I'm very pleased to introduce our speaker for this session, Dr. Lisa Guay-Woodford.

She's a pediatric nephrologist and an internationally recognized investigator, with a focus on inherited renal disorders. Most notably ARPKD.

She also serves in several director roles for the center for translational research at Children's National Research Institute, clinical and translational Science Institute children's at Children's National. The Children's National inherited and Disease program. The UAB childhood cystic kidney disease, core Center and more.

Doctor Guay-Woodford, so, thank you. Thank you so much. We always learn so much. I'm looking forward to the presentation.

So it's always a pleasure.

This is actually a meeting that I look forward to every year.

And what I'm going to do is to sort of talk about the basics of clinical care with an eye towards things that we should consider currently, but also an eye towards whats coming down the road.

So let me just go through the activity disclaimer, I'm a consultant for super Pharmaceuticals and so, this is my sort of first slide.

I thought I'd start with ADPKD and then segue into ARPKD.

So kind of a little bit reversed than the way it appears in the program.

And these are the objectives that I'd like to accomplish in the next 40 minutes or so. First, give an overview of what PKD is because I know that there are several people who are new to these meetings. And so really just understanding what PKD is, and of course, to do that, we have to understand what is the normal function of the kidney and the liver. The two organs that are most affected by PKD, particularly in childhood.

And then I'll start with ADPKD and talk about key issues in children, current treatment strategies, and then the promise of targeted therapies and then use this same format in talking about ARPKD.

So let’s begin with the normal kidney. So the kidneys are a pair of reddish-brown organs. As I always say to folks have you ever had chili, because the beans and chili really look like a miniature version of the normal human kidney.

They are located on either side of the spine, just below the diaphragm and they're about the size, a normal kidney is about the size of a fist. So if you're very petite person, you have a relatively small kidney, because that's the size for your body. And if you're a big, strapping six foot five, you know, like a lineman for a professional football team, then you have a much bigger kidney, but it obviously is appropriate to your size.

The primary function of the kidney is to remove waste from the body through the production of urine, and the kidneys also help regulate blood pressure, blood volume and the chemical or electrolyte composition of the blood.

So, here are the kidneys shown in this schema and then this is the kidney sort of cut in half and what you can see is, there are two parts. There's the outer part of the cortex, and the inner part of the medulla and, sort of the kidney is organized by these structures called nephrons.

And they're about somewhere around three hundred thousand to a million nephrons per kidney. And this is the structure that becomes abnormal in polycystic kidney disease, depending on the type of polycystic kidney disease the abnormality is distinct and separate, so, how did the kidney's help maintain health? Well, the kidneys remove waste and excess fluid from your body through the production of urine.

Therefore, when the kidneys aren't functioning, you need to have an alternative mechanism to remove those wastes, and the fluid from your body.

And that for many people the first approach is some form of dialysis.

So, let me just back up. So we talked about the normal kidney. Then we talked about how the kidney, we're talking about how the kidney maintains health.

So removing waste and excess fluid continuously, regulating body fluids and chemical composition, removing drugs and toxins from your body. That's why when your kidneys don't work really well, you have to be careful about the, the drugs that you take but the kidneys are also important in releasing hormones into your blood. Hormones that are important in regulating the bone marrow to make red blood cells, like erythropoietin, renin, which regulates blood pressure, and calcitriol, which is a form of vitamin D. That helps the intestine absorb calcium from the diet and therefore maintain healthy bones.

Now, the kidneys handling of salt and water is really, quite frankly, magnificent. The kidney filters about 200 quarts. And for those of you who are metric a quart is about a liter, so about 200 liters of water a day and we pee about, you know, on average about two liters of water a day.

So, the kidney is constantly, assessing how much fluid does the body need and holding onto the vast, majority of the water, that's filtered. And similarly, with salt, unless you're eating a large amount of salt and then the kidney is smart enough to say no, I don't need it and it dumps the salt.

The other major organ that is involved in polycystic kidney disease is the liver, and the liver is one of the largest and most complex organs in the body weighs about a pound in an adult and it's made of a spongy mass of wedge-shaped lobes.

Now the liver has many functions that are necessary for life and it’s really the factory at the bottom so it helps processed carbohydrates, fats, proteins, absorb food from the intestine and turn them into materials that the body needs for life.

That's not a part of the liver that's involved in either form of polycystic kidney disease.

The form of the liver that is involved is the bile ducts and the associated vein. So, the bile ducts are either side of something that's called the portal vein and these structures only make up about five percent of the liver. But that's where the abnormalities in both, the dominant form of PKD and the recessive form of PKD occur. So, for most patients, the normal functions of the liver proceed because the sort of brick-red tissue functions normally it's those bile duct structures that are abnormal.

Why don't you start by defining what polycystic kidney disease in terms of the definitions that we commonly use?

So, the dominant form of polycystic kidney disease. This is the genetic designation and, and it's important. As I'll show you in a minute to use the genetic designation versus the old term, which was adult polycystic kidney disease.

So, if we think about it genetically genes, we have about 25,000 genes. They're organized in chromosomes.

So say this is the gene in the typical family with ADPKD.

In the normal situation in ADPKD, there is a generational impact for the disease. And so for in this particular schema the father is carrying the disease gene and he has transmitted it to the affected son.

That's actually the classic form of dominant transmission, from father to son, but there are families where there are children that have what appears to be dominant polycystic kidney disease with no family history.

We can talk about that in the question period, about what that means in terms of the recessive form of the disease or ARPKD there are an abnormal gene carried by both the mother and the father. The affected child, inherits both copies of the disease.

So, again, autosomal recessive polycystic kidney disease has been referred to as infantile polycystic kidney disease, but that's really a misnomer.

And so I thought that it was important to sort of really start with you'll hear these things, you'll see them on the Internet, but we really want to talk about the dominant form and the recessive form of polycystic kidney disease. So, if we just kind of think globally about what, PKD is, PKD is a disorder that particularly in children affects the kidney and the liver.

And as I mentioned, if we sort of take a step back and we look at PKD in terms of its expression across the Life Span most patients with dominant polycystic Kidney disease, actually, come to medical attention in their teens or in their early adult years.

But there is a clinically significant subset of children who present with symptomatic disease. So these are, I’m not talking about the children who are diagnosed because you find cysts as an an incidental finding in an Imaging study for some other reason and they don't have any medical problems.

These are children, who come to medical attention because they have high blood pressure.

They may have protein in their urine.

They may have blood in their urine.

They may have urinary tract infections. So you can see that ADPKD does extend all the way down into the earliest stages of childhood and so it really is not appropriate to call it adult polycystic kidney disease. Similarly, ARPKD - most patients present in the first couple of months of life, or in the first couple of years of life but there are a subset of patients with clinically significant disease that are first diagnosed in adulthood.

So both of these disorders can affect the earliest, the youngest of children and can affect adults, the distribution of their impact is different for the dominant form of the disease again, primarily a young adult onset, versus ARPKD which typically has its onset very early in life.

So let's dig right in and talk about the dominant form of polycystic kidney disease.

So as I mentioned, ADPKD is the more, much more common form of polycystic kidney disease.

It is a prevalence of about one in eight hundred to one in a thousand.

There are two principal genes that are involved during the course of this meeting uou'll hear about a third, but really makes up a very small number of patients with ADPKD the renal disease in children and adults effects. This structure of it is called the nephron. And there are soap bubble like structures that bud off the continuity of the nephron. Interestingly it's only about one to two percent of the Nephron, that develop these sense, but they are sort of like the Bad Apple in the basket of apples and they impact the more normal nephrons and the more normal tissue around it and they can set up secondary processes, like, inflammation and fibrosis. That contribute to the progression of the disease. ADPKD in adults is a systemic disorder that can be biliary cysts or pancreatic cysts. Vascular aneurysms, hernias, even male infertility.

But in children, by and large, ADPKD is primarily a kidney disorder.

So if we think about the manifestations of ADPKD, I think it's important to kind of take the lens again of the lifespan. So on this side of the slide is, the dot is the adult onset of the disorder.

What I want to call your attention to, is there really are two groups of children.

There is the very early onset form of ADPKD, which actually, for all the world can look like ARPKD in the course of these children's life span. Particularly during their childhood this is a disorder that is dominated by a rapidly progressive form of polycystic kidney disease, with significant problems with high blood pressure in about 25 percent of these children by the time they are 18 years of age actually lose their kidney function and require renal replacement therapy. That's the rarer group of children, with symptomatic ADPKD. The vast majority of children can present anywhere between a couple of years of age into school age and then into early adolescence. This group of children that I'm talking about, again, are not children who are picked up with this because they were on an Imaging study. These are children who present because they've been noted to have high blood pressure, they’ve been noted to have protein in the urine or blood in their urine. And actually a tip on a normal physical, you know, exam that a pediatrician does for little boys who are at risk for ADPKD one of the clues can be that these little boys have a higher frequency of inguinal hernias. So, the normal cohort of children of little boys, that's about 3 percent inguinal hernias for children with ADPKD it’s a higher frequency about 10%.

This slide shows the management issues of kidney related complications from ADPKD. I would go through them in detail except I want to point out that much of this information comes from the adult literature. Actually is very little that we know in a primary way about children with ADPKD. So we know they have hypertension and we borrow from the adult literature to use ACE inhibitors such as lisinopril or to use an ARB such as losartan.

Our treatment for hypertension again borrowing from the adult literature, we know about abdominal pain, particularly in adolescence on that can be either acute because of cyst hemorrhage or infection or stones, or chronic, and we manage these using models from adulthood and it sort of goes on and on and on. I want to really punctuate the point that while we know lots about the clinical manifestations and the management of those in adulthood, we really don't know that much about the manifestations in childhood.

So there was a consensus group of International Group got together in 2019 and issued a consensus statement on the diagnosis and management of children with ADPKD, children and young adults with ADPKD.

They recommended that we not go looking with imaging studies to identify those children who may be asymptomatic who may have cysts. They say that in fact the recommendation from this group was that for children with a positive family history, they should be monitored for high blood pressure. They even recommended ambulatory blood pressure monitoring periodically and monitored for protein in the urine. So looking for signs that they in fact have the disease. If they in fact are diagnosed and they have high blood pressure thinking about ACE inhibitors again, like lisinopril as the first line therapy for these children.

Not just for hypertension, but also for those children who have protein in their urine and for those children who have a very high level of filtration, the term that we use is hyperfiltration and then children as adults should be low dietary salt intake is consistent with a standard American diet.

Now I show this diagram because all the things that I've just mentioned are treating the symptoms not treating the cause and so this is designed, this slide is a sort of a simplified version, think about it as a wiring diagram of all of the different pathways are what makes the cell go.

In ADPKD we know that there are certain defects, certain abnormalities and we know that there are drugs that are available that can address those abnormalities. So, again, in this conference you'll hear a lot about the fact that cystic epithelial cells, cells that are lining cysts have high levels of cyclic amp and it makes lots of things go haywire.

What drives the production of cyclic AMP is this receptor on the blood facing side of the cell called The V 2 receptor and that receptor is targeted by tolvaptan, which is also known commercially as Jynarque.

You'll also hear in this conference, when talking about adult ADPKD that there is the activation of what's called the mTor pathway. And the we have a whole series of drugs that can target the mTor pathway.

They've been very successful in animal models. Not so much successful in the clinical trials in adults with ADPKD.

And then there is a series of agents that target the abnormality that occurs on the urine facing side of the cell.

And again this receptor is overactive and triggers a whole series of Pathways that lead to these cells multiplying and contributing to the formation of cysts. And this, for those of you who have children with ARPKD you have heard of this trial, and it also is a trial that is being considered in adults for this agent that is call Tesevatinib.

So what are the recommendations for new therapies?

Well, listen to International consensus address that and they really felt very strongly that V 2 receptor antagonist, Tolvaptan and Jynarque, should not be offered routinely to children and this is for a couple of reasons.

Number one, Jynarque/Tolvaptan, is a drug that has significant side effects.

You know, we talked about the typical adult will pee 2 liters of urine. Adults that are on this drug will pee 4, 6, 8 liters of urine. That can be really very disruptive. So we need to be very clear in tailoring who is it that we would consider for using this agent in childhood.

In one demonstrated case is children with very early onset disease, due to ADPKD and I'll show you that study in a minute.

In this conference you'll hear about the use of statins. You'll hear about some at somatostain analogues. None of these agents are thought to have enough evidence to consider them as treatments for children with ADPKD.

So again standard care, control blood pressure, control hyperfiltration, watch and treat for protein in the urine. Treat urinary tract infections, and then for targeted therapy, the only one we mightconsider is Tolvaptan. But again, the information that underlies how we make those decisions is pretty thin in childhood. There is one really promising study that was done in the UK for a little girl that actually had to abnormal copies of the PKD 1G.

She had massive kidney enlargement, high blood pressure, low sodium levels in her blood and really significant problems breathing, and she was treated with Tolvaptan that really had a remarkable impact.

And so this is really a promising case report for children who have really severe ADPKD particularly the early onset form that again can look for all the world like the recessive form of PKD.

But this is the exception for right now and we don’t really know, for older children, how do we think about Tolvaptan use. So you can say, well, we’ll do clinical trials, that’s what part of this conference is about, but if you go to the international repository, sort of the bank if you will, for all clinical trials, there are only six trials being done in the world that involve ADPKD in children. And in Europe, they are looking at Tolvaptan in a small subset of patients with ADPKD. Those results will be published shortly.

But most of these studies actually are thinking about developing registries of patients, so we understand more about the specific manifestations in childhood.

So I want to take a minute and talk about this worldwide registry.

That we here in the US are part of. The registry was started by Dr. Mikela and Dr. Leevel. Dr. Mikela is from Belgium and Dr. Leevel is from from Germany. It's an international, longitudinal registry of pediatric ADPKD patients. As of June 2021, there are almost 1,300 patients that have been registered. The aim of the study is to collect longitudinal data from a large number of children. These children are diagnosed based on family history, renal Imaging, and for some of these children, they have genetic information. The data is taken from their medical record and is entered into a web-based database under very secure conditions.

So the data themselves are entered under a unique identifier, a code if you will, and the database itself is very secure so that that there is minimal risk. You can never say there's absolutely no risk that any child who's in this database could be identified or their family identified. And this effort I think is really important because it's looking across the world at children from every continent that's inhabited in terms of trying to get the largest number of children. So we can really understand the manifestations of the disease in childhood.

Let's switch gears and talk briefly about ARPKD

ARPKD is much rarer, incidence of about one in 26,500 live births the molecular genetics. Although there are a couple of genes involved, the overwhelming number of children have defects in a gene called PKD HD1. The renal disease involves the collecting ducts.

So, here's the nephron again, and here's the collecting duct and it is not soap bubble like-cyst, it’s a dilatation so it sort of balloons out. The cysts don't wall themselves off from this nephron. And so, the urine that's filtered here, goes through this system and leaves the body.

If we think about it a different way, here's the normal nephron.

Here's the cystic dilatation, and it can lead to kidneys that are massively enlarged. In terms of the liver, children with ARPKD always have a liver lesion. It may not be clinically significant, but if you were to take a piece of the liver tissue, there is always an abnormality and that abnormality is due to a defect in the modeling of the portal vein and the lattice-like network of ducts that should be associated with it.

So instead of it being sort of a robust, branching system of vascular structures associated with this, lattice like network of bile ducts. The vascular structure is abnormal and the associated bile ducts are abnormal and that then sets up an inflammatory and a scarring process that if we take a piece of that liver, we recognize as congenital, hepatic fibrosis. The reason this is a problem for children with ARPKD is here is the blood coming from the intestines. Into the liver, into the factory of the liver.

If you have this scarring around the blood vessels, when they get into the substance of the liver, that can increase the pressure in this vascular system, causing the blood in this very thin-walled structure, think about a paper straw, it's not going to be able to push against that resistance due to the scarring. And so the blood will back up into the spleen. That's why the spleen gets big and into the blood vessels around the stomach and around abdomen and around the stomach and the esophagus those blood vessels can actually be dilated and that's what we call varices. Not only have varices around the stomach and the esophagus you can have along, this vascular system basically is blocked because of the fibrosis in the liver.

So we actually undertook an effort to try to understand how common is ARPKD. We use the electronic health record.

Cerner is one of the major electronic health record providers in the US and we used a slice of Cerner data across the country. We were able to calculate that about one in twenty six thousand five hundred babies have ARPKD, we were able to calculate the mortality rate in the newborn period and we'll get back to that in a minute.

It's about 21 percent, but I think the most important number is, we were able to estimate how many children with ARPKD are there in the country. People talk about the fact that it is, you know, a very, very, very rare disorder.

Yes and no, it is a rare disorder but there are 1500 patients between 0 and 29 years of age that we estimate are affected with ARPKD in the United States, so a large number of potential patients that are available for further studies to really understand this disease and to think about enrolling in clinical trials, once we have that understanding.

In terms of patient survival, again ARPKD can be a deadly disorder, but those patients who die, typically die in the first week or two of life. We estimate that's about 21% of these patients.

When we think about that really should say newborns. I'm not sure why it says that. When we think about newborns, for reasons we don't really understand, these children are born early.

They typically are born, mother's go into labor spontaneously at 34 to 36 weeks.

The major issue for these babies is poor lung development and that's what causes the mortality in the newborn period. The kidney issues are this, this low level of salt, that actually is probably not because they're losing salt. It's because they're holding on to water in excess of the salt that they have.

So, it's a dilution of the salt level. Still an important issue, still needs to be treated and that's why these children very often are treated with salt supplements at least for the first few weeks of life. Decreased kidney function can be a major issue for these children.

Very, very large kidneys and hypertension for those children.

For those who survived the newborn period, again, there can be respiratory issues that are residual as subset of these children, perhaps 10 to 15 percent of them have chronic lung disease because they've had real problems being able to breathe on their own. They've required support of ventilators.

There is associated damage to their lungs and they can leave the newborn period and even early childhood, or infancy, with chronic lung disease. Not really, really common, but about 10 to 15 percent of the group. The kidney, it can be electrolyte abnormalities, high blood pressure, and declining kidney function. The liver again because of the scarring can lead to that portal hypertension effect that I talked about with the development of varices. Those varices that that swelling of those veins, again veins have very thin walls and so those varices when they're put under a lot of pressure can actually bleed and that's a major concern for a subset of these patients. And because of the dilated, bile ducts that can actually get infections in the bile ducts. We have to be very Vigilant about these babies and children. When they get a fever, particularly, if there's not an obvious cause of that fever, we have to be thinking about the liver and could there be an infection in that bile duct.

Feeding issues are a major concern. Again, probably just because of the mass of their kidneys, many of these children require the placement of a G-tube so that they can get supplemental nutrition at night. And then, I just want to just quickly kind of sort of summarize this by saying this is information that we've really put together with, two moderate sized studies of about a hundred and sixty patients. One done in the United States and one done in Germany, determining that many of these children are diagnosed prenatally, but not all of them. Many of them, but not all of them have low blood sodium levels, many of them, but not all have high blood pressure. Urinary, tract infections, more common than the children without ARPKD, but not universal.

There's a progression of their kidney disease with children actually going on to require renal replacement therapy with dialysis or even transplant during childhood.

There are growth issues for these children and it's not really clear, is this a primary issue with the disease with the gene defect or is this again because of the these children having difficulty getting the calories that they need for growth.

We talked about a subset of these children having chronic lung disease, but by and large, if these children survived the newborn period, they survived through childhood.

So we're back to this wiring diagram again and I put this up because I want to make the point that although the appearance of the cystic lesion in ADPKD and ARPKD is quite different. This wiring diagram, and what's wrong in this diagram, is common, in many ways, between ADPKD and ARPKD. Said another way, the therapies that are being developed particularly for adults with ADPKD have implications not just for children with ADPKD, but for children with the recessive form of polycystic kidney disease.

But again, there are very few Trials of children with ARPKD because we just don't understand enough about this disorder, its natural history. What the problems are?

Who's going to do what, in terms of the expression of their disease? So the potential is, we have related disease mechanisms and so ADPKD therapies may be effective in ARPKD, but ARPKD is a difficult disorder for us to be thinking about clinical trials because it's a disorder that develops very early. The kidney volume, which we follow in adults, and we think we can use in children with ADPKD, is not going to be a reliable marker of disease progression in kids with ARPKD. Kidney function is variable and doesn’t correlate with disease severity, so the bottom line is, we don’t have markers of disease progression. The reason that’s important because when you do a clinical trial you need to know well what would be the typical course of this patient, and if I give them drug X how will I know that typical course has been impacted and the disease has been attenuated in its severity.

So what do we need for ARPKD for clinical trials, but we need research-ready cohorts, and I'll talk about in just a moment, the international databases again.

Diseases in children are not common and so doing this at an international level so we capture a wide variety of children from different racial and ethnic groups. Thinking about the biology, that wiring diagram, what's common in PKD? And what’s specific to ARPKD? We have virtually no biomarkers for disease progression, so total kidney volume that we use in adults, it’s an imaging biomarker, so it’s really not going to be helpful in ARPKD, and then trying to think about the drugs that we will need to study in these in this cohort of children.

So I want to make a brief mention again about databases. The Europeans have once again been very, very effective in collecting a large number of patients. This is on their website. As of April, I know they have now well over 700 patients with ARPKD in their database. We have been collecting for years children with ARPKD and disorders, like ARPKD in the United States. And Larissa Kerecuk in the UK is connect as collecting data from children with ARPKD.

What's important is that we have taken all of these databases and made sure that they're very similar. Data from one database that we're collecting in one database is being collected by and large in other databases in the same way.

So that these, we can look across all these databases t to ask questions about this cohort of children with ARPKD. And that will be very important again, particularly for a rare disorder.

Lisa, we all have about seven minutes left. And I have just about a few slides. Thank you, perfect.

So, I just want to show you one of the things that has come out of the European study. So they looked at about 370 children with ARPKD, in the newborn period and they were able to really demonstrate the children who are born after pregnancy that has either all go hydrate videos or in Hydro amnios

They have large kidneys and renal cysts.

32% of these, there's a 32 percent risk for these children to go on to require dialysis or renal replacement by 12 months of age. And what I'd call your attention to is those children that had minimal problems, only one point five percent. So we're beginning to have clinical distinctions about different subsets of children with ARPKD and that will be very important in terms of thinking about the clinical trials that we want to do for targeted Therapies.

So to summarize PKD a clinically significant disorder in children, both the dominant form of the disease and the recessive form of the disease.

And while they are clinically distinct, there are many disease manifestations that are common, and the biology of these disorders is common. At the present time in children, our therapeutic strategy, our therapeutic focuses is on supportive management.

We need clinical trials to really examine drugs as potential targeted therapies. But to do that, we need to have information about the natural history of these disorders and prognostic and predictive markers and one response to that is research-ready cohorts.

Both for ADPKD. And again, we're collaborating with a worldwide effort for children with ADPKD and ARPKD. We are one of the large databases that are collecting information for these children and doing it in collaboration with other databases in the world.

So here's my contact information. You are always welcome to email me.

These are the websites both for the clinical inherited and polycystic kidney disease program.

And I see patients from all over the country, and then for my laboratory, for those of you who are interested, you go to these sites.

And then in the search terms, you look for polycystic kidney disease, or my last name. So, let me stop there and I'd be very happy to take questions.

Okay?

Actually one of them is from Rochelle.

She was asking about the blood pressure, like we always like what percentage should the children be at? Is it still between 50 to 90%?

Yeah, so this is a really good question.

So there was a large study that was done in Europe. Looking at children, with decreased kidney function, for all sorts of different causes. And what they were able to demonstrate, is in those children with chronic kidney disease, rigorous control of blood pressure slowed the continued decline of kidney function.

The problem is, we don't know that for the polycystic kidney diseases. And remember, I mentioned these kidneys are massive, they have cystic structures, they not only crowding out the other nephrons, they're crowding out blood vessels too. And so one concern that we have is if we are to rigorous with blood pressure control can we actually inadvertently do harm. Now, that's the first point.

The second point is we know from adult studies that rigorous control of blood pressure does slow disease progression in ADPKD.

So, will that be true in in kids with ADPKD? The bottom line is we don't know for either ADPKD or ARPKD.

So my practice is to control blood pressure, so it's less than the 90th percentile.

I don't make a, and that and that can be very hard to do just at that threshold.

I don't make a rigorous effort to get it lower than that because I don't have an evidence base to suggest it's helpful and I don't have an evidence base to suggest that by being more rigorous I'm not doing harm, inadvertent harm. So my target is less than the 90th percentile.

Okay, thank you.

This is also for Michelle. Maybe it kind of touches on what she just asked.

She said I remember hearing enalapril is good but not when function is declining. At what present percentage function do you change to another medication?

Yeah, so it really depends.

I mean, it's great question. And, clearly we worry about the Aces and the arbs when kidney function is declining. For those of you who are savvy about kidney function and the stages of chronic kidney disease, I start to think about, do I need another agent when children get to be at CKD three. You know, actually what I was just going to do is let me see if I can pull up, I have a little schema that I use to explain CKD to patients.

Let me see if I can just quickly put my hand on it.

Yeah, here it is.

Okay.

So every child that has a structural abnormality in their kidney, like PKD, has chronic kidney disease stage one. What it means is that they have structural abnormality, but their kidney is functioning normally. When you get to CKD stage three, that’s when I start to think about are these agents potentially not just benefitting the control of blood pressure, but on the dark side, doing damage to the kidney. And here I would be thinking about other agents and it really depends on what else is going on with the child. In terms of what, first of all, what is their underlying disorder? Is it ARPKD or ADPKD, and what else is going on, in terms of the number of other drugs that are at my disposal to choose. The one thing that we do know, and we actually put together an International Group in 2014, is it is probably not a good idea to have a child on both an Ace inhibitor and an arb. That actually has been demonstrated, when they're, when they're given together as causing kidney damage.

So, I certainly avoid trying to use them together.

And then it looks like we have one more question for now. I'm sure they'll be more. Do children with small stature tend to catch up to their peers at some point, or do they tend to continue being on the shorter side through adulthood?

Yeah. So that's a great question and it really depends on what's going on.

So if the problem is that they're just not getting enough calories, then those kids can catch up. There are children, and, you know, this certainly has been something that I've talked with people who are a part of this meeting, and certainly my own patients, with a just have short stature. They are evaluated by endocrinology and the different components that are really so critically important in growth in childhood all seem to be functioning okay, but then you try an empiric trial of growth hormone and the children respond.

So I think that's part of the reason for our inherited and polycystic kidney disorders clinic. We have as one of our multiple specialties available to see patients an endocrinologist, who can deal with these issues of growth, as well as a nutritionist. Is it an issue of too few calories? That these children just need a different amount of calories than what they're actually taking in or is this something that can be assisted by growth hormone supplementation?

Thank you, that's all the time we have right now.

Do you have any final comments?

No, I'm happy to be helpful to this group. I've been doing this as Michelle knows and is Paula knows for a long time.

And I have to say, this is a highlight of my year, so thank you very much for asking me to participate.

Thank you so much.