Complications of Liver Cysts

Elise Hoover: Let's get started. So hi, everyone. My name is Elise Hoover and the hospitality host for this session, thank you so much for joining us. This session is called complications of liver cysts with Dr. Neera Dahl. If you have any questions during the presentation, please go ahead and put those in the chat, you can send them to the group or privately to me if you prefer. And at the end of the session, we'll do our best to answer what we can. I'm happy to hand it over to Dr. Dahl.

Neera Dahl: Thank you, thank all of you for joining, we're really, really delighted to be able to have this time to share with you. For those of you who saw this talk at the last meeting. This actually is a completely redone talk because there's a fair amount of new information on live versus so I'm very excited about that and to show it to let me just advance the slides. All right, says me I'm at Yale and for the purposes of this talk. I'm also a member of the scientific advisory committee for the PKD foundation. Right, and what we will talk about today is PKD, but also a disease that's very similar called ADPLD or Autosomal dominant polycystic liver disease and talk about how liver cysts form and also who's most affected by the liver cysts, and then a little bit about treatment, both surgical and medical treatment.

And then I'll sort of wrap up with an algorithm for how we as clinicians think about managing those liver cysts. So, the first thing is that liver cysts increase with age. So here, what I'm showing you is how common liver cysts are. So, in the first group, I'm showing you, women and then here and men, and you can see that by the time women are 25 to 34, about 90% have liver cysts. For men at a slightly older age 35 to 46.

About 93% of them have liver cysts. So very, very common part of ADPKD. And then what's really interesting is we're getting that if this is study data from, you know, very selected cohorts of people. What we're also able to show now is what the data is that we're getting from the PKD registry. And for those of you who participated in the PKD registry go always already be familiar with what some of those questions are. But 73% of the people in the registry reported that they had liver cysts, and about 34% reported that they

had a diagnosis of polycystic liver disease. So again, more evidence that this is a very common problem with PKD. So, the two terms sometimes get used interchangeably. But let me talk for a minute about what is polycystic liver disease.

So, a normal liver volume meaning the normal size of an adult liver is about 1.5 liters or 1500 milliliters and that gives us a height adjusted liver volume of just under a liter per meter or 940 miles per meter. Assuming that the average height is about 1.6 meters. So, liver enlargement is due to liver cysts. And most ADPKD patients have liver cysts, but about 10% have very severe polycystic liver disease, which means the height adjusted total liver volume that's greater than three liters or three-point 3200 ml. And then a small percentage of people so one in 20,000 have severe polycystic liver disease, meaning such large livers that they're having complications, and that can be due to two diseases, either autosomal dominant polycystic kidney disease or autosomal, dominant polycystic liver disease.

And the umbrella term polycystic liver disease just means anybody with cysts, and they'll differ, but the causes of that are one or the other of these two diseases. So, what are these so autosomal dominant polycystic kidney disease is primarily clinically diagnosed by how in multiple cysts in the kidneys with large kidneys bilaterally, the liver may have a few or many cysts. And we know here that kidney size or total kidney volume determines the risk of progression. And 75% of patients will develop kidney failure by the age of 62.

This disease is caused primarily by the genes PKD-1, PKD-2 or another rare one called Ghana, in contrast, is the disease autosomal dominant polycystic liver disease this presents with similarly with cystic enlarged kidneys and assisted liver, but generally it's the cystic liver problems that predominate, the kidney disease may progress only slowly or not at all. So, these folks with these genetic defects may not have much in the way of loss of kidney function. Kidney Failure is rare. And the genes that are associated here, are listed here. So, ALG-8, PRKCSH sec 63. Ganache can cause both. So, you

see listed twice, and then sec 61B. So how do these things. And then here's just a little bit about the genetics. So, for the genes that cause ADPKD, it's about 10 people in 10,000, versus the genes that cause ADP LD, it's about 20 people in 10,000.

So, these genes, the ADPLD genes are more common. And that's important when we're thinking about what of making an actual diagnosis for someone. It may be more common, but that it's rarely, it's not as clinically significant all of the time, meaning there may be people who have liver cysts, who carry one of these genetic mutations who never come to clinical attention. And I'll show you some more of that. So how did these genes work together? So, I'm showing you a simplified diagram of what happens inside a cell. So, inside this cell, this is the nucleus that has the DNA, the coding information, and this is the place where all of the protein assembly and packaging happens. So, piece of RNA moves to this part of the cell to the endoplasmic reticulum, and then it's interacted on by all of these different proteins that cause ADPLD.

And these are like finishing proteins, if you want to think about it that way. They're adding sugar residues, they're sort of making sure that the protein is folding in an appropriate way. They're doing sort of those final quality checks. So, the protein that's important here is polycystin-1, which is encoded by the gene, PKD-1. And all of these other proteins, the PLD genes are making proteins that help that protein get appropriately packaged. And so, you can see here that the end result is to get these proteins polycystin, one and polycystin. Two, hooked up together and in the right place. And if that doesn't happen, then they're cysts that form either in the liver or in the kidneys. This is another way of looking at some of the things that cause liver cysts to form.

So, if you look here, there's this idea called ductal plate malformation. And here what's happening as the bile ducts where the cysts come from in the liver are forming. What happens is, is generally what happens is the cells start to form that cause the bile ducts to form these Qalandia sites, which are the bile

duct cells grow and form a normal bile duct. And what's happening in these polycystic livers is that there's impaired maturation, the differentiation for those Kalanchoe sites to form in the first place doesn't happen well, and then that leads to these very abnormal and sometimes unconnected, bits of bile duct. The other idea is that if you have a normal bile duct that has one gene that is disease causing, there has to be a second hit in that gene to knock out the gene both copies of that gene.

And when that second hit happens, that's when cyst formation starts. So, this idea of second hit is important both in kidney and liver cysts, but here showing you the pictures in the bile duct. That when that happens, there's abnormal growth of those bile duct cells, and then this form. And all of these different mechanisms then lead to polycystic liver disease. And then this is just showing you graphically what I mean by that. So, this is someone this is now what you're seeing is the liver here. These are the In the Green is the biliary system, the system that makes bile acid. And what you can see is someone with mild disease may have a few cysts. And then as those cysts grow, this is someone with more advanced disease. And then this is someone with severe polycystic liver disease.

And here, this is just showing you by imaging that you can't really tell some by imaging, always what the patient has. So, this is someone who has isolated polycystic liver disease from a mutation called PRKCSH. And the image I'm showing you this is the liver here. And all of the darker spots in here are liver cysts. So, all of these things in here are cysts within the liver. But you can see here is the kidney and the kidney looks really good. There are not very many cysts in that kidney at all. So, that is telling you that this is more likely to be in a disease that causes ADPLD, versus here you can see someone who has PKD autosomal, dominant PKD. And they have multiple liver cysts with a very, very enlarged liver. And if we saw their kidneys, you can see there's one kidney cyst here.

And we would expect to see more kidney cysts as well. So, knowing that liver cysts can be due either to ADPKD or to ADPLD, we then tend to treat

the patients who have liver cysts in the same way. So, one thing that's very important, if you have liver cysts to know to know is that the tests that we use to measure liver function called the LFTs, or liver function tests can be abnormal. And this is just looking at baseline values of people who had liver cysts and what those liver function tests look like. And what's important to know is that some of the common liver function tests so bilirubin, alkaline phosphatase, or GGT, may be elevated at baseline. And some of the cancer markers that are associated with the liver or maybe elevated at baseline as well.

So, CA 19 nine may be elevated and up to 45% of patients without proof of malignancy. But the important thing is, and PLD liver synthetic function remains intact. So, even though you might have mild liver function abnormalities, the work of the liver that sort of cleaning the blood detoxifying everything that still remains intact. And there can be minor abnormalities and other liver function tests and AST, ALT. And then in an enzyme made by the pancreas called amylase. And this is some of the new data now in in looking at liver cysts and thinking about liver cysts. So, a very big study that came out recently saying, well can we start to quantify and look at how quickly liver cysts grow.

So, this is a baseline study with 245 patients who had liver cysts out of this larger group of about 700 patients, and what you can see is that liver cyst volume, so the volume of the cyst growth is about 20% per year. And then if you look at liver volume growth, that's about 2% per year. And who are those people that are getting these increases in liver cysts. So, what we know is that there's a higher baseline liver cysts volume in women, and that that liver cyst growth rate changes in women after menopause. So, this seems this is the first hint that liver cysts growth may be responsible that estrogen may help cause liver cyst growth. But otherwise, you can see that there's a higher rate of growth in men compared to women.

So, what are those things that actually did not really seem to impact liver cyst growth? So, BMI did not genotype whether they were PKD-1 or PKD-2 did

not and then baseline total kidney volume did not so these All these things which are very, very important for kidney volume measurements are not important for liver volume, the liver volume seems to be responsive to other things, including maybe to estrogen. And what they did, and this will look very familiar to those of you already used to thinking about kidney cysts volume, this is looking now at liver cyst volume. So, saying that, based on the liver cyst volume and the rate of growth of those liver cysts, we can now start to identify people who are at very high risk of liver cysts growth versus those people who are at lower risk of liver cyst growth based on what their curves have been over time.

And now this is a different study an older study, and this is looking at what are the differences in those patients who have mild polycystic liver disease versus those patients who have severe polycystic liver disease. And the patients with the more severe polycystic liver disease were older. So, here 42 versus 35, they had more loss of kidney function. So, the GFR or the glomerular filtration rate in those with mild disease is 95. In those with the severe disease IS 84. They had similar size kidneys, but had larger spleens and importantly, they had only minimal reported worsening of quality of life, which is which is critical. So older, more likely to be women with some loss of kidney function where those who had the more severe disease. So, this the next few slides are going to talk about estrogen and the role of estrogen in in the liver cysts.

So, this is a very small study from 1997. And they looked at women who had severe polycystic liver disease. And eight women were controlled women, eight leadman, women got treated with Premarin at the time most women got treated with hormonal therapy after menopause. So, this wasn't unusual treatment. But what was unusual is that the kidney and liver volumes got measured after one year of treatment. And what you can see is after one year, there's a clear increase in liver cyst volume and in total liver volume in those women who got hormonal therapy. So based on this study, the literature and we all started to say that young women with PKD should avoid estrogen

containing birth control to minimize the risk of liver complications later in life. But this study was in 1997.

And clearly a lot of time has passed since then. So, I want to show you some of the more recent data after that. So, this is looking from the halt PKD study. And this is looking at height adjusted liver volume. And then looking at the percentage with liver cysts or their size of livers, either for patients who were never pregnant and never used oral contraceptives, or used oral contraceptives, or then had had pregnancy. And then here you can see it's one versus two pregnancies. And what's important here, oops, I'm sorry, is that there was no difference in the height adjusted liver volume with oral contraceptive use. Women who had had pregnancy had larger kidneys, but that was due to them being older and so when they adjusted for age, that difference went away.

And since then, there have been multiple publications that so no association between the use of estrogen containing contraceptives and total liver volume or total liver cyst volume. However, when they this is now another study that came out in 2018. And what they found was for each year of oral contraceptive exposure, there was about a 1.5% increase. Risk of have a higher total liver volume. And that again, here pregnancy is not associated with a change in liver volume. So, based on this, my practice is to make this a patient centered discussion. Clearly if I'm talking to a young woman that's in that category, I have a very severe liver disease, that's about 10% of patients, then all of us would counsel not to give estrogen containing therapy, but somebody else who has very mild disease, it may be appropriate for them to have some estrogen-based therapy, one sided conversation and sort of the risks and benefits are understood.

And this is a study that is just getting started. So, it's called against PLD. And the idea here is that if estrogen permits liver cyst growth can blocking the sex hormone production b be used as therapy. So, this is a study in which 36 pre-menopausal patients with very large liver volumes are being recruited. And they're giving Luke Perylene which is some of you may know is Lupron

which is used for treating prostate cancer. And what it does is it blocks the hormones that then lead to estrogen and progesterone release. And with the idea of, of seeing if you get this will that slow down liver cyst growth in these young women who may have an estrogen related growth in in this, and then they're doing some safety data here, some bone scans and some patient questionnaires as part of this study.

So, the next few slides are going to now talk about therapy. Here I'm showing you a picture of one of my patients. This is an MRI. So, this is a section where you're looking, her kidney is here, and her liver is here. So, she has a very, very large cystic liver, and also has large cystic kidneys. And here, this picture that I'm showing you, which is the cross-sectional picture, is just the picture showing you all of her liver cysts. So, she has a large total kidney volume, but also a very, very large total liver volume of almost nine liters. And she has some Renal Insufficiency her create mean that the time that I took this picture is 1.8. And you can tell she's very thin, there's almost no fat there between where the cysts are and where the outside is.

And you can feel her cysts very easily in the upper part of her abdomen. And she asks about, about therapy about treatment. So, this is to show you that the symptom burden changes with liver cysts as the liver cysts get more severe. So, in the blue are patients with mild liver disease, and in the green are those patients with severe liver disease. And as the liver cysts increase, patients are complaining of fullness of dissatisfaction with the abdomen of tiredness of limited mobility, of pain and pressure under the ribcage of something we call early satiety, which just means you feel full after a little bit of food but not having eaten the full amount of food that you ordinarily would. And then when they looked at, at physical components, scores of wellbeing or mental component scores with the severe PLD there was a clear decrease in those physical components scores, but not in the in the mental component scores.

And just more so the complications people can think of as the liver cysts are getting bigger and bigger. And so, this cartoon diagram at the bottom is just showing you here the lighter tan is a liver cyst. And then here are there are

more liver cysts here in this part of the liver. Here, more cysts here and then this liver is completely taken up with cysts. So, people notice back pain, flank pain, abdominal fullness, anorexia, loss of appetite, palpable masses. A lot of these things can be very common. And then then looking back at the PKD registry again, what are we seeing there? So about 78% of patients reported seeing a nephrologist to manage their liver cysts and I am a nephrologist. I see a lot of patients regarding their liver cysts. Only about 8% see a liver specialist.

As what people report so 27% said they report feeling full after eating 30% said pain or pressure near the rib cage, feeling bloated having abdominal pain having limited mobility, meaning difficulty reaching down or bending over and 14 said 14% said they were short of breath. About 43 had been told that their liver was larger than average. And about 58% had a history of family history of versus so what are the complications of liver cysts. As with any cysts, we worry about cyst haemorrhage, so bleeding into a cyst, the cyst can rupture or it can get infected. And then again, looking at the registry, about 6% reported a liver cyst infection 10% reported a liver cyst rupture and 9% had a liver cyst drained.

So, this is an image this is something called a PET-CT scan, where they do this CT scan and then they give a certain kind of tracer that lights up in metabolically active areas. So, in that looks like this orange color here so you can see the spleen is lit up because the spleen is metabolically active with all of the white cells there. And then here you can see in this part of the liver that looks like there's orange Halo surrounding assist that orange yellow is all the inflammation from the infection in that cyst. So, liver cyst infections are rare, but they can be life threatening. So, anything, so fever or really severe abdominal pain might be an indication of a liver cyst infection. And this is really to teach the other providers that when you're treating a liver cyst infection or any cyst infection, you need to use an antibiotic that penetrates into the cyst cavity.

Pain is also very common because of those liver cysts. So, what do we do for pain? So, I think the first question with pain, is it related to PKD? Is it not? Are there non pharmacologic ways of treating it? So, behavioural modification, physical therapy? And then what are those pharmacologic ways of treating it? And then we start to talk about minimally invasive therapies. Here for liver related pain, they talk about splink Knee nerve block, which is blocking the nerve so that you're not aware of the sensation of pain. And then other invasive therapies would be cyst fenestration or even removing part of the cysts of the liver. And I'll show you what that looks like in a minute. So, this is just showing you where those different nerve roots are, that either are part of the celiac Plexus, or are part of what gets blocked for renal nerve studies.

And so, this is a potential area of therapy of giving up doing nerve blocks to help manage pain. This is the other potential therapy. So here I'm showing you a picture of the Lipper with the cysts in this tan color. And so, you can put a needle in the radiologists will do this and pull-out fluid that's called cyst aspiration. And then sometimes they'll put in foam or alcohol or something else that causes the tissue to then sclerosis or scar down around the cyst. So, the cyst doesn't reform. So, this is aspiration and sclerosis. Then there can be fenestration which just means to make little holes in this so the cysts can sort of drain out into the abdomen. So, that's what this is showing you here. They're just cutting open assist and letting a drain into the surrounding belly.

So, how well do this work? Unfortunately, they're not 100%. So, after someone gets cyst aspiration with sclerosis, there's regression of this, this and about 22% and total regression and 22% and partial regression in 19%. So somewhere in the order of 40% of patients are getting some relief. But that means that 60% of patients are not about half or not. The cysts recurred in about 20% of patients. The symptoms improved in the majority of patients so that's the good news and continuing regression so it may take up to six months for complete improvement following that procedure. And I've had patients where we'll look and see if they have some dominant says we'll do some aspiration.

And sclerosis and then a year or two later they may come back because now the there's something bothering them again and we'll go through that procedure again. Where the cyst is determines the best kind of surgical therapy. So, if you have this picture where you have one large cyst here, then that would be appropriate for cyst aspiration or sclerosis. Here you can see one lobe of the liver is really affected, whereas the other one looks very normal. And, and so that might be an appropriate candidate for taking out that cystic part of the liver. And here, this is a picture that looks more like the picture of my patients that I showed you, where the entire liver is, is taken over by cystic disease. And this is someone that might then go to liver transplant.

And just to remind you, this is the rare patient with severe disease that's going to go to liver transplant. They're excellent long-term survival following either partial hepatectomy, meaning taking part of the liver out or with Spanish fenestration. So, really we're looking at survival up to 2530 years, that looks very good. And then you may have heard that there are exception points for people who have very large livers who are trying to get a liver transplant.

And these guidelines were updated, sorry, in 2021. So, it had to be previously it was having the very, very large cystic liver plus being on dialysis. And now that's changed. So, if your GFR is less than 20, you can get the meld exception points, or if you have evidence of liver failure, or you're on dialysis, so very big Lipper plus evidence of some significant kidney disease, and you can qualify for these meld exception points. Because livers and otherwise, the points for who gets the liver transplant is based on how much liver failure there is. And in PKD, there isn't liver failure per se. But there's just a space occupying problem from having a very large liver. And so, this is to try and level the playing field a bit so that patients with PKD or PLD also still qualify in a reasonable way for liver transplants. That's what these meld exception points are.

So, what are the outcomes after liver transplant. So, this is from another recent study 51 and patients who underwent liver transplant, either with

polycystic liver disease or with ADPKD. In their 50s and 60s, they followed these patients for about six years. And the survival was actually excellent, which is really, really encouraging. So, this is a huge surgery. But people do well. And that's good. What about medical treatment for patients with large stick flippers and so here I'm I will show you what the medication is in a minute, but this is someone on treatment. And you can see this cyst got better over time and still looks pretty good over time here. And but not everyone has a robust response.

So, if you look at this patient down here, patient three, you can see that this person throughout the course of the treatment, although they have a response, it's a little bit soft right there, they're still ending up with a liver volume that's over seven liters. The response to this therapy is highly variable. This is with octreotide or an octreotide analog. And the side effects include loose stools, increased blood sugars and an increased risk of gallbladder disease. So, Octreotide and Somatostatin these are the different names for the same drug. Somatostatin is a is a GI hormone, and Octreotide is just the name for that hormone, medical name for that hormone. And so, they pulled the data from all of these different studies with somatic statin or octreotide to come up with a sense of who are really those people who benefit from the medical therapy.

And what they found was that the therapy was most effective in young women under the age of 48. So, the pre-menopausal women, one of the liver function tests alkaline phosphatase may predict who responds and who doesn't. And some studies suggested that although deliberate growth resumes, there may be a lasting benefit after you stop the medication. So, it may still be worth trying. And I think that, the idea here is to if someone is very much bothered by the liver says to try the therapy for six months, and if there's no improvement after that, to stop treatment.

Elise Hoover: After all, we all are at 10 minutes.

Neera Dahl: Okay. And I'm nearly done. So, this is a slide showing that for people who have had kidney transplant, there's a drug that is not used as commonly anymore but had been used fairly commonly before. So, Rolla, Miss that

seems to have some benefit in in reducing polycystic liver volume after transplant. And so, for this patient, the treatment would be at the beginning to talk to her about estrogen use to consider conservative therapy to consider aspiration and sclera therapy, or laparoscopic fenestration or liver transplantation. And then if she's not a candidate for liver transplantation, then to consider the somatic statin or octreotide analogs. And my final slide is just to show you that there's always work in progress. So, this is work showing you all of the different areas that people are looking at for potential therapy.

So, hopefully a lot more to come. And I'm going to, to just show you a couple of studies that are ongoing now. So, this is a study by Whitney, Bessie, who's at Yale with me, and she's looking at for genes that cause liver cysts. And so, if you have liver cysts are interested in this study, then she would love to hear from you. And one more study for people associated with Yale, this is now looking for another kind of PKD complication called us cerebral aneurysm. So, if you have a cerebral aneurysm, and are interested in participating, please reach out to us as well. And then finally, I'm wearing my PKD foundation hat and saying, if you haven't looked at it already, then please take a look at the PKD registry, because we would love to hear from you within that registry. And this is how to contact me. It's neera.dahl@yale.edu. And then with that, I'm open for questions, if anyone has questions.

Elise Hoover: Fantastic. Thank you. Dr. Dahl. Yes, I do have a couple already. So, let's start with is there any relationship between polycystic liver disease and gallbladders risk of gallbladder disease?

Neera Dahl: So, that's a really interesting question. So, I didn't point it out. But the gallbladder is part of the biliary system. So, the gallbladder is where bile acids get stored. And so, you can imagine that there isn't a direct connection in that system form in the gallbladder. But you can imagine if you have a very cystic liver, that that might be putting pressure on the gallbladder or impairing the full emptying of the gallbladder. So, I would say it's not a direct relationship, but there could be a relationship there.

Elise Hoover: And what about the kind of contraception would you recommend to someone who has PLD? You mentioned that estrogen can increase risk factors. There's a specific question about Estradiol as well, you could comment on that?

Neera Dahl: So, in general, we recommend low estrogen. So, there are some progesterone only contraceptives or very, very low estrogen contraceptives, that we would that we tend to favor. I had a patient who was in, and I said to her, what about a diaphragm? Like you could think about that, and she looked at me like I had lost my mind. Like, that was such old-fashioned therapy that people didn't think about that anymore. But I think any of the non-hormonal therapies or non-estrogen containing progesterone therapies would be very, make it stop.

Elise Hoover: I'm going to just do a quick mute.

Neera Dahl: Okay.

Elise Hoover: And then I had to unmute Neera. Go ahead and unmute yourself.

Neera Dahl There we go.

Elise Hoover: No, I muted everyone's I couldn't figure it out.

Neera Dahl: Okay.

Elise Hoover: So, another question is, could you speak To any nutritional therapies or recommendations that you give your patients for, what might be beneficial for PLD?

Neera Dahl: So, this is a, I think an area that's very, very important. We're learning for kidney cysts, that diet matters a lot, right? So, for kidney cysts, we're saying, be careful of a high salt diet, eat a high potassium, sort of high fruit and vegetable diet if your kidney function is normal. And, and be careful of very high sugar because we think that sis preferentially use glucose as a fuel source. And so, we know that if sugar levels are too high, that might potentially lead to an increase in cyst growth. So that's the kind of dietary

information we're talking about already for PKD. We don't have that same richness of data for what is the right diet for, for liver cysts in particular.

But I think a lot of those things that we think are important for kidney cysts are probably very good. I know some of my patients who have early satiety or get full early there, the key for them seems to be eating more frequent meals, but smaller meals. And that seems to help with some of the symptoms, as well. So, I would say, to follow what we say for the PKD diet, but then sort of to modify it in a way that seems to be comfortable with having the liver cysts tissues.

Elise Hoover: We have a few questions here also about the pancreas. Do you have any comments on pancreatic cysts, or perhaps a woman had happened to the pancreas that the liver is enlarged and pressing on the organ?

Neera Dahl: So, I did not mention it at all. But having pancreatic cysts is actually part of PKD. And it's not uncommon for people to have pancreatic cysts as part of PKD. It can, it can be a little bit complicated because when the imaging comes back that shows the pancreatic cysts, there's a kind of an early precursor to cancer that can also look like a cyst in the pancreas. So, sometimes people with PKD will be asked to get follow up scans because they want to be very carefully looking at these pancreatic cysts in terms of so the pancreas has a big role in in secreting fluid and bicarb and things like that into the digestive tract. And that is usually completely intact in patients with PKD. But I can imagine that there could be cases where there's a cyst in in the pancreas, that's impairing some of the pancreatic duct flow.

I haven't seen a case like that. But I can imagine that that that some people might have complications with that.

Elise Hoover: Is there anything specific that post kidney transplant patients should know? We have a question about tacrolimus or any other medications that might influence fealty?

Neera Dahl: So, the only post-transplant medication that we know of is this Sirolimus Rapamycin, which seems to improve PLD seems to decrease liver cysts growth to (crollames) and the other medications don't seem to really changed liver cysts growth. We know that liver cyst growth continues after transplant. So, it's we've had patients where the kidneys working perfectly but there are complications related to that enlarging liver, but luckily that that turns out to be the minority of patients, and the same things that are available pre transplant. So, fenestration aspiration hepatectomy, all of those things can happen after transplant as well.

Elise Hoover: Great. And if there were one or two questions that you would urge patients to ask their doctor, if they know they have liver cysts, what would those be?

Neera Dahl: I would say, don't just think that this is normal, that you have to have a certain amount of abdominal pain, or you have to kind of just manage that. I would say, if you're uncomfortable, have a conversation about that and see if there's something that can be done about that. For those patients who have a predominance of liver cysts but don't have a lot of cysts in the kidneys.

That could be that other disease ADPLD and so I would ask for genetic testing. If you're not sure if the diagnosis I think that's a reasonable thing. to ask now we have pretty good access to genetic testing. And a lot of those things can be sorted out. So that might be helpful. But, you know, I would say there are therapies, the places where they offer therapies are in relatively specialized medical centers. But if you think that that's what you need, you know, to really ask and see if that's available for you.

Elise Hoover: Great. Well, thank you, Dr. Dahl. This has been great. I know that we didn't get to all the questions, so forgive us. If we didn't answer your question, please go ahead and message me on the platform, Elise Hoover and with the PKD Foundation, we'd be happy to get you some resources or some answers to that and enjoy the rest of the conference. Thanks, everyone.

Neera Dahl: Thank you.

Elise Hoover: Bye-bye.

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