Incremental Innovation and Pharmaceutical Productivity

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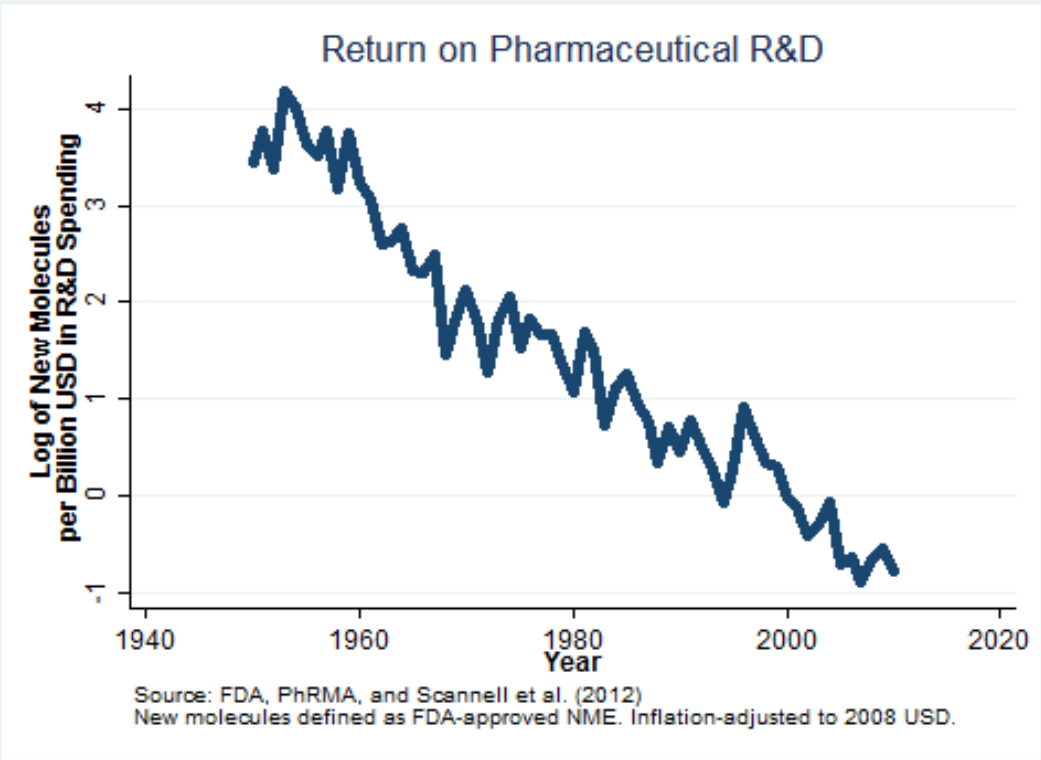
December 13, 2016

Outline

Motivation

- Pharmaceuticals are the second largest R&D industry in the US and are perceived to be in a "productivity crisis"



Observations

- Productivity should measure the health impact of innovation
- Novel innovation only captures part of innovation

Incremental Innovation

- Novel innovation: FDA-approved new molecules
- Incremental (or follow-on) innovation: modifications to FDA-approved new molecules

Outline

- Model and estimate how firms trade off between novel and incremental innovation
- Construct a dataset to measure the health impact of pharmaceutical innovation

Main Findings

- Trade off between types of innovation creates a dynamic allocation problem that helps explain past trends and predict future trends
- The productivity of pharmaceutical innovation increased between 1980 and 2009 by 30%
- Incremental innovation is the main driver and accounts for roughly half of the health impact of pharmaceutical innovation since 2000

Incremental Innovation

- FDA approval of a new:
  - combination
  - dosage
  - formulation
  - indication
  - active ingredient

HIV

- Innovation in HIV treatments helps illustrate impact of incremental innovation
- HAART was breakthrough HIV treatment in 1997
- Estimated to have saved 27 million life-years in US

HIV

Phase	Adherence Rate	Probability of Living 25 Years
Pre-HAART (1987-1996)	30%–50%	4%
Early HAART (1997-1999)	55%–60%	50%
Late HAART (2000-2005)	65%–70%	75%
CART (2006-)	85%	85%

Note: The probability of living 25 years is conditional on being diagnosed at age 25.

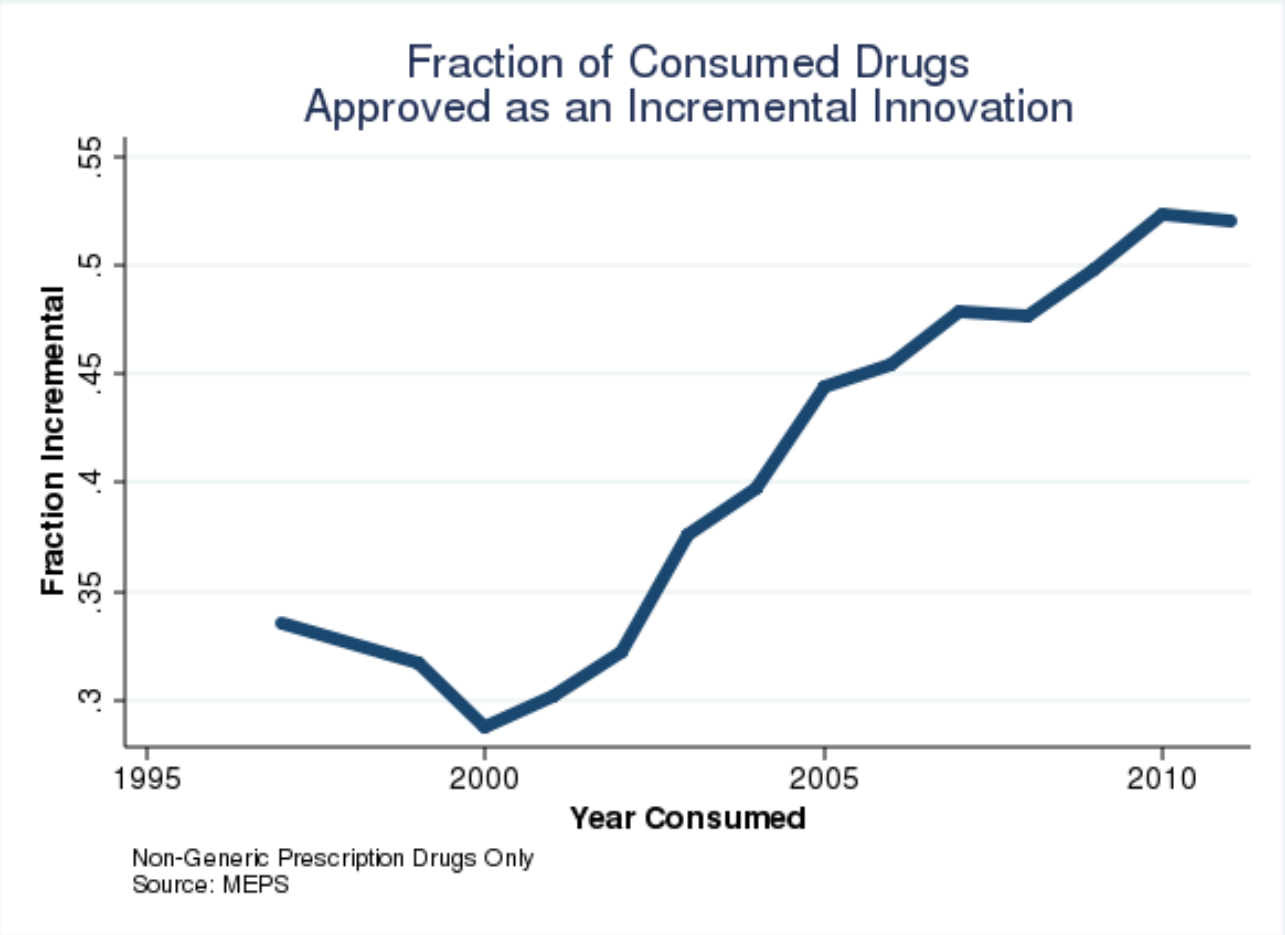
Table: HIV Outcomes

HIV

- More new molecules approved before HAART than during it
- Molecules approved pre-HAART accounted for over 75% of the market by mid-2000s
- Role of incremental innovation:
  - Improve efficacy
  - Reduce burden of treatment, increase adherence
  - Expand treatment population

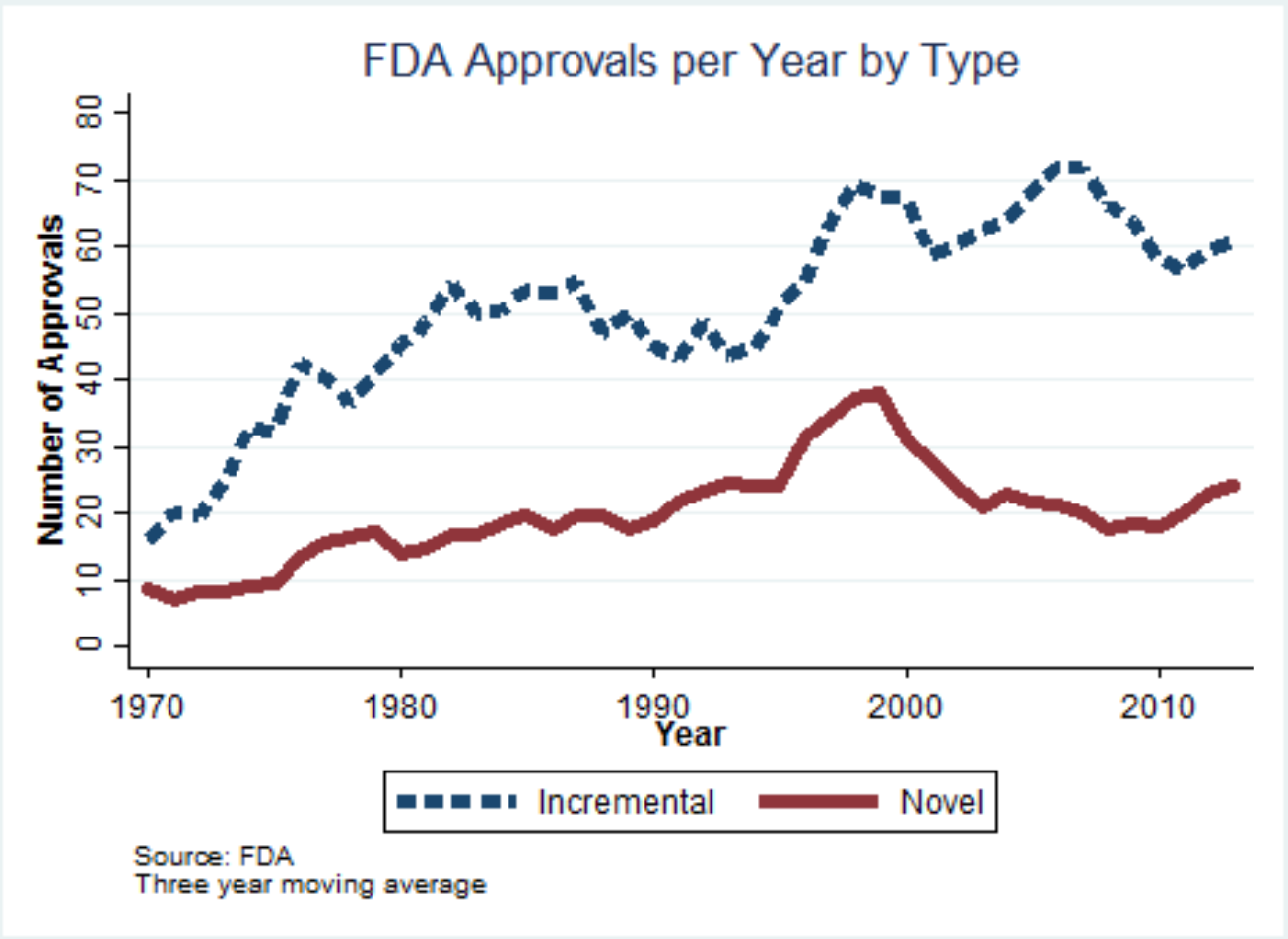
Incremental Innovation Facts

- Incremental Innovations is a growing and large fraction of non-generic prescription drugs



Incremental Innovation Facts

- Incremental Innovations have higher level and growth



Cost of Incremental vs. Novel Innovation

- Cheaper form of innovation (5-10% of the R&D cost per innovation)
- Quicker and easier to get approval (5 vs 9 years) and adopts quicker

Outline

Model of Incremental Innovation

- Related to Schumpeter growth model used by Acemoglu and Linn (2004)
- Flow rate of innovation per R&D dollar for drug j in year t:

$$n_j(t) = \delta_j z_j^N(t)$$

$$i_j(t) = \zeta(N_j(t), I_j(t))\delta_j z_j^I(t)$$

  - n, N: Flow and stock of Novel Innovations
  - i, I: Flow and stock of Incremental Innovation
  - $z_j^N(t)$: Novel R&D
  - $z_j^I(t)$: Incremental R&D
  - δ_j: Flow rate of innovation
  - $\frac{\partial \zeta}{\partial N_j(t)} > 0$ and $\frac{\partial \zeta}{\partial I_j(t)} < 0$

Model of Incremental Innovation

- R&D decision comes down to equalizing returns across novel and incremental innovation
  - Comes down to whether $\zeta(N_j(t), I_j(t)) \lessgtr 1$
  - If I assume $\zeta(N_j, I_j) = \beta \frac{N_j}{I_j}$, then in the steady state:
    - firms invest $\frac{\beta}{1+\beta}$ of their R&D on incremental innovation
    - firms invest $\frac{1}{1+\beta}$ of their R&D on novel innovation
    - returns are equalized and $\zeta(N_j, I_j) = 1$.

Estimating Model

- Test the assumption of the model about $\zeta(N_j(t), I_j(t))$ using a Poisson model similar to Acemoglu and Linn (2004):

$$E[n_{ct}|\phi_c, \bar{X}_c, \bar{n}_c] = \exp(\alpha_n \cdot \log M_{ct} + \beta_n \cdot \frac{N_{c,t-1}}{I_{c,t-1}} + X'_{ct} \cdot \theta_n + \phi_{n,c} + \mu_{n,t})$$

$$E[i_{ct}|\phi_c, \bar{X}_c, \bar{n}_c] = \exp(\alpha_i \cdot \log M_{ct} + \beta_i \cdot \frac{N_{c,t-1}}{I_{c,t-1}} + X'_{ct} \cdot \theta_i + \phi_{i,c} + \mu_{i,t})$$

- n: number of novel innovations in year t and drug category c
- X'_{ct}: vector of controls with drug category fixed effects (ϕ_c)
- μ_t: time fixed effects
- M_{ct}: potential market size
- $\frac{N_{c,t-1}}{I_{c,t-1}}$: ratio of the stock of novel to incremental innovation in the previous period

Estimating Model

- Estimate with a Hausman, Hall, and Griliches (1984) transformation of Poisson to get rid of the drug category dummies using QML

$$E[n_{ct}|\phi_c, \bar{X}_c, \bar{n}_c] = \frac{\exp(\alpha_n \cdot \log M_{ct} + \beta_n \cdot \frac{N_{c,t-1}}{I_{c,t-1}} + X'_{ct} \cdot \theta_n + \mu_{n,t})}{\sum_{N=1}^{T} \exp(\alpha_n \cdot \log M_{c\tau} + \beta_n \cdot \frac{N_{c,t-1}}{I_{c,t-1}} + X'_{c\tau} \cdot \theta_n + \mu_{n,\tau})} \bar{n}_c$$

- Observation is a disease category-year group (five year period) from 1975-2010 for 19 disease categories (ie. Antibiotics, Acid/Peptic Disorders, Antidepressants)
- Use FDA and MEPS data

Estimating Model

	(1) Novel	(2) Novel	(3) Incremental	(4) Incremental
Ln Market Size	2.204*	2.294*	2.421*	2.322*
	(0.355)	(0.352)	(0.208)	(0.202)
Novel Stock/Inc. Stock	-0.696*		0.377*	
	(0.349)		(0.169)	
Year Group Fixed Effect	Yes	Yes	Yes	Yes
Observations	152	152	152	152

Estimated by quasi-maximum likelihood (QML) with Hausman, Hall, and Griliches transformation. Huber-White robust standard errors are reported in parenthesis. The dependent variable in columns 1 and 2 is the count of novel innovation approvals, and in columns 3 and 4 is the count of incremental innovation approvals. Approval counts are from the FDA, market size is from the MEPS and CPS. Estimates are weighted by total expenditure for the category in the MEPS. Marginal Effect listed. Implied ratio of stock of novel to incremental innovation is 0.55.
* $p < 0.05$

Table: Effect of Stock Ratio on Innovation

Outline

Health Impact of Innovations

- Health impact of drug j in year y

$$h_j = \sum_y q_{jy} a_j e_j$$

  - q_{jy}: number of people taking drug j in year y
  - a_j: average adherence rate for drug j
  - e_j: average health impact of drug j (efficacy measured in QALY)

Health Impact of Innovations

- Health impact of all drug innovations across drugs and years:

$$H = \sum_{j \in D} \sum_{y} q_{jy} a_j e_j$$

- Increase in health impact from new innovations approved in year y:

$$\Delta H_y = \sum_{j \in D_y} [\Delta q_j a_j e_j + \Delta a_j q_j e_j + \Delta e_j q_j a_j]$$

Health Impact of Innovations

$$\Delta H_y = \sum_{j \in D_y} [\Delta q_j a_j e_j + \Delta a_j q_j e_j + \Delta e_j q_j a_j]$$

- Construct a dataset of six measures for each FDA-approved innovation (novel and incremental)
  - Δq_j, Δa_j, Δe_j, q_j, a_j, e_j
  - Doesn't include non-FDA-approved innovations

Data Sources

- Innovation data
  - FDA: Over 2,500 innovations from 1980 to 2009 listed by innovation type, date, and matched to national drug code (NDC)
- Survey data
  - Medical Expenditure Panel Survey (MEPS): 3.5 million prescription transactions from 1996 to 2012 with person id, NDC, and condition code
  - National Ambulatory Medical Care Survey (NAMCS): 3.2 million prescriptions from 1980 to 2010 with person id and condition code
- Cost-effectiveness data
  - Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry measures of QALYs for 6,500 cost-utility analysis studies published in peer-reviewed journals.

Relative Measure

- Health impact measured relative to novel innovation in 1980
- Measure within decades

Measuring Health Impact

- Health impact is measured from quality adjusted life years (QALY) using CEA Registry
  - QALYs measure the quantity and quality of life added by a treatment
  - q_y are measured as QALY levels
  - Δq_y are measured QALY relative to the standard of care
  - Measured by drug category, innovation type, and year average

Measuring Adherence

- Adherence for drug j (a_j) is measured in two ways from MEPS data:
  - Drug persistence: fractions of patients who remain on drug j across both survey years in the MEPS
  - Medical possession ratio (MPR): fraction of days that a patient had his prescription filled over the course of the survey
- Changes in adherence for drug j (Δa_j) is measured relative to the adherence rate of the other already-approved drugs that treat the same condition as drug j

Measuring Quantity

- Quantity for drug j (q_j) is measured as the number of users for that drug over the first 14 years the drug is on the market
  - Use drug shares from survey data (MEPS and NAMCS) matched to aggregate data
- Changes in quantity for drug j (Δq_j) is change in trend in quantity within narrowly defined disease category

Matching Across Datasets

- MEPS has data on 71% of innovations
- Disease category data for 93% of innovations

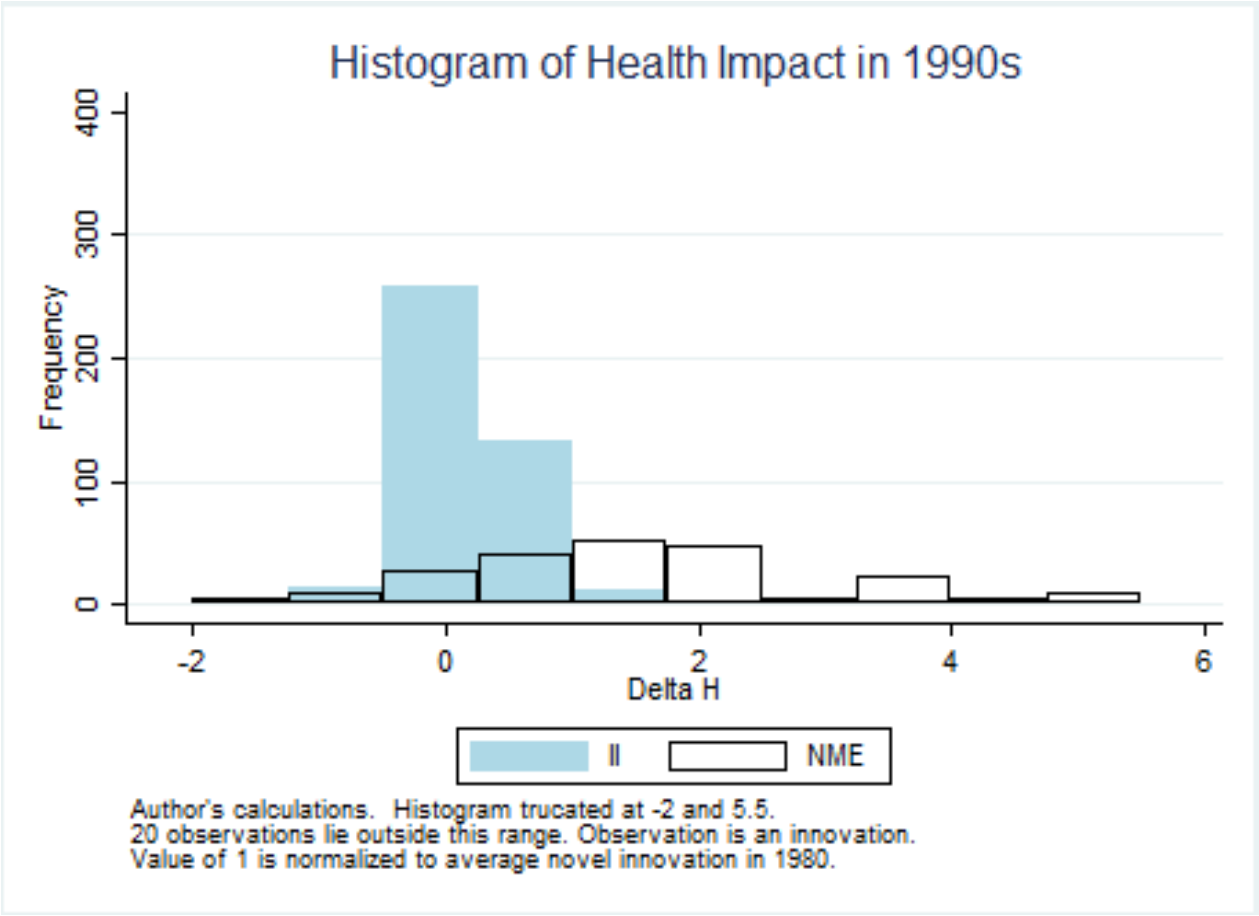
Role of Incremental Innovation in Pharmaceutical Productivity

	Novel Innovation		Incremental Innovation		
y	Health Impact Per Innovation	Count Per Year	Health Impact Per Innovation	Count Per Year	Incremental's Health Impact Share
1980s	1.0	18.7	0.1	51.7	20%
1990s	1.5	30.6	0.3	53.4	23%
2000s	2.0	20.7	0.6	63.7	49%

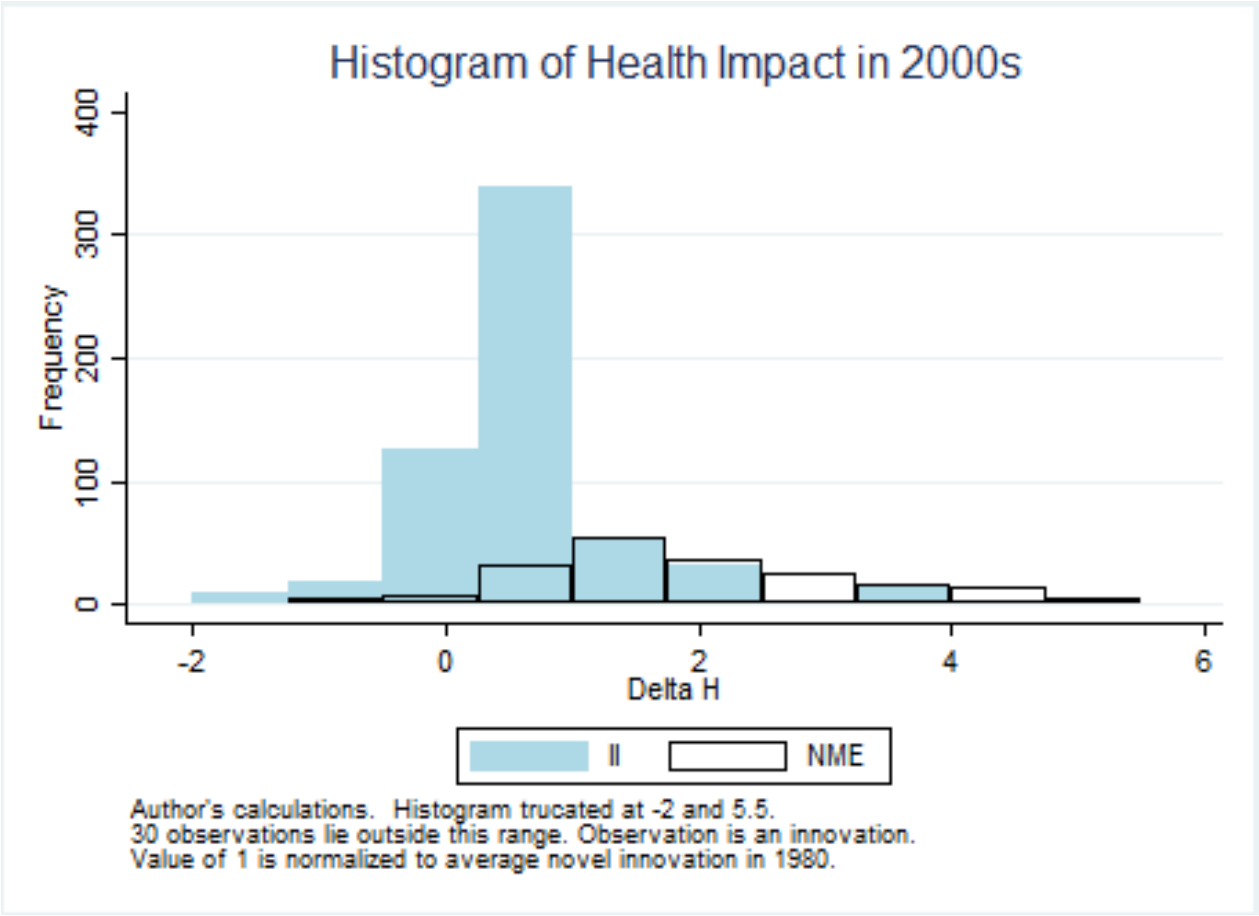
Note: All health impacts are relative to a novel innovation in the 1980s. The health impact of a novel innovation is $\Delta H_y^N / \Delta H_{\mathbf{1980}}^N$. The health impact of an incremental innovation is $\Delta H_y^I / \Delta H_{\mathbf{1980}}^N$.

Table: Health Impact Gain Across Decades

Health Impact 1990s



Health Impact 2000s



Role of Incremental Innovation in Pharmaceutical Productivity

- Productivity is measured as the relative increase in value of new innovations compared with adjusted R&D
- R&D is adjusted for inflation with the NIH Biomedical R&D Price Index, year adjusted to match R&D spending with outputs, and includes all federal pharmaceutical R&D funding

Measure of Pharmaceutical Productivity

y	Health Impact of Innovations	Adjusted R&D (Billions of USD)	Adjusted R&D
1980s	1.0	18.8	1.0
1990s	2.6	34.9	1.9
2000s	3.5	50.1	2.7

Note: All innovation values are relative to 1980: $\Delta H_y / \Delta H_{\mathbf{1980}}$. Adjusted R&D is per year.

Table: Productivity of Pharmaceutical R&D

Predictions

- Empirical calibration of the model tells us steady state trade off
  - 1990s: increase in novel innovation in 1996–1997, likely from PDUFA
  - 2000s: increase in incremental innovation from novel stock increase
  - 2010s: stock ratio below steady state, predict an increase in novel innovation

Extensions

- Understand the increase in health impact per incremental innovation
  - Role of technology, more complicated treatments
- Response to market conditions and market power
  - Orphan drugs
- Effect on prices, quality-adjusted prices?