How Effective is NIH Funding?

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We have two broad ways of encouraging innovation

"Pull" mechanisms: Reward innovations (e.g. patents)

- Benefit: gives people incentives to pursue highest potential projects
- Concern:
  - Distorts access to innovations afterward (high prices)
  - Only incentivizes commercially viable projects

"Push" mechanisms: Subsidize innovations (e.g. grants, tax credits)

- Benefit: Resolves some issues with the above
- Concern:
  - Can the government pick winners?
  - Is publicly-funded science useful?

Today:

1. Assessing the Quality of NIH Peer Review
2. Assessing the Impacts of NIH Funding

Part 1: Assessing the Efficacy of NIH Peer Review

Part 2: Assessing the Impacts of NIH Funding

Good peer review can be defined in many ways

1. **A notion of what good peer review means**
   - Give the best scores to the best projects
   - Give the best scores to the best projects that wouldn't be funded otherwise?

2. **Measures of what "best project" means**
   - Produces the most citations
   - Produces patents, drug candidates, medical devices, clinical trials, clinical protocols, etc.?
   - Leads to drugs and treatments that produce the most QALYs saved?

Research question: How well do scores predict outcomes?

Results: Peer review adds value

Percentile scores provide information about grant quality not available elsewhere.

- Among observably similar applicants, a 1 std dev improvement in percentile score predicts 16% more citations and 8% more publications.

Percentile scores predict high impact research

- Among observably similar applicants, a 1 std dev improvement in percentile score predicts 20% more high-impact publications and 15% more follow-on patents

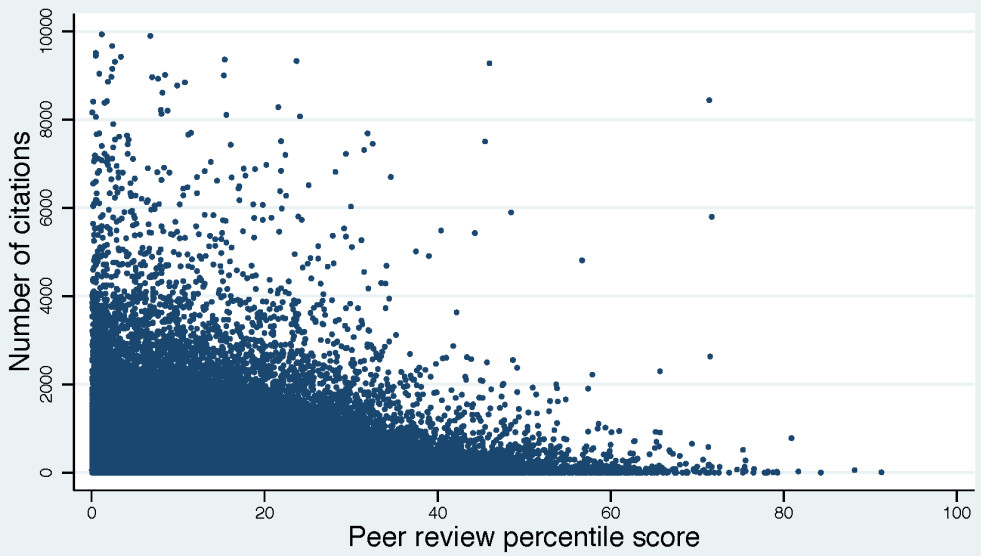
What we do

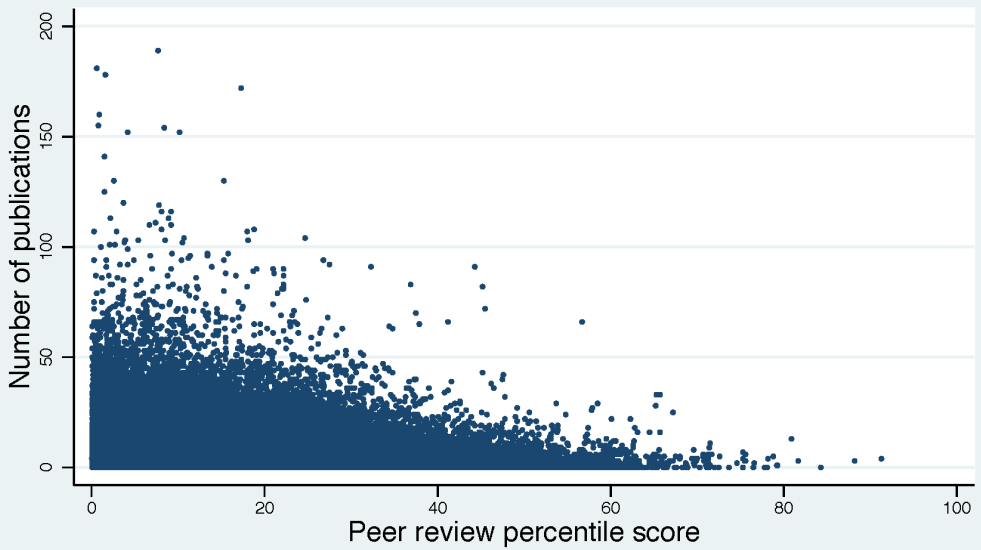
1. **Start with more data**: all NIH-funded R01 grants from 1980-2008

2. **Track grant outcomes**
   - # Publications: all articles that acknowledge funding from a grant.
   - # of Citations: all citations to those publications, through 2013.
   - # Hit Publications: very highly cited publications
   - # Patents: all patents that acknowledge funding from a grant.
   - # Patents building off this grant: all patents that cite publications that acknowledge a grant

3. **Control for applicant characteristics** (does peer review predict outcomes among observably similar candidates?)
   - Past publications, citations, grant history
   - Institutional affiliation

Raw Correlation, Scores and Citations/Publications





Statistically significant relationship: 5.8 fewer citations for every 1pp increase in percentile rank.

This could mean:

- Reviewers are contributing unique insights about the quality of an application
- Reviewers are aggregating information that is available elsewhere.
- Reviewers are doing anything that is better than random.

Defining Value-Added in Peer Review

Value-added: Can peer review tell us something about the quality of an application we couldn't have figured out otherwise?

- No value added: "This person has a strong publication record so this current proposal is likely to be serious as well."
  - Might be true, but could figure that out from a CV
- Value added: "This is just more of the same and is less likely to have the same impact because we know it already."
  - Would be hard to figure out without reading the application or some kind of human review.

Quantifying Value-added

Raw Correlation

$$\text{Research Outcomes}_g = a_0 + a_1 \text{Score}_g + \text{Error}_g$$

- a_1 is the average change in future outcomes for a 1 unit increase in score (want this negative)

Value Added

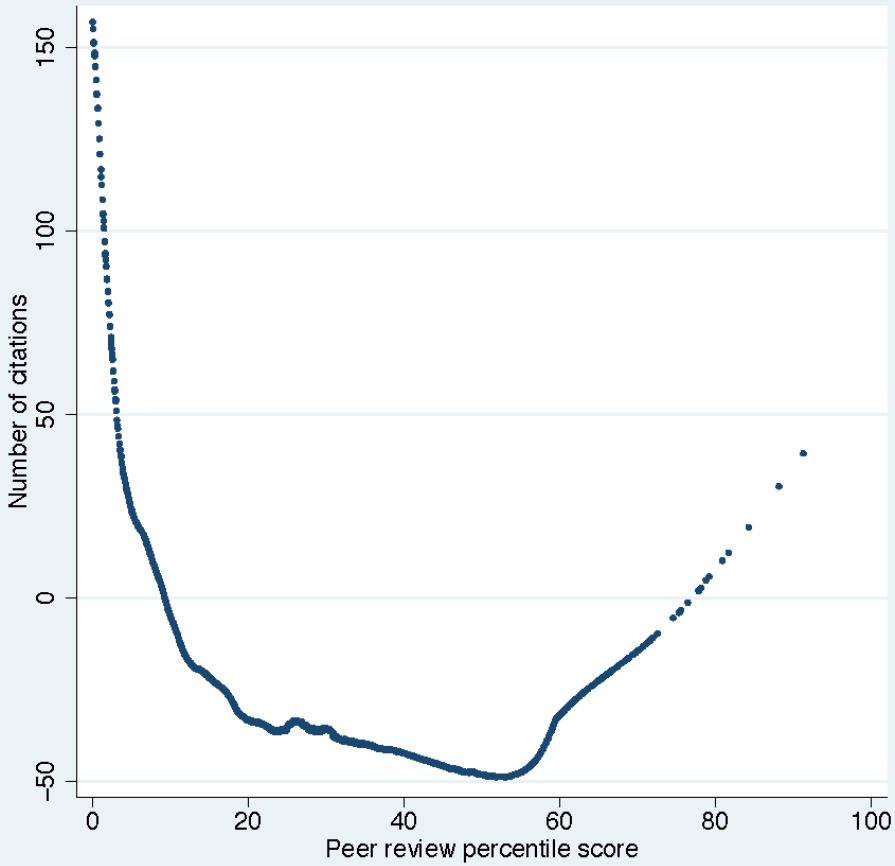
$$\text{Research Outcomes}_g = b_0 + b_1 \text{Score}_g + [\text{Applicant Characteristics}] + \text{Error}_g$$

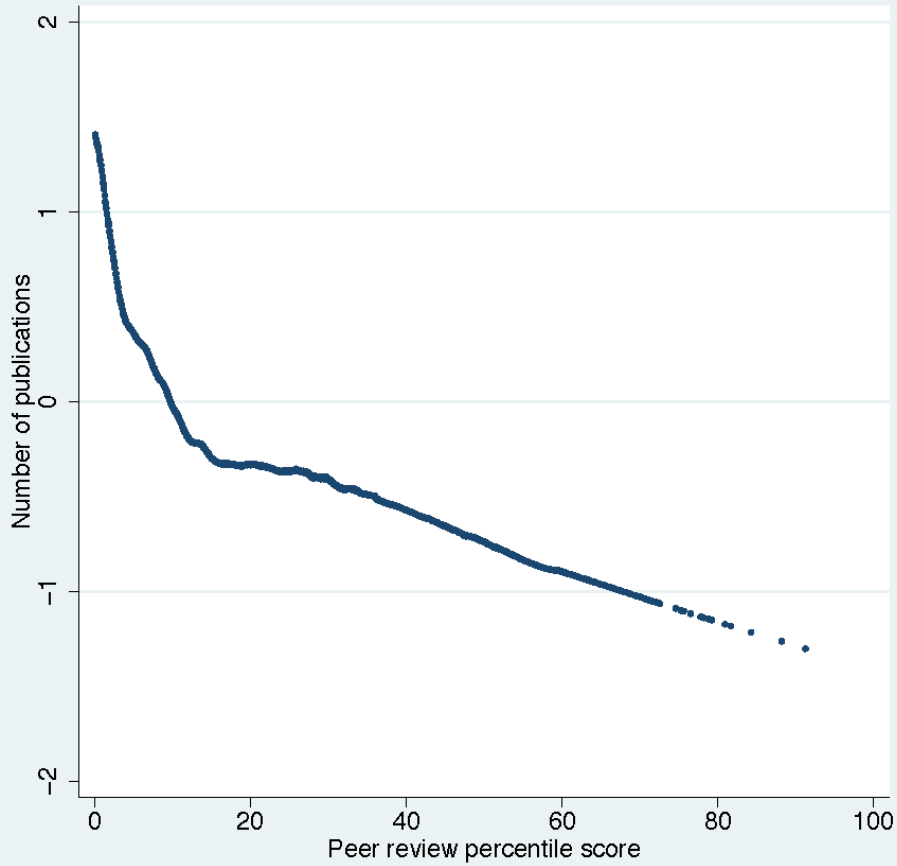
- Applicant Characteristics: publication history, grant history, degrees, age, institutional affiliation, etc.
- b_1 is the average change in future outcomes for a 1 unit increase in score – among **similar** applicants.

Applicant Characteristics

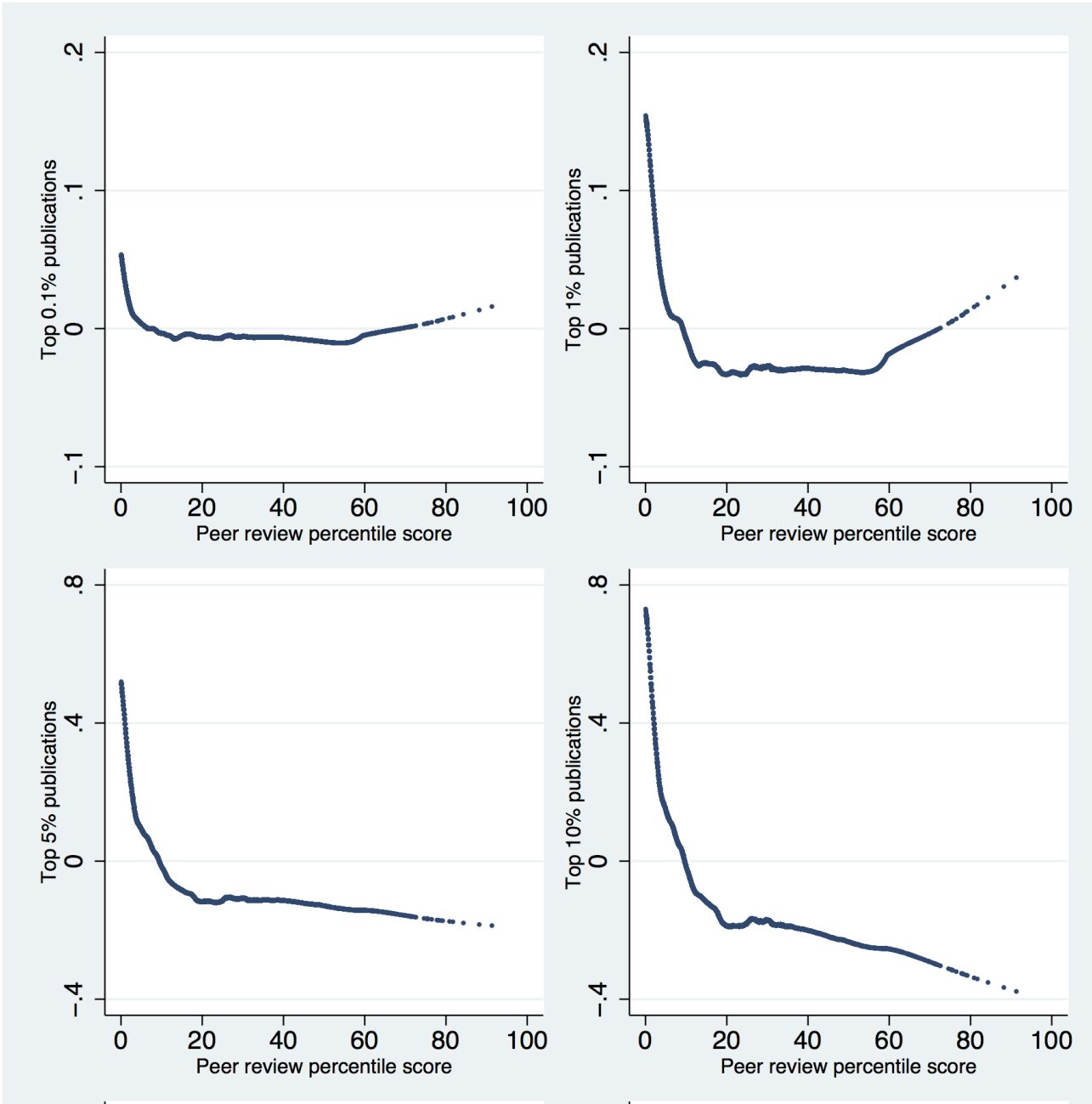
- **# Publications, past 5 years**
- **# of Citations, past 5 years**: all citations to date for those publications
- **# Hit Publications, past 5 years**: publications cited in top 0.1%, 1%, and 5% of the citation distribution for articles published the same year. Based on citations to date.
- Publication variables repeated for first/last author publications only.
- **Degrees**: M.D., Ph.D., or both
- **Grant History**: Prior R01 or other NIH funding recipient
- **Institutional Affiliation**: Ranked by number of NIH grants received.

Value-Added: Do Percentile Scores Predict "Surprise" Grant Outcomes?





Value-Added: Do Percentile Scores Predict "Surprise" Hits?



Part 1: Assessing the Efficacy of NIH Peer Review

Part 2: Assessing the Impacts of NIH Funding

What is the impact of science funding more broadly?

We spend a lot of (public) money on biomedical R&D

- Over 30 billion in the US annually

This funding is intended to generate research that leads to improvement in health and welfare

- For example, improved treatments for cancer and heart disease are credited with increases in life expectancy in developed countries

But most medical innovations are developed and brought to market by private firms

- Drugs, medical devices, etc.

Need to understand impact of NIH funding not just on publications, but on innovation by private sector firms.

Why is this hard?

Goal: Understand the causal effect of NIH funding on patenting by private firms

Two key challenges:

1. Where do we look for outcomes?
   - It is hard to know a priori what scientific results are relevant for a patent
   - We use new data to link grants with patents via explicit acknowledgements and citations, as well other measures of relatedness

2. How do we know funding had a causal effect?
   - Funding potentially responds to changes in innovative/commercial potential across disease or science areas
   - We use the structure of NIH grant review to generate plausibly random variation in funding for an NIH research area

Results

Baseline:

- 33% of NIH grants produce research that is directly cited by a patent
- 50% of patents associated with NIH funding are primarily related to a different disease area as the original funding source

Impact of additional funding:

- $10M leads to a net increase of 2.3 patents.
- 1% increase in public funding leads to a 0.5% increase in private sector patenting
- $10M generates $3.5M-$27.8M in PDV of drug sales.

Data Inputs

1. NIH Grants: 1980-2005
2. PubMed Publications: 1980-2012
3. USPTO Patents: 1980-2013

Outcome: # Patents that Cite NIH-Funded Research

Step 1: NIH Grants → Publications

Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions

JAMES U. BOWIE,* JOHN F. REIDHAAR-OLSON, WENDELL A. LIM, ROBERT T. SAUER

An amino acid sequence encodes a message that determines the shape and function of a protein. This message is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity. Comparison of different sequences with similar messages can reveal key features of the code and improve understanding of how a protein folds and how it performs its function.

specific positions in a cloned gene and uses selections or screens to identify functional sequences. This approach has been used to great advantage for proteins that can be expressed in bacteria or yeast, where the appropriate genetic manipulations are possible (*3, 8–11*). The end results of both methods are lists of active sequences that can be compared and analyzed to identify sequence features that are essential for folding or function. If a particular property of a side chain, such as charge or size, is important at a given position, only side chains that have the required property will be allowed. Conversely, if the chemical identity of the side chain is unimportant, then many different substitutions will be permitted

46. We thank C. O. Pabo and S. Jordan for coordinates of the NH_2-terminal domain of λ repressor and its operator complex. We also thank P. Schimmel for the use of his graphics system and J. Burnbaum and C. Francklyn for assistance. Supported in part by NIH grant AI-15706 and predoctoral grants from NSF (J.R.-O.) and Howard Hughes Medical Institute (W.A.L.).

Step 2: Publications → Patents

(12) **United States Patent**
Li et al.

(10) **Patent No.: US 6,867,006 B2**
(45) **Date of Patent: Mar. 15, 2005**

(54) **ANTIBODIES TO HUMAN CHEMOTACTIC PROTEIN**

(75) Inventors: **Haodong Li**, Gaithersburg, MD (US); **Steven M. Ruben**, Olney, MD (US); **Granger Sutton, III**, Columbia, MD (US)

(73) Assignee: **Human Genome Sciences, Inc.**, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 230 days.

(21) Appl. No.: **10/141,965**

(22) Filed: **May 10, 2002**

WO	WO 96/38559	12/1996
WO	WO 96/40762	12/1996
WO	WO 97/15594	5/1997
WO	WO-98/44118	10/1998

OTHER PUBLICATIONS

Beall, C.J., et al., "Conversion of Monocyte Chemoattractant Protein–1 into a Neutrophil Attractant by Substitution of Two Amino Acids," *J. Biol. Chem. 267*:3455–3459, American Society for Biochemistry and Molecular Biology, Inc. (1992).

Berkhout, T.A., et al., "Cloning, in Vitro Expression, and Functional Characterization of a Novel Human CC Chemokine of the Monocyte Chemotactic Protein (MCP) Family (MCP–4) That Binds and Signals through the CC Chemokine Receptor 2B," *J. Biol. Chem. 272*:16404–16413, American Society for Biochemistry and Molecular Biology, Inc. (Jun. 1997).

Bowie, J.U., et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science 247*:1306–1310, American Association for the Advancement of Science (1990).

Match Descriptives

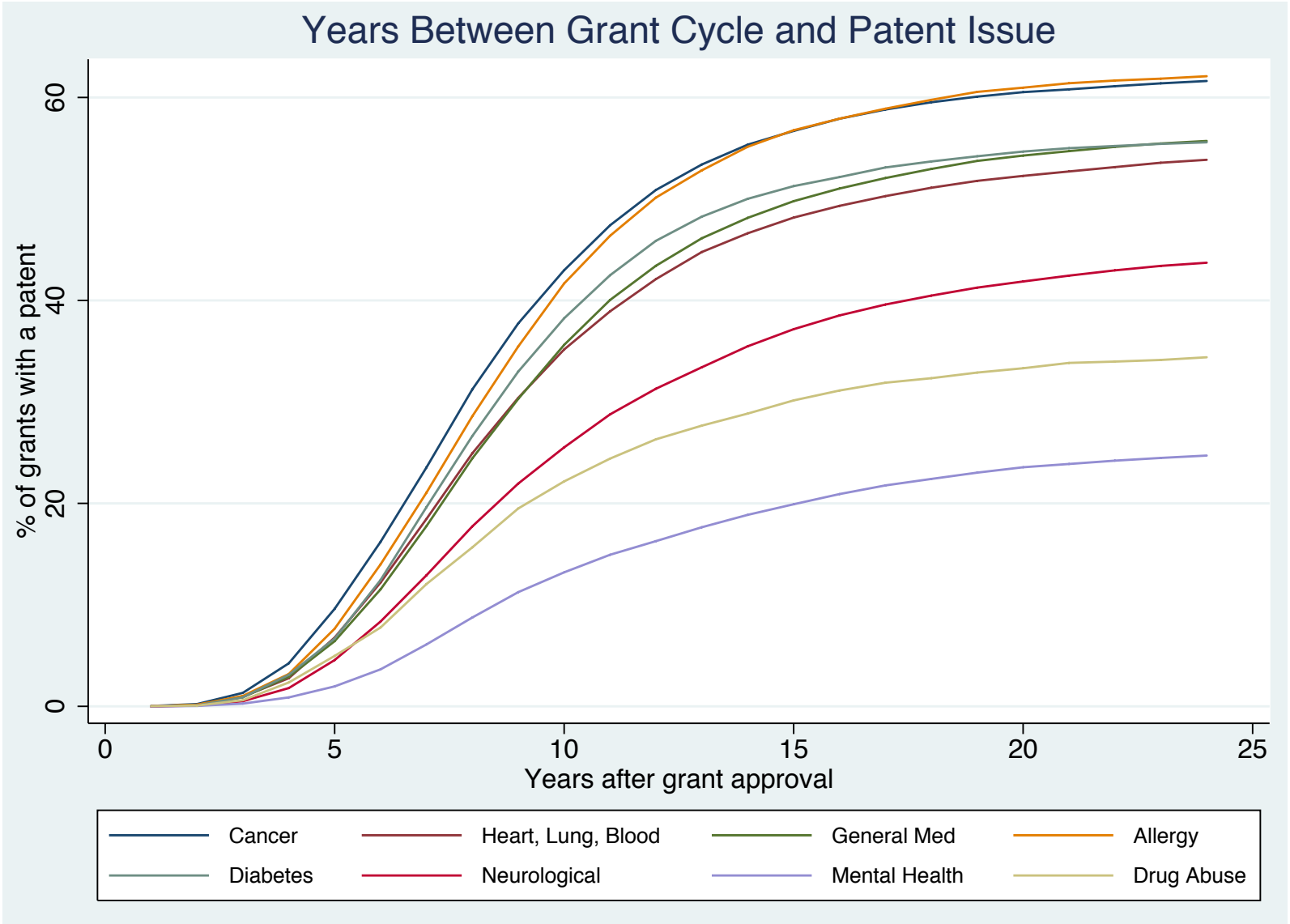
Initial Grants:

- All 153,076 NIH grants from 1980-2005 evaluated in chartered study sections from core Institutes.
- Funded by 17 Institutes (diseases); evaluated in 624 study sections (science areas)

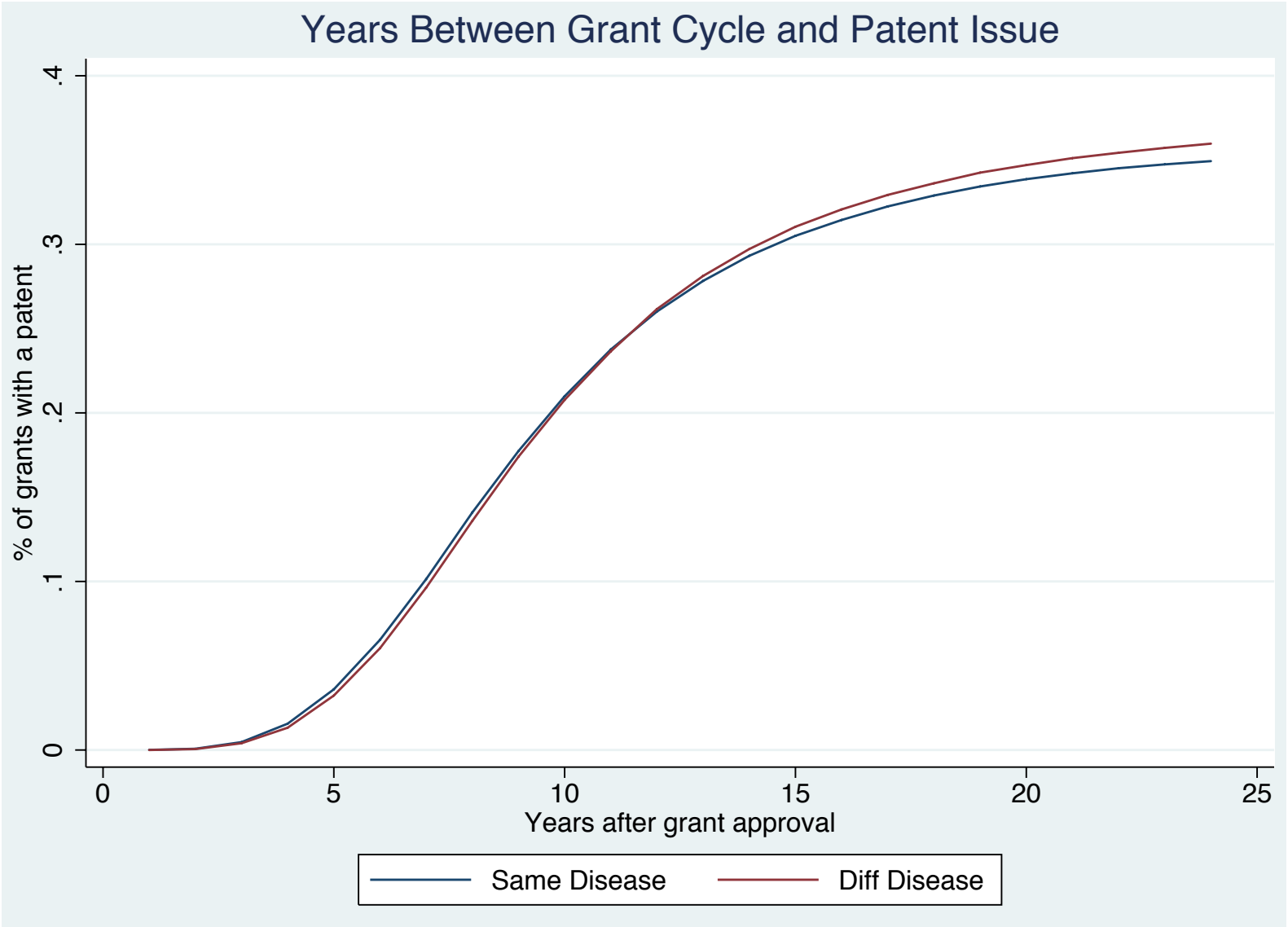
43% of NIH grants (66,085) produce research that is cited by a private sector patent

- 83,059 unique patents
- 17 ICs, 548 study sections, 8,886 DSTs.
- That's 83,059/232,276 = 36% of total life science patents issued between 1980-2012

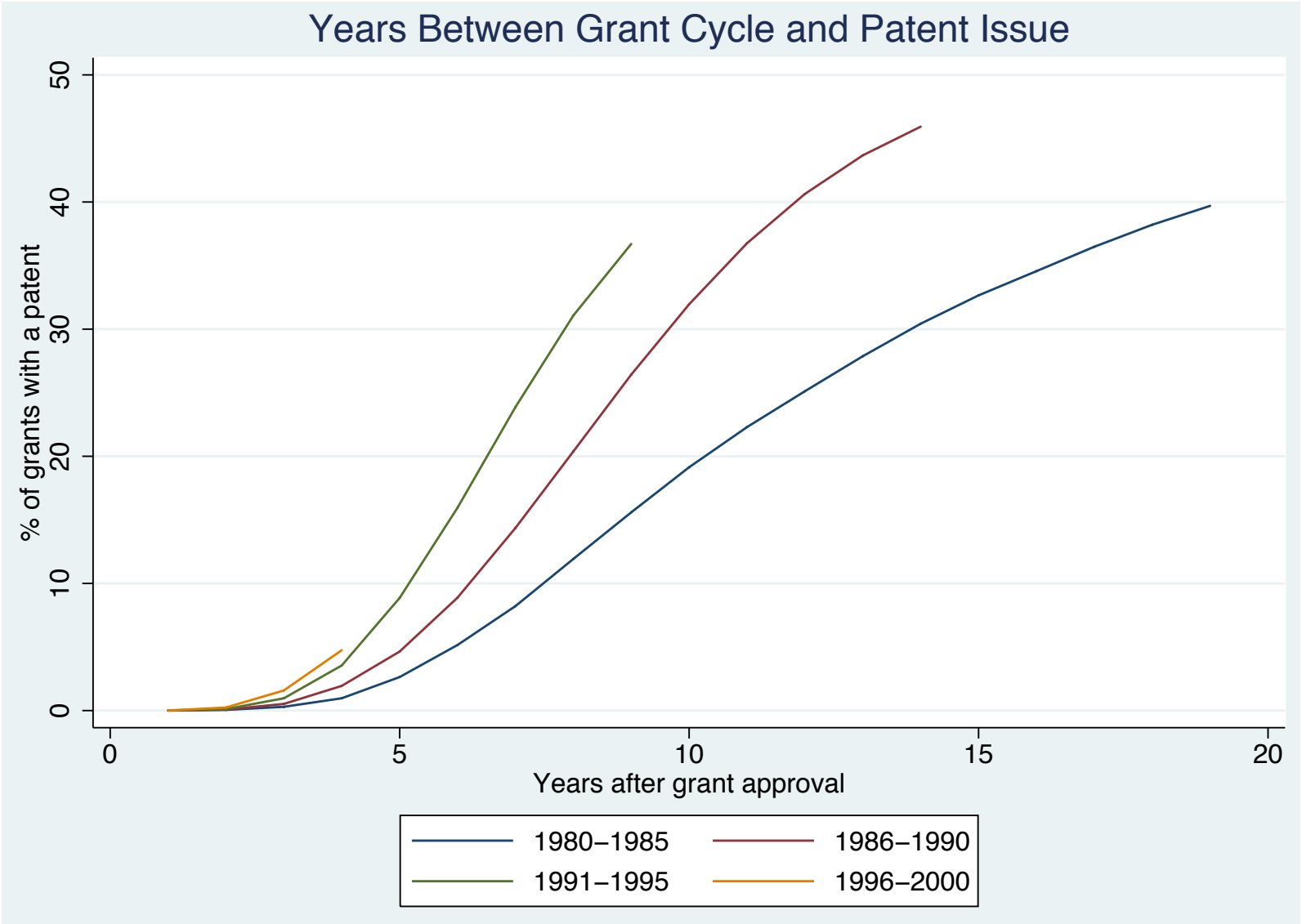
The amount of NIH-linked patenting varies by disease area



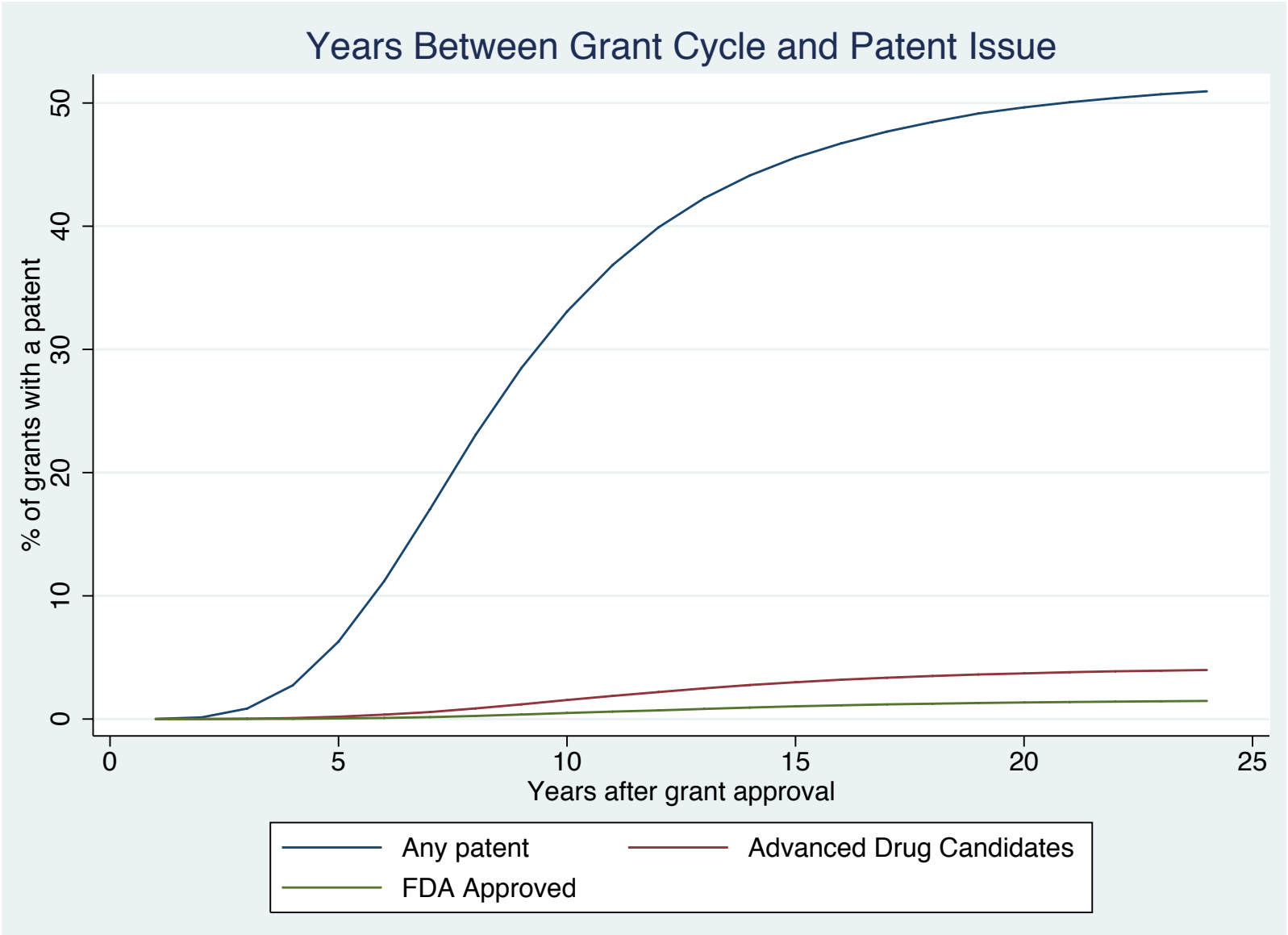
Funding for one disease area impacts patenting in other disease areas



Grant-patent lags have been shrinking over time



But few grants produce patents associated with high-value drugs



Assessing Causal Effects

Main Specification

$$\text{Patents}_{(dst)'} = \alpha_0 + \alpha_1 \text{Funding}_{dst} + \delta_{ds} + \gamma_{dt} + \nu_{st} + \varepsilon_{dst}$$

1. **Time invariant differences across research areas** (δ_{ds})
   - We care about cancer more than deafness
   - Genetics of breast cancer is easier to study than the genetics of schizophrenia

2. **Time varying differences across disease areas** (γ_{dt})
   - Increases in obesity may increase both private and public funding for diabetes research
   - Publicity surrounding AIDS epidemic increases both private and public sector funding

3. **Time varying differences across science areas** (ν_{st})
   - New DNA sequencing technologies make research in genetics more productive (increases returns or decreases costs)
   - Interest in personalized medicine declined from 2003 to 2004 once we figured out that there isn't a gene for everything

4. **Fixed Effects for # applications**
   - Proxy for time-varying potential in a DST with # of applications)

Is NIH funding useful to firms?

	(1)	(2)	(3)	(4)	(5)
# of Patents Citing DST-Funded Research: Mean=12.82; SD=19.17					
DST Funding (×$10 mln.) Mean=4.06; SD=4.36	2.595*** *(0.171)*	2.281*** *(0.267)*	2.242*** *(0.254)*	2.550*** *(0.294)*	2.450*** *(0.288)*
Elasticity	0.822	0.723	0.71	0.808	0.777
R^2	0.417	0.600	0.641	0.918	0.933
Observations	14,085	14,085	14,085	14,085	14,085
Year FEs	Incl.	Incl.	Incl.	Incl.	Incl.
Disease × Science FEs		Incl.	Incl.	Incl.	Incl.
Disease × Year FEs			Incl.	Incl.	Incl.
Science × Year FEs				Incl.	Incl.
Applicant Controls					Incl.

$10 mil $\implies$ 2.5 more patents; 1 patent for 3 additional NIH grants

Is NIH funding useful to firms?

	(1)	(2)	(3)	(4)	(5)
# of Patents in the Same Area as a DST: Mean=24.8; SD=28.0					
DST Funding ($10 mill) Mean=4.06; SD 4.87	4.177*** *(0.350)*	3.060*** *(0.662)*	3.193*** *(0.550)*	3.509*** *(0.504)*	3.264*** *(0.293)*
Elasticity	0.697	0.511	0.533	0.586	0.545
R-squared	0.511	0.774	0.801	0.974	0.980
Observations	14,085	14,085	14,085	14,085	14,085
Year FEs	Incl.	Incl.	Incl.	Incl.	Incl.
Disease × Science FEs		Incl.	Incl.	Incl.	Incl.
Disease × Year FEs			Incl.	Incl.	Incl.
Science × Year FEs				Incl.	Incl.
Applicant Controls					Incl.

$10 mil $\implies$ 3.3 more patents; 1 patent for 2 additional NIH grants

How large are these effects? An example

$10 million in NIH funding leads to....

$$\frac{\text{0.034 more patents associated with FDA approved drugs}}{\text{8 Avg. patents per drug}}$$

(Assumed patents are pure substitutes for the drug)

$\times$\$3.47 billion average PDV of sales

(Taken from the literature, DiMasi, Grabowski, and Vernon (2004))

$=$ \$14.7 million in sales for drugs.

Return to $10 mill in additional NIH Funding

	Advanced Drug Candidates *Mean=0.546; SD=0.864* (1)	**FDA Approved** *Mean=0.316; SD=0.532* (2)	**Pre-approval** *Mean=0.212 SD=0.358* (3)	**Main** *Mean=0.035; SD=0.084* (4)	**Drug-level** *Mean=0.059; SD=0.099* (5)
OLS					
DST Funding (×$10 mln.)	0.081***	0.046***	0.032***	0.005***	0.008***
Mean=4.06; SD=4.36	*(0.015)*	*(0.010)*	*(0.007)*	*(0.001)*	*(0.001)*
Elasticity	0.602	0.591	0.613	0.580	0.551
Implied Drug Value ($ mln.)	—	$20.0	$22.2	$17.4	$27.8
IV					
DST Funding (×$10 mln.)	0.053**	0.034**	0.017	0.001	0.004
Mean=4.06; SD=4.36	*(0.026)*	*(0.017)*	*(0.013)*	*(0.003)*	*(0.004)*
Elasticity	0.394	0.437	0.326	0.116	0.275
Implied Drug Value ($ mln.)	—	$14.7	$11.8	$3.5	$13.9
Observations	14,085	14,085	14,085	14,085	14,085

Concluding thoughts

1. The path from evaluating grant application to commercial innovation is complicated and uncertain.

2. Much of this research has required the collection and analysis of new large scale data linking funding inputs (scores, funding) to outputs (patents, publications, drugs)

3. The data in this paper span 30 years – because it takes time for the value of research to be revealed

4. In order to understand the impact of basic, often untargetted, science, we need to create metrics that are flexible and keep track of outcomes. Our future selves would be thankful.

Thank you!

Questions or comments? dli [at] hbs.edu