**Transcript**

**The Hurdles of Insuring Patients with Nano-rare Mutations with Alan Lotvin, M.D.**

**Stan:** Hello and welcome to the n-Lorem podcast series, the only podcast series that's devoted exclusively to the needs of patients with nano-rare mutations. I'm Stan Crooke, I'm chairman and CEO and founder of n-Lorem, and I'm your host on the n-Lorem podcast series. And today we have a very special guest person I've gotten to know over the last year or so who has lived in a part of the world that I understand very poorly. And I suspect most of you do, too. And so I'm really looking forward to this chat and to sharing and having Alan share his leadership understanding of these parts of the healthcare system, our special guest is Doctor Alan Lotvin. Alan is a, he's a cardiologist who practices cardiology and then moved on to do many other things that are fascinating to me and I think will be to you. So welcome, Alan.

**Alan:** Thank you Stan. I'm really glad to be here really glad to get to know you and what you've done and both at Ionis and n-Lorem and then you know I continue as much as you can teach me as much as I can teach you about the PBM industry you can certainly teach me much more about ASO's and the scientific discovery process. So, it's been great.

**Stan:** Well, it's been a happy marriage and look forward to continuing to to to expand it. So, I I'm assuming, Alan, you grew up in the New York metropolitan area.

**Alan:** Yeah, I did. I like to say I was born in Manhattan so I'm proud of that. My parents moved me to New Jersey and to Long Island and as soon as I was sent in, I moved back to Manhattan, went to medical school in well, I moved back to New York, going to medical school in Brooklyn, did almost all of my training at Mount Sinai and then lived in the New York area for a long time until I moved up to the Boston area and 20 something years ago and. I've been loving it in Boston.

**Stan:** Yeah, and you actually practice cardiology in the New Jersey area, right.

**Alan:** I worked out of a couple of hospitals in northern Manhattan called Columbia Presbyterian and then what now a huge one in New Jersey called Hackensack, which when I started there was not quite so huge and they've done a very, very nice job of building a world class Medical Center there.

**Stan:** Yeah, cool. And it is amazing to me the impact of endoscopic surgery on patients and of course as an interventional cardiologist, you were at the sort of forefront of all that. I just don't think people appreciate how profound the benefit of learning how to do surgery through a little tiny endoscope has impacted patients.

**Alan:** Interventional cardiology was sort of fascinating because I think people originally thought about it as a replacement for open heart surgery and what it really became was an augmentation and if you look at the best indication for angioplasty or stent placement now it's when you're in the middle of an acute heart attack. If you're in the middle of an acute heart attack you absolutely, positively want to get a revascularization procedure and it makes a huge difference. Whereas you know, bypass surgery tends to be kind of more treatment for symptomatic and creating longer term great outcomes, but they tend to be, you know, synergistic procedures and it was really fun doing it like when people asked me do you miss practice? And I miss a lot of aspects of taking care of patients and meeting new people and like being invited to become this incredibly, you know, intimate partner in their health. But I also missed like for a while I missed really missed doing procedures because especially when I was doing it early on like there was a technical aspect to it that was fun. You had to understand kind of the materials and how they would, you know, fold in three dimensions, in the aorta. That kind of stuff was really, really, really fun. So yeah, I miss it a little bit, but like everything else, you close one sort of set of fun things to do and you learn a whole other set of fun things to do.

**Stan:** And you did that, and that brings us to specialty pharmacies. I really am intrigued by how a nice well successful cardiologist should stumble into being head of a specialty pharmacy outfit.

**Alan:** So, it's a great question and you used a really good word which was stumble in and you know as the progression was, I realized in 1997. That despite our eagerness around revascularization procedures and coronary revascularization that it wasn't the panacea we thought it was. Again, if you're having a heart attack, it's perfect, but almost every other scenario, the procedures don't seem to have very much impact and I really struggled with how to maintain a referral practice. And I had a pretty big referral practice and not do something I wasn't really 100% sure was the best thing to do. So, I ultimately decided that I was going to leave practice and was kind of shocking to my partners at the time as well as my colleagues, you know, and I often credit my wife by being totally supportive and saying sure. And so, at that time, I was really interested in what we now call big data and what we called for while big data and population health management. And Merck happened to have a little ad in the New England Journal for someone to do this kind of work in cardiology. I'm like, you know what it’s Merk, I know them respectable organization in my backyard, don't have to move if I hate it, I can always go back into practice. And so, I joined there and what I learned I was actually joining a subsidiary of Merck called Medco, and Medco was a pharmacy benefit manager and I learned about what PBM's do and I know we'll talk about it. Like one thing that struck me as really interesting was they had this huge amount of data at that time it was I don't know 30 million people in the US, it was almost real time data and I thought it was really clinically relevant data in the sense that it reflected what was actually going into the body versus what someone wanted to get paid for, and I thought this is really cool and we can do a lot of work here and a lot of good things in terms of closing the gaps in care highlighting for patients and doctors, because we had a unique view in this world, we would see every prescription, no matter where it was filled. And so, we got to see and learn all sorts of things like how bad adherence and compliance and persistence is like, people don't keep taking their drugs long term. And we we looked one time, this was again going back 20 something years. But we looked at HIV meds, statins and imatinib. So, for leukemia, so two out of three drugs that absolutely like preserving. And we said, which one are people more likely to drop off of? And it turned out that it wasn't much of a difference at two years, only about 60% of people were taking any one of those. Yeah, even and obviously very especially at that time very different patient populations. And that was really instructive to me, and you know, learned a lot about why people don't take drugs and it's not simple, and there's no single answer. So, that's how I got into the PBM industry. And and after about a year or so, I realized I really liked it, and it was a place where you can see the ability to reduce the cost of care. You could see kind of a little bit of the future of what drug therapy looked like and it seemed to be an interesting place to be. So, I stayed there, I did a couple of, you know, you looked around the organization, everyone who was in charge and senior, they all had experience with clients. So, I raised my hand and said, hey, I'd like to get some client experience. They said, why don't you go be the chief medical officer for this new division we're building to manage United Health Group. I asked my wife if we could move to Minnesota, she said sure. My wife's fantastic, right? So, we moved to Minnesota and, you know, they offered me the job, and I tell the story to everyone and it was great, except for it kind of didn't feel like it was a real job. So, I asked the guy who gave me the job, a guy named Glenn Taylor, who I am eternally grateful to. I said, Glen, this is great, Can I have a real job too? And for reasons unbeknownst to me, Glenn gave me a $7 billion P&L to run. And that was sort of the transition into the business world. I did well at it, did another job and then Medco got spun out and they needed to build a specialty pharmacy. So, what's a specialty pharmacy? A specialty pharmacy is and was specifically for drugs that were expensive, 10,000 to $1,000,000 a year, usually have cold chain requirements which traditional pharmaceuticals, pills, tablets and capsules didn't need, often had some clinical, some incremental clinical requirements. Whether it was a REMS program imposed by the the Food and Drug Administration or other data needs that the manufacturers would put on, and often the manufacturers would limit distribution because they wanted really close control over the drug. And at that time, it was only about 1% of the drugs. You know, one of the drugs that was sort of common or common was a big one that was epoprostenol for pulmonary arterial hypertension, kind of a continuous infusion, needed a pump. It needed all sorts of support. And so, we built these pharmacies to meet the needs of those patients. And what happened was overtime with the wave of antibody therapies, all of a sudden the cold chain requirements, the all of those things, it went from being 1% of drug spent to being 54% when I left of drug spent. And people would say me, Alan, how did you know like specialty pharmacy was going to grow so much? And if I'm being obnoxious I say it's because I’m brilliant. And if I'm telling the truth, I say it was a hard problem that the company needed solving, and I was the right person to do it. Now I was smart enough to realize that this was going to be a good way to ride. And you know, so I helped build, you know, two of the largest specialty pharmacies in the country and we really sort of thought about how do we make the experience better for patients? How do we lower the costs? How do we help on the compliance and persistence side so that you know, if you're going to spend thousands of dollars a month on a product, you don't want the person to drop off it before the clinical benefit appears. And so, that's how I got into specialty pharmacy and I pretty much stayed in specialty from 2000 and one or two to about 2017. I had a couple of detours. Some of it was I was focusing on oncology and the drugs that are paid under the medical benefit versus the pharmacy benefit, but generally all of it was in specialty really until I took over care mark as a PPM, but it was a long story about my history. So, I apologize. Feel free to edit it basically.

**Stan:** No, actually you said a whole bunch of really important things that I want to parse. First of all, you talked about compliance. And focusing on Lipitor, for example, or statins, these are close to perfect drugs in that the side effect profile is de minimis. They're easy to take once a day does the job any time you take it is OK. And the evidence is overwhelming that taking it probably everybody should take it all their lives, no matter what, right. I mean, and yet as you said, two years out people are not taking their drugs and this continues to be a core challenge in therapeutics and in AIDS and cancer and whatnot you can understand some of it because at least in those early days there's a lot of side effects and there's still a lot of side effects and you could imagine people dropping out but but when you take a statin and ask why people stop? So, I've spent a lot of time looking at that. I'm interested if you had to pick the top three reasons people stopped taking statins, what would it be?

**Alan:** So, I'll give you the three reasons, but I think there's also something else that's not really talked about that much which is I'm not sure that we actually offer statins as broadly as we should. I have a lot of friends and neighbors who will tell me, you know, my cholesterol is whatever and, you know, my doctor said that, you know, he's not ready to start statins yet. And my perspective, you know, for what it's worth is you can't really have an LDL, that's too low, and you know the lower you have the LDL for the longer you have the low LDL, the less atherosclerotic heart disease you're going to get and it's still the number one killer in the world and it still contributes to the number three killer, which is, which is dementia. So why wouldn’t to your point there's such safe drugs. Why wouldn't you want to have your LDL, you know, below 70 all the time or lower and so I'm probably way out on the scale there, but to answer your question, what are the top three reasons? So, we did some work and it really turned out we found some academic work that there were 17 barriers to why people don't take drugs and we looked at it in our population and again it's a skewed population when you look at PBM data because it is by definition insured people. So, in general, insurance wasn't the biggest issue, but the copay was. So, there was a financial aspect and it's particularly gotten bigger as the list price of drugs has gone up and the prevalence of high deductible plans have gone up, so we'll lump in, like economic barriers, are absolutely one of the barriers. That's usually a barrier to starting therapy. It's not as much a barrier continuing therapy. I think the other big barrier to people in continuation of therapy, it's not that they forget despite all the gadgets and gismos most people use they're not forgetting, you know, yeah may forget the dose a week or so, but you're not forgetting reliably. I think there's a lot of it is that whenever you feel anything that's not normal and you're taking a drug, the the impulse is to ascribe it to the drug. And so, you know, I'm taking a statin, and my vision was blurry. Well, you know, OK. It's a statin. I stopped taking statin.

**Stan:** Or I had a muscle ache.

**Alan:** I had a muscle ache, or I heard you can, you know, it can be bad for your muscles. It could be anything. So that's the second big one. The third big one that I think is really, really, really, really really under discussed and then probably is not easy answer is people don't like to feel like they're sick. Right. They, you know, they don't want to feel like they, they need to take a drug because it makes them feel like they're sick or they're getting old. And often there's someone else they know some, you know, who said oh I had X disease and I took, you know, some miracle vitamin and some you know algal extract and I, you know, I danced under the line of the midnight sun and I was cured. And of course, that's not happening, right? But it's like oh if that worked for my neighbor and sometimes it’s not that egregious, right, it could be that, you know, the neighbor had, you know, I'll give an example. It's obvious. Like the neighbor might have been diagnosed as prediabetic and lost 60 lbs. And so now he's no longer diabetic. So I get diagnosed as prediabetic. My neighbors not, and neighbors oh, I just changed my diet and I stopped eating you know, whatever. And it went away, not realizing it was the weight loss that really did it and so that's, I think the biggest issue. People don't want to feel like they are sick. So, the combination of ascribing every eight pain symptom to the drug and really not wanting to take drugs are the biggest issues.

**Stan:** That's fascinating. And you know, focusing on statins, if the future of medicine is preventing disease, which it is, I think everyone who knows anything about where we are and health feels we should focus on health more and disease less then getting people to take medicine, despite the fact that they don't have symptoms is going to be one of the central challenges of the future, right? And I wonder how you would respond to also just the possibility that people are much more willing to intervene with themselves if they're feeling something, then they are if they're worried about what they might feel 20 years down the road.

**Alan:** So, I think that's true. I think there's three things. And by the way, I always think there's three things for everything, but I think there's three things that go into that. There's one is that people. You know, you know, prevention is hard, especially when all the other things we talked about in terms of ascribing products the 2nd is I think, and with all due respect to doctors, we not only do not teach doctors about prevention, there there's this idea that, you know, wait until something is at a certain point before you treat like you know the great example is you know hemoglobin A1C for diabetes, right if you're below 5.7 or below you don't have diabetes above 5.7 you do. Now, I'm not a diabetes researcher. I'm not an expert, but I refuse to believe that in your body there is some discrete quantum leap in physiologic process that says oh at 5.7 I don't you know, but at 5.8 or 5.71 oh, now all the bad things happen. You know it's most likely like everything else. It's on some sort of gradient and it may not be linear, it may in fact be, you know a curve but a gradient. That's an example where why wouldn't you want to be at 5 or 4.5 and especially if you can get there safely with statins we, you know, we talked about earlier, if you could get to, if you're an LDL less than 70 from age 30 on, I don't think you'd ever get coronary disease ever.

**Stan:** Unless you have an Apo A that's elevated maybe.

**Alan:** A great point in the absence of the 30% of the population with Apo B actually, elevated April. No, actually I'm sorry, really technically correct it's LP little A cause Apo B you can lower with statins LP little A you can't.

**Stan:** Well, you know, we've got a drug called that is in an 8000 patient out week, Ionis, the first Apo A inhibitor but worth that 8000 patient study is finishing and I think it will be the next major step forward.

**Alan:** Yeah. No, again. But if you could if you looked at a comprehensive lipoprotein panel like we talk about Apo A, Apo B, LDL, HDL, fractionated LDL's and LP little A you can create a scenario so I can treat all of these things to a greater, lesser degree get your LDL down below 50, right. You probably never develop coronary disease. Now again, I'm not. I'm not saying people should do that. The data is not there, I will tell you that that's what I shoot for myself, right? But that's my own. But that's me.

**Stan:** I don't know a single cardiologist who doesn't participate in my LDL is lower than your game.

**Alan:** My point is, there's generally, but among a lot of primary care doctors and a lot of specialists, there is a reluctance to start people on medication until some threshold is hit, because that's what the standards of care and I understand all the medical legal reasons to do that and all the other reasons, which is why I don't advocate it for anyone else other than myself. I know I'm not going to sue myself, so you know.

**Stan:** Well, and of course, then there is the misguided worry about cost, because if you worry about cost of a statin versus the impact of cardiovascular disease on cost you’ve sort of worried about a mole when you have cancer of the body, right? So.

**Alan:** Right. Well, that's the third part of it was you just hit on is there is noninsurance coverage often for preventive therapy and you can look, the poster child for that right now is Ozempic for weight loss. There's no question that these drugs help lose weight. There's no question that obesity contributes to all sorts of diseases. But if you look at the way a lot of these, a lot of, even though I won't even pick on the GOP ones for a second, let's look at bariatric surgery. Like people would say you had to be above a certain BMI body mass index to be eligible for bariatric surgery. Well, what a ridiculous incentive. So, if I'm just below the threshold instead of losing weight, I should go gain weight, right?

**Stan:** Actually, I know people who have done that, who deliberately gain weight so they can get bariatric surgery.

**Alan:** I have seen some you know authorization criteria or coverage criteria for the GOP ones that say we only cover it above a certain BMI than when people lose weight, they're no longer eligible for coverage you can't pay for the drug, people can't afford it. They gain back the weight, and you get into this cycling thing. It's, you know, when people say we don't have, we have a sick care system and not a healthcare system, that's not an indictment of the US that's the world. Right. And we really haven't reconciled yet the fact that we actually have the ability to at least for some diseases, to dramatically reduce your likelihood of developing them.

**Stan:** Or said in a more positive way we have the ability to enhance health.

**Alan:** That's right. And we're not good at doing it. We're just not, we're not good at like and that's partly the doctor's fault, but we got to take ownership here like it takes 20 years to get things out into the clinic for people you know out of the lab into the clinic for people to really start using them, you know aggressively and we have to sort of acknowledge that and so there's a lot of things we can do, which is probably adding to the whole little looking for gaps in therapy because I thought we could. Turns out it's a lot harder to get doctors to change their mind than I ever thought it would be.

**Stan:** So specialty pharmacies, then, are pharmacies that handle hard to handle drugs and expensive drugs, right?

**Alan:** Exactly so. So, they evolved to be, you know, hard to handle drugs, drugs that had cold chain requirements, drugs that required additional data capture, drugs where it was felt that the patients needed a greater level of support either to manage side effects or to avoid complications. So, you have a scenario where you have a group of people like pick something like, you know, cystic fibrosis, right. So, we have a service. I don't remember how many people, let's just make a number up two or three thousand patients with cystic fibrosis who our care team would take care of, and that's pretty much, you know, it's a good chunk of the number of people with cystic fibrosis in the country. Now how often is someone with CF going to walk into your local pharmacy and is your local pharmacy going to be holding a $250,000 vial of drug in stock? Of course not. So now you got to make another trip to the pharmacy, you got to schedule it. What we have found is that, you know, people get better, better adherence, better compliance, still not perfect, but better through the specialty pharmacies.

**Stan:** I want to move to PBM's, but there's one other thing that I think it would be very instructive to talk about. One of the numerous ways I've made people angry over the years is that I've argued that the right model for marketing is REMS. That REMS is a requirement to focus on patients who need the drug, and then managing them while they're on the drug. And we've witnessed over the last few years, an enormous growth in drug advertising on TV. I mean it's constant. And it makes me crazy because those ads are designed to get more people on the drug rather than keep people taking the drug which strikes me one it almost certain you get people who take the drug who shouldn't and it's almost certain that you lose people who should take the drug and so I don't want to get on that soapbox, but one of the things that I think the world is wrestling with our world, yours and mine, is what is it that we ought to do that's responsible with marketing drugs? And I've been arguing for a long time that our job should be to get the right people on the drug and keep them on the drug, and that's where money should be invested far more. I think your data argued very, very persuasively for that as well.

**Alan:** Yeah. No, I think again, I think if you look at the drop off right you get a prescription written a certain number of people never pick it up from the drugstore or get it delivered to their house by the time they're on their second fill like there's a big drop off between the 1st and 2nd fill. And I think that's a lot of that is either they're the economic because the coupon ran out, or it's that what we talked about earlier, ascribing any side effect to the drug. And then sometimes there's real side effects. And then there's just a steady drop off. But you know, there's also the issue that we touched on, which is you know, I don't think, you know, I know some of the data for high blood pressure, right? So less than half of people who really have high blood pressure have actually been diagnosed. And are the people who are treated only half of them are treated to goal? Right. So, there's another thing we even talked about, which is you're on the drug, but you're either not on enough of it, you're not on the right drug, you're on the right combinations of drugs. And this is the thing that, you know, like when I just talked about kind of big data and using large data sets, you know, back in the day, because again, I'm of a certain age, you know, before highly active antiretroviral therapy for HIV was available in one pill. But we knew that you had to take triple drug therapy. I'd looked in the drug database, and I would always see thousands of people who are on one of three two of three were the wrong three. And you sit there, and you pull your hair out because you're like I was a cardiologist. These papers weren't published in esoteric, you know, infectious disease journals. They were in the New England Journal of Medicine. And you just go crazy about it. So, like I agree with you that if we if we can take the same amount of money we spend on TV advertising that you know certainly raises awareness, we could say over raises awareness, and focus on helping doctors actually be better at their jobs and understand and you know what well I think the companies would be far better off and then if you add it on, alright, if I now invested a lot more money in keeping people on therapy or the same amount of money, the return is, again, I only remember the famous line about advertising. I only know half of it works I just don't know which half you know, at least when you spend money on adherence you can measure whether it worked or not.

**Stan:** You bet. No, I think you're right. Companies would be wealthier and they'd feel better about what they do as well. So now on to PBM's, pharmacy benefit managers. Briefly, can you tell people what a pharmacy benefit manager does?

**Alan:** So, your question that said briefly is a clear, clear evidence of the triumph of hope over experience since I haven't said anything. But I'll try to be brief so the PBM industry grew up as an amalgamation of different parts of pharmacy. And really if you look at it like a business study, essentially the industry grew up looking at where there were excess profits or profits that could be reduced right by bringing alternatives. So, companies started out initially as claims, like half the company started as claims processors. The other half started as mail service pharmacies on the theory that you know mailing something was less expensive than retail pharmacy, and those entities came together. And what would happen is they would negotiate on behalf of payers, meaning employers, the government agencies or health plans with initially retail pharmacies to lower the cost of or the reimbursement to pharmacies and they would use kind of the mail service alternative as essentially a cudgel way to do that. And that worked for a while and it worked well and they built the infrastructure kind of the claims processing infrastructure so you know pharmacy is the only part of medicine now when you walk into a pharmacy you may not know how much it's going to cost before you walk in but then while you're there you know what it costs it's not like you go to a doctor's office or a hospital and yeah, you get a bill six weeks later. You go oh okay, at least you're told in real time what it costs and so the PBM industry does all of that claims processing and it's, you know, at this point it's, you know 4 billion or something claims a year and they're you know the turn around time is microseconds and so it's a logistic fee. So that was mail service pharmacy. Then someone had the bright idea to say, you know, there's four different H2 blockers. You know Zantac, Pepcid, and I bet, these were before they were over the counter, I wonder if we ask patients, you know, to switch, would they? And I wonder if we went to the manufacturers and said would you be willing to give us the discount if we got and it turned out that people were and that became the beginning of formulary and kind of the “boogeyman” of rebates, right. So, people were able to interchange medications and you know, I think it's a great example of competition. You know, if you look at what happens to the list price of drugs when there's one, two or three in the category, it's kind of drifts down, but it gets to five, it accelerates, and eight it just falls off, and then it goes generic, right? So that was the second thing. Then the third big business model really was kind of coincident with when Zocor statins we were talking about when off patent in 2006, the percentage of generic prescriptions went from 42% in 2006, to about 92% now, and while generic drugs are much more expensive now than they were then, they're still 90% of the cost or 10, you know 90% discount generally to branded drugs. And the PBM's did a lot to drive the adoption of generic drugs. Now the skeptic would say, well, that's because they made money on it. Yes, that is true. And the the part about the PBM model that people hate is the lack of transparency about how these companies make money. And you know, I guess in the conceptual ideal world, people would like a PBM to go to an employer or a health plan and say, I'm going to pass through every single bit of discount, rebate, whatever, and you're going to pay me X dollars per claim. But that doesn't work for a couple of reasons #1, no one likes paying money out of pocket. Right. If I save 90% instead of 92%, I'm okay with that, right? I didn't have to pay out of pocket. That's one thing the second thing is, and I don't really hear people talk about this that often, is that if you're a health insurance plan and you actually earn covered under insurance laws, that payment comes out of your administrative bucket and that becomes, that means you can, it reduces your profitability. So, like the incentives aren't aligned. So, what's happened in the industry is there are these very sophisticated consultants who understand how the companies make money and so what each time the companies develop a new profit target to exploit whether it's pharma, pharmacies, generics. They make a lot of money for a little bit and then it gets competed away in order to win more business and they have to look for the next increase in the next business model. The fourth business model was specialty right was the idea that alright if I'm going to take care of all of your patients, and I'm going to take care of all your patients needs, well I have the largest specialty pharmacy that I'm gonna make them bigger by contract. And I'm gonna give you a better price if you let me fill all of your specialty pharmacy and became a virtuous cycle because you've got more patients. So, you could provide better service so you could get lower prices from the manufacturers, which allowed you to get more patients. So, you ended up with the scenario where you know two or three of the specialty pharmacies are now the largest, all owned by PBM's. So, in general, PBM's do three things right. They process the claims and do the plumbing, they negotiate with pharmacies to lower the reimbursement to pharmacies, they negotiate with drug companies to lower the cost of drugs, and they create plan designs that meet whatever the objectives, or try to meet whatever the objectives are of the payer, that's my concise my best attempt at being concise.

**Stan:** That's very helpful. And CVS Caremark was one of the largest and you built it, you were CEO.

**Alan:** Well, I didn't say it was the largest, but like I can't claim credit for credit where credit is due, in 2007 or so CVS bought Caremark, they were 50% smaller than Express Scripts which had recently bought Medco and a guy named Per Lofberg who was my mentor and just a fantastic man, one of the joined the company and really really drove the growth of CVS Caremark and then his successor, John Roberts. So I was at the end of a long chain of very, very successful people. I like to feel like I built on top of what they did like, you know, the expression is truly standing on their shoulders. But, you know, we were able to bring a different service, different level of compliance, conformance what our customers are looking for, and they voted with their feet, and these are sophisticated purchasers that's the thing that gets lost. I mean every blue fund is a sophisticated purchaser. They understand the market, everyone uses these three or four or five really smart consultants. So, you know, I get the lack of transparency and the concerns, I think the lack of transparency is far less because the contractual relationships are such that you have to be transparent with your customers. But you know, at the end of the day, some very, you know, people didn't like, people don't like what we saving money is great, right? But remember saving money from someone is costing someone else's income and naturally, there's a tension there.

**Stan:** Well, PBM's do have their various sources of animosity. Let's say that being a middle man is in the middle, but so CVS bought Caremark, so the PBM's are typically owned pharmacies or pharmacies, own them, and then then CVS took Caremark and I guess basically sold it to Aetna. Is that what happened?

**Alan:** No, no, no. What happened with CVS was the pharmacy, and then CVS bought Caremark to create CVS Caremark. And then CVS changed the name to CVS Health and we stopped selling tobacco in 2014. And then CVS Health bought Aetna to make a company. And so, what you've seen in this industry is it's like, everything is cyclical. A lot of the original PBMs in the 80s and 90s were owned by health insurers. They spun them out, then they were in the 90s, were bought by pharmaceutical companies. And then in the 2000s, they spun them out. And they started you know, enter PBM mergers. And so, they ended up with basically three large ones and United bought one that's now called Optum, CVS in the other way, bought Aetna, and then Cigna, which is a large health insurer, bought Express Scripts. So now you're kind of back to the early 1990s, the late 80s, early 90s, where the insurance companies and the PBM's are under one roof. And if I was going to make a bet, I would bet that cycles go like cycles for a reason and we will see another cycle.

**Stan:** Yeah. I mean, really what you described is different approaches to vertical integration. Who wants to vertically integrate, right? OK, so PBM's are there. They're going to continue to be there, and they play a useful role that there may be better ways to do it, but this is the way we're doing it in America, I want to finish now, Alan, with your interest in n-Lorem, and why I think n-Lorem and both the managed care and insurers should be a natural match in that we're giving drugs away for free. You don't get better than that. And for every patient who benefits the reduction in healthcare cost is extraordinary or potentially extraordinary. And so why is it so hard for n-Lorem to get to insurers to talk about all this?

**Alan:** So, it's a good question, Stan. And as you know we've been talking for about a you know a year. So, I've learned a lot. You kindly invited me to join the board. So, I'll learn a lot more. So, I will preface my answer by saying it's still a little bit of an answer of naivete. But I will tell you my reasons for wanting to join and help is I really thrive and enjoy solving hard problems with people are like to work with, and I think the problem of n-Lorem is a combination of small patient populations so, it's below the radar screen of most plans and employers. Even though you're not making a profit, the actual cost of goods for the drug is relatively high. And your incredibly clever approach to getting the FDA to allow you to do kind of n of one trials also completely gets in the way or allows every payer to exclude coverage. And so, all of those conspire to make it very difficult, but then you have a very good point, which is when you treat people, you lower the overall cost of care for these very, very sick people. So, you get into another problem, which is how long, and you know, this is a little bit of a problem of the US healthcare system is how long does anyone stay with any one payer?

**Stan:** And how long does the CEO last and what is his real timeline.

**Alan:** And so, you know if in an average in short population the churn is 30 or 40% and if the average you know if you think about some employers I know of have 50 and 60% turnover and even a Fortune 50 employer of choice is going to have some amount of turnover, people retiring people are going to another job. You know it gets all of that churn every whether it's five percent, 10% or 50%, it makes the return on investment harder and harder and harder. And then what? I'm super excited to learn with you is how do we tell a different story? How do we create a different environment whether it's expectations or regulatory or like or how do we work with the FDA like there are solutions here, some are really hard and require like you know, changing the way the FDA works or asking and some might be easier which are you know create a different sort of product that's you know relatively inexpensive that provides sort of coverage for these, for these, you know, really sick people. And then there's other business models we've talked about, which is when it goes from n of one to n of 100 or 200, how do we manage that? And does that create a funding mechanism where we can? There are all sorts of interesting things. The short answer is I don't know the answer. It's hard, I really believe in you know, I really believe that the right thing to do is to figure out how to provide coverage for people if we're going to live with our current system we have to figure out how to ensure that within our current system, people who require therapy when there is a proven therapy that exists should have access to it. And you know, we can talk a lot about how you know, there's some interesting ideas we can talk about how do we manage the price of those therapies, and what's a reasonable price, what's you know, do we use ICER type methods? Do we do international benchmarking? Like are there ways short of outright price controls to say to ensure that all actors are acting or are acting reasonably and in an aligned fashion. And it's a little bit of game theory. It's a little bit of, I mean, so I think that's where we have to think about it, and you know the idea that there's an unlimited that the free market and I'm look, I'm not a free market capitalist, but they do have the free market is it can fix every problem. We all know that they're in market failures, right. That's why there's something called the tragedy of the commons described like hundreds of years ago. So, not everything is amenable to a market solution. The question becomes how do we build a solution that's inside of a market mechanism so that you don't lose all of the market signaling? But you're able to constrain some of the challenges.

**Stan:** Well, you and I are again thinking along the same lines and I think the message I would give is that first of all, we didn't know nano-rare mutations existed until the technology made it possible. We know almost nothing about nano-rare patients. We're learning rapidly, and we're at the beginning of this process of finding a solution, and then n-Lorem is at the front of that, and there are many, many options that lie in front of us that we need to explore. We need all the good brains that we can to help us explore that and your addition with your experience just amplifies our ability to get there, and find a solution that is financeable and humane.

**Alan:** Well, I'm sure going to help try.

**Stan:** Yeah. Well, good. Well, listen, this has been a fascinating interview and you and I, I'm sure we'll have many, many long conversations about this, but we probably just overwhelmed our listeners but I think I would just end by saying that this conversation that we just had is a truly fundamental conversation about the future, and how we make a future that's better for health and patients than worse, because I think that's the option that's lying in front of us. It could get worse.

**Alan:** Oh yeah. No, no I think that that's absolutely true. So, I think that's a good way to end it.

**Stan:** Okay well, thanks so much, Alan, and I'll let you get off to running your new company.

**Alan:** My pleasure, Stan. I'm looking forward to talking to you some more thanks.

**Narrator:** n-Lorem is a nonprofit committed to discovering and providing personalized, experimental treatments for free, for life to patients with genetic diseases that affect 1 to 30 patients worldwide referred to by n-Lorem as nano rare, many of these patients progress and die without ever achieving a diagnosis. This is where n-Lorem comes in. They do the impossible by providing hope, and for those that they can help, free lifetime treatment. For more information about n-Lorem or today's episode, visit n-Lorem.org. Any questions can be sent into podcast@nlorem.org. Search n-Lorem on Twitter, Instagram, YouTube, LinkedIn, and Facebook to connect with us. This video is hosted by Dr. Stan Crooke and produced with the help of the following professionals. Thank you for watching.