Jay Gironimi

Well my name is Jason Gironimi, I usually go by Jay cause it's half the syllables. I was diagnosed with cystic fibrosis when I was 9 months old because I was a very lethargic baby. There are pictures of me from that time where you can see that kid ain't right. And I think I'm alive today through a very specific set of circumstances that when my parents went to the doctors and were like, 'Hey this baby sucks.' The doctor that they went to happened to work with a CF doctor in Yale, like they were partners on cystic fibrosis. So whereas I was a failure to thrive baby he knew exactly why I was failure to thrive and we were able to address that right away. So since then there has been a long journey and it hasn't been fun but I have been very lucky in most of my circumstances in that there's new medicines which aren't always easy to take but sometimes they work. I'm able to get insurance which is a real big thing and was a real problem for me for a lot of years.

And I'm actually doing okay now, I'm doing better now at 36 than I was at 26 which is not how this used to go. I was one of the first people to go into an adult CF clinic cause there weren't adults for a while and so that was weird, I kinda missed the slide from the children's clinic but what are you gonna do? I feel like everything about successful people with CF and I'm successful in the fact that I'm not dead yet, I feel like it's really important to mention how they got insurance.

And once again it's very specific circumstances for me in that I got very lucky in that there's two very large employers in my area who happen to offer insurance for entry level positions. And had that not existed at the time I wouldn't exist now. I'm also lucky in the fact that my job is a 9-5 job and I do not wake up that early so everyone was very nice when I was like, 'Hey I'm coming in at noon' and didn't question me. Cause it takes me a long time to get ready, it's a large production keeping this show on the road. When I wake up I don't feel great. I don't think anyone feels great when they wake up but I'm extremely aware of my lungs when I wake up, like I can feel them and you kind of do like a diagnostic check of the body, see what you've got going on.

And then I have a vest that I wear and there's been a recent technological advance in that in that it used to be a vest that sort of it was like a giant blood pressure cuff that you put around your chest and it would push air through and make a whole lot of noise, kind of like a poof-poof-poof-poof. Which now it looks like a jet pack and you wear it and it's got little pods that I think they're essentially speakers, they're not really allowed to tell me that but they kind of shake your chest, so they make more of an mm-mm-mm. And while that's happening I also have a nebulizer with which I inhale saltwater at first to salt up the mucus and encourage water to go to it and then the next step is a drug called polmozine which actually snips out parts of the DNA of your mucus somehow and thins it out. So trying to force water into it, trying to force it thin. The vest runs for three 10 minute sessions and inbetween each session you're supposed to cough and see if you can actually cough anything out.

Last week I actually had the occasion to cough out a large piece of sort of dried mucus that I could feel my bronchial tree imprint in it which is a strange feeling. So I do that, I have some extra pills I have to take. I have to take pills to eat that have I believe they're freeze dried pig pancreas, they actually digest the food for me. But if my stomach acid is too acidic they can't do it, I just tear up the pills. So I take omeprazole, so i actually take pills for my pills to work, so that's fun. Claritin which is an easy one and I gotta make sure that I get enough vitamin D because I also have osteopenia which is not osteoporosis but almost.

And then I go to work and I've got this all down into about an hour and then I do some work, I go home eventually, and I have to do the vest again when I get home which is another 30 minutes. I don't do the polmozine again but I do the salt on top of that and then I have to take a long-acting insulin before I go to bed because CF has done such damage to my pancreas that it gave me diabetes as well which is fun because people know what diabetes is and they will talk about that with you all the time where CF scares them I think.

	Something I learned in an old Swamp Thing comic is there's - some guy can see the future, I don't actually remember the context of it - but I don't think you're supposed to know the way you're gonna die. That was a very comic book-y thing, like 'Oh I can't tell you how you're gonna die, that'll change your whole life.' But that made me think for a long time cause for years I was sure I knew how I was gonna die. And it's become blurrier now, I'll give it like an 80% chance that CF kills me, there's a chance that something else could really come in and take the victory from it. But it made me incredibly morbid for so long because if I do have a gift or superpower mine is for most people comedy is tragedy plus time, I require very little time. When they happen to me obviously, I think most things are very funny right immediately and I think I made my family really uncomfortable with that.
	My grandmother who was wonderful to me for so many years was also one of those grandmothers who was like 'No, you're gonna be fine, everything's gonna be fine.' Like you don't know that. Anything could happen tomorrow and she'd be like, 'No, you're gonna live so much longer than me, you don't know that.' She was right but for me CF is a thing that I know and it is a thing that I do, it requires little to no bravery on my part, I just have to keep waking up and doing that. I have no other choice.
	But I think some people don't like to be confronted with the idea that their body could go into total rebellion at any point as mine constantly is. It shocking for them that I have a job and again it's not easy and there's no shame in not having that if you're dealing with CF but it's shocking for them to see someone doing quote unquote "normal" stuff while again, body in total rebellion at any given point. And I just think most people don't like to grapple with that when it's literally the only thing I wanna grapple with is how I'm going to die, when it's going to happen, what's wrong with me. I don't know.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	You just heard from Jay Gironimi who we had the most fun talking to this week.
Erin Allmann Updyke	The most fun.
Erin Welsh	He is an amazing author, musician, and just all around hilarious person. And we have more of his interview later in the episode, so do keep your ears out for that one.
Erin Allmann Updyke	Yeah, it was really thrilling to get to talk to him and we can't wait for you to hear even more of his story.
Erin Welsh	And there's one more thing that you should keep your ears out for at the end of the episode and that's a special song written by Jay specifically for this episode. It's called Complete Somatic Rebellion and we'll provide the link for download in our show notes. I think it seriously might be the coolest thing to happen on this podcast. Anyway, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	And today we're talking about cystic fibrosis.
Erin Welsh	That's right! Yes, this is our first genetic one, is that?

Erin Allmann Updyke	I'm pretty sure. I'm pretty sure that it is, yeah.
Erin Welsh	Yeah. Okay. So what are we drinking this week?
Erin Allmann Updyke	Our quarantini this week is the Dorothy H. Anderson.
Erin Welsh	Yes. Thus named because there was an amazing researcher named Dorothy H. Anderson who described I think or was one of the first people to describe cystic fibrosis and did tremendous amounts of research in her life on the condition. What is in the Dorothy H. Anderson?
Erin Allmann Updyke	Well there is pomegranate soda, lime juice-
Erin Welsh	A splash of ginger ale-
Erin Allmann Updyke	Tequila-
Erin Welsh	Always good.
Erin Allmann Updyke	And you've gotta have it with a salted rim and we'll talk about why throughout this episode.
Erin Welsh	Perfect, perfect.
Erin Allmann Updyke	We'll post the recipe for our quarantini as well as the placeborita which is our nonalcoholic version on our website and all of our social media channels.
Erin Welsh	And let's see, I think we do have a couple bits of business.
Erin Allmann Updyke	Do we?
Erin Welsh	Yeah. So one thing that I wanted to mention is that hey, we have merch. We have t-shirts, mugs, pins, and guess what? We have soap.
Erin Allmann Updyke	Oh we do! We do have soap. I think we did a bad job at telling you guys this but we have soap so you can wash your filthy little animal hands.
Erin Welsh	Also the label is the cutest thing you've ever seen, it's amazing.
Erin Allmann Updyke	It's adorable. You can find all of our merch at thispodcastwillkillyou.com if you just click on MERCH. Ta-da.
Erin Welsh	And the other thing is that I saw this on Reddit and I just wanted to share this because I was lurking briefly even though I haven't been on very much. So on the TPWKY subreddit there was a recent post or post a while back about what people wanted to call fans themselves, what they wanted to call themselves.
Erin Allmann Updyke	(laughs) Oh dear.
Erin Welsh	Let me pull up some of these things, actually. One of the top ones was Filthy Animals.

Erin Allmann Updyke	Of course.
Erin Welsh	Perfect. Another one was Vectors, which is amazing.
Erin Allmann Updyke	Ooh, okay.
Erin Welsh	Erindepiologists.
Erin Allmann Updyke	Oh my god. (laughs)
Erin Welsh	Erinfected.
Erin Allmann Updyke	Ooh, I like that.
Erin Welsh	I love that. Extremeophiles, Podcast Phages, Quarantini Fiends, Respiratory Droplets. I loved that one.
Erin Allmann Updyke	Oh my god, I want a t-shirt that says that. Just that.
Erin Welsh	The Herd.
Erin Allmann Updyke	The Herd. (laughs)
Erin Welsh	The Herd is also amazing. So anyway, I just wanted to tell you that I saw that recently.
Erin Allmann Updyke	Oh that's amazing.
Erin Welsh	Yeah, it was very fun.
Erin Allmann Updyke	That's really funny. Okay any other business?
Erin Welsh	Actually there is one more thing.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	This is our second to last episode of this season.
Erin Allmann Updyke	Oh my gosh! It happened so quickly.
Erin Welsh	I know. It happened so fast. And before you get alarmed by that news, we're only taking a relatively short break. We are coming back on October 29th for the premiere of our Season 3.
Erin Allmann Updyke	Woo-woo!
Erin Welsh	And so subscribe to all of our social media, subscribe to our podcast so that you see when the new episode drops.
Erin Allmann Updyke	Yes. And this is second to last, we're not leaving you high and dry, we've got another excellent episode coming out in two weeks.

Erin Welsh	Yes.
Erin Allmann Updyke	Okay. That's everything now?
Erin Welsh	I think so.
Erin Allmann Updyke	(laughs) Well then.
Erin Welsh	Let's get started. Tell me about the biology of cystic fibrosis.
Erin Allmann Updyke	I can't wait to.
Erin Welsh	Okay good.
Erin Allmann Updyke	We'll take one quick break.
TPWKY	(transition theme)
Erin Allmann Updyke	Cystic fibrosis. This is gonna be a fun one cause we haven't done a genetic disorder before so we're gonna talk a little bit about genetics before we get started on anything. And on top of that we get to talk about biochem which just for some reason is one of my favorite things to do on this podcast.
Erin Welsh	I guess so, yeah.
Erin Allmann Updyke	Even though it's one of my least favorite subjects. Okay. Cystic fibrosis is an autosomal recessive genetic disorder and it can be caused by actually a number of different mutations in a single gene. So it's always the same gene that gets messed up somehow but there's a lot of different ways in which the gene can be mutated that end up resulting in slightly different presentations of this disease or disorder. So first let's define the words 'autosomal recessive' cause some people might have never heard that. That basically means that you have to have two copies of this gene that are mutated in some way in order to actually have symptoms of this disease. So if you have just one mutation, you're what's called a carrier but you pretty much won't have any symptoms or be sick or have cystic fibrosis, you have to have two copies of the gene. And so that's what autosomal recessive means in this case. Cool?
Erin Welsh	Cool.
Erin Allmann Updyke	And 'autosomal' just means that it's not in the X or Y chromosome, it's in any of the other chromosomes.
Erin Welsh	Right.
Erin Allmann Updyke	Okay so the gene that is mutated in cystic fibrosis is called the CFTR, very creative, cystic fibrosis transmembrane conductance regulator gene.
Erin Welsh	Okay.
Erin Allmann Updyke	It's the cystic fibrosis gene.

Erin Welsh	Right.
Erin Allmann Updyke	This is a gene that codes for proteins that form channels through which ions pass. So this is where we're gonna go a little bit biochem. Genetics course over, biochem course beginning. Okay?
Erin Welsh	Okay. Here we go.
Erin Allmann Updyke	I'm not gonna get super into detail, I never do because it's not my strong suit and because we'd be here all day and there's a lot more interesting things than just the biochemistry of this disorder. So what you need to know to understand why cystic fibrosis is such a big deal is that your body is made up of cells, cells are just bags of water and electrolytes which are floating in a matrix of water and electrolytes. Okay?
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	Cool. We're bags of water, tiny little bags of water, floating in water and the linings of our cells are called plasma membranes. They're like the plastic of the water balloon that holds the water inside the cells. And these membranes only let certain things pass through them, okay? They're selectively permeable. And a lot of the ways in which things pass through this water balloon membrane is through channels and pores and it's proteins that make up these channels and pores in the membrane. Cool?
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay. So the CFTR gene codes for a protein that forms a channel that when it is normal sits in this membrane, across the membrane and allows for ions to pass across it.
Erin Welsh	Right.
Erin Allmann Updyke	Okay. That's your biochem course.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay. So if you have a messed up version of this protein in some way then you're not gonna be able to properly control what is going in and coming out of cells.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay. So the cystic fibrosis protein normally allows for the passage of chloride, that's the other half of sodium chloride, and also bicarbonate, $HCO3^-$. And by allowing these ions to pass through it also indirectly regulates other ions like sodium. Cause once you change the balance of one ion, you affect a whole bunch of other ions as well essentially if that makes sense. So what ends up happening is just dysregulation, you get messed up movement of sodium, chloride, and bicarbonate, all three of those across the membrane.
Erin Welsh	Okay.
Erin Allmann Updyke	And that's how you end up with all of the problems that we see in cystic fibrosis.

Erin Welsh	So can you elaborate a bit on what it means by 'messed up movement' or dysregulation of those ions?
Erin Allmann Updyke	Let's do that by talking about some of the different mutations that you can have and that will I think answer that question a little bit.
Erin Welsh	Okay, great.
Erin Allmann Updyke	So there's a number of different genotypes or different mutations that can lead to cystic fibrosis. They all result in this protein being messed up in some way. In one you have a mutation that leads to defective protein production, so your protein is either too short or too long or got cut off. So basically you don't have an actual protein being placed in this membrane.
Erin Welsh	So the one that's making up the pore or the channel?
Erin Allmann Updyke	Exactly. So you don't have a pore or a channel being formed at all which means you don't have any movement of chloride or bicarb across that membrane.
Erin Welsh	Nothing goes in, nothing comes out.
Erin Allmann Updyke	Exactly. Okay? So that's one potential mutation, class 1 mutation. Another one is a defect in processing of the protein, so you're making this protein which is supposed to form a channel but for some reason it gets stuck inside of the cell and it can't actually make it to the plasma membrane, so you make the protein but it doesn't actually make the channel. Does that make sense?
Erin Welsh	Okay, yeah.
Erin Allmann Updyke	So it ends up looking pretty much the same as the first mutation, right. No pore in the membrane for ions to pass through. So that's a class 2 mutation. Then there are a number of other mutations that can result in a protein that is made, so you make the protein, the protein forms a channel and makes it to the cell surface but it doesn't respond the way that it is supposed to to certain stimuli. So these are class 3 and class 4 mutations. And we're not gonna get into the nitty gritty of them but it basically just means that you have an ion channel that's there but it doesn't open when it's supposed to to say let chloride ions out or it doesn't close when it's supposed to to stop chloride ions from leaving. So you have movement of ions but not at the right time or at the right rate. Does that make sense?
Erin Welsh	Yeah. And so there's an association with these types of mutations or these classes of mutations and the severity of symptoms?
Erin Allmann Updyke	Absolutely. You can imagine that if you're not making any of this protein, you're probably gonna have more severe manifestations of disease than if you make some of this protein, it just doesn't quite work properly. Okay.
Erin Welsh	That makes sense.
Erin Allmann Updyke	Right. And then there's another couple classes of mutation, class 5 and 6 mutations where you make the protein, it mostly functions normally, you just do make quite enough of it. And so those might be the least sort of severe manifestations.

Erin Welsh	And so I remember reading that there are around 1000 different mutations that I guess are grouped into these different classes.
Erin Allmann Updyke	Yes.
Erin Welsh	Do you happen to know the distribution of... I know that there's one that's like the most common but what is the class distribution I guess?
Erin Allmann Updyke	Yeah. So the most common is a class 2 mutation.
Erin Welsh	Okay.
Erin Allmann Updyke	That's the F508 mutation is a class 2 mutation so that's a problem where you make the protein but it doesn't get trafficked to the surface properly, so it's not actually doing its function.
Erin Welsh	Okay.
Erin Allmann Updyke	Other than that I'm not sure how common the other classes are, there are I think multiple thousands of mutations.
Erin Welsh	Yeah.
Erin Allmann Updyke	It's bananas how many different mutations there are in this gene. Okay. So you can imagine that with all of these different ranges of mutations all affecting the same protein you can end up with a pretty wide range of manifestations. So let's talk about some of the symptoms. Okay?
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay. So as a recap, you have a malfunctioning protein in some way that leads to abnormal movement of sodium, chloride, and bicarbonate across cell membranes. Okay. So this channel protein, the CFTR protein, is found in a whole bunch of different organs and tissues, it's not just in one place in your body. It's most highly expressed in glandular epithelia. Fun word.
Erin Welsh	Okay. Tell me what that is.
Erin Allmann Updyke	It means in a few specific organs that have glands. So your lungs, your pancreas, your intestine, your sweat glands, and your reproductive tract.
Erin Welsh	Okay.
Erin Allmann Updyke	So you tell me where do you think we're gonna see symptoms of this disorder?
Erin Welsh	I'm guessing it's in all of those places that you just listed.
Erin Allmann Updyke	You're so right, oh my gosh. You're so correct about that. Okay. So yeah, lungs, pancreas, intestines, those are the biggest ones. Reproductive tract as well. Sweat glands, we don't have to talk about it unless you want to later.
Erin Welsh	I kind of do. But whatever.

Erin Allmann Updyke	We'll get to it. (laughs)
Erin Welsh	(laughs) Okay.
Erin Allmann Updyke	Okay. The truth is despite all that we know about how these mutations affect the CFTR proteins, we don't fully understand how this leads to the specific disease manifestations that we see. There's a lot of different theories and we'll talk about some of the possibilities but the main cause of morbidity and mortality, so the main cause of illness and sort of suffering in people with cystic fibrosis is airway symptoms. So when cystic fibrosis affects your lungs.
Erin Welsh	Right.
Erin Allmann Updyke	Okay. So we'll start with the lungs then and then we'll go kind of organ by organ. Okay. In your lungs if you have a messed up CF protein then you're gonna have less chloride and bicarb being secreted out of your cells and into the space inbetween your cells.
Erin Welsh	The negatively charged ions.
Erin Allmann Updyke	The negatively charged ions. This leads to less water being secreted onto the surface of your airway. So that means that your airway ends up not being very well hydrated.
Erin Welsh	Okay.
Erin Allmann Updyke	So this can lead to difficulties in the transport and defense mechanisms that your lungs normally have. So it can lead to super thick mucus being produced, less watery mucus that's more viscous, that can lead to obstructed airways.
Erin Welsh	So if you do not have one of these mutations, how does that ion transport prevent the adherence of pathogens or why is watery mucus more important?
Erin Allmann Updyke	Yeah. So watery mucus is important because it first of all just protects the lining of your cells to begin with so that they don't get dried out or anything by the air and things like that. But also you have something in your lungs called the mucociliary escalator which I think is an adorable name.
Erin Welsh	Escalator, that's very cool.
Erin Allmann Updyke	Yes. It's a combination of the mucus that your cells produce and cilia which are those little hair-like protrusions that we've talked about before. And the combination of this mucus and this cilia helps to sweep anything that you inhale into the bottom of your lungs up and out of your lungs.
Erin Welsh	Okay.
Erin Allmann Updyke	So if you've got a bunch of thick, non-watery mucus then it really impairs this mucociliary transport and it leads to obstruction of airways.
Erin Welsh	Okay, so it doesn't just slow down the escalator, it turns it into a stairway and says-
Erin Allmann Updyke	It blocks it. Yeah, not even a stairway.

Erin Welsh	With a gate in front of it.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay. Just a straight up cliff.
Erin Allmann Updyke	Right. So this can directly obstruct the airways but on top of that it can also lead to chronic infections. You're at much higher risk for bacterial infections because you can't clear anything that comes into your lungs out.
Erin Welsh	Right.
Erin Allmann Updyke	So it's a two-fold process where you have thick mucus that you're producing directly blocking your airways and on top of that you have infections that come in that you're unable to fight off.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	Okay? On top of that the cystic fibrosis protein has a role in helping to regulate inflammation through some other effects that it has on electrolyte transport so you can end up with excess inflammation coming into your lungs to try and help fight off infection which can actually further block your airways. So it's just basically kind of a mess in the lungs when you have this protein not working properly.
Erin Welsh	Yeah.
Erin Allmann Updyke	And honestly it's kind of the same thing that happens in other organs. So in your gut, in your intestines, you secrete a lot of mucus in your intestines as well as it's the same thing if you end up secreting really thick mucus instead of nice, clean watery mucus you can block ducts in the same way that you block the airways in your lungs. But in your guts, in your intestine that's gonna impair the cilia that are also there from absorbing a lot of nutrients. So you can actually end up getting malnutrition and things like that. On top of that it can lead to things like gastroesophageal reflux, acid reflux essentially and impaired bowel transit, so things aren't moving along your gut that way that they're supposed to because ducts are blocked kind of the whole way along. So in really small babies especially this can end up leading to intestinal obstruction on top of the malabsorption that you might be having.
Erin Welsh	Okay.
Erin Allmann Updyke	So that's in your lungs and then in your guts. And then we have your pancreas which for those who might not remember is a very important organ that secretes a whole bunch of enzymes that are important in digestion. And it's a very glandular organ.
Erin Welsh	What does that mean? It's very glandy?
Erin Allmann Updyke	It's very glandy, yeah. It's made of a whole bunch of glands.
Erin Welsh	(laughs) What's an example of a non-glandy organ?
Erin Allmann Updyke	Your heart.
Erin Welsh	Okay.

Erin Allmann Updyke	It's a muscle, your heart.
Erin Welsh	Okay. Not doing a lot of secreting.
Erin Allmann Updyke	No.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay so if you can't secrete these enzymes that normally do digestion then you're not gonna be able to digest your food properly, essentially. And so that exactly what happens in cystic fibrosis. Instead of being able to properly secrete these enzymes, you're pancreas is secreting thick, gunky stuff because the electrolytes and water are not balanced correctly. And this means that not only can you not properly digest foods, you end up not being able to absorb really important things like fat-soluble vitamins because the pancreatic enzymes are really, really important in fat digestion especially. And fat digestion is important in being able to absorb fat-soluble vitamins.
Erin Welsh	Right. So it's not just that your intestines aren't able to absorb, it's also that the pancreas is not even able to help you break down what you need to in the first place.
Erin Allmann Updyke	Exactly, right. And you might also remember that your pancreas secretes other important things like insulin.
Erin Welsh	Yeah.
Erin Allmann Updyke	So if the ducts in your pancreas get plugged up and aren't able to secrete insulin then you can end up getting diabetes. And that's actually a really important aspect of cystic fibrosis that I feel like is maybe sometimes overlooked at least just in common parlance. I think most people think about the lungs when they think about cystic fibrosis but the development of diabetes is a really serious complication as well. Diabetes basically is just not enough insulin in your body and if you don't have enough insulin then you can't properly regulate glucose or sugar, so then you could end up having really, really high blood sugars and then that can kill you.
Erin Welsh	Okay.
Erin Allmann Updyke	So in cystic fibrosis what diabetes looks like is a lack of insulin because you're not able to secrete it. So there's a number of different ways that you can get diabetes.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	Similar things, blocking ducts etc can happen in your liver getting plugged up with mucus, this can end up leading to things like gallstones or stenosis, it can lead to cirrhosis which is liver failure essentially. In people with uteruses and ovaries you can end up getting delayed menarche which is your first period and in people with testicles it's really common actually to have an absence of the vas deferens and that's the duct that normally carries sperm away from the testes, so that means infertility. So that's a lot. And honestly that's not even all of it because while this protein is most highly expressed in those type of glandular tissues, it's expressed in a lot of other tissues as well and so cystic fibrosis can end up affecting your bones which can increase the risk of fractures, it can increase your risk for anemia, kidney stones, chronic kidney disease, the list kind of goes on. It's pretty serious and it's a whole body situation.

Erin Welsh	So because this is a genetic disorder the onset of symptoms of very, very early. So what would that typically look like in an infant I assume?
Erin Allmann Updyke	I just love when you ask questions that are the thing I want to answer next.
Erin Welsh	(laughs) We did not rehearse this, I swear.
Erin Allmann Updyke	No we did not. Okay. So the next thing I wanna talk about is how we diagnose, how we recognize cystic fibrosis. Okay.
Erin Welsh	Snap. Excellent.
Erin Allmann Updyke	So with cystic fibrosis overall you have thickened secretions in a bunch of your organs, lung, pancreas, liver, blah blah blah. One of the ways that we actually can diagnose it is that you also end up with increased amount of salt in your sweat.
Erin Welsh	Right.
Erin Allmann Updyke	Okay, so sweat glands.
Erin Welsh	I know this.
Erin Allmann Updyke	Right. So that's one of the ways that we can actually diagnose cystic fibrosis and nowadays in the United States, in much of Europe, Australia, Canada, we actually do a newborn screen to test for cystic fibrosis.
Erin Welsh	Oh.
Erin Allmann Updyke	Because it is such a serious disease, such a serious disorder we test for it pretty much every single newborn that is born in a hospital gets a little heel prick and we can test for cystic fibrosis gene mutations. You also could do it by testing sweat conductance, essentially. You test to see how salty their sweat is which I think is just so interesting and cool that we can do that.
Erin Welsh	Well it's ingenious.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	And what's really great is that if you detect it in a newborn then you don't have to wait until these symptoms manifest to be able to start potentially treatment or at least preventative measures and things like that.
Erin Welsh	Right.

Erin Allmann Updyke	But if cystic fibrosis is not diagnosed by the newborn heel stick, then it's often diagnosed in childhood either because someone keeps coming down with recurrent respiratory infections or just has chronic respiratory symptoms. So we're talking chronic cough, signs of obstructive disease that we can see when we do X-rays, so their lungs will look like they're obstructed when we look at an X-ray or you can do pulmonary function tests but on a baby that's pretty difficult cause you have to be like, 'Now inhale and exhale.' And babies don't know those words.
Erin Welsh	And would it also be seen in like nutritional... Like would it be obvious in terms of malnutrition?
Erin Allmann Updyke	Yeah. So on top of the respiratory and sinus symptoms you can also sometimes get very commonly or used to be more common in very young infants something called meconium ileus which is obstruction of the bowels by a mucus plug. Or it can manifest at first with pancreatic disease which is basically what you said where you have malnutrition and malabsorption and then the child would present with what they call failure to thrive.
Erin Welsh	Oh yeah, okay.
Erin Allmann Updyke	So they're not growing properly etc because they're not able to absorb the nutrients that they're eating.
Erin Welsh	And so is this something where again if you're in a place where it is not standard to do the heel prick test that again the type of mutation you have might influence when those symptoms emerge?
Erin Allmann Updyke	Absolutely because it's also very possible that someone isn't diagnosed until adulthood.
Erin Welsh	Wow.
Erin Allmann Updyke	Especially if they have a mutation that doesn't result in a complete lack of the protein but is just one of these dysregulated proteins or a lower amount of a relatively normal protein. So in those people in adults who are diagnosed with cystic fibrosis they're more likely to present with GI symptoms, so just general like GI distress, maybe diarrhea, maybe really smelly or fatty stools. Diabetes is a common presentation of cystic fibrosis in adults because of that pancreatic dysfunction or they might not even be diagnosed until they try to have a baby and they're found to have infertility or lowered fertility.
Erin Welsh	Right.
Erin Allmann Updyke	Especially for people with testes that would normally be making sperm and they're found to have what's called azoospermia which means no sperm.
Erin Welsh	Yeah.
Erin Allmann Updyke	So if a person has these kinds of symptoms, maybe these GI symptoms, maybe new onset diabetes or chronic respiratory illness, then you might start to suspect maybe this person has a cystic fibrosis mutation. So that's when you get to do the sweat test.
Erin Welsh	Aha.
Erin Allmann Updyke	You also if that test is negative or for some reason if you can't do it, you can do what's called a transepithelial nasal potential test.

Erin Welsh	Oh.
Erin Allmann Updyke	Which means sticking two probes in your nose and testing for the electrical potential.
Erin Welsh	Yeah!
Erin Allmann Updyke	Yeah, right?
Erin Welsh	That's so cool.
Erin Allmann Updyke	Yeah. And then especially if those tests are positive but even if they're not and you still suspect maybe there's something going on here, then you would do genetic screening. And one of the reasons that newborn screening and genetic screening in general is really common these days is that there are a lot of new treatments available that we'll talk about in the current events section that are specific to the types of mutations that we see in cystic fibrosis. So that means that they'll work for people with certain mutations but they won't work for people with other mutations. So knowing exactly what cystic fibrosis mutation you have is important in determining the course of treatment.
Erin Welsh	That makes sense.
Erin Allmann Updyke	So yeah. That's it.
Erin Welsh	Oh.
Erin Allmann Updyke	That's the biology of cystic fibrosis.
Erin Welsh	Okay.
Erin Allmann Updyke	So tell me Erin, what do we know about cystic fibrosis and how did it come to be?
Erin Welsh	Well okay, big question here. Here we go.
Erin Allmann Updyke	Let's take one quick break first.
TPWKY	(transition theme)
Erin Welsh	Cystic fibrosis is an ancient disease which you might have guessed. But how do we know this? Okay well we know this for a couple different reasons. One is that it has left traces in old European folklore. So there's this old commonly quoted prophecy of quote: "Woe to the child who tastes salty from a kiss on the brow for he is cursed and soon must die."
Erin Allmann Updyke	No way.
Erin Welsh	Yes.
Erin Allmann Updyke	Are you serious?

Erin Welsh	Yeah. So that's like an old prophecy that's been found in several different things like an old Swiss-German dictionary, it was in an old Swiss almanac of children's songs and games.
Erin Allmann Updyke	That is so interesting.
Erin Welsh	Yeah. And we also know that cystic fibrosis is old because there was this description of an autopsy of a quote "bewitched" 11 year old girl done in 1595 and her pancreas was described to be swollen, hardened, gleaming, and white.
Erin Allmann Updyke	Ooh.
Erin Welsh	So that's a pretty tell-tale sign of cystic fibrosis as well. Okay so those are traces, those are written traces, right. The real smoking gun of cystic fibrosis' ancient origins - I don't know, there are lots of 'S's in that.
Erin Allmann Updyke	I don't know how you pluralize that.
Erin Welsh	Yeah. It lies in our genes. Okay so as you mentioned this condition is caused by having a mutation on the CFTR gene and tracing the geographic patterns of that mutation and of variations in that mutation or the types of mutations can tell us a lot about where and when the mutation probably first appeared.
Erin Allmann Updyke	I love it.
Erin Welsh	Yes. It was an interesting opportunity to dive into some of the evolutionary genetics.
Erin Allmann Updyke	Yeah.
Erin Welsh	Not in my wheelhouse whatsoever. (laughs)
Erin Allmann Updyke	But very fun.
Erin Welsh	Yes, very interesting. Bear with me, here we go. For a long time despite the widespread prevalence of this mutation, researchers had a really tough time pinning down exactly where it began and how it spread. So if you look at research from the early 2000s they're like okay, so the mutation probably originated anywhere between 3000 years ago to 52,000 years ago. You know, pretty big range.
Erin Allmann Updyke	Yeah.
Erin Welsh	And the geographic origin was even trickier to nail down. Ancient DNA analysis of skeletons from as early as 700 BCE did find the presence of the mutation in some samples which is amazing. Yeah, very fascinating. But that still left so many questions unanswered. Until last year. I found a recent study published in 2018 that claims to have resolved some of these longstanding controversies about the origin of cystic fibrosis.
Erin Allmann Updyke	Ooh.

Erin Welsh	Okay so what these researchers did is that they took DNA samples from people of European ancestry with cystic fibrosis and then they tried to get a wide geographic range of people spanning from all over Europe. Then they could compare their DNA sequences to see when the mutations likely emerged, overlay that with the geographic information that they had collected, and basically they could make this geographic timeline of the origin and spread of the cystic fibrosis mutation.
Erin Allmann Updyke	Just one of the mutations or multiples?
Erin Welsh	So this is just the most common one.
Erin Allmann Updyke	Okay. Okay, got it.
Erin Welsh	So this is...let me find out what the number is. Delta F508 is the one.
Erin Allmann Updyke	Okay. Yeah.
Erin Welsh	So yeah, so this is the one that's the most prevalent in the population.
Erin Allmann Updyke	Yeah.
Erin Welsh	So it turns out that after they did this their most likely scenario is that the mutation, this Delta F508 first emerged around 2700 BCE which is apparently the Bronze Age.
Erin Allmann Updyke	Okay.
Erin Welsh	Haven't really learned what that is yet. It's on my to do list.
Erin Allmann Updyke	It's the age of bronze, Erin. Obviously.
Erin Welsh	It's the age of bronze. Yes, I imagine the jewelry is fantastic. In small settlements living along the Atlantic in Western Europe, probably France or Portugal. Okay but then what they did was they teamed up with some archeologists to look at human movement patterns during that time to see if they could find anything that would account for the relatively rapid spread of the mutation throughout Europe following this early first appearance. And they found that there was a group called the Bell Beaker people that were known for their extensive migrations and cultural exchanges. Basically what they would do is move throughout the entirety of western Europe over 1000 years and marry or have children with people as they traveled.
Erin Allmann Updyke	As they traveled.
Erin Welsh	(laughs) Yeah.
Erin Allmann Updyke	Just like leaving babies in their wake.
Erin Welsh	Well I don't know how many generations-
Erin Allmann Updyke	Or bringing them.

Erin Welsh	Yeah, maybe it was like okay this time we'll stay here and then our kids will move to the next village and the next village and so on and so on.
Erin Allmann Updyke	Fascinating.
Erin Welsh	Yeah. So I think it's really cool that these geneticists teamed up with these archeologists and anthropologists to say okay what's happening here?
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay but why is it important to understand where and when the cystic fibrosis mutation comes from?
Erin Allmann Updyke	Yeah, why should we care?
Erin Welsh	Why should we care? That's always a good question about anything that you're learning, right. The first reason why we should care, this can be applied to any disease. So the more we know about a disease and how it spreads in a population or where it comes from, the better chance we have of controlling or curing it. And the second reason is that in the case of cystic fibrosis, understanding where the mutation came from can give us clues as to why it exists at such high frequencies. Because as we know, when you have two copies of this mutation it is often sadly fatal and it would have been especially more so in the time before modern medicine.
Erin Allmann Updyke	Right.
Erin Welsh	But this is one of the most if not the most common mutations of people of European descent with about 1 in 25 people carrying one copy of the mutation, of any of these mutations.
Erin Allmann Updyke	Yeah.
Erin Welsh	So why was it not selected out of the population? Why does it still exist basically? Cause usually when we see a lethal mutation with a high frequency it's a clue that it's doing something beneficial as well like as we saw in the case with sickle cell anemia protecting against malaria.
Erin Allmann Updyke	Heterozygote advantage!
Erin Welsh	There we go. Yeah so this heterozygote advantage is basically people who carry one copy of the mutation would benefit from the protection that that mutation offers while not being negatively affected by the presence of two copies of the mutation. Boom.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so that's what researchers thing might be going on with this cystic fibrosis mutation. So what are some of these hypotheses, right?
Erin Allmann Updyke	I love it.

Erin Welsh	Typically a lot of people immediately go to infectious diseases because that was such an important thing to protect against in times before modern medicine, antibiotics, etc etc. So some of these hypotheses include cholera, typhoid, diarrhea associated with lactose consumption, or tuberculosis. So the idea is that one copy of this CFTR mutation would protect against those diseases. There seems to be some physiological support for this or for at least some of these diseases, like the cholera toxin requires normal CFTR proteins to cause disease for example but it's still a little bit hand-wavey so other things don't quite add up.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	So in the case of cholera, cholera has occurred at much higher frequencies in tropical areas compared to Europe.
Erin Allmann Updyke	Right.
Erin Welsh	But the rate of the cystic fibrosis mutation is not correspondingly high there.
Erin Allmann Updyke	Yeah.
Erin Welsh	And same goes for typhoid. And no studies have confirmed that people with a cystic fibrosis mutation are more resistant to any of these diseases cause that would be a horribly unethical study.
Erin Allmann Updyke	Yep. It's just theoretically based on the channels and some mouse models it seems to hold water.
Erin Welsh	Right.
Erin Allmann Updyke	Get it?
Erin Welsh	Yeah. (laughs)
Erin Allmann Updyke	Wow that was funny, actually.
Erin Welsh	And so it could be that the mutation has a benefit other than protecting against an infectious disease or it could be that it protected against a disease that is no longer known to us.
Erin Allmann Updyke	Ooh!
Erin Welsh	I mean we don't know. In any case this part of the story of cystic fibrosis seems like it's still being written.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay, quick recap. So the cystic fibrosis mutation probably originated around 2700 BCE in Portugal or France.
Erin Allmann Updyke	Okay.
Erin Welsh	And it rapidly spread throughout the rest of Europe.

Erin Allmann Updyke	Okay.
Erin Welsh	Okay. We have these mentions in folklore and a few little anecdotal reports throughout the 1700s and 1800s. But it's not until the late 1930s that we get an official description of cystic fibrosis.
Erin Allmann Updyke	Wow. 1930s even though way back in the forever they were talking about salty kids.
Erin Welsh	Salty kids, yeah.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. And I mean I think part of this is because it does affect people differently and a lot of different organs in very different ways and it's hard to tie all the things together I think.
Erin Allmann Updyke	Yeah.
Erin Welsh	So then we have the namesake of our quarantini this episode, Dr. Dorothy Anderson. All right so let me tell you a little bit about Dr. Anderson.
Erin Allmann Updyke	Tell me all about her.
Erin Welsh	Because I did a little deep dive into her biography and it's just cool. All right so she was born in 1901 in Asheville, North Carolina which is an amazing place.
Erin Allmann Updyke	What?
Erin Welsh	Yeah, I love it. Dorothy was fascinated by science and medicine and she went to get her bachelor's in zoology and chemistry and then her MD and she did all of this by the time she was 25.
Erin Allmann Updyke	What? Dorothy. Killing me.
Erin Welsh	She worked incredibly hard to support herself having lost both of her parents before starting college and it seemed like she was well on her way to becoming a surgeon. She was doing an internship and everything and then she tried to do her residency at this particular hospital and was denied because she was a woman. That was the reason. Yeah, very frustrating.
Erin Allmann Updyke	Was she like uh uh, watch me go?
Erin Welsh	Yeah. She was like alright fine, I'll do research. And she got her PhD in endocrinology.
Erin Allmann Updyke	Like you do. What?
Erin Welsh	Just no problem.
Erin Allmann Updyke	Oh my gosh.

Erin Welsh	So she did eventually work as a pathologist and pediatrician at the Babies Hospital at the Columbia-Presbyterian Medical Center.
Erin Allmann Updyke	Wow.
Erin Welsh	And it was there that she noticed in one child that had died of celiac disease that there was this fibrosis of the pancreas which was not something that she had seen in other babies with celiac. So she wrote up her finding with this full description of the condition and she named this disorder cystic fibrosis of the pancreas.
Erin Allmann Updyke	Oh.
Erin Welsh	And that's how it got its name.
Erin Allmann Updyke	Wow.
Erin Welsh	And so that happened in 1938 and that's what that naming of it, that description, even though it had been mentioned in medical texts earlier in that century, that was the description that put it on the map, that started people to do research on it. And also a big reason is because this is what she did for the rest of her career. She worked on cystic fibrosis, she made these amazing observations that led to the development of the diagnostic sweat test-
Erin Allmann Updyke	Wow.
Erin Welsh	And she also hypothesized that it was an autosomal recessive disorder.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah.
Erin Allmann Updyke	I never thought about where it got the name 'cystic fibrosis' specifically.
Erin Welsh	Right.
Erin Allmann Updyke	And it's so interesting that it's from that she saw someone and it was a pancreatic disease, like that's where she saw it and that's where she diagnosed it when today we mostly think about lung issues. That's so interesting.
Erin Welsh	Well it's really interesting and I think a lot of people felt later on that it was a misnomer and there was a question of should we change this name, should we call it something else? And I mean at a certain point changing the name is just gonna lead to more confusion, so...
Erin Allmann Updyke	Right. (laughs)
Erin Welsh	But yeah, so that's the origin of the name.
Erin Allmann Updyke	Oh wow.
Erin Welsh	Yeah. Okay before I move onto the rest of the history of cystic fibrosis I just wanna tell you a little bit more about how awesome Dr. Anderson was because again, my deep dive.

Erin Allmann Updyke	Yes.
Erin Welsh	So she was incredibly meticulous and insightful in her research and she contributed so much to the field of medicine besides the work that she did on cystic fibrosis especially in things like cardiac medicine. She's just a huge inspiration because throughout her entire career she faced a ton of resistance, getting criticized or ridiculed by her colleagues because of her unkempt appearance or her unladylike hobbies because she loved to woodwork and hike and live in the woods and have these amazing parties. She was a stonemason, she championed women's rights.
Erin Allmann Updyke	What?
Erin Welsh	She was so cool! Yeah.
Erin Allmann Updyke	How BA.
Erin Welsh	But she also had a ton of loyal supporters and friends who just loved her and would always talk about how generous and kind she was.
Erin Allmann Updyke	And now she has a quarantini named after her.
Erin Welsh	Yes, thank you Dr. Anderson. Okay so back to cystic fibrosis. So research advancements didn't start immediately after Dr. Anderson's publication in 1938 and a big part of that is because of WWII. So a lot of medical research started to focus on war wounds, bioweapons, who knows. I don't know.
Erin Allmann Updyke	Yeah.
Erin Welsh	And during this time case descriptions were the most common reported thing, just building this recognition of 'this is what this person had, this is their case history' etc.
Erin Allmann Updyke	Right.
Erin Welsh	And it was during writing out these case descriptions that people started to recognize the familial nature of the disease. But researchers still didn't know the exact mechanism of autosomal recessive disorders.
Erin Allmann Updyke	Question.
Erin Welsh	Yeah.
Erin Allmann Updyke	When was Mendel doing his this with peas?
Erin Welsh	1860s.
Erin Allmann Updyke	Okay. So people knew a little bit about-
Erin Welsh	Yeah so like the concept of trait dominance had existed for a very long time but it was figuring out the location of the mutation that was a long ways away.

Erin Allmann Updyke	Right, okay.
Erin Welsh	And understanding the role of this gene vs that gene and how all those things functioned.
Erin Allmann Updyke	Right. That makes sense.
Erin Welsh	Yeah I think it needed the understanding of how DNA worked before we could make those leaps.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so as we know, figuring out the mutation was still a long way away but there was a lot that could be done in the meantime. So for instance the discovery of antibiotics greatly improved quality of life and the longevity of people who were diagnosed with cystic fibrosis because you could then prevent lung infections or cure lung infections that could cause irreparable damage to the tissue. And then also recognizing how important diet was, having the proper amount of fat and nutrient absorption, all of these things were starting to get recognized. But many doctors around the world were still unaware of this disorder or helpless against it and most children didn't survive to the age of 7 during this time.
Erin Allmann Updyke	Ugh.
Erin Welsh	And part of the problem was in correctly diagnosing the condition. So some of these procedures could be horribly invasive and others were kind of subjective. And so when the sweat test was developed in the mid 1950s it really helped to both start supportive therapy early for someone who had cystic fibrosis and to also give epidemiologists a handle on the widespread prevalence of the condition. Physiotherapy also started to be used around the same time and then doctors started to recognize the threat that chronic pseudomonas infections caused and then they started to recognize how harmful chronic antibiotic use could be. So it was a learning curve, this wasn't an easy thing to figure out, there was a lot of trial and error, a lot of 'how do we do this, is this the nest way to provide supportive therapy for someone with cystic fibrosis?'
Erin Allmann Updyke	Right.
Erin Welsh	And I think that the increased recognition also led to the formation of a lot of cystic fibrosis organizations. So in the 1960s when a lot of these organizations kind of got up and running, this allowed parents of children with cystic fibrosis or partners of people with cystic fibrosis to connect and form supportive groups and it also promoted the exchange of information among researchers once you have kind of a group of people together saying 'these are my experiences' or 'this is the research that I've found.'
Erin Allmann Updyke	Yeah.
Erin Welsh	And also these international collaborations were formed and that meant a lot of steady progress being made on treatment or at least supportive therapy. And you can see the progress in the numbers in terms of the life expectancy. So between the years of 1968-1977 the median age of survival rose from 14 years to 20 years.
Erin Allmann Updyke	Wow. In less than 10 years, yeah.

Erin Welsh	Which is a lot. In less than 10 years. And this increase wasn't consistent geographically or even across hospitals within the same country because many people could not afford around the clock care for their child. I mean can you imagine the hospital bills in the U.S. for all the hospital stays that you would need? All of the treatment, all of the care.
Erin Allmann Updyke	So high.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so despite the incremental improvements in therapy that helped extend the lifespan of children or people with cystic fibrosis, many researchers felt as in the dark about the condition as they did in the beginning of their career 30 years earlier. By the 1980s the gene that held the mutation that caused cystic fibrosis was still unknown. Like no one knew what that gene was.
Erin Allmann Updyke	In the 1980s? Wow.
Erin Welsh	In the 1980s. But during that time some progress had been made in understanding the biochemistry and so that was helpful.
Erin Allmann Updyke	Okay.
Erin Welsh	And it was finally in 1989 when the link was made between cystic fibrosis and a mutation in a gene on chromosome 7, so the CFTR gene.
Erin Allmann Updyke	Wow. That's in our lifetime, Erin.
Erin Welsh	In our lifetime, yeah!
Erin Allmann Updyke	How cool.
Erin Welsh	This was a big deal because once the location of that gene was identified, this meant that people could be tested for it to say are you a carrier, do you have the condition, etc. And I keep saying mutation but what I really mean is mutations plural.
Erin Allmann Updyke	Right, yeah.
Erin Welsh	Because there are thousands of different types of mutations. Okay and that's basically all that I have for the history but I kind of wanted to end cap this a little bit in a way because in doing the research for this episode I did something that I haven't done as much and that is read memoirs of people. And what it did was really remind me, it served as a great reminder just how important it is to read about an experience from someone else's perspective. And so reading these memoirs really hit home to me how difficult it is to talk about disease or wellness with our limited vocabulary. And I don't just mean you and my limited vocabulary but when we say words like 'this hurts', well how much does it hurt? 'A lot'. Okay, yeah we can use more descriptive language, we can use a scale from 1-10 but how can you understand a scale if you don't know what someone's baseline is?
Erin Allmann Updyke	Yeah.

Erin Welsh	One person who is like, 'Ugh, I'm feeling a bit cruddy.' Another person might be like, "Oh my god I'm in agony, I'm dying right now, this is extremely painful."
Erin Allmann Updyke	Yeah.
Erin Welsh	And I feel like our own baselines change over time. A hangover at 32 is a lot different than a hangover at 22.
Erin Allmann Updyke	Yes.
Erin Welsh	Personal experience.
Erin Allmann Updyke	Is there such a thing as a hangover at 22? I don't know.
Erin Welsh	Oh god. I don't think so.
Erin Allmann Updyke	No. (laughs)
Erin Welsh	And I think part of this issue of communicating effectively how we feel or what we're feeling is not just with this limited language but also it has to do with the difficulty in relating to someone what it's like to be you, to have your experiences and your memories and the way you see the world because that forms so much of how we perceive our own selves.
Erin Allmann Updyke	Yeah.
Erin Welsh	And also how we interpret other people's feelings or words. And that's something that I came across many times in some of these memoirs that I read for the episode. That for people born with cystic fibrosis, they have not known a life without it so you can't ask them hey, what's it like to have cystic fibrosis? Cause it's like well this is what I know, this is how I have lived, you know.
Erin Allmann Updyke	Yeah.
Erin Welsh	And also it would be like if they asked you what's it like to not have cystic fibrosis? It would be the same sort of thing. Well this is what I know, you know. And so for that reason we can't... I don't know what I'm trying to say exactly. I think it's very difficult to ever or impossible to ever truly understand what someone else is going through or what their experiences are but I think the most important thing is that we need to try, we should try because it builds empathy. Another thing that kept popping up in these memoirs was that other people use cystic fibrosis as an identifier for those people. It's one in the same. Their identity is cystic fibrosis. And that's not what it is, that's not the case, that's not what it should be. And Jay whom you heard from in the first hand sheds a little bit more light on what this is like for him and more about who he is.
Erin Allmann Updyke	So let's hear what Jay has to say in his own words.

Jay Gironimi

I growing up never enjoyed the tone of cystic fibrosis stuff, like I never felt like there was something for me. And I wondered if there were other people like me out there, I figured there had to be and writing the book was an easy was to find them. Because I grew up on the internet so I've seen support groups and things like that but they are not for people like me. Cystic fibrosis is also sometimes called by people '65 roses' cause there was the child how couldn't say cystic fibrosis and so they always called it 65 roses. I was not that kid. I knew exactly what it was at a very young age. I knew how to take my own pills at a young age which upset babysitters sometimes because when you have a little 6 year old kid and he's about to swallow six giant pills by himself, that's a real nerve-wracking moment.

But to see the inspirational quotes and everything like, 'I'm glad I have it, it's such a gift'. I do not consider CF a gift in any way. Not that I don't enjoy talking about it when people ask about it but my CF is like a vampire in that you have to invite it into the conversation, I usually won't just bring it up myself because I like to think that there's so much more about me than just CF which may or may not be true but it is actually why about half the chapters of the book don't involve CF because I think that it's very important to note that people get the disease, the disease doesn't get people. I hoped that there was a group of people where CF was a problem they had but not a defining portion of their personality and it has certainly changed my personality in ways that I don't know.

I like to talk about Swamp Thing more than CF most times or you can get me started on Iron Maiden or Amorphis, the kings of Finnish metal. Those things are very important to music is very important to me. CF is not important to me in that if it went away I'm sure it would be an adjustment for me but I'd be fine. I would just stop taking pills, it's not like I would lose a portion of myself I think. My favorite thing to do in the world is record music.

All Hallows Evil is the name of the project I do, it's usually just me, there were some other people in it for some time but I play all the instruments and everything. So I started that in 2002 is the first official album, so I have 17 years of albums where I recently went through and remastered them and remixed them and everything for public consumption again and it is painful to listen to because I remember that feeling like I didn't have anything to lose and there is nothing to hold back. At the time I would have been very offended if someone was like hey, are you okay? Yeah no man, this is just what I do.

And it's funny because I went back and was remastering all the albums and I dug up some things that I had written the first time we reissued the catalog. And I wrote that stuff when I thought I was okay back in like 2005 and looking at it now I'm like wow, I feel like I need to go back and apologize to everyone I interacted with at that time cause I was just... I had lost insurance a couple of times which is terrifying to know that you are one decision away from dying. I lost insurance, started coughing up blood, charged $2000 in drugs to my credit card, fixed that problem. But it took a long time to fix the mental problems there.

And I realized while I was making music easily now that it is one of the only times that I don't think about anything else. Like I am completely focused on what I'm doing while I'm recording instruments, while I do the vocals then I'm right back to thinking about CF because it's tough to breathe sometimes. But I think that's what I enjoy about it is it's one of the few things I can just really focus on and I can be really good at without worrying about like... Like I probably could be decent at running if I tried but it's difficult. Music, the barrier to entry was very low.

My entire life I've felt like I've had something to prove and I realized that I've always been trying to prove myself as someone who's disabled but able to do this stuff. And so I always thought when people were like, 'Oh wow, you're really good at this.' What I always heard was, 'You're really good at this for someone with cystic fibrosis.' And it was shocking the day I realized that there were maybe 2 people out of 60 at work that realized I have something wrong with me. The thing that I'd like people to understand is that I got very good at a lot of things because I have a chip on my shoulder and it is still there and it will never leave me because I know that I always started from way behind the starting line on most things. And the reason that I have been relatively successful, like I make a living at this point, has almost nothing to do with me and the fact that I'm good at those things because being good at those things means nothing if you don't have the right opportunity for it.

So if I were born 5 years earlier or like I don't know 70 miles to the west of where I was born, I'd be dead. I can't quit my job. I do not know how to quit my job because that's literally keeping me alive, more so than the money it's the insurance. My drugs cost $300,000 a year. There's no way, there no amount of money I could make. And the thing is, even if I did make that amount of money, they won't sell them to you. It was so difficult to get someone to sell me the drug and then that's when I found out that they wouldn't give me the insurance discount, I was paying cash and had to pay $400 more than an insurance company would've made.

There is such a specific set of circumstances and it kind of irks me when people are presented as like, 'Yeah, battling this disease and making it happen!' And it's like you don't realize... I hate to use luck but you have to be offered the opportunity to take it and those opportunities aren't open for a lot of people. And I'm lucky in that again I'm very good at a lot of different technical things which happen to be the thing that people want right now. If it turned out that our entire economy changed and now woodworking was the most valued skill, I'm out. I've got nothing for you because I can't breathe in the sawdust. To have those opportunities and be able to take advantage of them is kind of luck. I not only have been given the opportunities but I have skills to take advantage of these opportunities in the nest way possible and that is the only reason that I'm still alive. And I wish it were easier for everyone to be alive.

Erin Allmann Updyke	If you loved Jay as much as we did, you can find more of his writing at canteatcantbreathe.com.
Erin Welsh	And you can find his book 'Can’t Eat, Can’t Breathe, and Other Ways Cystic Fibrosis Has F#$%*d Me' on Amazon and any other place where you want to get your books. Seriously, go check out his book, it's incredible.
Erin Allmann Updyke	Yeah. We both highly recommend it, it's really great.
Erin Welsh	Yes.
Erin Allmann Updyke	And you can also find more of his music at allhallowsevil.bandcamp.com.
Erin Welsh	And that's also where you can find his latest album titled No Gods, Only Monsters. So go check it out.
Erin Allmann Updyke	And you can find him tweeting @allhallowsevil.
Erin Welsh	Okay so the last 80 years of cystic fibrosis have been big.
Erin Allmann Updyke	Yeah.

Erin Welsh	Since its first description 80 years ago, cystic fibrosis has gone from a disease of relative obscurity to one of the most researched genetic diseases out there. The expected lifespan has gone from 6 months to over 30 years and so much progress has been made in treatments and potential cures. So I'm hoping, Erin, that you'll tell me some good things about cystic fibrosis and gene therapies and other great things on the horizon.
Erin Allmann Updyke	I can't wait too. We'll take one more short break.
TPWKY	(transition theme)
Erin Allmann Updyke	So overall it's estimated that the incidence of cystic fibrosis is about 1 in 3000 among people of Northern European descent.
Erin Welsh	That's a very high incidence.
Erin Allmann Updyke	Yeah especially for an autosomal recessive disorder. The highest incidence is actually in Ireland which for some reason is not what I was expecting but there it's about 1 in 1400.
Erin Welsh	Wow.
Erin Allmann Updyke	Yeah. So it's very different in people of different descents. So in people of Latin American descent, the incidence ranges from about 1 in 4000 to 1 in 10,000. In African Americans it's between 1 in 15,000 to 1 in 20,000 and even lower in people of Asian backgrounds. And what I think is really important is that it's not to say that it's impossible. And one of the biggest gaps that we have in looking at all of these numbers is that these numbers all come from the U.S., Canada, Europe, Australia. So there's a lot of countries and entire regions of the globe from which we don't really have a handle on what the incidence of what cystic fibrosis actually is. Yeah. So we know that it's more common in people of Northern European descent but that doesn't mean that it doesn't exist across the globe cause it does, it's just lower.
Erin Welsh	Interesting, yeah.
Erin Allmann Updyke	Yeah. And a lot of the places that we do have a really good idea of the incidence are places where these newborn screening programs have been initiated. And I wanna talk about them for a minute because I think this is pretty incredible. These newborn screening programs have been shown to reduce mortality, like decrease the death rate, improve growth, and neurocognitive outcomes. Because babies who are diagnosed early can get treatment early, they have better brain outcomes. Which cystic fibrosis, we didn't even talk about it being able to affect your brain. And they've also been shown for those people who are keeping tally on these numbers to be very cost effective.
Erin Welsh	There we go.
Erin Allmann Updyke	So, you know. So newborn screening is routine in a number of different countries and it basically just is a heel prick and they actually test for the blood level of a protein that's higher in most infants with cystic fibrosis.
Erin Welsh	Cool.
Erin Allmann Updyke	So it's not a straight genetic screen right off the bat, it's just to test for the specific protein which is really cool.

Erin Welsh	Right but I imagine it's pretty rapid results?
Erin Allmann Updyke	Yeah, here I think you get them back within a week or two.
Erin Welsh	Okay.
Erin Allmann Updyke	So overall when we look at cystic fibrosis, even with these newborn screening programs, the prevalence of cystic fibrosis in the population is actually increasing. But it's for a very good reason and that's because major developments in treatment have improved survival. So more people are living with cystic fibrosis.
Erin Welsh	Gotcha. Okay.
Erin Allmann Updyke	Yeah, so it's a happy increase.
Erin Welsh	Yeah, that's great.
Erin Allmann Updyke	Yeah. In the U.S. between 2000-2010, survival improved by 1.8% per year.
Erin Welsh	That's amazing.
Erin Allmann Updyke	It's incredible. And today the median survival of children that are born today with cystic fibrosis is 56 years-
Erin Welsh	Wow!
Erin Allmann Updyke	It's still so young, like 56 is so young.
Erin Welsh	It's so young but when you look back at the history of the past 80 years, to go from 6 months to 56 years.
Erin Allmann Updyke	Exactly, it's amazing. And that's today and it's improving every year cause we're getting better at treating it every year which is amazing.
Erin Welsh	Yes. Yeah.
Erin Allmann Updyke	However a small caveat, not a small caveat, a big caveat is that overall when we look across the globe median survival is still in the mid 20s to early 30s.
Erin Welsh	Right.
Erin Allmann Updyke	So we're not better everywhere. But in places like in the U.S. where we have access to treatment it is getting better. And a lot of it does have to do with this early detection. In the U. S. in 2010 almost 60% of people that were diagnosed with cystic fibrosis were diagnosed by that newborn screen compared with only 8% of people in the year 2000 were diagnosed as newborns. Yeah.
Erin Welsh	Interesting.

Erin Allmann Updyke	So overall prevalence is increasing but it's because we're getting better at treating it and so that's what I wanna talk about next.
Erin Welsh	Yeah, tell me about the treatments.
Erin Allmann Updyke	Let's talk all about it. It's a really happy, fun, good stories. Okay. So there is so much research that is going into actual treatments. And for a long time all we could do to treat cystic fibrosis was treat the symptoms. So if you got recurrent respiratory infections, you would treat the infection. If you were having pancreatic insufficiency then you could give them maybe pancreatic enzymes. Okay? It's not gonna fix your pancreas but at least you can digest your food. But now there's all of these new drugs being developed and tested to target the cause of the disease, to target the messed up protein itself so that we can fix this disorder from the start rather than just treating the symptoms.
Erin Welsh	Wow.
Erin Allmann Updyke	The biggest difficulty is that because there are so many different mutations there hasn't yet been a single drug or a single intervention that can work for all of the different types of cystic fibrosis. If that makes sense.
Erin Welsh	Yeah.
Erin Allmann Updyke	As of yet.
Erin Welsh	But have there been any that work for at least one?
Erin Allmann Updyke	Oh there've been multiple.
Erin Welsh	Oh good.
Erin Allmann Updyke	And I do wanna say that I am not a cystic fibrosis researcher or expert and so I know that there's so much going on that I know I haven't covered at all and so for that especially if you research this, I apologize if I don't mention your current research. But I wanna talk about some of the things that have had the biggest impacts and some of what I think is the coolest and I'm biased because my friend actually did some of this research which is very cool. It's really cool research. Okay so one new drug that has been developed and works really great for some people and doesn't work at all for others is called ivacaftor. Have you heard of it?
Erin Welsh	No.
Erin Allmann Updyke	Ivacaftor. It's such a weird name for a drug. This drug works for people with a mutation, not the most common mutation but a mutation that affects about 4 people living with cystic fibrosis that one of those class 3 or 4 mutations that affects the way the protein works, the mechanism of the protein. So you have the protein, it's not misformed, it makes it all the way to the surface but it's not working properly. Okay? It's called a gating mutation. So ivacaftor can essentially improve the movement of electrolytes across this protein. It targets this bad gating protein directly and it's really, really effective. It essentially just allows for the movement of electrolytes.
Erin Welsh	How?
Erin Allmann Updyke	I don't know the details of it, Erin.

Erin Welsh	I don't understand. How?
Erin Allmann Updyke	That's when we get too deep into pharmacology that I can't handle.
Erin Welsh	I'm unsatisfied.
Erin Allmann Updyke	Well then you're gonna be more unsatisfied, okay.
Erin Welsh	Okay.
Erin Allmann Updyke	But it works. The point is that it works.
Erin Welsh	That's very cool.
Erin Allmann Updyke	If you have a protein but it's just not functioning correctly, it's not gating correctly, ivacaftor essentially combined to that protein in a certain way that allows for ions to move properly across that protein. Okay?
Erin Welsh	Cool.
Erin Allmann Updyke	But obviously that's not gonna be effective for people who maybe don't make any cystic fibrosis protein, right.
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay so there are some other options. There's two other drugs, tezacaftor and lumacaftor. These both are beneficial for the most common mutation of cystic fibrosis, that's the Delta F508. So that mutation is a mutation in the processing of the protein. so you make the protein in your cells but then you can't get it shuttled to the surface to actually insert in the membrane.
Erin Welsh	Okay.
Erin Allmann Updyke	So these two drugs help in the processing and trafficking of that protein to get it to the cell surface. Does that make sense?
Erin Welsh	How? How? Just kidding. That's cool, that's very cool.
Erin Allmann Updyke	Yes, it's very cool. So if you have a mutation where your body is still making the protein but it's not being trafficked properly, these two drugs can help with that. However what is even more interesting to me is that they've actually only been shown to be helpful when you give them in combination with ivacaftor. So ivacaftor helps the functionality of that protein which I would guess essentially just means that yeah, you're making it and the problem is that you're not trafficking it but there must be something else going on with that protein too that it's just not gating properly as well.
Erin Welsh	Right. Maybe it's slightly misfolded or something like that.
Erin Allmann Updyke	Exactly, right. But a combination of either tezacaftor or lumacaftor and lumacaftor - also these names...

Erin Welsh	Caftor? Can we talk about caftor? What does that mean?
Erin Allmann Updyke	Seriously. I don't know but it kills me.
Erin Welsh	Caftor. Okay.
Erin Allmann Updyke	But these drugs in combination are for people with this specific mutation hugely beneficial, like incredibly so. But even with these three drug options and their combinations, there's still gonna be a lot of people who straight up don't make the protein, right. Cause that's a whole class of mutation, I don't make any protein. Or others who just don't make enough of it. So helping to traffic it or helping it to gate, that's not gonna help, there's not enough of the protein. And so these drugs aren't gonna be helpful at all if that's the type of mutation that you have. So this is where I'm gonna brag.
Erin Welsh	Oh!
Erin Allmann Updyke	About a friend of mine, not about myself. Shout out to my friend Kat who did her PhD and worked on the development of a new drug.
Erin Welsh	Woo-woo!
Erin Allmann Updyke	This is brand spanking new, it came out in 2019. Not yet doing human trials but there was trials in cell culture and in pigs and this is so cool. This drug that she helped develop for her PhD straight up functions as a CFTR protein channel.
Erin Welsh	Whoa.
Erin Allmann Updyke	So she found a small molecule that's actually amphotericin B which is an antifungal medication that we already use which means that it's already been tested in humans which is gonna help down the road in terms of getting it through the process of testing, etc. You know what I'm saying?
Erin Welsh	Yeah, I gotcha.
Erin Allmann Updyke	Yeah, okay, anyways.
Erin Welsh	I read your mind.
Erin Allmann Updyke	So it functions as a small molecule that inserts itself into the cell membrane and allows for the transport of bicarbonate across this cell membrane.
Erin Welsh	Okay.
Erin Allmann Updyke	And bicarbonate is one of the things that is normally transported in this CFTR protein.
Erin Welsh	Cool.

Erin Allmann Updyke	It's so cool! And they found that when they gave this amphotericin B which again it's a drug that we use as an antifungal that's actually pretty gnarly when you give it at high concentrations, at really low concentrations it's highly selective to only allow these anions, this bicarb to pass across the membrane. So it's not gonna further mess up any electrolytes because it's not allowing just anything to pass through. And they compared the efficacy in changing the pH of the airway surface between this molecule, so amphotericin and ivacaftor which agan is one of those big drugs that they use, and they found that it had similar effects. So we know that because ivacaftor is working for people with cystic fibrosis with these certain mutations, it changes the airway surface pH in this way. Amphotericin B changes it in the same way but by actually acting as a protein, you don't have to have a protein there already for it to happen. Does that make sense?
Erin Welsh	I think so. And so this would apply to all different mutation groups?
Erin Allmann Updyke	Exactly! You don't have to be able to make any of the cystic fibrosis protein in order for this to be beneficial.
Erin Welsh	So would you have to take this antifungal medication for eternity?
Erin Allmann Updyke	That's a good question that we don't know at this point. But they did test it in yeast, in human airway epithelial tissue in culture, and then in pigs with cystic fibrosis and in all of those it worked. In the pigs especially it decreased the symptoms and prolonged these pigs living with cystic fibrosis.
Erin Welsh	That's very cool.
Erin Allmann Updyke	It is so cool. And again this is a molecule, amphotericin, that's already a drug that we use to treat fungal infections. So in terms of basic safety testing it's already gone through that so now it just needs... I mean it still needs a ton of work in terms of clinical trials but it makes it that much faster because it's not a completely new thing essentially.
Erin Welsh	So can you explain the difference between bicarbonate and chloride? Like is one more important than the other in terms of ion transport or ion regulation?
Erin Allmann Updyke	Yeah. This is a great question, I'm glad that you asked it because Kat was like, "Erin, don't forget to talk about bicarb' when we do this episode. So for a long time it was thought that the effects of the cystic fibrosis protein were mediated entirely through chloride. Like this is a chloride channel, so chloride moving across is what's causing all of these symptoms. But it turns out it's not only chloride that moves through this channel, bicarbonate also moves through and it might be even more important in some cases in actually causing and resulting in the symptoms that we see. So essentially both bicarb and chloride ions can move through this CFTR channel and in this case this amphotericin drug is only working on the bicarb but that alone is enough to actually benefit essentially without even touching the chloride. So it's likely that bicarb is a bigger player in the cystic fibrosis game than it has gotten credit for in the past.
Erin Welsh	So are there other things in terms of gene therapy and not medication?

Erin Allmann Updyke	There are, yeah. So gene therapy has also mostly been studied in the lungs so using like a nasal spray that has a viral vector that has a functional CFTR gene in it. And then the idea is that that virus will then go an infect your airway cells and put that functional CFTR gene into your airway cells and then boom, now you can make this functional cystic fibrosis protein. So there are definitely a number of different groups working on gene therapies. So far they haven't been super effective in long term trials but they are in trials. There's actually a huge group out of the UK called cfgenetherapy.org and it's the UK Cystic Fibrosis Gene Therapy Consortium and they're doing a ton of work on gene therapy.
Erin Welsh	Cool.
Erin Allmann Updyke	And that is probably a little further along in the process in terms of it has been tested on humans, it just hasn't been shown to be effective in long term so far.
Erin Welsh	Cool. Yeah.
Erin Allmann Updyke	So I think one of the biggest issues with generation therapy in general is figuring out how to administer it and how to get this gene to actually work the way that we want it to once it's inside of human cells. We don't have a lot of control over that as of yet. Another thing though that I think kind of hearkens back to what you were talking about Erin in terms of reading memoirs and understanding how cystic fibrosis... People live with cystic fibrosis their entire life and so understanding that effect is another big area in cystic fibrosis research has been on understanding that quality of life is just as important in many ways as just longevity. So in a lot of medical studies you'll only see reported things like morbidity and mortality and mortality is this one end point. But especially as we develop all of these new drugs that are allowing for people to live much longer lives living with cystic fibrosis, understanding how these drugs and these drug regimens affect your quality of life has become really, really important.
	And so a lot of research is taking this into account and quality of life studies over the past 10 years have really dug into this in trying to look at a few different issues. One is the importance of patient reported respiratory symptoms as one of the outcome measures. So not just maybe looking at how many infections did you get or something very quantitative but actually looking at the patient's reported symptoms. And then the growing perception that the prescribed treatments, even though we can say how incredible they are and how much they do, they're burdensome. Like we're talking about having to take pills for the rest of your entire life, multiple pills every single day.
Erin Welsh	And it's not just pills but it's also these machines that people need to take time every single day often to break up the mucus, to do this, yeah. And it's painful. Yeah.
Erin Allmann Updyke	Yeah. And there's huge differences according to socioeconomic and racial and ethnic status in terms of who has access to these new developments and who's included in these research studies and all of that.
Erin Welsh	Yeah I think that realm of research is really important and I was doing a little bit of a dig into some of the psychology papers around teenagers with cystic fibrosis and what are some of the minimization of symptoms or just language choices and how you talk about your physical feelings.
Erin Allmann Updyke	Right.

Erin Welsh	And also in terms of impact on family and divorce rates, these sorts of things. It's such a multifaceted thing where I feel like we follow this formula every episode, right. We talk about the biology, the history, and the epidemiology and I feel like that there's so much more to every single disease that we talk about, that we have talked about. And in this case it was definitely tip of the iceberg in terms of feeling completely ill equipped to tell any version of the story of cystic fibrosis and saying like well there's also this aspect of it, there's this aspect of it. Which is even more reason to talk about it, to say hey, share your experiences and so on.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah there's a lot of research and impact on aspects of cystic fibrosis that are maybe not immediately apparent or fall into the categories of medical or historical.
Erin Allmann Updyke	Right. Exactly. Yeah. So yeah, that's where we stand.
Erin Welsh	Seems like it's encouraging but yeah.
Erin Allmann Updyke	Overall encouraging.
Erin Welsh	Still hard.
Erin Allmann Updyke	Still hard and heavy.
Erin Welsh	Yeah. Sources.
Erin Allmann Updyke	Sources.
Erin Welsh	I wanna shout out a couple papers. So one is Rommens et al from 1989 and that is 'The Identification of the cystic fibrosis gene'. And so this article is where they identified where the mutation is located on which gene on which chromosome. And then there's a 2018 paper by Farrell et al and so this is where I mentioned estimating the age and origin of this most common Delta F508 mutation. And then there are three memoirs that I want to give a shout out to. One is called 'Alex: The life of a child' by Frank Deford. And so this is a memoir written by a father about his daughter named Alex who had cystic fibrosis. Another book is called 'My Foreign Cities' by Elizabeth Scarboro and so this is a book written by a woman whose husband had cystic fibrosis. And of course 'Can’t Eat, Can’t Breathe, and Other Ways Cystic Fibrosis Has F#$%*d Me' by our very own Jay Gironomi. All of these were incredible, I really highly recommend each one of these, I think it's just really valuable to read about someone's perspective, someone's experiences.
Erin Allmann Updyke	Yeah. I had two really great reviews actually that are super comprehensive about cystic fibrosis biology and covers a lot of their epidemiology as well. So we as always will post the links to all of our sources on our website thispodcastwillkillyou.com under the EPISODES tab. And there you can find sources from every single one of our episodes.
Erin Welsh	That's right. Jay, thanks again for everything.
Erin Allmann Updyke	Yeah, thank you so much, it was so much fun to talk to you. It was great.
Erin Welsh	Yeah. And thank you to Bloodmobile for providing the music for this episode and all of our episodes. And again to Jay for sharing with us this brand new song that you guys are about to hear, so get excited.

Erin Allmann Updyke	And thank you to all of you for listening. We really love making this podcast.
Erin Welsh	This is great. Okay well Jay has got one more nugget of advice for us all.
Jay Gironimi	The one other thing I need everyone to know is always wash your hands and never touch your face. That is the secret to everything.
Erin Welsh	You heard him, wash your hands.
Erin Allmann Updyke	You filthy animals.
TPWKY	(Complete Somatic Rebellion by All Hallows Evil plays)