovery to Launch



Source: *Measuring the Return from Pharmaceutical Innovation*, Deloitte (2014)

Therapeutic context helps explain variation in R&D costs

- Therapeutic context reflects:
  - Characteristics of the disease (the What)
  - Level of scientific knowledge (the Why)
  - Existing treatment options (the How)
- Relevant because it is the context for the regulator's determination whether benefits outweigh the risks
- Therapeutic context has implications for R&D cost through:
  - Its impact on study design
  - Its impact on the timing of trials

Characteristics of the disease: the *What* of therapeutic context

- Examples of impact on trial design:
  - In general, chronic/episodic conditions require long studies if no surrogate endpoints are available
  - Does the drug try to prevent an infrequent event?
- Examples of impact on trial timing:
  - Phase 1 might be combined with Phase 2 if drug is expected to have toxicity unacceptable for healthy volunteers
  - After establishing efficacy, regulator may accept a greater risk for severe diseases with few or no treatment options

Scientific knowledge: the *Why* of therapeutic context

- Understanding disease pathophysiology, biochemical and genetic underpinnings of disease helps:
  - Lower cash costs if firms do not have to do such research
  - Lower failure cost by pointing out dead ends
  - Identify which people are likely not to respond or likely to experience side effects
  - Cut trial length if surrogate endpoints are established
- Examples:
  - Disappointments in Alzheimer's
  - Success stories in HIV and cancer

Existing therapeutic options: the *How* of therapeutic context

- Therapeutic options determine the extent of unmet medical need for a given indication
- Impact on trial design
  - Active control may be used for ethical reasons
  - Generally, establishing superiority or non-inferiority may require a large sample size
- Impact on trial timing
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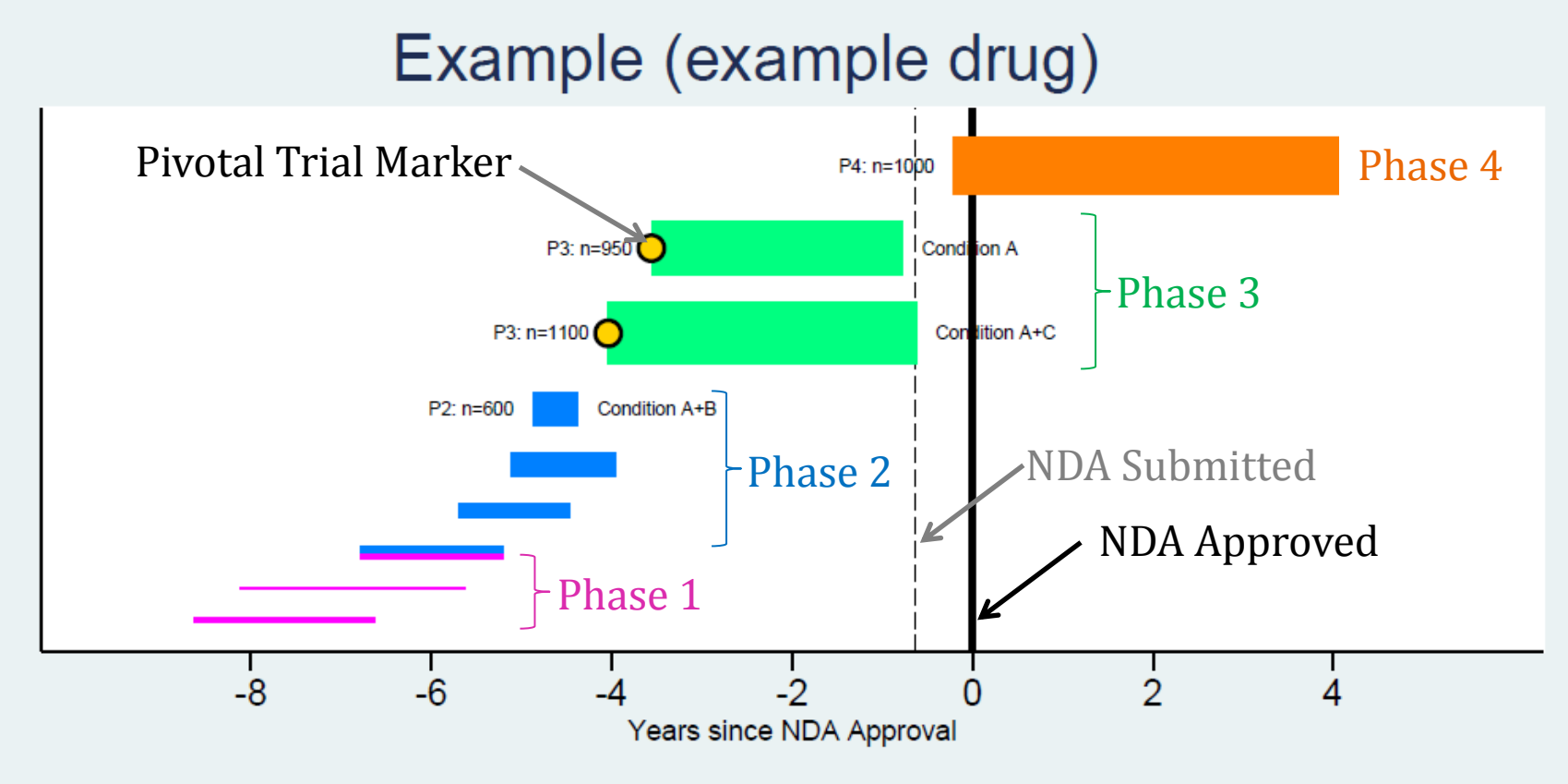
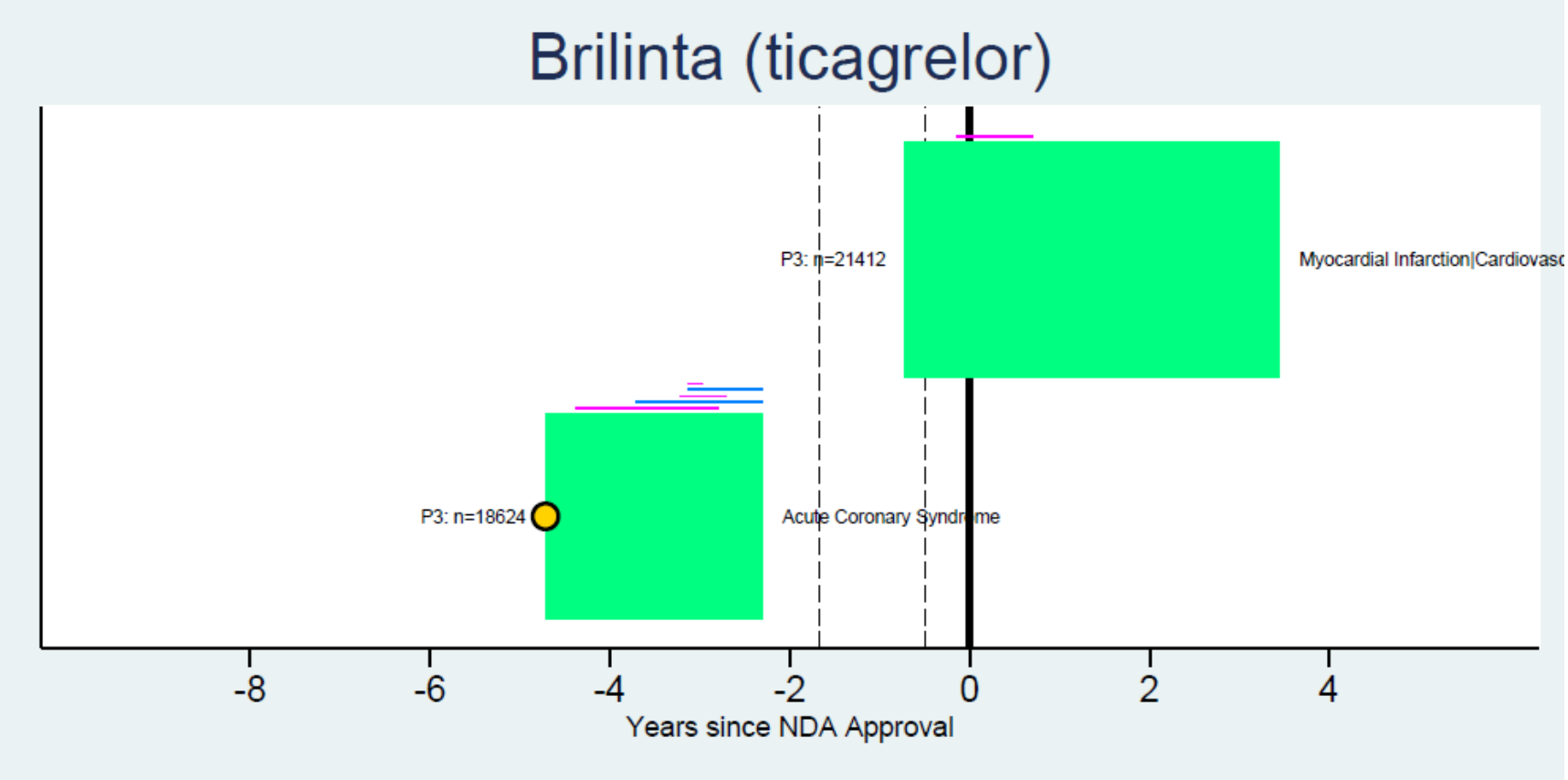
Visualizing therapeutic context in the clinical development process…





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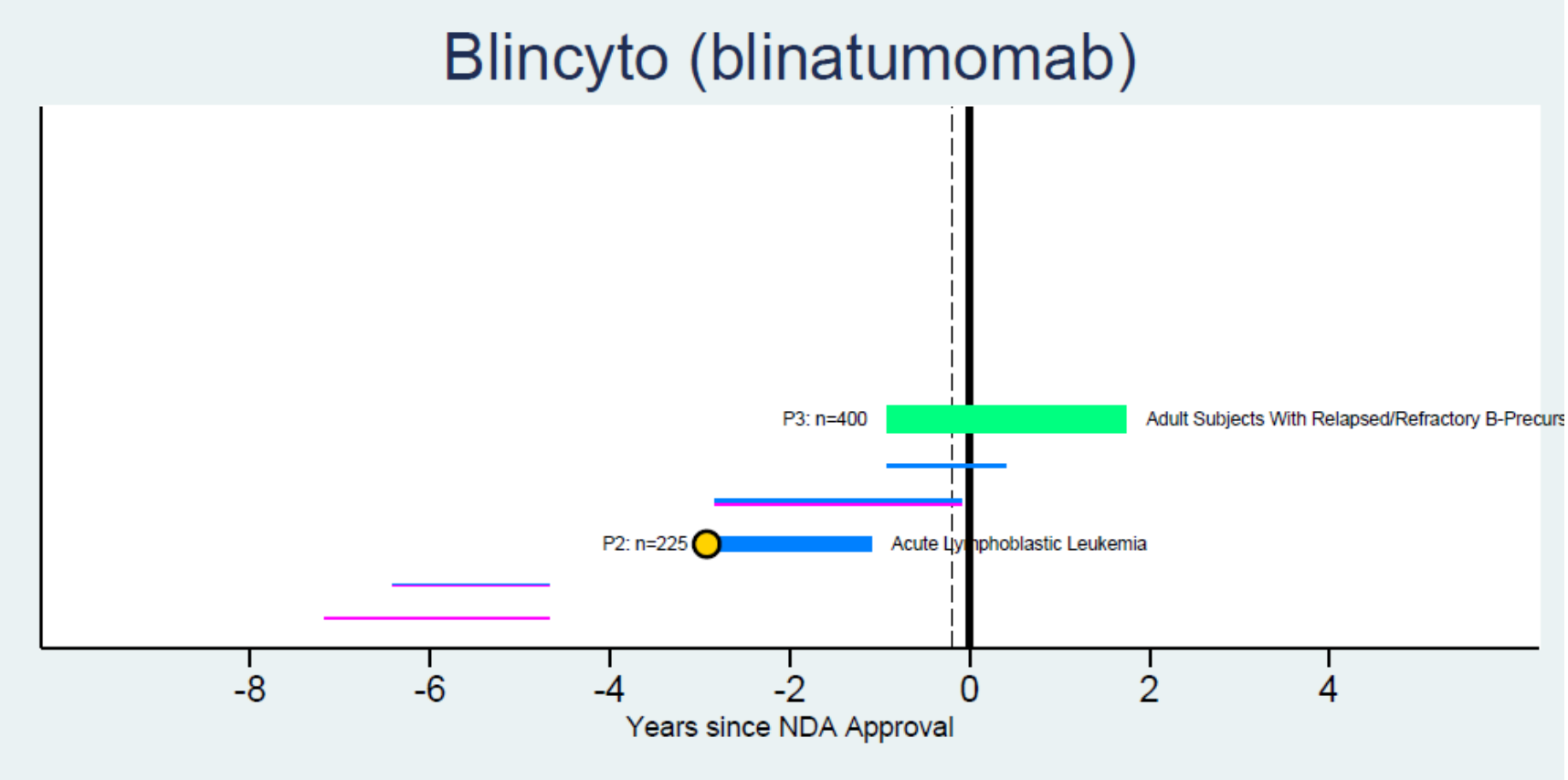

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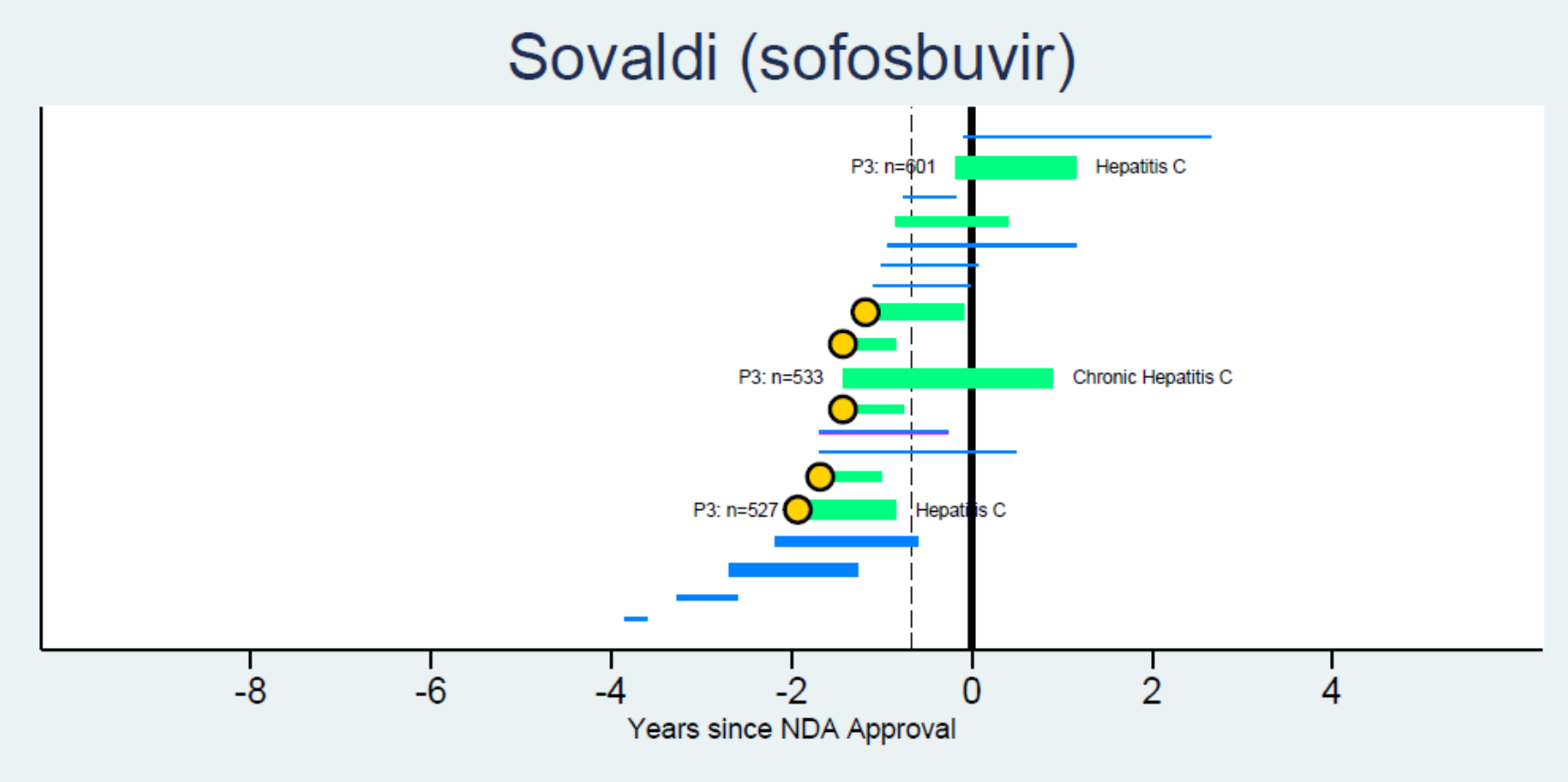

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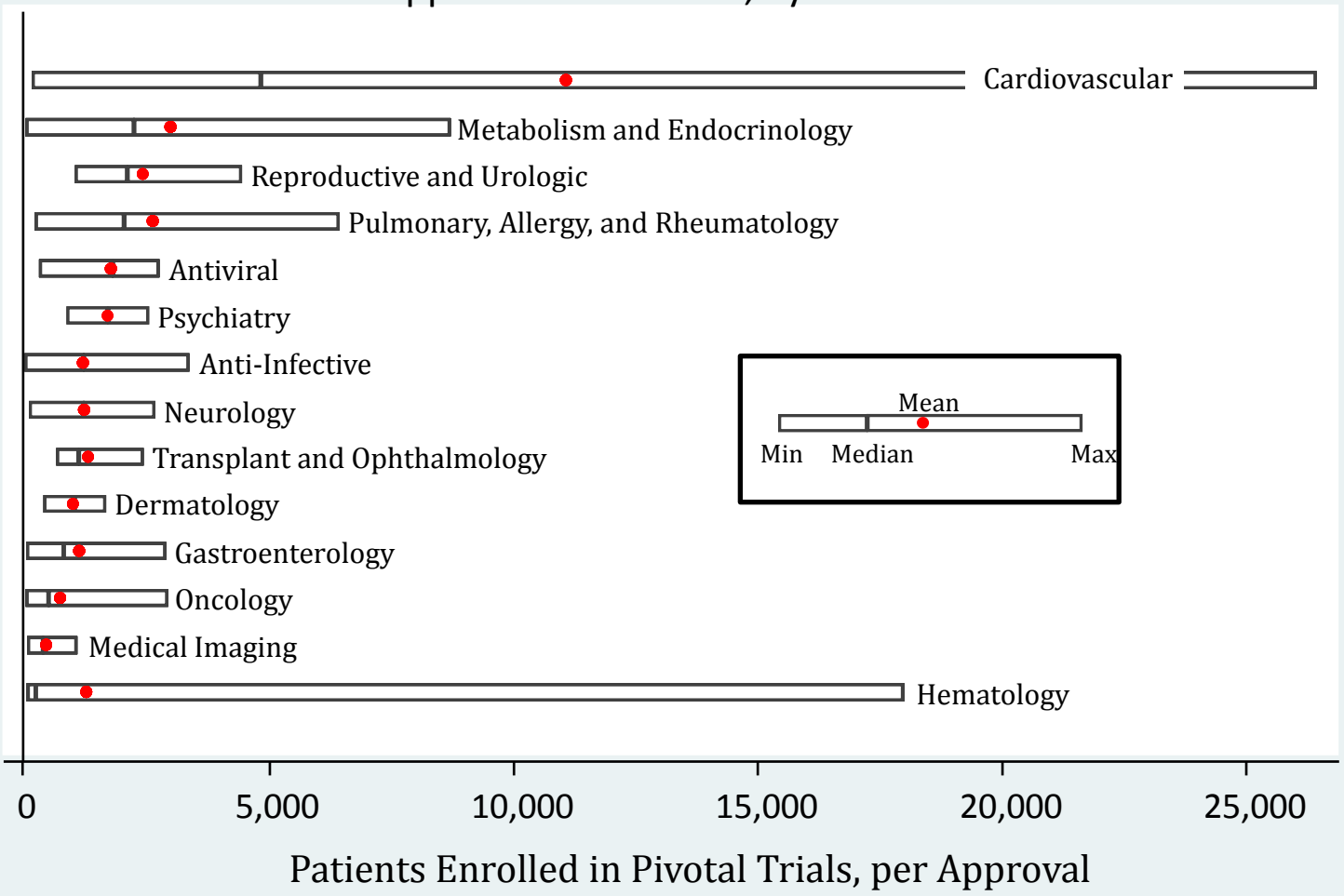
Summary of Enrollment in Pivotal Trials

NME Approvals 2011-2014, by Review Division



Therapeutic context is an important driver of drug development cost

- Implications for researchers:
  - When studying R&D costs and/or drug development timelines, account for the what, why, and how of therapeutic context
- Implications for policymakers:
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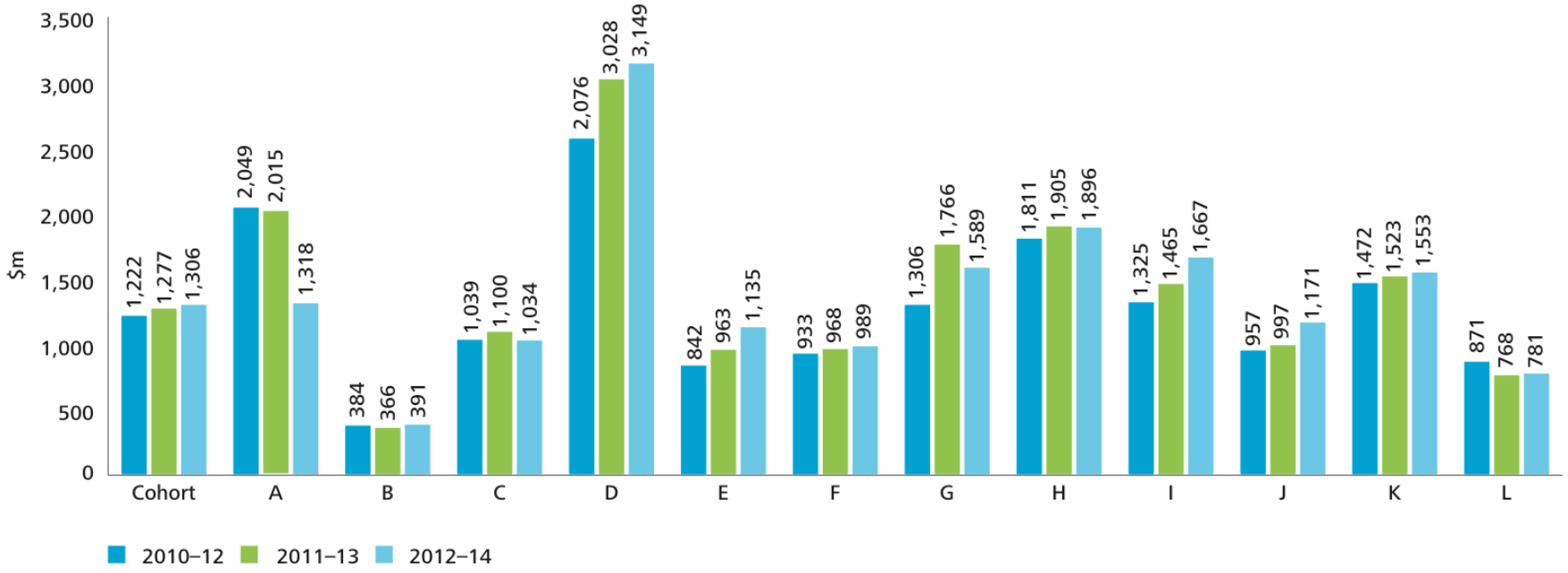

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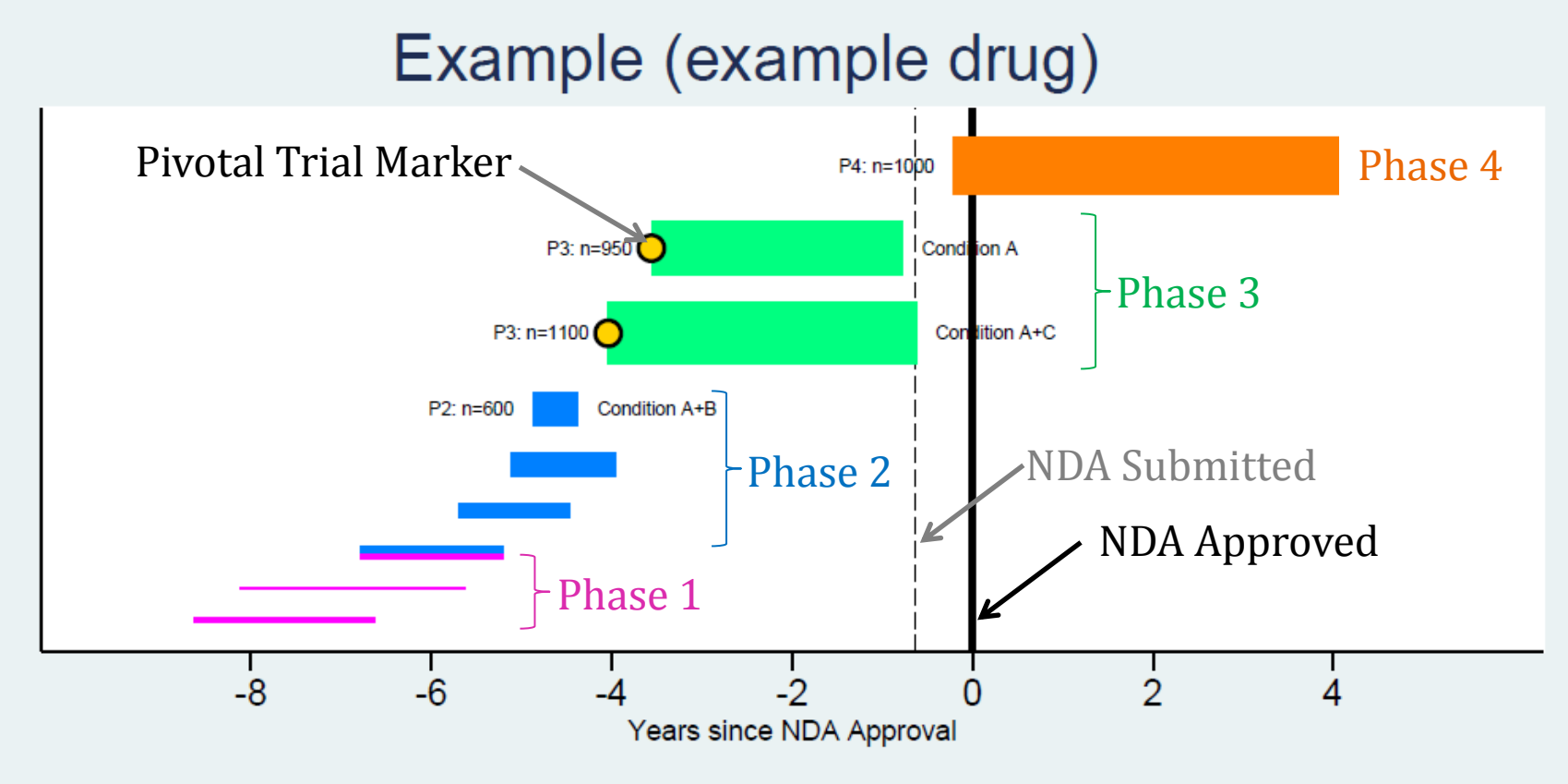

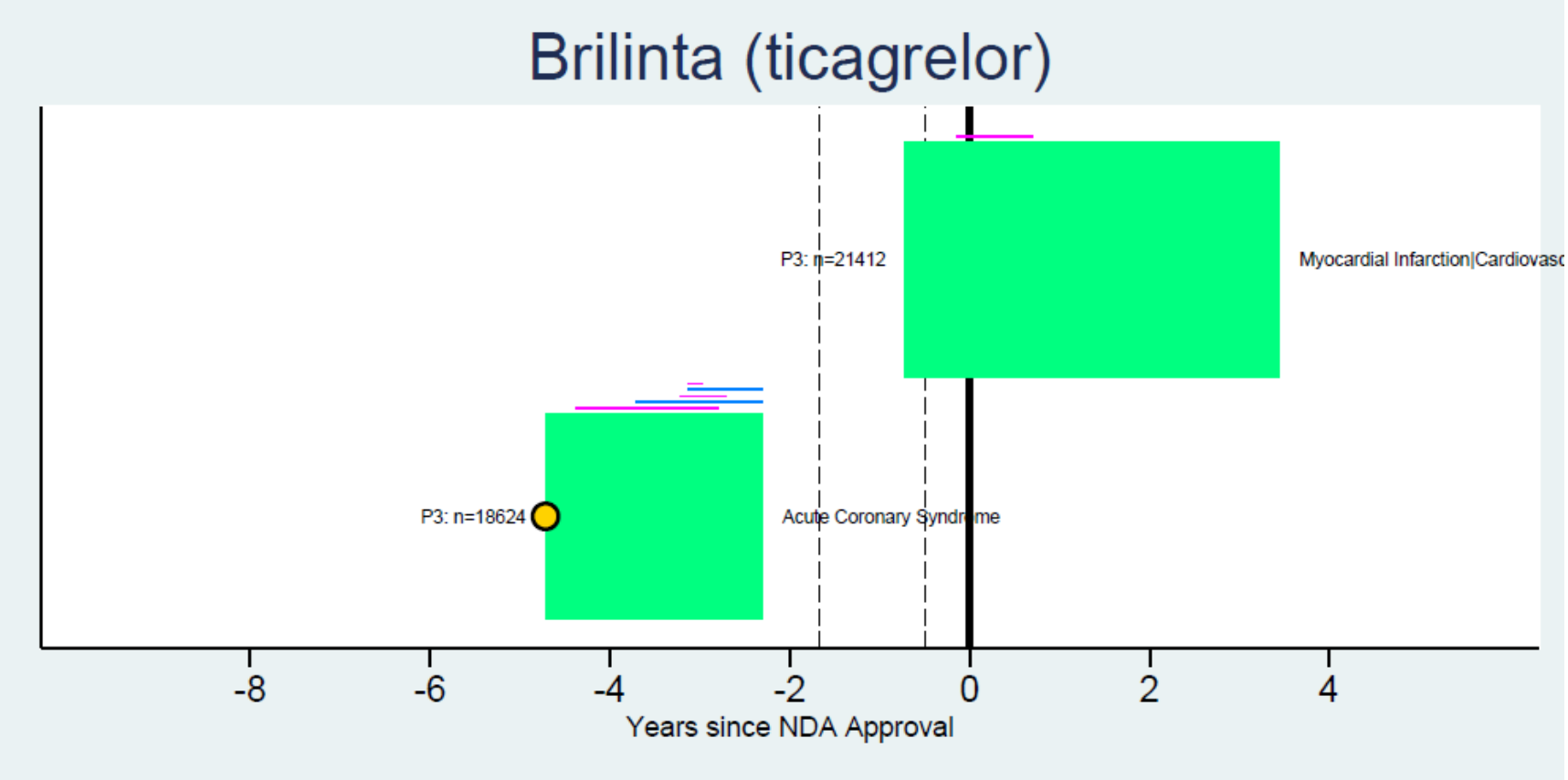

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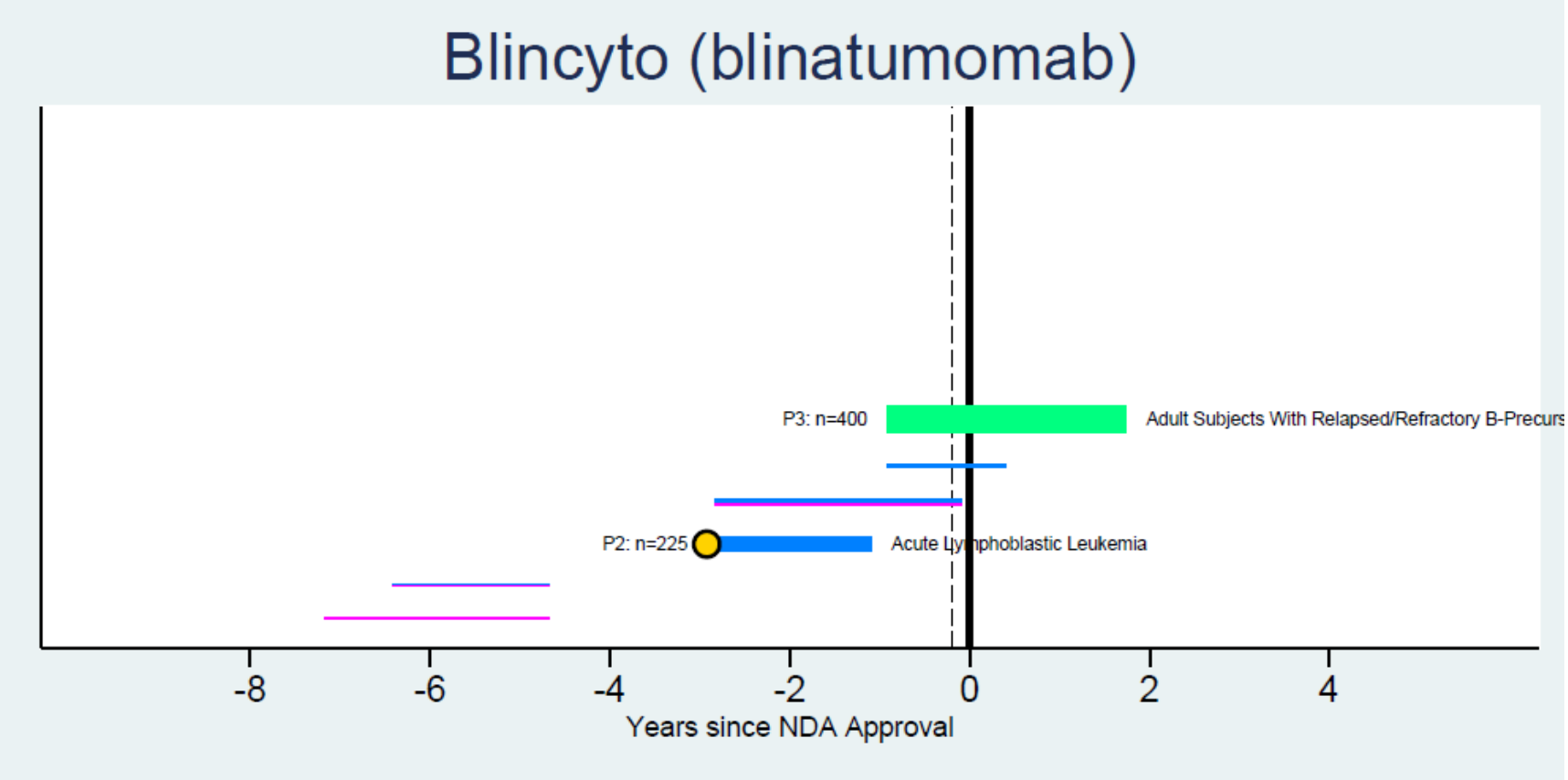

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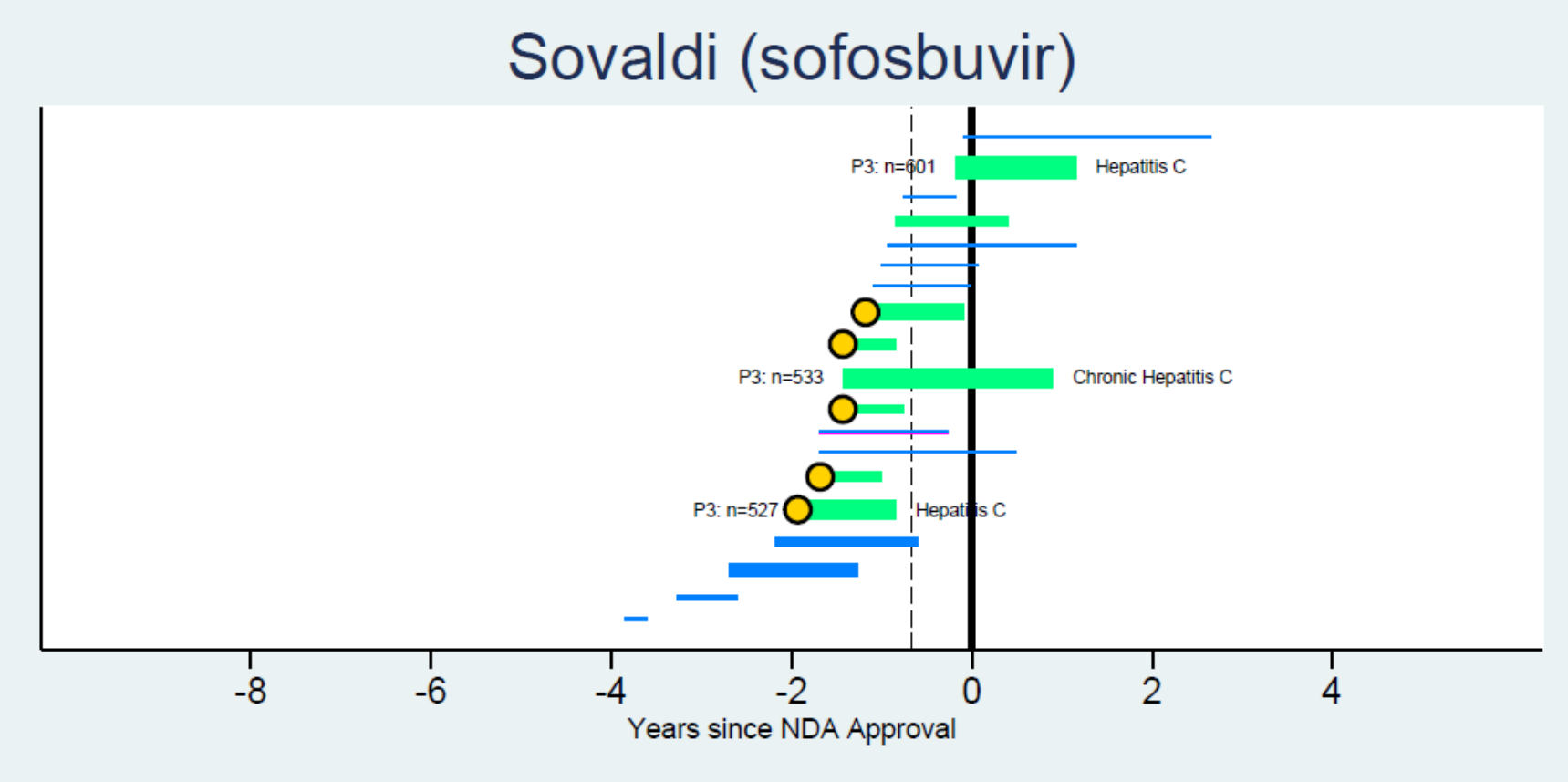

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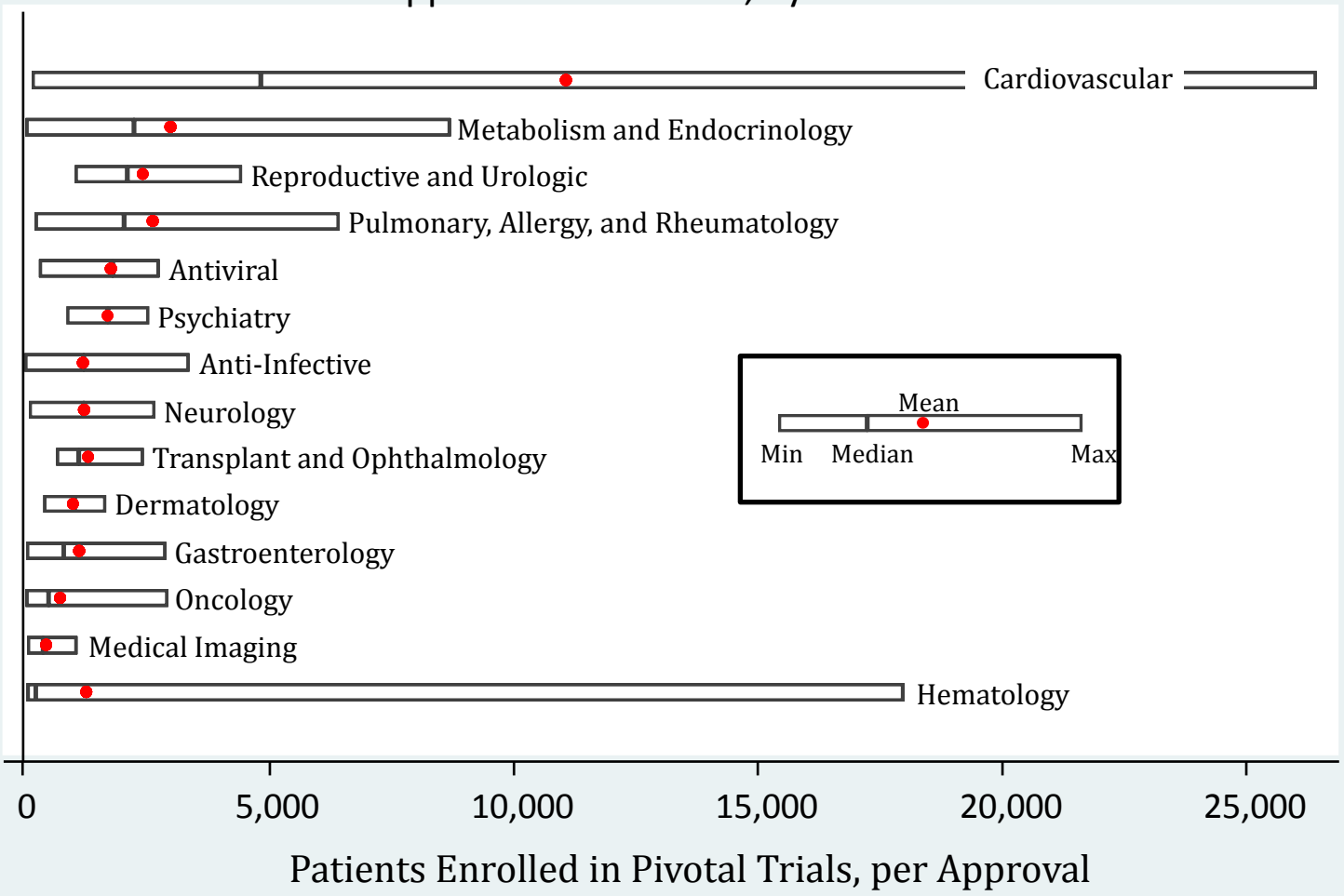

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