Missing Novelty in Drug Development

Joshua Krieger[1] Danielle Li[2] Dimitris Papanikolaou[3]

[1]Harvard Business School

[2]MIT Sloan and NBER

[3]Northwestern Kellogg and NBER

Motivation

Innovation and R&D productivity appear to be declining
(Gordon '16, Bloom et. al. '17, Kelly et. al. '18).

Why might innovative output be low?

- Are good ideas scarce?
- Or are firms just reluctant to develop them?

This paper: Do firms under-invest in *novel* drugs?

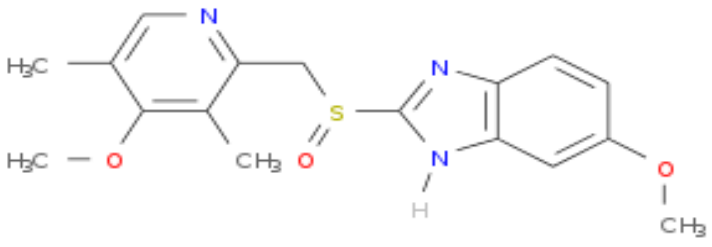
- We explore one channel that may limit innovation: risk aversion which can arise as a result of financial frictions.
- Potentially first order issue: drug development is expensive and uncertain—firms/managers may be reluctant to place large bets
- But is this important for large, public, and profitable firms?

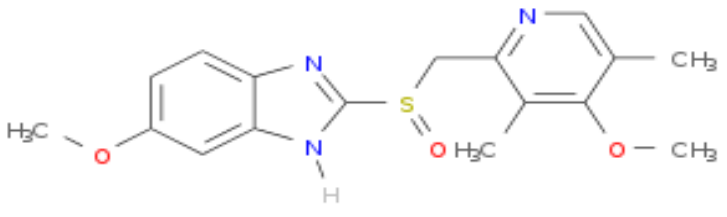
What we do

1. Develop (and validate) a new measure of drug novelty
    - Novel drugs are molecularly distinct from prior candidates.
2. Characterize the economic risk/return of developing novel drugs
    - Novel drugs are riskier but appear to have higher expected returns
3. Firms under-invest in novel drugs
    - Firms that receive a positive cashflow shock develop more drugs and shift toward more novel candidates—even in areas where project returns are unaffected.
    - Within subset of public firms, effect driven by firms with low levels of (pre-existing) cash holdings

Mechanism? Consistent with any model that generates firm risk aversion (e.g. a simple model with costly external finance)

"Me-too" Innovation: Prilosec and Nexium





"A new medicine that isn't any better for ordinary heartburn than the one it will succeed" (WSJ, 2002)

Measuring Drug Novelty

Measuring Drug Novelty

Want to understand the decision to *invest* in innovative drug candidates:

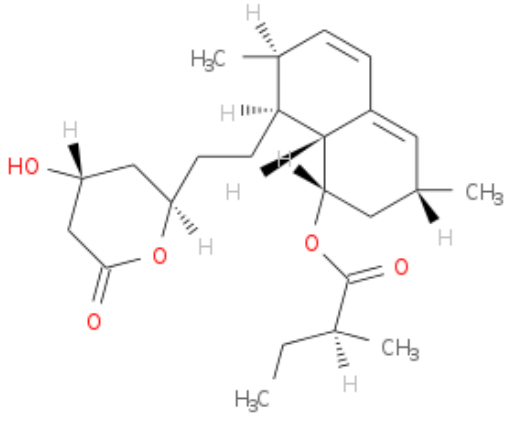
- Yet, most existing measures of innovation conflate novelty with ex-post success or market size
  - "Priority" status (Dranove et al., 2014) credit drugs as innovative only when they are successful
  - "First in class" measures miss innovation in larger markets

Our approach: Define a novel drug candidate as one that is molecularly distinct from prior candidates

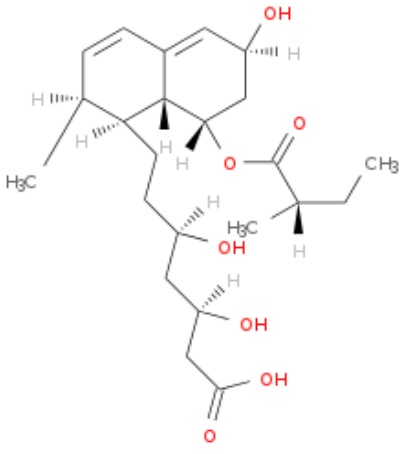
- Ex ante measure, observable when development decision is made
- Based on methods widely used by pharmaceutical chemists

Novel drugs are distinct from their nearest neighbour

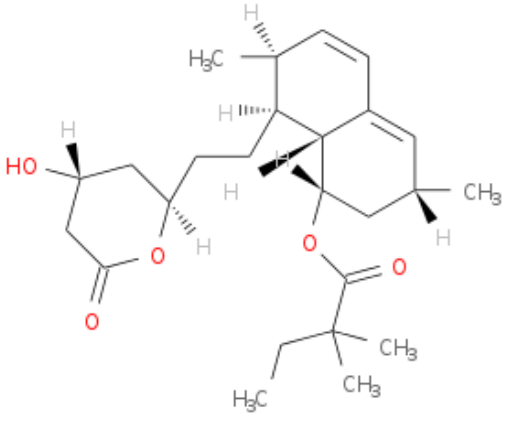
Novel drugs have low max similarity—Example:



Mevacor
(Similarity Score=0.25)



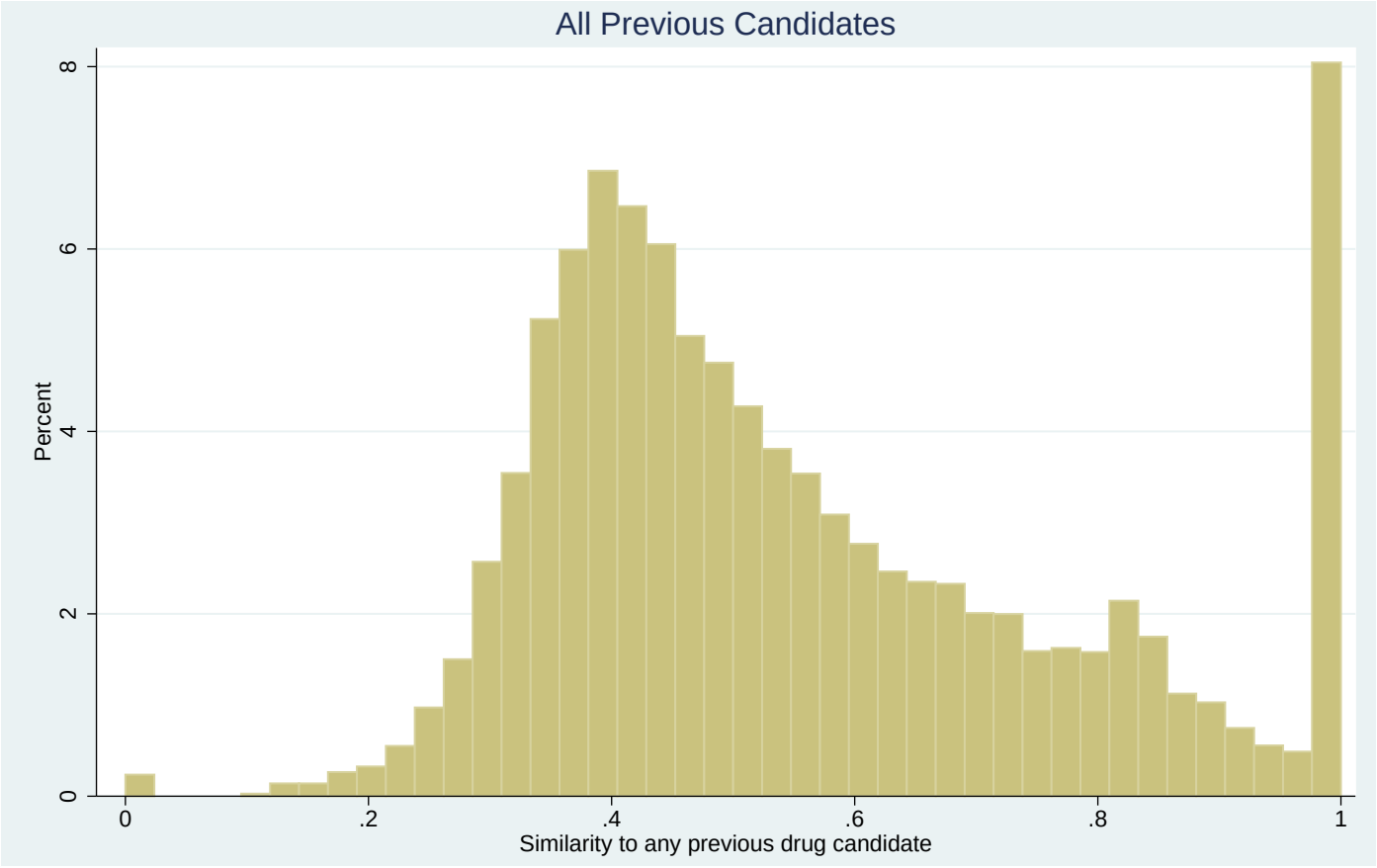
Pravachol
(Similarity Score =0.61)



Zocor
(Similarity Score =0.82)

1. Mevacor (Lovostatin) is 1st FDA approved statin (Sep 1987): maximum similarity to prior molecules is 0.25
2. Pravachol (Pravastatin) is 2nd (Oct 1991): pair-wise similarity to Mevacor is 0.61. Overall similarity to prior molecules is 0.61
3. Zocor (Simvastatin) is 3rd (Dec 1991): pair-wise similarity to Mevacor is 0.82; to Pravachol is 0.52. Overall similarity to prior molecules is 0.82

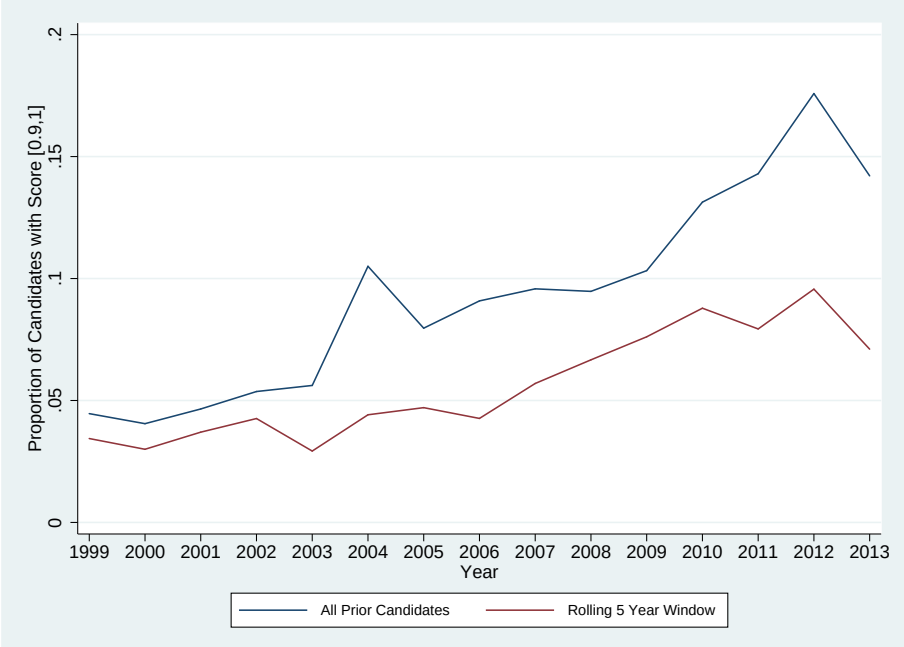
Overall distribution of novelty



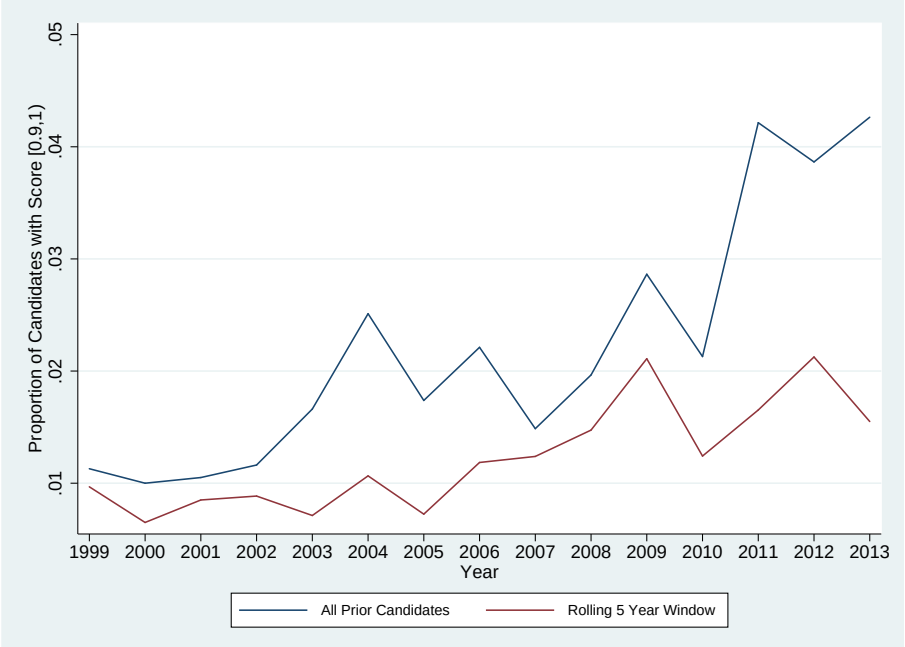
- 20% of drugs share over 80% overlap in molecular structures with prior drug candidates.
- 8% have a component that is the same (up to stereosymmetry) as a prior candidate.

Proportion of very similar drugs is increasing over time

(a) Similarity > 0.9



(b) Similarity > 0.9, excl combination



- Proportion of drugs that are 0.9 similar to a candidate within the past 5 years has doubled (4% to 8%)

Economic Characteristics of Novel Drugs

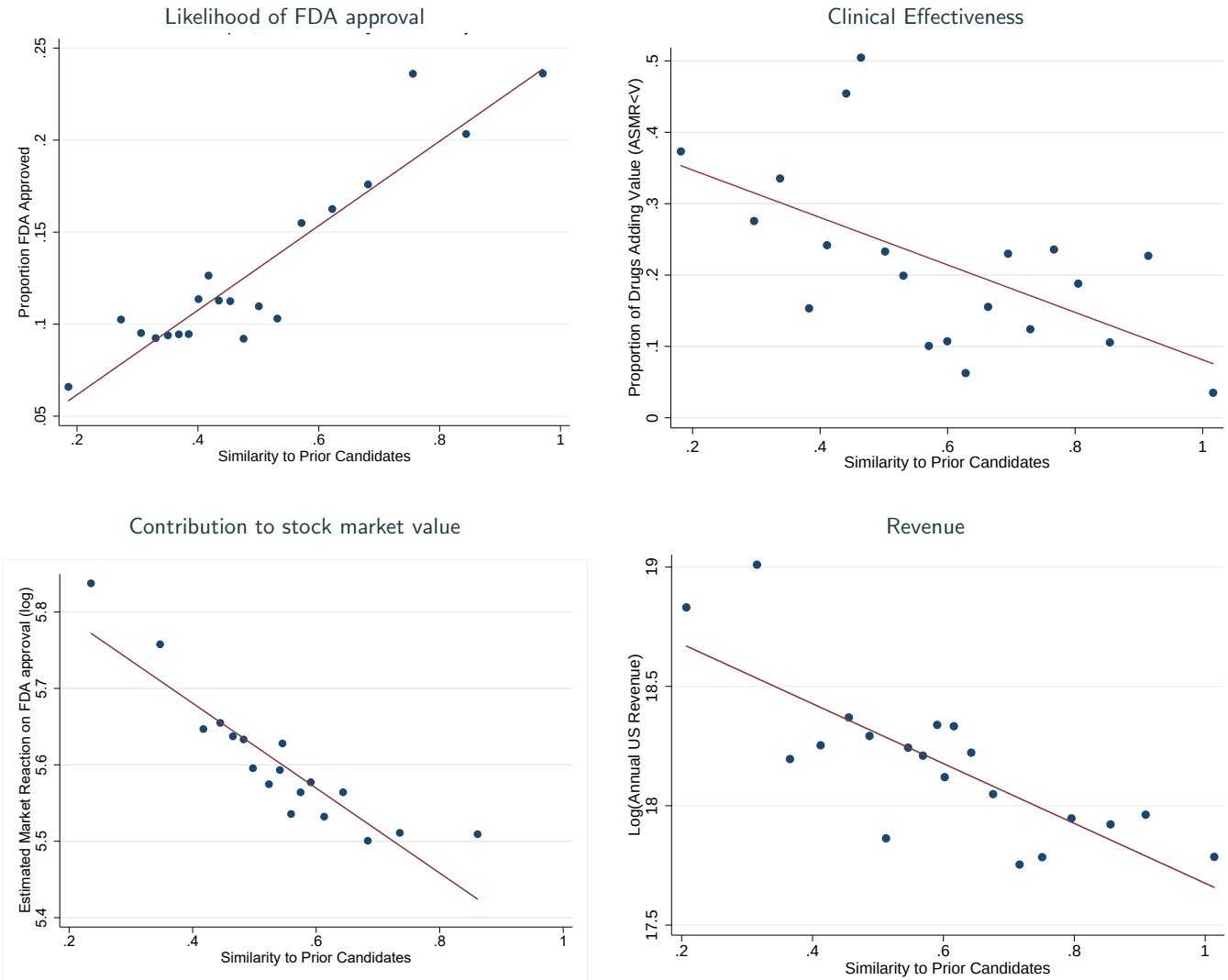
Novelty: Risk and Return

So far, we have developed a measure of novelty. But what are the economic characteristics of novel drugs?

Comparing drugs treating the same indication, developed in the same year, and by the same company, we find

1. Novelty and risk
    - Novel drugs are less likely to be approved by the FDA
2. Novelty and ex post value: among FDA approved drugs
    - Novel drugs are more likely to be highly effective (based on French Healthcare system classification)
    - Top-selling drugs are more likely to be novel
    - Nobel drugs contribute more to stock market value upon FDA approval

Novel Drugs are riskier, but successful drugs tend to be novel



Note: 1 SD increase in novelty is associated with ∼23% decrease in the likelihood of reaching FDA approval; ∼35% increase in the likelihood of adding a high level of clinical value; ∼20% increase in revenues; and ∼20% increase in stock market value of underlying patents, deflating by Pr(approval || phase 3). Figures control for indication; cohort; company FEs.

Ex-post vs. Ex-ante value

Novel drug candidates:

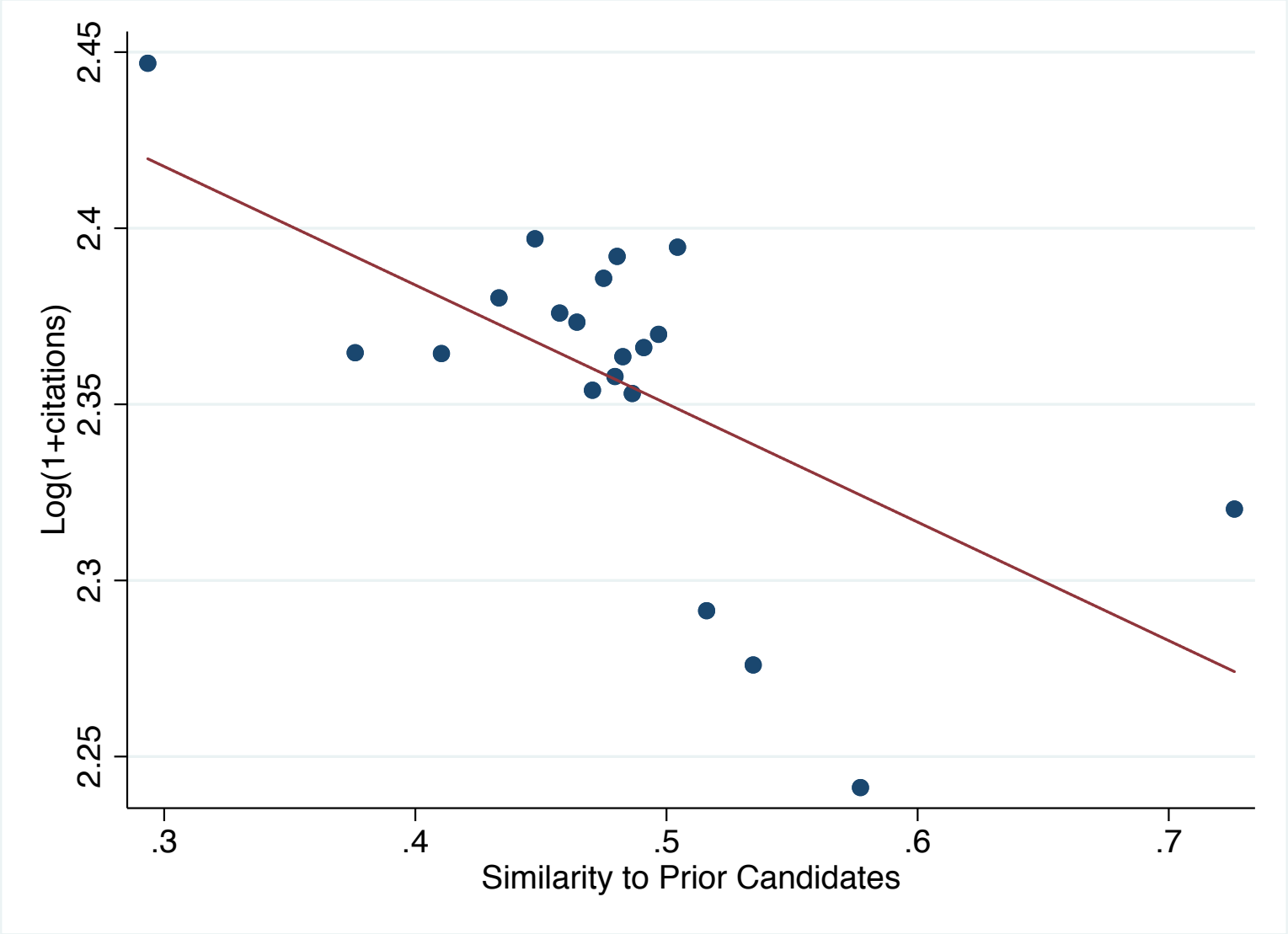
1. are less likely to be approved; but,
2. generate higher private/social value conditional on FDA approval.

But, are they better investments ex-ante?

Examine outcomes that are observable regardless of FDA approval

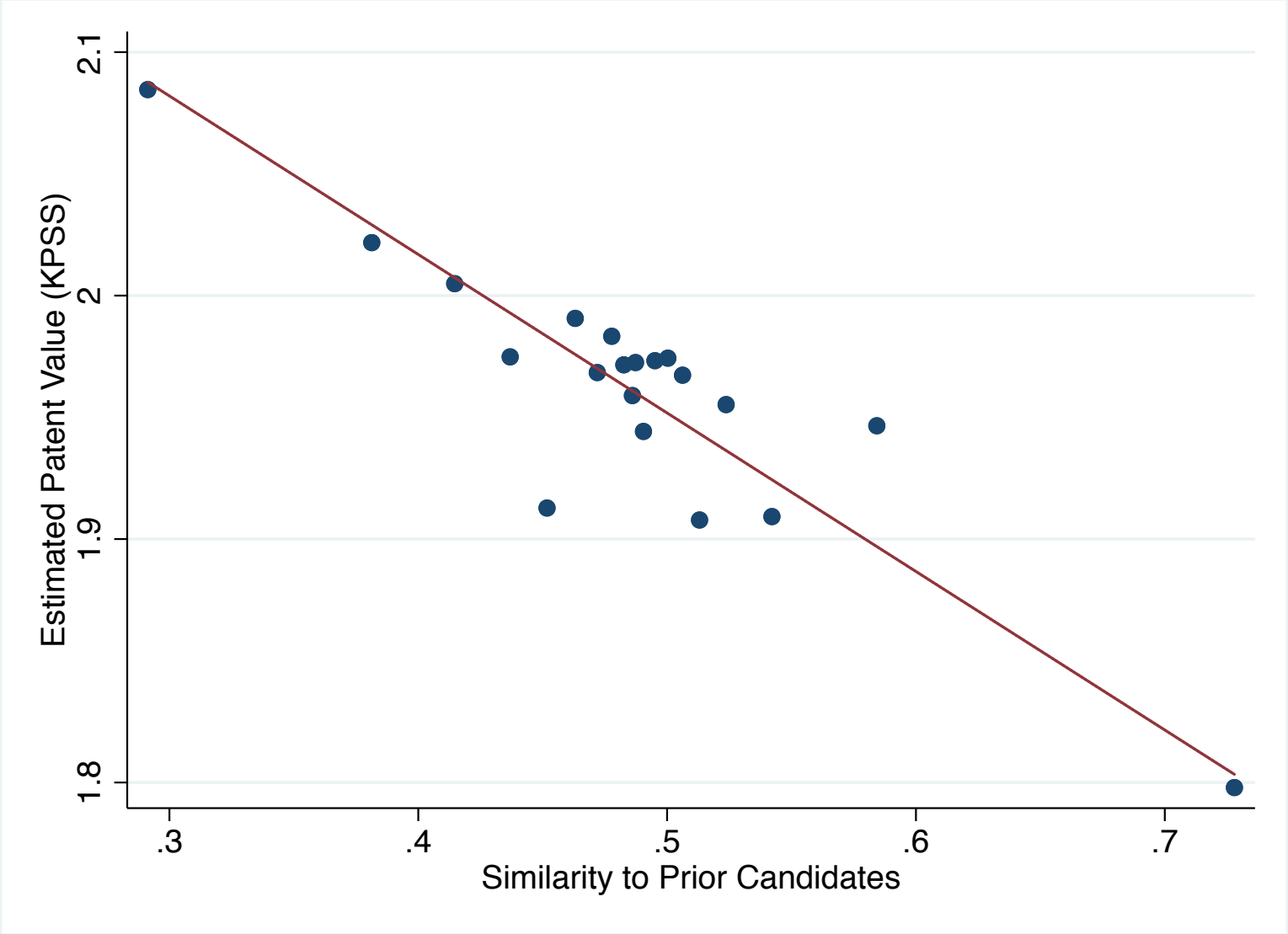
- Focus on early patents, filed very early in the development cycle.
  - Pre-approval patents are the key patents, covering active ingredients.
- Cost of patenting is low, thus firms patent all molecules. By contrast, drug development costs are back-loaded. Thus, focusing on the value of these patents is a good estimate of the ex-ante value of a drug.

Patents underlying novel candidates are more highly cited



Note: 1 SD increase in novelty (-0.21) is associated 25% more citations (relative to median) to underlying (pre-approval) patents

Patents underlying novel candidates have higher market value



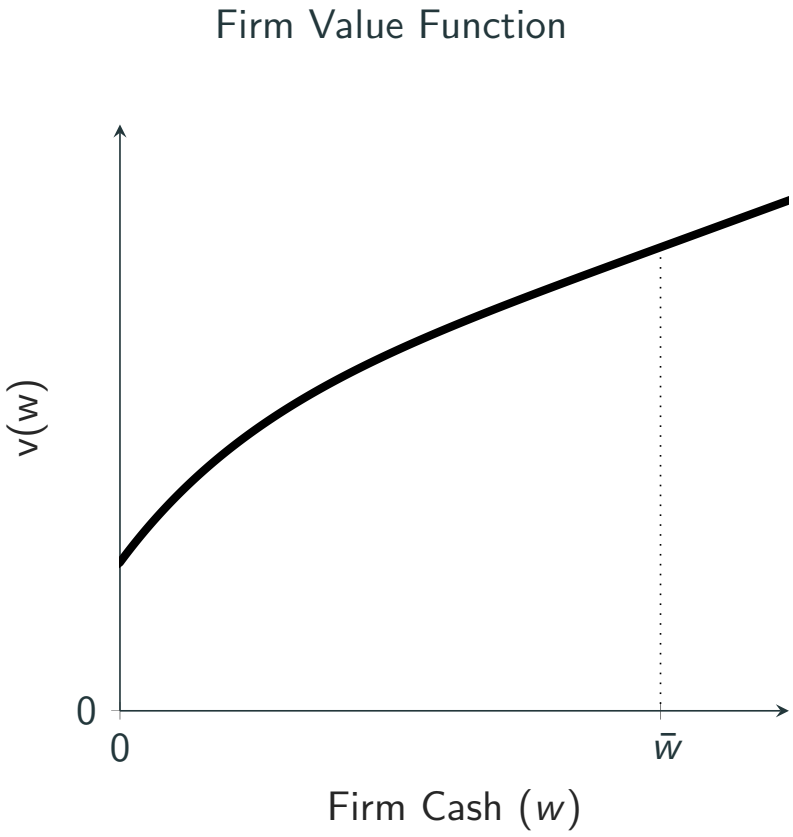
Note: 1 SD increase in novelty (-0.21) is associated with 10% greater increase in stock market value of underlying pre approval patents

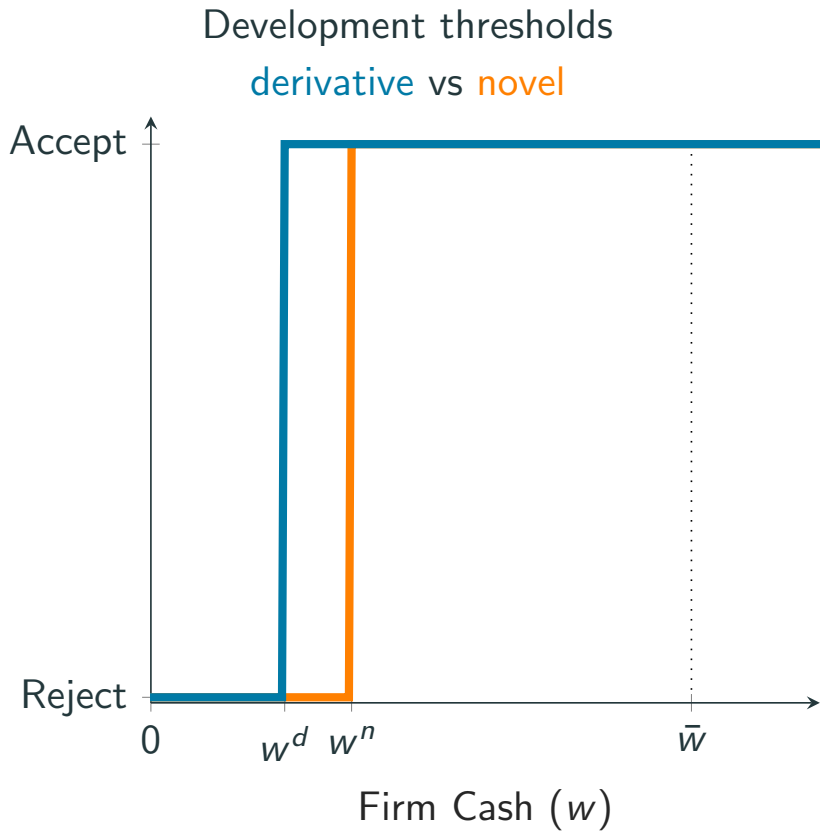
Do firms under-invest in novelty?

Thought experiment: Suppose we were to randomly endow firms with additional cash.

1. If there are no financing frictions, and ideas are simply scarce
    - No effect: firms are already investing in all available novel drug candidates.
2. If financial frictions impede innovation
    - Treated firms should respond by: a) investing in more drugs and b) investing in more novel drugs
    - Why? Models w/ financial frictions predict that (1) investment is sensitive to net worth, and (2) the possibility of needing to raise costly (external) capital tomorrow induces risk-averse behavior today.

Firm Risk Aversion and "Missing" Novelty





- Firms under-invest in all drugs (relative to the frictionless benchmark)
- Firms apply a higher threshold for developing novel drugs than me-too
- Threshold a function of current cash holdings, scaled by firm size

Cashflow Shocks and Drug Novelty

A Shock to Net Worth

Empirical test: Want a shock to firm (current and expected) cashflow while holding firms' investment opportunities constant.

The 2003 Medicare Modernization Act extended Medicare to provide prescription drug coverage for Americans over 65.

Differentially affected firms along two dimensions:

1. Proportion of drugs aimed at the elderly:
    - Firms with existing portfolio of drugs for elderly benefit more.
2. Remaining exclusivity period:
    - Firms with longer exclusivity periods benefit more.

We use both sources of variation in order to disentangle a shock to cashflows from a shock to investment opportunities.

Identification

We compare firms with the same MMS and same overall exclusivity remaining, which differ in how the exclusivity periods are distributed across elderly- and non-elderly focused drugs.

Example:

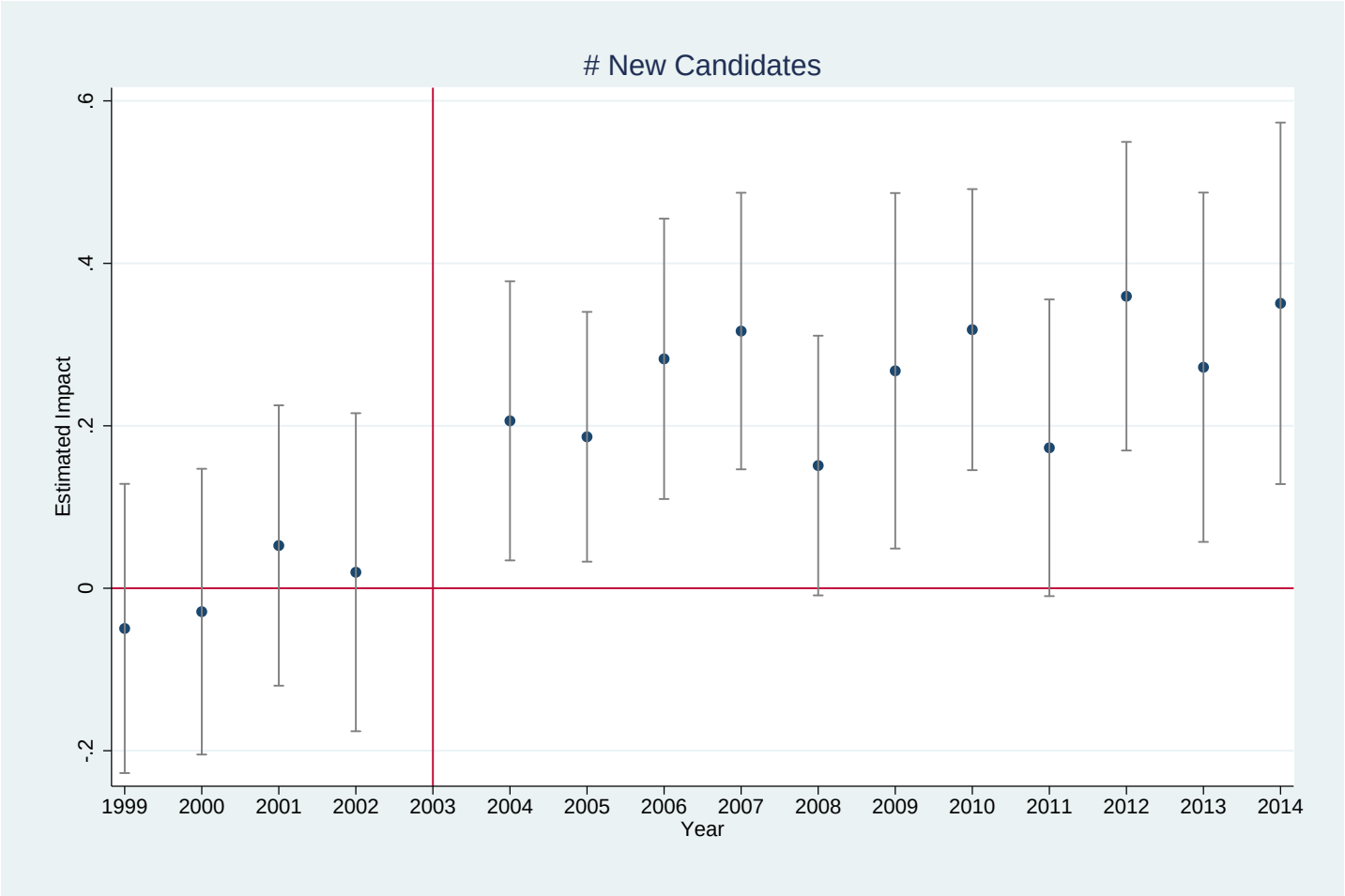
Firm A:
- O_A has a 75% medicare share and will remain on patent
- Y_A has a 50% medicare share and will not remain on patent

Firm B:
- O_B has a 75% medicare share and will not remain on patent
- Y_B has a 50% medicare share and will remain on patent

Firm A should benefit more from Part D: its longer patent life drug is targeted toward elderly people, while Firm B's is not

- Firm A's Treatment Intensity is: $\frac{75}{75+50} * 1 + \frac{50}{75+50} * 0 = 0.6$
- Firm B's Treatment Intensity is: $\frac{75}{75+50} * 0 + \frac{50}{75+50} * 1 = 0.4$

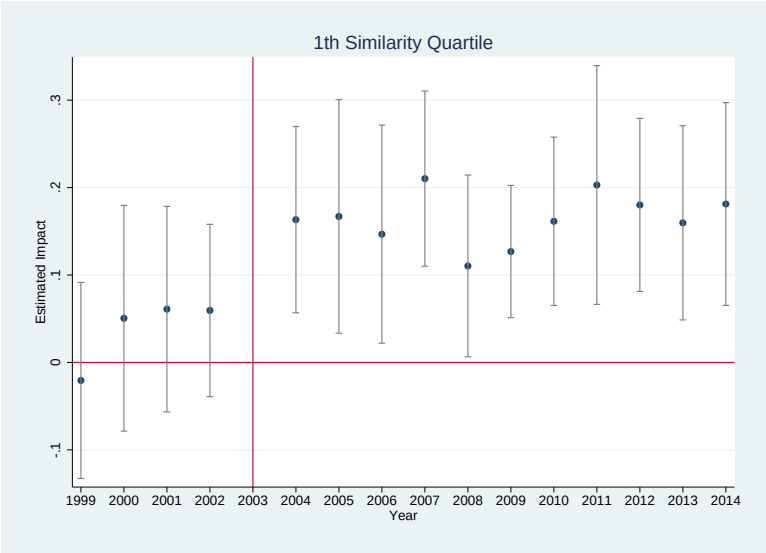
Treated firms develop more drugs



- Increase in drug development starts in 2004
- Part D implemented Jan 1 2006 $\Longrightarrow$ firm react to shock to expected cashflows Mechanisms →

Increase driven by novel drugs

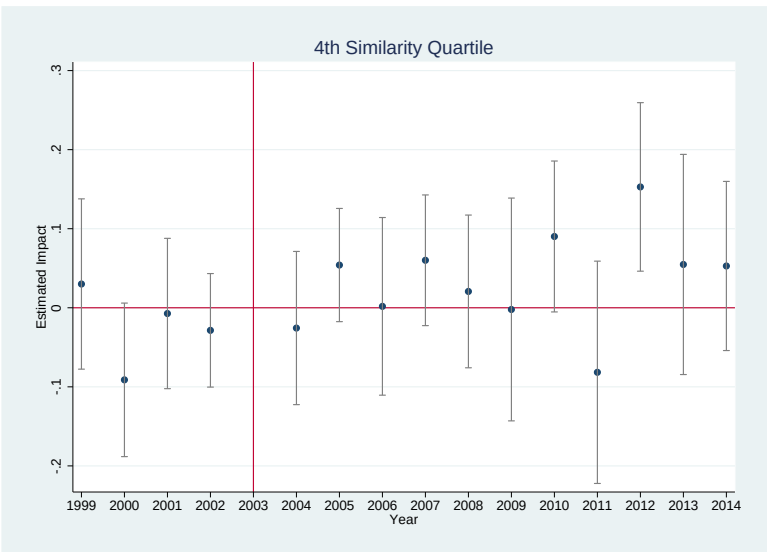
(a) Similarity Quartile 1



(b) Similarity Quartile 2

(c) Similarity Quartile 3

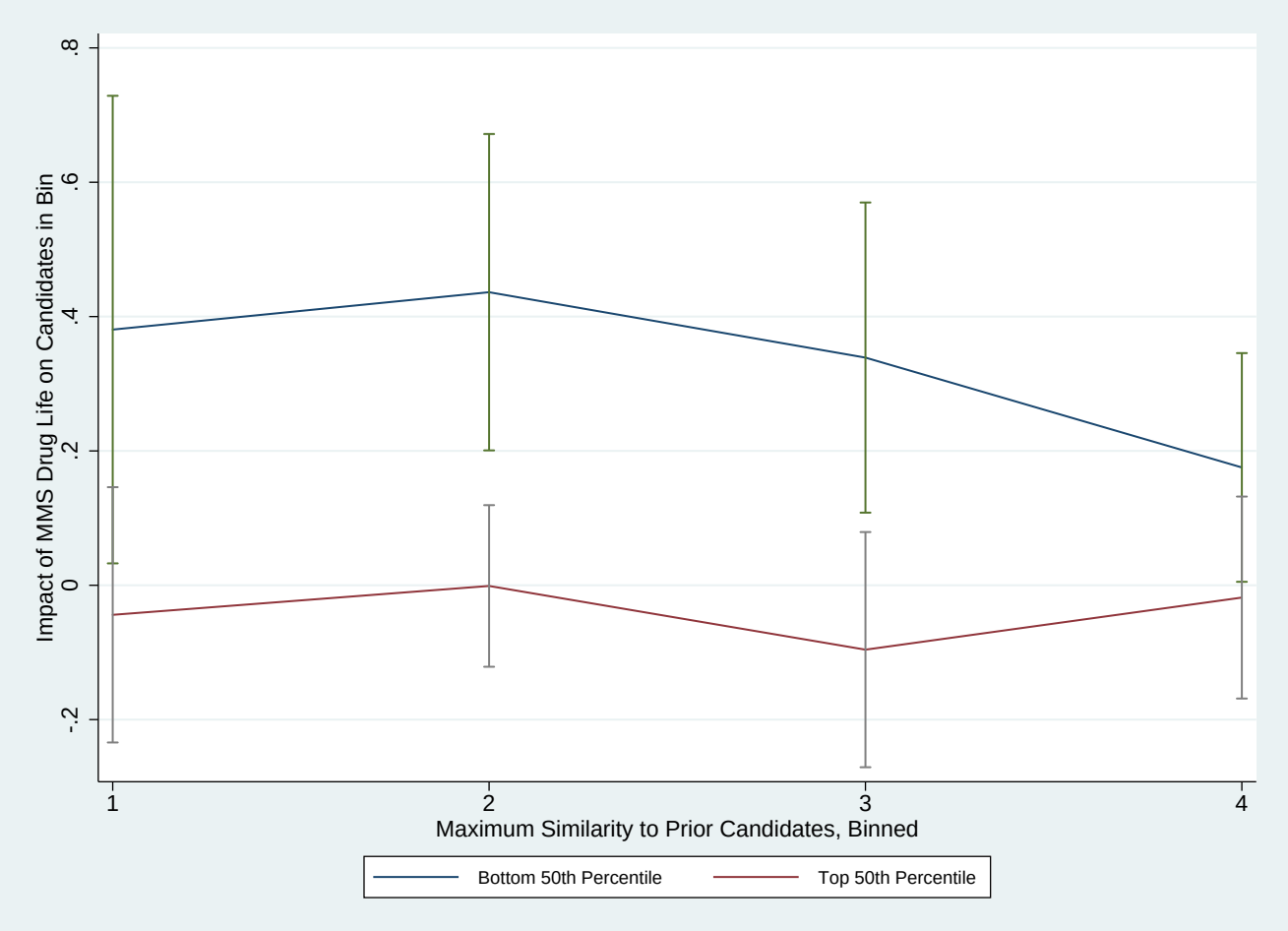
(d) Similarity Quartile 4



More novel drugs, even in unaffected areas

	Similarity Quartile	
Non-Elderly Candidates (Below Median MMS)	(Novel)	(Me-too)
Post 2003 X Medicare Drug Life	0.062**	0.016
	(0.029)	(0.019)
Pediatric Candidates		
Post 2003 X Medicare Drug Life	0.093**	0.040
	(0.043)	(0.030)
Youth Candidates		
Post 2003 X Medicare Drug Life	0.081**	0.026
	(0.037)	(0.027)
Company FEs	Yes	Yes
Qtr of Development FEs	Yes	Yes
Overall Drug Life/Firm MMS	Yes	Yes
Observations	16442	16442

Firm Heterogeneity: cash poor firms respond more



Among public firms (approximately half the firms in the sample)

- Firms with high cash-to-assets (pre-treatment) show no response
- Firms with low cash-to-assets (pre-treatment) respond strongly

Conclusions

1. Novelty is decreasing, the proportion of "me-too" drugs is increasing
2. Novel drugs are more valuable—but riskier—investments
3. Firms appear to prioritize derivative drugs, even though novel candidates appear more valuable
4. Focus on policies that change relative risk/return of novel drugs
    - Diversified portfolios (e.g. VC backed biotech)
    - Pay less for me-too drugs (e.g. closed formularies)