Newborn Screening

J: Hello, my name is Jessica. My second baby, Max, was born on my 38th birthday in 2025. Max has one older sister, and both of my pregnancies were pretty normal. Because I was considered to be of advanced maternal age, we were offered genetic testing each time. We were able to find out the sex of our babies very early because of this, and we held our breath through each round of waiting for the other results. Luckily, no abnormalities were ever found.

J: I had a scheduled C-section at 39 weeks, and I was in the hospital for four days but doing really well healing and nursing Max. Doctors, nurses, pediatricians, and lactation specialists were all in and out of my room from the hospital and from my own insurance company. I felt like Max and I were very well taken care of and watched over during our hospital stay. On day three, a pediatrician came into our room and sat down. As soon as she did, it felt like something was wrong. She began explaining that Max was given a newborn screening at 24 hours old. She explained that newborn screenings are a series of tests given to babies in order to identify certain metabolic, endocrine, and hemoglobin disorders. These conditions are serious, but many are treatable if they're detected early in a child's life. She told us that Max had tested positive for a condition called phenylketonuria or PKU for short. She explained that in very rare cases, a person's body cannot process one specific amino acid that is found in protein. In these people, the amino acid phenylalanine builds up in the blood and can cause brain damage and severe developmental problems if the condition is not treated.

J: She told us that a repeat test would be performed because false positives can occur. However, she let us know that Max's results were so high, she really didn't need to give that second test to confidently say he had PKU. She also told us that she had never seen a newborn screening come back positive for PKU and that it was very, very rare. My husband and I both had to be carriers and any children we had would then need to receive a recessive gene from each of us for the disorder to manifest in them. She asked about our first daughter who would've also been given a newborn screening, but we were not informed about any results with her. So it was safe to say she did not have PKU.

J: I was hearing the pediatrician's words, and I can reflect back on them now, but mostly I remember a blur of not understanding what was going to happen to my baby. Sorry. I know I cried for a good amount of time before finally managing to ask her what life would look like for Max. The part about protein poisoning his brain and severe disabilities played on repeat in my mind. Luckily for us, PKU is manageable with a very strict diet and medical formula. I could

talk on and on about our experience with PKU and the low protein world that I never knew existed before this, but I will stay focused on newborn screening for this episode.

J: Max just turned six months old, and we are starting to introduce foods. He gets to eat almost all fruits because they have very little protein and a specific list of low protein vegetables. Eventually, he will get to eat some medical foods that have the "Phe" removed from them, like rice and pasta. He is closely monitored with weekly heel pricks to test the level of Phe in his blood by his pediatrician who had not encountered PKU since medical school but has done an amazing job of research and reaching out to experts and by our wonderful genetics team at Emory, right here in Atlanta. Max is thriving and hitting every single milestone. He's even beaten his sister to some because she was a very late roller. However, absolutely none of this would've been possible if we had not caught this disorder as early as we did with a newborn screening. I will never be able to express how grateful and privileged I am to live in a place and in a time where newborn screening is the norm. If we were in another country, or if Max had been born 60 years ago, his life and ours would look completely different.

EW: Jessica, thank you. Thank you so much for sharing your story with us. It's, it is so meaningful, I feel like to hear firsthand the experiences of someone who was like, this information completely changed my life.

EAU: Yeah. Yeah, it's, it's really truly incredible and powerful and something that we could never express without your help. So thank you so much for sharing yours and your family story, and we're so glad that things are going well.

EW: yeah. Yeah. Hi, I'm Erin Welsh,

EAU: I am Erin Allmann Updyke

EW: and this is, this podcast Will Kill you

EAU: welcome to Newborn Screening.

EW: to Newborn Screening.

EAU: why I did Vanna White

EAU: Hands.

EW: I liked that. I would like you to do more of that throughout the rest of our show. Thank you. Thank you. I'm really excited for this episode, Erin, because I feel like it, we talk a lot about individual things that are, you know, individual conditions or medications or organs, gallbladder, but I feel like this has been a really interesting experience to learn about a screening, not like a diagnostic test, but like the process of screening and all of the good and weird and bad and, and you know, gray areas that come with it.

EAU: I also am biased, but screening is one of my favorite things, like,

EW: Yeah. it's amazing.

EAU: it's so incredible and I love it so much and we'll get to talk so much about it today. Um, but yeah. And I love newborn screening specifically, so I am, I'm really excited about this episode.

EW: I'm also excited that we have a very special guest that we're gonna be bringing on later, so stay tuned. Um, someone who's like, literally an expert on the ground developing the future. The future is now, and the future of newborn screening is now,

EAU: is. now, and they're doing it so like, kind of a big deal.

EW: But we will get to that in a bit

EAU: Mm-hmm.

EW: It

EAU: It's quarantining time.

EW: it is. Erin, what are we drinking this week?

EAU: drinking A Drop of Knowledge.

EW: We are,

EAU: It's a drop of blood in the, we? Don't, need to explain it every time, do we?

EW: we don't, we'll get to

EAU: Mm-hmm. We

EW: a drop of blood. Yeah. Okay. Yep. A drop of knowledge though, like the drink is, I was at a, a deli the other day and I saw that. Do you know like the, I think it's Dr. Brown's celery soda.

EAU: Yeah. I don't, I don't know what that is, but I love the idea of

EW: I feel like you would love this. It's so good. It's celery flavored soda, which sounds weird and maybe not good, but it's actually delicious and I thought what would make a good cocktail with this? Maybe a little bit of a drop of lemon juice, and if you would like some gin,

EAU: If you'd like, why not? We'll post the full recipe on our website. This podcast will click, you know, we actually haven't been posting it on the website.

EW: I know. I need to figure, I don't know how to do the embedded videos. I know that it's a simple google

EAU: Listen, they, they do get posted on all of our social media accounts, so check it out there.

EW: us there. But on our website, even though we might not yet have quarantini and placeborita videos up there, we do have lots of other things. We've got transcripts, we've got links to merch to bookshop.org affiliate page to our Goodreads list to Music by Blood Mobile. We've got a contact us form, so if you have any thoughts or episode suggestions, that's where you do it. And then we've got a firsthand account form. If you have a story of yours that you would like to share, uh, we probably have other things too. So check it out.

EAU: This podcast will kill you.com. While you're on the internet, you can also check and make sure that you are subscribed to the pod catcher that you enjoy, or the exactly right YouTube channel. Or you can also find video versions of my van, a White Hands. Um.

EW: Worth it. It's why we do it. It's why we do what we do.

EAU: mm-hmm. The end. Erin,

EW: end.

EAU: can you tell us, uh, we're doing this a little out of order. Can you tell us about the history of newborn screening? 'cause I know it's a good one.

EW: it is. Yeah. Let's take a quick break and I'll tell you all about it.

EW: In the 60 years since the first newborn screening program began, these screenings have prevented death and disability in countless children across the globe, making it one of the greatest public health achievements of the 20th century alongside some of our other favorites like antibiotics, vaccines, fluoride, and seat belts, which we should do an episode on seat belts,

EAU: I've never thought of doing an episode on seat belts, but I bet there's an interesting history there. Erin.

EW: Okay. I'm adding it to the

EAU: Sounds like a you episode that I get to learn about.

EW: I feel like there will be a lot that you will tell me about seat

EAU: I'd have to learn about forces and physics and that

EW: No, no, no. We don't have to do that. Or crash test dummies. Anyway,

EAU: Yeah, Okay.

EW: Yeah, yeah, yeah. But going back to newborn screening with one, just one drop of blood, we can screen a newborn baby for dozens of conditions that we can treat or provide some other medical intervention for.

EAU: It is like more than one actual drop, but like it's very few drops.

EW: a figurative, it could be one drop if it's a larger drop.

EAU: Yeah.

EW: Uh, anyway, so, but children who end up receiving a diagnosis for one of these disorders are now given opportunities that simply were not available at any other point in human history. Newborn screening has grown steadily over those past 60 years as our technology allows us to cast a wider and wider net. In the early years of newborn screening, you'd find just like one or two disorders

on the panel. Now, dozens. There are dozens. Soon it could be hundreds, and soon, meaning like very soon, like kind of. Now for some people, the, enormity of information that is contained in that tiny drop or large drop multiple drops is staggering. And we are just now starting to realize its full potential with whole genome sequencing. Which is, both exciting and overwhelming because determining whether a disorder should be included on the panel, that can be tricky to navigate. And it involves weighing things like treatment options, the feasibility of screening, and the potential benefit to the individual among other considerations. And I know that later on we'll talk more about the Wilson and Junger criteria,

EAU: Totally.

EW: but going through that process for each and every condition that we have, the ability to screen for that takes an enormous amount of time, resources, and combined expertise, but it is necessary to ensure that we are utilizing newborn screening to achieve the greatest benefit and equitability.

EAU: Yeah.

EW: Here in the us Currently, we have a standardized list of disorders that all states are recommended to include in their newborn screening. It's called the recommended Uniform Screening Panel, or RUSP,

EAU: RUSP. Yeah.

EW: And it includes 38 core and 26 secondary disorders. Two main bodies are involved in the decision making process for the RUSP. There's the head of hHS and there's the advisory committee on heritable disorders in newborns and children.

EAU: Mm-hmm.

EW: Ultimately, it's up to each state, which disorders they screen for, but all have at least those core ones that I mentioned on their panel.

EAU: It's like the recommended minimum.

EW: Yes. Yeah. And that, but that wasn't always the case, right? So like before 2003, which is not that long ago, um, that is when the, which is when the committee was unofficially formed. It was later, like formalized in 2008, but before 2003, some states maybe screened for just a handful of disorders while

others had upwards of 50 on their list. And so that made newborn screening like quite uneven across the us. And so since its creation, one of the major things that the RUSP has done has been to make newborn screening much more equitable across these states. And it has also provided an especially vital service as testing technology has advanced so very rapidly to like a mind-boggling degree, right? So like now we have whole genome sequencing on the very, very near horizon, and we need to be prepared for how to handle this massive influx of information because if we could incorporate whole genome sequencing to newborn screening, which spoilers we are

EAU: we will. Mm-hmm.

EW: Our screening capacity will expand enormously.

EAU: It totally changes the game.

EW: Totally, totally. Unfortunately, Unfortunately, in April of this year, 2025, the Department of Health and Human Services headed by Robert F. Kennedy Jr.

EAU: The one and only.

EW: Mm-hmm. Dissolved the Advisory Committee on Heritable Disorders in Newborns and Children. This is the committee that weighs in on the RUSP.

EAU: Yeah.

EW: The decision was quietly announced just a few weeks, just a few weeks before the committee was set to evaluate two new conditions for screening, so metachromatic leukodystrophy and Duchenne muscular dystrophy. And so far, no formal announcement has been made regarding whether this committee will be reinstated in some form or another, and if those conditions will be added to the RUSP, which is hugely disappointing to say the least. I think for these advocacy groups, the medical practitioners and researchers who have worked so very hard to nominate these conditions for inclusion to get them on the possible list.

EAU: especially just so depressing to think about how so many of the advocates for every one of these disorders that ends up being added to the RUSP are parents of kids whose diagnoses weren't caught because these things are not on the RUSP, despite the fact that we do have tests for them, and we do have treatments available where if things were caught earlier, their condition could have been different.

EW: Yep. Yeah,

EAU: So Yeah, this is a big deal.

EW: it is a big deal. It is a big deal. And you know, I think, just to put some numbers onto this, every year, approximately 13,000 infants in the US receive a diagnosis for a treatable condition. And it was initially detected through newborn screening,

EAU: 13,000. That's a lot.

EW: Yeah. And that number has the potential to grow as we are able to capture more individuals

EAU: The more things you add to the list.

EW: Exactly. Especially with genome, with whole genome sequencing.

EAU: Mm-hmm.

EW: But for that number to grow, for the number of conditions that we detect to grow, and for newborn screening to grow equitably.

EAU: Mm-hmm.

EW: We will need some sort of panel of experts to help sift through the tsunami of information that is now available thanks to genomic sequencing.

EAU: Yeah.

EW: Fortunately, this is like the, the hope on the horizon that does seem like it might be within reach. Because also in April of this year, so this is just before the announcement dissolving the advisory committee came out, the NIH Common Fund announced a research opportunity titled The Newborn Screening by Whole Genome Sequencing Collaboratory Initiative. That's like a lot of words. Like what, what does that mean? Yeah, so what it means is that the NIH has set aside a pot of cash so $4.8 million per year over three years. So a totaling $14.4 million. That's what the NIH has set aside to figure out how we can incorporate whole genome sequencing into the existing state-based US public health newborn screening programs. So basically this money is saying, okay, different programs, please apply to be the ones to help us, you know, use

our existing infrastructure to develop and implement whole genome sequencing for newborn screening across the US.

EAU: Like help us figure out how we're gonna convert from what we have now to whole genome sequencing at some point in the future. And we're gonna do it at these sites that we pick based on whoever applies to this

EW: to this init collaboratory fund. Yeah.

EAU: Okay. I mean, that's great.

EW: great. It's great. So the, yeah, the, the focus of this initiative is not like, how do we best develop whole genome techno, whole genome sequencing technology. We have that technology for the most part, but it's just how can we best, Yeah, fold it into the screening programs that we already have. So the, the other good news thing about this is that it's moving pretty rapidly. So applications were due in May, and the earliest start date was September 1st, 2025. So it's possible that by the time this episode is released, the project is already underway. So that's, that's pretty, that's pretty good. Right. There's still this issue though, of the dissolved advisory committee. So like, what is, what does it mean in light of that?

EAU: Yeah.

EW: It does seem that part of this new initiative involves determining a target gene list. So in other words, genetic conditions to include on the screening panel.

EAU: Which is really important. and we'll talk in a lot more detail about how those decisions are made later.

EW: important. Hugely. Yeah. And so this could conceivably supplement or eventually replace the RUSP as genomic sequencing, supplant traditional newborn screening, which is greatly expanding the number of conditions that we screen for in that process. And so this project seems like it would go a long way towards bringing, or it will go a long way towards bringing newborn screening into this new era of whole genome sequencing. And the panel that was dissolved would probably have had to change to incorporate this new technology

EAU: at at some point in the future, once it exists already.

EW: Right. So that's, that's, that's the sort of, the question is like. Is this a perfect replacement? It doesn't seem at this point like it is, right? Like I, the questions that I still have are what happens to the RUSP while this project slash Collaboratory gets up and

EAU: Mm-hmm.

EW: Will those two nominated conditions or, or any others that come up in the you know, in the next few years, will those be evaluated and added? Uh, you know, what happens if we're still a decade away from genomic sequencing being the norm at state public health departments like are states on their own until then, right? What happens also after three years when this project ends? Will the funding be renewed? I don't know. I dunno. So like I this in, I mean, this initiative is a really exciting and necessary step forward to meet the informational challenge posed by genomic sequencing technology because the future is here and this project will help us navigate that future carefully, thoughtfully, and with evidence to support our decisions. I still don't know what happens to newborn screening in the meantime.

EAU: yeah, I feel like that's what sounds very scary about it is it's like, yeah, we're gonna get all ready for this, but then it's like, so we're just, what, what are we, are we just gonna stay stagnant? Is one state, maybe like advisory board gonna take over, like supplant the thing, just informally, I don't know. Like is every state just gonna have to work harder to decide if they're gonna add things to their newborn screening list in the meantime?

EW: Will one state emerge as a leader and say these are the things that we should be screening for? You know, will someone take up that? Torch, I guess,

EAU: Let us know.

EW: Yeah. Yeah. But, okay. So now that we know what the future might look like, even if we still have questions about the present, shall we take a peek at the past to see the origins of newborn screening and how far we've come since then?

EAU: Yes, let's,

EW: Okay. On November 25th, 1961, a letter to the editor appeared in JAMA with the title Blood Screening for Phenylketonuria. End quote.

EAU: That's it. That was just the whole

EW: That's the whole title. This is a letter to the editor, by the way. So in just over 660 words, Dr. Robert Guthrie described a new technique for testing newborns for a condition called phenylketonuria. Briefly. It's PKUI won't keep saying that because it's difficult. Um, Erin, could you give us like a brief rundown of what PKU

EAU: Oh my gosh. Really? On the spot? Sure. so PKU is a, is a metabolic disorder where babies are not able to break down certain amino acids, and so then they build up in their bloodstream And can end up being toxic. That's the shortest way to say it.

EW: That's great. Okay, perfect. Thank you. I, um, probably should have written something out, but I was like,

EAU: No, you did great. I had nothing written. I felt my heart rate spike.

EW: Oh, no, I'm sorry. You did great. A plus. A plus. Um, so yeah, but this, this test that Robert Guthrie had written to the editor about, examined a spot of blood to see if there was an excess amount of an amino acid called pheno alanine. It was not a diagnostic test, but it indicated which individuals needed to be tested further to confirm that they had PKU. The blood screen was, it was inexpensive, it was easy to administer, and it produced sensitive results. And even better, one of the best things, the biggest improvements about this test was that it could be administered 24 hours after birth

EAU: Like super early.

EW: super early. Because there was an existing PKU test at this time. But what it did is what It used urine collected in diapers, and it was only accurate like six to eight weeks after

EAU: Mm. Okay. 'Cause you had to wait for things to build up? Probably.

EW: Exactly, so like enough of a marker. But then if you're getting that high enough, like once you were able to detect there, the baby might have already experienced irreversible brain damage due to the buildup of the amino acid. So, but in the letter, uh, Guthrie mentioned that they had tested over 3000 kids who were residents at a state school, 3000 already. Mm-hmm. And this, And the test had confirmed those that had already been diagnosed with the diaper test and detected at least two more that had been missed.

EAU: Wow.

EW: So like, this is 660 words. He was able to fit a whole lot into

EAU: crammed it all in there. Quite concise.

EW: Yep. And this, this, uh, Guthrie test, as it would become known, it would revolutionize medical genetics and public health. Because the potential was immediately seen for like, what this could do. Right. So in 1963, 2 years after this letter's publication, Massachusetts became the first state to mandate newborn screening.

EAU: Wow. Two years.

EW: years. And this is after successful campaigning by the Joseph P. Kennedy Jr Foundation and JFK's new task force, other states and countries shortly followed Massachusetts lead. And by 1965, 32 US states had laws for newborn screening

EAU: Wow.

EW: four years. That's very fast and. In medical, I mean, right. And so of those 32 US states that had, you know, included newborn screening, 27 had mandated it. And as the number of babies whose blood was tested, climbed into the hundreds of thousands and then into the millions, it was clear that newborn screening was not only feasible, it was changing people's lives and futures.

EAU: Wow.

EW: And so people were like, well, what else can we do with this? like, this is, has such a hugely positive impact so far. There must be more out there that we can screen for. And so researchers were looking into other conditions that could be treated early, and that could be easily included in this, um, blood drop, this heel prick test. And by the 1960s, the late 1960s, a few other conditions ended up being added to some country's screening protocols. And research was still underway to identify others as it will always be underway. And so along with this heightened interest in this area of research came this realization that like, okay, we have to figure out some ethical guidelines for what we should and what we shouldn't screen for. Like how should we prioritize research efforts to achieve the greatest benefit while also minimizing the potential for harm? Because knowledge, yes, knowledge can be power if we use that knowledge for good. If an early diagnosis, you know, allows us to intervene and prevent a disease from progressing further, or if it helps us to better look out for signs of disease later, like if we know that, oh, we should keep an eye out for this.

EW: But knowledge also has the power to harm. Sometimes it may be better not to know, especially if knowing doesn't change anything. If you get, if you test positive for something and there are no available treatments, what happens? What do you do? What does that knowledge give you? And that's like, I mean, there's, this is like a whole medical ethics philosophy. Yes,

EAU: a hundred percent. And it's all a very individual.

EW: Uhhuh,

EAU: It's an individual Right to know or not to know at the bottom of line. Yeah.

EW: And so, um, with all of the sort of these ethical questions swirling around newborn screening in 1968, the WHO published a report in which they outlined 10 principles for which disorders should be included in newborn screening programs. And this is the so-called Wilson and younger criteria, which I know you'll go into a bit more depth with this, Erin, but a couple of the key points include that a condition can be tested for, like, we have a, a, a suitable test that will, you know, help to not detect, it's not diagnostic, but like, yeah, I don't know why I can't find the words, but you know what I mean.

EAU: Right. You gotta be able to check

EW: You gotta be able to check for it. And it sounds fairly straightforward, but Yeah. Um, and then also the treatment exists, like some sort of medical intervention

EAU: Mm-hmm.

EW: And in the decades since these criteria were put forth, they've stayed quite relevant and helpful. But it's not always as clear cut as you think. Okay. A treatment exists. Check. Okay. Uh, this, a screening test exists. Check, right? Like, does it, there's a lot more new, there's a lot more gray area. And so, as technology especially has expanded our capabilities to detect a wider and wider array of conditions, these, these gray areas, this nuance has really grown with that. Newborn screening is not without controversy, and the harm benefit calculation is not always clear Cut. So let's get into some newborn screening nuance.

EAU: Okay.

EW: Every history of newborn screening starts with Guthrie and pKU, and I think it's worth asking why PKU and to some extent why Guthrie? Like who, who was

EAU: Who was he anyways,

EW: I'll tell you in a second. All right. So, I mean, aren't we all

EAU: Yes,

EW: we can all, yeah. Uh, PKU had only been described a couple of decades before Guthrie developed his test. So it was like actually fairly recent in Guthrie's time and had been described by a Norwegian pediatrics resident in 1934. So this guy Pfalling, examined a couple of siblings who were both intellectually disabled, and he unexpectedly found a dietary derivative of phenylalanine in their urine, something that he had never been described before. He was like, there's surely this is, someone has had to have written about this. Nope. So he wrote it up and was like, I think that this might be linked to the intellectual disability in these children. And a few other physicians were like, okay, well we'll take a peek too. And they confirmed this finding in other children who also had intellectual disabilities. And so it was like, okay, this is a stronger, stronger evidence for these two things being linked. Could it the intellectual disability that we have observed, um, caused by a buildup of phenol lain in the brain, and if so, could it be prevented through a diet that restricted phenylalanine? Because that is, that was possible. It's not like something that you are always constantly exposed to. Some foods have it, some foods don't, and so,

EAU: right. And it's not, it's not something that, like your body is just making willy-nilly. It's like you are consuming it and you're not able to break it down in the way that you're supposed to, and therefore it builds up to toxic levels. So if you are just never exposed to it, if you never consume it, then you can maintain low levels.

EW: Exactly, exactly. And so that, that is, that logic right there is exactly what a couple of British doctors used to create or propose this, uh, pheno, alanine restricted diet. And so they were like, if we administer this early enough, what is it possible to prevent the intellectual disability and some of the other symptoms associated with PKU? So they're like, well, let's try it out.

EAU: Yeah.

EW: The issue though, which is what I said earlier, was that pheno, laine sometimes took a few weeks to show up in the urine, at which point the child's brain made might already have been damaged. And so the advent of Guthrie's test was faster test was huge. Within 24 hours, you could say, oh yes, there is, like, we need to implement a ality restricted diet. But Guthrie Guthrie himself came from kind of an unusual background, right? He was not involved, he had no background in metabolic disorders or genetic conditions. He was a microbiologist by training. And he had been doing cancer research before he developed this test.

EW: So like how, how, how, did he go from point A to point B? Well, Guthrie happened to also have a son who is intellectually disabled, and he was involved in the local chapter of what was then called the Association for Retarded Children now called the Arc. And this is where he learned about PKU and the newly developed diet. He was talking, I think, to a speaker who had come and was discussing this, and he was like, but at the same time, I think he, he had heard about the limitations of the test and was like, gosh, we could really do something. If we could have a faster test, that could be huge. Maybe there's a better way. And so he was at the time working on a bacterial inhibition assay for cancer screening. And he was like, what if I just tweaked a few things here and there and used the same thing to look for phenylalanine? And that's what he did. He like was like, hmm, here's my idea, and here it is. It worked.

EAU: I love, I, I love stories like that where it's like, oh, I was working on this other thing, but I was like, huh, I wonder if I could do it for this thing. And then bing bang, boom. And now you've like revolutionized people's lives.

EW: lives. And I think it also just like goes to show sometimes that thinking outside the box, like approaching a problem as an outsider can really open up your perspective and be like, oh, and everyone else is like. Oh my God, the solution was there all along. I mean, I, I think I, I, I might be overstating the simplicity of it and like the work that he put into it, but still, I think it was like a flash of insight. Yeah. And so he, um, actually left his, his cancer work to, and took on a job at a children's hospital to continue his research on this. I know. And so in the midst of this work, prior to his letter to the editor, he learned also that his niece, who was severely intellectually disabled, had been diagnosed with PKU. And so that gave him even more like motivation, inspiration, knowing that this test could be critical in delivering time sensitive information that could prevent the effects of PKU.

EAU: Yeah.

EW: So when he announced his test in 1961, it was mostly though not entirely enthusiastically received.

EAU: Sounds about right.

EW: right. Yeah. I mean that's, I feel like an app, like a normal reaction

EAU: it's better than most, I would say.

EW: Yeah. This was a sensitive test that could help with a diagnosis for a condition that had a very clear and effective intervention if administered immediately (a phenol alanine restricted diet). But some people, including a prominent doctor, remained vocal skeptics saying things like, oh, well, I don't think it's pheno alanine that causes brain damage. Or saying like, well, I don't think the diet is effective, or It might be effective in only a few. And so this like led to concern that this was a costly diet that could harm or bother those who didn't need it. And also it was just like, why are you going through the effort of this if it's not going to provide a benefit?

EAU: They were like, we don't feel like, you know, PKU. Well enough

EW: Yes. I think that was one of the concerns, or it was like, this might be effective in some children with PKU, but not everyone like this is not, yeah. Right, right. Um, and a couple of the other complaints that were less, um, less medically focused, one was that newborn screening was socialism,

EAU: Oh,

EW: you

EAU: woo.

EW: Yeah. The boogieman. And also that, I found this one really interesting actually, that newborn screening would take focus away from social support programs for children with intellectual disabilities.

EAU: is an interesting

EW: yeah. I see where they're coming from with that. Because if it's, like, if we have a, a limited pot of money and we're now spending it on research rather than social safety pro, like social safety net programs, then,

EAU: You're gonna take our money And you're gonna shunt it over there rather than yeah, yeah, yeah. I

EW: And I, I don't know if that is actually what, like, was the pot of money the same, right? Was it the same source? But, um, but this was also especially felt, I think because kids with PKU made up a very small proportion of all kids who had intellectual or developmental disabilities. And, um, finally the, uh, last complaint was that the test was not accurate enough, or not specific enough. So meaning it either missed kids who had PKU or it led to False positives. False positives. Mm-hmm.

EAU: talk all about things like that, Erin.

EW: Yeah. We will, many of these objections faded away over the years as the test improved and as more data were collected on the efficacy of early intervention. But some objections remained not just for PKU, but for other conditions newly added or proposed to be added to newborn screening programs. Because especially as technology has allowed us to cast a wider net first with the incorporation of tandem mass spectrometry in the 1990s, and now with whole genome sequencing capabilities. One major area that people have expressed concern about is privacy. Right? How to ensure that our genetic information cannot be used without our consent, for instance, by insurance companies to discriminate against us, right? I think that's, that's a, um, a, a valid concern. Every newborn screening program has privacy policies intended to protect against this, and clear guidelines on how the information will be used, including restricting who can access it. Whether that's enough, uh, is beyond the scope of this conversation. And I think that like a legal podcast should definitely pick that up. That would be, I'd be fascinated to, to tune into that. Um, and I also wanna make sure that we, I talk about the other considerations for newborn screening.

EAU: Yeah.

EW: The first is what happens if a positive test ultimately leads to a confirmed diagnosis? Right? The path forward is not always clear when it comes to treatment. You know, I think that earlier we kind of touched on this, when in the criteria where we're like, is there treatment yes or no? Sometimes that answer is not obvious. So like many of the conditions that are included in newborn screening have a range of severity. And since these are rare disorders, we might not have as much data as we'd like for how effective some of these treatments or interventions are, especially in the long term. Sometimes deciding what to do, you know, should I do this treatment or that one, should I do one at all?

Sometimes that's not clear. Cut. Diagnoses can be inconclusive or intermediary. So for example, cystic fibrosis is sometimes is like, we don't know the severity based on whichever specific allele we're data deficient in some of these

EAU: yeah. Or like, we have great treatments for this type and less great treatments for this type, so there's still so many

EW: that treatment works. Yes. And this could leave parents to wonder, you know, if my child may never show symptoms, what should I be doing here? Right. And this is something absolutely that is taken into account when considering whether a condition should be included in the screening.

EAU: It's almost like that's why we need people who know what they're doing to make the decisions about what we should include on the panel.

EW: yes. Uh, yes. But, uh, we are also though approaching an era where someone's entire genetic information could be accessed by or provided to parents. Who does that information belong to? The child, the parents, or both? Like should parents be able to ask for all results, even if there are no interventions or treatments? That knowledge can weigh heavily.

EAU: Or things that like might not happen until adulthood, or maybe you're at higher risk of something as an adult, but not as a child. Like What

EW: Right. What is a parent allowed access to that? And so currently, these are largely hypothetical concerns, so we haven't quite gotten to that point with sequencing, but it's conceivable that we will have to confront them eventually. And then there's the other scenario. What happens if a positive test, positive screening test does not lead to a confirmed diagnosis? And this is very often the case. The high rates of false positives in newborn screening are a side effect of wanting to make sure that we catch every true positive, right? That is, that is often how screenings go. And it is a, it's not unique to newborn

EAU: No.

EW: And newborn screening is just that. It is a screening. It screens for certain conditions. It's not diagnostic at all. So if someone's newborn screening is flagged for a certain condition, that that baby will undergo additional tests to confirm or reject the diagnosis. And the vast majority of the time, like I mentioned, it ends up being a false positive, but that doesn't like, that doesn't undo the financial cost of the additional testing. Battling with insurance and the enormous emotional turmoil experienced by parents during those weeks of not

knowing or imagining the worst one. Study also found that most doctors do not discuss newborn screening with parents before the birth. And I know that we'll talk, there's like that I know. And and many, whether it's pediatricians or obs, feel ill-equipped to explain it. And then that's the other sort of question is like, are you getting your care from your ob? Is your O who should tell you about newborn screening?

EAU: Maybe you should have a family medicine doctor. I'm totally biased.

EW: But if you don't have a family medicine doctor, is your OB going to tell you? Is your pediatrician going to tell you? Are you going to see your pediatrician before You

EAU: No, usually not. Exactly. So, no, it's a total, it's a, it is a, it is a failure of the way that our system is set up, is that, yeah, a, there's usually not time in OB visits. The no one gets enough time in those, and B, you're not probably talking about newborn stuff in your OB visits.

EW: Right, right.

EAU: And then at your pediatrician visit, it's already done. So you get like, you're in the hospital, you just delivered a baby, and a nurse comes in and is like, okay, we're gonna do the screening. Or a resident comes in and is like, okay, we're gonna do the screening. And you're like, what?

EW: Or, or you don't even know that it's happening. I asked my mom, I was like, do you remember? And she goes, oh, did that did. Did that happen? I was like, yes, it did. It did. We were all of us. Like it's mandatory. Um, so it's, it, it is a, this is something that I think that that lack of communication can leave parents terrified and in the dark, seeking information from Dr. Google that could scare them even further. Right? Newborn screening saves lives and has had a tremendously positive impact over the past 60 plus years. But these positives can make it easier to brush aside the negatives, which can be substantial for some, you know, better testing that reduces the false positive rate would go a long way toward alleviating some of the anxiety and fear. Not to mention the cost of addit, of additional testing and having access to genetic counseling can be hugely beneficial in providing information, not just about the initial counseling, additional testing or what positive result might mean, but also what the options are if a diagnosis ends up being made. Um, genetic counseling is a tremendous field. we should, we should talk more about

EAU: We should, and we need more genetic counselors.

EW: Um, because unfortunately not everyone has access to a genetic counselor,

EAU: it's definitely not, like standard.

EW: not, it's not, and so it's really easy then to get overwhelmed by the vast amount of information and misinformation out there. So again, newborn screening though has saved the lives and improved the health of countless newborns around the globe. It is not perfect. There is room for improvement. You know, opportunities to reduce some of the harm and false positives, remove the uncertainty and what to do next for true positives and better communicate to all parents what the screening does. But if we wanna make any advancements in these areas, we need more investment in research communication programs, and a better healthcare system overall to make sure that this powerful knowledge can continue to make a positive impact. And

EAU: We should invest in public health, Erin.

EW: always, I will never stop saying it, except now when I turn it over to you to tell me more about how newborn screening works.

EAU: I can say it.

EW: Yes. Now it's your turn.

EAU: I I can't wait. Erin. Um, thank you. That was such a good setup. I love screening so much. I wanna talk for just a minute about like, what is the concept of screening? 'cause we've never gotten to on this podcast before, really. So the concept of screening means that we are testing. Asymptomatic people like entire, usually hopefully well-defined populations of people. So in the case of newborn screening, we're talking about testing every single newborn for a disease or a disorder or a suite of them before they show any symptoms. And in medicine we screen for so many things, like we screen everyone with a cervix for cervical cancer starting at age 21 or 25. We screen every adult over 45 for colon cancer or earlier, depending on your family history, we screen for high blood pressure. You might not even know that's what we're doing. We are screening for high cholesterol, diabetes, breast cancer, right? We are looking for evidence of a disease before you ever show any signs or symptoms of that disease.

EAU: Right. So in newborn screening, we are testing all of these babies right after delivery, usually within the first 24 to 48 hours of life for a whole suite of disorders that they may develop later in their life. And all screening, but

especially newborn screening because of the scale on which it's done is a process, not an event.

EW: Right. It is. Yes. I love that process, not an event.

EAU: And that process is dependent on a system that has a lot of different pieces that have to be in place. It has to start with our federal, uh, um, and state public health agencies deciding as a group based on expertise, what they're screening for. And then there are both hospital-based exams, which a lot of people might not realize are even happening, like a hearing test and a congenital heart disease screen, as well as the, uh, blood test or the heel prick test, which that test has to then be shipped and analyzed in a systematic way. And then there's all of the stuff that has to happen after that test. The results have to be reported to the families and the healthcare system in which they're a part of. There's then follow-up diagnostic testing that has to be coordinated and completed. There's all these additional appointments. Hopefully you have access to genetic counseling. There might be parental testing, and then there is some kind of treatment or intervention in order to prevent the harms of that condition for which we screened.

EW: Right. That's a lot.

EAU: It's a lot. It's not a small event,

EW: No, no, no.

EAU: and like I had mentioned, we think of the newborn screening test as just that blood spot test, the heel prick, but it is a lot more than that. There's like physical exam testing that is done on every single baby to like look for evidence of certain conditions. There's the congenital heart disease, there's the hearing test, but the blood test is what we're gonna focus on for this episode, and in that, what they do, if anyone hasn't seen this happen before, they take a little teeny tiny lancet like you would use to check your blood glucose and they prick the back of the baby's heel. Usually after you warm it up really good so that you've got good blood flow, and then you drop this blood onto a little filter paper. There's just these little circles. It's not like a whole vial, it's literally just like dropping it onto this paper in these little circles that you fill up and then you let it dry and you mail it to your public health department. Who usually is the ones who do the screening. And you had mentioned, erin, the different modalities. Today we use a bunch of different modalities actually for our blood screening tests. A lot of them use mass spectrometry. Some of them might use

hemoglobin electrophoresis. And then there are some genetic tests as well. It all just depends on what your screening for.

EW: Right.

EAU: And all of this screening generally happens at right around 24 hours of life

EW: It's a lot of information all at once and I, I just still, you don't, you might not even know that it's happening.

EAU: Exactly, exactly. And I'm not gonna give you a list. I'm not gonna go through like every single condition that we test for in the US and around the globe. There is not one single test. And you kind of walked us through, Erin, how this all got started, but it was after the introduction of mass spectrometry that things really kind of ramped

EW: Yeah.

EAU: But every single state in the US manages its newborn screening program a little bit differently and has slightly different things that they have on their blood tests. So some states test for a lot more conditions and some states really just rely on that recommended universal screening protocol that they use to make their list essentially. And all of that is now in question.

EW: Hmm.

EAU: Many of the conditions that we screen for on this blood test are what we call metabolic disorders like PKU, which means that they are disorders in the way that our bodies process foods or other things that can end up leading to the accumulation of toxic byproducts or sometimes deficiencies in other amino acids or things like that. There are really wide range of these metabolic conditions that we can test for. There's a lot of them on newborn screening protocols, but there's also disorders of hemoglobin, right, like sickle cell anemia is on most of the newborn screenings. There's diseases of the immune system, especially if they're caused by known genetic mutations like SCID, for example, or severe combined immunodeficiency. There's things like cystic fibrosis, congenital hypothyroidism, and. Most across the board. These disorders, without treatment, without identification and treatment can cause really significant impacts on growth and development, and in many cases can result in life threatening complications very early in life, in infancy and in childhood, and many of them have relatively straightforward treatments as far as all things

in medicine go, right, like specialized formulas, avoidance of certain foods. Sometimes it's additional therapies or immunizations. Some might be more involved. For example, with SCID, it might be something like a bone marrow transplant, which is very involved and not a decision to be taken lightly, but potentially allows for cure of a disease,

EW: Cur. Yeah. Curative. Uh, it's amazing. Yeah.

EAU: And so whenever we are talking about screening tests, not just newborn screening, but all of the screening tests that we do in medicine, there are, like you mentioned, a lot of factors that we have to consider to decide what populations we're screening and what types of things we're screening for and what types of tests we should use for that screening. So it was Wilson and Junger you mentioned who came up with this list of 10 criteria back in the sixties,

EW: 68. Yeah, yeah,

EAU: And those mostly hold up over time. Like they're mostly the same. But I did find a more recent paper from 2011 that what I liked is that they really tried to take into account how much some of these ideas that we think of are going to have to change as we advance into genetic testing.

EW: Right,

EAU: So there is a bit more of like an intensive framework about how to decide what we're screening for and how we're screening it.

EW: I think it's like, it comes, you know, down to what is the, how, how much does this predict? How well does, does this allele, this, uh, variant, genetic variant predict a disease versus predispose?

EAU: Exactly exactly right. There's a lot of, there's a lot of things that you have to consider, especially as you get into that genetic testing framework. But you kind of mentioned some of the biggest ones, and I wanna just, hi, like reiterate them. I think because they're so important, like, I guess what I'm trying to emphasize is how, what is being screened for is not a flippant decision,

EW: No, no, no. It's not like, Hey, you know what? We've got the capacity to do all of this. Let's just do it

EAU: Right. Let's just check everyone for everything. Like that's not how it's

EW: And I think that like the the other piece of the puzzle too is like this, there has to be individual benefit you think, okay, well, but if we, if we don't currently have a treatment for this, this condition, but we, if we screen for it and we could test it, then we could in the future. If we um, if we know that these kids have it, but like that's not, again, that's not what individual benefit is this kid getting if there is no existing treatment.

EAU: exactly. So some of like big picture, the biggest things that we have to have in place for a disorder to be like added to a screening list. We have to have a test that is appropriate for the condition that we're looking for.

EW: Mm-hmm. Mm-hmm.

EAU: And for screening purposes, what that means is that we have to have something that has what you mentioned, Erin, a high sensitivity, which means that we want it to pick up as many cases as possible. We don't want anyone to be missed and have a bunch of false negatives, because that means we are falsely reassuring people that you do not have this condition if we don't have a highly sensitive test. But the flip side of that is often though, not always, that screening tests can then have false positives, right? Which then means that we have to have additional testing that exists. That's really good and very specific to confirm a diagnosis if something is picked up on these screening tests.

EW: Mm-hmm.

EAU: And how good a test does, like how well it actually performs usually depends on how prevalent or how rare a disease is in the population. So we also have to consider some of the factors of the conditions themselves. Are they an individual health problem and are they a public health problem? we have to know, can we do something to prevent them if we identify them early? Because like you said, it is not considered ethical to screen for something that we can't do anything about. So we have to know that these conditions exist. We can't screen for things that we don't know about yet. And they have to have some kind of asymptomatic stage where this screening can be completed. And then we have to have some kind of treatment or intervention to offer something that can actually reasonably be accessed by everyone who you're screening.

EW: Right.

EAU: And then because this is public health, there's also always a cost consideration, right? Like we are gonna tell you that public health investment always saves money because it does.

EW: Always,

EAU: But the public health agencies also are gonna be doing this cost analysis and then like they have to weigh what is the cost of screening the entire population, plus the cost of the testing for both false positives and true positives weighed against the potential savings in medical care if we catch and treat these disease early and either cure them or prevent severe disease down the line. So all of this has to be considered when we are deciding what conditions have to be on this list to screen for or not. You need a lot of expertise and you need a lot of data.

EW: yes.

EAU: Yeah, and this list has been consistently updated over time as we've developed better testing or developed better treatments. A really good example of this is Spinal Muscular Atrophy, or SMA. This A treatment got approved in 2016, and before that we didn't have any treatment available for this disorder, which can be very, very detrimental. And because we now had a new treatment as of 2016, people started lobbying and recommending that this get added to the list of recommended universal screening, and it was added in 2018. It's still not on every individual state's list, but it is on the RUSP.

EW: I, yeah, it's, it's amazing. Like I feel like that has been, newborn screening has grown so substantially and cons, like consistently, well, not even consistently, exponentially over the years. And it, it, and it's evidence based, like we have, we have these criteria, we have reasons to include these conditions. Yeah.

EAU: Yeah. And all of that will change with the advent of genomic sequencing.

EW: Will change.

EAU: without a doubt.

EW: Yep.

EAU: Genomic sequencing, whole genome sequencing will and is enabling screening for a much wider range of conditions, but without substantial additional costs. Because right now, every single disorder, we have to make sure that we have a test that that test is cost effective and like a good enough test. And then we have to decide based on the treatments and all of those other things, do we add it to this list? Can people have the capacity to add this test to

their public health department? But with this switch to genomic sequencing, like the game has totally changed and literally every recent paper in the last like five years that has been written about newborn screening is about genomics and like the future of, and this future is here. Like you said, the UK has actually already made a commitment to switching all of their newborn screening to genomics within the next 10 years. This is happening. There is no going back. And like, like I said, in contrast to now, we won't need to do all of these different types of tests by sequencing the entire genome of an individual. We can look for so many different diseases and disorders. As long as there is an identifiable gene associated with this condition. You could at least in theory add it to the list of genes that you're looking for. But those same conditions and questions that we have mentioned will also apply when we are talking about using genomics, right? These conditions need to be identifiable. They have to have an asymptomatic stage. We should have some kind of treatment or intervention, right? You have to have confirmatory diagnostic testing. And then like you said, there's all of these additional questions that come with genomics. Like what about all of these genes where we know there's an increased risk of disease, but maybe not necessarily a disease? What about all of the rest of the data that comes by sequencing an entire genome? Who owns it? Who protects it? Who else is going to have access to that information? Do they want to know this information?

EW: How long does it, is it kept? How long, you know, like, can it be reaccess if you, if you want,

EAU: And for what? For what purposes?

EW: what purposes? Mm-hmm.

EAU: And so this comes with a lot of complications and a lot of potential for huge benefit. So we brought in an expert so that we don't have to tell you all about it.

EW: It's the best part.

EAU: Yes, that's right. We brought in one of the researchers who is involved in this huge project here in the US, which is very exciting, called The Guardian Study. Which has already begun, like it's already well underway, it has been screening really large numbers of babies in New York City using genomic tools. The Guardian study has been, it's been recruiting, it still is recruiting families with newborns at New York Presbyterian hospitals for over 200 genes associated with specific conditions known to affect young children. 200,

EW: I know from 38 to 200,

EAU: Yeah. Like the highest, at least that I could find. I think the highest, uh, state is California with like 75 or so conditions that are on our screening tests. So this is like x,

EW: than double. Yep.

EAU: Um, and some of these conditions that they're screening for are incredibly rare and they have had really interesting and important results already. Erin, your other podcast that you host, advances in care, had a really excellent episode on the Guardian study. So can you introduce US to our interviewee.

EW: I am thrilled to, yes, in that episode of Advances in Care, which was called Newborn Gene Sequencing, expanding early detection of Treatable diseases. It was released in March. It's such a good episode. The production team, everyone, the, all the physician scientists, amazing. Just really, really cool. Um, but, uh, one of the physician scientists featured in that episode was a one, Dr. Josh Milner, who is professor of Pediatrics and Director of Allergy Immunology and rheumatology at Columbia University Medical Center, who was involved in the Guardian study. And so yes, we're, we got to speak with, with Dr. Milner about the guardian study and about all of these different aspects of whole genome sequencing and what that could mean. And also, Dr. Milner is part of a group of immunologists who is working to make genomic sequencing a reality for newborn screenings across the country. And his role, one of his roles involves making recommendations for which conditions to include on screening panels. And he is extremely enthusiastic about the recent efforts in the UK that you mentioned, Erin, to incorporate genomic sequencing into newborn screening. And also that new NIH initiative that I mentioned at the top. And so in our interview, Dr. Milner shares some really fascinating insights about the potential offered by genomic sequencing for newborn screening. And we are so excited to bring these to you.

EAU: let's go to the interview, Erin.

EW: Dr. Milner, thank you so much for joining us today.

EAU: Thank you. We're thrilled.

JM: It's a pleasure.

EW: So, so far in this episode, we've discussed how standard newborn screening works as well as the history of its development, and we are really thrilled to hear from you about what the future might hold for this important screening process, especially with the application of genome sequencing. Could you give us an overview of the GUARDIAN study and how it's different from standard newborn screening approaches?

JM: So basically the idea of the Guardian study and generally speaking, doing genomic, uh, newborn screening is that when that blood spot is taken from, uh, the heel usually of, uh, a newborn baby. That the, uh, DNA be extracted and sent for sequencing for genes that might impact health. It's still the same sample, and it's the same process of sending it off to to screen. But when you do something like whole genome sequencing where you're getting the genetic code for the entire, uh, person, um, you actually can look for many, many more disorders. Um, where if you have a, what we call a variation, which used to be called a mutation, um, in a particular gene. That is known to cause, uh, a disease that that can actually be ascertained within the first few weeks of life. And what everyone does is essentially picks only genes where if you found a variation in that gene that there would be something you could do about it to prevent or cure the disease. Uh, and so, um, there are hundreds and hundreds of such genes on, on our list, and it's a, it's a constantly evolving process of, can we now there's something to do for this particular disorder. Oh, now we know actually this is a new genetic problem, but it already comes with something you could do about it. And, uh, then at least in the study, the way that it's been done right now, some of the genes. Do encode for the problem that you might pick up with the regular newborn, uh, screen that we already have. So those can be compared to make sure that the genetic, uh, strategy does not miss anything. But it also can actually even help clarify, uh, where you're like, well, I'm not sure why this particular problem came up on the regular newborn screen, but the genetic testing told me exactly what it was. More often than not, though the genetic testing finds something that couldn't be tested with the regular newborn screen. The thing about the genetic testing is every time you, you, you make a list of the genes that you want to be screening for, for mutations or variations. Uh, you, it doesn't cost anymore. It, it's, it's just, you know, it's the same analysis. Whereas with the regular newborn screening, every single new disease that you're trying to screen for, you have to make a new test. It, it's an extra cost. The development of that test is very, very difficult, and, and essentially you have to make the case that it's. Good for public health to be screening for something that's one in a million, right?

EW: Right, so it's using the same logic really as standard newborn screening, but you're leveraging this genomic sequencing technology, so you're able to cast an even wider net than standard newborn approaches screening approaches.

EAU: exactly a, a, a much wider net. So I'm wondering From like a parent's perspective, especially maybe someone who doesn't really have a medical background, how would this process of maybe being involved in the Guardian study or doing like a genomic screening on your newborn, how would that be different from a parent's perspective than just standard screening?

JM: So, um, again, a lot the, the, the same follow up sort of happens. You get called back, you might have something we need to bring you back, um, to see. We have a, a different type of a test to, to check to see, uh, if indeed this is a problem. Now, sometimes that different type of a test might be a genetic test, right? Because it's a different type of a test that says that, yes, this biochemical problem is there. Usually though, it's a, it's a different, you know, so for an immune deficiency, um, you know, we would look for. Cells in the immune system to see if they're missing or they're not missing, or something like that. Right. So you do, you'd have to come in for another test. Um, and, and during that time, you know, that is a fraught because we we're not saying definitively that we know that there's an issue, but this is, um, the way that we're gonna find out is with this extra test and that test might take. A, or two or three, you know, to come back. And that of course is um, uh, uh, you know, can be trying. Although, you know, that's not terribly different than what, what is already done with the regular, uh, newborn screen.

JM: And are. I'm wondering if there are any stories that you can share of children whose genetic condition was detected using this genomic screening you in Guardian after being missed by traditional methods.

JM: There actually are, are several stories, um, with a similar theme, which is, uh, again, my specialty is in genetic diseases of the immune system. Um, and so, uh, we have a, a huge number, a huge number of these that we've already, uh, put into Guardian, um, and many more, which we are. Hoping to incorporate into Guardian just because we know that many of these are, are actionable, right. Um, in some way or the other. Um, there's, uh, uh, one, uh, one of the cases that we saw was of a boy who had a genetic mutation that was associated with severe combined immune deficiency. The boy in the bubble. Okay. Um, and the boy in the bubble couldn't. Get that bone marrow transplant to work, uh, uh, because he was already sick and older. Um, but we do know 90 plus percent of, uh, babies who are transplanted before they get sick, usually before three months of age. Um, and will, uh, have lifetime, uh, survival, cure. Cure. Right. Which is incredible. Um. Um, otherwise there are life-threatening infections, which can happen. Once those infections happen, the survival drops substantially. Um, we, we are able to keep people alive much more than when, when, when the boy in the bubble was, was, was found, um, without having to

keep them in a bubble. But it's still, uh, you know, they must get a transplant, uh, to be, to be cured. Um, in this particular case, the variant that we found had been seen in two other people, both of whom did not have. Early onset infections. It happened later.

EW: Hmm.

JM: And, and so not surprisingly, we do have a screen in that chemical screen. There's, there's a screen for severe, one version of severe combined immune deficiency, um, that does not pick up, did not pick up this problem in this, in this boy. Um, and so, um, you know, there the parents were, were told this is the story, and the mom said, let's fix this as soon as we possibly can. The sibling was a matched donor. Um. Went to school the day, af whatever, after being a bone marrow donor. And what, what did you do, uh, last week? Oh, I saved my brother's life. Um, and, and, and that was what, you know, uh, the young sibling said, um, about this, uh, this child. Uh, and yeah, he's doing great.

EW: What a show and tell.

EAU: I know.

JM: and he'll ne he'll never know that he was sick. But the parents, you know, are quite thrilled that, that, um, this was, uh, this was

EAU: Yeah.

EW: Yeah.

EAU: How does it feel for you, you know, as a researcher, as a clinician to be involved in this kind of work?

JM: I'm trying to think of the, the best way to, to put it. I can't get enough of it. I, I, we we're, we need to be moving at light speed here 'cause there literally are kids who are being born where there is something to actually capture. Right. Um, and, and to do something about, not even as. Oh, maybe this, maybe that there are people with concrete things. There are people who are in the hospital now where if we had screened them, they wouldn't be in the hospital now. Right. I just feel an urgency, I guess is the best way to put it, to try to get this implemented as widely as possible and to be doing all that work to um, fill up the, the, the things that, that can be treated and have those treatments ready, right? To fill up the list, you know, to, to, to say these are things that we can do. Um, and then also where it is more ethically difficult that we start confronting

those questions, um, in advance so that, um, we are, we are able to move forward with a regular standard of of care, uh, for, for these types of things. right? There's a whole separate question about if you know about a syndrome that can't be

EAU: Mm-hmm.

EW: right.

JM: right? That's a separate,

EW: It's separate

JM: you know, completely separate question. Um, a uh, uh, but a question that might make it a little bit tricky is, well, are there somewhere we do want to know so that someone's working on it

EW: Right.

JM: that cure? Right? Um, and, and there may be ways of, of doing that type of a thing where you anonymize the, the, the medical records and the, and the sequences and that allows researchers like me to go into databases like that and, and say, okay, listen, I'm studying this particular gene or this particular variant. Um, what, what has this resulted in, in your, in your, uh, uh, database? Um, and then now I could start working on, you know, you know, understand why that gene causes a problem, right? And, and actually then, um, start working on a cure. So we need to have systems ready to do things like.

EW: Yeah, it's, I mean, and it sounds like there are so many different avenues for the wider application of the type of screening that, uh, guardian is doing. And then these, you know, ethical considerations as you discussed. And then just research opportunities. I mean, there is, it seems like we're really on. Or maybe even over the threshold of where genome sequencing will provide so many answers and also invite more questions. And this was just such a fascinating conversation and we really just can't thank you enough for taking the time to chat with us today.

EAU: Yeah. Thank you so much.

JM: It was a pleasure.

EW: Thank you again so much to Dr. Milner for taking the time to chat with us about the future of newborn screening and The Guardian Project. I just, I love it. And so, again, if you would like to know more about Whole Genome Sequencing and Guardian, there's a great episode of Advances in Care and also all of the episodes are amazing. But this episode is called Newborn Gene Sequencing, expanding Early Detection of Treatable Diseases. Again, it was released in March. It has some great information about some, about what this work has accomplished so far, which is a lot.

EAU: I love it. I love it.

EW: Yeah.

EAU: Well, uh, if you also just wanna know more by reading, we have a list of sources for you.

EW: we do, we do. I have a bunch of different, uh, papers. I'm gonna shout out three here. Uh, one is by Holtzman and Watson from 1997 called Effective Genetic Testing in the United States. Final report of the Task Force on genetic testing. And this was where I got a lot of the history of newborn screening and by, byec et al from 2022. Psychosocial issues related to newborn screening, a systematic review and synthesis. And then finally by McCandless and Wright 2019 mandatory newborn screening in the US history, current status and existential challenges.

EAU: Uh, Erin, I also read that psychosocial issues one, I really liked that paper.

EW: yeah. Yeah.

EAU: Uh, I didn't talk about it 'cause I felt like you did such a good job, but that's on my list too. Um, I also have a bunch of papers just about like, you know, newborn screen. I mean one was called an overview of newborn screening. It doesn't get more straightforward than that. That was from 2010 by Levy. There was also newborn screening from clinics in Perinatology 2015. I have a few though, like newer ones about the like whole genome sequencing aspect of it. And then I also have a link to, if you wanna know, like in your state, what are they testing for? Um, you can go to babies first test.org and they have a list of state by state. You can look up your state, figure out what they're testing for and all of that kind of stuff, which is great. Um, and there is lots more there on our website. This podcast will kill you.com under the episodes tab.

EW: check it out. A big thank you again to the guests that were featured in this episode. Jessica, your firsthand account. Thank you. Thank you. And Dr. Milner. Again, thanks for taking the time and providing such important context for this really amazing technology.

EAU: Yeah. Thank you. Thank you so much. Thank you also to Blood Mobile for providing the music for this episode and every single one of our episodes. Seriously,

EW: Seriously. Thanks, Dan. Thank you also to Tom and Lianna and Brent, and Pete, and Jess. And Mike and everyone who is involved at exactly right in helping make this podcast happen. Thank you.

EAU: we couldn't do it without you, quite literally.

EW: We literally, yeah, yeah,

EAU: Thank you. I mean to you all, like if you're listening still, I can't believe that you listened all the way to the end. That's wild. But thank you for doing that. And if you're watching, thank you.

EW: We're doing more Vanna White hands, by the way, for those

EAU: If you couldn't tell. I'm, this is why I don't have a job as a fan of White. But thank you so much for listening and watching and especially to our patrons for your support. It really does mean a lot to us, even though I am being ridiculous right

EW: I love it. I love it. Well, um, until next time, wash your hands.

EAU: you filthy animals.