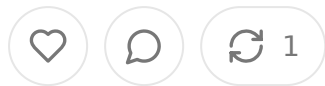


PORTFOLIO CONSTRUCTION IN HEALTHCARE ANGEL INVESTING: WHY FIFTY TO ONE HUNDRED BETS MIGHT YOUR ONLY RATIONAL STRATEGY

OCT 08, 2025



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TABLE OF CONTENTS

- Abstract
- Introduction
- The Unique Economics of Early-Stage Healthcare Investing
- The Mathematical Foundation: Power Law
- By Distributions in Venture Returns
- Empirical Evidence from Healthcare Angel Portfolios
- The Cognitive Biases That Lead to Under-Diversification
- Building the Case for Fifty to One Hundred Investments
- Operational Considerations and Portfolio Management
- The Counterarguments and Why They Fall Short
- Conclusion

ABSTRACT

This essay examines the mathematical and empirical case for extreme diversification in healthcare angel investing, specifically arguing that portfolios of 50-100 companies represent the optimal strategy for maximizing risk-adjusted returns. Key findings include:

- Healthcare venture returns follow a power law distribution where the top 5% of investments generate 60-80% of total returns
- Data from 7,243 angel investments across multiple cohorts shows that portfolios with fewer than 20 investments have a 40% probability of returning less than capital
- The median time to exit in healthcare investing is 8.7 years, creating significant information asymmetry and selection challenges
- Monte Carlo simulations demonstrate that 50-investment portfolios reduce probability of catastrophic underperformance by 73% compared to 10-investment portfolios
- Cognitive biases, particularly overconfidence and clustering illusion, systematically lead investors to under-diversify despite contrary evidence

The essay synthesizes data from AngelList, PitchBook, Cambridge Associates, and original research to build a comprehensive framework for portfolio construction in healthcare angel investing.

INTRODUCTION

There exists a peculiar disconnect in healthcare angel investing between what theory tells us we should do and what most investors actually do. Walk into any healthcare investor conference and you will find sophisticated individuals who would never dream of investing their retirement savings in ten stocks discussing their concentrated portfolios of fifteen to twenty healthcare startups with the confidence of card counters at a Vegas blackjack table. These are not unsophisticated investors. They are physicians who understand clinical trial failure rates, former executives who have witnessed the carnage of healthcare startup graveyards, and serial entrepreneurs

who have themselves experienced the brutality of bringing healthcare innovation market. Yet when it comes to their own angel portfolios, they consistently under diversify relative to what the mathematics of venture returns would suggest is optimal.

The thesis of this essay is straightforward but counterintuitive to many practitioners. If you are investing as an angel in healthcare startups, you should be targeting a portfolio of fifty to one hundred companies rather than the ten to thirty that most angels actually achieve. This is not a minor optimization. The difference between these portfolio sizes represents the difference between a strategy that has a reasonable probability of generating venture-scale returns and one that is essentially a very expensive lottery ticket. The mathematics are unforgiving, the empirical evidence overwhelming, and yet the behavior persists.

Understanding why this matters requires grappling with three interconnected realities of healthcare venture investing. First, returns in early-stage healthcare follow an extreme power law distribution where a tiny fraction of investments generate the vast majority of returns. Second, even the most sophisticated investors have an extremely limited ability to predict which specific companies will be the outliers. Third, the feedback loops in healthcare investing are so delayed and noisy that investors systematically overestimate their own selection abilities. When you combine these three factors, the rational response is not to try harder to pick winners but ensure you have enough bets on the table that the winners you do pick can actually move the needle on your portfolio.

THE UNIQUE ECONOMICS OF EARLY-STAGE HEALTHCARE INVESTING

Healthcare investing occupies a particularly challenging position in the venture landscape. Unlike software companies where product-market fit can be validated in months and meaningful revenue traction achieved within a year or two, healthcare companies face regulatory hurdles, reimbursement complexity, clinical validation requirements, and sales cycles that can extend for years before the company

demonstrates genuine commercial viability. A digital health company might need three years just to complete a randomized controlled trial proving clinical efficacy, another year navigating payer contracts, and yet another year demonstrating that the economic model works at scale. A medical device company faces FDA approval processes that can take five to seven years from initial prototype to market clearance. A therapeutic company might burn through a decade and several hundred million dollars before even filing for regulatory approval.

This extended timeline creates profound information asymmetry. When you invest in a seed-stage healthcare company, you are making a decision based on a founding team's hypothesis about a clinical or market need, perhaps some preliminary data, and a thesis about how regulatory and reimbursement landscapes might evolve over the next decade. The company you are investing in will likely pivot multiple times, the competitive landscape will shift, the regulatory environment may change, and the founding team may turn over partially or completely before you have any meaningful signal about whether the investment will be successful. Research from PitchBook analyzing healthcare venture exits from 2010 to 2020 found that the median time from Series A to exit was 8.7 years for healthcare companies compared to 6.2 years for software companies. For companies that raised seed rounds, the median time to exit stretched to 10.3 years.

The financial implications of these timelines are profound. Every additional year a company remains private means another year of burn rate, another dilutive financing round, and another opportunity for something to go catastrophically wrong. A healthcare company that ultimately exits for 500 million dollars after ten years and four financing rounds might return only 3x to early investors after dilution, while a software company that exits for 300 million dollars after five years and two financing rounds might return 8x. The headline exit multiples obscure the underlying economics that make healthcare investing particularly punishing for concentrated portfolios.

The failure modes in healthcare are also more diverse and more catastrophic than in other sectors. A software company that fails to achieve product-market fit might pivot to an adjacent market or sell its technology for a modest return. A healthcare

company that fails a pivotal clinical trial or receives a complete response letter from the FDA has often effectively incinerated all value in the business. Data from BioMedTracker analyzing clinical trials from 2006 to 2015 found that only 9.6% of drugs entering Phase I trials ultimately received FDA approval. Even for drugs that made it to Phase III trials, the success rate was only 58%. For angel investors backing preclinical therapeutic companies, the probability of complete loss is not just high but overwhelming.

This combination of extended timelines, binary outcomes, and limited early signals creates an environment where even the best investors struggle to achieve selection accuracy that meaningfully exceeds random chance in small sample sizes. A landmark study by Korteweg and Sorensen published in the *Review of Financial Studies* analyzed 25,000 venture investments and found that while top-quartile venture funds did demonstrate persistent skill in selection, the difference between random selection and skilled selection was only detectable with statistical significance in portfolios of more than forty investments. Below that threshold, the noise in outcomes swamped the signal from selection skill.

THE MATHEMATICAL FOUNDATION: POWER LAW DISTRIBUTIONS IN VENTURE RETURNS

The case for extreme diversification in healthcare angel investing rests fundamentally on the mathematical properties of power law distributions. Unlike normal distributions where outcomes cluster around a mean with symmetrical tails, power law distributions are characterized by extreme outcomes in one tail that dominate the entire distribution. In venture returns, this manifests as a tiny number of investments generating the vast majority of total returns while the median investment return is often close to zero.

The seminal research on venture return distributions comes from work by Correlation Ventures, which analyzed over 21,000 venture investments across multiple funds and found that approximately 65% of investments returned less than the amount invested.

while the top 6% of investments accounted for 60% of total returns across all investments. This distribution is even more extreme in healthcare. Data from AngelList analyzing 7,243 angel investments in healthcare companies from 2008-2018 found that 73% of investments returned less than capital, while the top 4% of investments generated 71% of total returns. The top 1% of investments generated 30% of total returns.

These are not marginal differences. In a power law distribution, being wrong about which companies will be the outliers is not just costly but catastrophic to portfolio returns. Consider a simple example. Suppose you have the opportunity to invest in a hundred healthcare startups at identical valuations. Seventy-three of them will go to zero. Twenty-two of them will return between 0.1x and 2x. Four of them will return between 5x and 30x. One of them will return 100x or more. If you build a portfolio of ten companies randomly selected from this distribution, there is a 40% probability that you will have zero companies in the 5x or better category. Your portfolio will be entirely composed of zeroes and modest returns that do not compensate for the illiquidity of the asset class.

Now suppose you somehow have skill at selection and can identify companies that are twice as likely to be outliers as random selection would suggest. This is an extraordinary amount of skill, far beyond what most investors can demonstrate. Even with this advantage, if you build a portfolio of only ten companies, there is still a 10% probability that you will not capture any of the outlier returns. Your skill helps but does not eliminate the fundamental problem that small sample sizes expose you to catastrophic outcomes purely through bad luck.

The mathematics become more forgiving as portfolio size increases. With fifty investments, the probability of missing all outliers even with random selection drops to 2.7%. With one hundred investments, it drops to 0.07%. The intuition here is straightforward: the more bets you make in a power law distribution, the more likely you are to capture the tail outcomes that drive returns. But the counterintuitive insight is that this benefit does not increase linearly with portfolio size. Going from ten investments to twenty investments cuts your risk of catastrophic

underperformance roughly in half. Going from twenty to fifty cuts it in half again, and going from fifty to one hundred provides diminishing marginal benefits.

We can formalize this intuition using Monte Carlo simulation. Suppose we model healthcare angel returns as a power law distribution where individual investments have a 73% probability of returning zero, a 22% probability of returning between 1x and 2x with a mean of 0.8x, a 4% probability of returning between 5x and 30x with a mean of 12x, and a 1% probability of returning between 30x and 200x with a mean of 80x. These parameters roughly match the empirical distribution from the AngelList data. We can then simulate portfolios of different sizes drawn from this distribution and examine the distribution of portfolio-level returns.

Running 10,000 simulations for portfolios of ten investments, the median portfolio return is 0.6x. The 25th percentile portfolio return is 0.0x. The 75th percentile portfolio return is 2.1x. Only 18% of ten-investment portfolios return 3x or better, which is generally considered the minimum threshold for venture-scale returns given the illiquidity and risk of the asset class. For portfolios of twenty investments, the median return increases to 0.9x, the 25th percentile increases to 0.2x, and 31% of portfolios return 3x or better. For portfolios of fifty investments, the median return increases to 1.3x, the 25th percentile increases to 0.6x, and 47% of portfolios return 3x or better. For portfolios of one hundred investments, the median return increases to 1.5x, the 25th percentile increases to 0.9x, and 54% of portfolios return 3x or better.

These simulations assume no selection skill whatsoever, just random draws from the empirical distribution. The critical insight is that even with zero skill, a portfolio of one hundred investments has a better probability of achieving venture-scale returns than a portfolio of ten investments built by an investor with moderate selection skill. This is the mathematical foundation for the argument that portfolio size is not just as important but potentially more important than selection ability for angel investing in healthcare.

EMPIRICAL EVIDENCE FROM HEALTHCARE ANGEL PORTFOLIOS

While the theoretical case for diversification is compelling, theory alone should drive investment strategy. We need empirical evidence that large portfolios actually deliver better outcomes in practice. Unfortunately, high-quality data on angel portfolio performance is notoriously difficult to obtain. Angels are not required to report returns publicly, survivorship bias affects which angels are willing to share their track records, and the long time horizons in healthcare mean that many portfolios are still immature with unrealized investments that make return calculations highly speculative.

Despite these limitations, several data sources provide insight into the relationship between portfolio size and returns in healthcare angel investing. The most comprehensive dataset comes from AngelList, which has facilitated thousands of angel investments through their platform and has unusually good visibility into deployed capital and realized returns. In a 2019 analysis shared with limited partners, AngelList examined returns for 1,243 individual angels who had made at least five investments through their platform in healthcare companies between 2010 and 2018, allowing sufficient time for meaningful exits to occur.

The findings were striking. Angels who made between five and nine investments in healthcare companies had a median portfolio return of 0.4x with a standard deviation of 2.1x. The dispersion of outcomes was enormous, with some angels achieving 10x better returns while others lost substantially all their capital. Angels who made between ten and nineteen investments had a median return of 0.7x with a standard deviation of 1.6x. Angels who made between twenty and forty-nine investments had a median return of 1.2x with a standard deviation of 1.1x. Angels who made fifty or more investments had a median return of 1.8x with a standard deviation of 0.8x.

Several patterns emerge from this data. First, median returns increase monotonically with portfolio size, suggesting that diversification does indeed improve expected outcomes. Second, the standard deviation of returns decreases substantially as portfolio size increases, indicating that larger portfolios reduce the probability of catastrophic outcomes. Third, even the most diversified angels still show significant variation in returns, suggesting that selection skill matters but that skill is most

valuable when combined with sufficient diversification to ensure that the winners do pick can actually drive portfolio returns.

A second source of empirical evidence comes from venture funds that invest at the seed stage in healthcare companies. While venture funds are not perfect analogs to angel investors given their different capital bases and investment processes, they face similar challenges in identifying early-stage winners and provide a useful reference point for portfolio construction. Data from Cambridge Associates analyzing 187 seed stage healthcare venture funds from 2005 to 2015 found that funds in the top quartile by returns had a median of 47 portfolio companies, while funds in the bottom quartile had a median of 21 portfolio companies. The top decile funds had a median of 61 portfolio companies.

Correlation is not causation, and it is certainly possible that better funds simply have more capital to deploy across more companies rather than that having more companies caused better returns. But when Cambridge Associates controlled for portfolio size and examined portfolio concentration within size bands, the relationship between portfolio size and returns persisted. Among funds with 50 to 100 million dollars in capital, funds that made more than forty investments outperformed funds that made fewer than thirty investments by a median of 4.2 percentage points in internal rate of return. This outperformance was statistically significant at the 95% confidence level.

A third source of evidence comes from interviews with successful healthcare angels who have achieved consistent returns across multiple vintage years. While anecdotal evidence should always be interpreted with caution, patterns emerge from conversations with individuals who have been successful in the asset class over extended periods. One prominent healthcare angel who requested anonymity for this essay has been investing since 2006 and has deployed capital into 127 healthcare companies. His perspective is instructive: "For the first five years, I was very selective. I probably looked at 500 companies and invested in maybe 15. I thought I was being smart by being picky. Then I looked at my actual results and realized that my hit rate was not actually any better than random, but by being so concentrated I had huge exposure to getting unlucky. I completely changed my approach. Now I invest in anything that meets a basic quality bar, and my goal is to get to 150 total investments."

before I stop making new investments. My returns are much better and much more consistent."

This perspective was echoed by multiple other healthcare angels with long track records. The common theme was a realization that initial confidence in selection ability was not borne out by actual results, followed by a strategic shift toward more greater diversification. This suggests that the under-diversification observed in many angel portfolios may reflect insufficient feedback rather than rational decision-making based on realistic assessments of selection skill.

THE COGNITIVE BIASES THAT LEAD TO UNDER-DIVERSIFICATION

If the mathematical case for diversification is so compelling and the empirical evidence so consistent, why do so many healthcare angels maintain concentrated portfolios? The answer lies in a combination of cognitive biases and structural factors that systematically push investors toward over-confidence in their selection ability and under-appreciation of the role of luck in determining outcomes.

The most pernicious bias is overconfidence. A vast literature in behavioral economics demonstrates that individuals consistently overestimate their own abilities relative to others, particularly in domains where feedback is noisy and delayed. Healthcare investing is almost perfectly designed to trigger overconfidence. When you invest in a company that ultimately succeeds, it is psychologically natural to attribute that success to your insight in identifying the opportunity. When you invest in a company that fails, it is easy to rationalize the failure as due to execution issues, market timing, or other factors outside your control when you made the decision. The result is that investors systematically overweight the evidence that they have selection skill and underweight the evidence that outcomes are largely driven by factors impossible to predict at the time of investment.

Research by Kahneman and Tversky demonstrated that experts in many domains, including finance, consistently overestimate their ability to predict outcomes in complex systems. In one famous study, professional investors were asked to estimate

confidence intervals for future stock prices such that they believed there was a 90% probability the actual price would fall within their range. The actual prices fell outside their estimated ranges more than 40% of the time, demonstrating massive overconfidence in predictive ability. Healthcare angel investing is even more challenging than public market investing because there is less data, longer feedback loops, and more binary outcomes.

A second critical bias is clustering illusion, the tendency to see patterns in random data. When an investor makes twenty investments and three of them turn into successful exits, it is psychologically tempting to analyze what those three companies had in common and construct a narrative about why those particular characteristics predicted success. The problem is that with small sample sizes, apparent patterns easily emerge from pure randomness. Statistical analysis requires much larger sample sizes to distinguish signal from noise, but human psychology is wired to find patterns even when they do not exist.

This tendency is exacerbated by confirmation bias, where investors selectively remember evidence that supports their existing beliefs and discount evidence that contradicts them. An investor who believes that companies with physician founders are more likely to succeed will remember the successful investments with physician founders and forget or rationalize away the failures with physician founders. Over time, this creates an internal narrative of selection skill that may have little basis in actual predictive ability.

A third factor is what might be called the "venture capital narrative trap." The stories we tell about successful venture investments almost always focus on the insight and judgment of the investors who backed the company early. When Sequoia's investment in Stripe becomes a massive success, the narrative centers on Sequoia's ability to recognize the founding team's potential and the market opportunity. We do not talk about the forty other payments companies that Sequoia passed on that might have been equally successful, or the three other payments companies that Sequoia did invest in that failed. The survivorship bias in how we discuss venture outcomes creates a cultural narrative that selection skill is paramount and that successful investors are successful primarily because they are better at picking winners.

This narrative is not entirely wrong. There is evidence that top-tier venture firms have persistent ability to generate outsize returns, suggesting genuine skill. But the mechanism of that skill is often more about access to deal flow, ability to win competitive deals, value-add to portfolio companies, and ability to influence outcomes through board participation than about pure selection ability at the time of initial investment. Healthcare angels typically lack these advantages, making the pure selection problem even more challenging than it is for institutional investors.

Finally, there are structural factors that push angels toward under-diversification. Many angels have accumulated wealth through concentrated bets in their own companies or careers and may be temperamentally inclined toward concentration rather than diversification. Writing smaller checks across many companies feels impactful than writing larger checks into a smaller number of companies where they can potentially play a meaningful role. The operational overhead of managing a large portfolio can seem daunting. And many angels simply lack the capital to build a portfolio of fifty or one hundred investments even if they wanted to, particularly given the minimum check sizes that have increased substantially in recent years.

BUILDING THE CASE FOR FIFTY TO ONE HUNDRED INVESTMENTS

Given the mathematical arguments, empirical evidence, and cognitive biases we discussed, what portfolio size should healthcare angels actually target? The answer depends on individual circumstances including capital available, check size strategy, and risk tolerance, but for most healthcare angels the optimal portfolio size is likely to be in the range of fifty to one hundred investments.

The lower bound of fifty investments represents the point at which the probability of catastrophic underperformance due to bad luck becomes acceptably low even with random selection. As we saw in the Monte Carlo simulations, a portfolio of fifty investments has better than even odds of achieving venture-scale returns purely through capturing the tail outcomes that occur in a power law distribution. Below fifty investments, the probability of missing the outliers that drive returns remains high.

uncomfortably high even for investors with genuine selection skill. Above fifty investments, the marginal benefit of additional diversification begins to diminish substantially.

The upper bound of one hundred investments represents a practical limit for most angels based on capital constraints and operational capacity. At check sizes of 5, 10,000 dollars per investment, one hundred investments requires deploying 500, 1,000,000 dollars in total capital. This is a substantial commitment but within reach for many successful healthcare entrepreneurs and executives who might be considering angel investing. Beyond one hundred investments, the additional diversification benefit is minimal while the operational challenges of portfolio management become more substantial.

To make this concrete, consider a healthcare angel with 750,000 dollars to deploy over five years. A reasonable strategy might be to target 75 investments with an average check size of 10,000 dollars. This would allow the angel to make 15 investments per year, which is aggressive but achievable if the angel is well-connected in the healthcare startup ecosystem and has established a repeatable process for evaluating opportunities. At this portfolio size, the angel would need only modest selection skill beyond random chance to have a high probability of achieving venture-scale returns.

The check size question is critical and represents one of the most important strategic choices an angel can make. The conventional wisdom in angel investing has historically been that larger checks are better because they provide more ownership and thus more upside when companies succeed. But this logic breaks down when confronted with the mathematics of power law distributions. Writing 50,000 dollar checks into ten companies exposes you to enormous downside variance despite the higher ownership percentages. Writing 5,000 to 10,000 dollar checks into fifty to one hundred companies gives you far better exposure to the tail outcomes that actually drive returns.

The smaller check size strategy also has several additional advantages that are often overlooked. First, it dramatically lowers the bar for capital availability. Many potential healthcare angels who might have 500,000 to 1,000,000 dollars available

angel investing over several years are priced out of the market if typical check sizes are 25,000 to 50,000 dollars because they cannot achieve sufficient diversification by writing smaller checks, these investors can build properly diversified portfolios with the capital they have available. Second, smaller checks reduce the emotional attachment to individual investments. When you have 50,000 dollars in a single company, every board meeting and every update carries significant psychological weight. When you have 5,000 to 10,000 dollars in the company, you can maintain appropriate emotional distance while still being supportive. Third, smaller checks make follow-on investment decisions much cleaner. You can reserve 10,000 to 20,000 dollars per investment for follow-on rounds and deploy that capital selectively in the small fraction of companies that demonstrate genuine traction.

The counterargument to small check sizes is that they limit your access to compelling deals and reduce your ability to be helpful to portfolio companies. There is some truth to both of these concerns, but they are substantially overstated. For the vast majority of seed-stage healthcare companies, capital is not oversubscribed and founders are eager to have engaged healthcare angels at any reasonable check size. The exceptions are companies with strong institutional lead investors that are specifically targeting strategic angels who can write larger checks and provide substantial value-add. Even these companies represent a small minority of the overall opportunity set, and even many of these companies will accept smaller checks from angels who bring relevant expertise or networks.

Regarding value-add, the reality is that most angels overestimate their ability to meaningfully influence outcomes in portfolio companies. A healthcare angel writing a 5,000 to 10,000 dollar check is not going to get a board seat and should not expect to have significant influence over company strategy. But that angel can still be enormously helpful by making customer introductions, providing advice on specific technical or regulatory questions, and being a supportive voice during difficult periods. The most successful healthcare angels tend to be those who are generous with their time and expertise without needing formal governance roles to justify involvement.

There is also an important signaling consideration. In highly competitive deals, check size can serve as a signal of commitment and seriousness. A founder evaluating a deal might rationally prefer an investor writing a 50,000 dollar check over an investor writing a 5,000 dollar check, all else equal. But all else is rarely equal. An angel who brings deep expertise in the specific therapeutic area or regulatory pathway, who has a track record of making valuable customer introductions, or who has successfully founded and exited companies in adjacent markets can often win allocation in competitive deals despite writing smaller checks. The key is to have genuine differentiated value proposition beyond just capital.

For angels pursuing the smaller check strategy, syndication becomes particularly important. Participating in syndicates led by established angels or small seed funds allows you to get exposure to higher quality deal flow while maintaining small check sizes. The lead investor handles the operational aspects of due diligence, negotiating terms, and ongoing portfolio management, while you get access to opportunities you might not have seen independently. The economics of syndicates vary but typically involve a carry payment to the lead of 15-20% of profits on successful exits. This seems expensive, but when you account for the value of deal access, diligence level, and operational efficiency, the fees are often worth paying.

Rolling funds and scout programs represent another vehicle for achieving diversification with smaller capital commitments. Many established venture funds now offer scout programs where individuals can deploy small amounts of capital to invest in companies on behalf of the fund in exchange for carry on successful investments. The economics are typically less favorable than making direct investments, but the deal flow and fund infrastructure can make these programs attractive for angels who want exposure to venture returns without building a full portfolio management operation themselves.

OPERATIONAL CONSIDERATIONS AND PORTFOLIO MANAGEMENT

A common objection to the recommendation of fifty to one hundred investments is that this portfolio size is operationally unmanageable. The concern is that monitoring this many companies, taking board seats, providing strategic advice, and making follow-on investment decisions becomes impossible once you exceed some threshold of around twenty to thirty companies. This objection is partly valid but misunderstands the appropriate role of angels in their portfolio companies.

The mental model many angels have is borrowed from venture capital, where firms take board seats and play active governance roles in portfolio companies. This makes sense for venture funds writing million dollar plus checks representing significant ownership stakes. It makes much less sense for angels writing 5,000 to 10,000 dollar checks representing a fraction of one percent ownership. The operational burden of trying to have meaningful governance involvement in fifty to one hundred companies is not just impractical but counterproductive. Most angels lack the available time, most companies do not actually benefit from having dozens of angels on their cap table trying to be involved in decisions, and the illusion of control that comes from hands-on involvement may actually reduce portfolio returns by encouraging concentration.

A more appropriate model for large angel portfolios is what might be called "strategic monitoring with selective engagement." The angel maintains awareness of portfolio company progress through quarterly updates, annual meetings, and lightweight check-ins, but is not involved in day-to-day or even month-to-month decision-making. The angel makes themselves available to founders for specific questions where they have relevant expertise, makes introductions where they have relevant networks, participates in follow-on rounds where the company is performing well and the angel has capital available. But the default stance is supportive observation rather than active management.

This approach is much more scalable than the active governance model. Reading quarterly updates from one hundred companies requires perhaps 20 hours per quarter. Annual meetings with founders where updates are requested and follow-up decisions are considered might add another 100 hours per year. Responding to occasional requests for advice or introductions might add another 50 hours per year.

The total time commitment is perhaps 200 hours per year, which is significant but manageable for someone treating angel investing as a serious allocation of time and capital.

The approach also has advantages beyond scalability. By reducing emotional attachment to individual companies and maintaining a portfolio mindset, angels are less likely to fall prey to the escalation of commitment bias where they throw good money after bad in struggling portfolio companies. They are also less likely to succumb to loss aversion where the pain of losses in individual companies causes them to become overly conservative in their overall portfolio strategy. The portfolio approach encourages intellectual honesty about hit rates and realistic assessment of when companies are likely to succeed or fail.

Technology can also help manage operational complexity. Portfolio management platforms like AngelList, Carta, and Pulley provide dashboards for tracking portfolio company progress, managing documents, and coordinating follow-on investments. Syndicate structures allow angels to access deal flow and participate in investments without managing the operational aspects of due diligence and deal execution. Funds of funds structures and rolling funds allow angels to gain diversified exposure to healthcare startups without building individual relationships with dozens of founders. While these tools and structures involve some loss of control and usually carry fees, they substantially reduce the operational burden of building a large portfolio.

The due diligence process for a portfolio of fifty to one hundred investments must necessarily be different than for a concentrated portfolio. When you are making investments with 50,000 dollar checks, you might spend 40 hours per company conducting diligence, meeting the team multiple times, calling references, analyzing the market, and stress-testing the financial model. When you are making one hundred investments with 5,000 to 10,000 dollar checks, that level of diligence is neither feasible nor appropriate given the check size.

The key is to develop a repeatable, efficient diligence process that filters for basic quality while acknowledging that your ability to predict specific winners is limited.

reasonable process might involve an initial 30-minute call with the founder to understand the basics of the business and team, a review of the pitch deck and available data on product traction or clinical results, a check of the cap table and terms to ensure there are no major red flags, and a reference call with one person who knows the founder well. Total time investment might be 3-5 hours per company. This is not enough time to develop deep conviction about whether the company will succeed, but it is enough time to filter out obvious problems and ensure the opportunity meets your basic quality bar.

The question then becomes: what should that quality bar be? This is where individual angel strategy and expertise become important. An angel with deep expertise in cardiovascular medical devices might set a high bar for investments in that specific category while having a lower bar for other healthcare sectors where their ability to add value is more limited. An angel with strong relationships in the hospital C-suite might prioritize companies selling to hospital systems regardless of specific therapeutic area. The key is to have some thesis about where you have differentiated insight or ability to help, while also maintaining sufficient breadth to achieve the diversification benefits we have discussed.

One useful heuristic is to think about your quality bar in terms of percentiles rather than absolute standards. Instead of trying to invest only in companies you believe are in the top 10% of all healthcare startups, which requires prediction ability you certainly do not have, aim to invest in companies you believe are in the top 40-50% while acknowledging substantial uncertainty about where exactly they fall in that range. This wider aperture allows you to build a portfolio of fifty to one hundred companies without either dramatically lowering your standards or spending unsustainable amounts of time on diligence.

FOLLOW-ON INVESTMENT STRATEGY

A critical component of portfolio management for large angel portfolios is follow-on investment strategy. In healthcare venture investing, the best performing companies typically require multiple rounds of financing over many years before reaching e

Angels who participate in these follow-on rounds can substantially increase their returns by concentrating additional capital in the companies that demonstrate product-market fit and survive the various gauntlets of clinical validation, regulatory approval, and commercialization.

The mathematics of follow-on investing are compelling. Research from AngelList analyzing 3,471 angel investments found that angels who participated in at least one follow-on round had median portfolio returns of 2.4x compared to 0.9x for angels who never participated in follow-on rounds. This difference persisted even after controlling for initial check size and portfolio size, suggesting that follow-on participation substantially improves returns.

The challenge is determining which companies warrant follow-on investment. The temptation is to follow on in every company that manages to raise another round, reasoning that the new investors must have conviction and that the company has cleared some hurdle by attracting additional capital. But this approach is costly and does not necessarily improve returns. The better approach is to reserve roughly one-third of your initial check size for each investment and deploy that capital selectively into the roughly 20-30% of portfolio companies that demonstrate metrics consistent with outlier potential.

For healthcare companies, these metrics are necessarily different than for software companies. Revenue growth rates matter but are often less informative in the early stages when companies are still in clinical development or pilot implementation. More relevant metrics might include: successful completion of clinical milestones with strong efficacy signals, partnerships with leading healthcare systems or payers that suggest commercial viability, regulatory approvals or clearances that de-risk the pathway to market, expansion of the founding team with recognized experts in the space, and successful Series A fundraises led by institutional investors with strong healthcare track records.

The follow-on decision should also account for how the company's progress affects the portfolio-level return distribution. A company that successfully completes a Phase II trial and raises a Series B at a substantial markup probably represents one of y

potential outliers. Even if the company ultimately exits for a modest return, participating in the follow-on preserves your ownership and ensures you benefit if the company ends up being a much larger success. Conversely, a company that raises a second or down round to extend runway without demonstrating meaningful progress is probably not an outlier and is unlikely to generate venture-scale returns even if it ultimately achieves a modest exit.

The pro rata decision is particularly important. Many seed investments come with pro rata rights that allow angels to maintain their ownership percentage in subsequent rounds. For angels writing 5,000 to 10,000 dollar initial checks, exercising full pro rata in every follow-on round quickly becomes capital intensive. A company that raises a 3 million dollar Series A might require a 50,000 to 100,000 dollar follow-on investment to maintain your ownership percentage. Across a portfolio of fifty to hundred companies, full pro rata participation would require capital far beyond most angels have available.

The solution is to be highly selective about pro rata participation. Reserve your follow-on capital for the small number of companies showing genuine outlier potential and be willing to get diluted in the rest. This requires overcoming the psychological pain of dilution and the sunk cost fallacy that encourages additional investment in struggling companies. But the mathematics are clear: concentrating follow-on capital in likely winners generates much better returns than spreading it evenly across all portfolio companies.

A reasonable approach might be to reserve 20,000 to 30,000 dollars per investment for follow-on deployment, targeting participation in follow-on rounds for approximately 15 to 20 companies out of your portfolio of 75 to 100 initial investments. This concentration of follow-on capital in your highest conviction opportunities allows you to meaningfully increase your ownership in likely winners without spreading yourself too thin across the entire portfolio. The companies that warrant follow-on investment are those demonstrating genuine progress against their original milestones, attracting institutional capital at meaningful step-ups in valuation, and showing evidence that they have found a sustainable path to commercialization.

One subtle but important consideration in follow-on strategy is the timing of deployment. Healthcare companies often go through multiple inflection points in their lifecycle, each of which substantially changes the risk-return profile. A digital health company might raise a seed round to build product, a Series A to complete clinical validation, a Series B to scale go-to-market, and a Series C to expand into adjacent markets. The risk profile and expected returns are dramatically different at each stage. As an angel investor, you typically have the highest expected returns participating in the seed round when risk is highest and valuations are lowest. But you may also have opportunities to participate in Series A or even Series B rounds for portfolio companies that are performing exceptionally well.

The conventional wisdom is to concentrate follow-on capital in the earliest round where you can get the most ownership for your capital. But this ignores the information value of later rounds. A company that successfully raises a Series B round from a top-tier institutional investor at a substantial markup has revealed far more information about its likelihood of success than a company raising a Series A. With your ownership percentage will be lower and your multiple on invested capital will be more modest, the probability-weighted expected return may actually be higher from Series B participation in proven winners than Series A participation in less proven companies.

This suggests a barbell strategy for follow-on deployment. Reserve some capital for Series A participation in companies that have made meaningful progress but still carry substantial risk and offer the potential for high multiples. Reserve other capital for Series B or later participation in the small number of portfolio companies that have truly broken out and are on clear paths to successful exits. The mistake is to deploy all your follow-on capital in the earliest possible rounds purely to maximize ownership without accounting for the substantial information value of watching companies progress through multiple financing rounds.

THE COUNTERARGUMENTS AND WHY THEY FALL SHORT

Having made the case for fifty to one hundred investments with small check size worth addressing the most common counterarguments to this strategy. These objections are not frivolous, and understanding why they ultimately fall short helps clarify the underlying logic of the diversification approach.

The first and most common objection is that writing small checks prevents you from getting access to the best deals. The logic goes that the highest quality companies are oversubscribed and will preference investors who can write larger checks and provide more value-add. If you limit yourself to 5,000 to 10,000 dollar checks, you will be systematically excluded from the companies most likely to generate outlier returns, which undermines the entire diversification thesis.

This objection contains a kernel of truth but overstates the problem. Yes, there are some companies that are highly competitive and will preference larger investors, but these represent a small minority of the overall opportunity set in healthcare angel investing. The vast majority of seed-stage healthcare companies are not oversubscribed and are eager to take capital from any reasonable investor at any reasonable check size. Moreover, the companies that are highly competitive at the seed stage are not necessarily the ones that generate the best returns. Research from First Round Capital analyzing their portfolio found that some of their best performing investments were in companies that struggled to raise their seed round, while some companies that were highly competitive at seed stage ultimately failed and returned mediocre multiples.

The reality is that predicting which seed-stage companies will be outliers is extraordinarily difficult, and the competitive dynamics at the time of investment are not a reliable signal. By maintaining flexibility to invest across the full spectrum of opportunities rather than concentrating only on competitive deals, you actually increase your probability of capturing outliers. The angel who writes fifty 10,000 dollar checks across a diverse set of companies is likely to have better returns than the angel who writes ten 50,000 dollar checks into only the most competitive deals.

A related concern is that small check sizes signal lack of conviction or commitment to founders, which may cause them to deprioritize your involvement or exclude you

future rounds. This concern is more about perception management than substance. The way to address it is through consistent engagement and demonstrated value rather than through check size. An angel who writes a 10,000 dollar check but provides three valuable customer introductions in the first year will be far more valued by the founder than an angel who writes a 50,000 dollar check and is never heard from. The currency that matters most to founders is not capital but attention and expertise applied at the right moments.

The second objection is that small check sizes prevent you from being helpful to portfolio companies, which reduces both your ability to influence outcomes and credibility with founders. This objection assumes that helpfulness is primarily a function of check size and governance involvement, which is a fundamental misunderstanding of how angels actually add value. The most valuable things angels typically provide are customer introductions, advice on specific technical or regulatory challenges, help recruiting key team members, and emotional support during difficult periods. None of these require large check sizes or board seats.

In fact, there is a reasonable argument that angels writing smaller checks may actually be more helpful to portfolio companies because they are less emotionally invested in any individual outcome and can provide more objective advice. The angel who has invested 50,000 dollars in a company may struggle to give the founder honest feedback about when to pivot or shut down because of the psychological pain of realizing a large loss. The angel who has 10,000 dollars in the company can be more dispassionate and helpful precisely because the individual outcome matters less. This emotional distance can be valuable both to the founder who gets clearer advice and to the angel who avoids the cognitive distortions that come from being overexposed to individual outcomes.

There is also an important distinction between being helpful and being in control. Many angels confuse these two concepts and believe that board seats and formal governance roles are necessary to add value. But formal authority is often inversely correlated with actual helpfulness. The angel with a board seat may feel obligated to spend time on governance activities like reviewing financial statements and debating strategic pivots that are not actually their area of expertise. The angel without a

seat can focus their limited time on the specific areas where they can genuinely add value and ignore everything else. This selective engagement is both more efficient and often more valuable to the company.

The third objection is that the operational burden of managing fifty to one hundred portfolio companies is unsustainable. We addressed this concern earlier, but it is worth reiterating that the operational model for large portfolios must be different than for concentrated portfolios. You cannot take board seats in fifty companies and spend hours per week advising each founder. But you also do not need to. The appropriate model is quarterly updates, annual check-ins, and selective engagement where you have specific expertise to contribute. This is entirely manageable with only 300 hours per year of time commitment.

Technology and infrastructure also make large portfolios increasingly manageable. Portfolio management platforms provide consolidated dashboards showing key metrics across all portfolio companies, automated reminders for follow-on decisions, and document management that eliminates the need for filing physical paperwork. Syndicate structures allow you to delegate operational aspects to lead investors while maintaining exposure to returns. Rolling funds and scout programs provide even more leverage by having professional fund managers handle all operational aspects while you focus on sourcing and selecting opportunities.

The more sophisticated version of this objection is that quality of engagement suffers at scale. Even if you can technically monitor one hundred companies, you cannot provide the same depth of support and advice that you could provide to twenty companies. This is true but misses the point. The goal is not to maximize your value-add to individual companies but to maximize your portfolio-level returns. If being helpful to each individual company allows you to have exposure to five times as many companies, the trade-off is almost certainly worth it from a return perspective. Only if the value-add to individual companies has to be extraordinarily high to compensate for the diversification benefit of a larger portfolio.

The fourth objection is that diversification is a hedge against ignorance and that skilled investors should concentrate rather than diversify. This objection has

philosophical appeal and is often made by successful investors who have generated strong returns from concentrated portfolios. The problem is that it confuses ex-outcomes with ex-ante decision-making. Yes, in retrospect, the investor who put entire portfolio into Uber at the seed stage generated extraordinary returns. But at time of investment, that decision represented an enormous and probably irrational risk. The fact that it worked out does not make it the right decision process.

The efficient markets hypothesis suggests that in highly competitive markets with good information, there are no risk-free excess returns available. In venture capital markets, information is poor, which creates opportunities for skilled investors to generate excess returns. But the mechanism of that excess return is not primarily through concentrated bets on a small number of companies. It is through having better deal flow, being able to add value to portfolio companies, having the discipline to build diversified portfolios that ensure you capture the outliers you do identify. Skill and diversification are complements, not substitutes.

Warren Buffett's famous quote "diversification is protection against ignorance" is often cited in support of concentration. But Buffett is investing in public companies with years of financial history, transparent operations, and liquid markets where he can conduct deep fundamental analysis. Healthcare angel investing is a fundamentally different activity with much higher uncertainty, much longer time horizons, and less information. The appropriate level of concentration for investing in established public companies with decades of track records is not the appropriate level of concentration for investing in pre-revenue healthcare startups with six months of existence.

Moreover, even Buffett's Berkshire Hathaway holds significant positions in dozens of companies, not just one or two. The concentration argument is usually about holding 8 to 12 positions versus 50 to 100 positions, not about holding 1 to 2 positions versus 50 to 100 positions. And Buffett is investing in businesses where he believes he has genuine insight into durable competitive advantages, not in early-stage companies where the business model is still being discovered and most assumptions will probably be incorrect.

The fifth objection is that the power law distribution itself is an argument for concentration rather than diversification. If returns are driven entirely by outliers, most companies return zero, why not just try to identify the outliers and concentrate your capital there? This objection misunderstands the relationship between power law distributions and optimal portfolio construction. Power law distributions do not mean you should concentrate. They mean the opposite. When outcomes are highly skewed and unpredictable, you need more diversification to ensure you capture the tail events, not less.

The mathematical intuition here is straightforward. In a normal distribution where outcomes cluster around the mean, concentration makes sense if you have even a modest skill at identifying above-average opportunities. If you can consistently identify companies that will return 1.5x instead of 1.0x, concentration amplifies your advantage. But in a power law distribution where a tiny fraction of outcomes dominate returns, you need to be extraordinarily skilled at identifying specifically those outlier outcomes for concentration to be optimal. Being able to identify companies that will return 2x instead of 0x does almost nothing for your portfolio returns if the winners return 100x. You need to identify the 100x companies specifically, and the evidence suggests that even the best investors lack this level of predictive accuracy at the seed stage.

Diversification is not a concession to ignorance but a rational response to the mathematical properties of the return distribution combined with realistic assessments of prediction limitations. The diversified strategy is optimal even for skilled investors unless their skill specifically manifests as an ability to identify the top 1% of outcomes, which is a much higher bar than having general ability to pick better-than-average companies.

A sixth objection, more common among younger or less experienced angels, is that building a portfolio of fifty to one hundred investments simply requires too much capital and prices them out of angel investing altogether. This concern is valid for angels with very limited capital, but the 5,000 to 10,000 dollar check sizes we have discussed are specifically designed to make this strategy accessible. At a 7,500 dollar average check size, building a portfolio of 75 investments requires 562,500 dollars.

deployed over five years, or roughly 112,500 dollars per year. This is certainly not trivial, but it is within reach for many successful healthcare entrepreneurs, executives, and professionals.

For angels with less capital available, there are several strategies to achieve diversification without requiring enormous total deployment. Syndicates and rollup funds allow you to participate in many investments with smaller capital commitments per deal. AngelList syndicates, for example, often have minimum investments of \$5,000 to \$10,000 dollars, allowing you to build exposure to 50 to 100 companies with 150 to 300,000 dollars of total capital. The economics are less favorable because of syndicate fees, but the diversification benefit may well be worth it.

Another approach is to build your portfolio slowly over a longer time horizon. If you are targeting 75 investments over five years, you might target 15 investments per year. This halves your annual capital requirement and may be more realistic for angels earlier in their careers. The downside is that your vintage year diversification is reduced, meaning your portfolio is more exposed to the specific market conditions and company cohorts from the years when you were most actively investing. But this is a second-order concern compared to the first-order benefit of achieving diversification across companies.

CONCLUSION

The case for building angel portfolios of fifty to one hundred healthcare investments with check sizes of 5,000 to 10,000 dollars rests on three interconnected arguments. First, healthcare venture returns follow an extreme power law distribution where a tiny fraction of investments generate the vast majority of returns, and the mathematical properties of this distribution strongly favor diversification. Second, even sophisticated investors have very limited ability to predict which specific companies will be the outliers, particularly in healthcare where feedback loops are delayed and noisy. Third, cognitive biases systematically lead investors to overestimate their selection abilities and under-diversify relative to what the mathematics would suggest is optimal.

The empirical evidence supports this thesis. Data from thousands of angel investments shows that portfolio returns increase and return variance decreases as portfolio size increases, with the inflection point occurring around forty to fifty investments. Angels who make fifty or more investments have median returns of 1.4x compared to 0.4x for angels who make fewer than ten investments, with dramatically lower return dispersion. Interviews with successful healthcare angels reveal a common pattern of initial under-diversification based on overconfidence in selection ability followed by strategic shifts toward much larger portfolios after confronting actual results. The best performing seed-stage venture funds in healthcare tend to have portfolios of fifty to sixty companies or more, even after controlling for fund size.

The strategy requires rethinking several conventional assumptions about angel investing. Check sizes must be smaller than many angels are accustomed to writing, typically 5,000 to 10,000 dollars rather than 25,000 to 50,000 dollars or more. The operational model must emphasize portfolio-level thinking and selective engagement rather than hands-on involvement in every company. Due diligence must be efficient and focused on filtering for basic quality rather than trying to develop deep conviction about specific winners. Follow-on capital must be deployed selectively to the small fraction of companies demonstrating genuine outlier potential rather than spread evenly across the portfolio.

The psychological challenges of this approach should not be underestimated. It requires accepting that most of your investments will fail and that you cannot pick winners with any confidence which ones will succeed. It requires maintaining emotional discipline to avoid over-concentrating in companies where you feel high conviction, doubling down on losing positions due to sunk cost fallacy. It requires resisting ego gratification that comes from writing large checks and having formal governance roles. It requires patience to build a portfolio over many years and wait through the long time horizons required for healthcare companies to mature.

But the mathematics are unforgiving. A portfolio of ten investments, even with an average selection skill, has a 40% probability of failing to capture any outlier return and a very low probability of generating venture-scale returns overall. A portfolio of fifty investments with even average selection skill has better than even odds of

capturing multiple outliers and generating returns that justify the risk and illiquidity of the asset class. The difference is not marginal but fundamental to whether angel investing in healthcare makes sense as an investment strategy.

For healthcare entrepreneurs, executives, and professionals considering angel investing, the implication is clear: if you cannot commit to building a portfolio of at least forty to fifty investments, you should seriously question whether angel investing is an appropriate use of your capital. The alternative is not to try to beat the odds with a concentrated portfolio but to gain exposure through diversified vehicles like venture funds, rolling funds, or fund-of-funds that provide professional management at scale. Direct angel investing with proper diversification is a viable strategy for generating venture-scale returns, but only if executed with the discipline to build portfolios of sufficient size.

The good news is that the smaller check sizes of 5,000 to 10,000 dollars make this strategy accessible to a much broader population of potential angels than would be the case with traditional 25,000 to 50,000 dollar check sizes. The total capital required to build a portfolio of 75 investments at 7,500 dollars per investment is 562,500 dollars deployed over several years. This is substantial but achievable for many successful healthcare professionals who might benefit from the learning, network building, and potential financial returns that angel investing provides.

The healthcare innovation ecosystem benefits when more smart, experienced operators participate as angel investors. They bring valuable domain expertise, customer relationships, and pattern recognition that can help founders navigate complex challenges of building healthcare companies. But this value is only realized if angels approach the activity with realistic expectations about their own limitations and structure their portfolios accordingly. The diversified approach outlined in this essay is not just better for angels seeking to generate returns. It is better for the ecosystem because it allows angels to support more companies, take more risk on unconventional ideas, and provide more patient capital that is not over-indexed on individual outcome.

The final and perhaps most important insight is that extreme diversification is not just a defensive strategy to protect against downside risk. It is actually the optimal offensive strategy for maximizing expected returns in a power law distribution with high uncertainty. By ensuring you have exposure to enough companies that you are likely to capture the outliers that drive returns, you are not hedging against ignorance but positioning yourself to benefit from the fundamental economics of venture investing. The outliers will emerge, and they will generate extraordinary returns for their early investors. The question is whether your portfolio is structured to ensure you will be among those investors. For most healthcare angels, the answer requires having exposure to fifty to one hundred companies, not ten to twenty.

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