**Understanding PLD**

Alright, it looks like it's time.

Hi everyone.

Welcome to the session.

Thanks for joining us.

My name is Elise Hoover.

I'm a Hospitality host. For this session, you have joined us for Understanding Polycystic Liver Disease. Before we get started, if you have any questions during the presentation, please go ahead and put those in the chat box and we'll try to get through as many as we can in the Q&A after the lecture. I also ask that you please keep your microphone muted, so we make sure we have good quality audio.

I'm very pleased to introduce our speaker for this session, Dr. Neera Dahl. Dr Dahl is a clinician educator, and an associate professor at the Yale University School of Medicine section of nephrology. Dr. Dahl is also a member of the Scientific Advisory Committee for the PKD Foundation. Dr. Dahl, it’s my pleasure turn it over to you.

Thank you very much.

I'm just going to pull up my slides.

Okay.

Are the slides visible, Elise. Are you seeing them all?

Yes, I can.

Okay.

All right.

It’s really my pleasure to be here today, and what I will spend some time talking about is complications of liver cysts and really kind of pointing out some of the newer therapies that are available for liver cysts and how we think about some of those, managing some of the issues that occur with liver cysts. And I'll go ahead and get started.

So this is a cartoon presentation of ,or representation of a liver, the liver is in the brown. And then, what's in the green are are all the bile ducts, or we call this the biliary tree.

And this is how bile is being created and then moves down into the intestine.

This is the gallbladder here for fat absorption in the intestine. And what's happening during development is that this tree is forming sort of like the buds on a tree form, and then as each branch occurs there's more and more of the, the tree forming. And what we think happens is that some of these little branches break off and then they can be dormant, and then over time, with the right kind of signals, grow into a cyst. So what you see happening in the top picture is a little biliary, a remnant of the biliary tree than, becoming this cyst that forms.

And we know with polycystic kidney disease, that there can be cysts in the kidneys, but also there can be cysts in the liver. So what I'm going to talk about today is the difference between polycystic kidney disease and polycystic liver disease. Who gets liver cysts and what that means in terms of treatment and what information we give patients. What the surgical treatment is. What the medical treatment is. And then putting it all together as a kind of stepwise approach to managing the liver cysts.

So there are two diseases that can look very similar to each other, in that they both cause liver and kidney cysts.

The first disease is the more common one.

Autosomal Dominant Polycystic, Kidney Disease. And this causes bilaterally large kidneys with numerous cysts in each kidney, the liver, may have a few or many cysts and the kidney size, or total kidney volume, determines the risk of progression in terms of loss of kidney function.

And what's important in PKD to remember, is even though there are liver cysts and the liver can get bigger, you never lose Lipper synthetic function. The work that the liver has to do, making clotting factors, making albumin, all of that, stays intact. PKD is unique in that 75% of patients will develop kidney failure by the age of 62. And PKD is caused primarily by a mutation in either the PKD one or the PKD two gene. And that is a, although the disease's look similar, it's distinct from a disease we call Autosomal Dominant Polycystic Liver Disease.

In this, there can be cysts in both the kidneys and in the liver. The key difference here is this, which is the kidney disease, may progress only slowly or it may not progress at all and that kidney failure is rare. And that the genes that cause this are genes that cause defects primarily in protein trafficking, and I'll show you what that means in a minute.

But this is something actually that we're starting to recognize more and more, that there may be some people who never have very fast progression of their kidney disease and it's because they don't actually have a defect in PKD 1 or PKD 2.

So, showing you a little bit more about what these can look like.

So I told you sometimes it's a little bit hard to tell them apart.

So this is someone who has polycystic liver disease with one of those mutations that cause causes ADPLDD and you can see the liver here.

So this is a cross section and this is a liver and these darker regions are the cysts within the liver. The liver here looks like what you might see in PKD with a lot of cysts in the liver. The kidney here, looks pretty normal. And here, they're just showing you across a different kind of cross-sectional view, so you can see the liver here, and all of the cysts in the liver. And then they're comparing that to this patient who has polycystic kidney disease and what you see again, so here's the liver and the dark regions are the cysts in the liver, and this person has a very large liver and multiple cysts.

And from this picture, what you see primarily are the diffusely enlarged liver cysts. We're not seeing any kidney slices here.

And so you couldn't necessarily tell but just by looking at the images who has polycystic liver disease and who has PKD with liver cysts, and that's important in thinking about the disease. And here, this is just showing that both of these cause cysts that form in the medium sized bile duct. So they form sort of in this area of the live. The very small size, bile ducts are here. The larger ones are here, and then over time these liver cysts expand and can often quite caused the liver to be very large.

So this is mild disease, Advanced disease, and then more severe disease. And the genes that cause PLD are really genes that are involved in the protein being formed and then getting to the part of the cell that's important. So what this is showing you is a part of the organelle inside the cell, called the endoplasmic reticulum and the proteins that cause PLD are genes that are primarily found in the endoplasmic reticulum. And they're important in making sure the protein structure is assembled correctly as that protein moves out of the endoplasmic reticulum and then, to the cell surface.

And the Protein that's primarily affected is a protein that will sound familiar.

This is poly system one which is the gene product of PKD 1. And so the reason these other genes cause a disease that looks like PKD is because the protein that is being effected by these diseases is Polycystin 1 one. So we think of all of these conditions being recessive at the cellular level. Meaning, your born with one defective copy of the gene, but in that cell, there has to be another hit that occurs for that disease process to start.

And that this protein Polycystin 1 is the gatekeeper. So the reason they're so much similarity and overlap between PLD and PKD is because of the effect on Polycystin 1. And then having an imbalance of Polycystin 1 leads to an imbalance in calcium versus cyclic A and P mediated signaling.

And that seems to be important for cyst formation.

So that's how the two diseases, which look similar to each other, but are from very different genes connect to each other.

And just to show you, again, these are the genes that can affect Polycystin 1 expression, but cause this disease we call polycystic liver disease.

So what we've learned from genetic studies is that we thought that these PLD disease states were fairly rare and that turns out not to be the case.

So this is a study looking at very, very large databases.

One is called Nomad and one is called Bravo. And these databases contain sequencing information on, in this case, over a hundred thousand patients. In this case, 78 thousand patients.

So lots and lots of individuals and these are individuals not with disease necessarily but all individuals that have been put into this database.

And what you see is that the PKD genes are about one in a thousand which is what we've always said that this is a very common gene PKD that has a distribution of about one in a thousand in the population. The surprise finding was that for PLD the distribution is about one in 500.

So these PLD genes are actually more common than the PKD genes.

And that I think matters when we're looking at people who may have a typical or mild disease and really trying to understand what their prognosis is going to be or what their disease is.

And then to put that new information in perspective in Olmsted County, which is in Minnesota. So this is a study done by the Mayo Clinic, they said okay well we get it. These genes are common, but it turns out that severe disease that leads to diagnosis and referral and a clinical phenotype, a patient label is relatively uncommon with the severe disease being one in 10,000 in Olmsted County.

So the genes are fairly common, but severe disease is fairly uncommon.

And this is something that we are interested in at Yale.

So there's a young researcher who's very, very interested in looking at the differences between PLD and PKD. And this is something if you are interested in later we can talk about, but just trying to sort out what that genetic difference is.

So for the rest of the talk, what I will talk about is PKD and this is Autosomal Dominant Polycystic Kidney Disease and talking about the disease that's primarily caused by either a defect in PKD one or PKD two and then talking about the liver cysts that can arise from those diseases and how we manage them.

So the first thing to know is that liver cysts are very common in PKD.

So this is looking at women, this is looking at men at different age groups. So as women get older so -from 15-24, from 25-34 to 35-46 by the time women are in their young adult years, about 91% of PKD women will have liver cysts. And for men, it's a little bit later.

By this age group 35-46, 93% of men will have liver cysts.

And what's clear from seeing patients, is that the two don't necessarily correlate.

So here in these images the cysts are the bright white balls. So this is a cyst, this is a cyst. This is a cyst, and these are our coronal images and what you can see here is the liver is here, and the kidney is here, and this person has only a few cysts in the liver, a few cysts in the kidney.

This person has very severe kidney cysts.

This person has a lot of liver cysts here but not very many kidney cysts. And this person has diffuse disease with both a lot of liver and kidney cysts. And in this, this is from the crisp cohort, there was no correlation between liver cysts volume and total kidney volume.

And this is another study, this is from the Halt PKD study and what they looked at here was they looked at the size of livers from people who are donating a liver.

So that liver size is about one point seven liters and they looked at the age and height of a person in the Halt study and they would have this size slipper but what they found was that the livers were actually larger and the growth in the liver is due to liver cysts.

So that was true for the men and for the women that the livers were larger than predicted in this study of early disease in PKD.

And then they further broke up the patients and they looked at patients with mild disease meaning a liver that's not very enlarged versus severe disease.

Meaning a liver that's quite a bit enlarged and what they found in terms of who has the mild disease versus who has the severe disease is that those with severe polycystic livers were likely to be older, they were likely to be women. They were likely to have more loss of kidney function, but with similar sized kidneys, but larger spleens and the good news is this is that there was minimally reported worsening of quality of life.

So, even though the livers were bigger, most people were tolerating that organomegaly, that large liver.

And this is something that is important to understand in PKD. So I told you the liver synthetic function, the job the liver does stays normal, even though the liver is getting cystic and getting bigger. And what is also true is that sometimes there can be mild abnormalities or mild changes from the normal for liver function tests. SO this is looking at the base line characteristics of 153 patients that participated in various tests where they looked at various aspects of liver cysts in PKD. And what they found was that some liver function tests may be elevated at baseline. So, Bilirubin, Alkaline Phosphatase, or GGT. And that’s important because sometimes we worry that if we see elevation in this, that means that means there's a gallstone that may be obstructing or something else that may be causing a biliary pathology and it may actually just be a normal part of PKD.

So that’s an important thing for you to know, or your doctor to know. And then there are some other markers that are a little unique in PKD. So one of the cancer markers may be elevated with out there being cancer present. And that the liver synthetic function, we talked about that, remains in tact. And there may be minor abnormalities in AST and ALT and in pancreatic enzyme called amylase.

Okay, and so the first set of data I showed you was from Crisp.

This is data from the Halt study and what they found was that having a PKD 1 gene or being female was associated with having larger liver volumes, meaning more liver cysts. And liver volume weakly associated with kidney volume in women, but not in men.

So looking at this again, it seems like maybe there's a weak association for women, but not for men, with liver cysts and with kidney volumes.

And something that if you have PKD that you may have heard, or you may have thought about is well, if this is a disease that is more prevalent in women, more women have liver cysts than, maybe it's mediated by estrogen.

And so this is a study that was done now, quite a long time ago in 1997, where they had eight women, who did not receive postmenopausal estrogen and 11 women who received Premarin, which is the standard postmenopausal hormonal therapy that’s used.

And then they looked at their kidney and liver volumes after one year. And what they saw was that there was an increase in liver volume and liver cysts volume for those women who had gotten estrogen.

And so based on this, we said maybe any exogenous, meaning prescribed estrogen, exposure is bad and so we said, hey, to young women like avoid estrogen-containing birth control pills or use them as

sparingly as possible. And avoid, to older women, avoid hormone replacement therapy.

And the newer data.

So this is now looking from the same Halt data from 2015 is that when they compared liver cysts for people who were never pregnant versus having a history of oral contraception, what they found was that there was no difference in height adjusted liver volume by oral contraceptive use. Women with pregnancy had larger livers, but this was not significant when adjusted for age.

So, the take-home message, which is this very strict prohibition against using estrogen either in the postmenopausal state or oral contraceptive therapy I think we’re walking that back a little bit.

I think it makes sense to still be cautious about exoginist estrogen use, but again, it's an individual risk-benefit analysis. So, another thing to be mindful of if you are thinking about the liver cysts and sort of thinking about what they're going to do in the future is that the normal history of the liver, is that it gets smaller with time.

So over time, the liver, which can start out being about two liters declines to about 1 liter, so over time, there's some loss of liver size and you can see that here the younger women have the bigger liver volumes compared to the women who are older. And this decline in liver cysts correlates around the time that women hitting menopause, right?

So the growth of liver cysts declines in women with ADPKD after the age of 48 and that difference was not seen in men.

And then this is just to give you some guide marks. A normal liver is about 1.5 liters severely.

Enlarged liver is over four literes.

And this now I'm going to move towards the treatment part of this talk.

So this is a patient of mine and now the sister and the white that is a kidney, that's a kidney. And then this is an image of her liver.

So you can see that most of her liver has been replaced with cysts and that her kidneys are also quite large and cystic. Here it looks like this side is smaller because of the way that kidney lies in the body, but it's not smaller.

Her total kidney volume is about 3 liters.

So she is large kidneys, and her liver volume, I told you a normal liver volume was about. 1.5 hers is almost nine liters and at the time of this image or creatinine was about 1.8.

And so, you know, she's very thin.

You can tell that she's very thin because there's almost no fat here between the organs and the outside and she is she's asking what she can do, right?

What is available to her in terms of treatment. And one thing that is that we know to be true is when we ask patients with the mild liver disease versus the moderate, or severe liver disease about their symptoms.

What you can see is that even folks with the mild disease, were complaining about tiredness or fear or anxiety.

But as the liver got bigger, there was much more reporting of symptoms. So, fullness, dissatisfaction with the abdomen, some limited mobility, some shortness of breath. I think that the biggest thing that people will say is that it’s harder to bend over to tie your shoes, that kind of thing.

Some nausea, some early satiety, which means feeling full before you've eaten completely and this then they looked at physical component scores. Meaning how did people report their physical functioning and mental component scores.

How did they feel emotionally?

The dotted line is an average population score, and you can see there was for mild or moderate disease, very little change in either the physical scores or the mental scores.

But with severe Polycystic Liver Disease, like, my patient had, there was a clear decline in that physical component score.

And so this is now a different study where they looked at complications of liver cysts. Here they mention leg swelling or ascites, which is fluid building up in the abdomen or hernias. And the patients are mentioning back pain or flank pain, or abdominal fullness or discomfort in the chest.

Or a feeling of not being able to take a full breath or feeling of not being able to eat fully.

And this is just a depiction here of what might be happening in the liver as the disease progresses and the liver becomes more cystic.

So some of the things that people talk about who have liver cysts are dyspepsia or reflux, sometimes this is called GERD, or G-E-R-D and just means that there's pressure on the abdomen. So the contents of the stomach are coming up into the back of the mouth and this can result in an acid or metallic taste in the mouth or the mouth filling up with water.

That's water brush or a chronic cough and really sometimes we try to manage this symptomatically by saying don't eat prior to bedtime, eat smaller meals, avoid triggers which could be coffee or alcohol or mint.

For this happening.

And then if all else fails, try elevating the head of the bed.

And there are some medications we can give for this as well. Early satiety, so again, this is the liver cysts pushing against the stomach and the sensation here might be feeling full after eating only small amounts

The trick here is just eating smaller more frequent meals if possible.

Some of the things we really worry about and these luckily are quite rare, is the development of jaundice. So if the skin is starting to look yellow, that could be from jaundice, or if the belly is filling up with fluid, that’s ascites, or compression of the intestines.

If there's a lot of abdominal discomfort, it may be worth looking to see if some of those liver cysts are pressing on parts of the intestines.

And then we really worry about sudden acute pain.

So in PKD, whether we're talking about a kidney cyst or a liver cyst, think there's a lot of understanding that there's background chronic pain. But what we really, as your doctors want to know is when does that pain become a cute and severe? Because maybe that's something else, maybe that’s a cyst Hemorrhage, meaning bleeding in the cyst or rupture of a cyst, or cyst infection.

Right. And so we're really keeping a close eye on those things.

And this luckily is a very rare complication which is a liver cyst infection. The test for this is a very specific test called a PET CT.

And so what this does is it's a CT scan and so you can see like the liver here, this is the spleen, but then in areas where there's a lot of activity that's when you get this reddish orangish color. And what I’m showing you here is a patient who has a cyst infection, and you can see that cyst sort of lighting up in the scan, showing that she has an infection. And so really it's this is something that we have a high degree of looking for because if it happens, people can get sick really quickly and so sort of recognizing it, treating it early is important.

Think the next big thing in terms of managing liver cysts and PKD is managing pain. And what this schematic is showing you is where the pain fibers are that control the upper part of the abdomen, so the liver, and then down here the lower part, including the kidney. So all of the fibers that control pain sensation from the liver are fed through a connection of fibers called the Celiac plexus. And so, sometimes you'll hear people talking about doing nerve blocks and they're talking about doing nerve blocks in the Celiac plexus, if we think it's a liver issue or around the renal around the kidneys themselves renal denervation potentially for pain around the kidneys.

And the management of chronic pain, first starts with non-pharmacological therapy, Behavioral Management, physical therapy and then kind of stepping up to pharmacologic therapy. Would be things like Tylenol, or Tramadol, or use very, very sparingly, perhaps NSAIDs, and then opiates. But knowing that there are a lot of complications with use of opiates and knowing that we don’t like to use them chronically. And then you move towards minimally invasive therapies, which in the kidney would be related to kidney denervation.

But in the liver, perhaps to a splanchnic nerve block and then more invasive therapies.

We'll talk about those more as they relate to the liver. Including things like liver cyst aspiration.

So here, if you have a cyst and particularly it seems like the cyst that are in the liver right under the ribcage or right at the Belt Line. Seem to be the ones that just because of where they are, give people the most trouble. So those cysts can be aspirated, which means we put a big needle into that cyst, pull out the fluid. And then sclerosis means we put in another agent there that can cause the cysts to sort of shrink down and not reform.

That's one treatment. The other treatment would be to simply go in surgically and open up these cysts and let them drain. And that is called unroofing or fenestration. And that just lets the fluid drain into the abdomen and decompresses the cyst.

So how often do these work? And what you need to know if you're considering this is that they're not perfect.

So about a quarter of the time, there's total regression of a cyst and about 20% of the time there's partial regression of the cyst, right.

So even if we're counting up, that means 50% of the time, there's a good outcome, but, you know, about that same amount of time, there isn't a good outcome. The cysts recur about 21 percent of the time, meaning that the fluid was pulled out, but then as soon as the patient got better, the fluid reaccumulated.

The nice thing is symptoms improved in a majority of patients and that regression can go on for some time. It can go on. So even though you don't feel immediate pain relief, you may feel pain relief later as the process continues.

And so this is in a, in a very graphic way showing you how we think about treatment. So, someone who has, so again looking at the liver in this cut and this has one very large cyst, so it makes sense to try and aspirate or sclerosis that cyst and perhaps these other smaller ones as well.

Someone who has a lot of cysts on one side of the liver, but the other side of the liver looks really normal may benefit from a hepatectomy, or liver surgery, and someone like my patient who I showed you, who had liver cysts throughout the liver, may only be a candidate for a liver transplant. May not really benefit from cyst aspiration or removing part of the liver.

And this is just to show you.

So this is looking 20 years after surgery.

Patient, survival is excellent and long-term survival is excellent following either partial hepatectomy or following a cyst fenestration.

There are people, so people that might be candidates for a liver transplant, because liver synthetic function is normal, and the waiting list for a liver transplant is based on how much loss of synthetic function there is for livers.

There's something called an exception point. So, people who might be candidates with PKD for liver transplants can get exception points, and can then, move up the listing criteria for a liver transplant

And the way they look at this is if it's someone who has renal failure from PKD, meaning already on dialysis, and is otherwise healthy, and has a liver that's diffusely cystic with no spare remnant normal-looking liver, those folks are candidates for these MELD exception points and then may be able to get that combined kidney/liver transplant earlier.

And here, this is looking at outcomes following either resection cyst fenestration or a liver transplant, and a liver transplant is a complicated surgery, so it's no surprise that this one leads to higher hospital complications with either drainage of ascites, meaning fluid filling up in the belly or bile leak, and liver transplant obviously is associated with higher mortality. These two are relatively straightforward procedures compared to a liver transplant.

And this is a slide now looking at outcomes for all three things.

So this is looking at outcomes for hepatectomy going out as far as 20 years.

And this is patient survival that looks pretty good. That's patient survival versus fenestration. That looks pretty good and then this is for liver transplant, and you can see that there's pretty good survival after liver transplant as well.

So you know it's a more complicated surgery that people do well.

So I'm going to move from that, from talking about liver surgery to talking about medical treatment for liver cysts. And this is really for people who have very large liver cysts and have impairment, functional impairment because the liver is so large.

And so this is a study where they were the patients were treated with a medication called Octreotide. This is sometimes also called somatostatin, but it's the same medication and what you can see is these are just serial images of the same patient that over time there's benefit like if you look at this one big cyst, it looks like that's cyst get smaller over time.

But in this case, right, the liver volume has gone down by about a liter, but this person still has a very large liver at the end of this. What we know from these medications is that response to treatment is highly variable and that there are some side effects of being on these medications.

And this is now showing you pooled data from these three trials with somatostatin, or octreotide, and what their take-home points were was that this may be most effective in young women with very severe disease, that one of the liver function markers called Alkaline Phosphatase may predict response and then whether there's a lasting benefit when you stop this medication is still being explored.

So some people will say, if you really have symptomatic liver disease and you're not up to the point of transplant to try this medication, if there's no improvement after six months of therapy to stop treatment.

And this is specific therapy now, for people who are post-transplant and looking at a medication called sirolimus, and what they're showing you is that with sirolimus use, there was a decline in liver volume with treatment.

So my patient here ultimately went on to get a combined kidney/liver transplant, but this is the pathway that we went through, in terms of thinking about how to take care of her.

So she has PKD with a severe polycystic liver, she clearly had symptoms, she didn't have a single dominant cyst, she didn't have just several large cysts that we could either reach laparoscopically for laparoscopic fenestration.

She did have an extremely impaired quality of life, she had prior, to having to stop. She had been a gardener, and, and grew all her own vegetables and had a very good life and I’m happy to say that after her combined kidney/liver transplant, she's back to that very good life. For people where this would not have been an option, conservative treatment is failing, then we would consider those somatostatin analogs.

And then what's down the pike, I think there's been a lot of discussion about what's coming down the line for managing kidney cysts in PKD, but there's also an equal sort of portfolio of drugs being developed for Polycystic liver issues and some of that are combination trials for using octreotide plus another growth inhibitor, or octreotide plus another sirolimus. It's one of the drugs that's used post-transplant.

So a few things this is pioglitazone and telmisartan until my certain. So drugs used for diabetes and high blood pressure and then other drugs that are in the in the developmental pathway.

Now, we have about 10 minutes remaining. Okay, terrific. And this is my very last slide.

This is just, I'm in Connecticut.

This is the Connecticut Chapter walk back when they were in person. Maybe in two years, we'll be there again.

And just a chance to say thank you to all of you for listening before I open it up for questions.

Excellent, thank you, Dr. Dahl.

Okay. Excellent.

Thank you so much for that great presentation.

We have a couple of questions.

So there were a few that came in. They were asking about considerations for post kidney transplants.

Are there anything any immunosuppressive measures should be avoided considering liver cysts or PLD?

Post-transplant the liver cysts can continue to enlarge.

I think we've had a few patients where the kidney is working fine. But over time there are complications with the liver cysts.

The only immunosuppressive drug that's actually been looked at that may have some role is sirolimus, but for various reasons I think sirolimus isn't used very commonly as an immunosuppressive agent. It has its own issues in terms of use. So that is the only one that we have data for. The same considerations as those liver cysts enlarge post-transplant are possible. So if there's one dominant cyst, that can be aspirated, if there's an area of the liver that can be removed, a hepatectomy can still be considered.

So, all of those other leading up to liver transplant, all of those other possibilities are still available after transplant.

Excellent, and obviously there's a lot of sorry, coordinating care for an individual's PKD can be really overwhelming, especially if you have these liver cysts or other complications and do you have any advice or recommendations for someone who's trying to make sure they're nephrologist and their liver specialist are talking to each other?

Well, I think that one of the things that has made that easier is actually the electronic medical record where everybody can very quickly get caught up on what the other doctors are doing for a patient. If you're in a hospital system, where all of your doctors are plugged into the same EMR than that makes it much, much easier for coordination of care. We tend to have a referral Network. So those of us that see a lot of PKD, there are some hepatologists within Yale that see a lot of the liver cystic disease, and so they’re our go-to people. So those pools of knowledge exist, I think within the major academic centers.

You also mentioned that study going on at Yale with Dr. Bessie. Could you tell us a little bit more about that and what the eligibility criteria look like?

Yes. Elise, do you mind if I go back to the slide, I'll just pull it on again.

So she, what this study is looking for is for people.

Okay, so for everyone to look at this, it's for people 18 years or older who either have numerous liver cysts and a few kidney cysts, so we're looking for people who the liver pathology is very different compared to the kidney pathology, when the PKD Foundation meeting. One of them, I believe the one in Orlando when it was in person, there was someone who brought us like an image that she had on her phone of her liver and her kidneys.

And when I looked at that, I thought, you know, that looks more like a ADPLD to me and not ADPKD.

And so I think if you look at your images, if you think about them, this is this is what she's looking for.

Because really, her interest is in finding more of the genes that cause polycystic liver disease, and, or if you've had genetic testing and you have what looks like PKD, but they didn't find a PKD mutation.

Those are the people that she's interested in and it's really just a single, one-time thing, a blood collection for the people who are interested in doing.

Excellent.

Thank you.

We’ve had a few other questions thinking about birth control, IVF, or pregnancy.

Could you clarify, is there's anything else you would add for someone is considering getting pregnant or taking IVF, or perhaps considering different birth control options.

So I think, you know, the so we're all driven by that first statement, right first, Do no harm. So I think if it's possible to there are some birth control pills that are very low estrogen or progesterone primarily, so those are reasonable options for young women that are looking for, for that kind of therapy.

And we still guide them towards that and say, you know, there's this potential risk of estrogen. We actually don't know how serious a risk it is because we haven't done those prospective studies, right?

We haven't, that first study in 1997 was you know, a total of 20 people. We haven't done it prospectively in young women to see if it makes a difference.

So I think that what we say is try to limit exposure to the high estrogen containing birth control pills and this is certainly a conversation to have with the GYN and sometimes the GYN will say, what do you think about this one?

Is this okay for someone that's looking for a long-term contraception, an IUD, or something like that, maybe an appropriate choice, or another form of contraception might be an appropriate choice. In terms of IVF and thinking about IVF, we're not really saying anything about that, right?

We're not limiting the ability to use IVF or to do IVF. Sometimes that's important for people who are thinking about pre-implantation genetic diagnosis. And so we’re not talking about that very small part of reproductive time.

We’re just talking about longer terms exposure of estrogen, which would be in the time prior to conception or in that time when you might be thinking about postmenopausal hormonal therapy.

Absolutely, thank you, Dr. Dahl.

That’s all the time we have for questions.

Thank you everyone for joining us.