MISSING INNOVATIONS

Amitabh Chandra

HARVARD BUSINESS SCHOOL

HARVARD KENNEDY SCHOOL OF GOVERNMENT and NBER

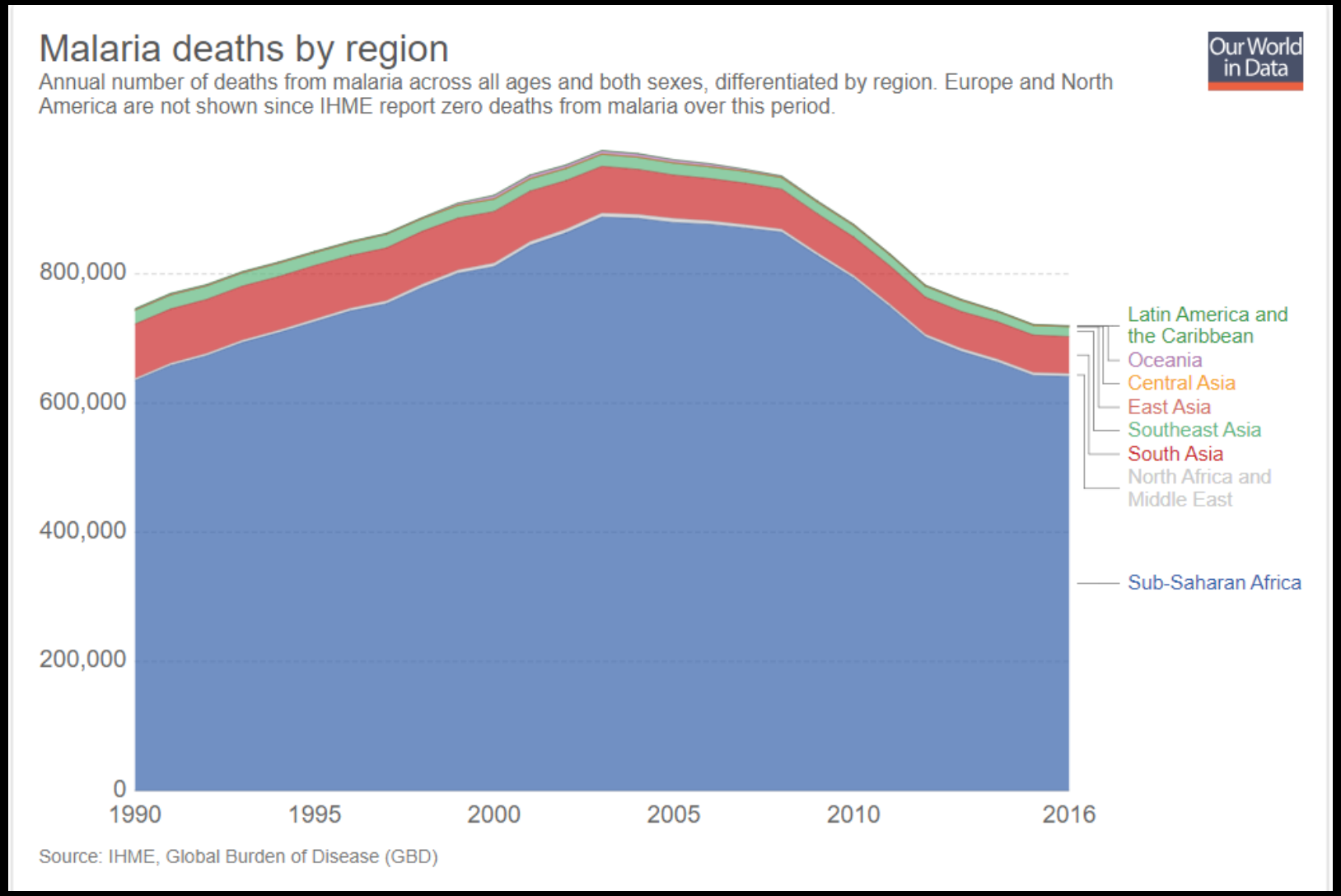
- Malaria

- Mosquito born illness that causes fever, chills and possibly death
- In 2016, 216 million worldwide
- These cases resulted in 445,000 deaths

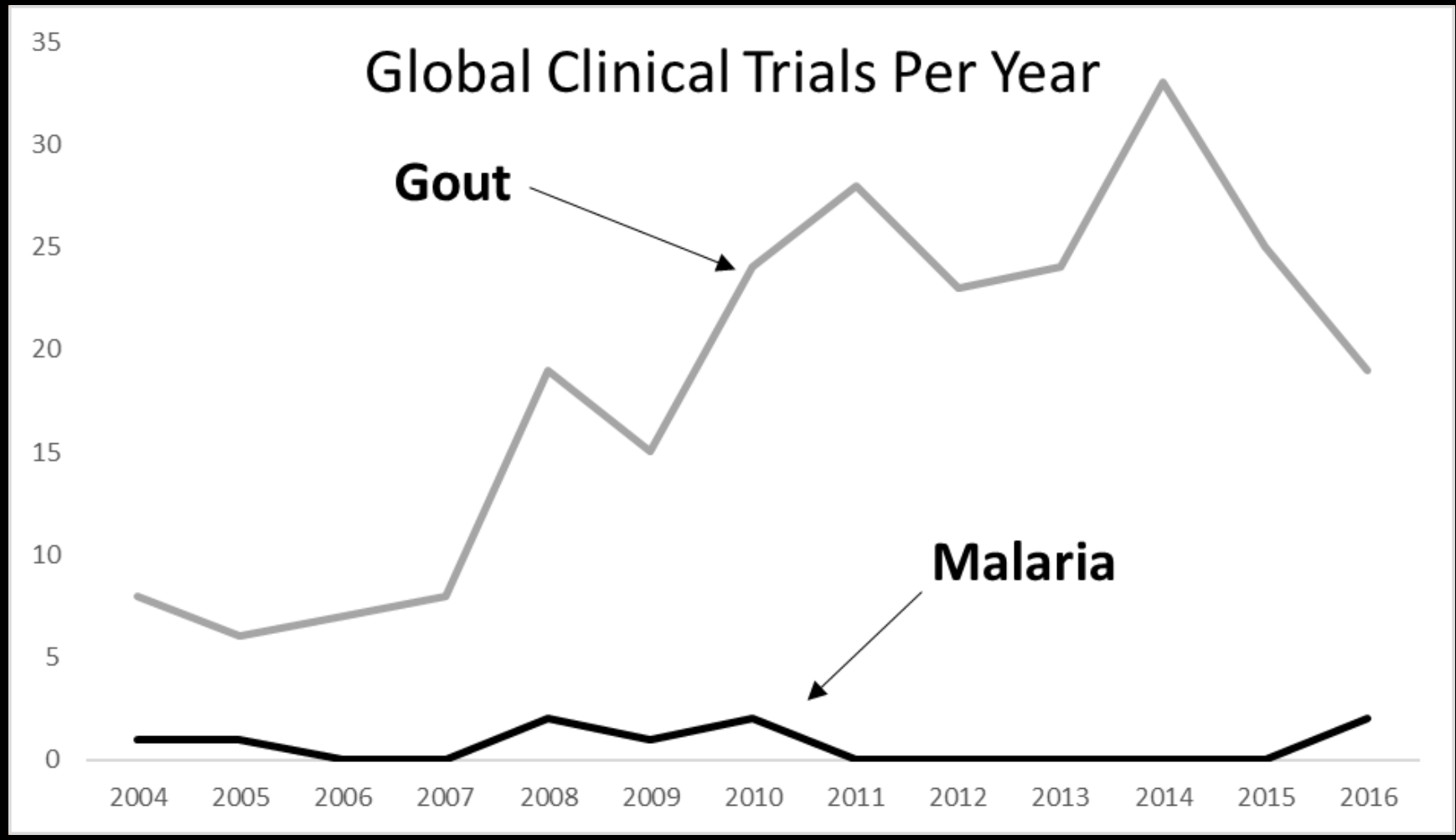
Gout

- Disease resulting in excess buildup of uric acid that causes exceptional joint-pain
- Exacerbated by fatty foods and alcohol
- 34 million cases worldwide

Malaria is not a small disease…



Malaria is not a small disease…but is to financial markets



The RAND Journal of Economics

Market Size and Pharmaceutical Innovation

By Pierre Dubois, Olivier de Mouzon and Fiona Scott Morton

"This indicates that when a market increases in potential size by 10%, that stimulates a 2.5% increase in the number of treatments to serve that market

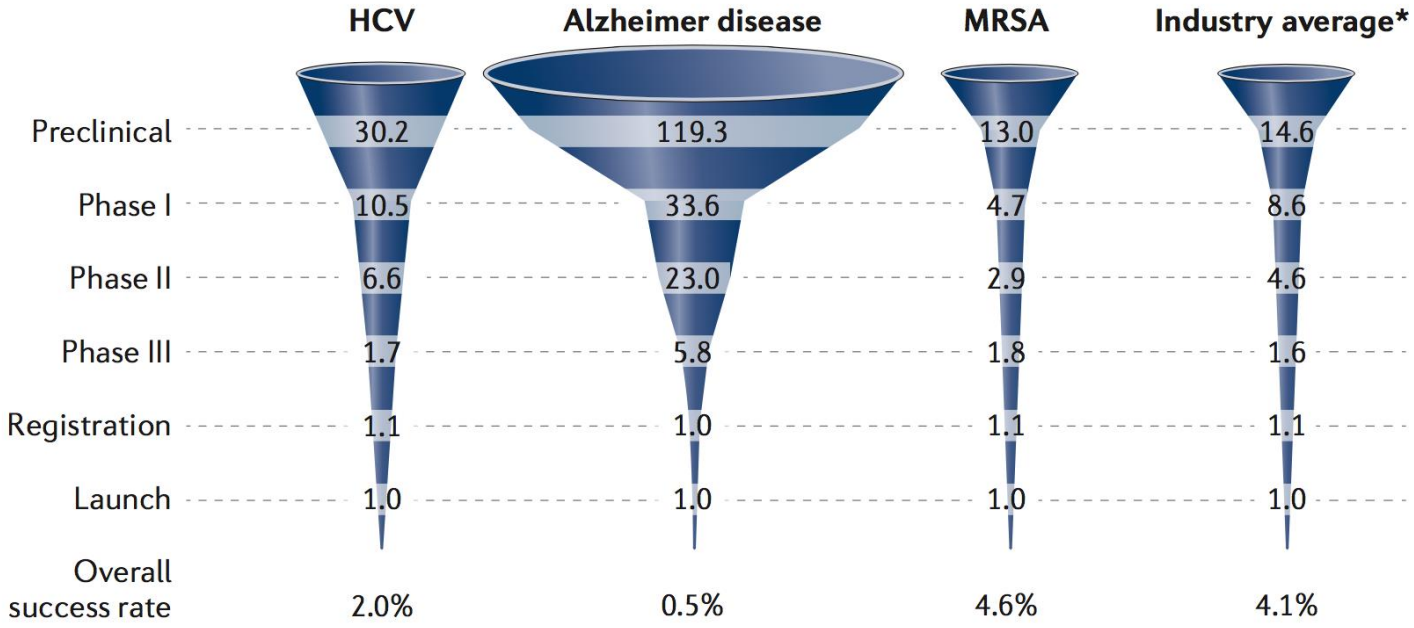
...

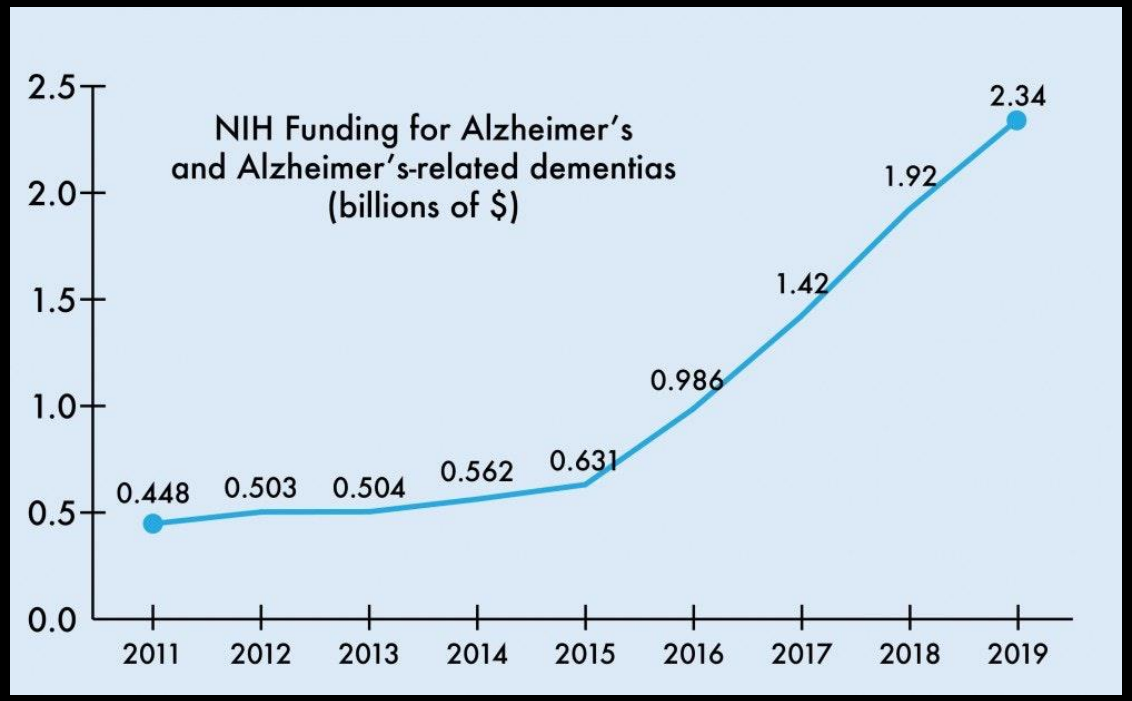
This suggests that, on average, $2.5 billion is required in additional revenue to support the invention of one new chemical entity."

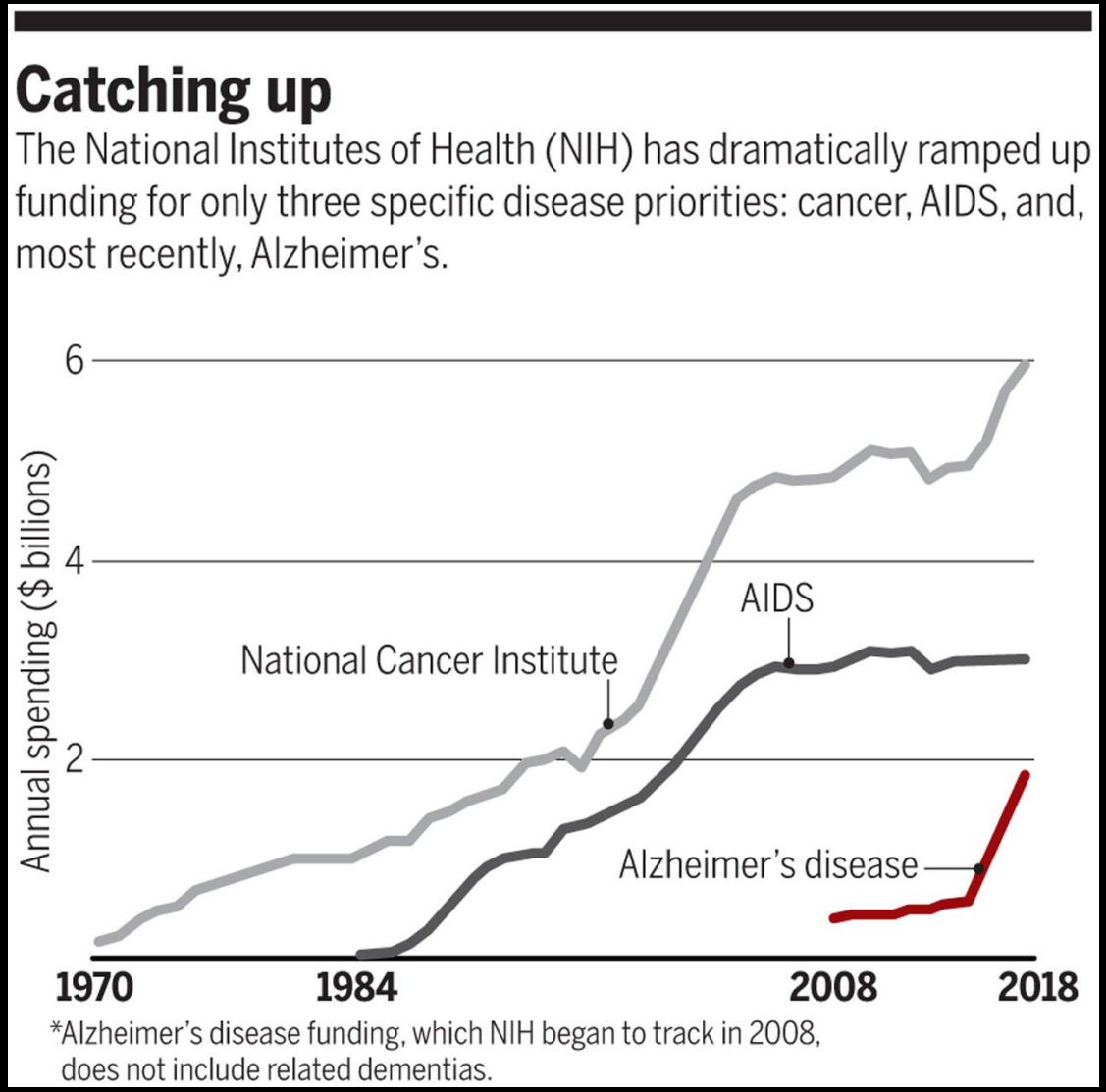
ALZHEIMER's: Amongst the World's Greatest Challenges

- Large Market Size
  - Growing incidence internationally
  - Declining competing risk
  - Demand from caregivers
  - Grey-area diagnosis
- Potential to claim large value–
  - US spending $500B/year
  - Different than other diseases where new drugs may increase spending

Attrition Profiles Across Therapeutic Areas




NIH Funding for Alzheimer's and Alzheimer's-related dementias (billions of $)
2.5
2.0
1.5
1.0
0.5
0.0
0.448
0.503
0.504
0.562
0.631
0.986
1.42
1.92
2.34
2011
2012
2013
2014
2015
2016
2017
2018
2019


Catching up
The National Institutes of Health (NIH) has dramatically ramped up funding for only three specific disease priorities: cancer, AIDS, and, most recently, Alzheimer's.
Annual spending ($ billions)
6
4
2
National Cancer Institute
AIDS
Alzheimer's disease
1970
1984
2008
2018
*Alzheimer's disease funding, which NIH began to track in 2008, does not include related dementias.

WHAT INVENTIONS ARE WE MISSING?

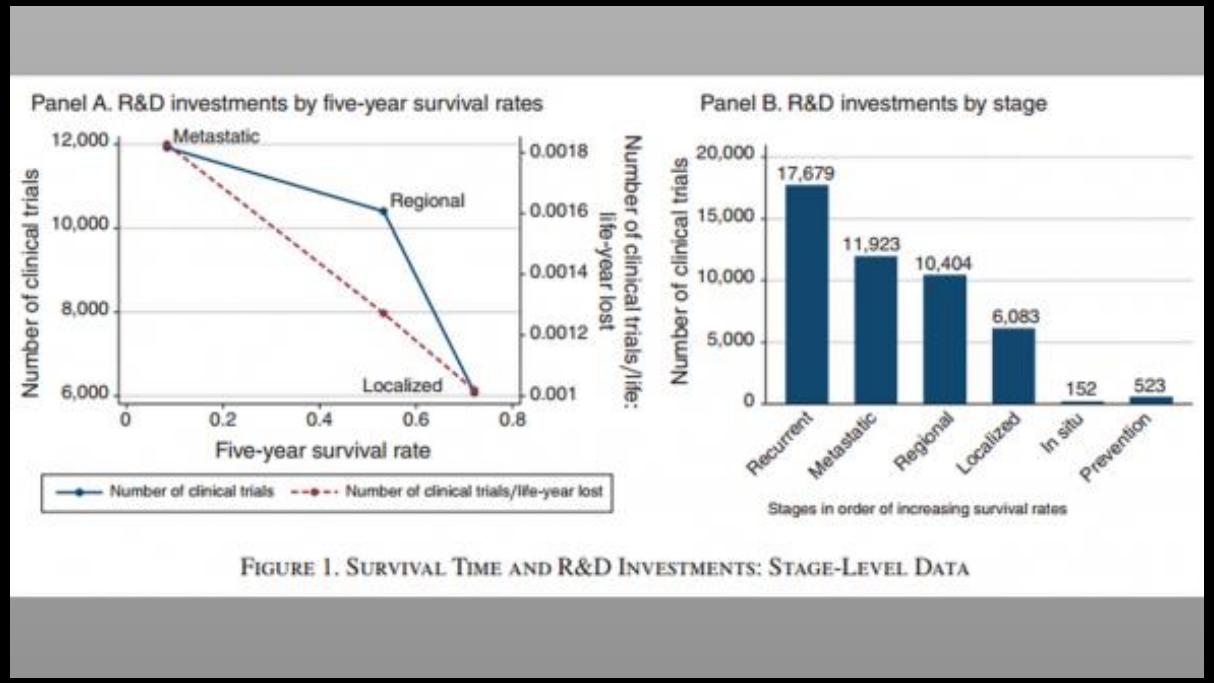
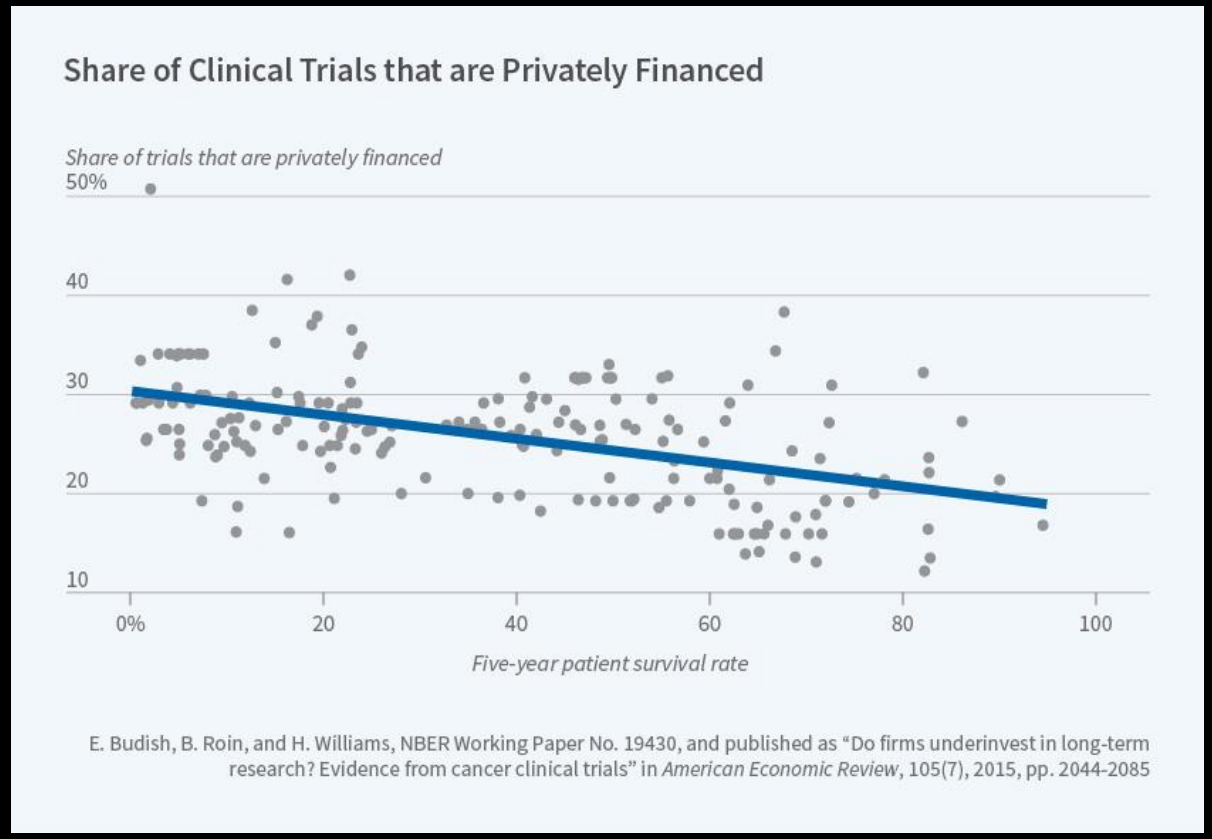
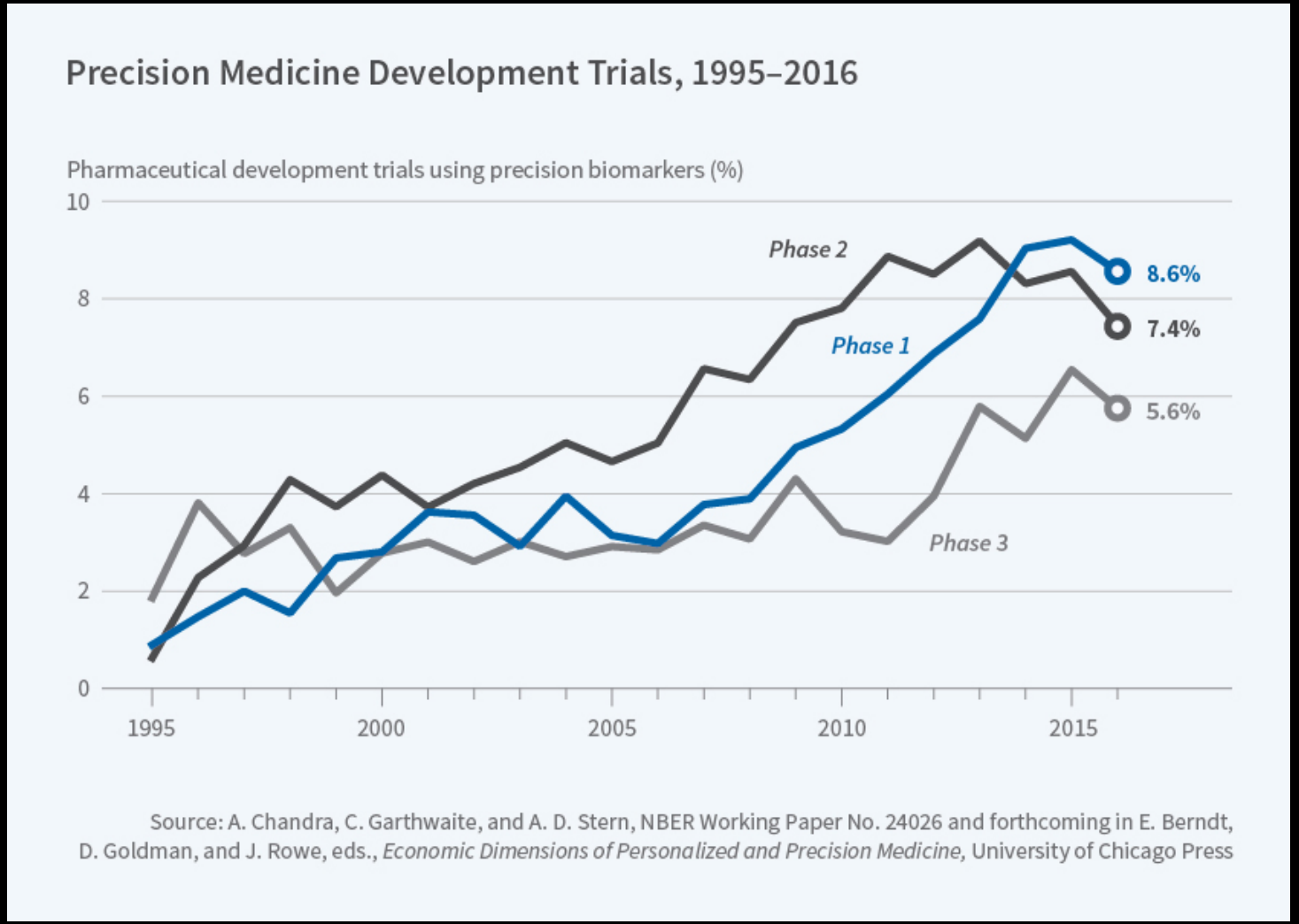


FIGURE 1. SURVIVAL TIME AND R&D INVESTMENTS: STAGE-LEVEL DATA



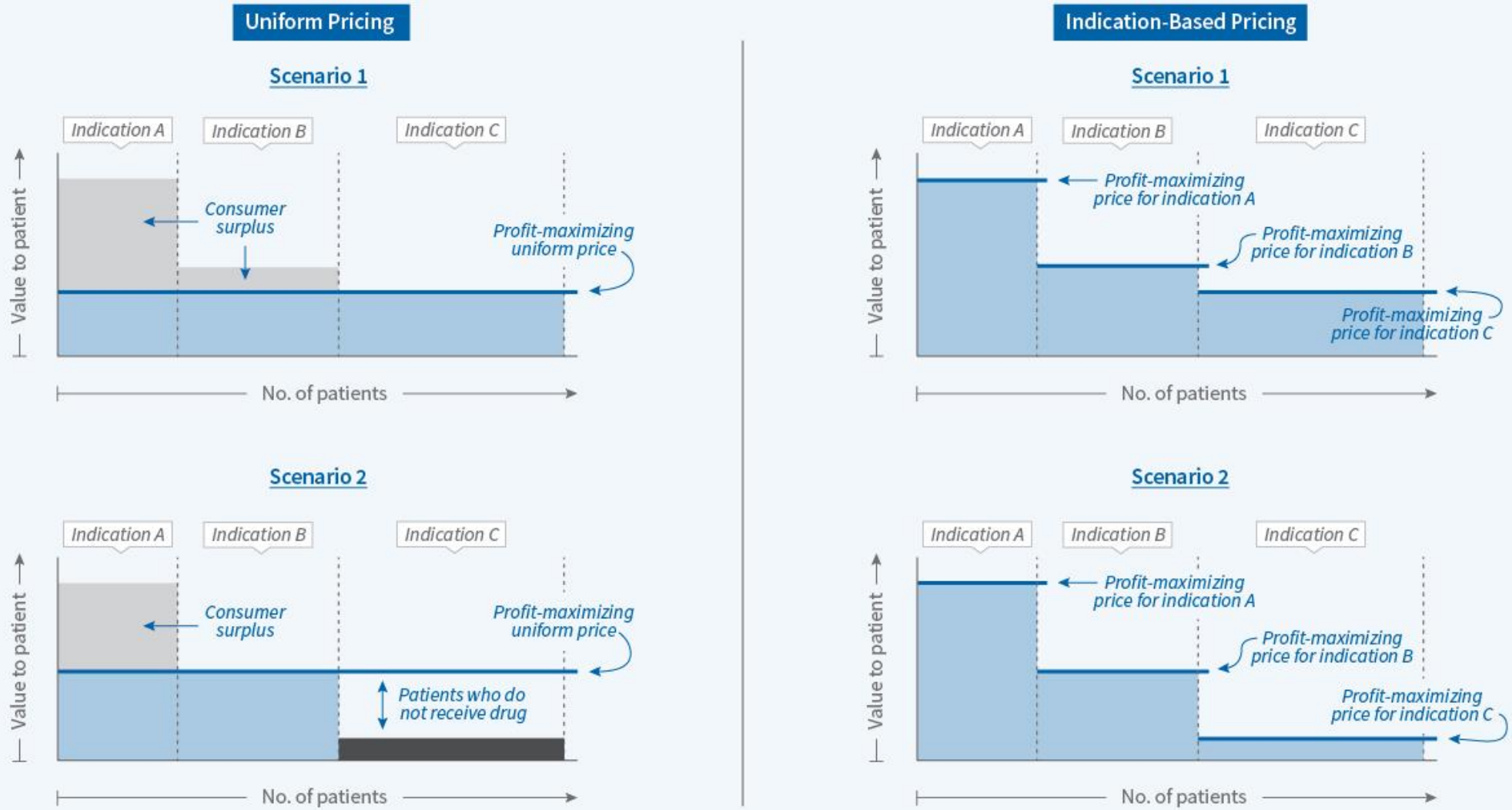
E. Budish, B. Roin, and H. Williams, NBER Working Paper No. 19430, and published as "Do firms underinvest in long-term research? Evidence from cancer clinical trials" in *American Economic Review*, 105(7), 2015, pp. 2044-2085

GROWTH IN GENOMIC AND PROTEOMIC BIOMARKERS



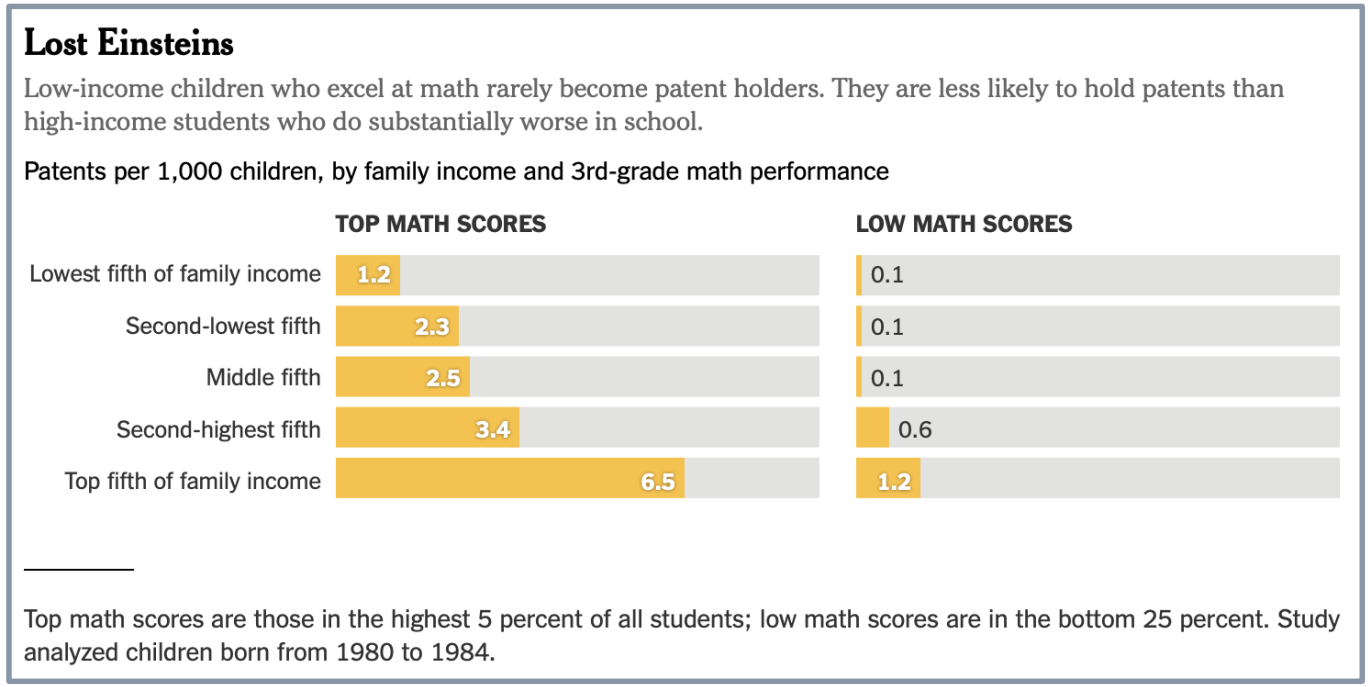
Source: A. Chandra, C. Garthwaite, and A. D. Stern, NBER Working Paper No. 24026 and forthcoming in E. Berndt, D. Goldman, and J. Rowe, eds., *Economic Dimensions of Personalized and Precision Medicine,* University of Chicago Press

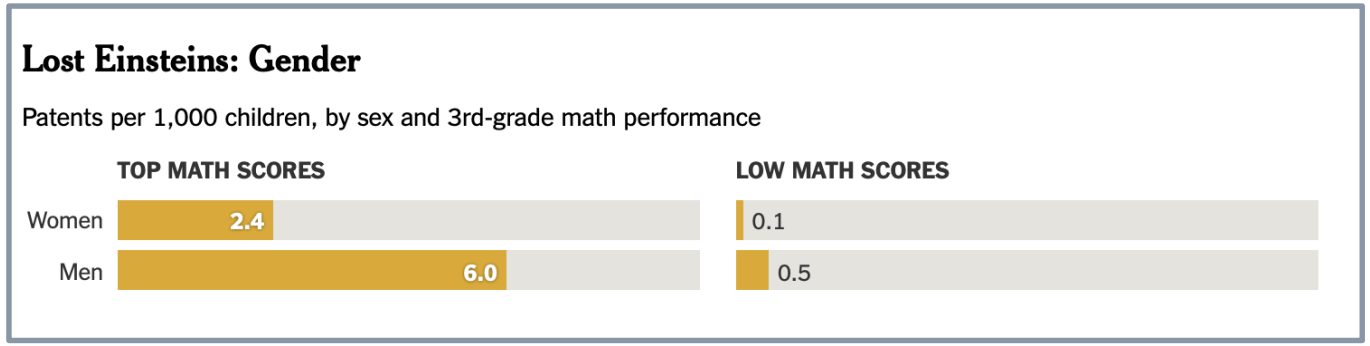
Market Scenarios for Precision Medicine Under Uniform Pricing and Indication-Based Pricing



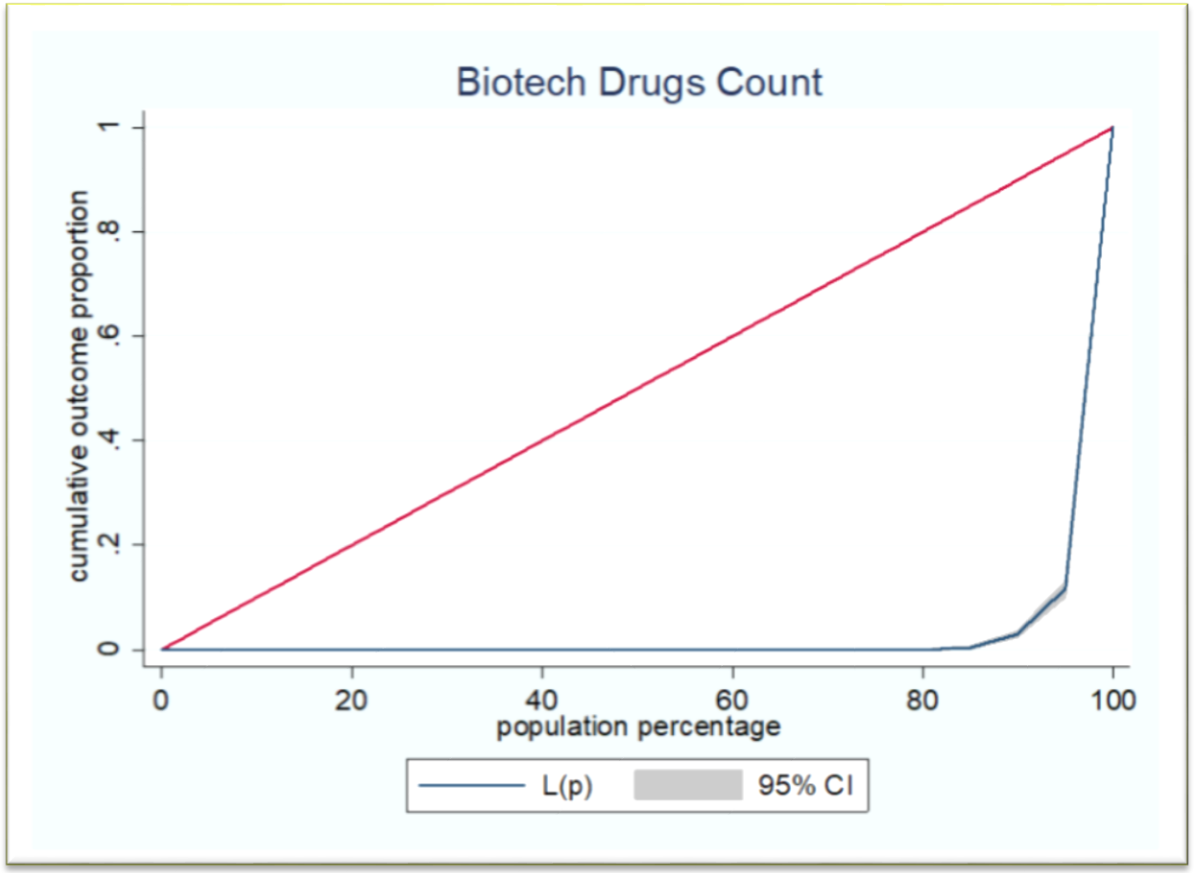
Source: Illustrative diagram based on author's theoretical scenarios

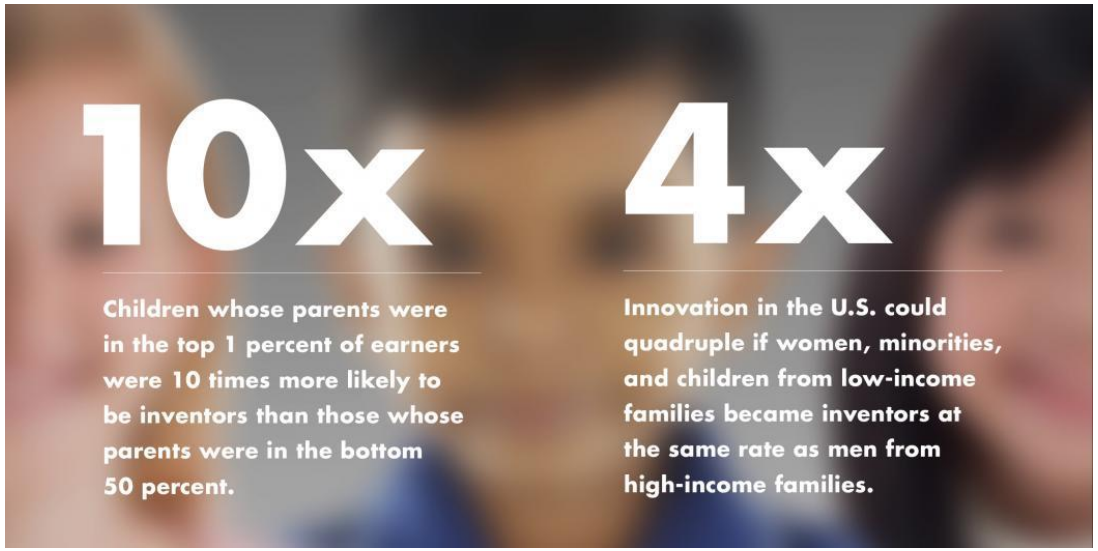
Lost Einsteins





Geographic Concentration of Innovation





What Innovations are we missing?

1. R&D requires **expected economic returns** > investors cost of capital
2. These returns depend on
   - Uncertainty and upside risk
   - NIH can reduce (some) uncertainty, but grossly insufficient for Rx Dev
   - IP + exclusivity are key for manufacturers to capture value
3. Validated prognostic biomarkers increase effective IP
4. Predictive biomarkers induce more innovation: more value capture
5. Other pricing models can also help– but negotiation with government is always fraught with classic 'holdup' problem
6. There are, poorly understood, non-price barriers to innovation: missing Einstein's and geography

New Actives Substances (NAS) Launched for the First Time in the U.S. in 2017

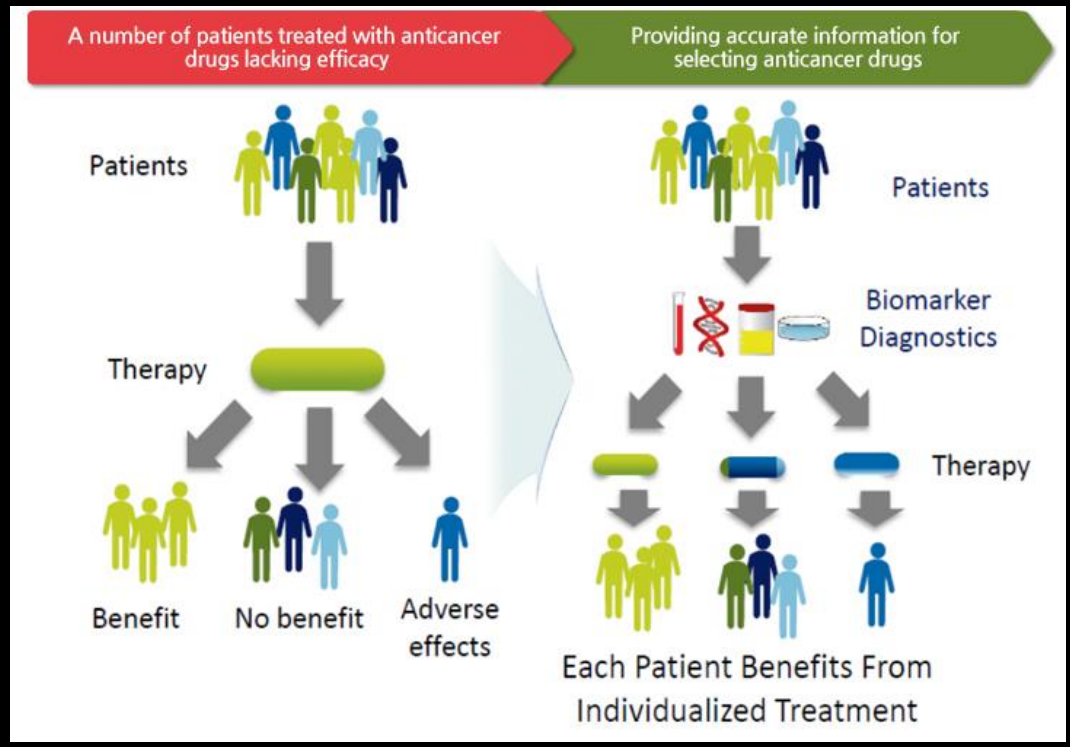
Orphan	mantle cell lymphoma	acalabrutinib	1	2	3	5		7	
	non-small cell lung cancer	avelumab	1	2		5	6	7	
	large B-cell lymphoma	axicabtagene ciloleucel	1	2		5	6	7	9
	Chagas disease	benznidazole							
	non-small cell lung cancer	brigatinib	1	2	3	4	5	7	
	Batten disease	cerliponase alfa		2	3		5	7	8
	relapsed follicular lymphoma	copanlisib	1			5		7	
	Duchenne (DMD)	deflazacort						7	8
	Huntington's disease	deutetrabenazine						7	8
	Acute cerebral infaction	edaravone						7	8
	haemophilia A	emicizumab		2					8
	acute myeloid leukemia	enasidenib	1		3	4	5	7	
	B-cell precursor ALL	inotuzumab ozogamicin	1	2				7	
	cytomegalovirus	letermovir		2				7	
	acute myeloid leukemia	midostaurin	1	2	3	4	5	6	
	ovarian cancer	niraparib	1	2				7	
	spinal muscular atrophy	nusinersen						7	8
	carcinoid syndrome	telotristat eitprate						7	8
	B-cell ALL	tisagenlecleucel	1	2		5	6	7	9
	tardive dyskinesia	valbenazine		2				7	8
	Sly syndrome	vestronidase alfa-vjbk							
Non-Orphan, New Mechanism	Clostridium difficile	bezlotoxumab							
	atopic dermatitis	dupilumab		2					8
	non-small cell lung cancer	durvalumab	1	2		4	5	7	9
	multiple sclerosis	ocrelizumab		2					8
	Parkinson's Disease	safinamide						7	8
Non-Orphan, Existing Mechanism	osteoporosis	abaloparatide						7	
	breast cancer	abemaciclib	1	2	3		5		
	severe asthma	benralizumab							8
	plaque psoriasis	brodalumab							8
	atopic dermatitis	crisaborole							8
	hepatitis C	glecaprevir+pibrentasvir		2	3	4			
	plaque psoriasis	guselkumab							8
	intraocular pressure	latanoprostene bunod							
	Type-II diabetes	lixisenatide							
	urinary tract infections	meropenem + vaborbactam						7	
	opioid-induced constipation	naldemedine							8
	HER2+ breast cancer	neratinib	1		3			7	
	constipation	plecanatide		2					8
	breast cancer	ribociclib	1	2	3			7	
	rheumatoid arthritis	sarilumab							8
	hepatitis C	sofosbuvir+velpatasvir+voxilaprevir		2	3	4			

Number of patients
- over 5 million
- under 5 million
- under 2 million
- under 200k
- under 50k

Trial or medicine feature	# of NAS with attribute
1 Oncology	14
2 Breakthrough	19
3 Predictive Biomarker	10
4 Companion Diagnostic	6
5 Approved based on Ph II	11

Trial or medicine feature	# of NAS with attribute
6 Single-arm trial	4
7 Single trial cited for approval	23
8 PRO data on label	18
9 Cell or Gene therapy	2

Source: IQVIA Institute, Mar 2018



LUXTURNA™
voretigene neparvovec-rzyl
for subretinal injection

NOW A REALITY: THE FIRST FDA-APPROVED GENE THERAPY FOR A GENETIC DISEASE

LUXTURNA is a prescription gene therapy product used for the treatment of patients with inherited retinal disease due to mutations in both copies of the *RPE65* gene, which can only be confirmed through genetic testing. You must also have enough remaining cells in your retina (the thin layer of tissue in the back of your eyes) as determined by your healthcare professional.

Incentives for Orphan Drugs

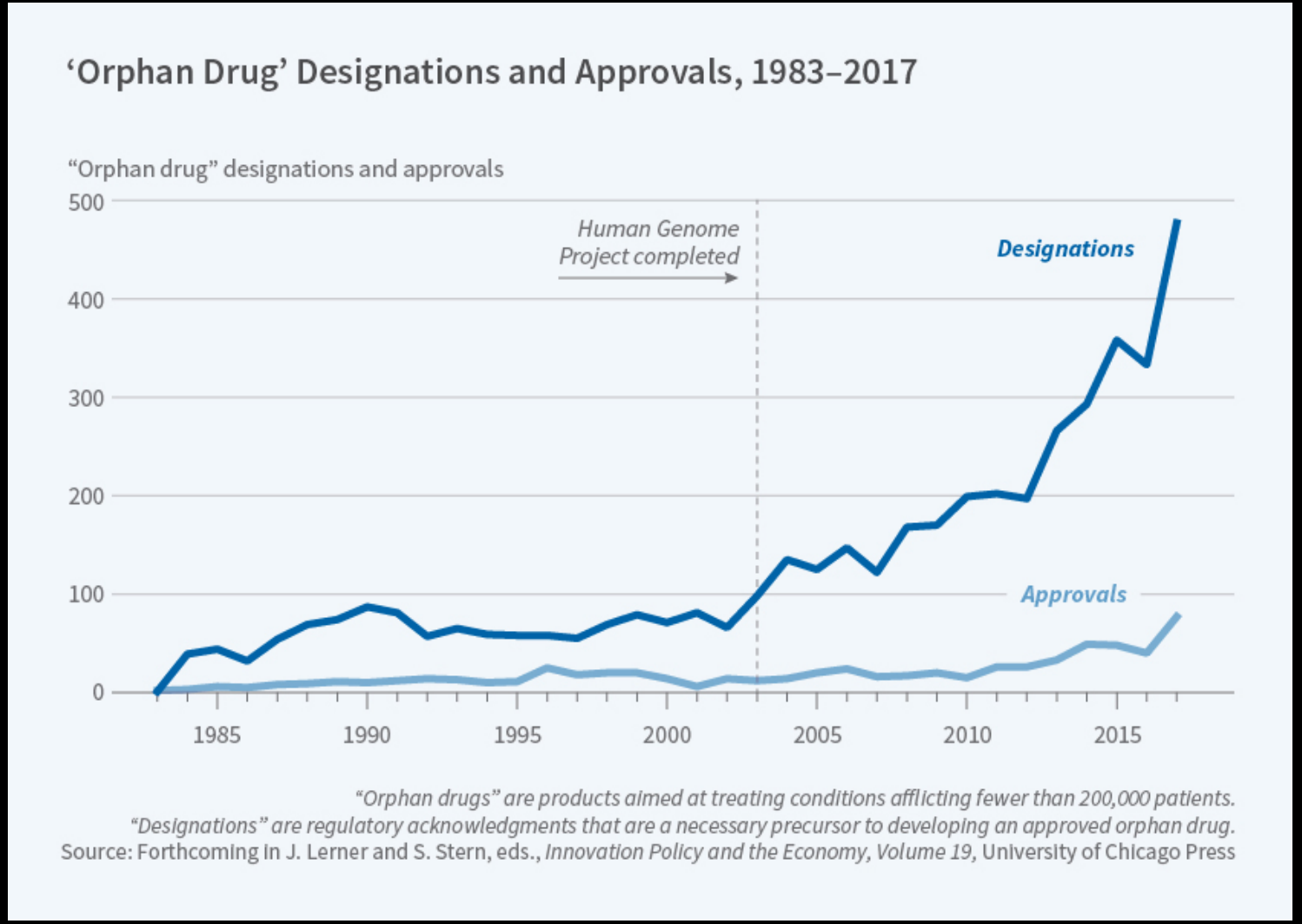
Country	Year adopted	Threshold for orphan drug status	Market exclusivity	Financial support for R&D
US	1983	Fewer than 200,000 patients in the U.S. (6 in 10,000)	7 years	Tax credits of 25% of R&D costs
Japan	1993	Fewer than 50,000 patients in Japan (4 in 10,000)	10 years	Up to 50% of R&D costs, plus 6% tax credit
European Union	2000	Fewer than 5 in 10,000	10 years	Varies across member states

Are these incentives too generous?

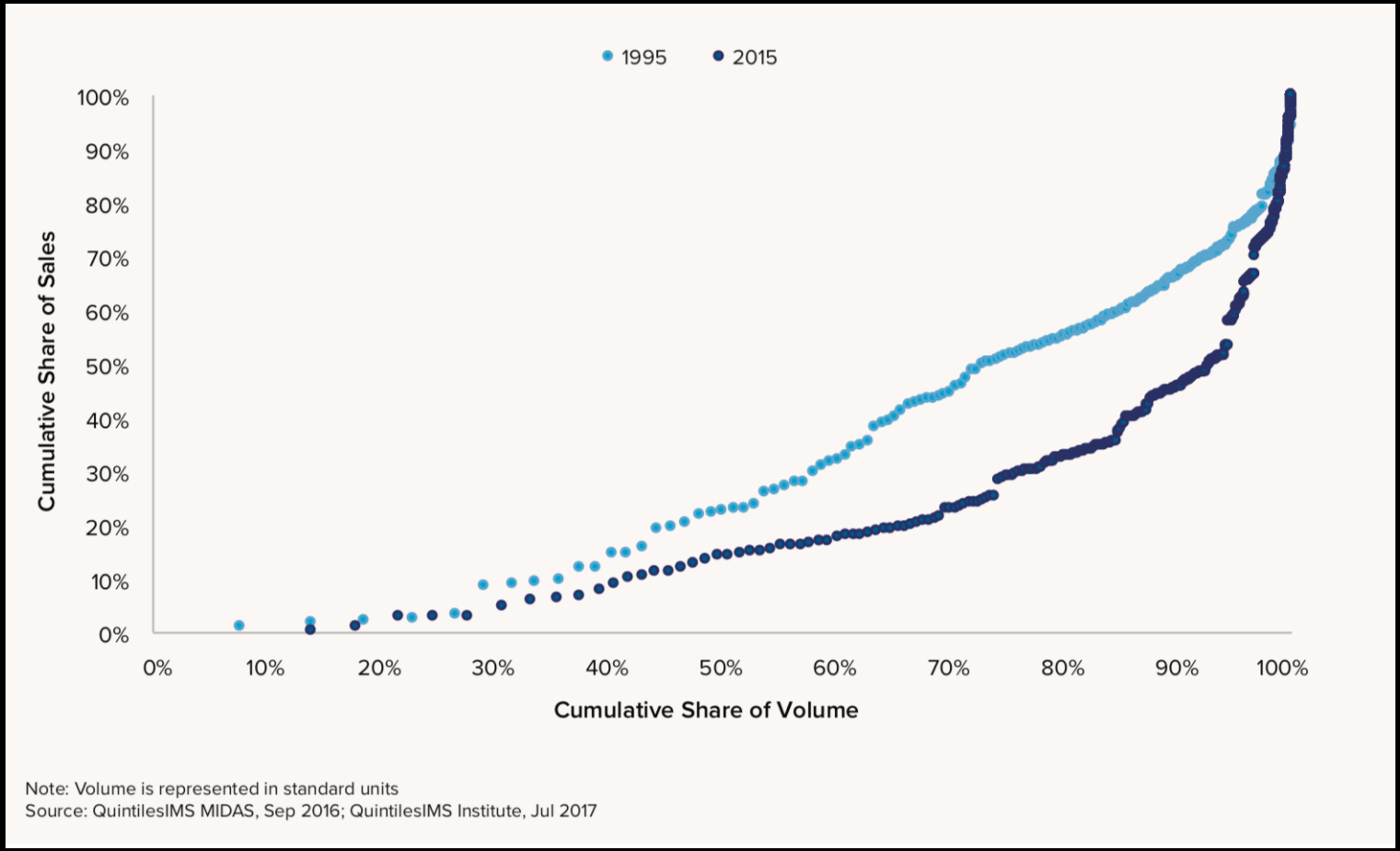
1. Changes in pricing dynamics including indication-based pricing have decreased threshold for an economically viable product
2. Firms increasingly seek multiple orphan indications for products, and often those products were approved for existing non-orphan indications.
3. Small size of patient populations targeted for orphan designations has created a set of natural monopoly-like conditions
4. Changes in the technology of drug development – surrogate endpoints and faster approvals-- may have lowered the cost of R&D

Incentives for RARE DISEASE R&D

- Firms undertake R&D as long as expected profits exceed a threshold
- Expected profits will be small for rare diseases



CHANGING PRICING DYNAMICS



Note: Volume is represented in standard units
Source: QuintilesIMS MIDAS, Sep 2016; QuintilesIMS Institute, Jul 2017

Table 1
Potential Prices by Indication

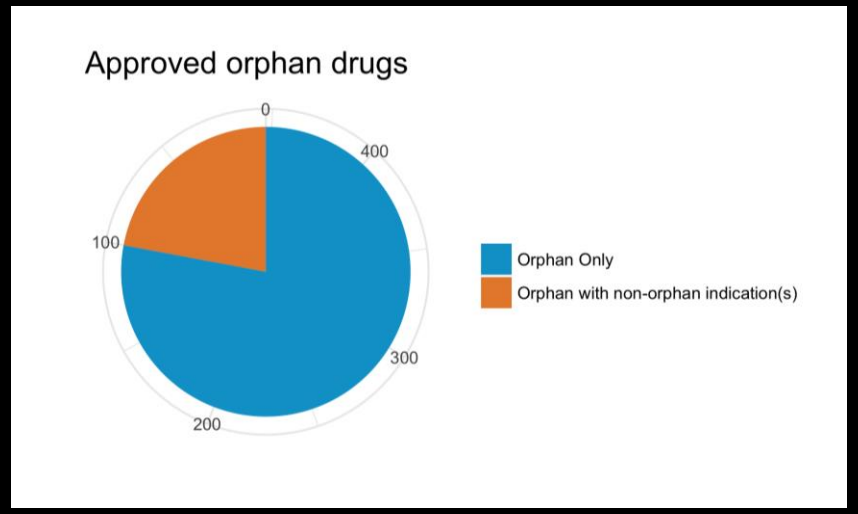
	Median Survival Gain, years[1]	Typical Treatment Duration, months[1]	Uniform MonthlyPrice[1]
Erbitux			
Locally advanced squamous cell carcinoma of the head and neck	1.64	1.39	$10,319
First-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck	0.23	4.16	$10,319
Herceptin			
Adjuvant treatment of breast cancer	1.99	12	$5,412
Metastatic breast cancer	0.4	10	$5,412

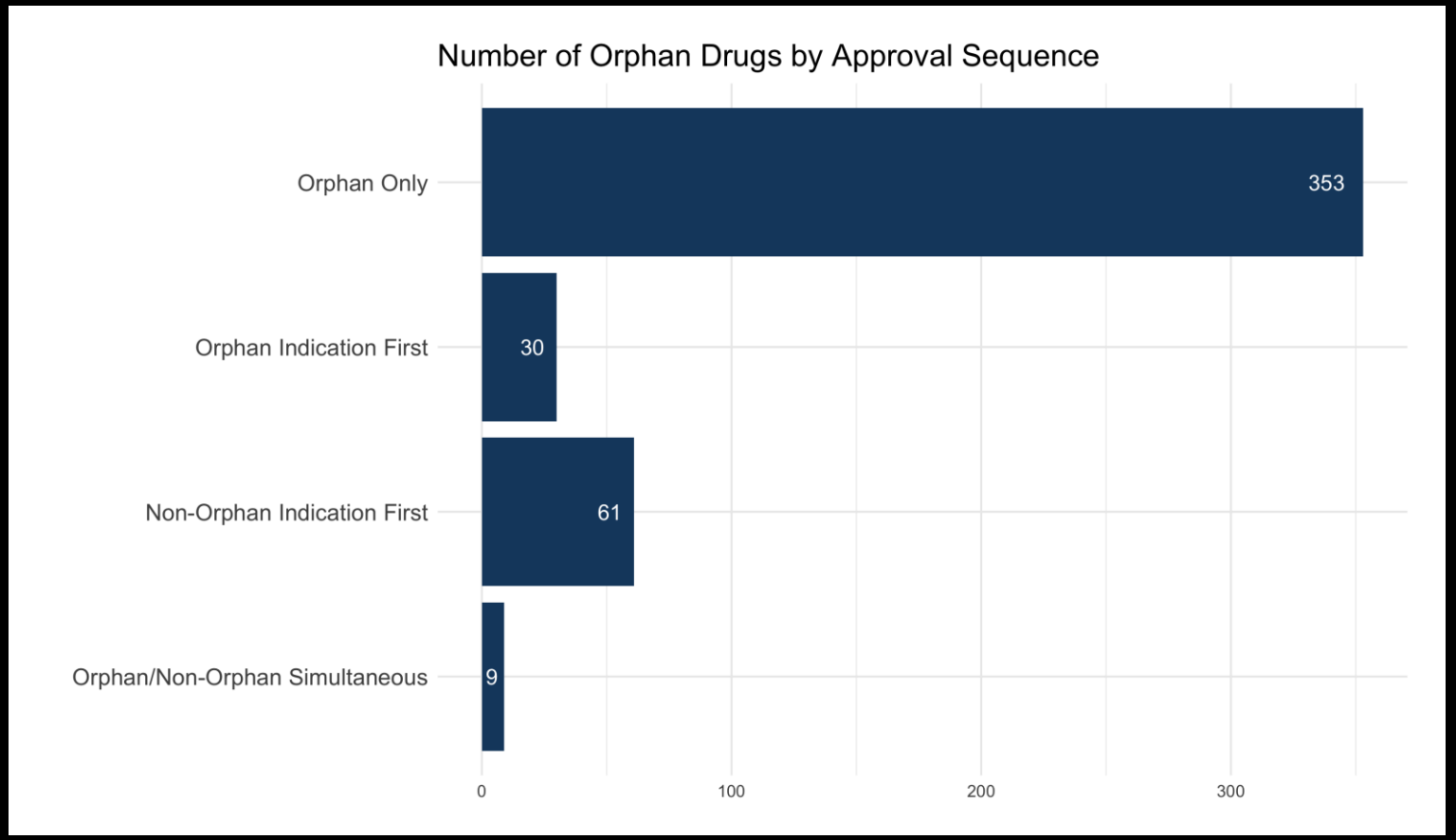
Source: Bach et al., 2015; authors' calculations in last column

Note: Indication-based price is calculated as the price that would be charged if patients value their life to the same degree as patients with the least effective, but still covered, indication. For Erbitrux, this implied value of a life-year is approximately $ 186,639 (in the low-value condition, payers are willing to cover 4.16 months of treatment at a monthly price of $10,319 for a survival gain of 0.23 years). The indication-based monthly price in the high-value condition for Erbitux will be $220,208 ($186,639 per life-year x 1.64 years of survival / 1.39 months of therapy).

Source: Chandra, A and Garthwaite C, The Economics of Indication Based Pricing, NEJM 2017

ORPHAN DRUGS with NON-ORPHAN INDICATIONS



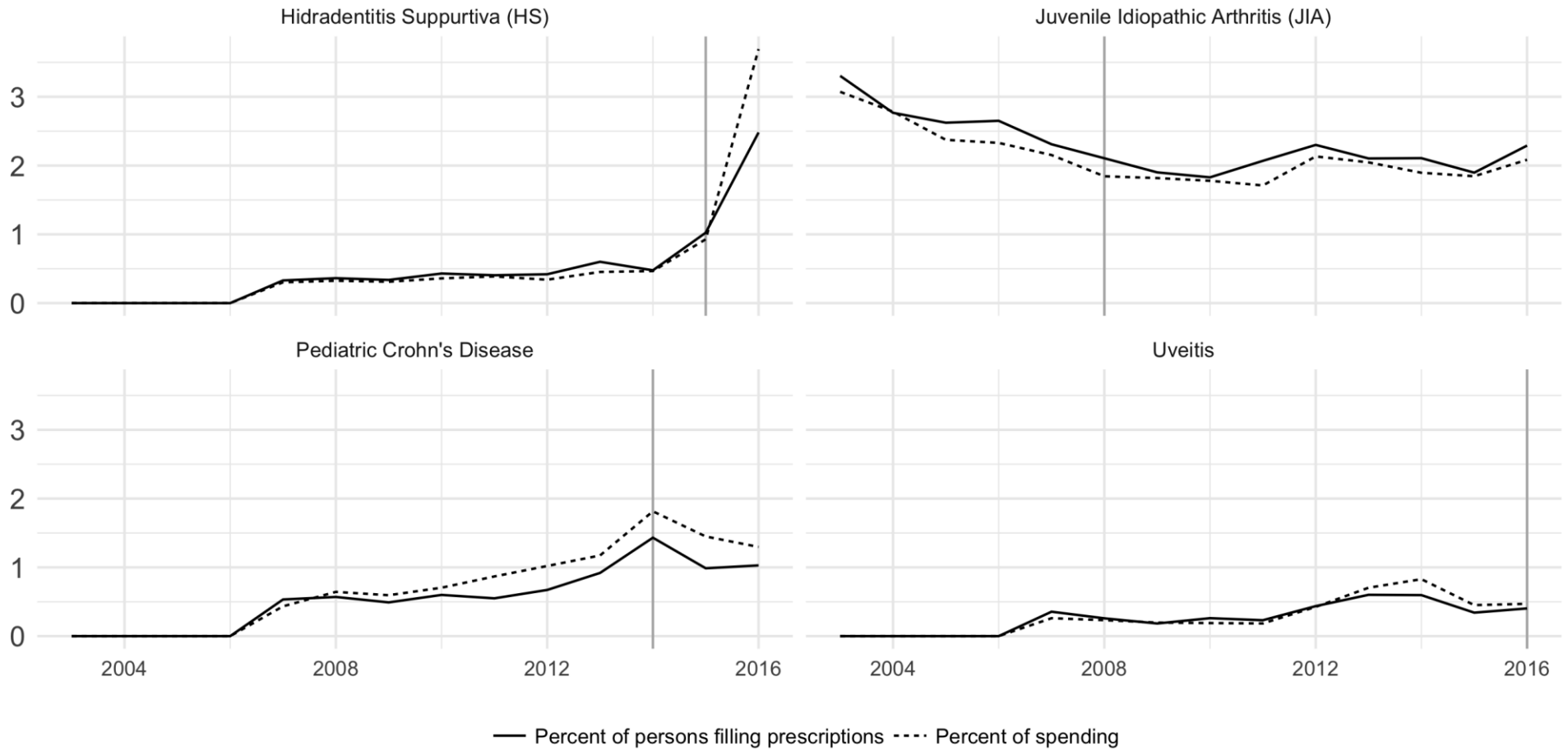


HUMIRA: a case-study

Date	Indication	Date	Indication
12/31/02	Rheumatoid arthritis	2/21/08	**Juvenile idiopathic arthritis**
10/3/05	Psoriatic arthritis	9/28/12	Ulcerative colitis
7/28/06	Ankylosing spondylitis	9/23/14	**Pediatric Crohn's disease**
2/27/07	Adult Crohn's disease	9/9/15	**Hidradentitis suppurtiva (HS)**
1/18/08	Plaque psoriasis	6/30/16	**Uveitis**

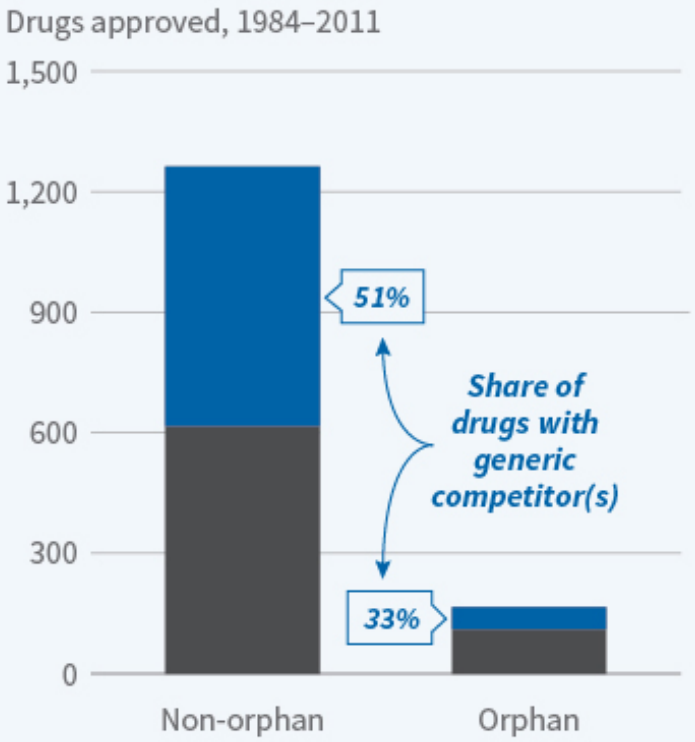
Percent of total Humira spending and use

By orphan indication



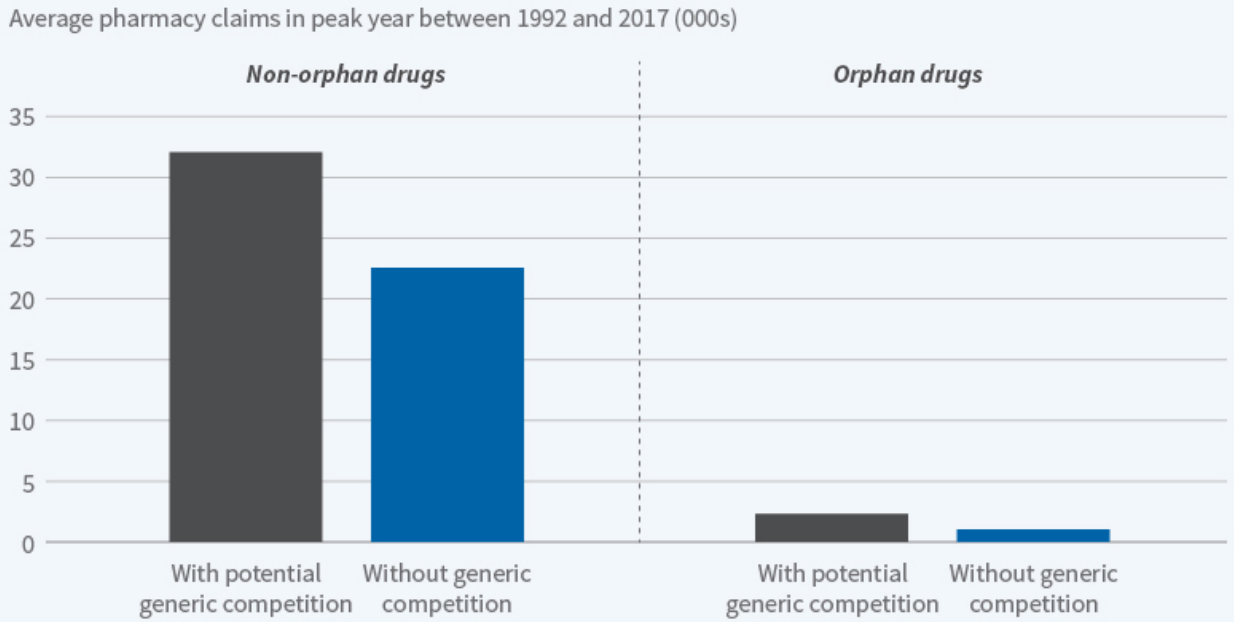
Each orphan indication is marked in the year of approval. Spending for each indication is reported as zero in years where ten or fewer persons were identified with the particular indication.

Generic Competition among Orphan and Non-Orphan Drugs



Data pertain to small molecule drugs
Source: Forthcoming in J. Lerner and S. Stern, eds., *Innovation Policy and the Economy, Volume 19,* University of Chicago Press

Demand for Pharmaceuticals with Generic Competition and Without



"Orphan drugs" are products aimed at treating conditions afflicting fewer than 200,000 patients.
Source: Author's calculations based on data from OptumLabs

Incentives for orphan-drugs require two determinations:

Which Products? Provide bigger incentives to products with little market potential and smaller incentives for those that are close to viability. Note that with biomarkers, vast majority of orphan drugs will command high prices with or without ODA

How to Structure? R&D Tax Credit is funded though general revenues; but orphan-exclusivity is a fee on patients with orphan diseases.

- Tax-credit is superior than orphan exclusivity: US may have moved in the wrong policy direction recently
- EU law allow a reduction of the exclusivity period when a drug is deemed sufficiently profitable. In Japan, manufacturers must repay R&D subsidies for drugs with annual sales that exceed a cutoff

A Role for Regulation? Perhaps use “cost based price regulation” for Rx that received ODA protections after exclusivity periods have run out?

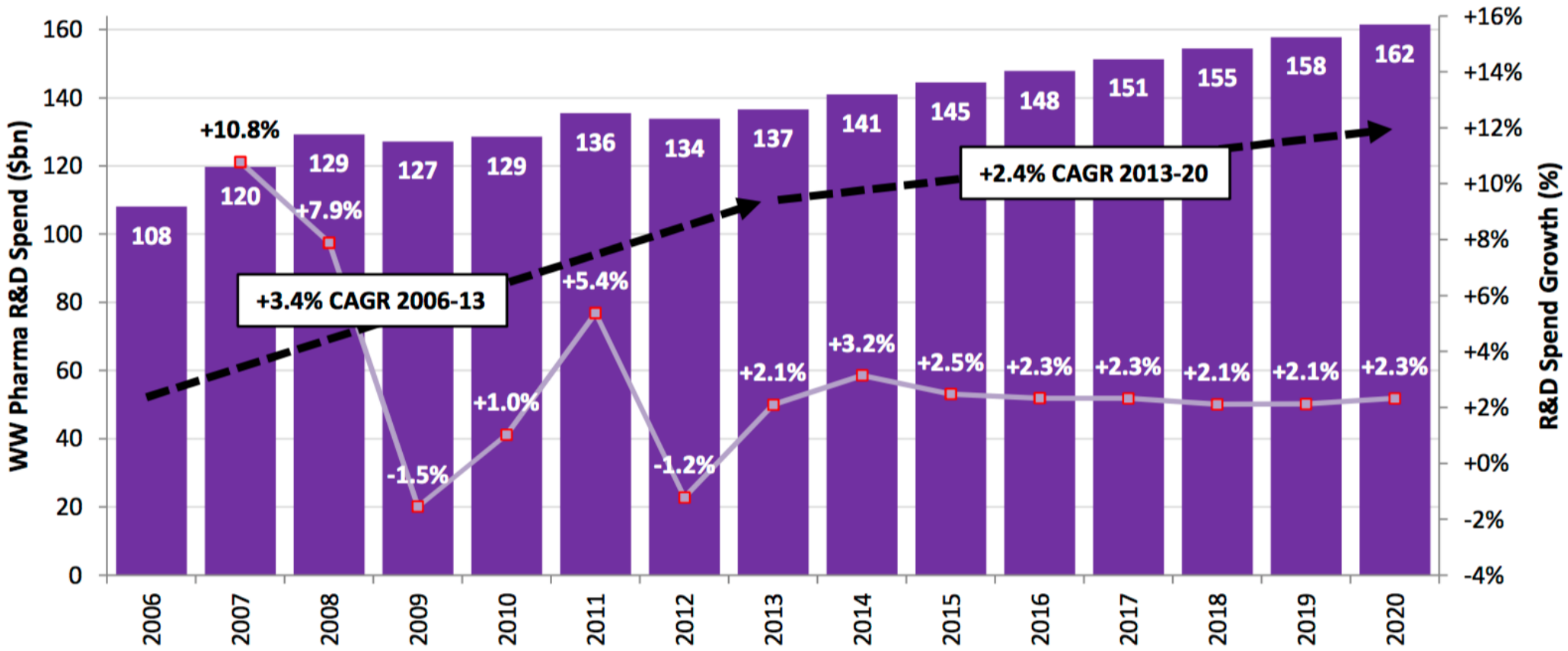
"Graveyard of pharma and biotech companies"

BIOTECH

STAT+

Biogen halts studies of closely watched Alzheimer's drug, a blow to hopes for new treatment

By ADAM FEUERSTEIN @adamfeuerstein / MARCH 21, 2019


WW Pharma R&D Spend ($bn)
R&D Spend Growth (%)
160
140
120
100
80
60
40
20
0
+16%
+14%
+12%
+10%
+8%
+6%
+4%
+2%
+0%
-2%
-4%
108
120
129
127
129
136
134
137
141
145
148
151
155
158
162
+10.8%
+7.9%
-1.5%
+1.0%
+5.4%
-1.2%
+2.1%
+3.2%
+2.5%
+2.3%
+2.3%
+2.1%
+2.1%
+2.3%
+3.4% CAGR 2006-13
+2.4% CAGR 2013-20
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020

POLICY & PHARMACEUTICALS

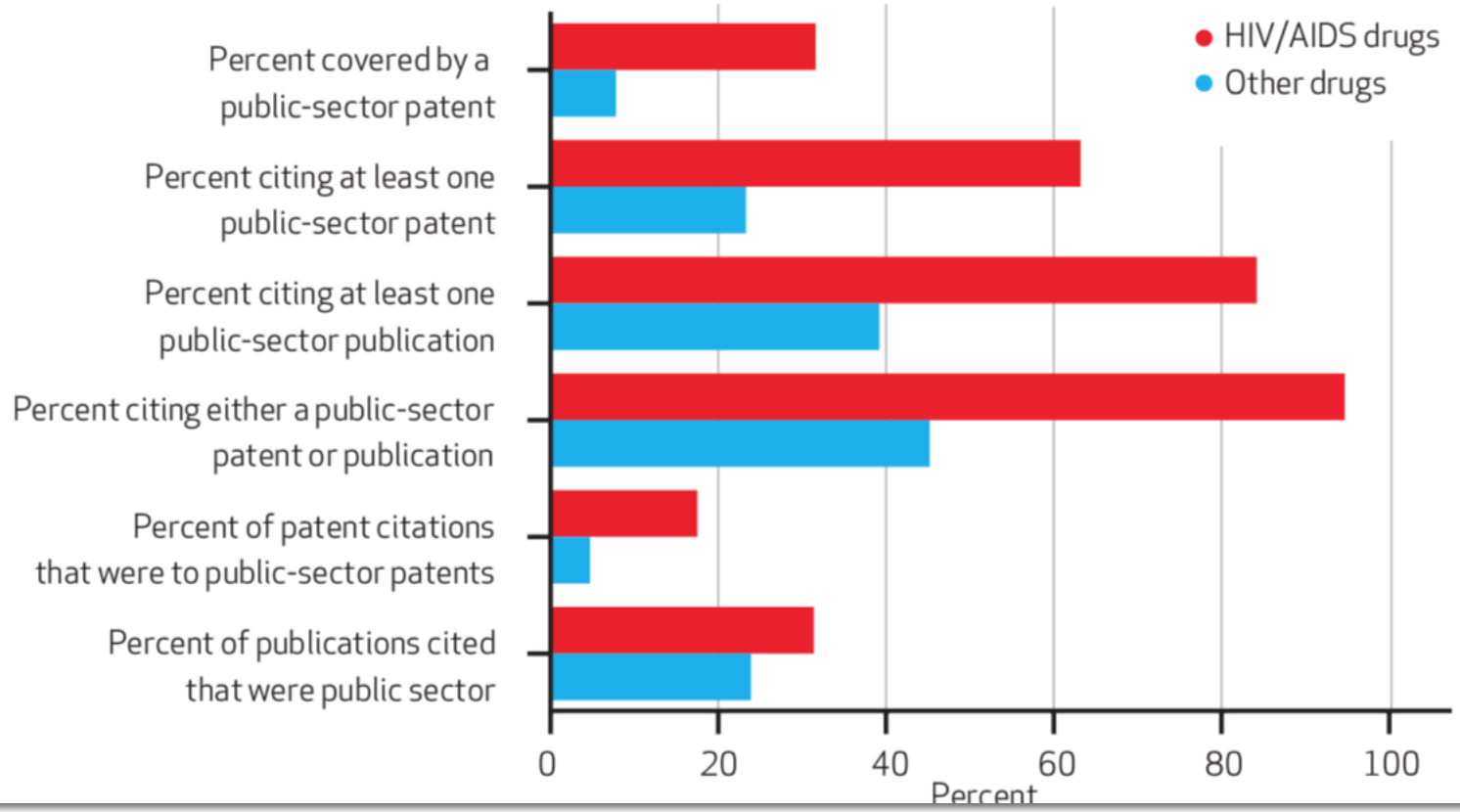
By Bhaven N. Sampat and Frank R. Lichtenberg

What Are The Respective Roles Of The Public And Private Sectors In Pharmaceutical Innovation?

DOI: 10.1377/hlthaff.2009.0917
HEALTH AFFAIRS 30,
NO. 2 (2011): 332–339

EXHIBIT 3

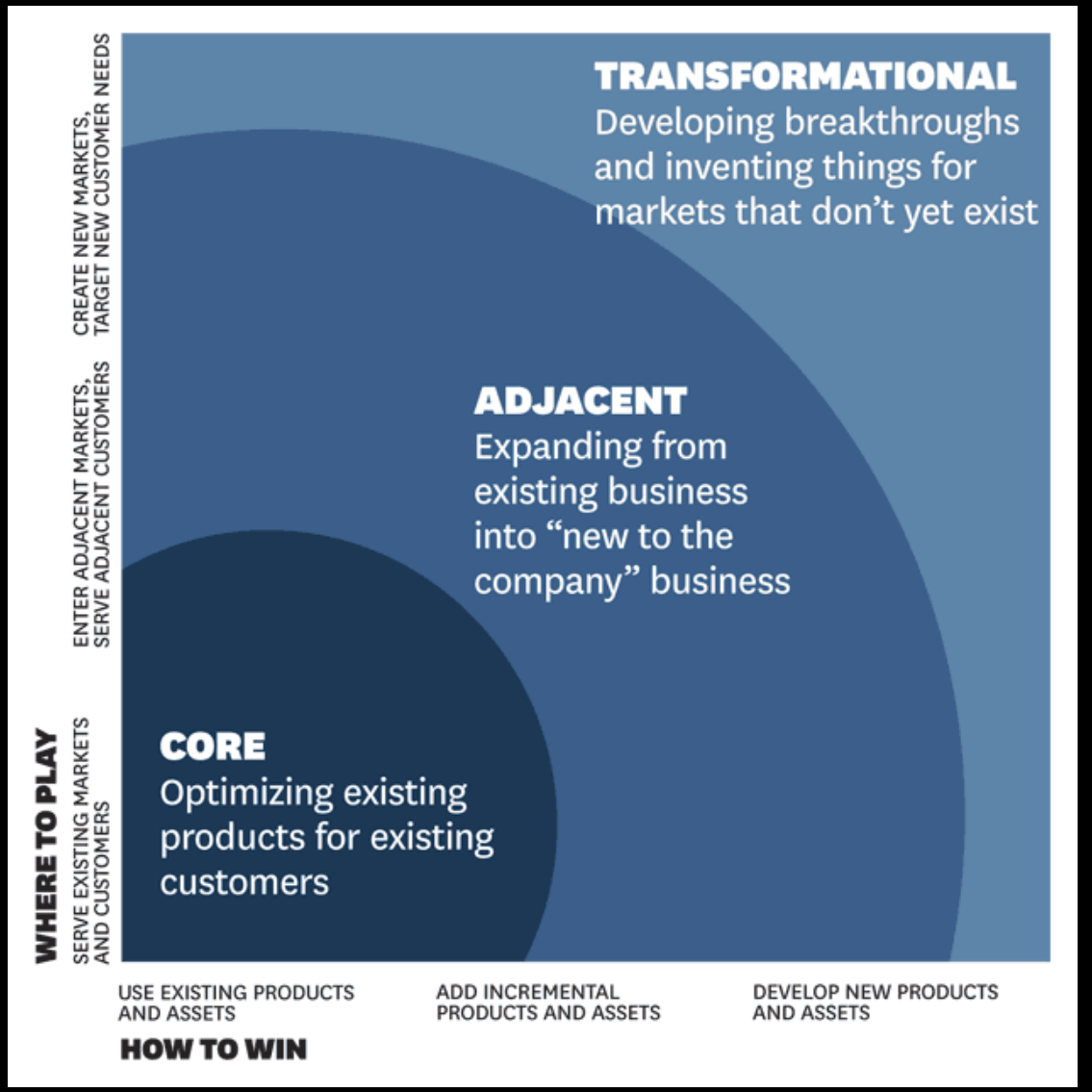
Public-Sector Influence On HIV/AIDS Drugs Versus Other Drugs



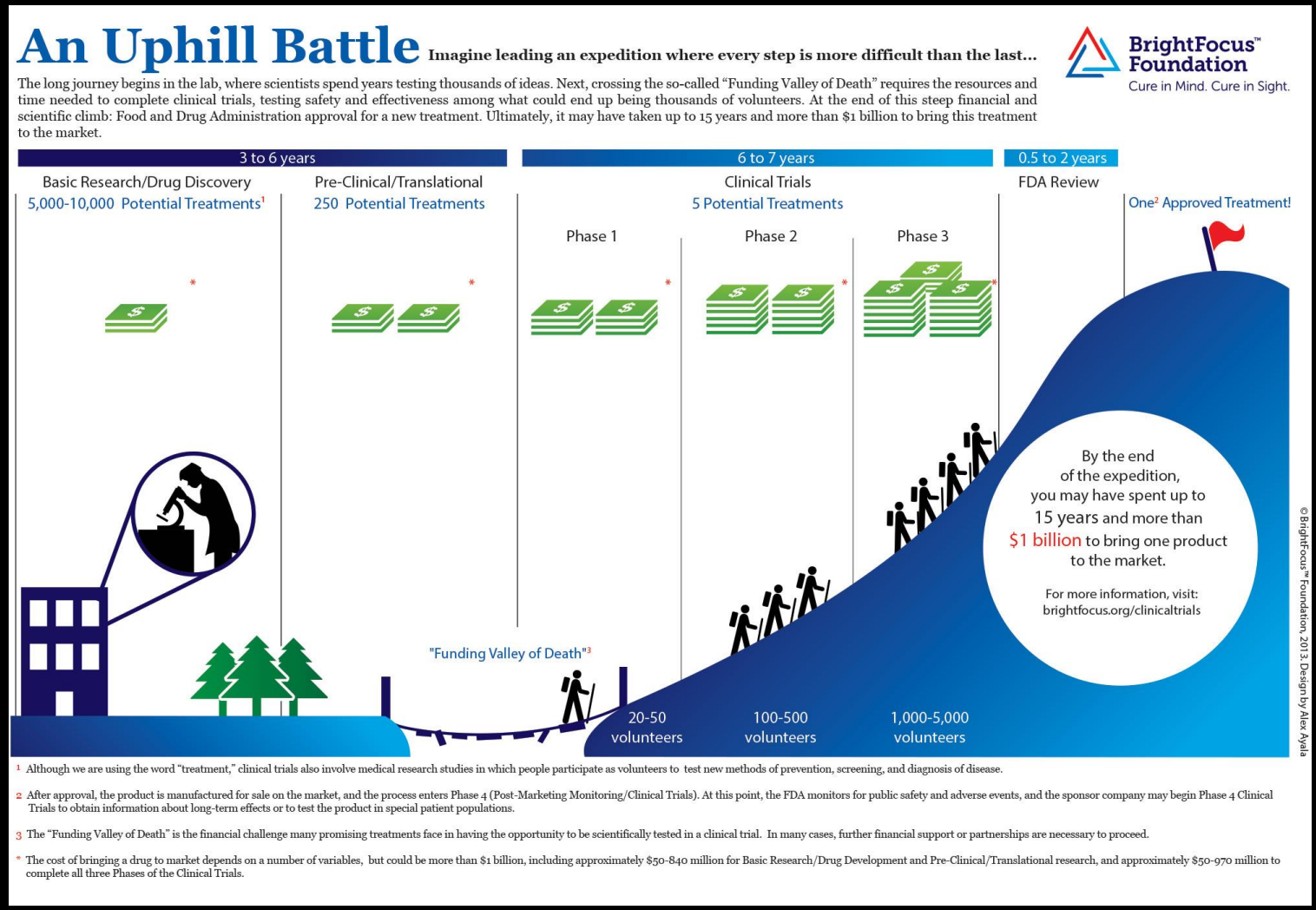
"Our results show that NIH funding spurs the development of private-sector patents: a $10 million boost in NIH funding leads to a net increase of 2.7 patents."

Public R&D Investments and Private-sector Patenting: Evidence from NIH Funding Rules
Pierre Azoulay Joshua S Graff Zivin Danielle Li Bhaven N SampaT, Volume 86, Issue 1, January 2019


HBR.ORG
Harvard Business Review
MAY 2013
REPRINT R1305C
SPOTLIGHT ON INNOVATION FOR THE 21ST CENTURY
Managing Your Innovation Portfolio


TRANSFORMATIONAL
Developing breakthroughs and inventing things for markets that don't yet exist
ADJACENT
Expanding from existing business into "new to the company" business
CORE
Optimizing existing products for existing customers
WHERE TO PLAY
SERVE EXISTING MARKETS AND CUSTOMERS
ENTER ADJACENT MARKETS, SERVE ADJACENT CUSTOMERS
CREATE NEW MARKETS, TARGET NEW CUSTOMER NEEDS
USE EXISTING PRODUCTS AND ASSETS
ADD INCREMENTAL PRODUCTS AND ASSETS
DEVELOP NEW PRODUCTS AND ASSETS
HOW TO WIN

Translational Research



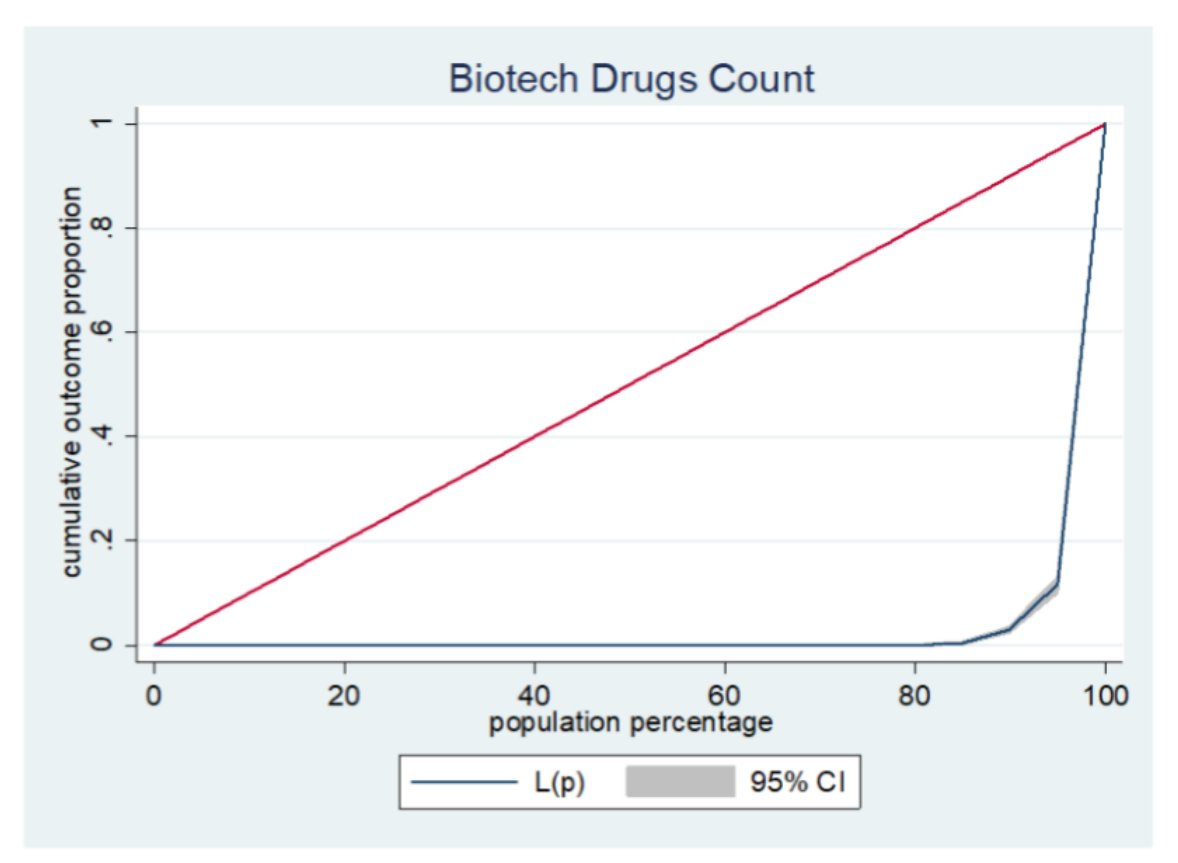
[1] Although we are using the word "treatment," clinical trials also involve medical research studies in which people participate as volunteers to test new methods of prevention, screening, and diagnosis of disease.

[2] After approval, the product is manufactured for sale on the market, and the process enters Phase 4 (Post-Marketing Monitoring/Clinical Trials). At this point, the FDA monitors for public safety and adverse events, and the sponsor company may begin Phase 4 Clinical Trials to obtain information about long-term effects or to test the product in special patient populations.

[3] The "Funding Valley of Death" is the financial challenge many promising treatments face in having the opportunity to be scientifically tested in a clinical trial. In many cases, further financial support or partnerships are necessary to proceed.

* The cost of bringing a drug to market depends on a number of variables, but could be more than $1 billion, including approximately $50-840 million for Basic Research/Drug Development and Pre-Clinical/Translational research, and approximately $50-970 million to complete all three Phases of the Clinical Trials.

Concentration of Innovation



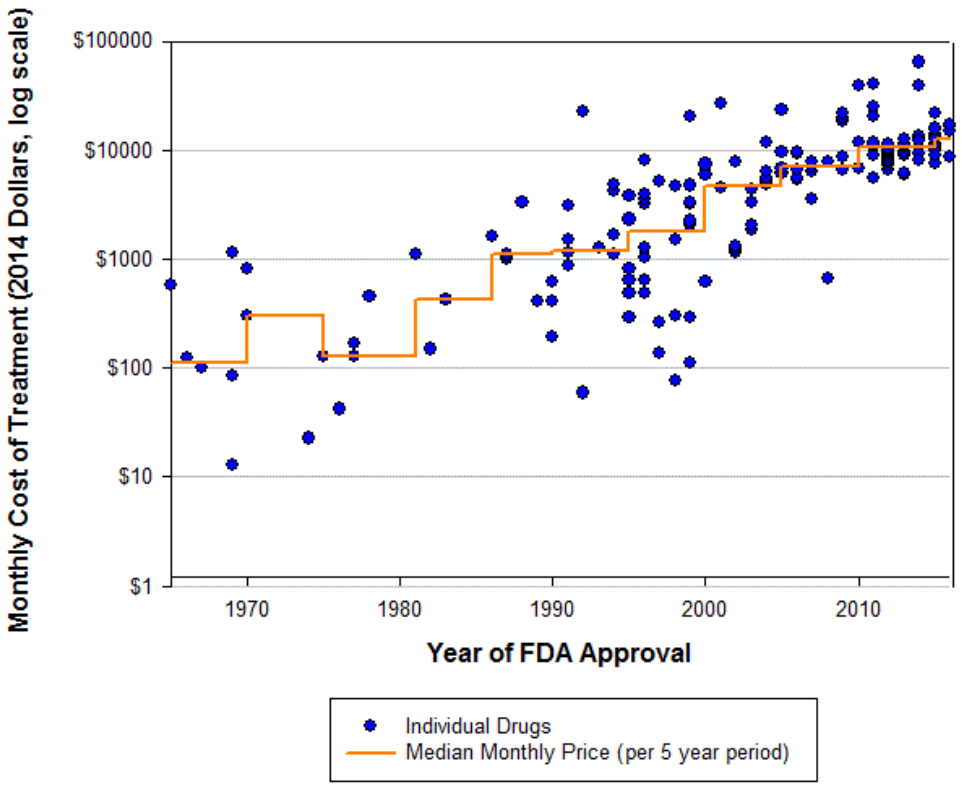
Public Attitudes about Health Care Costs.*

Attitude	Percentage of Responses
Health care costs as a national priority	
Reducing health care costs should be a top priority for President Trump and Congress in 2019†	69
Health priorities for the new Congress (top 5 from a list of 13; % saying "extremely important" priority)‡	
Lowering prescription-drug prices	92
Making sure insurance companies must still provide health insurance for preexisting conditions	91
Making sure Medicare benefits are not cut back	88
Lowering the overall cost of health care	88
Increasing spending on research to find cures for diseases	85
Reasons for high health care costs	
Reasons for rising health care costs (top 5 from a list of 12; % saying major reason)‡‡	
Drug companies make too much money	78
Hospitals charge too much	71
There is too much fraud and waste in the health care system	71
Insurance companies make too much money	70
New drugs, treatments, and medical technologies are often very expensive	62

Blendon et al., New Eng J Med, May 29, 2019

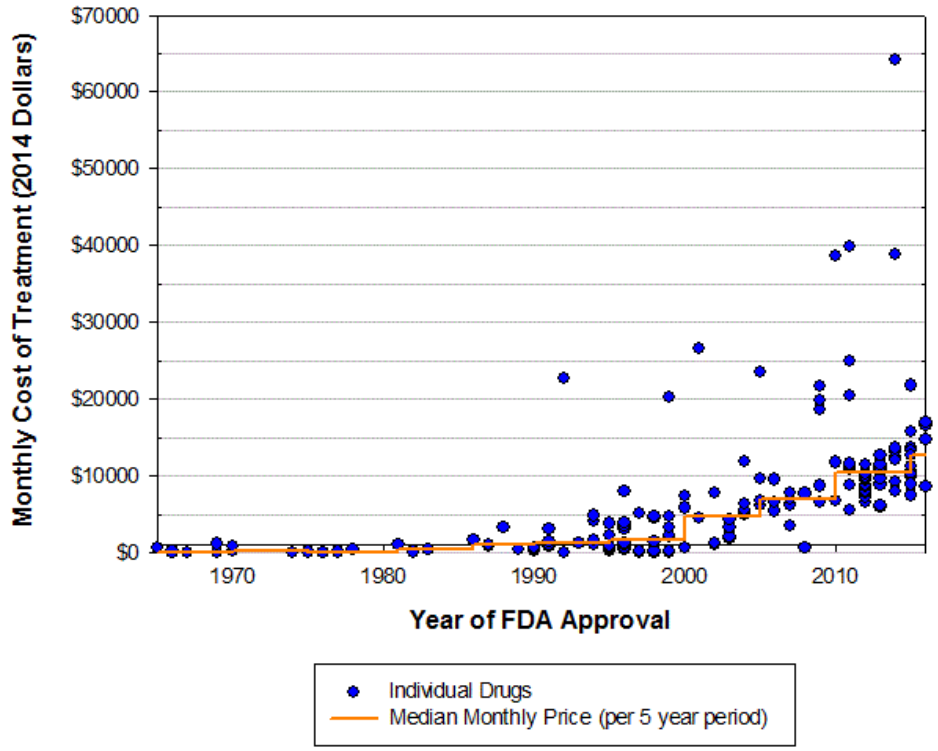
The NEW ENGLAND JOURNAL of MEDICINE

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965-2016



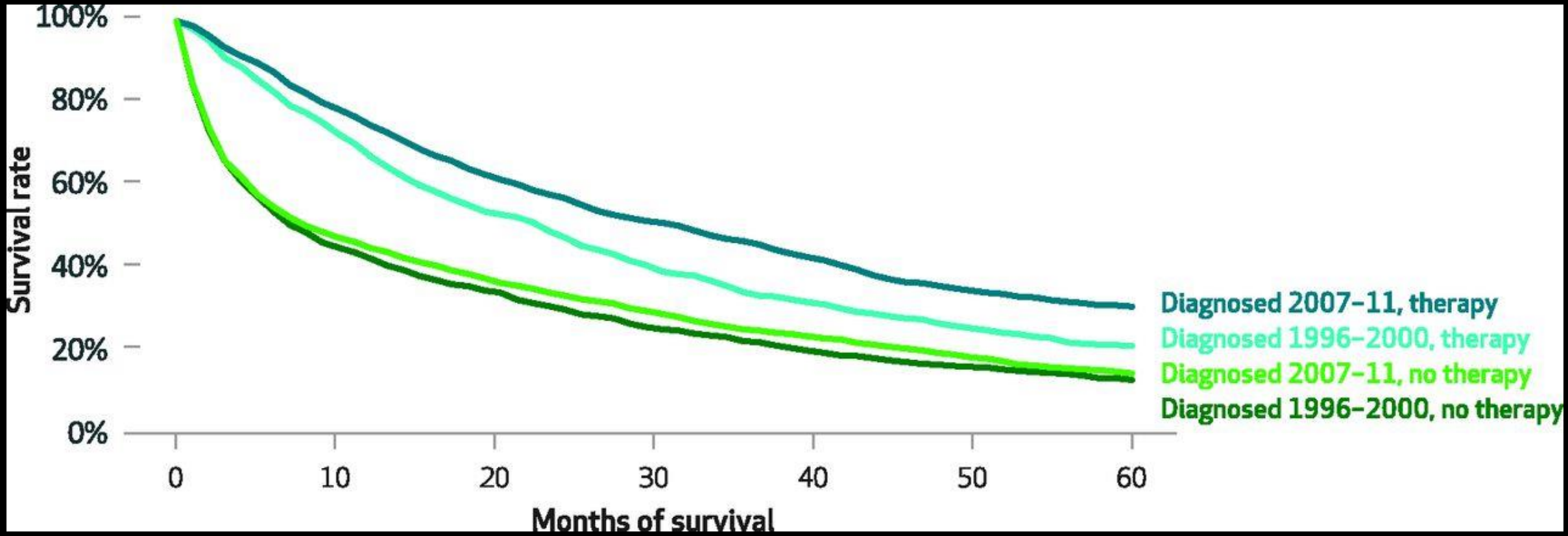
Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965-2016



Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

Breast cancer patient survival rates, by period of diagnosis and treatment.



David H. Howard et al. Health Aff 2016;35:1581-1587

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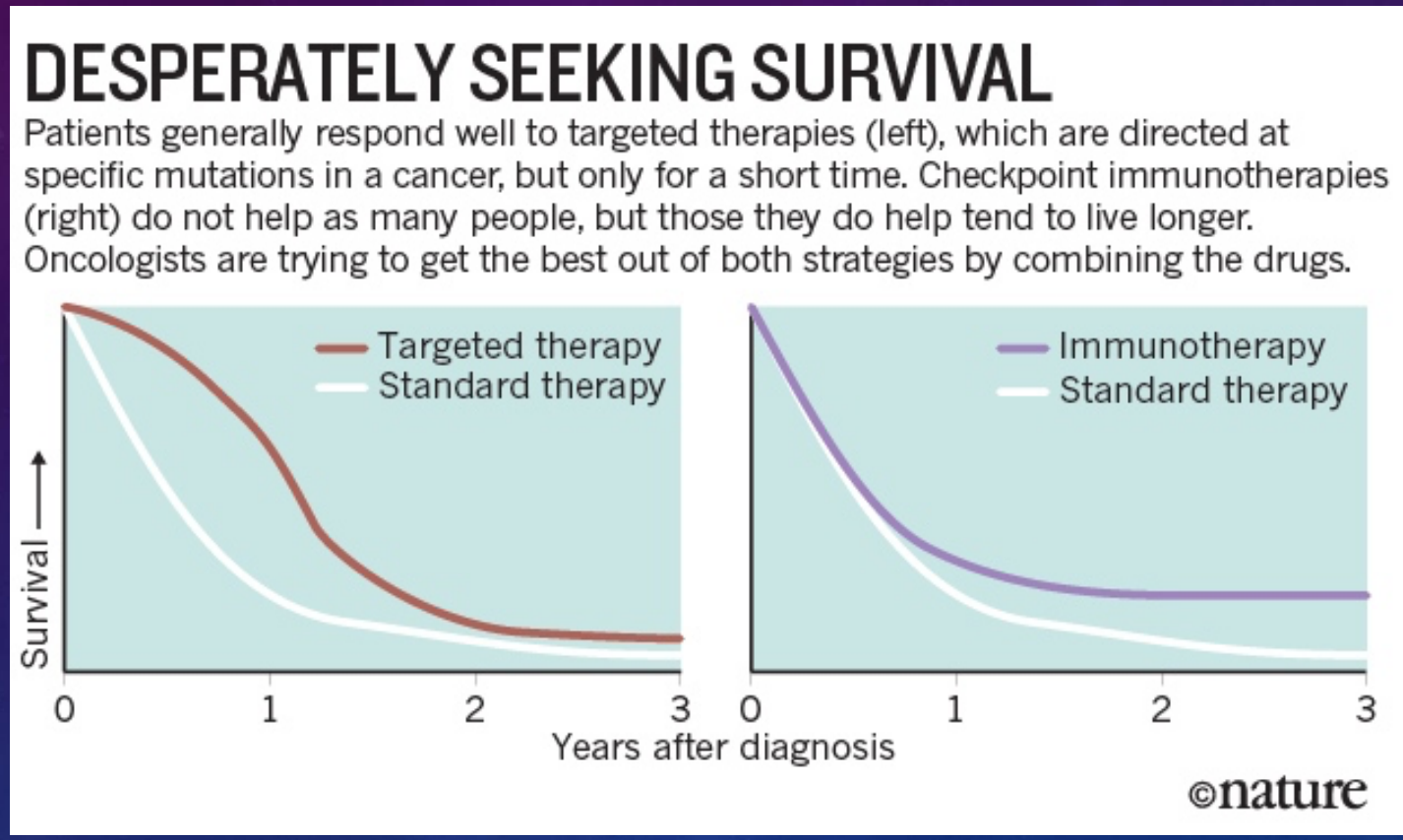
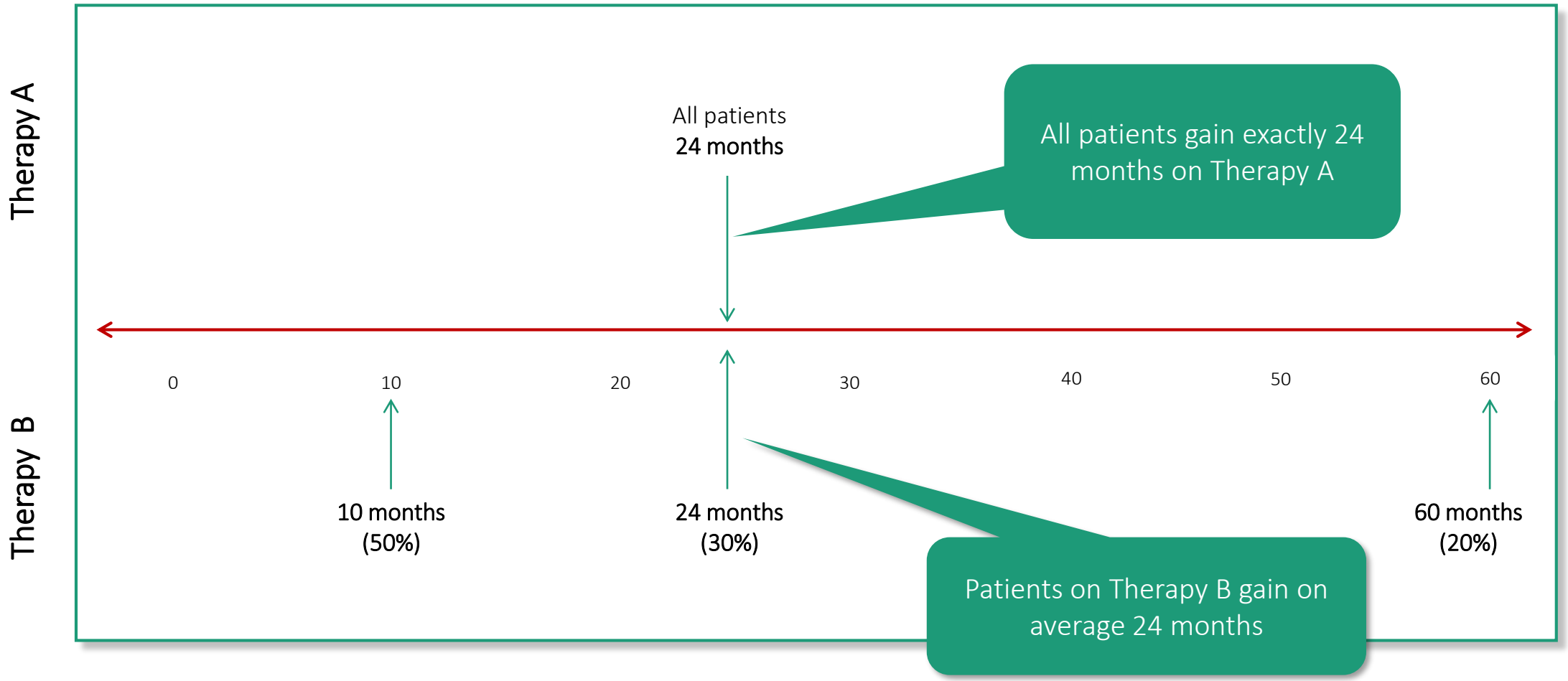
NOVEL SOURCES OF VALUE



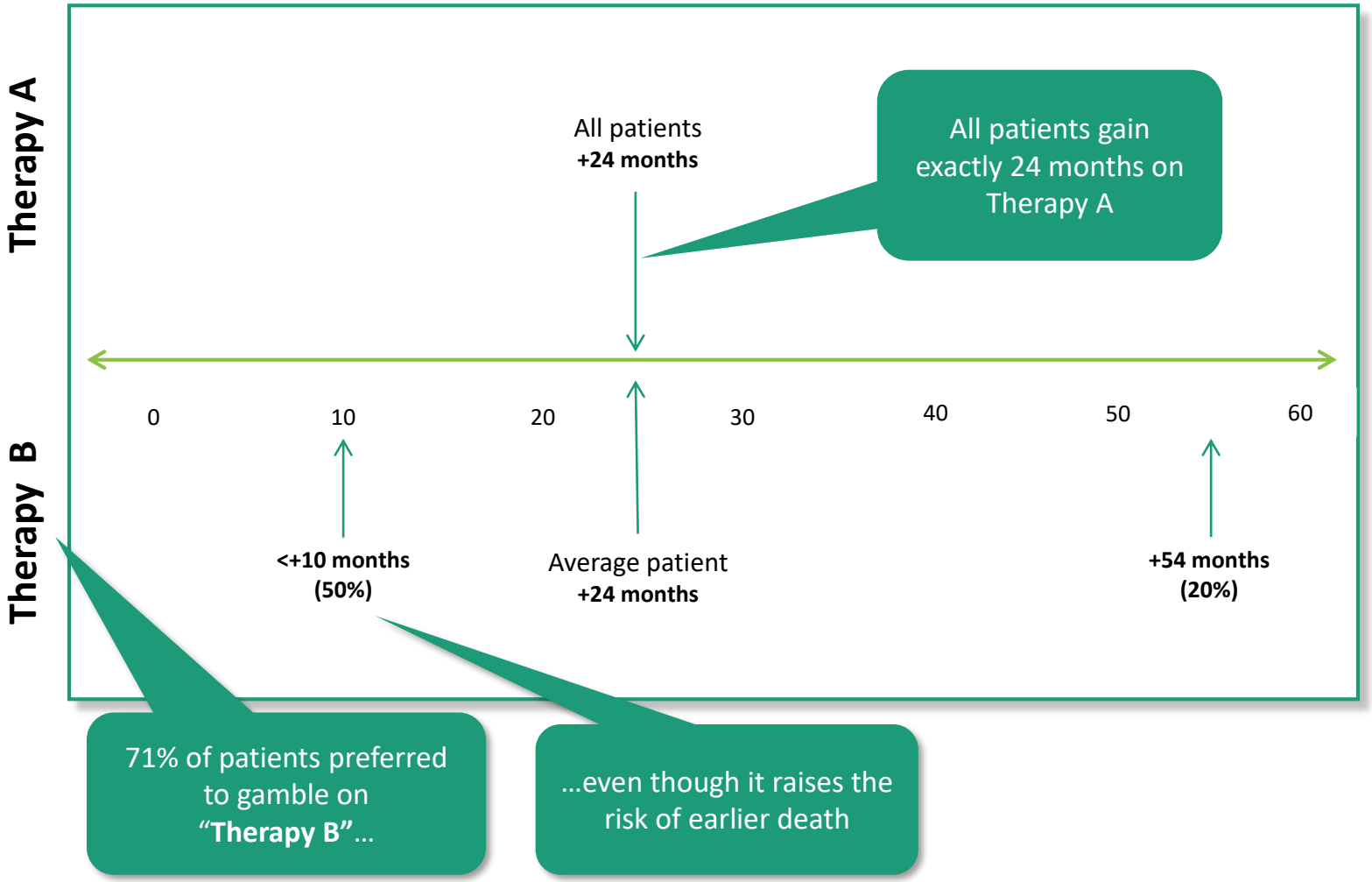
VALUE OF HOPE: SKEWNESS IN PATIENT OUTCOMES

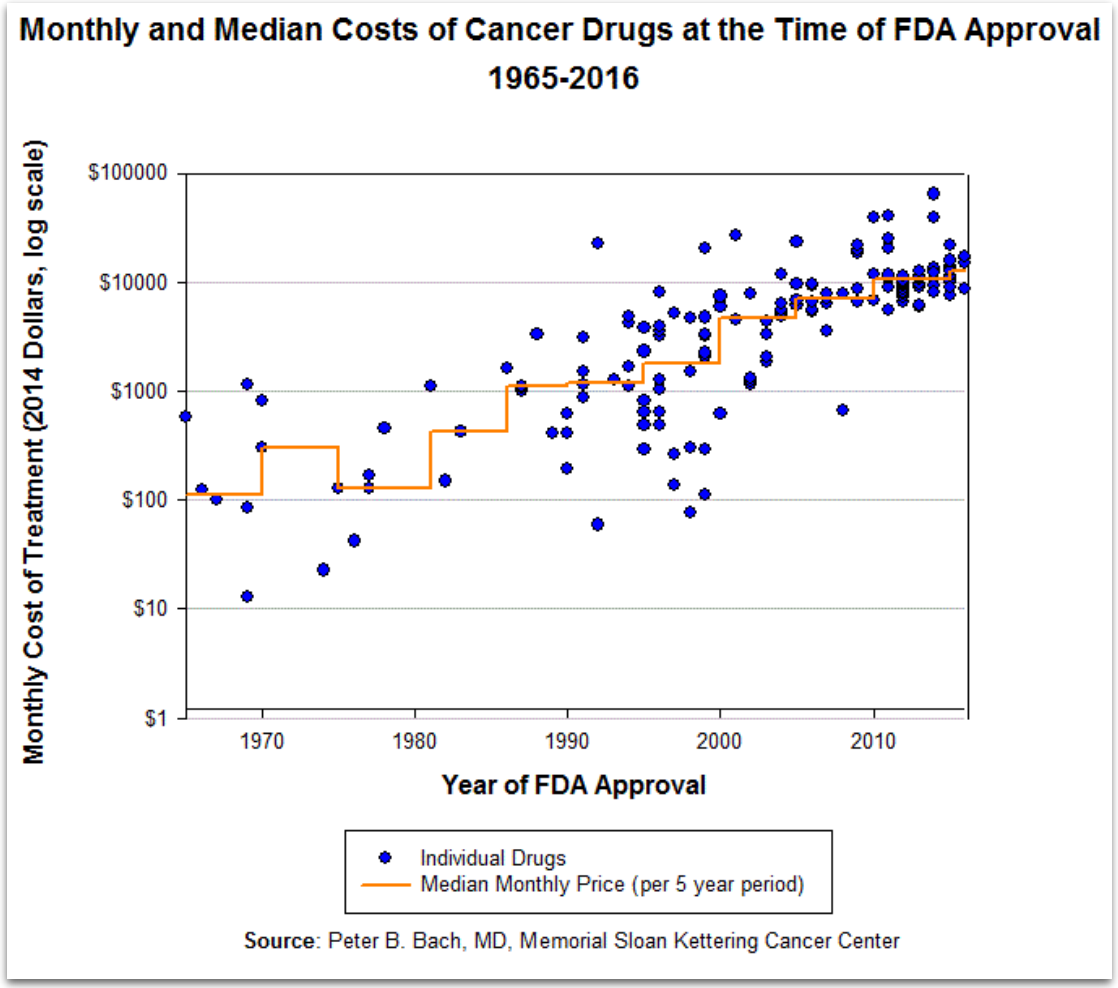
Illustrating the Value of Hope:
Which Therpay Would You Choose?

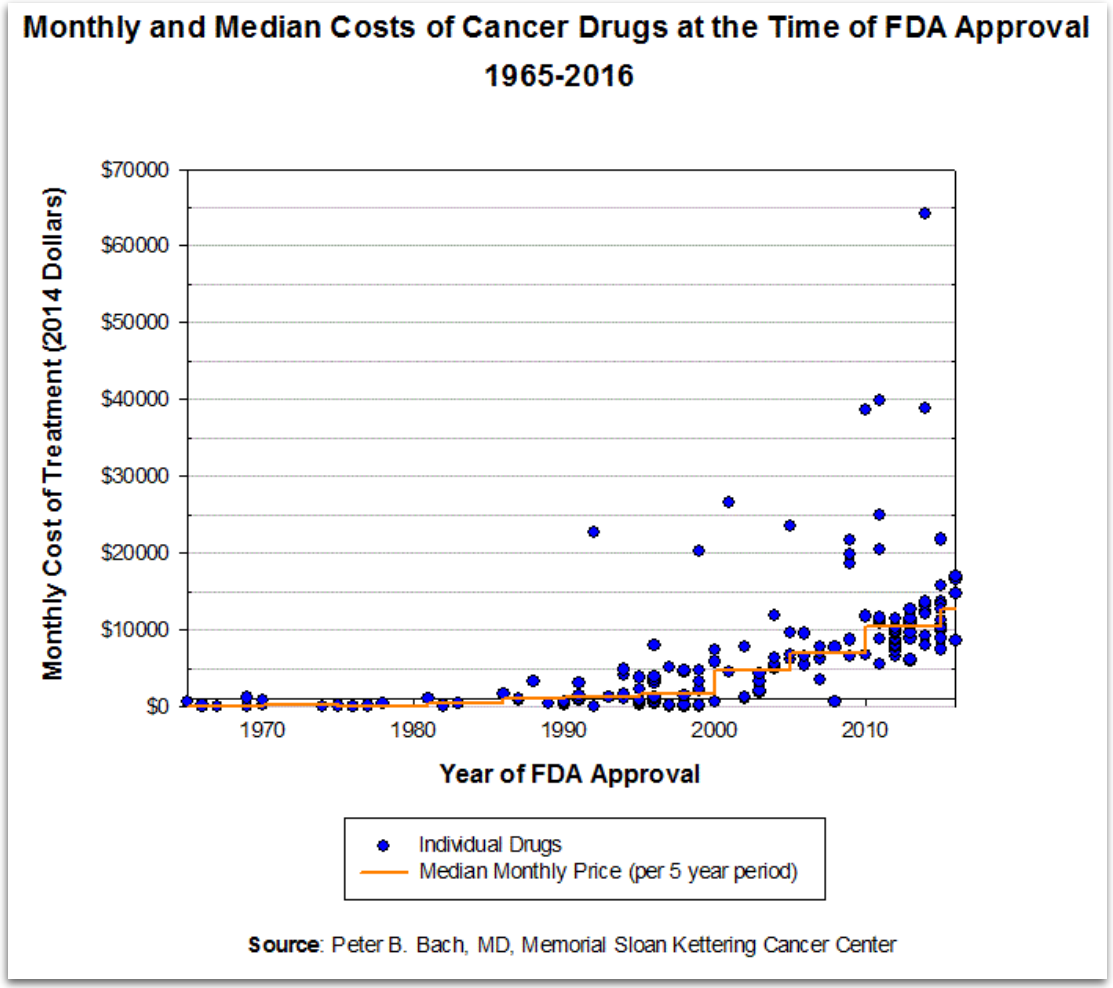


“Hopeful” Therapy a Popular Choice for Patients

In one study, 71% of cancer patients preferred “hopeful” therapy to a sure 24 month gain

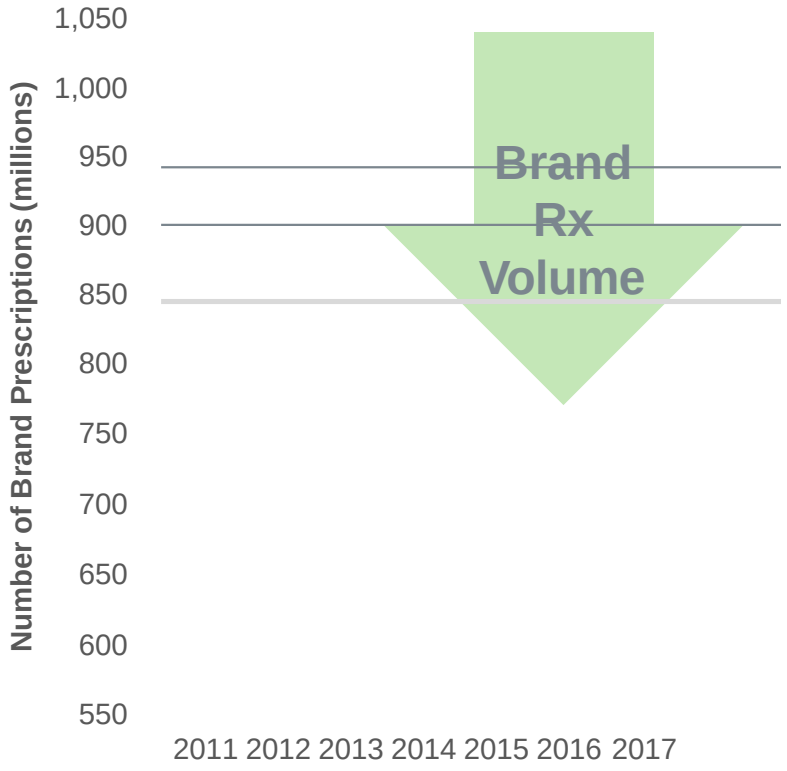



Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965-2016
Monthly Cost of Treatment (2014 Dollars, log scale)
$100000
$10000
$1000
$100
$10
$1
1970
1980
1990
2000
2010
Year of FDA Approval
Individual Drugs
Median Monthly Price (per 5 year period)
Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

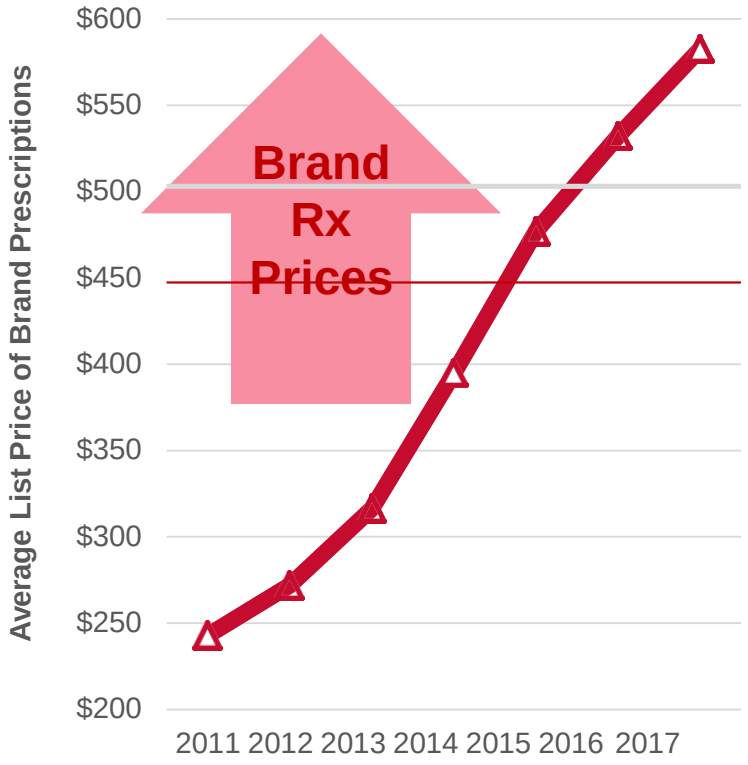

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965-2016
Monthly Cost of Treatment (2014 Dollars)
$70000
$60000
$50000
$40000
$30000
$20000
$10000
$0
1970
1980
1990
2000
2010
Year of FDA Approval
Individual Drugs
Median Monthly Price (per 5 year period)
Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

Why do Prices Increase? A Response to Shrinking Volume ?

Brand Prescription Volume Has Plummeted as Generics Have Replaced Brands

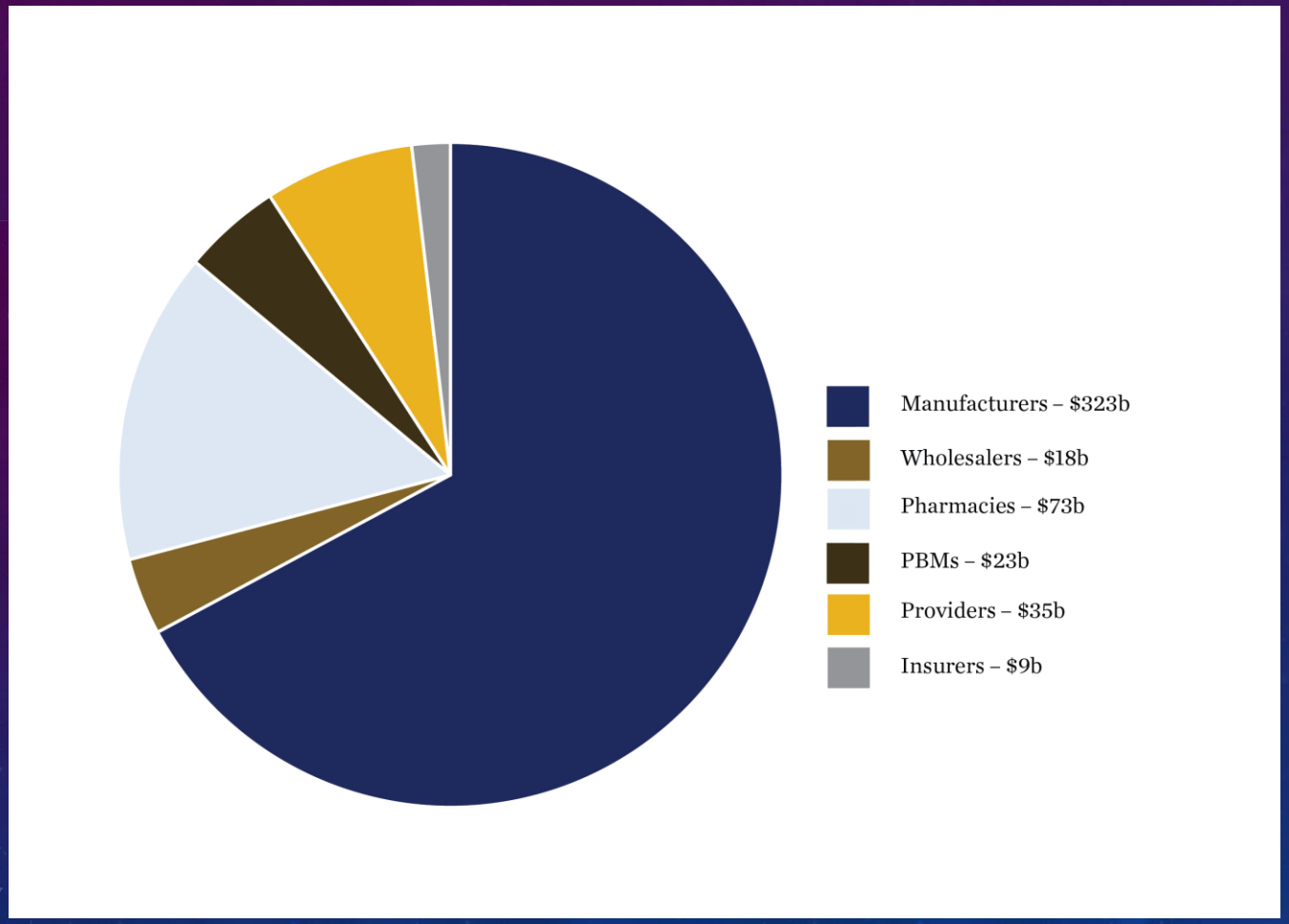


Meantime, Brand Drug Prices Have Skyrocketed to Maintain Revenues



Source: Visante analysis data published by the IQVIA Institute, 2018.

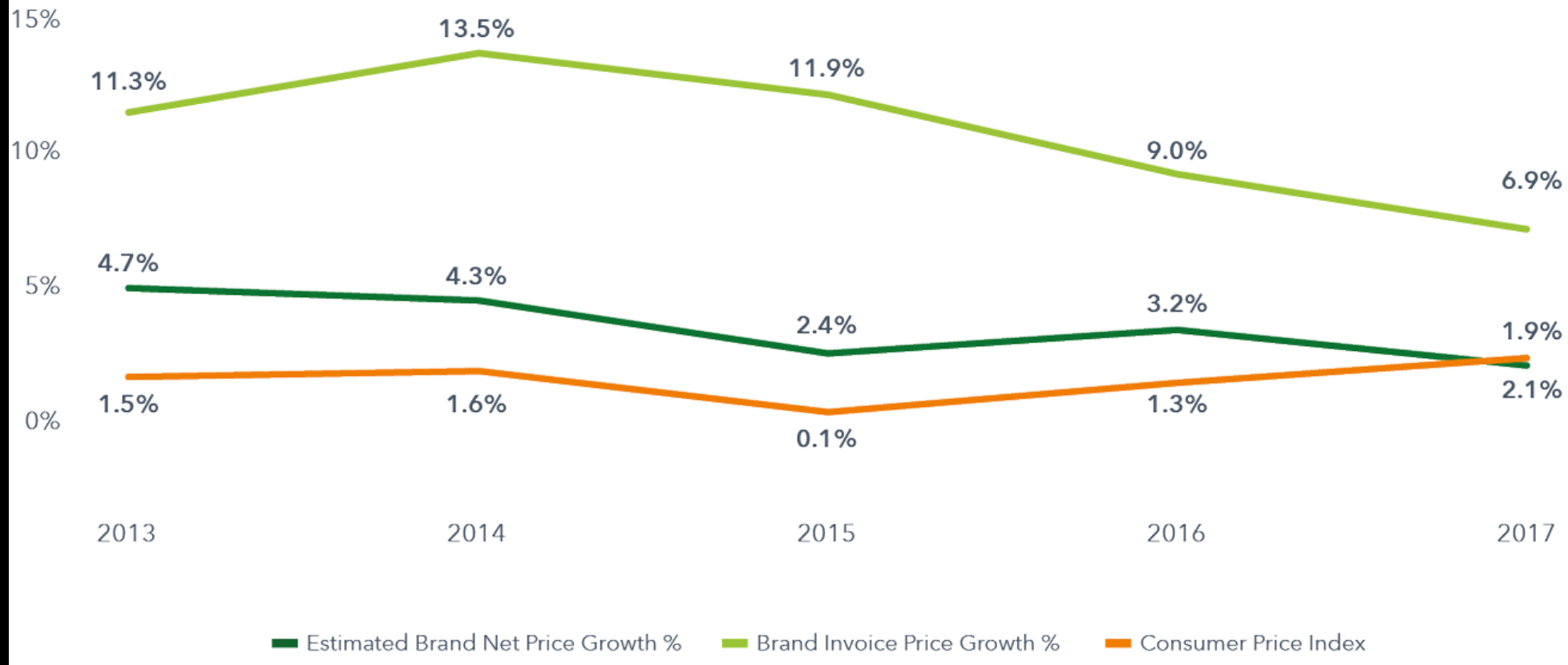
RETAINED REVENUE ACROSS US PHARMACEUTICAL SECTOR IN 2016 ($ BILLIONS)



HealthAffairs

“Spending On Prescription Drugs In The US: Where Does All The Money Go?, " Health Affairs Blog, July 31, 2018.DOI: 10.1377/hblog20180726.670593

Protected Brand Invoice and Net Price Growth %

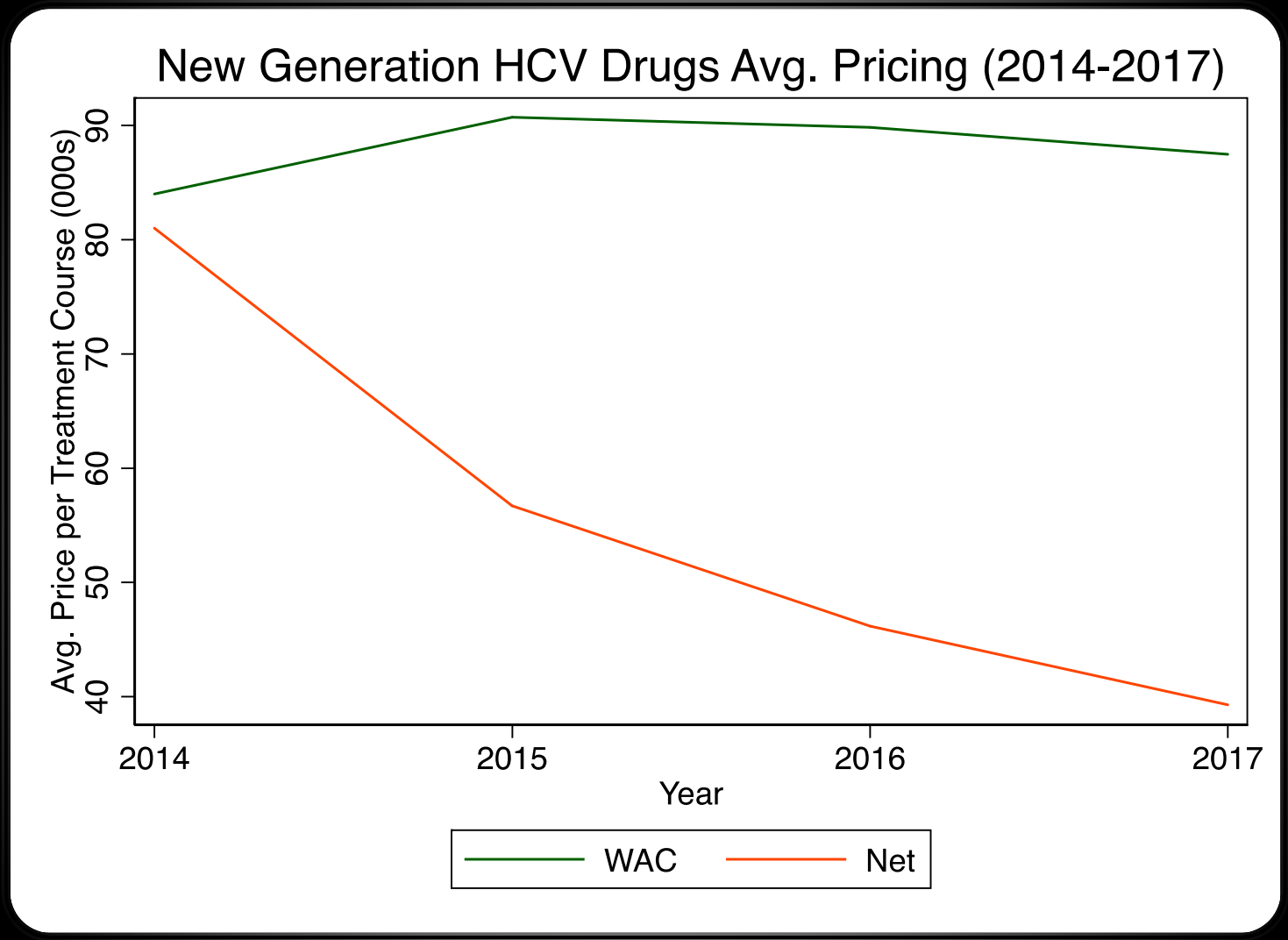


Source: IQVIA National Sales Perspectives, IQVIA Institute, Dec 2017

Chart notes: "Invoice" values are IQVIA reported values from wholesaler transactions measured at trade/invoice prices and exclude off-invoice discounts and rebates that reduce net revenue received by manufacturers. "Net" values denote company recognized revenue after discounts, rebates and other price concessions. Results are based on a comparative analysis of company reported net sales and IQVIA reported sales and prices at product level for branded products representing 75–93% of brand spending in the period displayed. All growth is calculated over same cohort of products in the prior year. See Methodology section for more details.

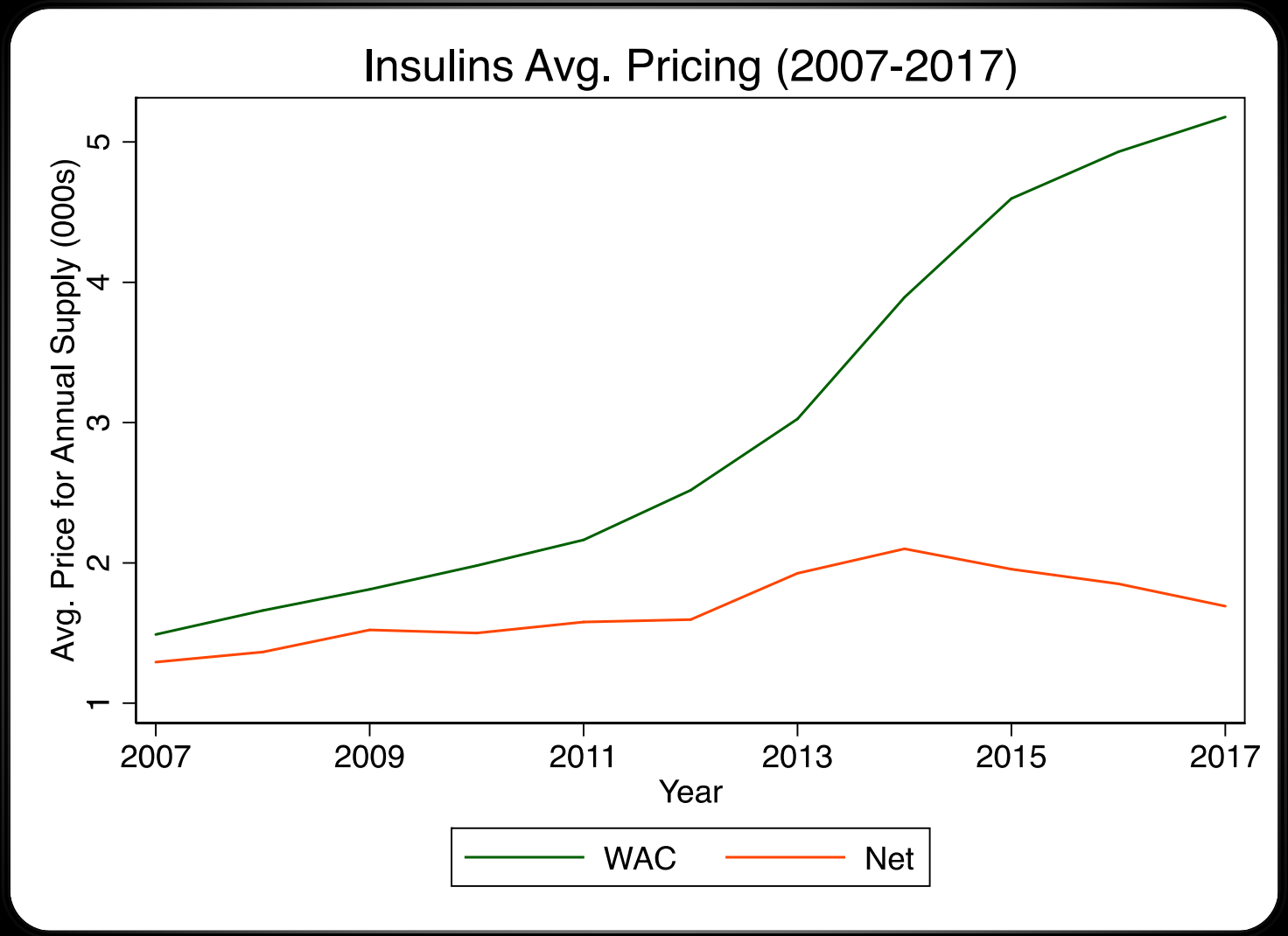
Includes all medicines in both pharmacy and institutional settings.

Report: Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022, Apr 2018



Net prices for New HCV therapies decreasing despite stagnant WAC

Includes drugs in SSR database approved after Sovaldi (2013) and before 2017: Daklinza, Epclusa, Harvoni, Sovaldi, Viekira / XR, Zepatier. Drugs weighted in proportion to average number of treatment courses sold from 2014-2017; Sovaldi and Harvoni account for 80-85% of total treatment courses sold; drugs are excluded in the calendar year of launch as sales data are less reliable.



Net prices for Insulins grew more slowly than WAC

- Includes drugs in SSR database: afrezza, apidra, basaglar, humalog, humulin, lantus, levemir, novolin, novolog, soliqua, toujeao, tresiba. Product formulations were weighted in proportion to average number of treatment courses sold from 2007-2017. For formulations with missing dosing information, the mean dose from the other formulations for that product was used. Drugs are excluded in the calendar year of launch as sales data are less reliable.