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**TRANSCRIPT - GR 04 01 22 "Updates in Membranous Nephropathy: PLA2R and Beyond "
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- Let's start with our reward.
- 00:15:56Okay, so the Herbert R. Farber award is in honor Dr Faber who graduated from the University of Virginia school of medicine in 1940 he's outside interests, besides being just wonderful internist his outside interests included accomplishments in sports and fine arts.
- 00:16:19The selection criteria for this award are for a graduating fourth year medical student who excels in the internal medicine purchase and demonstrates excellent in athletics or find or performing arts.
- 00:16:35So our recipient this year turned in an outstanding performance in the medicine production with glowing evaluation regarding clinical performance.
- 00:16:46And I have just a few of the comments of many to share with you, so this recipient was one of the best medical students, I have worked with.
- 00:16:54An overall function as a fourth year medical student on the medical icu rotation, despite being a third year student.
- 00:17:02Wonderful major strengthens your genuine inquisitiveness and enthusiasm for learning and her positivity only further bolstered our icu team dynamic.
- 00:17:11For presentations and notes were organized and showed deep understanding of the medical knowledge, she often went above and beyond.
- 00:17:18and looked apartment primary literature incorporated it into her presentations and taught rp I certainly helps you choose to train in internal medicine, but she'll excelled matter which career path she chooses.
- 00:17:32Another comment in her first week of her medicine clerkship she already has the clinical competence and medical knowledge of a first your package in terms, you can see the behavior.
- 00:17:44And another comment, a phenomenal medical students.
- 00:17:53So, as one of the other criteria this recipient meets the excellence in performing arts, so this recipient has been a classical musician playing the violin says ah sits in here, you can see here's a photo of her from age six or seven playing the violin.
- 00:18:12Here she's done many recitals and see just here and here's another example, and this is from a poster for a major violin recital that she gave at cobo hall.
- 00:18:25So our recipient this fear of the covert our former board is Irene Lee and i'm very proud to also tell you in case you're wondering we've had match day, so I really has matched it a little voice.
- 00:18:55alright.
- 00:19:01Alright, our next award is the dragon Alexander that's a word.
- 00:19:07So bratton out and your mentor Alex lives, he graduated from the school of medicine in 1983.

- 00:19:14 He was he went to university of Alabama for his medicine residency he won a lot of awards and accolades have been an outstanding medicine resident, he was named chief resident with very sadly he died in 1986 before becoming a true.
- 00:19:33 The late Dr disputes who's the chairman of the Tartan medicine it up at the time he wrote Alex was an intense and caring physician.
- 00:19:41 with both the patients, doctors and physicians doctor who love medicine had a wonderful knack for it and who gracefully combine the art and science, the participant.
- 00:19:52 criteria for this word excellent clinical skills outstanding ability to interact with patients zest and enthusiasm for the clerkship eagerness to learn good sense of humor and evidence of being a well rounded person.
- 00:20:09 Our recipient this year turned in an outstanding performance in medicine purchase she is blowing valuations across the board and you're just a few she was one of the best medical student I've ever worked with period.
- 00:20:23 She was always engaged and came to work with a positive attitude and she was able to.
- 00:20:29 Keep back in working backwards, using flavor to keep for more she'll be a great investment to interfere will take her and.
- 00:20:41 just so this is during this recipient was doing the workshop during the restrictions with business remote about.
- 00:20:49 And she got accolades for having aspirational communication skills and a comment here is choose always eager to talk to families and update them on.
- 00:21:00 Their what was in the hospital as impressed by not only the medical knowledge that her ability to communicate these concepts, with people to provide medical clearance.
- 00:21:11 She was truly a shining star or medicine service.
- 00:21:15 Now prior to coming onto the floor chip or recipient also I should mention is an md PhD student so she did her PhD work environmental engineering and you can see here in the live environment for any of you who have not known her outside clinical realm.
- 00:21:33 And here she is she has her PhD and see if she graduated with that and she says her mentor Kevin James written participate here that was beaming smile with any of you know her that's pretty typical.
- 00:21:48 For research has focused on uncovering regulatory here today, ladies and positive.
- 00:21:54 yourself she's had nine credit notifications today she's had a number of awards otherwise she said why.
- 00:22:05 Did you even replies sciences and the outstanding graduate student award.
- 00:22:12 She also does have a free time at.
- 00:22:17 magic.
- 00:22:18 In terms of free time that she talks a lot in volunteer work and hobbies fantasy she works at the shores of the clinic and.
- 00:22:27 She two years a lot, and she loves to read to me in between basically making history my favorite.
- 00:22:38 And I have one here.
- 00:22:40 recently said that she loves bacon and is the is the ultimate combination of scientific process decision preparation and of course I love.
- 00:22:51 I love it.

- 00:22:54 And our recipient is here of the alligator Luxembourg and i'm having sing and very happy to also tell you that Sean has match that her top choice and mass general four minutes.
- 00:23:44 So I'm just gonna freakin traction.
- 00:23:48 On shelves.
- 00:23:50 So today we welcome our very own Dr for your election to get apartment in medicine.
- 00:23:56 Dr cannot use it in Medical School they are university heritage college of osteopathic medicine and then pursued internal medicine residency and fellowship at the University of Louisville and Yale university.
- 00:24:08 Dr cabinets on the Faculty in 2019 is an assistant professor of medicine.
- 00:24:14 Dr Kevin as well down the residents and fellows in the room, and over zoom is a fantastic educator and this is reflected in receivable fellows teaching.
- 00:24:24 And department of medicine teaching.
- 00:24:27 off quite start from the teachers.
- 00:24:29 In the home around is it specific interesting blood Mary Lou disease, excuse me there and has started a little married or disease clinic at uva as well as the novel rheumatology and problems you combine.
- 00:24:41 These sub investigated for several multi-site research projects and, after several for soccer publications on grinding cockpits apology all at all he's a fantastic clinician and I personally experienced excellent teaching and it's deep commitment to our mutual patients for.
- 00:24:58 Today, we will discuss the evolving understanding physiology management metrics.
- 00:25:50 So I'm excited to give the talk today to serve share my interest in love so corner medicine emergencies.
- 00:25:59 So it's wonderful because the my first or one of my first grand rounds was actually in salon who came here, I was one of the founders of Members to proxy instead of uncovering everything, so if y'all remember pre covert era that was wonderful so.
- 00:26:16 A lot has transpired, since then, and our world of Members, the property so that's what we'll be talking about.
- 00:26:23 So apparently have no relevant conflicts of interest or financial disclosures pretenses talk.
- 00:26:29 So some of the objectives will be against describe the presentation pathogenesis appealing to our members and in frothy as well as the role of kidney biopsy evolving treatments and then novel discoveries, a new antigens.
- 00:26:44 So a little bit of background, so what is what is members to profit.
- 00:26:50 So we sort of learned in medical school.
- 00:26:53 It is immune mediated process, you have to remember all of these buzzwords like symbols.
- 00:26:59 So their deposits that sort of thing, and this is probably insurance of step one is probably one way if anything.
- 00:27:08 So there's a new data, disease and one of the most common causes of their products in the United States of America, although relatively rare at 10 to 12 cases per million it directly affects effects males.
- 00:27:23 But despite its rarity it is remarkably diverse, if you take nothing else away from the.

- 00:27:30takeaway that when we save and, reciprocally, that just means a pattern of anything it doesn't really tell you a lot about why or how or treatment so it's analogous to minimal change right that's just that's just the mythology is describing what they see and that's that's changing so.
- 00:27:48What do you expect to see clinically so vast majority of patients web products and and that's how they didn't recognize classically we do just sort of Sub acute or a long process, but often you'll get a rapid onset are rarely sometimes get a rapid onset.
- 00:28:05Minimal change our approach generic can be massive 20 grams a day and authority have some therapy macharia, albeit microscopic often on a preserve tfr normal blood pressure as well, so.
- 00:28:19And the hallmark is hyper limit Damien hyper flexibility within the products so keep a keen eye, if you see a DDT or the newly diagnosed, they have a little bit of a dilemma it's cheap disorder, the way you'd be surprised how many might catch everything.
- 00:28:37So, in terms of srt and a look at causes of yesterday in our country gn falls in around third place behind hypertension and diabetes and numbness is about second place in that category, so this is a graph showing us, obviously.
- 00:28:59that's important because this is a treatable disease, so we can prevent kids are being this population as opposed to hypertension, diabetes, which.
- 00:29:09We don't necessarily have.
- 00:29:13it's not just the srt though these folks come with a lot of co-morbidities as most kidney patients do.
- 00:29:19Not only the msrp risk but heart failure stroke venous thromboembolism coronary disease or ACS it tends to be more common in this population, this is a large HR database study.
- 00:29:35Out of Kaiser database of over 900 adults perfect did not purchase very nice medication so really this is telling you the risk associated with phonics.
- 00:29:46So it's not to be taken lightly.
- 00:29:51So, how did this all start.
- 00:29:53So the first major description of memorization of property was in the early 50s by Dr David Jones advantages of Syracuse.
- 00:30:04And that's where the Joan stained come from his name, otherwise known as the silver same, so this is an important staying for emergencies, especially number isn't a property that highlights the Spikes and holes.
- 00:30:17That you see with a keen eye, I found this sort of remarkable that just with a few patients sable sort of boil this down in his early years that in a Friday clarified as know triggering mechanism has been definitely established and.
- 00:30:34fragile Chester missions and exacerbations and auto antibody formation similar to acute gn appears to be President but it's mechanism, and that is a remarkable conclusion to make it really held true for way too many years and so we'll dive into that as well.
- 00:30:53It wasn't but a couple years later that sort of the first animal model came to light and to sort of explain the pathogenesis in early terms.
- 00:31:03But basically, it was 20 rats that had their kidneys rounded up in a super eight and we injected into them with Freud sentiment.

- 00:31:12 And it sounds yeah like excuse me sounds a little more rare our little rudimentary, if you will, but.
- 00:31:19 Ultimately, did show that a very, very similar pattern almost identical members of the changes in the rants occurred as humans.
- 00:31:27 And so that support the hypothesis this, this was an autoimmune disease, however, what list the antibodies targeting still remains one clear, it was ultimately masculine and the rat protein, but that is not so.
- 00:31:42 so fast forward 50 years.
- 00:31:47 The target antigen predominant antigen and Members the property that the antibodies targeting alternatively proved to be appealing to La.
- 00:31:56 And this is a story and again it's been told, in this very rope by by the man David salon to help discover this but, ultimately, this was in 37 patients 70% of them were found to have.
- 00:32:09 Without a secondary number is a frog a specific protein appealing to.
- 00:32:15 extract those proof by mass spec so taking this away, this is a huge leap forward to finally discovered the antigen and finally discovered the circulating antibody within spacious and get your path and Minister top notch and other customers use or second unit.
- 00:32:35 So what is it what is really to our eyes and transparent bring by composing its President.
- 00:32:43 Has a large extra silent domain in Tennessee subdomains its present on a wide variety of tissues in the body and importantly to upload a site part of the slip slip diaphragm makeup kidney However, its function within the getting into policy specifically as far as.
- 00:33:03 So to sort of understand the mechanism of what is exactly going on and how do we ensure our core slit diaphragm and say.
- 00:33:13 This is sort of a schematic to summarize our current understanding so let's circulating antibody ability to our specifically I do for subtype.
- 00:33:23 permeates people in our basement membrane and that's on the blood side leaking into the portal site and stuff epic space.
- 00:33:31 represented brings the antigen and blues the antibody and immune complex are formed to this international standards and on the potus a compliment is activated and through that injury of inflammatory process purchase currencies.
- 00:33:46 But it's a little bit more nuanced than that and just last year, a nice.
- 00:33:53 mechanism was put forth in cell culture experiment it's very hard at present tab appropriate animal model to explain this so we're still spending a lot of time doing human cell phone.
- 00:34:05 But basically Sera from patients with Pilates who are what were found to induce pretty license of two essential proteins in the photo site.
- 00:34:15 So you have to put it in F1 it's not critical that you understand this whole process in depth, but just understand it's not to put an F1 are critical.
- 00:34:24 For the structure of the site that maintains that slip diaphragm and holds back all the protein and one from leaking into the here.
- 00:34:32 So, as this antibody binds it stimulates compliment activation and the terminal compliment for MAC complex is inserted as well as C three and see five a.
- 00:34:45 compliment cascade or an activated and, ultimately, destroying snap to put in an F1 proteins and importantly from this study only man is binding, one of the Presidents of man is

binding leptin was this process propagate, so there is a critical roles and compliments specifically elected.

- 00:35:04 And the Buddha said expression appealing to our ability to work antibody was necessary, so without those two things not cause injury to the photo sites in the circles.
- 00:35:14 But that's only a piece of the puzzle other investigators have found roles for the classical alternative compliment pathways.
- 00:35:20 And really the landscape is moving towards that we're going to be targeting compliment gas stations, drugs, so that is probably the tip of the iceberg probably only you need for appealing to our Members, and not the other times.
- 00:35:36 So in keeping in mind that the antibodies critical to incite injury according to that model.
- 00:35:44 It would make sense that to target B cells that ultimately produces antibodies and that's really what I'm showing you here treatment algorithm.
- 00:35:52 So if you looked up our guidelines on how to treat members to propagate you might see that it's stratified by risk and that risk is associated with the not approaching area and the decline in CFR.
- 00:36:06 The higher risk patients are going to have a lower tfr more protein area one the products and Drummond perhaps a.
- 00:36:14 consequence of new products even like a DVD or TV and our first choice as remained for decades has been cyclophosphamide corticosteroids.
- 00:36:24 But now rituximab has moved up as an alternative first line therapy, whereas culture and ever like psycho sport is falling second place additionally purely to our values that you can check in the lab also play a role in your recertification I seen a high responsive.
- 00:36:46 So with that background information let's talk about some updates when talking about my Minister.
- 00:36:53 So I kidney biopsy is actually no longer necessary diagnosis, which sounds sacrilege but it's true.
- 00:37:02 So when you have a patient with no products syndrome and you're highly suspicious of remembering to step up the game diagnosis you got to go through a series of tests and if you've ever consulted us in one of these cases.
- 00:37:15 In patient it's kind of painful because we asked you to read all these strange things and everybody's worried they forgot something so.
- 00:37:22 First, you want to order the feeling to our antibodies course but addition to that you want to consider screening for cancers.
- 00:37:29 Age appropriate at least to start auto immune disease like an AMA or full exam skin joins searching for viruses like hepatitis B HIV Pepsi and an appropriate population syphilis.
- 00:37:45 Obviously, go into the drugs like an sets gold and penicillin and restarted outdated we don't use drugs anymore, they will see on board.
- 00:37:53 I think probably forever So in addition to that chest imaging is important to exclude sarcoidosis reasonable setting so there's also a list of other tests that others have advocated for specifically s corp like chains to exclude a techcrunch.
- 00:38:11 it's rare, but you will find it so.
- 00:38:15 Here, and as well as enabling it.
- 00:38:18 will probably be most common possible.

- 00:38:22 So the question I always get Why are you doing all this if you're just ultimately going to get the kidney biases seems like a huge workload or shock benefit.
- 00:38:33 And so, before I answer that question let's take a step back and sort of understand how we separate this up into this point.
- 00:38:41 So if you have memorized the proxy and you're concerned about an idiopathic or primary cause versus a secondary cause.
- 00:38:47 We previously defined this by what it wasn't a meeting, if you look through all the secondary causes that I just mentioned, like infection or drugs or malignancy are immune disease, and those are all negative yields are able to see the impact the name, however.
- 00:39:04 When feeling to our first discovered, now we have a reason to have memories of prophecy and we'll have all those other things, and it was just label primary.
- 00:39:16 systemic manifestations, so that really changed the game, but now we're digging into what are the causes of primary.
- 00:39:24 So a little bit more about feeling lar and testing for it so most centers now routine where you can send for analyzing and.
- 00:39:34 sterilizing testing to diagnosis as a variable sensitivity so just because it's a negative doesn't mean it's not feeling too, and that is.
- 00:39:44 For various reasons that I'll explain, but it is modest and sensitive but highly specific.
- 00:39:50 approaching 100% specific for the process of memorize the proper so that's really reassuring and when you compare it to the specificity of standing the biopsies appealing to our set of just the one test it's comparable, so why waste.
- 00:40:05 A little bit more about the field to are and why it's relatively insensitive is for this this graph so.
- 00:40:13 Today, take you through it, so if you were able to discover members that property at time zero when that first antibody bound to that first game and on the other side, before the season sued.
- 00:40:23 Its variable whether you see approaching our first or the serum fealty to our antibody first but, ultimately, they tend to hear each other.
- 00:40:32 With Pilates who are rising sooner and then falling sooner in relation to marry so as the disease progresses purely to artists are like the Canary in the coal mine.
- 00:40:42 If you have the antibody positive, you can bet in a few months that the protein area will become worsening with positive as well.
- 00:40:49 Unless you're treating the patient, where they go into remission repeal it to our in a body will fall in value and then switching area also fall behind.
- 00:40:58 So that's what I'm trying to show you with this graph and we refer to that is immunologic activity and then the clinical disease.
- 00:41:05 You want immunologic activity we control with a lower appealing to our because that's associated with better outcomes, as well as a result in a scenario reduction essentially disease.
- 00:41:21 So with that it's important to routinely monitor revealing random body, whether it's you're deciding on treatment and you see.
- 00:41:28 About ramping up if you're deciding I don't want to treat and it's ramping down on its own may hold off, so the take home point is this is an early biomarkers of disease.
- 00:41:40 Before approaching or a changes.

- 00:41:44 OK so again going back to the original update is you don't need a kidney biopsy, and this was supported by a couple of years ago by a retrospective study out of mail they took 132 patients and they'll clinic with feeling to our proven number and stuff rafi who had zero logic testing.
- 00:42:03 One of those patients they excluded 35 of them that had secondary causes being lupus or viral hepatitis or malignancy and we're left with 97 patients with no secondary causes but really turn lemons.
- 00:42:19 And they stratified those patients affording CFR, so if they're gsr is greater than 16 meaning of preserve tfr.
- 00:42:26 The kidney biopsy and those patients 60 of the 97 did not add anything clinically meaningful, so you did a biopsy relatively high risk procedures for no significant gain.
- 00:42:37 Conversion conversely, and the patient said more advanced TV two out of 37 actually had a meaningful change in their diagnosis or therapy.
- 00:42:46 to patients were discovered one to have a any other Jennifer percentage process would think of vasculitis so the takeaway point is.
- 00:42:54 Roughly 2% of the time, if you do a biopsy in the face of failure to our positive without a secondary thoughts, you have meaningful change which doesn't seem to work.
- 00:43:05 So with that information we wrote about proceeding with a reasonable algorithm on how to stratify these patients, a little bit of a busy slide but what i'll.
- 00:43:15 Do the take home point being is that if you've recently excluded secondary process with a list to the right.
- 00:43:23 And a for loop is a one see for diabetes he's gone through the drugs there's no causes of protein area there and you've done it says X Ray for certain point, as well as aspect to exclude.
- 00:43:34 Damien what you can do is check the eliza check in with our essence we're appealing to a positive and if you have no secondary cause with those positives you can skip one lab see.
- 00:43:46 However, if you do find a secondary cause or they have progressed kidney disease, you want to do.
- 00:43:52 biopsies and this year logic testing the reason for that is rarely or have only a positive psychological test with it the negative biopsy we've seen that.
- 00:44:01 Very rarely but also you want to follow that baseline feeling to our value and you want to see a change as time goes on to help you.
- 00:44:14 Okay So what are the issues with that, the main one, the obvious one is that it's a retrospective study of a little more than 100 patients, which doesn't sound very robust and it's not perspective is study meaning.
- 00:44:26 You wouldn't want to necessarily go forward with treatment and prognosis decisions based on a retrospective study that would be confounded.
- 00:44:35 Good news is is this study has been repeated a couple of times over, and a larger cohort a.
- 00:44:42 internationally and found very, very similar results, the biopsy just doesn't help you if you exclude secondary policies can you have a positive what tests are.
- 00:44:52 There are interestingly reports of false positives relevant and diabetes so definitely I always recommend a biopsy and the appropriate patient you have diabetes in a positive way to our.

- 00:45:04 It happens a lot you'll be spending a lot fulfilling to our emerging area and diabetes is so prevalent and you got to translate.
- 00:45:12 The reason for that false positive is not clear to say.
- 00:45:16 that it should be a shared decision making to skip the biopsy patients don't enjoy getting biopsies they don't enjoy talking about any biases so it's anxiety provoking and if you can tell them I'm going to do split test and skip it will be for.
- 00:45:33 false positives reality meeting that it's positive in a CRM and then on biopsy there's a correct.
- 00:45:41 Okay okay number two So if you don't need a kidney biopsy all the time that's great so that's a step towards precision medicine, but what about our therapies cyclophosphamide is called.
- 00:45:54 It is been around a long time, but now we're starting to look a bit more like Rheumatologists we're using redux of Mr isn't that great.
- 00:46:02 So the first line therapy is now protection or cyclophosphamide not cycle exploring, which is a big change and I'll explain the data behind that.
- 00:46:13 So it 10 years ago if you had a patient with the frogs and then, if you had to maximize on there as or art therapy and they still approaching area and if, after six months they had no improvement.
- 00:46:25 But they didn't spontaneous remission, which is a pretty common occurrence in numbers are probably 30 to 50% of their patients will spontaneously getting better without you doing much of anything.
- 00:46:37 So it's important we wait and give that time if there's no severe or high risk situation like a DVD of being we've got to fix this fast.
- 00:46:46 And then you can choose cyclophosphamide apart with steroids, what is our cyclophosphamide for Mr Eric regimen well that's about as diverse as.
- 00:46:54 As you can get if you ask 10 nephrologist you might get 10 different answers it's been everybody seems to have their own preference and how they want to give it the original what we call modified potentially regimen.
- 00:47:07 Is IV methyl pred over three days, followed by pred oral for 27 on odd days of month on 11 days you'd give more also toxin and that sounds strange, and it is.
- 00:47:21 And I don't have a good reason why we thought originally it was thought to have less than obedience or simultaneous by alternating.
- 00:47:30 Ultimately, this is the regimen and we will follow it to a TEE personally I tend to give them compressing at the same time for a shorter course so that nobody gets confused and that seems to be favorable.
- 00:47:45 So this was challenged in a randomized control trial, a couple years ago three.
- 00:47:52 In something called the mentor trial, so this was a comparison of rituximab to that cyclophosphamide or two cycles for just the second line therapy.
- 00:48:02 It was an open label multicenter nine if you're already dropped.
- 00:48:06 At his primary members, and these are relatively sick patients in terms of numbers and stuff rafi they had five grams of protein your it they went through three months threads running period with a sore arm.
- 00:48:16 And they were randomized rituximab recycle sparring and the complete are the primary outcome was.

- 00:48:24 Positive complete or partial remission at two years with respect to purchase area there and so really The goal is to get rid of protein in there.
- 00:48:33 So table one on these folks as you might expect, it was predominantly male.
- 00:48:39 They had seemed to get approached in areas we talked about, as I explained.
- 00:48:44 They had a low history of immunosuppression only about a third of them had previously been exposed to new suppression, which is good.
- 00:48:52 And the importantly the appealing to our value was considered in this trial tues is one of the first randomized control trials, where that was but for us it wasn't a primary endpoint, but it was still.
- 00:49:04 check frequently is considered positive if is greater than 40 I we don't use that threshold for anything, this was an in House as a meeting it's not the essay we currently use.
- 00:49:15 Solid are available so don't necessarily say Oh, it was over 40 minutes severe a we don't use this anymore, so we can't it's apples to oranges for our class.
- 00:49:27 So what it ultimately show well the.
- 00:49:31 where it talks about for cyclists born and then fight.
- 00:49:36 So, so the complete or partial or mission at the end of one year was 60% and ever talks about growth comparable by not inferior a cyclist born in 52%.
- 00:49:49 However, the end of the two years we're talking about the map continued at about 60% complete or partial permission, whereas cycles born fell off around 20% so at two years.
- 00:50:00 35% saw complete remission with chuck's gun it's like this morning had 00 complete remissions after two years, set in another way for talks to map so 40% patients fail and cycle sponsor 80% of patients fail.
- 00:50:15 If you're new to Melbourne is you're kind of going wait a minute you're telling me a disease that remains, about half the time and you have a therapy that fails 80% of the time.
- 00:50:27 that's not it's not great, so we have a lot of work to do, but this, I think, especially with the zero complete remission that two years firmly established, is this the second line fair.
- 00:50:41 In addition to the approach and area response it's important to look at the ability to respond so.
- 00:50:46 As I've been explaining that really to our it's a biomarker it's necessary for the injury and appealing to our Members.
- 00:50:52 And although this wasn't a primary endpoint what you have is rituximab after two years, this is purely to our values and the y axis and time on the X.
- 00:51:01 They dropped precipitously in the first six months, whereas psycho sporran wasn't nearly as big of a drop now it's not statistically significant this was in the primary endpoint, mind you, but.
- 00:51:14 Time after time, the ability to our value as i'm showing these red boxes here, those are the raw values.
- 00:51:19 Was you know four to five hold higher for their cycle sparkler compared to text me so what you're getting you're not getting immunologic control to disease and second spot and that's really.
- 00:51:29 it's where it fails So why did they get better why did, why did psycho sport at least help at all.
- 00:51:37 The answer is probably this there's early approaching Eric response with cyclists born and the mechanism is psycho sport probably.

- 00:51:46 prevents synaptic vesicle degradation by stabilizing set of skeleton, so this is really interesting because.
- 00:51:52 We don't necessarily want to target T cells with cyclists born in a B cell mediated process that kind of doesn't fit, so why does it help and it probably is a direct action on the site itself.
- 00:52:04 which opens up the door for new therapies targeting the the photo site itself in its structure so.
- 00:52:11 That likely is pointed it also explains why there's a higher rate of relapse if you're not getting important feeling to our reductions with this drug soon as you stop the drug disease washes right back because you haven't done a really to our, which is the driver's seat.
- 00:52:28 Okay, so some take home points this firmly established that be cell targeting therapy, especially with rituximab was here to stay in a superior to cyclists born.
- 00:52:38 Future trials really should target for generic reduction and immunologic production so we're hitting it at both points.
- 00:52:45 The start and the end of sort of the process, if you will psycho sporran it's definitely a second line and then you know 40% of patients did not respond to a text message there's a lot of work left to be done and as I'll explain later on.
- 00:53:00 So, how would this compare to cyclophosphamide so, is it is it the same as an equivalent this doesn't really tell us which should be first line.
- 00:53:09 And this was attempted to be answered at least last year by scolari and colleagues and a randomized trial and open label is mostly Italy.
- 00:53:21 These patients had fealty to our Members to probably mostly they weren't nearly as sick they had only three and a half grams of protein areas compared to five and mentor.
- 00:53:31 But they were assigned rituximab and one gram on day one, and another grand one day just chain like mentor, however, they did not get a reduced it six months if they were responding, unlike mentor.
- 00:53:43 Their primary outcome again was pretty generic reductions for complete remission at one year and they did use modified on a chilly as a comparison.
- 00:53:51 So, unfortunately this study was not big enough to show statistical superiority or inferiority for one of the other but.
- 00:54:01 What it what it does show is that Pilate to our reduction with her toxin that was unbearable.
- 00:54:07 to sacrifice my that I'm showing you here so on the y appealing to our values at the start, and at three years 52 are on the wire here with the modified pot of chili or that sacrificing literature, as well as approach area.
- 00:54:21 Reduction so ultimately you could say that perhaps cyclophosphamide had it much quicker action and reducing the good your value but.
- 00:54:33 what's critical to appreciate is going forward is you don't really know.
- 00:54:38 What the feeling to our values in this trial and the other tribes you don't really know what the ability to our value is doing prior to treatment.
- 00:54:44 Was it going on, was it coming down, was it flat the whole disease process could be changing under your nose and just because you started patients at time zero doesn't you don't really have a good understanding of the natural history for the patient.

- 00:54:55 So it's to be taken with a grain of salt, but they both seem to work and so look at the the data on there, the hard numbers on this basically after one year other not statistically significant.
- 00:55:09 The reduction map was no better no worse than cyclophosphamide this held true as time went on at three years they're pretty comparable.
- 00:55:20 it's a saw study it's a pilot study, but ultimately didn't really show one was better than the other.
- 00:55:29 Where the conversation really comes in, in terms of directly in front of the patient is the adverse events.
- 00:55:35 cyclophosphamide associate with malignancies associated infections simultaneous the steroids, are going to cause hypoglycemia and a lot of patience.
- 00:55:43 And I've had patients flip to starting to use diabetes, which is you have those conversations and maybe.
- 00:55:50 They don't enjoy it and on the flip side of that were texting that comes up a lot of fusion reaction and so you'll see comparatively the adverse events wasn't really different 19% never talks about group.
- 00:56:02 serious adverse events verses 14% and it's like the mastermind group, but this is really the conversation, are you willing to accept the opinions pneumonia risks that will be a small versus the intrusion reactions with your text message.
- 00:56:17 that's where a lot of the conversation.
- 00:56:21 So why, why is it still a tire what makes us choose one or the other, or why very high risk patients still getting second possible.
- 00:56:28 rituximab has yet to prove its benefit in the long run sacrifice it's been around a long time has been shown to reduce rates of yesterday, our toxin that has not been shown to do that just yet, although time will tell.
- 00:56:41 it's not excited and advanced kidney disease so oftentimes if you have someone who's well advanced in their chronic kidney disease with Members to probably reflects what's going to take a while.
- 00:56:51 we're a sacrifice one seems to work faster and.
- 00:56:56 The cyclophosphamide tends to reduce the ability to are from higher heights meaning the worst you're appealing to our is in terms of absolute value sacrifice and appears to be the.
- 00:57:07 The better drug and observational study so it's still still in the high risk category you're going to want to sacrifice my first and perhaps that will change.
- 00:57:18 And so Lastly, the third update you should be aware of is that we're sort of putting away the term primary and secondary managed properly that's going by the wayside.
- 00:57:26 And this is essentially the most exciting part about Member supremacy today.
- 00:57:32 So again, when we define primary memory rather saying all right, this is only a disease that affects the kidney we used to call it a bad thing that really to our came around those are great we have.
- 00:57:41 A primary metrics and things we know why everything else is secondary if it had multi organ involvement or systemic manifestations, cancers and back in 2019 life was so simple wasn't it we just had a few antigens we were known about coated wasn't here this great.
- 00:58:02 feeling to arm and a little more than half of cases another antigen called promise bonding was discovered.

- 00:58:08 And 2014 that was great we got used to that now, one is another antigen that was discovered that came a couple of years later, and then access towson.
- 00:58:19 So these antigens are piling up, we were getting more and more specific with our primary and secondary members to practically causes.
- 00:58:27 And then 2022 we have eight more, and now it feels like alphabet soup, we have so many proteins to go through, and all these new discoveries, where do we put them.
- 00:58:38 All these new antigens that are potentially on photo sites are secreted from photo sites are now the targets of antibodies causing us to practice how.
- 00:58:46 The heck do we define this so going back to the to the separation 25% of time you have secondary and I'm going to 75% of the time, the primary.
- 00:58:56 But all of these entities that were discovered, where do we put them, are they all primary now because they're the target antigen.
- 00:59:02 Or they don't have secondary causes well it is state so and I large retrospective studies, looking at all of these cases are many of these cases with the antigen identified some of them novel.
- 00:59:16 Take home points or miss whether that malignancy was rare and you're appealing to our positive cases So although you should still practice that you do routine cancer screening.
- 00:59:25 Age appropriate just know that in 5% of patients are going to a positive head cancer verses 22% are appealing to our negative so malignancy associated nearness to property.
- 00:59:37 is pretty uncommon for purity one, on the other hand, autoimmune disease is very, very common around 50% guilty to our negative so and it behooves you to search for it.
- 00:59:48 Whereas it's pretty rare only 5% for purely to a positive cases.
- 00:59:52 Alright So what about the other ones, what are the other antigens really tell us so novel ones that we're not going to go through in detail what they mean or their process, but just to give you sort of a.
- 01:00:03 glimpse into clinically why they're meaningful so semi three b's and novel antigen is discovered that's pretty common and pediatric population at 10%.
- 01:00:11 contacting this is seen in patients who have CDP or other denominated partner opportunities so gives you a clue if you have a patient person area and prevention CDP maybe that's why it is an antigen target on the potent.
- 01:00:27 malignancy pregnancy associate member set properly seem to be much more common and promised on it, or the Th es de seven eight antigen now one or PC pH seven So those are more common with malignancies compared only 5% affiliate to walk.
- 01:00:45 And then lupus lupus test, you have specific antigens to so and cam excess towson tgf beta or three they are all.
- 01:00:55 There are making up a huge portion of the target antigens and move this madness and felt that the two so we're getting much more defined and much more specific and defining our movies.
- 01:01:06 So how do we use this, how can we possibly apply this I mean are we just collecting baseball cards here are we actually doing something clinically meaningful.
- 01:01:15 So i'll give you an example, I had a call from a former fellow who ran a case by me, he says six year old man is history smoking, hypertension know what's in production or my weight loss.

- 01:01:27 And its tissue diagnosis was consistent with primary members, but the appeal to our and the drama spawn and teach us to seven eight or negative, so the antigens not identified yet.
- 01:01:37 The routine cancer screening was up to date, but negative so I have weight loss, I have a guy smoking, I have memories from they have how aggressive Should I be and my response was well, did you stay for now, one yet.
- 01:01:49 No, so what is before we go into no one what is malignancy members, the property.
- 01:01:56 So the relativity agreed upon criteria for malignancy and associated Member and as a proxy is it should occur at the time of diagnosis, maybe you should have malignancy and they want us to probably in a reasonable time frame about one to two years from the diagnosis of the moment.
- 01:02:12 You should go into remission if you treat the cancer, it should relapse causing number struggling to come back if it comes back and there should be some sort of link between into some sort of pathophysiology.
- 01:02:24 background is that cancer tends to be pretty common in membership probably about 10% of patients.
- 01:02:30 Is a three fold increase in the incidence of malignancy compared to the general population of commerce and memories copy.
- 01:02:36 And that sort of confounded by the fact that these patients have to be older, they were exposed to cyclophosphamide which causes cancer.
- 01:02:43 Some folks really aggressively screen for cancers others do not so your instance it's going to be different members of properties, the leading positive net for onyx and your patients with malignancy so it always gets your attention, and you can see in front of everything.
- 01:02:59 So what is no one and Why did I suggest, my fellow stain for it or form.
- 01:03:04 So this was discovered a couple years ago by sounds he said, the end of mail and an international court of 10 210 patients who are appealing to our negative, but had memorized probably 16% were discovered.
- 01:03:16 To have no one positivity and novel antigen on the site using laser dissection and mass spectrometry.
- 01:03:23 If you're trying to figure out whether it's a similar way we tight amyloidosis in a similar mechanism of discovery.
- 01:03:31 So the predominant it G or the bottom one is http 184 with Pilates you are and we previously, so I just wanted to comment and malignancy.
- 01:03:43 from Members I circulating, no one had a body was found in five patients so that's great news daily to artists are doing and writing a one is they're going to anybody.
- 01:03:52 Perhaps we can monitor it for relapsing recovery now one is highly expressed on the nervous tissue and it's active during development but not rich and express on photo sites so that's strange why, why was photo sites if readings protein.
- 01:04:08 If it's not within the express what's going on the site that remains to be determined, but just adding to the diversity of Members that are up to date is not just an antigen it started by an antibody it's on the place.
- 01:04:21 So it happens to be now the studies are hard to pull off, but it's the second most common primary numbers right the second most common antigen and remember this.

- 01:04:31 So, to get to the cancer point.
- 01:04:35 There was a study just last year by causing colleagues that 91 patients.
- 01:04:42 91 patients with Members about the no one in their large database at.
- 01:04:48 The 33% of the 91 patients and identifiable malignancy 19 of which were ongoing at the time of diagnosis so fitting with our criteria of malignancy associated numbers.
- 01:05:01 nine of the 12 are treated for malignancy without immunosuppression targeting governance so if you treated the cancer.
- 01:05:09 Nine of those 12 saw at least a complete impartial mission other members of property, so that also fits with our criteria.
- 01:05:15 For malignancy associate members and what's more interesting to me is that when an exceptional biopsy of a lymph node for this particular case of follicular lymphoma in the.
- 01:05:27 picture below that standard positive for now, one so now you have an antigen is present on the tumor as well as the photo site and so hypothesis is are being generated but.
- 01:05:39 Could you to target an antibody towards the cancer and that incidentally targets and antigens secreted from the photo site and it's a cross reactive situation.
- 01:05:48 That remains I'm clear but there's your path of physiologic link that explains how long you been seeing numbers sort of intertwined potential.
- 01:05:58 So we did have the patient's tissue stands for now, one, and it was positive, which is great, and so I said why.
- 01:06:06 search search keep looking and, ultimately, I think, a few months later he had some trouble swallowing or something and stuff to cancers discovered so.
- 01:06:16 not something you routinely think about, but certainly the risk factors, or maybe we've gotten there any way, but certainly keeps our index of suspicion high.
- 01:06:27 So how should we describe numbers are probably going forward so if you read my clinic notes, I try and adopt this, but no longer see you necessarily say just primary or secondary, we should probably, and this is from scientists at these brain.
- 01:06:42 that perhaps we should be calling number is disruptive with respect to the target antigen associated Z so you might say, memory so probably feel a to our energy and positive without associated sees.
- 01:06:53 remembers probably no one positive there's malignancy so the point being we're getting more specific.
- 01:06:59 we're getting more focused and ultimately these antigens are probably have a very different natural history pathogenesis and conceivably the treatment will be different and the outcomes will be different so it's important to be specific about what you're talking about.
- 01:07:16 So as more antigens like Pilates who are identified more we understood about its pathogenesis one before so it's much more diverse than I'm probably explaining and more to come.
- 01:07:29 Most of the antigens also have a circulating antibodies that's very exciting, for us, you order.
- 01:07:35 DNA for rheumatology you may be ordering the members of the panel for us where that's going to have all this target antibodies and perhaps in years down the road you often not do a biopsy for members of the group who's to say which will be kind of said I like cooking classes, but.

- 01:07:52 made it so all considered it's a step towards precision medicine it's a step towards patient focus care and getting more nuanced.
- 01:08:04 So where do we have to go from here 40% failure is not acceptable, and that was true for both protection of acts like a Boston.
- 01:08:13 So what's coming down the line, for us, the next generation CD 20 targeting therapies like or texts or effort to to map the price and letter and apology.
- 01:08:25 we're not even targeting the plasma cells is probably the antibodies are the self-producing the antibody were concerned about so.
- 01:08:34 plasma cell targeted therapies are coming as well, are being tested Belinda man recently saw FDA approval for lupus net Freitas, this is being studied in primary or previously known as primary Member scruffy as well, even carty selfish.
- 01:08:50 If you want to talk about killing a fly with a sledgehammer.
- 01:08:53 party cell therapy is also really wouldn't that be nice if we could just print money and have that happen great.
- 01:09:01 So anti compliment therapy is also so I explained that this can't happen without the antibody but compliment is often necessary to.
- 01:09:10 So it's under investigation, but a lot of the small molecules drugs are targeting various pathways left and pathways mass to see three effectively as the alternative pathways so.
- 01:09:23 Maybe that will play steroids and cyclophosphamide it's already are placing steroids in the vasculitis going to target compliment so very exciting time.
- 01:09:33 And I had three minutes left, so please ask questions.
- 01:09:46 I'm sorry if you mentioned this and maybe I should just know this, but what is, you talked about like protein lyric.
- 01:09:54 I'm remission if you want her mission, what would an African patients get bar look like, when you say they have permission does it get better and then they fail, do they just give us.
- 01:10:07 yeah so The good news is, if you achieve for generic or mission meaning lesson for today, the odds of hitting is, are we are finishing small.
- 01:10:19 So you can almost guarantee unless there's already some scarring similar process but that's, the only thing going on getting particular permission that's stable is here.
- 01:10:30 The reason for worse than getting function and setting those it's not clear to all these years, why do we have a guy and then we'll change disease that's a for boys out what.
- 01:10:42 That means, and so I can't say exactly why does kidney function anonymous.
- 01:10:47 But certainly a response to treatment so yeah The goal is still person, on the other hand, feeling to are going negative after therapy as a metaphor risk reduction and relaxed So if you get an idea I mean completely negative attention to our that.
- 01:11:09 What is the role-play to our measurements in a transplant patients yeah rigorous so.
- 01:11:18 he's been suggesting that perhaps you should check billy to our before transplant to suggest values, you know, greater than 50 or so will tend to increase your risk of relapse and numerous.
- 01:11:31 Is not uncommonly relapses lung transplant whether we should be testing for it and treating it preemptively or giving them, you know suppression after transplant.

- 01:11:42I think has not been sorted out yet I'd advocated and safe and effective just treat it beforehand, depending on the risk factors and looking at the patient, but yeah it's a it's a question I think some just treated some let's see what the game.
- 01:11:59yeah I'm curious as a trans.

Unknown Speaker

01:12:03You.

UVA IMR

01:12:06awesome time.

- 01:12:08Cancer antigen piece of things, but it's really interesting patients come in with either new member to the property or, worse, can you see it sort of check.
- 01:12:18In oh very good question yeah so you think you sort of unleashed things with the checkpoint inhibitors and what the immune system one wow is, to my knowledge, not very common to have a member s relapse i'm sure it's been rewarded.
- 01:12:32But yeah that's he tend to think of memory as a sort of a multi hit process I didn't explain to you, but there's definitely a genetic predisposition if some mutation Hla or feeling to our gene specifically.
- 01:12:45Why is it 50 years later you're 50 years old, you get paid to our Members that's unusual vanishing rare in pediatrics we often don't see it's a unicorn pediatrics so.
- 01:12:56You know why Why then, and would check one inhibitors exacerbated, it makes sense, make sense, I have not routinely see I don't know.

Unknown Speaker

01:13:13Yet.

Unknown Speaker

01:13:20You can see a fish.

UVA IMR

01:13:24Even for people that.

- 01:13:27Are that gotta check.
- 01:13:32Was he was to take the cancer that complaint, but now there's just in the last week and published novel antigen for stem cell transplant.
- 01:13:42So there's even antigens unique to do that not even just cancers after stem cell transplant with graft versus host disease there's unique antigen so yeah it's a more nuanced.
- 01:13:59yeah.

- 01:14:01But.
- 01:14:05If you are please press one wise into them.
- 01:14:10And I know you I.
- 01:14:13was not here, he would have added he's already asked her that question that's a great I don't have to answer, I suspect, maybe it's local inflammatory environment of the photo site, perhaps, or something about the Buddha says expression ability to our that allows for better binding.
- 01:14:30it's a really good question was daily to our is expressing the lungs and there have been observational studies that in areas of China with high.
- 01:14:39aluting volumes that seems to increase the risk of ability to our Members so maybe there's some.
- 01:14:46You know priming action that occurs in the lungs and you don't really see a clinically but it produces the antibody to target the kidneys and that's where you see clinically meaningful disease.
- 01:14:56In my mission is, and so you know we think 40% of patients feel relaxed and sacrifice with line that's like 40% of the.
- 01:15:0650% of patients have permissions to give a small percentage of a small percentage of what's already as policy get, how do you like recently study these patients.
- 01:15:14For like clinically meaningful outcome or they're like good like can you follow the protein levels that relate to our and I was able to take those are good surrogate markers.
- 01:15:25yeah that's it's almost a you have to it's a part of our guidelines and recommended that at least every three to six months when you're.
- 01:15:35deciding on therapy following the ability to our value and approaching area, but what your point is good, like this is a, this is a long process, it takes to kill kidneys.
- 01:15:45How do we really know studies aren't huge I mean I'm talking like 100 patients, so it takes friends, so you got to work together and different.
- 01:15:53different universities patch together and create different consortiums and that sort of thing to get to the bottom of it which studies are getting bigger and bigger and work together, but you know, in terms of drug trials that are involved in I hope to get one or two a year.
- 01:16:09So it's really hard it's really hard.