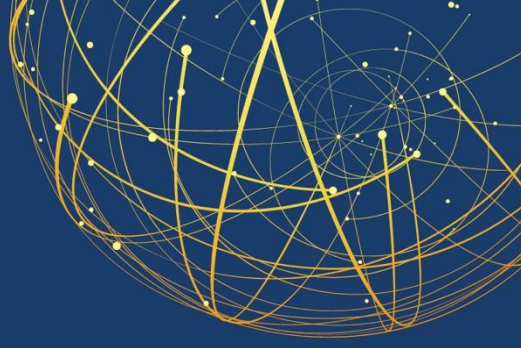

PART 2: ALIGNING INVESTMENT AND OPPORTUNITY IN HEALTH

Caitlin MacLean 00:15

Okay, good morning. We're standing between you and lunch. We just heard what the federal government has planned in terms of the health of all of us sitting in this room, and I think what we heard as well was that we need more capital to make a lot of that happen. And so thankfully we have a group of panelists who represent all of the types of capital going into building our stronger healthcare system in the US and truly around the world. So, thank you for joining us today. We will get into your feedback and your thoughts about what we just heard from the federal government perspective. But I would love to start thinking about framing, because oftentimes when we get into these conversations, we're about to get into transactions and M&A and sort of where we should be investing in AI and China. But fundamentally what we're talking about is getting more capital so that all of us are healthier. And I think we all have lived experience as patients and as humans, and we understand what some of the challenges are in our health system and what some of the exceptionalism is, as you just heard in the previous panel. But we do need to think about not just how we are living as humans and Americans and patients now, but how we're going to be living in the future, and how are we thinking about changing the way we invest in health, in life sciences, and in healthcare to change and to meet where we need to be in the future. So, Phil, let's start with you.

Philip Ross 01:52

Okay.

Caitlin MacLean 01:53

Where is the capital going? Where is it coming from, and where is it going as you're seeing it right now? We're seeing an increase in M&A activity, sometimes even earlier than maybe expected. Why don't you talk a little bit about some of the trends you're seeing in where the investment is coming from and when and where it's going?

Philip Ross 02:12

Yeah. Well, thank you for—it's a privilege to be here and to be with these panelists. As I'm pinching myself, they're all so brilliant, but it's my first Milken conference, and it's absolutely incredible. I was thinking about where are we this year versus last year? Well, the world's actually a little worse. It's not better. The geopolitical environment's a little bit more complex. I think we don't say that, and we're all trying to deal with these macroeconomic factors that are happening from things outside of healthcare that are impacting us. But it all comes down to one thing. Whether you're financing innovation through the private sector or the public sector, it doesn't really matter. We're all trying to move the bar higher and higher for human health. So, I go back to the need for one thing and one thing only. It's growth that gets fueled by innovation. So, if you think about Liberation Day, which was about, I don't know, a couple of weeks ago, a year ago, the S&P's up 35 percent since that day. But the XBI, this index that we track for some reason, no other than just to judge where we are in sentiment, is up 65 or 70 percent. And most of that is because of how people are thinking about growth. So, I've been a broken record on something that to fuel growth, first you have to focus. So, companies like large pharmaceutical companies finally went through what I think is the hardest 10 years they've ever dealt with, which is corporate clarity. Things that we take every day, whether it's Tylenol or use Listerine or a Band-Aid, they've sold off every one of those businesses. All animal health businesses are gone. So, they're pure play pharma companies for the most part. These are the large top 14 players in the world. And then they said, "Wait a minute, how do I get bigger?" Well, you can't get bigger in doing things that are “me too” or slightly “me better” because we just heard from two panelists that say no one's going to pay for that. And then what you say is, "I go out and I hunt for innovation." And unfortunately, they all need a lot of growth. In fact, we calculate somewhere in the order of $70 billion of risk-adjusted sales just to grow at 4 percent a year for the next five years. So, they went on this hunting spree to go buy things, and that's because great people on this panel finance companies earlier in their life cycle. And to give you a sense of how that's worked out, $140 billion was spent to buy public companies in the last six quarters. $105 billion has been spent to buy public—this is just public company M&A—since the beginning of April 1st of 2025. And that capital has now been, we call it recycling or redeployment of capital, and that's been a very good thing in terms of pushing money back out to, I say, the ecosystem of public and private companies. And investors like the ones on this panel get rewarded with some of that capital, but they don't go sit that and put that in their pocket. They go and fuel the growth of more and more companies. I'll be done in a sec. You asked a tough question.

Caitlin MacLean 04:55

[Laughter]

Philip Ross 04:46

Then what we had is, okay, so we have the depth of capital that can now go back into the public markets, and we're now at a point, this point of this year, where about $20 billion of that capital's gone back into public companies that already exist that want to raise more money. And not only that, this time last year, they couldn't even do that. They could barely get $100 million. Now they're raising on average $250 to $400 million. And then even more exciting, that we're seeing now, is we're seeing IPOs finally come back to life. But the difference, given your question, is these companies are actually much later stage. We went through a cycle in 2019/2020 in a very low cost of capital environment to fuel the growth of a lot of

exciting companies, and we measure everything by the probability or the likelihood that it happens. We call it probability of success. The average company that went public then, their probability of success was probably less than 10 percent. They're preclinical assets that we all hope will work, but attrition makes sense. So, some of the have-nots are going away and now this new batch of companies. And we hope, in addition to that recycled capital, that the generalist investor, those that don't wake up every day and think about healthcare, will start to wake up and realize that this ecosystem is probably in the second inning of where tech was 10 years ago. So far, that's a good way to set the stage. But I invite my fellow panelists if you have any other thoughts on.

Caitlin MacLean 06:14

So Peter, would love to hear your thoughts. As Phil just mentioned, some of the kind of market signals, the cost of capital, kind of the later stage activity. You drive a lot of investment into innovation on the earlier side. Would love to hear your thoughts about where you're also seeing some of those market signals, whether it is from the capital markets or whether it is from unexpected kind of players across the health system.

Peter Kolchinsky 06:39

Sure. So indeed, everything Phil just talked about is sort of my day-to-day, right? The decisions around which companies to fund, which ones might fill a gap that some pharma company has, what might they acquire later, generate a return, generate liquidity for me. But let's step back a little bit and consider that all of the innovation that we see here is in pursuit of the rewards that are offered by the US market. The United States spends about $400 billion per year on novel medicines. That's only about 8 percent of total healthcare. And that spending by the US market creates the incentives for all of the investment in R&D, about $300 billion per year, that gives us hope of tomorrow's medicines. How that $400 billion is actually spent on exactly which drug. You have multiple competing drugs against any particular class, like one GLP-1 sells better than another GLP-1. We study that. We study that very carefully. Why is it one drug is outselling the other? And we try to invest in medicines that are more like that, more like the successful ones. We're constantly gathering market signals to try to make sure we direct our capital to the kinds of medicines that any of you might want if you find yourself in that situation. And as you study how that money is directed, right, all that $400 billion of US spending, mostly by US insurance companies, you discover some really fascinating people deep in our healthcare system that nobody even thinks about. For example, you might think that a patient has a given disease, they have rheumatoid arthritis, and there's a novel medicine on the market, and a doctor will prescribe it. All right, so that's revenues for the drug company, right? Well, not quite, because odds are, if that drug just launched, it's probably not covered by many insurance plans. And so, the first thing that will happen is that that person's insurance plan will probably reject it. They may have a prior authorization requirement. So now that's a burden on the doctor. The doctor has to fill out a prior authorization form. The doctor probably is not the one who's going to fill out that prior authorization form. There's probably a billing director in that doctor's office. That might be one of those people that you pass on your way in to see the doctor or leaving behind some window. And that person is getting tons of these insurance rejections and requirements for prior authorizations. There may be 20, 30, 40 that they have to fill out in a given day. What if they only have time for 15? Will they prioritize your prior authorization?

And if that person ultimately connects with you, if that person understands what rheumatoid arthritis is, like the kind that is refractory to all the available drugs we have. You tried Humira, you tried the other drugs, it doesn't work. You're in pain. You're 38 years old. You are facing this pain and disability for the rest of your life, and yet you should be in the prime of your life. And if that person can empathize with you and decides that yours will be the one they will prioritize and push through, then insurance will cover it, and you will get your medicine. But more importantly, that insurance plan is going to be like, “Damn, people keep filling out those prior authorizations for that drug. I guess people really care.” Because it's a burden on them, too, right? To reject and to handle prior authorizations is a burden. So, when they see that society cares, that billing directors care, and they're fighting for that drug, that's the kind of drug that the inventor—I don't call drug companies manufacturers, I hate that term. They're inventors. The inventor, in their negotiations with each plan to secure coverage, will have a leg up because the insurance plan looks and sees, yeah, people fill out those prior auths, and we are covering it. All right, let's enter into a coverage agreement. Let's cover that drug. And now that drug sells. And that drug sales provides the signal to me that we should fund the development of more drugs like it. So, what will the billing director prioritize? And a really smart sales rep, by the way, won't just go into a doctor's office and convince the doctor, “Here's the data. Here's why you should prescribe this.” They'll pause, and they'll spend some time with the billing director, and they'll tell a story. Here we are in the story capital of the world, aren't we? Right? Hollywood finds stories and creates stories. As an industry, we have to tell the story of what it is that we are solving, the unmet need. And we have to make sure that the billing director hears the story and ultimately cares. And there are others in the whole chain. I could go on and on. But I think that when we talk about money transferring, whether it's a royalty or M&A dollars or whatever, we lose sight of the fact that it's a little over $3 per American per month that is funding the $400 billion directed by decisions by people like that billing director, who just feels overworked, that is ultimately sending the signals of what R&D is going to get funded next. I would love for all of us to examine those little details more. I think it might change the way that our drug industry conducts its own direct-to-consumer advertising, for example. Maybe someday it'll be some kind of ad that expresses appreciation for billing directors. Watch for it. You heard it here first.

Amy Schulman 12:55

Well, Johnson & Johnson famously did advertisements thanking nurses and nursing staffs, and I think has always been thought of as the kind of approachable human biopharmaceutical company because many of us associate J&J with baby powder and baby lotion. And so, I'm thinking about this notion that healthcare is the most intimate decision. When people talk about healthcare, how many of us go to the doctor and still our heart pounds when we go because it's like, what are we going to hear? What are we going to learn? There's a lot of anxiety and consternation around healthcare on an individual patient level, but also on an investor level. Because when you're investing in what I do, which is super early-stage academic science spun out of universities, investors are just as scared about that as they are about going to the doctor because it feels completely opaque. And I actually have been doing this for almost 40 years, and my ability to predict the future is no closer now than it was 40 years ago. It's just that I think part of my contrarian view is that we actually have to trust the scientists, and that none of us sitting here or anywhere else are actually better equipped than people who are living on the frontier as clinicians and scientists treating patients. The problem is, not every academic innovation is a company, and not every incremental improvement in patient care, as meaningful as it is to many patients, deserves to actually be formulated into a company. And I think that's where professional capital comes into it. But it's so ironic that, as you said, Phil, all of us—I mean, when I was at Pfizer, we sold our nutrition business, we sold our

animal health business. After I left, we sold the consumer business. As you say, we're becoming pure play Big Pharma, and yet consumers and patients have never been hungrier for accessibility for information. We use agentic AI to kind of outsmart our own physicians. And the pharma companies would love to talk in an unmediated way to all of us, but of course, they're not allowed to because the learned intermediary is a very important kind of break between pharma and us. So, I think this notion that there's a rise in consumer desire for accessibility and information, and actually more and more opacity is an interesting potential collision that we haven't really thought of yet.

Caitlin MacLean 15:43

At the same time, that AI provides opportunities for that information, some positive, some negative, and also hopefully addressing some of those opacity issues. Pablo, why don't you talk to us also, I think if you go to any of these panels, we hear about AI, we hear about China. We just heard from the session just before this, talking about US competitiveness. Would love to hear your thoughts about some of the market signals you're seeing as we move further into the year about where investment is going to go in driving innovation.

Pablo Legorreta 16:19

Sure. So, thank you for the invitation to be here, and I think, Phil, you set the stage of what's going on in this industry beautifully, and particularly in the more recent timeframe. There's been a huge amount of talk about China, and we heard it in the last panel, and issues that the world faces because of the way they behave and they compete. But there's no question that innovation is really strong in that market, and there's been an exodus of scientists from the US and other parts of the world to China, which is something that is concerning. I think there's huge excitement about China, but the one thing that we have to remember is that there's probably half a dozen companies in China that are global, and they want to become global and imitating the bigger companies. But the vast majority of Chinese companies, which are many thousands of biotech companies, are local. And the issue they're going to face is that they want their medicines to be actually sold, marketed in the US and Europe, which are the two big markets. But how is that going to happen? Because they do not have the infrastructure to actually run clinical trials in the US and Europe. They do not have the infrastructure to market the drugs in the US and Europe. So, what's really happening when we look at what's going on, and has gone on for the last two, three years, is that all of that innovation that has been occurring in China has moved to the hands of US Big Pharma and biotech companies who are then developing the drugs clinically and eventually will commercialize them. So, it's an interesting thing to just think about because, yes, the technology is generated there, but it's in the hands, it's being controlled by actually US and European companies, to the point where the US and European companies who license the Chinese innovation don't do it just out of China. Chinese companies have to take those inventions, put them in offshore companies, because the US companies, European companies want to do a deal with an offshore entity, a subsidiary of a Chinese biotech in the West. So, it's an interesting phenomenon. It is one that's going to require also huge amounts of capital because it is very difficult to finance Chinese companies. So, we'll see how that plays out. But it is an interesting phenomenon that we're now seeing. We were talking also a bit about AI, and I—

Amy Schulman 18:58

—Can I just say a word about China?

Pablo Legorreta 18:59

Go ahead. Yes.

Amy Schulman 19:00

Just two things to add on, because I completely agree with what you're saying. One is we are seeing also our kind of phase one biotech companies in the US going to China to accelerate their clinical development.

Pablo Legorreta 19:15

Yes.

Amy Schulman 19:16

Because the speed of clinical trials in core areas, not in some of the more obscure areas, is so much faster in China. And the question of intellectual property protection has gotten much more robust. And so one of the real, I think, important issues for us to grapple with over the next five years is what are we going to do about the translation of clinical trials in how much are we going to have companies replicate in the US and Europe phase one and phase two results in China? Because we're seeing companies go there who are earlier-stage biotechs, the way they used to go to Australia and Ireland and other places. And the other thing I would say is you are completely right that early-stage companies that have too many Chinese investors on their cap table have a very hard time raising money in the US. And that is a huge problem because there is an enormous amount of intellectual capital in China, capital that is intellectual, not just intellectual capital, and they want to invest in innovation. And it actually, ironically, can hurt these companies because some of the US investors will say, "It's hard for me to understand what it means to have so much Chinese money on the cap table." And that's another problem that we really need to solve in a kind of global healthcare world, I think. Sorry.

Pablo Legorreta 20:36

I agree with you, and you're right that for some companies, running early-stage trials in China is quick and much cheaper, and it will give them a sense of whether a molecule is potentially a real drug or not. But then the later-stage trials will have to be run in the US and Europe with the standards that are required here, with a good representation of US and European patients. So, it is an interesting thing that we'll see how it plays out, but presents significant challenges.

Philip Ross 21:06

Peter, can I ask you a question about this? Because you just talked about $3 per capita in the US. What if we could get that down to $1.50 using China? And what does that do for—we had this panel just before us. Sorry, I didn't mean to hijack it.

Caitlin MacLean 21:19

Please.

Philip Ross 21:21

What does that do in terms of, I don't want to say talent drain, brain drain, innovation here in the US? How do you square that when you think about that? Because doesn't that ultimately get it to 400 billion has the purchasing power of 800 billion if you can compress cost, speed, and innovation?

Peter Kolchinsky 21:39

So I actually think that when you reduce the cost of something, you don't necessarily spend less on it. You may get more of it. The fact is that America has revealed that it is willing to pay $400 billion per year, or I should say 8 percent of total healthcare spending. It's a really interesting percentage because America has spent 8 percent of its total healthcare spending on novel medicines for decades. That was the percentage back in the '80s, '90s. These drugs, they keep going generic, and we keep selling new drugs to earn that 8 percent. So, about every 14 years or something like that, all the drugs you've invented have gone generic, and if you're still making that 8 percent, it's because you've invented a new set. And so, we've been expanding our drug armamentarium dramatically from all of this compounding, and yet it's still only 8 percent. And that's a little over 1 percent of US GDP, and it is supplemented by Europe, Canada, Australia, Japan, pitching in a little. People say that we are subsidizing Europe and all these other countries. I don't actually think that's true. I think that America's very focused on its own needs. I think if no other countries existed, if they all sank into the ocean and there were only the US, we would still be spending $400 billion. We have that willingness to pay for progress. But we would now be doing without the few hundred billion dollars that is contributed by all these other countries. So, are we worse off that other countries happen to exist and are pitching in a bit? No, it doesn't make us worse off. If anything, they don't just pitch in a bit by paying a little bit for drugs. And don't get me wrong, I'd rather that they paid what these drugs are worth and made the total incentive pool even bigger and incentivized even more innovation. But they don't just pitch in a few hundred billion dollars. They also allow us to run these clinical trials on their patients. We need tons of patients to enroll into all these clinical studies, many of which fail, and we just don't have enough of them in the US. Europe contributes. We run a lot of phase one trials in Australia. Sometimes Canada, UK, are faster places to run a trial. Do you remember during COVID, the insights that IL-6, that dexamethasone could save lives? Those came from a UK study. The UK did a better job of running a well-designed trial to come up with answers, whereas we had a clinical trial traffic jam because we were so uncoordinated.

Pablo Legorreta 24:26

We see Dr. Landray in the audience, the guy that did those trials. Thank you.

Peter Kolchinsky 24:31

Awesome. Right. *[Applause]* So as much as I really resent the UK for having NICE and doing this skimpy math and claiming that drugs aren't worth what the US pays for them, I also have to appreciate what each country contributes. It contributes its scientists. Thank you. It contributes its patients. Thank you. And it pitches in a little bit on the incentives. Fine. And along comes China. That is barely a market for actually generating revenues, right? China's not yet wealthy enough to generate huge amounts of revenue. Now, in 40 or 50 years, at the rate that China's growing, if it spent 1 percent of its GDP on novel medicines, wow, that is a huge contribution. Even at 25 percent of whatever the US pays for a drug, China's massive population would mean that it's spending $400 billion a year on novel medicines. And any scientist anywhere in the world, backed by any investor anywhere in the world, is drawn to the chance to earn a piece of that global pie. And today, the global pie is two-thirds US. But in the future, as the rest of the world gets wealthier, if we can prevail upon them to pitch in their fair share and not free ride on the US, then that pie could be a lot bigger. Now, Phil, you asked the question, but might that result in Americans paying maybe only a dollar and a half? Maybe. And if that means the rest of the world's paying more, that doesn't mean that the incentive shrinks from 400 billion to 200 billion. It may just mean that the incentives are spread more evenly over the whole wealthier world. That might be nice.

Philip Ross 26:26

And what about the amazing scientists that are domestic here, that then leave? Do you think that makes us, as a country, less well off in terms of being the innovators for the world?

Peter Kolchinsky 26:46

Where the market is for a product doesn't necessarily have anything to do with where the scientists are or even where the factories that produce the drug are, right? We've decoupled all that. We've globalized. GSK and AstraZeneca are based in a country that barely pays anything for drugs, right? They got great scientists there. So, it's annoying that Denmark pays barely anything for Ozempic and yet is fracking America's obesity for its national budget. It doesn't even have the decency to pay a US price for Ozempic and be like, "Oh, yeah, our drug is totally worth it." So those things are annoying, but we also shouldn't be so annoyed that we end up passing policy like MFN that backfires on us, that robs us of the contributions other countries make for us to get what we want here for ourselves as patients, and that just hands the rest of the world to China.

Amy Schulman 27:41

And it also is a reason to keep on supporting academic science here in the US and to fund research and development. Because you're right, there are terrific scientists all around the world, but I spend a ton of

my time in Singapore, which has incredible academic research and a really organized and thoughtful approach to healthcare systems. But what it doesn't yet have is a huge innovation pipeline and a population that loves to take risks, and an ecosystem of private capital, public capital, academics, and big pharma that supports that kind of innovation flywheel. And I think that is something that we need to be protective of in the United States. And I think, as I look at some of the market dynamics and the shift away from investing in early-stage innovation into China, this is something that I'm tremendously concerned about. And as well as I am with policies that make it hard for us to attract scientists and welcome them here from around the world, which is a huge and important part of our thriving academic and innovation ecosystem, is our hospitality to research and academic researchers and our support of them, and we need to stand behind that.

Caitlin MacLean 29:06

But one of the things that's interesting about Singapore is the amount of incentives that they do provide in terms of trying to build out their ecosystem, their capital, their incentives in terms of bringing talent onshore, not just scientists, but also early-stage investors to build out that ecosystem. We're talking about China as well in terms of the geopolitical kind of shift of what this landscape looks like. And obviously, there are kind of market dynamics there—But I want to go to the AI piece, because Pablo, you were starting to talk about that. We've talked about cost. There is, I think, a huge hope that we are going to see drugs go to market cheaper and faster because of AI. Do you think that that is a real signal in the market? Do you really feel that AI will have kind of a major transformational effect on the way we do clinical trials, the way we market to patients, and talk to the billing directors? Everyone. Everyone's going to now go talk to their billing director, I think, at their doctor's office. Thank you, Peter. But Pablo, I would love to hear your thoughts, given that you focus on the later stage piece, what are you most excited about in terms of AI, and does it have that possibility that we all hope it does to truly revolutionize how we do drug development?

Pablo Legorreta 30:25

Yeah. So, this morning, there was another panel on manias and booms, which was quite interesting. And there was a discussion there about how AI could create the biggest—time the world has ever seen. And I found it quite interesting, but Peter and I were talking about this before we got to this panel, and it's very difficult to see how AI is going to, in the near term, sort of influence, facilitate, power drug development per se. Human biology is so complex, and we need to learn a lot more about it. And we were talking about how all of this, LLMs have to be trained with data, and the data that exists for human biology, and then interactions between our biology and potential drugs is also complex. And again, there's data that needs to be generated to train those models. That's in the future. I think where we're going to see, and I would love to hear your views, but I think where we're going to see a much bigger impact near term with AI is in the delivery of healthcare, because there's so much inefficiency there. And you talked about it today—about what happens when a doctor writes a prescription and all of the steps they have to go through up to get to reimbursement. I think there, there's definitely going to be huge savings impact, gains in efficiency, which will benefit the patients, which will potentially lower the cost, which also should increase access. The other area where I think we're going to start to see some impact is in running clinical trials. Because there, there is a ton of data that could be fed into these LLMs, and there's now companies that are working on this, a dozen or so that are advanced. And what they now claim, and we've met with several of them, is that you

can actually increase the potential success of a trial by designing it better with the knowledge that AI brings. And could you increase the chances of success of a trial by 20 percent/25 percent, potentially? Could you reduce or make things like recruiting patients easier, more efficient, maybe finding better patients for your trial that fit better with the enrollment criteria of the trial? So, all of those marginal efficiencies, and maybe they're not marginal. I mean, 10, 15, 20 percent is not marginal. But if those things—we start to see how that plays out, then that would have a meaningful impact in maybe cutting by a year or two the time to develop drugs and reducing the cost to develop drugs by, again, 20 percent. But also, on the other side, if you increase the chance of success also by a meaningful amount, all of these things will add up, and I think we're going to start to see that impact soon. And I think it will end up also impacting cost of developing drugs—but love to hear your view.

Peter Kolchinsky 33:40

So, you mentioned the amount of data that you need to train an AI. Machine learning feeds on data, right? We have millions, tens of millions of books. You can train AI with that much data. You want to train it on traffic data, you've got tons of data generated every day. But how are you supposed to train an AI that operates at the level of millions, tens of millions, billions of data points when we've only got a few thousand drugs that we've approved over an extremely long period of time? And when the problems that we're trying to solve are the most difficult problems that remain after all of the problems that we've solved, by definition, they're very different problems than all the ones we've solved. And so, I think that what we just fundamentally don't have are the data to train AI models to be trustworthy predictors of, "This molecule will work, trust me," in a clinical study. So, we're just going to have to run trials. And if a company came to you and said, "All right. I'm not saying that every molecule that we are going to put into development will work. But historically, it's been a 10 percent success rate. I'm telling you we're at 20 percent." Okay, that's a claim. How many drugs would you need to see that company actually put through clinical trials and have a 20 percent success rate for you to say, "Oh, yeah, you have statistically proven to me that you are, in fact, at 20 percent"? I mean, if they developed 20 drugs of which four worked, is four versus two statistically significantly different? No. 50 drugs of which 10 worked, is that clearly better than five versus 10? It starts getting there. So, it would take an incredibly long time for such a company to ultimately do 50 at-bats and hit the ball 10 out of 50 times for you to be like, "All right. I believe you. You have a 20 percent success rate." And so, it is the slowest learning and validation loop of anything that we could put AI to. And so, when people say, "Oh, AI's going to revolutionize everything. That's it. We, on the West Coast, are going to crush the East Coast. Those old school biotech dinosaurs, we're going to displace them." Bring it on. We've heard this before. But drug development will crush the hopes and dreams of everybody in AI. Not that AI won't help. There's plenty of things that can be optimized. In fact, I can't wait to use AI to shorten the times for filing approval submissions for the FDA.

Caitlin MacLean 36:29

It's operational, not scientific.

Peter Kolchinsky 36:31

Operational, sure.

Caitlin MacLean 36:32

Right.

Peter Kolchinsky 36:32

And of course, we can make better molecules. We can come up with AI models that better predict when a molecule will bind to a protein. Because there, we've got millions and billions of data points. We just can't be sure that that means it will be a commercially successful drug.

Caitlin MacLean 36:47

Right.

Philip Ross 36:47

It's actually not even an investable business. So, when I think about AI, it's a tool that you apply to something, and that something then produces value, and then that value could be either on a patient level or a capitalist level—however you want to do it. Every time that somebody's put what we call tech-enabled drug development, TEDD, and AI just plugs into that, people have gone out and tried to form a company around it. And every time they've done it, we've never seen a perfect meshing of a pharmaceutical investor with a tech investor. It just doesn't happen. And when that happens, once that company says, "Aha, I've got my 20 percent probability of success," they go, "Guess what? I'm a drug company now." And they start developing the drug, and if they don't, then they lose their whole focus in terms of how they can navigate the world, whether it be a capital markets world or just a way to—because as you mentioned, $400 billion, whether it's coming out of each of our pockets, investors' pockets, institutional money pockets, or pharma's pockets, has to get allocated. So, then it becomes a defeating purpose in terms of trying to build a company. So that's the other big issue with AI is just, it's a tool, it's not a standalone business.

Amy Schulman 37:55

Just to make that very clear for people in the room, because I think it often sounds very abstract. If you are a tech-enabled biotech, then you're essentially a SaaS business model, and you're getting paid as a services, and that has a completely different rate of return on your capital and a different investment rate. And you also have different people working there. They're not animated by making medications that are going to go through the therapeutic process. On the other hand, the kind of goldmine of, "Okay, we've

actually made a drug that we can trace back to this AI model," has two problems. If you are doing something de novo, you're taking on all of the risk of biology that we've talked about with that timeline, that need for clinical trialists at your company, regulatory, and everything else, and then you have a traditional biotech investor, not a tech investor. Or you prove the validity of your model through going after a known target, but that's completely uninteresting from an investor model. And so you've then wasted time in going around waving it as a proof point, and it doesn't actually translate into the novel medicine. So, I think that's the reason there's such a disconnect between tech bio and what biotech investors are seeing. Because I think sometimes we say that as if it's obvious why that's the case, and that was just a primer on it.

Caitlin MacLean 39:22

So we're coming down to the wire here, and there is a QR code for you to ask questions. One of the questions that's come in is a question on therapeutic areas and a question of, are we seeing any shifts in where investment dollars are going? We heard the previous conversation talking about prevention and early detection as more of a focus of the US government's funding. Are you seeing a shift based on GLP-1 success? Based on the work we do at the Milken Institute is largely in our health pillar. One of our big projects is about women's health. Are we seeing more investment into women's health, things like menopause? We're obviously seeing—continue to see quite a bit of investment into oncology. Where are you all seeing precision medicine? Where are you seeing a shift in therapeutic areas of where dollars are going?

Peter Kolchinsky 40:16

Yeah. I'll offer an area where I'm seeing things shift away from. We are seeing a lot less development of small molecules for non-orphan diseases of aging. So, small molecules for colorectal cancer, for general heart failure, for Alzheimer's. Because the US government passed a law that said, "If you develop that drug, we're going to price control it nine years after you launch." They call it Medicare negotiation. That is a very clear shift away from where we would otherwise free range, and if the science says, "Oh, this might work, this might solve an unmet need," I'd be like, "Great, I'm going to fund that." And now I have to consider this policy dead zone that was created all because the American public said, "Drug prices are too high. People can't afford medicines. I demand a fix." And instead of our policymakers saying, "You know what? You're right. Why is insurance raking you over the coals? You paid your premiums your whole life. You got sick. Your doctor prescribed chemo, and then they charge you more than you can afford, all in the name of skin in the game?" What, people fake cancer to score free chemo, right? And due to that misdiagnosis, we got price controls on novel medicines instead of insurance reform. And so, there's this exact dead zone. If somebody pitches me a small molecule or an oligo for Alzheimer's, some preclinical program, I say, "I can't fund it," because essentially, it's as if you're telling me, "I only have nine years of patent life. My drug will go generic nine years after we launch." So that is the one area where we're not going. As long as you're not in that dead zone, we're investing in everything. It's amazing. It's glorious. If it's an antibody, no problem, you get 13 years. If you're orphan, you're exempt entirely. Plenty of patent life left. We can make the math work. We'll get a return on our investment if it works. But if it's in that one zone, forget about it. Can't fund it. And I do worry that we have more proposals coming out of Congress to say, "Hey, let's not just make it Medicare negotiations so that it's diseases of aging. Let's make sure that on

behalf of all insurance plans, we will be able to come in and just price control the drugs." So now it'll be diseases of any age. And then they're saying, "And let's not just make it small molecules, let's make it all drugs, biologics, and let's do it five years after they launch." Will this happen? I think before 2022, Pablo, we would've said, "Come on, America would never be that stupid. It would never override its own market-based, patent-based system and crush an area of R&D, especially related to cures." But it happened. In 2022, the Inflation Reduction Act passed this thing we call the pill penalty. And it continues. We continue to get this threat.

Caitlin MacLean 43:30

So there are those unintended or intended consequences of our public policy. But I think that kind of goes to a broader point and another question that's come in about the disconnect there between what we as a population need in terms of innovations for our healthcare, and for the diseases that we all live with, versus what the market thinks is attractive as an investment because of the potential kind of revenue generation attached to it and the reimbursement that goes with that. And so, is anyone else seeing an interesting area where there is a medical need, a human health need, a population need?

Pablo Legorreta 44:10

CNS.

Amy Schulman 44:11

CNS, exactly. And depression and things that are related to CNS, for sure. And if you look at the GLP-1s, for years people thought obesity was not something investable in, and they had the kind of fen-phen scare, and it was this kind of notion that you only lost 10 percent of your weight and you always gained it back, and so this was something pharma completely steered away from. I think we are now seeing in the neuropsychiatric and the CNS space, and in areas like intractable depression, schizophrenia, investment dollars, even though those are very hard and we don't yet have really good surrogate endpoints.

Philip Ross 44:51

It's important to talk about—

Pablo Legorreta 44:51

—There's been—

Philip Ross 44:52

—I'm sorry. Go ahead, Pablo. Go ahead—

Pablo Legorreta 44:53

—Yeah. No, I was going to say there's been incredible innovation in inflammation immunology. It's amazing how that has really made diseases that were hard to treat very treatable, and we have so many alternatives, so great innovation. There's another area where I'm involved, not so much on the Royalty Pharma side, which is organ failure, and that's a tsunami that's also coming. There's 450,000 Americans that die from heart failure every year and 135,000 that go into dialysis. So, I think there's now a possibility of actually getting to those issues with pig organs and we're at the cusp of it. Clinical trials are starting, and that could be a really interesting area because people don't die of many things because of the advances, but as they get older, we have heart failure, lung failure, kidney failure, liver failure, and it's very expensive and actually, there are solutions in the near term.

Caitlin MacLean 46:00

Amazing. Phil, you were going to say?

Philip Ross 46:01

I was going to say, so this IRA phenomenon that Peter mentioned, when that happened, the world of specifically precision small molecule oncology collapsed because what do people do? They test their molecule in the sickest, most brittle patients, fifth line plus. That means you've gone through four things and it still didn't work, so let's try and help you with something. You do that. You get that drug approved, and now you're eating through your nine years as you're just trying to get to first line for that patient when they're first diagnosed. So, it didn't work. So now what we're seeing is with innovation, whether it's small molecule or biologics in oncology, we're seeing people showing long durations of therapy, but they're really steering away from ever trying to get approved in fourth or fifth line plus, which is not helping any of us. So, I think the whole thematic thing is, is there something that's clinically meaningful, and what's the definition of that? Sometimes the payer says it has to have big old outcomes data. That means we've looked at longitudinal data over a decade and we said, "You improve morbidity and mortality by this much," which is 50 percent, which is like 0.001, eighth of a percent more than the half a percent that had already—trial design is complicated. But what folks want to do is, if they had their choice, is develop drugs that are given to patients chronically, not an immediate cure. That are given for a long period of time at the earliest diagnosis, because that's the economic model to get the free cash flow back in to cycle out more development. That's where the system breaks, because now we've left how many patients behind, Peter? Millions? Like millions.

Peter Kolchinsky 47:24

Yeah.

Philip Ross 47:24

So that's the conundrum, I think.

Peter Kolchinsky 47:26
I think the bottom line is that if any of you guys work for large companies that are self-insured, you have a head of HR that probably chose what kind of health insurance your company has. And you can look across all your employees, all your colleagues, and look at the various diseases they have and what their needs are. And if you see colleagues that are having a difficult time getting a medicine that they need because an insurance plan is rejecting it, and if you are not seeing all the other employees rise up in defense of their colleague and go to the head of HR and say, "That's unjust. We want this person to get help." If people don't care, then ultimately all of us sitting here will get that market signal because that drug doesn't sell, and we won't make more such medicines. Everybody has a role to play in signaling in this American market, really the only market in the world that figures out what do people care about. Every other market, it's just a government committee that decides. But here, truly the people are involved in expressing their views—this matters. And so, look around and consider what's important to you, what's important to others. Will you each stand for each other? Will you go to the head of HR, and will the head of HR call up Aetna and say, "Yeah, we're going to need you to improve coverage of that, or we're going to switch to United." Once Aetna gets that phone call, they'll tweak their coverage, and maybe insurance premiums will go up by 25 cents per person. A $4 billion drug is just $1 per person per month. That's all it is. That's how America affords a new blockbuster. All of this is affordable to all of us, as long as we pay through premiums and don't dump it on the heads of patients.

Caitlin MacLean 49:17

I think what you're saying is we all can be that market signal that we need to make sure that the investment dollars flowing from each and every one of you are going to places that will have the impact that we are trying to achieve, which is a healthier population. So please join me in thanking this amazing panel, and enjoy lunch.

Announcer 49:41

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