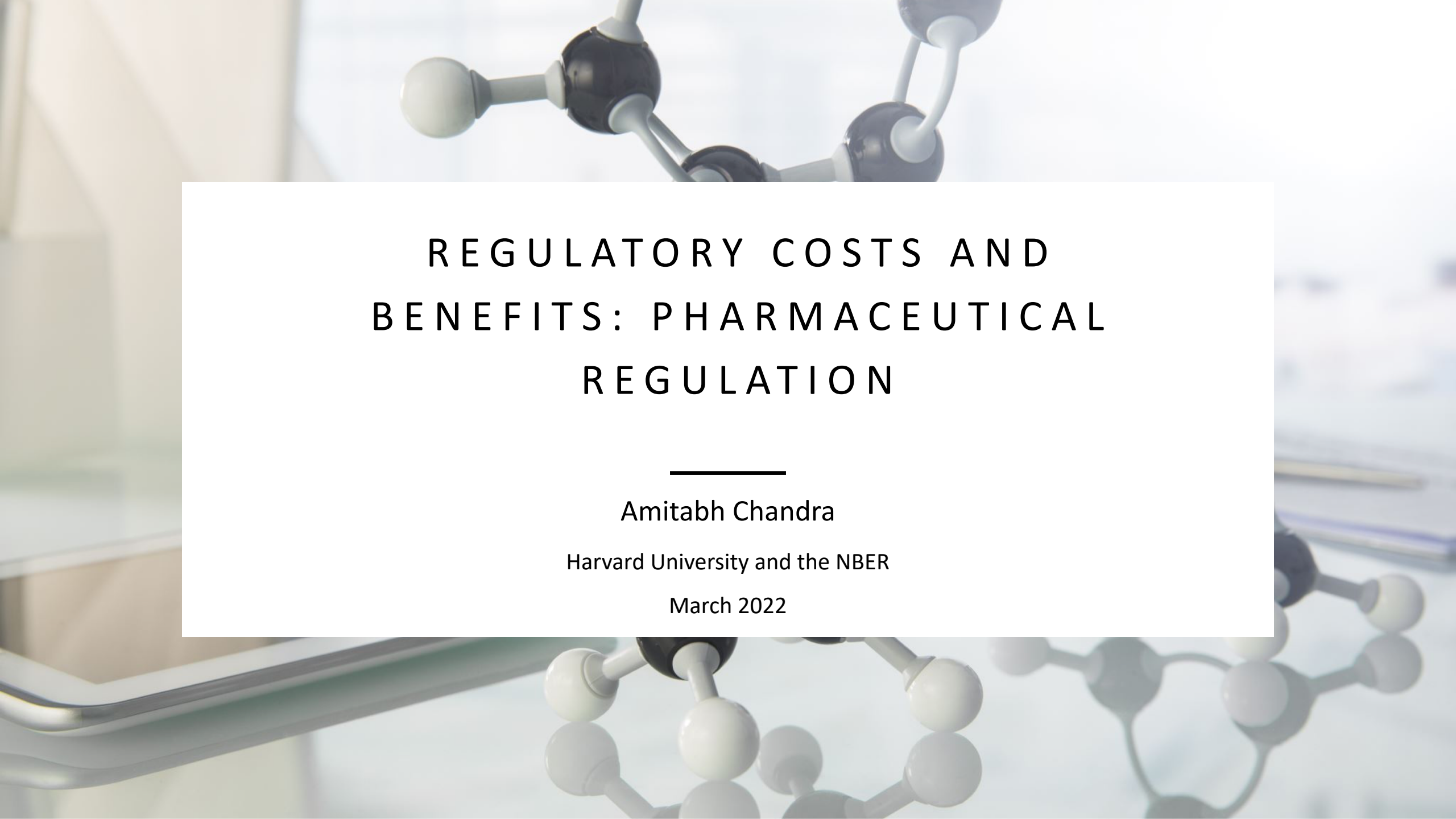
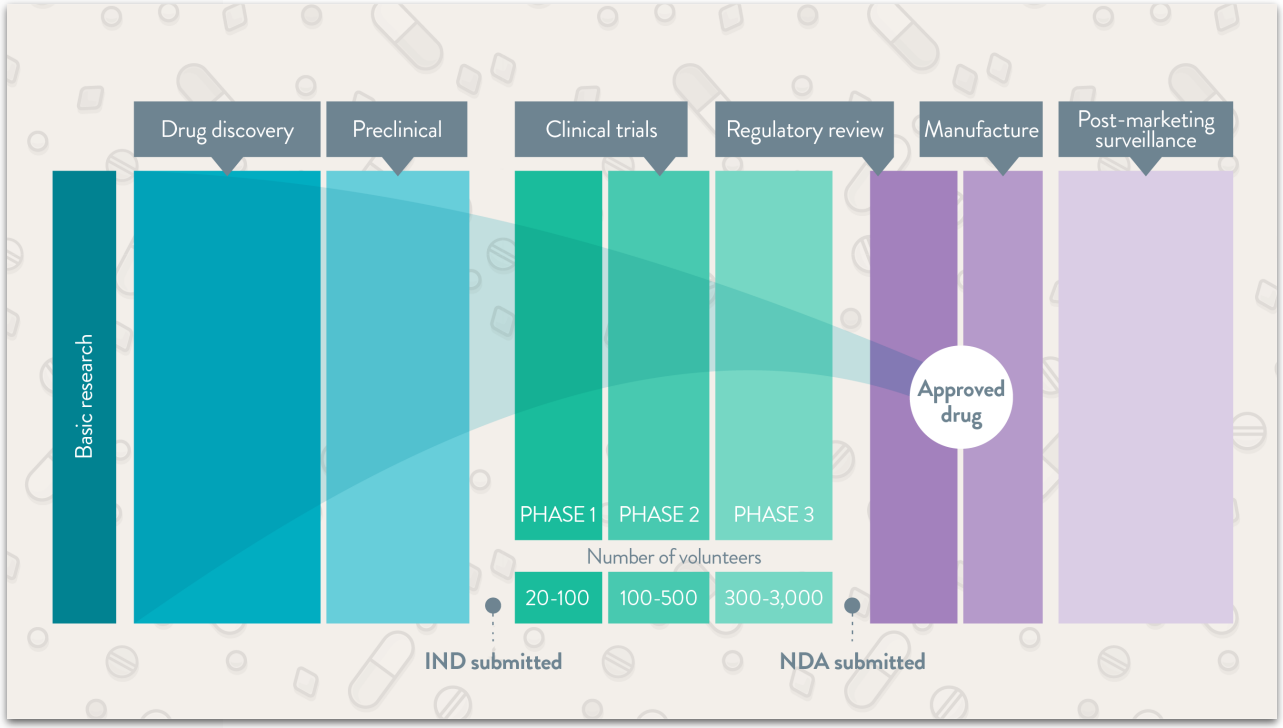


REGULATORY COSTS AND BENEFITS: PHARMACEUTICAL REGULATION

Amitabh Chandra

Harvard University and the NBER

March 2022



I. **FDA Regulation**

- Speed/Safety Tradeoff
- FDA Regulation and Market Size
- Marketing and Welfare

II. Regulation and Innovation

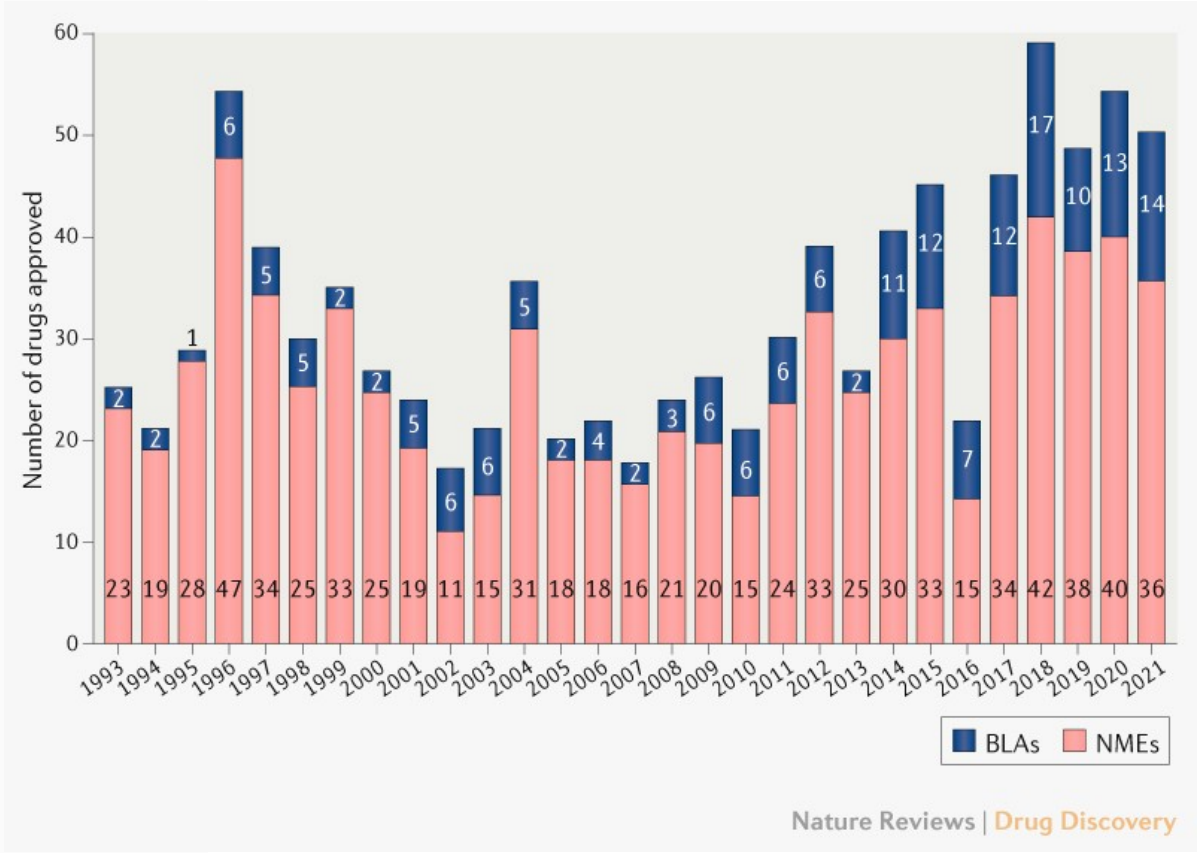
- Regulatory incentives: ODA
- Quality of Innovation: not just medicines

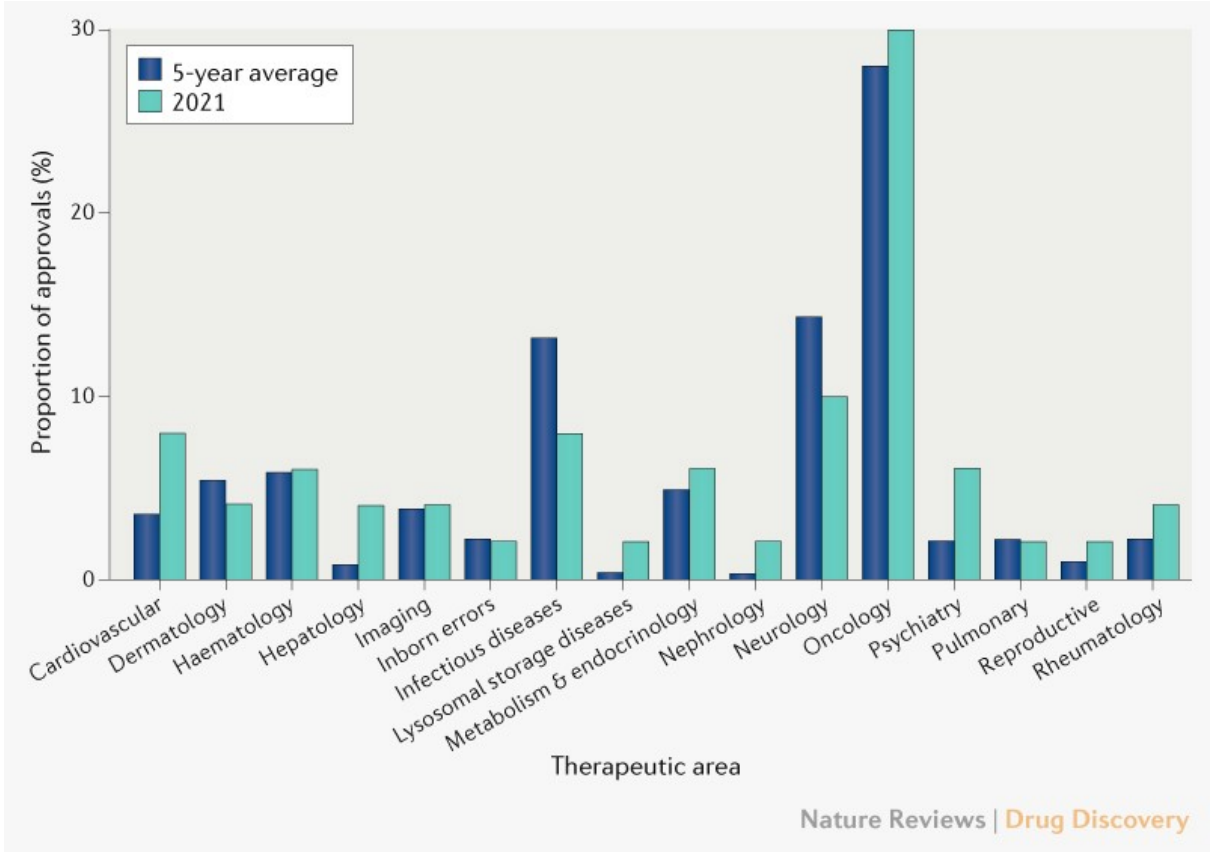
III. Drug Price Regulation

- Myths vs. Facts
- Regulation of Price Discrimination
- Regulation of Plan-design

2018				2023			
RANK		COUNTRY	% OF U.S.	RANK		COUNTRY	% OF U.S.
1		U.S.	100	1		U.S.	100
2		China	28	2		China	27
3		Japan	18	3		Japan	12
4		Germany	11	4		Germany	10
5		France	7	5	▲ 2	Brazil	7
6		Italy	7	6		Italy	6
7	▲ 1	Brazil	6	7	▼ 2	France	6
8	▼ 1	U.K.	6	8		U.K.	5
9		Spain	5	9	▲ 2	India	5
10		Canada	5	10	▼ 1	Spain	4
11		India	4	11	▼ 1	Canada	4
12		South Korea	3	12	▲ 1	Russia	4
13	▲ 1	Russia	3	13	▼ 1	South Korea	3
14	▼ 1	Australia	3	14	▲ 3	Turkey	3
15		Mexico	2	15	▲ 4	Argentina	2
16	▲ 1	Poland	2	16	▼ 2	Australia	2
17	▲ 9	Turkey	2	17	▼ 2	Mexico	2
18	▼ 2	Saudi Arabia	2	18	▼ 2	Poland	2
19	▲ 27	Argentina	1	19	▼ 1	Saudi Arabia	2
20	▼ 2	Belgium	1	20	▲ 6	Vietnam	1

- Actions by firms and US regulators have enormous implications for patients and spending around the world
- For these reasons, I will focus on US actors, but there are important lessons to be learn other large markets such as Japan and Germany


Number of drugs approved
60
50
40
30
20
10
0
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021
2 2 1 6 5 5 2 2 5 6 6 5 2 4 2 3 6 6 6 12 6 2 11 12 7 12 17 10 13 14
23 19 28 47 34 25 33 25 19 11 15 31 18 18 16 21 20 15 24 33 25 30 33 15 34 42 38 40 36
BLAs
NMEs
Nature Reviews | Drug Discovery


Proportion of approvals (%)
30
20
10
0
5-year average
2021
Cardiovascular
Dermatology
Haematology
Hepatology
Imaging
Inborn errors
Infectious diseases
Lysosomal storage diseases
Metabolism & endocrinology
Nephrology
Neurology
Oncology
Psychiatry
Pulmonary
Reproductive
Rheumatology
Therapeutic area
Nature Reviews | Drug Discovery

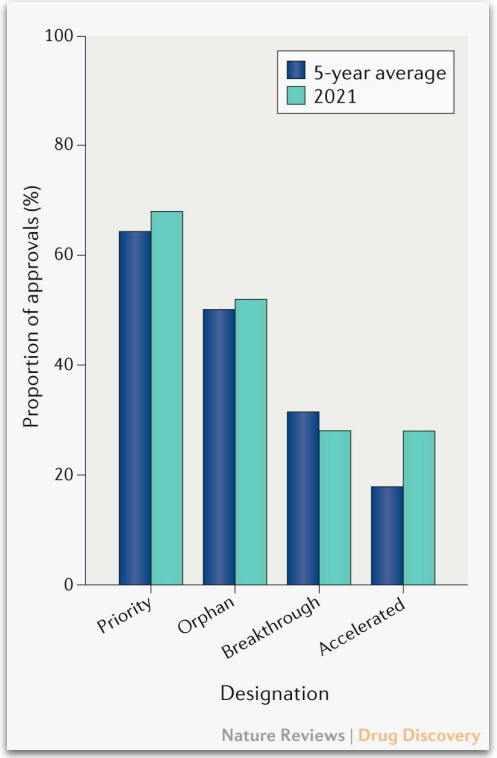
Understanding the Tradeoff between Speed and Benefit

EXHIBIT 1

Overview of the Food and Drug Administration's (FDA's) Expedited Drug Approval Programs

	Fast track	Accelerated approval	Priority review	Breakthrough therapy
Date established	1988	1992	1992	2012
Qualifying criteria	• Must be intended to treat a serious condition • May address an unmet medical need • Supporting data can be clinical or nonclinical	• Must treat a serious condition • Early evidence shows substantial improvement over existing therapies • May use surrogate endpoints to demonstrate clinical benefit	• Must treat a serious condition • Provides significant improvement in safety or effectiveness over existing therapies	• Must treat a serious condition • Early evidence shows substantial improvement over existing therapies • Supporting data must be clinical
Time frame for application and FDA response	Can be requested with an investigational new drug (IND) submission or any point after applying. The FDA has sixty days to respond to request.	No formal process. Drug sponsors are encouraged to discuss the possibility with the FDA during drug development.	Requested at time of drug approval application. The FDA has sixty days to respond to request.	Can be requested with IND submission or any point after applying. The FDA has sixty days to respond to request.
Key program features	• Earlier and more frequent communication with the FDA during development • Rolling review of application • Designation may be withdrawn if drug no longer meets qualifying criteria	• Approval is granted on a conditional basis. Drug sponsor must conduct post-approval trials to confirm benefits • Application is submitted in one package • Drug is subject to expedited withdrawal	• Drug review process is shortened to six months (from the standard ten months)	• All fast-track designation features • Intensive FDA guidance throughout development process, involving senior FDA officials • Designation may be withdrawn if drug no longer meets qualifying criteria

SOURCE Information in this table was adapted from the FDA's "Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics" (June 2013).



Problems with surrogate measures: Safety

Drug	Use	Surrogate	Actual Outcome
Aprotinin	High-risk cardiac surgery	Decreased need for transfusion	Mortality
Clofibrate	Increased cholesterol in healthy men	Decreased cholesterol	Mortality
Doxazosin	Hypertension and other CV risk factors	Decreased blood pressure	Congestive heart failure
Encainide	Ventricular premature beats post-MI	Decreased ventricular ectopic beats	Mortality
Erythropoietin	Anemia due to chronic renal failure	Increased hemoglobin to >12.0	Mortality
Estrogen/ progestin	Cardiovascular disease prevention in postmenopausal women	Decreased LDL cholesterol and increased HDL cholesterol	CV disease and breast cancer
Flecainide	Post -MI patients with ventricular premature beats	Decreased ventricular ectopic beats	Mortality

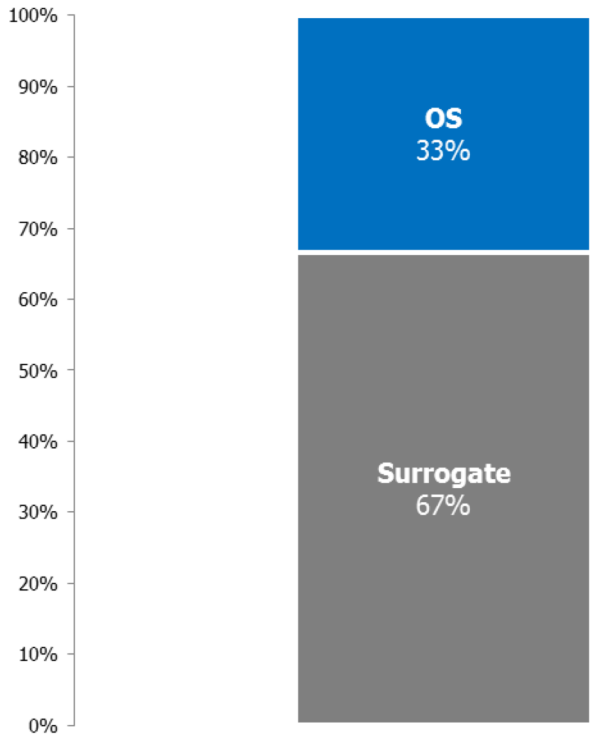
Drug	Use	Surrogate	Actual Outcome
Flosequinan	Chronic congestive heart failure	Improved ventricular function	Mortality
Fluoride	Fracture prevention in postmenopausal women with osteoporosis	Increased bone mineral density	Nonvertebral fractures
Ibopamine	Severe congestive heart failure	Increased exercise tolerance and decreased vascular resistance	Mortality
Metoprolol	Patients with CV risk factors undergoing non-cardiac surgery	Decreased postoperative myocardial ischemia	Mortality
Milrinone	Severe congestive heart failure	Increased cardiac contractility	Mortality
Moxonidine	Congestive heart failure	Decreased plasma norepinephrine	Mortality

Svensson et al. JAMA IM, 2013
Slide is from Aaron Kesselheim at Harvard Medical School and PORTAL

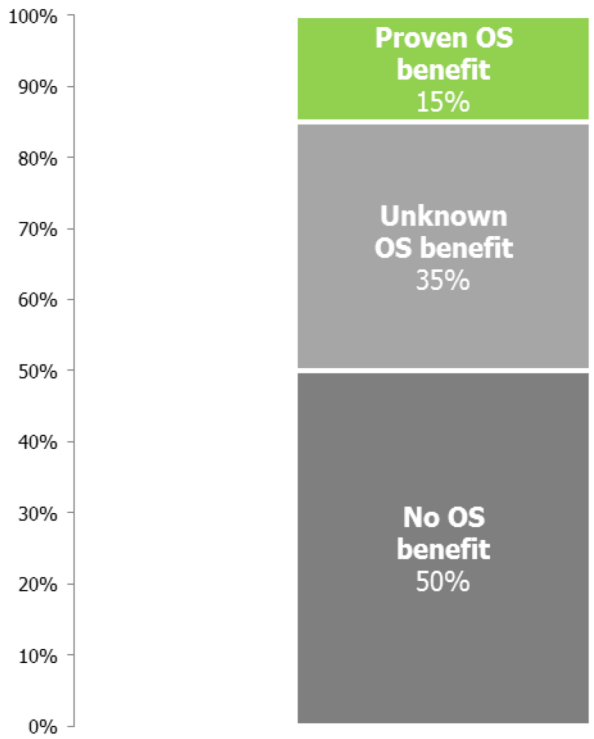
PORTAL
Program On Regulation, Therapeutics, And Law

Problems with surrogate measures: Efficacy

% of approvals based on surrogate



% of surrogate approvals with OS benefit (with follow-up)



Kim, Prasad, JAMA Intern Med, 2015. Includes all cancer drugs approved by FDA between 2008-2012.
Slide is from Aaron Kesselheim at Harvard Medical School and PORTAL

Is mortality (OS) the only benefit?
How would we know if Acc Approval is balancing speed against benefit correctly?

Does Regulation Always Reduce Profits?

- Higher bar for evidence increases cost of development
- Higher cost of development lowers NPV of project
  - What if FDA approval increases market size through a certification effect?

REGULATORY APPROVAL AND EXPANDED MARKET SIZE

Benjamin Berger
Amitabh Chandra
Craig Garthwaite

Working Paper 28889
http://www.nber.org/papers/w28889

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
June 2021

(1) follow-on approvals increase the share of patients taking a drug with that indication by 40%
(2) little market learning prior to, or following the approval of follow-on indication
(3) effect is larger for uses in a different disease area (4.5 yrs of market-learning)
(4) FDA approval, not the initiation of clinical trials, generate expansion in market size

Pharmaceutical Marketing and Welfare

Ask Your Doctor? Direct-to-Consumer Advertising of Pharmaceuticals

NBER Working Paper No. w21045

55 Pages • Posted: 30 Mar 2015 • Last revised: 2 Jan 2022

Michael Sinkinson
Yale SOM

Amanda Starc
Kellogg School of Management, Northweste

Date Written: March 2015

Abstract

We measure the impact of direct-to-consumer television advertising (DTCA) by drug manufacturers. Our identification strategy exploits shocks to local advertising markets generated by idiosyncrasies of the political advertising cycle as well as a regulatory intervention affecting a single product. We find that a 10% increase in the number of a firm's ads leads to a 0.76% increase in revenue, while the same increase in rival advertising leads to a 0.55% decrease in firm revenue. Results also indicate that a 10% increase in category advertising produces a 0.2% revenue increase for non-advertised drugs. Both the business-stealing and spillover effects would not be detected through OLS. Decomposition using micro data confirms that the effect is due mostly to new customers as opposed to switching among current customers. Simulations show that an outright ban on DTCA would have modest effects on the sales of advertised drugs as well as on non-advertised drugs.

Promoting Wellness or Waste? Evidence from Antidepressant Advertising

Becker Friedman Institute for Research in Economics Working Paper No. 2018-14
American Economic Journal: Microeconomics

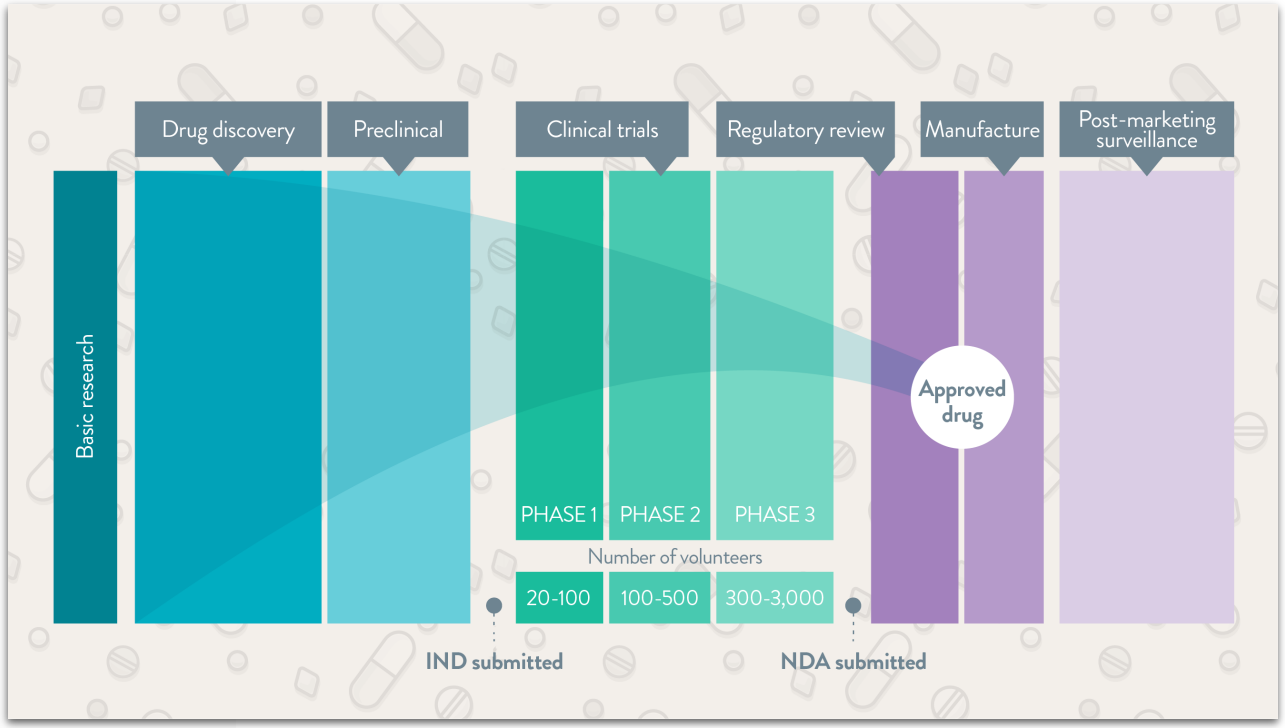
55 Pages • Posted: 6 Mar 2018 • Last revised: 2 Apr 2020

Bradley Shapiro
University of Chicago - Booth School of Business

Date Written: April 1, 2020

Abstract

It is taken as given by many policy makers that Direct-to-Consumer Advertising of prescription drugs drives inappropriate patients to treatment. Alternatively, advertising may provide useful information that causes appropriate patients to seek treatment. I study this dynamic in the context of antidepressants. Leveraging variation driven by the borders of television markets, I find that a 10% increase in antidepressant advertising leads to a 0.3% ($32 million) increase in new prescriptions followed by reductions in workplace absenteeism worth about $770 million. I find no effect of advertising on prices, generic penetration, drug switches, adverse effects, non-adherence rates or therapist visits.



I. **FDA Regulation**

- Speed/Safety Tradeoff
- FDA Regulation and Market Size
- Marketing and Welfare

II. **Regulation and Innovation**

- Regulatory incentives: ODA
- Quality of Innovation: not just medicines

III. **Drug Price Regulation**

- Myths vs. Facts
- Regulation of Price Discrimination
- Regulation of Plan-design

The Trillion Dollar Question: Are we getting the right medicines?

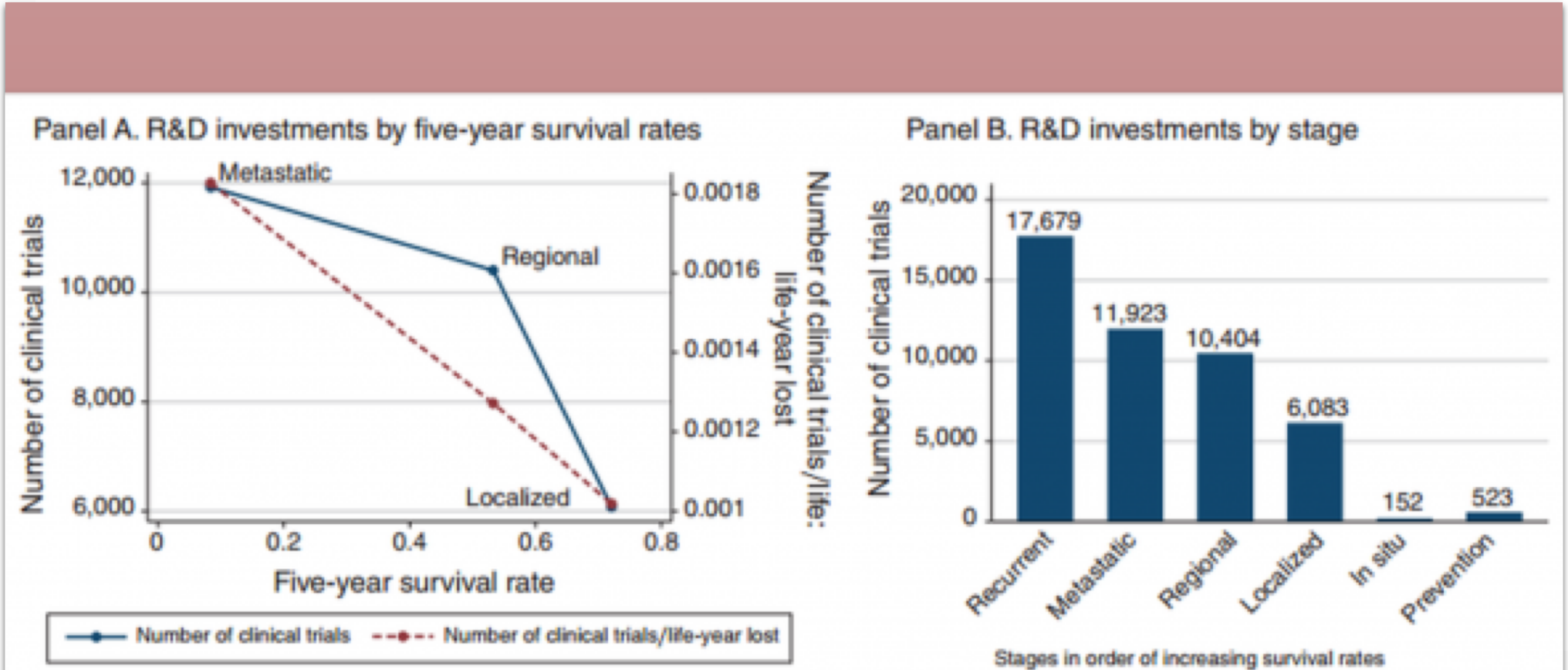
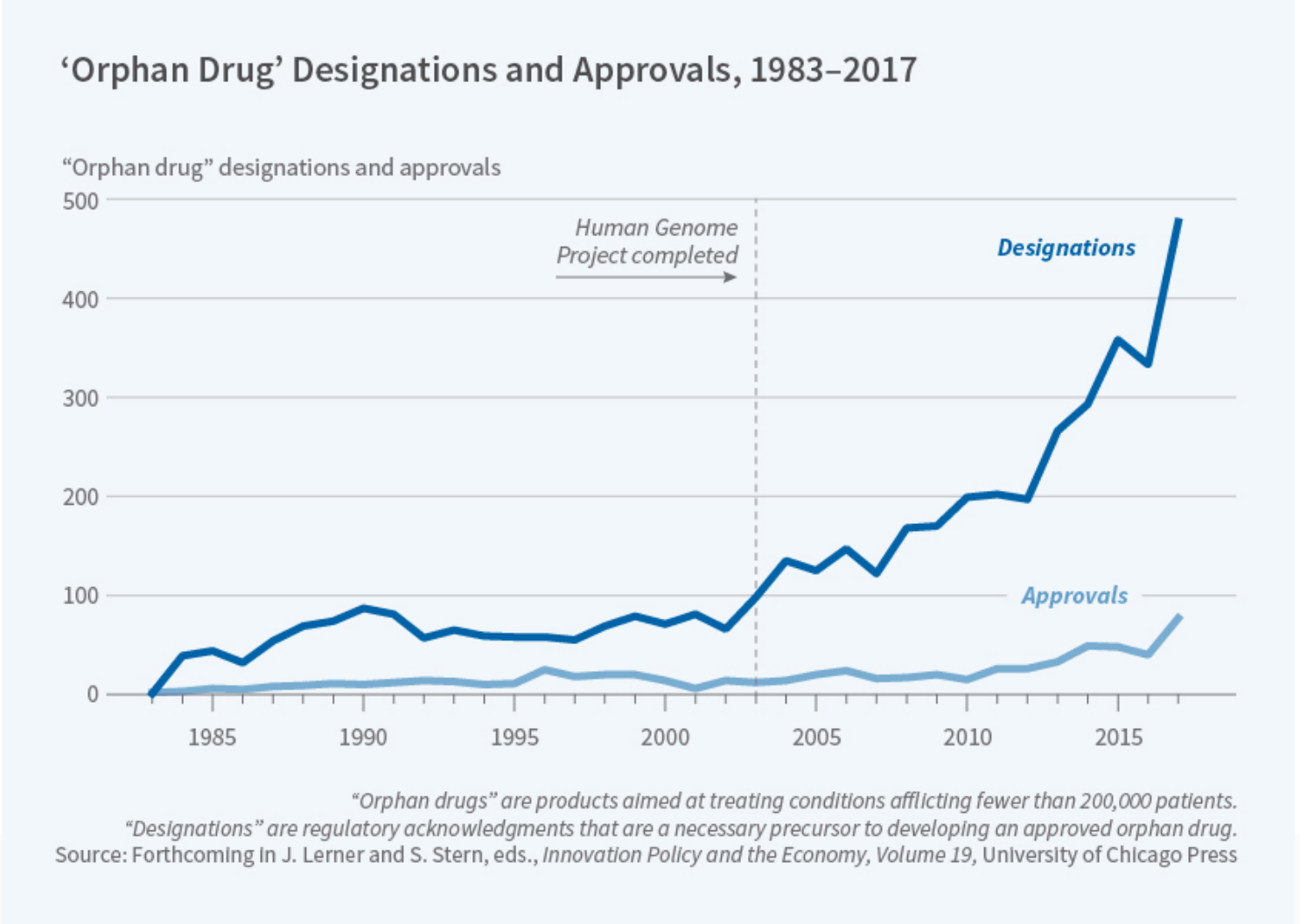
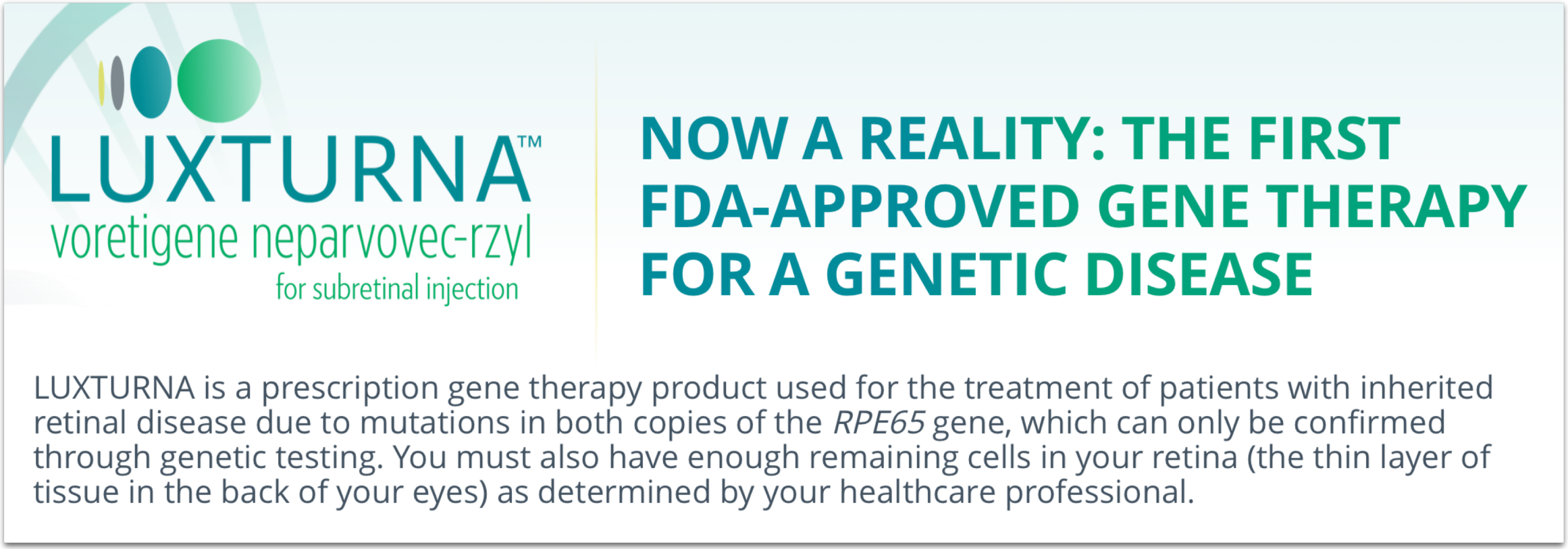


FIGURE 1. SURVIVAL TIME AND R&D INVESTMENTS: STAGE-LEVEL DATA

How does Regulation Affect the Shape of Innovation?

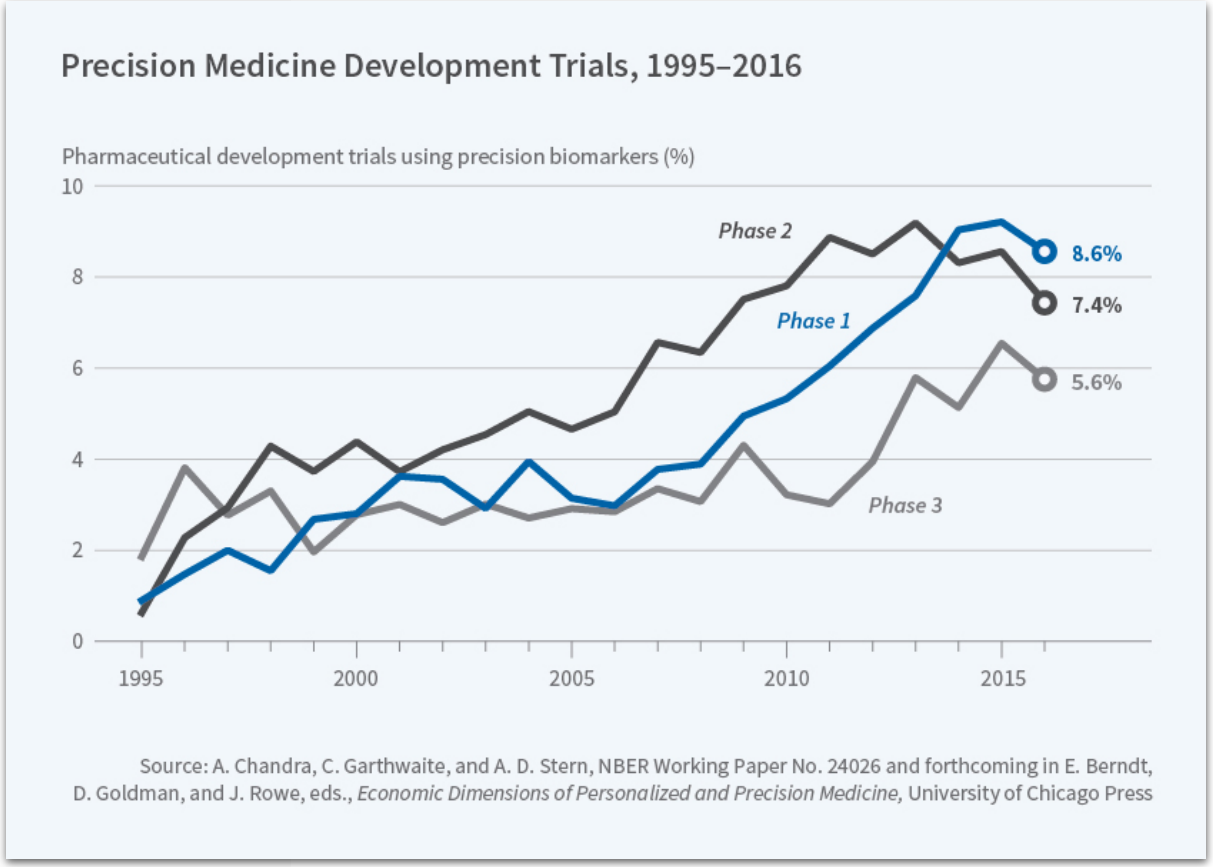
- Firms undertake R&D as long as expected profits exceed a threshold
- Expected profits will be small for rare diseases
- ODA is an attempt to rectify this





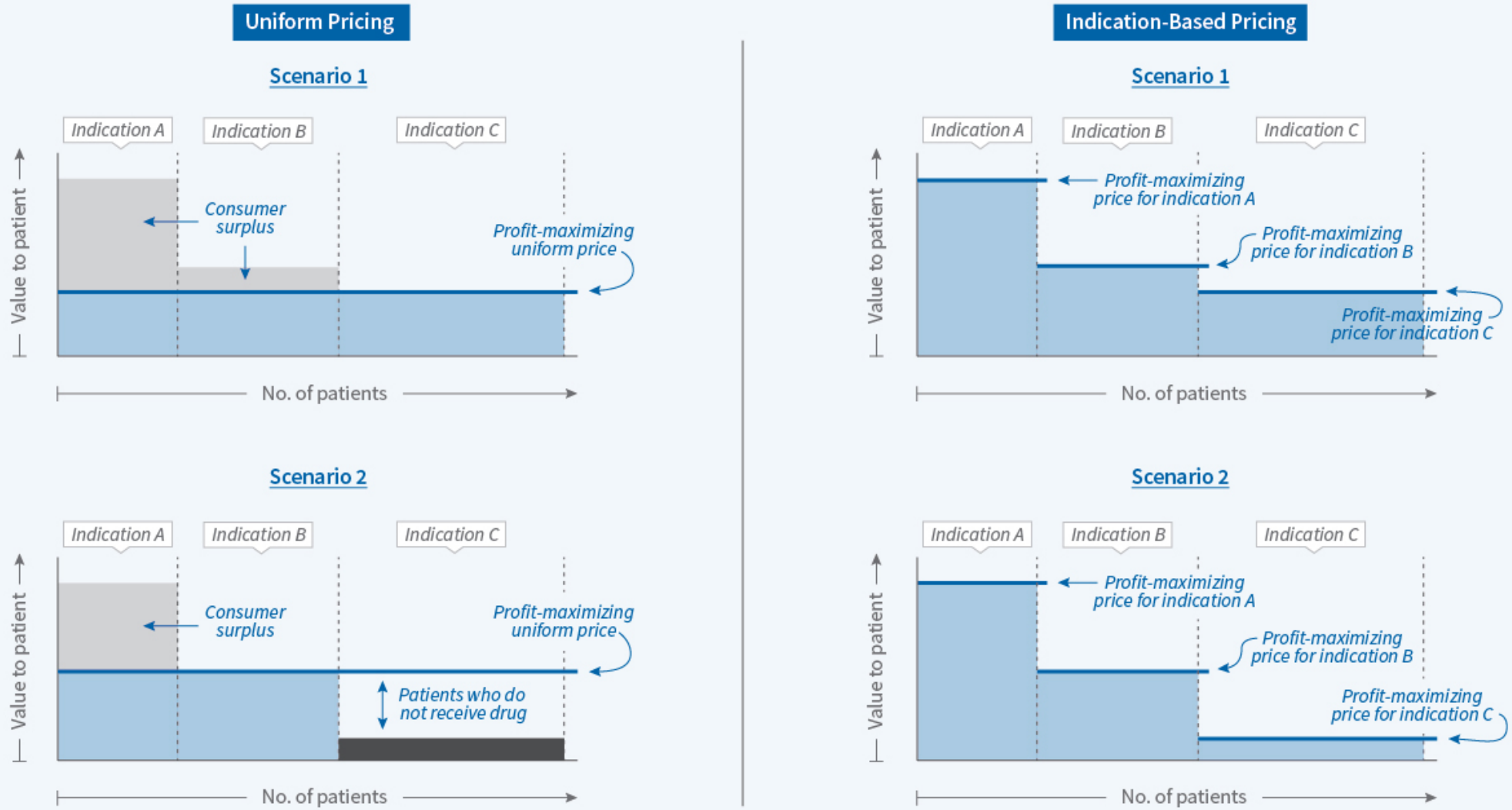
Precision Medicine allows for Price Discrimination

Are these incentives too generous?



1. Changes in pricing dynamics, such as indication-based pricing may have decreased threshold for an economically viable product?
2. Firms increasingly seek multiple orphan indications for products that were approved for 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 end-points, novel approval pathways) may have lowered R&D costs?

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



Source: Illustrative diagram based on author's theoretical scenarios

Table 1
Potential Prices by Indication

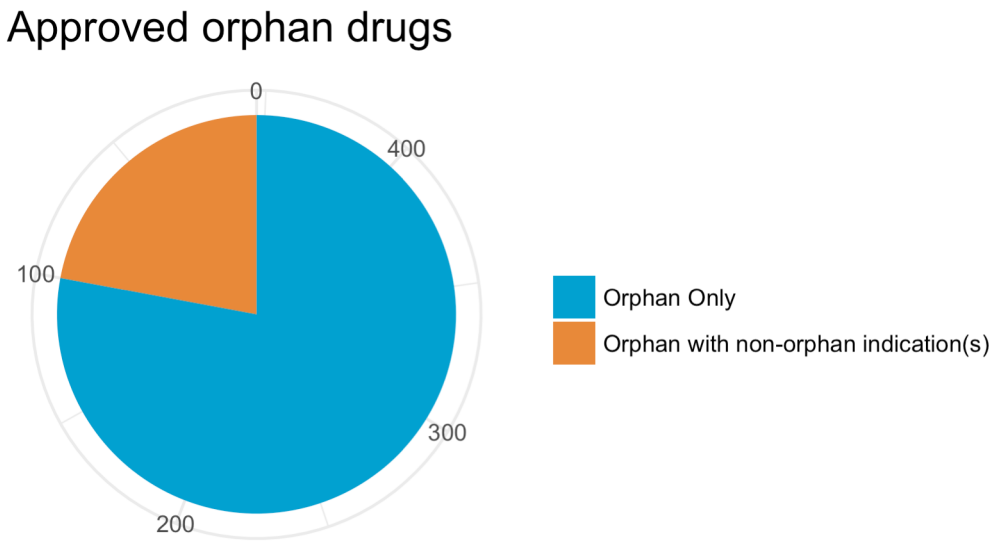
	Median Survival Gain, years[1]	Typical Treatment Duration, months[1]	Uniform MonthlyPrice[1]
Erbitux			
Locally advanced squamous cell carcinoma of the head and neck	1.64	1.39	$10,319
First-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck	0.23	4.16	$10,319
Herceptin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

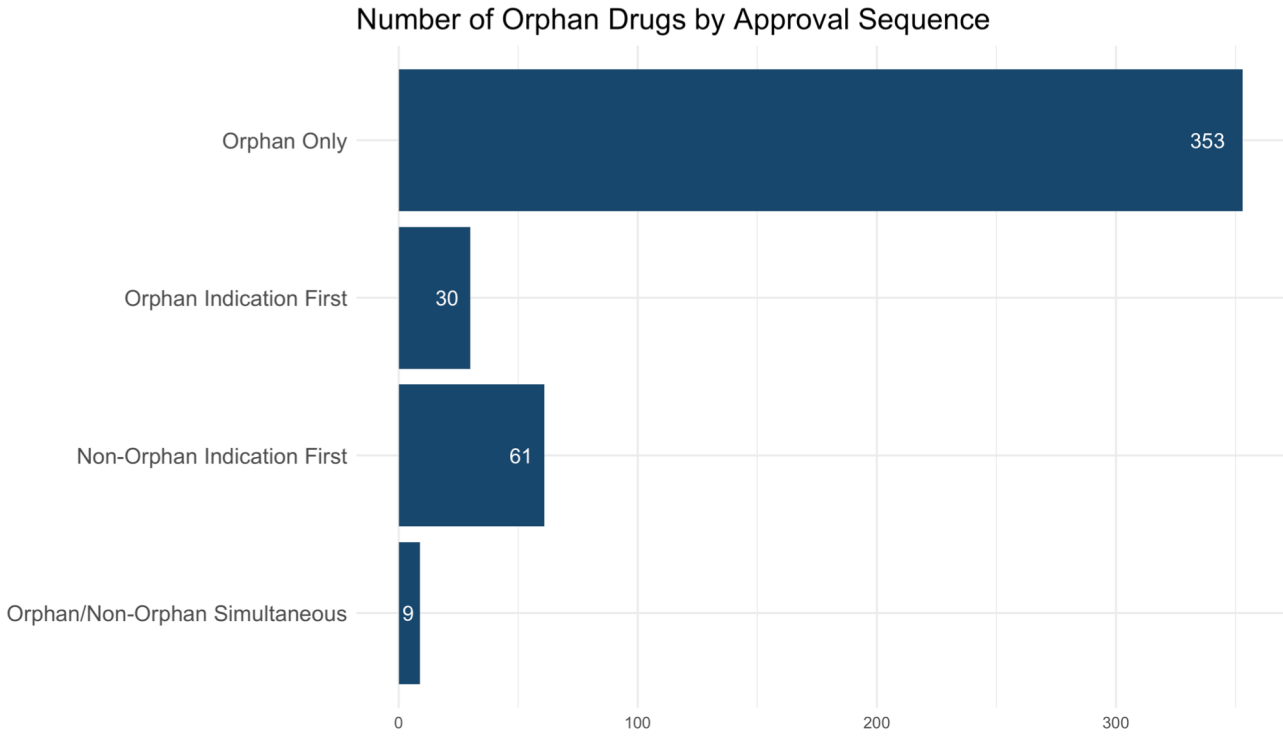
Source: Bach et al., 2015; authors' calculations in last column

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

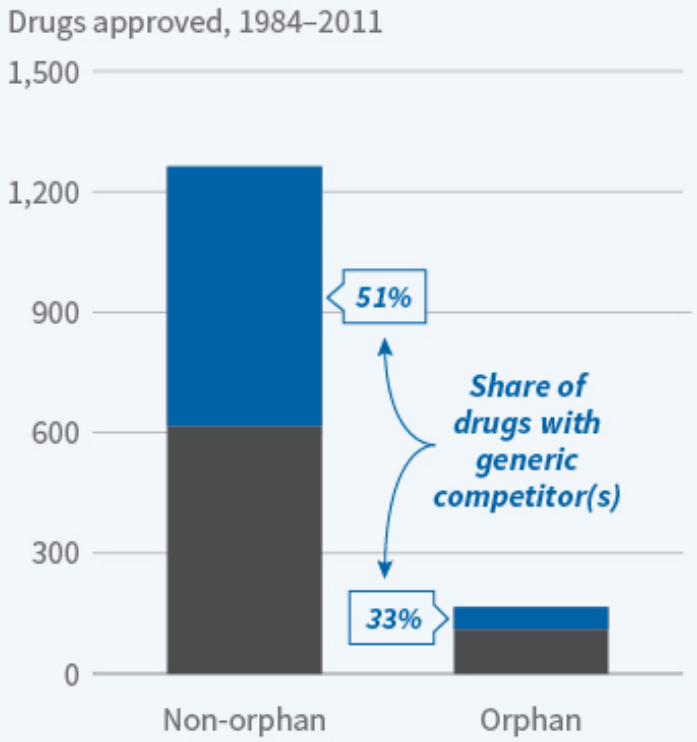




HUMIRA: a case-study

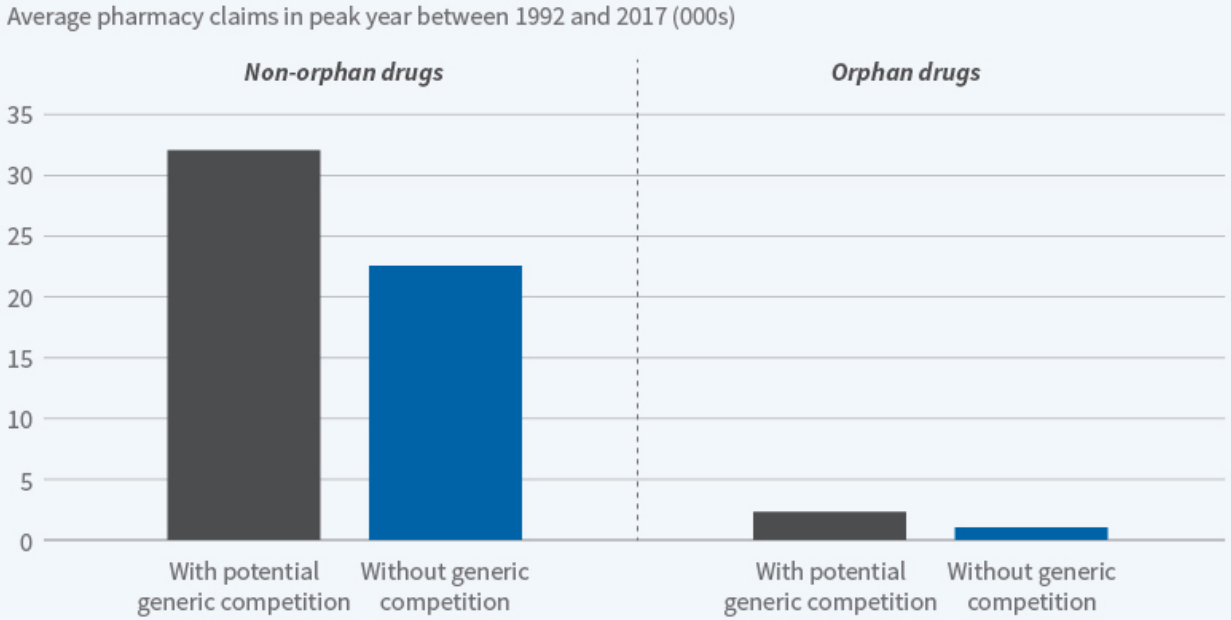
Date	Indication	Date	Indication
12/31/02	Rheumatoid arthritis	**2/21/08**	**Juvenile idiopathic arthritis**
10/3/05	Psoriatic arthritis	**9/28/12**	Ulcerative colitis
7/28/06	Ankylosing spondylitis	**9/23/14**	**Pediatric Crohn's disease**
2/27/07	Adult Crohn's disease	**9/9/15**	**Hidradentitis suppurtiva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

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

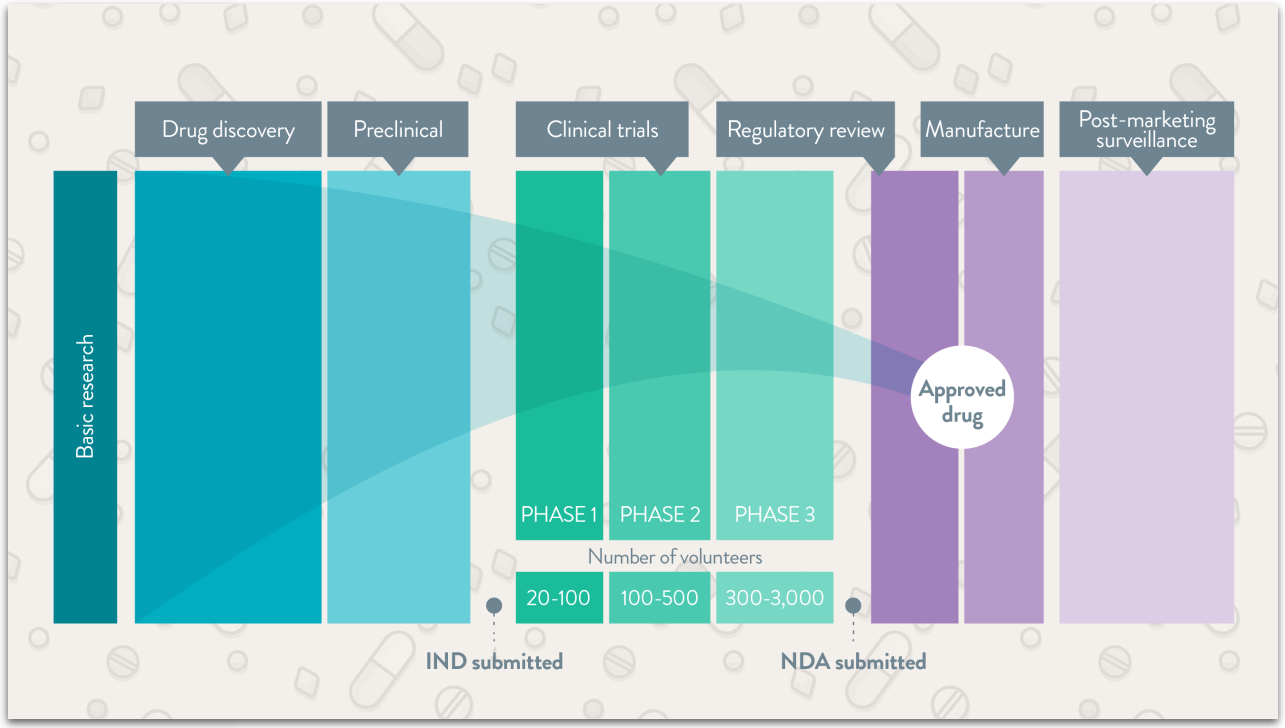
Demand for Pharmaceuticals with Generic Competition and Without



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

Research and Policy Questions

- **Which Products?** Provide bigger incentives to products with smaller market potential. Note that with biomarkers, vast majority of orphan drugs will command high prices even 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
  - 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?** Use “cost based price regulation” for orphans that receive ODA protections after exclusivity ends?



I. **FDA Regulation**

- Speed/Safety Tradeoff
- FDA Regulation and Market Size
- Marketing and Welfare

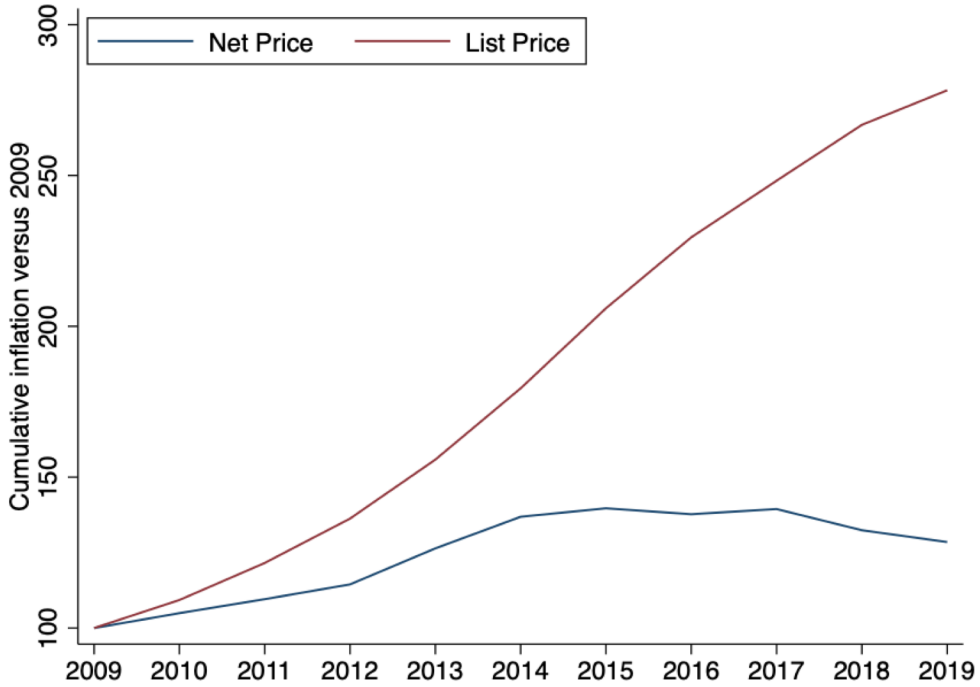
II. **Regulation and Innovation**

- Regulatory incentives: ODA
- Quality of Innovation: not just medicines

III. **Drug Price Regulation**

- Myths vs. Facts
- Regulation of Price Discrimination
- Regulation of Plan-design

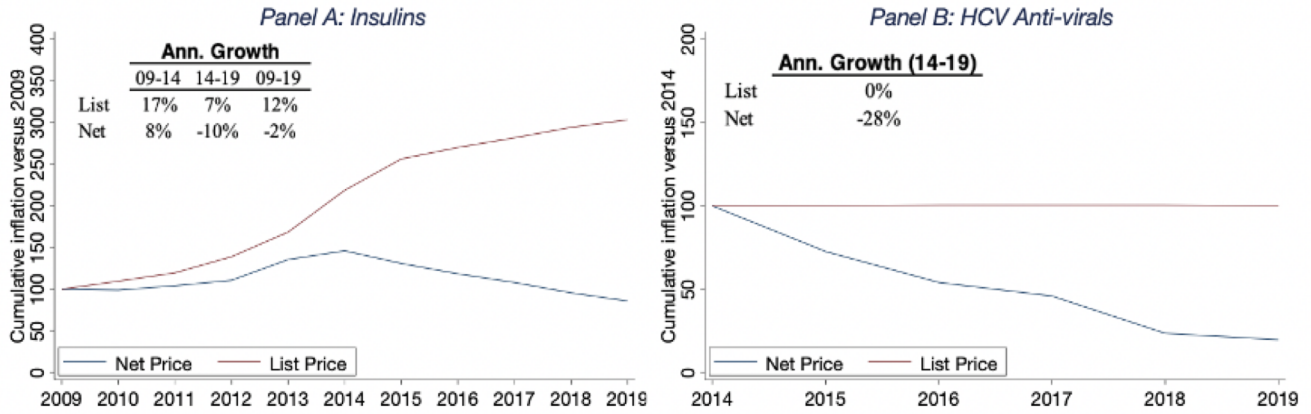
Panel B: List and Net Price Inflation



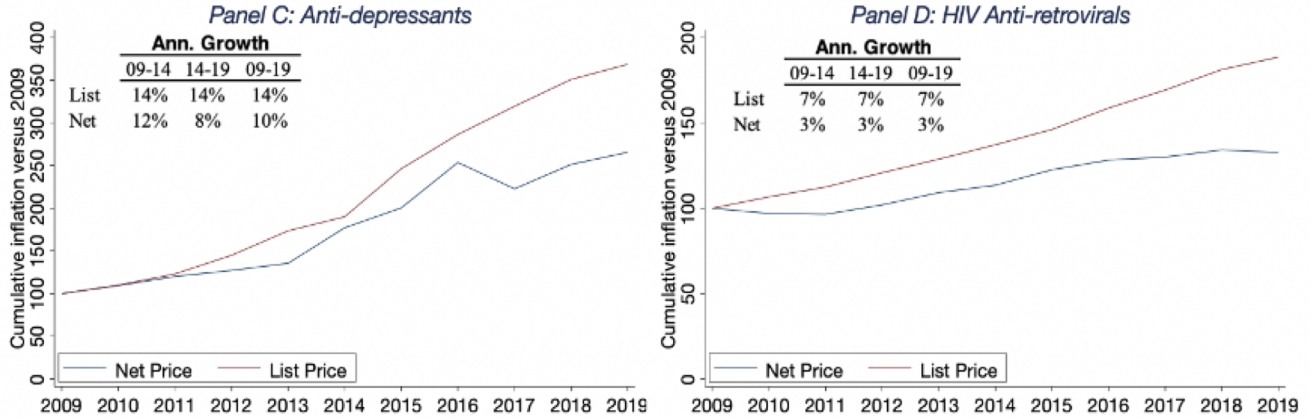
											Avg. annual inflation		
Year	**09-10**	**10-11**	**11-12**	**12-13**	**13-14**	**14-15**	**15-16**	**16-17**	**17-18**	**18-19**	**09-14**	**14-19**	**09-19**
List Price	9.3%	11.2%	12.1%	14.3%	15.2%	14.8%	11.4%	8.2%	7.5%	4.3%	12.4%	9.2%	10.8%
Net Price	4.9%	4.4%	4.5%	10.4%	8.3%	2.0%	-1.4%	1.2%	-5.0%	-3.0%	6.5%	-1.3%	2.5%

Notes: Both panels reflect analysis of 1250 brnaded product-formulations sold in retail pharmacies for non-rare conditions, but the sample varies in each year due to entry and exit. Samples differ by year due to product entry and exit. See text for further details on exclusions. Panel B reflects list and net price inflation calculated using a Laspreyres Price Index for each year-pair. This reflects a chainweighted approach using the balanced sample of products in each pair of adjacent years. Annual inflation is compounded year over year to estimate cumulative inflation relative to 2009. Prices in 2009 are benchmarked at 100 percent.

Figure 2: Growth in rebates, list prices, and net prices in select categories (2009-2019)



Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2014	2015	2016	2017	2018	2019
Rebate	18%	26%	29%	35%	34%	46%	59%	64%	68%	72%	75%	6%	39%	52%	53%	63%	65%



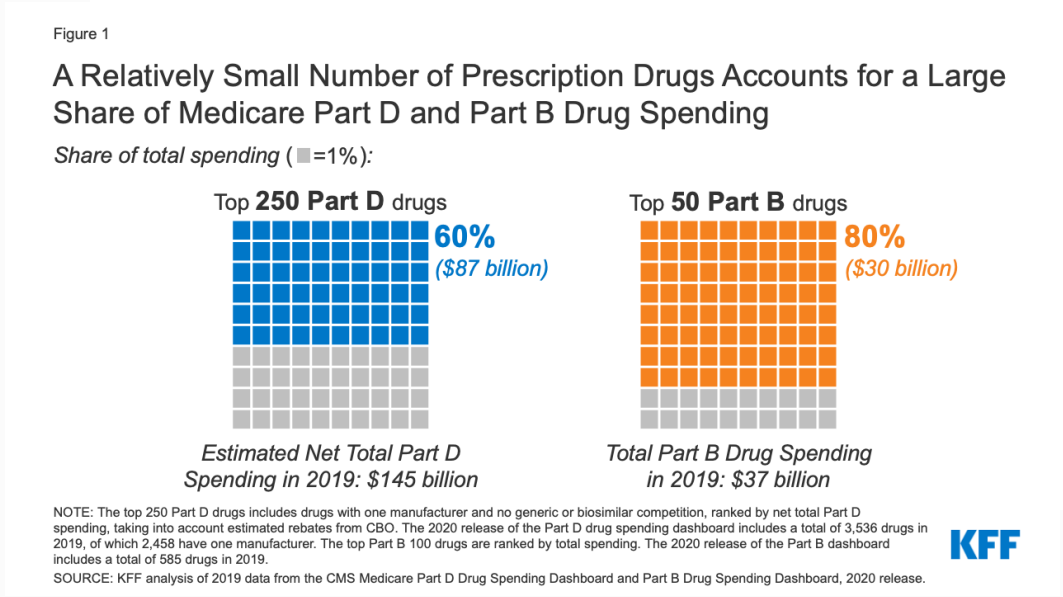
Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Rebate	18%	19%	20%	23%	30%	23%	33%	31%	42%	44%	45%	23%	30%	35%	35%	33%	34%	32%	33%	33%	34%	35%

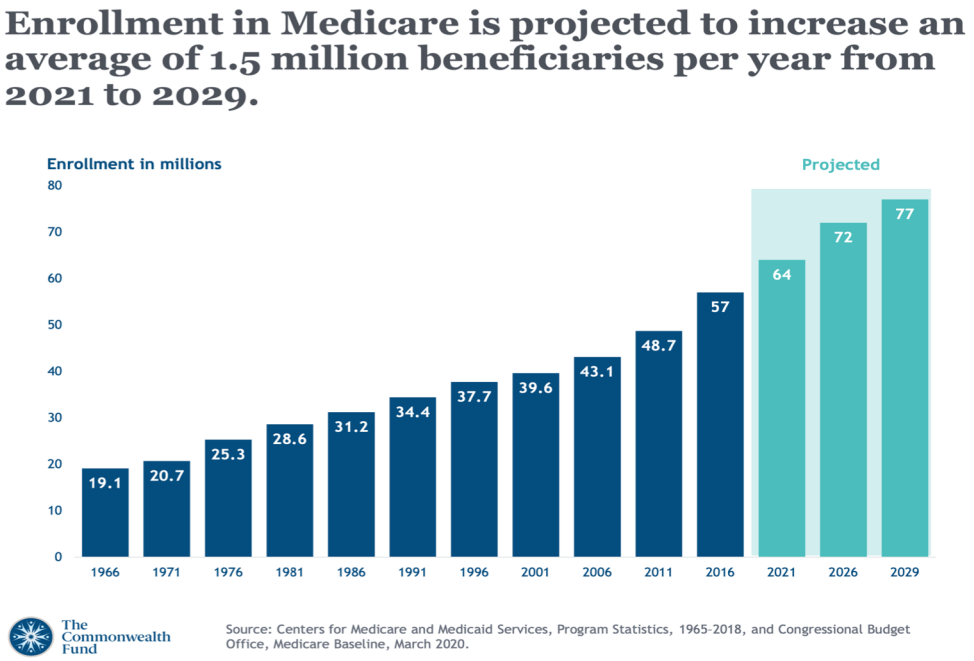
Notes: Insulins included are in ATC-level 4 categories A10AB (fast-acting), A10AC (intermediate acting), A10AD (fast-acting with intermediate or long-acting), or A10AE (long acting) and includes 27 product-formulations: afrezza (2 formulations), apidra, basaglar, humalog / mix (8 formulations), humulin / mix (8 formulations), lantus (3 formulations), soliqua, toujeo (2 formulations), and xultophy. The HCV anti-virals category (ATC4 category J05AP) includes 14 product-formulations: daklinza (3 formulations), epclusa, harvoni, mavyret, olysio, sovaldi, victrelis, viekira / xr, vosevi, and zepatier. HCV products shown starting in 2014 due to launch of Sovaldi in late 2013. The anti-retroviral drugs are identified as the subset of ATC3 category J05A (direct acting anti-virals) that is approved for HIV and include 71 product formulations: atripla, biktarvy, combivir, complera, crixivan (3 formulations), descovy, emtriva (2 formulations), epivir (3 formulations), epivir hbv (3 formulations), epzicom, fuzeon, genvoya, intelence (2 formulations), isentress (5 formulations), juluca, kaletra (3 formulations), lexiva (2 formulations), norvir, odefscy, prezista (7 formulations), reyataz (6 formulations), selzentry, stribild, sustiva (4 formulations), symtuza, tivicay (3 formulations), triumeq, trizivir, truvada (4 formulations), viread (5 formulations), and ziagen (2 formulations). The anti-depressants category (ATC3 category N06A) includes 58 product-formulations: aplenzin (3 formulations), celexa (3 formulations), cymbalta (3 formulations), fetzima (5 formulations), lexapro (4 formulations), pristiq (3 formulations), sarafem (3 formulations), savella (5 formulations), trintellix (3 formulations), viibryd (5 formulations), wellbutrin sr (5 formulations), wellbutrin xl (2 formulations), and zoloft (4 formulations).

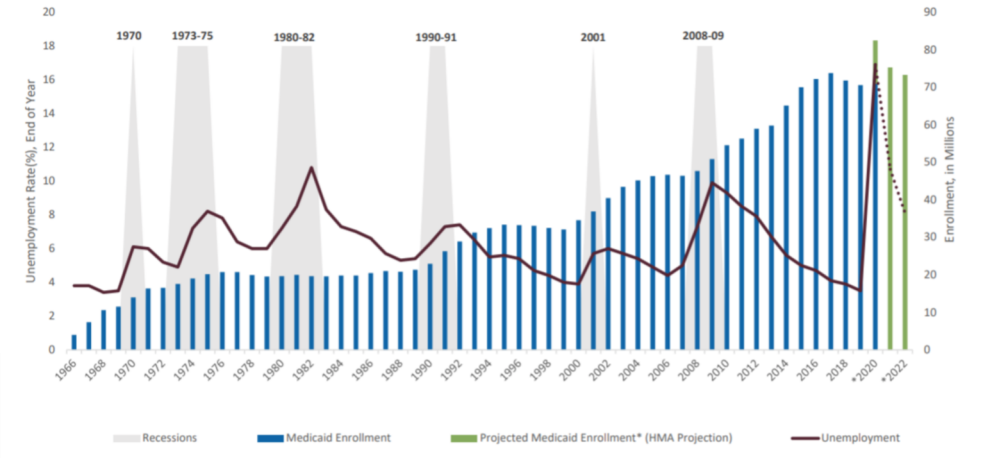
What is not working in drug pricing

Government Payers:

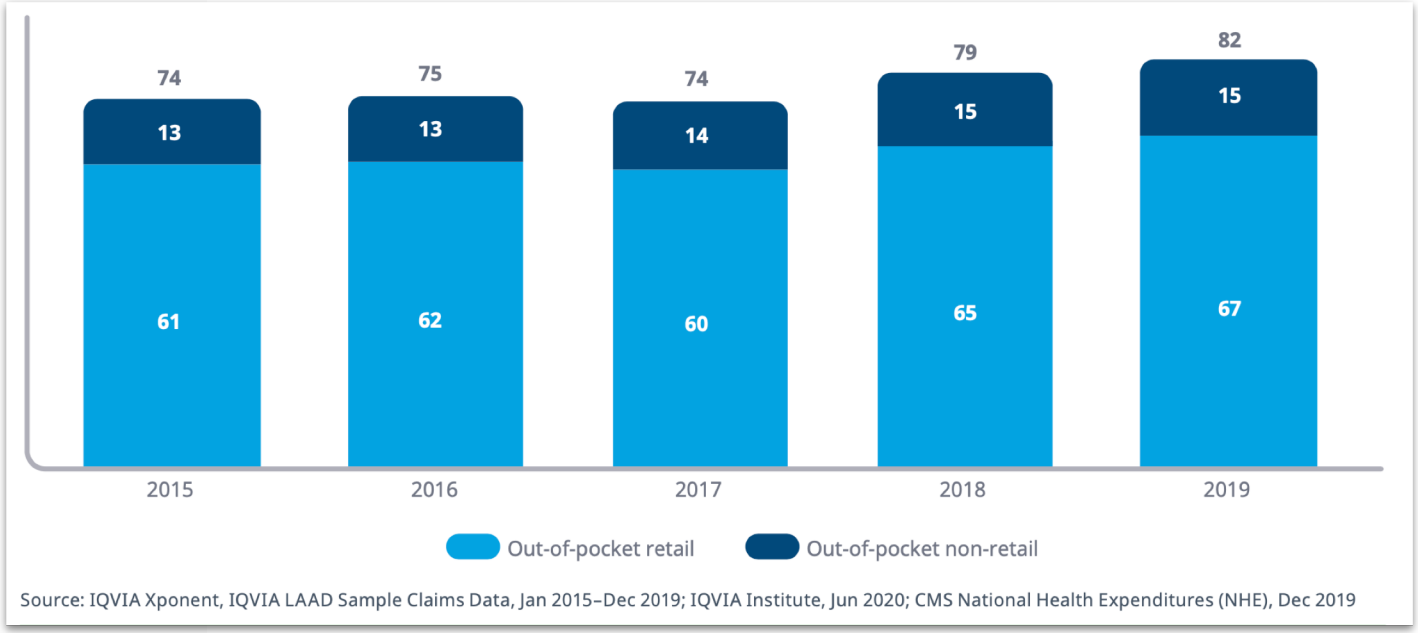
1. Medicare can't functionally negotiate for physician-administered drugs (45 billion)
2. Medicaid gets statutory rebates, but can't negotiate ($70b)



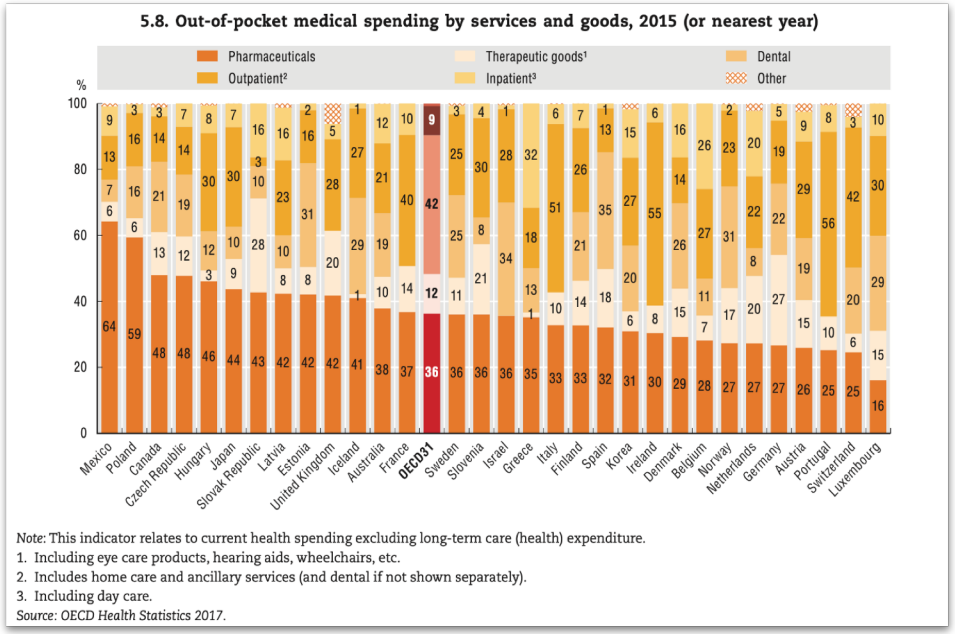




Cost-sharing is everywhere in health care



Source: IQVIA Xponent, IQVIA LAAD Sample Claims Data, Jan 2015–Dec 2019; IQVIA Institute, Jun 2020; CMS National Health Expenditures (NHE), Dec 2019



Note: This indicator relates to current health spending excluding long-term care (health) expenditure.
1. Including eye care products, hearing aids, wheelchairs, etc.
2. Includes home care and ancillary services (and dental if not shown separately).
3. Including day care.

Source: OECD Health Statistics 2017.

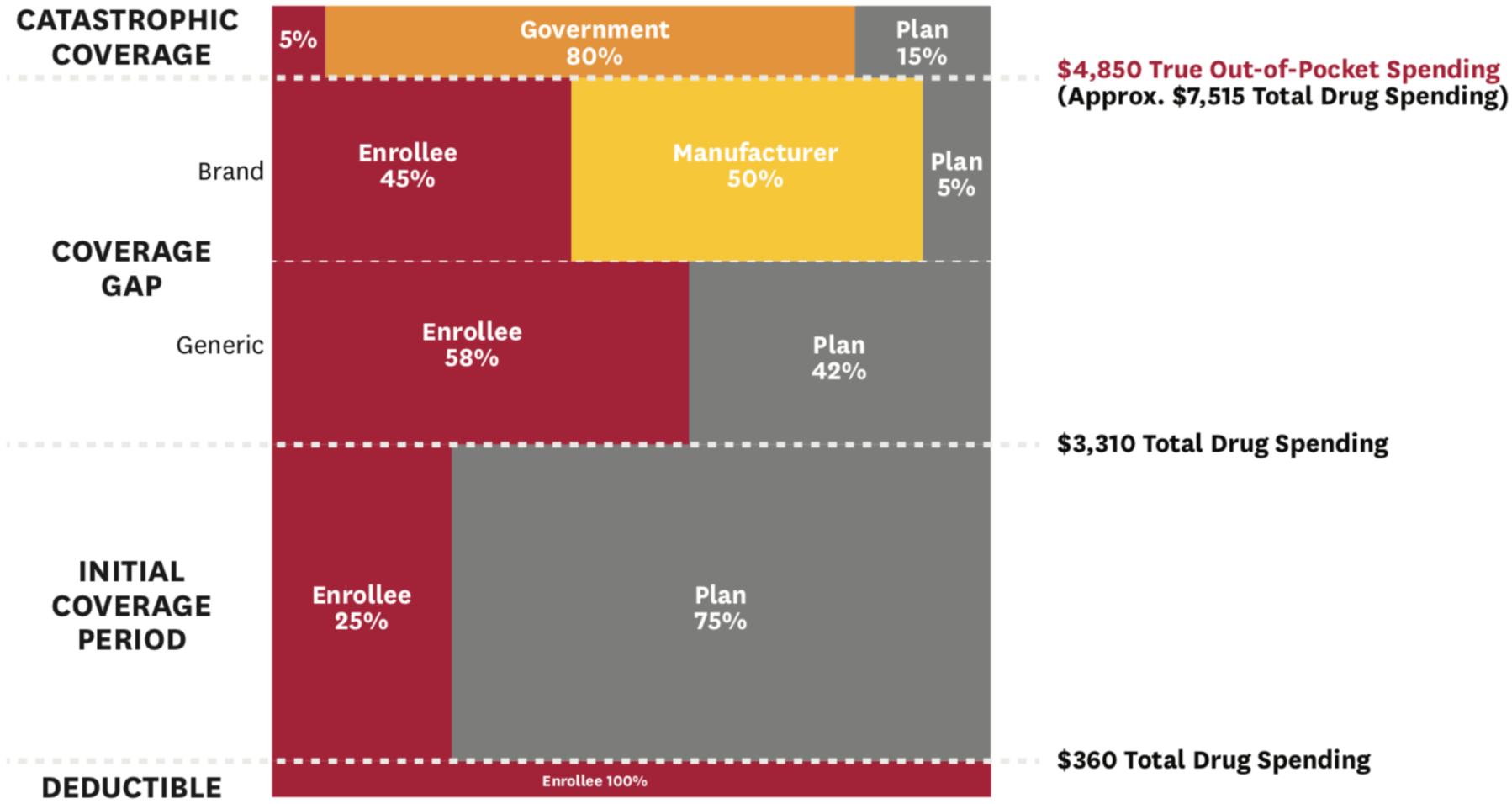
- Goal is to reduce wasteful spending on health care
  - Cost-sharing is efficient, if care is over-used (moral hazard)

- A growing literature suggests it can reduce health
  - Patients cut back on high-value care
  - Behavioral hazard, if benefit misperceived

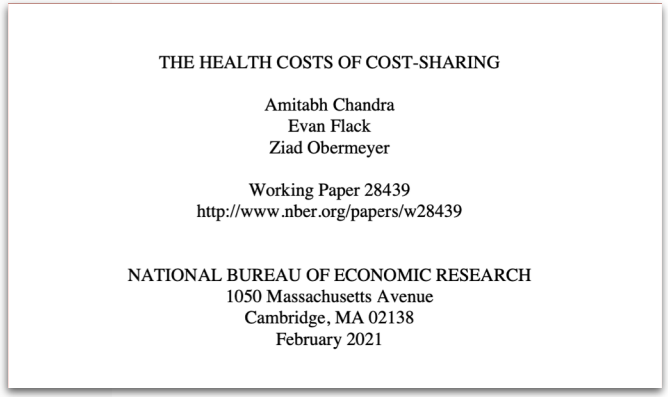
[1]Baicker et al. (2015); [2]Brot-Goldberg et al. (2017), Chandra et al. (2010), Geruso et al. (2020), Choudhry et al. (2011)

- But demand response (price-elasticity) ≠ welfare (outcomes)
  - Would need n=325,000 to detect 10%Δ on 1% mortality

Medicare Part D (Prescription Drug Benefit)



Does Plan-Design need to be Regulated?



THE HEALTH COSTS OF COST-SHARING

Amitabh Chandra
Evan Flack
Ziad Obermeyer

Working Paper 28439
http://www.nber.org/papers/w28439

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
February 2021

ABSTRACT

We use the design of Medicare's prescription drug benefit program to demonstrate three facts about the health consequences of cost-sharing. First, we show that an as-if-random increase of 33.6% in out-of-pocket price (11.0 percentage points (p.p.) change in coinsurance, or $10.40 per drug) causes a 22.6% drop in total drug consumption ($61.20), and a 32.7% increase in monthly mortality (0.048 p.p.). Second, we trace this mortality effect to cutbacks in life-saving medicines like statins and antihypertensives, for which clinical trials show large mortality benefits. We find no indication that these reductions in demand affect only 'low-value' drugs; on the contrary, those at the highest risk of heart attack and stroke, who would benefit the most from statins and antihypertensives, cut back more on these drugs than lower risk patients. Similar patterns exist for other drug–disease pairs, and irrespective of socioeconomic circumstance. Finally, we document that when faced with complex, high-dimensional choice problems, patients respond in simple, perverse ways. Specifically, price increases cause 18.0% more patients (2.8 p.p.) to fill no drugs, regardless of how many drugs they had been on previously, or their health risks. This decision mechanically results in larger absolute reductions in utilization for those on many drugs. We conclude that cost-sharing schemes should be evaluated based on their overall impact on welfare, which can be very different from the price elasticity of demand.

PHARMACEUTICAL REGULATION

- Regulation in the Pharmaceutical area has first-order implications for societal welfare through 3 channels: NPV of Project, shape of medicines, market learning about product
- Important role for economists to study this space, and clean up a variety of misunderstandings and political advocacy
- Natural to think about FDA regulation as central, but a variety of other regulations on payers or on pricing also affect innovation and patient welfare
- I have left out a number of important topics and authors