Paving the Way: Follow-on Innovation and Spillovers in Drug Development

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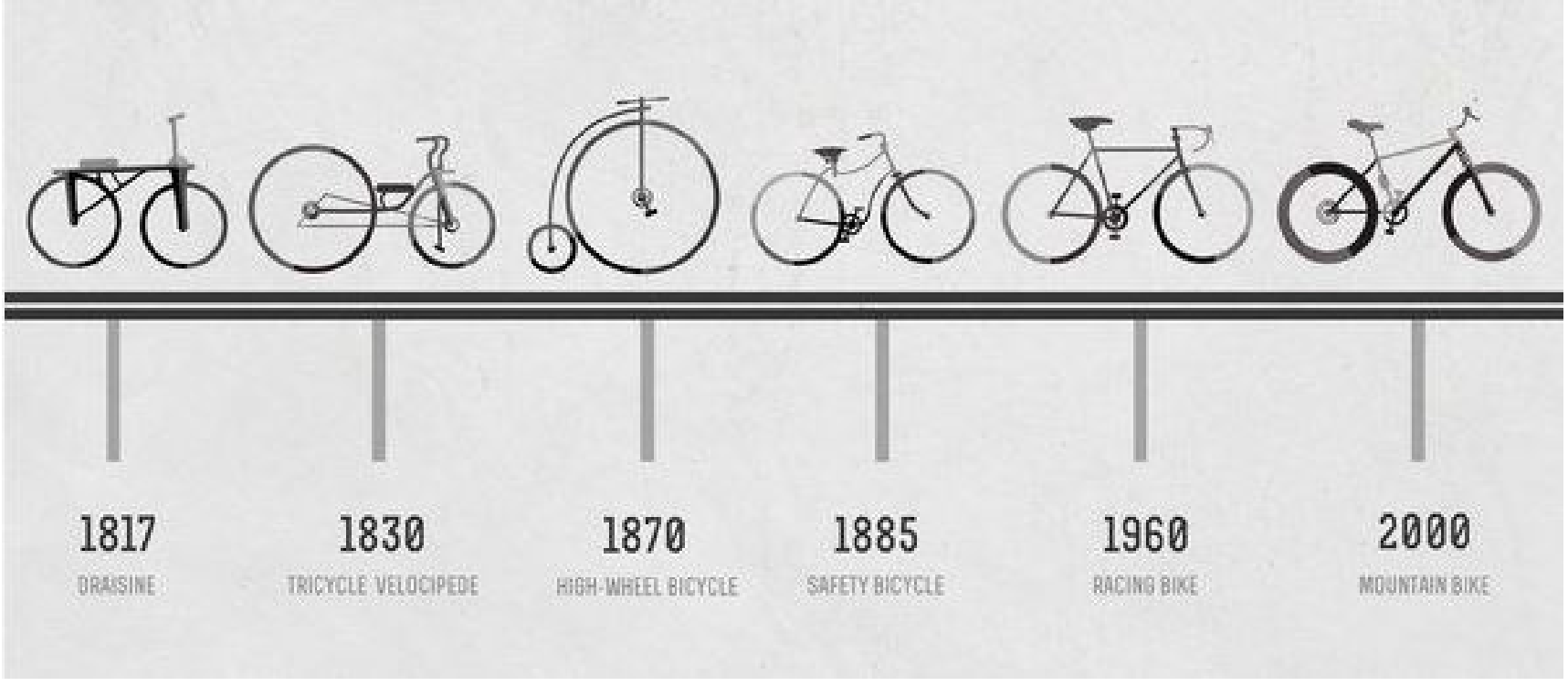
Motivation

- Innovation is often thought of generating research spillovers and positive externalities. However, these are challenging to identify empirically.

- Whether and how such spillovers distort R&D incentives depends on...
  1. What type of projects generate them?
  2. Who captures them?
  3. Whether spillover beneficiaries undercut the pioneering innovation?

Motivation

Some forward spillovers seem purely good, regardless of who captures them:



Motivation

...but sometimes spillovers mean free-riding problems, and that initial innovators are not rewarded for taking risks (i.e., the "penguin effect")

Today

- We focus on the pharmaceutical industry:
  - We propose new measure(s) of follow-on innovation (based on similarity)

- Armed with our new measure, we ask the following two questions:
  1. What type of drugs are more likely to generate positive spillovers?
  2. Who captures the benefits?

Today

- We focus on the pharmaceutical industry:
  - We propose new measure(s) of follow-on innovation (based on similarity)

- Armed with our new measure, we ask the following two questions:
  1. What type of drugs are more likely to generate positive spillovers?
  2. Who captures the benefits?
  3. **Next up: How competition changes the flow of follow-on investment**

Our Findings

1. More successful drugs are more likely to experience follow-on innovation
   - Follow-ons enter after success milestones
   - Larger number of follow-on attempts
   - But also, more successful follow-ons on average
2. Novel drugs also generate more positive spillovers
   - Fewer number of follow-on attempts
   - But much more successful follow-ons on average
3. Majority of spillovers captured by other firms
   - Though own-firm follow-ons are on average better, most follow-on attempts are by other firms.

Measuring Chemical Similarity

Want to identify influence on follow-on innovations

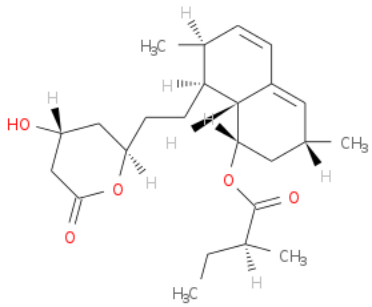
- Attempts to measure future impact and knowledge flows (e.g., patent citations) don't capture similarity of product features

Our approach: Use information on molecular structure similarity

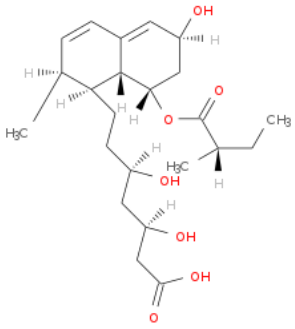
- Molecularly similar compounds have similar properties and biological activities (Johnson and Maggiora, 1990)
- Identify a drug candidates *future impact* based on its similarity to future drug-candidates

Tanimoto Examples: Cholesterol Reducing Drugs

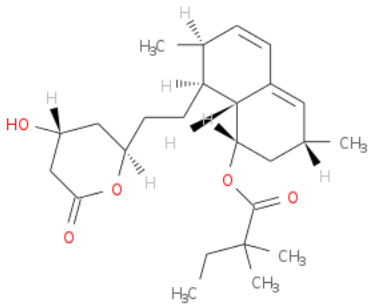
Lovastatin



Pravastatin



Simvastatin



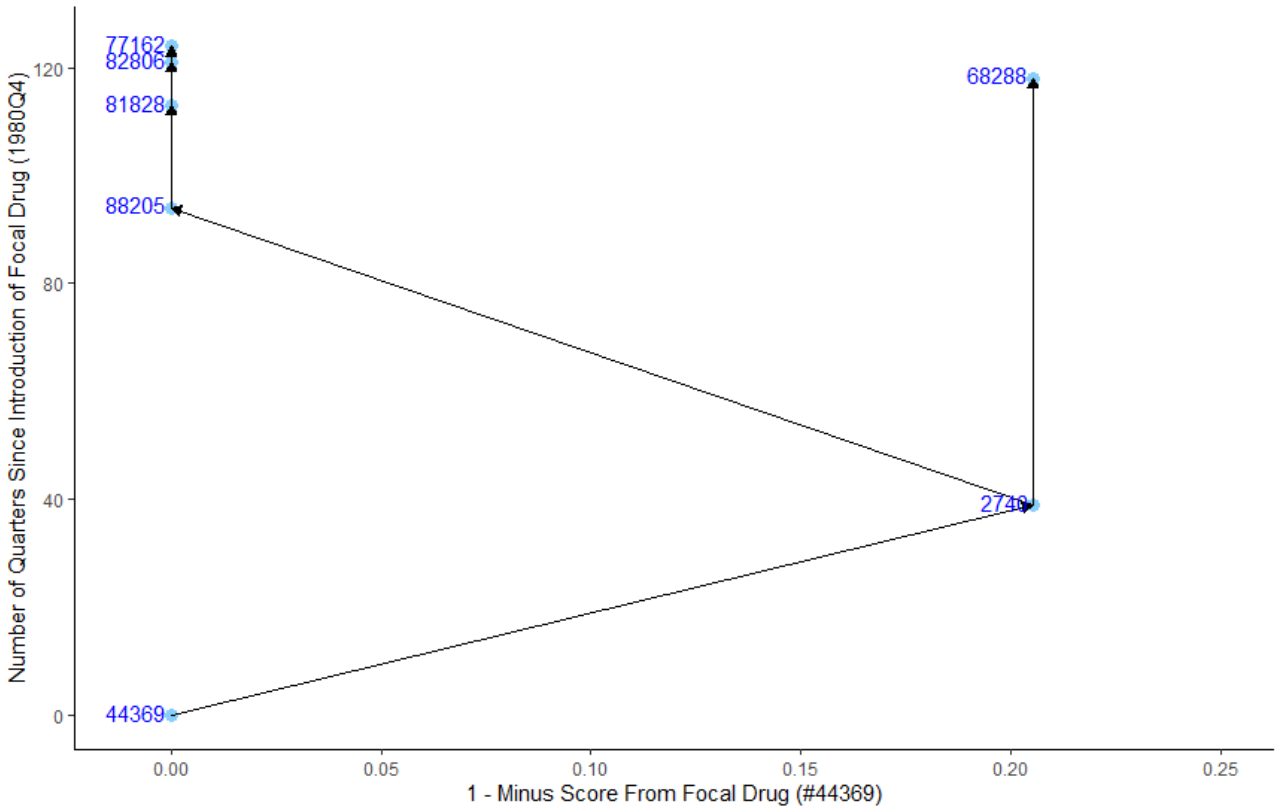
Timing:

1. Lovastatin is 1st FDA approved statin (Sep 1987)
2. Pravastatin is 2nd (Oct 1991): not very similar to Lovastatin (similarity: 0.61).
3. Simvastatin is 3rd (Dec 1991): is similar to Lovastatin (similarity: 0.82) but not very similar to Pravastatin (similarity: 0.52).

Summary: Simvastatin follows on Lovastatin (based on a threshold similarity ≥ 0.75)

Crediting Follow-On Innovation

- Proxy for chain of inspiration. Both novel and derivative compounds can inspire subsequent innovation



- Focal drug is Cefotaxime, an important antibiotic used for multiple infections, developed originally by Aventis. The first follow-on (2740) is Cefpodoxime, a similar antibiotic first developed at Sankyo. More recent follow-ons include a combo antibiotic using Cefotamine by a Chinese company.

Ex. Quiet Failure Sparks Years of Follow-On Investment

Etacstil:

CCC(=C(C1=CC=CC=C1)C2=CC=C(C=C2)C=CC(=O)O)C3=CC=CC=C3

- Selective estrogen receptor degrader (SERD) for estrogen receptor-positive breast cancer
- Developed in 90s by Duke / Glaxo / Dupont
- Abandoned by Dupont for non-scientific corporate reasons
- Followed on by structurally similar (> 0.8 score)
  1. Glaxo's GSK-232802, developed in the 2000s by Glaxo (last active in PII 2009)
  2. Early stage compound developed at Stony Brook in 2009 (no record of clinical trials)
  3. Aragon Pharmaceuticals Brilanestrant (bought by Genetech/Merck for

Forward Credit Allocation

Two Versions

1. **Earliest:** gives full "forward credit" to earliest developed drug with similarity $>= 0.75$
2. **Timing:** gives partial "forward credit" to drugs based on how early the focal drug was within the follow-on's set of similar ($>= 0.75$) predecessors
   - Credit for a given follow-on must sum to 1
   - $PCtimng = (N - Rank + 1) \times \frac{1}{\frac{N^2+N}{2}}$
     - N=number of drugs $>= 0.75$ similar
     - Rank=order of entry within the set similar drugs N
   - For the purposes of this talk we focus on the latter

Data: Sources and Measurement

- Cortellis: Drug Characteristics and development dates
- ChemMine: Chemical Similarity
- IMS: Drug Revenue
- Drug Revenue drug fixed effect from a regression of annual revenue on cohort and time FE $\rightarrow$ apples-to-apples comparison of commercial "success"

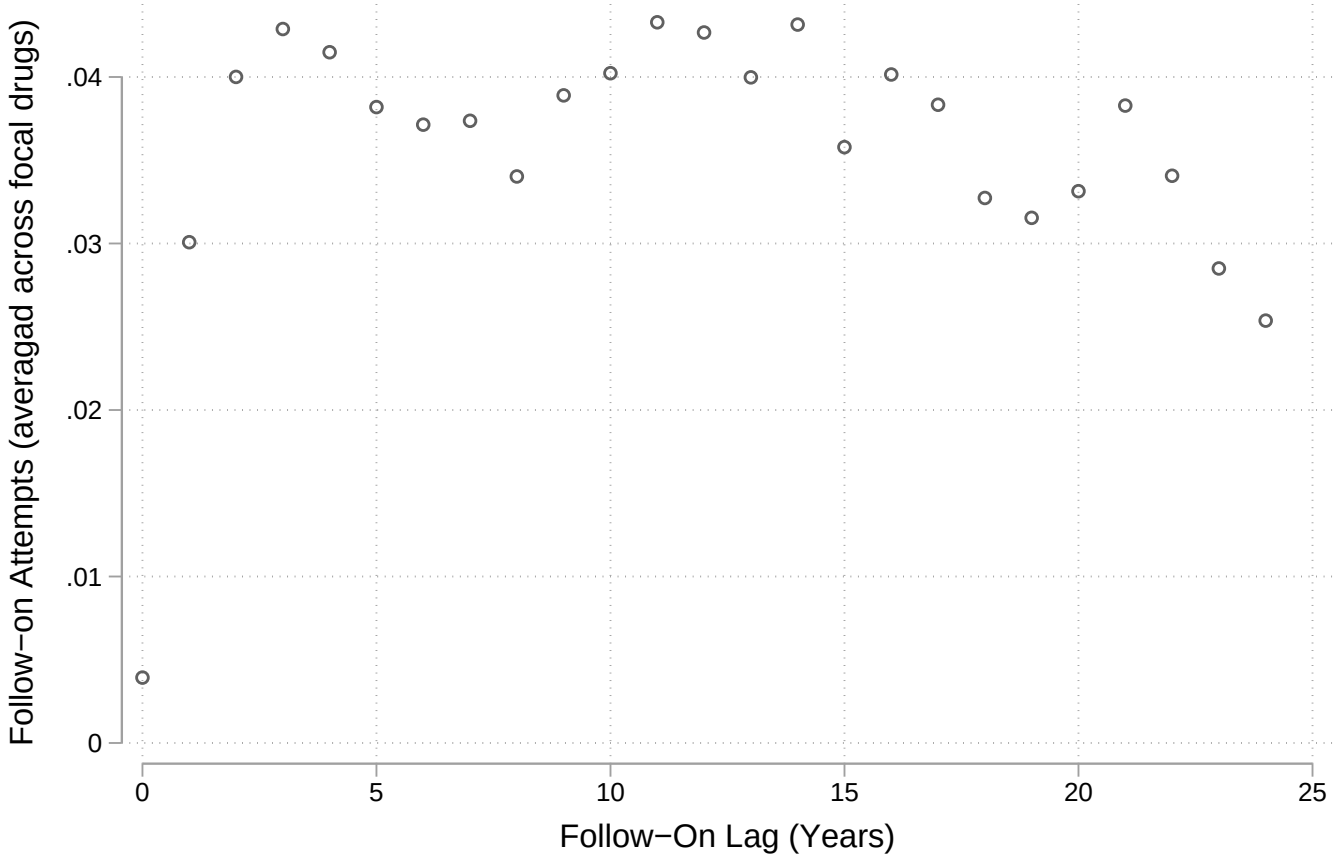
$$\log(\text{Revenue}_{i,t}) = \text{Drug}_i + \text{Calendar Year}_t + \text{Launch Year}_i + e_{i,t}$$

Dealing with Selection and Forward Truncation

- Cortellis has a much more comprehensive coverage of drugs that enter Phase 1 Clinical Trials than drugs still in discovery mode.
  - Drugs in discovery mode largely self-reported
  - **Our approach:** restrict sample to drugs that complete Phase 1 Clinical Trials; treat Phase 1 date as entry date for focal drug
- An inherent difficulty in measuring forward impact is data truncation:
  - A drug developed in 2010 will mechanically have fewer follow-ons than a drug developed in 1990.
  - **Our approach:** Scale number of follow-on attempts by number of years since focal drug completed P1 trials.
  - Implicit assumption is that number of follow-on attempts per year roughly constant as drugs age.

Cumulative follow-on attempts scale linearly with time

Figure: mean number of follow on attempts per year since focal drug completes P1 trials.

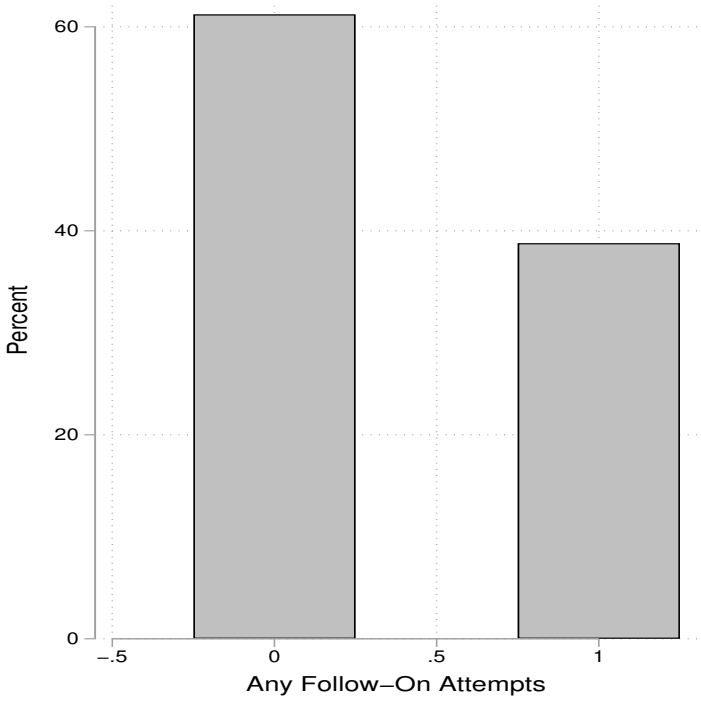


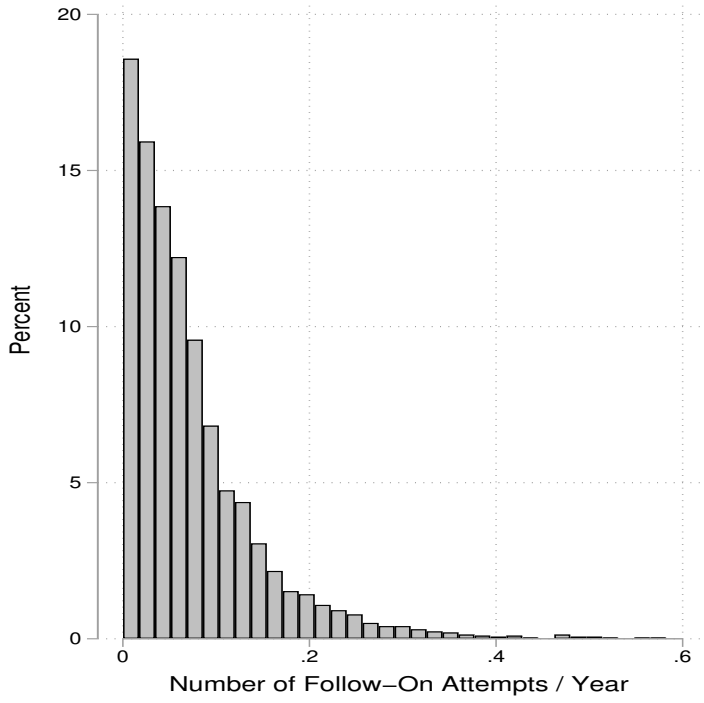
Measuring spillovers

In measuring spillovers, we focus both on the extensive as well as the intensive margin

- Likelihood of follow-on attempts
- Likelihood of success (generate positive revenue)
- Distribution of revenue of follow-on attempts

Distribution of Follow-on Attempts

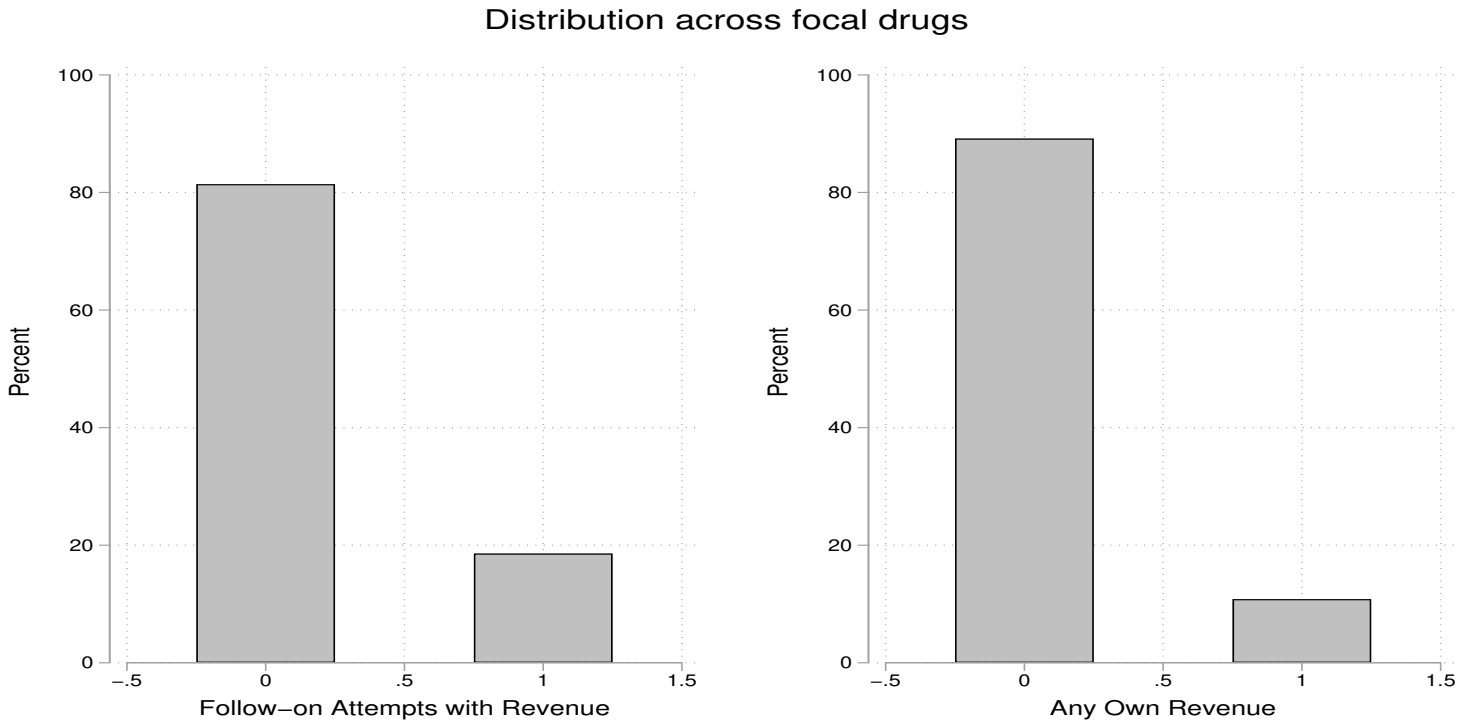




Distribution of follow on attempts is highly skewed:

- Approximately 2/3 of the drugs in our sample generate no follow-on attempts
- Within the remaining 1/3, distribution of follow-on attempts is highly skewed

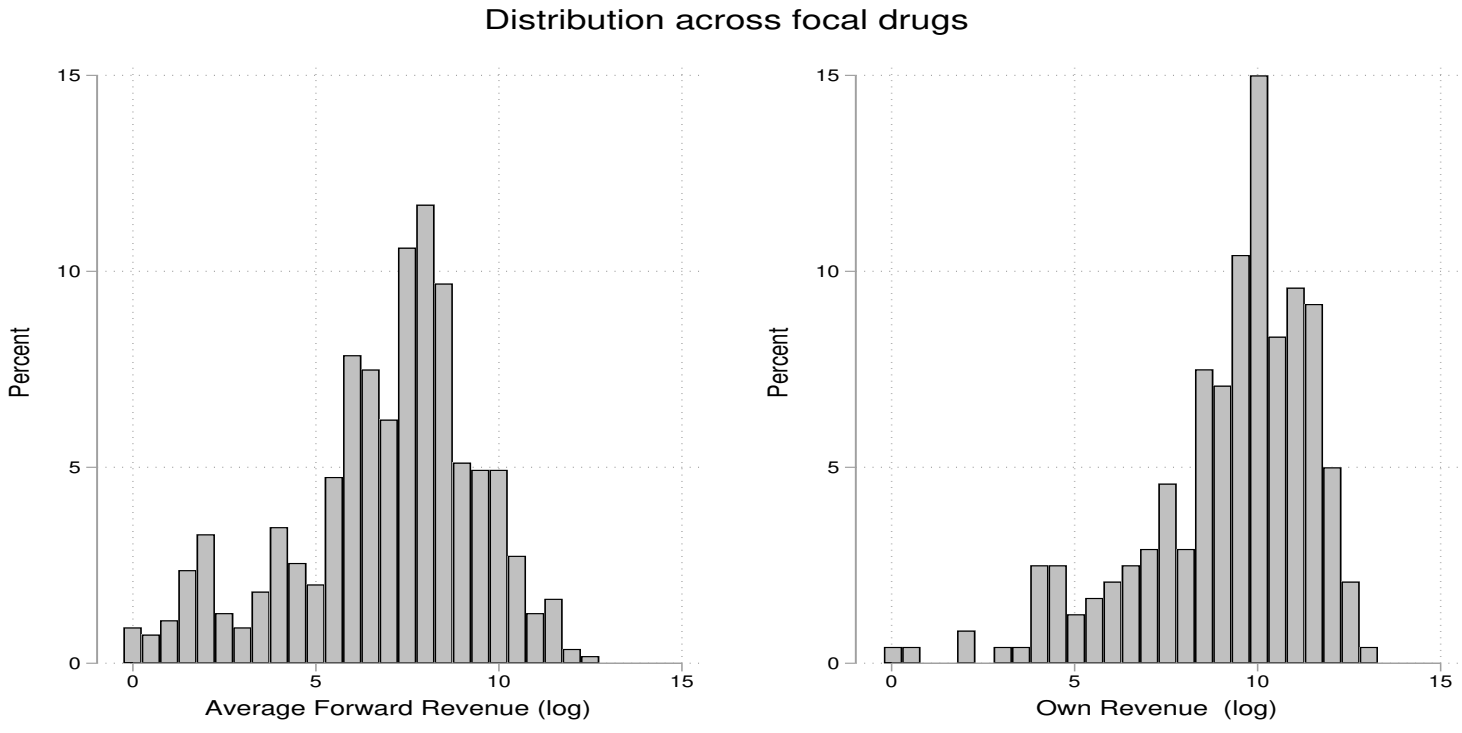
Most attempts are unsuccessful



Small fraction of forward attempts successful in our sample

- Approximately 1/5 of the follow-on attempts generate revenue
- Which is higher than the likelihood that the focal drug has revenue (cond on P1)

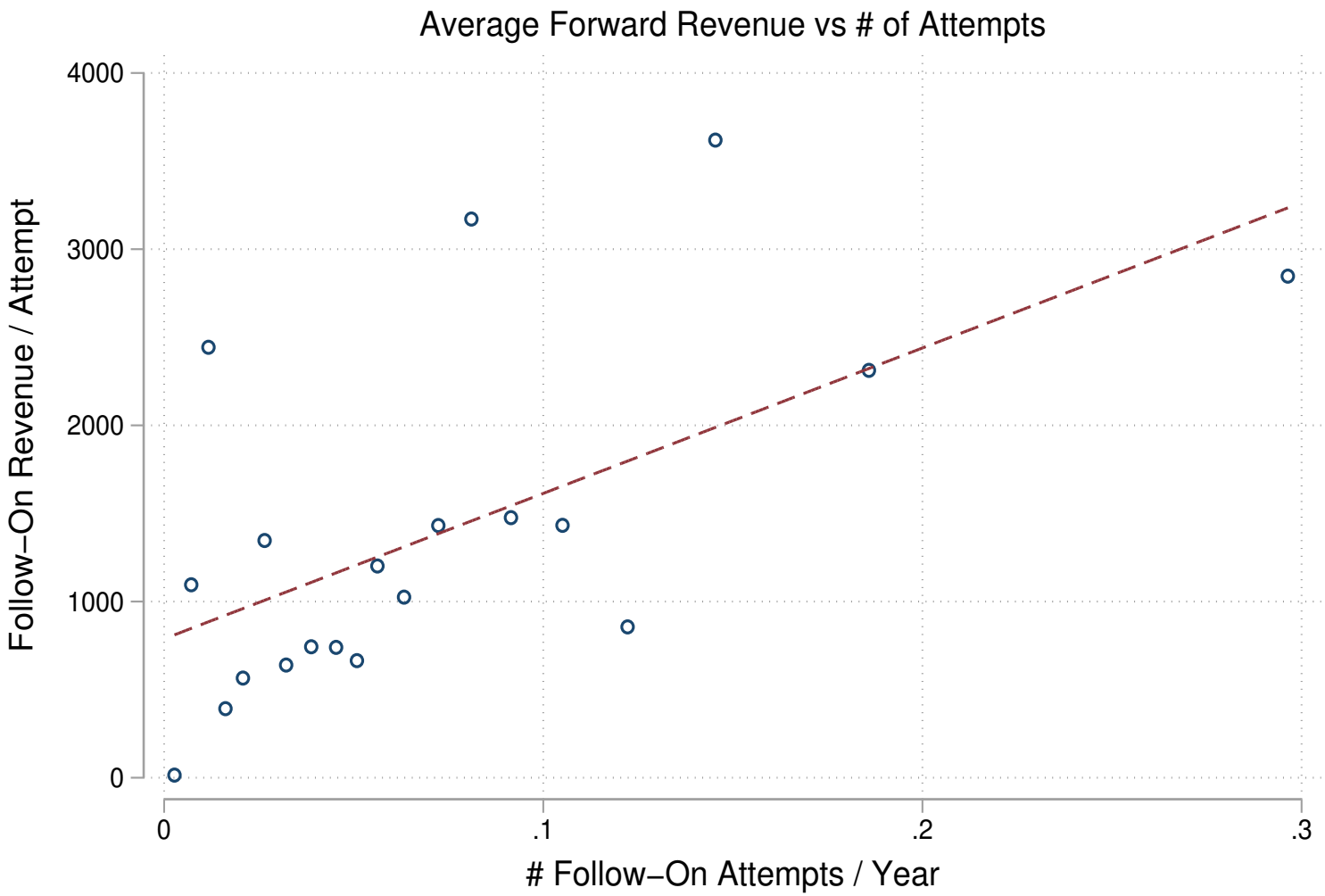
Considerable dispersion in revenue even among successful attempts



Considerable dispersion in average revenue of follow-on attempts

- Dispersion similar, though mean appears lower

Average forward revenue is increasing in the number of attempts

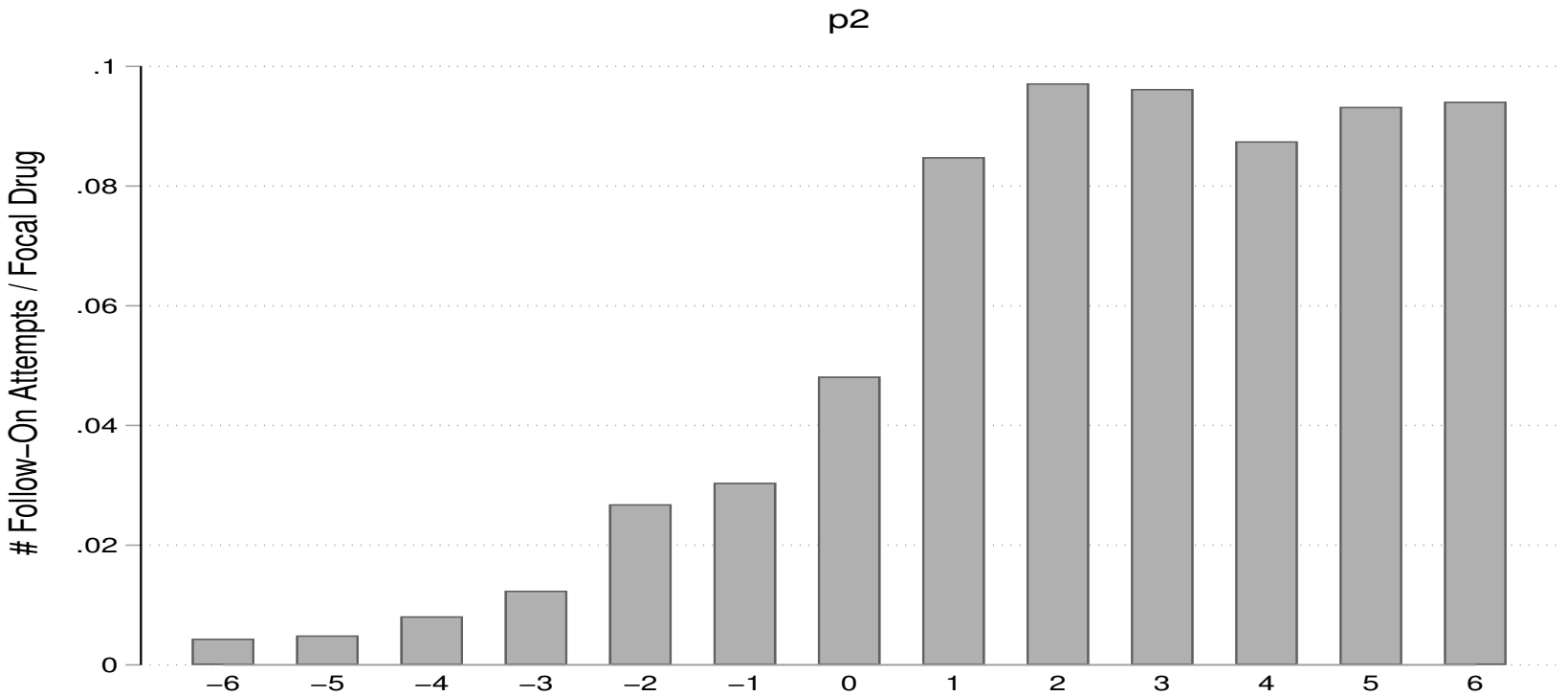


What explains this heterogeneity?

Does the distribution of future spillovers vary with....

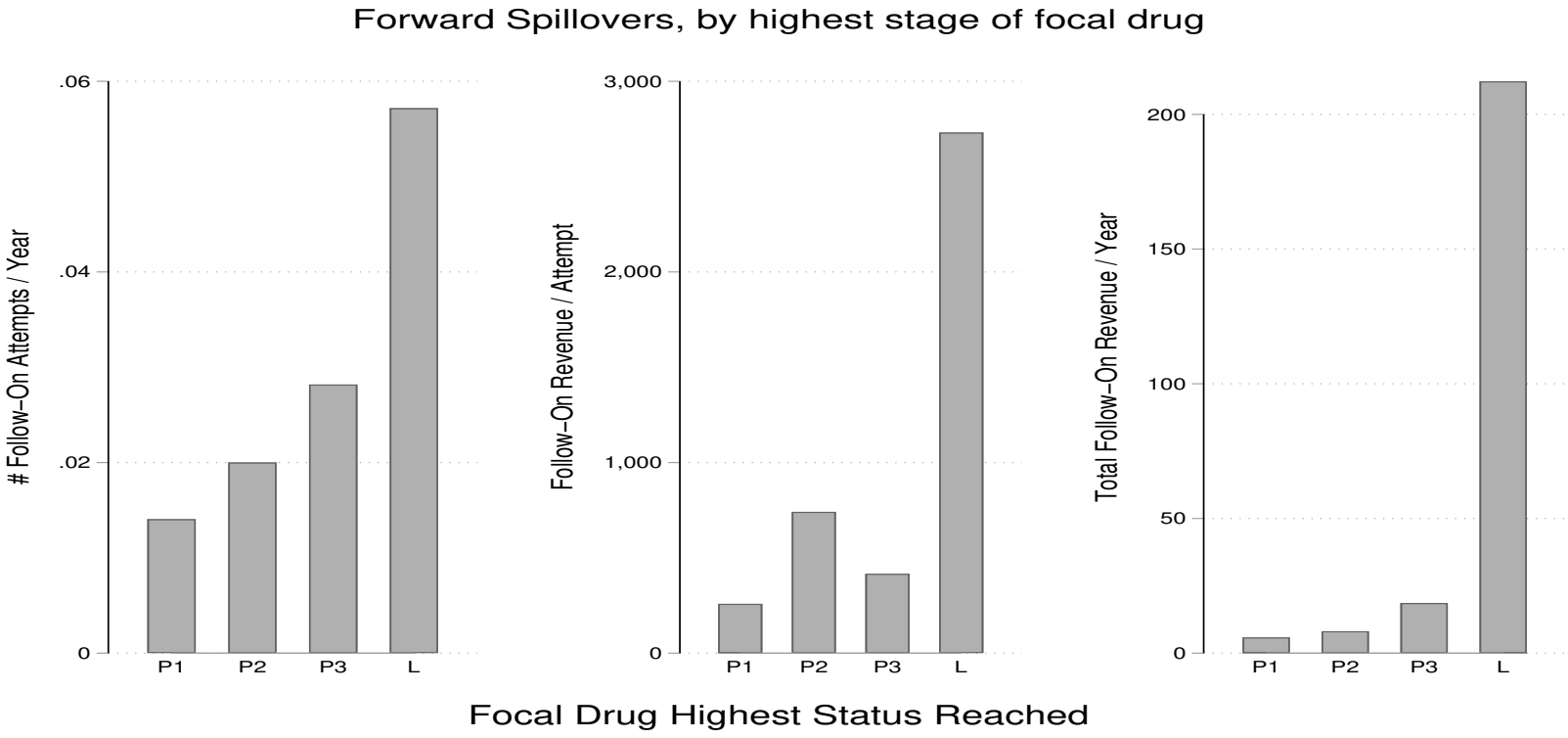
- The stage of the focal drug?
- The (eventual) success of the focal drug?
- The novelty of the focal drug candidate?

Follow-on entry peaks right after focal drug milestones (Phase 2 Entry)

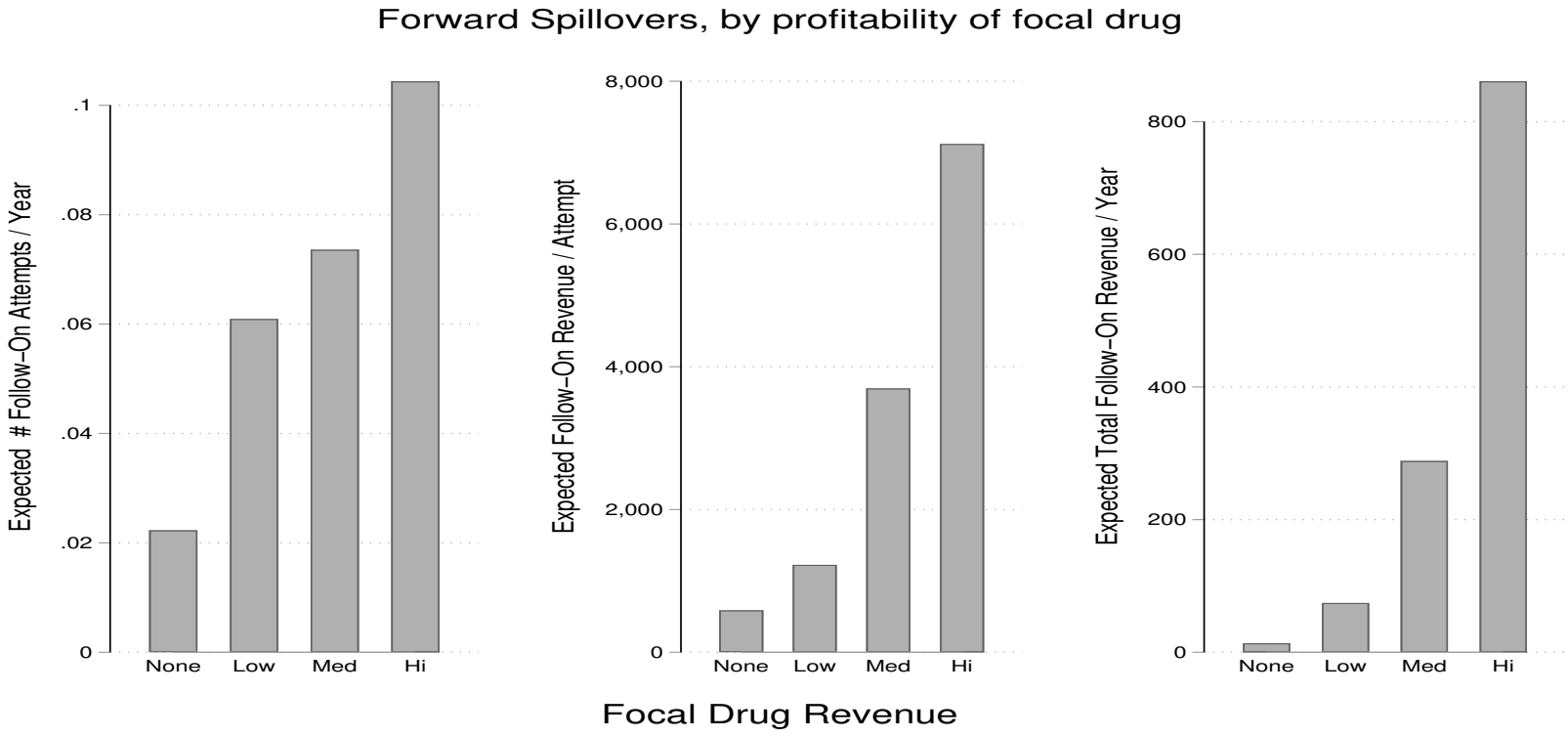


- Similar for P3, more gradual for approval milestone ▸ P2 P3 Approval
- Average Revenue per attempt also jumps after milestones...but returns are skewed... ▸ Revenue

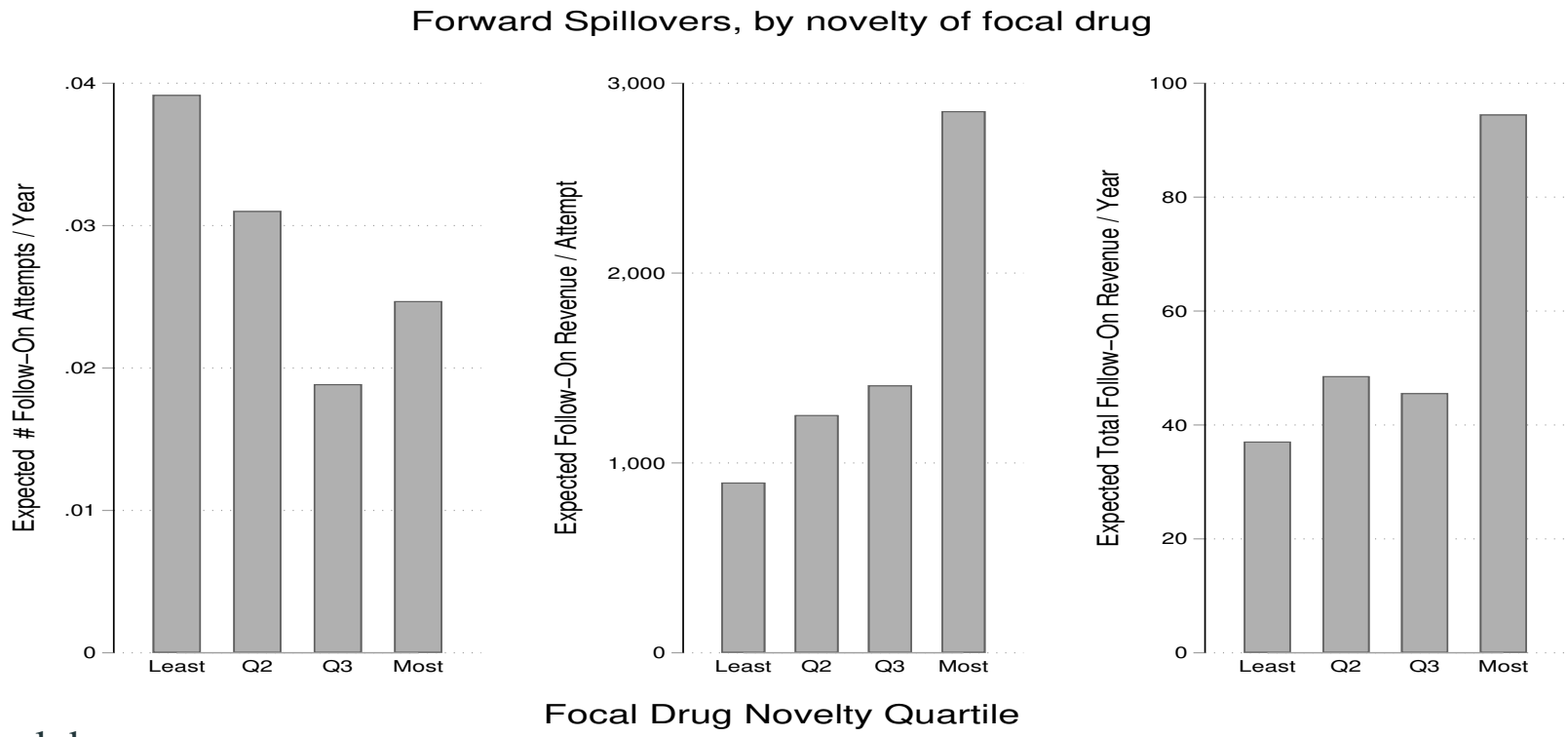
Successful drugs generate more positive spillovers



Successful drugs generate more positive spillovers



Novel drugs generate more positive spillovers



Novel drugs:

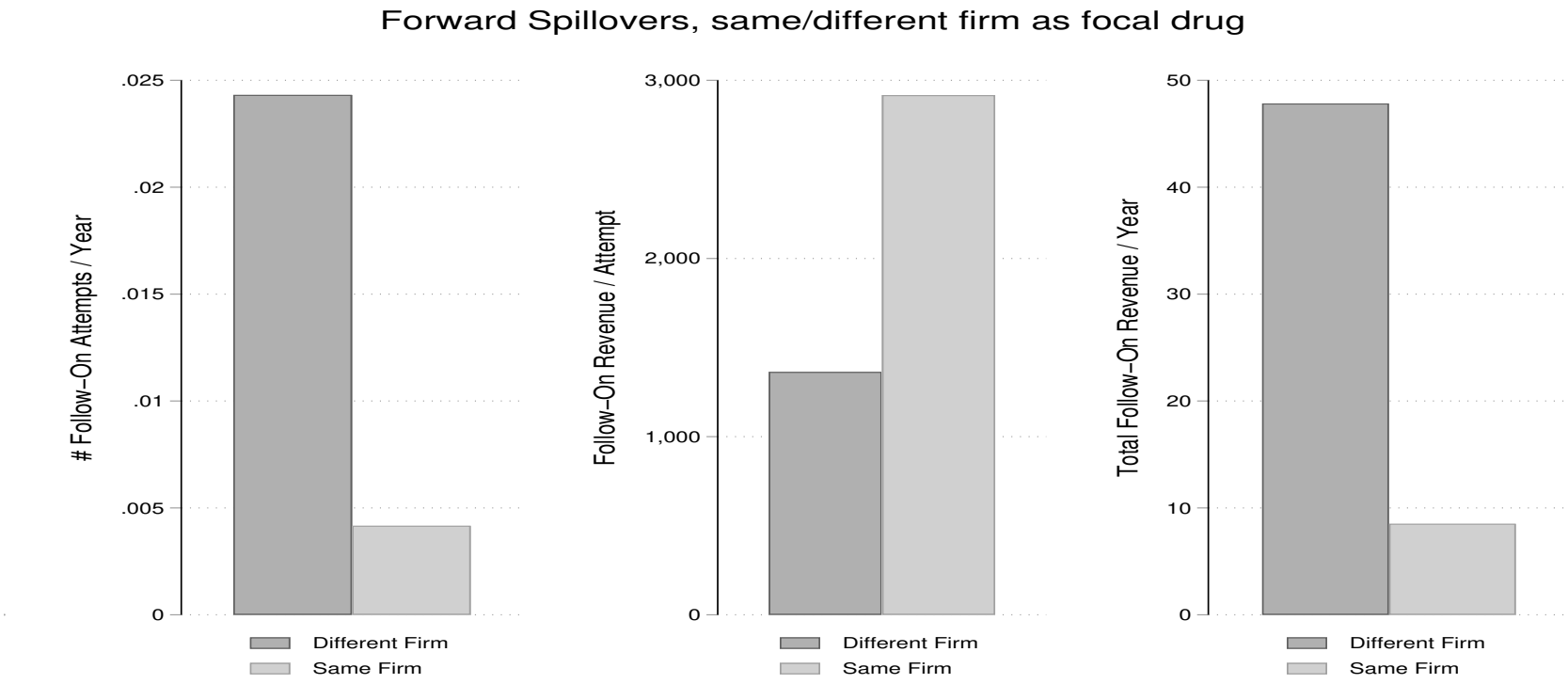
- generate fewer follow-on attempts,
- ...but each attempt is of higher quality.
- Net effect: Novel drugs generate more forward spillovers

Who benefits?

Are these positive spillovers ...

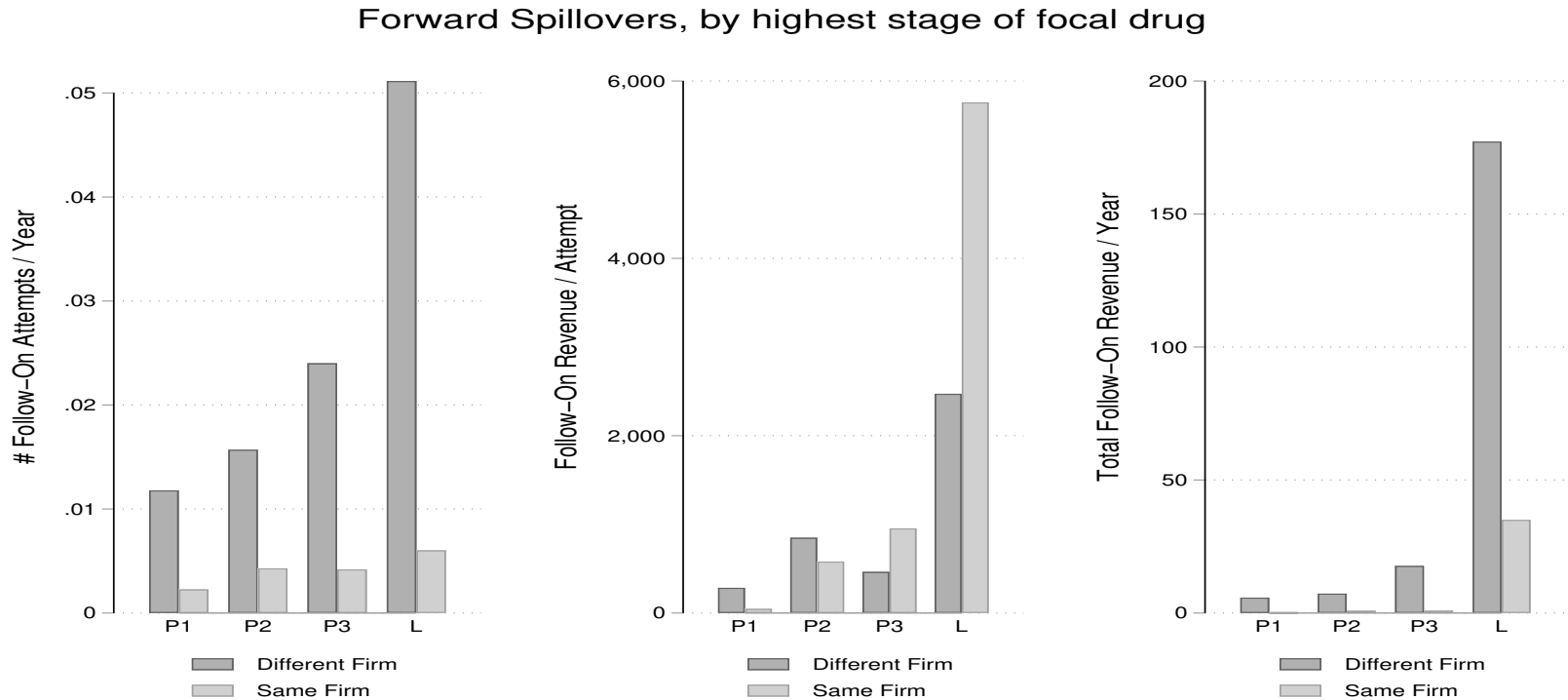
- captured by the same firm that developed the focal drug?
  - i.e. are part of the **private** economic value of the drug
- or are they captured by competing firms?
  - i.e. are part of the **social** value of the drug

Successful drugs generate more positive spillovers

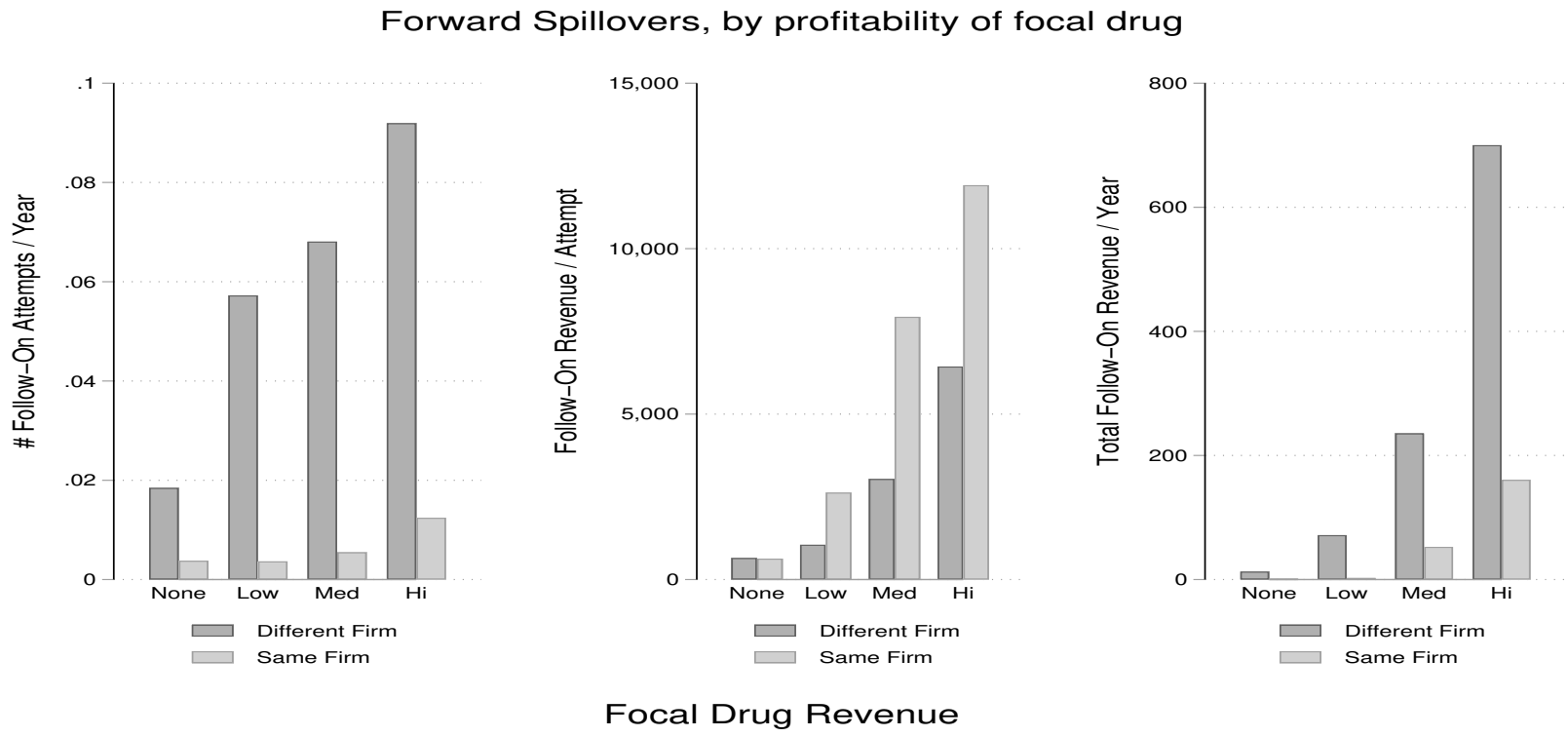


- Most follow-on attempts by different firm...
- ...though follow-on developed by the same firm are on average better.
- Net effect: On average, other firms capture most spillovers.

Pattern does not depend on the success of the focal drug

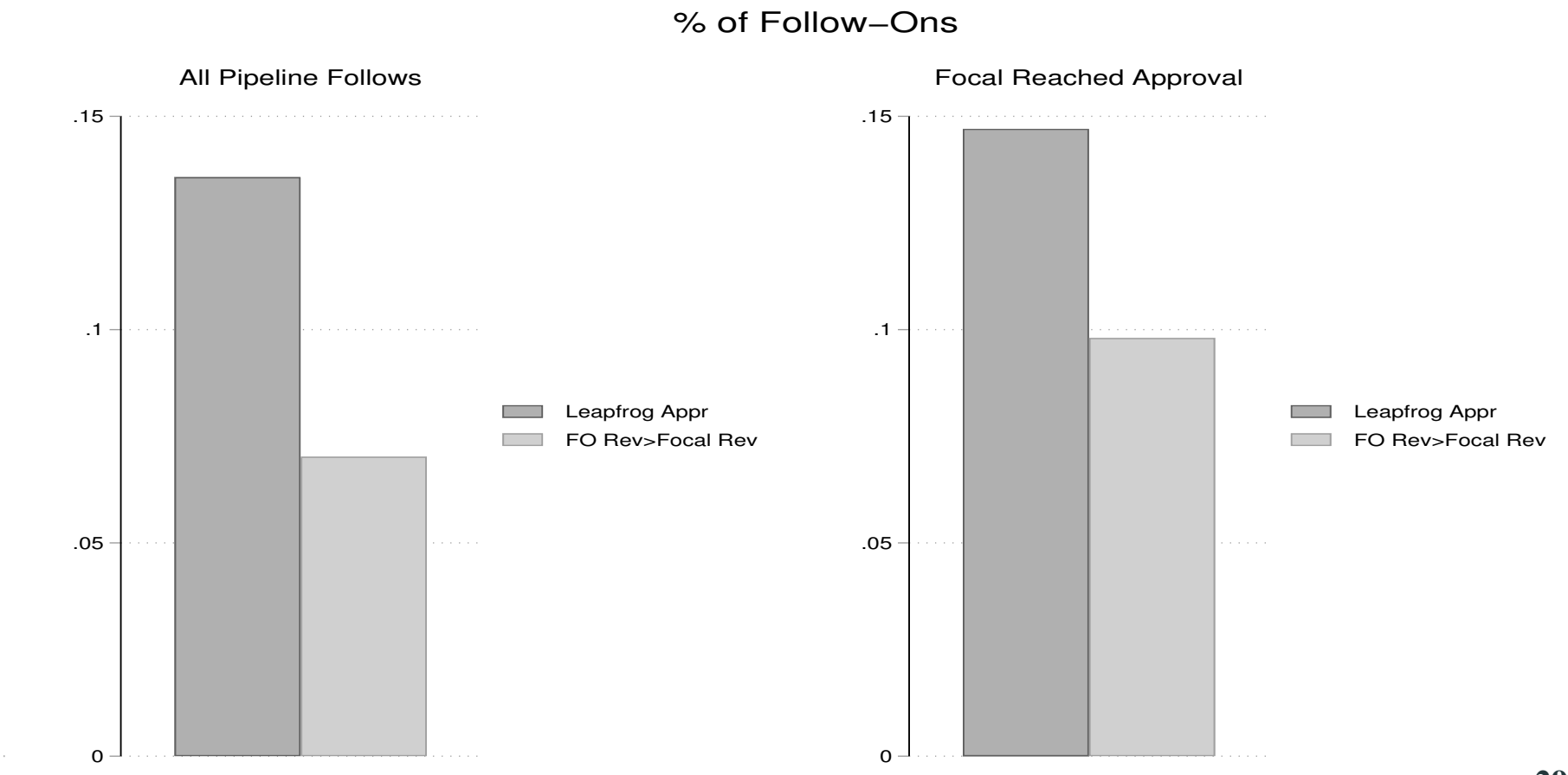


Pattern does not depend on the success of the focal drug (cont)



“Leap-frogging” is Rare

Few follow-ons beat the focal drug to approval or surpass the focal drug’s commercial success



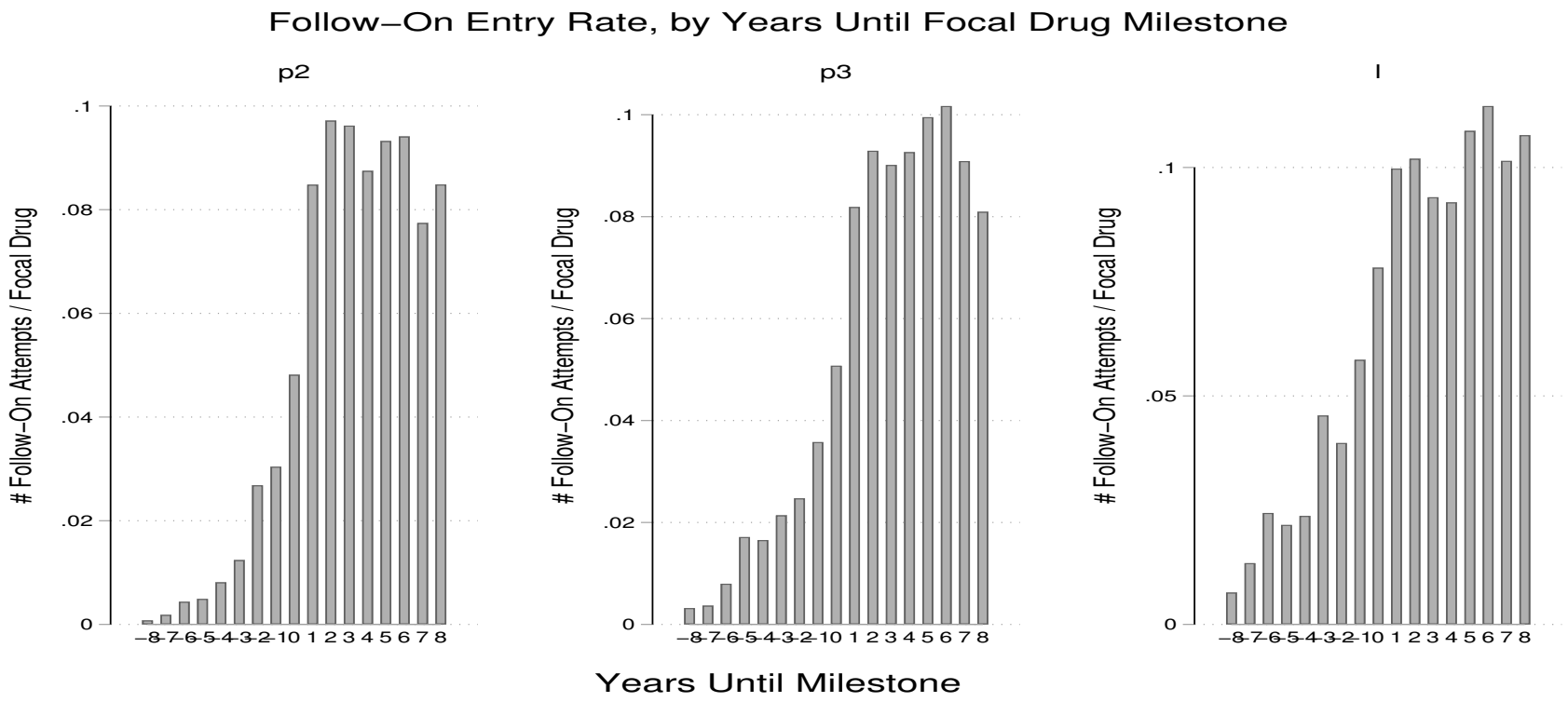
Summary and Next Steps

- Developed a new measure of forward spillovers
  - More successful or more novel drugs generate higher spillovers
  - Majority of spillovers captured by competitors...
    - ...though own firms have an advantage
  - Innovators generally enjoy substantial head start

- Next steps:
  - Interpret these patterns through the lens of a model of competition
  - How flow of follow-on effort shifts based on competition and information shocks

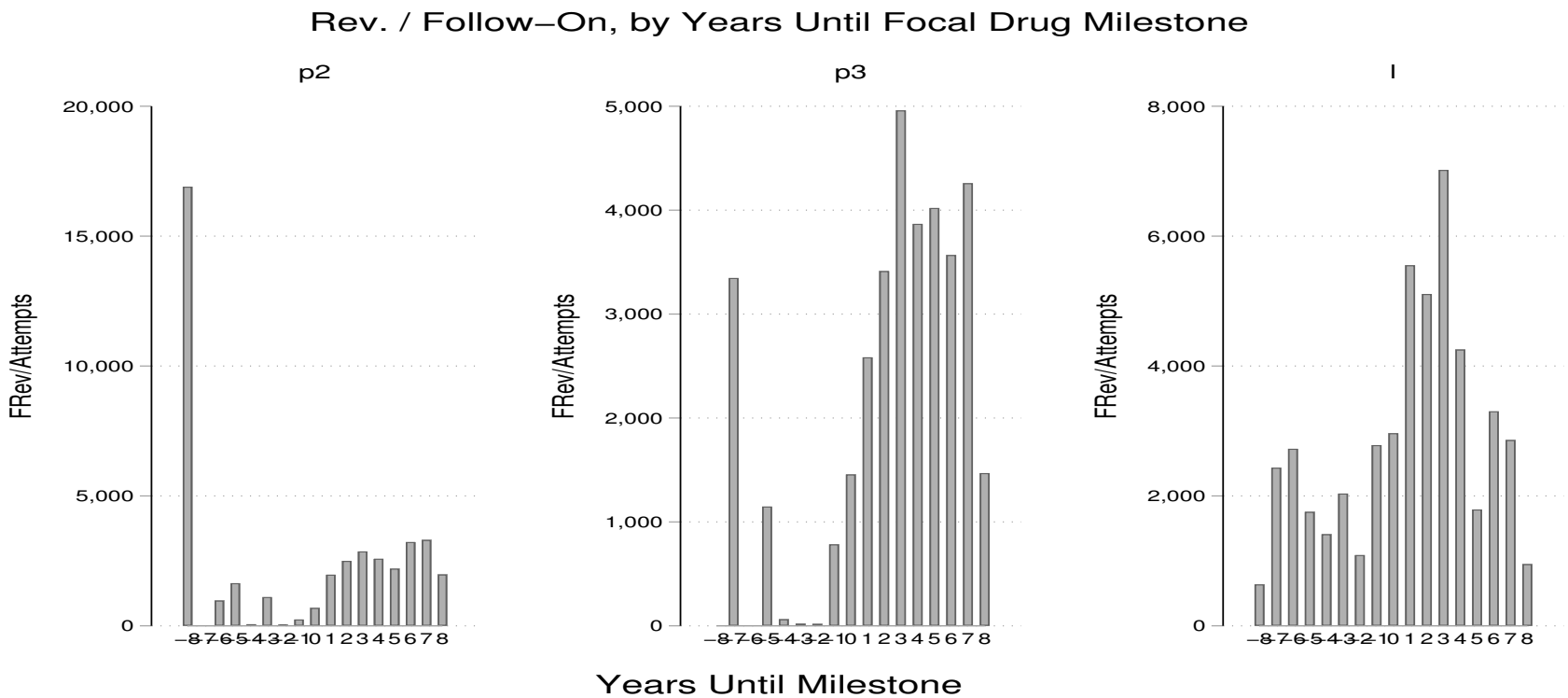
EXTRAS

Follow-on entry peaks right after focal drug milestones



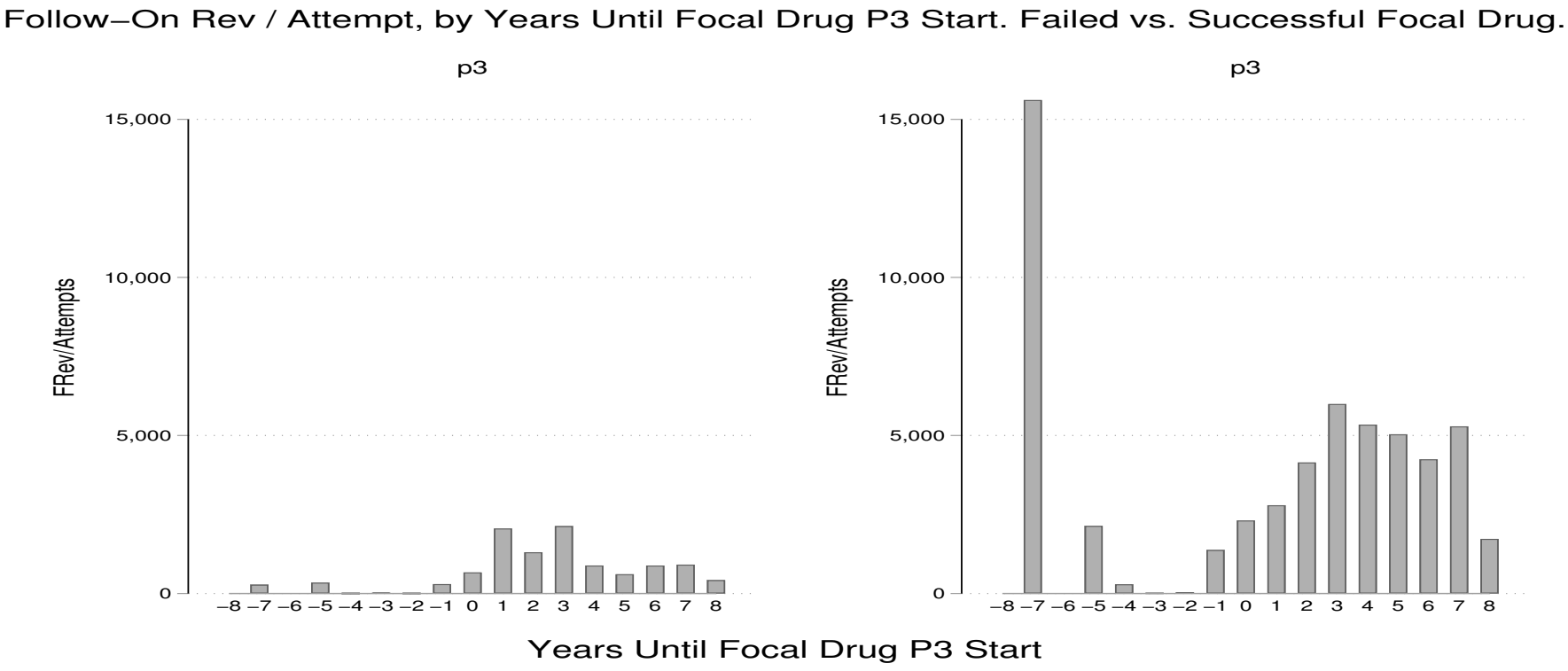
▸ BACK

Follow-on entry peaks right after focal drug milestones)



BACK

Follow-on entry peaks right after focal drug milestones)



BACK

- Better to follow a winner, but not much benefit (on avg.) of following pre-P3 milestone