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TRANSCRIPT - GR 05 16 25 **"Membranous Nephropathy: Diagnosis and Treatment in the Era of PLA2R Antibodies"** guest speaker Fernando Fervenza, MD, PhD from the Mayo Clinic

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Internal Medicine Grand Rounds

- Hello, everyone, and welcome to Department of Medicine grand Rounds. We're delighted to have Dr. Fernando Frevenza speaking with us here on membranous nephropathy. I'll take us through our Cme. Slides and then bring up our Nephrology division. Chief Dr. Marco Cusa. To introduce the lecture speakers. Presentation Objectives disclosures credit for Cv. For faculty within email as well. Shortly now, Dr. Agusa, to introduce the Doctor Butterson, our distinguished lecture hall.
- Thank you, Brian welcome to medical grand rounds. This is the W. Klein Bolton Lectureship, and it's really a privilege to introduce this. W. Klein Bolton distinguished lectureship which was established to bring to the University of Virginia in terms of glomerular disease, research, and clinical care. And this year we're honored to welcome Dr. Fernando Provenza, who's a professor of medicine at the Mayo clinic in Rochester and Dr. Asanta. But I'd like to take this moment to reflect on Dr. Bolton's legacy. He couldn't be here today. Usually he does come, but he couldn't make it today, and he's a pioneering nephrologist and a real national international authority on Rpg. And good pastor Syndrome, and he was the 1st to demonstrate cell media immunity which alone can cause pulmonary arthritis, and he identified epitope spreading as a autoimmune mechanism in glomerular lipid his early work has also established the use of pulse, methyl prednisolin in Rpgm.
- Dr. Bolton earned his medical degree at Uva, trained at Harvard and University of Chicago, and he returned here in 1973, he led the division of Nephrology between 1988 and 2,008 to 81, and he was a true academic physician, scientist.
- He's also mentored a delegation of physicians and scientists at the University of Virginia. He has helped shape the Nephrology department as well as the Nephrology, practicing Demo through his leadership, insight, and his generosity. And I'm personally grateful for his membership during my early careers here.
- So we are honored to honor, Dr. Bolton through this lectureship, and with that I'll turn this over to Dr. Hassan to introduce Dr. Thank you.
- Well, good afternoon, everyone. It's my distinct pleasure to introduce today Dr. Fernando Preventa so a little bit about him again, he's a professor of medicine at the Mayo clinic in Rochester, Minnesota. He graduated in medicine at the Rio Grande and underwent clinical and research training in Internal Medicine, Oxford University and Stanford University, where he completed his postal by college.
- He's a member of the American Board of Internal Medicine Pathology Section, and up-to-date section editor for Glomerular Diseases.
- His research interests include a number of interventional studies that focus on new treatments for glomerular diseases, including pneumoniasmopathy, iga, glomerulonephritis, focal and segmental glomerular sclerosis lupus nephritis and inca- associated vascularis in addition to understanding the role of a number of pathogenic families in their response to therapy.

- We're very excited to host you for grand Rounds day. As a result of the distinguished lecture. So please join me in all it.
- Thank you very much, and I'm very honored to be invited to present to the distinguished client could have been a better opportunity.
- Now I'm a clinician, and then I, opening what I do is see patients on a regular basis. So my presentation is really a clinical based presentation and I see the learning objectives I think I would like to convey to you is how to use serology to guide diagnosis, how to use serology to guide treatment, to recognize early markets of responsibility. And if we have time, discuss new target engines in the protocol.
- Now this slide, which was incorporated by Dr. Sal, who has been a previous life. Bolton, speaking here, shows a classical findings available on the property that you have thickening of the glomer basin member or liveoscopy. You have the position of Itg and complement, and if a patient with clearly who are positive this Igg is Igg 4, predominantly, and you have the submit.
- Memory. Property, of course, is the most common cause of nephetic syndrome in adults and the prognosis of memory is dictated by the response of therapy, and this is not just, but also true to patients with any portocytopathy like primary Fsgs. In other words, if you get into complete remission of proteinuria, the long-term outcome is excellent. Not a single patient will go on dialysis.
- Even patients. We go into partial remission. And this is lines from Toronto's group. About 20% or 80% of those who will still be dialysis free 15 years on the road. And I will tell you later if we get time, that this is probably an underestimation. It is based on the fact that this consideration of remission was based solely in proteinuria, but new developments have now bring it into the forefront that the mission should not just be date based over the year. But we should base in chronological relations.
- But what is all known is that if a patient goes into no remission, remain nephrotic, then about 60% of those patients will go to required patient 15 years down the road. Now there is no question, therefore, then, in patient memory. The goal of therapy is to reduce proteinuria, because this will prevent progression to end stage.
- Now for years we have treatment for Member nephrogative that were based on either the Ponticelli regime. That was a combination of steroids alternating with cyclophosphamide or chloropusil or we have calcinating inhibitors.
- The problem with those regimes is that, as you know, the cycle of cytotoxes have a risk of probability goes, so you cannot really use double information relapse, you cannot really retreated, because then you increase the risk of blood, cancer, dysplasia, leukemia, apart from infertility. If you are dealing with a early young man or woman and in the calcium inhibitors we had the problem that a lot of those patients will become calcium dependent, and you know that calcium is nephrotoxic for a long time.
- Then you run the risk of those facing develop hypertension, nephrotoxicity, loss of kidney failure.
- So there was for a time a need for something new to those patients, and have good efficacy with less toxicity. And this came about back in 2022, when Dr. Rabuzzi, in Bergam and his group treated 8 patients with Rituximab. That's a more important antibody against CD 20 positive P. Cells. And what Ramulusi treated those patients, the 8 patients and followed them for a year, and found that 2 patients at 12 months were in complete remission. 3 patients were in partial remission, and another 3 patients had lost more, had dropped about more than 50.

- So that was the 1st demonstration that A B cell approach, using a more target therapy was effective. Now at that time, as Mayo.
- We I was working with doctor respects with an expert in vascular, and we were doing the studies in Mayo was the 1st wave that
- Rituximab had been used to treat Pain associated arthritis.
- We reported that in the art flags very much has been 2,001, and then Genentech, able the money to do another pilot study. And then this pilot study resulted in the brain. Study the protocol, study that we all you are all familiar with. So that we genentech at that time it was easy to have access to study. You didn't need to. You just wrote like 4 pages, basically what you were here, whatever you said there, and usually it was approved very fast. All right.
- So with that, I wrote to the ask for money to do a pilot study to see what happened to to. We got money to do a 15 patient study. And I'm going to show you this today. But it basically showed we did those patients with Rituximab one gram on day, one and one gram in day 2.
- The reason why is that is because been approved apart from the lymphoma program for rheumatoid arthritis and the approval for one gram twice a day. So I initially proposed to do 4 doses, but then I got a call from Genetic and said, If you want to do 4 doses, we are not funding your study, but if you want to do 2 doses, we are going to fund your study. Suddenly the scientific merit became period. We did 2 doses, and we did 12 months, but for the 1st time we took the opportunity at that time to do pharmacokinetics and pharmacodynamics. So we start doing to see how happened to the T. Cells, how fast they recovered what happened to the Redoxima, and we found out that redoxima, the B cells. Usually, if we do, a patient T cells are depleted for at least 6 months, 9 months, 12 months.
- But what happened is your patient with nephronic syndrome? These cells, because it goes out into the urine by 3 months. The majority of those patients have these cells back into circulation. So I went back to Genentech and asked them, Can we do a new study? Then, using the 4 doses that we do against the pharmadynamics.
- And then we did that, and we changed the outcome because we saw the opportunity going down. And if you look at the complete studies. In fact, you can see that every 6 months more and more people will go into emissions. Hotel has to change the endpoint from 12 months, maybe 4 months.
- We did the 4 doses. And then what we found we did again, pharmacokinetic, pharmacodynamic, and we found that if you transpose those patients for longer. In fact, at 2 years you get it, you have an 80% revision. This is important to understand, because people don't, what we are going to discuss. I'm going to show you about the mental study inventory study. The remission rate is 60% that people get it. So they said, battery toximab is 60%. But the issue that detail the inventory study because we included a clause that because we are randomizing against cyclosporine and we didn't believe that was ethical to keep patients that was calling for a year, even if we knew that after 6 months they were likely to respond. That's why we create the exit. So if a 20, a 6 month more, they didn't show more than 25% reduction for the year, they will consider failure in exit.
- But this shows you that if you give Rituximab to a patient in nothing and you don't have you just follow it.
- Then we got 80% response rate at 24 months.
- So then again, we had the pharmacokinetics. We had the pharmacodynamics, and again, then, a couple of years later, multi 100 patients, and it showed that indeed, in

members of the property it takes time to get upper failure between 18 and 30 months. If you are going to do a randomized study in member of the property and your endpoint is proteinuria remission. You cannot do unless you believe that your drug is matching, or as a growth factor or something like that, to regenerate profile, to get rid of deposits in speed away. You should not put that endpoint of 6 months or a 12 months, because you are going to miss the boat until that is why I didn't show you, doctor the money is not going to show any different, because we know the date time now in 2 when we going here. Oh, sorry then it was a revolution. Remember that until that time we were all idiopatic member of the property. We knew that it was. But the Revolution came when David Sulland and Larry Beck in 2,009, published the discovery of the receptor as a target for about 70% of patients with membal nephroma. All right. So this was a change, or different, because now we have a market of the disease.

- So at that time I contact.
- And I said, because I have in this storage in the freezer the samples of those patients that I have done the 15 patients in the 1st study, and the 20 patients on the second study, I suppose, to Boston. We did at that time. We were done by Eliza, the by Western one, all right. And then what this study show is that if you have the Tl. 8, 1 here and the t. 8 1 goes down. The proteinuria will form. If you have Tl. 8, 1 here, and the Tl. 8 goes down. Proteinuria will form.
- You should live with oxyman, and the clearly one does not go down. Then the protein here doesn't go down, and, in fact, we had one patient that they was into complete what I call complete immunological emission, meaning the clearly one is until complete.
- But once the antibody came back this was default. What he lost. So this is not a hundred percent proof, but it's quite, very strong evidence that the antibody correlates to the activity of the disease.
- So we thought at that time, and I'm going to say something very politically correct even. But I think from Brazil as you describe, and you know, what can I say phonetically? Just this form, so I cannot contain myself. So we then remember we had them 2 studies that we have the pharmatis. We knew the T cell population.
- How fast we reconstitute. We knew how one level was there, and now we had a biomarker that would predict how the patient will respond.
- So, Doctor Daniel Katherine, who is my good friend and mentor from Toronto, Canada.
- This now it's time to do a randomized control trial to see if this drug really is effective because we try to use the insurance company or not paying so. But who are we going to fund the biomarkers?
- My private foundation said, How much money do you need? And we calculated that 10 million dollars that we shouldn't accept no interest because the market for this is very small, the rare disease we don't want to do. And that a private foundation said, well, we give you half 50% of their money.
- So I went to genetics. And now I have 50% of the money, they said, well, if you have 50% of the money, we will give you 25% of the money. This is an excellent, then let's write a research for the National Institute of Health to see if we get it funded to do the 1st randomized or small in many of the property in years, more than 30 years, where we had all the markers.
- Then we have cost the institution nothing, because all we have been done with private funds. Right? It was reviewed by the led the committee said, was excellent,

but of course, as Dr. Knows, they never fund unless you really understand that first? st So they asked a few questions but the committee, the Administrative Committee Executive Committee of the 98 did not allow us to resubmit.

- All right. So we are sort of short sighted that they never even say, Well, you are asking, because we're basically asking them was $500,000 a year for 5 years. That's what they die all the time.
- Instead of saying, Yeah, he was asking 500,000. You know, we are short of money whatever because we have to pay this money to the zoom, you know. And this patient here we are not really interested is correct. Whatever we just give you
- $100,000 a year we would have taken. In fact, that's how Rave was done as rave. We went to the National Institute of immunology and allergy. And Ray said in the in the said, Well, we can only give you 10%. Well, Gene and Tech gave 90% of their money. Nayak gave 10%, but they got the credit. Every publication, every presentation we give about rave we go funded, supported by not the analyticaid. They. So I went to Genentech, gave the reviewers. So this is why I called the Not anymore Nih, but I called them the National Institute of Animal Health, because they are only interested in animals. You know the story. We did that, but then brings me to the story. We then went again and did the why I'm showing you this study. This is just how we went that you reach the endpoint showing the Vitoxima was superior to why I'm showing this to you because it comes to the client story. You see, we needed to have a data safety monitor board for this study.
- They are
- Dr. Said to me, why about? Why did you contact Dr. To see if you would like to be the chair of the data which I did?
- And he, very gentleman like said, Yes, no problem when. And he wants the Data Safety Monitor Board and he they have meetings every 6 months for like 4 years.
- I don't see. I don't remember. I don't think we pay him anything, but he was there. He supervised all the data, all the side effects whatever, so we're very grateful that this is at the bottom for having done this and for holding us honest to the 2, getting all the side effects all this, and and supervising the conduction of the study that well in this time.
- Now one important thing that the mentor show us also is exactly in a bigger way is what we already have done with Dr. Fallon is the effect of the antibody on proteinuring. All right, so you can see that here.
- The antibody I mean the negative is below 40, but it goes there. It goes to negative by 6 months in the majority of those patients, while the calcine inhibitor here is more is lower in to get into remission, and by design mandatory study would treat those patients for 12 months, and then just continue that. And you see it shows that if you just continue that in a patient who has Pn. Is still positive not surprised, the antibody bounces back and yet explain why we had positive results in the reduction, because the protein and proteinuria, as we already knew, continues to go down while in the calcium inhibitor. Antibody went up, and then you bounce back the protein urine.
- So then the other thing is important. I seem to have to show, because I mean, you have to show you. This is this fact and those creations go into remission. This is the creatinine cadence 25. You see, they have atomine cadence of 93. The cyclosporine level is 98 bye.
- At 6 months, 12 months, you see, the clearance goes t093-94-9698, but at 2 years they cleared us a hundred percent.

- And so you gain normalized innovation. On the other hand, you see the group treated with the inhibitor.
- The clearance goes to 98. Here at 12 months they clear the 71. But they said, What is surprise? Why are you so? I mean, you're giving a calcino inhibitor that's expected. Yes, but at that time they stopped the calcium inhibitor. So the surprise is here that 12 months later they are not on calcidine inhibitor. The clearance is still below what they expect. So it tells you that 12 months of a calcid inhibitor is nephrotoxic, and that price is not healed by 12 months of the calcium inhibitor because with that, and also because your immune remember, a lot of this was at the time we didn't have your immune. But then the assay came around. Mayo was the 1st place in the in the Us. Was working to validate one by Eliza and then I was using this for free, because it was part of the validation process in patients in clinic, etcetera. Then, together with the data of said, Well, you know, Pn is excellent. So in 2,016, I mean, this is 17. But the paper was accepted. 16 was online. Interestingly, we put together with Doctor Glass of again was the first, st Drussen tells me. Well, the 1st Clivel lecture here. We put this a proposal for a senological approach to memory. Well, we said the old approach, and just me just looking for risk based on proteinuria now, is not enough. We now can use the serological approach using pn in what we wrote in this. And then I tell you, for the I don't know if it's true or not, at least in this time. It's an example for the one of your faculty we have. We wrote that in what we wrote into this business we say that measure of pla 2 are a patient comes with nephrotic syndrome, we measure that the patient has period. Yes.
- Does. This patient has secondary disease, meaning has hepatitis. Cancer has drugs or autoimmunity. Lupus. No?
- Then this patient has pla 2 R associated memory. You do not need biopsy. This is the diagnosis.
- Then we put all this business here, and of course the reviewers gave a hard time about this, and they want that, and then but at the end they left alone, and it even was published. But what I'm trying to make a joke is that the elephant was here in the room? They didn't look at the name. They went after this all right, because the elephant it was all based in Bs. We didn't have any data to support the scene that we are saying that they didn't know about right. But then one of the fellows at Mayo Clinic Shane Popat was there, and like Shane. So now why don't we try to see what we said is, makes any sense. So we went there. We pick it up all the that we had done from 2,015 to 2,018, and we had done period testing in 800 patients, of which 142 of those patients are positive. And then we got rid of the 32 that we thought they were secondary members of the property because they have autoimmunity, malignancy. And we went to 97 patients. And basically, we divided those 97 patients into patients who have no longer meaning Egfr more than 60 and less than 60. And to end the story, we wrote this, and we said the patient, who had nephrotic syndrome, who are pna 2 R. Positive, who have a normal Egfr. They have no secondary cause, meaning. They have no hepatitisis, no lupus, no malignancy, no sarcoidosis and they have no diabetes.
- It is no point, no need to biopsy this patient, because the biopsy is going to show you nothing else, the property or nothing else that is going to change how you manage this patient. So they did not need a biopsy. They had a fear related.
- Now, this was 2,019. So of course, a lot of my colleagues, because Europe, whatever said, Yeah, but this is Mayo. This is only Mayo. That's not we still going to biopsy? All right. Well, then, I got into Barcelona and we said, Well, what about your

patients? Just say so we got our patients. And basing to get on the story short, we found out another well, 276 patients, or this 79 of those new patients with Iegfr greater than 60 that had no separate disease. The biopsy showed nothing whatsoever that it that was different. And we published this as a non-invasive diagnosis, a validation study. We published this in 2021, and this is just to illustrate one of those patients. So this is like a 57 years old, or something that I saw back in 2,020. This patient comes. He has. This is the the argument we can see, the argument is going down. The patients continue initially here the peak goes up. I check this. Platy is positive he had nothing. I did not biopsy this patient, I said, let's give. Rituxima gave him 2 dose of Rituxima, and you can see the protein went down. We've normalized this patient has been information because of this, you see the Rituxima perturbation, incomplete immunological remission, and this was followed by clinical edition, and that business came through the Kdigo Guidelines in 2021, saying that the patient in contrast to previous guideline. If a patient now has pla 2 r positive insulinology, you don't need a biopsy. I don't quite agree with this, because that's not what we said. We said that if they have normal kidney patient they don't know biopsy. But then that's what they do but regardless, I still have friends, and I still want to biopsy because biopsy. In fact, if they could probably do biopsy, both did this all right. So the story of Max Blank, who was a Nobel Prize for physics in 1918, who said that the new scientific truth does not triumph by convincing his opponents and making them to see the light but because of the phone, it eventually died and a new generation brought up that is also needed. So in that thing. We also gave recommendation that used not only for diagnosis, but we also use the antibody pla just to see who are you going to treat. And we at that time we said, if you have very high, you don't need to mess around giving 6 months of conservative therapy, because just torturing the patient right?

- I remember one of those patients came from London. He was orthopedic surgeon, all right. He had 20 grams of proteinuria.
- For 18 months that Guy had been in conservative therapy, and for the last 9 months previous. He cannot enable company to do surgery because orthopedic surgeons have to be 8, 7, 9 h. There the amount of edema so much is included. So just because of the idea that this will go into spontaneous remission. This is Ps. If you have a patient with certainty, you treat the screen remission and has remained in remission until now and then we put into that, and you use the antibody. I'm not going to go into detail on this, but you use antibody level to also to monitor which one is likely to go into remission or not and you use the antibody also to guide how you are treating this patient, because if you give whatever immunosuppressive therapy you are, and by 6 months you have more than 90% reduction in antibody. Then it's likely this patient is going to remission. You can stop what you are doing. Now stop what you are doing is a misconception also, because if you give redoxygen to the guy, you are going to stop nothing because the T cells have been deleted, and you just have to wait 9, 12 months until the result. If you give cyclophosphamide for 6 months, the Diesels are going to be limited for exactly the same time or longer. So the only thing that applies is, if you're giving a calculator inhibitor, then you are going to stop right if you give them and diet. 6 months later you have not 100% reduction of everybody else.
- Still, between 50 and 90, you just need to continue doing what you're doing forever. But if up there 60 now.

- I don't have time to show you. But after 3 months you don't see any significant change. Their antibody doesn't come back by 25%. Then it's changed here because this page is unlikely to respond.
- And then just going through the paper with Dr. Radakrishna sitting here just to illustrate the point of how to use pla 2 r to guide therapy. So this is a paper that came. We saw that Mayo had in 2015. He had a proteinuria at that time about 15 grams. He was pla 2 r positive. You can see more than 1,500 there we give Ritaximab 3 months later the patient protein went down a little, but 3 months later the protein was back to 14 grams, and the patient was losing kidney function. You can see that the Creatine was going from 1.5 to 2.5 in one day. He gave was 3.3. At that time I said, Pra. 2 R. Was still in change, more greater than 1,500. I put the patient on.
- I gave one pulse of Metalprenizone and Dr. Boldone, and using the pulse, I gave my order with it or steroids, and you can see that 2 months later the period one has become 0, and lo and behold, if you get rid of the antibody, the proteinuria has to go down, and indeed the proteinuria came down, and the patient has been in remission ever since, so use the antibody as a market of if the patient is going to respond to therapy or not.
- Now a lot of people is. Still. I told you about the misconception that 60% is not 60% is more likely 70, 80% of which will respond to production.
- But of course, a lot of people say, yeah, but reproximately working, it doesn't really matter, because now we have a new antibody that is coming. That means available to produce a more profound T cell depletion. And as we wrote this cases in 2020, and that is why, then, an intent. And now Roche did a randomized control trial now looking for an indication using Obituzumab compared to Tacroli was into.
- See if that is going to produce some more uniform that can be FDA approved and etc. And I think by the end of this year we'll finish. I mean, the study is complete, randomization complete. We just need to do the 2 years 18 months follow up together.
- So with the last few minutes. What I want to do is a few cases, just to illustrate the case. What I was saying to you. 57 years old woman, came from the south of the United States. She had a biopsy done in 2016. That was not pla 2 r. Positive at the time. Diagnosed. She has 6 gallopia normal kidney function. Pla 2 R. Was 560 and treat the conservative. The proteinia went to 3.7 4.9 6.1, and the Pr 81 levels was 56578700400.
- And then, just to tell you that don't be dogmatic in clinical medicine because you should be dogmatic in clinic medicine, because you have not seen patients enough, because you always will find deception right if you see patients long enough. So the patient came back in January 2,017, and at that time she had a proteinuria. This one had clearly 800 views. So what I said to you is that this patient not going to voice for television? I told you with that later right?
- But this is the p. 12, antibody from 800 to 0. And this is the protein unit. He went from like 4.5 to I have more follow up, but, like I see now, is like 500 acres, and the question to you which therapy I gave illustration story short, I gave her nothing. And I say, why? Because, remember the 1st thing that goes up when the patient is going to respond. Not only members of the property but in Fsgs only, is still an argument and when she came to me I had the benefit that I saw that her argument was already going up. So at that moment I said, Wait, this tells me that this patient is probably going to go. I'm going to do nothing. I'm going to continue. And I

continue. And you can see the argument went for 3. So pay attention always to the argument, because it's the 1st thing that is going to start going on the right direction, and the patient is going to respond to them not in case the 47 year more men. Pra. 2 are positive. Well, he got edema. He got kidnaps in January 2024. He had Pra. 2 are positive antibody, 730, creating an album of 2.5 in March 2023, 2 doses. But, as you can see, there uses the It's still low, and this is the protein union he got when the baseline 13 grams. But 2 months later this proteinuria was 20 grams. So this patient is a failure to therapy, all right. And in fact, this is the Ritoximum level was 534 in March, but in April was 42, and in May it was a hundred 46. So, in other words, this explain why the patient was responding. So you say, well, he's resistant to Riptoxin you know, this is again this, just because you need to be careful what you say. What happened, in fact, is because the patient had all that all the Ritoxima was going into the urine. So you see that following Ritoxima, his B cell go to 0. But one month later, the B cells, where it's already back to 425. So he had records. Not that he was resistant is that he's all this ritoxin going to the urine.

- So we then gave him a more powerful managed to get global circulation. And then Bingo, his period went to 0 a month later in his proteinuria, as you can see, went from 10, goes to 12 in the 3.5, and then we have further testing. So showing that you always have to.
- The devil is in detail to explain if something is.
- I can tell my fellows. Yes, so it's very easy, all right, if you just do a little couple of sinking clinical medicine any idiot can do. See my example right around here. The difficult is like putting a rock into the morning bringing back. But to do clinical medicine, you just have to do a little bit of thinking, and it makes all always makes sense all right in 90 from 5%. Right now, I see this is probably the last game I want to show to you 67 years old white male radiologist. I just tell you that radiologist is at that time he was already just retired, who had a 20 years history of type, 2 diabetes and I was found to have argument in the year in 2,011, and and became the project 11.3 grams and an outcome of 2.5, and also he had all the evaluation complements, immunofixation, monoclonal protein, hepatitis. All was negative and also Pna 2 was negative. So I saw one day when the biopsy. He showed a member of Nephrog, so he came to see me at Mayo because he wanted treatment. There was no evidence of diabetes of that biopsy and this is what I saw, sweet.
- This is when I saw him. Oh, I don't see this is not going to work. But anyway the person behind well, somehow it doesn't all right, because the the story was going to show you it should have been the bottom line is ignore the second part. So when he came to see 11 point 2 grams and like 6 weeks later, his protein was down to 2.7 grams, and the story is that what I wanted to, because it should have been secret. What therapy I gave to this patient? And then phosphamide cytoxin, I mean nothing.
- Because, remember, I told you this radiologist has been 20 years to answer. Type 2 diabetes.
- Now, have you ever seen a type? 2 diabetes that is close to you? Normalcy? No, in fact, that the pressure when he gave to me, and a measure of 1 83. So I gave him a ras inhibition to the point that 6 weeks later this serum, his blood pressure went down to 96, 47. So I didn't back off because I think I was pushing too much, but this tells you the effect of blood pressure control can do all right. You don't just go give him muscle pressure because he has 11. You have to think about the story, and if I we never treated him with muscle pressure, this is what happened to his ultimate

controlling the blood pressure, this protein. This kid they function went to 71, 11 years, 18 years, or 81. So this is to take the wrong message. I think this pump patients with positive nephrotic, syndrome period, one positive, no secondary cause. You don't need a biopsy. They have period, one associated memory property, patient with very high levels of the body as well. But if you are facing on this patient, treat them with opium to begin with if, of course, hypophospha is as effective, but that is the problem that is toxic, and if you, in the patient relapse you cannot use it. But all the therapies of the evaluation. But do not forget the basics. Treat the patients. Blood pressure control, low protein diet, low salt diet, control the steroids because you have does not remember you have a patient then noticing we have 2 windows more or not.

- So one bill beyond Pn. So in the old days we had the classification. That was how it was, it was divided. Patients in primary member of the property or secondary member of the property, and of course, then found Pr 8, 1 positive in 70%, and then, a few years later, found positive in one to 3, 5% of the patients.
- What was the cause for the secondary? What about the cause of under 70%, we would say, Well, this opportunity, maybe. But what was the Antigens? Now, this is my colleague, Dr. Who is a renal pathologist, Mayo clinic and he was doing a master in. When we're doing the cases of Mentor he will tell you the most boring part, because we ask him to do mass spectrometry looking for the complement task of art classes. Right? So he start doing all the mentor slides for them. But the 1st thing I start looking at it, he found, if you do mass spectrometry. One lady, said Fernando, who get started by mass spectrometry we would have found pla 2 r. Because in the pla 2 are positive. The 1st thing that you see in the spectrum is the pla 2 enormous expression, all right. So in there.
- So then it was at 1st that we do the same diagnosis. We do the detail, but then we don't do biopsy. But then you have all the other biopsies that were not Prd positive. So he started looking at the Prd. 2 R. Biopsy, and again my grievance with the National Institute of Animal Health asking for money to move there and they triage not even went to the long story short, we start doing that. And the bottom line is that. Then we discovered Exostocin one and Exostocin 2. They've associated with secondary cause, remember nephrogative, especially in patients with lupus or disease, and the second one that we found was now, which is now the second most common cause of Hemo's deformity, is associated with malignancy, but associated with skin pain, especially in India, they look a lot of they like to skin. There's a lot of form in there. It's associated with lipoic acid associated with sarcoid. Also there.
- The 3rd one was associated, especially in pediatric young adults there essentially found protocol in 7, usually 4 men. The biopsy is characterized because there is no or very little c. 3 in the compell when we stay. And then the patients have developed. In the majority of cases we didn't know the Antigen well, we do now is when we found out about patients who use nsest, and they are due to the Pck. 6. The last one was patients who had Ndnf that is associated with syphilis.
- So this, in fact, has created a new. Now we know basic 90% of the properties. And so this is led to us have a Mayo meeting like a couple of years ago, when the proposal was that we should not now anymore talk about primary or secondary. But what we should we should do.
- I mean the ideally we do mass spectrometry, and then you classify what's the target you know and you classify is the Pl 8 throposponin. 7 A is the because then we'll

guide you not only what you can do, how you should evaluate this patient, so I think we are now lucky, at least in the part of in a new era, or that we can personalize, approach, diagnostic therapies. And of course we can have this, the future. The vision is that all these antibodies in the future, like, if you have developed, then you can have a not just appeal. You can have an I. 1. Serology. So if the patient has an I 1 positive. Normally. Gfr. In no secondary. Why are you going to biopsy this patient, who should be the same story all right and the pathologists are not very worried because the amount of biopsy they get from diabetic nephropathy is more than enough to keep them going, so they don't need us. I have to acknowledge all the people who helped me over the year and Mentor and Dr. Katherine in Toronto, of course, and of course, again, I'm very grateful to Dr.

- Who want the the chair of our Data Safety Monitor for thank you very much.
- Thank you so much, Dr. Provenza, for an excellent talk, so I'll open it up. For questions. I'll ask my 1st question for the end of your talk you were referring to, you know, these various different you know different targets and their association with various diseases. I was wondering, for pla 2 are you have that slide where it says like there's no known diseases associated. But I was wondering if in your clinical experience, you see, like a certain demographic population, some type of patients who appear to have higher titers of pla. 2 are that you may rather than like a disease finding or a disease association.
- No, I mean, of course, remember you, you have to do the basic right. So I don't see an association between Asian and equality but you have to remember that you should always be because a lot, indeed, I mean, some patients have concern so, and he is like older than 60. Maybe it's a colonoscopy for sure, but just because they they? But I don't really think there is an association. It's very difficult to prove that between the majority of patients that we see the cancer is concomitant, but you should make sure to evaluate because amazing body of work. Thank you for coming. I'm going to ask a transplant question that never made sense. So in transplant. When we use CD 20 antibodies ov rituximab, it never works to stop antibody rejection, never is it? It always fails. And yet in an antibody, mediated or Antibody Associated kidney disease, primary kidney disease. One or 2 doses will put you into potential remission, as you showed.
- Why? Is that? Because I think whatever the basic science is sitting there, remember that. But still we do need therapies for the patient, because even with open, the worst patient is the patient, in fact, the patient that therapy period one negative, because they come in 2 favors, they come period to a level negative that have a criteria of 5 grams and allowed, you know, 3.3, and then whatever you give, they go away.
- But then they have another version. They come with protein, 20 grams and album 2, and they respond to nothing. You give them rituximab cycle. Now I don't have. I don't show you, I think, but one of them I gave end up giving more than the patient then responded, so how would I assess that?
- But again is I? I don't know can tell you, but I don't think that that's the answer. One of the explanation that is, I could say is that the business of the rejection is because they are made by the plasma cell, which ritaximate does not kill all right kills after stem cells and before they are plasma, plasma blast. So you say that the patients that are resistant to redoxy are in one.
- The immunology has developed to a level that the antibody production is not even done anymore by the B cells, but are done by the plasma cells that we are using.

And I think that I would say in the rejection, that's the story. They are not low level, they are higher level. Therefore they're not pla to our antibody producing plasma cells in the system process. You just develop new logical processes. Remain for until longer then and if you are still messing around, and this is then in the process until the stimulation, then they become plus month plus.

- So it is so I would say there is a question of time, and how much they have stimulated, or 7 until they enroll into them.
- And this is a group that I think probably this patient that I treated with with for those of you that is in that category. So they have been, we just, you know, and we do. I mean studies from the from Doctor
- Mary. She did because she she published like 2 or 3 years ago, whatever you found that their patients who have been Kelly, who are positive for years in separation before you manifest the disease. So I would say that that probably that's my ignorant view of my how we feel.
- Middle of Siberia. The American Siberia, which is Russian approach of human knowledge, depends on where you are in the political. You are dealing either with short leave. Long live, or then you are living with the problem. Go ahead.
- Yeah. Thank you for the talk 2 quick questions for insurance coverage. Do you have ever a problem getting their text map or open to zoom app if you don't have the bar option?
- No, I haven't got any. I mean, you know the story they are. You sure? I'm sure here, right, but May or they'll get in the past we used it didn't get much. But now every other patient I have to write a little letter. So what happened is, I already have a lot of letters that I got my secretary. If they deny Rituxima, then I write a standard. I said, this patient, whatever this would be beneficial to this patient and if they deny again, or they deny it the 1st time. So there's 2 ways to do. Web gives you free of charge to the patient. If they make less than 1,900.
- As a company they make less than a hundred or 150,000. It changes, I don't know what, but it was 100,000 a year. Then they get free of charge, and then we just ordered and from Genentech and drug arrives, and may or of course, may you charge them for the fusion fees, and all right, but they shouldn't always stay that there. They don't want to. They don't worry about it. So that's 1 way.
- The only way is that I usually do is that when they really deny whatever. Then I write a letter very friendly to them, they said, you know I can tell you that I no delays at all.
- I believe that free Proxima or Ncc. 20, would be beneficial, and if you deny this. I will have no hesitation to stand by them with the patient in the court of law, claiming that it was your failure, disease, with all the social, economical, and financial problem that this this outcome will define. And I can tell you that I have insurance companies like calling me on Friday, because it's easy to understand. This problem is because it's a jury problem. So you can imagine a nephrologist saying this patient should have been treated a jury there sitting there and then the insurance company decided to say. But what are you done? Based on what? Because of the cost of the medication game over?
- But send them, and they get like that if they have to go online, apply, they get to drop if they make better than a hundred 1,000.
- And my second question, if it's a plar 2 positive that's gone into remission. How frequently are you monitoring their plar? 2, to determine if they need more rituximab in the future? Yes, I see it as an excellent question.

- I think if they go into a region and I would, because remember all this patient is treated. Eventually they they would relapse. We had it into the rate study. We had a 5% relapse rate at 2 years. Right?
- But I would say that 5 years you have about 20%. But what I do is that we also we cannot get the patients completely crazy. Right? So you check for the 1st year after the initial for every 6 months and then usually I say to the patient, if it is incomplete, clinician, I give them a restriction for all these things they can say once every month. You just check your unit if you start seeing bubbles in the unit. Then, because also I haven't seen and I have seen. I do clinics 3 times a week, one week, 4 times a week the other week.
- I haven't seen it done. Period wise, not like anti-gbm scenario that Dr. Bolton gave major contribution. It goes up slowly, if they are negative, suddenly becomes 12, and the next month or 2 months later. And then so it's not something that is going to. So we check every 6 months, and then once a year, those patients. I see this enough.
- Thank you for a fantastic talk really enjoyed it. If someone has to design a new, a trial for a new therapeutic agent for members, probably, and then looking at the spontaneous remission rate, it's it says, let's 30 to 60%. So what kind of a trial this person should be looking at? N type 2 receptor group, or the many 30%, which is negative.
- Yes. Well.
- I know, because now is they are all suddenly, because, you know, I'm lucky to be. Don't get offended. The other parts of the Nephrology. You see, I'm lucky, because in the last we have been I. When I came to Mayo in 99 predecessor was Dr. Donario, he had retired 5 years later. There was nobody in Gn, he said, well, why don't you develop gn clinics? You know what I mean, whatever.
- So I developed now, I think, as you can see, we have all this. We have not only membros, I mean, we have complement disease. We have new drugs, you know. You have Iga, we have. You have the other centers on Novartis. You have all these drugs, all the antibodies. So I would say that became the excitement in the story. Because if you are on dialys, okay so open up front is very good. Yeah. The 1st date is going to be dedicated to ATM. Then you do nothing with her. The second day is going to be dedicated, and then you just stop the drug. So, and then the rare occasion that the patient has a gn then you refer to a Gn expert. So I make a fun of them. So the industry is the same. So everyone is interested in doing another studies, and they told me I said, Well, yes, but the study again should be 18 months can do production area faster and and unless you have a drug that you are going to compete with what we have in the city 20. So there is drugs available. I get this frequently they have a this and this. But again like, what are you going to do again? Much as your drug is to drop your drug, like, for example, wants to do anti complement therapy, or I tell. But the question is, if anti complement therapy is not going to cure the disease, so which patient is going to like to receive Iv complement every 2 months when you get a CD 20 monitoring body, and then it's done right for twice, and then probably 70 80% of the patient is going to be long term results. So I got so unless you've come up with these others like,
- I forgot the name now published in kid international report last year. They use Ntcd 38. It moves to your colleague right? Which say, well, then, CD. 8, fantastic, because then you just go to the plasma cell and you blast them. And whatever. Well, unfortunately, it's not so good meaning that the majority of those patients had

nothing to do with the plasma cell. You can give them a cell. The results were very poor. That's what at the end end up in kid international report.

- And that's why we haven't seen a randomized control trial. Because, in fact, the majority of those patients are not plasma cell mediated are clearly into the end, or the short lived or long live memory cell. So
- I see the the trial again. That's what.
- Yeah. And there's a lot of retailers now doing trial, because all this they wanted to make money all right. So they went now to go there. I frequently get, oh, we have a trial. Yeah, go ahead. But the you have to. You come with a drug that's going to be better than just getting 2 infusions provide better results that we have. So
- Thank you.