

SEMPER MAIOR: SPIRITS RISING

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A year ago we published the [first “Semper Maior” piece](#), making the case that biotech was on firm ground and ready for a reboot. We put out the second piece last summer, when it felt like the rebound was underway. Had the year ended in October or even November... well, you know. But here we are after a general market and XBI surge feeling like biotech is now truly recovering from its prolonged downturn, having been distilled to a more valuable core. So let’s mine the data, as we have before, to get a sense of what happened in 2023 and what lessons to take with us into 2024.

SEMPER MAIOR: **ALWAYS BETTER**

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LET'S BEGIN: THE BOTTOM LINE AT THE TOP

In the spirit of putting the bottom line at the top, 2023 was a year of interest rate/inflation-linked volatility which the sector ended on a positive note. The public portion of the sector is now more heavily weighted towards mature, derisked, well-capitalized companies ripe for acquisition and on strong footing for continued strong performance.

WE GOT HERE THROUGH WHAT WE'LL CALL SUSTAINED DISTILLATION:

1. the usual rate of failure,
2. a notable culling of companies that started the year impaired,
3. an aggressive rate of M&A, and
4. fewer new companies going public.

During 2023, biotech has been on stronger footing than many people appreciated because they were distracted by stats based on simple counts. While there are still hundreds of weakened companies, as always they have a smaller weighting in most portfolios than their number suggests and therefore are not the problem reflected in basic stats that fail to weight for size.

The sector performance we've witnessed over the last couple months might give people the impression that the rising tide is lifting all biotech boats. However, acquisitions have accounted for the majority of the sector's gains this year. Our analysis of the companies left behind suggests that 2023 was a much tamer year than it might first appear (from end to end, with insanity in between). Still, tame is good. Tame would be welcome in 2024. Tame means that, with prudence, good science can still advance and drive returns.

We think 2024 will be a year of continued maturation with an activation of the private-public conveyor belt; biotech crossover and public funds have enough cash from recent M&A, public names have been substantially depleted, and there are scores of high-quality private companies held by those same crossover funds. We'll see many of those companies finance via crossover and/or IPO rounds.

To purely public investors, this will look like fresh stories entering the sector. But to those of us who operate across the private-public spectrum, these are stories we know well; they will merely be moving around within our portfolios and only the visibility of their valuations and who can buy their stock will change.

With another election looming, our progress could be challenged by heightened anti-pharma rhetoric and new drug pricing policies. The set of potential good policies bouncing around Congress (those that promote both affordability and innovation) is very small while the number of bad ideas there is truly expansive. In September, CMS will put out its prices for the first 10 drugs targeted for price "negotiation." That will create some noise but hopefully people remember that early-stage investors don't care about what this administration does to existing drugs this year but rather what some future administration is doing over a decade from now, which no one can predict. This therefore impacts our ability to invest confidently in the development of drugs that don't exist yet.

In 2024, more people will step off the sidelines in support of affordable innovation; more investors will recognize that bystanding is unbecoming and more companies will recognize that “scientific isolationism” (i.e., “well I’m working on biologics so the IRA doesn’t impact me and I don’t have to get involved”) is myopic.

Our collective acceptance of the *biotech social contract*—the biotech industry’s commitment to develop better medicines that will go generic without undue delay and society’s commitment to make all appropriate treatments available to the people who need them through proper insurance, which means low out-of-pocket costs—**must mature into a broader, sustained campaign to win the public’s support for sound policy.**

Without such a campaign, we should all recognize that bad policy won’t stop at the nine-year small molecule penalty; that was just a small victory for those who won’t stop until they achieve H.R.3-like price controls on all drugs at launch, which would defund all biomedical R&D. For that reason, as Peter Thompson, a Managing Partner at Orbimed and one of us (Peter K) [wrote last year](#) and hundreds of executives and other investors co-signed, achieving the 9-13 fix isn’t just some item on the menu of issues we must address as an industry; it’s the menu itself, without which there are no other biotech issues to worry about... not patent waivers, not CFIUS, not clinical trial diversity, not supply chains, not anything.

Ultimately, with enough sustained effort, there’s a version of the future [where we get a 9-13 fix](#) (i.e., have Medicare “negotiation”

kick in after 13 years for all medicines, not just biologics) and possibly other modifications to the IRA that preserve affordable innovation. The law currently trades away innovation under a false pretense that price controls solve affordability for patients (which only proper insurance with low out-of-pocket costs can do, something the IRA helps with by setting a \$2,000 annual cap for Medicare but is not actually improved by the IRA’s price setting). More than that, a successful public-facing campaign that achieves a 9-13 fix today is also the kind of campaign that can shield innovation from bad policy tomorrow.

Many CEOs and investors have gone above and beyond to defend our ecosystem. Some investment firms have sat by quietly, thanking those doing the work for their effort in private but refusing to take a public stand, claiming that their LPs (the limited partners whose money we fund managers deploy into biotech companies) would rather they keep quiet. Based on our experience, we’re skeptical of that excuse. By the end of this piece, you will be too.

Bystanding is becoming conspicuously unbecoming of those with senior titles who present themselves as leaders.

We’ve learned a lot through the challenging markets and damaging policy decisions of the past few years. Let’s carry these lessons with us as we enter 2024.

HOT OR NOT: A QUICK LOOKUP OF LESSONS TO TAKE WITH US INTO 2024

WHAT'S HOT IN 2024	WHAT'S NOT
Defending our ecosystem to win public support for sound policy that preserves innovation. Signing up to be a NPLB First Responder .	Bystanding because a bad policy will just “go away” or “won’t affect me.”
Spending money like it's 2023 (prioritize, focus, save money wherever possible).	Spending money like it's 2019-2021.
Saving money on the small stuff: negotiate for lower D&O, low-cost ATM fees (25-50bp for reverse inquiries, 1% or less for open market sales), financings without banks when you know which investors want to invest to save on fees.	Overpaying on fees; thinking you’ve negotiated enough by paying 2.25% for an ATM; paying bankers 6% on a mostly-insider financing you could have done with a lawyer as a private placement or by taking reverse inquiries off your low-cost (25-50bp) ATM.
Not judging books by their covers: investors taking meetings with impaired companies to look for gems.	Declining meetings assuming a company isn’t worth your time.
Doing things that make sense based on first principles even if they seem unconventional.	Unexamined assumptions and conventions, such as the idea that a good company should only do a conventional IPO, disregarding all the reasons for deviating from convention.
Executives incentivizing the investor behavior they want by making it clear how and why they’ll allocate their shares.	Spreading allocations thinly to everyone or letting bankers dictate allocations.
Running efficient and effective board meetings with clear pre-reads and scenarios laid out on a detailed elephant slide (learn more on Gateway).	Long decks without clear bottom lines; long board meetings where management presents the deck; little time spent planning for unpleasant scenarios.
Doing a Generalized Cost Effectiveness Analysis (GCEA) on your drug as soon as you have Phase 2 data so that you anchor the world to the societal value of your medicine before ICER and NICE do.	GCEA what? I’ll just let ICER do its simplified math, declare my drug not cost effective, and end up having to dig myself out of a hole.
Assessing sector health using company performance that takes various parameters like holders and market cap weightings into account.	Assessing sector health based on company counts (e.g., number of companies trading below cash) and equal-weighted average performance, allowing tiny companies to skew the results to the point of irrelevance to most audiences.
Signing up for RAReport and Gateway .	Seriously, they are free resources.
Writing longer RAReport pieces.	Writing RAReport pieces merely as long as the ones we wrote in 2023.

PART 1: 2023 SLICED AND DICED EVERY WHICH WAY

BY THE NUMBERS: THE GREAT DISTILLATION OF OUR SECTOR

At the start of 2023, the public biotech drug development-stage universe consisted of 655 companies, a statistic that's barely useful for reasons we'll get into.

We include only US-listed, not-yet-profitable companies with valuations under \$10B. There are too few companies listed ex-US to impact the results of this analysis. Based on 13F data as of 3Q22, we know which of these companies were owned by at least one of 41 peer specialist investors, representing what we call the Core set of 387 companies. The 268 other companies we call Peripheral.

LIKE MAKING SPIRITS: SHRINK BY VOLUME, INCREASE IN VALUE

By the end of the year, the Universe consisted of 599 companies, down -9% from the start of the year, with 327 Core (-15%) and 272 Peripheral (+1%). The public biotech Universe and especially the Core set have been shrinking by this measure. And yet, the Cumulative market capitalization of the Universe climbed slightly (+8%) from \$324B to \$351B. The majority of that is Core, which climbed +11% from \$282B to \$312B. Peripheral deflated by -6% from \$42B to \$39B.

So maybe the Universe didn't shrink. **Rather, it was distilled to fewer but more highly valued companies. In particular, specialists really tightened up their holdings. And as you'll see, Core was where the action was.**

TABLE 1 shows many of the major stats that will inform the analyses below. If you haven't read a Semper Maior piece before, hopefully you'll be able to follow along with the explanations we include throughout. However, the **first of this series** introduced these concepts in more depth, so you may want to read that.

A QUICK NOTE ABOUT PERIPHERAL COMPANIES:

To be clear, we're not saying that these companies don't matter to humanity. They just don't matter to the returns of specialist investors or their Limited Partners and, as you'll see from the weightings, they barely impact the indices. Peripheral companies may not be owned by any specialists because they have no compelling programs or maybe they have a good program but specialists consider them overvalued. In case you doubt the wisdom of a herd of specialist investors, then consider that 99% of M&A dollars flow to the Core set; acquirers see almost nothing they value enough in Peripheral companies to acquire them. These sets are not static. Core companies lose their specialist shareholders and become Peripheral companies and Peripheral companies gain specialist shareholders and become Core. So think of specialists as simply being blood hounds... they sniff out value ahead of Big Pharma.

TABLE 1:
THE BIG TABLE

	UNIVERSE			CORE			PERIPHERAL			IBB			XBI		
	2022 YE	2023 YE	% Change	2022 YE	2023 YE	% Change	2022 YE	2023 YE	% Change	2022 YE	2023 YE	% Change	2022 YE	2023 YE	% Change
Total Number of <\$10B Dev-Stage Biotech Drug Companies	655	599	-9%	387 (87.1%)	327 (88.9%)	-16%	268 (12.9%)	272 (11.1%)	1%	208 (19.3%)	190 (19.5%)	-9%	118 (72.5%)	98 (66.1%)	-17%
Positive Enterprise Value: PosEV	441 (94.8%)	459 (96.3%)	4%	269 (95.0%)	255 (96.8%)	-5%	172 (93.5%)	204 (92.2%)	19%	188 (18.8%)	159 (18.8%)	-15%	116 (71.9%)	94 (64.9%)	-19%
	Negative Enterprise Value: NegEV														
	214 (5.2%)	140 (3.7%)	-35%	118 (5.0%)	72 (3.2%)	-39%	96 (6.5%)	68 (7.8%)	-29%	20 (0.6%)	31 (0.6%)	55%	2 (0.6%)	4 (1.2%)	100%
	New NegEV:														
	214 (5.2%)	46 (1.4%)		118 (5.0%)	26 (1.0%)		96 (6.5%)	20 (4.7%)			21 (0.3%)			3 (1.1%)	
Lingering NegEV:															
	94 (2.3%)			46 (2.2%)			48 (3.1%)			10 (0.3%)			1 (0.1%)		
Number with <2 Years of Cash	429 (34.8%)	408 (41.9%)	-5%	209 (31.6%)	182 (38.7%)	-13%	220 (56.2%)	226 (67.1%)	3%	80 (6.2%)	92 (7.7%)	15%	36 (24%)	40 (28.3%)	11%
<2 Years of Cash and 25% Burn/MC Ratio	361 (12.4%)	317 (8.1%)	-12%	169 (10.5%)	129 (6.6%)	-24%	192 (25.8%)	188 (20.1%)	-2%	52 (1.6%)	52 (0.9%)	0%	19 (8.5%)	14 (5.5%)	-26%
Cumulative Market Capitalization (\$B)	\$324.0	\$351.2	8%	\$282.3	\$312.1	11%	\$41.8	\$39.0	-6%						
Cumulative Annual Burn: All (\$B)	\$61.6 (19.0%)	\$54.1 (15.4%)	-12%	\$49.2 (17.4%)	\$43.6 (14.0%)	-11%	\$12.4 (29.6%)	\$10.5 (27.0%)	-15%						
	Just those with <2 Years of Cash (\$B)														
	\$32.4 (10.0%)	\$30.5 (8.7%)	-6%	\$23.2 (8.2%)	\$22.3 (7.1%)	-4%	\$9.2 (22.1%)	\$8.2 (21.0%)	-11%						
Just those in Danger Zone (\$B)															
\$24.7 (7.6%)	\$19.5 (5.6%)	-21%	\$17.0 (6.0%)	\$13.2 (4.2%)	-22%	\$7.7 (18.5%)	\$6.4 (16.3%)	-18%							

DANGER ZONE

This is the mega table of data that we cite throughout this article. We include not only the number of companies that qualify for a category but also, in parentheses, the weighting by market cap of that category. While it's not entirely intuitive to use, we hope you get the hang of it based on the examples that we provide here. So, for example, at YE23, there were 327 Core companies that made up 89% of the Universe by weight (the percent refers to the Universe, which is the row). But once we are examining Core, we see that there were 182 Core companies trading <2 years of cash, which had a 39% weighting by market cap within Core, so the percent refers to percent of the Core market capitalization (which is shown lower in that column). And XBI had 98 companies that belonged to the Universe as we define it with a combined weighting of 66% within that ETF. We hope you enjoy this table. Side effects include bleeding from your eyes. Cheat sheet: Universe means all public cash-burning drug companies <\$10B market cap; Core means owned by at least one of our 41 peer specialists (inclusive of our firm) as defined in the [first series](#); Peripheral means not owned by any of these specialists; Lingering NegEV companies are those that were NegEV at YE22 and remained NegEV at YE23, whereas New NegEV companies are those that were PosEV at YE22 and were NegEV at YE23; Danger Zone means <2 Years of Cash and 25% Burn/MC Ratio (spoiler—maybe this isn't so dangerous—read on for more). When we talk about Burn, the percentages we show are burn as a percent of the cumulative market capitalization of that category; so as of YE23, the Universe had a cumulative burn rate of \$54B which was only 15% of the cumulative 351B market cap of the Universe.

SOURCE: Bloomberg, FactSet, RA Capital

FIGURE 1 shows what happened to the 387 companies that entered 2023 as Core with a cumulative valuation of \$282B. 32 converted to Peripheral, another 32 were acquired, 21 were delisted, 3 vanished due to a merger with another Core company (admirable considering how complicated public mergers can be), 2 graduated to profitability (well done!), and 1 graduated by exceeding \$10B in market capitalization (congrats!), leaving just 296 with a cumulative valuation at the end of 2023 of \$278B. What partially replenished the Core set were 21 companies that converted from Peripheral to Core when specialists showed up as shareholders on their 13Fs, 8 companies that entered the Core set via IPOs (welcome!), 1 company dropping into Core from a higher valuation down into the <\$10B zone, and 1 company starting to burn cash again (pandemic revenues declined), bringing the total number of Core companies at the end of 2023 to 327 and their cumulative valuation to \$312B.

So at the end of 2023, Core biotech was worth +11% more than a year earlier but consists of -16% fewer companies. The average value of a Core company is now \$954M compared to \$729M a year ago, which is +31% higher. Because companies raised money along the way, that's not the same as their stocks appreciating.

In the past, we have also tracked the dynamics of the Peripheral set, but we see little reason to spend the time on that; these companies are simply too small to matter to sector returns, adding up to a mere 11.1% of the market cap of the Universe. We

think what matters is that there are 272 at the end of 2023 that currently no specialists own and yet may be underappreciated gems. 21 companies converted from Peripheral to Core in 2023.

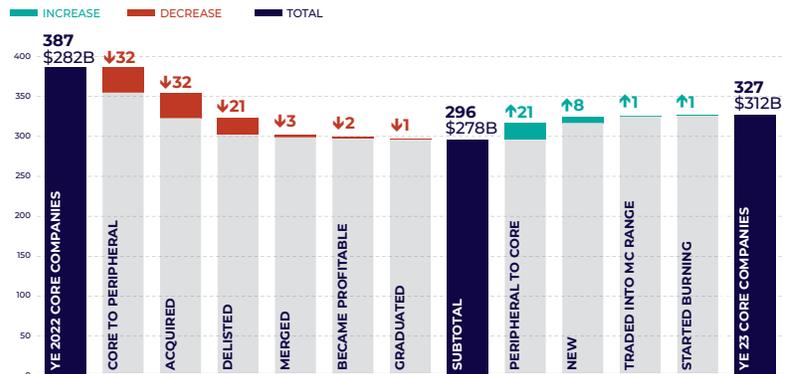
Let's see how many Peripherals convert in 2024. Our team will be looking.

**NEGATIVE EV:
RELEASING THEIR CLAIM
ON SOCIETY'S RESOURCES,
BUT SOME CLING ON**

FIGURE 2 shows that across the Universe, there were 214 companies with NegEV at the start of the year and 140 at the end, which may make it seem like this category shrank by only a modest -35%, but let's go deeper into what really changed before drawing a premature conclusion that the sector didn't really tighten up by much.

Of the 214 NegEV companies at the start of 2023, 84 exited the

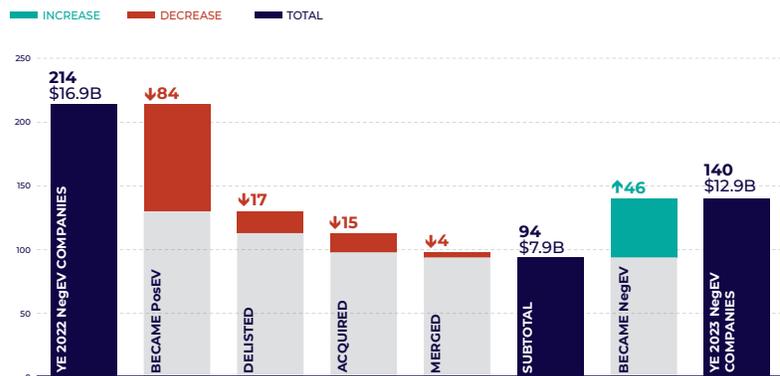
**FIGURE 1:
DISTILLING THE CORE**



The number of Core companies shrank from YE22 (which is based on 3Q22 13Fs) to YE23 (which is based on 3Q23 13Fs) as companies lost and gained specialist shareholders, some were delisted, others acquired, and some graduated out of and into the <\$10B valuation limit, though more left than entered the set. Yet it stayed at about the same valuation. It's worth pointing out that of the 21 companies that were Peripheral and became Core, only 1 did so through a reverse merger while 20 appeared to win specialists over with some version of the pipeline they already had.

SOURCE: Bloomberg, FactSet, RA Capital

**FIGURE 2:
FEWER NegEV COMPANIES LAY A SMALLER CLAIM
ON SOCIETY'S RESOURCES**



The number of NegEV companies shrank from YE22 (which is based on 3Q22 13Fs) to YE23 (which is based on 3Q23 13Fs) as companies' cash and market caps fluctuated. Some were delisted, others acquired or merged, and some were able to inspire investors enough to become PosEV. Far more companies graduated to PosEV than became NegEV.

SOURCE: Bloomberg, FactSet, RA Capital

set because they graduated to a PosEV, 17 because they were delisted¹, 15 because they were acquired, and 4 because they merged with another company. So in number, that set shrank by a more impressive -56% to 94 companies.

But we shouldn't be concerned with just the counts. Merely by existing as a listed company, the only resource we know the company is squandering is a stock symbol, which isn't worth much. More important resources are cash and people. We don't have clean data on the number of people these companies employ (we're working on that) but we can look at cash.

Over the course of 2023, the \$31B cash held by 214 NegEV companies shrank by -54% to \$14B cash held by the 94 remaining companies in this set, roughly proportional to the reduction in counts. The 94 lingering NegEV companies were burning \$5.9B at YE22 and are now burning \$5.2B as of YE23, a modest -12% reduction.

These impaired companies, willingly or not, are yielding their claim on society's resources – its cash and people – even if we might wish they were doing so more efficiently. It's one of the virtues of biotech that companies constantly need to finance; that they have a finite amount of cash and time after becoming impaired before they cease to exist unless they can inspire investors to believe in them. This ensures that investors serve as a second governing body, beyond boards, voting with their capital on which companies are pursuing compelling R&D.

So when companies become impaired, though it's difficult to reclaim the cash on their balance sheets, the markets quickly and dramatically cut back on the cash these companies are able to raise until they come up with a better plan. Those that can't proceed wither, shedding employees who are hired by stronger companies. These companies functionally remove themselves from just about every measure that matters except for the most useless measure of all... the simple count of surviving companies.

Cash constraints are an important forcing function that can help focus companies, especially when boards do the hard work of recognizing when their companies are constrained, as [we urged back in Spring 2022](#).

What should **FIGURE 2** look like? We suppose ideally we would see that every company that started 2023 with a NegEV was no longer in that category by the end of the year, either because it has won back investor support for its plan and now had a PosEV (even if that meant reverse merging) or because it has been reassimilated into the ecosystem (for example by being taken private at roughly 90 cents on the dollar by investors willing to do the work of dismantling a company if not actually employing its intellectual property in some way).

But just lingering in that NegEV zone for a year, as 94 companies have, is likely a sign that society's resources are being squandered. Think of the cash trapped at these companies (**TABLE 2**; about \$14.1B as of 3Q23 financials, which is about 11% of all the cash held by the biotech Universe).

¹ Delisting doesn't mean that waste isn't being averted, but the 17 delisted companies held only about \$560M in cash at the start of 2023, about \$33M each; we don't know if any of that was recovered after the delisting but it's a lot less than the average \$150M cash held by all the other companies, so we won't consternate further on how to think of delisting. Out of sight, out of mind will do.

Is it being put towards its most productive purpose?

For what it's worth, **TABLE 2** also shows that 84% of that captive cash (\$11.8B) is held by just the half (46) of these Lingering NegEV companies that are currently Core. The other half (48) of the Lingering NegEV companies are Peripheral and only lay claim to \$2.3B. That's still a lot (almost enough to get one drug to market) but it's only 2% of the Universe's cash, even though these companies represent 8% of the count (48/599).

The data make sense to us. Even among the NegEV companies, the ones that managed to remain or become Core by 3Q23 managed to hold on to more cash. While not proof of anything, it certainly generates a hypothesis that maybe these companies have something of value that one or more specialists are keyed into.

We'll be looking at whether the resurrection rate in 2024 among the 46 Lingering NegEV companies that are Core is higher than among their Peripheral cousins.

Meanwhile, PosEV companies routinely become impaired (which doesn't always mean they flip to NegEV); that's just how science works. They need

some time to process and adjust course. As **FIGURE 2** shows, 46 companies dropped into NegEV territory during 2023 and remain there at YE23. But while the final count of 140 NegEV companies is only -35% lower than the 214 that started the year in the NegEV camp, the new entrants factored into this stat shouldn't overshadow the fact that more than half the publicly listed NegEV companies at the start of 2023 were no longer in that camp by the end of 2023.

What **TABLE 2** shows us is that, of the total cash fueling the biotech Universe, the cash trapped in Lingering NegEV companies at YE23 is a modest 11%. Meanwhile, another 7% is currently held by companies that entered NegEV over the course of 2023. We hope that none of the 140 companies starting 2024 with a NegEV will end the year in this category. Either they will create value or repurpose their capital to something society will value (i.e., as evidenced by a positive EV). **The lesson of this most recent downturn is that every dollar must be put to good purpose.**

TABLE 2:
CASH IS CONCENTRATED IN COMPANIES THAT SPECIALISTS VALUE

	COUNT	CASH (\$B)	Percentage of Universe Cash
CORE PosEV	255	\$91.7	74%
PERIPHERAL PosEV	204	\$10.3	8%
CORE New NegEV	26	\$5.6	5%
PERIPHERAL New NegEV	20	\$2.5	2%
CORE Lingering NegEV	46	\$11.8	9%
PERIPHERAL Lingering NegEV	48	\$2.3	2%
TOTAL:	599	\$124.2	

This table tracks the amount of cash held by the Universe companies, broken out by Core/Peripheral and Pos/Neg Enterprise Value. Specifically, the NegEV companies are broken out into New ones that turned NegEV in 2023 and Lingering ones that were NegEV at YE22 and remained NegEV at YE23, which strikes us as wasteful. Note how small a fraction of the Universe's cash is trapped in Lingering NegEV companies and that the 255 PosEV Core companies (only 43% of the total companies in the Universe set) lay claim to 74% of the Universe Cash.

SOURCE: Bloomberg, FactSet, RA Capital

Meanwhile, let's not overlook that most (74%) of the cash in biotech is in the hands of the 255 PosEV Core companies (43% of the Universe) that specialists still value. That reflects a >1.7X enrichment of cash in favor of Core companies beyond just their numbers.

In the extreme, if there were 10,000 companies but all the cash and therefore all the jobs were concentrated in 100 companies, would we be talking about 100 companies or 10,000? (Does the word "count" make you nauseous yet? Shall we stop merely counting?)

PERFORMANCE: WEIGHT FOR IT... A GOOD YEAR FOR SOME

So let's look at how the Universe as a whole and our Core and Peripheral subsets performed in 2023. Keep in mind that in 2023, the biotech-focused XBI was up +7.6% and the IBB, an ETF more weighted towards larger caps and more diversified with exposure to generics and other healthcare sub-sectors besides drugs, was up +3.8%.

But wait! How shall we weight our portfolio? We did it three ways. The bottom line is the same: 2023 sector performance was driven by Core companies.

SPECIALIST-OWNED CORE COMPANIES HAD A SOLID 2023

First, let's buy \$1000 of every stock, a small enough amount that every company is liquid enough to be represented in the portfolio. That's our Equally Weighted (EQW) portfolio.

In this EQW case, **FIGURE 3** shows that the development-stage biotech Universe was up +3.9%, Core was up +16.6%, and Peripheral was down -14.3%.

But this portfolio adds up to under \$1M and hardly reflects the realities of investing. You might think that you could scale this up to a larger portfolio by buying more of each stock but that's where reality kicks in: most of these companies are tiny and their stocks are thinly traded. For a larger portfolio, they are barely relevant.

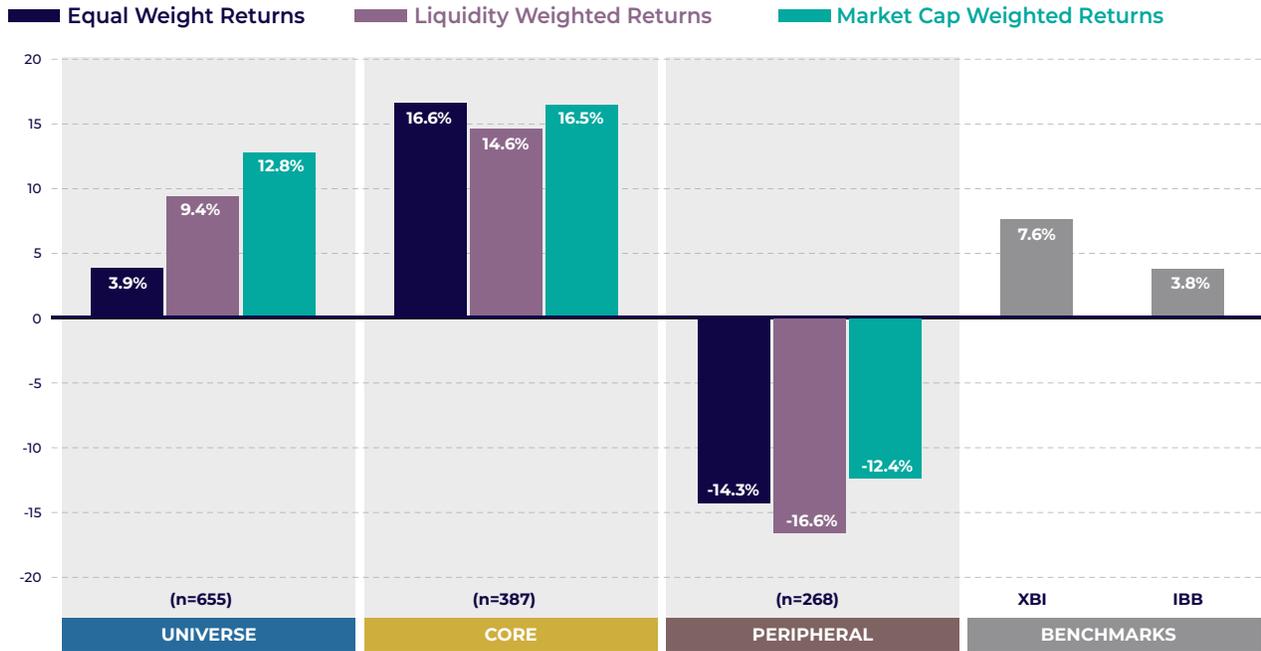
LET'S STOP COUNTING

Just counting companies is misleading and makes the sector look like it's in worse shape and less efficient than it actually is. We can talk about the sector's inefficiencies but first let's quantify and bound them appropriately, weighting for size in some way.

When you show returns of an equal-weighted portfolio, that's just counting. It ignores liquidity and how big an investor's positions could even be. When you ignore the size of a company's balance sheet and the number of employees and count every company the same, you misjudge how society's resources are allocated. So you can certainly start an analysis with some counting, as we have, but any real conclusions require deeper analysis.

We urge anyone still merely reporting counts to consider either 1) discontinuing that practice or else 2) wrapping it all in adequate caveats so that it's clear what utility you think counts offer. For example, simply counting public companies is informative to vendors involved in the base operation of any public company, such as auditors, as well as for headhunters wondering how many CEOs and CFOs might be poachable from struggling companies. Unless that's the audience you're catering to, there's no need for counting.

FIGURE 3:
STRONG PERFORMANCE IN THE CORE



Here we show 2023 performance of the <\$10B public development-stage biotech drug-focused Universe, including the Core and Peripheral subsets of companies. We present three ways of weighting the companies and also performance of two biotech/healthcare ETFs, XBI and IBB. Core and Peripheral classifications are based on 3Q22 13F filings. Performance is reported through YE23. As you can see, Core biotech dramatically outperformed Peripheral. Since Peripheral companies tend to be smaller and less liquid (making up 13% of the cumulative Universe market cap, 7% of XBI, and <2% of IBB as YE22), they are already underrepresented in the Universe and benchmarks when you use LCW and MCW. We argue that everyone should look at biotech on a liquidity or market cap weighted basis so that the impact of Peripheral companies is not overstated.

SOURCE: Bloomberg, FactSet, RA Capital

Let’s say that one spent a week buying each stock, constrained to 20% of the daily volume, up to a \$10M position (i.e., the lower of \$10M or the daily average trading volume of a stock at its 12/31/2022 closing price). We’ll call this Liquidity-Constrained Weighting (LCW). In that case, one would have a portfolio of roughly \$1.6B, which is at the scale of what a professional investor might manage these days.

Here we see from **FIGURE 3** that, on a LCW basis, the portfolio was up +9.4% in 2023, with the Core portion up +14.6% and Peripheral down -16.6%. For the average specialist investor (who only invests in Core), 2023 was a good year.

We could also look at a portfolio that is Market Cap Weighted (MCW). In that case, **FIGURE 3** shows that the Universe was up +12.8%, Core was up +16.5%, and Peripheral was down -12.4%.

We consider LCW and MCW returns to be more relevant than EQW for understanding how professional investors experienced the sector. LCW and MCW performance isn’t so different largely because liquidity is somewhat correlated with market cap.

Consider how different the returns are between the EQW portfolio and LCW/MCW. **Clearly, when you weight the Universe by liquidity or market cap, you see that the performance of the Universe looks a lot more like Core and has much less weighting to Peripheral companies.** The underperformance of Peripheral companies in 2023 shouldn't be overemphasized by simply looking at counts of companies (i.e., equally weighting everything). At YE22, Peripherals made up 41% of the Universe by count but only 13% of the cumulative Universe market cap and only 7% of XBI and <2% of IBB.

How did this Core set generate its returns? There are two ways, after all. Did these stocks simply go up and therefore might still come down? Or were these returns the result of acquisitions that reflect a permanent, realized return?

DEFINING CORE: A QUARTER'S LAG MATTERS ONLY A LITTLE

Note that we defined Core by holders as of 3Q22. This means that anyone could have looked up the 13F data by mid-November and planned out their 2023 strategy based on these data.

We can now use 4Q22 13F data that came out in mid-Feb 2023 to redo our analysis by what Core/Peripheral looked based on which companies actually were Core and Peripheral at the moment they entered 2023. However, since our forward-looking definitions of Core and Peripheral rely on 3Q23 filings, it's reassuring to see from **FIGURE 4** that the results are not materially different when one looks at 3Q vs. 4Q filings to classify Core vs. Peripheral for 2023 analysis. Though note that the 3% difference is in the logical direction... over the course of that one quarter, specialists did further enrich for companies that performed better.

FIGURE 4:
LITTLE DIFFERENCE FROM DEFINING CORE BASED ON 4Q22 VS. 3Q22 13Fs



Using more up-to-date 4Q22 13F data to define Core vs. Peripheral categories shows that performance wasn't so different from using 3Q22 data, though specialists did skew their portfolios by a few dozen companies towards ones that would go on to outperform in 2023, slightly outperforming a portfolio based purely on what was known at YE22. If you wanted to invest in a basket of Core companies today and bet on their 2024 performance, you would have to use 3Q 13F data. To use 4Q22 data, you would have to wait until February 15th. Because we would like these analyses to be reproducible and testable prospectively, we do all our 2023 performance analysis using Core classifications based on 3Q22 13F holder data.

SOURCE: Bloomberg, FactSet, RA Capital

No matter how you look at it, Core drove 2023 biotech returns. What does this mean? Only that using the low bar of whether a company has at least one specialist investor show up as a holder dramatically enriches for a set of companies for which 2023 would appear to have been a good year.

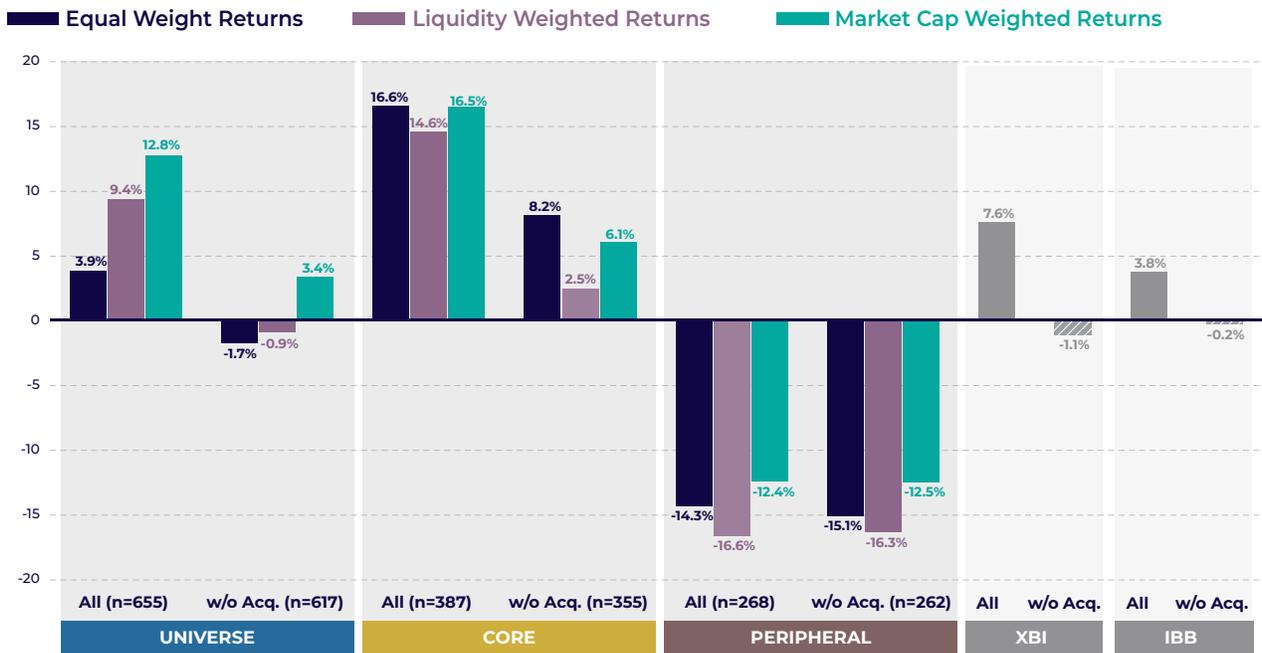
CORE-FOCUSED M&A DROVE RETURNS, WITH LITTLE HELP FROM THOSE “LEFT BEHIND”

There were a lot of acquisitions in 2023. We count 36 cash transactions this past year from our Universe, of which nine were take-private transactions meant to clean up struggling companies and 27 were the kind of M&A by strategics we think of as driving returns.

Buyers gotta buy. And their buying drove returns this year. But what about the rest? Because when we look forward, 2024 will obviously be defined by the performance of the companies that haven't been acquired in 2023. What if they had a horrible 2023? Wouldn't that change the way you look at things? Well... it's not so bad.

FIGURE 5 shows the returns of the various sets of companies when we remove all the companies that ended up being acquired in 2023. Since there were almost no acquisitions of Peripherals and even then not for big gains, those numbers are largely unchanged. But acquisitions accounted for most of the Universe and Core returns. Removing them results in the Universe's shedding 9.4% of its +12.8% return, ending up only +3.4% on the year. Core's +16.5% sheds 10.4%, ending up +6.1%.

FIGURE 5:
ACQUISITIONS DROVE RETURNS IN THE CORE AND ETFs



When you remove acquisitions from the Universe set (almost all of which were actually within the Core sub-set), performance over 2023 is notably lower for the Universe and Core. 2023 clearly wasn't a strong year for the un-acquired (aka, the Left Behind). But it wasn't horrible, and that's better than it could have been. We estimated the 2023 return without acquisitions for XBI and IBB.

SOURCE: Bloomberg, FactSet, RA Capital

That's just for MCW; the effect is more dramatic by other weightings. Across the whole Universe, the average company left behind was down slightly on the year (i.e., on an EQW or LCW basis).

So strip out the acquisitions and the biotech Universe and even the Core companies left behind had a pretty modest year. The median company was down substantially – Universe (-28%), Core (-20%), and Peripheral (-44%) – though that's probably true most years since biotech is a business of outliers.

Does that mean that the mood in San Francisco next week will be dour? Hardly. Again, consider that larger companies send more people to the conference and all the specialists, by definition, are invested in Core, so most of the people at the conference will have experienced at least a slightly positive year, not to mention the bounce in the step of those coming off acquisitions thinking about their next act. And those attending from private companies have a basis for optimism that the public markets will be more welcoming in 2024, which is reason for cheer.

We expect M&A to continue to drive biotech returns. **But it's best not to count on being acquired**, so every company should expect to be among the ones "left behind" at the end of 2024 (many would even prefer to be!). So if 2024 is anything like 2023, it won't be nearly as good as indices driven by acquisitions would suggest 2023 was. It could very well be flat. That's okay. That would be way better than 2021 and 2022, which spanned a period of heavy, broad-based decline.

But it means that companies should plan for challenging market conditions and stick to the ethos of doing more with less (i.e., let's stay vigilant for wasteful spending).

THE FIRST DERIVATIVE OF CORE: THE 92 CLIMBERS DROVE RETURNS OF THE LEFT BEHIND

So far, we have only looked at companies by whether they were Core or not. Now let's look at what happened to companies that saw a change in the number of specialists over the course of 2023 (i.e., the first derivative, for calculus fans).

TABLE 3 shows that it was the mere 92 companies (about 36% of the Core set by market cap) that started as Core and saw a notable increase in the number of specialist holders that had a really good year, up +18% on a MCW basis. Those that saw little change in specialist holders were flat. Those that saw a decline in specialist holders performed poorly. Perhaps not surprisingly, Peripheral companies that entered Core by attracting one or more specialists (generally through unexpectedly positive data) performed best on an EQW basis and reasonably well on a MCW basis. However, there were few of these companies and they have a low weighting within the Peripheral set, which is why Peripheral companies overall had a bad year (although these high-performing gems are also why we always keep our eye on companies in the Peripheral set that may graduate to Core with positive data).

Is it necessarily true that losing specialists should correlate with poor performance? No. After all, the specialists we're tracking tend to focus on development-stage biotech and most would sell their positions if a company matured to a high valuation. Alas, 2023 wasn't the year when many stocks got too rich for specialists.

And who said specialists are the only ones capable of driving a stock up? There are lots of generalists out there. So it was not a given that Core companies that saw little change in their specialist count couldn't have had a positive year. But that's not what we see.

So, 2023 was a good year for the companies that were acquired and for the quarter of the Left Behind Core companies that saw a notable increase in the number of specialist holders by the end of the year (i.e., the Climbers). Just holding onto one's specialists was not enough and losing them was bad.

Recall that the Universe was up +12.8% in 2023 but only because Core was up +16.5%. But Core was only up that much because of acquisitions. Without acquisitions, the Left Behind Core was only up about +6.1%. And so now we're pointing out that without the quarter of those that were Climbers (92 companies), all the rest of Core was actually down slightly on the year. There were no doubt plenty of positive performers in that depleted set, but we've simply run out parameters by which to define them as drivers. NegEV at the start of the year could be a positive predictor but these companies were too small to count as sector drivers.

TABLE 3:
THE 92 CORE CLIMBERS LEAD THE PACK

		EQW	MCW	# of Companies	Cumulative YE23 Market Cap \$B
STARTED PERIPHERAL	STARTED PERIPHERAL AND STAYED PERIPHERAL:	-20%	-20%	217	\$28.4
	STARTED PERIPHERAL AND MOVED TO CORE:	81%	9%	21	\$12.2
STARTED CORE	CORE CLIMBERS: (started Core and increased specialists)	51%	18%	92	\$102.8
	CORE UNCHANGED: (started Core and no change in number of specialists)	5%	-5%	98	\$55.5
	CORE DECLINERS: (lost specialists but stayed Core)	-2%	2%	108	\$78.6
	CORE TO PERIPHERAL: (lost all specialists)	-10%	-24%	33	\$8.2
	CORE CLIMBERS:	51%	18%	92	\$102.8
	LEFT BEHIND CORE W/O CLIMBERS: (sum of "Core Unchanged" and "Core Decliners")	1%	-1%	206	\$134.1

Here we show performance of companies that remained listed at the end of 2023 based on their change in Coreness. We looked at results for both a simple increase or decrease in the number of specialists and also an increase or decrease of at least two specialists. Results were similar, so we stuck with the simpler definition of any increase or decrease.

How is any of this actionable? We're not proposing that any company can engineer its own success by any means other than just executing well on its plan. If you cure cancer and decide to raise entirely from retail investors and generalist funds, your stock will no doubt still do great, because what matters is curing cancer. But it's rarely so easy. Companies often study 13F changes with their boards to try to understand how investors are thinking about them. So now our analysis poses the hypothesis that companies really should be concerned about losing the absolute number of specialists they count amongst their holders. It seems to bode poorly for

Before we assume more specialists is better, though, note that gaining specialists was important but starting with a large number of specialists was not. In fact, the number of specialists at the start of the year was a poor predictor of average returns; those companies that were still trading at the end of 2023 and started the year with seven or more specialists returned 0%, on average, while those with three to six specialists returned an average of +27%, and those with one to two specialists +5%. This is just a hypothesis since we're still engaging in egregious data mining and will need prospective 2024 before we bother to probe for causality.

stock performance and therefore access to capital. It's worth trying to understand why those specialists are selling even if you are happy to be picking up other shareholders.

BUT WASN'T 2023 PERFORMANCE ALL ABOUT INTEREST RATES?

XBI performance in 2023 was punctuated by several macro events: the failure of SVB and other regional bank weakness in March along with several meetings of the Federal Reserve's Open Market Committee (FOMC, the group responsible for setting rates). But we ended the year roughly where we started: with the 10-year yield at YE22 vs. YE23 at 3.88% vs. 3.84% (link), respectively, or, inflation-adjusted, 1.58% vs. 1.68% (link). Certainly, 2023 performance would look different had the FOMC stuck with the dreary tone they set in September due to

concern that there really would be much higher inflation for the long run – but they didn't, which is why we focus our analysis on sector fundamentals vs. some of the macro drivers that contributed to sector volatility during the year (FIGURE 6).

While many people would cite interest rates as evidence for why development-stage biotech was out of favor (since profits are distant and more heavily discounted), that never struck us as the real reason people were staying away. After all,

when duly inspired by AI or obesity drugs, investors were quick to bid up those assets. We think interest rate talk was an excuse for something else. The fact is that most generalists never really understood biotech enough to have conviction in its fundamentals. During times of fear, they sell whatever doesn't feel safe. To buy biotech, either they need to understand it well or else fear missing out more than they fear the uncertainty of biotech. Obesity drugs inspired the fear of missing out. Most other companies didn't.

To specialists, biotech can feel safe; we love nothing more than a robust data set to reassure us that a company is likely to prosper, even if its stock is cratering due to something the Fed said. But to generalists, when they don't really understand the data, then watching stocks decline likely makes them wonder what they are missing. That's how we feel about most stocks outside of biotech; we have no conviction in McDonald's or Disney because we can't account for people's tastes as far into the future as their valuations require us to look. Other investors seem to understand these things better but to us consumer preferences for food and entertainment feel shaky.

FIGURE 6:
2023's LONG, STRANGE MACRO ROUND-TRIP



A tour of 2023's relevant macro events, emoji-annotated for SVB crisis (came and went in a matter of days) and that interesting time in the fall when the Fed (FOMC) talked the world into a case of the flu, gave biotech Ebola, and then said "okay, y'all have had enough."

SOURCE: FactSet

BUT WASN'T 2023 PERFORMANCE ALL ABOUT INTEREST RATES? (CONTINUED)

On the other hand, we do know that people prioritize better health and avoidance of suffering. That's not a taste. That's the essence of life itself. The way we look at it, in the long run, if anything is going to be inflating when there's inflation, it's going to be medicines. Novel medicines have pricing power and are one of society's best tools to combat inflation in healthcare services (because hospital costs only climb and they never go generic but drugs keep us out of hospitals and eventually go generic, continuing to keep us out of hospitals inexpensively). And that's what anchors us to biotech even when interest rate talk is scaring others away; biotech is a safe harbor in the storm.

So while we can correlate biotech's performance over 2023 with interest rates, we don't actually believe that such fluctuations necessarily merited such volatility. Rather, much as fear of a bank-run is self-fulfilling, we think fear of inflation and interest rate increases being bad for biotech is self-fulfilling. So interest rate fluctuations were a real driver of biotech performance because people thought they should be... except when they didn't let that stop them buying up companies that really excited them.

Now that more investors are dropping the interest rate excuse, more biotech companies will hopefully find it easier to remind investors that they are also part of an exciting future and offer returns well in excess of long-term, low-risk rates.

**BOTTOM FISHING AMONGST THE NegEVs:
REWARDS FOR THOSE WHO CAST THEIR NETS**

Now let's turn again to companies that started 2023 in positions of weakness, with negative enterprise values (NegEV).

Classifying companies based on Core vs. Peripheral reflects the subjective judgements of only specialists. But valuation takes the whole market's judgment of companies into account. When a company trades below cash, that's a sign that investors don't see much value to their business and maybe even consider it a liability that the cash is going to be squandered. That's pretty damning.

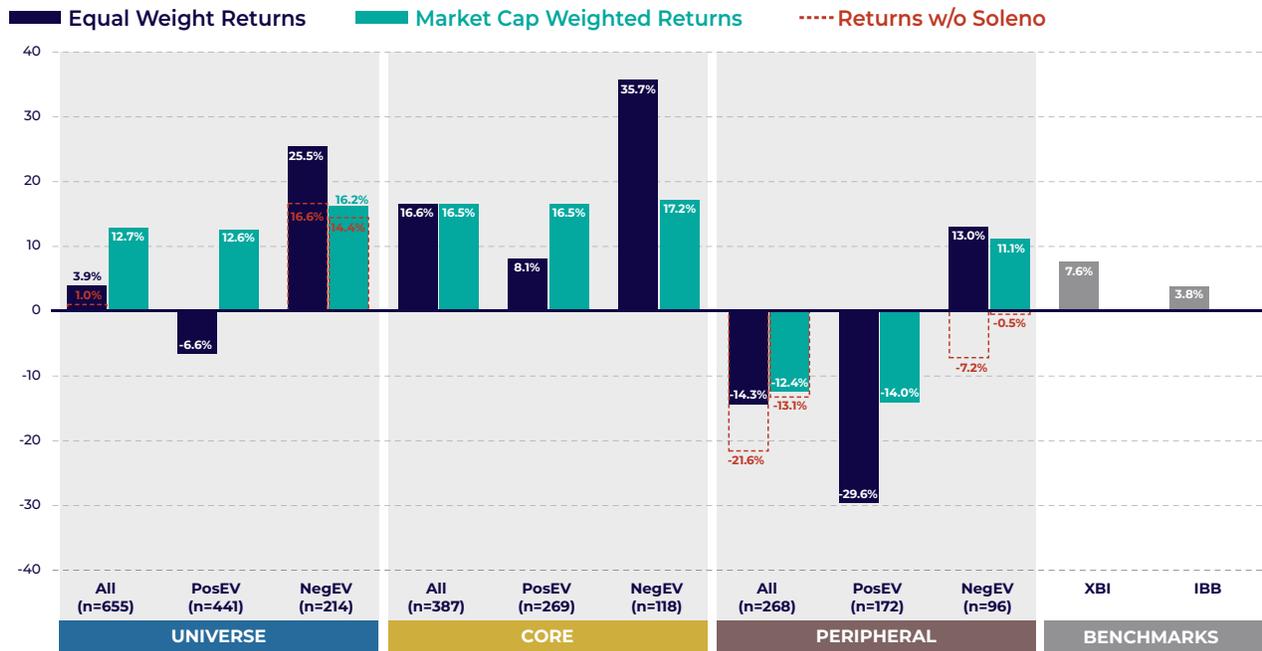
Here's the bottom line: While too small to drive returns for the sector, Core NegEV companies performed fairly well in 2023, offering an attractive set of opportunities for funds willing to do the work.

We looked at NegEV vs. PosEV for the Universe, Core, and Peripheral sets. To make room for the extra data cuts in **FIGURE 7**, we'll now drop the Liquidity Constrained Weighting and only include just Equal Weighting (EQW) and Market Cap Weighting (MCW).

Note how EQW yields more erratic values than MCW. That's because EQW gives tiny microcaps equal standing with the larger caps. That's absurd and unrealistic for professional investors who direct most of the capital that flows to development-stage biotech; MCW is more appropriate for them. NegEV companies make up only 3.7% of the Universe on a market cap weighted basis (**TABLE 1**). Still, you have both perspectives here and if you want to take the perspective of a tiny fund manager or retail investor, then EQW is an acceptable measure.

FIGURE 7 shows the NegEV companies performed comparably to if not better than PosEV companies in 2023. Why might that be? After all, when a company trades below cash, isn't that the market saying that it offers nothing of value? The market isn't always right, of course, but it is strange to see it be so wrong. Maybe these stocks had declined in 2022 and were extra depressed at YE22 due to tax loss selling and rebounded in 2023, especially with their cash cushioning against much further downside.

FIGURE 7:
NegEV OUTPERFORMANCE: NICE RETURNS IF YOU CAN GET THEM



Universe, Core, and Peripheral are now split into companies that started 2023 with a positive enterprise value (PosEV) or negative EV (NegEV). What we see is that NegEV held up pretty well and arguably outperformed, especially if you have a small portfolio and can buy stakes in NegEV companies that are meaningful to you, which larger investors can't since the whole NegEV class makes up only 3.7% of the Universe by market cap (Table 1). Because Soleno was a component of the Peripheral NegEV set and surged by over +1900% in 2023, it single-handedly drove that group up, so we also show what happened if you removed Soleno (dashed bars).

SOURCE: Bloomberg, FactSet, RA Capital

Also, there were a few star performers among the NegEV set. Ambryx is worth calling out as a company that started 2023 in the Core NegEV category and surged over +500% in 2023 on the back of responses in a small oncology study. According to our analysis, Soleno started 2023 as a Peripheral NegEV company and surged by over +1900% on positive data from their Prader-Willi trial (and is now owned by multiple specialists and is therefore Core). In fact, Soleno was such an outlier that it alone moved the entire Peripheral NegEV category from being negative on the year (see dashed bar in **FIGURE 7**) to positive. When you look deeper, you'll see that Soleno actually did a structured financing in 4Q22 that wasn't picked up by 13F filings, so even in this case, it was kind of Core. We think it's cool to see specialists sniff out a gem like this among the Peripheral companies.

NegEV companies are denigrated by some and certainly no board or management team would ever relish having their enterprise value wiped out. But these companies offer opportunities for

bottom fishing for those with the wits and courage to do the work. Kudos to the management teams and investors who unlocked value from these NegEV situations. Let's do more of that in 2024.

DANGER ZONE: THE REAL DANGER LIES IN A SMALLER ZONE THAN WE THOUGHT

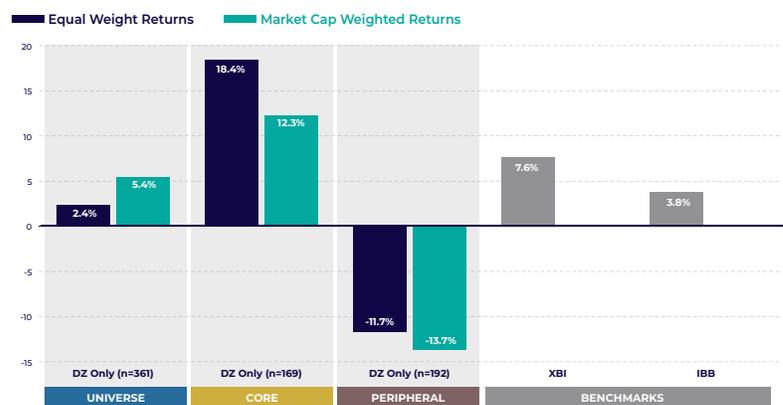
If we told you that a company has less than two years of cash and a burn rate that is at least a quarter of its valuation, would you find that uncomfortable? Odds are, that company will want to finance in the next year and to raise even one more year of cash, it would need to sell over a quarter of its market cap. So consider how a company with a \$400M market cap burning \$100M/year would need to raise another \$100M just to extend runway by a year, let alone longer. That's quite a bit to ask of specialists when the company's low valuation suggests it's probably low-ranked in their portfolios. You might expect that financing to be done at a discount. Would you want to buy that stock ahead of the financing? And once they finance at a discount, that financing probably would absorb a lot of demand, so would it even perform all that well thereafter? Now imagine that the burn rate is half of the market cap! Yikes, right?

A year ago, when we first defined the Danger Zone (DZ) as <2 years of cash and >25% burn/market cap ratio (burn/MC), we did so precisely because most people would agree that this felt dangerous and to point out that DZ companies have a low weighting in the Universe, Core set, and specialist portfolios and therefore don't actually represent much risk to the performance of the sector.

But now we're a year on and can look back to see how those stocks performed. **FIGURE 8** shows that DZ companies did not do all that poorly. DZ Core was up +12.3% on a MCW basis, only a little worse than the +16.5% performance of Core overall. DZ Peripheral companies were down -13.7%, only slightly worse than the -12.4% of Peripheral companies overall.

Okay, so being a Peripheral company (no specialist holders) sets a company up for difficulty, DZ or no DZ. But for Core companies, it seems like maybe the Danger Zone isn't so dangerous. Isn't that odd? Does cash runway and relative burn rate just not matter?

**FIGURE 8:
DANGER ZONE WASN'T SO DANGEROUS**



We say a company is in the Danger Zone if a company has <2 years of cash and is burning >25% of their market capitalization since a financing seems likely in the near term and yet may prove challenging. While companies in the Danger Zone slightly underperformed the whole set (not shown but see **FIGURE 3**), Core DZ companies did well enough that we have to admit that the Danger Zone doesn't seem as dangerous as we thought.

SOURCE: Bloomberg, FactSet, RA Capital

So we ran this to ground with... what else?... MORE DATA! (TABLE 4.)

NARROWING THE DANGER ZONE

Turns out, one's burn/MC ratio doesn't play a very important role in defining the Danger Zone. It comes down to years of cash. Those companies with >1YoC performed well. Those with less did terribly, for the most part.

So how could it be that a Core company that started 2023 with only 1-2 years of cash but a high burn rate, even in excess of even 50% of its market cap, performed well? One answer may be that they started the year with a low enough market cap (and therefore their burn rates were not actually as eye-popping as the ratios would lead one to think) that they offered more upside than downside. In the more extreme cases, they were NegEV companies, which we already saw performed well.

TABLE 4:
NARROWING THE DANGER ZONE TO <1 YEAR OF CASH

Burn/ MC Ratio	<1 YOY (CORE ONLY)						1-2 YOY (CORE ONLY)						2+ YOY (CORE ONLY)						ALL YOY					
	EQW returns	MCW returns	n	Avg. MC (\$M)	Avg. EV (\$M)	w. Core	EQW returns	MCW returns	n	Avg. MC (\$M)	Avg. EV (\$M)	w. Core	EQW returns	MCW returns	n	Avg. MC (\$M)	Avg. EV (\$M)	w. Core	EQW returns	MCW returns	n	Avg. MC (\$M)	Avg. EV (\$M)	w. Core
<25%	6.4%	16.1%	5	\$939	\$886	2%	37.2%	19.0%	35	\$1,568	\$1,379	19%	8.5%	18.6%	109	\$1,576	\$1,192	61%	15.2%	18.6%	149	\$1,553	\$1,226	82%
26% - 50%	13.0%	-17.5%	11	\$347	\$287	1%	15.5%	17.3%	37	\$413	\$274	5%	8.2%	-3.8%	39	\$463	\$110	6%	11.9%	3.5%	87	\$427	\$202	13%
51% - 75%	-27.0%	-14.5%	10	\$199	\$161	1%	45.8%	23.4%	21	\$169	\$3	1%	8.6%	15.9%	14	\$164	\$(2)	1%	18.0%	11.6%	45	\$174	\$37	3%
>75%	-21.3%	-21.7%	39	\$29	\$10	0%	49.5%	36.7%	51	\$74	\$(5)	1%	37.3%	27.6%	16	\$59	\$(95)	0%	21.6%	23.9%	106	\$55	\$(35)	2%
>0 (ALL)	-14.2%	-3.8%	65	\$179	\$147	4%	37.3%	19.7%	144	\$538	\$388	27%	11.0%	16.5%	178	\$1,085	\$745	68%	16.6%	16.5%	387	\$729	\$512	100%

We show all of Core broken down by years of cash and burn/MC ratio, with negative performance represented by red cells. Since Core was up +16.5% overall, being positive doesn't mean that a given segment didn't underperform. Still, we are looking for what the true Danger Zone might be and would expect that to be where we see red. We are surprised to see almost no red for companies with >1 year of cash, even when they have a very high burn to market cap ratio. For each category/group, we show the number of companies, average market cap, average enterprise value (EV), and percent of the total Core market capitalization that the group represents, which shows that most of the sector is in a strong financial position

SOURCE: Bloomberg, FactSet, RA Capital

For example, the average company with 1-2 YoC and a 50-75% burn/MC ratio was trading at cash with a market cap of \$169M and needed to raise ~\$90M to fund another year. That's doable for the right company and indeed there were a handful of companies that started 2023 in this zone that got the funding they needed and performed well. Notably, in this group of 21 companies, Eyepoint and Ambrx both climbed >500% in 2023 on good data.

We shouldn't give the impression that this zone isn't dangerous. Most companies in this set had negative returns (median: -18%), but then again the median Core company was down -13% in 2023, so we're saying that this seemingly risky zone wasn't all that riskier than Core biotech in general.

Go to the even riskier companies with 1-2 YoC and burn rates >75% of their market caps and you find 51 companies with an average market cap of \$74M and therefore an even more modest burn

rate, but these started 2023 with an average EV of -\$51M. This group did very well and had a lot of transformational activity. Many slashed their burn rates to extend their runways. Several of these companies were taken private for close to the cash on their books. Data can rescue companies from sticky financial situations. Outliers include Olema and Sigilon with >400% returns sparked by good data (the latter was acquired by Lilly). Inozyme and TScan were both up over 250% on good data, while Orchard was up over 300% on being acquired by Kyowa Kirin. Having <2 years of cash and a high relative burn rate still feels dangerous, but it's clearly not dangerous enough to keep companies from persevering and doing well for their shareholders.

Notice the one red spot among the >1YoC companies? Is that real? It's the MCW performance of companies that had 2+ YoC and 25-50% burn/MC ratios. We think it's a fluke because 1) EQW performance is similar, so the effect is likely driven by a few large blow ups and 2) even riskier companies with 1-2 YoC and the same burn/MC ratio had a similar market cap (\$413M vs. \$463M) and higher EV and performed well.

When you get below one year of cash, we see a very different story. Now, the burn/MC ratio matters a lot. Companies with <1YoC and a >25% burn/MC ratio underperformed in 2023. We think the most likely reason for this is adverse selection. Most companies try to raise before they fall below one year of cash. So if they started 2023 in that condition, they likely had failed to raise sometime in 2H22. That means that 0.9 years of cash and 1.1 years of cash are not just slightly different; they are qualitatively different. The former are companies that were vetoed by specialists at maybe even any price and the latter might not yet have tried to raise and so include companies that have not yet been vetoed.

...our hypothesis is that a company is in danger only when it tries to raise money but fails.

Do we have proof?

Why is one year special? Because when a company falls below one year of cash, it earns a "going concern" clause. It's actually a minor issue from an operating standpoint (nothing much changes) except that most companies avoid it like

the plague thinking it's a big deal to investors (it's not). If a company with a year of cash and key data expected in a few months simply decided not to bother trying to raise until after data, then it would not necessarily be subject to adverse selection; we wrote recently in ["A Going Clause Isn't Always a Concern,"](#) a couple of companies appeared to do just that with aplomb.

So there is a Danger Zone but it's not where we thought. The Danger Zone on its surface appears to be getting below one year of cash. But our hypothesis is that a company is in danger only when it tries to raise money but fails. Do we have proof?

It's not definitive, but take a look at the set of companies that had less than a year of cash but <25% burn to market ratio. There were just five of them and this group performed well. Why might that be? From the data, we see that specialists valued them more. These five companies had an average market cap (>\$900M) that was notably higher than other companies with <1 YoC.

In fact, three of them have products on the market and growing revenues; while none of them were projected at the end of 2022 to be profitable in 2023, their burn rates were clearly not static but rather linked to growing sales. And they had a downside protection from their marketed products; for example, they could avail themselves of a royalty financing. The other two companies didn't have marketed products and cratered by ~70% of the course of 2023.

For companies in the Core, “financing overhang” doesn’t matter... until you discover that you can’t raise, and then it matters a lot.

So in the case of the few companies with <1YoC and low burn, we think we are witnessing positive selection by specialists for companies that, despite getting to an unusually low amount of cash on their books, still offered something special that kept investors engaged, notably commercial products. And when these companies need to raise, financing isn't all that hard considering how low their burn rates were relative to their valuations.

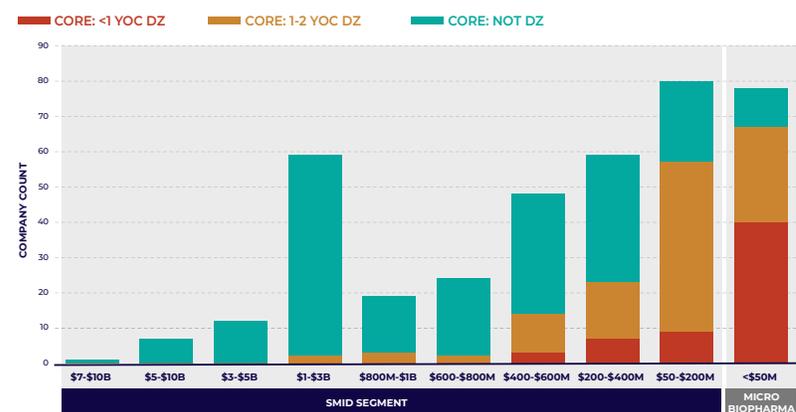
We found these new insights on Danger Zone companies liberating. For companies in the Core, “financing overhang” doesn't matter... until you discover that you can't raise, and then it matters a lot. Provided you believe the company is doing something worthy of attracting additional capital, even exceptionally high burn to market cap is not a sure sign that the share price will suffer.

SPECIALISTS ARE IN LITTLE DANGER

Whether we define the Danger Zone the old way or tighten it up, specialists have little exposure to these companies when we adjust for their market capitalizations.

FIGURE 9A shows the number of Core companies by market cap and colors the ones we classified as being in the Danger Zone. While both red and orange meet the old criteria for being in the Danger Zone (<2 YoC and >25% burn/MC ratio), only the red now meets the new criteria (<1 YoC and >25% burn/

FIGURE 9A: SAFETY IN THE CORE: FEW COMPANIES IN THE “NEW” DANGER ZONE

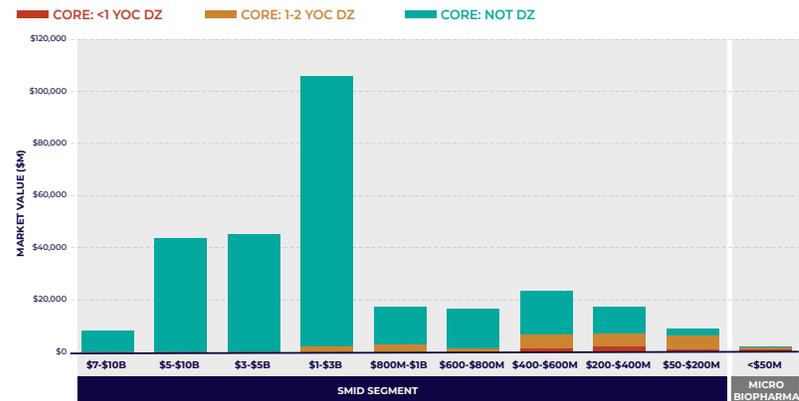


We show the number of companies in market cap segments in degree of “Danger” based on their YE23 valuations and 3Q23 financial statements. Note how there are far fewer companies in the “new” danger zone (<1YoC and >25% burn/MC ratio), mainly concentrated in micro caps.

SOURCE: Bloomberg, FactSet, RA Capital

MC ratio). Even just looking at the red, the counts sure do make it look like there are a lot of companies in danger. And yet, **FIGURE 9B** shows that when you adjust for market cap, you barely can discern any red at all. There's not even much orange. This is what the sector looks like to specialists. It feels reasonably well capitalized and financeable. And now that we have adjusted the parameters of the Danger Zone, it's even less dangerous than we thought.

FIGURE 9B: SAFETY IN THE CORE: WHERE DID THE DANGER GO?



When we look at the “new” Danger Zone on a market cap weighted basis, the weighting to Danger Zone – already low with our old definition – all but disappears.

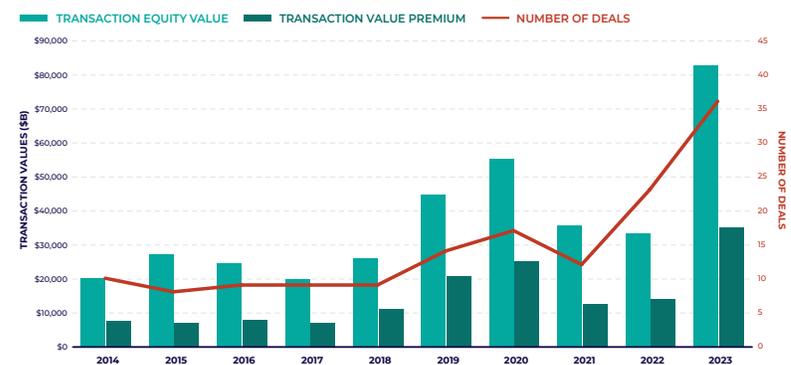
SOURCE: Bloomberg, FactSet, RA Capital

PART 2: BUYERS GOTTA BUY

Let's return to M&A, which set new records in 2023. **FIGURE 10** shows that 2023 M&A levels exceeded past years not only in the number of deals but also the total M&A dollars deployed. Considering the depressed valuations, that's saying something.

We also plot a number that we don't see elsewhere but that is really the most important M&A number worth tracking: the cumulative premium dollars paid. Only that number represents a gain to investors. If M&A weren't done at a premium, it would simply serve as a liquidity event, which is useful, especially for the taxman. But it's the premiums that generate a return on investment, and the \$35.2B returned by M&A in 2023 was notable considering the \$324B cumulative valuation of the Universe at the start of 2023 (+10.9% return).

FIGURE 10: A RECORD YEAR FOR M&A IN THE DEVELOPMENT-STAGE BIOTECH UNIVERSE



2023 was a record year for M&A within the biotech <\$10B public development-stage Universe in terms of total deals, total M&A dollars to equity holders, and total M&A premium. We include acquisitions of companies in the Universe by year of announcement and calculate premiums based on the deal price vs. the average price in the 20 days before the deal was announced. For companies with CVRs, the acquisition premium is based on where the stock was trading immediately prior to close, which reflects the expected value of the CVR to investors.

SOURCE: Bloomberg, FactSet, RA Capital

Again, it's not enough to merely count acquisitions since we see that there are more acquisitions in 2023 than ever before yet the total dollars only slightly exceed those of 2020 (and yet the percent returns from M&A were lower then because total valuations were higher).

FIGURE 11 shows that 99% of that cash flowed to Core companies. This is simply to say that before a company is acquired, at least one peer specialist manages to get there first. As we've said, it's a low bar to be called Core, even if only 59% of the biotech Universe made the cut at the start of 2023. When we raise the bar, we see that 94% of M&A cash goes to Double-Core and 92% goes to Triple-Core (companies owned by at least two and at least three peer specialists, respectively).

Only 34% of the Universe made the Triple-Core cut. That's quite an enrichment to see that in 2023 >90% of M&A gains flowed to the third of the biotech Universe owned by at least three specialists. It's worth noting that this is consistent with data for past years, which we presented in the Semper Maior article we pushed last year.

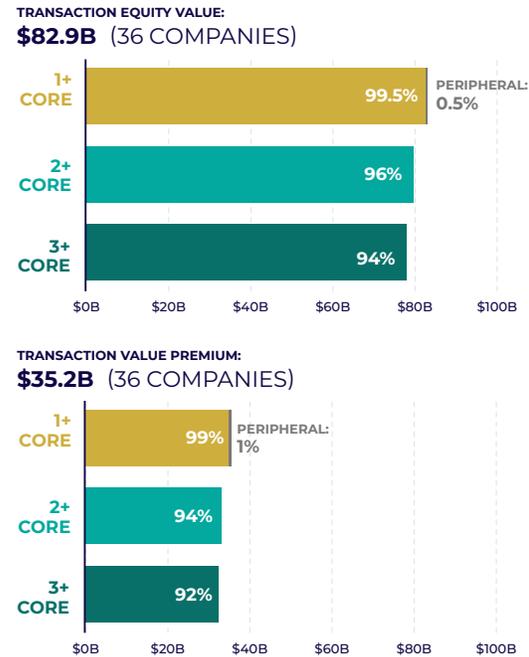
This means that 99% of the \$35.2B premium, or \$35B, flowed to the \$282B cumulative valuation of Core companies (as of YE22), generating a 12.4% return.

We lay out these data in **TABLE 5**.

In the case of double core, the return from M&A was +13.5% (94% x \$35.2B divided by the cumulative valuation at the start of 2023 of 2+ Core companies, \$246B) and for triple core it was +15.8% (92% of \$35.2B divided by \$204B). Keep in mind that we calculate M&A return as of the day the deal is announced, not closed; that's a better reflection of when investors generated their return since many could sell on the news.

For investors who pride themselves on originality, it's a bit unnerving to see that M&A returns are higher for companies owned by more specialists. And yet, 2023 was an unusual year in that companies with high-quality, derisked assets traded at such low valuations (presumably because many generalists cut back on their biotech exposure indiscriminately) that many specialists saw the same \$100 bills lying on the sidewalk and reached for them.

FIGURE 11:
M&A DOLLARS AND PREMIUMS FLOWED TO THE CORE IN 2023



Share of total M&A dollars and M&A premium dollars that went to Core vs. Peripheral. We include here not only regular Core (defined by having one or more specialist shareholders at the time of acquisition), but also Double Core (two or more specialists) and Triple Core (three or more). Bottom line is that a few specialists almost always get to a company before it is acquired.

SOURCE: Bloomberg, FactSet, RA Capital

TABLE 5:

HIGHER RETURNS FROM M&A FOR COMPANIES WITH MULTIPLE SPECIALISTS

	Number of Companies (as of YE22)	Cumulative Market Cap (\$B, as of YE22)	Share of 2023 M&A Premium (% of total)	Return (using proportions from 2023 M&A)
ALL	655	\$324	\$35B (100%)	10.9%
≥ 1 CORE	387 (59%)	\$282 (87%)	\$35B (99.5%)	12.4%
≥ 2 CORE	287 (44%)	\$246 (76%)	\$33B (94%)	13.5%
≥ 3 CORE	220 (34%)	\$204 (63%)	\$32B (92%)	15.8%
1-2 CORE	167 (25%)	\$78 (24%)	\$3B (8%)	3.5%
PERIPHERAL	268 (41%)	\$42 (13%)	\$0.2B (0.5%)	0.4%

Return from M&A to the Universe, Peripheral, and Core as defined by number of specialist holders as of the time a deal was announced. Strategics rarely buy Peripheral companies and we see more of the returns accrue to Core but especially to companies that had more than two specialist holders.

SOURCE: Bloomberg, FactSet, RA Capital

If we had to guess, we would say that if only one or two specialist investors saw value in a given company, then odds are that they were either stuck in a struggling name (e.g., from having founded the company) or were new to a name and seeing an opportunity that still needed time to mature before strategics would be likely to take an interest. So one wouldn't expect those to be acquired. In fact, we see that the return from M&A to the set of companies that had only one or two peer specialist shareholders was only +3.5%.

Kind of makes you wonder what the return was for those that had more specialists.

The most peer specialists that any company had at the time of acquisition was 11 (which is pretty modest considering that we track 41 specialist firms), and that one company was acquired (can you guess? Answer in the footnotes²). Leaving that aside, it seems the sweet spot, as evidenced by the absolutely horrific post hoc data mining we present in **TABLE 6**, is having at least six specialists.

There were 83 companies that had at least six specialist holders at YE22 (based on the 3Q22 13F), adding up to a cumulative valuation of \$100B as of YE22; since companies with 6+ specialists captured 75% of the \$35.2B of M&A premiums we saw in 2023, we estimate that the return to 6+ Core from M&A was an impressive +26.6%.

Although the FTC seems determined to throw sand into the works, we think the current pace of M&A is rational for as long as there are quality assets to buy since big pharma is always looking to replenish their sales forecasts to offset revenues they expect to lose due to patent expiries and, soon, Medicare “negotiation.”

² Iveric [ISEE], acquired by Astellas for 64% premium.

TABLE 6:

JUST FOR FUN: WHAT NUMBER OF SPECIALISTS GENERATED THE HIGHEST RETURNS FROM M&A?

CORENESS: Number of peer holders at time of acquisition	Number of Companies (as of YE22)	Cumulative Market Cap (\$B, as of YE22)	Share of 2023 M&A Premium (% of total)	Return (using proportions from 2023 M&A)
≥ 12	5	\$16	\$0B (0%)	0.00%
≥ 11	7	\$18	\$4B (11%)	20.6%
≥ 10	14	\$26	\$5B (15%)	20.1%
≥ 9	18	\$29	\$8B (22%)	26.0%
≥ 8	37	\$56	\$8B (23%)	14.3%
≥ 7	56	\$75	\$18B (50%)	23.6%
≥ 6	83	\$100	\$27B (75%)	26.6%
≥ 5	118	\$138	\$28B (81%)	20.6%
≥ 4	166	\$185	\$31B (89%)	17.0%
≥ 3	220	\$204	\$32B (92%)	15.8%
≥ 2	287	\$246	\$33B (94%)	13.5%
≥ 1 (CORE)	387	\$282	\$35.1B (99.5%)	12.4%
≥ 0 (ALL UNIVERSE)	655	\$324	\$35.2B (100%)	10.9%
= 0 (PERIPHERAL)	268	\$42	\$0.2B (0.5%)	0.4%

Absolutely horrible post hoc data mining of M&A returns to groupings of companies based on the number of specialist shareholders they had at the time of acquisition. Return from M&A is calculated as M&A premium over the cumulative market cap of companies by “coreness” (cumulative market cap includes companies that were acquired as well as those that were not acquired). The more specialists, the higher the return from M&A, to a point. So clearly CEOs should shoo away any specialists if they don’t want their companies to get acquired. Note that we calculate the value of all companies with a certain number of shareholders by looking at 3Q22 13Fs and YE22 valuations. However, when the acquisitions actually happen, we look at how many holders there were just prior to the acquisition. In some cases, we referenced 13Fs that came out after the acquisition was announced. If an acquisition is announced in mid-April 2023, the company might have had five specialists as of 3Q22 but had eight by the end of March 2023, something we would only see by inspecting the 1Q23 13F issued in mid-May 2023. So we would score it as a win for the 8+ category and use 3Q22 13F data to identify all the 8+ companies and then use their YE22 valuations to estimate the total YE22 valuation of all 8+ companies. We could have done this analysis in a variety of ways but we had more important things to do than more post hoc data torture.

SOURCE: Bloomberg, FactSet, RA Capital

What we find particularly interesting is just how small the pool of targets is relative to the strategics’ Free Cash Flows (FCF). As **FIGURE 12** shows, it would take only 3.3 years of FCF (at 2023 level) for the strategics to acquire all remaining Core companies for a 100% premium. This is well below the levels of 2020 and 2021 and in the zone of 2017-2018. What’s interesting is that, if Core companies stay at their current prices, then the ratio will drop down to 2.6 years over the next couple of years simply from strategics’ FCF growth. .

Just as counting companies doesn't tell us much, neither does looking at the cumulative valuation of biotechs; everything is relative. And in this case, we think it's relative to the size of the strategics and the free cash flows that they both need to sustain and replenish.

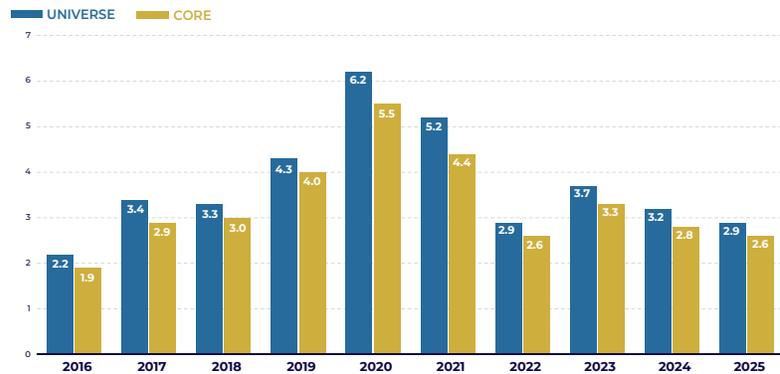
And now let's look forward two years to YE25. Consider that the Core market cap at YE23 stood at \$312B after more than \$80B of market capitalization was removed via M&A over the course of the year. If we see even \$50B of M&A in each of the next two years, then Core would be almost one third smaller than we project, which would make the 2025 ratio stand at 1.7 years of FCF, lower than the nadir of 2016. And we mustn't overlook that plenty of companies will fail in the next two years, so the acquisition ratio of the Left Behind companies two years from now would be lower still – unless they increase in value and/or the public pool is replenished with more companies crossing over. And that's saying something because we would argue that today's set of target companies is a lot more mature (i.e., later stage, more derisked) than the companies we had back then. Big Biopharma's FCF is much greater than it was in 2016, but that's also the point: that they are growing and need to ingest more to sustain themselves.

We think the next two years will see investors earning a return not only from acquisitions but from the appreciation of the companies left behind, which will in turn attract more companies to cross over to the public side, replenishing the pool and keeping the acquisition ratio within historical norms.

We've spoken so much of acquisitions that we must clarify that we are well aware that not all companies wish to be acquired. As investors, we certainly don't wish for every company to be acquired. Wouldn't it be remarkable to create another Vertex?

But even if one wished to be acquired, wishing is pointless. As experienced board members and investors know, companies are bought, not sold. If a company has funding to get through Phase 2 proof-of-concept data and then hopes that an acquisition will spare it from having to solve for how it will fund expensive Phase 3 trials, then disaster looms, because strategics may not feel like

FIGURE 12:
YEARS OF STRATEGICS' FREE CASH FLOW NEEDED TO ACQUIRE BIOTECH UNIVERSE WITH A 100% PREMIUM



Years of Strategics' Free Cash Flows needed to acquire the whole Biotech Universe for a 100% premium. We're not doing this to suggest that strategics would or should acquire all biotech companies for a 100% premium; that would be silly... it should be a 200% premium. Okay, no... we're just doing this to show how small the target pool is relative to the cash flows that acquirers generate. We're not even counting all the cash that strategics already have on their balance sheets. Because this was created as part of a different historical analysis that predated the Semper Maior series, it is based on data that exclude companies <\$50M in market cap (and it's a ton of work to redo going back to 2016), but this impact of this is so tiny that it doesn't change the results anyways.

SOURCE: Bloomberg, FactSet, RA Capital

getting out of bed at that moment. A company needs a path to success on a standalone basis because M&A cannot be engineered or relied upon. When there is an interested potential buyer, and often there is only one, they won't pay much of a premium if they smell financial weakness and desperation. However you look at it, success requires operating like you won't be acquired.³

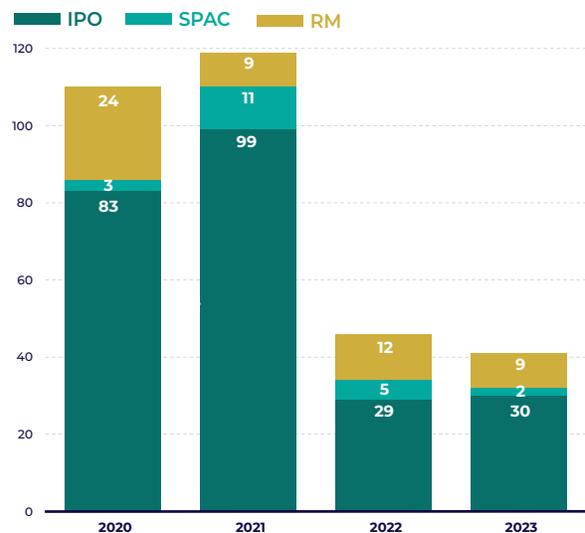
PART 3: RESTARTING THE CROSSOVER CONVEYOR BELT

This whole article so far has been about public companies; it makes it seem that private companies somehow don't matter when in fact they matter a lot. Our team spends a lot of its time on private companies. We got to know most of the companies in our public portfolio while they were still private. Our future portfolio is likely being seeded by our private investments. We analyze public data because that's where the data are rich; between financials, pricing data, and 13F statements, it's nerd nirvana. The public markets are also directly relevant to private companies' financing prospects. There's much less information to work with on the private side.

We meet with thousands of companies each year, most of them private. Many of those are little more than a few people with a slide deck. Some have raised too little to be credibly engaged in drug R&D. You can't just count everything as the same. To give you a sense for the scale, Pitchbook tracks over 3600 private biotech companies (not counting devices or diagnostics) that raised at least \$10M in one financing with at least one VC involved within the last three years, with another 1500 that raised smaller amounts.

For the last few years, with less crossover activity, the private and public sides of the sector have likely felt separate to many people. Everyone with private portfolios had to figure out how to survive being trapped on the private side and make the most of the cash available there, because the public markets seemed like frozen tundra not worth venturing into (with few exceptions). Investors who could invest in

FIGURE 13:
HOW PRIVATE COMPANIES WENT PUBLIC



41 private R&D-stage biotech companies went public in 2023. Note that this means that only 32 new entities entered the Universe pool (this drops to 31 when we remove RayzeBio, which was acquired soon after IPO'ing) since reverse mergers don't change the count.

SOURCE: Bloomberg, FactSet, RA Capital

³ Those who wish to learn more about M&A strategy and tactics can look forward to more on these topics from seasoned directors and bankers featured in RA Capital's [Gateway](#), a resource for executives and current and future board members.

publics seemed to focus only on publics; it's like private companies were invisible.

And yet, biotech is one sector, private and public. Even when the crossover conveyor belt slows for several years (**FIGURE 13**), that's still a short period of time. The future of the public biotech sector was developing these last several years on the private side. If they aren't acquired first, the best of these companies go public. They almost have to. Very few private companies manage to get through drug development to profitability while staying private. That's not failure, it's reality; the sums required to fund R&D get so big that one has to access the public markets (or else partner or sell, which isn't necessarily more compelling). It's just a question of valuation, and maybe how to choose among the menu of options for going public.

Indeed, we think we'll see more crossover financings and companies going public in 2024. After the surge in valuations in December, we don't think our prediction is all that controversial, though realizing this prediction won't be all that easy. Consider, for example, that including the December surge, the valuations of the Left Behind Core companies only increased about +6% in 2023. Since pre-IPO private companies typically have to compare themselves to public ones and those public comps were valuation-challenged throughout all of 2023, we're not yet in dramatically different territory. Crossover investors are likely to be quite selective.

So let's delve a bit deeper and consider which companies might realize this prophecy.

REASONS FOR REACTIVATION

There are two reasons for the slow pace of companies going public these last two years, one on the demand side and one on the supply side. On the demand side, crossover and public investors simply had too many deeply undervalued, derisked, and comparatively liquid public companies to invest in to go hunting for crossover rounds and IPOs. Of course, demand can be stimulated by lowering the price of a deal, but that then gets to the supply side of the equation: Many private companies were anchored to their last private valuation. If that valuation was set back in 2021, it was most likely too high given where the markets sat throughout most of the last two years.

Such companies likely preferred insider flat rounds when necessary, putting off as best they could the down-rounds typically required to attract new investors, especially into an IPO. Whether they could do that depended on whether their shareholders had the cash to keep bridging them. When some of those existing shareholders ran out of money or just weren't willing to put more in, either new investors were needed or the other insiders were obliged to put in a super pro rata amount, which made them valuation sensitive. In those cases, companies tended to get repriced or were saddled with non-standard provisions (e.g., 2x participation), which is functionally like a repricing.

Of course there were exceptions (GLP-1!), which helped remind everyone that the crossover and IPO machinery wasn't broken. As always, it's just a matter of fundamentals and price.

By this point, quite a few private companies that have survived this downturn (many didn't), have matured their pipelines and/or done down-rounds such that they are more likely to be able to attract investors to a crossover and/or IPO.

Many of the companies ready to go public were formed prior to this downturn and therefore have been subjected to the crucible of cash constraint. They may have stayed private much longer than anticipated. If they have made good progress with their pipelines, they are further along now than they expected to be before going public and will be able to cite more attractive public comparables. Public companies without proof-of-concept data are still struggling in these markets.

A third factor likely to push companies to consider the public path is that crossover funds are probably still pretty full on the private sides of their portfolios since there have been few crossover events these last two years. Due to their structures, they simply don't have the fresh funds to participate in a private round (including a crossover round). They need to create room for private rounds by moving some of their existing private companies to the public side. So all else being equal, these investors are likely to offer their companies bigger checks if they opt for an IPO than if they stick to private rounds.

As companies 1) find there is less cash for private rounds and more cash for public rounds and 2) if they have modest-enough valuation expectations and are 3) far enough along in derisking their pipelines that investors perceive risk-adjusted upside relative to existing public comps, they will find that they can go public and would even prefer it to trying for a private round.

The fourth ingredient is the courage to recognize that an IPO is just another financing and not all that complicated, once you get through price discovery. And if you can do price discovery for a private round, you can do it for any financing.

PRICE DISCOVERY:

A RARE SKILL THAT REQUIRES TRADING ALLOCATION FOR INFORMATION

What we've witnessed these last two years is that many management teams really struggle with price discovery. They don't know what to do when term sheets don't come in. They don't know how to mobilize their own existing investors to reveal their interest or disinterest early in the process so that everyone understands what the company is working with. Eventually, someone throws out a number... if it's high, there's silence. If it's low enough, a discussion ensues.

“So the key with private rounds is to find ways of guiding the discussion to a price range where investors fill the silence with their interest.”

The beauty of the public market is that it gives you that price every moment. It's usually easy to price a public round for any company outside the Danger Zone since some price in the neighborhood of where it's trading will get a deal done (if it's in the Danger Zone, that's where bells and whistles might be needed, in which case one might have to go through some awkward silences before someone broaches the idea of warrants).

So the key with private rounds is to find ways of guiding the discussion to a price range where investors fill the silence with their interest.

If you wonder why investors don't want to go first, it's because they have learned that you get punished for going first. If CEOs and boards want to avoid a downround, then there's no sense being the bad guy who suggests a lower price. Let someone else do it and take the arrows. Then come in with a slightly nicer offer and cut the other investor out. Such mercenary behavior is encouraged by many companies that want to optimize for their own outcomes. It's kind of pointless to berate anyone for doing it because even if only 10% of companies did it, investors wouldn't know when a new company was in that mercenary 10% and so would act accordingly.

CEOs should know that this behavior holds many investors back from filling awkward silences with low bids. When investors aren't offering a company terms, either they won't invest at any price or they would invest at a price lower than they think management wants to hear, and they don't want to say that price first.

As CEO, you should want to know which is the case. A low bid is better than no bid.

So how can a CEO spark a pricing discussion? The key is to reward the investor behavior you want. For example, a CEO could sincerely promise to investors that they won't be ghosted if they offer a term sheet that the company ultimately doesn't accept... in fact, they will get the first call after the company has signed the term sheet it plans to take, ahead of all other investors who didn't submit a term sheet. We should point out that this only works with credible investors. You can imagine that speculators would quickly abuse this promise by throwing out low-ball term sheets at every company and then demand to be let in on whatever round materializes.

Even when you are sincere, you won't always be able to honor your promise to the investor who goes first. Sometimes the winning term sheet comes in from a syndicate that takes the whole round. But then at least the losing investor hasn't lost anything by bidding since they weren't in the winning syndicate. But just maybe you can make an effort to make room for them. At the very least, sincerely commit to calling those investors who gave losing term sheets first in the next round, and if it's an IPO, take their willingness to bid on the crossover into consideration when allocating.

 *...reward the investor behavior you want.*

Rewarding the behavior you want is actually the key principle at the heart of the [Series I IPO](#): if you want to know how much insiders really want to buy in an IPO and at what prices, then reward them with a designated allocation in the IPO. For game theorists, we're just talking about a Dutch auction.

WHEN IS A COMPANY READY TO BE PUBLIC?

Many believe that a company has to have good data in hand to go public and stay public. That's not actually true. If you consider that most companies are really just options on the possibility

that their programs work out (which is why scores fail and collapse every year), then waiting until you have good data is perfectly fine, but you could actually go public one round prior to that.

What you want to avoid is stumbling short of good data while public. When a company goes public, it should aspire to either achieve a no-regret definitive fail or succeed and keep succeeding.

Basically, if a company goes public with enough cash to get to its “hero/zero” inflection and is prepared to live or die by its timelines and outcome of its value inflection, then go for it. But if their cash will only get the company halfway to a hero/zero inflection, then beware. It’s kind of like embarking on a trek across the desert with only half the food and water you’ll need. While it’s possible that you’ll find food and water along the way, you might not. So be prepared to accept death. And if you are traveling with a group of people, be prepared for the possibility that some might get eaten to increase the odds that others make it across (i.e., companies will often jettison parts of their pipelines when they find themselves short of cash to get their lead programs to a hero/zero inflection).

All this can happen in the private markets too. But sometimes VCs allow a company to believe it’s not happening by just extending flat-round bridge financing. If as a CEO you have such backers, be both grateful and wary of how easy they make things for you. Setbacks are an expense. The public markets have a way of making those adjustments in real-time so they don’t accrue like bad debt. Private companies that enjoy repeated bridges can delay a revaluation but often don’t escape it.

In that regard, if you do have setbacks, sometimes the public markets can make things a lot simpler for a management team. Because the valuation adjusts in real-time, it’s clear to a CEO

A CASE STUDY

Say a preclinical company has two programs that are two years and \$150M of spend from generating proof-of-concept Phase 2 data. And let’s say that based on public comps, successful data in just one program should make the company worth \$1B. As long as investors give those programs each a 50% probability of success (75% that one of them works), then any post-money valuation under \$500M offers investors a decent expected return over two years.

The company should want more than two years of runway, both in case timelines slip and to have some runway after positive data to plan for the next stages. So they might want to raise \$225M, which means keeping the pre-money to <\$275M. If the last private round was at \$400M, this requires a downround. If the last private round was \$200M, then the IPO should be at a modest step-up. If the company doesn’t have many crossover investors and would feel better IPO’ing after a crossover round, then it might need to raise \$50M at a \$200M pre-money to leave room for a step-up to the \$175M IPO at a \$325M valuation, thereby ending up at the \$500M post-money. If the company’s last valuation was \$275M, then a crossover round would require a downround whereas the IPO might be done flat.

What’s important here is that the company must be sure that if both programs fail, it’s prepared to accept annihilation. And if their timelines slip significantly, maybe because the FDA puts the trials on clinical hold for a year, then it should be prepared for a potentially punishing extra financing while public. What the company is foregoing is being able to just pretend that the clinical holds didn’t impair its valuation by counting on its insiders to extend bridge financing.

and board at which price they can raise if they want to raise. Sure, it might be dilutive, but at least you know you can do it. With a private company, polite silence on price can give the impression that a company will be able to raise painlessly when it needs to. The management team often only finds out that its investors actually don't want to invest more when the conversation is forced, typically close to when cash is running out. And if emotions run high, it can be hard to have a discussion about offering new investors a downround, sparing them the awkwardness of having to suggest it first. Management can find itself rapidly burning down its runway without a clear sense of whether the company will raise more cash. So however difficult the public markets may seem, being the CEO of a private company experiencing setbacks and delays can be its own hell.

There's one school of thought that every company should be public from inception. It's not a serious recommendation but more of a provocation for discussion. However dumb that may seem, it's not without its benefits.

And sure, it costs more to be public, but that's about \$2.5M/year. Compared to the costs of developing a drug, the monetary costs of being public are not the reason to stay private.

We were going to tell you about how reverse mergers are, under certain circumstances, compelling alternatives to IPOs, but a recent shift in the SEC's stance on reverse mergers has potentially tilted the calculus squarely in favor of IPOs, particularly those done with proper insider price discovery. So we'll save the reverse merger discussion for another day and remind you that we've written extensively on how to conduct logical, data-driven IPOs (see [last year's Semper Maior piece](#), our resources in [Gateway](#), and the [RA Capital website](#)).

But all such discussion is moot if a pen in Washington checks the wrong box.

Continue to the next page for part 4.

PART 4: THE STROKE OF THE PEN THAT WE MUST COLLECTIVELY REDIRECT



There's a type of risk facing every sector that is known as "the stroke of the pen," referring to the possibility that Congress might just pass a law that will wipe out a fundamental precondition for the work that we do. Imagine if patents were optional. They are just pieces of paper. It's not a given that they will be honored. Imagine if the government could just dictate the price of a drug from the moment of launch, or only five years after launch, or let's just say nine years after launch, even though your patent still has another five years on it?

When we're asked about this risk, we acknowledge that it's real—after all, how could anyone doubt that after passage of the IRA with its nine-year penalty on small molecules and other NDA-path drugs?—but that we're optimistic that this first real exposure to the "stroke of the pen" has served as a vaccine, mobilizing our ecosystem's defenses and therefore reducing this risk in the future.

But what kind of vaccine was the IRA? How robust a response will we mount to that one shot? Is it a two-dose or even three-dose vaccine? Must we experience even worse policy than the nine-year penalty before all available B and T cells activate? Or might one exposure be enough?

Stroke of the pen risk is mitigated through civic duty. Anyone who thinks that just supporting BIO and PhRMA is enough need only consider that the IRA passed in its current form, with its myopic nine-year small molecule penalty, despite their best efforts. Just because we've delegated the work of preserving innovation against stroke-of-the-pen risk to BIO and PhRMA doesn't mean that innovation is protected. It's important that we have these organizations doing what they

do, but that doesn't obviate the need for all of us to consider our civic duty in achieving our professional mission to continue bringing new medicines into the world (assuming you consider that your mission).

Civic duty means using one's voice to teach. It can extend to political lobbying, but that doesn't mean that this is what is required of everyone. It can be as basic as just helping to inform the public. And even lobbying can be as modest as co-signing a letter you agree with that makes our case to our elected officials.

If you want to take it a step further, most people in our industry have the standing to write an op-ed for their regional newspaper. No Patient Left Behind has started cataloging pieces that we call **"Community Quests"** in which innovators address their communities that way. Check that page out; notice how our colleague and Givax CEO Mario Barro links his quest to develop a norovirus vaccine to the efforts and interests of others in his community in Virginia. Similarly, Ventus CEO Marcelo Bigal wrote a piece for the Bucks County Herald in Pennsylvania, laying out the dividends to everyone of his company's work on Parkinson's, epilepsy, and lupus. Now imagine hundreds of these pieces in regional papers all over the country.

JUST STANDING BY: THREE WEAK REASONS FOR BEING A BYSTANDER

I find that there are three main reasons people give for not getting involved in any way to defend biomedical innovation.

1. SOME THINK THAT SINCE DEMOCRATS NO LONGER FULLY CONTROL THE GOVERNMENT, WE DON'T HAVE TO WORRY ABOUT MORE PRICE CONTROLS.

If anyone thinks that Republicans will save biotech, recall that Republicans proposed International Reference Pricing, ostensibly aiming to import ex-US prices, which are based on price controls. Republicans also stripped away the insurance mandate from the ACA that would have seen fewer Americans suffer the consequences of being uninsured (whenever that results in a person going without a necessary medicine, that's yet more antipathy for the drug industry).

Innovation won't be safe from bad policy until 1) everyone is properly insured, by which we mean "has insurance with low out-of-pocket costs," 2) price controls are kept at bay for the period of time enshrined by Hatch-Waxman (~14 years... so 13 is close enough but nine is not), and 3) America believes that it is getting value for what it spends on new medicines out of premiums and taxes, which means we have to engage in the math to showcase the value our medicines offer (i.e., Generalized Cost Effectiveness Analysis becomes as commonplace as NPV modeling).

And while Democrats tend to favor lowering out-of-pocket costs and extending insurance to everyone, some Republicans prefer to see individuals make a choice for themselves whether to pay for more generous coverage, a potentially logical position

if one were also consistent about making people suffer the consequences of their choices. Healthy people often don't appreciate the degree to which any given plan leaves them exposed to financial risk if they fall ill. The fine print is daunting. And yet, they aren't the only ones who pay the price for miscalculating. We all do.

If we're going to pay the cost of emergency care for anyone who needs it and automatically cover anyone who needs dialysis and a transplant, then it simply seems prudent to fully cover insulin for people with diabetes to prevent them from getting to that stage. It's simply not logical to demand even so much as \$35 a month from a person with diabetes for their insulin. Who fakes diabetes just to joyride insulin shots? We pay a higher cost for under-utilization of insulin than over-utilization.

And it's not just diabetes and insulin. Who fakes cancer to joyride chemo? Who fakes just about any disease to get whatever medicine it indicated for it? Consider that no one can get a medicine without a licensed physician prescribing it and, if it's expensive, then payors can use prior authorization to make sure that the medicine is right for the patient and, if it's in a competitive class, it's the one for which that the plan has negotiated a favorable price (rebate). There's no risk of over-utilization at the expense of premium payors. Even GLP-1s, with all their off-label use, can simply be rejected by insurance, forcing off-label use to be entirely funded out of pocket. The idea of charging any out-of-pocket for insulin or chemo is a strange hold-over from another era. It's an unexamined tradition that we should be challenging.

Who fakes cancer to joyride chemo?

But however logical you might find what we're saying, know that this argument for lowering out-of-pocket costs won't get in front of hundreds of millions of Americans and hundreds of policymakers without a campaign and funding

for that campaign. Waging that campaign is one of [No Patient Left Behind](#)'s top objectives. Don't just watch for it. Support it. If you're with a company or investment firm, a suggested amount to contribute is one basis point—one one-hundredth of one percent—of one's market cap or assets under management. For most companies, that's a tiny fraction of the cost of hiring a single government affairs professional, yet it will make a greater difference than hiring one amidst a sea of currently uncoordinated government affairs professionals. Besides, there's only so much government affairs professionals can do when the public flat out hates our industry. What we're really talking about is a public relations campaign with a government affairs spillover.

2. SOME "SCIENTIFIC ISOLATIONISTS" THINK THAT SINCE THEY WORK ON BIOLOGICS OR BECAUSE THEY WORK ON DISEASES OF PRE-MEDICARE-AGE PATIENTS, THE IRA ISN'T THEIR PROBLEM.

Consider that before the IRA, no one had any reason to think that the nine-year small molecule penalty was their problem. They didn't see it coming. None of us did. HR-3 targeted all drugs for Medicare "negotiation" at the point of launch. But then the IRA

passed and it turns out that biologics are largely spared. That's no reason to think that the threat codified in HR-3 has passed. Already there's the "SMART" Act, proposing to impose price setting just five years after any drug launches, whether biologic or small molecule, and other bills proposing to extend those lower prices to commercial plans. And then there are the state-level PDABs, government committees with the power to just set the price of any drug they consider expensive. Colorado went after Trikafta, a drug for cystic fibrosis, a disease that affects patients normally too young for Medicare (but transforms their lives so profoundly that many will live to get Medicare someday). Maryland, Washington, and many other states are watching Colorado and will no doubt attempt to impose price controls in their own way.

The way these PDABs work is that they penalize any plan, which is to say any employer, that dares to pay more for a drug than the price the PDAB authorized, no matter how much the payor wants to. So even if plans in Colorado would have paid the going rate for Trikafta, they wouldn't be able to pay more than the Colorado PDAB allowed. It's a true price control.

PDABs might seem like a small problem because they are state-level. So what if Colorado price controls a drug? The genius of the anti-pharma camp's strategy is that it would force companies to pull their drug from that state or else see "best-price" spillover to Medicaid across the whole country. That's a lot of bad press for drug companies. And if families move to other states to maintain access to that drug, then Colorado would be rewarded for its price controls, dumping its sick onto other states. Such adverse selection would create extra motivation for other states to pass similar price controls until all the states are equally ungenerous. The rules of insurance are that within any region where people can readily move about (i.e., a country), all insurance has to be comparable. Otherwise, the sick will move where insurance is best and the healthy will move away from there until they are sick.

So when a region or plan deviates from the norm by cutting its coverage, either society must be prepared for all plans to follow its lead or it must voice enough outrage to

nudge the deviant back into alignment with society's values. Patient groups have a big role to play in that, but we all have a stake here because patients are all of us, now or eventually. For example, Gunnar Esiason, a CF patient advocate and founding advisor of No Patient Left Behind, penned a powerful op-ed rallying opposition to the Colorado PDAB's misjudgment of Trikafta's societal value. Gunnar cited the Generalized Cost Effectiveness Analysis NPLB conducted for Trikafta showing that it was actually cost-saving for society, which is pretty much the opposite of ICER's claims that it wasn't cost-effective. Ultimately, the Colorado PDAB dropped Trikafta. But it and other PDABs are on the hunt for other drugs that society won't object to seeing price controlled.

So what if Colorado price controls a drug?

So whatever type of drug you work on, consider whether you would be okay with having a PDAB target your class of medicines. And if you don't take a stand for other classes, what makes you think there will be anyone left to take a stand for yours?

There's no place for such "scientific isolationism." We must all stand together in defense of the fundamentals that make affordable innovation possible.

There's also a version of scientific isolationism that we can call "indication isolationism." For example, some orphan disease advocates favor pushing for expansion of the orphan exemption in the IRA to preserve interest in the development of medicines for orphan diseases even if a drug is approved for multiple orphan indications (right now, the exemption only applies if a drug is approved for a single orphan indication). Indeed, there's a lot of sympathy for people with orphan diseases that might make such a fix palatable in Washington. However, what makes heart failure unworthy of adequate incentives? Or Alzheimer's or colorectal cancer? Changing nine to 13 would restore incentives for the development of all medicines, without the need for an exemption. Orphan disease advocates should stand together with all other advocates in support of progress in the treatment of all diseases. Besides, all drugs should go generic without undue delay—that's a big part of our industry's value proposition to society—so we shouldn't be too eager to push for exemptions.

3. SOME JUST DON'T BELIEVE IN GETTING "POLITICAL."

This is a pretty facile objection, but we think others have made the case against it better than we can.

Steve Potts, a biotech CEO who recently testified before Congress in defense of innovation about the harms of price controls, wrote [an inspiring piece last year in The Timmerman Report](#) analogizing R&D to the intense workout of running and biking up and down mountain trails. Those trails don't maintain themselves. Some, like Steve, mountain bike while carrying tools with which to fix the trails when they get washed out by rain.



Everything is politics. Action and inaction. It's the rain. It's an umbrella. It's wet socks. It's a chainsaw to remove fallen trees across a path.

So our friends at many bystanding firms can tell themselves that they are doing important work by forming and funding biotech companies to work on cures for many diseases for as long as the conditions are favorable for engaging in such R&D. But maybe they can also look at themselves honestly in the mirror and acknowledge that

they are freeriding on the work of others when they can't even be bothered to so much as sign a letter to Congress let alone pen an op-ed, show up in Washington, or cut a check in support of public education about the value of biomedical innovation and the merits of the biotech social contract. They may think "we don't do politics," and yet like the rain and the wind, "politics" will affect us all nonetheless, wash away our trails, and knock trees across our path. Not "doing" politics is a comfortable falsehood built on the work of others. Inaction is its own politics... the politics of not giving a damn.

LPs certainly aren't expecting their fund managers to stay silent. Just ask them. We did—we asked a few experienced capital allocators to share thoughts that we could pass along here.

RICK SLOCUM, CIO of Harvard Management Company (which manages Harvard's endowment):

In our experience, asset allocators respect managers who are active in the ecosystem in which they invest and have a keen eye for larger policy developments, especially when the mission is as important as healthcare. We all care about healthcare at a very personal level. Policy that preserves affordable innovation isn't just about returns. It's ultimately about all our hope for better health. Thoughtful and effective engagement is not just appreciated, but essential for all of us.

YEHUDA SPINDLER, Chief Investment Officer, and
MARSHALL HENDLER, Vice President, at Optima Asset Management:

As investors, we strive, where possible, to seek managers who actively engage more broadly in their sector/strategy beyond simply managing a portfolio of financial assets. We see incremental positives whether that comes in the form of investors who take board seats, contribute time to policy groups, engage with regulatory bodies, and/or spend time with global thought leaders to drive positive change. This is to ensure that policies and regulations make sense for the end-users and foster innovation and development in a financially thoughtful way, as this generally leads to better outcomes for all participants.

We are cognizant that regulatory changes are inevitable. However, it's important that these changes are implemented in a way that continues to democratize access to healthcare and improve patient care. As a result, we look to our various industry experts to be advocates not only for their portfolios, but for the sector as well. Without a compelling investment case and future opportunity set, capital will surely leave the sector which will be detrimental for performance and society.

DAVID MOREHEAD, Baylor University's CIO:

We all have a stake in new and better medicines as well as a role to play in their development. This isn't just about generating a financial return for any of us.

But even if it were, that's not at odds with speaking publicly and with policymakers about the fundamental economic concepts that make productive investing possible. We count on healthcare managers to understand healthcare well, and if they can help inform wise policy to preserve innovation and keep it affordable for patients, we would certainly hope they speak up. We also imagine that, all else equal, inventors and management teams would appreciate those investors who defend innovation over those who just sit by, so it would seem prudent just from a deal flow standpoint for an investor to show they care about preserving the policy framework that makes it possible for their portfolio companies to raise funds and innovate.

STEPPING OFF THE SIDELINES AND HOW TO ENCOURAGE OTHERS

CEOs ultimately can inspire bystanders to come off the sidelines in two ways.

1. CEOs CAN LEAD BY EXAMPLE:

You don't have to actually testify in Congress as Steve did (though that's service at the highest level), but consider writing to your Senator, penning an op-ed (e.g., a Community Quest piece), getting involved with and supporting No Patient Left Behind, and certainly encouraging BIO (when you're in a meeting) to offer up the biotech social contract as a solution to Congress.

Consider the tireless efforts of Paul Hastings, CEO of Nkarta and until recently the Chair of BIO. Paul is now a member of [NPLB's Innovation Council](#). As CEO of Nkarta, a cell therapy company, Paul has plenty to lose from supporting policy that would end rent-seeking (i.e., profiting from old drugs not being able to go generic and therefore remaining profitable). He could be a scientific isolationist, since the IRA exempts his technology. But instead he called out the Landlords in our industry who would milk old drugs for profit, earning a reward not for innovation but for gaming patent and regulatory loopholes.

The public struggles to tell the difference between a high price earned for innovation and one extracted via other means, but we know the difference, and Paul has spoken publicly about it. Even as Chair of BIO, he was vocal about standing for the biotech social contract and recognizing the merit of policy that would ensure that all drugs go generic, if not from competition then indeed through price regulation after a patent-intended period of time (e.g., 13 years, not nine).

When a Texas court suggested that the judiciary should have final say over a drug's marketing authorization, Grace Colon and Amanda Banks (both NPLB Innovation Council members) and others from the Biotech Sisterhood stood up in defense of the FDA's primacy when it comes to making benefit-risk judgments. They waged an impressive campaign that inspired over a thousand others to stand with them. This and other letters to Washington are available on the [NPLB website](#). Open each one to see who signed.

Signing a letter may not seem hard, but it does take some courage to put your name out there, especially when you also sign with your position and affiliation. It shows that you're willing to justify your stance to your board and colleagues, who might include people who would prefer to "stay out of it." Bystanding is many people's default but leaders lead their colleagues into the zone of uncomfortable discourse from which history emerges. Of course, it's easier to sign when many others do. So if you sign, know that you are offering protection to others. It's like herd immunity. The more that sign, the easier it is for others to sign, and the more people sign, the more effective the action. So don't just sign... be quick to sign. Those early signatures catalyze many more signatures. That's why NPLB refers to its supporters as [First Responders](#)—become one today if you aren't already signed up.

And consider the tremendous commitment that John Crowley is now making by stepping into the role of BIO's President; it's a role that requires diplomacy because BIO operates on consensus, so whatever John might personally wish, he can't make BIO take a formal position that doesn't have the support of every BIO member unless he is willing to lose BIO members. If you think that shouldn't be hard, consider who pays BIO. The lion's share of BIO's revenues, as in the case of PhRMA, come from large, profitable companies, at least some of which are still milking profits from old drugs (i.e., what NPLB refers to as rent-seeking, Landlord-like behavior). We hope John will ultimately pivot BIO to be more effective at defending innovation by offering solutions that allow for affordable innovation (i.e., lower out-of-pocket costs and conceding that all drugs must go generic without undue delay). If he's to be successful he's going to need enough support from Builders (hopefully you) to withstand the negative lobbying of the Landlords who would have BIO protect the milking of old drugs (e.g., secure IRA exemptions for gene therapies, which can't go generic) or simply not offer up solutions that include an end to such rent-seeking

2. CEOs CAN ALSO SPECIFICALLY INFLUENCE INVESTORS BY MAKING IT CLEAR THAT THEY TAKE NOTICE OF WHO HELPS TO MAINTAIN THE BIOTECH TRAILS AND WHO MERELY FREERIDES ON THE EFFORTS OF OTHERS.

As a CEO, if you find yourself in a position to decide which investors to allocate your shares to, simply ask them what they have done to preserve the trails, not just fund companies to run them. Ask for evidence that they actually care about preserving the affordable innovation framework. If you hear excuses, you decide if that matters to

you. Because there are investors who are making an effort to protect the trails from the rain... and their money is actually greener.

Steve Potts' article takes a data-driven approach to listing out everyone who bothered to so much as sign a letter, but we can tell you from our own travels that we've seen many peers roll up sleeves, write op-eds, engage with Washington directly, fund educational campaigns (e.g., NPLB), and cut checks in support of all kinds of relevant projects: ARCH, Atlas, Boxer, Braidwell, Deep Track, EcoRI, OrbiMed, RTW... thanks to them and everyone else who steps up.

So whether you're doing a private round, an IPO, or a follow-on round, if you find your round over-subscribed and most else is equal, consider making "biotech trail maintenance" one of the factors by which you decide to whom to allocate. And make it clear that this was a criterion for your decision. The one thing that any investor will definitely hate more than being forced off the "political" sidelines is being left on the sidelines of a hot financing. And when LPs see a manager left on those sidelines, they will definitely start asking managers what they have done to contribute to maintaining the trails. And then bystanding will become the exception, not the norm.

Such is the power of CEOs to elicit constructive participation from everyone around them.

By the way, the same approach can be taken to building boards. Who do you want on your board? Those who keep their heads down in the face of a challenge or those who step up to be part of the solution? So just consider working it into your evaluation process of candidates for your board.

IT COMES DOWN TO MISSION. HAVE YOU GOT ONE?

If biotech is a job, it's a job. We could argue that one would be more professionally successful by chipping in on the affordable innovation campaign. But if battling disease is also a mission, then it's harder to understand how someone's mission ends with their formally defined professional duties. Being mission-driven means thinking about how to achieve a goal even when you're not on the job and helping achieve it even in ways you're not asked to or that aren't written into your job description. Most biotech leaders would claim to be mission-driven. So probe that a bit. What have they done to defend the biotech trails? There are tools to carry, gravel to spread, and fallen trees to remove. Or do they just wait for others to do it... for others to fix the nine-year penalty... before they bike those trails again?