THE THREE Cs OF HEALTHCARE INVESTING

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Andy Acker, CFA, provides a framework for investing in healthcare stocks. The healthcare industry remains a great growth industry, but it is fraught with risk. Acker discusses how to manage the following risks when investing in healthcare stocks: clinical risk, commercial risk, and construction risk.

ANDY ACKER, CFA: What are the three C’s of health care investing? So, these are some of the risks that we try to manage when we’re investing in this sector. A key theme for us is to invest in novel therapies, addressing high unmet medical needs. And it’s our view that these kind of therapies can do well regardless of the reimbursement environment.

So, most of the talk today is going to focus on investing in therapeutics, mostly drugs and biotechnology companies. But when investing in these kind of companies, there is significant risk. So, novel therapies with new science — there’s great upside, but also significant downside. And we’re going to talk about how we manage that.

So, the first aspect is the clinical risk, so we want to understand the science, as well as the business. That’s a key aspect of how we invest, and most of the members of our team have scientific backgrounds. So, I studied biochemistry. Ethan Lovell, the co-portfolio manager with me, studied chemistry. Dan Lyons is a PhD in immunology.

So, understanding the science is really important, but we also try to go beyond that to actually understand the statistics behind clinical trial design. And in doing so, to try to estimate the probability of success for these molecules. And that’s important, because actually only 1 in 10 of the molecules that move into human clinical testing ever make it all the way to market.
So, the second aspect would be commercial risk. So, this means that once a drug makes it to market, in our experience, the consensus estimates from Wall Street are wrong approximately 90% of the time. And those estimates can either be way too high or way too low. And as many of you know, if you want to find a stock that goes up, you want them to beat expectations. And if they don't make or beat expectations, those stocks frequently go down, and that can be even more severe in the health care sector.

And then the last aspect is construction risk, so this is how we put the portfolio together and especially how we deal with single-stock risk when we're dealing in an extreme environment, as we often see in health care.

So first, I'm going to start with why I think the health care sector is an exciting one to invest. And first of all, the key aspect that we're seeing right now is an acceleration of innovation. And you could actually say we're going through a revolution in biology right now because of our better understanding of the genetic causes of disease that are allowing us to develop far improved therapies from anything we've seen in the past. And we're also getting many more new drugs coming to market, which also provides opportunity for fundamental analysis that can create alpha generation.

The second factor is demographics, and I think you understand this well. But we have aging populations, not just in the US, but around the world. And the elderly spend significantly more on health care than the rest of the population, so that's going to be another longtime driver of health care spending.

And then we have globalization, so as countries get wealthier, not surprisingly they tend to spend more of their income on health care. And then finally, health care has defensive and diversifying characteristics, and we'll talk about that.

So, innovation in health care, why does this matter? So, we're trying to address some of the largest unmet medical needs in the world. And number one, I would say is cardiovascular disease, and we were talking about this last night. But we're spending over $800 billion a year treating cardiovascular disease, and yet it is still the number one cause of morbidity and mortality in the world.

In fact, we have somebody dying of cardiovascular disease every two seconds. So that's a huge unmet medical need. And we're actually very excited, because there are some new therapies being developed now — two of which have recently launched in just the past year — that we think can be game changers.

And so we were talking about statins, and I personally take a statin. I recommend everybody get tested for their levels of cholesterol, and if it's high, consider taking a statin. Because these are drugs that can reduce the probability of having a heart attack or a stroke by an incremental 30% to 40% if your levels of bad cholesterol are high.
But these new therapies that were recently approved, we think can actually lower your risk even further. And so they can lower your levels of LDL, or bad cholesterol, by an incremental 50% on top of the best available therapies today. And just three days ago at the American Heart Association meeting, one of these therapies was tested where they did ultrasound of the coronary vessels and found that they could actually remove the plaque in the vessels that are believed to be the causes of heart attacks and strokes.

So, that was really important data. We’re going to actually get for the first time outcomes data with a 27,000 patient trial early next year that we believe will show these drugs can actually reduce the rate of heart attacks and strokes even further from what we can do today.

Cancer is the number two cause of death, and virtually all of us know somebody who’s been affected by cancer. This is a huge unmet medical need. Eight million people worldwide are dying of cancer, and the risk of getting cancer continues to increase as we have an aging population.

Fortunately, we’re starting to make some real progress, and some of the new therapies that have been coming out are called immuno-oncology agents. And for much of the last 17 years of investing in health care, we were making very small incremental improvements. So generally, improvements with new therapies for cancer are measured in months, so we’re talking about the median survival.

So, instead of the average patient living for 6 months or 8 months with a very severe form of cancer, maybe they could live for 10 or 12 months. And that is progress, but not the kind that really makes you feel good in terms of if it’s a friend or a loved one that’s impacted. But now we have new immuno-oncology agents that can actually activate the immune system to identify and kill cancer cells.

And it turns out cancer cells are very smart. They’ve found a way to hijack part of your natural immune system that allows your immune system to differentiate between self and foreign material. And so they have essentially — cancer cells have a way of putting the brakes on the immune system. And I’m a Star Trek fan, and so it’s kind of like the cloaking device. So they say, “Don’t kill me. I’m one of your own cells.” And your immune cells can be right next to a cancer cell and not recognize it, and so they just sit there.

But now with these new checkpoint inhibitors — and one of the leading ones is called Opdivo from Bristol-Myers — now you can take the brakes off the immune system and identify and kill cancer cells. And that’s important, because now we’re getting long-term functional cures in previously incurable cancers. And so we have new treatments that — some of these have now been approved for lung cancer, head and neck cancer, skin cancer, and kidney cancer.

And to put in perspective with melanoma or stage four skin cancer, just a couple of years ago, for the best standard of care therapy, the median survival at two years was about 20%. Now that has
moved up to over 65%, just in the last couple of years. And what we’re really excited about is now we have monotherapy, but soon we’re going to be combining two different immuno-oncology agents or potentially one of those with a cancer vaccine or with traditional chemotherapy. And we think we’re going to get to a much higher percentage of patients that can get these long-term functional cures — so really starting to make progress.

And then we have diabetes, which is a worldwide epidemic that now affects over 400 million people. Nine percent of Americans have diabetes, and that trend keeps growing. So as we get older, and unfortunately as we eat more sugar in our diets, and have too much McDonald’s, the trend is such that we may have one in three Americans ultimately develop diabetes.

So, there’s another major problem, but again we’re making progress. One of the things that we’re excited about is continuous glucose monitors. So, patients when they get further along in diabetes or if they have type 1 diabetes, they need to monitor their glucose levels very frequently. So, many of them have to use finger sticks, and they have to stick their finger to measure the glucose in their blood as often as five or six times a day.

And so they start to feel like a pin cushion, and that’s not really fun. And so, very few people actually monitor as often as they should. And because of that, their glucose is not well controlled, and if your glucose is too high, then you can develop end-stage organ failure, whether it’s kidney disease or they often have a higher risk of dying of heart disease.

And if your blood sugar gets too low, then you can get what’s called hypoglycemia, which can also be life threatening. But now we have continuous glucose monitors where you can put a small sensor under the skin, and it can continually monitor your glucose every five minutes. And not just tell you what the levels are, but also what the trends are.

And that gives you much better control, and now you can actually track it on your iPhone. Or if you have a child that has diabetes, a parent at home can monitor for their children and make sure that they’re staying within control. So again, we’re making significant progress.

Now, we talked about the trend accelerating. And how many of you are familiar with Moore’s law? Anyone? I had some people that had never heard of it, but I always thought of it as a very important law. And obviously, that means that the amount of information on a microchip doubles every 18 months, and that’s resulted in the computer revolution and the fact that an iPhone has more transistors than a supercomputer of years ago or of a rocket ship that could go to Mars in the 60s. You now carry more power than that in your pocket, if you have an iPhone.

So, we’ve made obviously dramatic progress, but the progress we’re making on genetic interrogation, genetic productivity has even dwarfed Moore’s law. So when I started at Janus back in
1999, we were just completing what was known as the Human Genome Project. And do you guys remember the Human Genome Project?

So, this was a giant global collaboration to sequence the first human genome, and it was completed around 99. And the first actual sequence was completed in 2000, and it was celebrated as a great success. And biotechnology stocks all did very well back then, and everyone was excited about the potential of this new genetic information. Because the genetic code is the book of life for all organisms. We have 3 billion base pairs, and so deciphering these letters, this was going to be the key to figuring out all disease.

The problem is that project took 13 years to complete and cost $3 billion. And so if every time we want to get genetic information, it cost $3 billion and takes 13 years, that's not very helpful for drug development. So, there was a long period where we didn't get that explosion of new medicines that we were hoping for, and that led to a period of disappointment.

However, very quietly in the background we've been making dramatic progress in terms of our ability to get this genetic information. So, now we can actually — just about 16 years later or 17 years later, we can sequence a human genome in one day and do it for $1,000. So that's a 3 million fold productivity improvement. And what does that mean?

That means now scientists have a much better understanding of the underlying genetic causes of disease, and they can develop drugs that directly address those underlying genetic defects. So, the net result of that is we're getting more new drugs, and they're better new drugs. We're getting revolutionary changes instead of evolutionary changes.

And you could see at the chart on the right, just in the last three years alone, there were 113 new drugs approved, which is 60% more than what we were seeing just six years ago. And last year alone, there were 45 new drugs approved, which was the most in 19 years. Now, all these new drug approvals are important for two reasons.

So, the first is that in health care, the lifecycle of a new product is much longer than in other industries. So, generally a company that gets a drug to market has 10 years or longer before the patents begin to expire, and so the revenues, and the earnings, and ultimately the cash flow from those new launches tends to increase over time for many years. And in the initial couple of years, companies often lose money as they're launching the drug, but the penetration increases over time.

The second aspect, though, is that these new launches, first of all, whether a drug actually makes it to market, and then second of all, once it makes it to market, whether it's successful or not are huge inflection points in value. And this is where I think an active management approach can really be helpful.
I’ll go through these others a little more quickly, but aging demographics. So obviously, we’re in the time where the Baby Boom generation is reaching retirement age. And in fact, in the United States, we have 10,000 Baby Boomers that we’re expecting to reach retirement age every day until 2030. So obviously we have an aging population in the US. It’s also true in the rest of the world. And why is that important for health care spending?

Because we actually spend three times as much on the elderly in health care as the rest of the population and four times as much as on pharmaceuticals. And that continues actually after retirement age, so the bottom chart on the right shows Medicare spending. And you spend about $5,000 for someone who’s 65, but that doubles as they turn roughly 80. And then it doubles again as they get to 95, so that’s going to continue to drive higher health care spending.

Globalization is also a reason for higher health care spending. So, as countries get wealthier, it may not be surprising, but we spend a higher percentage of our GDP on health care. And so especially in emerging markets where the spending per capita is so much lower than everywhere else in the world, as countries like India and China catch up, they’re spending more on health care. And it’s estimated that there will be $1 trillion of incremental spending in those emerging markets by 2050.

And the last characteristic is the defensiveness of health care. So, we looked at major downturns over the last 15 to 20 years, and how did health care hold up versus the broader markets? And as you’d expect, health care is defined as a defensive industry for a reason. It’s because if the economy slows but a patient has diabetes, they’re still going to need their diabetes medicine. And if someone gets sick, they’re still going to need to get treated or go to the hospital.

So, health care tends to hold up better than the broader markets during down cycles. And in fact, health care outperformed in four of the five last down cycles. The most recent one was the only one — and this is 10% corrections or more — the only one where that wasn’t true and this most recent one, and that’s because of the special circumstances of the last year, which we’ll probably get to in the Q&A. But we’ve had this election cycle where drug pricing has been a major issue, and that had weighed on the sector.

But health care also has a lower beta than the market and a lower standard deviation, so that’s why I think health care is interesting. But why take an active approach? And at the dinner last night, we were talking about how few active managers can actually outperform on a sustainable basis. And so we were arguing, should investors just be investing in ETFs or index funds?

And I think health care is really unique in that there is the biggest disparity between the winners and the losers in health care of any sector. And this is because — we talked about it a little bit — but health care is prone to extreme outcomes. So, a drug, essentially, that’s being developed, it either works or it doesn’t. That’s what we call a binary event. There’s only two outcomes. And then once the drug gets to market, it can either be extremely successful and sell billions of dollars and
generate great returns for shareholders, or it can be a complete commercial failure and potentially go bankrupt.

So, those are extreme outcomes, and this chart shows the difference between the winners and losers. And this is only stocks over $500 million in market cap in the Wilshire 5000, but what was the difference between the winners and losers over the last 10 years? And you can see it’s pretty extreme.

This is the top five and bottom five. But you could cut it any way that you want to, and the results are the same. But you can see here that the top stocks over the last couple of years went up three-to four-fold in a single year, and the bottom stocks were down 70 to 80. They didn’t like the stocks going down that much.

So, now you can see that the black line that’s kind of surprisingly close to zero is what you get if you own the MSCI World Health Care benchmark. So, that looks — our goal actually in active management is to try to own and find more of those winners that do really well and then avoid, or at least mitigate, the impact from the losers.

And we call this our framework for investing in health care, and this is probably the most important slide of the presentation today. But we call this the 90/90 rule. So what do we mean by that?

The first part of the 90/90 rule is the clinical risk, so this is the first C. And what we mean is that 90% of drugs that move into human clinical testing will never make it all the way to market. So, this is why companies spend so much to develop a drug and to get it to market. The average estimated cost for each drug that makes it to market is between $1 and $2 billion per molecule.

So most drugs will fail, and so a big part of our process is trying to identify that needle in the haystack. Which are the drugs that actually have what it takes to get all the way to market? And so our process is to try to understand the science, as well as the business. And so most of the members of our team have scientific backgrounds. I studied biochemistry, and we have a PhD in immunology. So, we want to understand that.

But we go beyond that. We want to understand the statistics behind these clinical trial designs, and so we’ve developed proprietary statistical models to analyze the probability of success and then, ultimately, try to estimate that, and what we found is both the market and even the companies themselves are not always very good at differentiating between drugs that are highly likely to work from those that are a coin toss or worse. And so, that can be a significant inflection point in value, and we’ll talk about some examples.

But even if we identify that needle in the haystack, the 1 drug out of 10 that makes it all the way to market, then you have the commercial risk. So even though we have a lot of very smart analysts
that are looking at these companies, in our experience over 17 years, those consensus estimates are wrong virtually all the time. And they’re either way too high or way too low.

So, our approach here, we call it the three P’s, and so those are physicians, patients, and payers. So, we want to understand the perspective of each, because the reality is these new drug launches are very difficult to estimate correctly. And this is why everybody gets them wrong. The consensus view often takes an average estimate of what a launch could look like, but very few or almost no drugs are average. Either everything lines up perfectly, and then the drug is much more successful than expected. Or something goes wrong, and then the drug can be a commercial failure.

So, to get a better understanding with the three P’s, I’ll talk about a few examples. So, let’s start with clinical risk.

So, this is an example that was recently in the news this year, and this is a company called Medivation. So, we came upon Medivation back in 2012, and Medivation had developed a novel therapy called Xtandi, and this was a treatment for prostate cancer.

Now, Xtandi had already proven success in late-stage prostate cancer, so this is for patients that were pretty far along in their disease, had actually already taken and failed chemotherapy. So at that point, patients literally have only months to live — about six months on average.

And they showed that by giving this drug that the patients could live a little bit longer, and so we thought that was a modest market opportunity. And the stock was reflecting that kind of reality, so they had about a 500 — we thought that drug could do about $300 to $500 million in sales. The company had about a $2.5 billion market cap, so we thought it was appropriately valued for that opportunity.

But we also knew that the company was doing a large study in over 1,000 patients, looking at early-stage prostate cancer. So this is before the patients had taken and failed chemotherapy. And it was our belief that this drug actually had a much higher probability of success than was being priced into the market. And in fact, we thought they were getting almost no credit for this drug working in late-stage prostate cancer.

Now, why did we think it was going to work? So first of all, there’s another drug that was similar to this drug Xtandi by Johnson & Johnson, and that drug was called Zytiga. And all of the head — not head to head, but comparable trials — all showed that the Medivation drug was at least as good and probably better than Zytiga in terms of efficacy and tolerability.

And that drug had already shown success in the early-stage prostate cancer, so we used our statistical models and assumed that Xtandi would be only as good as Zytiga, even though we thought it would be better. And when we modeled this out, we actually came out with an 80% to 90%
probability that this drug would work. And yet the stock was pricing in almost nothing for that opportunity.

And then we had to look at, well, what would success look like? What if it did work in that setting? And our understanding was that the opportunity was about 10 to 12 times larger for the early-stage prostate cancer opportunity. So we became a significant shareholder, and over the course of 2012 and 2013 Janus became a top five holder — I think the number two holder of Medivation.

And then indeed, in October of 2013, the company announced the results of their Prevail study, which showed the largest survival benefit ever demonstrated in the early-stage prostate cancer opportunity. And on that day, the stock was up 30%, but we thought that was still an underreaction. In fact, over the next few years, the stock went up meaningfully higher.

Now that drug Xtandi not only got approved, but this year will do almost $2 billion in sales. And Pfizer just earlier this year acquired Medivation for $14 billion. So, that was one example.

The next example is Puma Biotechnology, and so this is — before we were talking about prostate cancer, but we don’t want to leave the women out. So we have to develop something for breast cancer.

And this is a particular kind of breast cancer called HER2-positive breast cancer, which affects about 20% to 25% of the cases of breast cancer. Now there’s a very good drug already approved for this indication called Herceptin, and Herceptin is an antibody that targets this HER2 receptor.

The problem is — and that drug has been extremely successful. It’s selling about $7 billion worldwide today, and it’s approved for both early stage or the adjuvant setting, which is what you give for early-stage patients after you remove the tumor surgically. You give chemotherapy and this drug Herceptin to try to prevent the cancer from coming back, as well as late-stage cancer, which is metastatic once it’s spread.

Now, this drug is called Neratinib, and this is a pill that blocks that same receptor, but in this case inside the cell. And in 2013, we knew that that drug worked for the late-stage cancer setting, so you’re going to see some parallels here. But the question was, would it work for early stage?

And in this case, they were looking again at the adjuvant setting. But Herceptin is given for one year, and they wanted to give this drug for an additional second year of therapy. And in 2014, the consensus view was this is very unlikely to work. And why did people feel that way?

It was because another drug being developed by Glaxo that had a similar mechanism had just at the June ASCO (American Society of Clinical Oncology) conference failed in development. So everyone said, well, that one failed, so this one clearly won’t work either.
Again, we ran our statistical analyses, and we believed it actually had a much higher probability of success. Because this molecule was actually much more potent than the one that had just failed, and the trial was very well powered for success. So, we thought the stock was pricing in almost nothing for a potential successful outcome.

And in July of 2014, indeed they did announce that this drug worked and actually improved disease-free survival in this indication. And the stock was up 299% in one day, so that’s essentially a quadruple, which is one of our best single days. And that obviously was a very unexpected result for consensus, but based on our work, we thought it was much more probable than it was being priced in.

Now, this doesn’t always go the right way, so I don’t want to mislead you that we’re right all the time. Because this was a very painful example that still leaves a scar, but this was all the way back in 2006. And this is a company called Nuvelo that was developing a novel therapy for peripheral vascular disease, so these are patients that have a clot in their leg, for example. And often that needs to be fixed surgically, and so it would be great if we could have a medicine that would clean out those clots.

So, this was a drug that was actually developed from vampire bat venom, and it actually makes sense. Because when a vampire bat wants to suck your blood, it wants to loosen it up, so it has a blood thinner in there. So, the mechanism made sense. We talked to a lot of doctors. They all believed it was going to work, and we had a big position in it.

And unfortunately, it didn’t work. It actually worked no better than a placebo, and the stock had run up because of high expectations that it would work. And so the stock was down 74% in a single day, and we made two mistakes that day. The first is that we owned the stock, which was obviously really dumb in retrospect. But even more importantly was our position size was completely wrong. We had a 4% position in the portfolio, which means that cost us 300 basis points of absolute and relative performance in one day. So that meant it wasn’t just a bad day, but it was a bad month and a bad year. And that really weighed on our results.

So, that single example was actually the reason why we adopted what we call a value-at-risk approach, and we’ll talk about that later. But in essence, what this means is we have to actively manage the position size. So, even though we can run statistics and we think a drug is likely to work, there’s always scenarios where it doesn’t or an unexpected safety issue emerges. And so it’s very important that you vary your bet size essentially and mitigate the impact from a worst-case scenario.

And so in early 2007, we implemented this value-at-risk approach where we wanted to set the maximum position size so that in a worst-case scenario, the impact to the portfolio would be 1% or less, or 100 basis points. And so we’ll talk about that in a little more detail soon.

So, let’s talk about commercial risk. So, the clinical risk is really exciting. We’re dealing with binary events. Now the drug has made it to market, and how do you decide what’s going to happen? And
so the first example is Regeneron, and so this is a company based in New York. And you might have heard of it, but this drug was approved in late 2011.

And this is a drug called Eylea, and this is for a disease called wet AMD, which is one of the leading causes of blindness for the elderly. Now, there was already a drug to treat wet AMD, and it’s called Lucentis. And Lucentis was very successful. It was selling about $2 billion in the US, but this drug is coming second to market.

And the expectations for the launch were good but relatively modest, so the stock was around $80 a share. And this is where the three P’s come into play. So, we’re always looking. Is the consensus too high? Is the consensus too low? What are they actually going to sell in that first year? And the consensus estimates were they were going to do about $250 million in sales in the first year, which would be considered very respectable.

So, we want to understand the perspective of the three P’s. So first we start with the physicians and actually with the science. So how does this drug work? It turns out this drug was about 100 times more potent at binding to the target, which is called VEGF, than the old drug Lucentis. Why does that matter?

So first of all, it turned out that by binding more tightly, the drug had better efficacy, especially in more difficult to treat patients. So the doctors tried it in their hardest to treat patients and found it worked much better than the old drug Lucentis.

But the second aspect is because it was binding so much more tightly, it stayed on longer. It meant that you could give it less frequently, and so these drugs unfortunately have to be injected in your eye. That doesn’t sound fun, right? But if you’re going to go blind, then getting injected in the eye is worth it. (And actually it’s not as bad as it sounds — the patients don’t really feel it.)

But with the old drug Lucentis, you have to come in once a month, and it affects the elderly. So, it’s often a child taking their mother or father in to the doctor every month, but this new drug could be given every other month instead of every month. So, now you could get it 6 times a year instead of 12 times a year. And as the CEO of Regeneron, Leonard Schleifer, said, I’d rather have one stick in the eye than two sticks in the eye. And that seems kind of obvious and intuitive, but that was very attractive for the patients.

So, you have to understand the physicians liked it, because it was more effective. The patients liked it, because they could come in less frequently.

And then finally you have the payers, so you have to understand the perspective of the payers. So, are they going to cover this medicine? Do they think it’s cost effective? Are they going to create access issues? And here the company did something brilliant, which is they had a better drug that
could be given less frequently, but they charged less for it. So, they actually priced it at a 15% discount, which is actually somewhat unusual in the drug industry.

So, now you had a drug that could be economically superior in every way. It’s better for the patients, better for the physicians, and better for the payers. And it costs less. So, the result was much more rapid adoption than expected, and in fact, in that first year, they sold almost $800 million. And today, that drug is annualizing over $3.5 billion. And that stock has gone from $80 a share to roughly $400 a share today. So again, getting these right, these new launches can drive tremendous economic value.

The next example is Pharmacyclics. So, Pharmacyclics had developed a new drug for a form of leukemia called CLL, or chronic lymphocytic leukemia. Now, this drug launched, and initially it was approved for late-stage leukemia patients.

But in 2014, the stock was very weak, and actually I don’t know if you can tell on the chart, but the stock was down roughly a third from when it had launched. And the reason is, there were a lot of skeptics out there. They said, oh, this market’s not that big. The stock is pricing in too much success. There’s a lot of competitors coming. Maybe there’s side effects.

And when your stock is down, and it’s essentially on sale, you have to decide, am I wrong? Was my thesis incorrect, and maybe the consensus is right? Or maybe the consensus is wrong, and so that’s when you really have to batten down the hatches and essentially double down on your research process.

And so, we spent a lot of time talking to key opinion leaders, talking to physicians that were getting experience with the drug, conducting surveys — and that’s one of the key aspects. We want to understand from the physicians that are using it. We want to get the perspective of the key opinion leaders, but also the community doctors that represent 80% of medicine’s use. What’s their experience with the drug, and do they see using a lot more of it?

And the feedback we got was actually very encouraging. So, instead of chemotherapy, this is a once a day pill that had very few side effects — so much better tolerated. And then it had remarkable efficacy, and so, one of the things we think the street was missing was that because the patients were doing so well on this therapy, they could be on it for many years.

And we thought in the first line setting, the median progression-free survival was measured at seven years, meaning every year there’s about 5,000 new patients that get this disease, every year. But those numbers would keep adding on. They actually now call this the Gleevec effect, because Gleevec is a drug for another form of leukemia that initially people thought would do a couple of hundred million. And it ended up doing multiple billions. Because the patients do so well on it, they stay on it year after year, and you keep adding new patients.
So as it turned out for this drug, the consensus estimates for year two were for them to do about $650 million in sales. And we thought it was going to be closer to $1 billion in sales. And then in early 2015, the company actually came out with guidance to do $1 billion in sales. And then shortly after that, the AVI actually made an acquisition offer for the company for $20 billion. And just six months earlier, it had been trading at $8 billion.

So again, this is an opportunity. This was about a 150% move over a six-month period.

Now again, we’re not always right on these things, so I don’t want to mislead you. And part of what’s so tricky about these launches is they can change. Sometimes a new launch is going great, and expectations keep building. Because again, if you have a company with $1 billion market cap, and they come out with a new drug, and it ends up selling $1 billion, that stock’s probably going to be a $5 billion market cap. So, there’s an enormous upside.

But what happens when things turn? So, this is a case study, a company called Aegerion, which was developing a new therapy for cholesterol. And we talked about cholesterol as a huge unmet medical need. This was a pill that could lower your levels of bad cholesterol by an incremental 30% to 40% for the most severely affected. So something that’s called homozygous FH, or familial hyperlipidemia, sorry.

So, these patients have severe levels of high cholesterol with their bad cholesterol measured at 200 or 300, and the drug actually worked. And so initially, the uptake was very rapid. The problem is that it was very difficult to tolerate this drug, and patients had to be extremely restrictive on their diet. So they had to have a very low fat diet. They couldn’t eat pizza. They couldn’t eat ice cream, all the fun stuff that we all enjoy. And they had to do that for life, and if they didn’t, then they would get really bad GI side effects.

And so, what happened is initially the patients would take it, but then gradually the tolerability issues and their diet would loosen. And then they just couldn’t tolerate the drug anymore, and so we have what looks like Mt. Everest there. But the stock had initially did extremely well, and then things turned. And the company kept missing expectations, and you can see what happens to a stock when they start missing.

So, in this case, the stock got as high as almost $100 a share. We ultimately sold out around $25 a share once we finally, belatedly realized that we were wrong. And now the stock is probably a couple of dollars a share, so it shows you the extremes of what can happen when these launches go well or when they go poorly.

So, the last C that I’ll talk about is construction risk, and this is really the broader view of the portfolio. We’ve been talking about two very specific aspects, but how do we put the whole portfolio together? Because we do have a health care fund, not just biotech and pharma.
And so, first, we have to create an investable universe, and so we look at all of the different companies. And we look at the qualitative and quantitative aspects, and there are roughly 600 stocks within the health care universe that have sufficient liquidity that we can consider in the portfolio. And that’s when our team of six analysts actually starts really digging in, and this is the fundamental research.

So, our team is traveling around the world, attending medical conferences in every therapeutic area from oncology to heart disease to diabetes to autoimmune disease. We’re talking to physicians and interviewing key opinion leaders in each of these therapeutic areas. We’re reading the scientific literature to find out what are the major medicines that can have an impact and change the way we treat disease.

And we’re also meeting with management teams — although that’s a smaller aspect — conducting detailed surveys. We develop a proprietary prescription database to analyze both volume and price to try to get a better sense of revenues. All this is incorporated into detailed financial models where we’re looking at the key leverage points and focusing on the revenue and earnings, and ultimately the free cash flow of the business.

I know you spent some time with Ashta Motorne yesterday. He taught us a long time ago about how to do a DCF, and so valuation is ultimately what we focus on. We’re looking for companies that traded at least a 25% discount to our estimate of intrinsic value. And we use a discounted cash flow approach to estimate that.

And then, we put together a portfolio that represents the best ideas of our health care team, and so the portfolio has 70 to 100 holdings. Today, it’s about 85 to 90 holdings, and 85% to 90% of that portfolio is rated buy/strong buy by our team. But then, we also look at we want to have a balanced and diversified approach, so we have about half of the investments in core growth companies. These are companies that have dominant franchises, that we think are market share gainers that generate strong and sustainable free cash flow generation.

A good example here would be Celgene, which more than 10 years into the launch of their leading therapy Revlimid, which is for blood cancers, in the most recent quarter is still growing revenues at 28% year over year. Then we have emerging growth companies, so these are companies that have a new product that we think can drive an acceleration of revenue and earnings.

A good example here that we didn’t talk about on the commercial risk is Gilead. So, Gilead a few years ago acquired a new therapy for hepatitis C, and we believe that even though Gilead was already profitable — they are the leader in HIV therapies — they acquired this treatment for hepatitis C. And a year before the launch of that medicine, the consensus estimates were for them to do about $1 billion in sales.
As it turned out, they did $12 billion in sales in the first year, and that incremental $11 billion in revenue at 98% gross margins caused Gilead’s earnings to quadruple and their stock to go up about five-fold over a three-year period. So, that would be the emerging growth category. That would also include companies that are development stage that don’t actually have a product on the market, but a single product can make a big difference for them.

And then the last category, which is another 20% to 30% of the portfolio, would be opportunistic investment. So, these are companies that are suffering from short-term market misperceptions that we think should resolve over time. Often this involves restructurings and spin-offs. A good example here is Baxter, which split into two companies about a year ago.

And then we have Baxter and Baxalta. Baxalta has already been acquired, and Baxter has been a strong performer as the new management team has been able to significantly improve the margins of that business. Now, we have a balance within this portfolio across the different subsectors within health care. So, we have investments in pharmaceuticals, biotechnology, medical devices, and health care services.

And we try to maintain that balance, so generally no one sector would represent more than 30% to 40% of the portfolio. And that can vary over time, but we look different than the benchmark. We tend to be overweight biotechnology and underweight pharmaceuticals. Because, frankly, that’s where we’re finding more of the innovation and more of the growth.

Now, this last slide — I had referenced that value-at-risk approach. This is a graphic depiction here, but the idea is that we actively manage the position size so that in a worst-case scenario, the impact would always be 100 basis points or less. So, if we had a company that had a key product where if it failed in a worst-case scenario, the stock would be down 33%, we would never have a position above 3%.

If a company had a product that failed and it could be down 50%, we’d never have a position more than 2%. And in the case of Nuvelo, we should not have had a position more than 1.4%. So having that 4% was a big mistake.

And that little box on the right shows how we construct the portfolio where two key parameters determine our position size, and those are conviction and risk. So, our biggest positions are the ones in which we have the highest conviction, which means we believe we have investment insight based on our research that the market doesn’t appreciate, but are also lower risk. So, we don’t want big positions to be the ones where if we’re wrong, there is tremendous downside.

And then the ones in the bottom right are those higher risk opportunities, where it may be in front of a binary event, so we haven’t been de-risked yet. So, we want to have exposure, but again
we want to limit the position size so that in a worst-case scenario, it won’t really damage our performance.

So, those are the three C’s of health care investing. We talked about the clinical risk, the commercial risk, and the construction risks — all of which we try to manage in order to ultimately achieve long-term risk-adjusted results that are ahead of our peers, ahead of the broader markets, and ahead of the health care sector. So, how have we done? Has this worked?

And so, this is the one slide I’ll refer to. But we looked at, have we actually outperformed the benchmark? Which is, for an active manager, what we think we need to do to justify our existence. And so we looked at the last 10 years, every rolling three-year period, every month, and what we found is that we had outperformed the benchmark in 85% of those rolling three-year periods. But that actually includes the period in 2006 when we had that terrible Nuvelo stock and some other binary events that went against us, and it was before we implemented the value-at-risk approach in early 2007.

So we looked at, how have we done since we implemented that value-at-risk approach? And in that period, we’ve actually, since early 2007, have outperformed our benchmark 95% of the time. So, I think that’s a testament that following these three C’s of health care investing can actually work to drive our performance.

And I guess, just when we look at historically how have we done versus our benchmark, over the nearly 18 years of managing this portfolio now, we have roughly doubled the performance of the benchmark, outperforming by over 570 basis points. And against the broader market, we’ve also more than doubled the performance of the S&P 500 for almost 18 years now and outperformed by about 600 basis points a year for 18 years. So with that, I’ll open it up to questions.

SPEAKER 2: Thank you very much. We have a fair amount of interest here, Andy.

ANDY ACKER, CFA: OK.

SPEAKER 2: So the first segment of questions I’m going to focus on is more like people are very curious about digging deeper into your investment process and decision-making rights. So, can you elaborate on the statistical techniques you use to improve your success in pricing a commercial winner?

ANDY ACKER, CFA: OK, so those are — it’s really two different aspects, so I’ll start with the statistics. So, this is something that we developed over the last 8 to 10 years, and what we found is initially — and I think the way many health care investors approach investing — is you try to look at the clinical data. And then you talk to smart scientists in that field and ask them, do you think this drug is going to work?
And that was our approach, I would say, for the first eight years of managing this portfolio. But what we found is that approach didn't really work that well all the time. So, we found it was like throwing a dart at a board, because the doctors actually — the whole design of these trials is they're double-blind trials, meaning neither the patient nor the physician knows which therapy the patient is getting. And we found they weren't very good at estimating whether a drug would work or not.

So we thought, is there a better way? And so we started to bring statistics into the equation, because ultimately a clinical trial has a statistical hurdle. So, the FDA sets a hurdle where a drug has to be statistically significant on the efficacy endpoint, meaning there is only — and they call that a \( p \)-value. So, you have to have a \( p \)-value of 0.05, meaning there's only a 5% chance that that outcome was a result of chance.

And you have to do that generally in two different studies, so two different studies both have to show there was only a 5% probability that that was not because the drug worked. So how do you approach this?

We actually designed these proprietary statistical models, because essentially every drug has a true effect size. And then the clinical trials are really just an estimate of what that effect size is. And so for example, let's say a drug — in testing some drugs, they look at what is the response rate of the drug. So, is it 30%, 20%? And there's often a placebo response.

So, let's say a placebo would give you a 20% response in the average patient. Then companies conduct three different stages of testing: phase one, where you're testing generally in healthy volunteers; phase two, where you're looking at a dose ranging and trying to get an estimate of the treatment effects size; and then phase three, the pivotal trials where you're actually trying to prove that a drug works.

So, what we do is we take generally the phase two data, which give you both an estimate of the treatment size — so let's say we got 30% versus 20%, so the estimate of the treatment effect size would be 10% — but then we also know the variability around that, so it might be 10% plus or minus 5%. And so, that essentially gives you a distribution of probabilities, and then we can put those inputs into the design of the phase three pivotal study, which generally is a bigger trial.

And what we find is we have an estimate of the treatment effect size plus or minus a certain amount. So, if you look out two standard deviations, then you know there's a 95% probability that the true treatment effect size will be within that range. And then you look at the pivotal study and say, how is this study powered? How much of an effect size do we need?

So, what we find is that some studies are designed so that we actually have an 80% or 90% confidence that even if this trial shows the drug effect size is at the low end of that probability
distribution, we’re still going to get a positive trial. And other times, it comes out more 50/50, and we find the street and companies are really not good at estimating that. So, by understanding all of these variables and what essentially matters in the trial, we find that can actually really help us in terms of estimating the probability.

It’s a bit complicated to explain, and there’s a lot of proprietary aspects of it. So, I can’t explain to you exactly, but that’s essentially what we try to do.

SPEAKER 2: How long do you hold an individual stock? And does your model tell you how long to hold them?

ANDY ACKER, CFA: So, what we look at is I have a spreadsheet with every stock in the portfolio, including our target price, which is our estimate of intrinsic value. And obviously stocks are volatile. They’re constantly going up and down.

So, as the stock is appreciating and starts to approach our estimate of intrinsic value, we tend to trim it. And then if it reaches our estimate of intrinsic value, then we would sell it. At the same time, a stock is pulling back, then we have to again reassess our thesis, make sure we’re still confident in it. But if we aren’t and our thesis hasn’t changed, now the discount to intrinsic value is growing. And so, we would be adding to that position.

But generally, our holding period — we’re looking for stocks that we can own on a multi-year basis. Usually, that represents about three years on average, but we’ve had many stocks like Celgene, which I mentioned earlier, which we’ve known for more than a decade. And as long as that value keeps increasing, their drugs are growing, they are developing new drugs in their pipeline, our estimate of intrinsic value can keep increasing. And so, we can own drugs for multiple periods, multiple years.

SPEAKER 2: Can you talk about the process you go through to decide when to exit a profitable trade? And how much of a gain is enough to realize profits? And do you hedge, and if so, how? So, definitely more technical again.

ANDY ACKER, CFA: Yeah, so again, for us it comes down to, where is the stock trading relative to our estimate of intrinsic value? And so, we would look to exit a profitable trade when that stock reaches our estimate of intrinsic value. Because at that point, we think the market has caught up to our beliefs about the value of the company. And so, continuing to own it at that point, we don’t think would be a good strategy. We’re constantly trying to essentially maximize the discount to intrinsic value for the overall portfolio, so that happens by varying the stocks and varying the weights within the portfolio.
SPEAKER 2: This next question is a little bit of a clarification. They’re saying when you invest in a winner drug, then the drug company often has multiple drugs. Some are winners. Some are losers. So how can you weigh that and get a sense of how much the impact will be on the stock?

ANDY ACKER, CFA: Yeah, so Regeneron’s a good example. So, we initially got very excited, because we thought, this drug Eylea — the consensus estimates were missing how big this drug can be. And now this is looking like it’s going to be a $5 billion drug or more. But then, you also have to look for those sources of hidden value, and as it turned out, we mentioned that there’s these new therapies that were just approved in the last year.

It turns out Regeneron was also developing one of these drugs called a PCSK9 inhibitor. So, these are the drugs that can lower your levels of cholesterol by an incremental 50% on top of the best available therapies today. And the reason we got so excited about this drug, there’s actually an experiment in nature where there are certain individuals that are born without this particular protein. And what this protein does is it actually gets rid of the receptor in your liver cells that removes your bad cholesterol.

So, when you don’t have this receptor, it allows your cholesterol to accumulate. The patients that were born without this particular protein have almost no heart disease. So, there was an 88% lower rate of heart attacks, strokes, and death if you’ve never had this protein. So, that is a point of evidence why we think it’s very exciting. At the time, no one was really talking about that drug, which was also in their pipeline.

They have another drug that we’re really excited about, which is hard to pronounce, but it’s called Dupilumab. And this is a drug for allergic disease, and so it turns out it blocks this particular pathway in the allergic cascade. And when you block that — so there are patients that suffer from something called atopic dermatitis. So, this is a skin disease where patients have inflammation on their skin that causes severe itching. And so, for the moderate to severe patients, this can be extremely debilitating. So actually many of the patients, they literally can’t sleep, and there’s a high suicide rate. And there’s nothing that really works. Steroids work for a while, but you can’t take them long term. But this drug is showing incredible efficacy for that disease, and also for allergic asthma, and other allergic diseases. We expect that drug to launch next year, and again, we think that could be another big seller.

So, we have to look beyond the drugs that are on the market into the pipeline, and that can be more a source of hidden value.

SPEAKER 2: Just to put this question into context, we had a fantastic speaker yesterday, Marcos Lorenzo de Pareto, and he talked about how in scientific studies, 30% of these studies are eventually rescinded as not being correct mathematically. So, this question is there is increasing concern that most published research findings are false, and much of what medical researchers conclude
on their studies is misleading, exaggerated, and flat-out wrong. Pharma funding for studies only exacerbates the problem. Do you want to comment on that?

ANDY ACKER, CFA: That’s an interesting one. So, these studies generally — and I think sometimes those studies that are wrong are usually early-stage studies. So, a scientist will do an experiment in their lab, and then a key part of the scientific process is that you have to actually confirm those results in another independent lab. And so, when they try to do that, sometimes they can’t actually replicate that data. And so, the original data might have been fraudulent.

It happens with public companies with drugs or products on the market, but it’s much more of a rare occasion. So, these studies that are in thousands of patients, those data are very heavily scrubbed by many sources, including regulators around the world. And so, it’s much less common for that to happen, but we have actually — there have been cases of fraud with public companies.

We owned one of them a few years ago, a company called Sequenom. Had turned out they were the one that developed the first test that has now actually become commonly used. But this was for prenatal screenings, so for women who wanted a noninvasive prenatal test to see if their child might have Down syndrome. But unfortunately, that initial dataset turned out to be fraudulent, so that was not a fun day. The stock was down about 75%.

But as it turned out, you actually can do that kind of testing, and that’s now becoming much more commonly used today. But for most public companies, that data is much more validated.

SPEAKER 2: Are there any promising treatments on the horizon for Alzheimer’s?

ANDY ACKER, CFA: Yes, so we talked about cancer and heart disease, which are some of the leading causes of death. And hopefully we’re going to make progress there, and so we’re all going to live longer and longer. The problem is, as we live longer, we’re at increased risk of dementia. And it turns out for every five years of life beyond age 60, your probability of getting dementia doubles. So, if we’re all going to be living into our 90s and 100s, unfortunately, we’re all going to get dementia, so we’ve got to do something about that.

Fortunately, we are making progress there, and we talked about the revolution in biology. We have a much better understanding of the cause of Alzheimer’s disease. We’re actually going to get data in just a couple of weeks from one of these first therapies from Eli Lilly, a drug called Solanezumab, which is targeting the a-beta plaques in the brain. So, we’re hopeful that this one will work. It’s not that clear cut.

But there’s another therapy from Biogen Idec called Aducanumab, and that one, the early data looked even more promising, where they actually showed this drug, which is an antibody, could actually remove the plaques from the brain that are believed to be the cause of Alzheimer’s disease.
And that in doing that, it actually correlated with an improvement in cognition or the ability to think. So, that drug is in the final phase three, pivotal testing. And we’re optimistic that that could show some efficacy.

SPEAKER 2: And unfortunately, I have a lot of really great questions, and we don’t have a lot of time. So, I think that the one that seems to be most prevalent is in this new political regime, what’s the outlook for your sector?

ANDY ACKER, CFA: Sure.

SPEAKER 2: And the changes that may occur.

ANDY ACKER, CFA: We’re 68 minutes and 24 seconds into the presentation, and we’ve got our first question about the election. So this election — the last year has been very challenging for health care investors and especially for biotechnology investors. So, there’s been a lot of discussions and a lot of political rhetoric about drug pricing, a lot of concerns. And so, many investors have been avoiding the sector.

It was our belief that these concerns are overdone. We did expect some changes on the margin, but drug pricing has been an issue on and off in the United States for the last 30 years. It generally comes out more around presidential election cycles, but the United States has always come out on the side of free market pricing. And so we had believed that that view would emerge again and that trend would continue.

I think now with President-elect Trump and Republicans now controlling both houses of Congress, many of those concerns are significantly diminished. We also think that we have a higher chance that we’re going to see corporate tax reform, potentially lowering the rate of corporate taxes, allowing repatriation.

So, many of these companies have billions of dollars of cash that are trapped overseas, so they can’t bring them back into the United States. We think there’s a good chance that that could change, and potentially we move to a territorial system where companies also have more free access to cash.

In that scenario, we think companies will be potentially picking up their M&A activity and acquiring many of the smaller development-stage biotechnology companies, which is where we often find a lot of great opportunities. So we think that this new cycle will actually be good for biotechnology investing, and actually in the last week alone, we had the largest week of inflows. After a year of outflows, we had the largest week of inflows into biotechnology ever measured. It was about $2.7 billion, so I think investors are starting to get the opportunity.
SPEAKER 2: Well, thank you, Andy. You certainly inspired a lot of interest here — both in how do you do it, and personal questions on things like what vitamins do you take, and a whole bunch of very specific things about drugs. So, they were very keen on your comments.

So, please join me in thanking Andy for an insightful presentation.

ANDY ACKER, CFA: Thank you.