Laurel Willig: So, we're going to talk today about congenital hepatic fibrosis from fundamentals to the future. I don't have any relevant financial disclosures, but I am claiming I am a pediatric kidney doctor by training. So, not an expert liver doctor like Dr. Fisher. But

Ryan Fisher: Yeah, and I do have a couple of conflicts. I speak for Albireo and Mirum Pharmaceuticals, they're not subject to this talk. So, hopefully, that won't be any quite an issue at all. And then I wasn't smart enough to be a kidney doctor. So, I ended up doing liver medicine.

Laurel Willig: So, we're going to kind of the objectives of the talk todays to review, sort of the - what, when and how of polycystic liver disease with really a focus on congenital hepatic fibrosis. And we'll talk to you about the genetic sort of the "what", what is wrong? The prognosis, the if, when will deliver quick, question and then treatment. I'm kind of how might - we fix the congenital hepatic fibrosis. So, just a real basic overview of the different kinds of liver disease that can happen in folks, we have polycystic liver disease as part of the ADPKD disease diagnosis.

Again, that's usually cyst formation and accumulation of cyst a liver, in concert with kidney cysts. This can show up as early as kind of age 15 to 25. And by you know, age 40, about 94% of folks will have some liver cysts, congenital hepatic fibrosis and we'll go more into this and what happens but it's basically a ductile plate malformation that eventually leads to fibrosis and portal hypertension.

Generally, starts in childhood and occurs in about 45% of those with ARP KD. There are some other genetic conditions for which it can occur and as well, but we won't probably focus too much on that. And then there's autosomal dominant polycystic liver disease, which are liver cysts, typically without kidney cysts. So, they don't have that ADPKD kidney disease.

This happens a little bit later in life kind of in the 40s to 60s and is a pretty rare condition in the general population. I think we can go to the next slide.

Ryan Fisher: Yeah, there we go.

Laurel Willig: And I just, I'm a kind of Harry Potter nerd. And this is, it's supposed to say guess it's not showing that we're supposed to say, it's silly-ar, not sillier. So, really, these diseases, all of them stem from a problem with the cilia, which is this little finger like projection on most cells in the body. And in polycystic kidney disease and polycystic liver disease, it tends to be that something has gone wrong, in terms of how the cilia functions, which then sort of translates into kind of some dysregulation of these downstream effects and the camp regulation pathway. I think that's - can go to the next slide.

So, really briefly, just because it's not so much the focus of our talk, and I think there was a talk yesterday about polycystic liver disease specifically, but basically insists formation in the liver, what we think happens, you have that genetic change either in one of the PKD genes or in a couple of other genes response that can drive this cyst formation. That change leads to a problem with how the cilia functions. And you end up getting this sort of cyst initiation event where you have sort of abnormal protein formation that then affects that cilia signaling pathway and cyst starts to form.

And then as you accumulate cysts, they cause kind of local changes around them, that then lead to even further sort of abnormal signaling pathways and allow for more cell proliferation and more cysts formation as the disease progresses.

And really quick, and I think Dr. Fisher may go into this in a little more depth, a little further down the line, but congenital hepatic fibrosis, this is really something that occurs while the liver is forming. And so up at the top here on the slide, so kind of the ‘A’ Pathway the normal sort of formation of your portal triad, or the kind of main working functioning unit of the liver.

So, you have your central vein. And then the ductile plate is sort of this area out here, which forms that with the bile duct precursors, they slowly along with sort of forming these smaller veins slowly start to kind of work in concert with the smaller veins and join up with the portal vein. And then you eventually get this kind of this beautiful mature bile duct and Portal triad. With congenital hepatic fibrosis, instead, you have more of this malformation of the so basically, these, these things that started as immature bile ducts don't undergo maturation as they should, and you end up with sort of, not beautiful artwork here, but more of like what my first grader would draw with bile ducts that don't communicate very well with the venous system. And this creates kind of ongoing fibrosis in those areas.

Ryan Fisher: Yeah, and as I kind of, you know, tell people that when you when you have congenital hepatic fibrosis, it's really those processes related to those abnormal genes and the development of that liver, where the remodeling goes wrong. And you can see in the cartoon over on the right, that really the portal track and the portal vein, work together to try and create nice tubes that that go through our liver. And with the bile ducts carrying bile out in the portal vein bringing blood in. But then when you have congenital hepatic fibrosis, CHF, you'll see that there are malformations, and not just say fibrosis in the area, but also really these dilated bile duct tools that that proliferate and become problematic for kids and adults as they get older.

When you when you take a look at this under a microscope, and we can do this by getting, say a liver biopsy, you can see on the left side, that there's what we would consider a normal portal triad, so that that large space is the portal vein. And there's a bile duct up to probably on the nine o'clock side of that blue area with a hepatic artery coming in at the 12 o'clock position. And that's the way it's supposed to look, it's supposed to have that that nice triad appearance with a little bit of fibrous tissue around it, which is in blue, and then normal hepatocytes encircling that.

And you can see that really clearly on the left. And then when you head over to that right side, you can see what happens in CHF is that you get not just increased fibrosis so things that really increase that stiffness in the liver, but you can see those abnormally formed and dilated bile ducts that that occur because the remodeling didn't happen correctly. The cilia that Laurel talked about didn't, didn't work, right, we didn't, we didn't get good connections. And we have those big, dilated spaces with a lot of extra fibrosis and what ultimately leads to significant liver disease early on in ARPKD, especially. And to kind of, you know, show it off again, if we did an MRI of someone who has ARPKD or congenital hepatic fibrosis, and this is this is one of my patients over on the right but on the left, you can see what should be normal.

And I don't know if I can get a pointer to work on this. But up at the top left-hand side of that MRI is the liver, it's kind of got a nice shape to it should kind of look like a pyramid basically, or a triangle on this two-dimensional view. There's a large gallbladder that you can see filled with fluid. And then you can see actually bile ducts going up into that liver and kind of making that Y shape. Heading to the right and the left side of the liver.

That's the way it should look. Now if we take our eyes over to that right side, you're going to get what we see as an abnormally formed gallbladder which is a little tough to make out on this picture. But where the green is highlighted, that's a measurement of larger kind of dilated, common bile duct with really dilated ducts scattered throughout that liver and in that liver (plank) of mine, so if you look on this side, you'll see kind of those big fluid filled cysts.

And this happened in, I believe this patient was only two or three years old. So, you can get some really advanced disease quite quickly. This can develop more slowly over time and some kids. But again, it all goes back to those abnormal mutations. And then finally, it can just get ugly. And so, this isn't, and he doesn't like the doorbell anyway, that said, this is a good example of a liver that's got really dilated bile ducts within it. And they show what that liver looks like if you were to take it out of someone. And then there's a

picture of a CT scan, actually, same liver, on the left-hand side with those with those dilated areas throughout that liver.

And so, I think that's the you know, to us, what we see and what we know can happen and truly represents how this disease can advance in some kids and adults. I think kind of digging down, we do want to know, how does this occur? And I've got I think Laurel is going to share a little bit more about that.

Laurel Willig: Yeah, so I think I'm sort of I feel like part of the fun of me giving this talk is that I get to talk a lot about like the new kind of discovery things and things that I think are coming and how sort of some of the research that's been done in the last few years has really kind of is coming to fruition, I guess, hopefully for patients.

But defining, the what, we this is where genetics is really important and often had been historically kind of overlooked in ADPKD especially, and also to some extent in ARPKD, I think so there's lots of genes that we have identified related to polycystic liver disease, and congenital hepatic fibrosis. But as you can see on this slide here, so we can find about a 93% of the genetic reasons for why someone might have polycystic liver disease associated with ADPKD. With ARPKD, we're a little bit less likely to find the reason we're kind of at the 80 to 85% mark, but you know, it has just all the genetic testing that folks have been doing either clinically or on a research basis has led to kind of finding a new gene.

So, the D's - that one L is kind of a relatively newer gene related to ARPKD. And then in polycystic liver disease, we actually there's several mutations that have been found. But we still have a long way to go in terms of understanding the genetics of, of just purely polycystic liver disease without any associated renal disease, because at this point, we really only diagnose about 40% of people, or we can only find a genetic change and about 40% of people with polycystic liver disease, despite the fact that we know it's a genetic condition.

But like taking this a little bit further, so how does this help us other than kind of identifying the change, so that you can talk to family members about it or that kind of stuff. And as we do more genetic testing, we learn more to about how different changes in the same gene can lead to different outcomes for people.

And so, this is a relatively recent study in congenital [0:34:20], ARPKD, in terms of developing portal hypertension. And it not to go into tons of detail. It's a very busy slide. But what they basically learned was, it's not just the exact type of mutation like when if you hear truncating, or missense, or that kind of thing, but it's also where that change happens within that gene protein structure. So, what that's showing over here, kind of up at the top, it kind of says exons and amino acids. And so, the color coding on these bars, or on these survival charts on the right-hand side, are based on which amino acids were affected by that genetic change.

And so, what you can see here is that folks who have an amino genetic change that leads to an amino acid change and kind of this latter part of PKHD One have are more likely to develop portal hypertension. So that's what this curve kind of shows is as time goes on, the faster it goes down, the more likely you are to have portal hypertension by a certain age. And then that if you look down at the bottom, you'll see that there again, sort of in similar fashion, that depending on where your gene change was in this amino acid, you'd be either less likely to have any hepatic complication, or more likely to develop a hepatic complication depending on where your gene changes.

So, this can help doctors maybe like Dr. Fisher say, maybe I only need to see you once every couple years or three years, because you're in a group that you know is less likely to develop significant liver complications or maybe I need to see you a little bit more often because you're in this group that generally develops liver complications kind of at an earlier age, in time.

And so, then we take this one step further with all the genetic testing that we're doing. And this is a recent paper where they basically now can grow hepatic organoids. So, in this paper, they take stem cells from patients who

had ARPKD the most common ARPKD mutation is actually what they use in this paper, these are actually normal organoids.

So, you they grow, you know, they take the stem cells, the stem cells differentiate into a little kind of mini portal triad. And so, you they form a bile duct, they form a portal vein and artery. And they form hepatocytes. So, that's kind of what these pictures over here on the right-hand side show you is kind of similar to Dr. Fisher's normal slide that he showed you for the portal triad. Here you have it's not zoomed in quite as much. But there is your portal triads that these little mini organs are forming. Here's your hepatocytes. And these staining basically kind of show you yes, there's hepatocytes. And yes, there are these kind of portal triads that these organoids can form.

And so I'm going to let you go to the next slide. And so, then what they were able to do is, again, they took the most common genetic change in PKHD-one, in this experiment, and developed organoids, from using that or with that gene change in the cells. And as you can see, you get a lot more of that kind of disorganized appearance to the little organoids we don't form, here's the control groups with their nice kind of portal veins, and bile ducts. And here you can see, again, it looks like Dr. Fisher's picture that he showed you of the congenital hepatic fibrotic liver, again, very disorganized. And they also found that, because again, these ducts are supposed to kind of as they mature, they're supposed to be fewer of them. But instead, in this experiment, because you're left with kind of these immature bile ducts that don't kind of resorb like they're supposed to, in the affected organoids, they have a much higher fraction of duct material.

And then they can look at those and say, well, what's different about these Qalandia sites that form those portals or those bile ducts and healthy ones? And where are they different what cell populations are affected, and then that can start giving them an idea as to sort of what changes at like a signaling pathway standpoint are they seen, that might give you an idea of what pattern, you know what pathways that you could target for treatments, it would allow you if you had a drug that you were kind of using to target something, you could follow the expression levels, so all of these, this is a single cell

experiment, so they were able to a kind of shows the breakdown of the different types of cells they found in the organoids, but you can see over here and be the control versus ARPKD that there's different kinds of breakdown of cell populations.

So, there are extra cell populations and air PKD that you don't find in the control organoids also similarly, you find some control populations of cells that you don't find in the ARPKD population. And so again, you can look at like for instance this population nine and say what does what kinds of cells are these what's different about them than maybe they're kind of normal control group organoid cell and then that allows you to start kind of looking at differences and gives you an idea of at a kind of very small molecular level sort of what is different about them what is causing this disease to kind of move forward or progress.

Ryan Fisher: Yeah, and it's tough because, as you said, you know, Laurel there's an important movement that that we're now experiencing where we're getting this information and learning about these pathways, but we still really don't have a true therapy to improve the liver in these kids. And what we'll end up doing is as liver ducts, when we get to see them is that we'll focus on trying to manage and minimize some of those long-term complications as best we can.

We do this with, you know, multi-pronged approach. One is making sure that we give kids with ARPKD other forms of congenital hepatic fibrosis, immunizations, including one against hepatitis A and B. And, and really recommending the full gamut, even things like HPV, to make sure that we are doing everything we can not only to prevent liver disease, but to prevent potential cancers in the future. And things that would otherwise complicate someone who's already got enough complications to deal with, will monitor the growth of the kids that we see their development and the nutrition that they have, will want to focus on vitamin supplementation, we know that when you do have advancing liver disease, it can sometimes be tough to absorb nutrients as well.

So, you may need more calories, or you may need things like fat soluble vitamins, vitamin A and D and E and K to help you reach your potential will certainly counsel everyone and I know the doctor will, group would do this too. But we would always recommend that they that they avoid alcohol, that you avoid unhealthy lifestyle choices with highly processed or high sugar containing foods and drink that can lead to obesity. And we'll recommend that they don't use non-steroidal anti-inflammatory, like ibuprofen, because everyone thinks oh, hey, you know, and this probably isn't as big a deal for someone say that's been dealing with kidney issues anyway, because we know that that's where a lot of those get metabolized.

But sometimes people will say, well, my livers got in really rough shape, and I don't want to do anything to hurt it. So, I'm not going to use Tylenol. Well actually acetaminophen or Tylenol is okay, for use in someone with advancing fibrotic liver disease, those liver cells themselves are actually still working well. And we'd prefer that someone use that as opposed to doing something to hurt the kidneys or, make it more difficult to clot, which we know that those things like ibuprofen can do. And then finally, there's going to be some real basic stuff that we talk to our patients about, including trying to stay away from high context sports to prevent any kind of damage from occurring related to portal hypertension, where the liver gets kind of sick and makes the spleen larger, we'll talk about that in a couple minutes.

But that large spleen could potentially rupture if it gets hit really hard during high contact activity, and that can be devastating to a child. And then finally, there's some things that come along the lines when you might need an antibiotic because you do have that big, dilated bile duct sitting in there that's kind of like a hot tub for a bacteria, that maybe create an infection.

So, they may need some something you know, if they get a fever and, and have high liver numbers, and some pain over on that liver side, gosh, probably need admission for some IV antibiotics. And we can even use some other medications to try and help bile get out as easily as it can. Those things that we call kind of bio thinners or choleretic. agents like Ursa dial can be useful.

But again, nothing that can really change at this point, the fibrosis and the progression of that fibrosis that we see. And here's just a nice cartoon about what we mean when we talk about fibrosis and the portal hypertension that can develop with congenital hepatic fibrosis. And the cartoon simply shows just a really roughed up liver kind of looking lumpy and bumpy. That's what happens when it gets that fibrotic tissue in there. It kind of scars up and creates what we call cirrhosis, or that advanced fibrosis.

And you can see on that cartoon, the portal vein is marked, well, that portal veins trying to put blood into the liver. Unfortunately, when the livers really scarred and beat up, it becomes a traffic jam. And it's hard for that blood to get through there, that that blood is coming from our intestines, our stomach, or esophagus and even our spleen to get into the liver. And what happens is when that has, you know, a backup when it's a traffic jam, you'll see that those veins get larger, it's not a big deal. And for the most part, except for right around the food bite that esophagus and the top of the stomach where those veins can get large enough and the wall of those organs is thin enough that they can actually bleed.

So, sometimes, you know if one of those does bleed, you'll see a child throw up blood or have a bloody stool and that can be a pretty dramatic event. Similarly, that spleen is trying to push blood into the portal vein and into the liver and if that's backed up that spleen will get enlarged and that's what I just talked about something that could rupture potentially and be devastating for a kid as well.

Laurel Willig: Ryan, we have one question that I think is probably more that you then we can answer. Have you seen people with RPKD congenital hepatic fibrosis who have developed a focal nodular hyperplasia type of liver nodule? Is there anything known yet related to which people with CHF end up developing and FNH kind of liver nodule?

Ryan Fisher: Yeah, I don't know of, say, a scientific association between what we would call focal nodular hyperplasia, which is a really specific type of liver nodule, versus those who are getting what we would call the nodules of advanced

fibrosis or cirrhosis. We do know that about one to 2% of the population can develop a focal nodular hyperplasia, regardless of if they have disease or not complicating their liver, and we'll see them in kids without any known background of any kind of fibrotic disease.

My thought, not having done a lot of research into that particular question would be that it's certainly possible to develop focal nodular hyperplasia, when you have ARPKD, whether it's more common in that setting, I don't know that for certain, I know that I haven't necessarily seen it.

The good thing is that for the most part, if someone does develop focal nodular hyperplasia, as opposed to the nodularity, of cirrhosis, and advanced fibrosis, focal nodular, hyperplasia is fairly benign, meaning that it won't really transform into anything more. And as long as it doesn't get too big, staying underneath five or six centimeters, or really, you know, two or three inches in diameter, there's not much that you do to worry about it. And in fact, if we have one, and we see that it's relatively stable in size, we don't typically follow those up.

But I would, you know, you definitely piqued my curiosity with the question, and it's probably something that I'll just take a quick look at, in the near future here to see if there's if there's truly some kind of association. I don't think there is. And I don't know that I would worry too much about relatively small focal modular hyperplasia, we can certainly see kids get really large ones. And that becomes a little bit of a different story. And at the interim, I'm certain that we can get some time to talk more about that, too. We're only I think this is your slide.

Laurel Willig: Yeah. So, we kind of talked a little bit about what, so what causes the liver disease? But then it's sort of the next question is kind of identifying because it's not everybody who has liver disease associated with their ARPKD is sort of like saying, who, who's going to have liver failure - liver failure, or liver issues? And when might they happen, right. That's always a question for folks. And also, a question that Ryan and I have to talk a lot about, because if we have a kid who needs a kidney transplant, and the liver is not very

healthy, do we do the liver transplant, all of those questions kind of come into play.

So, 70% of people with ARPK, do have some portal hypertension, and 61%. And like a bigger study have had progression of that portal hypertension. But still 70 to 80% of patients have a functioning liver at age 50. So, it's a pretty still small group who ended up needing a liver transplant, you know, prior to age 50, there doesn't seem to be a sex difference. So, kind of male females are equally at risk for needing a liver transplant.

And it doesn't necessarily seem to be related to the type of genetic mutation when you look at, again, that's a little different than that first slide, what they're talking about here is like, do you have a mutation that would cause the protein to not form at all, or just change one little part of that protein? That's what they're talking about here. And so maybe we've been looking at this question a little bit wrong based on the other graph or the other study, and like, maybe what we need to be focusing on is where in the gene is the problem, not the type of change that is happening. And it does not seem those with bad liver failure do not necessarily have worse kidney disease, or vice versa.

So, it's not necessarily related to the how bad their kidney disease are. About 13% of folks will need a liver transplant. But you can see here the age in that study was pretty wide from nine years old to 59. So, we still have ways to go on this kind of prognostic part of things.

Ryan Fisher: Yeah, and so I think that's, you know, it becomes important, how do we predict who might progress to that more severe form of liver disease?

Laurel Willig: And so just to kind of again, in an area that's becoming a big, this, a big focus is again, because people want those quick. - We want to be able to answer those questions for patients and that's what patients want us to be able to help them with to, um, as this big push it to identify biomarkers things that we can use to predict who is going to have a problem and hopefully, sort of identify

those who are progressing faster than others so that it's not a surprise or a shock to someone if this is happening.

And again, then also will help us with that. If you need a kidney transplant, do you should we go for the liver transplant to or not sort of questions, so this is actually just an example of how research is helping us answer these questions as well. So, this is a MRE which is like an MRI with elastography so and Ryan can probably talk more about elastography in general, but basically, this MRI device has been around for over a decade, they've used it for a long time and other diseases that cause hepatic fibrosis, so not so much ARPKD and congenital hepatic fibrosis, but other diseases.

It's relatively noninvasive, the only issue is in little kids, they would need to probably be sedated. Because just like for any other MRI you kind of have to hold still, when you do it, it basically you put this little pad thing, that's what this passive driver is on the belly, you can kind of see that here on this mannequin guy. And then there's an active driver, this generates these acoustic waves that generate kind of, you know, movement in the liver. And then based on that sort of movement, or how stiff the tissue is that it's those sound waves are kind of moving through, they get this readout of the different areas that are you know, stiffer or less stiff, based on the different coloring patterns. And then that lets folks kind of tell where there might be more fibrosis or scarring, I think you can see that a little more on the next slide.

So, they did this in a very small group of folks who had ARPKD. So, you can see up here at the top, and there was a difference in they were able to tap there was a difference in the stiffness based on this. So here and see up in the top left, you see lots of purple, right and then over next to that control healthy control group, you see an ARPKD ad without portal hypertension. So again, a lot of kind of purple and blue, not a lot of red and yellow. And then down below you can see a patient who had more portal hypertension, and then up above an A and B, you can see they were able to tell a difference in stiffness between the control group and those with ARPKD overall. And then if you look you can see actually sort of a - what seems like a progression of stiffness between healthy controls those without portal hypertension, but who

probably have some kind of mild, you know, possibly mild disease that's kind of undetectable currently with what they use in clinic and then the folks who had the more severe portal hypertension had a much more stiff sort of reading on their MRE.

There haven't been any longitudinal studies where they actually follow patients, you know, this is how you look in 2022 and this is how you look in 2025, but it has some potential to pretend to maybe start telling Dr. Fisher Hey, this liver is getting more fibrotic this liver is getting more disease versus this isn't.

And then other biomarkers, this is sort of my thing. So, I'm I've been doing some cell free work and kidney disease, but this is for liver disease. This is not in congenital hepatic fibrosis, but I think it's certainly something that we can use. So, cell free DNA is something easily accessed from the blood. And in fact, we know especially that liver is actually one of the primary cell types besides blood cells where the cell free DNA comes from.

So, it's, it makes it kind of a nice potential marker for, for studying liver disease and a noninvasive way without a biopsy or that kind of thing. So they, you can take that cell free DNA from multiple different cell types. And using the methylation patterns actually say this, these, this DNA came from the liver, this DNA came from, you know, the spleen, this DNA came from white blood cells, by just looking at its methylation pattern. And then you can take that a step farther and look at the methylation patterns to sort of start predicting, maybe the disease progression.

So, what you can see in this the slide, so this was in a MPSC, which is primary sclerosing colon giantess, I think I said that, right. And so, you can see sort of that they found difference in the methylation patterns. And the amount of certain genes that are particularly involved in this disease process. So, they kind of focused on these ones, primarily, and that they could tell the difference between a healthy person and a person who had this disease. But not only that, they could tell the difference between a healthy person, a person

who had kind of early onset, like earlier disease, so not as severe yet, and late kind of fibrotic liver disease related to this condition.

And so, it may also serve as you know, we're because we already get blood work often on folks who have ARPKD and congenital hepatic fibrosis. So, it may be something in the future, again, something we can track to say like, this looks like it's getting worse, this looks like maybe it's time for some more imaging or that kind of thing, based on what we're seeing. So, I think we're going to see a lot more of these biomarkers in the future to try to help tell us when things are getting worse and will also probably let us study, again, how you respond to therapies and that kind of thing.

And then, really, the current therapies are like, are supportive. For the most part, Dr. Fisher probably is more expert at this than me, but there is steel banding, systemic shunts, you can take out parts of the liver that are merrily fret, you know, a fibrotic. If there's, if it's part you know, just partial some places, sometimes the liver is having more disease than other parts of the liver, you can take those out if they're causing a lot of problems, and then ultimately a liver transplant.

Ryan Fisher: Yeah, and that's, and that's where we really do try and help out as much as we can in the management of these kiddos is that is that we make sure that we, you know, get involved as soon as we can I love it when Laurel sends patients to us, for us to see just even if it's early in the disease course, you know, it's something where we can where we can start off by saying not only just introducing ourselves becoming part of the team, but check that exam and look for any of those clinical findings like a big spleen or maybe some prominent vessels on the wall of the abdomen that would say, you know, we looked at on paper, but I'm wondering if there's more to the story.

We can check bloodwork looking at lab studies, including platelet counts, to see how big that spleen is, the platelet count drops as the spleen gets bigger. You can check INR, which is a measure of coagulation to make sure the liver cells are doing their job and making the proteins that help us clot. You can check the bilirubin and GGT, which are enzymes that are associated with the

bile ducts. When those go up, we tend to think that there's more stress on those ducts that we need to worry about.

And certainly, we can do imaging, we tend to use ultrasound a lot, but I love what Dr. Willig mentioned about the fact that we have MR technologies, and even ultrasound technologies that can measure liver stiffness. And I feel like those need to be a part of our management of these kids. And something that we'd love to do on a regular basis when we do get to see a kid with ARPKD or CHF.

And then finally, there's some things that Dr. Willig mentioned, just prior including varices, where we can go ahead and do a scope a GI doc and versus being a liver doc. So, we can do a scope and look to see if those things are developing. We can sometimes see that, hey, things look good or that they're getting a little worse over time. And again, these are things that may not show up even on the exam or the imaging and lab work and it all becomes part of a large component of just making sure we're looking at every single aspect of the patients that we see.

This is a good example of a scope that we might do on the left. That is a normal looking esophagus. That's the way it should be nice and pink on the right. That is a esophagus that has large bear seas within it. And you can even see some signs of a little bit of bleeding there where that these varices have gotten so big that they get a little bit leaky, I don't know if this person came in for vomiting, but at this vomiting blood or having bloody stool, but this would certainly be someone who could be at risk for that.

The good thing is, when we do see that we can help, because we can take our scope and actually kind of, for lack of a better word, suck the varices into a small plastic cap and then throw a rubber band around it. And that can eliminate that varix. And while it doesn't take away portal hypertension, or the liver disease, it can eliminate some of the risks that we might associate with a bleeding episode like that.

This one is a good example of this shunt surgery; the Dr. Willig talked about where we've got a cirrhotic liver and we can see that the blood going into it is having a hard time. But you can reroute that blood. And so, you can see that this vein coming from the spleen is now going down into the renal vein. And then it goes through the system. That's a complicated procedure. But it could be something that works if the livers otherwise doing okay, and we don't think this person is, is ready for transplant or isn't a good transplant candidate.

There are some other options that can definitely be discussed with your team I've met. *[Crosstalk] [1:00:46]* thank you so much. But there are certainly good reasons for considering liver transplantation including recurrent bleeding, recurrent infections, or maybe you know, just the face of renal disease needing a transplant. And what we know is that, as Dr. Willig mentioned, when you get earlier disease, and you have more disease upfront, you get a higher likelihood of progression to transplantation.

That's something that we have to keep in mind when we see someone at a young age have a lot of liver injury, they're probably going to have a harder time holding on to that liver and not needing a transplant in the future compared to someone who may be presents later in life. But what's nice to know is that patient and liver survival following transplant is excellent and congenital hepatic fibrosis, this is old data, it's gotten even better since then, where I look at families myself and say, you know, I'm expecting 100% survival of you, and the liver that we give you, we know that there's things that affect that. But really staying above that 90% line is important to every single program and every single person that manages kids with this type of liver and kidney injury.

Laurel Willig: So then, really briefly, just what's on the horizon, and this is where the hope lies, I think we're in why we do our jobs, but from all of those cell experiments and DNA experiments, they have generated a lot of pathways that we know are disrupted in congenital hepatic fibrosis, so you can see them all here. And then there are currently treatments being developed, you know, oral or IV treatments for several that target kind of several of these

dysregulated pathways that that people are, are either trying or studying in an animal model, which are the little mice or there's been some even clinical trials in people that are either ongoing or just completed.

So, I think there's a lot of room for hope on where we have other therapies besides just waiting until you need a liver transplant for this. And then really kind of the most multi-pronged approach. I don't know, Ryan, if you can play this (video), but this is where I think we're going to end up, but this was amazing and recent work, I think in just the last year or so where they're actually able to take those little organoid types that science and implanted into bile ducts and this was done in liver transplants that maybe they were trying to repair for some reason or just studying and were able to actually grow bile ducts healthy, normal bile ducts in a diseased liver.

And I think, you know, at some point that might be what we're talking about is more cell therapy. In the unhealthy livers. It doesn't look like it's going to work maybe with sorry, it worked in my presentation, but I would encourage you I think it was in Colombia that they did this or at Columbia, but I can put it up in the chat. But basically, we can grow healthy bile ducts now with the work we've been doing, and they've done it and actually been able to do it and liver, human liver transplants. And so maybe coming for other folks as well.

Ryan Fisher: And sorry, I can't get that to pull up. I didn't I didn't practice that before the presentation. It looks like when I switched it over. It didn't work. So, my bad.

Laurel Willig: That's okay. So really, that's I think wraps up what we have to talk about, but really, this is why we do our work. Hope is the thing that with feathers that *[Unclear] [1:04:30]* sings the tune without the words and never stops at all. And I think that's really where we are with PKD both kidney and liver, and in just in medicine in general. And if we have, we have like one minute for questions or people can just, you know, and you're welcome to just instead of writing them in the chat, just say them out loud.

Krystn: Well, that was great to the hour. Thank you so much. We've put a survey in the chat. If there's no other questions. Oh, I see something coming up. Just a big thank you. And I'll offer my thanks too. Thank you so much for this informative presentation. We have a survey. There's lots more sessions to be had. And I wish everybody a good afternoon. Thank you.

Laurel Willig: Bye, everybody.

Ryan Fisher: Thank you guys.

[Audio Ends] [1:05:29]