

SPEAKER 1: Well, I appreciate the opportunity to talk today about a topic that has been extraordinarily important to pediatric urology. I am a pediatric urologist, and our field was really founded on the diagnosis of vesicoureteral reflux. So I know my title today might make some pediatric urologists a little bit nervous. But I think when we walk through this, you'll see that there is a different way to look at how we diagnose and manage reflux and urinary tract infection.

I also want to focus on population health, which is an area that, as pediatric urologists in the clinic, we don't think about very much. We really think about our patients from a very individual point of view. And I hope that I will get across the fact that when we think about patients as individuals, we miss opportunities to really use our resources as wisely as we might.

Sadly, I have no financial disclosures. But I do have two other disclosures. And one is that I am a suit. So although I'm a pediatric urologist, for the last 10 years, I've been the chief medical officer of the Children's Hospital of Pittsburgh. And as a suit, as someone who's on the administrative side of the house, I tend to look at clinical issues a little bit differently than I used to from the point of view of the clinic. And that informs, I think, a little bit of what I'll talk about here today.

The second is a quote from Huxley that I like and that I think I will represent today. The nature of oratory is such that there has always been a tendency among politicians and clergymen to oversimplify complex matters. From a pulpit or a platform, even the most conscientious of speakers finds it very difficult to tell the whole truth. And I do promise that I'm going to oversimplify and avoid telling the whole truth during this talk. And it really is because I'm trying to make a point.

So I'm going to talk about population health in one slide. There have been books written about population health, so I'm not going to do it justice. But this is really for those of us who don't think about it every day. Population health, very simply, is looking at improving the health of the entire population. And in our case, that would be the population of children. That is done through activities that haven't typically been ours to handle, like health promotion and disease prevention, focus on socioeconomic factors and the physical environment. And in order to really affect this, we need to have very broad systems of data sharing. If you look at our electronic health record, it only represents those children who come to us because they have significant illness.

If you want to understand the health of the entire population, you need health plan data, you need data from schools and community organizations, you need all sources of data to understand the entire population. And we are really just at the tip of the iceberg of understanding how to bring all of the data together to understand the population's health.

One of the examples that I like to give about the difference between looking at health from the point of view of the individual versus the population is asthma. And it's a really good example, because I know nothing about asthma. But when we take care of asthma today, we are very focused on the individual. And even more so than the individual, on the bronchioles of the individual.

And we're very good at managing those children who come into our emergency department who are sick enough to be admitted to the acute care floor, or who are sick enough to be in critical care units. And we can recover them to health by focusing on relaxing those bronchioles. And when we do that we're also very careful to capture the complexity of our care with appropriate coding. Why do we code appropriately? So that we can get reimbursed appropriately for our care. Very important to keep the health system running. Because we do get compensated for care, we also want to make sure that when your child has an asthma attack, they wind up in our emergency department and not somewhere else. This is kind of the way we focus on the individual when it comes to asthma.

But if we look at asthma from a population health point of view, it really is very different. We might advocate with the government to reduce particulates in the air. We might work with community resources to get into the homes and reduce mold and dust, give out HEPA-filtered vacuums, for example. We might work with schools to enhance asthma education, and to get our school nurses focused on preventing acute exacerbations. We would educate our families and primary care providers in providing day-to-day care in early intervention.

And the whole idea would be to keep children out of our emergency department, keep them out of our hospital, keep them healthy. That's what population health is. I refer to it as external medicine, because we're really focused on everything outside of that child that might impact their likelihood of having an exacerbation.

It's clearly the right thing to do. So why don't we do it? And there's one minor problem. We don't get paid to do any of these things, at least in the current system. And I am not here to talk about payment or payment models. This is the only mention I'll make of it. This is a slide that I've borrowed from the advisory board, basically showing that there are new models of payment that are coming into the health system that may help to correct these incentives that cause us to think more about acute care than preventative care. Not the point of today's talk, but I am looking forward to the day when we can be compensated for improving the health of the population as opposed to the other way around.

So let's say you are a pediatric neurologist or a pediatrician. The question is why do you care about this. You are really focused on taking care of children, not on the money. And as a urologist, very focused on taking care of kidneys. Well, so let's talk a little bit about urinary tract infection and reflux, and try to make this personal for the urologists and the pediatricians out there.

The traditional teaching when I was a resident was that all children who have a urinary tract infection get a voiding cystourethrogram. That's the study, for people who aren't familiar, that allows contrast to be introduced into the bladder through a catheter. And during voiding, evidence of reflux of that contrast to the kidney makes the diagnosis of vesicoureteral reflux. If reflux is found, then all patients get prophylactic antibiotics to prevent infection. That's a once-daily dose of a first-line drug. And then that antibiotic is given until the reflux goes away either on its own, because we know that reflux does have a tendency to resolve, or the reflux is surgically corrected. Much more fun for those of us who are surgeons. That's the traditional management.

And the way that we, in the past, dealt with reflux is we always try to detect it if it's there. And then we go to our national meetings and argue about how it should be managed. And we argue about things like should we use prophylaxis or not. Should we just watch and wait, and see how these children do? Should we correct higher grades of reflux preemptively? Should we correct if there's breakthrough infection? And if we do correct, what of the many, many different ways to correct reflux should we use? Transvesical, extravesical, robotic, et cetera.

The outcome that we have measured and that we've reported, and if you look in the reflux literature, is the outcome of reflux resolution. That is making the assumption that reflux is the disease and that resolution is the cure. And I'm going to make the argument that that's really not the way we should be thinking about it. So what's our role today? Our role today really should be to argue about the real issues. And the real issues, in my mind, are does vesicoureteral reflux matter at all; if it matters, does it matter for everyone who has it; and do we need to care whether or not a child who has a UTI, particularly a first UTI, and has normal upper tracts by ultrasound has reflux, is this important?

So we know from a number of wonderful studies, this is an example of a study done here in Pittsburgh, that about 40% of children who have a first urinary tract infection will be found to have reflux. And the majority of them have lower to middle grades of reflux, measured on a scale of 1 to 5. But when we look at normal children, and that's defined as children who've not had a urinary tract infection, what is the prevalence of reflux? Well, I was always taught, and we've all been taught, that it's less than 2%. And this comes out of studies that were documented five, six decades ago, and really have been quoted for all of these years. Here's one study showing seven out of 535, or 1.3%, children without a history of urinary tract infection were found to have reflux.

So if you think about it, if we say that less than 2% of children have reflux, and we say that 5% of children will have a urinary infection prior to age 7, and we know that very well, and then we say 40% of that 5% will have reflux, the calculation is that 2% of children will have reflux and a urinary tract infection. Which implies that every child with reflux has urinary tract infection. If you believe that, and if that's true, then reflux is clearly a very important diagnosis to make. I question whether or not our understanding of the prevalence of reflux in the normal population is true and appropriate.

First of all, we can look at a number of diagnoses for which VCUG screening has been done. One is we know that siblings of children who are found to have reflux have a relatively high incidence of reflux. And back when we thought, and some people still do, that it was very important to know about reflux if it's there, we felt that we needed to screen all of the siblings of a child who had an infection and was found to have reflux. So that if they had reflux they could get preventative antibiotics and we could prevent that infection that might otherwise cause kidney scarring in them.

So there have been a lot of studies looking at sibling screening. Here's just one example. 47 of 108 siblings who were screened for reflux were found to have it. That's about 45%. 40 of those were followed for three to seven years on prophylaxis. And it turns out that only two of those 40 had a urinary tract infection. Much lower than we would expect of the population of children who are found to have reflux after a urinary tract infection. Turns out that none of these children had progressive renal scarring. And there are many, many studies like this, to the point where most of us today don't recommend sibling screening.

To me, the high incidence of sibling screenings suggests that there may be reflux out there in the population that is causing no trouble whatsoever. And we know that it's true, because somewhere between 30% and 50% of siblings of children with urinary infection and reflux are walking around with reflux and having no problems.

Second example that I would use is multicystic dysplastic kidney. For many, many years we screened all children with a multicystic kidney on one side for evidence of reflux on the other side so that we can use prophylactic antibiotics to prevent infection. Here's just one study coming out of Indiana. Looking at 133 newborns with a one-sided multicystic dysplastic kidney, all followed for at least two years, 23, or 17%, were found have vesicoureteral reflux. And it turns out of the 133 original children, six had a febrile urinary tract infection. Only two of them were children who had reflux. So 16 of the 18 children found to have reflux were completely asymptomatic with their reflux. Granted, they were on prophylactic antibiotics for a period of time.

So Sargent, back in 2000, following a similar line of reasoning, looked at more than 250 articles where children were screened with a VCUG for many different conditions. In most of these, he found the prevalence of reflux in the children without infection was very similar to the prevalence of reflux in children with infection, and estimates the overall prevalence of reflux in children with normal kidneys as 17%. Much, much higher than 2%. Once again suggesting that just having reflux does not imply that you have a disease.

So leave all that aside for the moment. You can't really talk about reflux without talking about what I think is the most important study that's been done in this area, and that's the RIVUR study, or Randomized Intervention for Vesicoureteral Reflux study. This was a multi-center randomized placebo-controlled trial. Children were entered anywhere between two and 71 months of age for a first or second diagnosed urinary tract infection and found on VCUG to have reflux grades 1 through 4. Grade 5 reflux was excluded. They had to be diagnosed with infection within 112 days of randomization. And they were followed for two years, looking at the impact of trimethoprim-sulfamethoxazole prophylaxis on primary outcome recurring UTI and secondary outcomes renal scarring and anti-microbial resistance. The first time an adequately powered randomized control study has been done to look at the impact of antibiotic prophylaxis, a treatment that we've been using for more than five decades.

The study looked at renal scarring, and looked at scarring in a very systematic way, defining scarring as mild, moderate, or severe-- or grades one, two, three-- based on the number of segments when the kidney is divided into 12 segments that are impacted by renal scarring. Any scarring impacting four or more segments is defined as severe renal scarring. It's important to think about that term as it's used, because you can have scarring impacting four segments of the kidney with really no impact on overall renal reserve. So even though we define it as severe scarring, it really doesn't necessarily have implications about future renal function.

So I want to take a very complicated study and distill it down to this one slide, and think about the results. Most importantly, the impact of antibiotic prophylaxis was found to be a 50% reduction in the likelihood of breakthrough or recurrent urinary tract infection, down from 25% to under 13% with prophylaxis. However, prophylaxis had no impact on renal scarring. None at all. Neither renal scarring in general or severe renal scarring, exactly the same in both groups.

Now there was another study that was done in parallel to this study called the CUTIE study, or Careful Urinary Tract Infection Evaluation. This was the study that looked at those children who were found on VCUG not to have reflux during screening for the RIVUR study. They had the same follow up and the same outcomes that were measured, although none of them had antibiotic prophylaxis. And so the results were combined in a wonderful article in *Pediatrics* with the no-prophylaxis arm of the RIVUR study to look at the risk factors for urinary tract infection, including reflux. I'm going to distill the results of a complicated study down to one slide.

And the bottom line is that if you look at those children with reflux, no antibiotic prophylaxis, their likelihood of having a recurring urinary tract infection, as we already mentioned, is 25%. But when you look at those kids without reflux, their recurrence rate is 17%. Not that much lower, and still a significant recurrence rate. Looking at renal scarring, interestingly enough, we find 8% renal scarring in the group with reflux-- we already saw that-- but only 4% in the group without reflux. And that is statistically significantly different. More likely to have renal scarring if you have reflux. Looking at severe renal scar formation, less than 1% in the reflux group, zero in the no-reflux group, not statistically different.

So what do people conclude based on these studies? Very reasonably, people conclude that reflux is a significant risk factor for renal scarring. It is. That continuous antibiotic prophylaxis reduces the risk of infection by 50% in children with reflux. We clearly saw that. And so, because of these things, screening for reflux is warranted after a first urinary tract infection in early childhood. I'm going to argue with that just a little bit.

First of all, when we look at the likelihood of finding renal scarring, what we've seen is that that likelihood is decreased over time. When we look at studies from the 1990s, about 40% of children diagnosed with reflux were found to have preexisting renal scarring. Now that number is 2% to 4%. The difference, we believe, is that both emergency physicians and pediatricians are much more keyed in to fever as a possible sign of urinary tract infection. And so these infections are diagnosed and treated promptly. And we believe that delay in diagnosis and treatment is really the most significant risk factor for renal scarring. It's not reflux, it's delayed diagnosis and treatment of urinary tract infection. And there's very good evidence to bear that out.

Secondly, when we look at the risk of end-stage renal disease in children with reflux, it's one of the things that we always talk about. But if you look at patient populations with end-stage renal disease and reflux, it turns out that they are overwhelmingly male. But if you look at the children who present with urinary infection and are found to have reflux, they are overwhelmingly female.

So what's the difference? The difference is that boys present with high-grade prenatally diagnosed reflux. That is often associated with renal dysplasia, congenital renal dysplasia. So the renal failure that they experience is not related to recurring infections and recurring renal scarring, it's related to congenital dysplasia and a lack of renal reserve to get them through their lifetime. And there are a couple of examples of this.

In this one quoted here, 118 of 278 children with congenitally acquired kidney and urinary tract anomalies who were found to be in stage three to five chronic renal failure had reflux at presentation. When you look at that group of 118 that had reflux, 77% were male. Once again, overwhelmingly male. Then as those children were followed longitudinally to see whether or not they progressed to end stage renal disease, and how quickly they progressed, whether or not they had reflux had no impact whatsoever on their likelihood or their rapidity of progression to end stage renal disease.

There was a paper put out in the 1990s by Stark using mathematical modeling to estimate the risk of a woman who had a first urinary tract infection as a child progressing to end-stage renal disease because of reflux. And the risk was considered to be about one in 10,000. That was re-analyzed in 2012 because there were concerns about the mathematical modeling and so a number of different models were used to look at that risk. And you can see that widely varying risks were calculated using these different models. But what was considered to be the best model estimated the risk in the United States to be about 1 in 200,000, which comports with our experience. It's vanishingly rare. It's something that is almost never seen.

So we talk about end stage renal disease, and it's very difficult to say that it can't happen. But we know when we look at the population that it hardly ever happens. So let's think again about what it feels like in the clinic when a family comes through the door and there's a child with a urinary tract infection. So the way that I was taught to counsel families when a child was brought in with a febrile infection is, number one, that child might have vesicoureteral reflux. If so, they might go on to have recurring infections and renal scarring. And if so, it's possible that that child could advance to renal insufficiency, the need for renal transplantation, and even early death.

So imagine what a parent's face looks like when you have that conversation. And the scary thing is that, for this individual child, it's all true. I can't say with 100% certainty any of those things won't happen when I'm talking about an individual. And that's why we need to think about the population when we counsel a family instead of thinking just about what could possibly happen to that one individual patient. Because after this conversation, this mother in this picture wants me to do anything I can to diagnose and treat vesicoureteral reflux. But I'm not sure that's really the right thing for this child.

So when we look at reflux from the point of view of an entire population, I think things look a little bit differently. So here's an example. 1,500 children that I'm responsible for in a population. Statistically, 100 of those children will have a culture-proven urinary tract infection. I'm going to make the assumption that we have a sophisticated health care system. So their infections are going to be diagnosed and treated promptly. And we're also going to make the assumption that all of these 100 children had normal renal ultrasounds. So we're not advocating a nihilistic approach. We do want to look at the kidneys with ultrasound. If they're abnormal, they are not the people that we're talking about here. They need aggressive management and aggressive diagnosis. But for this population, all of these ultrasounds are normal. A very simple example.

So here is our group of 100 children out of the 1,500 that have had a urinary tract infection. And because I happen to be omniscient, I know that those who are colored red have vesicoureteral reflux. We've not done any testing to prove that at this point, but I just happen to know it's true. So what happens to this population over two years? Well it turns out that, as you can see, 21 of these children will have a second urinary tract infection over a two-year period of time.

And interestingly enough, even though the odds of having an infection are a little higher if you're in the reflux group, it's about half-and-half between children with reflux and without reflux who have a second urinary tract infection. Now if we look at those children who've had a second infection, and see how many of those are going to go on to have a third infection, what we'll see is that it's a significant number of those. They're at higher risk than the first 100. And once again, there is a split between those children who have reflux and those children who don't have reflux.

Now what's the likelihood that we're going to see severe renal scarring in these children over two years? Well, it turns out that it is less than 1%. So in that group of 100, we may have one or we may have none. The likelihood that there will be enough renal scarring to cause eventual renal insufficiency in this group turns out to be essentially zero. So let's look again at that likelihood of a third urinary tract infection. What you see is that these are children who clearly appear to be at very high risk. So these are children, in my mind, who warrant intensive diagnosis and intensive management.

So how do we manage? Well the tool that we've used the most over the last five decades is continuous antibiotic prophylaxis. And we already know that that reduces the incidence of urinary tract infection by 50% over two years in children who are known to have reflux. But if you think about it, for every 100 kids who has a urinary tract infection, we do 100 VCUGs, which is not a fun test, and we treat 40 of them with antibiotic prophylaxis, and we prevent five urinary tract infections if you do the math. And remember, we're expecting 21 urinary tract infections in that group when you include the children with and without reflux. So we haven't accomplished very much, but we've done a whole heck of a lot of work. So why do we do it?

Well, we think about antibiotic prophylaxis in our specialty even though there's no evidence that it reduces renal scarring because we say urinary tract infections carry a certain amount of morbidity. And so if we can prevent them this is a good thing for the children. However, when you look at the children with reflux, the 40% of children who've had a UTI or have reflux, we know that only 10, 25% of those children, are going to have another UTI. So 75% of those refluxers are getting antibiotic prophylaxis to no benefit whatsoever.

So if that's the case, I would make an argument that we should use antibiotic prophylaxis in kids without reflux as well. 17% of them are going to have a urinary tract infection. And if that's a morbid event we should prevent it in that population as well. And when you look at the totality of the 100 children who've had a urinary tract infection, if we treat all 100 of them, 79% are treated without potential benefit. That's about the same as 75%. So if you believe that we should do it when 75% get no benefit, then I would say we should do it when 79% get no benefit. Or we shouldn't do it in either group.

But whether or not you believe we should use antibiotic prophylaxis in these kids to prevent infection, my argument would be we don't need to know whether or not they have reflux to make that decision. It's all about whether or not we think it's worth preventing a relatively small number of infections in a large number of children.

The attitude toward antibiotic prophylaxis is informed by a number of different things. Of course, one of them that's very important is antibiotic resistance. And we know from a number of studies that the likelihood of seeing a resistant organism in breakthrough infection in a child with reflux is related to whether or not they're on prophylaxis. And that might give us pause about using antibiotic prophylaxis. But I'm not really here to argue about the pros and cons of prophylaxis. Really I'm just here to talk about whether or not we need to diagnose reflux to make that decision.

Now I've gotten pretty deep into it talk about urinary tract infection without talking about BBD, which is Bowel and Bladder Dysfunction. And it's hard to talk this long about urinary infection without getting to this, but finally we're here. Because what's interesting-- when we look back at the CUTIE and the RIVUR studies, the most significant risk factor for urinary tract infection is bowel and bladder dysfunction. It's not reflux. So if you look at this estimate of two-year UTI recurrence rates, you'll see that in children without reflux, 35% of those with bowel and bladder dysfunction will have a subsequent urinary tract infection. That's more than any of the children with or without reflux who don't have bowel and bladder dysfunction. And the numbers just go up in the populations with reflux.

So if we think about our 100 children who had a first urinary tract infection, it turns out that there are 12 of those children, statistically, who would be diagnosed with bowel and bladder dysfunction. And when we do the calculation, we realize that of those 12 children, six will have recurrence of urinary tract infection. That's a 50% recurrence rate. And that might warrant continuous antibiotic prophylaxis. But once again, for that population, we don't need to know whether or not they have reflux to know that they have a 50% likelihood of having a subsequent urinary tract infection.

So with all of this information that I've given you, what would I propose that you do? This is just one proposal. I think it makes a certain amount of sense, but you could certainly come up with something that is different than this that might make just as much sense. But let's say we have that population of 1,500 children, 100 of them have a first urinary tract infection. They all should have an ultrasound, because if you've got abnormal upper tracks, you're talking about a different category. They need aggressive management.

Let's assume they all have a normal ultrasound. Then let's examine the group to see which one of them are toilet trained and have bowel and bladder dysfunction. We know that they have a 50% likelihood of recurrence of an infection. We might want to start continuous prophylaxis in that group. I might avoid it in the rest of them. Now if these children present with a second urinary tract infection, I might consider antibiotic prophylaxis even if they don't have bowel bladder dysfunction, because remember, we've identified that they're at relatively high risk for developing a third infection.

If they develop a third infection, and that is going to be fewer than 11-- and why do I say fewer than 11? Well, because we're treating some of these kids with antibiotic prophylaxis. And remember, when we saw 11 children with a third infection, that was a group with no antibiotics. So I suspect it's going to be half that number. But let's say it's somewhere under 11. Well, in those children I would do a VCUG. I would diagnose reflux if it's there. And if it's there, I would treat it. And I would treat it aggressively. But now we're talking about a very small number of children. If they don't have reflux, I would consider doing a renal scan to look for any evidence of significant scarring. And if that's there, I would also treat them very aggressively, as if they had reflux. Once again, very small number of children.

So here's a demonstration of resource utilization in a population of children who have urinary tract infection. And for this graph I've used the example of the AAP's recommendation for reflux screening, which actually is waiting until the second urinary tract infection, not even as aggressive as what I've recommended here. But in the blue in the background, you see resource utilization for our traditional management of reflux. You've Got 100 kids with infection, and 100% of them have a VCUG. About 40% will have reflux. We treat all of those with antibiotic prophylaxis. And if you look all the way to the right, the most important resource of all, the pediatric urologist's time. The Pediatric urologist is going to see all of those 40% of patients.

A very small number of those patients will have multiple breakthrough urinary infections and require surgery. Now if you look at the front group, looking at VCUG only after a second UTI decreases resource utilization very significantly because you're only going to do VCUG on that relatively small number of kids who has a second infection. You're going to detect an enriched group of refluxers because that group is at higher risk, but it's still a much smaller group than were detected before. And any management that you use, whether or not you choose to use prophylaxis, will be used on a much smaller group of children, including that pediatric urologist's time. Now the pediatric urologist is seeing many fewer children.

But if you look back at multiple recurrent infections and the need for surgery, it's exactly the same. You're still going to identify those children at high risk who wind up needing repair. So it's a much smarter use of resources with, in my opinion, no change in outcome for this population.

So I don't want to imply that any of these ideas are brand new. Here is a slide that comes from Ron Keren at Children's Hospital of Philadelphia. And this slide actually was developed many years ago. And I've been using it for years in talks, with permission. And I think it illustrates the same principles. So our conceptual model is that reflux causes urinary tract infection, that that combination can cause renal scarring, and renal scarring can lead to end stage renal disease, hypertension, or complications during pregnancy, which we haven't talked about today.

So how do you manage that? Well, either prophylactic antibiotics to prevent infection, or surgery to correct reflux. Either one of those would hopefully interrupt that cycle. But the modified conceptual model would suggest that, yes, renal scarring can lead to end-stage renal disease, hypertension, or complications of pregnancy. But the cause of renal scarring is a little bit different than what we thought before. Number one, we know that most of the children and adults who go on to end-stage renal disease with a diagnosis of reflux in fact had renal dysplasia congenitally. It was not the result of recurring infections. And secondly, we believe that most of the renal scarring that was seen in the past was due to delayed diagnosis and treatment of urinary tract infection, and not necessarily the combination of urinary infection and reflux.

So how do you manage in this situation? Well, prompt diagnosis and treatment of infection is important, and prophylactic antibiotics certainly might make sense as a way of preventing recurring UTIs. But what you see kind of missing from this picture is reflux. How does reflux really play into this? So this concept has been around for a long time, and I think we now have the data, because of the RIVUR and CUTIE studies, to really put some meat on those bones.

So just to recap what we've talked about today. Number one, I think that the prevalence of reflux in the normal population is unknown. I think it is much, much higher than we've assumed in the past. And what that means is that most children with vesicoureteral reflux are running around and doing just fine. It's not something that we need to know about. Secondly, when you look at any kind of process from the individual level, anything can happen to that individual if there is a statistical probability. You have to make decisions about an individual based on the risk to the population. Otherwise you make decisions that don't make sense from a resource utilization point of view, and frankly, from the point of view of morbidity for that individual patient.

I believe there's very little reason to know whether or not children have reflux after a first or maybe even a second urinary tract infection for the reasons that we've talked about, that antibiotic prophylaxis may be very useful, but it's not specific to children who have vesicoureteral reflux. And I don't think reflux is completely negligible. Children who have multiple febrile urinary tract infections are at higher risk and that suggests aggressive diagnosis and management of reflux. But that's going to be a very small number of children.

So I want to talk a little bit about words and get back to the title of the talk. A phenotype is defined as the observable properties of an organism that are produced by the interaction of the genotype in the environment. That is reflux. Reflux is a phenotype. A disease is an illness that affects a person and prevents the body or mind from working normally. That's bowel and bladder dysfunction and urinary tract infection. Those are the diseases that we need to be treating. Reflux can sometimes complicate those diseases, but most of the time reflux is an innocent bystander. It's a phenotype that we don't need to know about.

Here's a quote that I think sums things up reasonably well. If we want to ensure that limited health care resources are appropriately distributed, we must have a reasonably clear idea, first, what a disease is, and second, which diseases are most worth the investment of time and money. And I would suggest that we've spent a lot of time and money on a phenotype that really is A, not a disease, and secondly, has much less impact than we've suggested that it's had in the past.

And here's a quote from one of our own, John Woodard from 35 years ago. As one looks back over the last 30 years of reflux history, it is ironic that urologists have become so expert at its surgical correction before understanding much about its natural history and true clinical significance. I think those words are as true today as they were 35 years ago. So thank you very much for your attention.