[Transcript] FYI - For Your Innovation / The Future of Genetics in Pediatric Care with Dr. Caleb Bupp

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Welcome to FYI, Arc's four-year innovation podcast.
My name is Simon.
I'm the director of life sciences research, and today I'm lucky to be joined by Dr. Caleb Bup.
He's trained in both medical genetics and pediatrics, and he's currently the division chief of medical genetics and genomics for Corwell Health West and Helen DeVos Children's Hospital in the great state of Michigan.
Thanks so much for coming on.
Thanks so much for having me.
So unlike me, I think our audience hasn't had the luxury of getting to know you.
So would you mind just recapping a little bit how you initially became passionate about genetics and pediatrics, and what led you to land in Michigan?
Sure thing.
I think my journey has been one of kind of falling backwards into the next step, which is one way of doing things, but it also in retrospect shows you that one thing kind of leads to another.
I actually grew up, my dad is a pediatric dentist who specializes in kids with special needs, and kind of just looking back, you wonder how the things in your childhood kind of mold you and shape you.
I ended up being a science major without sort of a particular plan in mind, and then I had the opportunity to go on a medical missions trip in college, and I went to Kenya for a couple of weeks and worked in a dirt floor church, and people walked from a couple miles away with things that required a fairly simple intervention, but were quite life changing, and that's what kind of opened my eyes to pursuing medicine as a career.
And as I went along, I really found myself drawn to taking care of kids, because a lot of the health issues that kids have aren't something that they chose to happen, and I think there's just kind of a special way that we get to give kids care, because you and I, we should probably eat better, we should probably exercise more, and kids, you know, when they're sick, it's typically not their fault, they get better quick.

And when I was on my first year of pediatrics training, I was working in the hospital during one of the winter months, which is crazy busy, and a little girl got admitted with RSV, respiratory virus, and she had Pompey disease, which is a rare genetic metabolic disorder, and she got admitted, she has this condition, and she was on enzyme replacement, which at the time was pretty new as a treatment.
So there's this little girl, she has this rare disease, I've read about it, but now I'm seeing somebody who actually has it in person, and there's a treatment for it.
And that is what kind of sparked my brain for the idea of genetics, pediatric genetics is, is kind of my career choice, and, you know, I went through some additional training for that, and I've landed here in Michigan, and I've really been part of a period of fairly unparalleled growth and expansion for the use of genetics and medical care.
You know, I'm about nine years in as an attending physician, and even when I started, we had like a fraction of what we have in our tool belt right now.
So it is a good time to be in genetics and healthcare.
Yeah, and I wanted to ask you, you know, you and I, we met initially at the Genetic Health Information Network Summit, which is in Nashville.
It's put on every year by one of my favorite, you know, private companies in the space called Concert Genetics, and we'll get into that a little bit later.
But that was late last year.
And one of the things I think I enjoy most about that was the fact that that conference brings together so many people in the stakeholder system that are passionate about provisioning, you know, medical genetics, especially, you know, and the topic of this year was a lot about pediatrics and rare disease.
So it was, you know, diagnostic labs were there, clinicians like yourself, insurers, government, et cetera.
I wanted to ask you, how did you initially get involved with that conference, with Concert? What do you remember about the conference?
And yeah, I'd love to just know more about, you know, your experience there.
When I started as a genetic physician, you're at school, first big boy job, I was seeing patients, right, some patients come to clinic, we try to figure out what's going on, we maybe order a test, get a diagnosis and do what we can.
But the more time I was spending there, I started to see all these other pieces.
Like you said, who are these other stakeholders that are tangentially, but now more directly related to the care that I'm giving to my patients, you know, their insurer, their insurer's policy for genetic testing, what's going to be covered, the different health systems and the different genetic testing labs, the different technologies that are emerging, what's an experimental test, and then again, like we, you know, kind of mentioned treatments that are here and treatments that are coming.
So there are just all these other pieces outside of the clinic that are playing a role.
And you know, healthcare is complicated right now, let alone if you have a rare genetic disorder that's, there aren't many people and there's not a lot known about it.
So that was the experience I was starting to have.
And then my hospital in 2018, 2019, started to look at where is kind of the future for

pediatric care when it comes to genetics and from a hospital side, the use of genetics in the hospital historically has been really, really small because most genetic testing would take you weeks, if not months, to get a result back.
It was really expensive.
So inpatient genetics care was a lot of looking at patients saying, yeah, maybe this, this might be genetic.
I don't know.
We don't really have a test that we can order to figure it out.
And that is a really challenging place to be at when you're looking at a critically ill child that'll look like a kid who might die today or tomorrow.
And we've seen this shift over the last five or 10 years where the speed of genetic testing has gone up and the cost has come down.
And this door has kind of opened of using broad rapid testing quickly to get diagnoses.
And it's really shifted the paradigm of inpatient pediatric care.
So our hospital was looking at this and we heard about the folks at Reed Children's, their Institute for Genomic Medicine, who were really pioneering rapid and ultra-rapid whole genome sequencing.
So we started to work with them as the first in Michigan to really offer that testing for the kiddos that were in our hospital.
And turns out that if you have a sick kid and you can do a test to figure out why they're sick really fast, you give better care.
And it's always kind of crazy when there are these like no-brainers that just shift the way that you give care because the way I think about it now is we can take care of sick kids and know why they're sick or we can take care of sick kids and not know why they're sick.
And one of those is better.
So we started to use this at our hospital and we were really happy with the impact it was having clinically.
But the thing that I think draws us back to the Nashville piece is it actually reduces the cost of health care when you're using genetic testing that's not cheap because the cost of the test is far outweighed by cost savings from all the things that you don't have to do in getting to that precise treatment right away.
So that was kind of what was going on and we can talk about what was happening in Michigan, but that's kind of what got me connected to the summit.
Yeah.
And I remember there were some initial presentations about and we can get into, you mentioned Rady's
which the state of California has been relatively progressive with underwriting kind of the Medicaid policies around reimbursing this type of testing.
I think people that follow our researchers are probably familiar with a couple concepts that you mentioned.
So, you know, the cost of whole genome sequencing has declined six or seven orders of magnitude since the turn of the century, which is, I mean, unprecedented, right?
And I think what it's done is it's allowed us to go from like single, you know, hypothesis

driven single gene testing to panels to large panels and now to whole genome.
And I think the future is going to be looking at, you know, other sorts of orthogonal pieces of data like the transcriptome or the epigenome to try to triangulate what exactly is going on and figure out like what are the mechanisms that are driving that phenotype.
So we'll get into that in a minute, but I know people are familiar with that.
You mentioned speed and this is the place where I really wanted to pick your brain a little bit because maybe it's not intuitive, but for folks who don't know, like when you're doing whole genome sequencing, you'll often have to sequence the parents too in some context to try to figure out, well, you know, is this variant hereditary?
Is it de novo, which I know you have some work that you contributed to the field.
We'll talk about that in a little bit too.
But for how expensive that that is, the overnight stays in the neonatal and pediatric intensive care units, the NICUs and the PICUs, correct me if I'm wrong, but they're terribly expensive.
And that's one of the reasons why you get cost savings is if you can shrink the amount of time you've got to, you know, have a kid in the overnight ward, you can save a lot of money.
Is that right?
Yeah.
I think it's a rough rule of thumb is the cost of a rapid whole genome is about one day in the NICU.
And the idea of saving one day, it's really not that much when you get a diagnosis that changes management because if you sit and talk or if you look at a NICU census, kids will be in the NICU for months.
Some kids will be in the NICU for over a year.
So if literally saving one day makes the cost of the test go away, man, you knocked that off right away.
And now you're starting to get to significant savings.
And again, things I've learned over the years that I never thought I'd say, you know, in the NICU population, there's this concept of an outlier and how payments happen when a kid has been there a long time, the payment structure changes.
So this is in health care, the rare win-win-win that it's good for the patient and the family.
It's good for the medical team providing care, and it's good for the hospital and the payer as well.
And you don't get a lot of things that check everybody's box too often.
Yeah.
I mean, I think that's one of the reasons why you mentioned it is rare.
I mean, it's completely unprecedented, I think in a lot of cases, to get a situation that's like that order of magnitude cost declined between $10,000 and $1,000.
And now we're on the next one is like so important for this type of thing.
And still, sometimes it's frustratingly glacial, like how slow these things permeate.
It's kind of a patchwork quilt, state to state, I know.
But I wanted to ask you and zoom in on a concept you mentioned.
So sure, if you're able to hand a diagnosis back or figure out, you know, a treatment

that you could marshal on a condition, that's tremendous.
And when you're thinking about clinical utility, especially from the perspective of payers, I often hear that it's about changes to medical management.
But in cases where you can give a diagnosis, but there's not really a therapy developed yet, there must be some sort of tangible value, certainly to the family that just have a name to put to what's happening.
Can you talk about that from your perspective?
What is this intangible value of delivering that information to parents and to the patient?
I think the field of genetics over the years, we've kind of gotten maybe a little bit of a bad rep, you know, when we just get diagnosis, we don't really change much.
And I sat with enough families over the years, inpatient and outpatient, and you give them a diagnosis and yes, there's no medicine, there's no new doctor or anything like that.
But they will look at you and say, thank you.
Even if you've given them a very, you know, bad diagnosis, because these families have lived with days, months, years, decades of worry, fear, regret, guilt around, you know, was it something that I did during pregnancy?
Is it because I ate that thing?
Is that, you know, so giving families answers from a psychosocial standpoint is immensely valuable, but it's hard to quantify that.
I think the other piece that I've seen is when you can give somebody a diagnosis, it really is a bit of a marker for moving forward, more empowered and more reassured for knowing what's going on.
You're not crazy.
It wasn't something you did wrong here.
And it is kind of a marker for them of, all right, well, now we can be more sort of more aggressive.
We want to settle into where we're at with a routine and where we're at with life.
And again, that may not even be a new medicine, but it's being able to go to the school and push for an IEP or, you know, work more with physical therapy.
So there are some options there that I think make a big difference for families.
So I wanted to ask you another question about something that came up in the conference that I think is pertinent to this discussion.
And that is the idea of genetic exceptionalism, which is like this notion that genetic testing or genetic information is somehow separate or unique or maybe it's too complex to other forms of medical data.
And I wanted to ask you about that because I know it's not necessarily a new concept and maybe people are getting more familiar with layering genetic data in with other types of phenotypic information.
So I'm curious if you had any updated thoughts on that topic.
I think as a society, we've gotten a lot more comfortable with the idea of our genetic information.
You know, the direct to consumer genetic testing companies have, I think, just lowered the threshold for people to do genetic testing on themselves to find things.
So I think it has softened quite a bit.

And I think also this is something where the horse is out of the barn as well.
And as a genetics community, we have to find a way to meet patients and meet society where they're at and help make sure people are informed.
You know, I always wonder a little bit about false reassurance for folks when it comes to genetic information, you know, just because you have a genetic test or look for something in your genetics, you know, if you don't find something, you're not off the hook.
You know, I think of something like cancer.
Yes, there are hereditary cancer syndromes, BRCA one and two.
But people who don't have changes in those genes still develop cancer.
So I think, you know, we just have to, we have to keep talking about it and have it to have our dialogue around genetic information continue to rise because again, it's not going to go away and it's only going to become more integrated into health care, but also just, you know, society in general.
Right, right.
Another thing that I wanted to talk about here was kind of the state of genetic testing now versus what it was like when you were finishing, you know, I know you did a genetics fellowship, I think, and it was after your pediatrics training or no.
Pediatrics first and genetics.
Got it.
Okay.
Going back to that time and thinking about where we are today, clearly the field has changed pretty drastically, but is there anything that surprised you kind of positive or negative on the pace of change with genetic testing specifically in the context of rare disease, you know, in the pediatric setting?
When I did my training, there was a lot of emphasis on, you know, examining patients, looking for physical features for clues that might suggest a particular diagnosis, you know, some things are very recognizable like Down syndrome, you know, most people can pick that out of a lineup and there are other genetic conditions that an expert, we would call it like a dysmorphologist can look at somebody in the shape of their eyes and where things are placed and kind of think that, well, this person might have more rare syndromes, William syndrome, creature shat, you know, things that maybe the average person wouldn't be quite as familiar with and you could do a targeted test for that.
Well, as the cost of testing has changed, it's actually cheaper for me now to do a gene panel or do a broader test than to do a single gene test or at least it's pretty close.
So it starts to put you as a clinician and the standpoint is how confident are you that you're right and are you willing to bet in this case, you're kind of, you know, betting me the cost of the testing that it is that one thing or one of a handful of things versus doing something like a microarray or exome sequencing or genome sequencing and you're going to figure out whether you were right or not for that one thing, but also kind of look at everything else too, because I tell learners sometimes that, you know, all our patients don't read the textbook and they don't look the way that they're supposed to look and they don't have the health issues that the book says they should have.
So the spectrum of a genetic disease that has kind of classically been right in the

middle, well, there's more severe and more mild findings of that.
And as we do more and more broad testing, we're understanding that the disease again has a lot of different ways of showing itself.
We've certainly learned that with some of the neonatal testing, because these babies would die.
We wouldn't know what was going on, the child would pass away, well, now we at least can find out what's going on, maybe save their life, but say, oh, my word, I never would have thought that they had that because there's never been a neonatal case of that before.
So it's really expanded phenotypes.
Yeah, so the way I'm interpreting that, correct me if I'm wrong, is, you know, a while ago, the downside was real cost, right?
Like you'd rely on your training and you try to take a hypothesis-driven approach because all you could really afford was a single gene test or a small panel, but now the conversation has changed to be about the opportunity cost of not doing a whole genome or an exome or something brought because, you know, that's just within the realm of feasibility of cost.
You know, I think, you know, exomes are down to what, like 45 or 50 bucks on reagents alone.
So it's really changed quite a bit over the last decade.
Yeah, yeah, that's an excellent way of restating it.
And when you look at everything, again, say you're targeting it towards a rare disease or a pediatric issue, when you look at everything, you can find everything.
So you get into the place of adult onset things, treatable adult onset conditions, non-treatable adult onset conditions.
So we kind of open the box and we have to be prepared to deal with what we find once we look at everything that's inside.
I did want to talk about Project Baby Bear in California and then, you know, keep it over to you on Project Baby Deer in Michigan.
But before I get there, maybe just a last question about this topic.
So the field is clearly moving in the direction of more information for less money.
There comes a point, though, especially when you're thinking practically about the level of genetics training that clinicians have and how quickly the field is changing and how they have to keep up with everything.
Is there a point where the amount of information almost becomes like inundating for clinicians and the interpretation becomes the real challenge?
I mean, I know diagnostic labs are doing their best to try to, you know, do the interpretation for you and, you know, at the same time, the American College of Medical Genetics is also broadening what it considers to be, you know, necessary, reportable findings, right, that might be incidental.
And then all of a sudden you might be on this kind of wild goose chase.
So there's a push and pull when you think about how much information is the right amount in these contexts.
So I wanted to ask you about that as well.
Yeah, Simon, it's gotten to the place where a week doesn't go by where I don't get a result back, that's something I've never heard of before.

And you could maybe put that on me and maybe say I should know more, but it's just we're finding so many more things that it is impossible for any one physician, expert or not, to keep up with everything.
So it's kind of forcing the world to get smaller at the same time as it gets bigger and I'm spending a lot of time now connecting my patients with who's the expert on this gene, who's published on it, who's working on it, because, you know, one team can't work on everything.
So I'm excited for the way that as, again, the world's gotten smaller.
There's more ability for patients who get a diagnosis, you know, typically with something that's a little bit rarer to start to connect with other patients and families and what's happening in that because you don't have to travel across the world now to make those kinds of connections.
Right.
Yeah.
And to your earlier point you made about giving a diagnosis over to parents, I imagine that's probably very helpful too in terms of, you know, perhaps allowing them to join like a patient advocacy group that's built around a specific condition and helping those people network.
And maybe even that becomes an opportunity for drug development companies to actually be able to get in touch with, you know, people that have a very rare genetic disorder so they can learn more about the, you know, the etiology of the disease and perhaps even develop, you know, drugs against that target.
Yeah.
I mean, the amount of medical progress that's been driven by patients and families and rare disease, it may be the largest piece of the pie because those people live it right 24 seven there and it's not a patient on their schedule or, you know, a part of your research portfolio.
They're living it every day.
So the motivation to push for research and treatment is very, very powerful within those organizations and, you know, there aren't a lot of other options.
So you kind of have to figure it out for yourself.
It is.
It's the right thing to do.
It creates that microcosm that the drug company that the researcher can connect with, that's what you need to take something elite forward for development.
Got it.
Got it.
So Project Baby Bear, California, Medicaid, let's talk about that for a second and then we'll take it over to Michigan.
But I wanted to, I know that was the one of the main early topics at the Nashville conference and I think it was because there were some initial tranches of health economic data, some of which we've talked about already in terms of cost savings.

But I wanted to learn from you, like what you felt that study, the impact that it had not just on reimbursement policies on the West Coast, but in general, like what it contributed to the field, you know, major learnings about implementation, perhaps that you carried with you to, you know, doing a similar program in your home state, just learning a little bit more about Radies too and the importance of rapid sequencing.
So what can you tell me about those things?
Yeah.
So Project Baby Bear taking five different hospitals that are at different places in the state, for me, somebody in Michigan who's at one of many hospitals to show that the same test at multiple different hospitals, diagnosis kids, changes outcome and reduces cost.
That's exciting because, you know, your genetic code isn't, every ZIP code has genetic code abnormalities in it, right?
So it shouldn't matter where you live, whether you have access to testing and diagnoses and, you know, what we tried to do in Michigan was move that even further to say it's not just five, it's every hospital in the state.
Because again, it shouldn't matter where a kid lives, whether they can get a diagnostic test.
So I was, I loved that in California and that when you kind of take the reins off a little bit and let physicians use this testing in a more free flowing way, you do see the diagnosis rate that's been seen and now multiple other studies of, you know, about 40% of the time you're going to find something in these really sick kids and then you're going to change their management in a quarter to a third of them and have, you know, significant improvements in their care and in their cost.
So it was really, it was the first one, right?
It opened the door for all these other states to start to look at how could we do this on a broader basis, because that's what a tool like this is going to really be used best as at every hospital, regardless of whether you have genetics, whether you're a level three, a level four NICU, regardless of where you're located at, there's kids there that could benefit from graphical genome sequencing.
And that, that project, I think helped, you know, galvanize the creation of a blues plan coverage policy, right?
In California, it was a Medicaid program and then commercial.
Yep.
Okay.
Yeah.
Yeah.
Cause I think, you know, partnering with payers and work like this is really important because you can kind of say to each other, what do you need to feel like this will work for you?

And as a clinical team, as an insurance team, and then engaging patients and families, I think there's the opportunity for everybody to get something out of this.
So maybe tiling over to Project Baby Deer.
I know you published a manuscript recently with a few updates on the program.
There was a coverage policy.
So I wanted to maybe ask you a few rapid fire questions about this.
And I also understand, maybe before we get into those questions, that you did a panel or a presentation about this recently at a conference.
Would you mind kind of telling us a little bit about, you know, what you talked about, maybe some interesting questions that you heard from the audience or during that panel discussion?
And then I'll have just a few follow-ups that stuck out to me as I was reading the paper.
Yeah.
So every year, Raidi does their frontiers and pediatric genomic medicine conference, and it kind of brings together stakeholders from around the world that are interested in pediatrics, genomics, and the various applications of that.
And so, yeah, we talked about the Baby Deer work.
We talked about how we expanded the age inclusion.
So in California for Project Baby Bear, they just did it on kids.
I'm like really the youngest of the young.
In Michigan, we said, hey, up to age 18, which was a huge leap.
So the oldest patient that got rapid genome in Michigan through that project was actually 17 years old.
Because again, we talked a lot about neonates, but older kids have genetic conditions too.
They get critically ill.
So there's opportunity there.
It was all centers and Michigan had access to Project Baby Deer.
And then the other thing that we did was work with Michigan Medicaid for that coverage policy.
And the key piece in Michigan was that that coverage policy pays for rapid genome sequencing as a carve out.
So as a separate payment from kind of the daily rates.
And that is really a game changer for really opening the doors to using this testing, because when it's rolled into the daily reimbursements, it really disincentivizes hospitals to use this testing because it's a loss for them.
Essentially, they lose the cost of the testing.
And so it just makes it much harder to activate that, particularly at centers that maybe don't use this testing a lot.
Would you mind elaborating on that a little bit?

So you're talking about a diagnosis related group, right?
Like a DRG billing scenario.
Yeah, would you mind just unpacking that a little bit in terms of understanding what you mean by a carve out a separate policy and how the incentive system may work on the side of the hospital?
Sure.
So if a kid's in the hospital, when they're in for the day, the payment is made as a lump sum.
And like you said, it's that diagnosis related group.
So depending on what the illness is, the acuity, the hospital gets a certain amount of money.
And regardless of how much testing was done or not done, treatment done or not done, that's how much they get.
So if you try to add in a genetic test that costs thousands of dollars, that's going to suck up that DRG payment pretty quickly.
And so why would a hospital want to kind of burn their DRG payments on a genetic test?
So that's why most hospitals will say no, or will strictly limit the utilization of inpatient genetic testing.
So with the carve out payment saying, Hey, you're still going to get that lump.
And then we're going to give you a separate payment to cover the cost of the test.
That's where from a clinician standpoint, now I don't have to fight with my send out department about sending out this test and tell them it really is going to, I promise, I promise this is the right thing to do for the patient.
And to be honest with you, most hospitals are incredibly gracious and supportive of that because we want to do what's right for patients.
But when you can take that piece of the conversation out, that's when this really starts to get teeth and make a, and make that more, more precise, more dramatic impact on care and the cost of care.
Was this one of the first examples of that, that, that you know of on a state level?
It was the first.
Wow.
Okay.
And it hasn't been mimicked anywhere else since.
So the other states that have started to copy this policy, some of them have done it, not all of them.
And so, you know, when I talk to folks, I really do encourage them that this carve out is a key part of the messaging around this, because otherwise these policies are fairly toothless, to be honest.
Got it.

Okay.
And, you know, in that manuscript that you put out, I noticed you mentioned the importance of having diverse, you know, quote unquote, clinical champions within a health system.
Would you mind elaborating on that a little bit, what you meant by that and what that means?
One of our key learnings with baby deer was it really takes somebody who is passionate about this and is willing to endure getting this set up and push forward to that clinical champion.
And we saw in Michigan that that took various forms, you know, in some places it was geneticists, other places it was a neonatologist who was really championing this.
One of our sites, it was a pediatric neurologist, you know, a lot of neurologic conditions, genetic counselors were a huge part of advocating for this.
And then we also knew that within a state ecosystem for something like baby deer, you know, we had the Michigan Health and Hospital Association that was incredibly helpful and just making the connections with policymakers, with lawmakers, with healthcare executives.
This is not a hard sell.
I mean, I haven't had, you give me 60 seconds with somebody and hopefully it reflects even in this conversation.
60 seconds is all it takes to convince somebody this is the right thing to do.
So it is, it's easy to talk about, but implementing things is always hard, especially when it's something that's new.
Right.
And the other thing I wanted to ask you about was the, in addition to the, the DRG carve out, you know, you also mentioned the, the timeframe with which you can actually still get reimbursement for testing.
I know previously, or maybe it was in a different policy.
I read there was like a one year cut off and I wanted to ask, you know, one about the importance of, of expanding it to, you know, kids that are a little older.
But in addition, this concept of like a, you know, kind of a, an optimal therapeutic window where you can intervene and, and the therapies are much more effective.
I understand that, you know, some conditions that might be recalcitrant to therapy, when you're a little older, if you intervene early, you can really, you know, help improve the condition, you know, of a child afflicted with, with one of these conditions.
So is there any, any truth to that?
And can you speak to that?
Earlier is always better than faster is always better.
I think that's why there's starting to be a lot of conversation around what does

this look like as a newborn screen with whole genome sequencing.
Sure.
The sooner you get the results, the sooner you can change medical management.
Your cost savings is greater.
So yeah, you're absolutely spot on with that.
That applies to a newborn like day of life, zero day of life, one, but that also applies to the teenager who develops seizures for the first time in their hospitalized.
There's not often a good reason that a child, a teenager develops something like epilepsy, so genetics is high on your list.
So hitting that hard and fast with genetic testing gives you the best chance of optimizing that therapeutic window, like you said.
Okay.
Yeah.
And I guess to your point on this, you know, distinction, maybe it's, it's subtle, but it's an important one to touch on is that, you know, a lot of these admissions to the hospital may be phenotypically driven or symptomatically driven, and that's what leads you to have mom and dad, you know, take a kid in.
But in other cases where, you know, the penetrance of a genetic condition may not, I mean, really happen until later in life.
Like this is the point you're bringing up about screening is like, okay, well, what if we can do this proactively very early on, kind of like how some states have the, the heel prick panel of things that they're looking for it and make whole genome sequencing, you know, for, for neonates, like really what we do.
So we can catch conditions that, sure, you'd want to act on them early, even though there's maybe no symptom, you know, set of symptoms yet.
So that is a really interesting proposition.
I think, you know, you have to consider the cost of screening generally, you know, and underwriting proactive healthcare procedures like that is not something that we've done a tremendously good job at, I think in the US.
It's very expensive.
And oftentimes, you know, the false positives become a real issue over diagnosis is becoming a challenge, especially with cancer screening, for example.
But I wanted to ask about, about those things, the way you feel about them.
And also maybe some of the ethical concerns, you know, secondary findings that you have to report and what that could look like on a population scale, where you're testing, you know, a whole state's worth of newborns.
And I'm generally just curious how you think that space is going to involve in terms of proactive testing.
There's a lot of evolution to happen.
The metabolic newborn screen, the heel stick you talked about, that's one of the greatest, like, public health successes of probably the last hundred years.
Taking a condition that you can treat with a simple diet change

and saving someone's life, it's unbelievable.
And the opportunity to expand that to other things is really attractive.
You're right.
There are a lot of ethical questions around that.
And some of them, you know, multiple studies have shown that families
and parents, I think, are a lot better than we sometimes give them credit for
of making informed decisions, feeling comfortable with the amount of information
that they have.
But there is a part of me that when I sit in the ICU, face to face
with the parent talking about, let's say, you know, genome sequencing,
where we might find a BRCA one or two variant, it's hard to feel
like I'm getting true informed consent.
If you have your child's life hanging in the balance, how clear are you really thinking?
But on the other hand, these kids that are critically ill are going for surgeries
and they're getting treatments that we're consenting them for from a health care perspective.
And I don't think anybody worries too much about that because, you know,
we're doing our best and we hope that they're making informed decisions.
So I think we've got a lot to build on and a lot of experience, like we said,
with that newborn screen and a lot of really good lessons to learn.
And I'm hopeful that there will be a steady cadence of progress, thoughtful progress.
And I think there's a lot of interesting work going on in like the UK and in other countries
in Europe looking at newborn screening when it comes to using, you know, genomics
and molecular testing to identify a larger set of diseases that could benefit from a treatment.
So switching gears a little bit, I would be remiss not to bring this up.
But when I think back to the presentation that you gave this really impassioned discussion,
you know, back in Nashville, you spoke about a specific patient that you and your team discovered
had a novel de novo variant in the gene ODC1.
And I know that you repurposed kind of an existing, it was a WHO essential medicine,
right, to come back and be able to help, you know, ameliorate some of their symptoms.
So I was wondering if you wouldn't mind just filling in a little bit of detail.
I mean, it's a really amazing story. It certainly was when I heard it.
And I wanted to learn a little bit more about that and also, correct me if I'm wrong, but
there were a few more patients that you found recently that had a similar variant in this
gene that I don't know if they were also treated with that drug or not.
But I was curious to learn more about that too.
Yeah, it's probably the coolest thing I've ever been involved in in my life.
We don't know where the next years will take me, but it's going to be hard to top this.
You know, this started with a patient that came to our genetics clinic with developmental delay,
which is probably one of the most common reasons we see patients in the outpatient clinic.
And the question of is it something in their genetics? The answer is typically maybe.
So this little girl came to us several years ago.
We gave that answer of maybe and the family elected to not do any genetic testing at the
time. They wanted to see how things would go. She had this interesting history, though, of being

born with a full head of kind of silver gray hair and the parents saying that it fell out in the first couple of days of life and chunks as they bathed her. And for those who have endured personal hair loss or taking care of kids, that's pretty unusual. And it just stuck in my head of like, well, that's kind of weird. So the family came back to us several months later and she wasn't making any progress. We're ready to do genetic testing. And eventually we found the change in her odc one gene. And that gene was not known to cause any syndrome at the time. And so it's one of those what we call variants of uncertain significance. So it kind of went back on the shelf with my office and well, we found something we don't know what to mean of it. I was at Grand Rounds several months later at our children's hospital where one of the intensive care physicians was talking about some work he was doing about organ failure. And he was working with a researcher and they were looking at this pathway called the polyamine pathway. And I honestly just remember that it was kind of a funny sounding word. And nothing clicked in the moment until I was looking back at my patients results a couple months later. And saw that the odc one gene is involved in the polyamine pathway. And so I called my colleague who was that intensive care doc and he connected me with the researcher he was working on. And this was a gene that he had been studying for 20 plus years. And we we just ran into a series of beautiful coincidences where there had been a mouse model made of changes in this gene in the mid 90s. And those mice were born with hair and it all fell out. And when they gave these mice this drug eflornithine or DFMO the mice re grew their hair. So with some basic science work we were able to basically prove this and publish it as a new syndrome. And then we faced the possibility of using this drug for treatments but as kind of a novel drug repurposing treatments.

You're right. DFMO has been around since the 70s. It was developed as an anti-cancer drug. Didn't really work super well but it works really well for West African sleeping sickness. So WHO had kind of kept it around for years and years. It has been used in pediatric neuroblastoma.

So what we got from that was safety data in kids. So we had an animal model. We had safety data. And

then we took fibroblasts from our patient. Treated them in the lab and saw promising signs. So we were able to go to the FDA and ask them for a compassionate use IND investigation on new drug approval to try this treatment. And so our patient came in. We were able to get the drug donated by Sanofi. They shipped us some that they had in the warehouse. And we gave her the first dose. And we didn't see anything that was a concern. And about a month later her family sent me a picture. It was a couple days before Christmas and she had sprouted eyebrows. And I just like stared at that picture like oh my word it's working. And this is a little girl Simon. When we started her on treatment she didn't roll. She didn't talk. She essentially couldn't do anything. And we're about three years into treatment now. She's got a full head of hair. She can use sign language. She has some words and her family kindly shared with us even a month or two ago that she's starting to take some steps. So you know repurposing a drug for we were 15 months from publication of the syndrome to first dose. That's a really remarkable story. And also we hope that it's a good encouragement for rare disease for treatments and for just kind of science in general. And we do have two more patients on treatment now. One that was actually diagnosed through rapid holding sequencing. And we were able to start that patient on treatment at 11 weeks old. And that patient has done unbelievably to the point where there's almost no impairment with this child. And that is that's the holy grail of rare disease discovery

treatments and doing it efficiently and fairly simply. I mean it's an incredible like you said set of beautiful circumstances that let you be able to intervene in that way. And it's almost amazing. I mean it's like a movie about it being available and getting a hold of it. And there being safety data in children. I mean there are just so many things about that that I think are really remarkable. And I'm curious how much of that pathway as it pertains to like the multiple different trait changes that she had and that these kids have how much of that pathway have
you fully elucidated. And do you understand like I mean I'm just generally curious how much the field understands about how it's ephornithine right. Like how that actually acts to change so many different traits. It seems just incredible that it's able to do that.
The polyamine pathway there's about 20 or 25 genes in it. And from the mid 60s until our syndrome one syndrome had been discovered 40 years one syndrome in the last four years there's been four new syndromes discovered in the pathway. So there's still probably another 15 or 20 that they're all in that area that from a therapeutic standpoint really raised the question of whether DFMO or other related drugs might help a bunch of other new or yet to be discovered syndromes. The question around the the impact of the drug to be a bit of a biochemistry nerd our particular syndrome Bachman up syndrome the protein is it sticks around it's not degraded so the enzyme hangs around and keeps acting and DFMO is a is a suicide inhibitor of the enzyme so it just gobbles it up and some of the data that we have showed that really even within the first week of treatment everything went back to normal which is really exciting.
So this is a gain of function mutation in odc one. It functions like a gain of function it's more complicated for people to understand that more than I do but yes it basically is a gain of function which is not the most common when it comes to genetic conditions and it certainly makes it more amenable to treatments. But what we're excited in particular when we talk about this with others is whether the whether the bones of this journey we've been on over the last few years that can be applied to other situations for discovery repurposing even just the the the ability to activate a compassionate use protocol and treatments. These are fairly heroic efforts is just the amount of time and effort that it takes you know particularly when you know you're not at a huge academic center that has a clinical trials division and you know this was done on the back of a lot of really well-intentioned generous people at my institution who did it because it was the right thing to do. Right once this started working did you like go out and try to like down select from a list of other pre-existing drugs that have that same tolerability profile and try to like reverse engineer like are there other genes or or pathways that you could have a drug repurposing effort or is this like a very rare and unique circumstance that let this work?
It's a little bit of both. It is a bit we'll use genetic exceptionalism. This was an exceptional situation that we got ourselves into. There are certainly other opportunities for this though but you know not as a complaint more as reality the amount of time and effort that it's taken even to treat three patients we haven't had the time or the ability to look to other ways of doing it and I and again I don't mean that as a complaint but I'm just trying to speak to the reality of the challenges of developing treatment for rare diseases. There's a reason that it's not financially interesting to drug companies right you have a treatment for we know of 11 people worldwide at Bachman Bup syndrome so how does that work with these kinds of rare diseases so it kind of falls on the back again of patient and family organizations or is it the right researcher

or clinician or does it take this perfect combination of circumstances to get us to a place where you can actually do something here? Yeah and that's I mean we could have a whole another conversation about it that is one of the frustrating things about I was just having a conversation about someone with this about you know rare diseases I think a lot of people like to say they're individually rare collectively common you know affecting several hundred million people ostensibly throughout the world and yet when you're trying to develop a drug against any one of these diseases to your point you'll have a very small number of them scattered across the world difficult to find difficult to get into trials and yet you know if you develop a therapy let alone a curative one then it's just it's hard to make it make sense as a pharmaceutical company right you've got to leverage all these different resources to build up a drug discovery campaign against the target and the failure rate is going to be high so I think that is a challenge for the field and I'm interested in in just seeing how you know as we see more companies start to you know marshal really interesting techniques to lower the you know the likelihood of failure or improve speed to market it's going to take a while I think to improve r&d efficiency to that point but hopefully in the future you know these these conditions yes there's a huge humanitarian impact even if it's for one person but hopefully the the financial incentives start to make sense for more companies to go after rare disease so I don't want to meander too much on that but it just an interesting you know way of thinking about the problem maybe the last thing to say I know we're we're you know about at time here but going forward to I think it's in September or October you know we'll be back in Nashville hopefully having you know another conversation what do you hope
you know to see from the field over the the next half year you know maybe what would you like to see us talk about at the next genetic health information summit meeting and then I'll broaden the question because I know six months not maybe not a whole lot can change but by the waning years of this decade what are some major improvements in the ability for us to dole out you know genetic testing in the pediatric setting what do you hope that that looks like by 2030 I think access to care right now is something that I'm concerned about you know we are not going to put out enough geneticists and enough genetic counselors to keep up with the demand but there are so many other medical providers how do we get the comfort level there with using genetic testing diagnoses treatment in a way that doesn't make access to this kind of medical care inequitable or maybe even let's just say continue the inequities
that exist you know so I'm in Michigan and there are kids in a different peninsula of my state they're literally a lake away right how do I make sure that they can get testing and diagnosis and treatment just as easily as a kid who lives the street down from my children's hospital and the answer isn't going to be putting more geneticists there or you know so I think that's something that we need to that we need to be cognizant of I think the consent piece that we talked about is important just our people understanding what they're getting into and then when you have that information how portable is it you know people change their insurance company they change their healthcare system they move how do you make sure that you know let's say something like pharmacogenomics or we didn't talk about that but that that kind of information is very important and you know if you go to an ER when you're on vacation somewhere and they're going to prescribe you a drug if you have something in your pharmacogenomic profile that should alter that how do we make

sure that it gets there so I just I'm I'm hopeful that this the world gets bigger and smaller that this stuff does go with us and it will matter less about what we have and don't have or where we are where we might go so that care can stay consistent yeah no absolutely and hopefully we'll hear some updates on that later in the year and I look forward to seeing you again and catching up but otherwise thank you for spending an hour with us and giving us kind of your expertise and walking us through everything I certainly learned a lot and yeah looking forward to the next time we can speak so appreciate your time again absolutely I was good to talk arc believes that the information presented is accurate and was obtained from sources that arc believes to be reliable however arc does not guarantee the accuracy or completeness of any information and such information may be
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