Title: Do We Have the Right Incentives for Rare Disease Biopharmaceutical Innovation? A Study on the Trends in Venture Capital Investment for Rare versus Non-Rare Disease Innovation

Authors: Hanke Zheng, PhD[1], Julie A. Patterson, PharmD, PhD[1], Frank S. David, MD, PhD[2], Jonathan D. Campbell, PhD[1]

Affiliation:
[1]National Pharmaceutical Council, Washington, D.C.
[2] Pharmagellan LLC, Milton, MA, USA and Department of Biology, Tufts University, Medford, MA, USA

Background: Venture capital (VC) funding supports emerging biopharmaceutical companies and funds that advance preclinical and early phases of new drug development. Throughout the 2000-2010s, investors increased venture capital funding into rare disease treatments, likely reflecting policy initiatives alongside market considerations. Orphan drug approvals more than doubled following this time of increased investment. Despite these recent approvals, 94% of rare diseases still lack an available treatment option. Recent changes and uncertainty in market and policy environments have shifted economic incentives surrounding capital investment in biopharmaceutical innovation. Since 2021, post-COVID macroeconomic pressure, including rising interest rates and inflation, combined with headwinds from government drug pricing policy and FDA regulatory unpredictability, act as barriers to healthcare investment. Although such investment headwinds are relatively well known from 2021-2025, evidence is lacking on how much VC investment has shifted away from rare disease innovation when compared to other biopharmaceutical innovation investment. In order to inform policy discussions on the current U.S. climate around the incentives for innovation in rare disease, this study characterizes VC investment patterns in biopharmaceutical companies primarily focused on rare diseases, compared with other biopharmaceutical companies, from 2018 to 2025.

Methods: We examined trends in completed VC deals and capital raised for biopharmaceutical companies from January 2018 through December 2025. Data was sourced from the PitchBook database, a third-party investment data provider that tracks global investment activities. We identified completed investments categorized as seed, early-stage VC, or late-stage VC for biopharmaceutical companies during the study period. Eligible biopharmaceutical companies were required to have at least one U.S. office and record of at least one interventional clinical trial involving a therapeutic product. Companies were classified based on whether their primary focus is on rare diseases. VC investment deals < $1 million were excluded. We examined the VC investment activity using the number of completed transactions and capital raised. Monetary terms were inflation-adjusted to 2025 USD using the Consumer Price Index. Using linear regression models, we first included year fixed effects to test the variations in VC investment deals and capital raised each year relative to 2018. Additionally, we quantified the overall temporal trends as quarterly percentage change using a log-linear ordinary least square regression. Both models were adjusted for seasonality. Additional models are being explored to directly estimate the relative difference in trends between rare and non-rare disease VC activity.

Results: The analysis included a total of 2,741 biopharmaceutical VC deals completed from January 2018 through December 2025, with 7.2% (n=196) for rare disease companies. The median number of VC investment deals into rare disease companies per quarter was 7 (IQR: 3-8.3), and the median quarterly total capital raised by these firms was $366 (IQR: 226.1-486.1) million. Annual observed rare disease-VC deal count was 48.4% lower in 2025 (n=16) than 2018 (n=31) ($p<0.01$), and total capital raised was approximately $1.8 billion, or 68.6%, lower (2025: $845.2 million; 2018: $2.7 billion; $p<0.01$), suggesting a shift to fewer and smaller-size VC transactions (2025: $52.8 million/deal; 2018: $86.7 million/deal) (**Table 1**). In non-rare disease VC transactions, deal count was 39.2% lower in 2025 (n=233) than 2018 (n=367; $p<0.01$), and the capital raised was 12% lower

(2025: $14.6 billion; 2018: $16.6 billion; $p > 0.05$), suggesting a shift to fewer but larger-size transactions (2025: $65.5 million/deal; 2018: $45.2 million/deal). Log-linear regression indicated statistically significant downward trends in VC investment from 2018 through 2025, with estimated average quarterly declines in deal counts of 4.5% among rare disease-focused companies versus 2.3% among non-rare disease-focused companies (both $p<0.01$). Similarly, capital raised declined by an estimated 5.2% per quarter among rare disease-focused companies versus 1.4% among non-rare disease-focused companies (both $p<0.01$).

Conclusions: Our findings suggest declines in biopharmaceutical VC deals and capital raised in rare disease and non-rare disease companies from 2018 through 2025, with disproportionately greater percentage reductions in rare disease investment. Amid the changing policy environment and market dynamics, the evidence suggests increasing investor risk aversion to rare disease VC transactions, raising questions about whether current incentives are sufficient to sustain and advance treatment innovation.

Acknowledgement: This research received no external funding. HZ, JP, and JC are employees of the National Pharmaceutical Council. FD is a paid advisor to NPC. He earns additional consulting income from numerous parties in the biopharmaceutical industry (incl. manufacturers, drug developers, investors, and advocacy organizations) through the advisory firm he leads, Pharmagellan. His wife is employed by a biotechnology company, from which she receives cash, equity, and options.

Figure 1. Relative percentage changes between 2025 and 2018 in biopharmaceutical venture capital investment.

	Rare disease companies	Non-rare disease companies
Deal count	-48.4%*	-39.3%*
Capital raised (USD, million)	-68.6%*	-12.0%
Average capital per deal (USD, million)	-39.1%	44.9%

*Notes: * $p<0.01$.*