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TRANSCRIPT - GR 07 22 22 ***"Onco-nephrology"*** – Amanda Renaghan, MD from the University of Virginia

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- Okay, so today, we have our hosting Dr Amanda ran a hand for medicine grand rounds, many of you are undoubtedly familiar with her she's been a faculty Member here since 2017.
- 00:42:49surgeon multiple roles already in are still young career as a teacher mentor researcher patient centered clinician.
- 00:42:57or inspired me or impressed me the most was when I went around preparing for this introduction and talk to people and said oh she'll be presenting today.
- 00:43:04There are a lot of happy faces a lot of smiles a lot of people kind of lit up and said oh she's great she's wonderful.
- 00:43:10I think it's really highlights her commitment to like a genuine commitment to her was like a mentor and in clinical instructor.
- 00:43:16She is an alumni of Boston college she left Boston to do residence or to do Medical School here at uva and then went up to cornell for her medical residency and fellowship and nephrology.
- 00:43:29She has focused her academic career in the field of unco nephrology studying the effects of hematologic malignancies.
- 00:43:36And pair approach anemia is on the kidney as well as well as the effects of immunotherapy and effort toxic chemotherapy in fact she's gone so far as to establish an ongoing nephrology clinic here to Emily her cancer Center and with the express goal of caring for such patients.
- 00:43:54She is also the uva would say, maybe site director is, this is an appropriate to turn to us for the STOP covert investigator group so multicenter collaborative research effort to study the effects of.
- 00:44:06And outcomes and patients who are critically ill with coven it's very fruitful investigator group and as part of English dozens of papers, since the beginning of the pandemic, so please give a warm welcome today to Dr Amanda ran a hand.
- 00:44:32Thank you, Sam for that very generous introduction.
- 00:44:37I have no relevant disclosures.
- 00:44:40Good afternoon, and thanks so much for the opportunity to speak with you all today about a topic that I think is really interesting and ongoing ufology.
- 00:44:49But before I get into the real meat of the talk I did want to say a few brief words about ongoing ufology and our clinic here at uva.
- 00:44:56Over the past four years I've had the great privilege of building this clinic along with a wonderful care coordinator Kelly Phillips and immense support from the divisions of nephrology and oncology.
- 00:45:05We get to care for really amazing patients living with cancer and kidney disease, whether it be our protein-associated kidney disease kidney dysfunction after stem cell transplantation.
- 00:45:15electrolyte disturbances after cisplatin exposure renal toxicity from immunotherapy or patients living with one kidney after renal cell carcinoma.
- 00:45:24it's been a to collaboration and i've been so fortunate to work with such fantastic colleagues in hematology oncology urology and pathology.
- 00:45:33To really try to figure out the best way to care for these patients, while also keeping them on their anti-cancer therapies as much as possible, so thanks very much to my colleagues at the ECC.
- 00:45:43So let's get into it protein associated kidney disease is a constantly evolving field.

- 00:45:49And it's a huge topic so we won't be able to cover it all, but I really wanted to hit some of the highlights that I think are important to understand for both nephrologists and non nephrologist to like.
- 00:45:59The goals of this talk or to define monoclonal come up with the adrenal significance and distinguish it from monocle and have them apathy of undetermined significance or am Gus.
- 00:46:08To understand the spectrum of fair protein associated kidney disease to understand the advantages and.
- 00:46:13disadvantages of several different screening methods looking for monoclonal proteins enter review strategies for treatment of a pair of protein associated kidney disease, using a clone directed approach.
- 00:46:27What is a pair of protein it's a monoclonal.
- 00:46:33Things should be a.
- 00:46:36pair of protein is a monoclonal light chain heavy chain or intact immunoglobulin present in the blood or urine.
- 00:46:42pair of proteins are produced by plasma seller be so clones, resulting in a pair of anemia, which is also called the monoclonal ganapathy the responsible clone may or may not meet criteria for cancer.
- 00:46:55So now for just a second let's take it back to MED school and remind ourselves of what an immune globulin looks like see if I can get the pointer to work.
- 00:47:03Each immunoglobulin is made up of two light chains and too heavy chains, each with variable regions here in orange and constant regions here in blue.
- 00:47:14Light chains have one variable region and one constant region heavy chains have one variable region and three constant regions ch one stage two and ch three.
- 00:47:24And each region has its own job the fema region or variable fragment mediates antigen binding the ch one domain, which we'll talk about later is important for allowing the heavy chain to bind to its light chain.
- 00:47:37And the FC fragment here mediates and organ or downstream effect or functions through compliment activation and also through binding to innate immune cells.
- 00:47:46There are five immunoglobulin subtypes type of their story I GG ign IDA I G and add I did use the most common and two types of light chains Kappa and Lambda.
- 00:48:02em Gus is a term that was introduced into the literature and 1978 and it stands for monoclonal them up with the of undetermined significance.
- 00:48:09This is essentially a pair of anemia without over at cancer or and organ damage in em goes there's no increase in morbidity, mortality related to the clone.
- 00:48:18The serum and protein concentration is low, less than three grams per deciliter and there are fewer than 10% colonial plasma cells in the bone marrow.
- 00:48:27And Gus is quite common found in 3% of the population over 50 years old and it's two to three more times more common in African Americans, and it also increases with age.
- 00:48:38there's a low risk of progression to multiple myeloma limbo proliferative disorder or immunoglobulin associated amyloidosis about 1% per year and this low rate of.
- 00:48:48progression is depicted in the graph down here so we've got time from diagnosis and then progression per year and I'm just fine it's just kind of drifting up slowly.
- 00:48:57The risk of progression to avert malignancy is higher in patients with a higher CRM protein so greater than a gram and a half of.
- 00:49:05Protein in the serum when it's a non je je and protein, for example, an idea or an iga and when patients have an abnormal serum free light chain ratio and we'll talk about that a bunch later.
- 00:49:20smoldering myeloma also called asymptomatic multiple myeloma is characterized by the presence of a higher tumor burden.
- 00:49:27But, specifically the absence of any organ damage so patients have an m protein of greater than three grams per deciliter in the serum or more than 500 milligrams per day in the urine.

- 00:49:37And they have more Colonel cells in the marrow but they still have not experienced in my aloma defining event and they don't carry a diagnosis of amyloidosis.
- 00:49:45And, unlike these patients their risk of progression to avert malignancy is higher, about two thirds of patients progressing by 10 years.
- 00:49:58I had a little fun with the clip art for this.
- 00:50:01So, in contrast, is moldering myeloma over to symptomatic myeloma is defined.
- 00:50:05by the presence of a higher tumor burden and the presence of end organ damage, and we all are very familiar with the crab criteria from Medical School Piper calcium, you have renal dysfunction anemia and bone lesions.
- 00:50:17In 2014 the international myeloma working group added three additional criteria for the diagnosis of myeloma recognizing that these predict, I strongly predict the progression to symptomatic myeloma.
- 00:50:28And these include greater than 60% bone marrow involvement by Colonel plasma cells, a serum free light chain ratio of greater than 100 with the level of the involved free like chain being greater than 10 milligrams per deciliter.
- 00:50:41And more than one focal lesion on MRI, and so the crab became a slim crab and I want all of our residents and students who are watching to remember this, for your exams.
- 00:50:52And, of course, this is a talk about kidneys so I want to draw your attention to the renal insufficiency criteria and part of the crab criteria.
- 00:51:01This is really limited to kidney injury resulting from casting a frothy light chain cast in the property is actually considered a myeloma defining event is nearly all cases meet the tumor burden criteria.
- 00:51:12However, pair of protein associated kidney lesions other than casner for apathy do not satisfy the renal impairment criterion for symptomatic myeloma.
- 00:51:20myeloma can't be diagnosed in a patient with monoclonal immunoglobulin deposition disease, for example, unless other crap criteria are met.
- 00:51:31And the reason that any of this is really important is because historically treatment was not recommended until progression to a work crab.
- 00:51:39criteria for myeloma so here you have em Gus and smoldering myeloma and really treatment was not recommended outside of the bounds of a clinical trial.
- 00:51:49So as late as 2010 the international myeloma working group guidelines suggested that those patients with em Gus, by definition, not meeting criteria for malignancy should be followed with an s and a CBC every six months, with no specific treatment unless part of a trial.
- 00:52:06But clearly there's a gap here, so we all frequently see patients who have an m spike that's a low level they've got less than 10% colonial plasma cells in the bone marrow but they've got kidney impairment, possibly related to a pair protein or clump.
- 00:52:25Until the question is.
- 00:52:28Are there dangers associated with smaller quantities of em protein and lower tumor burden or, put another way, can small clones be dangerous.
- 00:52:36So as early as 1991 it was recognized the bench Joe team branch Jones proteins, which are just monoclonal like chains.
- 00:52:43isolated from patients with power protein related kidney diseases could actually replicate the same disease when injected into animals.
- 00:52:51demonstrating that some, but not all monoclonal proteins have intrinsic properties that cause and organ damage.
- 00:52:57So you have mice over here and humans on the right, and you see crystals amyloid deposits and tubular cast from pair of proteins that have been injected into the mouth so even in the absence of a high tumor burden these animals developed disease.

- 00:53:12In 1992 hellman and colleagues published this retrospective study of 19 patients with light chain deposition disease 12 of whom had em Gus.
- 00:53:22one and five year patients arrival were 89 and 70% one and five year renal survival were 67 and 37% which is pretty small.
- 00:53:32And if patients with the creating of greater than 480 2% progress that yesterday.
- 00:53:37However, the patients who had a creating have less than four did show a partner reduction and stabilization or improvement in their kidney function with treatment and in this study these patients got Mel flan and print ozone are clear and we're still in prison.
- 00:53:51In 2011 NASA and colleagues reported on for patients with a history of proliferative loma Linda Freitas with monoclonal immunoglobulin deposits or PG and mid and kidney transplant.
- 00:54:03Disease record only four months after transplant with aloe graph dysfunction and protein area.
- 00:54:09Three of the patients got high dose steroids and rituximab one got high dose steroids and cyclophosphamide they all showed a reduction in portland area and three header reduction in their sphere and creating.
- 00:54:21The last steady i'll show is from lorenza who in 2010 reported on about 1300 transplant biopsies from the Mayo clinic.
- 00:54:28They found 29 cases of recurrent Member know proliferative gloomier Linda Freitas or mpg in.
- 00:54:34and have these 29 six had a circulating and proteins and one had a monoclonal I mean a globulin that was deposited in the kidney.
- 00:54:42those patients who are found to have an identifiable and protein had higher rates of recurrence as well as a trend toward earlier more aggressive disease, though the latter wasn't statistically significant.
- 00:54:53The recurrence rate was 71% enough seven patients who had him on monoclonal protein identified compared with 29% for the patients who did not at an average follow up with 53 months.
- 00:55:10Until we've seen that pair of proteins can have never toxic properties, independent of the number of plasma cells or the quantity of the protein.
- 00:55:18That certain pair of protein associated kidney diseases are associated with mortality and yesterday.
- 00:55:24And the recurrence that recurrence may occur in the Telegraph but that these entities can be treated successfully if identified and managed properly.
- 00:55:32And all of this led to a landmark paper published in blood in 2012.
- 00:55:37When the international kidney and monoclonal them up at the research group introduced the term monoclonal them out, but they have regional significance would really represented a paradigm shift.
- 00:55:46in how we look at monoclonal diseases affecting the kidney the group noted that, despite their non malignant nature and drs lesions are associated with a great deal of morbidity and mortality and distinguish them from em guts.
- 00:55:59And so, now we fill this gap we've got patients with a low tumor burden they don't have crab criteria they don't meet criteria for my aloma or clo or my league malignant lymphoma but they have renal dysfunction attributable to a monoclonal protein.
- 00:56:20before the storm was introduced many of these lesions that will discuss like mid mid PG and mid were not treated.
- 00:56:29And so I think this whole story is really relevant because, like a lot of things in medicine it's a lot easier to treat something once you've named it.
- 00:56:35So this is a CS this is acute abdomen this is m drs Okay, we need to do something about this when you decide which this patients kidney function.
- 00:56:46Historically power protein disorders, affecting the kidney have had a poor renal prognosis after diagnosis, with about half of patients progressing as RD by two to five years.
- 00:56:56Really, with the notable exception of light chain proximal to be lot WiFi which takes about 10 years to progress it yesterday.

- 00:57:03These diseases present independent of tumor burden accepting like gn casts the properties mentioned earlier, which is a myeloma defining event.
- 00:57:11Importantly presentation is determined by the nature of the pair of protein and not by the type of cell or the type of clone producing it.
- 00:57:19So the molecular characteristics are really important, for example, we talked about for about the heavy chains and light chains.
- 00:57:27And in a disease called heavy chain deposition disease you've got a deletion, and the ch one constant domain here.
- 00:57:33which basically renders that heavy chain unable to bind to its light chain and resistant to produce thermal degradation.
- 00:57:39letting heavy chains be secreted out of the cell when they normally wouldn't be and then, subsequently, leading to deposition and tissues.
- 00:57:47The functional properties of these power proteins are also really important we have some that are able to activate compliment others that are able to induce autoimmunity.
- 00:57:56And also Importantly, these pair of protein associated kidney disease disease power proteins can deposit in any renal compartment so gloomier tubular interstitial and vascular and patterns of injury may co exist, so you can have someone with.
- 00:58:10Multiple pair protein associated kidney disease is going on at the same time.
- 00:58:18Our protein disease associated kidney diseases don't have to be limited to the kidney and i've highlighted a couple of examples here.
- 00:58:25So we all see patients with Al amyloidosis who have cardiac involvement and severe cardiac involvement is a main predictor of morbidity and mortality and these patients.
- 00:58:34or patients with Type one and Type two crowd globulin you MIA these are also Mrs lesions that can have multi system involvement presenting with perper arthralgia is and life threatening vasculitis with GI pulmonary CNS cardiac and other manifestations, in addition to kidney disease.
- 00:58:52And so, these may be better described is n gcs lesions or monoclonal come up with these of clinical significance, since it's not just the kidney that's involved.
- 00:59:01The diagnosis of em drs almost always requires a kidney biopsy with interrogation of the biopsy specimen for evidence of light chain restriction meaning.
- 00:59:11deposition of just capital and capital gains or just Lambda light chains and the presence or absence of an organized substructure to the deposits on electron microscopy.
- 00:59:21Special techniques may also be necessary, for example, Miss mass spectrometry which is really the gold standard for amyloid typing when you find.
- 00:59:29fibro suggestive of amyloid on electron microscopy and you have a sample that's Congo read positive.
- 00:59:35Patients with Mrs Mrs lesions are generally considered to have the same bleeding risk from biopsy as non Mrs patients about 4%.
- 00:59:44with the possible exception of patients with amyloidosis who may have a Co op.
- 00:59:48coagulate apathy related to a factor of 10 deficiency or my head deposition and the small capillaries that increase their bleeding risk, and so in patients, where you have a higher suspicion for amyloidosis.
- 00:59:59Perhaps it's preferable to start with a bone marrow or fat head biopsy that carries less risk.
- 01:00:06And if you look in the literature you'll see lots of scary looking charts trying to organize the different m drs lesions out there.
- 01:00:14I chose this one, because it represents the most up to date, classification from the International kidney and monoclonal come up with the research group.

- 01:00:21And because no nephrology talk would be complete without some obligatory images of blueberry lie, and I hope you're able to see it pretty clearly i'm sorry, the text is small there's a lot to say about all of these but i'll be brief, to try to keep everyone awake.
- 01:00:36These lesions are broken down into those with and without monoclonal immunoglobulin deposits and those with deposits are further broken down into organized or non organized deposits.
- 01:00:49Many of these entities, you may be familiar with those some of them are more rare and you may not have seen them.
- 01:00:55Here in the fibro group, you have immunoglobulin associated amyloidosis, which is the most common em drs lesion.
- 01:01:02down here we have monoclonal February Ilona Freitas, this is also caused by fibro definite deposition actually the minority of patients with February gn.
- 01:01:15it's really the minority that have a monoclonal protein and majority or poly colonial diseases, but a sub sub group of them are associated with a pair of Mumia.
- 01:01:25Here in the microbial group, we have amy no tax legal marijuana Freitas, which is a Reno limited disease.
- 01:01:31Compared to cry globule anemic have Type one and Type two and drs where you have multi system involvement as I previously mentioned.
- 01:01:40We have patients with light chain proximal to the law apathy in the crystal or inclusion group and here you're not looking at a glimmer aerialists you're looking at two bills and you have.
- 01:01:50deposition of crystals in these proximal tubular cells that have just become so overwhelmed by these toxic light chains and they're accumulating in the lives of stones causing in some patients frank Fanconi syndrome.
- 01:02:04crystal storing his do psychosis is quite rare and can have widespread extra renal distribution.
- 01:02:10In the bone marrow lymph nodes is the novia a cornea so lots of different places are really interesting and pretty rare disease and then at the bottom, here we have crystal romulan email gn also multi.
- 01:02:24Multi system disease with thromb by that can deposit in the glimmer of the capillaries but also the smaller arteries the arterial is causing vasculitis and drawn by.
- 01:02:34mentioned previously in a non organized group, we have monoclonal immunoglobulin deposition disease, which is MIT.
- 01:02:41And then proliferative gn with monoclonal immunoglobulin deposits or PG in mid we don't have to remember all of these names.
- 01:02:49These lack and organized substructure in mid.
- 01:02:52These pair of proteins they're kind of characteristic properties that they're negatively charged and that causes them to deposit in both the mayor and tubular membrane so that's sort of the hallmark.
- 01:03:02and PGI mid is really a gloomier limited disease and we'll talk a lot about that one later and actually think some of the more interesting am drs lesions are the ones here on the right side that don't have any monoclonal immunoglobulin deposition.
- 01:03:20This one over here see three give them a lot with the when patients are biopsied they've got an abundance of C three on immuno fluorescence but they actually don't have a monoclonal protein deposited.
- 01:03:32This entity is caused by constitutive activation of the alternative compliment pathway.
- 01:03:36And a subgroup of these patients will have a monoclonal gum apathy that we think is acting as a C three and a critic factor or an Anti factor H anybody causing compliment dysregulation and subsequently compliment deposition and the kidney.
- 01:03:51Pretty recently robotic micro-algae off, but he was added to this classification under provisional status i'm not sure why.
- 01:03:59I guess they're still working it out the pathogenesis is not entirely clear.

- 01:04:03There are some patients who have both robotic micro-algae apathy in the kidney and also micro and geo pathak humility anemia in the blood.
- 01:04:11And it's thought that perhaps their power protein is acting as an auto antibody to cause compliment dysregulation.
- 01:04:19And then in patients with poems syndrome, they can develop the robotic micro angie apathy in the kidney without any micro and geo pathak anemia in the blood.
- 01:04:28And the thought there is that the tma is caused by a cytokines mediated endothelial injury, so a lot of really interesting things going on in this area that are still being worked out.
- 01:04:37And then down here and pink we have some had the miscellaneous group and really that's the group that's characterized by mimicking poly colonial diseases, so a pair of protein that produces members Marilyn apathy or anti gbm disease.
- 01:04:56And so, now that we've taken a whirlwind tour of the drs lesions I wanted to turn our attention to, I think, really challenging clinical conundrum what patients with em Gus should be biopsy.
- 01:05:10This is a visual abstract from a recent study published in the journal of the American society of nephrology zan and colleagues from Mayo looked at the rate and predictors of finding em drs lesions on kidney biopsy in patients who had an Gus.
- 01:05:26And they did this because, for patients with the combination of monoclonal them apathy and kidney disease quote great angsty remains among the nephrology Community over who to biopsy.
- 01:05:37Especially in the elderly, where pair approach anemia and ck D frequently coexist.
- 01:05:43So they looked at 6300 patients with monoclonal them apathy, who were diagnosed between 2013 and 2018 and they found that only 160 or 2.5% of these patients were biopsy.
- 01:05:56Their patients, had I mean age of 66 they were mostly male mostly white with a mean creating a 2.4 and a median protein area of about 1.6 grams and 23% of this group was diabetic.
- 01:06:09And what they showed was that 40% of these patients who had em Gus who were biopsied actually had an m drs legion with the most common being Al amyloidosis followed by the other setting mentioned.
- 01:06:22But 60% of patients did not have an m drs lesion in them arteriosclerosis was the most common followed by diabetic neuropathy and ankle associated vasculitis and a second study has.
- 01:06:35demonstrated similar findings that about 40 to 45% of the patients with monoclonal them apathy and kidney dysfunction who get biopsied actually have an md or escalation.
- 01:06:45All about 55 to 60% of patients don't, and this is obviously a skewed sample because there's a reason that some patients get taken a biopsy and other patients don't.
- 01:06:55Also, really, interestingly.
- 01:06:57In this study the strongest predictors of em drs lesions were prone area of greater than 1.5 grams per day.
- 01:07:04He material greater than three red blood cells for high power field and an abnormal serum free light chain ratio and we'll talk about this more later, but they did correct and patients with far less than 60.
- 01:07:15For the fact that they had ck D, which impacts, the normal quote normal light chain ratio.
- 01:07:21In these patients the median involved to uninvolved free like chain ratio was about 5.6 so a capital Lambda Orlando Kappa Kappa ratio about 5.6 and the M drs folks compared to about 1.8 in the non m drs group.
- 01:07:40it's, of course, really essential for us to distinguish patients who have em drs from patients who have them Gus but at the same time, we need to be thoughtful about who we expose to procedural risk.
- 01:07:51I think kidney biopsy should be considered in patients who have high urinary protein level greater than 1.5 grams per day and abnormal free light chain ratio for microscopically materia, as highlighted in the previous study.

- 01:08:04I think patients with monocle and have them apathy and an unexplained rapid loss of kidney function even patients who have long standing diabetes or hypertension, if you don't have a good.
- 01:08:16understanding for the worsening and it doesn't fit your typical time horse these patients may weren't biopsy.
- 01:08:23Because m Gus is so uncommon in patients who are less than 50 if you have a young patient less than 50 years old, who has a pair of pants anemia and kidney dysfunction they weren't the throw workup, of course.
- 01:08:35And kidney transplant candidates with monocle and have them apathy and nuclear costs for their ears 30 may also weren't biopsy.
- 01:08:42Because you really want to do everything you can to prevent recurrence and aloe graph once they're transplanted and so you really want to know what that cause of yesterday was.
- 01:08:50And this is assuming that the kidneys aren't already small and shrunken if they are then your biopsy yield is going to be lower and you're bleeding risk is higher so kind of weighing risks benefits there but.
- 01:09:01Being on dialysis isn't necessarily a country indication to by seeing the setting.
- 01:09:08Now, sometimes we have the kidney biopsy results first and we start looking for the PowerPoint anemia and sometimes it's the other way around, that we have some of the power protein markup which leads us toward kidney biopsy.
- 01:09:18But, since this is a kidney centric talk I figured we would jump off from kidney biopsy so you've identified an abnormal finding in the urine.
- 01:09:28or either blood or hematology or protein or abnormal kidney function This prompts you to do a kidney biopsy this lead you to find monoclonal immunoglobulin deposition what do we do next.
- 01:09:42We have to shift our attention to finding evidence of a circulating pair of protein and underlying plasma seller be cell clone that's producing it.
- 01:09:54So we've got to find a pair of protein and we need to make sure that it matches the monoclonal protein that we've identified on kidney biopsy so we're really linked them together and we can do this by ordering several different tests, a few of which i'll highlight here.
- 01:10:09The first test is a serum protein electro for Rhesus and I know we've all ordered a lot of these.
- 01:10:14proteins are loaded onto a jail or a capillary tube separated by electrical current based on charge and size and then staying for visualization.
- 01:10:22proteins migrate into five zones or fractions albumin alpha one alpha to beta and gamma and albumin should be the most abundant protein in your serum.
- 01:10:33But when you have a Monaco teen monoclonal protein President you'll get a sharp band here and that's called the spike.
- 01:10:40Now, keep in mind, I have grossly oversimplified this from my mind, but we really benefit from having our pathologist interpret these studies, because there's really a lot of nuance here in terms of.
- 01:10:53Being able to pick up or identify that something looks wrong on this study and then reflecting through additional studies.
- 01:11:00What are some of the advantages of as fat it's a quantitative test, so it gives you a number for how much protein, you have, which is helpful for diagnosis and to monitor treatment in the future.
- 01:11:09But the major limitation is that it's not sensitive enough as an isolated screening tool, so you miss about 12% of my illness and about a third of amyloidosis cases, for example, if you just use an s prep.
- 01:11:21And it doesn't tell us if it's it G or IBM what kind of subtype you have, which has implications for therapy going forward.
- 01:11:29You pad or you're in protein electric Rhesus is run by the same principles as an SF has similar advantages and disadvantages, but of all the tests that will mention has the lowest sensitivity for.
- 01:11:42identifying a pair of protein, and so you can increase the sensitivity, by doing a 24 hour you pep and that helps account for some of the compositional changes in your urine.

- 01:11:52Over the 24 hours but it's still not the most sensitive test it does provide a breakdown of protein in the urine I think i'll.
- 01:12:00move on from this part in the interest of time, but something to talk about in the future.
- 01:12:05The next group of tests are the immuno fixations, and these are performed in the serum in urine.
- 01:12:10In our lab, and these are usually reflex tests and they get run when the ESP or the you pep looks abnormal or when there's a history of unknown monoclonal come up with the.
- 01:12:20samples are electro for research in parallel lanes and then antibodies against heavy and light chains are applied to each lane separately, if you get a sharp band here, and here it helps tell you what kind of pair protein, you have.
- 01:12:35A manifestation techniques are much more sensitive than electro for races so adding that to an s step is going to increase your ability to text.
- 01:12:42to detect myeloma by to 94% and amyloid to about 74% it identifies your protein which is important for your therapy choice later on the major disadvantage is that it's expensive and it's qualitative only meaning, it can tell you there's a protein or there's not.
- 01:13:03But it can't really tell you how you're responding.
- 01:13:06If there's a low level or a higher level won't be able to tell you that.
- 01:13:11So this is just the two of them together you've got an SF with an m protein in the beta region, the use of immuno fixation identifies a sharp band for iga and Kappa until you have an iga Catherine monoclonal protein as little blurry smudges a poly colonial I GG.
- 01:13:34serum free light chain these essays were introduced in the early 2000s, and they use antibodies to episodes that are normally hidden.
- 01:13:42In the intact immunoglobulin so right here and right here and they're able to detect in a very sensitive fashion concentrations of free Kappa and free Linda like chains.
- 01:13:53In the serum Mano a Mano commonality is inferred with an abnormal Kappa to Lambda ratio, the ratio is really high you think about a Kappa clone if it's low you think of a Lambda clone.
- 01:14:06This slide depicts the interpretation of the free light chain as say the Kappa ratio is on the X axis the serum Lambda ratio on the y axis and then the chart at the bottom sort of.
- 01:14:18correlates and the colors match up so we'll go through this, you have a normal Kappa concentration you've got a normal Lambda concentration you've got a normal test.
- 01:14:29No concern here for a monoclonal process, you have a normal Kappa concentration, with a highlander concentration your ratio gets low.
- 01:14:38And you become concerned about a Lambda monoclonal come up the end the reverse here in black for a Catholic clone.
- 01:14:46And when you have both a high Kappa and a high Lambda concentration, where you have a near normal ratio.
- 01:14:52that's when you think about renal impairment, sometimes inflammation and very rarely a by colonial GM apathy, or you have to clones one has gone rogue and made a bunch of campus one has the same has done the same, and made a bunch of Lambda light chains, but not very common.
- 01:15:08very critically it's really important for us to know that the accepted free light chain ratio with kidney insufficiency shifts upward.
- 01:15:17So why, why do we accept a different ratio for COPD patients compared to face with normal kidney function.
- 01:15:24So Kappa free light chains are normally produced at twice the rate of Lambda free light chains, and this is related to January arrangements that occur during the sale differentiation.
- 01:15:34lamb does exist as diners and they're cleared more slowly by the kidney resulting in slower clearance, so that the median free like Jane ratio, if you look at all conferences about Point six or it's usually less than one.

- 01:15:45With kidney dysfunction the kidneys have trouble getting rid of the light chains and then the ridiculous endothelial system.
- 01:15:52Of the body takes on a bigger role and free light chain clearance without regard to whether or not this is a dimer or a.
- 01:15:59monitor and so, if you're producing more campus and your campus and Lambda is are now being cleared at an equal rate that ratio is going to shift up so we use point 372 3.1 and people who have.
- 01:16:11Severe kidney insufficiency and using this new range increases the specificity of the free like chain ratio for patients with kidney disease.
- 01:16:21Some of the advantages here is a quantitative test it's very sensitive.
- 01:16:25you're picking up now, some of the myeloma that were previously thought to be non secret tori you're picking up more of the amyloid cases when added to an aspect or an immuno fixation.
- 01:16:34The disadvantages again monocle analogy is inferred you may be missing something like a by colonial them out, but the or something that's a little bit more unusual.
- 01:16:46I wanted to talk a little bit about mass fix, which is also called immuno enrichment based matrix assisted laser disruption ionization time of flight mass spec.
- 01:16:58So I think mass fix works better, and there are several advantages over serum even a fixation.
- 01:17:05It has a higher sensitivity and specificity.
- 01:17:08it's able to distinguish therapeutic monoclonal proteins that somebody might be getting for treatment so it'll pick up your dare to my bad or it'll pick up your texts, a map when you're trying to figure out is this person responding to treatment and.
- 01:17:21It can identify something called light chain and like constellation which is associated with Al amyloidosis and cold a gluten in disease and in patients with em Gus is it, so it is associated with a higher risk of progression to over malignancy so at the Mayo actually since.
- 01:17:40Mass fix has entirely replaced serum and the fixation I think we are just still doing serum even station here, but maybe that's something in our future.
- 01:17:50This was a pretty recent study that was published in The Lancet hematology they tested.
- 01:17:557000 individuals from the promise study in front of mass general Gregor biobank, these are all patients who were considered to have high risk for myeloma self identified as black or head of positive family history of my aloma.
- 01:18:07or some other he malignancy and they identified a substantial increase in the prevalence of Angus using mass fix compared with the lecture for resistant immuno fixation so.
- 01:18:18And these are patients over 50 so in the same group of patients 6% were would have been called em Gus by conventional methods 13% using mass fix so.
- 01:18:32Something that I think has a ton of potential to increase our ability to detect pair of proteins to monitor disease, the same time, it probably.
- 01:18:40will open up a whole can of worms because you're going to be getting a whole lot more em Gus patient and trying to figure out what to do with them so.
- 01:18:47pluses and minuses there, and this is just a brief summary have for pair proteins detection main test your SPF 24 hour you pep your immune to fixation and you're free like chains.
- 01:18:58There is a urine free life chain essay but it hasn't been validated it's not really clinically useful we don't send it and then in the appropriate clinical setting and with the guidance of hematology and pathology some of these other tests like mess fix.
- 01:19:14So now we've identified the circulating pair of protein and it's time to turn our attention to finding the clone.
- 01:19:21This is my reminder to all of us into myself at the end organ damage caused by pair of proteins it's not necessarily proportional to the size of the clone so the chicken and the egg maybe very, very small.

- 01:19:33And this is when as nephrologist as an ongoing for i'll just i'm calling and help from our hematology and oncology colleagues to help guide workup and collaborate on going forward with next steps.
- 01:19:45When you're looking for the clone you can start by taking a cue from the type of care protein.
- 01:19:50b cells and limbo plasma citic cells, which are very late stage be sales, like those seen involved and drums tend to produce ign plasma cells produce I do D more than iga or ign.
- 01:20:02That can give you some clue about what you might find in the uncle nephrology community, we think that bone marrow biopsy is indicated in the vast majority of patients were found to have an m drs lesion.
- 01:20:15The possible exceptions here are maybe patients with CA ll where that diagnosis could be or a CLS type clone or the diagnosis could be made by peripheral blood flow.
- 01:20:26And perhaps patients with PG and mid who don't have a circulating pair protein that you've been able to find.
- 01:20:33So this figure is from a case series of PGA and mid patients, there were 60 patients biopsied and found to have this diagnosis at Mayo 20 of them did not.
- 01:20:44give consent, I think what 40 did, and they look to see sort of how often you were able to find the clone on bone marrow biopsy in.
- 01:20:54When you had a positive or negative free light chain ratio so for people who had a positive serum immuno fixation and an abnormal light chain ratio ratio on bone marrow biopsy you found the clone 100% of the time.
- 01:21:06in patients with a negative immuno fixation and a normal freely chain ratio you found the clone I think zero percent of the time so potentially you could spare a patient of bone marrow biopsy here but.
- 01:21:18it's up for debate.
- 01:21:25It time correct Sam 30.
- 01:21:28I won't profess to be an expert on bone marrow biopsies but i'll tell you what I know what i've read and seen.
- 01:21:35All bone marrow biopsy sample should be evaluated for cell morphology and immuno staining supplemented by flow cytometry to find the B cell phone or the plasma cell clone.
- 01:21:45genetic testing in bone marrow biopsy specimens can be really critical and as an increasingly important role, and there are implications for therapy.
- 01:21:54For example, and amyloid patients who are found to have a translocation, for you know 1114 they may have an inferior response to bore testament so knowing sort of the genetics of.
- 01:22:06The clone can really help guide you in therapy and there are numerous examples of this.
- 01:22:10off to the right, we have a bone marrow biopsy with extensive involvement by abnormal plasma cells kind of crowding out the normal or eliminating replacing.
- 01:22:20The normal trial any traumatic we says up here on the top right, you have cell standing for CD 138 which is.
- 01:22:28A marker of infiltrating plasma cells here taking up about 65% of the bone marrow and then on the bottom, here we have negative campaigning and positive land and immuno history chemistry.
- 01:22:40telling us that we have a Lambda restricted neo plasan so kind of a similar.
- 01:22:46approach to kidney biopsy.
- 01:22:49additional studies may be necessary looking for the clone This includes peripheral blood flow cytometry which is really the gold standard for detecting the cells.
- 01:23:00pet CT may be important for patients with lymphedema apathy or looking for plasma say tomos lymph node biopsy skeletal survey, so this really takes.
- 01:23:09A coordinated effort with oncology to help us figure out what tests are appropriate and where do we go from here in order to identify this clone and then move toward treatment.

- 01:23:19This figure is just a quick summary of the workup for clone detection, so your clinical suspicion hematology approach area abnormal kidney function prompted a biopsy.
- 01:23:30Your biopsy showed monoclonal deposition you go searching for your pair of protein, hopefully, you find it go searching by bone marrow and with potentially some of these additional tests to look for your clone.
- 01:23:43We talked earlier about see through gmail apathy, this is a potentially am drs lesion where you don't have deposition of the immunoglobulin because it's kind of out there.
- 01:23:55activating compliment and just leading to deposition of C three and in that case, if you have any patients with see three C three gn.
- 01:24:03or alchemy, a lot with you ought to send for monoclonal come up with these and see if, then you should be doing additional work up if you find it bone marrow biopsy and other work of is slightly indicated.
- 01:24:18it's important to note that clone detection rates will vary by these MDS lesions and it really depends so in patients with mid the vast majority are going to have a detectable clone that you can find.
- 01:24:29But in something like pg&e mid only about 30 in only about 30% of cases you'll be able to find that pair protein circulating in the blood or find it in the urine and.
- 01:24:40you'll only be able to find the clone on bone marrow 25% of the time so that.
- 01:24:44poses a real unique challenge when it comes to figuring out how to treat these patients, especially because in PG and mid when you do find a clone half of the time it's a plasma cell clone and half of the time it's a B cell clone so.
- 01:24:58hard to figure out if you don't have a pair of protein or don't have a clone on bone marrow biopsy what age and you're going to treat them with.
- 01:25:06us.
- 01:25:08So if you're lucky enough to find a clone The next step is to kill it lets me have to salvage these kidneys.
- 01:25:16Who should we treat it of course there's always a question of who should be treated and why what's presented on this slide is based on published literature and expert opinion.
- 01:25:27There really are no natural history of natural history studies comparing people presenting with more severe versus less severe presentations of these lesions but generally.
- 01:25:36If the kidney function is stable the urine protein is low level, less than a gram conservative management and Ross blockade is probably appropriate.
- 01:25:44Those with worsening kidney function and heavy protein area should be considered at least for a clone directed therapy, and this requires collaboration with humans and we treat small clones like large farms.
- 01:25:57And all of this really does need to be informed by taking patient characteristics into account, so how old is this patient what are their co-morbidities how much scarring do they have in their kidney biopsy is there really any kidneys to salvage.
- 01:26:10And do they have any extra renal involvement some other organ system that would benefit from treatment and then, what are the risks and benefits of therapy.
- 01:26:19If we do treat the goals are preserving life trying to preserve kidney function, and also to prevent recurrence after transplant.
- 01:26:28So you would consider treatment, even after the development of srt if a patient to transplant candidate and we can get really good guidance from this paper which was published in blood.
- 01:26:38called how I treat em drs, and this is the consensus guidelines from the International kidney and monoclonal come up with the working group so i'll refer you here kind of for an expanded discussion of treatment options.
- 01:26:49But just briefly you've diagnosed the lesion and you've identified your pair of protein and a path is extremely clear not at all.

- 01:27:00And so, Mrs lesions, we know that they respond poorly to me know immunosuppressive regimens that are used to treat autoimmune conditions.
- 01:27:09Google corticosteroids calcium iron inhibitors Michael fennel eight and, instead, the best outcomes have been shown when therapy is directed against the clone.
- 01:27:16So what therapies, could you use again keep in mind this is expert opinion their cases are limited, a few.
- 01:27:24are able to find a B cell clone makes sense and no patient qualifies and it's reasonable to treat them make sense to use of anti be cell regimen lymphoma regiments.
- 01:27:34plasma cell clone and by plasma told treatments and you have no clone that you found, but you have an idea and protein chances are.
- 01:27:43going to be a be sale so on Pyrrhic and i'd be so therapy, but if you're wrong and the patient doesn't respond with you know, two, three cycles, you can always change course.
- 01:27:52Targeting a different clone and then the special challenge clone negative non ign meaning an ID or an iga ideally if you could get insurance to cover it.
- 01:28:03You could consider targeting both with something like or testament again this is expert opinion not extensively studied but ongoing studies.
- 01:28:12Here are some of the potential treatment options that have been used for em drs lesions and they fall into several categories which i've outlined here.
- 01:28:19Including steroids produce inhibitors side of toxic agents monoclonal antibodies and Amina module satori agents high dose chemotherapy and that's all stem cell transplant has been used in a few cases of mid.
- 01:28:33The majority of these drugs when use they're not used alone they're used in combination.
- 01:28:38And when considering what drugs to us, we do need to take into account the potential for an effort toxicity, as well as other organs side effects, and also whether or not people require a dose adjustment for their kidney function.
- 01:28:50This table summarizes some of the key characteristics of these drugs.
- 01:28:54or testament really is an ideal agent for em drs because it can be given, without regard to somebody kidney function, and it also doesn't need to be dose adjusted for renal insufficiency.
- 01:29:03But of course it has its own downside, including peripheral neuropathy car fields and mib doesn't need to be dose adjusted, but can cause kidney toxicity and including a KPI and robotic micro 20 apathy so kind of used with caution.
- 01:29:20monoclonal antibodies here retested based regimens really the mainstay of therapy for be cell clones Derek to my map has.
- 01:29:29An anti CD 38 anybody and it's shown efficacy and Al amyloidosis and it's.
- 01:29:34Their ongoing studies at the mail, looking at the use of data to embed for mid and PG and mid and that would be a really great option to add to our our momentary them, given the high response rates and the relatively low rate of adverse effects side of toxic agents like mouth LAN.
- 01:29:53next page right here, you do want to use with caution, if this is somebody who may be considered for a stem cell transplant in the future, given toxicity to stem cells.
- 01:30:04And I would suggest using caution with things like the limiter lenalidomide.
- 01:30:09solidified associated with hyper Columbia and renal failure is just needs to be monitored lenalidomide dosing isn't really well established in patients with renal insufficiency and then I crossed out a couple that we really ought not to use given.
- 01:30:23Need for potential for acute kidney injury potential for bed malice depression and patients who have far less than 30.
- 01:30:32So now, the patient's been treated and we have to figure out how to monitor them going forward.

- 01:30:38So we don't have clear guidelines dedicated specifically to em drs to help us monitor response or recurrence so we have to take a page out of the myeloma and amyloid playbooks.
- 01:30:48This slide just shows the accepted criteria for him response in patients with myeloma and want to pay attention to patients with the criteria for a complete response and very good partial response.
- 01:31:02you're looking to see how deep of a response you got from these patients, based on their email fixation and the tests that we talked about earlier.
- 01:31:10This slide just summarizes the acceptance criteria for adrenal response in Al amyloidosis we're really looking at changes in protein area and whether or not their.
- 01:31:20kidney function declines in patients with myeloma we're hopefully looking for improvement in their ground clearance over time.
- 01:31:31In myeloma and Al amyloid hematologic responses have been validated a surrogate outcomes for improved morbidity and mortality, including renal outcomes.
- 01:31:41For em drs lesions with the detectable protein that you can actually follow in the blood or urine complete response or a very good partial response by myeloma criteria has also been associated with improved outcomes, this is best studied in mid.
- 01:31:58Following treatment your organ response your improvement or changing kidney function that you're going to get from this therapy is going to be delayed after the human response, sometimes by as much as 12 months.
- 01:32:08And patients with amyloidosis, for example, and so you have to judge the efficacy of treatment by the quality of the hematologic response.
- 01:32:16And this is just a study on demonstrating that in patients with MIT who essentially showed improves your Bible the improved renal survival, the.
- 01:32:27Deeper the response that you got until your response is going to occur before your renewal response and the deeper your hematologic response, the better your patients are going to do.
- 01:32:40So your hematologic response will be followed, whenever possible, when your pair of protein or clone is present with tests like as a 24 hour you pep followed until negative.
- 01:32:51Then, your immunizations are valuable once the electrical resource becomes negative, so you can confirm and ongoing complete remission.
- 01:32:59The free light chain ratio should be followed, even as the M spike decreases there's a phenomenon of light chain escape were a clone may stop producing intact immunoglobulin but may continue to secrete light chains.
- 01:33:11And then you could consider again with hematology and put repeatable now or flow.
- 01:33:19In these pair of protein negative clone negative patients like PG and mid.
- 01:33:23What do we follow, and unfortunately we're sort of left with the usual suspects, creating potent area materia and consideration of a repeat kidney biopsy.
- 01:33:33And so it's really important before you start kind of embarking on a treatment plan for these patients to know what you're going to follow and figure out how you're going to measure response in your patient.
- 01:33:45And so, just to summarize, Mrs is a small plasma seller B cell clone with renal disease that's directly through deposition.
- 01:33:53or indirectly through auto antibody activity compliment activity or production of cytokines induced by the secreted monoclonal immunoglobulin.
- 01:34:02Protein associated kidney diseases may be associated with higher morbidity and mortality, if not treated properly.
- 01:34:08Your type of lesion in the kidney is dictated by the nature of the protein and its unique characteristics, the treatment of the lesion is dictated by the nature of the clone that produced it.
- 01:34:19kidney biopsy is essential for diagnosis, followed by a search for the pair protein, which is the egg and the clone, which is the chicken.

- 01:34:26treatment is aimed at Oregon preservation preservation of life and prevention of recurrence after transplant and select patients.
- 01:34:33and effective diagnosis, treatment and monitoring require a multidisciplinary approach to care with close collaboration among nephrology hematology oncology path and primary care.
- 01:34:44Thank you all, and a special thanks to john hogan formerly from Japan for helping me understand this complicated topic better and also for granting me permission to.
- 01:34:54use this chicken and an egg analogy, which was not my own, but would I, which I think is the most useful and most entertaining approach to this disease that I have found.
- 01:35:16cleaver I think that was me.
- 01:35:19Now thing to do.
- 01:35:30So amanda, thank you for great talks, especially speaking from the primary care perspective I think we've all been in that situation, initially, where you go.
- 01:35:38good to know about the light chain ratio, because I think it's something that you can stumble into with this complex.
- 01:35:44nature of the older patient with renal impairment and what is that coming from so just for us on the primary care side thinking about looking at that.
- 01:35:56higher than your normal range of acceptable like change what degree of room renal impairment, do you think about expanding this normal range of the light chain ratio to.
- 01:36:09And and is that something that is a little bit more of a flexible concept, depending on the degree of renal impairment over time as well, so.
- 01:36:16So so help those on those of us on the general medicine world to to not sort of you know kind of panic too too much or too quickly with like gene ratios, thank you.
- 01:36:30So the kind of adjustment up for your free life chain ratio.
- 01:36:36With COPD, it is a pretty flexible concept even pretty mild levels of renal impairment you'll start to see that ratio shift upward and so.
- 01:36:45There I don't remember the exact cut offs, there was a paper.
- 01:36:49By Hutchinson, I think, in 2008 where this was really like flushed out and they looked at the ratios in different groups and different stages of COPD and you can kind of see that they all sort of drift up, so I.
- 01:37:02think probably start seeing it with I had to guess I don't remember off the top of my head, you know do far less than 60 you're going to start to see this kind of drift, I can find that paper and send it out to you guys if anybody's interested in trying to find the exact numbers.
- 01:37:37Top cut off is like three 3.1.
- 01:37:46Thank you so much, Dr anyone, and so you were mentioning the addition of communication in screening tools and, in addition to that, as.
- 01:37:56My understanding currently is it that's a reflex test and based off of the APP do we gain additional sensitivity with using it as a reflex test, if you have to see an abnormality the SPF before that test is obtained.
- 01:38:12A very good question you know I haven't really thought about it and i've not looked into whether or not these sensitivities are.
- 01:38:21Related to order to set test separately versus whether or not they were reflex test, so I don't know the answer to that question, I mean, I think.
- 01:38:30Either way, you're going to gain sensitivity, I just don't know you know if you didn't order the immune fixation separately and you just waited to see if it reflects I think you are going to pick up more I mean we often have people who kind of have a sort of.
- 01:38:44funny looking as step, are you pet profile not quite a huge jump spike that are pathologists are really good at sort of picking up an abnormality and reflex, and so I don't know if you'd pick up like that full 100% or near 100% of my illness.

- 01:38:58Relying on a reflex, but I think it's getting closer Okay, so, in practice, it still makes sense to just from like a.
- 01:39:06Cost conscious care standpoint to continue to proceed with it as a reflex test that's what I do i've had maybe one or two cases where I was really suspicious and called the lab and said, please run this for me.
- 01:39:20But typically I just use it as a reflex Thank you very much.
- 01:39:33Thank you, that was fascinating.
- 01:39:36So I guess you mentioned a study in from Mayo in there, trying to look at people who had em gas.
- 01:39:45How do you who needs biopsy and then looking at those clinical risk factors, so I pro ternary I he material.
- 01:39:52Are there any efforts, one thing I think we don't do it, maybe I just don't there's some reason I don't know but we don't really image, the kidney like with MRI to restaurant five people for like what might be the underlying problem.
- 01:40:07Besides just having to do biopsy, certainly in the cardiology world, people will get a cardiac MRI is a lot of time.
- 01:40:14But I guess one question was, is there any role for like actually imaging the kidney with like.
- 01:40:19More detailed.
- 01:40:22modalities then another one was do we characterize those proteins differently so you mentioned that you know, having like a one of the mutations and.
- 01:40:31Heavy chains makes it more likely to create problems in the kidney is there a role for looking at the proteins, the pair proteins.
- 01:40:41In a more detailed way to decide, like oh if it's an iga and it has this mutation it's more likely to cause renal disease or if it's a is there any role for either of those two things, maybe that you've heard people talk about her um well I might need you to repeat the second one, but.
- 01:41:00I have read a lot of papers on this topic, I have not seen anywhere, the role for MRI or any imaging of the kidneys I mean you can have.
- 01:41:11malignant infiltration of kidneys from a variety of malignancies, in which case they may be big or they may be small.
- 01:41:18And they may have you know distinct pockets that look like they've been infiltrated or they could be diffuse Lee and large like an amyloidosis you can see, but for the purposes of like diagnosing and Mrs lesion I really not seeing that at all.
- 01:41:31I don't know if it I don't know if it's possible like in a.
- 01:41:37Regular clinical setting to really drill down and find out too much more about an individual pair of protein know this is being you know looked at, because obviously people are looking at these like ch one deletions to try to figure out.
- 01:41:51You know, changes in therapy and that kind of thing I don't know about would be useful.
- 01:41:58Because I think the main things really are.
- 01:42:02Seeing what kind of pathology you have on your biopsy so you can name it so like if you found heavy chain deposition disease those almost always are going to have that ch one deletion, so it doesn't really matter.
- 01:42:14In my mind what exactly the nuances of that deletion are because then you just want to find the your pair of protein Finder clone and treat it yeah you know, so I don't know if there's a major role for like trying to drill down to an individual person's.
- 01:42:31You know mutations in their pair of protein, as long as we can identify like what the disease entity is on that big chart yeah that makes sense, great Thank you.
- 01:42:45swati RAL had a question.

- 01:42:48She asked for recommendations from monitoring for recurrence of the monoclonal process in the post kidney transplant period.
- 01:42:57that's a really good question and I don't think i've read.
- 01:43:02Enough papers on this topic to be able to give a clear recommendation I mean I know you guys are always monitoring when they're coming in your analyses to look for you know pro scenario look for him material, and if you find those.
- 01:43:16In a setting where the original disease also would have caused it like a glue marijuana Freitas, and you see blood pop up or.
- 01:43:24You know mid where you start to see prone area pop up I think that's sort of a reason, then, to more aggressively.
- 01:43:34Look, for these lesions and potentially consider repeat kidney biopsy but i'm not really seen.
- 01:43:39You know recommendations for like routine power protein studies in these patients as a really good questions why you don't have to look into that.
- 01:43:53Oh, Dr Ralph says as for email discussions with Dr lungs and Nelson long from a oh is like the power protein associated kidney disease guru.
- 01:44:02She said they do every three months aspect you have an immediate fixation and they actually do protocol kidney biopsies at three and 12 months, thank you, money.
- 01:44:39Thank you very much.