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Polycystic Kidney Disease: The Basics Part Two of Two



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00:00

Diagnostic Testing

1. **Ultrasound diagnosis**
2. **Genetic diagnosis**
3. **Presymptomatic diagnosis**

Diagnostic testing

Let's continue with diagnostic testing. What I want to do is to put this in real terms, 1999 terms. How do we think about making the diagnosis of ADPKD? In fact, the mainstay in our diagnostic armamentarium is imaging studies, and specifically renal ultrasounds. We are going to touch on genetic diagnosis because as many of you know, the two principle genes that cause ADPKD have been identified. I would imagine your question is: If we know the genes, why can't we just look at them to see if there is a mutation? I will explain why that is complicated. Then I want to touch on what for me, perhaps particularly because I am a pediatric nephrologist, is a very important and I think difficult question. That is the issue of presymptomatic diagnosis.

00:00

Diagnostic Criteria - Ultrasound

Age (in years)	Cysts
15-29	2 in one or both kidneys
30-59	2 in each kidney
≥ 60	4 in each kidney

Diagnostic criteria for ADPKD by ultrasound

Here are the diagnostic criteria that are currently accepted for the diagnosis of ADPKD. Someone asked a question about her 41-year old sister who has a single cyst in her kidney.

Let me point out that the development of cysts in the kidney is a normal phenomenon, not many cysts, but a few. So seeing a cyst in a child is very, very unusual, but seeing a cyst in an adult could be well within normal.

If you are less than 15 years old, any cyst in the kidney should raise the antennae of the pediatrician or the pediatric nephrologist, and that should be investigated. If you are a child less than 15 years old and you come from a family with ADPKD, even one cyst is strongly suggestive that you, too, have ADPKD.

If you are between 15 and 29 years of age, two cysts--either both in one kidney or one in each kidney, meets the diagnostic criteria for ADPKD.

Between 30 and 59, two cysts in each kidney meet the diagnostic criteria for ADPKD. As you can see, if you are greater than 60 years old, you need to have at least four cysts in each kidney to meet the diagnostic criteria for ADPKD. So you could be 60 years old, have two cysts in one kidney, one cyst in the other, and be considered within the range of normal.

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Ultrasound Diagnosis in Children		
Age range	False Negative Rate	False Positive Rate
All children	25%	2%
3 mo - 5yrs	38%	11%
5 yrs - 10 yrs	19%	0%
10 yrs - 15 yrs	23%	0%
15 yrs - 18 yrs	22%	0%

False negative and false positive rates of ultrasound diagnosis by age

This is relatively recent data about ultrasound diagnosis in children. This again comes from the wonderful study that has been conducted for well over 25 years at the University of Colorado in Denver. This is a busy slide. It has a lot of information. Suffice it to say ultrasound is not great for making the diagnosis of ADPKD in children under five. There can be false positives and false negatives. It certainly can be used. It certainly can make the diagnosis, but it doesn't have optimal sensitivity and specificity.

If you are older than five years of age and you don't have any cysts in your kidney, the chances are still about 20 percent that you can go on and develop cysts in your kidney. If you get to the age of 30 and you have no cysts in your kidney, then probably your chance of carrying one of the PKD genes with a mutation is less than 5 percent. On the other hand, the false positive rate in children over the age of five... so that you would see something that would make you think a child has the disease but they really don't, is zero. If

you see cysts in the kidney in a child greater than five years of age, particularly in a child who comes from a family with known ADPKD, that child has ADPKD by our diagnostic criteria.

00:00

ADPKD - Genetics

The diagram shows two chromosomes. Chromosome 16 is a large, light blue chromosome with a yellow band at the top labeled 'PKD1'. Chromosome 4 is a smaller, light blue chromosome with a yellow band in the middle labeled 'PKD2'. The numbers '16' and '4' are written below their respective chromosomes.

Incidence ~1:1,000
> PKD1 - 85%
> PKD2 - 15%
> PKD3 < 1%

Genetic diagnosis of ADPKD

Let's talk about genetic diagnosis. As many of you know, there are two principle genes that cause ADPKD. One is PKD1, and it causes about 85 percent of the disease. In fact, the lion's share of the clinical data that I have just shared with you comes from studies of patients who have mutations in PKD1. There is a subset of patients who have a mutation in a second gene, called PKD2.

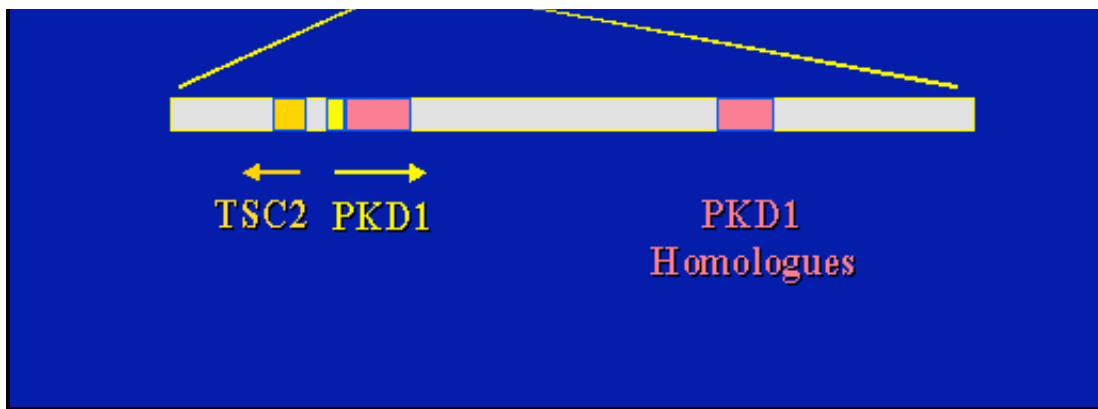
PKD1 sits on the short arm of human chromosome 16 at the very end. PKD2 sits about a third of the way down the long arm of human chromosome 4. For most of you in this room who have ADPKD, you have mutations in PKD1. That gene was identified in 1994 and really thoroughly characterized by 1995. But it is a complicated gene and it really at this point is not amenable to a clinically available diagnostic test. This is the reason in a nutshell.

00:00

Gene-Based Diagnosis: Difficulties with PKD1

Chromosome 16

The diagram shows a horizontal representation of Chromosome 16. It is a long, thin, light blue chromosome with a yellow band at the very end, representing the location of the PKD1 gene.



Problems with genetic diagnosis of PKD1

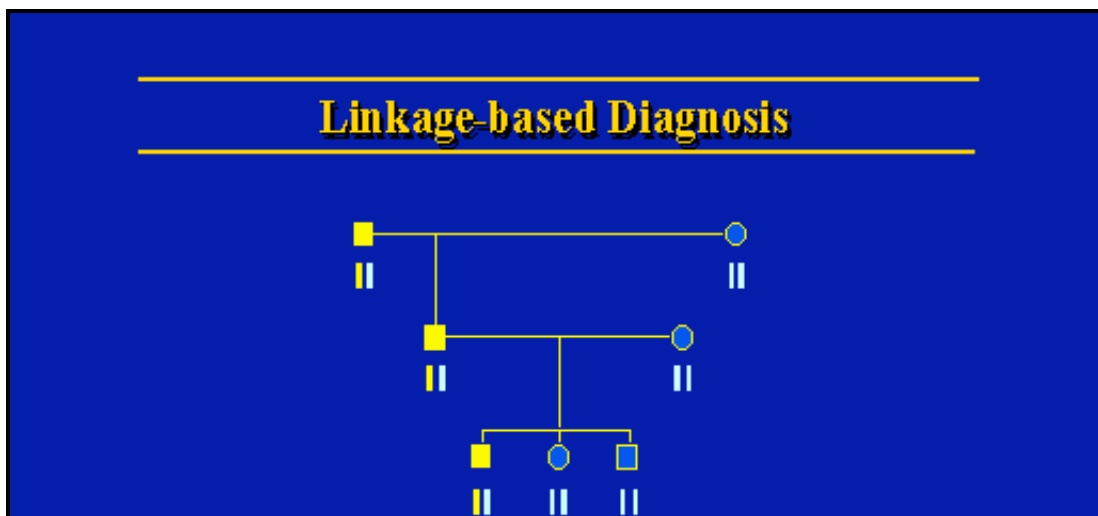
This is the region that contains PKD1, out here on the short arm of human chromosome 16. The PKD1 gene, if you will, sits tail-to-tail with one of the genes that causes another cystic kidney disease called tuberous sclerosis. It is almost as if you have two animals on the fence facing in opposite directions. The problem with the PKD1 gene is only that very tail portion is unique. Two-thirds to perhaps three-quarters of the gene is duplicated on another region of human chromosome 16, not just one copy but in three copies.

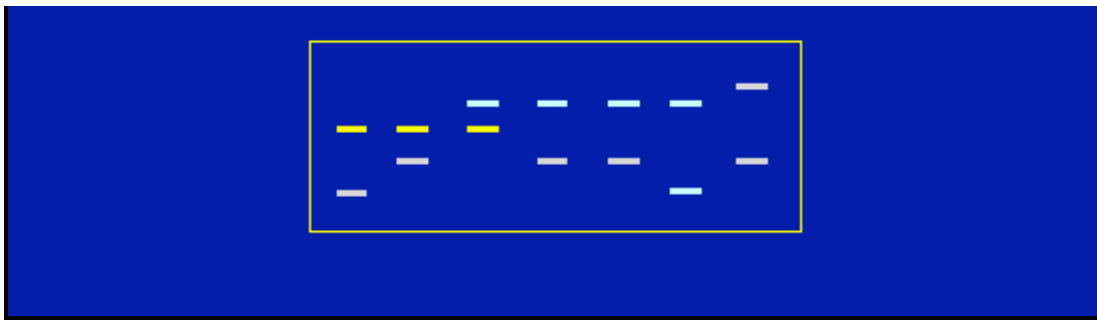
The way that we do gene-based diagnostic testing is we use a series of molecular biologic techniques to basically amplify this region so we can study it. The technique involves the polymerase chain reaction, or PCR. Any of you who watch crime shows know about PCR. What happens is that you take a series of primers on either side of the gene, and you make many, many, many copies of it so that you can then study it. You can study the sequence information in that gene. You can see if you start amplifying this region, how do you know that you're looking here instead of here? That in a nutshell is what complicates gene-based diagnosis right now for ADPKD. The principle gene is PKD1, and PKD1 is genetically complex.

Does that mean that it will never be possible? No. It is just going to require the development of more sophisticated, more novel strategies before it becomes clinically available.

Can we use any of this genetic information to make a diagnosis? Yes, we can use what is called linkage information. We know that PKD sits out here on chromosome 16. In other words, we know its genetic Zip Code. We know its genetic address, and we know the neighbors on either side of that genetic address. We know the neighbor to the right, and we know the neighbor to the left. If we use those neighbors as surrogate markers of the disease gene, we can follow the transmission of those neighbors, those immediately adjacent neighbors, through the family.

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Example of linkage-based diagnosis of ADPKD

Here is an illustration. Here is the pedigree or the family structure that I showed you at the beginning of this talk. Here are the family members who are affected. Let's suppose we weren't sure this fellow was affected; we wanted to test him. What we need is to have at least two family members who are known to have the disease. That is very important for linkage-based studies. Let me actually repeat that. To do a linkage-based test for ADPKD, you need to have two members of the family participating who are known to have the disease in addition to the patient who is being studied.

So if we look at this particular patient without knowing whether or not he has the disease, we see that he got the yellow copy from his father and the blue copy from his mother. His father got the yellow copy of this particular marker from his father, and both his father and he have the disease. Now we have chosen this particular marker because it sits right beside the gene. So we would say that the whole stretch of the chromosome that contained this yellow copy of the marker also contains the disease copy of the gene. Because this patient inherited that same yellow neighbor, that same yellow marker, this patient has the disease as well.

That is shown on the bottom of this slide. If we look here, the grandfather has a yellow copy and a grey copy; the father has a yellow copy and a grey copy, this time that he got from his mother; and our patient of interest got the yellow copy from his father and a blue copy from his mother. He has the disease. His sister, who got the grey copy from her father, and his brother, who also got the grey copy from his father, inherited the normal copy of the gene from the father. Does that make sense? Okay. If it doesn't, we can go over it again. I think it is a very important thing because we get to the issue of presymptomatic diagnosis.

00:00

ADPKD: Presymptomatic Diagnosis

Advisable:

Family history of intracranial aneurysms
Living-related transplant donor

Available:

All "at-risk" persons 18 years of age or older

Issues:

Indirect test - PKD1

Psychological burden Insurance/employment risks

Indications for presymptomatic diagnosis

Part of what I am going to say is supported in the literature. Part of what I am going to say is based upon my clinical experience. I believe, and I think the literature supports, that adolescent patients who have a family history of intracranial aneurysms should know whether they are carrying the disease gene because there are reported cases of ruptured intracranial aneurysm in patients as young as 18 and 20 years old. While unusual, the first presenting symptom could be a rupture of an intracranial aneurysm. I think that is not an advisable situation.

So for patients who come to me who have family histories of intracranial aneurysm, I discuss and actually advise that they consider linkage-based testing for their adolescent children. We will get to that in a minute because I think there is a wrinkle to that. Certainly once they get to be 18, I think that needs to be discussed with the patient himself or herself.

The other situation that I think is very important is that there are a lot of 20-year old siblings who want to give a parent a kidney or an older sibling a kidney. When you are 20 years old, you have between a 15 and 20 percent chance of having a negative ultrasound but still carrying the disease gene. Why would you want to have someone give you a kidney that is ultimately going to develop PKD? Why would that person want to give it up, and why would you want to get it? So I think linkage-based testing is a very useful thing to consider, particularly for donors who are at that age where you can't be definitive using imaging studies alone.

The other situation relates to the following observation: I just flew here. I actually went from Birmingham to Cincinnati to Dallas, down to San Antonio, and then we hugged the Mexican border because there was such bad weather. If my airline pilot had ADPKD and came from a family that had intracranial aneurysms, you can be sure I would want to know whether he was at risk for having an intracranial aneurysm so we didn't end up in some canyon someplace. So if you have a high-risk job where sudden loss of consciousness would be a disaster, both for the individual and the people with him, I think that is also a situation to consider.

What I am getting at is I think in 1999, knowing that you have the disease before you are symptomatic doesn't have tons of advantages. It is not as if we have therapies that we can institute very early that will attenuate the course of your disease.

What you should have if you come from an ADPKD family is careful medical follow up. You should have your blood pressure checked. You should have your urine checked for blood or protein. You should have your kidney function checked. But do you need an imaging study? I think the answer right now is no. On the other hand, I think if you come from certain situations, the answer probably is that it should at least be discussed. I think it raises a very particular issue in terms of age. If you are 18 years or older and the devil you can live with is the devil of knowing, then you should talk to your physician about getting a linkage-based study. If you are less than 18 years of age, I think there are many ethical concerns.

Let me say this as delicately as I can. Parental curiosity, in my mind, is not justification for putting a child through a diagnostic study who is completely asymptomatic. I think an alternative course of action that is extremely responsible is to have the child's blood pressure followed, to have the child's urine checked once or twice a year, and to have their kidney function followed and a good physical exam. Problems that you would want to be jumping right on top of will come to medical attention with that type of screening. What you run the risk of is having a child know they have a disease that we can't do anything about and that they may not want to know... the devil they can live with is the devil of not knowing. We have to respect that. I know there has been a recent discussion about this in the PKD Newsletter. These comments are purely a matter of my opinion and my clinical

experience.

When presymptomatic diagnosis can have negative consequences

I will tell you just a little story because sometimes "The Journal of Anecdotal Medicine" is very useful in adding color to a situation. I have a 16-year old boy whose father was going to have a renal transplant. The new pediatrician found out the father was going to have a kidney transplant for ADPKD and had all six children in the family screened. Four of them have ADPKD. All four of those children are asymptomatic.

The 16-year old wanted to go to West Point. He now knows he can't go to West Point. What he has decided is he has a chronic disease, he is going to need a transplant, and he is just not going to go to college. His grades have fallen and he really HAS had a hard time. I think what that points out is that he wasn't prepared to know that information. He wasn't at an age where he really could have informed consent. So I would caution you. Please, as parents, think about it. Think about all the issues. It is important for you as parents, but it is also important for your children. Now, of course, all of this changes if we have something that we can do that attenuates the course of the disease. Then I would completely change my view on this. Enough preaching.

Issues about linkage-based testing.

It is an indirect test. That means that to do this... suppose you have an 18-year old child who says, "Yes, I want to know." They have to get two family members who have the disease to participate in the test. That means it is not a typical laboratory test, like you could walk into the doctor and have a urinalysis or a cholesterol test, and it is not a private test like an HIV test. You have now involved other members of the family. That should be discussed because it is not like many other medical tests. I talked a little bit about the psychologic burden of knowing. That particularly is important, I think, when you think about children.

Insurance issues

Insurance issues are important. In 1996, there was a law passed that says you can't be discriminated against in terms of getting insurance because you have a pre-existing illness, but that doesn't mean they can't raise your rates. Believe me, the insurance companies think in actuarial terms. So if they know you come from a family with ADPKD, already your rates have gone up. If they know you have a positive ultrasound, they are going to go up even higher. You have to take that into consideration if you are presymptomatic. There are still some lingering employment risks because, unfortunately in our society, there are still issues of discrimination in a whole variety of regards.

00:00

ADPKD: Treatment Issues

Kidney

- Hypertension
- Gross hematuria
- Urinary tract infection
- Stones
- Dialysis and transplantation

Other

- Pain syndromes

- Symptomatic cystic liver disease
- Intracranial aneurysms

ADPKD treatment issues:

I just want to emphasize hypertension, very important; prompt treatment of gross hematuria, bedrest, plenty of water, trying to get this to remit; urinary tract infections need very quick and aggressive attention; stone disease needs careful attention; dialysis and transplantation will be discussed in great detail tomorrow in two sessions. Dr. Janet van Adelsberg will talk about dialysis, and Dr. Andrioni will be talking about transplantation. Other issues to consider--pain syndromes. Last year, for those of you who were here, there was a very good session on pain issues by Dr. Ted Steinman. This year, unfortunately that is not going to be repeated because we are doing lots of other things. There are transcripts, I believe, for those of you for whom this is a big issue. Symptomatic cystic liver disease--Dr. Torres, who really is a world expert in this manifestation of PKD, will be giving a session on cystic liver disease. Intracranial aneurysms, particularly intracranial aneurysms and hypertension, will be discussed at some length by Dr. Ron Perrone.

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ADPKD - Genetics

PKD1

16

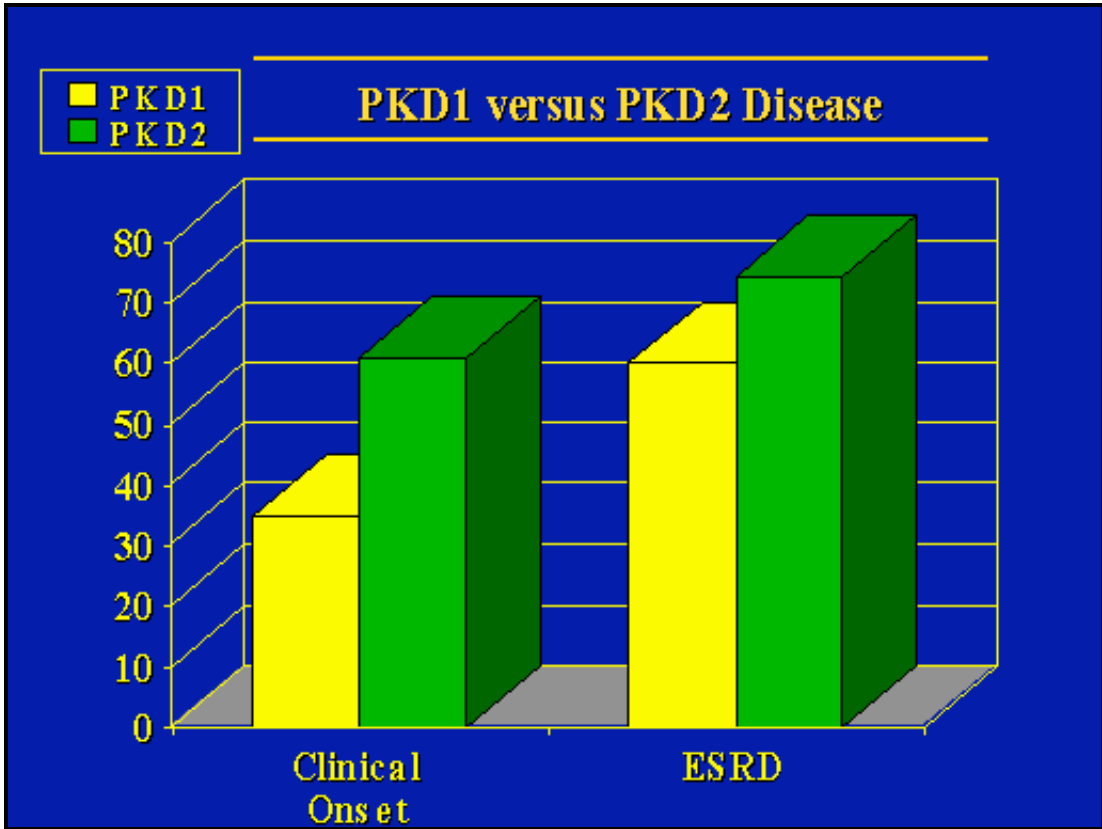
PKD2

4

- **Incidence ~1:1,000**
 - > PKD1 - 85%
 - > PKD2 - 15%
- **Very early onset ADPKD -> PKD1**
- **Infant diagnosis often identifies an affected parent**

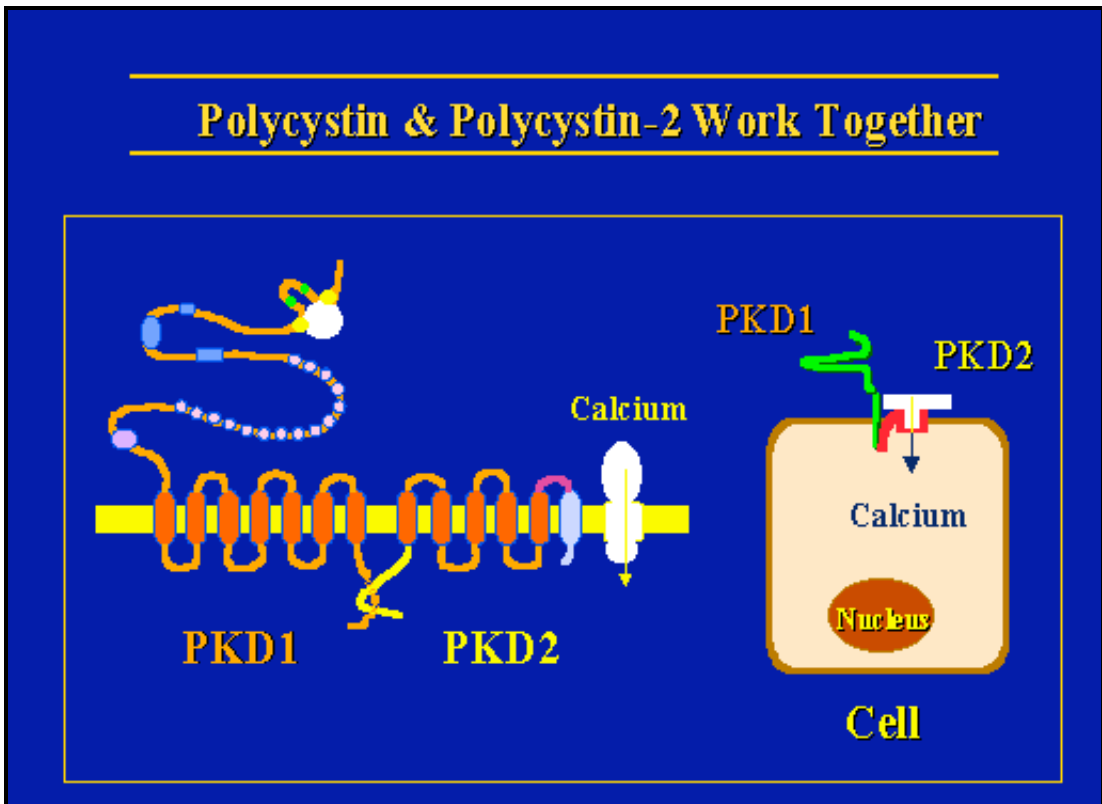
Basic mechanisms of PKD disease

Let me talk a little bit about the genetics in terms of thinking about the basic mechanisms of the disease. We have already talked about the fact that there are two disease genes. Let me also point out that it is not unusual for babies who are born with ADPKD to be the reason that the transmitting parent is first diagnosed with the disease. That is why pediatric nephrologists ask parents who have children who are born with polycystic kidney disease to have screening ultrasounds. This is the basis for it. You could say, "There is no family history at all." And someone asked me the question, "You know, I don't have any family history. How come I have this disease?" There is probably a 5 to perhaps as high as a 10 percent spontaneous mutation rate; in other words, it shows up in an individual for the first time. But then that individual is fully capable of transmitting it to subsequent generations.



Clinical comparison of PKD1 and PKD2: PKD2 has later onset

I mentioned that most of what we talked about is PKD1-related disease. PKD2-related disease is for all the world identical to PKD1 disease except it has a later onset. The clinical onset is later, and the progression to end-stage renal disease tends to be later than in PKD1.



Basic mechanisms of PKD: "two cats sitting on a fence"

Let's spend a little bit of time with a synthesis of what we understand about the basic mechanisms. These are models of the protein products of the genes that we are talking about. This is the protein product of PKD1, and this is the protein product of PKD2. The gene for PKD1 and characterization of the protein was done in large part by Dr. Greg Germino's lab at Johns Hopkins University, by Dr. Peter Harris's lab at the University of Oxford, and by the group in Leiden in the Netherlands.

What these cumulative studies have suggested is that the protein that is coded for by this gene is a protein that goes back and forth, almost like a serpent, through the basement membrane. There is a little tail in the inside of the cell and there is a whole big portion of this protein that hangs outside of the cell. There are whole series of motifs or domains in this portion of the protein that suggests it facilitates the interaction of cells with other cells and cells with their basement membrane or their matrix, and I will explain to you what that is in just a moment. That protein, and the protein made by the PKD2 gene sit side by side in the membrane and physically interact by their tails. Again, you can think of these two proteins as two cats sitting on a fence, like in Lady and the Tramp. That really is a very good analogy for the interaction of these two proteins. They interact in a direct, physical way.

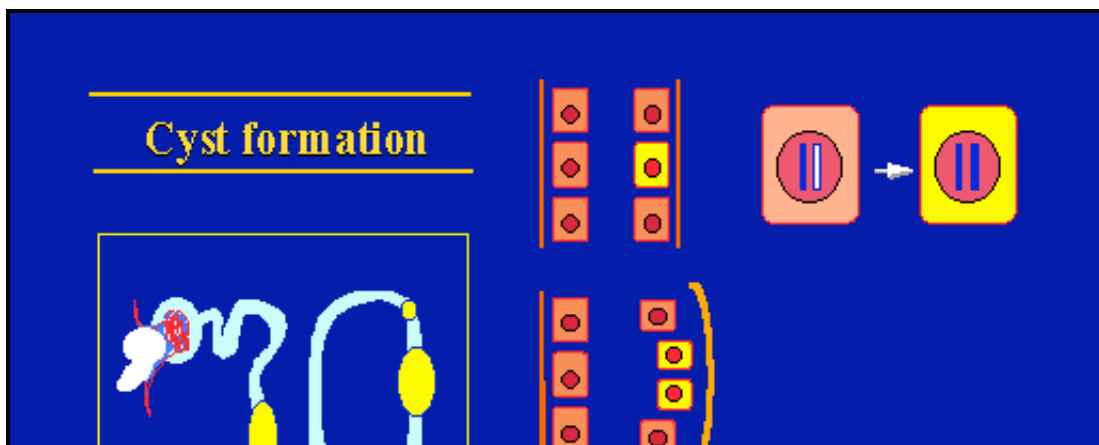
PKD2 protein is also like a serpent through the membrane except this protein seems to encode a calcium channel. So if you will, PKD1 seems to act as a receptor by binding to its appropriate contact on another cell or in the matrix. It sends a message via this physical interaction to the PKD2 protein. In response, the PKD2 protein allows calcium to enter the cell and sets up a whole signaling pathway that seems to be very important in kidney development, in developing the kidney, and in maintaining the normal structure of the kidney epithelium and the normal function of the kidney epithelium.

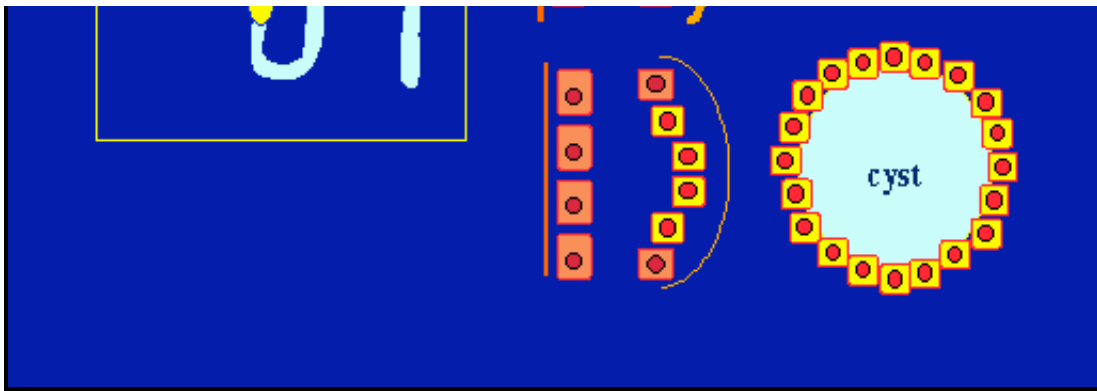
ATM machine analogy

One other analogy that sometimes people think is helpful--this whole scenario is kind of like an ATM machine. You put your card in here. It stimulates this receptor that talks with something immediately on the other side of the face of the ATM machine and sets up a whole series of reactions. Instead of the readout being cash, the readout is the cell does what it is supposed to do. If you disrupt anything along that pathway, the card won't go into the machine, the machine won't read it with these early events, then you don't get the readout, you don't get what you are looking for. That is what seems to be the functional consequence of PKD mutations.

You could say, "I don't understand this. Every cell in the body has one abnormal copy of the PKD gene, whether it is PKD1 or PKD2. You told us only one to five percent of the nephrons have cysts. Not everybody has hepatic cysts. Not everybody gets intracranial aneurysms. How is it that only a minority of cells seem to be affected when EVERY ONE is carrying the disease copy?" Recent data is beginning to shed light on this.

00:00





The "TWO-HIT" hypothesis

This is what is called the two-hit hypothesis. I will briefly go through this... let me put it another way, simply go through this. Dr. Stefan Somlo is going to be here tomorrow to talk about advanced genetics of PKD. He will be talking about this in more detail. It is really a very exciting recent series of discoveries because it is shedding light on what is going on. Over here is our nephron with cysts. This is in the one to five percent.

Here if we cut this tube sort of this way and just expose the inside... this cell has one abnormal copy of the disease gene, but all of the cells of the similar color have the same abnormal copy. The reason I have now drawn this cell in yellow is because that normal copy was lost.

So, if you will, at a cellular level ADPKD seems to be acting as a recessive trait. Remember I told you we can learn things about the recessive disease from ADPKD and about the dominant disease from recessive PKD? Well, at a cellular level, ADPKD seems to be acting as a recessive trait. What happens is when you then lose function in both copies of the gene? The cell loses all its normal checks and balances. It starts to grow. It starts to divide, to proliferate. It does that in an unregulated way. It doesn't interact with its basement membrane in a proper way, and that give rise to a cyst.

00:00

Abnormalities in ADPKD

ADPKD

Normal

- A. Fluid movement**
- B. Cell proliferation**
- C. Basement membrane**

Second hit occurs sporadically, causing only some tubular cells to be affected

This second hit only occurs periodically, and therefore probably accounts for the fact that only one to five percent of the nephrons are involved. But in those nephrons, those epithelia are no longer regulated.

Functional consequences of cystic tubular dilatation

As a consequence of that, several things go wrong. Number one, over here are the normal nephrons, those nice little epithelial cells sitting on their basement membrane. By and large the function of this tubule is to move salt and water across this membrane from the inside back into the blood. When you have this kind of event occur, the cells start to divide; they start to multiply. They can even pile up on one another causing what are called microadenomas. Those cells don't interact properly with the matrix; so instead of the matrix being nicely organized, it becomes disorganized. Too many matrix proteins are made. The composition of the membrane is not well regulated. Most importantly, perhaps, fluid starts to move in opposite directions. So instead of moving out of this lumen into the blood, it starts to be pumped in. Remember I told you when these cysts form, they wall themselves off from the rest of the nephron, so they increase in size, it appears, as a function of this abnormal movement of fluid.

Why caffeine ingestion might exacerbate cyst enlargement

Wouldn't it be a great thing if we knew a way to block this abnormal movement of fluid? Someone asked about caffeine. This process seems to be regulated in part via a chloride channel, in fact the chloride channel that is involved in cystic fibrosis. Let me be clear--that is not to say ADPKD patients have cystic fibrosis. It is just the protein that happens to get picked off in cystic fibrosis is important in kidney epithelia. It is by this mechanism that an ADPKD epithelia that have gone awry, chloride and water and salt, can move into this space and make a cyst grow bigger and bigger.

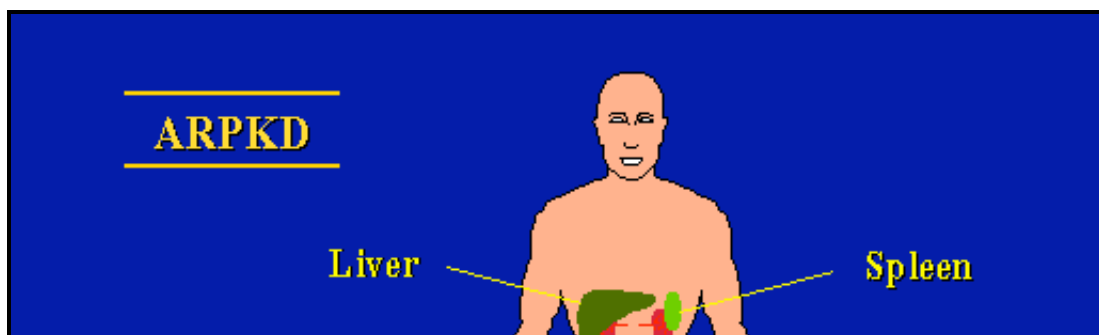
Effect of caffeine on cyclic AMP, which regulates a chloride channel

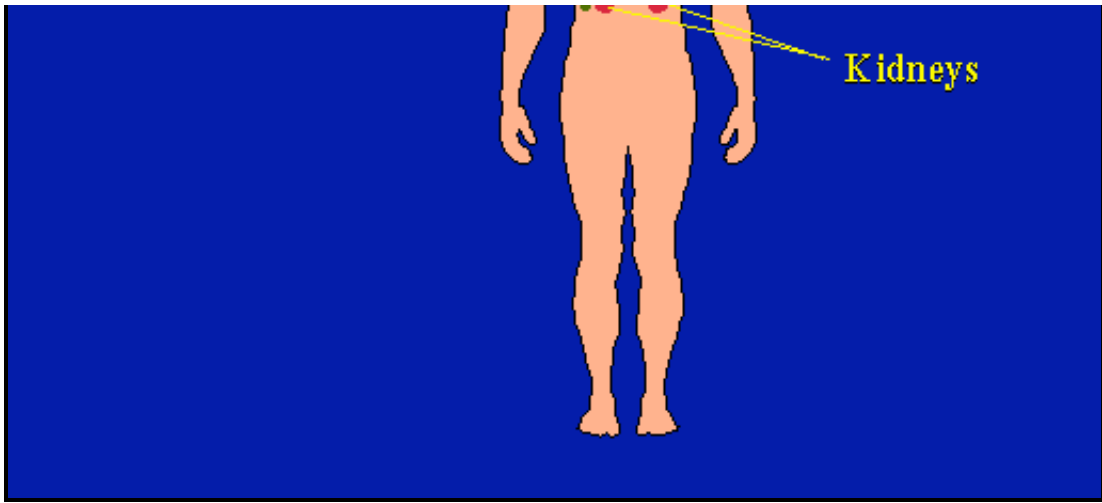
That whole process can be regulated by a substance called cyclic AMP, and caffeine is something that can increase that effect. That is why people write about it. It is a theoretical basis. Don't drink lots of caffeine because cyclic AMP seems to be important in this fluid secretion process in ADPKD. There are studies in animals that suggest caffeine actually can cause cysts to increase in size. That data are not precisely applicable in humans. But again, it is kind of that logical thing.

Green tea drinking in the South

In the Deep South, people are weaned from breast milk to sweet tea. It is really true. Kids all drink sweet tea. So they have a very high caffeine load. The first thing I always say to parents who come in with kids with ADPKD is, "You've got to keep the sweet tea to a minimum, preferably decaffeinated sweet tea." Now it is not something that is going to hurt a child not to have their requisite component of sweet tea. In fact, probably all of us could do with not having excessive amounts of caffeine. I would caution you--the data are borrowed from animal studies and they are inferred from our understanding about the physiology. Specific data in human cystic disease is not available; but it is a simple thing to do, so don't drink too much caffeine is probably very reasonable advice. That same sort of cyclic AMP-mediated process seems to be important in the progression of cystic liver disease. So you get two bangs for the buck by curtailing your intake of caffeine.

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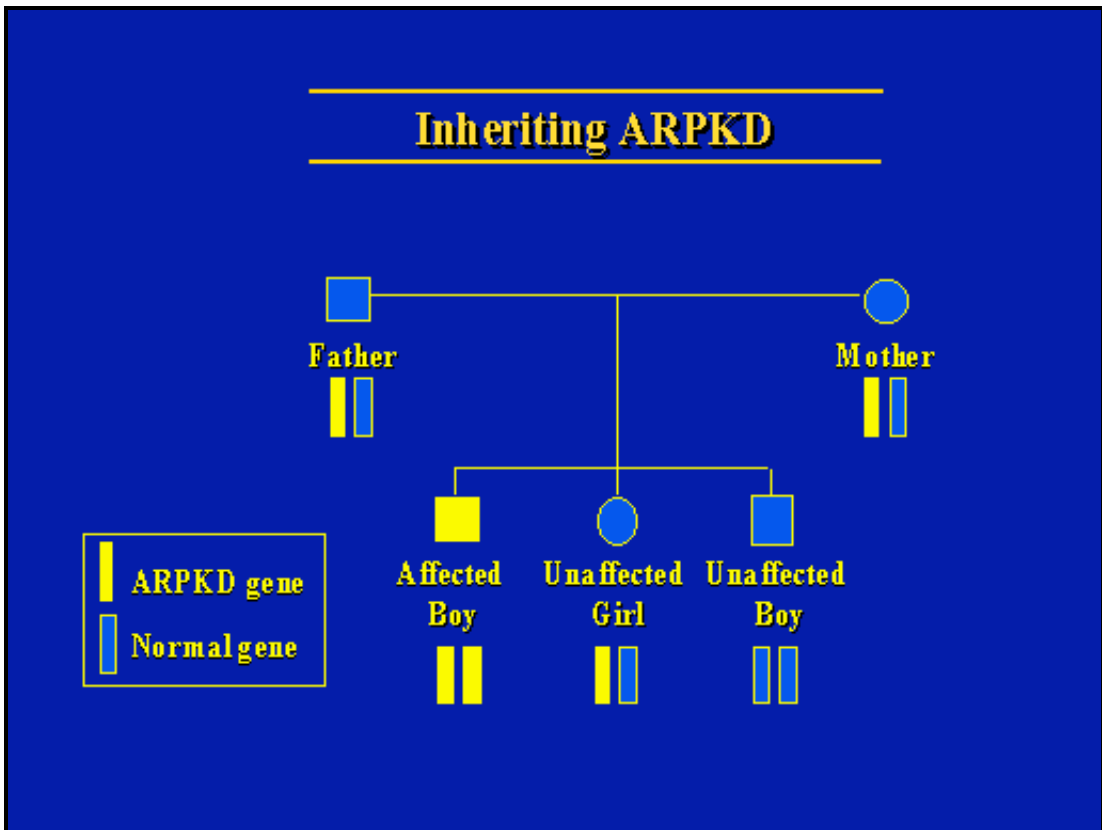




ARPKD

Let me switch for the last few minutes of my talk to talk about ARPKD. As I mentioned, it is a disease that primarily involves the kidneys and the liver.

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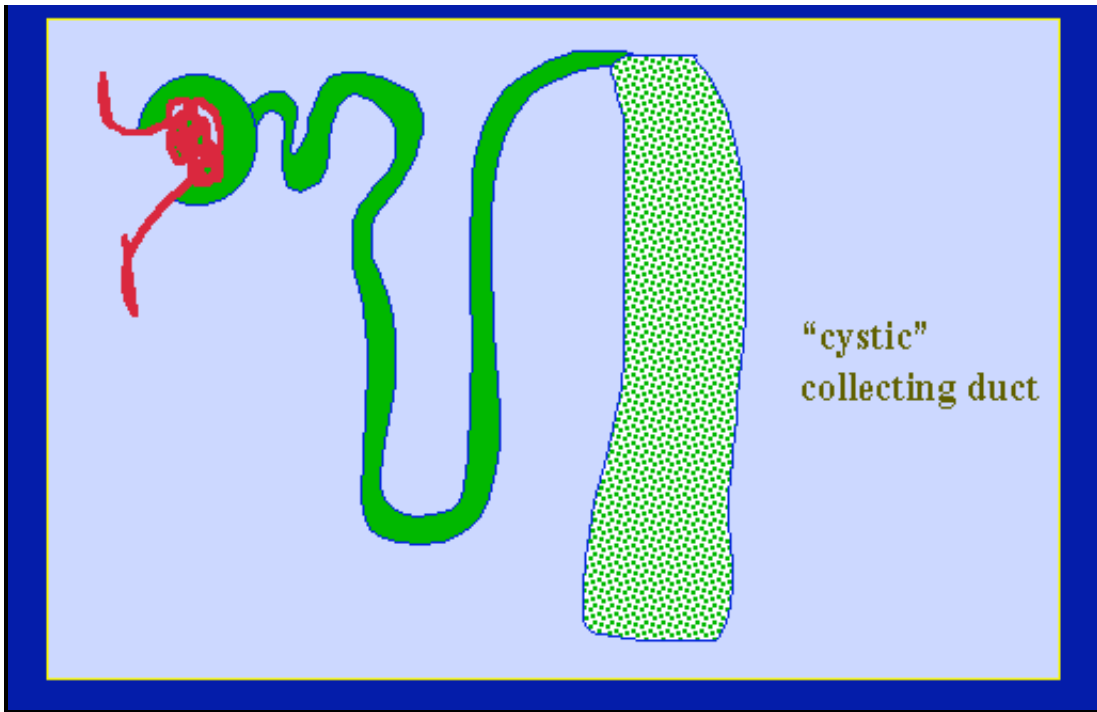


ARPKD has a RECESSIVE inheritance

Recessive inheritance, unlike dominant inheritance, the transmitting parents each have a diseased copy of the gene, but they are completely asymptomatic. To be symptomatic you need two copies, two disease copies of the gene. In ADPKD, this may be happening at a cellular level for specific individual cells that lose the good copy of the gene. But in ARPKD every cell has lost both copies.

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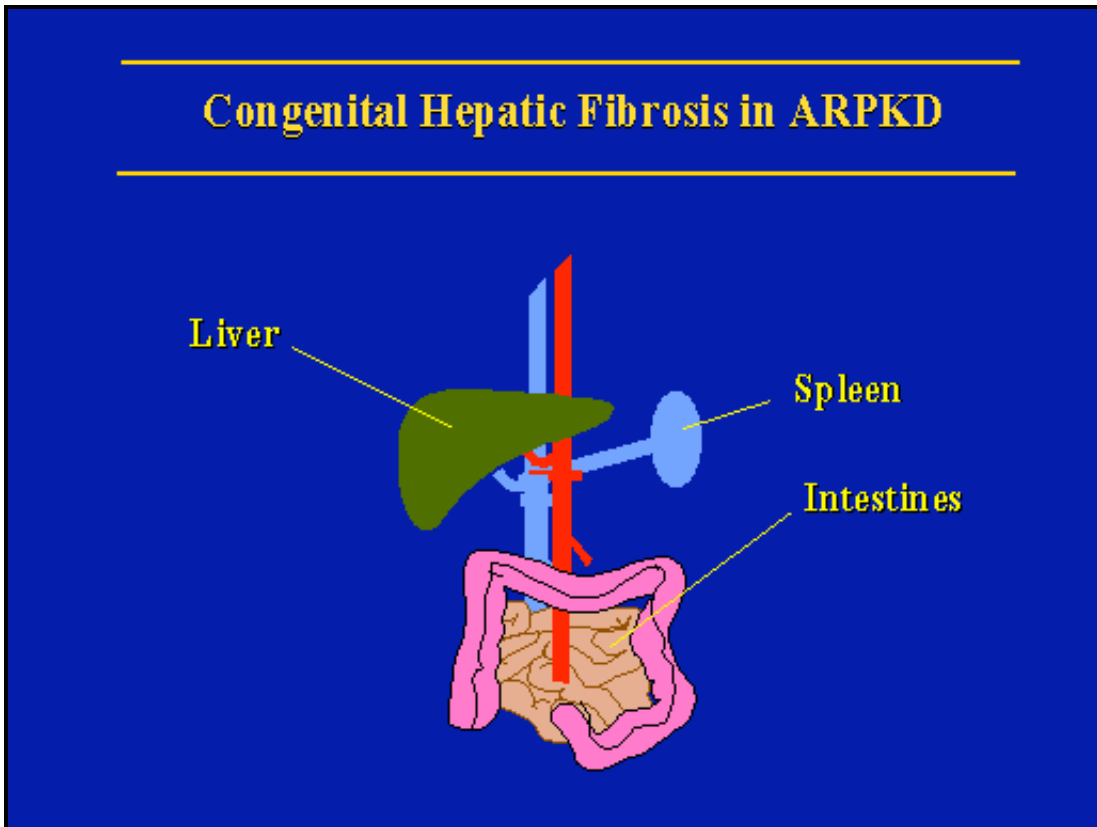




In ARPKD, the nephron is affected differently

This is the ARPKD nephron. Very interestingly, the cysts involve the collecting duct almost exclusively.

00:00



Liver is involved more severely in ARPKD

In the liver the problem is a scarring around the biliary ductules, those tiny little structures that transport bile into the bowel. As a result of that, blood coming back through the veins from around the intestines backs up because the pressure in the liver is too high and blood, like water, flows where there is least resistance. So it can't make it through the liver and

backs up into the spleen. The spleen of these children can get quite big. When the spleens get big, they can take on abnormal biologic activities. They can start to eat blood cells. Also that back up of blood can cause distension of the blood vessels around the esophagus and those can rupture and cause bleeding. Those children can come to medical attention because they are vomiting blood. They can lead to what is called venous distension around the intestines, and that can be a problem for some children in terms of eating.

Further talks on ARPKD at the current PRK Foundation meeting

There is a whole series this weekend devoted to ARPKD... to a large extent This is a credit to the Foundation and to the singular magnificent efforts of Colleen Zack. There is a whole session on ARPKD on Sunday for those parents in the audience who have children with ARPKD. In addition, tomorrow in one of the break-out sessions, Dr. Ellis Avner is going to talk about ARPKD in some detail, so I am going to give you the highlights here.

00:00

	UAB Database (n=70)	Zerres et al. (n=115)
Prenatal dx	40%	10%
Hypertension	57%	70%
UTI (girls)	31%	25%
ESRD	16%	10%
growth retardation	21%	25%
chronic lung disease	10%	--
portal hypertension	12%	46%
1-yr survival	96%	94%

Clinical course of ARPKD

This was a large study done in Europe by Klaus Zerres. This is a study that is ongoing at the University of Alabama at Birmingham looking at North American children from both the United States and Canada.

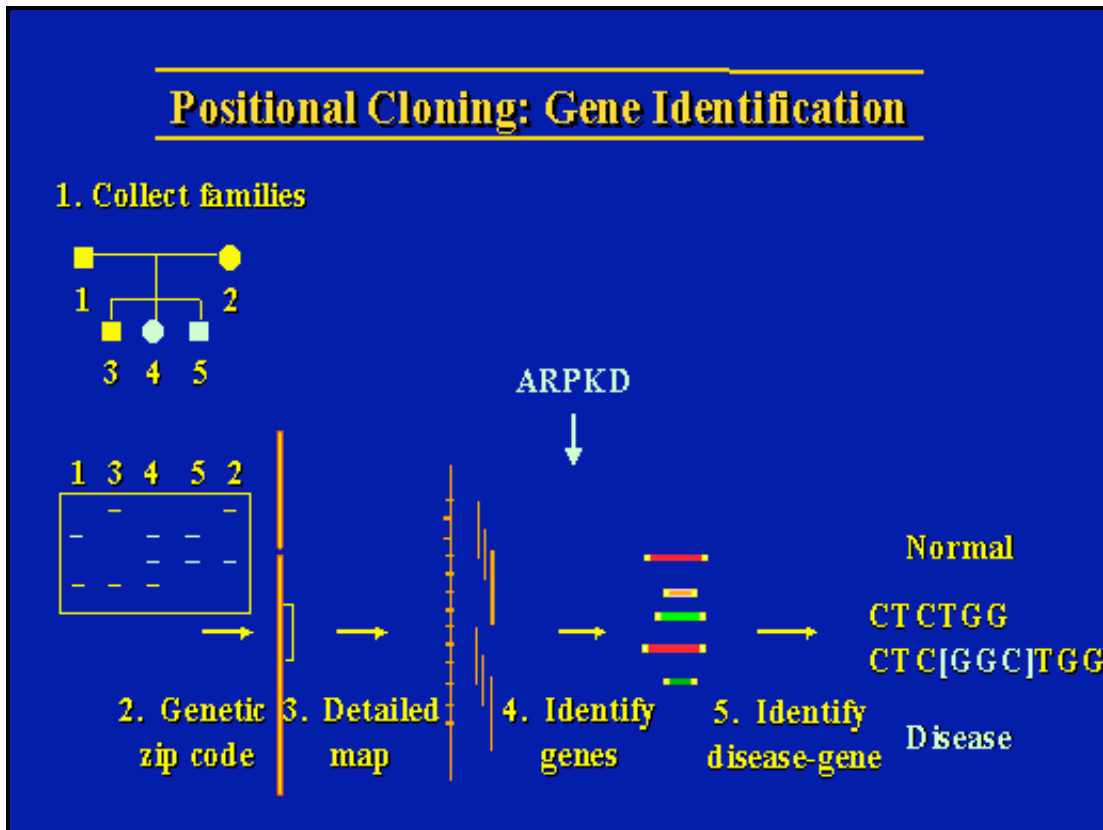
What you can see is hypertension is very common in both European and American children in ARPKD. Urinary tract infection, in girls is very common. Progression to end-stage renal disease, interestingly, only occurs in about 10 to 15 percent of these children. I point this out because there are still people who think the recessive form of the disease is an obligatory death sentence for these children. It is true that probably 30... maybe a little bit higher percentage of these children who present in the first few hours of life die as a consequence of their lungs not developing properly because in utero their kidneys didn't work well. But it is not a uniform death sentence, and I want to stress that.

I also want to stress that if these children survive the perinatal period, they have an excellent one-year survival. As our data grow and as the data from Klaus Zerres grow, it appears that these children have a very good 5- and 10-year survival, as well.

Complications of ARPKD

The complications. They tend to have problems with growth. Some of these children have problems with chronic lung disease. Again, their lungs don't develop properly because their kidneys didn't work in utero very well. And they have problems with this portal hypertension. The cohort that Klaus studied is a little bit older than ours, and this discrepancy may represent an age-related phenomenon.

00:00



Prenatal genetic screening for ARPKD

In terms of the genetics, we are using exactly the same strategy in ARPKD that was used in PKD1 and PKD2. In fact, it is a consortium effort. My lab is involved; Greg Germino's, who was very much involved in the identification of the PKD1 gene; and Stefan Somlo's lab is involved, his lab being the group that cloned the PKD2 gene.

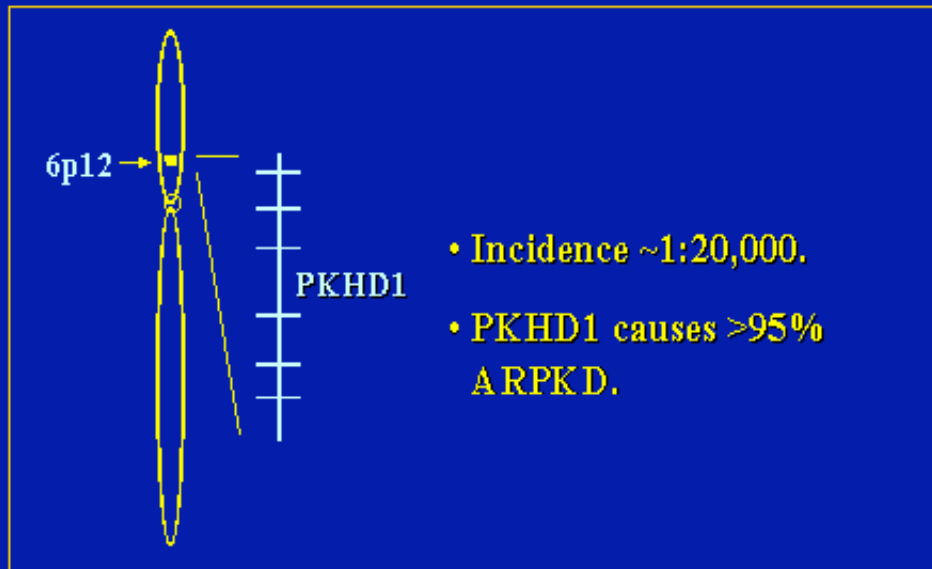
Basically the way this works for all these diseases--you identify a collection of families; you determine the genetic Zip Code--where is this gene because we don't have any idea how to get there otherwise. You make a very detailed map of that region and in fact identify clones that contain pieces of DNA from that region. So you basically take this whole region and a series of clones, overlapping clones, that you can then put into your refrigerator to study.

By study, I mean that you examine those clones/pieces of DNA to identify the genes and then you look at those genes in patients who have the disease to find a mutation. Here is where we are with ARPKD. We have a genetic Zip Code, we have a detailed map, we have identified most of the genes in the interval, and we are systematically screening them looking for mutation that will identify the ARPKD gene.

A question on the minds of parents in this audience... Colleen always asks me, "When are you going to get the gene?" The problem with this sort of approach--we could have it tomorrow; we could have it in two years. There is just no way of knowing. But there has been substantial progress, and the Foundation has supported some of that progress. They certainly have supported the database for ARPKD.

00:00

ARPKD - Genetics

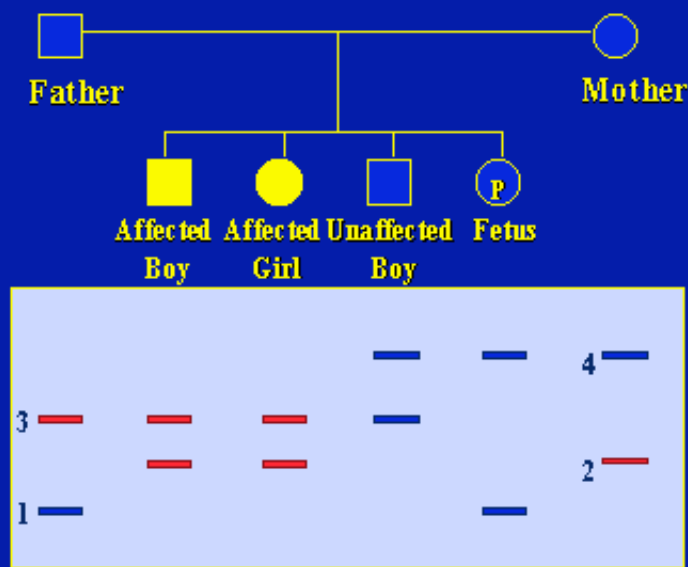


ARPKD genetics

This gene on the short arm of human chromosome 6 accounts for the vast majority of the disease. So unlike ADPKD, there really seems to be one gene for ARPKD.

00:00

Linkage-based Prenatal Diagnosis

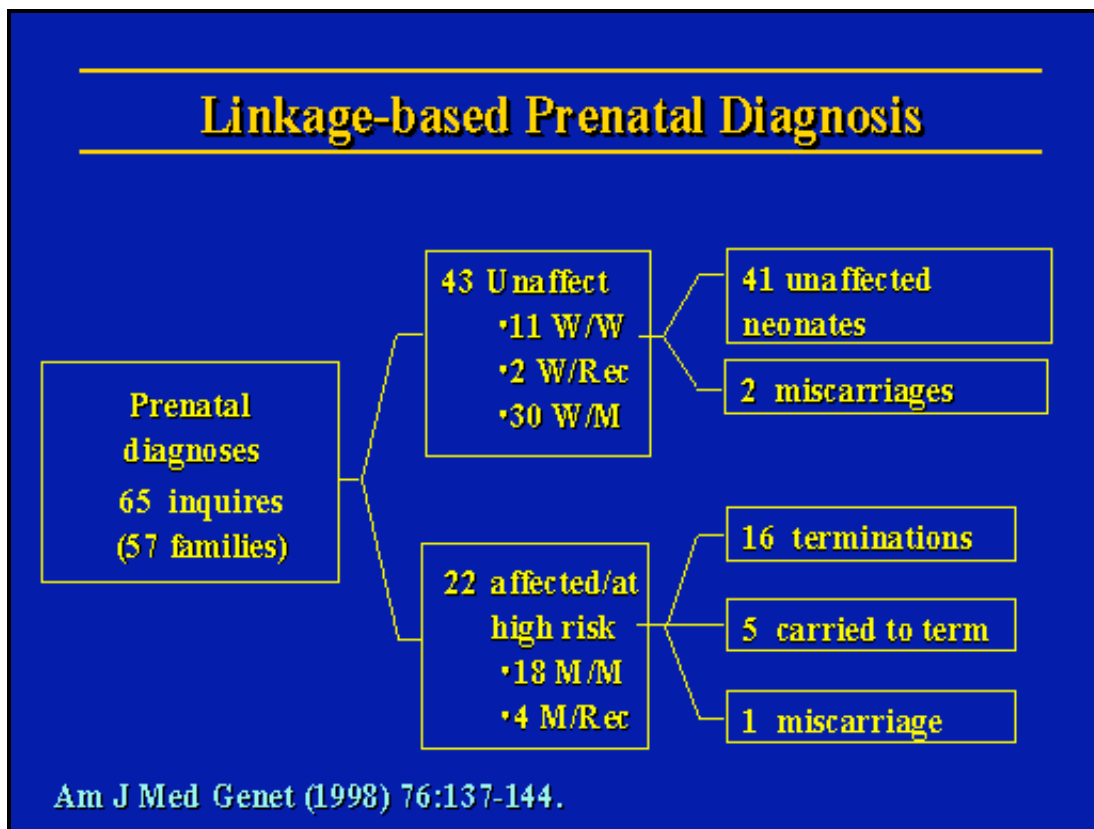


Linkage-based prenatal diagnosis of ARPKD

We can use that information for linkage-based prenatal diagnosis. I think that is very important. I have taken you through linkage analysis in the context of ADPKD. Let me point out to you that many of these children die in the newborn period. Parents have decisions to make about pregnancies at risk. Every pregnancy in this case has a 25 percent chance of being at risk.

If you live in a small town in western Nebraska and you know that you have a child with ARPKD, you have a decision to make about each pregnancy. Do you go to the big center that is 300 miles away to deliver another baby that may well die within 24 hours because your first child did? Do you terminate the pregnancy? How do you think about these things? It is a very vexing, very personal, really very difficult decisions.

00:00



For many of these people what they want is the most reliable test so they will know whether the pregnancy is affected to at least simplify some of their decision making. We can use the same genetic neighborhood information to do prenatal diagnosis. What this slide shows in some detail, and we published this in The American Journal of Medical Genetics in 1998, is that linkage-based testing for prenatal diagnosis of ARPKD is both feasible and reliable.

In fact, in the last two years at the University of Alabama at Birmingham, we have done 50 prenatal diagnoses, 100 percent of the families have been informative with those genetic markers that we are using. In every situation what we would predict based upon the genetic information has been the outcome of the pregnancy. So if we said a child had a very high risk of being affected, that child was affected. If we said the child was probably not affected, in fact at this point that child looks like they are not affected. So I think this has been a very important addition, even before we get the gene, to our treatment of ARPKD.

00:00



Perspectives

Perspectives

Let me try to put ALL OF THIS INFORMATION in the last few minutes into perspective for you.

00:00

Milestones in PKD Research

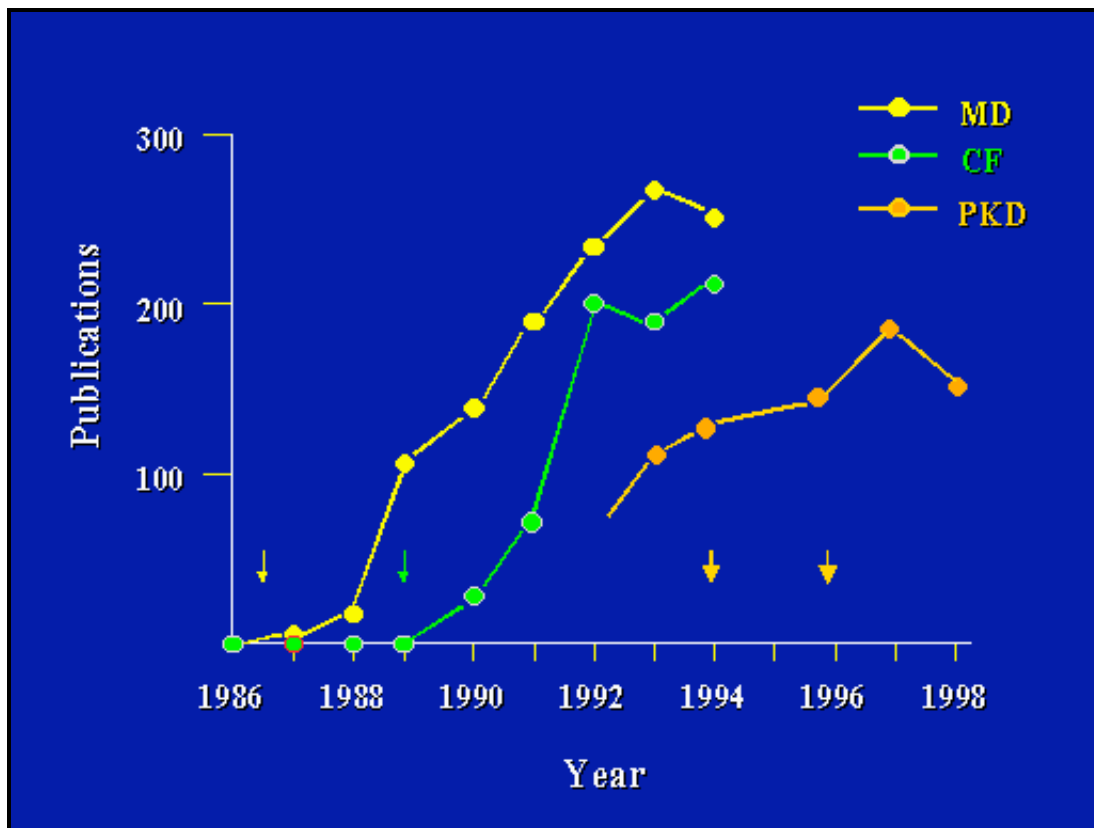
- 1888 PKD first described
- 1957 ADPKD defined as an inherited disorder
- 1982 PKR Foundation founded
- 1985 PKD1 gene mapped to Chromosome 16p
- 1993 PKD2 gene mapped to Chromosome 4q
- 1994 ARPKD gene mapped to Chromosome 6p
- 1994-5 PKD1 gene isolated and characterized
- 1996 PKD2 gene isolated and characterized
- 1997 PKD1 and PKD2 interaction
- 1998 PKD1 and PKD2 mouse models

Milestones

These are the milestones in PKD research. In 1888, PKD was first described. In 1957 in a seminal report, Dalgaard determined that autosomal dominant polycystic kidney disease is actually an inherited disorder. In 1982 Mr. Breuning and Jared Grantham founded the PKR Foundation. All of these subsequent achievements have been funded at least in part by the PKR Foundation. The mapping of the PKD1 gene, the mapping of the PKD2 gene, the mapping of the ARPKD gene- -work that was done in my laboratory, the identification of

the PKD1 gene, the identification of the PKD2 gene, the determination of some of the biology that these gene products interact, and the creation of mouse models so that the disease can be studied was all funded in part by the PKR Foundation.

00:00



Gene discovery increases the number of publications for a given inherited disease

Here is a slide that I think is quite helpful. In the yellow is muscular dystrophy. In the green is cystic fibrosis. In the orange is polycystic kidney disease. The downward pointing arrows show when the genes were identified.

The gene for Duchenne's muscular dystrophy was identified in late 1986, and there was explosion of reports in the literature. Productivity and publications in the literature bespeak progress in our understanding of disease processes. That same pattern was followed after the 1989 discovery of the cystic fibrosis gene.

In trying to recapitulate this sort of story for PKD, it is a little harder because there are at least four human genes that are involved, the three genes for ADPKD and the gene for ARPKD, and there are a plethora of animal models. So it is a little hard to tease apart. But what you can see is certainly during the 90s there has been an increase in publications. In that increase in publications, there has been real progress in our fundamental understanding of what is going on.

00:00

*... So Horton kept sitting there, day after day.
And soon it was Autumn. The leaves blew away.
And then came the Winter ... the snow and the sleet!
And icicles hung
From his trunk and his feet.*

But Horton kept sitting, and said with a sneeze,
"I'll *stay* on this egg and I *won't* let it freeze.
I meant what I said
And I said what I meant
An elephant's faithful
One hundred per cent!"

Horton Hatches the Egg
Dr. Seuss

Closing comments

My postdoc said, "Can you kind of end this slide by saying, 'that is all great, but where was the real impact for patients and for patient care?'" I could spin a lot of stories, but I think what people are really asking is for that substantive breakthrough, that breakthrough that will attenuate the course of the disease, that breakthrough that will change us from 50 percent of people going on to end-stage disease by age 60 to less than 10 percent or maybe even no patients going on to end-stage disease. We are not at that point yet. I think perhaps the most appropriate way to close this talk in 1999 is to call on someone I consider to be ONE OF THE great social philosopherS of our time. I will quote you something from one of MY favorite works. This is from "Horton Hatches the Egg" by Dr. Seuss.

"So Horton kept sitting there day after day, and soon it was autumn and the leaves blew away. Then came the winter, the snow and the sleet, and icicles hung from his trunk and his feet. But Horton kept sitting and said with a sneeze, 'I will stay on this egg and I won't let it freeze. I meant what I said and I said what I meant. An elephant is faithful 100 percent.'"

This kind of work takes persistence, it takes faith, it takes patience, and it really takes a belief that we are going to get there. Horton hatched the egg. We are going to find cures for PKD. They may not be what we envision right now, but that breakthrough is going to come. Part of it is going to come because of you and your interest, because of your support of the Foundation, and because working together we are going to achieve that. I will close there. Thank you.

DISCUSSION PERIOD

Moderator:

The first question was a request to clarify the need of testing for aneurysms.

Dr. Guay-Woodford:

I think that is a very important question. Thank you for asking. Thank you for remembering to ask. The story that I presented is really the story of screening patients who come from families that were known to have intracranial aneurysms. But remember I told you about 10 percent of patients with ADPKD can have intracranial aneurysms. We don't know the natural history of intracranial aneurysms in ADPKD precisely.

We do know the following: Some patients with ADPKD can have an aneurysm and they can develop another aneurysm. Or they can have one aneurysm that ruptures and have several other aneurysms that have been asymptomatic. What that suggests is that at least in some patients with ADPKD the disease involves the cerebral arteries, the biology of the cerebral arteries. If you have been identified as someone with that kind of complication, probably you need more frequent screening.

In terms of having precise algorithms of how to do this, I think here we borrow from the

general population and particularly from a subset of the general population who have familial intracranial aneurysms. So here I would defer to your neurosurgeon about how frequently that would be done. My sense of things is it is about every two years or so in someone who has already declared themselves as having this particular biology. Does that answer your question?

Moderator:

The question is for women who are starting estrogen replacement or hormonal therapy if you would clarify your comments about that.

Dr. Guay-Woodford:

We know that postmenopausal estrogen therapy is associated with an increased risk of developing more hepatic cysts. One of the alternatives is to have transdermal administration of that estrogen. The other thing is I think this is one of those places that common sense is important. Cystic liver disease is a problem in ADPKD. But osteoporosis is a very big problem in women who are postmenopausal, and estrogen therapy clearly has a benefit. It also has a benefit in cardiovascular disease. So what if you come from a family where on one side came ADPKD and on the other side came a bad history of osteoporosis and cardiovascular disease?

I think here it becomes a thoughtful, judicious tradeoff--the tradeoff of trying to administer the estrogens in a way that is going to have limited effect on hepatic cysts, and maybe a transdermal approach is one of those ways. But the other is to pay attention to things that have very high morbidity and even mortality. As you know, the risk of mortality for women from cardiovascular disease goes up dramatically in the postmenopausal years. That kind of issue has to be paid careful attention to. Therefore in summary, I don't think there is a simple answer. I think there is a tradeoff.

Moderator:

The question has to deal with the process of potentially draining cysts when there are a number of them in each kidney that are causing problems.

Dr. Guay-Woodford:

I think that there are a number of ways to address symptomatic cysts in the kidney. One is to just put a needle in, particularly if you have a set of dominant cysts that are really big and that are causing problems. You can put a needle in and take out the fluid. Most of the time, not always, but most of the time that procedure is just a stop-gap measure because often that fluid will re-accumulate. So if people do that procedure, what they will often do is put a substance in like 95 percent alcohol that will kill all those cells lining that cyst so they won't be able to pump more fluid in.

If your problem is that you have a number of cysts that are causing pain, causing discomfort, then a more reasonable approach may be to use a laparoscopic approach and to just basically take little pieces off the roofs of all of those cysts. These kinds of things are judgement calls certainly when you get into laparoscopic approaches and surgical approaches that require the consultation of a surgeon. The idea, again, is above all, do no harm. You don't want to set someone up where the good news is we opened the cyst; the bad news is we left you with a series of complications.

Let me digress further on that point to just say one more thing. We know that when we decompress cysts that blood pressure can get better. But by and large, the indication to go after cysts is pain because the blood pressure effect is rather unpredictable.

Moderator:

The question is: Since cyst bleeding is not good, is there any contraindication to lithotripsy?

Dr. Guay-Woodford:

Let's examine what lithotripsy is. It is taking sound waves and targeting them in on a stone. It works best if the stone is less than 2 cm; 2 cm is less than an inch. So if you have a really big stone, this isn't going to work. But if it is less than 2 cm, you have a very good chance that it will work. The stones aren't in the cysts. The stones are in the collecting

system of the kidney. Because it is targeted sound waves, the sound waves themselves shouldn't disrupt the cysts and therefore if there is bleeding this probably doesn't have the same significance as a bleeding cyst.

Moderator:

The question had to deal with if there is another method other than genetic linkage testing to determine whether or not you have the disease, I guess before birth, especially if you don't have other members of the family who are living and can be tested.

Dr. Guay-Woodford:

Yes. I think the situation comes up in two possible scenarios. One is before you were symptomatic but you new there were family members who had died of the disease. That may be one reason you're asking the question. The other is you have been diagnosed with this disease, and you want to be sure it is ADPKD. Let me take the first situation.

The first situation--the short answer is no, right now. Because before you are symptomatic, particularly if you have already had an imaging study and you are less than 30 years of age and you don't have cysts in your kidney-- at this point we could scale up and do a more sensitive imaging study--CT and MRI are better at picking up small, little cysts. The only reason I would really push that issue though is if the reason you don't have any surviving relatives is because they died of intracranial aneurysms. If they died of intracranial aneurysms and they had an autopsy, we can get DNA out of autopsy material. We do it all the time for ARPKD because many of these children die. So that is something that could be explored with your physician and with one of the genetic diagnostic companies in the United States, like for example Genzyme, whether they would be willing to think about doing that. In that situation, you really want to know if you have the disease because you want to know, "Should I be starting to be screened for these kind of complications, for intracranial aneurysms?"

If the situation is the other situation where you have the disease and no one in the family was known to have it, as I said, there is about a 10 percent... perhaps as high as 10 percent spontaneous mutation rate. But here we fall back on clinical patterns: big kidneys, lots of cysts, cysts in the liver, no evidence of any brain involvement in terms of seizures or cognitive impairment, no evidence of any significant pancreatic involvement, evidence that these cysts are simple and not something that is associated with tuberous sclerosis, for example. All of those sorts of things we pull together in a clinical pattern to say this pattern looks most like ADPKD.

Moderator:

Thank you. I think you have a bit of a picture of some of the wonderful people who represent our organization from a scientific/medical standpoint. One thing you need to know is these doctors don't get paid a penny for what they are doing here this week. All we are able to do is provide for their travel expenses and so on. They do this out of the goodness of their hearts and their love and their desire to serve PKD patients. I really want to hire the folks who cloned Dolly and clone Dr. Guay-Woodford and all you others because there are so few of them around. Let's express our gratefulness to Dr. Guay-Woodford.

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