



The Voice of the Patient Report Meeting Transcript

*Externally Led Patient-Focused
Drug Development (EL-PFDA) Meeting*

C3 GLOMERULOPATHY (C3G)

Public Meeting: August 4, 2017



National
Kidney
Foundation®

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OPENING REMARKS

Dr. Vassalotti: I want to welcome all of you. We have a tremendous amount of energy in the room here, and we have participants on the web that I want to welcome as well. I'm Joseph Vassalotti. I'm a nephrologist. I'm the National Kidney Foundation's Chief Medical Officer, and I'm really thrilled here to welcome you to the Externally-led Patient-Focused Drug Development Meeting on C3G, C3 glomerulopathy, dense deposit disease as it goes. This is a disease that a typical nephrologist might see a handful of times in their whole career, and we're really fortunate to have two experts here, our co-chairs who have a wealth of experience to help guide us.

We're really looking forward to hearing your voice, how you experienced this disease, how it impacted on your life, and we really want to benefit from that in terms of our future plans. Our real goal here is to have a Voice of the Patient Report that will go to the Food and Drug Administration, and that will help guide innovations in not only therapy for this disease, but also hopefully improvements in the diagnosis.

So, on the next slide we have a list of who our participants are, and I think we're having a little problem with the technology here, but I want to acknowledge the patients, first of all, for their commitment, for their time, for their travel, for your courage and presenting your story. I want to acknowledge the caregivers and your support of them through the trajectory of their illness. I want to acknowledge our web participants that we have, the individuals from America and Canada here, but I also wanted to recognize- there we go. So, individuals that have come from other countries as well. So, we have on the web Israel, France, Switzerland, Australia, and the United Kingdom.

And I also want to acknowledge the FDA. I want to thank you for considering the patient voice in drug development, and I want to thank you for your presence and for listening. I want to thank the pharmaceutical industry for supporting this and making it possible. You all, at least in the room here, have a program book, so just a little bit about our day, what's it going to be, on page two. So, we'll have two presentations from our expert co-chairs on C3G. Dr. Bombback will talk about the natural history of the disease and treatment. We'll hear about the challenges to clinical trial design from Dr. Carla Nester, then we'll have welcoming remarks from Norman Stockbridge of the FDA and we'll go into our patient discussion.

So, there'll be two aspects of this. There'll be one, living with C3G disease symptoms and daily impacts, and that will start with a panel, and then we'll open it up with a facilitated discussion to the larger audience, including that audience that's participating via the web, then you may want to plan your morning for a break at about 11:05 till 11:20, and then we'll continue a second topic discussion on challenges in treating C3G, and again, that will just start with a panel and then we'll open it up to the larger audience. We'll have closing remarks from the FDA, closing remarks from the National Kidney Foundation, and at the conclusions at about 1:00, we will have a box lunch that you can take with you as you leave. So, without further ado, I'm going to introduce our first expert speaker, our co-chair, Dr. Andy Bomback who is at Columbia University in New York City where they have a practice that sees over 100 patients with C3G, and he will talk about the background of C3G and the natural history of the disease and available treatments.

HISTORY OF DISEASE AND TREATMENT

Dr. Bomback: Thank you, Dr. Vassalotti. I'm setting a timer. That's why I have phone out, to make sure I only speak for 15 minutes because we really want to spend the day hearing patients, not doctors. I want to start by just thanking the National Kidney Foundation and our sponsors for putting this together today. This is really an exceptional meeting to have patients together in a room sharing their stories, and personally, they are patients of mine I've known for almost a decade who have constantly said, "You should meet this person," or, "You should meet that person and share your stories with each other," and now we can finally do it in the same room, so thank you.

I'm going to briefly just review what a C3 glomerulopathy is to make sure we're all on the same page, go into how we work up patients who are diagnosed with this disease, and then get deeper into what's the prognosis, what do we know of the natural history now, and how are we currently trying to treat this disease, and how do we hope the treatment will become in the future.

So, what is a C3 glomerulopathy? As many of you know in the room, we do a kidney biopsy to diagnose glomerular- the disease, inflammation of the kidney filters, and traditionally we'd look at three different types of microscopes, a light microscope, the type of microscope you would use in a science classroom, electron microscopy, which

is a very high-power microscope to look at the ultrastructural details of the kidney filters, but then we look at something called immunofluorescence microscopy where we can stain for different types of proteins including antibodies and complement proteins.

Usually when we look at a kidney biopsy, we see a combination of antibodies and complement proteins, and what that tells us is that the body's complement system, which is part of the immune system, has been triggered along its classical pathway, and these are usually what we see in autoimmune diseases of the kidney or diseases of the kidney that are prompted by infection, and these are the more common forms of glomerulonephritis, and so when we look at a biopsy and we see the presence of complement proteins like C3, but we also see antibodies like IgG.

In both, the complement proteins and the antibodies are depositing on the kidney and causing the inflammation and subsequent damage that can happen to the kidney. In contrast, the disease we're talking about today called C3 glomerulopathy, when we do that immunofluorescent staining on the biopsy, we only see the complement protein, C3, or if we see any other components, they're very trace, and it's really the dominance of C3 that sticks out, and that's why we call this a C3 glomerulopathy. And then this very large term of C3 glomerulopathy can be subdivided into dense deposit disease and C3 glomerulonephritis, and the distinction between dense deposit disease and C3 glomerulonephritis currently is based on what we see on the electron microscope. Where these deposits of complement are landing will either label the patient as a dense deposit disease or a C3 glomerulonephritis, but they all fall under this umbrella term of C3 glomerulopathy.

And so, in contrasting it to the first instance, this is what we see on a C3 glomerulopathy. All complement without any real contribution from antibodies, and so the complement proteins themselves are mediating the damage to the kidney. That's a complement mediated form of glomerulonephritis, what we call C3 glomerulopathy, and because complement itself is what's driving the injury, and there's no antibodies that are activating complement to incite this inflammation, we call this antibody independent complement activation, and that really focuses us on part of the complement pathway called the alternative pathway.

This is a pathway that is constitutively active in all of us but at a low level, and what happens in C3 glomerulopathy is that this low-level activity becomes hyperactive, so whereas if you look at normal kidney tissue, there's a little bit of C3 and a little bit of

what we call the membrane attack complex, which is the more distal effects of C3 activation, but if you look at biopsy in C3 glomerulopathy, there's a lot of C3 and there's heavy deposition of the membrane attack complex.

So, what we really are seeing in this disease is a shift from normal controlled activity to uncontrolled hyperactivity, and that leads to glomerular inflammation, and if that inflammation is unchecked, glomerular damage and subsequent chronic kidney disease and in many cases progression to overt kidney failure- end stage kidney disease requiring dialysis or transplant. So, when we get a patient diagnosed with C3 glomerulopathy, what we're trying to do from a diagnostic standpoint is figure out if this alternative complement pathway is hyperactive. If we've shifted from controlled activity to uncontrolled hyperactivity, how can we figure out where that shift occurred? Where did this patient lose control of the complement pathway? And we tried to dive into the components of this alternative pathway. The alternative complement pathway, which is a series of proteins is usually tightly regulated. There are some proteins that push this pathway forward, which I've pictured here in green, but then there are some proteins that pump the brakes on the system. These are regulatory proteins. In states of health, the regulators and the activators should be well balanced, and that's what keeps us at a low-level activity.

But you can imagine that if one of the activators becomes overactive, or if one of the regulators becomes underactive, the system could get thrown out of whack. And so, some of the ways that can happen are variants in your genetic code, what we could call gain-of-function mutations of an activator or loss-of-function mutations in a regulator. Or, you can acquire an antibody, a protein that's directed at one of these activators and makes that activator essentially immune to regulation, or an antibody that's directed at a regulator and turns off that regulatory activity. And to complicate matters, there are a number of patients who have both genetic variations and autoantibodies. We have to tease out which of those abnormalities is contributing to the loss of control of the system.

And this is important because the better we can understand why a patient's complement pathway has gone uncontrolled, the better we might be able to understand what's going to happen to that patient. Because one of the things that is really striking about C3 glomerulopathy, and I think you'll hear this today, is that it is not a one-size-fits-all diagnosis. There are some very mild versions of this disease, and there

are some extremely aggressive versions of this disease, and those patients are carrying the exact same diagnosis. So, we think this is an incredibly heterogenous disease, and we think that there's not going to be a single therapy that works for everyone, but rather, the goal of the nephrologist and the pathologist and all the caregivers working for this patient should be to figure out where is the abnormality and what is the best therapy for that specific abnormality and it's not going to be just a one-size-fits-all answer to that. We think there's going to have to be a personalized approach to this.

Now, in terms of what we know about the natural history of the disease and the prognosis, and this data, I should tell you, a lot of this is historic, and what we hope is that data 20-30 years from now, which reflects what we're doing now, will look better than this. But, this is the best data that we have right now. The dense deposit disease version of C3 Glomerulopathy has traditionally carried the worst prognosis. If you look at most of the series, whether they're series in adults or children, the average person progresses to end-stage kidney disease at 10 years. So that means 50% of the patients will be in kidney failure by 10 years from the time of their diagnosis, requiring dialysis or transplant. If you contrast that with the C3 glomerulonephritis variant of the disease, this looks milder. So, the C3 glomerulonephritis variant still is a progressive disease, but it seems to progress slower than the dense deposit disease version of the disease. Doesn't mean these patients aren't at risk for going to kidney failure. It just means that they traditionally progress slower.

So, one of the questions that I was asked last night and again this morning, what's the difference between C3 glomerulonephritis and dense deposit disease? Currently, the way we define the difference is based on the biopsy. Where do the proteins deposit on electron microscopy? Predominately in the intramembranous region of the glomerular-based membrane, and they're very dark and osmiophilic, we call it dense deposit disease. If they're not, we call it C3 glomerulonephritis. That's still just a descriptive term, and it will be better to have a distinction that's more based on the physiology of the disease.

Personally, the way I approach this, is I think there's a spectrum of disease. And I think they both fall along that spectrum, and I have seen plenty of patients diagnosed with dense deposit disease who have done exceedingly well, despite that data on natural history. And unfortunately, I've seen patients diagnosed with C3 glomerulonephritis who have had awfully aggressive versions, down to kidney failure very quickly. So that's what the data says, but again from a natural history standpoint, these are the average

patients, and I do think that this is the type of disease that is often better approached on an individual basis.

Now, this is data from our own cohort of patients at Columbia, and this is data we presented at the American Society of Nephrology, and we're putting it together now in a manuscript we're submitting. This is interesting because in our experience this distinction between dense deposit disease doing worse than C3 glomerulonephritis, has not held up. So, this is data following over 100 patients for an average of about seven years. And if you look at progression to what we would consider to be hard endpoints, doubling of your creatinine, progressing to CKD Stage 5, which is the point where you need to plan for dialysis or transplant, actually going to dialysis or transplantation, or dying; 40% of the patients, whether it was C3 glomerulonephritis or dense deposit disease, met that endpoint within six years, with no difference between the groups.

The data that I showed you earlier, and much of the data on C3 glomerulonephritis versus dense deposit disease, comes from European cohorts. So, is the American version of this disease, which has more diversity in its representation- in our series, only about 65% of these patients are white, so 35% are non-white. So, is the American version of this disease, which is at least 1/3 non-white, a more aggressive version of this disease, and that's why we're seeing similar versions of the outcome? We don't know.

There are a number of series, and our data holds this up as well, which suggest that the earlier your diagnosis, the better you do. And so, this is just looking at progression to those hard outcomes, and you see that if you're diagnosed before the age of 18, you do better than if you're diagnosed between the ages of 18 to 50 years. And then, if you're diagnosed after the age of 50, you seem to be doing the worst. We suspect that this is what's called lead time bias, and that we're just catching these patients earlier, but they still have the progression, it's just happening later. We've just caught it earlier. Because when we do all of our adjustments, when we adjust for things like what the biopsy looks like, what the genetics look like, what the proteinuria levels are, what the patient's ethnicity is, there doesn't seem to be that difference in age on multivariate adjustment. And so, this gets to the idea that even if you're looking at data and the natural history looks better because you're diagnosed younger, if you do nothing, those patients will still be progressing.

One of the hardest parts about managing C3 glomerulonephritis or dense deposit disease, is that the patients do go to kidney failure despite our best efforts. And the story does not end at that point. Most of these patients are getting transplanted because they're young and they deserve to get transplanted, and we try to keep them away from dialysis. But once you're transplanted, the story unfortunately does not end. The rates of recurrence for this disease are exceedingly high. So, this is data that's quite recent, looking at C3 glomerulonephritis, which is again supposed to be the milder variant of the disease, and if you look at 10 years, about 70% of those patients have recurred within 10 years of transplant. And unfortunately, when recurrence happens, the graft has a more likely chance of failing. So, the disease coming back increases the risk that the transplant will fail. If your disease doesn't come back, your transplant will do better.

This is data in dense deposit disease, and it shows that unfortunately dense deposit disease patients do worse with their transplants. Their kidney allografts, their kidney transplants, survive at a significantly lower rate than other transplanted patients. And if you compare them against other glomerular disease, they do worse. We think this is obviously happening because the disease is recurrent. So, the prognosis after transplant is unfortunately very guarded. We expect the disease will come back. Seventy to 80% will recur within the first 10 years. And we expect that when it comes back, it will have an adverse outcome on the transplant survival. So, this is why we need to really work on trying to focus on the disease, not just before transplant, but there's so many patients out there that will need help after the transplant.

So, how do we treat this disease? Well, currently, we have some therapies that we use that are nonspecific. But, we hope that the future is therapies that are targeted at complement. So right now, our main version of treating this disease is a combination of mycophenolate mofetil and steroids.

We basically borrow this treatment regimen from lupus. And in our experience, which is small, about 30 patients who were treated long-term with this, 20 of the 30 showed some version of response. But I will warn you, and I say this to the patients, just because you "responded" to this regimen, doesn't mean we had any impact on your disease. I consider a response in this series to be a stalling. We've stalled the disease. We've kept it in check until we can find a therapy that's actually targeted at your disease. And this is actually my last slide, because this is where I think we're headed.

This is a very complicated slide with a complement cascade, and here you see the alternative pathway, which is what we're focused on in this disease, and you can see in these red boxes, these are all the agents that are under investigation, under development, targeted at different levels of the alternative complement pathway. And this, I think, is what we're looking for. This is the type of treatment that can actually modify the disease, potentially stop the disease, and get patients into sustained remission. So, the nonspecific therapies are stalling. This is where we hope the therapy is headed towards. And as I mentioned earlier, because it's such a heterogeneous disease, I suspect that we're going to need to use some of these on some patients, some of these on other patients, some of these on other patients.

Once we figure out where the defect is, we can pick and choose from these available therapies, I hope, to treat these patients effectively. And so, the last thing I'll say is that there are tons of unresolved questions as we move into this field. How can we test patients to figure out where their abnormalities are? Can we safely target at the higher levels of the complement pathway versus the lower levels, where there already are some drugs that are developed? And then if the therapies emerge and they work, how early should we be using them? Many of these therapies, we think, will be lifelong, and so how early to do you want to start somebody on lifelong therapy? So, these are some of the questions that I have, and hopefully Dr. Nester will be addressing some of them, as she talks about where clinical trials are trying to answer these questions. Thank you.

CHALLENGES TO C3G CLINICAL TRIAL DESIGN

Dr. Nester: I'll try to do the same thing with my clock here. So, I've already been sort of set up, because I don't think I have any answers for you to that slide. But I am going to try to at least give you some of the challenges that I think we face in the clinical world about how you would actually do a trial. So, let me start with doing a recap of exactly what I think is a starting point for why are we even considering trials right now. The first thing is that, as already has been pointed out, I think we have some very good evidence that we know what the underlying pathology is. We know that it's abnormal complement activation, deposition, or regulation. So, we know that piece, and that's absolutely key when you're trying to decide what treatments might be an option.

We also know that this disproportionately affects the young, and I don't mean four-year-olds. I mean in general young people who still have a long life ahead of them, in theory,

if their kidney stays healthy, if their health is appropriate to sort of get them through that long life. So that's a high burden of disease we're talking about for this group of patients. End stage to 50% in 10 years, maybe sooner according to some of the data that was just presented to you. But even also very discouragingly, the risk for recurrence, these are reasons to think about a trial right now. There are no disease-specific treatments, but there are several in the pipeline. That's the important piece here, and I was talking to some of the people last night in the small group I was sitting at, and I deal with lot of glomerular diseases.

We don't have great treatments for a lot of our glomerular diseases. This disease happens to be one of perhaps very few, if not the only disease, we might have the opportunity to actually choose disease-specific therapy for. And then I think the other key piece before you can move forward to a trial is you have to understand how to diagnose the disease. And because of the consensus, and granted it is expert opinion, but in 2012, published in 2013, we now know that this disease is biopsy- it's a biopsy diagnosis. So, you don't need a biomarker. You don't need to prove you have specific complement abnormalities. You don't need to have a particular clinical phenotype, you know you're very hypertensive, etc., etc. You don't need any of that. You need a kidney biopsy that says you have C3G.

And that's now been codified. We now know exactly what the diagnosis should be for all of the patients that actually have C3G. So now let's now take sort of- with that as a background now, let's sort of go forward. And I'll sort of- this is my challenges/obstacles slide, if you will. So, let's talk about some of the problems with actually creating trials in this disease.

The first thing is it's rare. You knew that part already. And if you sort of accept the fact that it's one to two people per million that actually might have this disease, then the first thing that comes to your mind, probably, is that this is very geographically dispersed. You know that based on who's in this room here.

Any trial that is going to have to consider a treatment in this disease is not going to be able to do it at one center and actually get a large enough number of patients to satisfy, I presume, the FDA or any science person who's actually going to be interested in proving a therapy. And then the question, and I've highlighted two specific challenges here, because I want to get back to them a little bit. But the last part of this particular bullet is that are there enough patients to test all the drugs that are in the pipeline?

It's something that has to be considered, and I think it's a definite challenge for us. Something that was clearly a problem for us previously is whether we had some degree of diagnostic uncertainty, and I would say that most of us are very comfortable making this diagnosis. There are probably some sort of people who have never seen the disease, perhaps, have a little bit of difficulty with it. But the important point is that the consensus was very clear about this, and most physicians who actually work with C3G very much, it's very clear. There are mimics of this disease. There are biopsy findings that if you gave the clinician no other evidence at all or no other clinical presentation, they would not be able to tell the difference. Is this C3G? Or is this some other disease? I'm going to throw that out there. And, again, I don't mean to make it sound- we are clear in our heads, those of us who work with this disease a lot, but you have to be clear- you're making a trial that you don't include patients that are actually secondary forms of this disease or complement activation, but not dysregulation, and it's an important point.

Then as has already been talked to you, there is some heterogeneity to this disease, and we do have a little bit of a problem in trying to decide- if you're going to run a trial, do you accept only DDD patients? Do you accept only C3GN patients? Do all of your patients have to have a C3 that's less than 10% of normal? Must they all have C3 nephritic factors? Or must they all be just hypertensive and proteinuric, which is obviously a lot of what we have in a number of our other glomerular disease trials. I think that it's a large issue for a clinical trial design- to decide who should be treated, meaning who are you going to enroll. Is there a kidney biopsy, for instance, that has very advanced sclerosis that you don't want to enroll in your trial, because you can't impact that kidney biopsy if that's one of your outcomes?

And also, you don't necessarily want to enroll patients that are incredibly indolent or that are going to have a good outcome anyway regardless of what the treatment is, because then if you do have a placebo arm, both arms are going to look the same. What about clinical equipoise? Well, for those who don't know that term, it's kind of a hard term. But basically, it sort of tells you how likely is a clinician going to enter a patient into a trial if they think that you're going to take away all their good drugs or all their drugs that they think might be helping and say, "Okay, this patient might be on placebo." And what it really means is that, is there enough uncertainty in the treatment world to

accept the fact that it is reasonable to have a trial design that allows the patient not to be exposed to drug for a period of time.

And I think that this classic thing you say is it ethical, and that's not really the right word here. Are you going to be able to recruit? Are you going to be able to get physicians to enroll patients, because they are in agreement with you having two separate arms, one with the treatment, which they think is going to work, and one that might be actually placebo? And then, of course, there are outcomes. And I actually have a- there's not only renal outcomes, which is something that clinicians are used to working with. I'm sure the FDA is used to working with certain renal outcomes. These are things that actually tell them that whatever has been just trialed, whatever you're trying, whatever drug it is, was it effective?

And so, you have to decide on what those outcomes are. I'm going to provide a few views of why we have to be a little bit careful about the outcomes we choose. And then, of course, there's biomarkers. This has already been eluded to.

This is a complement based disease and so should there be complement bio markers involved in any trial? And it is a challenge trying to decide which markers, for instance, Dr. Bombback will know, we've gone through phases of saying, "Well no one should be entered into a trial unless they have an elevated membrane attack complex." You know that sort of distal protein that was talked about. So those are the sorts of things that have to be solved before you can move towards actually making your trial design.

Very busy slide, and it's very similar to the one Dr. Bombback gave you, but I want to just point out those two boxes. Those two boxes, and again, if I can show you the alternate pathway is the pathway that's on the right here. Those drugs that are listed there and this is from Dr. Wickline, or previously from Penn, I think he's actually moved somewhere else now, but the point is that those 21 drugs that are shown there are, in theory, in the pipeline.

And I'm not a pharmaceutical person, so I don't know exactly what in the pipeline means in terms of where we are in terms of how soon they could be out, but all 21 of those that I've flagged, if I put my scientific hat on, they may have a role in this disease. So that's fantastic right? We didn't have all of that not so many years ago. But if you have 21 drugs, and if each of your pharmaceutical companies require 60 patients per drug,

so 30 in the placebo arm or 30 in some sort of cross over arm etc., etc. then we need 1200 patients to do these trials.

How hard do you think it's going to be to find 1200 patients with this disease? So, I think the reason I flagged this on my earlier slide is because this is, in my mind, one of the largest challenges, is trying to find the right patient for the right possible drug for them and making sure that patients get directed into the direction that they need to go to and make sure that everyone gets an opportunity to try it. Try a drug, or every pharmaceutical company gets an opportunity to trial their drug in patients, but it perhaps is going to require some creativity in figuring out how to make that happen.

So, the usual way we define outcomes in how we would think about clinical trials would be you get some improvement in kidney function, so renal function, your GFR is improved or your creatinine is improved. Stabilization is okay for some trials, but also if you're getting some improvement in urine protein, and what I want to provide to you here are two patients.

One is- let me show you this patient and so I will just say that it's a little bit hard to see in this light, but can you see the two yellow entries on to this person's chart? The first one was anti-complement therapy, then she went off of anti-complement therapy and then she's back on anti-complement therapy. And I want to point you to the fact that the blue line is her creatinine, so it didn't change at all, but what did change is her urine protein, which is the green line. Changed substantially and when we took her off drug, her urine protein went back up again, we put her back on drug, her urine protein went back down again.

So, success for this patient is a change in urine protein. We did not see a change in her creatinine and we can argue, and Dr. Bomback and I were talking about this just before, we can argue that as a clinician I might know exactly why that potentially happened, maybe we started too late, but the point is we didn't have a change in creatinine so that's not going to be a standard outcome that would be useful for this patient if I had chosen to enroll her.

And importantly we didn't see a change in her C3 at all. And I think that there are many of us believe that in order to help patients with this disease, if they have an abnormal complement system, we have to be affecting the complement system as part of a treatment course and so, and again there is some disagreement in the communities

about how we're going to achieve that, but the example I'll offer again is this patient clearly has essentially an undetectable C3.

But when he was placed on drug again, he actually gets an excellent urine protein. Completely normal urine protein, his blood pressure is now easy to control. He has no more edema, swelling of his legs etc. He is actually feeling very well and that's actually going to be the next point is that both of these patients absolutely feel one hundred percent better. Are back to work, are back to their normal lives. So, this drug did have an effect on them. It may not have changed the creatinine in either one of them and it certainly didn't change the C3 in either one of them, but actually they had some improvement.

Part of the challenge to clinical design is deciding whether is that good enough to get something an indication? Is that good enough to say that you've had success? There are many of us in the field believe that you actually have to do better, it has to be part of it, there is no doubt, but you have to do a little bit better than that perhaps to actually be the best choice for patients. It's a problem.

So if we go back now, this is why I said I'm set up just a little bit- because I don't have the answers for you, but I'm going to try to take that same group of figures and say, for instance, if your problem is rare disease then what you have to do is you have to have a consortium approach or you have to have some way of actually recruiting patients from multiple centers where they can be clearly diagnosed, clearly screened and actually then get them entered into a trial. And that's the best way. So obviously you can't have patients driving or flying across the country regularly for most trials that you're going to try.

The next piece of this is we are going to have to approach personalized medicine. I know that's a very- it's a crazy catchphrase that obviously a lot of people try to use right now, but we're going to have to try to figure out, out of those 21- and I'm just choosing those 21 medications because that's what Dr. Wickline had in his slide, but we're going to have to be able to choose which of these medications are actually going to be the most suitable for a given patient.

Do I believe that there may be some medications that would be good for mostly all patients? I know Dr. Bombback said that may take multiple meds, multiple opportunities to actually treat a given patient, but I think there's probably some medications that could be good for most patients. Other medications are going to be good for only a

certain cohort of patients and that's going to have to be something we'll have to take into consideration.

I think that the decision about diagnostic uncertainty has essentially gone away now that we have the consensus guidelines and we now know that we can biopsy, we can confirm the diagnosis and we can rule out the two major mimics of this disease, as far as I'm concerned. So, I think that we've solved that problem for our clinical trials.

Heterogeneity of the disease, what that really means is we have to be very careful to use the term phenotyping or deep phenotyping. We have to really just understand what the patient's story is. How low is their C3 or how active is their complement system or how high is their urine protein, have they been getting nephrotic syndrome, so the swelling issue? We have to really understand those patients before they're entered into the trial in order to try to figure out the effect on their heterogeneity or the effect of their part of their disease.

And then of course we have to expand this issue of natural history studies, registry studies and there are- we of course have ours and there are others going on throughout the world, we need to be able to maximize what we get out of those in order to understand what patients should be enrolled and at what stage of their disease.

The clinical equipoise issue, I think that the bottom line for that is that yes, what we might not like to agree to that, but there is clinical equipoise, there is not treatment that is preferable for any given patient at this time, so anybody who makes that decision is clearly biased. Having said that, it does mean that when someone is devising a clinical trial, they clearly have to be innovative about how they're going to do it. And one of my favorite- I threw this one out because I think this is one of my favorites, where you have a response adapted to design. If patients are responding in a given arm and patients in the other arm are not responding at all, then maybe you need to be- I know crossover's not a very happy design for a lot of people, but I think we need to think about whether patients can cross over to treatment if we do decide to go with placebo control.

And then finally I think we have to be very innovative about our outcomes. We can't use standard- if you use proteinuria as the outcome, and as Dr. Bomback said, we know that even the treatment that was used there is not disease specific. I already told you, we don't have disease specific treatment so the anti-complement therapy that was being used there did not go to where these patients' problem was. They both had genetic abnormalities, so it did not go to the problem. So, is just proving that you improve the

proteinuria in those two patients enough? It probably is not, you're going to have to expand that to consider other renal outcomes, perhaps biopsy and I think, again, a little bit of bias from me is that I think you're going to have to include complement biomarkers.

So finally, here's the solutions and again obviously you might wish you had a crystal ball, you might wish that you could figure out exactly who the patients are you need to treat and exactly what their treatment is, and maybe that's what the- I mean of course the FDA wants science, but maybe they would accept the idea of a crystal ball.

So, maybe dating myself, but perhaps what you really want is a tricorder. Do you guys remember what a tricorder is? Maybe if you sort of wave this tricorder over the patient you could figure out exactly what their complement problem is and then aha, you'll know exactly what their treatment is, perhaps that could happen too. Of course, we don't have those so what we really need to do is we need to maximize our natural history studies. We must really figure out what complement means in this disease and we have to- I mean we obviously, we think we know, but we have to prove that we know that, and we have to actually prove that that needs to be one of the biomarkers that needs to be addressed.

We also need to have strong collaborations obviously, between clinical, between pharma, between universities, between the FDA, etc. We have to have collaborations with the groups that make the decisions about how to bring medications to patients. Then, finally, the last two is we are going to have to think about some innovative trial designs. We're not going to be able to use the standard trial designs in this disease. We won't be able to trial- we won't get enough patients to do what we need to do and then finally, we need to think about the endpoints. Thank you.

WELCOMING REMARKS

Dr. Vassalotti: Great. Thank you both Dr. Bombback and Dr. Nestor. Those are wonderful presentations. Crystal clear and very helpful.

I want to remind you, you can tell in the room that you will be photographed during the proceedings and for those in the room and those on the web, we will be recording this

because it's very important for us to capture all your voices.

Without further ado, I'm going to introduce Dr. Norman Stockbridge. He has an MD and PhD in physiology from Duke University. He's worked at the FDA since 1991 and since 2004 he's been the Division Director of Cardiovascular and Renal Products. Dr. Stockbridge.

Dr. Stockbridge: Thank you. I wanted to spend a few minutes and try to highlight why I'm particularly glad to have the patients and their family members here today. To do that, I'm going to start and give you a little bit of background about what the Food and Drug Administration is about- what our role is and then it'll be clearer, I think, why it's important to have you all here today. It is the Food and Drug Administration, but in fact, that's not really the right name for the place. We're actually the food and medical products administration. The medical products piece of the Food and Drug Administration is up the road here about a mile at a facility, a campus, that doesn't have nearly as nice a meeting facility as the one we're at here today. We're all fortunate to be here and not there.

The medical products parts of FDA include a center for devices, a center for biologics that includes vaccines, cell-based products, and blood derivatives. Then the center for drug evaluation and research, which is where I work. The office of new drugs in the center for drug evaluation has 16 new drug review divisions. My review division is one of those and deals with most of the drugs that deal with cardiovascular and renal disease. We're about 50 people, a third of whom are physicians or clinical reviewers. A third of them are non-clinical reviewers, they're pharmacologists and toxicologists. And, a third of them are the, what we call project managers, but in fact they're the people whose career is around understanding the process of laws and making sure that we follow standard procedures.

We're part of a somewhat larger family that includes maybe another 50 or so people on a routine basis who contribute other aspects of expertise- statisticians, pediatricians, clinical pharmacologists, a whole range of different groups. Our assigned role, really, is to monitor the drug development process. The drug lifecycle from the point at which a compound is ready for its first test in humans, throughout the time it is studied for use and then later is on the market. While our nominal responsibility has something to do with making sure the products that get approved meet certain criteria, in fact every single person who works on that campus a mile up the road believes strongly that a

major part of what our responsibility is has to do with fostering drug development- fostering product development.

Our basis for approving things has several components to it. One of them is establishing that the product is effective in doing something that matters to patients. We're here listening to you today to try to figure out some of what it is that matters to you about your disease because these are going to become reasonable candidates for somebody to show that a drug is effective- does something that is beneficial to you who have the disease. Unfortunately, drugs seldom do only what you want them to do and so part of our approval process is trying to figure out whether or not the benefit that's been achieved with a particular product is worth the risk or harm that accompanies it. In diseases that affect many people, hypertension, coronary artery disease, diabetes, it's relatively easy to design clinical development programs that give you pretty good insight into what the harms are that accompany a drug.

In the case of rarer diseases like this family of diseases, it's simply impossible to actually work out in the usual way what the real risk and benefit attributes are. So, one thing that we're going to be listening to here today in addition to trying to figure out what aspects of the disease are that matter to you, the other thing that what we're going to try to be listening for is something about your level of risk tolerance. There are going to be things that accompany approval of these products that aren't going to be extremely well characterized with regard to risk. We need to understand something about what your level of risk tolerance is for things that aren't really adequately characterizable. I hope we're more or less back on schedule at this point and I'm looking forward to the next session of discussions with patients.

Dr. Vassalotti Great. So next is really the highlight and very much looking forward to having Moderator moderate this. He's an expert, actually I think he told me this is his fifth PFDD meeting, and without further ado, James?

PANEL #1 DISCUSSION ON TOPIC 1

Living with C3G: Disease Symptoms and Daily Impacts.

Moderator: Good morning everyone. It's my pleasure to be here. I'm James Valentine, I'm an associate at a firm here in Washington DC, Hyman, Phelps and McNamara. We're very proud to represent the National Kidney Foundation, and I am honored to be here with

you this morning to be your meeting moderator for what is really the whole purpose of today, which is to hear from you, patients and caregivers that are living day to day with C3G, and help those that are here in the room- our colleagues at FDA and from industry- those that are developing products to hopefully help treat your disease, can learn from you and guide their development process, and eventually help inform FDA's regulatory decisions as Dr. Stockbridge was just noting.

Before we get started, I wanted to give you a little bit of an overview of the meeting today. The meeting, this Patient Focused Drug Development meeting, follows a format that was really well established by the Food and Drug Administration as part of its patient focused drug initiative, which was really an initiative launched about five years ago where FDA committed to broadening its efforts to bring the patient voice to FDA and it actually hosted a number of meetings on its campus, which Dr. Stockbridge mentioned, it's not quite as nice of a facility as we have here today.

This meeting, which was requested by and granted by FDA to be hosted by the National Kidney Foundation follows a similar format to those hosted by FDA. I'm going to talk to you a little bit about that, so we're all on the same page in terms of how it is we're really going to be soliciting your input through the course of the meeting.

As was highlighted at the beginning of today, our discussion is really divided into two topics. The first topic is going to be on the symptoms of C3G that matter most to you. So, we're going to explore issues of symptoms that have the most significant impact on your life, how those symptoms affect your ability to do specific activities, and then we're also interested in how those symptoms and burdens have changed over time.

In the second part of our meeting, we're going to then build on that earlier discussion and discuss your current approaches to treating your C3G. So here we're going to be asking you what you do to treat your disease. This will include not only drug therapies, but other medical procedures or even things that you do in your daily life like lifestyle modifications or diet or exercise, really anything out there that you might do to attempt to manage your disease. We're going to ask you how well those things are working and treating the most significant symptoms of your disease, what are the biggest down sides of those treatments, and then we're going to turn looking to the future and ask you a little bit about what you'd like from an ideal treatment.

So, to help answer those questions the meeting is structured in a way to get your input

in a variety of ways. For each of the topics we'll first hear from a panel of patients and caregivers. This panel presentation will help us set a foundation for the broader audience discussion that we'll move to, and the panelists were selected by the National Kidney Foundation to reflect a range of experiences with the disease. To help set the stage for that discussion.

After each of the panels, for all of you that are here in the room, as well as those of you that are on the web we're going to turn to answer some polling questions. These are questions that we've designed to help aid in our discussion and kind of get a sense of your burdens and treatments before we open it up to an actual audience discussion.

For those of you that are in the room, you can do this by using your cell phones. I'll give you instructions once we get to our first set of polling questions. Then for those of you on the web, you'll be able to use your web browser to participate as well.

We do ask that only patients and caregivers, caregivers being those that provide direct care, such as spouses or parents of patients, participate in the polling responses.

After we move through our polling questions, we'll then broaden the dialog by including patients and caregivers again in a facilitated audience discussion here in the room. The purpose for this is to build on the experiences shared by the panels, as well as through the polling questions. During this time, we'll ask you- all you have to do is raise your hand and I'll be facilitating that conversation and we'll have a dialog here in the room. We do just ask that you state your name before answering so that way when we go back and look at all the input we receive today, that will help us putting together a summary report, which was mentioned, which is called the Voice of the Patient Report.

We do only have so much time today, so we understand that there may be things that you want to say that we won't be able to get to, or maybe as you leave the meeting today you'll have thoughts that you're going to continue to mull some of these topics over and you'll have more input that you'd like to give, or if you're on the web or listening to the webinar and you obviously can't participate in audience discussion, there is going to be a way for you to provide comments after the meeting in written format. We'll provide those instructions at the end of the meeting. The National Kidney Foundation will be collecting those until September first of this year. Those will also be included in that Voice of the Patient Report.

One final piece of business before we actually move into our first set of demographic

polling questions, is I want to discuss a couple of ground rules for our dialogs today. I mentioned that we're here to listen to patients and caregivers. I really encourage all of you to participate in the dialog. In terms of participating, we do ask that this be just caregivers and patients that are participating in this.

Our colleagues from FDA, Industry, clinicians, and researchers are here to listen. So, while we're asking that they not participate in the discussion periods, also worth noting that we're not going to be directing any questions to them to respond to. They're here really to absorb what it is we're going to be talking about today.

The discussion is going to be really focused on symptoms and burdens of your disease, and approaches to treatment. There may be other topics, policy topics, or other aspects of your experience that you want to talk about. We ask that you table those for today. National Kidney Foundation would love to hear about that from you, but for today's session we're going to stay focused on the questions that we have.

I do understand that your views that you're going to be sharing today are very personal ones, and that they can even be very emotional, so I just ask all of you to please be respectful of one another, which I'm sure you will. We're going to try to give as many of you an opportunity to share as possible.

So, with that, we're going to move to our first set of polling questions, so go ahead and pull out your cell phones, and if you're on the web you can go ahead and open up a browser. I'm going to explain to you the instructions as we work through our first question.

First, to give you some instructions for getting logged in and part of this polling system is- I even recommend for those in the room to use the URL web link through a browser over texting, although both are available. Those on the web, obviously if you're at a PC you can use your browser, but if you go to that URL pollev.com/nkf17 then that will, as we progress through polling questions, those questions will appear for you and you can respond to them.

For those of you that would prefer to use text messaging, if you send a text to the number 22333 and send the message of the text is NK17 that will put you in the system, and as we go through each question you'll be able to enter your responses and send those, and they'll be captured here.

I'll go ahead and read our first question, give you all a chance to log into the system. If you have any issues accessing it just lift your hand and someone will come by to help you. But our first question is a simple one. Where do you live? And here's stuff that applies to you, A: East Coast, B: Midwest, C: West, D: West Coast, or E: Outside of North America.

Looks like our responses have stopped trickling in. It looks like we have about- it looks like we have the majority of our representation from the east coast with about half of our participants being from the eastern time zone. A close second is those from the midwest and the central time zone. And it looks like we do have some representatives from the west coast. Those of you on the west coast on the webcast, thank you for joining us so early in the morning out there.

Next question. Sorry about that.

So, we can keep moving and working through these technical issues. So, our second demographic question for you is, "What is your age?" So here again, select one, and one thing to mention is for those of you that are caregivers responding for patients. For here- and as we move throughout the remaining questions we'd like you to answer them for the patient that you care for. In this case it would be what is the age of your patient? Or, if you're a caregiver, what is the age of the patient you care for? So, here, the options are A: Under 18, B: Age 18-29, C: Age 30-39, D: Age 40-49, E: Age 50-59, F: Age 60-69, or G: 70 or greater.

Okay I'll go ahead and let you respond to that. And feel free to raise your hand if you are having any issues accessing this.

All right, so it looks like almost two-thirds of our participants are representing patients that are aged 18-29. The next is a little under 20% are representing those aged 30-39; we also have representation for those under 18, 40-49, small representation of those aged 60-69.

Our next question is if you identify as male or female. Again, we're asking this about the patient. If you are the patient, or the patient you care for. And this is on A: male or B: female. I'll give you a few more seconds to get your responses in for this question. I think this might be an unprecedented event. Exact equal distribution of male and female patients represented here today. Thank you.

So, our fourth polling question is, "What is the length of time since your diagnosis of C3G or the patient that you care for? The response options are A: Less than one year ago, B: One to two years ago, C: Two to five years ago, D: Five to ten years ago, E: More than ten years ago, or F: Not sure.

I'll give you a few more seconds for this question. Looks like a couple of more responses are trickling in. All right, so, it looks like we have a broad range of representation of the length of time since diagnosis of the disease. It looks like about a quarter of you represented here today were diagnosed more than 10 years ago. Also, five to ten years ago and two to five years ago. Near equal representation from those diagnosed less than one year ago, but very few that were diagnosed in the one to two year ago range. And nobody was unsure about how long since diagnosis.

Thank you for bearing with us as we deal with some technical issues on the webcast front. So, our fifth demographic polling question is, "Do you have a kidney transplant?" A for yes, B for no. I'll give you a few more seconds on this polling question.

It looks like a little more than two-thirds of you represented here today have not had a kidney transplant. A little under a third of you have had a kidney transplant. So, that's certainly exploring your experiences with your progression to needing a kidney transplant in Topic 2 of our discussion today.

And our final polling question for demographics is, "Are you on dialysis?" A for yes, B for no.

So, it looks like the overwhelming majority of our participants are currently not on dialysis. Although we do have some representation in the room and on the web for those that are. We'll also be exploring this in Topic 2 of our discussion today.

So, that concludes our demographic polling questions. I'll invite our first panel up as I introduce our first topic. As I mentioned not too long ago, our first set of input we're asking of you is to help us understand the symptoms that matter most to you. Our panel here today is going to be discussing some of these same issues that we're then going to turn and ask those of you in the audience about. We're going to be again exploring symptoms that have the most significant impact on your life. How those symptoms impact your ability to do specific activities in your daily life and how those symptoms

and burdens have changed over time.

Today, our panel that we have for you is, Shannon, Tori, Dave, Jenna, and Nicholas. They will be sharing their stories with you. Then we will move into our audience participation.

Without further ado, Shannon-

Shannon: Good morning. My name is Shannon, and I live in Grove City, Ohio with my husband Matthew, our three amazing children, Logan, 13, Allison, 11, Ian, 5, and our dog Nila.

I'm here on behalf of my daughter Allison. Beginning at three months of age, Ali had frequent UTI's. Later in her toddler, and beginning school age years, she had recurrent infections that would symptomatically mimic a UTI. Her culture results were always negative, but always presented with blood and protein.

In July 2014, after consulting with a new pediatrician, he recommended seeing a urologist. The urologist ordered a series of tests, none of which gave us a diagnosis.

After the urologist could not diagnose Ali, she was referred to a Nephrologist. Five months later, in January 2015, we were seen at Nationwide Children's Hospital.

After even further testing, with an unconfirmed diagnosis, we proceeded with a kidney biopsy. We were certainly not prepared for the diagnosis we would receive.

In early February 2015, at eight years old, my little girl was diagnosed with C3GN. I had no idea what this meant. It was hard to explain something to my child that I didn't even understand. I felt helpless and I was scared. I wanted so badly to take this from her. The fear of the unknown is a fear like no other. This was my daughter, and all I could think about was what I could do to help her.

Allison was the first case at Nationwide Children's Hospital. Even they weren't sure of what a C3GN diagnosis meant. Getting the information we so badly needed was challenging. I set out on a mission to gain as much knowledge as I could.

After hours searching C3GN on the internet, and from nephrologists who knew what that term meant, I contacted Cincinnati Children's. The nephrologist on staff was

accepting new patients, so we transferred Ali's care.

From May 2015 to July 2017, Ali made wonderful progress and we were able to gain further knowledge to better understand what we were dealing with.

Last month her nephrologist relocated. I was on a search again. After a lot of conversation with my husband, and using our forum's C3G support group as a resource, we decided to transfer her care, yet again, to the University of Iowa.

Taking time off from our full-time jobs, finding care for our two boys and traveling, is not the ideal situation. It was an hour and a half car trip from the nephrologist in Cincinnati, and now would become eight hours when we make the trip to Iowa.

Due to the lack of local physician education and knowledge around C3G, we are committed to doing this, so we can get the best care for Ali.

We are extremely thankful that Allison began with and continues to have normal kidney function with minimal symptoms. Though she has experienced headaches and sporadic high blood pressure, the most prominent symptom was fatigue. She would complain that she was tired all the time, and had dark circles under her eyes. Even after a full night of sleep, it looked like she had been up for 24 hours. It was extremely hard for me to see her so exhausted.

Though this was a challenge for her, she powered through and didn't allow it to affect her day-to-day activities. Ali began taking lisinopril daily and prednisone every other day. I monitored the protein in her urine by using a dipstick every day, and recording it.

We worked together with her physician to monitor her urine on a monthly basis. This gave us a good indication of how well the medication was working. During the time she was on the prednisone, the hardest thing for Ali was the weight gain. She gained approximately 20 pounds and was hungry all the time.

The biggest obstacle she faced was with her self-image. Even though we never made mention of the weight gain directly to her, she knew she had physically changed, and would often remark about being fat, not something I wanted my daughter to look in the mirror and think of herself. It was heartbreaking to see Ali struggle with her self-image, due to something beyond her control.

Emotionally the hardest time for Ali was right after diagnosis, having to take medicine

every day was difficult, and a constant reminder of something she didn't understand. She had a hard time talking about it with us, because we weren't experiencing the same thing. We had to work through those feelings with her by giving specific examples of how there are many people who take medicine, just like she has to.

She needed to understand that she was just like every other normal little girl out there who can accomplish anything she wants to. I expressed that even though we are not personally experiencing the same thing she is, we are here to help her through it; to gain the knowledge and understanding we can, so that we can be an advocate for her, until she is able to be an advocate for herself. But even then, we will still be there.

As a mother, my biggest worry for Ali is the uncertainty of the future, and what it will mean for her. The absence of available treatments could result in declining kidney function. Finding a knowledgeable physician to care for her in her adulthood, and the potential complications of having children as she gets older.

During pregnancy patients aren't able to take lisinopril, due to the risks associated with the medication. So, what is the chance of her coming off the lisinopril and having a successful pregnancy without any complications? Does this mean her health will severely decline during that nine months? What options will she have to bear children of her own?

In closing, I pray every day for Ali and all the others affected, and for continued progress in the research and treatments of C3. Thank you.

Tori: Hi, my name is Tori. I'm 22 years old. I'm originally from Knoxville, Tennessee.

December 21st, 2015, I married my husband Brandon and moved to Grand Forks Air Force Base in North Dakota, to become a military wife. I work for the library on base, and absolutely love my job.

We have three wonderful fur babies, Simon, Lily, and Evy. Then we also have two beautiful angels, Grayson and Willow.

August 14th, 2016, ten days from now, I found out we were going to be growing our family. August 16th, we saw that we were having twins.

I've always been healthy, so I had no worries. On October 6th, at 11 weeks, I learned

my twins had stopped growing, and they had passed. I had to have an emergency D&C done.

My doctors say they passed for unknown reasons, but I believe they died so this could be brought forth. My angels gave their life for me. 24 days after my surgery, I started having swelling in my legs. I couldn't walk without extreme pain or difficulty. My OBGYN thought it was related to chronic anemia, the only health issue I've ever had.

Doctor after doctor blew me off. Finally, I found an internal medicine doctor that ordered a urine in December. It came back with 10.48 grams of protein in my urine. My albumin was a 2. She immediately referred me to a nephrologist, who ordered a kidney biopsy and a bone marrow biopsy. It confirmed C3G. All I could think of is, what on earth is that? Before long, I was on plenty of medications, such as prednisone, Lasix, losartan, potassium, Bactrim, iron supplements, sodium potassium, and finally CellCept, only with the help of other specialists, because he'd barely heard about this, much less saw it before.

I felt angry and I felt betrayed by my body. How could swelling and exhaustion lead to a disease, that in my doctors' words, would put me on dialysis by the end of the year, if we didn't get it under control because it's killing the filters in my kidneys?

Despite everything, I kept fighting. I kept digging to understand. My doctor recommended I go visit Dr. Nester at the University of Iowa, twelve hours away. She helped me understand what was truly happening to me, what my future would hold.

I also got approved for the genetic test. Once tested, it came back that I had the Factor H mutation. I'm still kind of lost on what that means. But, my understanding is that every time I get really sick, or my body gets really stressed, this will happen again, if we ever get it under control in the first place.

This year has been rough, to say the least. I had to have a port placed and had an allergic reaction to the materials the port was made of, and had to have it removed. Between this reaction, and then insurance denial, because eculizumab isn't an approved medication, this is currently not an option for me.

Testing and doctor's visits have slowed down a bit to see if my current regimen will work. My husband went from being my partner to my care giver. Due to being so far

away from family he had to take care of me, he would leave food beside the couch for me while he went to work because I couldn't even get up. He would sit in the bathroom while I showered because I was so weak and would become lightheaded. I could tell you about the symptoms, I mean everyone will, I could tell you how bad it is, but none of that can possibly compare to the grief and the pain that my husband and I feel, the loss of my health and the loss of a normal life for me. The loss of our babies, and the loss of probably ever having any future ones, that definitely outweighs anything that this disease can do to you. Thank you.

Dave: Good morning, my name is Dave. I'm a 43-year-old father and husband from Yorkville, Illinois. I live in the suburbs of Chicago with my beautiful wife of 23 years, Nikki. We have two awesome boys, Jackson, who's nine, and Griffin who is seven. In 2008 at the age of 34 my life was turned upside down when a routine exam for life insurance turned into a life altering event. After many tests and eventual kidney biopsy I was diagnosed with C3G dense deposit disease. Since my diagnosis in 2008, my health has taken many ups and downs. I've gone from initially noticing very minor symptoms, to now, much more severe, impactful, and painful symptoms. To name just a few, I have high blood pressure, gout on a fairly regular basis, significant pitting edema in my legs, feet, and hands, fatigue, decreased kidney function, and wet age related macular degeneration, due to drusen in my eyes.

The progression of this disease was not unexpected, and although my doctors provided me with information regarding my prognosis, I thought I would not succumb to the side effects that my doctors warned me could happen due to my diagnosis. You see, since my early teens I've always maintained a healthy lifestyle, so that, along with following doctor's orders as a result of my diagnosis, I really didn't think I could or would get sick. "You don't look sick," is a common phrase I hear when people learn of my disease. What most people don't know are the daily struggles that I, and I'm sure many of us with C3G have to deal with. The constant and unavoidable reminder of the excess protein in my urine every time I use the bathroom. The swelling in my face, hands, feet, and legs that can make it difficult to stand and walk, the medications I take on a daily basis for high blood pressure, high cholesterol, and edema. The gout, which makes it painful to wear shoes, walk, or even wear socks, and most impactful, the blurred vision in my left eye as a result of the drusen deposits.

My vision struggles have been most difficult and scary to me because without my vision

I literally lose this part of the world. It started at a golf outing about a year ago. While most people were having fun, I had a startling reminder of my disease. A simple glance at a golf ball changed my life forever. I couldn't focus on the ball, actually balls as it appeared to me. It was at that exact moment I knew something was drastically wrong. A week later at the eye doctor for an exam, I was told I had the eyes of an 80-year-old. My doctor explained to me that the drusen in my eyes mimicked what she would see in her older patients with wet age related macular degeneration. From that day forward, I began a series of shots, and not just any shots mind you, but shots in my eye, in an attempt to save my sight. These monthly shots will most likely continue for the rest of my life, as my doctor does not believe I could continue to see without them, and although painful and costly, it's worth it to save my sight.

On my good days I go about my life with very little challenges, on my worst days I feel the toll the disease is taking on my body, such as the edema I experience. This can make it difficult for me to perform simple chores around the house, such as mowing the lawn, and more importantly being active with my wife and kids, playing sports, or just chasing my boys around in the yard. These are things I enjoy more than anything, so the thought of not being able to do so devastates me. What's most difficult is knowing that time is not on my side. Since my diagnosis nine years ago my condition has worsened, I'm slowly watching my kidney function deteriorate. Quarterly tests continue to show negative change in my GFR. Without a viable drug treatment, I know that maintaining a healthy diet, exercising, and following doctor's orders will not stop the progression of this disease, eventually resulting in kidney failure. This absolutely frightens me, because I know the difficulties of dialysis and transplant that I would face due to my kidney failure.

As I think about how my condition has changed over the past nine years, I contemplate almost daily about what the next nine plus years will bring. Of most concern is the potential loss of kidney function, and loss of eyesight. I can only imagine things getting worse, and I have no expectation other than things getting worse, because there are no treatments available to provide hope for my health to improve. This expectation leaves me feeling desperate. What will come next? What new symptoms will present themselves over the coming years? Without a treatment option, only time will tell, so all that I can do is wait and worry. Worry about the years to come and whether I'll be a burden to my wife and kids, worry about the ability to be involved in their lives actively, or as a spectator on the sidelines. Worry about whether I'll actually see my children grow, worry about whether I'll be around to see my children get married and have

children of their own. Worry if I will grow old with my wife, worry about the unknown and the inability to do a darn thing about it. Thank you.

Jenna: Hi, my name is Jenna, I am 31 years old, living in Seattle, Washington where I work as a building information modeler. I have lived with C3G DDD for the past 24 years. My medical history starts with me at the age of seven where C3G was rapid and progressive, going from normal renal function to ESRD in just months. From seven to fourteen I treated with home peritoneal dialysis, fourteen I received a transplant where C3G showed signs after the first month. The next year and a half was spent doing plasmapheresis to combat the disease progression. Sixteen, I went back on dialysis until now, where I've been doing home hemo, five days a week for the past 15 years. The chapters of my life living with C3G have been exciting and challenging. In these next five minutes I'd like to paint what those challenges have looked like for you.

To start, as a child I was one in a family of six. It was a hot summer afternoon in Iowa when C3G decided to make itself known to my life. After playing dominoes with my brother, I fell into a deep sleep on the carpet. Waking up groggy and to a fever, my mother was immediately concerned. That evening, fear shot through my seven-year-old core after going to the bathroom and seeing red in the toilet where I should have been seeing yellow. That began the cascade of medical tests, appointments, biopsies, and surgeries.

After starting PD, many previously unforeseen modifications were made to my life. Some of these include being removed from gymnastics class, to prevent how back handsprings might compromise an abdominal catheter. The inability to attend sleepovers due to the requirements of nightly dialysis, challenges of swimming for fear of peritonitis, and the myriads of foods I was banned from eating. In addition, one of the biggest anomalies with my situation is that I was born with an identical twin sister who doesn't have the disease.

Including the exhaustion that has plagued me for most of my ESRD days, there have been a huge number of differences that have established themselves between us. Where her endurance increased, mine decreased, where her flexibility increased, mine declined, and where she now stands at 5'6, I'm four inches shorter. Where I trailed her in endurance, height, and physical development, there are many times when she would show her commitment to me only as a twin knows how. When she taped an abdominal catheter to her stomach to pretend she was me, or stand up to the bully

who challenged our twinliness when I had edema where she had none. Or those other moments where, for lack of explaining the medical anomalies we found ourselves to be in, instead of following up “we are twins” with identical, we chose fraternal, for sake of explaining what no one seemed to understand anyways.

As I live now, with dialysis as my only sure resort to living a healthy life, I have been challenged physically in many additional ways. Of note have been my experiences with severe foggy brain in my declining months of transplant where classes and social involvement were compromised, strangulated and obstructed bowels from seven years on PD, daily battle of red, inflamed eyes as a result of sensitivities to phosphorus, ovarian cysts as a result of excessive abdominal surgeries, living with bone pain three years as a PTH value of 400 slowly escalated to 2,500.

In the worst of times prior to my parathyroidectomy, I had physical limits to running as it caused me immense bone pain. Where I would be involved in multiple sports, I could only do one activity once in a two-week time frame. The rest of the time was spent healing from pain caused by activity, pain that felt like tiny fractures throughout my bones. Even when lying down, the pain would persist. I had to take great care when hoisting myself out of bed, take two steps per stair, walk delicately, and take the elevator for just one floor.

Post-surgery in light of better days, while I still get severely exhausted, I can hike, dance, run, and in addition, dig into my cuts when playing soccer or Frisbee, a notable action I hadn't done for likely a decade. In addition to these physical challenges, I am also faced with emotional traumas.

For me, processing has taken many forms. Laughter, as it helps transmute the seriousness that can get overwhelming. Silence, walking, and reflecting to process and recognize what I do have and am grateful for in life. Frustration, because I don't know if it's ever going to end. Depression, when the frustration gets too much to handle.

That's when I break down. I bawl my eyes out. I want it all to just go away. I want a body that doesn't attack itself. I take a deep breath, sigh, wipe away tears, and slowly pick myself back up again. Talking helps me to be open about C3. This makes it feel like just another thing instead of a big medical burden.

Connecting. I love connecting with new patients, as it gives me the opportunity to help someone out of the darkness where so many have helped me. Amongst the challenges

we face, the beauty of life is that we all have the opportunity to manipulate it, to some extent, and align it with what we want to experience and feel.

I have chosen to be lighthearted as I can in my views of C3, as in the days when my machine, Jamal, got his name. Friends were over hanging out while I did dialysis. The machine beeped, and someone explained, "Oh, stop yelling so loudly," with a pause where a name only felt right. After deliberation, Jamal was dubbed.

Aside from these lighthearted moments that entwine my life, I also live with concerns for my future. What will it look like? How much more will my health decline? Will I keep feeling broken? Will I be able to keep handling it? Didn't I say I would attempt a second transplant in two years 10 years ago? Should I go for it and just try again? Wouldn't that be ridiculous, knowing the outcome? Do I want a hand in my current situation in exchange for a kidney, a suppressed immune system, and a life likely followed by cancer [inaudible]?

What's better? What happens if my blood pressure continues to steadily drop? Can I even qualify as healthy enough to get a transplant? All I know is that instead of fighting as I once used to, I've come to terms with where I am. I live taking steps at my pace and believing that everything turns out as it is meant to in the end. With that, I believe that someday soon there will be an answer for all of us with C3G.

Nick: Good morning. My name is Nick. I'm from Buffalo, New York, and I have a PhD in Medieval History. I'm currently living in Boston doing research for a book and then I'm moving to Greece in a few weeks. I'll be 33 years old in a few months and I developed C3 glomerulonephritis soon after my 13th birthday in December of 1997.

I woke up one night to go to the bathroom and noticed that I had blood in my urine. C3G was almost unheard of at the time, so I joked to my father, who happens to be a nephrologist, that they should name the disease after me. But he said that diseases are usually named after the doctors who discover them, not the patients who suffer from them.

During the first 12 years of my condition, it was usually stable. With relatively low levels of proteinuria and creatinine and mild doses of immune suppression. There are occasional flare-ups of the disease. They're usually triggered by a cold or the flu or something like that. Often, I couldn't really tell apart the symptoms of the passing illness from those of C3G.

But they usually included a general sense of unwellness and fatigue. At this stage, however, my main difficulties were not with the disease itself, but with the treatment. There was the hassle of regular tests and keeping track of my medicines. There were also the side effects of the meds, especially prednisone. But otherwise, I was able to live more or less normally, to go to school, work part-time, and play sports like most people my age.

The disease and the drugs did keep me from being as athletic and as competitive as I would have liked, which was frustrating for me as a teenager. But my main focus was on my studies, so I didn't let it bother me too much.

Then as I got into my 13th year with C3G, around 2010, I started feeling the toll from the accumulated scarring of my kidney. An attempt to treat me with an experimental drug, with eculizumab, failed and things got steadily worse. I really started feeling unwell as I got into my 14th year of C3G in late 2011.

At first, the main symptom was chronic fatigue, which affected me in my work and play. I had a harder time focusing on my doctoral research. I couldn't make it through a half-hour intramural basketball game without doubling over with a hacking cough. Worst of all for my daily activity, I developed gout in my big toes and my right knee and my right hand.

I was in Rome the summer of 2012 for a Latin course and outside of class, instead of getting out and exploring the Eternal City, because of the pain from gout I stayed in bed and read novels. Up until then I had dealt with things pretty well because I'm generally stoic, and because I could understand why my body was feeling the way it was. But now, the fatigue and the pain were wearing on me mentally, especially since I wasn't quite sure what was going on.

I didn't really discuss the gout symptoms with my nephrologist as much as I should because I thought they were unrelated to my kidneys. I was going to an orthopedist at the time and even though he knew I had kidney problems, he didn't think to diagnose gout, so it went untreated for a while.

Finally, while in Rome that summer an Italian doctor figured it out and prescribed medicine, allopurinol. Now I was pain-free but still dealing with extreme fatigue. At the end of the summer, a bad cold that I caught while at summer camp left me totally

wiped out. That's when I really got scared because I never felt so exhausted in my life before.

At this time, in late August of 2012, lab tests showed that I was below 20% kidney function. Because of the slow decline until then, it'd take me a long time to really feel the acute symptoms. I was like the proverbial frog in the slowly boiling pot. Now, I was eligible for a transplant. Fortunately, I didn't have to wait long since my mom volunteered to donate right away.

Thank God, after just a month of dialysis I got a healthy kidney on November 20th, 2012, after almost 15 years of C3G. Since then, I've been in great shape. I still have to worry about tests, drugs, biopsies, etc., but my day to day health is back to normal. My energy level is excellent, and I am able to do strenuous exercise without feeling exhausted. Some of my joints are still residually sensitive to gout, but my allopurinol keeps it from developing.

Then what about the C3G? The electron microscope evidence from my recent biopsies shows possible activity, but at an insignificant level. It seems that for now, my anti-rejection drugs are keeping the disease at bay. Due to my feeling of normal health day-to-day and the fact that my C3G is under control indefinitely, although I know the disease is still there, I'm not so anxious about it.

I feel that knowledge of C3G has come a long way in the past 20 years, even though treatment is still in its infancy. I hope that whatever problems crop up in the future, there will be better solutions. For now, having grown up with a chronic disease, I feel that I can face whatever the future holds as an adult with a certain amount of wisdom based on experience. Thank you.

LARGE-GROUP FACILITATED DISCUSSION ON TOPIC 1 Living with C3G: Disease Symptoms and Daily Impacts.

Moderator: That was very powerful and illuminating. Please join in thanking our panel for sharing their stories.

Now we're going to move into the pulling questions for this topic, Living with C3G: Disease Symptoms and Daily Impacts.

The first question which we have for you, is to please select how much does your C3G interfere with your day-to-day life in general. Your options are A: not at all to minimally. B: moderately, or C: a significant amount. I'll give everyone a few more moments to get in your responses to this first question on living with C3G.

So, it looks like about 44% of you that are represented here today, there's patients or patients that have caregivers here representing them- are not at all to minimally affected in your day to day life. And then about equal proportions of you, or a little less than 1/3 each are either moderately affected or not affected to a significant degree.

Our second question for you is a question- is the first such question where we're asking you to select up to three responses, so if you're doing this by the web browser, you can just select up to three or if you're doing this by text, you can enter in three different letters with spaces in between them. But please pick which three of the following symptoms most negatively impact your daily life A: swelling. B: being tired, exhausted, or fatigued. C: anxiety and or depression. D: headaches. E: not being able to concentrate or think clearly. F: GI problems. G: weight gain. H: altered appetite. I: insomnia or J: other, something that's not listed up on this slide. So, I'll give you some time to think about this and get your responses in. Which of your three of the following symptoms most negatively impact your daily life? While some of the final results are trickling in, I'll note that it looks like the top symptom that you rated as most negatively impacting your daily life is being tired, exhausted, or fatigued. The second most negatively impactful symptom being swelling in the ankle space or other areas, and then the third highest being anxiety and or depression. We do have each of the other symptoms being denoted by some of you as most impactful and we do have some other symptoms as well, which we'll want to explore when we get to the moderated audience discussion in a minute.

So, our third question for you about your living with C3G, is in your daily life: what bothers you more? A: symptoms of C3G. B: side effects from medicines you take for C3G. C: both, the symptoms and side effects are equal, or D: you can't tell the difference between the effects of C3G and the side effects from medicines.

So, it looks like a little under half of you, just over 40%, said that the symptoms of C3G are what bothers you more in your daily life. The next highest rated response is both; about 25% of you said that they equally affect your daily life and then just under 20% say that the side effects of medicines actually impact you more, and 13% said that you can't

tell the difference between the two. So, we're certainly going to want to explore the symptoms that impact you from your C3G and then for those of you that maybe both impact you or you can't tell the difference, we'll still want to explore those as well and see what your thoughts are in terms of whether you think they're from C3G or a medicine, or if you can't tell, it's still important for us to know what it is that's burdening you.

Our fourth question is, which have you experienced while coping with C3G? And this is one where you can select all that apply, so you can enter up to five responses. A: depression. B: anxiety. C: low self-esteem. D: social isolation or E: difficulty with relationships outside of the family. And again, select all that apply.

So, it looks like anxiety may be slightly ahead of the others in terms of the most experienced of these while coping with C3G, but there is quite a deal of experience with depression, low self-esteem, and social isolation. There's less experience with difficulty with relationships outside of the family, but there are a number of you that did note that as being something you've experienced.

And finally, our last question for you about living with C3G is, which of the following statements is true? And here you can select all that apply. A: that you miss work or school. B: family stress is common in your life. C: others don't know what it's like to be affected with C3G, and D: I cannot participate in sports or other physical activities I enjoy. So, select all that apply.

So, it looks like many of you have stated that others don't know what it's like to be affected by C3G. Many of you cannot participate in sports or other physical activities that you enjoy and also miss work and school, and perhaps less of you experience family stress that's common in your life.

So, thank you for participating in our polling questions. You've now heard from the panel, some of their experiences and their story with living with C3G. You've also now responded to some questions, hopefully that's gotten you thinking a little bit about your own experiences and now we'd like to explore with you all more, in some more detail, about your experiences living with C3G. So, on display up here are our topic questions for our session now, which are the same ones that the panelists were asked to respond to. As you'll see, a lot of these relate to the polling questions you answered as well. So, as we move forward into the discussion, look over these questions and think about those things in your experience that really relate to the most burdensome

impacts on your life. What are the symptoms of C3G that is most impactful? Why is it most impactful? How does it impact activities or other things that are important to you? We're also interested in knowing not just necessarily what is the case right now, but how have your symptoms changed over time. Do your most burdensome symptoms wax and wane day-to-day and can you tell us about that, and how has it changed over time, perhaps as your disease has progressed? Then ultimately, what really worries you the most about your disease, given your experience, with symptoms and burdens of it? You've all started to give us some input.

I'd like to open it up first to anyone in the audience that maybe had something different that was a top burden to them that they either mentioned that they responded to "other" on one of the polling questions, or maybe you didn't really hear from the panel, or maybe your experience is a little different from the panel on what burdens you most.

Just raise your hand. I'll call on you, and you can say your name. Just to speak, all you'll have to do is hit the talk button on the mic. The little red light will light up, and then once you're finished, you can hit the button and the mic will turn off. Do we have any volunteers to get our discussion kicked off today?

I know it's the morning, we've got to get warmed up. Hopefully you've all had your coffee to get going. I'm sure some of you have had different experiences than others, that we've talked about so far, but maybe it's easier to start with stuff that we've already started to explore.

I'm really interested to know, and I think FDA wants to know, what are commonalities also that are experienced by patients within the patient community? We have a sample of five up here, but we really also want to know what really are the most common significant burdens of the disease, and then those that maybe aren't as common? If you have those experiences, how maybe even if you have the same symptom, they impact you differently? Would anyone like to share their top tough symptoms? Yes.

Chris: I'll speak a little bit. I'm a little nervous. I got diagnosed as-

Moderator: Start with your name.

Chris: My name's Chris.

Moderator: Thanks Chris.

Chris: All right. A little nervous. I was diagnosed this disease when I was seven, so it took about 10 years for my disease to fail. That's the range I guess. I've been through kidney failure three times in my life. Each time you go through the same process. It happens slowly. Swelling, like the question stated, isolation, everything like that. I have a bad pride issue, so I don't really talk about feelings or anything. I kind of keep everything to myself.

I don't talk about anything with my friends or anything like that, but you don't really get the full spectrum until you've been transplanted. It's like night and day. You go through failure. Dialysis isn't so bad because you get some of your life back. The swelling goes away for the most part. You can eat better. But it's still very negative. You don't feel the same. You can't think the same, a constant reminder.

You're always going to worry about it. It's always going to be on your mind. You're always thinking. You can't really plan for the future as well as you want. You don't know where you're going to be next year, you know? It's a constant stress almost. But I try to block it out and enjoy the moment. It's the best thing you can do, I guess.

It's tough, so a lot of hospital visits and stuff like that. Right now, I'm being, I guess that's the second part, but I'm being treated with eculizumab. I guess I'll save that for the next part. They did a very good job up there, kind of going into detail on each range of where the disease affects you.

Moderator: Thank you, Chris. You mentioned that as you were progressing, before you needed to do dialysis perhaps, that you said that once you went on dialysis you got your life back. What were the things that you had lost leading up to that point that you're referring to there?

Chris: When I went on- before my first transplant, I was only on dialysis for like a month and a half because I had a cousin that was giving me the transplant. I was in high school, and before the transplant you get really tired, you're swelling, you don't want to be seen with puffy eyes and stuff like that. You're tired a lot so you're not- I'd go home and sleep a lot.

Then you go on dialysis, and I don't really remember that range of dialysis, but then transplant, it's like night and day. You get your energy back, you get color in your face, you're out, you're doing stuff, you have a life again, basically. Then, slowly the disease, I have recurrence of it just slowly. The disease takes effect again, and because it's gradual, that's what you don't realize.

It's gradual so you slowly get tired. Then your transplant, you get your life back like I keep saying. It's the same thing. Second time around, I let it go a little- I'd get a little worse. I walked around like 155, 160 pounds. I was 210 pounds before I went on dialysis because I dreaded hemodialysis. I didn't want to get the catheter. I didn't want to get a fistula.

I was supposed to get a transplant, but it fell through, so I had to go on dialysis. Before that, I was lying in bed all day just sleeping. Like I said, I had like 50 pounds of edema on me. Just constantly tired, cold. The only times I'd get out of bed was to go to the doctor basically, and go downstairs to eat. I'd watch a lot of TV. It kind of takes your life away.

I was working with swollen ankles. I think I was working at like 185, just walking around at like 30 pounds on me. You're just tired. When I got back from work, I was trying to fix the house, and like my ankles were the size of my thigh right now. It was kind of tough. Then you go on dialysis, and you get some of your life back. The swelling's off of you, you can eat better, you're able to go out and enjoy life a little bit.

Then you just don't realize that even that is not that good, you know? It's not good at all compared to a transplant, or compared to healthy kidneys. If you just get the stability in your life, that's what I want, just some stability. Just to know that maybe it'll hinder for like five, ten years or something like that. I could just plan a little bit better. Something like that.

Moderator: Yeah, that's useful to know. Thank you. Thank you for letting me dig in a little bit with you. I know it's-

Chris: That's okay.

Moderator: We heard in the presentation this morning that about 50% of you will have end-stage renal disease in a 10-year period, so like Chris was just explaining his progression, would anyone else like to kind of describe to us their progression, how either quick or gradual it was, and what it was that you experienced, what symptoms, and maybe things that you lost in your life as you led up to that point of end-stage renal disease? Would anyone else like to share on that topic? No? It's okay.

We'll have plenty of time to circle around to a lot of the same topics that we've been talking about. I'd also like to hear from individuals that maybe have not yet experienced end-stage renal disease, maybe a little earlier in their progression. I'd like to hear what

really has been impacting you?

Martin: Okay, my name is Martin, caregiver for Lucille. Lucy here is usually not very shy. She likes to be the center of attention, but she decided not to speak at the moment. She was also diagnosed at age seven. She's 11 now, and has not experienced a whole lot of symptoms from C3GN. She had a lot of immune system issues, which is what led us to this. A lot of illness, a lot of infection as we've heard some of the other stories, so there is some commonality there.

One of the hardest things that I had to do as a parent is say to our physicians that the biggest impact on her life, up to that point, was the amount of time she was spending in hospitals. I noticed this because some of my friends, and some of my co-workers were familiar with what we were dealing with, and every time I saw them they said, "How is Lucy?" My answer was always, "She's fine."

But I was taking time off work every couple of weeks to take her to the hospital to have blood drawn, to subject- at the beginning, there's a little stick, no big deal. Towards the end it became an all-out- like literally her holding onto things, and crying, and us having to pull her just to get a blood draw because it had happened so many times.

I finally said I know this disease progresses. Some of the stories we've heard, we know what's going to happen, but right now she's healthy, and the biggest impact that is happening to her is us bringing her in to not be treated, to simply be monitored. It was really hard for me as a parent to say, "I'm going to pull back from that. We're going to dip her urine at home. We'll bring her in twice a year, but we're not coming here."

We're lucky just geographically, we're very close to actually multiple wonderful children's hospitals. We're not looking at five-hour drives. We're looking at one-hour drives. But I had to pull back because she was not having a high quality of life, and she was not being treated at the time because there was no treatment that was better than the symptoms.

So, that's why this venue was so important to us to come, is because if there is a chance at a real treatment that's not going to have her in hospitals for infusions all the time and things like that, then we're going to jump all over that, but for now, to simply slow the progression of something that we don't have a crystal ball, every story's different. We don't know what's going to happen but destroying the quality of life that she does have

right now would not be a good option for us.

Moderator: Yeah. So, you did that balance of whether the blood treatment options were available outweighed what symptoms were there. Can you explain a little bit what Lucy's symptoms have been before?

Martin: Illness, after illness, after illness, mostly minor, mostly what would be considered typical childhood illnesses, but just beyond- if there's a range of normal from healthy kid to sickly kid, she was not in that range. She was way past that range. Denial by pediatricians that there was a problem until we finally found one who just on the off chance, no visible blood in the urine, but dipped and found blood in the urine and found protein in the urine, then did a blood draw, found no C3, no C4. The C4 started to come back up. We assumed this was because of her latest bout of strep, but she had had strep three or four times in the last, what, year, couple of months, but the C3 never came back up, and that's when the initial- you're going to CHOP or Dupont. Pick one.

Moderator: Yeah, yeah, yeah.

Martin: Like I said, we're lucky that we had a choice of either. When they initially did do the biopsy and diagnosed, started her on the prednisone, didn't seem to help- the weight gain, some of the other side effects, the knowledge of the long-term hit with the bone development and things like that. Pulled her off that, had her on an ARB as well. That seemed to help a lot, but if she forgets a dose, almost immediately massive headaches, and other things that we're always worried about, so a lot of the symptoms that she's had up till now were immune system related, and that's why treatments that target shutting down part of the immune system are a concern to me.

Moderator: Yeah. Okay. That makes sense. Thank you, Martin. Lucy, if you choose to talk at any point, just raise your hand. I'll be happy to call on you. A comment up here in the front.

Lindsey: Hi. I'm Lindsey. I wanted to talk a little bit, kind of follow up on Martin, because I was really glad that he explained a little bit of what Lucy had experienced because I feel like those immune system issues are something that really get bypassed a lot and don't necessarily get the attention that they need, and I don't know if that's just because not every patient experiences it, or if we just don't understand the connection well enough yet, but I too experienced chronic infections from a young age, and early in my life the kidney symptoms, the renal symptoms, were very minimal, and so were mostly ignored.

The immune system issues, I was hospitalized for life threatening infections, and it took until I was 33 before that connection started to be made. And I had all those red flags all those years, but nobody put the pieces together, and I feel like a lot of patients probably have those experiences, but they don't get connected, and so they get left out, and so the patients who are coming after us go through the same thing over and over, all those unexpected parts of our disease that aren't recognized. You feel like you go through it alone and that there's no help for it, and you don't get treated for it properly because it's not all being connected together.

Moderator: So, for your experience, Lindsey, you said it was essentially a chronic experience, but how frequent does that mean? In your words, how frequently were you having infections? How often did they result in hospitalization?

Lindsey: Right. I had all types of chronic infections. I had strep infections, ear infections, UTIs, yeast infections from a very young age, upper respiratory, lower respiratory. If there was anything for me to get, I was going to get it. I was sick all the time. I missed a lot of school. I had to have tutors because I couldn't go to school because I would just get sick over and over and over. It got better as I got older, but yeah, I was hospitalized for a week when I was eight for pneumonia, for 10 days when I was 10 for osteomyelitis. I had surgery three times before I was five for chronic infections, so it was spaced far enough apart, and I would have trouble with one type of infection for a while, and then that would start to resolve, and then it would be a new thing, and it was just always something new.

Moderator: Yeah. So, could I see a show of hands from patients and caregivers for your loved ones that- how many of you have experienced these chronic illnesses? Let's see. I see some hands up in the front. I see it looks like about maybe six or seven of you in the audience, and maybe three of you up on the panel, so yeah, thank you both of you for sharing about this. Oh, Shannon, do you want to add?

Shannon: Yes, I do. I'm going to follow up on what Lindsey said, too. I think part of it is that the physicians aren't connecting it to C3G, but it's also that when you approach them about it that they don't think it's directly related because it's kidney disease. I think they relate it to just any normal patient that has kidney disease because it was acute renal failure, or it was from being diabetic, but with this disease it's not the same, so I hope that they can start looking at it like that and kind of relating these other symptoms with the disease process, too.

Moderator: Yeah. Okay. Yep, right here in the front?

Matthew: I'm Matthew. I'll just add on to my wife. Our daughter, she went through, as she said, the constant looks of UTI, never actually having UTI. There were other things that she was constantly- sore throats, always do a swab, never end up with strep or anything like that. We had her tonsils taken out before she was diagnosed. I'll get emotional, so I'm sorry.

Moderator: That's okay, Matthew.

Matthew: It's little things. It's like going from a normal, healthy kid to all of a sudden having a rash because she was playing in grass, never had any symptoms before. It's just random, just comes out of nowhere.

Moderator: Sure.

Matthew: We're lucky because she's extremely healthy, but it's little things like she's said- what's going to happen when she gets older, so that's all I really have.

Moderator: Thank you. Before we move off of this topic, does anyone have any other experiences to share related to the chronic illnesses? No? Okay. We can talk about other symptoms as well. You can share whatever you'd like, but for the rest of the audience, think about some of these. I know we talked- most of you mentioned tiredness and fatigue for example as a top burden. I'd like to explore a little bit with you about what that means for you, as well as some of the other top symptoms like edema and gout, but Mimi, if you have something to share on this topic, feel free to jump in.

Mimi: Just very briefly, and I will be atypically brief, to follow on what some of the caregivers are saying and something I think that is often overlooked with a disease like this: you have the patient, in the case of the parents who are talking- you have your child, who is diagnosed with this scary, mysterious, life-threatening disease, and the child has the disease. The child has all of the things that go along with the disease, but the family also gets all these things that go along with the disease. I'm listening to parents who are crying, and I've been there.

The anxiety is spread throughout an entire family. Siblings are affected too. I look at this gentleman and I can't see- Dave's children are watching him go through what he's going through. That affects the kids emotionally. Brothers and sisters are shorted a lot of their parents' time because their parents have to spend so much time dealing with

the problems that come along with this disease. It's the patient who's affected, it's the caregiver who's affected. It's every sibling in the family who is affected as well. Really, it spreads out beyond just the physical symptoms that people experience and goes with the whole family life, the family experience, family interactions and so forth.

I think that sometimes gets overlooked, but over the long term in a family, it can be pretty important.

Moderator: If you don't mind, is there a particular experience or example of that that you've experienced in your family that you'd be willing to share?

Mimi: From the time Laura was diagnosed when life suddenly revolved around her diet, keeping her properly nourished and healthy, we used to visit my parents in Chicago frequently until my father died and then my mother. We used to visit John's family. Most of his family lives in Indiana. Laura hasn't been into Indiana since she was diagnosed. Our son Ed has been once. The relationships that we're developing with cousins were pretty much cut off. We were afraid to travel. We were afraid to make plans. We were afraid to do much of anything. Things like that- then you look back on it and think, "Oh my goodness, an entire part of our life was just basically erased because something else had to be the focus."

It was very important, but other things had to drop off. And those things that you drop off while you're focusing on dealing with the effects of this disease are sometimes very important things.

Moderator: You're referring to the burden of the treatment or the unpredictability of the symptom onset?

Mimi: The unpredictability, the day-to-day in caregiving, the doctor's visits which means you have to plan to not do other things because you have to do all these things. With Laura, it was pretty minimal. I listen to other people and with her it was pretty minimal, but I'm listening to a lot of people who are talking. This is taking up big, big piece of life if there are other kids in the family. That's attention those other kids aren't getting. It's affecting those other kids whether we recognize it or not.

Moderator: Thank you very much. Would anyone else like to share some of their top symptoms that have burdened them? Again, I specifically have some interest in exploring maybe how fatigue or tiredness maybe varies amongst you. We heard some experience of that from

our panel. I know a lot of you experienced it from our polling question as being most burdensome. I'd like to get a sense of how that looks in your day-to-day life. At some points, we heard that might mean not getting up out of bed all day. Maybe that's not always the case. It may change even for you from day-to-day. Some experiences with this?

Nate: Hi, my name is Nate from Milwaukee. I was diagnosed when I was around my 19th birthday. My transplant the day after my 22nd birthday. So, I was kind of dealing with that for about three years. My experiences with fatigue that I had were I would be at work. I would go to take a break, maybe just drive around for a little bit and I would have on a few occasions were my coworkers would come out and find me sleeping in my car- not because I didn't get a good night's sleep, just because everything I did made me tired.

Sometimes the same day, I would drive home. It would be late at night, and my parents would find me sleeping in my car as well. The fatigue was a huge problem when I went through symptoms of C3G. Like I said, I had the transplant about two and a half years ago. Like he mentioned before, it's night and day. I was told my eyes were sunk in. I had been losing a lot of weight, but I couldn't tell because that was just normal for me. Right after I had the transplant, everybody could tell that it was a huge difference. I could tell as well.

Moderator: That's fabulous to hear. With the fatigue, you felt this constant feeling of tiredness and then occasionally you'd just need to sleep?

Nate: I couldn't- my eyes just wouldn't stay open.

Moderator: Did those little naps if you want to call them that, did that help with the fatigue?

Nate: Not really. It's just what I needed to do at the time.

Moderator: Thank you. Do others have experience with fatigue or feelings of tiredness? Maybe in that case it wasn't related to the ability to sleep, but maybe you have had issues sleeping and that might cause tiredness?

Sarah: Hi, I'm Sarah Bernhard. I'm Drew Bernhard's mother. He was diagnosed when he was 16.

Drew: 17.

Sarah: 17. He'll interrupt me when I'm wrong about stuff, which is fine. I hear all these stories. We're very blessed that he didn't struggle with the chronic illnesses. We also live in Cedar Rapids, Iowa so we're 25 minutes from Dr. Nester and University of Iowa which I think plays a huge role. I know that you guys talked, Shannon, you talked about the availability of physicians who are aware of the disease, understand the treatment of it and medication. That's huge. It hurts my heart that you have to travel so far and the burden it puts on your family.

Speaking of fatigue, I didn't realize how much it impacted him until he had his transplant last year.

Moderator: Take your time, Sarah.

Sarah: He's going to kill me. He had his transplant April 7th of 2016. Like you mentioned, it's night and day. I didn't realize how sick he was because he slept all the time. You think, "He's 25 now." You think- no disrespect, young men, but they work, they sleep, they eat. You know what I mean? Repeat. You just kind of assumed that was a typical lifestyle. He only had to do dialysis for a few weeks. That was more preparation for transplant. But in the last year, definitely you see a difference. That fatigue is overwhelming because living it, I think it just becomes their normal. As caregivers, we watch it and it becomes our normal. Then when you see them healthy, you're like, "Wow."

Moderator: What does that healthy look like compared to the coming home from work, sleep?

Drew: Same as it does now?

Sarah: He's moved out, living independently, coaching football, working, doing the things that he loves. Does he still probably sleep a lot, probably.

Just happier. I know Monica and Dr. Nester can probably attest to just knowing Drew for the last eight years, just a difference in what that lack of fatigue and being healthy looks like.

Moderator: Did that fatigue, was it all prior before it got- I guess you were describing it as all encompassing. Was it always that way? Did that fatigue increase as he got older?

Sarah: I think it increased as he got older. Do you? I'm going to be honest. It was hard. When he was first diagnosed, it was one of those unknown. Nobody knew a lot. We didn't have

anything to compare it to. I would say definitely as his disease progressed, he did have swelling, but not to the degrees that a lot of people are discussing. But it definitely, I would say, within the last few years prior to his transplant, the fatigue was definitely more a part of his life than not.

Moderator: Were there any other symptoms that you think really got worse right before transplant?

Sarah: I would say maybe headaches. Swelling?

Drew: I think that's from dialysis. Myself-wise, I think I got more tired once I started dialysis because it takes more out of you. I mean, for the most part, I've been able to do everything else compared to most everybody else here. I've been able to do everything I've wanted since I was diagnosed. I played football, I finished high school, I played two and a half years of football in college. I coached high school football. Now, it's been five years, it's been eight years and two weeks since I've been diagnosed. So, in the eight years it's not like I haven't been able to do everything, including with my younger sister but, you know?

Moderator: Is there any one aspect of the disease that is most burdensome to you? Even if you're still able to do everything you want, is there still something that to you is the key symptom or key problem?

Drew: I've got no control, so, that's about it.

Moderator: Yeah, no control over the progression. Thank you very much. Both of you.

Okay. Anymore thoughts on fatigue or tiredness? If not, I want to ask about the swelling-the edema. I know that came up a good deal on our panel discussion. Again, a number of you mentioned it in the polling. I'd be interested to know the frequency and what you experience the swelling. How severe it is and how that might impact you. I know it can vary a lot and even- we want to know the full range so it's important to us even if you don't have extreme swelling that maybe you need to be on bed rest or something like that until it goes down, it's still important to know your experience with that and how it might change over time.

Would anyone like to share experiences with edema or swelling?

Bradley: Brad, I think about six months ago I had a large gout flare up that was combined with swelling in my knees, ankles, all the way up. I cut my slippers to put shoes on to try to

get to work and was unable to get them in after cutting them fully off the sides.

Moderator: Oh wow.

Bradley: Yeah, so, I don't get things too often but that was one that was pretty bad. And again, it's very infrequent so it's weird when it comes in, but it came in very harsh that time.

Moderator: And how infrequent is that?

Bradley: I might have a little bit of swelling every month or every other month maybe just for a few days. But this one was I never had anything like that. But otherwise I have compared swelling to my girlfriend's 80-year-old grandma before, I think I beat her on a few occasions.

Moderator: On the more typical swelling, not this particular instance where having to try to cut the slippers, so the more typical swelling- does that prevent you from doing anything- like can you still put on your shoes and go to work?

Bradley: Yeah, not currently- it's not terrible. So, it's a little hard to get my hand on this for those several reasons but typical day-to-day, it's not affected by the swelling in my ankles.

Moderator: Okay. Yes.

Lindsey: I think the swelling is probably one of the first symptoms that I really noticed and for me it comes and goes. Even now, with treatment and with improved kidney function I still experience the swelling, especially when the weather is really hot. I work in a building with no air conditioning in the fall and I have to choose my footwear carefully because what may fit in the morning may not fit by the time I've been at work for two hours. And the last thing I need is the straps of my sandals cutting into my feet all day.

By the time I get home a lot of times, my ankles are so swollen that I can't bend them, so it becomes very painful to try and walk. It's very difficult to walk when you can't bend your ankles so you just kind of hobble around. And then for me personally a lot of times I put my feet up, and by morning, a lot of times it's better and then just start all over again on a new day.

Moderator: So, it's pretty much a daily symptom?

Lindsey: For me now, depending on the weather, it just depends. But I did experience it very

regularly when my kidney function was less.

Moderator: Sure. Any other?

Yes, Tori, thank you.

Tori: Obviously, Tori. I think I touched a little bit when I spoke on it, but whereas everyone else seems to only have it sporadically, mine is every day. If I don't personally bring additional clothing for myself, my husband keeps an additional pair for me to bring to me because what I wear in the morning will not fit half-way through my day. I can't walk. When I wake up in the morning- this year has been horrible, so I do a lot of crying normally. I can't open my eyes in the morning because my face is so swollen.

They're having to, we're discussing upping my Lasix now, which is my water pill because I just can't fit in anything. And it's not just because of the prednisone, because the prednisone, I think we all know, makes you gain a lot of weight, makes you really hungry. But, just the excessive swelling, it's hard getting in and out of the chair and it's 11:00 in the morning, for me I mean, that's 10, but I feel like that shouldn't be happening. It's crippling at some points because you can't move, and it keeps you from doing your job. It keeps you from just, like I can't go to the grocery store. I have to send my husband with a list and he thinks, "Oh, they don't have this. I'll just get this, this is okay."

Moderator: You were kind of describing your usual experience. Are there days where it's even worse than that? You said you can fit in one thing in the morning and then you have to change by the afternoon. Are there days where the whole day- where it's from the time you wake up to the time you go back to bed, where maybe you would be in that second pair of clothes?

Tori: Normally Wednesdays are my worst because I try not to miss work. I don't get very many sick days, I don't get very many days off, so I try to reserve those for if I do get hospitalized, because I never know. But I'll start out at the doctor usually around seven in the morning and go until I have to be at work and by the time I get to work I've got compression socks on, I've already changed pants once. I've kept my pregnancy pants and they have an elastic waistband you just have to- they let you blow out a little bit. I'll keep going until 8:00 at night and sometimes- we have a split-level home and my husband will have to come and get me out of the car and carry me into the house because I physically cannot just climb the stairs.

The laundry, I separate upstairs, he carries down for me and does it and carries it back up, so I can fold it and put it away. I can't do dishes because I can't stand that long. The swelling just pools in your feet and it's to the point where my friends used to say I had cankles and it's just, its-

Moderator: Thank you Tori.

Chris.

Chris: I just wanted to tie everything in. The fatigue, the swelling, the diet. It happens gradually, it doesn't happen all at once, you're not just like swollen one day, it's going to slowly progress and that ties into the instability of the disease, being at the mercy of it. It's just horrible all around. You know that you're slowly going to get worse. It's going to lead to dialysis. Maybe get prolonged kidney function out of it, I guess we can talk about that next.

Moderator: Thank you. Comment here in the back.

Holly: He'll kill me for this as well. But just in the different aspects of the disease and what he was saying, he had the opposite experience and that he feels guilty for being here, for doing well, but he had a year from hell. They assumed for a couple of years that he had blood in his urine when he was sick. He ended up finishing his finals at college real sick but determined to finish. Came home and they said he had the flu. Ended up for two weeks in the hospital, creatinine of 12, emergency dialysis, all kinds of testing. His doctor there even said, "I'm familiar with it but if you can find somebody better, go ahead." All kinds of viruses, treatments, etc. etc. Came home and dealt with the horrible effects of prednisone.

In September, ended up in the hospital with Bell's Palsy and a spinal tap and an MRI and different things. In January, ended up in the hospital again with a strep and a different type of virus. This is all on a 19-year-old boy. He feels guilty for doing okay but in contrast he had a year of hell. Just the point of being that, how it can happen over many years, it can hit you like a brick wall in a year, but it is very different and there are many different aspects of how it can really get to you.

Moderator: What was Justin's experience leading up to that year from hell? [inaudible].

Justin: Well it was like you said, it was the end of my freshman year of college but probably

about half-way through my senior year of high school I started seeing blood in my urine. I went to a nephrologist and they said, "Well, I don't know." They thought I'm not sick and nothing was wrong, but they'd just keep an eye on it. I went every- I don't know- six months maybe just a couple of times. But then during finals week about a year and a half later I got real sick. I figure it's my first year I'm just stressed. It's college, you know, freaking out but I got home and when I went to the doctor they said, "You have the flu really bad, nothing we could do just go home and ride it out." I figure, all right this is going to suck for a few days, but I'll be all right, but then it just got worse and worse.

The next day my dad looked at me and he was like, "Yeah, we should probably go to the hospital." Then they told me your kidneys are shutting down. We were like, what, where did that come from? I mean she could probably tell you a lot more about my hospital stay because I don't really remember too much. At the end of it I thought I spent two days in the ICU, but I really was there for five. Fluid in my lungs, I had the mask on and everything, but we had no idea. I couldn't have seen this coming. It just hit us like a wall.

Moderator: Yeah and after that year from hell, how have the things, have they gone back to the way it was before?

Justin: Yeah, pretty much. I see Dr. Bombback about every six months. Every time I go it's always, "Oh, your levels are looking good. You're all right." There, everyone's surprised that I'm doing as well as I have been. I haven't had a problem since. Like she said, I've been in the hospital a few times during that year but other than that, I've been fine. Every time I get sick my urine might get a little dark, but I drink a lot of water and it goes back to normal and then I'm fine. I really haven't experienced too many problems with it so far but I'm always tired, so I mean that's probably just from me being a young man who- but so far, I've been all right.

Moderator: Okay. Thank you for sharing that. This is important to know the differences and the experiences. We've heard quite a range of them already today. I think we're about at the end of our time.

PANEL #2 DISCUSSION ON TOPIC 2

Current Challenges to Treating C3G.

Moderator: We are now shifting to the second part of our conversation today, which is about current approaches to treating your C3G. Our panel that we have assembled for you are going to be exploring topics of what they are doing to treat their C3G as well as how well those treatments are actually impacting their symptoms and other impacts of the disease on their life. They're going to tell us a little bit about their biggest downsides with treatments as well as what they might be looking for from an ideal treatment. After our panel, we'll then broaden the discussion again with more polling questions and audience discussion. Without further ado, I'll introduce our panel. We have Ned, George, Allison, Bradley, Mimi, and Lindsey. Ned, take it away.

Ned: Okay. My name is Ned. I am a 27-year-old that lives in Wayne, New Jersey. I was diagnosed with C3 glomerulonephritis at 13 years old. At 20 years old I had my first kidney transplant, which I had received from my mother. After seven years the C3G reoccurred in my new kidney and quickly led to kidney failure. The disease was very aggressive and within one year I had end stage renal disease. Last January, I started dialysis treatment and I am waiting for my second transplant. Before I started dialysis, I had extremely low hemoglobin levels, which were eventually corrected after treatment with Epogen. To control my hypertension, I am taking three blood pressure medications amlodipine, losartan, and labetalol.

After my first transplant in 2010 I was placed on immunosuppressant drugs, mycophenolate, and Prograf. After my donor kidney failed my doctor wanted me to continue these drugs. I needed to stay on the immunosuppressant drugs to prepare me for my next transplant, which will hopefully take place next month. Before my first transplant I was on drugs that treated symptoms of my kidney disease. In order to attempt to bring my disease to remission I was placed on steroid and rituximab therapy. Unfortunately, I was unresponsive to these medications and they only caused further damage to my kidneys. My doctors had tried to treat my symptoms in order to slow down the progress of my disease.

In 2010, I received my first kidney from my mother. After my first transplant, the C3G

returned into my kidney only after a few weeks. At the time, my doctors placed me on the experimental anticomplement therapy eculizumab, which preserved my kidney function for seven years. After seven years of my disease being under control, it eventually became aggressive and led me to kidney failure within one year. My current treatment is dialysis three times a week. This helps keep my blood clean from toxins. When I first started dialysis six months ago it was very difficult and time consuming. I am taking blood pressure medicines that I take to control my hypertension and relieve me from constant headaches.

Due to my non-functioning kidneys I retain water in my body that causes me swelling and discomfort. The swelling causes pain in my legs and ankles and prevents me from enjoying my favorite outdoor activities such as soccer and volleyball. To treat the swelling I take a water pill diuretic, which most of the time is not very effective. To control dangerous levels of phosphorous and potassium I must be on a special diet and take two to three phosphorous binder pills with every single meal.

Dialysis is not an ideal treatment for kidney failure. Although it does keep you alive, it lowers your quality of life. I no longer have energy to play sports that I used to enjoy. Even long walks feel strenuous on my body. I currently have a dialysis catheter that is in my chest. This interferes with certain activities such as swimming and even something as simple as showering. I must be careful not to get the catheter wet because it could cause infections. My symptoms that are hardest to treat are swelling and cramping. The most effective way to control the symptoms is to manage fluid intake and being on the kidney friendly diet. If the diet is not followed it can lead to swelling and cramping that could last for a few days.

Another downside to my disease is the restrictive diet and controlling phosphorous and potassium levels. Anytime I eat something I must take my phosphorous binders to keep my levels at a normal range. This diet regime restricts me from enjoying foods that I enjoy. My only chance for a normal life is to receive a kidney transplant. Assuming there's no cure for my disease the best treatment for my disease would be a medication that slows down the progress. For now, the best treatment options would be improvement in proteinuria, edema, and hypertension. If these symptoms are controlled, it will lead to the overall slowing down of kidney disease progression. Thank you.

George: My name is George and I'm a 63-year-old retiree. My kidney condition spans a bit over

30 years. I was diagnosed with MPGN in the Spring of 1987 after a biopsy. They pretty much told me I had five or six years until kidney failure, and my first indications would be high blood pressure. Right on cue, in 1993, my blood pressure became an issue and has continued for the past 25 years. No added salt diet and meds had done pretty well until the last five years.

We've been trying different drugs and combinations. I've taken enalapril, hydrochlorothiazide, and lisinopril. Currently I'm taking furosemide, amlodipine, and minoxidil. In the early '90s, my doctor had me try a high dose of prednisone and that really lit me up. I think there was a week or so that I could only get 20 minutes of sleep a day. I took vacation time from work since I was in a safety-related job. In December of 2013, we tried CellCept/MMF that I reacted badly to. I wasted away and quit weighing myself when I saw 137 pounds on the scale. I was very dehydrated and so they gave me IVs and fluid to rehydrate me. I got some better and then they tried Myfortic/CellCept, only to have the same effect.

I was weary, trembling, cold, and shaking. Thankfully I was near enough to retirement age, early retirement age, so I could retire. I couldn't do my job in the condition I was in. In April 2014, in preparation for eculizumab, I had a meningococcal vaccine of Menactra and a booster. I started infusions of eculizumab for about six months of every other week. From home to check-in desk would take about 45 minutes. With labs, drug delivery, infusions, and observation, it could be another three hours.

It seemed to stabilize my decline. I then had my third biopsy. Insurance and expense were an issue with this drug, since my retirement insurance was capped. I'm going through my primary insurance. It chewed up most of my supplement insurance.

About two and a half years ago, I developed gout, and so I've added a suppression dose of allopurinol to my daily drugs. In March of 2016, I had a stroke, so now I'm on a statin. I had started azathioprine four months before my stroke and discontinued it then.

I've also been dealing with anemia the past couple years. I recently started giving myself a shot at home of Procrit to increase red blood cells. I'm taking iron supplements of ferrous sulfate. Started taking calcitriol for my calcium absorption and a large dose of vitamin D2 once a month. My phosphorus was high, so I had to give up most dairy. Currently I'm taking cyclophosphamide, an immune suppression drug that has started in March. My protein spillage is down to 2+. This improvement had my doctor

wondering if this drug is helping, but it's still too early to tell.

My concern with taking this drug is that I'm also taking a suppression dose of acyclovir for Herpes simplex, which develops on my nose and then turns into a Staph infection that has hospitalized me a half dozen times or so. I started having these infections on my nose after my first kidney biopsy in 1987. I have not had to be hospitalized for the infections in about the past eight years. Due to this reduction with my kidneys, I'm taking half the dose of acyclovir. In July, my labs showed more decline as my GFR has now dropped to 12.

Other than low energy, my swelling of especially my ankles, legs, hands, another daily struggle. Fluids tend to need to be relieved an average of every two hours a night, so I don't sleep very much. I end up in my recliner a lot to get my feet up. If I'm on my feet most of the day, it can take a couple of days for my swelling to go down. When I wear my compression socks, my knees puff up so much that I can't bend my legs very far.

Of course, I want a fix to stop my kidney decline. Next best would be a way to tie up unfiltered electrolytes and elements that cause fluid retention for removal. I can't ask for a better way to fight anemia since I'm early in that struggle. Something I'm currently doing might help.

Thanks for your time and consideration.

Allison: My name is Allison and I am from Marquette, Michigan. I am 18 years old and I graduate high school this spring. I'm planning to attend Concordia University Wisconsin this fall for a master's degree in rehabilitative science and occupational therapy.

A year ago, I noticed blood in my urine. My parents thought that it could be just from a menstrual cycle, but I already had it that month. The blood went away in a few days, but came back later in September 2016, when urine and blood tests confirmed high amounts of protein in my urine. Later a biopsy confirmed I had dense deposit disease.

I still remember my local nephrologist, who has practiced for many years, tell us that he has never seen a case of this disease. He then referred me to a team of nephrologists at UW Madison who started me on my current treatment. I received conventional therapy to help treat my symptoms. This means steroids like oral prednisone, which I take with Zantac to help my stomach. I also receive intravenous prednisone known as Solu-Medrol.

I also take lisinopril for blood pressure and I also take atorvastatin since I had borderline high cholesterol, but I may stop this soon since my cholesterol is not an issue now. I also take mycophenolate since my nephrologist eventually wants me to stop prednisone because of its side effects. I also take a vitamin supplement and Tums for calcium, since dense deposit disease can cause weakness in bones and joints.

My treatment started to change this past March when my urinary protein levels were half as much as before. I don't have to take a baby aspirin every day since I no longer am at risk for blood clots. Starting in May, my Solu-Medrol infusion was once every week, but since this past June, I receive it every other week. In December, I started with 80 mg daily of prednisone, and then this spring it was cut back to 60 mg every other day.

Since my last visit this July, I now take 40 mg every other day, since my nephrologist has seen improvement with my overall kidney function and the amount of protein I am peeing out. My treatment has addressed my proteinuria well. My nephrologist says that I respond very well to high doses of prednisone because that is when we notice big reductions in my proteinuria.

The symptoms that are not addressed well are first, water retention, since being on prednisone causes water retention. Another symptom that is not addressed well is being immune-compromised, since I easily get sick, and being sick damages my kidneys and causes me to pee out blood and my proteinuria to rise. Getting sick easily is not only a result from the drugs I take, but from the disease, as well.

Since I was very responsive to high doses of prednisone, it has been hard lately to have huge progress in my proteinuria since I am on a low dose of the steroid. But my nephrologist wants to keep me off those high doses.

The most significant downside to my current treatment would be for one, weight gain. My mom and I have spent over \$100 on new clothing for me since I have gained 25 to 30 pounds since being on prednisone. It also caused me to get stretch marks which make me self-conscious when wearing cute summer clothes, I love to wear. I worry that if other people my age see my stretch marks, they will think that I am pregnant and will judge me. It also gives me a moon face which I got many comments about when I'm working at my part-time job at Wendy's, and it is really hurtful to me since I can't help it, and also makes me no longer thrilled to take pictures with my friends.

Since this weight gain has really hurt my self-esteem, I hired a personal trainer and I go

to the gym a few times a week. But it is frustrating since I haven't really been able to lose any weight. I also don't like how the prednisone makes you really hungry and you never feel full, so that contributes to the weight gain.

Another downside of my treatment is it compromises my immune system. This past March, it seemed like I was sick almost every week. I even tested positive for influenza which I never had got before in my life, since I always get the flu shot every year.

An ideal treatment would not require me to take steroids or have the same bad effects of steroids. I would love a treatment that doesn't make me gain so much weight or doesn't compromise my immune system. I would love to have a treatment that is more affordable, so it would be available and would help patients with this disease be able to live the most normal life possible.

Lastly, I'd love to be able to have kids someday, but I know if I am on these medications, it could cause harm to the unborn baby which would make it hard to have a healthy pregnancy. Thank you.

Bradley: Hi. My name's Bradley. I'm 28 years old and I live in New York City. I've always considered myself extremely lucky, not for having C3G, but for all the opportunities I've been blessed with since the diagnosis nine years ago.

I was part of an experimental trial at Columbia University for eculizumab, which consisted of biweekly infusions and labs done onsite. I showed great results throughout the trial, but seeing my kidney function plummet back to pretrial numbers at the end of the trial, when I no longer received eculizumab, was really the kicker. I realized that if I wanted to keep stable kidney function, I had to make sure to stay on eculizumab.

With the proof that eculizumab was working for me, I was given it again.

I received treatment through Compassionate Care, because while still under my parent's insurance, I was unable to be covered for it. Throughout this process, and with the major success of my treatment, I was able to play college hockey, and I even played in two seasons of Double A Pro Hockey.

While playing hockey, whether it was in college or professional, there was always the constant of every other Monday morning, I would be in the infusion center at Columbia Medical. In an already heavy traveling profession, adding a trip back to Columbia from

either Buffalo or Atlanta became extremely over burdening. I did what anyone else would do in that situation, I moved to New York City and found a real job. As fate would have it, this company covered my insurance claim for eculizumab. Of course, it would not be that easy. Every six months to a year, my insurance company would dispute my claim, and I must file appeals to have it covered again. Multiple times I've missed treatments because of the back and forth with insurance. I've a very stressful job, but nothing compares to the stress I feel when I have to fight for coverage of my drug - and that gives me a normal life.

One of the worst experiences I was faced with the insurance company happened in 2015. I was already set up with at home infusions, but I was contacted by a nurse representing my insurance company. She told me that my treatment was being fulfilled out of network, and that although I met my max out of pocket on my first infusion of the year, I could be four million dollars in debt because of balance billing. She then worked meticulously to help me cancel my current out of network claim and put in a new in network claim. This resulted in the same insurance company that she works for to reject my new claim, causing months of missed treatment. After multiple appeals put in by myself and my doctor and my mother, this denial was eventually overturned, and approval was given for the next six months until the next review cycle.

Currently, my treatment regimen is not too different than it was six and a half years ago, just a lot less travel. Wednesday nights, the pharmacy drops off my drug and medical supplies after eight PM to my apartment. My nurse administers the drug on Friday after work or Saturday morning, it's a smooth operation.

Most of my peers would not even know I have a disease, let alone a biweekly infusion, if it wasn't for the disabling gout I get once a quarter like clockwork. Gout is the most external side effect I have for C3G. Gout causes crystallization of uric acid in joints anywhere from my feet, wrist, to shoulders, but most predominately in my big toes. On multiple occasions, I've gotten it simultaneously in both big toes. I'd like to paint a picture of a 6'5" man grimacing every step walking on the outside of his feet through Times Square Subway Station, trying to make his morning transfer to get to work. It wasn't a pretty picture.

After listening to my other panelists, it's extremely apparent that I'm on the lucky end of the spectrum. My largest symptom of my current treatment is not physical but mental. I feel stuck, handcuffed to exactly what life is now, with the fear of any change

in variables could result in the loss of treatment. As different opportunities present themselves, I'm always constantly having to ask the question, is it worth the risk of losing treatment? The answer is always no. With the current state of insurance and the lack of FDA approval for the only treatment of my disease, I will remain stagnant, timid, unable to take risk and live my life to the full potential.

Again, I do consider myself extremely fortunate. I have the best nephrologist in the world. I have the most tenacious mother, who took it upon herself to knock on every door and become extremely educated on my disease, which I also found out is not just her. It seems like every parent's that way. But the reason I feel the most fortunate is because I don't have a list of symptoms that I need to be fixed. While I'm extremely grateful for eculizumab, the normal life it has given me, what I want most out of a new treatment is to know that I can take a risk in my professional, personal life and still receive treatment.

Mimi: Are we still talking into this?

Moderator: Mm-hmm (affirmative)

Mimi: Hello.

Hi. My name is Mimi, and my daughter, Laura and I are here from Minneapolis, Minnesota. Laura was diagnosed with dense deposit disease at age 11 and received a kidney transplant from her dad at age 15. Laura's treatment before her transplant was primarily supportive because the disease is so rare, and there's just not much available to treat the disease itself. She took medicine to manage blood pressure and anemia, and she followed a strict renal diet. These worked well to address some of the issues with failing kidneys, but they couldn't keep the disease from progressing. Ultimately, all we could do was keep her as active and healthy as possible while we watched her kidneys continue to fail.

Our focus now is on avoiding rejection and keeping Laura's new kidney healthy. She takes two immunosuppressive medicines, Tacrolimus and CellCept, twice a day, the antibacterial Bactrim, to prevent infection due to immunosuppression, and blood pressure medicine. She follows her medications schedule carefully, eats a low sodium diet, and drinks lots of water every day to stay well hydrated. Her kidney is doing well after three and a half years, so the medicines are doing their job, but they don't always play nicely with others. Some side effects are no big deal. Others are a problem. The

Tacro raises Laura's blood pressure, so she takes blood pressure medicine. The blood pressure medicine has caused her gums to swell, which has altered the alignment of her teeth, so she needs to be extra careful about dental hygiene. The CellCept lowers her white blood count, so she takes filgrastim shots twice a week to maintain a safe white blood count. These things are annoying, but we're used to them. They're part of our normal now. They're no big deal.

Other side effects are more difficult. For example, CellCept causes Laura to have frequent, often severe, cold sores around her mouth and nose. They're painful, they're ugly, they bleed, and at one point she had four of these at once. It hurt to eat, to brush her teeth, even to smile. She now has a prescription for Valtrex to take as needed for the cold sores, but she must be careful of taking it too often as the Valtrex itself can be hard on her kidney. It's a constant balancing act.

Laura's early antibacterial post-transplant, dapson, dropped her hemoglobin so much that she was constantly exhausted. For the first eight months after her transplant, she actually had less energy and felt worse than she did even during the weeks before her transplant when her kidney was around or below 12%. Laura's a very active athletic hockey goalie, who played in a tournament, seven days before her transplant surgery, but after her transplant, the dapson-induced anemia left her so tired she'd get winded walking up a flight of stairs.

She went back to playing hockey, but the fatigue was so bad that she was ready to quit hockey. She was ready to quit what she loved most. Even with a well-functioning new kidney, the constant fatigue was causing her to become depressed. It was really scary. John and I wondered just what it was we had agreed to for our child. Was this transplant a good idea?

The prescribing doctors don't always understand these side effects or what they can do to a person's life. It took a visit with a hematologist to pinpoint the problem and get Laura's medicine changed from dapson to Bactrim, and for us to see our happy, energetic daughter re-emerge.

We've been really lucky so far. Laura's new kidney has functioned well. Her body hasn't rejected it, and so far, the disease itself has stayed quiet. We also know this could all change tomorrow. My family's greatest hope is that new treatments will be suitable for patients who have had transplants, as well as those who have not.

People who have had or who will need transplants will need to protect their kidneys from this disease, so an ideal treatment would be compatible with the medicines transplant patients take to maintain their kidneys, would slow down disease progression long enough to make the medicine and the side effects worthwhile, and would have manageable side effects that don't cause too much damage to the rest of the patient's body. A kidney transplant is a wonderful, remarkable gift, but transplant surgery, followed by the strict lab and clinic and medications schedule, is a lot to go through if the patient is ultimately just buying some time before the disease takes out the kidney again.

On the other hand, we know that treatment for this autoimmune disease was probably going to target the immune system in some way. For patients with transplanted kidneys this presents the problem of layering immuno-suppressive treatments on top of each other. The big question for transplant family is, or transplant patient is, would a treatment, even if effective, create too many problems for someone already taking immunosuppressive medicines with their side effects and the increased susceptibility to infection? Would the person's life be better or worse than if the person just proceeded to kidney failure and dialysis?

We desperately want Laura to have a well-functioning kidney and the normal, happy life it gives her, but above all, we want her alive and feeling well enough to really participate in and enjoy her life. If a treatment for this disease could work for patients both with and without transplants, that would be a true miracle.

Lindsey: Thank you.

Good morning, my name is Lindsey. I am sixth grade teacher from Blue Mound, Illinois, and I am 37 years old. I was diagnosed with C3GN almost five years ago. My experience with this disease is unique because my C3G is hereditary.

I am a patient, but I was also the child of a patient. And I am the parent of a patient. I've lived intimately with this disease my entire life. I am currently on eculizumab to treat my C3G. I began this drug a year and a half ago after spending two years convincing my doctors and my insurance company to let me try it.

I also receive iron infusions and take several prescribed supplements due to nutritional deficiencies. I take Avapro to control blood pressure and proteinuria, allopurinol for gout, wear a fentanyl patch to control chronic pain, and require a daily antihistamine

year-round due to hard to control allergies. Some of these medications treat typical complications of kidney disease. Others treat symptoms from higher-than-normal inflammatory and histamine responses that are believed to be related to my complement dysfunction. These medications do give me some relief, but it is minimal.

For most of my life, because I was undiagnosed or incorrectly diagnosed, I was prescribed a series of drugs aimed at controlling my misunderstood C3G-related symptoms. I experience a great deal of inflammation, so I was given high doses of NSAIDs despite my renal symptoms and an alarming family history of renal failure. I took immunosuppressants due to a misdiagnosis of lupus. I was given antidepressants, nerve medications, and high doses of diuretics in an attempt to manage various symptoms. None of these medications were very effective, and most had unpleasant side effects. My renal symptoms were never treated at all.

Eculizumab has been a successful treatment for me. Before beginning this treatment, I had reached stage 4 kidney failure with a GFR of 27, and my symptoms made it almost impossible for me to live a normal life. My function has improved to stage 2 with a GFR of 74 and is no longer steadily declining. My inflammation and allergy symptoms have also improved. None of my symptoms have been fully addressed, but I can once again enjoy activities like baking and gardening that had become impossible.

I still have days I wake up with a painfully inflamed joint or tendon, but not every day. I still struggle to keep my fluid and electrolyte levels balanced, but I no longer become so swollen that I can't walk. Taking eculizumab does have drawbacks. It's inconvenient, as it must be given by IV. I travel two and a half hours one way to receive my infusion every other week, missing a half day or work each time. I go to work when I am sick because I must conserve my limited sick days for treatments. My husband must also miss work since I cannot drive home after receiving the medication. My son sometimes has to accompany us on these trips and often needs to complete his homework while sitting in a waiting room.

I typically spend about two hours at the hospital with each treatment, and then have a two and half hour drive home. Between the profound fatigue caused by C3G, the demands of working full-time while fighting chronic illness, and the effects of the medication, I sleep an average of 12 to 14 hours once I arrive home. When I began this treatment, I experienced nausea, headaches, and back pain. Fortunately, these have lessened over time and now occur only occasionally.

One drawback of the treatment is the need for rest after an infusion. I must limit my activity for a few days afterward, or I experience side effects and excessive fatigue that last up to a week. My treatments are scheduled on Fridays to give me time to recover before I return to the demands of my job. Two weekends of every month are off-limits for most activities, which is detrimental to my professional life, family life, and social life.

Despite the limitations and drawbacks of eculizumab, I am profoundly grateful to have access to this medication. Since it is incredibly expensive and is not approved for C3G, it is very difficult to obtain. Despite the drawbacks of eculizumab, any treatment is better than no treatment. Dialysis is not a pleasant way of life, and transplant without treatment is often unsuccessful.

The majority of C3G patients have no effective treatment to prevent kidney failure. We have no way to avoid a lifetime of dependency on a dialysis machine or a series of failed transplants. We need timely, effective treatment to preserve the function of both native and transplanted kidneys. My ideal treatment would not only protect my kidney function, but would also relieve the fatigue and inflammation that are so destructive to my body. But when you have no treatment options at all, ideals become negotiable. C3G patients need effective treatment that we can obtain, and we need a variety of treatment options to fit our diverse patient population. In our current situation, that is the ideal. Thank you.

Moderator: Thank you all for sharing what ... [audio stopped momentarily]

So now we're going to move into our polling questions for the second topic, which is Current Challenges to Treating C3G. So, if you can get your phones out, and those of you on the web go to the first polling question. The first question is, "How well does your current treatment reduce the most significant symptoms of your disease?" Select either A: very well; B: moderately well; C: poorly or not at all; or D:) I do not currently take any treatments.

The question is about how well does your current treatment reduce the most significant symptoms.

All right, so it looks like responses have stopped trickling in. Looks like about half of you have said that your current treatments address your symptoms moderately well. So, we'll explore a little bit what moderately well means to you. It looks like a little under a third of you say that your current treatments reduce your significant burdens to a

degree where you consider it very well reduced. Only 14 percent of you said that this doesn't- your current treatments address your symptoms poorly or not at all, and then there's a small number of you that do not currently take any treatments.

Our second question for you- there's a lot of options here, and it's a select all that apply, so I'll read through it and give you a chance to think about it. "Which symptoms do you have that are not addressed fully by your current medications?" So which symptoms do you have that are not addressed fully? A: swelling; B: being tired, exhausted, or fatigued; C: anxiety and/or depression; D: headaches; E: not being able to concentrate or think clearly; F: gastrointestinal problems; G: weight gain; H: altered appetite; I: insomnia; J: your kidney function, for example, your eGFR; K: proteinuria or protein in your urine.

Please select all that in which your symptoms are not adequately addressed by current medications. I'll give you a few more moments to get in. I know there's a lot of responses here.

So, it looks like our top symptom that you have that's not well-addressed is being tired, exhausted, or fatigued, followed by anxiety and/or depression. After that, we've got a lot that are of similar degree of not being well-addressed including swelling, headaches, not being able to concentrate or think clearly, weight gain, altered appetite and insomnia. And it looks like maybe to a little bit of a lesser degree your proteinuria, gastrointestinal problems, and kidney function are symptoms that are- maybe only a few of you do not have them well-addressed.

Our third question is, "Is the side effect profile of a new drug", or, "If the side effect profile of a new drug was more severe than you currently experience with your treatments, but you thought the drug would significantly slow the progression of your disease and/or improve your quality of life, how likely would you be to take this drug?" A: I would never take it. B: not sure. I might take it. Or C: I would absolutely take it. Again, this is if the side effect profile of a new drug was more severe than what you currently experienced with your treatments, but you thought it would significantly slow the progression of your disease or improve your quality of life, how likely would you be to take that drug? All right. I'll give you a few more moments to get in your responses.

It looks like it's a pretty close 50/50 split. Slightly more of you would absolutely take it, and then slightly less than half of you are not sure- you might take. I guess that might depend a little bit on the exact benefit-risk profile of that particular product. And then none of you said that you would never take it. Okay. So now we have another question

for you about deciding to select a course of treatment. "Select up to three factors that are the most important to you when deciding to select a course of treatment." A: whether the treatment is taken by mouth, by IV, or as an injection in the muscle. B: how often you have to take the treatment. C: evidence in C3G patients that the drug improves specific symptoms most bothersome to you. D: the number of side effects known for the drug. E: the severity of side effects of the drug. Or F: cost and whether it would be covered by insurance. So, pick your top three factors that are most important to you when deciding to select a course of treatment. I'll give you a couple more minutes.

It looks like some responses are still coming in. All right. So, it looks like the top factor for you all is the cost and whether it's covered by insurance. It would make sense that access would be a first line consideration. After that, the next highest factor for you for deciding to select a course of treatment is the severity of the side effects. I think we've already started to hear a bit about the severity of current treatment side effects. So, I would be interesting to also hear the audience's views on what severity of side effects would be important to you. After that, it looks like the kind of next tier of factors are the route of administration of the product, evidence that the product improves specific symptoms that are most burdensome to you, followed by how often you have to take it, the number of side effects, and then lastly what your physician recommends.

Our fifth question for you. This relates to participation in clinical trials. So, we'll ask "Which of the following is true regarding a C3G drug. A: I have participated in a clinical trial. B: I attempted to participate in a clinical trial but was unable. For example, you did not meet the eligibility criteria. C: I would be interested in participating in a clinical trial, but I have not attempted to participate. D: I have not considered participating in a trial. Or E: I have considered participating in a clinical trial, but I chose not to do so."

Well, it looks like certainly no one has considered participating but chose not to do so. Meanwhile more than half of you are interested in participating but have not attempted to participate at this point in time. Looks like just under one in five of you have participated in a clinical trial. 15% have not considered participating as of this time. And only a small proportion, 9% have attempted to participate but were unable to.

And our final polling question for you is, "Which one of the outcomes below would be most important to you in a new drug?" So, we give you a series of options here. The first is a drug reverses the decline in kidney function. In other words, it halts the progression

of C3G, but it induces moderate to severe side effects. B: the drug significantly reduces some signs and symptoms of C3G, but does not affect kidney function or disease progression, but the side effects are tolerable. C: the drug slows but does not halt progression of C3G and has minimal to moderate side effects. Or D: the drug extends time to dialysis or need for transplant but induces moderate to severe side effects.

So, select which of the following would be most important to you in a new drug of these options. The good news is we're asking you to make a hard decision here, but we'll get a chance to talk about what it is that you would like, and it might be multiple things that you're looking for and multiple things that you'd be willing to trade off for that. But for here, just for this purpose, we're asking you to try to rank the top one.

All right. It looks like just under two-thirds of you now dropping closer to half of you. Some last-minute responses here- looking for a drug that would reverse the decline in kidney function, but induces moderate to severe side effects, so you'd like to see a halt of the progression in C3G.

Just under a third of you would like one that slows but maybe does not halt the progression of C3G and has just minimal to moderate side effects. Then there's about 14% of you that would like a drug that significantly reduces signs and symptoms, even though it doesn't affect kidney function or the disease progression, but the side effects of this drug are tolerable. And it looks like there might be one response that says that you'd like a drug that extends time to dialysis or need for transplant, but it induces moderate to severe side effects.

So, we've concluded our polling questions. I think this has given you a lot of food for thought already. And now we're going to explore our audience discussion questions, which again our panelists have so nicely started the conversation for us on.

LARGE-GROUP FACILITATED DISCUSSION ON TOPIC 2

Current Challenges to Treating C3G.

And so here we want to know- we're going to start going back to talking about what you're currently doing to help with your treatment. And then towards the end of our time we'll talk about future treatment options. So, for now, what I would like to know is what are you doing that works? Or maybe more importantly to you as an individual, is

what are you doing that really hasn't worked. Maybe you aren't even doing anymore, because it's not worth it to you, because it wasn't really helping, but maybe it came with side effects. But whichever it is, in your experience, where you have either something that's worked really well or something that hasn't worked, I'd be interested in your experience with that.

Looks like there might be a pair of glasses someone's missing. Yes.

If you have an experience with some kind of treatment- this can be a drug treatment, this could be a medical procedure, or it could be some other approach, some lifestyle modification. We heard someone talk about diet and exercise, even dietary supplements. Interested in knowing your experiences with what might already be out there. We'll start here and then go over-

Chris: My name's Chris again. My first transplant, I didn't do any- I've had three transplants. My first transplant I didn't really do anything to help the disease and it progressed. I think I had it for about three years. The second transplant my doctor said there was a medication out there and I believe she put me on eculizumab around six to eight months later. Maybe the disease had already taken its course for the most part. That one failed about three and a half years. The plan going forward was to have eculizumab before transplant and then right after it, and continue it. You do need insurance to do that, it is the most expensive drug in the world.

Prior to the third transplant I actually went to Iowa to take part in one of the research drugs, a clinical trial on a CDX 1135, which in my opinion worked. It worked for a little bit and then I had- I guess it went from good to bad there. It was working and then it turned- it had a negative impact. To go there and do that trial, I had to stop eculizumab. That's probably what hurt me the most. When I got back to New Jersey I was taking eculizumab and this CDX. It wasn't until after they ended the trial, because they saw no changes, that like that next week I actually started peeing off a lot of fluid to where the drug looked like it was actually working.

My couple of things with me is eculizumab, we'll see if it works this time around, if it prolongs my kidney and hopefully it does because I did start it earlier. Working with two medications, like Dr. Nester said that people, it might be specific to each person, so I might need eculizumab and maybe something else that works the complement system somewhere else. Yeah, maybe a clinical trial that allows me to still be on eculizumab because taking me off I feel is like a risk. I don't want to risk myself. Then of course,

opening up clinical trials to people with transplants and who have their native kidneys too.

Moderator: When you were talking about going off eculizumab and going into the clinical trial, you said you thought that worked. Was it your kidney function? Was it symptoms?

Chris: After my transplant, they biopsied me six months later and I had the disease again. I think there was a slight increase around eight months. I was put on eculizumab and my creatinine went down, and protein went down so it seemed to be working. Then, I think it was in about the third year of my transplant that there was this clinical trial that came up. In order to do it they don't want you to have another medication in your system, they don't want two medications, they just want theirs to work. I had to come off eculizumab and I did see a bump in my creatinine and protein, and I had a little bit of swelling in my ankles.

Then I went to Iowa, tried this new medication, and my numbers actually came down to better than post-transplant numbers, my numbers might have been like 1.2 after transplant and it was down to like one. I was doing really well, I don't think there was- I think there was decrease in protein, I had no edema on me, but then it actually started to uptick to a point where it was actually worse than when I got there. Something was off so my doctor back in New Jersey- I think they just wanted to end it at that point to see if I could kind of stabilize my kidney again back on eculizumab.

I went back to New Jersey, and then I think they did a Compassionate Use where they tried both drugs at the same time. The study actually ended before they could see the results. It was starting to work towards the end, it took about a month and a half to two months before, because I was on low dosage of the CDX 1135. Those two together probably would work.

Moderator: That worked for you.

Chris: Yeah.

Moderator: Thank you. Do we have a comment over here? Jenna.

Jenna: When I had my transplant, like I was saying earlier, the C3G signs came back after the first month so it was again, rapid. What we did do for the next year and a half was plasmapheresis treatments as a way of attempting to remove those C3G proteins and

slow down the progression of the disease. It showed that was being effective in what it was doing, but ultimately after that year and a half, kidney function was low enough that dialysis did seem to be a better option at that point. Eventually, had to start that but I would say the treatment was three days a week and it was, I think about two hours at a time, if I can remember. It was not enjoyable at all. It was very painful, I wouldn't recommend it. It gave me a little bit prolonged time before going back on dialysis. It was difficult.

Moderator: How long was that that you had plasmapheresis?

Jenna: It was for, oh probably about a year and five months or so that I did that. A hundred treatments was what it ended up being.

Moderator: Right. Then that was up until the point where you then went to dialysis instead.

Jenna: Yeah.

Moderator: Thank you. Other experiences with other approaches to treatment that you might have tried? Worked, didn't work? We heard a lot about diet. I'd be interested in knowing how well has diet worked. How easy or hard is it really to comply with the kidney friendly diet? How has that been a burden on you, if at all? How has it actually worked for you? Has it at all helped you maintain healthy kidney function compared to when you're not on the diet? Does it help with any of your symptoms?

John: Hi, my name's John. I was one of the- I'm that one Canadian guy who's on the map. In regards to the meds, I was on MMF, prednisone, sulfatrim, ramipril, rosuvastatin, ranitidine, and calcium pills so you can imagine, that's a lot of pills. In regard to the diet, the kidney friendly diet, I'm actually quite disciplined in that sense of things so I try to keep my diet up too. I was in taking about 800 to a thousand milligrams of sodium. Just to give you an idea, like a slice of bread has 300 milligrams of sodium so you can imagine, it's very hard. You essentially can't go out for food. Going out for dinner with your parents, your friends, going for brunch, that's not really an option. I was also a student and I was a researcher at a hospital. You have really long days, you don't pack food, you can't really go get a sub, that's extremely hard. I don't know.

Moderator: How well is your overall treatment regimen working for you?

John: Prednisone was tough, as a lot of you probably know. I was one of the lucky ones that didn't have a lot of Cushing symptoms. The lack of sleep was really tough. Mood swings, it was tough on me but also those surrounding me, my family and my friends. I can't be in the sun for too long obviously for increased risk of skin cancer from MMF, prednisone, and even sulfatrim, the antibiotics. I can't really travel properly because of the diet. I've got to take a box of pills just to go away for a week.

Moderator: Has that been helping manage your symptoms? Do you consider them well managed?

John: I'm not really sure what's working right. I mean, I'm taking eight pills. I know that my proteinuria got a lot better, but got a lot better is from 16 grams per day to 4 or 5. So, I mean we'll have to see. I still got a long way to go for sure.

Moderator: Okay, yeah thank you very much for sharing.

Drew: I'm Drew, but as for the diet- as you can tell by this petite dancer's figure I have- I started out when I originally was told to do it anyways. It's not like I ate poorly anyways from the standpoint of- I was an athlete, so I know how to eat for the most part. But even though now- you just kind of have to know what you can and can't take. Do I strictly follow the diet? No, but I also know what I can and can't eat because it'll affect me to a certain extent.

Of course, you know the biggest assumption is when they say, "No sodium." It's not like I ever put salt on anything, but it does make you realize how much sodium there is in stuff. Like John said, as soon as you go and look at bread, you're like, "Huh." You wouldn't think that there's that much sodium in bread. But you kind of just have to work your way around it- figure out what you can and can't do.

Moderator: Yeah. Do you feel that the diet that you've been on which you said is difficult to comply with and you've kind of found what is working for you? Has it been working for you?

Drew: Yeah, for the most part. From the point I was diagnosed to even now, I've maybe gained five pounds in eight years. It's fluctuated. I of course lost like 20 pounds right after my surgery. But myself always kind of being a bigger guy, I've not gained- there's a time when I gained a bunch of weight of course when I was swelling up and all that stuff, holding water but other than that- true actual weight, I've maybe gained five to ten pounds at most. But it stays about the same.

Moderator: Gotcha, okay. Lindsey?

Lindsey: I think a lot of people really don't understand how difficult it is to eat a kidney-friendly diet especially the further that the disease progresses. When you are trying to limit protein and limit potassium and limit phosphorus- each, the further you go there just- and limit sodium.

You reach a point where you feel like there is not anything you can eat, and it becomes very difficult to balance all those different pieces and to keep track of what has how much of this and how much of that, and how much you should have. It's very difficult. Not to mention that a lot of the food isn't really all that enjoyable to eat once you get rid of all those things. Kidney diets just- let's be real- they suck. It's bad. I knew- at one point I had a friend who knew I was struggling with that. She called me on the phone and she said, "Well, what have you eaten?" She asked something about what I had eaten that day. I said, "Well, I've had a piece of toast and gummy bears," because I can't figure out what else I can eat. I mean it's really, really difficult.

Moderator: Any other experiences with diet that anyone wants to share? Yes Jenna.

Jenna: I do dialysis almost every day and so I'm lucky in that I can basically eat pretty much anything. Dialyzing that often allows you to, because it also will remove the retention of water, since I don't urinate at all. But I do find that when I travel on vacations, it's more difficult because, for the majority of the time, I'll schedule at a clinic and so that will be on clinic hours, which is every other day, depending how long I vacation.

I do find that I have to be a lot more strict with my sodium and my water intake. For the most part with the sodium, it's just so that it doesn't trigger your thirst factor so that then you retain that water. Since I've been doing dialysis for so long, I have- I'm very tuned in to my body and have discovered that because I know I will have limited treatments, I can do things like working out, which will make you sweat and that will get rid of the liquid and the salt. So, I've resorted to that a lot of times is working out more, doing something to get rid of that extra fluid in that way. But it doesn't make sticking to a dialysis-friendly diet any easier.

Moderator: I think for those that haven't experienced a kidney friendly diet, I hear the box lunches are kidney friendly, so we'll all get a chance to try that out after today's session.

One of the big symptoms that was talked about earlier this morning was fatigue. I think

that was one of the top symptoms that came up as being- or it was the top symptom that came up as being unmanaged for most of you. Has anyone tried anything that has worked? Is there any amount of rest that can help with this? Or can someone describe for us really how little, whatever they have tried, has worked since it does appear to be essentially unmanaged in this patient community. Anyone that has- yes, Chris.

Chris: I just want to say something about the dieting cause we're in treatments now. The diet doesn't treat the illness. Nothing like that treats it. You could be as healthy as you want. You could eat vegetables every day when you're healthy, but the disease- if it's going to- it's going to still progress. The diet is basically just saving your body from other high potassium and your heart will stop. So, it's not really a treatment as it's like what you have to do while you're declining.

For fatigue, I took EPO shots. They seem to work a little bit, but I didn't do anything with my diet to increase energy if that's what you're asking.

Moderator: Oh no, just generally anything to increase energy or reduce fatigue. The EPO shots- how often did you get them? How would you describe how well they worked?

Chris: It was- what was it? Once a week, something like that. Once a week subcutaneously.

Moderator: Sub-Q. -

Chris: Yeah, subcutaneously.

Moderator: Yup. What was the difference from before you received-

Chris: My hemoglobin was up like 7. I think it bounced up to like 11, something like that- 10 or 11.

Moderator: And that made you feel much less fatigued?

Chris: Well yeah but I just didn't like giving myself a needle-

Moderator: Yeah, yeah, yeah.

Chris: So, I would kind of blow it off. Then you're just tired again. It takes about two weeks to kind of kick in again. Once it kicks in, you're like "Oh I may not need it," and then you just decline again so- like that was me.

Moderator: Okay.

Chris: People are probably more disciplined with- if they do that, so.

Moderator: Wow, thank you. Jenna?

Jenna: I found that the increase in doing dialysis increases my energy level- so the higher frequency. Then also, even though I get exhausted by doing activity, the more that I do the more I can build up my endurance even though compared with a kidney, it's still significantly less. But that does help.

Moderator: So, can you- for both of those things, can you either, through an example or maybe a before and after comparison- the dialysis. How much more energy do you feel like you have? How much does trying to build up endurance actually work?

Jenna: So, the before and after dialysis. When I was doing it three days a week, on the off days I would be significantly more exhausted. I kind of always attributed that to the excess of water that I would be holding on and the breakdown of foods and whatnot that I was just kind of retaining and not able to get rid of. So mentally I always sort of attributed the exhaustion to that. So, there's that. Then I guess just immediately following dialysis after you've kind of balanced out, is when you really have your most drive to want to be able to accomplish things and do things. So, by doing dialysis so frequently now, I'm for the most part able to go forth and do what I want to pretty normally. But when I do have a day off, I can tell right after I do dialysis that I feel a lot better.

Moderator: When you said doing activities helps you build your endurance, is that physical activities?

Jenna: Yeah, physical activities. I think that's a fair statement across the board whether you have C3G or not. I think it's just that with C3G, it's still a struggle. You still get exhausted, but you'll also notice that build-up of energy, just maybe not as much as if your kidney works.

Moderator: I know there was only 9% of total respondents, that includes the web, that are on dialysis now, but are there others that are on dialysis, or anyone who was previously on dialysis that can talk about the effect that had on their symptoms and activities that you can do in your daily life? Was it universally a positive experience that people have had? I know there's the burden of actually doing dialysis. Have people had experiences with that that they want to share?

I know we've talked about that a little bit. Another one- and many people have mentioned that they've taken- that I'd like to hear your experience about, is steroids. There's been a talk about their use. I'm interested in what benefits to you as an individual you've experienced from taking steroids and how has that balance worked for you in terms of- obviously there's been a lot of talk about the downsides, the side effects of steroids and your own personal weighing of their benefit versus risk. If there's anyone that has chosen not to use steroids because of that personal decision, I'd be interested to hear your thoughts behind making that decision. Martin?

Martin: In Lizzy's case, they initially started her on the oral prednisone and an ARB. The weight gain was so severe, and she was so young when she started them, they knew they didn't want to keep her on them, long term anyway. They tapered them off and the proteinuria did not rise at all. Eventually they stopped completely. Again, the proteinuria dropped initially when they started her on the prednisone and the ARB. When they stopped the prednisone, it did not rise at all.

The doctors came to the conclusion that this was not impacting the progression of the disease and clearly because of the side effects we just chose to keep her off of it.

Moderator: Sure. Thank you. Yes?

Nick: In my case, before my transplant, it was a constant- not constant, but every year or two- I don't know the frequency, but I responded well to prednisone. Of course, at the very beginning, it was necessary to stabilize me when I first got the disease and I had IV pulses, but then with my doctors over the years, they would taper me, and I would be fine, but then there'd be a flair. There's this constant trying to balance the need to not be on prednisone, or minimize the use of prednisone with the effect. Because I had these flairs, it was really a game almost to walk the tightrope. That was a very difficult thing to do.

Then there were also disagreements with my doctors sometimes and my dad who's a nephrologist. He'd have a different opinion. That was hard to balance between that as well. I'm very happy now that I'm not on prednisone. That's one thing that I'm very glad. Fortunately, didn't have terrible symptoms from prednisone. I did have some moon face, but not enough to make me self-conscious. I had bad acne, but that was probably just genetic in my family to have bad acne. I was fortunate enough not to have terrible symptoms. I could deal with it. I did have symptoms and I sympathize with having to do-

Moderator: How long would your on and off periods be?

Nick: I don't remember. Do you remember Dr. Bombback exactly? I think it was every year or two.

Dr. Bombback: [inaudible]

Nick: That sounds about right.

Moderator: We can see maybe where the tension is.

Nick: I think maybe every year or two. When I was in college, it was four years, it was at the beginning, and then I think it was pretty stable for most of college. It varied too.

For me, one of the problems long term was the bone problems. I had some running injuries and things like that. That was a worry too. Fortunately, I haven't had terrible bone problems, but it was a concern long term.

Moderator: Sure. Other experiences with steroids, using them, maybe tapering them off, no longer using them, or decision of not using at all? Tori.

Tori: As soon as we had the idea that this could possibly be C3G, they immediately started me on prednisone. I went immediately to 50 milligrams. I'd never really taken steroids before. It really didn't affect me that much because at the end of January, I was 105 pounds. Now I weigh 148. That's a significant difference in such a little amount of time. I'm really not gaining anymore or I'm really not losing anything. It's staying stagnant, but I experienced the moon face. Because they're tapering me, it's finally starting to go away, but really from what I've read, unless you go under 10 milligrams, it won't fully disappear.

My face, like high school, they always call you pizza face if you have a lot of acne. Totally had pizza face. I was so irritable. Red head, you're kind of irritable to begin with, but it adds to it. Stretch marks, during pregnancy, I was like, "Okay, I want a couple. I want that scar. I want to be proud." Now I have it just because. My mom told me they're not stretch marks. You just fought a tiger and won. Just embrace it.

The prednisone definitely- you eat so much, and you never feel full. I would eat my husband, who's twice my size, under the table. Now that I'm tapering, I can barely touch a plate full. I don't- the side effects from decreasing them, you're shaky. You're always-

it's almost a paranoid type thing. I don't know exactly how to describe it. Your mind is just scrambled. You can't focus.

I didn't necessarily have all the sleep loss, or insomnia that came with the prednisone, but now that I'm tapering off, I'm definitely sleeping a ton more. I'm also developing carpal tunnel because the swelling is coming back up. They can't put me on steroids because I'm already on them. There's a lot that comes with it.

Moderator: Thank you. Are there any symptoms that we haven't talked about trying to treat that either you've been able to successfully treat, and it's helped impact your quality of life? We've talked about a whole range of burdens of this disease. We obviously won't have time to go through every single one of them, but are there any that are really outstanding that nothing seems to help that you want to share with the audience today? Anything left untreated?

C3G Treatments for the Future

I think we've explored a lot- your current approaches to treatment. I'd like to use our remaining time to ask you all to think about what you'd like from future treatment. We had a couple pulling questions to help you think about this. One, what is the benefit you're looking for? What would be a meaningful benefit to you? Is it a slowing of progression or a halting of progression of the kidney disease? Or is symptomatic relief more important to you? We had a number of people respond that it'd be nice to be able to have some of the signs or symptoms reduced even in exchange maybe for less side effects than a drug that actually reverses or halts the kidney disease but comes with more severe side effects.

Interested in what would be important to you and if you have thoughts about it, what would you be willing to take on in terms of risk to have that benefit?

Chris: Do I have to say my name?

Moderator: For the record.

Chris: For the record, Chris. I wrote down three things. They were fast tracks, stabilization, practicality. Those, above all, would be what I would like to see. I have a kidney transplant now and I'd like to keep it as long as possible. Meds in the future, hopefully

they get here quick. Hopefully they can be used with other drugs as well because like I said, I wouldn't want to come off eculizumab to try another drug that might not work or doesn't work as well without it, you might say.

Then practicality, because eculizumab is every other week. I have to go to an infusion center every other week. That's not that bad. I can still take trips with that and everything, so that's not that bad. Practicality, if you could pop a pill, that would be very convenient.

Then the risks, it's a kind of tough one. If it's a risk that's something that could be vaccinated against, then sign me up. If it's like cancer, if it's a big risk of cancer, I don't know about that. Then I like my hair. I have pride in my hair. I don't want to lose my hair, but I could give that up.

I don't want to grow anything. There's this law suit on TV sometimes, people grew breasts or something, I wouldn't want that. In the spectrum of reality, let's say not cancer. I don't know.

Moderator: If you think about some of the burdens about the therapy you're already taking, that might be a good way to help you think about risks that you would or wouldn't be able to take. There are certain things that drugs you're taking give you that you wouldn't want a future drug to also give you for a similar benefit or a different benefit. That is useful to know. Who else has thoughts about what would be a meaningful benefit?

Martin: Martin. We were focusing in the first part of this about treating the symptoms which is certainly important, but as yet, my daughter is asymptomatic. However, every time I look at my little girl, I know that C3 is accumulating in her kidneys. I'd really like to see something that treats the disease and hopefully that would also resolve the symptoms for people who do have symptoms. By treating the disease, are we going to regulate or fix the regulation in the alternate pathway? Are we going to shut down the alternate pathway? Can the kidneys flush the deposits of C3 if they're not being further damaged?

Those are the things I kind of made our poor nephrology fellow who first diagnosed her crazy about when she was saying, "Here's how we're going to treat the symptoms." And I'm like, "I don't want to treat the symptoms! I want to make the disease go away!"

Then absolutely to reiterate what we've already heard, especially what Chris said about

that, I definitely agree with that. I definitely am sympathetic to the horrible symptoms that people are dealing with, but can we make this disease go away?

Moderator: I thought for a second maybe Lucy is going to say something.

Sarah: Still Sarah.

Moderator: Yes.

Sarah: I think when that question is asked, it's quality versus quantity. As a mother of a patient, that's a very difficult question for a caregiver to answer and for a patient to answer, because what are you willing to give up in order to gain? I think as we hear getting both, suppressing the disease, slowing down the kidney failure with minimal side effects. The perfect drug or the crystal ball, or something, but I think to pinpoint, "I would give up swelling, but take on severe headaches and nausea versus this versus that" is a very difficult question to pose. I know we're focusing on treatments, so addressing the disease and being that it is rare, understanding how to slow it down and then treating the symptoms. It's that quality versus quantity. At the end of the day, that's not a question I ever want to have to answer as a mother and I hope my son doesn't ever have to answer as a patient.

Moderator: Another way to maybe think about this that I think is also useful for our discussion is not just what trade-offs would you want, but what really is it that you want? What is left based on what you currently have? Because, the whole meeting we set up- what are the burdens? What do we have to treat it? How well does that work? There's obviously downsides to treatments. What is it that you- are your priorities of what you're looking for short of a cure. We would love a cure, but what would you want that next treatment down the line to do?

Sarah: I'm hoping- we're a little over a year out from transplant. He had complications where he ended up with pancreatitis and diabetes; NODAT is what they call it, "new onset diabetes after transplant." For me, I would love some sort of treatment that's going to prevent the disease from attacking this kidney. That would be my dream.

Moderator: Thank you. That's exactly the kind of thing we're hoping people would share. Chris, and then we'll go up to Lindsey.

Chris: It's basically stability, just correcting the disease and being able to plan for the future

and have that stability that you know if the disease is suppressed and under control that you will have longevity out of your kidneys or your transplanted kidneys. Definitely that.

Moderator: Lindsey?

Lindsey: I think this disease has so many parts and so many pieces. There are a lot of things I wish a treatment could address or would address, but for me personally, at the end of the day, I need my kidneys to function because- some of us know, because we've been there, but once your kidneys stop functioning, life is never the same again, never ever. I watched my dad go through four transplants and years of dialysis. It's an incredible burden. Your life just is never the same again.

For me, I will go to pretty great lengths to preserve my kidney function. That is my number one priority. There are a lot of things that I wish could be addressed and wish could be different, but that is my number one goal. I'm pretty tough. I can take a lot of things to make that happen. I still have to weigh against- with a defective immune system and the immune-suppressants after a transplant, a current treatment. Are those side effects really worse than what I would go through on dialysis or with those transplant drugs? What are those side effects going to be when I get there? Is that really any better than what I might experience with a drug now?

Moderator: Right. Any other final thoughts from any of our patients or caregivers on what you would like from future treatment? Yeah, Nick.

Nick: As you said, Nick. I don't know if this directly answers your question, but being at this conference has helped keep me aware because I've been so successful with my transplant and I've had the remission of the disease or keeping it under control. So, I'm actually very grateful to be here to put what I'm experiencing in perspective. I just guess my response is it would be nice if I could stay the way I am. But I know that's something that could change. It's useful for me to keep aware of what might be in the future, not to get worried about it, to be grateful for what I have now, just that awareness.

Again, that didn't direct answer your question but-

Moderator: I think it actually did. Thank you, Nick. Any other comments? Yes, Jenna?

Jenna: Jenna. I think to go along with all that, it would just be to kind of put that worry at bay of when you go into a transplant, that's just a constant worry. What are the lab results

going to show? Just to show that at least with a drug to have a handle on that and know what that outcome is going to be and to be more aware. Just kind of to deal with the rest of the complications of normal transplants, and not the C3 factor on it.

Moderator: Right.

Jenna: Yeah.

Moderator: Okay. That's valuable. I see a lot of heads are shaking in the room, too. Okay. With that, I want to thank you all for giving me the opportunity to be here with you today and ask you some probing questions. Hopefully it wasn't too hard to answer, but I do really, really appreciate you being open and sharing. It is all very personal. I think that- we'll soon find out from our FDA colleagues how this information will be used and how important it will be for their decision making moving forward. [inaudible].

CLOSING REMARKS

Drs. Aliza Thompson and Jonathan Goldsmith, FDA

Dr. Vassalotti: Okay, thank you all. That was amazing. Next up is closing remarks from the FDA, and I'm pleased to introduce Eliza Thomson. She's the clinical team leader in the Division of Cardiovascular and Renal products, and also notably she's trained as a nephrologist. Also, speaking with her will be Jonathan Goldsmith, and he is the associate director of the Rare Diseases Program, and that's out of what we affectionately call CDER's Office of New Drugs, and he is trained as a hematologist. Thank you.

Dr. Thomson: I think we were told we could sit. Is that okay?

Dr. Vassalotti: Sure.

Dr. Thompson: Do you want to- okay, I'm going to sit. Can everyone hear me? Great. I want to start off by thanking all of you for sharing what were very personal stories about your experience with C3 glomerulopathy. I think that your stories really highlight the urgency with which we need to find effective treatments for this disease, and also treatments that had better safety profiles than those that are currently out there.

As was mentioned, I trained as a nephrologist, and since that time I've been at the FDA for about 10 years working on drug development for kidney diseases. What strikes me

is that this is really a very exciting time for C3 glomerulopathy. I think that there have been tremendous advances in understanding the science of what is really a collection of diseases- probably also tremendous advances. I think though, much more needs to be done in terms of understanding the natural history of the disease, how it progresses, and how that progression varies from patient to patient.

I also think it's an exciting time because we have drugs that are out there that target what we understand to be at least at this point, some of the driving forces behind this group of diseases. Finally, I think it's, most importantly, why this is an exciting time is because we have you all, meaning the patient, engaged in this process, shaping this process, and ultimately, I believe you'll be driving this process.

That is not to say that there are not challenges here, or that this will be easy, and I think some of that comes out of the points that Dr. Nester made this morning when she spoke about the challenges of studying a rare disease. Challenges also, I think, of studying a disease where patients can present in so many different ways, and have such different types of symptoms and complications of disease, and sort of the rapidity of the disease and disease burden.

I think that many of these issues have come up in discussions that we've had with those in industry when we've met with them and talked about developing therapies for the treatment of this disease. I just want to point out that there are some issues that haven't come up today, but I think are important to raise, and hopefully we can discuss in the future.

One of those issues surrounds the use of biopsies in trials and getting sort of protocol biopsies in patients with this disease as a way to get an early sense of whether or not the treatment's effective, and the willingness of you all to do that.

I think another issue that's come up in discussions but hasn't come up so much today are some of the issues with enrolling children in trials, particularly when drugs at early stages of development, and really when it's acceptable, and when it's appropriate to do so.

But really, these are all discussions that we need you to be a part of as well. I'm just going to look down at my notes to see what other points I wanted to make before I turned this over to Jonathan.

I think most of the time I can't say anything with certainty, but there is one thing I can say with certainty, and that is that the stories that you shared with us today, your experiences with the disease will certainly impact how we at FDA will think about this disease, will approach our discussions with sponsors moving forward, and will really shape the development in the future of therapies for this disease.

Just before turning this over to Jonathan, I want to add that I hope this is part of a continued dialogue, that this is just not a one-time interaction with you all, but that you'll continue to be involved. Obviously, the therapies are being developed for you, and moreover, you will need to be involved in the trials that establish their efficacy and safety, so the trials have to be trials you'd want to participate in.

I wanted to make that point. My final point was: Even though I'm sitting up here today, and Jonathan's sitting up here today, there were others from the FDA who- some may be listening remotely, but some who are in the room, and I just want to ask them if they could stand up. We have had really a team of people who have been involved in these programs at FDA, in particular want to highlight- so Norman is my boss, but his boss is standing in the room. I won't point him out, but he is one of the people standing.

I want to also highlight we've had a lot of help from our staff who focuses on pediatric drug development, and also some of the ethical issues there. Thank you so much for sharing your stories with us.

Dr. Goldsmith: Hi, my name's Jonathan Goldsmith. I want to thank the organizers, the patients, the families, members of regulated industry, academia, government, all my colleagues for coming here today. This is a pretty big lift- to come this distance, and to gather together, and to try to bring your thoughts to the fore and to present them to FDA and to each other. It's both.

As was said before, my background, I'm a hematologist. Hematology is full of rare diseases, all the diseases in hematology, almost, are rare diseases so before we kind of invented this discipline of rare diseases, I think I was in the business, I just didn't realize I was.

I've had a background in regular industry for a long time as well as in academia. I've been involved in clinical trials, efficacy and safety of products, and even in in vitro diagnostic tests, so I have a pretty fair overview of how things go and how drug development works.

FDA's been interested in hearing about the voice of the patient for some time now, and by way of background, we're in this transition from the patient focused drug development meetings that we've developed and run for about five years under the FDAegis, and we're now moving to these externally led patient-focused drug development meetings, although I think we're up to about seven or eight of these already. It's a very popular venue.

The patient focused drug development meetings support its systematic, scientific approaches to methodologies and analyses. FDA's a science-based organization, and we'd like to have things put inside that particular perspective. From those meetings, FDA learned and confirmed that patients and families are uniquely positioned to inform FDA about their disease and its impacts.

The current mechanism that we were using to obtain patient input is time limited by law, the way it was set up, and our fiscal and personnel resources. We now have embraced this transition to the externally led patient focused drug development meetings.

These are really important from a rare disease perspective. I don't know if you're aware of this, but about- well over 40% of the new molecular entities, the novel new drugs at the center for drugs approved every year are for treatment of rare diseases. So, this is especially important in a rare disease space. These meetings have confirmed the voice of the patient and how valuable it is to reviewers, and to those in the rare disease drug development space that is regulated industry outside.

We heard a couple of great talks today from your scientific support, from your medical experts about C3 glomerulopathy, and dense deposit disease. We heard about it being a serious disease, has multi-organ effects, things that I don't need to tell you about, or repeat.

From this meeting today, which I should tell you is really a very well attended meeting. I know people say, "Well, we only had 50 or 100 people." This is a very well attended meeting. There was a breadth of opinions and observations and points of view that we got to hear.

We heard about the commitment and the love for your children, and your courage and determination as adults, children, and teens. We heard about the heavy burden from disease from patients and families, from your heartfelt descriptions, things that are

common in the world of rare diseases is a so-called diagnostic journey.

I heard at least one of you is like 30 years, I think, of trying to get to a diagnosis. This is a tough road to hoe.

We heard about the challenges of activities of daily living, and that many of these are progressive. We heard about the profound fatigue and weakness that people experience, and how it impacts their lives every day, and their family's lives.

We heard about joint problems secondary to gout, and kind of tardy diagnosis of this problem by some of my medical colleagues. They probably could've done earlier interventions, and earlier treatments.

We've heard about difficulties of managing complicated medical care at home, doing dialysis at home or peritoneal dialysis, is not so easy.

We've heard about the impact of frequent and often prolonged hospitalizations and more routine but frequent physician visits. That impact of the disease isn't always very clear, it's a loss of time. It's a changing of your life as a result.

We heard about the family impacts of the disorder including social isolation, mental health issues, and neuropsychological complications. We've heard about a long list of losses, including a normal, or a near normal life, and independence. We've heard about a loss of energy and how it impacts your ability to go about your daily life. We've heard about problems with planning, uncertainty: Will I be here next year? What will my health be? What kind of life decisions can I make?

We also heard about problems with memory during some of the polls that were shown, and mental efficiency issues. We also heard about the potential impact of the disease on special senses, such as loss of vision.

We heard a lot of discussion about the complications of currently available treatments, and the interaction. Many of you just ran through a list of about eight or 10 medicines, and obviously there's a lot of drug interactions, and drug-disease interactions- and all of these problems have to be addressed- and make management of your disease much more complicated.

We also heard about your views on new treatments, and those potentially under development regarding possible drug treatment effects, and what kind of risk you were

willing to accept as part of drug development.

Your voice, as I think you'll begin to learn, or maybe you know already, does help FDA as we perform our public health mission to evaluate and approve new drug in biologic applications. We applaud your efforts to support drug development, and your interest in drug development, which is obvious.

We hope, as you think about drug development, that you'll support efforts to gain insights into the natural history of disease, because that's very helpful as drug development has progressed, because if we understand the natural history very well, we may be able to do different kinds of trials to find out about the efficacy of a new therapy.

We also know that you'll play a potential role in clinical trial recruitment, and retention. In rare diseases we have small populations we study, and we have to use them wisely. It's like human capital, and that people who come into trials, we hope to be able to keep in trials until we get to the end and find out something about the product.

We also hope that you'll be able to support study and rigorous development of potential biomarkers that might be part of drug development. We heard about these as possibilities today.

Just to close, I want to thank you for including me and the FDA in your excellent program, and fostering this strong sense of collaboration that is helping to bring new therapies for C3 glomerulopathy to patients and families. Thank you again.

NEXT STEPS

Dr. Vassalotti: That was wonderful, thank you very much. That was a very nice summary of our day, today. On behalf of the National Kidney Foundation, I just want to say this has been an incredible meeting for us. I feel moved to hear your stories, the courage that I've heard from patients and caregivers, and we feel inspired to do something about it in the future. We're really looking forward to our next steps.

Now, I want to acknowledge especially the patients and their caregivers in the room, but I also want to acknowledge those from other countries and on the web that have paid attention over the last four and a half hours.

There might have been some things that you didn't want to say publicly today, that you would've liked to have said, or maybe in the next few days and weeks you'll think of something that you want to share with us. We want to give you that opportunity, particularly those who are participating on the web, and on this slide is an email address that you can share written comments with us for additional feedback. We're also looking for other feedback, not necessarily related to your experience, but also about the process, too, we'd be interested to hear from you.

We heard from Dr. Thomson that they would like to hear about kidney biopsy and enrollment in trials, so how do you feel about that? That was one thing we didn't address. Also, the enrollment of children. Those are two things would be great if we could hear about them through this email address.

We will have what is called a patient voice report compiled. That's our next step. That's going to be publicly available in the future. You'll all be able to see that. I think we have a lot of energy and excitement around this problem, so I'm looking forward ... [audio stopped].