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Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation

Moderated by Dr. Peter Nickerson

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Reported by: Richard Livengood

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A P P E A R A N C E S

List of Attendees:

Dr. Jacqueline Corrigan-Curray, Principal Deputy Center Director, CDER, FDA

Dr. Ozlem Belen, Deputy Director for the Division of Rheumatology and Transplant Medicine

Dr. Emilio Poggio, Department of Nephrology and Hypertension of the Glickman Urological and Kidney Institute, Cleveland Clinic

Mr. Paul Conway, Chair of Policy and Global Affairs, American Association of Kidney Patients

Dr. Aliza Thompson, Deputy Director of the Division of Cardiology and Nephrology, CDER, FDA

Dr. Peter Nickerson, Max Rady College of Medicine, Rady Faculty of Health Sciences

Dr. Ergun Velidedeoglu, Transplant Team Leader, Division of Hematology and Transplant Medicine, FDA

Dr. Jeffrey Siegel, Director of the Office of Drug Evaluation and Sciences

Dr. Hrefna Gudmundsdottir, Chief Medical Officer of the Icelandic Medicines Agency

A P P E A R A N C E S (Cont'd)

List of Attendees:

Dr. Amanda Klein, Executive Director, Transplant Therapeutics Consortium, Critical Path Institute

Dr. Nadia Chaudhri, Medical Officer, Division of Rheumatology and Transplant Medicine

Dr. Roslyn Mannon, Professor of Medicine at the University of Nebraska Medical Center

Mr. Kevin Fowler, Board of Directors, Kidney Health Initiative

Dr. Karin Hehenberger, Lyfebulb

Dr. Ken Newell, Professor of Surgery, Division of Transplantation, Emory University

Ms. Molly McCarthy, Kidney Transplant Patient

Dr. Sundaram Hariharan, Medical Director of Kidney and Pancreas Transplantation, Medical Director of Transplant Nephrology, University of Pittsburgh Medical Center

Dr. Angela Maldonado, Medical Director, Hansa Biopharma

A P P E A R A N C E S (Cont'd)

List of Attendees:

Dr. William Fitzsimmons, Senior Advisor, Transplant Therapeutics Consortium, Critical Path Institute

Dr. Vijay Kumar, Medical Officer, Center for Biologics

Mr. Calvin Henry, Patient

Dr. Nicolay Nikolov, Director of the Division of Hematology and Transplant Medicine

Dr. Michael Mengel, Chair of Pathology, University of Alberta, Edmonton

Dr. Roy Bloom, Professor of Medicine, Medical Director of Kidney Transplant, University of Pennsylvania Medical Center

Dr. Karen Higgins, Senior Statistician, CDER, FDA

Dr. Steve Woodle, Director of Solid Organ Transplantation, University of Cincinnati

Dr. Peter S. Heeger, Professor of Medicine, Director of Transplant Research, Recanati Miller Transplant Institute, Icahn School of Medicine

Dr. Chris Weibe, Associate Professor, Max Rady College of Medicine, University of Manitoba

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P R O C E E D I N G S

REID: Okay. It is 8:00, so we're going to get moving here. Can everyone see me? And can everyone hear me?

MULTIPLE SPEAKERS: Yes.

REID: I'm very sorry about that. Okay. So welcome to the Endpoints and Trail Designs to Advance Drug Development in Kidney Transplantation. My name's Reid, I'm part of the FDA staff. Myself and my co-workers will be assisting you and the speakers throughout the day.

If you have any questions, you can find us at the long table in the hallway, or back there at the AP table. That would be Brittany and myself.

So a few housekeeping things to keep in mind. If you were not told at the registration desk, the deadline for lunch orders is 9:30 a.m., and you can go to the kiosk in the main hallway to pick up a lunch during break.

Now, lunch can be eaten within the room, or at any tables in the main hallway, or I

think, it might be nice enough outside. Also outside.

Bathrooms are located behind the kiosk in the main hall. So if you go passed the kiosk, down that hallway on the left, you'll find the men and women's bathrooms.

Any phone calls should be taken in the main hall or outside the presentation room. If you need somewhere more secluded, once again, contact one of our team members, and if there's an open conference room, we can see if we can get that for you.

Now, there will be an opportunity to ask questions. We have two microphones in the main hall, right there. However, those will be designated for the open panel discussion sections of the meeting. So please, during and presentation or any formal discussion, please refrain from trying to use the microphones. There will be a time and they will let you know.

Now, with all that in mind, again, welcome. And our first speaker with be Dr. Corrigan-Curray.

DR. CORRIGAN-CURRAY: Good morning. I'm Dr. Corrigan-Curray. I'm the Principal Deputy Center Director for CDER, and I'm so pleased to be here and have the opportunity to say a couple of words before you really launch into this important topic.

It's great to see some of you in person and thank you for everyone who's joining us online. I want to also thank our co-sponsor, the University of Manitoba Transplant Center for supporting this conference, and for its leadership in scientific research and innovation around kidney transplantation.

I want to also recognize the Critical Path Institute, who is here. I think we're in our 20th year of collaboration with the Critical Path Institute, and it's been a very productive partnership to advance drug development across a spectrum of diseases. And I know today it is our Critical Path Transplant Therapeutics Consortium, which amongst other activities, has been working to advance the -- the novel iBox Scoring System, and I know that will be discussed some today.

You know, the field of transplant medicine is just one of incredible innovation. You know, going back and sort of refreshing myself on this, you know, realizing that the first kidney transplant was done about a decade before I was born. I want to keep that a little vague.

And then, they moved on to, of course, kidney, pancreas, liver, heart, and lung in the '80s, a time when probably more people in this room can remember.

And then, as we hear about the second person, I think it was, to receive an experimental pig heart, it's easy to think that we've achieved everything that we need to do in human organ transplantation. And I know if you're not on the front lines as you are every day, it may seem like that.

I don't know, but I would suspect that the average person really thinks about, aside from organ availability, which is a large issue. Once, you know, there is a transplant, we're sort of good, and

everything is fine.

And of course, for kidney transplant being, you know, one of the most common, and I understand we're over 560 kidney transplants as of September 23, and 25,000 a year. It really seems like this has become part of routine medicine, which perhaps it has. And it's incredibly good news, but like many things in medicine, there's usually still an unmet need.

You know, in April of '23, and I think most of you might have seen this, New York Times published a guest essay entitled, My Transplanted Heart and I Will Die Soon, and it's a title that really catches your attention.

And many of you who've read it, you know, read about this young woman who had two heart transplants and it was not the failure of the transplants, but a secondary cancer that was attributed to the immunosuppressive regimen.

And the author raised an issue that probably does not receive attention about the price

that patients pay for their immune suppressants, both daily side effects, and that are perhaps, that are non-life threatening, but then the more life threatening and serious.

And she quotes an unidentified doctor saying that the current medications are insufficient, they don't prevent the long-term rejection. And if they do, then unfortunately, their effects can become deadly.

And she refers to a gratitude paradox, where those given the gift of an organ may feel like they cannot complain, and she identifies this unmet need that is probably too unfamiliar -- too familiar to those in the room.

I understand that the last new drug that FDA approved in the prophylaxis of organ rejection was belatacept, and I'm sorry if I mispronounced that, in 2011. So I went back in 2011 and said what else was going on in drug development.

Well, 2011 was actually the year that two new drugs were first approved for melanoma after a

13-year hiatus. And in the intervening years, there have been multiple drugs approved for melanoma, probably eight or nine drugs, building on a successful targeting of BRAF mutations and other knowledge.

So we know that drug development is not easy, and then in the transplant setting, the stakes are high, as in many others. We also know that identifying appropriate endpoints and trial designs can really facilitate development, as it has done in cancer and other fields, and accelerate investment and interest.

So there's an incredible amount of talent in this room, and online, and from patients who know what it is to live with this experience, to those treating patients every day, and to my colleagues who are really here to engage in a dialogue that can move the needle forward.

So I want to thank you all for taking the time out of your busy schedules to -- to meet with us, to work with us today. I'm going to end my talk, because there's so much, many more important things

that we need to discuss, and I look forward to hearing about what you achieved. Thank you for your attention.

DR. BELEN: Good morning. My name is Ozlem Belen, and I'm the Deputy Director for the Division of Rheumatology and Transplant Medicine, in short, the RTM in the center of drug evaluation and research at the Agency.

On behalf of the Agency, I would like to welcome all of you to this collaborative workshop, co-sponsored by the FDA and University of Manitoba, titled Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation.

This is our first workshop for kidney transplantation since 2018, and the start of the pandemic. We have been informed that over 700 people had registered to attend this workshop, close to 100 in person, and over 600 to attend remote -- remotely.

During the last decade -- during the last decade, the scientific understanding of transplant medicine, including transplantation has

made significant progress, including but not limited to, the changes in organ allocation system, and antibody mediated rejection, importance of medication adherence, HLA molecule mismatch, and the revisions to bath classification.

We identify challenges we would like to discuss in order to promote the development of new, safe, and effective therapies in this -- in kidney transplantation.

The goal of this workshop is to have a public dialogue to help address barriers to drug development in this space. The topics discussed will include efficacy endpoints for kidney transplant prophylaxis of rejection trials, biopsy proven acute rejection as efficacy failure, non-inferiority trials, and secondary endpoints.

Personalized immunosuppression and enrichment as a tool in trial design. We assigned ample amount of panel discussion time for questions from both the audience and remote attendees, and we expect to clarify any points that need further

discussion from each session.

In order to ensure a robust discussion today, we recognize the importance of having a broad representation as the objectives of this workshop relate to multiple stakeholders.

I would like to note that this is a public workshop and not an advisory meeting. However, this workshop is a part of ongoing and much needed dialogue, and a forum for open discussion between kidney transplantation experts in academia, industry, the nonprofit sector, government, and patients, with the hope of expediting drug development of safe and effective treatments in kidney transplantation.

Therefore, everyone's input perspective and ideas are valued. The planning committee included members from the Agency, including our own review division, Division of Cardiology and Nephrology, Office of Drug Evaluation and Sciences, Office of Biostatistics, and representatives from our co-sponsor, University of Manitoba, including Dr. Peter Nickerson, as well as members from the ASD, AKP,

Critical Path, specifically TTC, representing transplant academic community and investigators. And most importantly, patient voice.

We -- we sincerely thank you for your time and dedication for the past months to make this workshop possible. Today's agenda is quite busy, but we are hopeful we can adhere to the schedule so that we have sufficient time for a robust discussion in each session panels.

Once again, I thank you for joining us today and we're looking forward to a very productive meeting. Thank you.

DR. POGGIO: Good morning, everybody. Thank you very much for inviting me to present. And the title of the presentation is Are Long Term Outcomes After Kidney Transplantation Improving?

So I started the -- the presentation with a question, and the answer; yes. I'm going to show you some data, now.

As we all know, we need transplanting more and more. We actually doubled the number of

transplants -- a over 20 plus years from about 14,000, we're about 26, 27. We will do more this year. This is mostly at the expense of deceased donor transplantation, not so much at the expense of living donor transplantation, is another area where we have to work. But we are doing more and more transplants year after year.

Now, this is a -- an adjusting graph survival data from UNOS, and you can see that at one year, this is graft survival. If you get a living donor kidney, very few kidneys -- very few kidneys will be lost, for any reason.

As time goes on, of course, survival decreases, and a significant number of kidneys are lost within three years of transplantation from living donors. Outcomes a little worse for deceased donors, 93 percent, 7 percent the kidneys will be lost within one year. And as you can see here, after three years, 25 percent of the kidneys are not functioning anymore.

This is patient survival. You can see also here, this is from UNOS, too, unadjusted data,

you have, of course, younger people live longer. We have an issue with older recipients where they tend to die within five years of transplantation. And with that you lose grafts, functioning grafts.

So a few years ago, we -- we look at -- we wanted to know if kidney outcomes were improving in the long term, over the last 20, 25 years. So we look at this LTR data from 1996 to 2017, because we wanted to have at least five years of follow up. Sorry, how do I go back here?

Here you see, this is donors, living donors. You can note here you have all kidney transplant recipients divided by in five different groups, based on when they received the kidney transplant. '95 to '99, 2000 to 2004, '05 to '09, '10 to '13, '14 to 17. And this is a graft survival. And you can see that every five years survival is getting better and better. And this is adjusted for all sorts of comorbidities and variables that can affect survival.

Same thing with living donors, the

impact is smaller, but you can see, also that every five years, graft survival is improving in the United States.

You can now say, also that in 1995 If you got a kidney from a deceased donor, you have life -- the half-life of that kidney was eight years. Now, it's expect it to be about 13 years, so you have about -- or 11 years, I'm sorry. So you had about 25 percent increase in survival, in half-life of the kidneys.

Where living donation is much more pronounced, it used to be 12 years, now you can expect 15 to 19 years of graft survival. So we are doing better.

All groups, all different subpopulations may get impacted differently by this improving survival. Within one year, note this, one year of improvement, in one year survival, the improvement is only four or five percent. We are already kind of like maximized. This is over -- this is over 20 years, from 1995 to 2017, about 12 years.

So you can see that there is improvement in different subpopulations, especially in the older population, they tend to live a little longer, compared to a younger population. African Americans they have improved survival -- more survival improvement than other races, et cetera. Yet, the survival improvements only five years or one year, because we already do very well at one year.

Now, if you go a little farther out, this is five years, you can see the impact is much more significant, even up to 25 percent improvement in some subpopulations. Note that this is a -- if you get a -- if a recipient got a kidney between 2014 and 2017, they have at least 60 percent less chance of losing the kidney than if they got it back in 1995.

Similar data was shown by -- by Hariharan, who is here, similar analysis. And you can see the same thing for living donation and deceased donation, graft survival, and patient survival is getting better year -- year after year.

There's a nice -- this is a nice

picture here because what we are looking here is at the rate of graft loss and patient loss, and this is time. And you can see that from all the transplant, only three -- three percent were lost at some point here, early on, but then the rate at which we are losing grafts and patients is less -- is lower and lower over time.

So the answer to the question is yes. But are we there yet, and absolutely not, as we all know. Look at this, it's very complex. It's very complex. This is a nice diagram, in where you can see how complex is a kidney transplantation, in contrast to, for example, native kidney disease. I'm not saying that native kidney disease is not complex, either. But I'm saying this -- there are many more factors here.

We have donor factors, we have recipient immunosuppression, we have common disease, patient death, everything leads to graft loss. And therefore, it's very difficult to choose one surrogate, or one outcome, or one -- one tool to

estimate endpoints.

We are not doing that well. Here, I can show you that for 13 percent of the patients that were transplanted between 2014 and '17 are retransplants. So we are losing grafts with patients being in good shape to get another kidney. This is not even counting those patients who lost a graft, and they can't get on the transplant list, or they cannot get another transplant. And so we need improvement there too.

This figure is being shown many times, but I want to show here that back in the day we were looking at one-year outcomes. You can see that this is a one-year allograft survival and rejection rate, and all the drugs were developed from 1960 to 2010, the last one being "Bela" in 2011 or 2012.

All these drugs brought the survival -- graft survival to very high, rejection rates very low. And they're all directly at T-cell immunity, mostly. Nothing about antibody immunity mentioned here. It's all about aiming at lymphocytes and acute cellular

rejection, which is kind of -- which is kind of like the most common cause of graft rejection within the first year. So our goal was one year. That's what's been there for a while.

But you can also see here, this is data from -- and these are biopsies for different reasons. And note here that I could see the rejection, the -- rejection is very -- is very significant in the -- at the beginning, within one year of transplantation. But as time goes on, the -- the condition that really affects kidneys and eventually leads to graft failure is antibody mediated rejection, where we haven't made much progress.

We know, hear about if you develop the donor -- donor specific antibodies and with different the different characteristics, you will lose the graft. But this happens late, it doesn't happen within one year. It doesn't happen within two, three years. It may happen over 10 years. So the events occur after one year and it take a while or take a long time before we lose the graft.

In all the grafts that are not lost, we have antibody mediated rejection, can be lost to this condition of chronic allograft nephropathy, what we used to call. Multifactorial, very complex, no treatment either. We don't have treatment for AMR, we don't have treatment for this. So we are losing grafts from this conditions that they have no targeted drugs.

So traditional endpoints now, I think, in my opinion, they are not sufficient. As an example, we cannot focus on graft rejection within one year, which is mostly serial rejection. Look at this, this is data from UNOS. We are talking about five, eight percent of cellular -- graft rejection, mostly cellular, within one year. That doesn't mean graft loss. So we are talking about something that we are really doing very well at preventing, which is rejection within one year.

If you look at GFR as a marker, people talk about, it's very difficult, too, if you look at it alone. Look at the distribution of GFR in between

transplanted patients, depending on the age, it's all over the place. So if you say, "I'm going to do 40 percent change in GFR," is not the same if your GFR is 20, versus 60, versus 30. So it gets complex.

So when they account for the improvement of graft survival and patient survival of time, we don't have new immunosuppressive drugs since more than a decade ago. None of the drugs in the market addresses antibody mediated rejection, for example.

However, we have many new drugs in cardiovascular -- to prevent cardiovascular disease. We have a ton of drugs now, to control and cure cancer. We have a lot of antibiotics, we have a lot of antivirals, this helps to help the patient keep that organ, a longer and patient life. And even now, real week -- last week, tons of new drugs to treat GNs, novel GNs.

So we have a lot of medications we can treat common causes of patient -- of a graph loss and patient death, such as recurrent disease,

cardiovascular disease, malignancies, et cetera. But we don't have a drug that really -- a drug that really look at what we do as kidney transplant physicians, which is prevent organ rejection.

So new -- what do we need? A new immunosuppressive drugs directed at conditions that manifests late in the transplant process, but they take years to evolve. We have to rethink our endpoints and find new surrogates or tools that protect the expected outcomes, rather than wait for the outcome to occur. We cannot do wait for five years, try -- try a drug for five years before we know if you -- if works or not. And these new tools will likely incorporate several surrogates and not a single one, I don't think a single one will be enough.

So in conclusion, short term outcomes such as rejection within a year of transplant are excellent, and basically, I think they are maximized if you really want to look -- use them as an endpoint. Covering shorter outcomes do not address the graft loss. We can have excellent outcomes at one years,

yet we lose a kidney at five years.

Long term outcomes are improving but likely to advance in the overall care of patients in general, I think. And there is a need for surrogate outcomes to facilitate novel drug development directly that late immune mediated graft loss and related conditions. Thank you.

DR. NICKERSON: Go ahead, Dr. Conway, or Paul. Go ahead.

MR. CONWAY: Thank you very much. My name is Paul Conway, I'm from the American Association of Kidney Patients, and I have the pleasure of serving as the Chair of Policy and Global Affairs. And I'd like to thank the FDA for the opportunity for the opportunity for AAKP to participate today.

And I'd especially like to thank fellow patients around the country, who obviously have a vested interest in this, and helped make this meeting as big as it is today. The credit goes to the patient voice. And we'd also like to thank the congressional staff of the United States Congress. On October 19th,

the American Association of Kidney Patients did over 130 meetings on Capitol Hill and encouraged congressional staff to attend this meeting and to listen. And we've committed to do a post meeting patient impact statement to the Congress after this meeting.

And the reason why is because we believe there's a disconnect, right now, between the direction of the country in terms of national policy and patient interest, and the intensity and action of the FDA to move forward on new transplant drugs. So right off the bat, we're going to talk about three myths, three realities, and three important questions that we think should frame today's discussion.

So first myth is that there are no unmet patient needs. We hear this from time to time. We also hear that status quo is good enough in transplant medications, and we reject that. And third, we've heard that science in regulatory decisions are too complicated sometimes for patients to grasp, and they occur separately from patients and

policy set by the President and the Congress.

We find this interesting and it's worthy for the discussion, because what's happening today is a discussion in full candor, and collegiality with the FDA, and with many of the experts there in the room. But make no mistake about it, the FDA is in the process of making decisions on a regulatory pathway for the next generation of transplant drugs.

This is a United States government agency that is deliberating data that will determine the access of American patients to new drugs. And it will also impact the practice of transplant medicine, and the industries that have decided to either be in this space and develop drugs, or to leave the space because there's no pathway forward.

So let's just take a look at one quote here on the next slide, which I think is very important. This is a quote from Dr. Robert Califf, the Commissioner of FDA, who we believe deserves a tremendous amount of credit. These are quotes that were taken from his introductory remarks at the

patient engagement advisory committee in September of 2023, and they really characterize the spirit we believe, of FDA. And it says, "I'm pleased to be with you today to help kick off this meeting addressing the most important areas of focus at the FDA, how we incorporate into the patient voice in support of the development of new products to treat disease."

He also said, "The FDA as a whole is committed to better understand and advanced diverse patient perspectives, preferences and unmet needs inform our work." And he also said, "One of the most important aspects of our mission is to protect and promote public health to -- involves the responsibility to consider, to the extent we can, the needs and characteristics of all people and populations in the policies we advance, the science we support, and the workplace in which we operate."

Dr. Califf deserves a tremendous amount of credit, because many of the patients there in the room and who are watching online, remember Dr. Califf's words of eight years ago, in front of kidney

patients, as he listened patiently to patients describe what they go through with kidney disease and the lack of innovation, including the lack of innovation in drugs.

And after listening to this, Dr. Califf, who is very esteemed in many different areas, as a researcher and as a practitioner, got up to an open microphone as a U.S. government official and said, "If he were a kidney patient in America today, he'd be pissed off," and he's right.

Next slide. This is how at FDA, over the past eight years, has listened to patients. They've leaned forward to hear the needs of patients in the context of multiple meetings. In eight years, including today, the FDA has conducted five meetings to consider what the future of transplant medicine is, and a number of different factors, and they've been open to listening to the patient voice, which is very important.

It's also important to point out that over the past eight years, that amount of time is

longer than it took the U.S. to win World War II with our allies. It's almost as long as it took from John F. Kennedy's speech about putting a man on the moon to a man actually landing on the moon. And it's actually longer than it took for Bono, of U2, to work with a bipartisan coalition in the United States and to move forward with an effort that broke the back of HIV transmission in Africa between mothers and their babies. I think it's always important to benchmark how much time it takes for government to do something.

Next slide. So in light of this meeting coming up in November, the meeting we're at today, AAKP did a survey that evolved over 1200 kidney transplant recipients, and organ donors, and patients. And we asked several questions to go to the issue of unmet needs.

And we asked patients when they first thought about getting a transplant, did they think of it as a treatment that was better in terms of their health and renewed capacity to do what they want it to do in life, in comparison to dialysis? Ninety-eight

percent said yes.

Next slide. And then we asked them as a transplant recipient, would they like to know how long their transplant might last before going ahead with a decision to get a transplant? Seventy-seven percent said yes, 13 percent said no, 10 percent said they weren't sure.

Next slide. We asked this question, when they first thought about getting a kidney transplant, did they discuss it with a family member, or a friend, or a loved one, and how long it might last? Fifty-six percent said yes. The reason why we asked this question is because one of the stakeholders that is often not talked about is the family of the transplant recipient for the person that's on the waiting list. And that is another stakeholder that's impacted by delays or by organ rejection.

Next slide. And we also asked whether or not they thought a kidney transplant, how long it should last to make the surgery worthwhile, to make donation worthwhile as a transplant recipient. And

you can see here that patients are saying, almost half of them, that they think that a transplant should last longer than 20 years. Forty-eight percent of them. Thirty-six percent say 10 to 19 years.

And what's interesting about this is when you consider the previous presentation, which was superb, you have the patient expectation for how long a transplant should last, and then you have reality.

Next slide. So then we asked, what did the medical team tell the transplanted patient, how long the kidney might last if they took their medicines exactly as they were supposed to do? Only 15 percent were told that the kidney should last more than 20 years. The majority, 57 percent, were told 10 to 19 years, and about 25 percent we're told five to nine years.

This is very important, because the long-term outcomes for transplant recipients matter to the recipient. And so while statistics might say that "Hey, we're doing well at 10, or 12, or 14 years," we're still not meeting the patient need, which has

been very clearly articulated over the past eight years to FDA.

Next slide. So patients as influencers. I just want to take on this point that we think is a myth, that somehow patients can't understand the science of some of these discussions. This is very important.

So the Clinical Journal of the American Society of Nephrology is highly respected throughout the kidney community and throughout the world. But you should know this, 40 percent of the top 10 all-time pieces that have appeared in CJASN have been written by patients in just the past five years. They do an indicator on there, a metric. It's called altimetric, and it's about the spread and impact of articles. And so the average score is 30.8 on a piece that's published in CJASN.

But in fact, the number one article of all time, you can see it right there, of all the articles, almost 4000 articles, the article that rates number one, was written by the current president of

AAKP, who is a U.S. Marine Corps veteran with kidney disease.

We don't know if a transplant is in his future, but he's concerned about all patients that are in need. And one of the interesting things that he wrote in a piece called 12 Tips for A Nephrology Team, writing as a Marine, was "leave nobody behind." Never underestimate the innate human desire to live and prevail and remember your responsibility to make certain your patients are not set adrift in the care system or left to fully coordinate the burden of their own care. I think it's important for folks to think about that as we proceed throughout the day.

Next slide. That brings us to three realities, as we see it in comparison to myths about transplant survival. Longer transplant survival is the priority of the United States government and the American people. Longer transplant survival matters to patients and donors, families, taxpayers, and industry. And number three, kidney disease is both a U.S. workforce and health care issue.

Next slide. How do we know it's a priority for the United States? Because multiple presidents have made it a priority. On September 22nd, President Biden signed a bipartisan piece of legislation that overhauled the transplant system in the United States. And patient advocates and doctors, who are our allies, and medical societies have worked on this and push for it for years. And the reason why is because it's not good enough right now, and we're not going to settle for the status quo.

He signed that legislation to bring in greater transparency and accountability innovation to increase transplantation, reduced the waiting list, and also, underlying all of these policies that you see here, is the idea that a patient who loses their transplant and goes back on the transplant list, that's not a success. We need to do better in making certain that when patients are transplanted, that that organ lasts as long as possible.

And you can see this reflected in U.S. policy. Under President Trump, we had the Executive

Order on Advancing American Kidney Health, that prioritized transplantation over dialysis.

From 2018 to 2019, Secretary Azar, whose father was on dialysis, awaiting an organ transplant, came to meeting after meeting at his conference table, as a U.S. cabinet officer, with transplant recipients and donors and talked about many different things. And one of them was the lack of innovation and transplant drugs. That's a U.S. cabinet officer spending that time.

Next slide. In 2018, we were able to work with the Secretary of Labor to extend the Family Medical Leave Act to organ donors to increase transplantation and to reduce waiting lists for more living donors. That was done because of an analysis of congressional discussion in intent that FMLA would extend to organ donors in the United States.

2016, President Obama and the White House Office of Science and Technology, had a fantastic summit on organ donation, where again, the focus was on how do we get more people to donate

organs? And how do we make certain that organs that are received by a patient and they become a transplant recipient, that they last as long as possible?

And in 2013, after many, many decades of fighting to get this done, and through the great science and advancements of FDA and the transplant community, President Obama signed the Hope Act, which gave inspiration and lifegiving gifts of kidneys and organs to HIV patients. So you have HIV positive to HIV positive organ transplantation.

That is 10 years of policy in the United States government that's been enacted that has prioritized transplant and making certain that transplant lasts as long as possible. And what we are seeing is a disconnect between national policy and the action and order to sustain the policy. And that's concerning.

Next slide. Going back to our survey, we asked a couple of questions to gauge other stakeholders here. We asked kidney donors, when they first asked about potential treatment for patients

with kidney failure, was the medical team for the donor able to say how long a transplant might last? Only 60 percent were able to get that knowledge before they donated a kidney.

Next slide. We also asked whether or not FDA went forward and approved new primary or co-primary clinical endpoint that could lead to innovation. Whether or not people will be more likely to donate a kidney to somebody that had kidney failure that was on dialysis. And knowing that something could actually last longer, the survey indicated that 75 percent of them thought that that would make an impact. Think about it, getting more living donations.

Next slide.

DR. NICKERSON: Paul, we've lost your audio. Sorry, just --

MR. CONWAY: To a lot of folks, there's a barrier there that, if you're on dialysis, you don't want to take a risk because you hear about the side effects and you don't think it's going to last that

long. Eighty-five percent of the people that participated in our survey thought it would make a significant difference in the minds of dialysis patients.

Next slide. And then we also asked whether or not -- what the impact of a setback would be. If FDA fails to move forward in adopting a new primary or co-primary endpoint or an amalgamated endpoint, what would the impact be on the industry? Would it be a setback? Ninety-two percent of the recipients understood that if there is not a pathway through regulation to greater innovation, there will be a setback if industry leaves the space.

Next slide. So in terms of the true impact, one of the other realities that was on the list of the three, was that kidney disease is both a healthcare and workforce issue. And we know this, and the appointed and elected leaders that we work with know it as well.

These are two quotes from Secretary Azar when he appeared at the Global Summit on Kidney

Disease Innovations this past summer and received a global award for his leadership. "These patients understood that kidney disease was not simply a medical issue. They saw it as both an economic and workforce issue. For many, their lives were a testament to the fact that kidney disease denies people the opportunity to pursue part-time or full-time work, the ability to care for their families and the chance to build a secure retirement."

And he also said, "Earlier disease detection, faster interventions, improved dialysis technologies, greater opportunity for organ transplant, and new transplant drugs, and artificial and regenerative organs, are now the future of kidney medicine." And that was in the context of explaining how a President of the United States could sign an executive order that would transplant -- transform American kidney care, because he held the roundtables that formulated the policy that a President of the United States signed, and the current president has sustained and moved even more forward. That all came

from patients.

I think it's important to understand that kidney disease and these issues that we're talking about, about an organ not lasting as long as possible for patient, they impact families, they impact the economy, they impact people's ability to earn a living and stay independent and retire securely.

Next slide. So to the folks that are in the room, and to the patients, and the congressional staff who have joined us online today, again, we thank you. And we think there are very important questions that the FDA should answer. And it should be answered in the forum that we're having today.

The first question that everyone should be able to answer is this, does today's meeting recognize the known, unmet patient and donor needs for longer lasting organs? Does today's meeting defend or excuse the status quo in transplant drugs, which patients have said very clearly for eight years, is

totally unacceptable.

And three, does today's discussion advance pathways to spur innovation and transplant drugs within this decade. And I emphasize within this decade for a very important reason. In 2019, the Executive Order on Advancing American Kidney was held, was signed. And in 2019, the American Association of Kidney Patients declared the decade of the kidney to focus national attention on moving innovation forward across the spectrum of kidney disease for all kidney patients, including transplant drugs.

It's about to be 2024, halfway through that decade, almost. And the question that we would like to know is, within our lifetimes, before we lose more friends and tremendous advocates, as we have in just the past couple of months, will we be able to see drugs that have a better future and have organs last longer for the folks that are coming behind us? And I think FDA needs the answer that question, because they're about to make a decision that will impact the lives of Americans to have kidney transplants and want

kidney transplants.

But just as importantly, the decision that FDA will make in the next several months is actually the operative whether or not national policy will be operationalized or not. And that's a significant concern, and it should be, to the Congress and to the President, because policy drives science as much as science informs policy.

And you have three presidents now, multiple cabinet officers, that put it on the line for patients because they listened, and you have multiple congresses. The question is, will FDA act? Government has the power to convene, and they have a duty to act. It's important to have the discussions and the open debates that we're having today.

But FDA is not a think tank and is not a faculty lounge. It's an agency that's responsible for protecting the lives of all Americans. And it's an agency that's responsible for ushering innovation when the president of the United States and the U.S. Congress have said to move forward, and they have been

very clear about moving forward. The patient voice is clear, and it will be well represented today.

I congratulate my fellow patients that are there in the room, I would love to join them. But on behalf of all the patients, especially those who are no longer here, we ask folks to consider these things because we think they are vitally important. And we think that patients have a disproportionate interest in any discussion that happens about transplant drugs. Thank you very much.

DR. BELEN: Before I introduce the next session, I have a housekeeping reminder, especially for FDA employees who are attending this session. Please order your lunch in the morning because the cafeteria will be closed at noon today.

I'm happy to introduce the next session, Efficacy Endpoints for Kidney Transplant Prophylaxis of Rejection Trials. And our moderator is Dr. Aliza Thompson and Dr. Peter Nickerson.

DR. NICKERSON: Thanks, Ozlem. I want to just acknowledge excellent opening by both Dr.

Poggio and Paul Conway. I think you've heard the -- the clear, shared interest of unmet needs. I would agree with Paul that there is absolutely ongoing unmet needs, and I think we're all here today to try and identify those and figure out the path forward that will allow new and innovative drug development in this space. I think that's also a shared interest of everybody in the room.

So I commend both speakers for their -- their introductions, and I look forward to this session where we're going to go through various states of where we're at. I think the -- we're going to be hearing lots of data, and with the end of the talks, we're going to invite everybody to come and share their thoughts and ask questions. We're hoping to focus on the data and keep as -- as Paul said, this to be collegial and driving to where we can get new ideas on the table.

So with that, I'm going to introduce Ergun as our first speaker from the FDA, go ahead, Ergun.

DR. VELIDEDEOGLU: Good morning, everybody. My name is Ergun Velidedeoglu. I'm the transplant team leader within the division of Hematology and Transplant Medicine here at the FDA.

I first, want to extend my special thanks to all attendees, both online and in person, and especially to our patient representatives, to Paul Conway, to Kevin Fowler, and other patient representatives, both online and attending in person.

I carefully listened to Paul Conway's talk, and I can say that we share the common goals of extending the life of transplant patients, not just kidney transplant patients, but all transplant recipients and their allograft survival times. And we have been working really hard to achieve that. And this workshop that we are holding today, is a testament to that.

Now, the title of my talk is Current State of Primary Endpoints in Kidney Transplantation Trials. In the first part of my talk, I will try to give a brief history of the advances in the science of

transplantation and what type of primary endpoints have been used for the approval of immunosuppressants. And in the second part, I will be talking about special attributes of the BPAR, biopsy proven acute rejection endpoint, and why we believe that it is still a relevant primary endpoint.

I'm trying to advance the slide. Okay. So this is my disclaimer. So starting with the history, first successful kidney transplantation between monozygotic twins with long term graft survival was accomplished long time ago, in 1954. And long-term graft survival was achieved. And obviously, no immunosuppressive treatment was needed.

Subsequent outcomes with immunosuppression requiring transplants were not so encouraging. As presented at the 1963 Human Kidney Transplant Conference, held in Washington DC, out of the 244 kidney transplants reported at that meeting, only 11 allografts survived more than 12 months. And a patient that was excessive, over immunosuppression was incriminated as the main cause of death.

So on this slide, you see the landmarks, or some of the important landmarks, in the history of kidney transplantation, starting with 1954, ending until the first BANFF conference, which was held in 1991. And as you can see that success was accomplished based on many factors, not just based on the approval of new immunosuppressant drugs.

And parallel to those scientific advances, you see that the rejection rates have decreased, and patient and graft survival times have increased. So the evolution of the primary endpoint followed the scientific progress. Since one year survival rates and kidney transplantation approach 100 percent, patient and graft survival endpoints were replaced by acute rejection endpoint. And but that's -- and graph losses are still imputed as events.

So the first immunosuppressant drug approved by the FDA is Azathioprine, and that was approved back in 1968 for the prevention of rejection indication, base -- based on five-year patient survival rate. And second drug to follow was the

equine, the horse anti-thymocyte globulin, that was a Seaver approval in 1981. And that was approved for the management, or in other words, treatment of allograft rejection, based on rejection resolution endpoint.

Cyclosporine, which was a groundbreaking discovery, was approved in 1983, based on one year graft survival endpoint. OKT3, which happens to be the first monoclonal -- monoclonal antibody ever approved by the FDA, was approved in 1986, for the treatment of acute rejection based on reversal of rejection, and one year Kaplan Meier graft survival rate.

In 1994, a milestone event took place and that was the Biologic Response Modifiers Advisory Committee. The meeting was convened to provide guidance to sponsors. Advisory Committee members were asked whether they agreed a decrease in the proportion of patients experiencing a rejection episode in a set time interval is an appropriate primary endpoint for approval of new agents. The committee agreed, and

after that advisory committee in 1995, CellCept was -- Mycophenolate mofetil, was approved based on the BPAR endpoint, the biopsy proven acute rejection endpoint, and superiority was demonstrated.

Tacrolimus, with the brand name Prograf, was approved in 1997 for the kidney indication, but at the time it had already been approved for the liver indication in 1994. And the regimen that was approved was Prograf plus azathioprine.

Subsequently in 2009, Prograf plus MMF regimen was approved. The first approval with azathioprine was based on similar one year patient and graft survival rates, and the second approval in 2009, was based on BPAR rates and Symphony Elite Trial was utilized for that purpose.

In 1997 and in 1998, two CD-25 monoclonal antibodies were approved back-to-back for induction immunosuppression. The first one was Daclizumab and subsequently in the following year, Basiliximab was approved. Both were approved based on

BPAR endpoint. Here you see Basiliximab approval.

Anti-thymocyte globulin, rabbits, which has the brand name of Thymoglobulin, was first approved for the treatment indication, meaning treatment of acute rejection, in 1998, based on a renal function-based endpoint. That was return of serum creatinine back to -- back to the baseline within 14 days. Subsequently Thymoglobulin was approved for the induction, or in other words, prophylaxis of rejection indication in 2017, based on BPAR endpoint.

Sirolimus was first approved in 1999, based on BPAR endpoint as a fixed dose regimen. Subsequently, it was approved with therapeutic drug monitoring in 2003, following cyclosporine withdrawal based on graft survival endpoint.

Myfortic, mycophenolate sodium, was approved based on BPAR endpoint in 2004. And Sirolimus, I -- I'm sorry, Everolimus was approved, again based on BPAR endpoint. This time it was treated BPAR, in the context of a noninferiority trial

in 2010.

Belatacept, the first monoclonal antibody for maintenance immunosuppression in transplantation, was approved in 2011, based on two randomized control trials, which utilized BPAR endpoint and noninferiority was demonstrated in both trials.

So regarding the clinical endpoints in general, a clinical trials endpoints measure the outcomes in the trial. A clinical outcome assessment is a measure that describes or reflects how a patient feels, functions, or survives. Efficacy endpoints are measures intended to reflect the effects of a drug.

Coming back to biopsy proven acute rejection, some of the important statistical considerations are, BPAR is a clinically meaningful and sensitive endpoint, makes calculation of noninferiority margin possible. And intent to treat analysis is recommended. All patients are followed for outcome, regardless of treatment compliance.

Patients with death, graft loss, are

considered as having intercurrent events, which are handled using the composite strategy. This means that these are also counted as events in the analysis. Missing data, loss to follow up, should be minimal. Initially, they are imputed as failures but different types of analysis with and without imputation are also conducted.

Regarding the important clinical considerations of BPAR endpoint, in other words, how it relates to how the patient feels, functions, and survives, acute rejection is a direct measure of immunosuppressive efficacy, which is the main purpose of the treatment. Diagnosis and treatment of acute rejection is associated with significant morbidity, graft biopsies, or invasive procedures.

Hospitalization is generally likely during the diagnosis and treatment of an acute rejection. Rejection treatments are associated with increased risk of infections, malignancies, cardiovascular events, hyperglycemia, diabetes, and gastrointestinal complications.

Acute rejection, in addition to being a clinical endpoint, as demonstrated above, impacts long term graft and patient survival. So as an example, this slide shows the 36-month outcomes of deaths, graft losses, and combined death and graft loss rates in the belatacept trials that supported approval. In the upper half, you see the benefit trial. Outcomes in the lower half, you see the extended criteria trial outcomes.

By the way, all this information is in the package insert, not in tabular format, but in textual format. And you can also find this table in the publicly available BLA review, the FDA BLA review.

So you only need to pay attention to the numbers in bold, which present the combined death and graft loss rates. And if you look at the benefit trial, the upper half shows the patients who experienced BPAR initially. And the lower half shows patients who did not experience BPAR. As you see, there's a common trend of increase death and graft loss rates in patients who experienced BPAR, based on

the 36-month outcomes.

Just as an example if you look at the first regimen, that's not the approved regimen, but it's, you know part of the trial. Moderate intensity regimen, the -- this rate was 6 percent among patients with no BPAR, versus 16 percent in patients with BPAR. In the approved regimen, which is the lower intensity regimen, the middle column, the combined death and graft loss rate was only 4 percent in patients who did not experience BPAR, but it was 22 percent in patients who experienced BPAR.

In the cyclosporine arm, the trend is not conspicuous, and that's mainly because the Banff grades of rejections in the cyclosporine arm were just too low. It was mainly 1As and 1Bs. And if you look at the benefit, extended criteria trial, again, you see the same trend with belatacept and my regimen being the outlier here, but I don't want to go into the details because that's the -- that's outside the scope of this talk.

It did -- a few additional

considerations on BPAR. There is a concern in the community that despite the decrease in acute rejection rates and excellent one year patient and graft survival and kidney transplantation, long term outcomes are lagging behind. And we have just seen in Dr. Poggio's presentation, and also as published by Hariharan, long term outcomes are improving -- improving, have been improving. Despite the usage of lower quality organs because of the expanded donor pool.

But that doesn't mean that, you know, we have reached the ceiling. There is certainly a lot of room for improvement, and we will keep striving for the better. Those rates should continue to go up.

And another additional concentration on BPAR is the seven year follow up data from the belatacept trials that supported FDA approvals, suggest that belatacept patients have better or similar long-term patient and graft survival compared to the control arm, despite a high rate of acute rejection with belatacept.

So we would like to remind that the long-term extension trials, which included data up to seven years, are not randomized control trials. So over 30 percent of the original randomized patients were not enrolled in the seven year follow up long term extension studies. That precludes meaningful assessment of comparative efficacy and safety. You can find further information on these in belatacept package insert, in Section 14.

So in summary, effective prevention of acute rejection enables successful transplantation, BPAR continues to be clinically relevant and BPAR at one year can establish clinical benefit. Given the great success on lowering the BPAR rates at one year and acknowledging the room for improvement in long term graft survival rates, additional endpoints may further inform the potential of a therapeutic intervention for long term graft survival, if supported by adequate data. Thank you.

DR. THOMPSON: Thank you, Ergun. Our next speaker in this session is Dr. Jeffrey Siegel,

who is the Director of the Office of Drug Evaluation and Sciences. Jeff.

DR. SEIGEL: Thank you, Aliza. Good morning, everyone. In my talk this morning, I'll be discussing surrogate endpoints and the evidentiary standard for accepting surrogate endpoints and reasonably likely surrogate endpoints.

So the FDA, along with colleagues at the NIH, discussed a number of years ago, the different types of biomarkers and how they could be used in drug development programs and put together the best resource to finding these different types of biomarkers. These different categories of biomarkers are shown here, with the top ones being measures of disease presence and status, such as diagnostic biomarkers and prognostic biomarkers, and the ones down below being measures of aspects of response to treatment.

And a particularly important category of the latter are pharmacodynamic, or response biomarkers, including the very important category of

surrogate endpoints. When we think about biomarkers, we think about the best biomarker category, such as a surrogate endpoint biomarker, and the way that biomarker will be used in a clinical trial, or clinical development program.

When we evaluate the data to support their use, we think about the extent of evidence needed for qualification, including the analytic validation and the clinical validation. And what we mean by analytic validation is the sensitivity, the specificity, the reliability, and the accuracy of the biomarker.

For clinical validation, we're talking about the relationship between the biomarker and a particular clinical concept of use. So one particular consideration for clinical validation is the benefit risk for that biomarker. And the benefit risk is quite different than what we're talking about for a new drug.

For a biomarker, the benefit would be the benefit for clinical development program, for

example, for allowing for shorter, smaller clinical trials. And the risk would be the risk to patients of accepting use of a biomarker and a clinical development program if the biomarker actually does not measure the concept -- clinical concept of interest.

There are three different ways that biomarkers can be accepted in clinical development programs. One is by scientific community consensus, which is used sometimes. Another is for pharmaceutical companies to submit the data supporting the biomarker directly to the review division, the FDA, for its use in a particular development program.

And the third is the biomarker qualification program. This is a program where biomarker developers can submit a letter of intent saying what biomarker they're proposing to develop. Then, if that's accepted by FDA, a qualification plan is submitted, describing how the biomarker will be validated.

Finally, the biomarker -- the full qualification package is submitted with all the data

supporting it's used for a particular concept of -- content -- context of use. If that full qualification package is accepted, then the FDA will qualify the biomarker and share that publicly. And any drug developer is free to use that biomarker for that particular context of use in their drug development program.

In general, the FDA will approve a new drug based on evidence that it improves the way that a patient functions, feels, or survives. In some situation, biomarkers can be used to support drug approval, if they're -- if they're shown to reflect the way a patient functions, feels, or survives.

And two particular categories of surrogate endpoints that can be used in this way. One is a validated surrogate endpoint, one that's accepted by FDA based on evidence that the biomarker predicts a specific clinical outcome, validated endpoints have strong and diverse evidence supporting the relationship between the biomarker and the outcome. And these types of biomarkers are used to support

traditional approval.

In contrast, a reasonably likely surrogate endpoint is an endpoint supported by strong mechanistic and/or epidemiologic rationale. So it's believed that the effect on the surrogate is expected to be correlated with a clinical benefit but has not yet reached the standard for full validation.

Reasonably likely surrogate endpoints are used for accelerated approval for a product intended to treat a serious or life-threatening disease or condition. It's important to consider the limitations of surrogate endpoints. They're not a direct measure of the way a patient feels, functions, or survives. Instead, they're intended to predict the clinical benefit, but don't measure directly.

So the benefit risk assessment for a new drug, based on a surrogate endpoint, is based on assumptions and predictions of benefit. And in some cases, biomarkers actually have not predicted clinical benefit. For a surrogate endpoint that's reasonably likely to predict the clinical benefit, is relied upon

to support accelerated approval. For these situations post-marketing, confirmatory trials are required to verify the clinical benefit.

Let's discuss a few ways that surrogate endpoints may have limitations for use in approval of new drugs. The simplest situation is where a biomarker is on the causal pathway to disease. If a drug has an impact on the biomarker, then it's inferred that it will have a causal impact reducing the clinical outcomes.

In other situations, the biomarker is not on the causal pathway, but it's correlated with clinical outcomes. In this situation, an effect on the biomarker may not impact clinical outcomes.

And in other situations, the biomarker may actually be on the causal pathway, but other events may prevent an impact on the biomarker from predicting an impact on clinical outcome. One would be where the drug has a negative impact on the clinical outcome, and another situation would be where the drug has a toxicity that counterbalances the

clinical benefits.

There are many different types of surrogate endpoint biomarkers. Some are shown on this slide, and I won't go through all these. But sufficient to say that some are causal biomarkers. So these would be, for example, HIV, viral load for HIV disease. Others reflect pathways or mediators in different pathways leading to disease. In this situation, it's important to consider they may be multiple pathways leading to disease.

So the effect on a biomarker may or may not predict clinical benefit. Other biomarkers reflect organ function, and these are the ones that could be closest to clinical outcomes.

LDL cholesterol can serve as a good example of a sort of a validated surrogate. As shown on this slide on the left, 25 trials of statins showed that the impact on LDL cholesterol was directly related to the impact on the risk of cardiovascular events. Furthermore, as shown on the right, in eight non-statin trials, it was shown that the impact on LDL

also was associated with the impact on cardiovascular outcomes.

However, there are other situations where biomarkers have not served as good surrogates, even though the initial data indicated that they might. One example of this is HDL cholesterol, where epidemiologic data, as shown on the left here, was very closely associated with -- showed a close association between HDL cholesterol levels and the risk of cardiovascular events. Where higher HDL cholesterol levels were associated with lower risks of cardiovascular events.

However, when a drug was developed, that effectively increased HDL levels, as shown by the two red circles on the left, the outcome of the study of this CETP inhibitor, torcetrapib, showed that even though it increased HDL cholesterol levels, it had no impact on cardiovascular outcome events. It's not known exactly why this is, but it's just a cautionary tale that makes us be thoughtful about use of surrogate endpoints as approval endpoints in clinical

trials.

There are a number of different sources of data to support validation of a surrogate. Randomized trial data at the treatment group level showing a relationship between the change in the surrogate and the change in the clinical endpoint are particularly impactful. Individual patient level data for interventional trials are important. Observational data can be very helpful, showing relationship between the biomarker at one point in time and the clinical outcomes later.

And then other sorts of data include mechanistic data, pharmacodynamic studies, showing the change in the surrogate, leads to modulation of important causative pathways of disease. And then human genetic data and translational animal models, in some situations, may support use of a surrogate.

On the right is shown how these different types of evidence play into validation of a reasonably likely surrogate, versus a validated surrogate. The mechanistic data are very important

for supporting reasonably likely surrogates, but the clinical data, including randomized clinical trial data, are very important for assessing whether a biomarker is fully validated for use in clinical development programs.

I'm going to begin by -- end by sharing two examples of recently developed, reasonably likely surrogate endpoints. The first is the use of total kidney volume in -- as a reasonably likely surrogate endpoint for autosomal dominant polycystic kidney disease. The effort to validate this biomarker was developed by a consortium led by the Critical Path Institute.

They aggregated data from many different sources and were able to put together a model that related total kidney volume at baseline take into account covariates, such as baseline estimated glomerular filtration rate and age, with the long-term rate of loss of kidney function.

As shown on the right, you can see that for a particular level of total kidney volume, 1.7

liters in this case, and particular age, that you could predict quite accurately what the rate of loss of kidney function would be. So that at seven years, it was expected that 50 percent -- there would be 50 percent of patients with a 30 percent loss in kidney function.

These data were used to qualify total kidney volume as a prognostic biomarker for autosomal dominant polycystic kidney disease and subsequently was applied in individual drug development programs, and the data allowed acceptance by the FDA review division of total kidney volume as reasonably likely surrogate endpoint for accelerated approval.

The second example I'd like to share of a reasonably likely surrogate endpoint is proteinuria for IGA nephropathy. Here, the data consisted of three types. One is mechanistic data, tying urine protein, to kidney damage. The second was epidemiologic studies, showing a consistent association between the severity and duration of proteinuria and loss of kidney function. And the

third was interventional trial data, showing an association between change in proteinuria and clinical outcomes.

This graph shows the relationship between different levels of proteinuria on the x-axis, and the slope of loss of kidney function on the y-axis. If you look on the far right and IGA nephropathy, you can see with increasing levels of baseline proteinuria, there's a clear and consistent increase in the rate of loss of kidney function, with each grade of increased proteinuria.

In the middle graph, in focal -- focal segmental glomerulosclerosis, there is a relationship but it's less clear. It's only at high levels of proteinuria where the association is most marked. And in the left, membranous glomerular nephropathy, you can see there's even less clear association, where only at the very highest levels is there any association between baseline proteinuria and loss of kidney function over time. This shows that a surrogate endpoint for one condition may not serve as

a good surrogate endpoint for others.

The third category of evidence was the relationship between interventional trials showing improvement in proteinuria, and the impact on loss of kidney function over time. In this graph, you can see the circles on the right are for studies where there was relatively little effect of the intervention on proteinuria. And there was also relatively little effect on the rate of loss of kidney function over time.

In contrast, the circles on the left showed that for treatment trials, where there was an improvement in proteinuria, there was a concomitant improvement in the rate of loss of kidney function over time.

So to end, to support a surrogate, getting to acceptance, there are a number of important considerations. One is it's context dependent. In rare, serious diseases with unmet medical need, there may be more of a imperative to consider use of a surrogate endpoint versus other settings. It's

important to consider the impact of accepting the surrogate. What are the risks of approving a drug based on a surrogate.

Different levels of evidence are needed for validated surrogate versus recently likely surrogate. And multiple sources of evidence are important, including biologic plausibility, supported by varying extent of clinical pharmacology, and clinical trial evidence.

And finally, convergence of evidence between these different sources of data are very important to provide confidence that this surrogate is truly likely to predict clinical outcomes. And with that, I'll end and thank you for your attention.

DR. THOMPSON: Jeff, thanks for that great overview of surrogate endpoints and evidentiary considerations. Our next speaker will be joining us remotely and is Hrefna Gudmundsdottir. And Hrefna, I very much apologize for mispronouncing your name. Hrefna is Chief Medical Officer of the Icelandic Medicines Agency.

DR. GUDMUNDSDOTTIR: Thank you. Can you all hear me?

DR. THOMPSON: Yes.

DR. GUDMUNDSDOTTIR: Okay. Very good. Thank you so much for inviting me. I wish I could see the audience. It's always more fun to be able to read the faces, you know, see if people fall asleep or if they are awake, and alert, and so on.

But I saw the room before the start -- we started, and I saw how it's set up. So that's a little helpful and I've seen you. Thank you. So I think we are good to go.

So I'm here to talk about iBox as an endpoint. The EMA perspective, this is came to us for qualification opinion to -- you can go to the next slide -- to determine if this could be used as a -- one slide, yes. If this could be used as a surrogate endpoint to predict the graft survival at five years in order to use in clinical trials and approve novel immunosuppression.

And we can go to the next slide. So

the -- this -- you will hear more of the -- of the group doing the work in the -- in the lecture to come. But this work started in France, Europe. And the initial work was to assess this as a prognostic marker. This marker in transplantation, and later it evolved to use this as a surrogate marker.

And this is the derivation dataset they used, is shown there for thousands of participants in -- from Europe. And I will explain later the difference between the full and the abbreviated iBox, the follow up for ten years. So this is quite my typical. Can we go to the next slide?

Now, for the results of the derivation dataset, we abbreviate the factors going into the abbreviated iBox and the full life of the cylinder to the right. We abbreviated health GFR as a continuous variables, qPCR, proteinuria, and then don't -- then antibody -- donor specific antibodies as a binary variable less than greater than -- than 1400.

And then the full life of the results are -- the result of a biopsy -- a biopsy, to

fibrosis, atrophy, and inflammation of various -- and glomerulopathy. So this is from the -- from the derivation dataset, and you can see the -- the beta coefficient -- coefficient efficients in the tables together. So that's the impact of each of these factors. And we'll go over that later on.

The next slide. So when you put all of this together, you'll see that the distribution of the -- of the iBox score, in yellow, those who do not have a graft loss, and those who do have a graft loss. And having a lower iBox is better, is less graft loss compared to the ones to the right. But there's a lot of overlap, clearly.

And you can go to the next slide, then. And, of course, part of assessing this association between the iBox and the outcome is, of course, a curve and the -- the performance here is modest. You would, of course, want to have as few true negatives as possible and as many true positives as possible. And you know, if there's a difference of minus two, then the associated is the only model. And this is

from the derivation datasets. So there's already some concerns in the performance of this of the surrogate.

So next slide. Now, to validate this -- the validation of this surrogate included four datasets from Mayo and Helsinki and Finland, and then control times the benefits of the benefit extended donors on GCP, the numbers in these trials, 1500 or 1700, depending on if the biopsy data was included and -- and 10 years of follow up.

Next slide. And looking at the -- the -- if you pause it a little bit and go over the -- the factors going into the iBox, you have the GFR and you have the proteinuria, and you have the antibodies, and the transplant scores from -- from the -- not the transplant, but biopsy scores.

And for GFR, of course, has a -- has a great impact. And because you have -- it's a continuous variable, so it adds up if the difference becomes greater. The proteinuria, that was some concern with the proteinuria in this because out of the four trials, three of them only had 60

proteinuria. So what they did was to impute the dipsticks to -- to us the UACR, but one -- one nephrology will tell you that that is really valid. Difficult because the dipstick does not take into consideration, or actually, it doesn't correct for the -- the concentration of the urine, whereas UACR correct for how concentrated the urine is, and so reflects the protein in our urine, proteinuria. So it doesn't really tell you exactly the same thing.

And another consideration with the proteinuria is transplant nephropathy. Of course, as you heard, a lot of different causes and but most of these do not cause a lot of proteinuria. And if you see a lot of proteinuria, you would probably think it's -- everything was returning. And so your approach would be not to expect a -- a rejection, chronic or acute of any kind, of the original disease.

Now, the GFA, it was a binary variable. The -- the -- it was assessed very thoroughly, and I think, from what I understood, is that the -- the data really did not allow this to be a continuous variable,

so this is what we have.

The -- one would think that the transplant -- the biopsy scores would add a lot, but in truth, it was surprising, really, the -- the impact that the -- the transplant -- no, the biopsy -- transplant biopsy had.

And you can go to the next slide. This here, we have the four trials that we used to validate the data. You have the compound observational studies from Helsinki and from -- from Mayo, and then the combined randomized control trials. And you have the observed and the predicted event. Of course, you want this to be the same as you want the P value to be close to one.

The -- the observed and predicted are very similar for the compound -- for the randomized control trials, but it is in a different direction for the Helsinki and the Mayo -- Mayo trials. The -- these datasets from Helsinki and from Mayo, they were a little different. There was more living related donors in one of the -- and -- and induction therapy

was different in TP3 versus anti IL2 two, so I don't know if this would explain it. But of course, in the validation data set, you would want to have different types of -- of treatments in the dataset.

So next slide. And we mentioned that the -- the having the biopsy results did not really add them, up until we see the t statistic for both the full iBox and the abbreviated iBoxes, did not include the biopsy results. And the -- the statistics really are very comparable. Somewhat surprising, I would say, but this is what the data showed.

Now, if we continue to the next slide. Now, finally, and this is probably the most important slide, this is a trial level surrogacy for the -- for the -- for validation dataset. And on the x-axis, you have the treatment effect, meaning the change in -- the difference in iBox score between two treatment arms. And how much that really translates into graft failure on the Y-axis. And if there's no change in iBox, so why accept this as zero. There's no change in -- in graft failure, but the line is really not

very steep, and the confidence interval is really very broad.

So you can go to the next slide. With that, the conclusion from -- from this evaluating process was that this could not be approved at the surrogate or a primary efficacy endpoint to support efficacy or to support regulatory approval in -- in transplantation. However, that was the easy part of all of this, was the need for such a surrogate input was clearly, we were all in agreement with that. So that did not require a lot of discussion.

And the overall validation approach was endorsed, because the consortium did a very good job in -- in the assessments that they had. The context of use was modified and refined. And so the -- the problem here was really that the database was very limited in the size. There was a very low numbers and events, and there were some issues, as I mentioned, with the with -- the factors going into the iBox. And so many things that prohibited us from approving data as a primary efficacy endpoints, surrogate

endpoints.

However, in order to encourage further evidence generation, we thought that this could be used as a secondary endpoint in order to create data and text, in order to move this forward. Now, the -- the qualification opinion is open to the public and you have the number of the documents there, and you can also just Google qualification iBox -- qualification opinion iBox and EMA, and then you would have exactly that come up. So thank you very much.

DR. NICKERSON: Thank you very much, Hrefna. Our next speaker is going to be Amanda Klein, from the TTC, CPath Consortium. Amanda.

DR. KLEIN: Can you hear me okay? Okay. All right. Well, thank you for the invitation. It is an honor to present on behalf of the Transplant Therapeutics Consortium.

Next slide. Oh, that's me. Let's see. Thank you. All right, these are my disclosures. Okay. So in 2017, the American Society of Transplant Surgeons and the American Society of Transplantation

partnered with the Critical Path Institute to create the Transplant Therapeutics Consortium.

TTC is a public private partnership among scientists from the biopharmaceutical industry, diagnostic companies, academic institutions, professional societies, and their patient advocacy groups, and government and regulatory agencies all dedicated to advancing the regulatory science needs of transplant.

Thanks to current immunosuppressive therapies and management, and clinical practice, graft survival a one-year post transplant is excellent. Unfortunately, long-term graft loss remains an unmet need that is not adequately addressed by current therapies. So TTC's focus has primarily been seeking FDA qualification of the iBox as a reasonably likely surrogate endpoint for long-term graft survival after kidney transplantation.

My presentation today will focus on why iBox, as a reasonably likely surrogate endpoint, is currently the best option for bringing new therapies

into transplantation for kidney transplant recipients.

The current regulatory standard for the primary endpoint and immunosuppressive therapy registration trials is not adequate to address long-term graft loss. No therapy is approved for preventing long-term graft loss. All currently approved immunosuppressive therapies are indicated for the prophylaxis of -- of organ rejection, as Ergun had shown earlier.

BPAR, while correlated with long-term graph survival is neither prognostic nor predictive of long-term graft survival. And in transplant, traditional approval of immunosuppressive therapies have required two phase three RCTs. This has impacted immunosuppressive therapy development for transplantation.

No new immunosuppressive therapy demonstrating improved efficacy has been developed for over two decades. No new immunosuppressive therapy has been approved for the prevention of organ rejection for more than a decade. No new

immunosuppressive therapy is currently in phase three clinical trials.

The inability to improve upon the current efficacy failure endpoints, and the lack of an endpoint prognostic for long-term graft survival has stifled new immunosuppressive therapy development and transplantation. Several composite scores have been proposed as surrogates, but iBox, as described in Loupy, et al., 2019, led by the Paris Transplant Group, is the best surrogate for late graft failure.

The iBox is based on extensive epidemiologic and prognostic data, the largest data set of 4000 kidney transplant patients, and is specifically designed to predict long-term graft survival.

From a mechanistic standpoint, the iBox includes measures of kidney function. You'll see eGFR and proteinuria, alloimmune response to the donor kidney in the form of donor specific antibody, and damage to the transplanted kidney, the histopathological findings on kidney biopsy.

So while eGFR is a driving component of the iBox, the prognostic ability is further enhanced with each additional component of the iBox, allowing for a comprehensive assessment of kidney graft health.

In close collaboration with the Paris Transplant Group, TTC translated the work from this publication into a regulatory endpoint for long-term graft survival. We developed two versions of iBox that Hrefna had described previously, with and without biopsy. And this was based on feedback from the transplant community that obtaining biopsy samples tends to be problematic due to compliance issues. Therefore qualifying two iBox models will provide sponsors the flexibility in clinical trial design, whether they want that surveillance biopsy.

So this -- this table describes the evidentiary standards from --for qualifying a surrogate endpoints between FDA and EMA. FDA defines a reasonably likely surrogate endpoint as an endpoint with strong mechanistic and/or epidemiologic rationale, but without sufficient clinical data, that

is clinical trial data showing that it is a fully validated surrogate endpoint.

EMA does not have an endpoint analogous to an FDA reasonably likely surrogate endpoint. A validated surrogate endpoint is an endpoint with clear mechanistic rationale and clinical trial data to show that the effect on the surrogate predicts a specific clinical benefit. And this is consistent with the evidentiary standards for EMA.

TTC agrees with Hrefna that more evidence generation is warranted to make iBox a fully validated surrogate. We believe that the only way to generate more evidence is by qualifying iBox as a reasonably likely surrogate endpoint, which will include the mandatory five year follow up data that everyone is looking for.

TTC believes that iBox meets criteria for a reasonably likely surrogate endpoints supported by strong mechanistic and epidemiologic rationale, and without sufficient clinical trial data.

A reasonably likely surrogate endpoint

can be used for accelerated approval of drugs. iBox meets all criteria for FDA accelerated approval pathway. Does it treat a serious condition? Yes, graft loss is a serious and life-threatening condition.

Does it provide a meaningful advantage over available therapies? Yes, it allows the superiority of a new therapy and a new indication. Remember, all currently approved immunosuppressive therapies are indicated for the prophylaxis of organ rejection.

Is the endpoint reasonably likely to predict a clinical benefit? Yes, iBox is a reasonably likely surrogate endpoint at one year is prognostic for five-year graft survival, demonstrated in over 5000 kidney transplant patients across all immunosuppressive therapies globally.

TTC has a determination letter for the iBox as a reasonably likely surrogate endpoint. TTC recognizes that the proposed reasonably likely surrogate endpoint cannot be used alone as a sole

primary endpoints, nor can it replace efficacy failure. As such, TTC submitted the qualification plan, the second stage of the three-stage process, to FDA this past July, with a modified context of use to include co-primary with efficacy failure.

This option does not compromise FDA's current standard, and in fact, would be held to higher standards than the current efficacy failure endpoints while providing sponsors a pathway to accelerated approval.

TTC conducted analysis comparing the prognostic performance of iBox to BPAR for long term graph survival. This was demonstrated in discrimination and calibration analyses. For iBox, C statistic values of at least .7 were consistent across data sets, indicating good discriminatory ability, while the C statistic values were below .7 for BPAR. And remember, BPAR is defined as TCMR grade 1A or greater.

So likewise, the calibration analyses demonstrate the iBox has good prediction accuracy,

while BPAR does not. iBox is superior to BPAR as a prognostic indicator of long-term graft survival. And lastly, Fitzsimmons and Naesens literature review showed that BPAR is not predictive of a treatment effect on graft survival.

TTC has developed an example draft language for labeling a new immunosuppressive therapy for kidney transplantation approved based on the iBox as a co-primary endpoint with efficacy failure under accelerated approval. This indication would be for the prophylaxis of organ rejection, consistent with the current standard for immunosuppressive therapy approval, and now with an improvement in the iBox in kidney transplant, this indication can be modified after the five-year mandatory confirmatory evidence, demonstrating an improvement in long-term graft survival.

We know what the accelerated approval pathway with surrogate endpoints has done to stimulate and incentivize new therapies and oncology. Still, there are also non-oncology indications, HIV,

Alzheimer's Disease, sickle cell disease, Fabry Disease, IGA nephropathy.

Let's dive more into IGA nephropathy, as an example. In 2020, there were no approved therapies. In 2023, there were two drugs approved, both through the accelerated approval pathway. And presently, there are five therapies in phase three development. Although not directly linked to the accelerated approval pathway, all prior accelerated review approvals have been based on one pivotal trial.

All right. So let's look at outcomes for patients living with IGA nephropathy and kidney transplants. You'll see this figure shows the end stage renal disease-free survival, meaning not on dialysis, needing a kidney transplant, or having a diagnosis of CKD stage five, over time, for patients with IGA nephropathy in red, versus a matched cohort from the general population.

Over 50 percent of patients living with IGA nephropathy have functional kidneys out to 30 years. When we overlay this figure with current

kidney transplant graft survival outcomes in the United States, graft survival is only 74 percent at five years post-transplant.

Now, let's look at patient survival. Patients living with IGA nephropathy have survivals out to -- over 75 percent out to 20 years. Comparatively, patients living with a kidney transplant have survivals of only 84 percent at five years. Graft loss is a serious life-threatening condition in which there are no drugs approved for preventing long-term graft loss.

TTC is united with patients in wanting to advance the development of new immunosuppressants, just as the accelerated approval pathway has done for other therapeutic areas, including IGA nephropathy.

I'm going to summarize why iBox is our best option for bringing new, innovative therapies in transplantation for kidney transplant patients in these six bullet points.

iBox is the only endpoint in the FDA biomarker qualification program addressing patient

regulatory and clinician needs. It is the best prognostic endpoint for long-term graph survival. It allows the superiority of a new therapy and a new indication. It does not preclude traditional approval on efficacy failure, if iBox fails, but meets non-inferiority on efficacy failure.

The current efficacy failure BPAR and endpoint remains, and we believe BPAR remains a relevant endpoint, which should be used as a co-primary endpoint with iBox as a reasonably likely surrogate endpoint.

And lastly, it is the opportunity to incentivize the introduction of innovative graft preserving therapies through accelerated approval compared to traditional approval.

We've spent five years collecting and curating all the available data. And we know there are no more RCTs to obtain to use in the FDA qualification submission. Qualification of the iBox as a reasonable likely surrogate endpoint for the use in the accelerated approval pathway will include the

mandatory five year follow up data to generate the evidence everyone is looking for.

TTC believes iBox can revive therapeutic development in kidney transplantation directly addressing the unmet patient need for new therapies to improve the quality of life and extend the life of their transplanted organ.

So thank you for your time and thank you to the TTC for your ongoing support and dedication to transplant drug development.

DR. THOMPSON: Thank you, Amanda, for that overview of the iBox, as well as the CPath and TTC perspective.

Our next speaker is Dr. Nadia Chaudhri. Nadia is a medical officer in the Division of Rheumatology and Transplant Medicine.

DR. CHAUDHRI: Thank you. Thank you to the panelists, thank you to our virtual and in person attendees. I'm actually trying to figure out -- okay.

So I'll be talking about estimated GFR as a surrogate endpoint from a regulatory perspective.

Okay. Oh, let's see. Okay. This is my disclaimer slide. This is not intended to convey any official US FDA policy, and I do not have any financial interests or conflicts of interest to disclose.

Here's an outline of my talk for today. I will first define -- introduce some definitions of kidney function as a surrogate endpoint, and then provide a brief reference to the CKD space where eGFR has been used as a surrogate endpoint. And then discuss a potential confounder in the use of this surrogate endpoint. And then describe some publications that have evaluated clinical outcomes and how they relate to the relationship of eGFR and clinical outcomes in kidney transplant.

So this slide provides a very brief summary, an introduction into potential definitions, which could be a topic of a workshop in itself, in terms of how to define kidney function. The first on your right in the box in the top right would be looking at a large change in serum creatinine, such as a doubling of serum creatinine.

But as many of us know, in the nephrology and transplant community, that creatinine can be confounded by non GFR determinants, including muscle mass, muscle breakdown, as well as medication effects from CNIs and others, such as trimethoprim sulfamethoxazole.

The next option would be looking at a reduction in the rate of GFR decline, which is also not perfect, and can be confounded by reversible medication effects. I will be providing some examples of use later.

So this slide provides a summary as a reference to how eGFR is used in the CKD space. The top box describes the clinical endpoint of end stage kidney disease defined as treatments, dialysis, transplantation, and eGFR less than 15 mls per minute.

Below that is an accepted surrogate of doubling of serum creatinine, which correlates approximately to a 57 percent decline in estimated GFR. And as we have learned, there were two surrogates that were approved through the DCN division

with -- in two separate workshops. One was in 2012 that was sponsored by the NKF and FDA. And based upon data analyzed and presented at this workshop, this was a greater than 40 percent decline in eGFR was considered a validated surrogate endpoint.

Subsequently, in 2018, the NKF, FDA, and EMA came together for another workshop to evaluate relationships of GFR to clinical outcomes in kidney disease for earlier stages of kidney disease. And the conclusion of that workshop was determined that a GFR slope reduction of a specified amount measured over an adequate time could be validated as a surrogate endpoint.

But I'd like to highlight that it is important to note that CKD, as we know, cannot be equated fully with chronic allograft injury, and that there are specifications about how these endpoints are even used in the CKD space.

And more importantly, reversible effects of treatment as highlighted in summaries of both of these workshops on the treatment of GFR may

complicate both interpretation of treatment effects and trial designs using such endpoints.

So this is a brief discussion about the reversible hemodynamic effects of CNIs, that many of us who treat patients, are aware. CNIs commonly lead to acute, functional, and generally reversible declines in kidney function, commonly associated with higher trough levels attributed to alterations in intra renal hemodynamics, primarily related to acute afferent arteriole vasoconstriction.

The important caveat -- take home note from this is that this hemodynamic effect on an eGFR based endpoint may complicate interpretation of treatment effects and trial designs.

I will next describe some publications that evaluate relationships of eGFR and various definitions of eGFR with potential clinical outcomes in kidney transplantation.

This first study was conducted by Kaczynski and colleagues and published in 2011. And they looked at data from the port or patient outcomes

in renal transplant study. They looked at 12-month eGFR and subsequent graft outcomes, which were defined as all caused graft failure or death center graft failure, and death with a functioning graft. And they analyzed 13,671 patients, for whom eGFR was reported.

This slide will provide an highlight some of the summary of the results, they had grouped EGFR into CKD stages. So as you can see, as you go down the table, the GFR declines, and there's a stronger association with graft failure that is slightly stronger if censored for death. If you look at the first row in table three, there was a slight blip with a hazard ratio of 1.41 noted, and you can see in the graphs on the right, that that was -- that the highest GFR had a slightly higher risk of graft failure, which goes away when you censor for death.

They do hypothesize certain reasons for this potential increased mortality, which we don't have time to go into today. What I'd like to highlight is a comment from the -- a statement from the article itself, that "The lower kidney function is

associated with worse clinical outcomes. It's not possible to infer that specific measures that alter function will necessarily alter outcomes. And we cannot determine whether different immunosuppressive medication regimens can alter function and thereby outcomes. Only randomized trials can do this."

The next study I'd like to highlight was published in JSON in 2016, and conducted by Clayton and colleagues, where they analyzed data from the Australia New Zealand Dialysis Transplant Registry, evaluating the relationship between percentage of eGFR decline between end of year one and year three post-transplant -- transplant, and kidney transplant clinically -- clinical outcomes defined as death or death censored graft failure. Their -- their analysis included 7949 kidney transplants, with up to 8.5 years of follow-up.

So this slide also highlights and summarizes some of the results that they published. In this table, they looked at different percentage declines of eGFR, categorized here as greater than 10,

20, 30, and greater than or equal to 40 percent. I've highlighted in red to just sort of remind you, as a reference, that the greater than 40 percent eGFR decline was considered acceptable in the CKD space and is also associated with a high risk of graft failure based upon this study.

And then this following table just provides a reference of the doubling of creatinine, which has also even higher association of 9.87.

Finally, the final paper I'd like to discuss is a consensus report that was developed by the European Society of Organ Transplantation and submitted to EMA in 2020. And this slide highlights the bullet points that the Committee for Medicinal Products for Human Use, which is abbreviated as CHMP here, as a part of the AMA -- EMA, excuse me. And this slide summarizes some of the advice from the CHMP based upon this report.

And these are not all the -- some points highlighted in the paper, but what I'd like to direct your eyes to are the final three bullet points

that clinically relevant magnitude of effect size is important. "Clinical significance of the proposed difference and slow progressions between treatment arms should be defined for this specific development. Analyze loss of GFR does not meet all the criteria for a valid surrogate -- surrogate endpoint but is considered a valuable measure of efficacy in addition to the currently accepted hard clinical endpoints, and it should be supported by other clinical measures."

So as a take home and takeaways that I'd like the audience to recall, is that the reversible hemodynamic effects of CMIs will need to be considered and accounted for if eGFR is proposed for future trials. And late graft failure, as Dr. Poggio had also mentioned, is more complex and has multiple different insults, and cannot be equated with native kidney disease.

But for kidney transplantation in particular, we need to remember -- remember that a quantifiable, proposed change in eGFR as a surrogate endpoint, will need to show both a clinically

meaningful and statistically significant effect on clinical endpoints in kidney transplantation. Thank you.

And we're over. I'm sure some of everybody's watch might be, you know, reminding you to stand up. So feel free to stretch your arms in the interim.

DR. NICKERSON: Thanks very much, Nadia. I just want to say for everybody here in the audience, because I've already addressed it online, the slides will be available. They are being posted after the meeting.

It's my great pleasure to introduce Ros Mannon, who doesn't really need any introduction, past president of the AST, and who has contributed abundantly to these forums in the past and is now a Professor of Medicine at the University of Nebraska Medical Center. Ros.

DR. MANNON: Thanks, Peter. Apologies to the UNMC logo, but our students picked the lab as our logo. These are my financial disclosures.

I just want to remind everyone in the room after the last several talks on reached on regulation, why we're you're here. And I will reiterate as a clinician scientist in this space for a very long time, that long-term graft survival is still the challenge we face and the data that Dr. Poggio showed is incremental, at best.

It includes both non-immunologic and immunologic entities, and the latter really have no approved therapies, including chronic active antibody mediated rejection. And our current management decisions for induction and maintenance immunosuppression are really based on early outcomes, which is the status quo, and you've seen as quite good.

Therapeutic development of new agents lacks any regulatory pathway to assess long-term outcomes. And to develop new agents to address these unmet needs, we need methodology that informs us whether a therapy may improve long-term graft outcomes.

I've been to a lot of these meetings; and I will say we've met a lot, but I haven't seen much change. I've attended and participated in the 2012 meeting, the 2015 meeting, the 2018 meeting, the latter of which was on context of use in the best criteria.

And importantly, in the 2015 meeting, we even had a two-day workshop after that, sponsored by the Transplantation Society that included FDA members from transplant. And at that meeting, we published that the surrogate endpoints of one year that correlate with subsequent graft failure will further enhance trial feasibility. That was over eight years ago, and we discussed eGFR and proteinuria that were prognostic of late graft loss. We also recognize that other biological markers, including biopsy histology, and HLA donor specific antibody were predictive, and that success could be obtained by combining both of these markers to uniquely inform graft outcomes.

However, I was here today to talk about

estimated GFR as a nephrologist, and so I will talk about it as a proxy for allograft function. I will address Tacrolimus; I actually study TAC and CSA toxicity in the lab. I'll show you some dissociation of clinical data with eGFR in terms of outcomes. I'll talk a little bit about the iBox in terms of improving the eGFR prognostic ability, and I was also asked to address eGFR slope in the first year after transplant.

So some comments about GFR. In this room, I, as well as many of the kidney patients here, know that GFR is really important. It's clinically important and it is strongly associated with graft failure. But as demonstrated 20 years ago by Kaplan and Meier, accretion showed, eGFR is not reasonable to utilize alone as a surrogate for graft loss. Twenty years ago we identified that.

The clinical monitoring in adults requires serum creatinine. We don't use a Cystatin C in adults. It also has some problematic issues in transplant patients. And there are many equations, we don't have time to talk about them. They may not be

perfectly performing, but as clinicians, they're accepted in practice, and they certainly have been accepted by regulators. There's a bevy of them, including a new kidney transplant race free equation.

Shown here are data from Sumeet Mohan and colleagues assessing what were clinically relevant changes in eGFR and studies. This is the data they show from clinical trials. Again, strong correlation not disputing that of eGFR at one year, inversely related to death censored graft loss.

But I also want to point out, and a great example of where eGFR is, is the Elite Symphony study where the two standards -- and that's shown in purple -- where the standard and low dose cyclosporine arms performed almost similarly, very similar eGFRs and graft loss. And surprisingly, the lower dose Tacrolimus arm, which is highlighted for you, actually had higher rates of graft failure and lower estimated GFR. Again, counterintuitive to the intent of the study, which was to reduce CNI exposure.

So let me put it to rest. The

hemodynamic impact of cyclosporine therapy is very different than Tacrolimus. If you look at infused rats that are anesthetized, which are not human beings, you don't see the same renal vasoconstrictive effects that you do see with cyclosporine. If you look at humans that are treated that are healthy for two weeks, the parameters such as estimated renal plasma flow, GFR, renal blood flow, and vascular resistance are significantly different in cyclosporine. But the Tacrolimus group is really similar to the baseline.

And finally, there's a smaller study that you can observe were giving consistent treatment and with Tacrolimus in kidney transplant patients, they actually have lower resistive indices and mean arterial pressures compared to cyclosporine. And I'm not even going to get into the data that show maybe less fibrosis, it's a completely different comparison. Though functionally, and immunologically, they work very similarly.

Another interesting phenomena has been

comparing the belatacept studies that we have and comparing the TAC arms, the Tacrolimus maintenance arms to Bela, and similar estimated one-year GFRs. And whether you're looking at the Adams-Emory Experience, which is a huge, enormous clinical experience, Steve Woodle's randomized control trial comparing bela versus TAC, or Kumar, which is a meta-analysis that includes Ken Newell -- Ken Newell's C TAC study, they all demonstrate very similar estimated GFRs, whether you're looking at the belatacept arm or the TAC arm, and I just give you some of the mean estimated GFRs, one that, you know, ranging. And this is for all the studies, the meta-analysis had about five. But again, pretty respectable.

The Grinyo Conversion Study is another example where there was no significant difference in eGFR after you converted from TAC to Bela, comparing the TAC and Bela arms. But there's still, after conversion one year later, were significant differences between cyclosporine and Bela. So again, I just want to point out that these are two different

calcineurin inhibitors.

And finally, another sort of interesting phenomenon. This is a randomized control trial performed by Mark Stegall at the Mayo Main Ship in Rochester, comparing attack-based maintenance therapy to Sirolimus, which is shown in the right column.

And interestingly though, the estimated GFRs at one year were similar in both arms, that -- that did not reflect the significant improvements in tubular interstitial fibrosis, vasculopathy, and overall fibrosis quantitated by serious red. These significant improvements in histopathology that many of us feel are critically important for long-term survival, were not picked up by estimated GFR.

So we -- I think it's important to compare the prognostic ability of estimated GFR and long-term graft survival, and I'd like to demonstrate the improvement in that prognostic ability, if looking at the full iBox on the current sets we've talked about, the derivation cohort, and then the validation

cohorts, using both a discrimination analysis shown on the left, and then the calibration shown on the right.

And you can see that, you know, eGFR does quite well, it's above 0.7, with the exception of the benefit study. But there is significant improvement in the prognostic ability when you utilize the full iBox, and I think that calibration shows you that there is significant improvement in that prognostic ability, using the iBox, which is indeed including estimated GFR.

Lastly, I'll address this trajectory in the first post-transplant year. And as many of you know, you know, GFR in the first year is subject to a lot of things. We deal with organ procurement, brain death, and its inflammatory function, and innate activation, implantation, reperfusion injury, the quality of the donor, and also recipient factors that include medications that we provide patients for intermit periods of time, such as trimethoprim, sulfamethoxazole, and H2 blockers that blocks creatinine secretion, as well as potentially innate

immune responses, alloimmune responses.

And interestingly, in that complexity, the TAC and Bela regimens have actually shown, when you look at Emory data, that those individuals on Tacrolimus actually have a slow rise and improvement in their GFR over a year. Shown on the right is work by Kaczynski and colleagues at CPath, looking at GFR over the first several years, but importantly focusing on the first year.

And really, in terms of eGFR trajectories, the first-year post transplant is nonlinear and very individualized. And interestingly, that's reaffirming to me that after all these years of work, whatever I see in the clinic is actually shown in the data. And I think this creates challenges for applying a linear slope or percent change for evaluating kidney function in transplant patients within the first year.

But I do think there is real value in the trajectories after the first year, and this is work by Marc Raynaud and colleagues at Paris

Transplant Group, 14,000 patients. 15 centers across the world, had to have at least a few measures of eGFR after the first year. And using -- using machine computation, they identified latent classes of baseline and trajectory of eGFR.

And again, the red groups are the people that I'm very familiar with, and some of you in this room are. Again, certainly they exist and have an opportunity to affect those entities. But we'd like to see patients like this, stable, functioning over long periods of time, regardless of their baseline GFR.

So I'll summarize by saying that estimated GFR is indeed an important prognostic factor of kidney allograft. But with some caveats, and the change from cyclosporine-based control arm to TAC as a standard of care does affect estimated GFR comparisons. If we use belatacept as a CNI free, as an example. And even so, I'd like to point out that we don't know what new drugs are out there that might affect the GFR differently than Bela; there may

actually be improvements over it.

I think, and I believe that the additional of the features of the iBox multicomponent biomarkers significantly improves the prognostic performance of estimated GFR. And those include measures of proteinuria, histology, and DSA. And yes, many centers are measuring DSA in stable patients in the first year, now.

And finally, I think the first-year slope of GFR is really limited in its utility, but the slopes of eGFR and proteinuria may have value. And it appears that my last slide was removed, but I just want to say that I was attending the American Society of Nephrology meeting last week. There were 16 drug approvals last year in nephrology. The exhibit hall was packed, the attendance was high. This is the most important aspect that has revolutionized kidney disease, and it's great for me as a lifetime clinician. And in transplantation, what do we have in the last 10 years -- 12 years? Nothing. Thank you.

DR. NICKERSON: Thanks very much, Dr.

Mannon. Myself and Dr. Thompson are going to host the discussion of the panel. The mics are open here. We have questions in the -- in the -- on the online. Dr. Thompson is going to monitor those while I try to host the discussion here.

And maybe as you come to the mic, introduce yourself and state your -- your representation, if you have -- have one. And we open the floor.

MR. FOWLER: Yeah, I am Kevin Fowler. I'm representing the Kidney Health Initiative on the Board of Directors. So here's a volunteer.

I'd just like to maybe make a couple summary comments. Just want to clarify, too, when we say graft loss, it's not a serious issue. Patients prefer to die versus going on dialysis. So for anyone that thinks that that's an acceptable alternative treatment, just want to clarify that; it's not.

I've been to every meeting that was listed since 2015. The only one I didn't attend was 2017. So can someone tell me here, what's changed?

Anyone?

DR. KLEIN: Well, we do have the TTC. So that took five years to establish by 2018. So you know, my vision when I was coming in as president, Kevin, was that this would revolutionize, that we would have a trusted third party integrating massive amounts of data, harmonizing it, and doing independent statistical analyses.

So that is the one thing that has changed, but therapeutically, no.

MR. FOWLER: Okay. And so I just want to say that I'm a patient person, but my patience is gone. Right? And so, I guess my expectations after this meeting, that there's going to be a clear path forward to accelerate innovation.

We've had all these meetings and I just want to say, you know, to amplify Ros's comments, what's happening in nephrology is something I never thought I'd see in my lifetime. And one of the people here responsible for it is at the table, Dr. Thompson.

And I think we could do the same thing

here in this field, but I think what's missing is accountability, collaboration, and elevation of the patient voice. And that's what I like to see done.

But I mean, I'm just telling you, I'm a patient guy, but my patience is gone. Thanks.

DR. NICKERSON: Thanks, Kevin.

DR. THOMPSON: And I just want to echo Kevin, thanks for being a patient advocate and patient lawyer. And I think that there is widespread acknowledgement, as evidenced by the workshops over the years, that this is a very serious issue that FDA takes very, you know, understands its importance.

I do want to emphasize that I think this workshop is like many of the workshops we've had with the community that led us to the endpoints in our spaces, and that we're trying to make these data driven, you know, discussions and decisions.

So really appreciate everyone in the room joining today for having such a science-based discussion, and we have a tremendous number of people participating remotely, which I think is a testament

to how many people view this as a very, very important issue.

DR. HEHENBERGER: Hi, my name is Karin Hehenberger. I'm also a patient, a two-time kidney recipient, but I also represent an organization called Lyfebulb, and I -- for me, it's the first time I'm here. I'm also an MD and a PhD. So I studied medicine in my home country of Sweden.

So I think there's a constituent that we're not talking about today, and it's the donor. In my case, I was very fortunate, I had two living donors, my father and my sister. And my sister gave me a kidney only six months ago, so it's pretty recent.

But again, I was very fortunate to have these two living donors. And one of my -- my biggest actual thoughts before I got my second kidney was how I disappointed my father. Because when he gave me his -- one of his kidneys, he's still doing very well, went to climb K2 base camp at the age of 78, with only one kidney a few months ago. But was that I had not

succeeded in keeping that kidney alive. And I think that I didn't realize, despite my medical education and my scientific education, how toxic the actual drugs were, that were supposed to keep his kidney alive.

And yes, I'm grateful because I did experience dialysis and the difference between dialysis and transplantation can't even compare. I mean, I would never want to go back on dialysis again, and that's a separate issue, how people on dialysis are being treated.

But I do think that we need to consider those individuals who stand up and give those kidneys, and we, as a community, need to do better because it is incredibly important to value them as well. And there aren't that many kidneys out there. So for every new kidney I need, you know, I have two sisters, I hope -- I hope I don't need to use my second sister.

And we -- we are removing the opportunity for another patient. So just wanted to mention that because I don't think we have -- we have

discussed that a lot that -- that impact on those individuals as well.

But thank you for having this discussion and for all the important data.

DR. VELIDEDEOGLU: This is Ergun Velidedeoglu. I'd like to make a comment in general, not in response to a particular person, but in general.

It's -- I hear that there's a sentiment, it has been going on for a while, maybe not always explicitly, but implicitly. FDA has been blamed for not fostering or enhancing drug development in transplantation.

So I'd like to point to a fact in response to that, there are several different regulatory agencies all over the world. It's not just the FDA. There's a regulatory agency in Canada, there's a regulatory agency in Europe, in Japan, in Australia, in other parts of the world.

So if there had been a discrepancy in drug approvals in transplantation between those other

regulatory agencies and the FDA, then there would be more reason to blame the FDA. And that's not the case.

There is general lack of innovation in the field of transplantation, unfortunately. And that may have various different reasons, not just one reason. But the pharmaceutical industry also carries a big chunk of the responsibility in that it's not like that the other regulatory agencies are approving new drugs. But when it comes to the FDA, FDA has been the obstacle; that's not the case. That's one thing.

Second thing, drug development in transplantation is a tall order. You are making comparisons between other therapeutic fields, nephrology, cancer, et cetera, but if you think of transplantation, you have a patient in kidney transplant, with end stage renal disease, starting with a baseline morbidities, either diabetes, hypertension, or autoimmune diseases, losing the native kidneys.

On top of that, you are transplanting a

kidney, either from a live donor or a deceased donor. In the case of deceased donor, there are additional factors, and you are trying to improve the survival. Which we have made progress, just to name a few. I mean, there have been recent advances in kidney allocation.

Meaning, we don't need to look at the field only from a drug development perspective. Starting in 2014, there have been a drastic change in kidney allocation. And there have been advances in HLA matching, molecular mismatch has been a big advance. And the benefit of that is we start to learn the existing drugs in a better, more meaningful way.

And there have been other, you know, in organ preservation, and the all these advances are reflected in the outcomes. I mean, we are not moving in leaps and bounds, but we have made significant progress, despite the use of lower quality organs, because the donor pool has expanded.

We -- we started using organs from older age donors. So those advances, those

accomplishments should not be overlooked. So I just wanted to make a general comment. And thank you.

DR. THOMPSON: Sir, and maybe just before we get to the other speakers in the room that we do want to hear from you, is maybe just to field a few questions from the chat. Is that okay? I think we got some questions about the iBox. And so Amanda, maybe you can help us with those.

One question about the iBox scores was about the iBox scores are for Denovo, another term -- in other words, first time transplant. The question or questioner is asking whether this is correct, and if so, is there any utility for individuals with repeat transplants?

DR. KLEIN: That's a great question. So the intent of the iBox is to use a Denovo phase 3 clinical trial. The data that we have to support is data from baseline, which is time of transplant. The data regarding whether someone's a re-transplant or not was limited in data sets to fully incorporate, but I imagine that there were patients with re-transplant

included in the data sets.

DR. THOMPSON: Great. Maybe we'll just take one more question from the chat and then return it to you. And instead of doing -- we do have a follow up question on the iBox, I will come to that later, maybe I'll ask a question that came in earlier. And Jeff, I think this question may be best addressed by you.

How in practice is the distinction made between validated and reasonably likely surrogate endpoints? And then, also question of whether there's actually a list of validated endpoints?

DR. SIEGEL: So the answer to the second question is easy. The FDA has a website where we list all the surrogate endpoints that have been used for drug approvals. And that's freely available on the web.

Can -- can you repeat the first part, again?

DR. THOMPSON: I think the first part of the question was pushing us a little bit further to

speak to how in practice we actually distinguish between our validated surrogate endpoints, which serve as a basis for traditional approval and are reasonably likely surrogate endpoints?

DR. SIEGEL: So in general, any type of surrogate endpoint rests on a strong mechanistic understanding of how the surrogate endpoint relates to clinical outcomes. And the degree of change in the surrogate endpoint that's expected to have a meaningful impact on clinical outcomes later.

A key distinction between the two is the amount of clinical data that's available to validate the surrogate. In the case of validated surrogates, showing evidence on a trial basis that the change in the surrogate in that intervention in the trial correlates with a change in the clinical outcome is particularly important for validated surrogates.

Sometimes some data is available on that relationship for a reasonably likely surrogate, but often, generally less than for valid surrogate.

DR. THOMPSON: Thanks. And maybe we'll

return to the room.

DR. NICKERSON: Thanks. Dr. Newell.

DR. NEWELL: Good morning. My name is Ken Newell, I'm a transplant surgeon at Emory. I'd like to start by thanking the FDA and the University of Manitoba for holding this workshop. I think, although there have been a number of them, this one has the real potential to make changes.

I particularly enjoy medical history, and I enjoyed reviewing the FDA's approval of agents over the timespan of transplantation. I enjoy that and it reminds me my presidential address I gave as president of the American Society of Transplantation, where I started by acknowledging the great strides made by the pioneers in our field. They undertook risk, they were thoughtful, and hugely benefited. Their pioneering spirit benefited patients directly. Everything they did was driven for patients.

And while I appreciate what we have achieved together with the FDA and patients to this point, our patients today, we heard very clearly,

expect that same sense of innovation, that same commitment to change, not incremental, small steps. If I see a patient, I tell them, "Really good news. If I was seeing you five years ago, your survival, the you know, your graft survival at 10 years would be x. Now it's, you know, improved slightly." No one's going to pat me on the back.

And so that's me pontificating, but what I'd like to say is, and I liked the slide, and I've made the same slide myself, looking at the approval of cyclosporine. What was it 230 some total patients? Why was it such a small number? You improved graft survival by -- or you decreased the rate of acute rejection by 50 percent, if I recall right, and you could correct me. But it was about 90 percent pre-cyclosporine, about 45 percent afterwards.

So with one intervention, you benefited half of the patients undergoing transplantation. And BPAR is a huge thing. No one here would argue that, you know, biopsy proven rejection is not an issue. But I would say today, if you accept that acute

rejection rates are single digits, pick number 9.

If I could have the same effect, I reduce acute rejection by 50 percent. Now, I've gone from 9 percent of patients to 4.5 percent. What is the impact of that long-term? How will we ever approve new drugs? If everything's approved based on non-inferiority, what I'm telling Kevin is great news, I'm going to develop a new drug, that's going to give you the same rate of acute rejection, basically as now. And if I did reduce it by 50 percent, there are other things that are going to have far more dramatic impact on your outcome.

So all this is to say, if we're to have the courage of our forefathers who established this field, I think we need to embrace innovation and, well as academics, we always find a way to say, you know, "I love what Peter says. His ideas are great, but mine's slightly better." You know, I think patients don't want to hear us have that debate anymore. They want us to say what can you do today? If it's not perfect, at least it's better than where we are. And

it doesn't mean that perfect can't come down the road when somebody discovers it, we just don't have it yet.

So I'd like someone to say how we're going to use acute rejection as a way to bring transformative therapies into the field of transplantation, that really benefit patients.

DR. HEHENBERGER: What he said. Thank you.

DR. NICKERSON: The only thing I'm going to say, Ken, is I think we are going to talk about that in the next session. So I think your comment's very well stated, and in the next session, I think we're going to address maybe where -- where we're lacking in BPAR as a diagnostic tool, at the moment. And I get your point. I agree. I agree.

DR. MANNON: Amen to that, Ken. And I want to follow up something that Ergun said. The United States is the leader in transplant innovation, and always has. With the exception maybe of ex vivo perfusion, where Canada, and the Netherlands, and the Belgians are exceptional. So expecting Canada or

expecting Japan to change things is unrealistic. We're the innovators, it's our country. We have the most patients in the world. We don't have such great outcomes, so I don't agree with that.

DR. NICKERSON: We're Going to have Ozlem speak, and then we'll come back to you.

DR. BELEN: I just wanted to say a few things to the patient representative, as well as physician. I forget your name, I apologize. You, yes.

So I hear your remarks about your experience, it was very well said. I appreciate that. We are also paying attention to safety endpoints as claims and in the trials. We are trying to collect those as endpoints that are well defined in the existing products, but also for new products that may come to the market.

So there's a session in the afternoon that we'll talk about that. Maybe that does not answer your question, totally. But I think, looking at safety outcomes, in addition to efficacy endpoints,

when we look at new trials going forward is important. And we hear you, I just want to acknowledge that and thank you for your comment.

DR. NICKERSON: Please go ahead.

MS. MCCARTHY: Thank you. Good morning, or afternoon, wherever, wherever we are. I live in Seattle, so I'm not entirely sure what time it is. It's morning, thank you.

Molly McCarthy, three-time kidney transplant recipient. Mom donated first; dad donated second. I completely empathize with a sense of responsibility of doing the right thing by your donors. Deceased donor the last time after a six year wait.

Thirty-two years that I have been a recipient and so seeing some of the history felt very much like a walk down memory lane for me, and I think refresh my experience and memory of at 1991 when I had my first transplant at Iowa, I was realizing like holy Schinke's, I was like five years old, right. Like I had lost sight of that.

I completely agree with you in the context of really trying to focus on bringing patients along in these discussions. One thing I would add is, you know, we're the ones that you let us out after three- or four-days post op. And while, I think, in the media, and in most of kind of public life that we try to go back to it seen, "Well, you got your transplant. You be good, you got enough, don't you dare ask for more and go back to normal life."

And so when I think about kind of the innovation, or candidly the lack of innovation, and that's not said to point fingers. I'm going to add to that and say, there is much to be done, you have a very active and I would dare say confident set of patients that want to get in the game and back you up.

Consider us, put us to work, if it's money that you need, if we need to storm the Hill to go after driving more innovation, both in practice as well as like anything that it would take in that space, put us to work on that behalf.

I would also say, too, you know, it's

not just about living a year after your transplant or five years or however many years. I was saying last week, I actually just turned 50. And to be quite candid, I never thought I would live this long, right. But it's not just about being on the right side of the graph. The other side is the quality of life.

And I vividly remember, I'm now seven times in with skin cancer. I remember the last one that was on the back of my neck, and literally the surgeon was sewing me up saying, "Gosh, we have gotten so much better about telling transplant patients that they're going to have a lifetime of skin cancer." Like haven't we progressed?

And well, as a patient, literally under the knife at that moment, I empathized, and she's right. But it also comes to mind like, why is that then the burden that comes with transplant? Like why can't we be healthy for the rest of our lives and not have to have three transplants before you turn 40? Like, that's the world that patients really want to start to see.

I'm with you, Dr. Ros, and I do take a little bit of effort around like, well, you know, nobody else is outpacing us. I'm American, sorry. I pay a lot in taxes. The government loves me. So I would expect more, I want more. But with that criticism comes an offer of put us to work on your behalf. We're the lucky patients, and we're willing to work for and demonstrate our gratitude in that way. So thank you.

DR. NICKERSON: So I say, thanks very much for those comments. And when we had the -- the workshop that was the patients talking about the side effects that they had to tolerate to keep their graft, and how impactful that was on patients' lives, it's absolutely true.

And I see that every day in my clinical practice of patients who -- who are tolerating the drugs that they have today. So we do need to do better. And I think it's clear on the need.

Dr. Hariharan.

DR. HARIHARAN: Yeah. Good morning. I

am Dr. Hariharan, long-term clinician. I decided to join FDA. Today is day number five, so I don't know, I'm just getting my feet wet. I have one academic question and one academic comment.

First to Dr. Poggio. You clearly showed the long-term survival has improved, but not good enough. I agree with you. You clearly showed the rejection rates are lower in the first year after transplantation over the last 20 years or so.

So the question is, if you are focusing on long term survival, are we dealing with a lot of late rejection, which is a problem? Or are we dealing with smoldering rejection with the first year which we are missing, which are manifesting after the first year?

These two things are very important as we try to focus on the long-term survival. I would like to hear your comment on this, your answer on this, or your opinion on this, then I will go to the comment about the other one.

DR. POGGIO: Thank you very much for --

for your question. And you're totally right. You know, we don't know whether subclinical rejection actually -- you have some -- some data you showed, you know, within the first year in patients who undergo protocol biopsies. They do have injury, they do have -- they don't have a normal kidney allograft. And that's not manifesting as GFR, proteinuria, whatever you want to call it within one year, and then make -- be clinically evident a few years after that.

We are learning. I think is not the only thing. I think some patients get to one year with completely normal kidney allografts and then develop an event after that. So I think it's much more complex than -- than the simple cut off of one year or not.

DR. HARIHARAN: I agree. The second one is a comment for Dr. Klein.

Comparing BPAR to iBox is not a perfect comparison, because one is an acuity, and one is acuity plus chronicity. When you have acuity and chronicity, you're going to correlate higher odds of

graft failure and in acuity and BPAR alone, all of them are treated or nearly all of them are treated, and some of them are reversed. That may be the reason you may not find good correlation with outcome. Okay. So the comparison is slightly different. We have to keep that in mind. Thank you.

DR. KLEIN: I'm happy to comment on that. So when we did the comparison of iBox to BPAR, we first did a comparison of knowing iBox is a continuous measure and knowing BPAR is defined as presence of great TCMR, 1A or greater for regulatory purposes. So the critique as well, you're not talking apples to apples.

So then what we did is if we took the -- maximized the specificity while holding sensitivity stable, knowing eGFR, you want to maintain specificity, but still have reasonable sensitivity. How does a binary iBox compared to a binary BPAR, once again defined in the regulations for efficacy? And even with that, we have better prognostic of iBox compared to BPAR.

And as Dr. Mannon also showed on that sensitivity specificity curve, you even see that as well.

DR. HARIHARAN: Okay. Thank you.

DR. KLEIN: Thank you.

DR. NICKERSON: We're -- I'm just going to do a time check. We're into our last 10 minutes. So I'm just going to say, if we could have -- there's a whole line, which is great for those who aren't in in the room. If you could keep them short, and we'll try and get through as many as we can.

DR. MALDONADO: Thank you. My name is Angela Maldonado, and I'm medical director of Hansa Biopharma. So I did -- did want to address the comment about the perception of FDA being a barrier. And I -- that's not my perception.

This is my first FDA workshop and I'm actually presenting the Unmet Need of Patients Who Are Highly Sensitized. So we have a phase three desensitization trial right now in the U.S. And hearing about the endpoints that are being discussed

for trials primarily designed for prophylaxis of acute rejection is very different from what we're trying to achieve.

So do want to, one, say that, you know, we recognize the unmet needs of patients. I came from clinical practice and now in industry, but you know, as we talk about trials and kidney transplantation, there's a whole field coming up in desensitization, tolerance, and other areas as well.

And so as a company, Hansa's really looking forward to the creative ways that FDA and Hansa can work together because our trial is very different from the ones I'm hearing about today.

And so, we wanted to say, you know, we had a very positive experience with EMA, so Imlifidase is conditionally approved, you know, in the EU for desensitization.

So we're looking for a very positive engagement and how we can look at creative trial designs that are outside of what I'm hearing about today, and what you presented in your past review and

what I'm, you know, looking forward with my colleagues and other industry as well. Thank you.

DR. NICKERSON: Thanks for that comment.

DR. FITZSIMMONS: Bill Fitzsimmons, I'm here representing TTC and CPath. I previously spent 29 years working at Fujisawa and Astellas, starting with the development of Tacrolimus in 1990. So I really wanted to address, Ergun, your -- your comments about whether the FDA is a barrier in other countries.

And from the -- I think we all know, the largest pharmaceutical market in the world, whether it's for any drug, or for transplant immunosuppression, is in the U.S. So that decision, to be sitting in the room as a pharmaceutical company, is based on our U.S. market first and foremost.

And if that doesn't pan out in terms of return on the investment, the tendency is not to develop that therapeutic in other places. So I don't think we can expect to see someone going around the U.S. and bringing new innovation in the rest of the

world, but not bringing it to the U.S. The U.S. will be the driver.

FDA is considered the gold standard regulator in the world. There are plenty of other great regulators. The reality is you guys are the best and that's what the rest of the world holds us up to.

And so I think that's we have to look at. I sat in the room where we're debating at the company that brought Tacrolimus forward, should we bring new immunosuppressants in the transplant, and the answer was no, because they couldn't show superiority to TAC and MMF on the efficacy failure endpoint.

So if you look at that through that lens, you say it's up to all of us, the industry which the biopharmaceutical industry is in the U.S., the commercial potential is in the U.S., the best regulator in the world is in the U.S. So we need to bring those together, I think, to bring the new innovation into this area.

DR. VELIDEDEOGLU: Can I just briefly respond? I just want to briefly respond. Thank you for your comment. I agree, I mean, U.S. has been the leader of innovation and I mean, we should continue as such.

But I also would like to remind, you know, your prior company, Fujisawa, I believe that was a Japanese company, and also Sandoz, a European company. I mean, they seek marketing preferentially in the U.S. because there's a much larger market, I fully agree with that. But sometimes innovation comes from outside of U.S. and embraced in U.S. So I just wanted to remind. Thank you.

DR. KUMAR: Hi, I'm Vijay Kumar. I'm a medical officer in Center for Biologics, here. I have a few comments.

Two of the, you know, long-term challenges in the transplant field is the chronic graft dysfunction and also the chronic toxicities of the immunosuppressive regimens. Of these, the metabolic complications and the cardiovascular events

have accounted for a lot of the -- the deaths in the patients who have died with a functioning graft.

From a regulatory perspective, when we look at the study data, we are focused on if there is an uneven distribution of random or relevant variables that can have a confounding impact on the outcomes. Specifically, as Dr. Mannon mentioned, there has been a lot of recent approvals in the cardiorenal drugs.

We know the impact of the SGLT2 inhibitors on one of the -- there are two surrogate endpoints that were discussed. One was the eGFR and the second one was the iBox. We know the impact of the SGLT2 inhibitors on eGFR, and recently there was a news item that one of the GLP products, Ozempic, the trial was discontinued one year early because it had a positive impact on renal outcomes.

So how do we -- my understanding is that the iBox has not been studied in a randomized control trial. So in absence of an randomized control trial, how do you account for these confounding variables?

DR. KELIN: I'm happy to take that question. So the iBox was derived in a large observational cohort, and then validated into RCTs that completed. The only two RCTs that have that five-year long-term data. And iBox is prognostic for death censored graft survival, understanding the reasons individuals living with a kidney transplant lose a graph are different than, you know, dying with a functional graft.

In the context of a regulatory framework and as a construct of death censored graft survival, by pursuing qualification as a co-primary, it ensures that the regulatory standard for the primary endpoint based on efficacy failure remains accounting for death, graft loss, loss of follow up and BPAR, while now allowing an opportunity for an endpoint that is prognostic for iBox on death censored graft survival to complement the current standard and then allow pathway for accelerated approval.

So in that case, you're not compromising the current standard for regulatory

approval, but you're allowing a new endpoint that is prognostic for death censored graft survival.

DR. KUMAR: So unless these confounding variables are evenly distributed in your randomized control trials, how will you be able to show that the iBox is predictive?

DR. KLEIN: The issue with demonstrating predictive, as defined FDA, to be able to show a treatment effect requires RCT data. We know that there is limited RCT data that has all the variables necessary in iBox, as well as five year follow up data currently.

So there's two limitations, is the number of events to be able to be sufficient to be able to power to demonstrate that treatment effect and the number of RCTs. We believe the only way to get additional RCT data to support a fully validated surrogate is by sponsors implementing iBox as a reasonably likely surrogate endpoint, and that's after qualification.

Because remember, with a reasonably

likely surrogate endpoint, it is linked to the accelerated approval pathway with the mandatory five year confirmatory follow up.

If I was a sponsor, why would I willingly just follow patients out to five years if I can get approval at one year. With the accelerated approval mandate, this ensures that we do get that five-year outcome data that we all want to need to be able to demonstrate fully validated surrogate. Thank you.

DR. KUMAR: Thank you.

DR. THOMPSON: Yeah, I'm just -- it looks like we only have a few minutes left. I think we will give priority to the people in the room. But I just do want to thank all of you who asked questions in the chat. I think many of them echoed, you know, some of the concerns we heard during the meeting, as relates to these endpoints, and there are also a number of other great questions and I'm just very sorry, we won't get to them.

DR. NICKERSON: Here and then, I think,

Nikolay, you also wanted to make a comment. So maybe we'll end with this question. Sorry, Roy, you'll have chat time later, and then we'll go to Nikolai, please go ahead.

MR. HENRY: Sure. I'll be as brief as possible. Comments, really not a question. My name is Calvin Henry, northeast -- from Northeast Georgia. I am not a -- I'm a patient, but I am not a kidney recipient. I am an almost 11-year double lung transplant recipient.

One of my concerns is as a patient, 11-years out, and one of the many advocate -- advocacy efforts that I've leaned into is mentoring organ -- other organ recipients. And not just lung recipients, kidney recipients as well. And we have an annual conference in the Atlanta area called Trends in Transplant, where we discuss what are the new innovations that are improving patient lives.

The very first conference I attended talked about belatacept, nothing since then. And patients are frustrated, I heard some comments from

fellow patients in the room where patients would rather die than go on dialysis. And patients would rather not get a transplant if it means having to go through the current immunosuppressive regimen.

So an additional comment I heard, I listened to a webcast that Karin sponsored last year, I'm sorry, I can't remember your last name, where it was discussed were the latest innovations in immunosuppressive therapy, probably about a decade away. There's no driving force behind it, there is no, you know, push toward using or looking at the off-label drugs to investigate whether they would work for patients.

The only comment I would say is, again, echoing the comments in the room already, as a patient, we -- use us. On our behalf, we will -- whether it's, you know, to your colleagues at the FDA, pharmaceutical companies, on the Hill, as patients, we really, really urge innovation within immunosuppressive therapy.

Personally, that's something I've

talked with my transplant center about. We talked about, you know, 11 years out, we're already getting referred for kidney transplants because of the toxic effects on our kidney. So that's something I'm personally worried about, to the point where I've actively worked with my transplant center to reduce my own medication, sort of a personalized focus for me.

So once again, just reiterating the thoughts in the room on anything that we, as patients, can do to use our voice to help push for innovation. Happy to do.

DR. THOMPSON: I think that's a great way to end it. Thanks so much for the comments. And I'm sorry, that I think we're just trying to stick to the clock. There will be other opportunities to make comments and ask questions, we promise.

DR. NIKOLOV: I was given the podium, so I'll take it. My name is Nicolay Nicolov, and I'm the Director of the Division of Hematology and Transplant Medicine. I'm currently the acting office director of the Office of Immunology and Inflammation.

And I just want to be open and transparent to say that it was not without trepidation that we put this agenda and this workshop together, fully expecting the criticism that we will get squarely at the FDA.

We get it, we hear you, and we understand our role as regulators to incentivize drug development and make sure that there is, you know, appropriate pathway for development of products in that space.

I want to make sure that we are on the record to say that we fully recognize the high, unmet needs to improve long term survival, graft survival, and patient survival. And we also want to reaffirm our commitment, not just now, but all along the way to help address this unmet need.

I want to recognize my colleagues here who have been working over the years to do that. And I also want to recognize the patients in the room, you know, who participate and raise all of these important questions.

Again, thank you for sharing this, providing this information to us and -- and we are taking that seriously. Again, I want to make sure that we are, you know, open and sharing this -- our thinking with you and we will be working with all stakeholders to address this unmet need.

This workshop is an example of our effort to try to tackle the scientific questions to get to that point. Thanks.

DR. NICKERSON: Thank you, Nikolai. I want to say we're done this session. There's going to be lots more time for discussion. Roy, we're going to hear from you as a speaker in the next session, so you'll get your time.

We have 15-minute break, we're going to start right on time at 11, just to keep to the day. Thank you.

(Off the record.)

DR. NICKERSON: We're going to get going, everyone. If everyone can take a seat, we're going to start our second session.

Chairing this session is Dr. Ros Mannon and Dr. Ozlem Belen, and it's the Biopsy Proven Acute Rejection Efficacy Failure.

DR. MANNON: We know that, thank you. I'm going to go ahead and move on. We'll be presenting Defining Biopsy Proven Acute Rejection, Past, Present, question mark Future. Dr. Michael Mengel, who's Chair of Pathology at the University of Alberta at Edmonton and Director and Trustee of the BAM Allograft Pathology.

DR. MENGEL: Thank you very much for the opportunity to be here. And this will be a pathology talk. I saw there's one other pathologist in the audience.

So can I have my first slide? Can I do this? I don't think so. I can -- I can see my slide here, but not up there. If I only share them with myself, that might be boring. Do I have to do anything?

DR. THOMPSON: I believe there's a green arrow on that window.

DR. MENGEL: I advanced to that, oh, and then, it's maybe the next one. Okay.

DR. THOMPSON: There we go.

DR. MENGEL: I -- I -- now, now I understand the concept. So going back, so defining BPAR. And I apologize, I should not -- I should have explained the abbreviation in the title. But while I listened to the first session this morning, I realized maybe there are, in our heads, different definition of what the A stands for in this.

So the B stands for biopsy, we can agree on that. P stands for proven, A stands for acute, I think per definition, so far, and R stands for rejection. And maybe the A needs to be reconsidered, what it stands for, after -- at the end of my presentation.

So here are my disclosures. And I will talk about the Banff classification, which I'm heavily involved in. And I have this slide of a bit of a historic overview. I will now go through this in detail.

But our understanding of what rejection is, and how it works, and what the mechanisms are are nicely summarized in this review paper by Phil Halloran, has been evolving and is evolving significantly since the fundamental concepts of immunology and then in the context of transplantations have been studied.

And that needs to be taken into consideration that probably historic definitions of rejection are not applicable anymore, today, in the same version, or even in the same implication what it means for graft.

Just fundamentally a concept, rejection is not like or most diseases we have in health and medicine, are not a yes, no, thing, black and white. There is cause postulate that you have an infection which is the prototype of what a disease is, and pathology, you have an agent, a bacterium, which causes an infection, and you treat it, and it goes away.

But rejection is the inevitable,

natural response of your body to the transplant you received. And it is a continuous process, and in these animal models, you can study it, how it unfolds with time. You transplant, your immune system recognizes the transplant as non-self, or allo, in general, and then ramps up an immune response. And that manifests in the graft with a certain pathology.

And this pathology at the bottom is usually after a week to three weeks, when you're not immunosuppressed, developed as inflammatory immune cells invading your graft and unfolding, a fairly standardized immunological inflammatory response. And to diagnose this, before 1991, it was in the eye of the beholder of the pathologist who received the biopsy. There were no real standard criteria.

But in 1991, the first Banff meeting took place in Banff, Canada, and the group of 12 individuals had a conversation around standardizing how to diagnose the pathology of rejection. And you see the concept behind this was the more immune response you see in the graft, the more rejection you

have.

And the two key features in kidney are interstitial inflammation and what we call tubulitis, so that lymphocytes invade the nephron. And there is the data at the time, that this pathology is associated with an increase in creatinine and functional deterioration.

Already in 1991, everybody was aware that this is not black and white, that somebody who received an allograft and has no rejection, has absolutely no inflammation or tubulitis.

But everybody will have some rejection, but also being aware that immunosuppressive drugs have severe side effects, the consensus was that we need a threshold of saying everything below this we tolerate and accept or is not worth increasing immunosuppression at the expense of more side effects. But everything above this threshold, which is 25 percent of non-scarred cortex in a kidney biopsy, inflamed, warrants more immunosuppression, because the risk of losing the graft is higher than the

anticipated side effects of the increased immunosuppression.

So the diagnosis of rejection is established based on consensus thresholds of a continuous disease pathway. And this hasn't really changed since 1991, this concept. And even major molecular studies haven't changed this. Studying all 21,000 genes in your body revealed that when you have more T-cell genes, you will have more T-cells and free infiltrating your graft.

The molecular signature in every single gene has been studied, correlates with this fundamental concept of pathology. More inflammation, more tubulitis, worse outcome, worse function, worse other things.

And immunosuppression just brings you below this consensus threshold. There is no single gene which is absolutely specific of the diagnosis of rejection in itself, and there is no single pathology lesion which is absolutely specific of rejection and only seen in rejection. Every pathology described in

a graft can be seen in a different context, which are non-rejection associated as well.

So when I studied now, 22,007 published, 15 years, sometime ago, more than 15 years ago, this concept of continuous inflammatory response in the graft in a large cohort of protocol and clinical indicated biopsies, which are all around the first year, first 18 months post-transplantation, under the standard immunosuppression, which we probably use today with -- with MMF and Tacrolimus.

What you can see is two important findings is that 87 percent of all biopsies show some inflammation. There is essentially, almost no graft out there which has not some inflammation at some point. And that when you have inflammation, it's not good, so to say. You develop more fibrosis in follow up, you have less function in follow up.

So there is this graph on the right, which was on the cover of AJT, is that the more inflammation and the more compounding inflammation you have, reverses your function.

Footnote to the audience, I use the term rejection and inflammation not interchangeable, not interchangeable. Rejection is a consensus definition of how much inflammation you should have to call it rejection. Okay. So please, don't get confused by these terms of being the same. And it gets more confusing.

AMP rules say you diagnose acute rejection, back then, only in areas of non-scarred kidney cortex, that area. You should not score nodular infiltrates, you should not score perivascular infiltrates, you should not score infiltrates too close to the capsule. Only something what is diffusely here, should be scored to define BPAR. Nothing when it is scarred.

So if you technically have a kidney biopsy, which is totally scarred, you can't reject. But why would you not reject scarred? It's still allo. So there are consensus conceptual challenges at the Banff classification, the definition of BPAR. And especially when you take time post-transplantation

into consideration. The longer you are out post-transplant, your scarred compartment gets bigger. So your likelihood to diagnose BPAR gets lower, the longer you're out. But that does -- of course, that's not what it is, mechanistically, right?

That's a -- that's a flaw in the Banff classification from 30 years ago, where biopsies were mostly done in the first year, and grafts lived for one year, where you didn't see scarring. But we made so much progress that grafts live longer now, and we see different pathologies depending on time post-transplant when the biopsy is taken.

And this work, this understanding and evolution drove several studies which showed that the type of inflammation in fibrosis and tubal atrophy, called i-IFTA, which was ignored initially for diagnosing rejection and BPAR, or being at all relevant, is one of the strongest predictors of allograft survival. And not the infiltrator type, which is used to diagnose BPAR.

However, follow up studies showed is

that i-IFTA, so inflammation in scar areas, is nonspecific. Many diseases can cause i-IFTA. But i-IFTA is a feature of activity. i-IFTA is the strongest correlate of molecular signals of acute active nephron injury.

So the acuity, and my question is, does the A stand for acute or active, is a molecular feature activity in areas of chronic inflammation. Again, all these terms of acute, active, chronic are conventions.

Two very large studies have clearly proven that acute or active acute T-cell mediated rejection can lead to i-IFTA, besides others. But a subset of cases with i-IFTA are the secular of earlier T-cell mediated rejection. And these findings altogether lead to their most recent change of the Banff classification to introduce the diagnostic category of chronic active T-cell mediated rejection.

So the concept morphed from acute rejection and events, towards persisting inflammation, defined under a phenotype of chronic active rejection.

Which is, actually, in most biopsies we see today under current immunosuppressive protocols, the most common phenotype and mixture of activity and chronicity in the setting of rejection.

If you thought it was complicated to this point, here's the next layer of complication. So when you have inflammatory events, T-cell inflammatory events and grafts, and this is the work from the Winnipeg group, early on you have a probability risk with later events, which are not T-cell mediated, but antibody mediated. So the novel, donor specific, anti-HLA, antibody development has an association with earlier T-cell mediated events, sub-chronically, borderline even below BPAR thresholds.

Cases with antibody mediated rejection phenotype, again also at the molecular level, have a T-cell component. This landmark study in Lancet from the Paris Transplant Group, clearly showed that we have three categories of phenotypes of rejection that do both, a T-cell mediated rejection type phenotype, an antibody mediated rejection phenotype, and

phenotypes where they overlap.

We have various band pathology lesions which overlap between rejection phenotypes. And we have overlap between acuity, or activity, and chronicity. So rejection becomes a Venn diagram, where you can be as a patient, in with having various components of rejection.

And as Phil Halloran said, as maybe we need a test which can give you a number of your ABMR risk and your TBMR risk. And I'm just trying to choose my words carefully, because I don't want to oversimplify that the conclusion is, well, it's all rejection. Whatever. It's like saying to our cancer patients, "Well, you have cancer. I don't care what cancer you have." But there is a significant difference between what type of cancer you have for your prognosis, survival, or treatment you need, and we know this from the cancer world.

So the challenge is really to dissect your rejection phenotype, in the individual patient, at the given point in time when a biopsy arrives. And

that's the major focus of the work of the Banff group, at the moment. And at the 2022 Banff meeting, this is the example of this conceptual thinking for antibody mediated pathologies.

And again, I choose my words purposeful. It is an antibody mediated pathology, and that's an association, because we also know, now, that a certain pathology, which we discovered in the setting of anti-HLA DSA, can be seen in the setting without anti-HLA DSA, for example, missing self. Different mechanisms, same pathology, which might need different treatment than when you have an anti-HLA DSA as the cause of the rejection phenotype and the graft.

So there is mechanistic components to rejection, and a big component is timing. And again, then the clinical components, what is your GFR at the time where you developed the phenotype? What other comorbidities do you have? What co-histologies you have? How much i-IFTA do you have, how much vascular lesion do you have? What type of antibody do you have? What are the attributes of the antibody, as a

complement fixing, or has it a higher affinity to the graft or not.

So there are multiple components which can change over time dynamic into your rejection phenotype, and that translates into your prognosis. So what I'm saying is there is many, many phases of BPAR.

And the molecular diagnostics are reflecting this by saying you have a probability of X for a certain phenotype of rejection. So you can't have 30 percent, and that was always Phil Halloran's concept, is saying is we -- we tell you how much your load of a certain molecular pathology is. And all these molecular correlates, your probabilities, you have your half histological correlates. So the biopsy and the histology reflect them to a very, very similar extent.

And it doesn't matter what your favorite gene is and what phenotype, you can -- all of you can have your personal favorite diagnostic gene in this setting.

So where is -- where is the rejection diagnosis going in, in this integrated concept? The Banff pools went beyond just poor, semi-quantitative thresholds of interstitial inflammation towards combinations of other variables and components to allow for the diagnosis of rejection.

Furthermore, the diagnostic category gives you an overall idea of the Banff lesion scores within a category carry additional information for your prognosis. So that the most recent approaches have been where you put these individual lesion scores into automated machine supported approaches, like the i-score, as we discussed earlier today, which takes the different variables from histology, not just the diagnostic category, but the Banff lesions which are overlapping between different diagnostic categories, and the relevant other prognosticators, and ways it in the individual patient, usually done at a time of a biopsy.

And your i score five years ago, iBox score five years ago when you had a T-cell mediated

rejection episode, is calculated differently and weighs things differently than five years later when you developed a donor specific antibody. And that makes sense, because those two rejection episodes require different clinical management.

And therefore, you need to assess the prognosis and the effect of different treatment approaches in a weighted fashion.

So to conclude, BPAR, I think the A should not stand for acute, but active. We could not ignore the chronic active components because they are a major driver for long-term allograft outcome.

Secondly, I would challenge from the past the unit dimensional dichotomy and histology only endpoint, yes, no, you have it, and our goal of the trial is to not have it, towards more the several dimensional overlapping phenotypes, at least be more granular and say this drug is for T-cell mediated rejection. It is without chronicity, it is with chronicity, or it is for an antibody mediated rejection, towards future concepts, where we have

probabilistic archetypes and we see how your probability changes after a treatment, and to improve your outcome in that association.

So it is not one-size-fits-all. And what we have learned from the cancer world is stratifying your trial groups for targeted treatment made trials being more successful, instead of lumping them all together into one category with one very nonspecific endpoint.

And also, the concept of having rejection as the endpoint, I think, can be challenged. It would be like saying, we give all of us here chemotherapy, and then we do a biopsy and see who has cancer, rather than saying we diagnose patients with a certain phenotype of rejection, and then give a targeted treatment to cure rejection. Maybe that's another approach to how we can do it. So thank you.

DR. MANNON: Thanks so much, Dr. Mangel. Next, we'll hear from Dr. Roy Bloom, Professor of Medicine at the University of Pennsylvania Medical Center, and Medical Director of

Kidney Transplant on managing BPAR and contemporary immunosuppression, from the transplant clinician perspective. We can tee up his slides.

DR. BLOOM: Okay. Thank you again, for the invitation to discuss today, and these are my disclosures.

So I'm going to try and cover four objectives in the course of this -- this brief talk. First, to discuss the clinical relevance of BPAR in 2023. Second, to review existing data regarding treatment of BPAR. Third, to highlight what the guidelines tell us regarding BPAR therapy. And finally, to describe how transplant clinicians typically treat BPAR.

So we've seen this slide before, transplant outcomes have improved, albeit somewhat incremental. This is also a figure that we've seen showing the relative improvement in graft survival, comparing an era between the late '90s and 2010, to 2013, and showing that the relative improvement has basically been demonstrated in all subgroups,

regardless of donor source, regardless of donor age, race/ethnicity, or comorbidities.

And why we see this prolongation in graft survival beyond the first post-transplant year, there are probably lots of reasons. TAC is more efficacious than cyclosporine. We heard earlier that it's associated with less nephrotoxicity. We've also primarily been using depleting antibody induction therapy over the past couple of decades, and we have markedly improved HLA technology.

So if we look at why kidneys failed, death censored graft loss, we have data from both studies with surveillance or protocol biopsies, as well as with full course biopsies. This is data from the Mayo Clinic, where they looked at a cohort of patients who had sequential protocol biopsies. They clustered the causes of graft -- of death censored graft loss into these five buckets, and you can see that approximately a third of the grafts failed because of a histological diagnosis of i-IFTA, about four to six months prior to the kidney actually

failing. And about a third had glomerular disease.

But if you look at the patients that had i-IFTA, about 25 percent had a history of rejection. If you look at the patients who had glomerular disease, about 40 percent had transplant glomerulopathy, highlighting the importance of -- of rejection as a cause of long-term graft loss.

This is a more -- a more recent study, also in looking at for course biopsies though, and in this study, they looked at the causes that they identified multiple factors that contributed to graft loss. But here, I'm just showing the primary cause, which was defined by the cause responsible for a persistent eGFR loss of more than 50 percent of the maximum GFR. And again, you can see that combining both T-cell and antibody mediated rejection, rejection was the leading cause of long-term graft loss.

So this is something that we recognized 20 years ago, 30 years ago, and essentially it still hasn't changed. Now, if we look at how common clinical TCMR is, we have data from a number of

randomized control trials. Most of these are registration studies. You can see that starting in as a TAC, MMF era, where there were rates of rejection in the 90 percents, the impact of Tacrolimus, reducing that significantly in the late 1990s, plus the addition of mycophenolate, and in more contemporary times, we now have -- oh, there we go. Anyway, in more contemporary times, we now have rates of rejection of around 10 to 20 percent.

I do want to point out that the Symphony trial, which ultimately became the trial that guided our sort of current benchmark of TAC, MMF, and prednisone, had a low rate of rejection. And that was published in -- in 2007.

So some of the limitations of these registration trials that we need to be aware of is that they did not specify the grade of rejection, and they did not -- most of them did not incorporate borderline rejection, either. And this is important because of the increasing recognition of the association between borderline rejection and outcomes,

and that is not well established in indication biopsy studies.

Now, we do have a number of studies and trials that have looked at subclinical TCMR with protocol biopsies. This is not every study, but it's -- it's a number of them, all in the prevalence -- all looking at the prevalence in the -- the TAC, MMF era, and what you notice is that most of these studies were either observational, retrospective, there was one RCT here. But the time to biopsy is right, you know, typically every one to three months in the first year, a couple beyond that time point.

And what you notice is that total TCR mediated rejection, the rates of rejection with these protocols that it is not that different than was observed in the RCTs that I showed you in the previous slide. But what is notable is that most of these -- most of the rejections that occur in protocol biopsy studies, the overwhelming preponderance is because of -- is because of borderline T-cell mediated rejection.

So should borderline rejection be

considered TCMR? So this is my perspective as a transplant clinician. This study from the Sydney Group nicely demonstrated that borderline clusters with acute TSMR, using principal component analysis, we know that it associates with adverse outcomes. Borderline TCMR is basic a broad diagnostic phenotype.

I'm not a pathologist, but you know, obviously, it includes a spectrum where you can have less -- a combination of less inflammation, and less tubulitis, to having more tubulitis and less inflammation, and vice versa, more inflammation and less to tubulitis. So it really does encompass -- doesn't encompass a broad phenotype. This has potential for overlap with TCMR, and as we just heard, it really does represent that this is more a spectrum.

There are issues with sampling error. But I think even if you, you know, quibble about what the appropriate phenotypes are, or anything, we will all accept that borderline rejection is consistent with under immunosuppression.

In addition, there's been some

correlation of borderline rejection with some of the emerging acute rejection biomarkers. And what is important is that there may be a difference between clinical and subclinical borderline, in terms of whether it should be treated or not, just based on clinical practice, which I'll go into in a little while.

So if we move into treating BPAR, what is the data that we have from randomized controlled trials? So this is just to remind everyone that the last multicenter RCT that was published was in 1998 and was basically the registration trial of pharma globulin. But if we look at a relatively recent systematic review of all the RCTs that have looked at treatment of -- of the first TCMR, usually in the first post-transplant year, there are a total of 17 studies comprising about 1000 patients.

And these were trials you can see how far back they go, 1973 to 2000. You can see the different comparisons with antibody therapy, either steroids, steroids versus steroids alone, one antibody

versus another, or antibody versus another treatment altogether. And if you look at the outcomes that the analysis looked at, look at the first outcome of failure of reversal of acute rejection, antibodies where treatment was associated with less failure of rejection. This was with moderate certainty, and it indicates that antibody is probably better.

If you look at recurrent ACR, preventing recurrent ACR, there was a moderate level of certainty in favor of antibody being better. That sense of graft loss was a low level of certainty, suggesting that antibody may be better. And adverse effects were high with antibody and probably reduced by steroids. Notably, there was no difference in death at 12 months post -- post treatment, and within the first post-trial -- post-transplant months.

So to summarize this historic data, pretty much all the data has been in the cyclosporine, Azathioprine era, and likely included antibody mediated rejection at that time, since the criteria for diagnosing ABMR was not well established. There's

very limited data with contemporary immunosuppression. Some of the knowledge gaps include related to not having well defined rejection grades in these studies. Obviously not knowing what the optimal therapy should be, how to define response to therapy, and then the issue of subclinical rejection, which has -- has not been -- was not addressed in any of these trials.

This is a more recent systematic review. This is from Dr. Nickerson's group, looking at more real-world data in patients on TAC, MMF based regimens. Here, there are 12 studies that they investigated, and was a more contemporary era, 2015 to 2021. And the different spectrum of all these studies, one RCT, a number of observational studies, and a few retrospective studies. Rejection diagnosis was both by protocol biopsy, as well as indication biopsy.

And if you look at the spectrum of TCMR that they saw and how they treated it, you can see subclinical borderline rejection. About half the studies, no treatment was given. There were variable

practices in terms of increasing maintenance immunosuppression or using steroids, with clinical borderline. Again, a combination of maintenance immunosuppression, steroids, and variable practice with around those, becoming a bit more consistent with sub clinical and clinical rejection for Banff 1A, for example, using steroids that are given intravenously, steroid resistant pharma globulin. And with more advanced grades of TCMR -- TCMR, using pharma globulin.

Now, you see the heterogeneity in treatment for subclinical rejection. This raises the question, does treating a subclinical rejection make a difference? So this is the only study that I'm aware of in using contemporary immunosuppression, where they looked in a randomized control trial, at using surveillance biopsies. And what you see is that about half the patients were randomized to get biopsied more frequently. The control group had biopsies at six and 24 months.

And what the findings were is that at

six months subclinical TCMR prevalence was only 4.6 percent. At six and 24-months of note is that there was no difference in kidney function, patient, or graft survival, but there was more fibrosis in the biopsy group.

So the authors concluded that treating subclinical rejection did not prevent chronic injury, oops, just need to go back a sec. Two limitations of the study is that they didn't treat borderline subclinical TCMR, and whether that might have had an impact is unknown. And the follow up was relatively short, it was only 24-months.

So here's additional data regarding whether or not borderline TCMR should be treated. This is a retrospective study from Nankivell, again, over 1000 biopsies in 550 patients. These were based on an index biopsy or 12-months post-transplant, included to 201 patients with TCMR. And the spectrum of treatment of borderline TCMR varied from none through to rATG and increased immunosuppression.

So of the 146 patients who had

borderline TCMR, 54 were diagnosed on indication biopsies, on which of whom 83 percent were treated, and 92 were diagnosed on a protocol biopsy, on which about half the patients were treated.

So if you look at the outcomes in these groups, so if you look at all patients, 72 percent on a follow up biopsy showed resolution. But note that about 30 percent had late acute rejection. If you break it down by the biopsy approach, on the indication biopsies, about 75 percent resolved. On the protocol biopsy group, about just over 70 percent resolved, as well.

Now, if you break it down by whether the patient's protocol biopsies were treated or untreated, you can see that in the in the group of patients who had a protocol biopsy, there were about -- I'm sorry, in the group of patients where protocol biopsy were treated, there were about 14 percent that had persistent, and 8 percent that had worse histology on a subsequent biopsy. And about 25 percent had had a subsequent rejection.

But of note, I'm sorry, there's a formatting problem here. But in the protocol group that did not get treated, about 61 percent of patients in the second column, resolved the biopsy altogether without treatment.

So what are the guidelines tell us? This is the KDIGO guidelines. There are other guidelines that, essentially, have similar recommendations. So the major recommendations are obviously biopsy and before treating. They suggest treating subclinical and borderline rejection and recommend steroids initially. For patients that were not on steroids, restarting steroids. For patients with steroid resistant rejection, adding a lymphocyte depleting therapy. A number of different recommendations for -- for treating antibody mediated rejection. And if patients were not on mycophenolate, either starting it or adding it if they were on azathioprine.

So important, and you can see most of these recommendations are either low or very low

quality of evidence. In KDIGO, unresponsiveness was defined as function marked back to baseline after the last dose of therapy, but doesn't determine what their timeframe was after that last dose. No distinction between persistent versus recurrent rejection, or the use of a repeat biopsy to assess response.

It also does not provide guidance for treatment of acute rejection in terms of specific drug dosing, based on the rejection grade. If the sub-clinic TCMR, or if the rejection was diagnosed by indication or protocol biopsy.

So finally, what do transplant physicians say they do? And we have three surveys that I'm going to share -- that have been conducted in the past five years. And I'm going to share with you, the first is from the Canadian group. Here they had 47 respondents out of 196 members of the Canadian Society of Transplantation. Other respondents, 28 percent perform protocol biopsies, and the practice represented the majority of transplant centers in Canada.

There was a subsequent study in -- in among us transplant practitioners, where there were 104 respondents out of 470 patients who were surveyed, representing about 88 out of 235 transplant centers. Among the respondents, 40 percent of protocol biopsies and induction was the primary -- R82 was the primary induction use.

And then, the most recent survey, which is not yet published, but it's courtesy of Dr. Naesens, is from -- is from Europe, where there are 129 respondents, representing 129 transplant centers. And in the centers, 36 percent of centers that protocol biopsies as a standard of care, and other 21 did biopsies in specific subgroups. Induction was either basiliximab or rATG.

So essentially, we have insight into practice in 235 transplant centers in North America and Europe. So this is going to end up being a fairly complicated slide, so I'm going to explain to you what this represents. The three studies on the left, this shows -- I'm going to break it down by the grade of

clinical TCMR, which is on the x-axis, and the immunosuppression, the different bars, are representing different colors are different immunosuppression. The lower legend represents the U.S. and European study. The upper legend represents the Canadian study.

So if we first look at treatment of clinical TCMR, you can look at borderline TCMR and you can see that -- oh, and then the table at the -- in the bottom right, is looking at these different grades, and looking at the harmonization, either within each study across different practitioners, or between the different countries, or different regions.

And so if you look at treating clinical borderline TCMR, you can see most centers, either in increasing immunosuppression, mostly use prednisone or -- or steroids rather, IV or oral. Notably, in the U.S., about 20 percent of centers do not do -- do not treat clinical borderline TCMR.

So if we look at the table, there's some harmonization in terms of increasing

immunosuppression and using steroids. But less harmonization, say within the U.S., were they about 20 percent of patients that don't use any change in immunosuppression and then, even some that use anti-thymocyte globulin.

So next, we'll look at recommending steroids for the initial treatment of acute cellular rejection. So this is grade 1A rejection, and here you can see that the -- the European group combined both 1A and 1B into one category. And I think that if you look at 1A, at any rate, there is a lot of harmonization, since mostly the treatment that's used is steroids. Although, again, some use of pharma globulin in the in the U.S. population.

If we look at 1B, I think there's pretty much no harmonization in the U.S. over 60 -- the majority of patients get treated with rATG, whereas steroids are used both in Canada and in Europe. And then if we look at grade two TCMR, I think there's no harmonization, because again, steroids and rATG are used in both Canada and in

Europe, but the vast majority of patients in the U.S. are treated with -- with rATG.

This is exactly the -- I'm not going to go through it so systematically again, but this is just treatment of subclinical rejection. So if you look at borderline rejection, there's again some harmonization. But there are five to 20 percent of patients across these different respondents were not treated at all. Most, there was some increase in immunosuppression.

Again, grade 1A, I think there's good concordance with most -- excuse me, centers using steroids and/or increased immunosuppression. And then, looking at 1B and grade two TCMR, I think it's a bit more all over the map. Again, a higher likelihood of using rATG in U.S. patients.

Lastly, as far as in the -- in the surveys, looking at assessing the response to therapy, across all the studies, frequent -- more frequent bloodwork was -- was the most common response in virtually all patients. Surveillance, or follow up

biopsy was recommended -- was the practice in about 40 of Canadian and U.S. respondents. It was a lot more frequent in -- in patients in Europe.

And one question that was placed -- that was given in the Europe survey, which I thought was really instructive, is what the respondents -- respondents were surveyed for, what they considered the timeframe of a treatment failure. And you can see about a third of respondents said within a week. About a third said within two weeks of treatment, and another third said within one month of treatment.

So thinking about when to do a surveillance biopsy, this is some insight into practice from -- from a group of transplant clinicians.

DR. BELEN: Dr. Bloom?

DR. BLOOM: So most importantly --

DR. BELEN: I apologize, Dr. Bloom. Can we wrap up, we're over time? Thank you.

DR. BLOOM: Sorry. So most important is most standardization of post -- post rejection

treatment in a number of different parameters. So in conclusion, rejection remains the commonest cause of death censored graft loss. There are no large RCTs that have evaluated BPAR treatment under contemporary immunosuppression. There's tremendous heterogeneity in treating BPAR in terms of when, whether to treat, how to treat, how and when to assess response to therapy. And the optimal management of BPAR remains to be established. Thank you.

DR. MANNON: Thanks. Our last speaker for this session is Dr. Peter Nickerson, on Long Term Impact of BPAR in the Modern Era, What do we Know?

I know we are running a few minutes behind, so we'll either cut the discussion down, or maybe cut lunch down to try and catch us up a little bit.

DR. NICKERSON: So I was going to talk about efficacy of modern immunosuppression, immune suppression on BPAR a little bit, discuss relative impact of things like DGF, TCMR, and ABMR, and talk about some future directions.

So there's been a lot of intense focus on DSA and ABMR. This is a paper from the Paris group showing that at one year, if you had subclinical ABMR, you had a really bad outcome by eight years. I would just highlight that 80 percent of these one-year subclinical ABMRs were associated with preformed DSA, which is not really the type of patient that we typically deal with going into a clinical trial.

In our own cohort, what we saw is that by four or five years, if you were developing a de novo DSA, that was really a bad marker and it pretended a poor prognosis of up to 10 to 11 years, as compared to those patients that did not develop a de novo DSA.

And I think the other thing we haven't appreciated enough is what drug combination you give makes a big difference in whether you're going to develop a DSA or not. And this is just showing the improvement in the rate of de novo DSA, free survival based on attack MMF pred combination, as compared to cyclosporine, MMF, and pred.

Now, it not only matters that you're giving TAC, MMF, and pred, but it also matters how much you're giving. So this is a study out of Colorado, where they were targeting levels of six to nine the first three months, and then four to 12 or five to eight in the next -- between four and 12 months. And what they achieved in their study was that a quarter of the patients had a mean TAC level of eight, the majority had a level between six and 7.9. And about 20 percent had mean TAC level less than six.

And what was astounding in this study, which was a one-year study, was that the rates of de novo DSA by 12 months was 21 percent, which seems remarkable.

But when they actually started looking at it relative to what targets they achieved and their TAC levels, what they saw was at the moment you were less than an average of eight in the first year, you had a slightly increased odds ratio of developing a de novo DSA.

But certainly if you were between four

to 5.9, or between zero to 3.9, versus on an average of eight, you had a marked or increased risk for de novo DSA, acute rejection, and death censored graft loss. So the adequacy of the drugs that we're giving really matter.

In our own cohort, where we looked at 50,000 levels over 12 years and almost 500 patients, and these were our targets and what we actually achieved, what we saw is that about 95 percent of our patients over the first year had an average level of eight or more, and the de novo DSA rated at 12 months if you gave that level of immunosuppression was 1 percent.

When we looked beyond that, and we asked what -- what threshold was giving you increased risk for DSA, what we found was that those patients who were spending time below a trough level of five were having an increased rate of de novo DSA, and that was true for any trough level below that. But for any level above that, what we saw is that there was no difference in the rate of developing de novo DSA.

So essentially, what we were seeing was that long-term, if you didn't keep your levels above five, you're increasing your risk for developing a DSA.

And this study, actually out of France, was a multicenter randomized control trial where they took a standard cohort of patients that would go into a randomized controlled trial. They had no pre transplant DSA and they gave them IL-2 receptor induction, they gave them TAC, MMF, and a steroid taper to make them steroid free.

If they remained BPAR free at three months, they randomized them to stay on a lower dose of TAC, at an average level greater than three, versus standing on staying -- on standard dose TAC of seven to 12.

They achieved that, they achieved a real separation in TAC levels between four and 12 months. There was a highly significant difference. What they didn't see was an improvement in eGFR. The eGFR was identical between the two groups. They'd

hoped by giving less TAC, they'd have an improvement in the eGFR, but that didn't show up. And maybe that goes to Ros's point that there's not so much of a vasoconstrictive effect as we think with TAC, as compared to earlier drugs, like cyclosporine.

But what they did see was that when we lowered the immunosuppression and didn't give enough TAC, they were paying the price of having more BPAR, 11 versus 3 percent, more de novo DSA, five -- six versus zero, and the majority were class two, which are the ones we don't want. But they did have less BK viremia, which you'd expect them to have, because they gave less drug. But when they got to a protocol biopsy at one year, they had a much higher rate of an iScore greater than one, going into Michael's point about inflammation is not necessarily rejection, but inflammation is showing suboptimal immunosuppression here, as compared to standard dose Tacrolimus.

And so their conclusion at the end of the study from this randomized trial is that you should probably try and keep your TAC level in the

first year, on average, at seven or higher. And if you don't, you're going to pay the price.

This is a multicenter Canadian trial; I'm not going to go into the complexities of it. But what it was essentially trying to look at was low dose versus high dose or standard dose TAC, and it also had a randomization on ace inhibitor and no ace inhibitor.

The point I want to make here is that we actually had a clear separation of those that got standard dose versus low dose TAC. And when we looked at BK viremia, same things we saw in the Paris study, those that were on standard dose had more BK viremia versus the low dose TAC.

But when we looked at rejection in this cohort, and we looked at protocol biopsies at six months or 24-months, those that were on standard, those TAC, actually had a borderline or higher rate of rejection with 30 percent. So this is again, using borderline as our definition.

If we used our classical, Banff grade of 1A, we saw the standard was TAC -- the rejection

rate was 4.2 or 7.2 percent, telling us that most of the information we're seeing in these graphs is at a borderline level, not at a Banff 20 or higher.

We also saw that those that were on standard dose TAC, by one year, there was an average of 1.5 to 1.6 percent of de novo DSA. By two years, it was up to three to 5 percent. And on standard dose TAC, by five years, it was between five and 7 percent. So again, showing what the expected -- expected level or development of de novo DSA, if you gave adequate immunosuppression.

And this brings me to the question of, well, where is acute T-cell mediated rejection? Is it still an opponent that we need to be thinking about? And there's two studies that we put out last year, one from Chris Wiebe, who's here, and Dr. Julie Ho, who did the meta-analysis that Dr. Bloom referred to.

So if we use borderline or higher as our definition, and borderline meaning, I1, T1 or higher as borderline, and we looked at all the biopsies we did in this cohort out to five years. In

the top, you're seeing the four cause biopsies. Here's our protocol biopsies, and the majority are at six months. And you can see that the cumulative Index of borderline in our cohort was about 23 percent in one year. And it got up to about 30 percent by five years.

When we looked at these rejections, the first TCMR that was occurring, the majority were pure TCMR, alone. There were some mixed rejections with ABMR, and the median time of diagnosis was six months. There was some ABMRs without TCMR, there's only seven of those. But the median time of an ABMR in our cohort that was pure was 22 months, much later.

Now, this kind of goes to where Michael was talking about. When we looked at our cohort on cyclosporine, MMF, and pred, we saw a lot of Banff 1As, 1Bs, and 2As, and even 2Bs. And we had borderline, even on cyclosporine, of 32 percent. What happened when we went to MMF and pred was we push the grade down, and we got more normal biopsies, all the way up to 70 percent with no TCMR.

But we still had 18 percent borderline is our predominant diagnosis. And in this cohort, when we looked at on surveillance or for cause biopsy, it didn't really matter. The primary diagnosis on a for cause or surveillance biopsy was the borderline rejection.

And on the -- we did see on the F4 cause a more higher rates of 1A and 1B, and then, 2A. All this to say is that borderline is the most common diagnosis we see today, and it's not something that's been used in clinical trials to define BPAR.

Now, Michael alluded to this, this was a threshold that was set by the community back in 1993. And setting a threshold in the Colt V [ph] article was designed to so that false positive rate in the diagnosis should be very low. But it has the potential for frequent false negatives, depending on the prevalence and impact of Banff borderline on TCMR on our graphs.

So that took us to looking at time dependent covariate analysis to look at death censored

graft loss and all cause graft loss. And in this modeling, what we looked at was three factors when you adjusted for all the baseline variables. And what we saw was delayed graft function at first cellular rejection or an ABMR were all independent predictors or correlates of deaths censored graft loss, and all cause graft loss. And the importance here is that the first TCMR was an independent covariant of graft loss from ABMR. They both held risk.

When we did a sensitivity analysis and we looked at whether the first TCMR was found on a for cause biopsy or found on a surveillance biopsy, there was a clear association of those found on a for cause biopsy, independent of ABMR, as correlating with risk of death censored and all caused graft loss.

If it was found first on a surveillance biopsy, if it didn't reach statistical significance, the p-value is .08, but it did have a hazard ratio of almost 2. So I think, had we had a larger sample set, we probably would have gotten there.

When we looked at the grade of

rejection and asked whether or not did it matter if it was Banff borderline or Banff 1A or higher, it really didn't; either one has highly correlated with death censored graft loss. The Banff 1As were correlated more with all cause graft loss, as compared to the first TCMR Banff borderline.

Now, when we went and did follow up biopsies, looking at what happened to these patients who had a TCMR that was treated, what we saw was that up to 50 percent of our patients were actually having ongoing rejection, either persistent or -- or subsequent. Persistent meaning it was occurring within the next six months. In fact, the median time to the next diagnosis was 1.7 months, and the subsequent was generally after six months.

Now, you could say well, that's Winnipeg, and maybe you're doing something differently there, and your rates of persistent rejection are just abnormally high. So this was why we did the systematic review and meta-analysis. And what we found when we looked across the literature,

restricting ourselves to those patients who are on TAC, MMF, and pred, we saw that in the aggregate, 39 percent had a initial TCMR that was Banff for borderline. We had persistence of borderline or higher, 39 percent. And if our initial TCMR was bad Banff for grade 1A or higher, we still had 39 percent that we're having persistence of their TCMR on follow up biopsy.

Now, if we looked at persistence of Banff borderline after treatment of clinical, greater or equal to Banff borderline, we saw that it was 41 percent. If we looked at persistence of Banff borderline after treatment of subclinical Banff borderline, it was still over 40 percent.

And interestingly, when we looked at persistence of Banff borderline after untreated Banff borderline or higher, it was 61 percent, suggesting that the treatment actually had some restriction on what would have otherwise happened, had you not treated it. Suggesting again, I think, that the these persisting processes are -- are related to the degree

of immunosuppression that we're giving.

So we then looked at the question, what's the impact of a second TCMR? And we found that that was highly significant, both for death censored graft loss and all cause graft loss, and independent of whether there's an ABMR or not. And if we looked at whether it was persistent or subsequent, it didn't really matter. Both were highly correlated with the risk of death censored graft loss and all cause graft loss.

So it really brings me to the point that, I think we've been making all day, there's a lot of unmet needs still in transplantation. We do a transplant, some patients will develop a DSA without a preceding TCMR, and go on to ABMR, and chronic, active ABMR. But I would say the majority of what we see when we do have rejection, it's TCMR, that many times is not treated adequately. It leads to persistent TCMR or a tips over into an ABMR. And both ABMR and persistent TCMR can go into chronic, active ABMR and chronic, active TCMR. And these are things that we

are not having treatments for at the moment. And that will lead to reduce graft survival.

If we could treat TCMR and put it into a remission, we still are in the current immunosuppression that we have, we're going to have to deal with CNI toxicity, which is still real and prevalent in the combination that we have. But they still do relatively better than compared to those that are having ongoing inflammation in their graft.

So I think, in terms of where we need novel therapies, we need it to prevent and to treat TCMR and ABMR, and I think as we've been discussing throughout this whole session, we really have nothing new since the 1990s, in terms of trying to address these problems. And I think treatment of a rejection, given the high prevalence of persistence, and if you look for it, you'll find it, is a real opportunity to bring new therapies into the field.

And with that, I'll just acknowledge my coworkers and stop.

DR. BELEN: Thank you, Dr. Nickerson.

I just want to announce that I think we're going to have to shorten our panel discussion to maybe about 25 minutes, I apologize, so we can get to lunch.

It will be still late, but we -- maybe we can add five more minutes at lunch. So with that, we can go into questions. So far, we don't have any questions from the remote audience, and we can start any questions here.

DR. MANNON: I would say I there's a summary of several individuals in the chat, Dr. Deirdre Sawinski, Dr. John Gill, past president of AST, Michel Joseph, President of ASN and a transplant nephrologist, all indicating that this has been an interesting session.

But the implication of just focusing on BPAR in the absence of an RSLE is not going to transform our field. And to circle back to this morning's discussion, to rethink about how we're doing this. These are, I think, interesting academic questions and important when I think about a patient, but we're talking about drug regulation and

innovation, and I think that's what they're getting at. Trying to channel the online audience, sort of.

DR. BELEN: Okay. Please, go ahead.

DR. KEN NEWELL: Thank you. So never one to shy away from diving in, I'm going to try to simplify my understanding. I think this is a really good discussion that points out the heterogeneity and the opportunities to improve, both in our diagnosis and in a more standardized management that will improve outcomes.

But when I think of all the people participating here, to look at simply, I'm going to go back to the question I asked before, and I tried to look up some data while I was sitting there, which is fortunately easy to do.

So if you look at the most recent OPTN SRTR report from 2021, the rates of acute rejection published registry data, but huge numbers. I think we all believe this is real. The rate of acute rejection in the first-year ranges from 9.3 percent in 18- to 34-year-olds, to 5.3 percent in people like myself,

who are 65 or older.

So you say, let's pick an average of 7.3 percent, reduce it by 50 percent. So we're going to say, you know, if I can reduce it to 4 percent, now, big improvement; 50 percent reduction, I've reduced it to 4 percent. If you look at the five-year survival for those populations, unfortunately, for my age bracket, it's 68 percent. For 17- to 34-year-olds, it's 81 percent. You pick an average of 74 percent.

So if you're following my math, if every one of those acute rejection episodes that I've presented, that 4 percent, lead to graft failure. And if I could stop that 100 percent of the time, I've now increased the five-year survival from 74 percent to 80, to 78 percent, right.

So it's not to say we can't do it, but it's incremental, it's a bigger squeeze, to -- to get not a lot. And I think that we have to do that. No one's saying that we shouldn't focus on biopsy proven acute rejection. Every one of us as a clinician wants

to avoid it, our patients do. I take Ergun's point, the -- there are a lot of consequences, other than graft loss, associated with BPAR that need to be prevented.

But I still don't think, and I'd like the patients to weigh in. You know, if I tell you, I'm focusing this energy here, but with the current endpoints I have, I can tell you, I expect to improve your outcome in terms of graft survival, not other important things, by 4 percent. I think we need to do that, but we need to think of a companion to that.

So I don't think anyone's saying we should ignore the impact of rejection. But I think we have to look a little bit beyond that. And so I want to understand how we're going to, without new endpoints, really transform the experience for our patients. And I hope maybe patients online can comment or other people, because I think that's the real issue as I see it.

DR. MENGEL: Yeah. So I think, Ken, one problem here is that the 7 percent or 8 percent of

acute rejection episodes is those we detect. We detect many patients with chronic lesions where we probably miss the episode. And kind of the data are suggesting, and I think it has not really been proven is, when we have a standard immunosuppression with zero rejection, we have zero chronic problems in a trial, where we control them.

DR. NEWELL: But what I would say, Michael, is even if I'm wrong. Say --

DR. NICKERSON: Use the mice for the audience. No, like the online audience.

DR. NEWELL: So say the registry data is missing 50 percent of rejections, even if you double those numbers and even if you assume that every one of those rejections would create graft loss, and I now have a way to prevent it, it's still a incremental gain.

So I'm trying to use the data that every one of us, that's how we're judged by CMS, that's how -- everything uses SRTR data. I think it's a safe thing to do.

But let's pick number and say it's actually 12 percent. And I can reduce it to 6 percent. It's going to mean that I've improved outcomes from 74 percent to 80 percent within a year. And that's not what our pioneering forefathers did.

I mean, if you look at the data presented, they kept doing transplants, where out of -- what did you say, 244 patients, only 11 survived the year, the graft function? They took bold steps.

I mean, if I had that sort of success at Emory, they would ask me to retire. And so I think we need to -- I think we need to set a higher bar and we need to be bold and adventuresome. And while we should absolutely focus on squeezing everything we can, whether it's preventing BK, or I mean, that's not going to transform our field and I'm not going to feel proud at the end when I tell Kevin, "Hey, I got an extra 4 percent."

DR. STEGALL: Just sort of a related comment, but the idea of what we've seen this to Peter, it's what you can really achieve in a patient

with -- with the medicines that we have, right. And that's the reason I think that we see -- most of these patients are somewhat maxed out on their systemic immunosuppression.

And the focus on the levels, it's a sort of an idealized number, it's a mean. But you know, very many of our patients are on lower levels of drug and not on MMF at all, don't tolerate it. And that's the reason I think that focusing on -- it's only one aspect of the overall patient management issue, that has to improve. And I think that's the reason we would advocate something more broad than just focusing on the rejection piece.

And I think that's the reason that maybe rejection doesn't have the same impact that it used to have on survival of the graft, too, because you know, there's so many aspects polyomavirus, and -- and leukopenia, and everything else, that you end up -- I think that's the reason that the subclinical rejection rates are all over the board, too. Because it's a lot of patient management issues that lead to

getting to that number.

UNKNOWN SPEAKER 1: So I totally agree with you, Mark. I think the issue that I would argue here, is that there are patients who are going to have rejection with what we're doing today. And they're going to keep having rejection with what we're doing today. Which is, for that subset, they've got a problem that we're not addressing. And we should try and address that.

And I would agree with you that the majority of our patients, probably 60 percent, I would say, maybe 70, don't have that problem. They have a problem of drug toxicity, of leukopenia, nephrotoxicity, of neurotoxicity, that they want to get away from, and where's the new drug that's going to help me get away from those.

So I think that's where we have to start getting into what are our patient needs. And the approach that we take right now, is one size fits all. It's -- we're going to bring a new drug in and we're going to give it to everybody. And we're not

trying to tease out which group actually needs what. Because I would argue, there's probably a whole bunch of people that could do better on less, and with less nephrotoxic drugs. And we should be finding those patients to do with drug development with. And then, the patient who has -- going to have a real hard time with their rejection, they probably need something new as well. It's completely different, right.

But we're lumping everything together in our approach today. And what I would argue is we need to get a little bit more into precision medicine about what we're doing. And so I think, there's no -- I don't think -- I think there's multiple pathways here, that we're talking about.

So one pathway is, how do we actually get and address problems that a subgroup is going to have? Because for them, it's a real problem. For the majority, they don't have that problem, but they have another problem, and we need to fix that for them too.

So I would say, there's multiple things that we should be doing, not just thinking of one way

to get there.

DR. BELEN: Before going to the next question, I'd like to read a question from our remote attendees. And Dr. Helen Thoreau says, "As Dr. Mengel very nicely pointed out, PCMR is a continuum, and not a yes or no variable. In addition, borderline changes often warrant treatment and is associated with worse outcomes. But it's not defined as BPAR. Seems definitely like not a very useful binary endpoint. Any comments on these issues by the FDA?"

DR. VELIDEDEOGLU: This is Ergun Velidedeoglu, and I will try to tackle that question.

It's, I mean, this discussion has been going on for some time, and we had discussions about this with Dr. Mengel on the phone, as well. So we have the Banff grading system. But that doesn't necessarily correlate well with the outcome.

There are publications that, I mean, as far as I could look up, showing some correlation. But there are also outliers. I mean, for example, in one recent publication that I, you know, looked at, 1B

rejections seem to have, you know, worse outcome than 2As, and maybe 2Bs. So it's not a perfect correlation.

But Dr. Bhutta and his group published about it back in 2014. I believe that Dr. Wu was the first author, and there are similar publications. So currently, we don't know how to -- how to scale the intensity in terms of outcome and rejection episodes. Regarding counting borderlines and probably subclinical rejections as events, I'm fully on board with that.

We just need to get an appropriate submission, with the rationale, and we are willing to consider that. I mean, that sounds a reasonable approach. And it will also provide the benefit of increasing event numbers. So if you have too few event numbers or too many event numbers, that requires much larger sample size to demonstrate superiority. But if you start using borderlines, and subclinical rejections, that may be helpful from a sample size perspective and make studies more feasible, especially

for the demonstration of superiority.

So I don't know if I have been able to answer the question, I mean, acute rejection endpoint has served us well. And we are in a comfort zone now, just because we are able to prevent it effectively. And the rejections we are seeing under immunosuppression are the blunted versions of what would have otherwise happened. And we have seen one example of that when you give belatacept based immunosuppression, and that's in the label, in the absence of corticosteroids, it's I mean, you get very high rejections and some of them may end up in graft failure.

So we should not be in a false comfort zone just because we have effective immunosuppressive treatments.

DR. BLOOM: You know, and I just want to add, and this partly responds to the comment that Ken had made as well.

So it may be that, you know, more than greater or equal to a grade 1 TCMR, may only be eight

to 10 percent. But you know, we know, from the data that I showed, that most patients -- most rejection is borderline, and whether or not it even contributes to an adverse outcome, depending on you know, which side of the fence you are.

The reality is, we know from the surveys that patients are still being treated, and if the treatments, and those are not necessarily being captured as rejections and even as I say, if the rejections -- the borderline rejection is not affecting the outcome, the fact that patients are being treated is leading to additional comorbidities and contributing to death, which is the main reason that kidneys fail.

DR. MANNON: Okay, Kevin, go ahead.

MR. FOWLER: Yeah. This is Kevin Fowler, from Kidney Health Initiative. I'd like to go, I think, along with what Dr. Newell said, and then also the people online. And I just ask you to take this under consideration.

But you had the meeting five years ago,

and I looked at the iBox was the pathway, right? And so my concern is, and we talk about these areas that are important, that Dr. Mengel talked about a few and Dr. Nickerson. But we go off, sometimes, it gets us away from the larger issues that we need to galvanize around.

And so I think where my concern is, is trying to look at these meetings to continue. Are we moving forward, or going back to my opening question, what's changed in these meetings, right? And so I think I keep going back to that question, are we advancing in that direction that's going to benefit the greater good or are we going to go back and open the meeting with the same question again, and that's where my concern is.

And then I -- and then, just one thing I would just ask, too, is that whenever you come to the point, I think Nickerson said there may be multiple pathways, right, which would be great. But just to make sure the patient community is not at the end, putting the icing on the cake, but it helps build

the cake, and builds the ingredients so that we have a collective. Because our risk tolerance has been shown, sometimes to be different than what physicians are. So that's it. Thanks for consideration.

DR. MANNON: Thanks, Kevin. You know, we have a very short time, Michael. Can you summarize in a sentence?

DR. MENGEL: Look, I know -- I want to -- I think you are making a very important point and I'm not sure what this workshop is actually about, because -- sorry for saying that. But when I look at our practice as pathologists, the smallest fraction of biopsies we get our early events post-transplant. Ninety percent of the patients are doing just fine. They never get a biopsy.

The events you see associated with failure are way later and have nothing to do with BPAR or an acute rejection. They are a different pathology.

And I think there is a false notion that when you avoid an early acute rejection, you will

never see the late pathology. But I'm wondering why we see hundreds of biopsies with the late pathology, when everybody gets standard immunosuppression at the front end. There is something missing in between.

And that's where the iBox comes in where it is waiting. So a patient can be totally fine up here, and you treat BPAR, but there is something, which is maybe it's missed or not picked up, or it is -- we don't know that in all cases. But the iBox takes all the pathology showed into consideration, also at later time.

So is the goal preventing an acute event over here for a few or is the goal to extend long-term allograft survival for all patients, where there are other events laid here.

And maybe the drugs we have to avoid the acute event early are good, and they don't get better. But we have no drugs tackling the late events.

I'm not sure they are associated. That's what the statistics show. But are they the

same? Is there -- the research of druggable targets of i-IFTA just oversimplifying?

So what's the purpose and the goal of today is discussing endpoints around treatment over here or is it just assuming whatever that we do better here, at the beginning, we will never see this late, which I doubt personally.

So that's what I hear when you speak, to be honest.

DR. MANNON: That's a very long single answer, but appreciate the clarification, very much. So, I do. Karin?

DR. HEHENBERGER: Thank you. You know, I -- I appreciate the -- the answer from you, Dr. Nickerson, that -- that it's not easy to live with the levels that are recommended. Because if you're looking at the levels of Tacrolimus, and the trough level being 8 or above, you know, for a patient to go on for years and years with those levels, you're going to -- it's not just about fibrosis, and CNI toxicity.

But it's also the actual side effects

that are, you know, impacting work. You know, cognitive dysfunctions, it's tremors, it's headaches, it's hypertension, diabetes. It's all these effects that -- that may limit the adherence to the program.

So although, it is interesting to look at, you know, let's up the immune suppression, we do need to find other drugs that are more immune modulatory in nature, and less aggressive to the whole body. You know, 40 percent bioavailability doesn't really cut it.

You know, the other point I wanted to make in addressing the comment that industry is not doing enough. You know, if there's no regulatory pathway, there's no financing of industry. You know, we have seen in oncology so many drugs and so much investment. I mean, I'm -- I'm sad to see the lack of investment in this industry, from venture capital, from Wall Street, and so on.

You know, it is because there are no real regulatory pathways. There is no diagnostic beyond a biopsy, which for a patient, is pretty

traumatic.

So we need to look at better ways to segment the population. If we even look at us who are here today, the patients, we all look kind of similar because we're educated, we can speak. You know, if we look at the kidney transplant population in general, it looks very different. And we need to look at individualized treatment like that, and therefore, we need better diagnostic. And I think we heard that as well, today.

You know, it's not -- it's like type one diabetes. It's not type one diabetes, we now have different stages of type one diabetes. We need to look at kidney transplantation and kidney disease as something that is not just a one, fit all.

You know, Tacrolimus, as being given to me at 120 pounds, and someone who's 250 pounds, you know, it's similar dosing. So we have to -- we have to really, I think, dig deeper; and that's to academia and industry. But we need to create the pathways and the incentives to do so. So thank you.

DR. BELEN: Thank you, Karin. Actually, we are going to take one last question from remote, Dr. Hariharan. And we'll get back to you in the next session because we're already over.

This is from Jessica Voss. "In short," I'm trying to summarize this question. "Other disease areas, including lupus, as well us TAC. And the disadvantages of using it to the kidneys is widely -- widely accepted. Can the FDA comment about why the nephrotoxicity in kidney transplant is just accepted as it is what it is; whereas in other diseases, it is not?" Maybe I'll just tackle it, and then we'll end this session and go to our lunch.

So in general, when we look at benefit risk for any new therapy, it's accepting what the benefit is versus the risk. So if you have a new product with, let's say, comparable efficacy, even maybe slightly less, but far less toxicity, we do take that into account. So the status quo is not acceptable for each product. We make that benefit risk assessment.

Having said that, even for already approved products, we do continuously do that benefit risk assessments when we have new safety issues, we do that, take it into account.

Sometimes in other areas, we did change our indications to indicate that this new safety issues that came about changed our benefit risk analysis.

So I'd like to say, in short, that I -- I do not think that we are happy with status quo of nephrotoxicity as an acceptable safety outcome for these patients. And we strive to have new products that where we can say this is less and we can accept new protocols, new medications, looking at this as a safety endpoint and as a claim. Which -- which might give him incentive to new innovators as well.

I hope I tackle this a little bit. I know this is far complicated question than what I'm saying right now, but this is in our minds. Thank you.

DR. NICKERSON: So I think we're ready

for lunch?

DR. BELEN: Yes.

DR. MANNON: And we're going to start at the same time, because we have people with trips to be on to, and the like.

(Off the record.)

DR. CHAUDHRI: If everybody could take a seat, we will try to get started.

Good afternoon. Hopefully, we were able to enjoy some sun on this rare November day. We'll start with session three. The topic is Non-Inferiority Trials, What have we Learned? And our first speaker for this session is Karen Higgins, who is a Senior Statistician in CDER, at the FDA.

DR. HIGGINS: So hello, everyone. So thanks, Nadia.

Yes, I'm a statistician at the FDA. I support the division of rheumatology and transplant medicine. And I was asked to talk about considerations in determining a non-inferiority margin.

This is a very different talk than the talks you've seen, so far today. Actually, as a statistician, I have the least amount of data in my talk, compared to everybody else. Just enough for a small motivating example.

So my disclaimers and disclosures. So I'm going to talk about -- give an example about setting a non-inferiority margin. But prior to that, it's really good to talk about non-inferiority in general. And then, to motivate that, I always like to give a little bit about superiority trials. So that's the direction of this talk.

So superiority trials, the objective -- and I'm focusing on efficacy, really the demonstration of efficacy. The objective of a superiority trial is to show that a new treatment is effective by showing it's better than a control.

It's kind of the gold standard. It's what everyone learns in statistical classes. The control could be placebo, an active drug, a lower dose of a test drug. We've seen superiority designs in

transplantation, people have talked about them already, today.

We have placebo-controlled superiority trials that are typically of an add on design. And that just means, because we have a multi-drug treatment regimen, is that patients are randomized to a new drug or placebo, but that everybody receives a standard background regimen. And an example of that was, with MMF, plus cyclosporine, plus steroids was superior to placebo, plus cyclosporine, plus steroids.

We've also seen active control superiority trials. Similarly patients are randomized to new drug or an active control. Again, everyone receives the same standard background regimen. And an example of that was cyclosporine and steroids, superior to Azathioprine plus steroids.

There's some important considerations to think about with superiority trial designs, despite them being kind of the gold standard and the demonstration of efficacy. Is that we do need to make sure that statistically significant results point to

efficacy of a new product, rather than merely the lack of a safety concern.

And as an example, superiority in the rate of new onset diabetes after transplantation of a new drug, compared to Tacrolimus, wouldn't be evidence of efficacy. I'm not saying that showing better safety isn't still very important. But when it comes to determining an efficacy -- the efficacy of a product, that wouldn't be a demonstration of efficacy.

Though sometimes superiority trials are not ethical or feasible to conduct. So in situations when a new drug is meant to replace an existing, effective product, the use of placebo might not be ethical. And we might not expect the new drug to actually be superior to that existing, effective product.

Or even if it was, even if we thought it might be superior to the existing, effective product, it's often that the treatment effect that you might want to find would lead to such a large sample size that designing your trial as a superiority trial

might be infeasible.

So in those cases, we can consider non-inferiority trials. So very similar objective with the non-inferiority trial, we want to show that a new treatment is effective. But this time, we're showing that it's close enough to an active control. It's -- it's okay to be better than the active control, that's great. But it's -- it's not okay to be too much worse than the active control. And that too much worse highlighted in red, is because that's kind of a hard number to figure out, how much is too much.

So here, just to -- I like to picture things. So this is just the way I picture these superiority trials. We have a number line that has all kinds of possible estimates of the treatment difference between test and placebo. So this is a superiority trial.

Where to the left would be results that would favor placebo, to the right would be results in favor of the test drug. And I've my 95 percent confidence interval. That confidence interval

excludes zero and it's on the side in favor of the test drug. So that's comparable to having a statistically significant result with like a P value less than .05. So that's just how you picture the superiority results.

Now, to show how it's different with non-inferiority, in a way the criteria is relaxed a little bit. Now, we have on the left, in favor of the active control. On the right, still, in favor of placebo. But rather than that confidence interval having to show superiority to that active drug to be, you know, excluding zero in favor of the test drug, we allow it to kind of dip down to -- to a certain level. And it's that non-inferiority margin is where we allow that confidence interval to go down to.

So just an example, I know we've talked about trials in the past, and a lot of drugs have been approved for transplant based on non-inferiority designs. But here's an example of Nulojix, or belatacept, where subjects were randomized to either Nulojix or cyclosporine. Everyone received the same

background regimen of basiliximab induction, MMF, and corticosteroids.

Here are the results of biopsy proven acute rejection at one year for one of the studies. And we see Nulojix had a 21.7 percent rate of BPAR, and cyclosporine had 16.7. The confidence intervals go -- the confidence interval goes from -13.2 to 3.3 percent.

And one thing we always need to do when we're looking at confidence intervals, especially for non-inferiority trials, is what side of that confidence interval are we focusing our energy on. And in this one, we're going to look at the lower bound, because I'm looking at cyclosporine minus Nulojix, and it's a -- it's a rate that we don't want too high. It's kind of a negative endpoint.

So in general, this confidence interval is the -- the increased rate of BPAR could be as much as 13.2 percent. So with a non-inferiority margin of 15 percent, this trial would conclude non-inferiority of Nulojix to cyclosporin.

So next, I'm going to go into a little more terminology about that non-inferiority margin. All of this information comes from the FDA guidance on non-inferiority trials. So in much gory detail, it's -- it's described very clearly in that.

So M1 is the estimate of how much better the active control is compared to placebo. So it's -- it's how effective that active control is. We estimate M1 based on historical, relevant data. So it has to be data that we think would be meaningful, with the current non-inferiority trial. And it should be a conservative estimate.

M2 is based on clinical judgment. It's the maximum amount of the treatment effect that we would be willing to lose. It's a difficult concept; you take into account considering the severity of the disease, the outcome you're measuring, and the potential benefits of new treatment. And then, the margin used in the trial is the minimum of -- of those two values.

So just expanding on this M1 a little

bit more, again it's based on historical data. The best way to estimate M1 is to have multiple studies comparing your active control to placebo. You get an estimate of the treatment effect of that active control, pool it all together, and you get an estimate for your M1.

Alternatively, you can determine M1 by comparing two kind of comparable sources of data. You can get some information on your active control, and some information on placebo, and kind of compare the two. And then, the guidance also gives alternative methods.

But important, no matter how you estimate this -- this treatment effect, again, you got to keep in mind that the data has to be comparable to the -- to the non-inferiority trial you're designing. So the design should be similar, the endpoint should be similar, the time point that you're measuring the endpoint, patient population, background therapy. No non-inferiority margin justification is perfect, but you need to consider all this, and consider how this

would impact your estimate.

And then, just a quote from the guidance says, "The validity of any conclusion from a non-inferiority study depends on the choice of M1 and its relevance to the current non-inferiority study." So it's just an important thing to consider.

So just an example of the determination of M1 for a transplant trial. Going back to belatacept, again, reminder that patients were randomized to Nulojix or cyclosporine, with the background regimen of basiliximab, and MMF, and corticosteroids.

Ideally, we would get a margin justification based on a bunch of trials comparing cyclosporine to placebo, with every one receiving the same background regimen.

But there were no studies like that available. So we had to look further, or the sponsor had to look further. And in the end, the non-inferiority margin was justified based on six studies that looked at the treatment arm of cyclosporine, a

more general induction treatment, MMF, and corticosteroids, and compared that to one study of induction, plus MMF, plus corticosteroids. And I have the reference here and at the end of the slides that describes this in more detail.

But again, I like to visualize things to just help you visualize where this margin came from. Here, is my -- my number line. On the X-axis is the rate of BPAR. The image is just for you to be able to visualize it, the -- the image itself, isn't exact.

But imagine we have the six studies, all of that active control treatment arm. We would -- we conducted a meta-analysis to get a confidence interval of that effect that went from 17.0 to 26.

So you can imagine the rate of BPAR, kind of the highest rate, a conservative estimate of a rate of BPAR for this active control regimen that we're going to be using in the -- in the trial, was 26.

And we had one study looking at kind of

this putative placebo. That same background regimen, but without cyclosporine, that would tell us what cyclosporine adds to the regimen. And we got a confidence interval of 47.9 to 68.4.

And then a conservative estimate, we'd compare the upper bound of one to the lower bound of the other. So it's 47.9 minus 26, gave us an estimate of M1 of 21.9.

You know, this data is not perfect. It's kind of a cross study comparison. We only had one study for the putative placebo. You know, there -- there are some drawbacks to the margin justification. And for that reason, you know, we kind of rounded it down to 20, but.

So that was M1 and how we calculated an M1 for a specific transplant study. But how do we come up with an M2? And this is, you know, it's less scientifically based. It's -- it's more of a clinical judgment. 20 is that minimum of kind of showing a drug is effective, showing that it's better than placebo. So that's that M1.

But we might want to preserve some of that benefit, we might not want to use that full amount as our non-inferiority margin justification. So let's say in this case, we wanted to preserve about 50 percent of that benefit. So the leftover piece would be our M2. That's kind of the amount we'd be willing to lose, and then our margin would be based on the minimum of those two, which in this case, would be M2.

We could think of, maybe it's -- maybe we're looking at mortality. Maybe, for some reason, we felt we needed to preserve more of the benefit, the benefit preserved would be bigger, but we'd have a smaller M2, and a smaller non-inferiority margin. Or we might -- maybe the new treatment is going to add -- potentially add a lot as another choice to people who maybe couldn't take other things. Maybe we'd be willing to have a smaller preservation of benefit and a larger M2. But either way, that M1's fixed and the M2 is -- is more nuanced, in a way.

So then you think, well you know, why

not have as small an M2 as possible, right? Preserve as much benefit as possible. And the reason is, is because as quickly as M2 gets smaller, the feasibility of doing a non-inferiority trial really increases the infeasibility.

So here, I just have the sample size for various rates of BPAR from five to 30 percent. It's a sample size per arm, in a situation where we have 80 percent power, 5 percent two-sided error, and the test equals control. That's my assumption for my non-inferiority trial.

So if I had a trial of -- with a 15 percent margin, my sample size per arm is under 200. When I get to a 10 percent margin, the sample size, as you can see, increases. But when I get to 5 percent, it really explodes. So when we consider M2, we really need to consider about how feasible this trial will be.

And then going back to belatacept and some considerations for M2. You know, M2 could equal M1. It could be that 20 percent. And that would

demonstrate an effect over placebo. You know, that's not a terrible thing. We're showing that it works. But again, we would need to consider should that margin be smaller than 20 percent.

We need to consider the severity of the outcome, the benefits of the new treatment. And just an example, an M2 of 15 percent would preserve at least a quarter of that cyclosporine estimated treatment effect, which we admit as a conservative estimate. And in this case, we would still conclude non-inferiority, because that 13.2, -13.2 would be greater than that -15 percent.

So just in conclusion, I'd say non-inferiority trials play an important role in assessing efficacy when superiority trials are not feasible or ethical. The trial requires a valid non-inferiority margin justification. It requires an estimate of the treatment effect of that active control M1, based on comparable data.

And it's not always possible to conduct a non-inferiority trial if we don't have any estimate

of the effect of that active control. And it requires a discussion of kind of a limit in that loss of effect you're willing to consider.

And just something to keep in mind, the conclusion of a non-inferiority trial really doesn't mean that the new drug is worse than the control. The non-inferiority margin is a limit of that negative effect we want to exclude. And similarly, like we exclude zero for superiority trials.

And here are my references. Thank you.

DR. BLOOM: Our next speaker is going to be Dr. Steve Woodle, who's coming in remotely, who is the Director of Solid Organ Transplantation at the University of Cincinnati.

DR. WOODLE: Can you -- can everybody hear me?

DR. BLOOM: Yes.

DR. WOODLE: Okay. Good. Good. So in the next 15 minutes, I'm going to try to share with you some of our perspectives on endpoints and get at some of the issues, hopefully, that have arisen around

the endpoint of rejection and a trial.

So you've heard today, already, about primary endpoints in registration trials, that combinatorial endpoints is the way that this -- these are done nowadays. And the combinatorial endpoints traditionally have been patient survival, graft survival, loss of follow up, biopsy, proven rejection, and renal function.

I won't spend a lot of time talking about renal function because it's -- it's extensively covered in some of the other talks. And in some cases, co-primary endpoints have been used, for example, in the belatacept trials.

And I'm not sure how I can control the slides here. Okay. Good. So secondary endpoints for a sponsor are important, because they can be used to make claims and post approval marketing. And so in discussions with FDA, as a design the clinical trial, they can talk -- have discussions about the endpoint and what they will or won't be able to say about -- really harbors around the robustness of the

observation as a secondary endpoint.

And it also is a mechanism and a potential for future endpoint development. For example, if a sponsor wants to try a non-traditional endpoint, and FDA is considering this, this is one of the things they can do in early phase trials, have a secondary endpoint that evaluates the potential for future primary endpoint.

Examples of secondary endpoints, DSA was specifically mentioned for me to speak about, so I'll talk a little bit about DSA. Renal function, as I mentioned, is covered by a lot of other people. You've heard a lot about iBox, today. The one thing that I would say about iBox, is that think iBox primarily suffers from a lot of subjective endpoints that include Banff criteria.

If iBox scores improve, I think it's going to have to move away from the subjective components and elements and move towards objective components. And I think this will happen as pathology approaches, such as some that I'm going to describe

today, improve over time.

Cardiovascular risk and cardiovascular events have been very difficult. You heard some comments about NO-DAT [ph] just a little while ago in the previous talk. And this has proved to us in our steroid elimination trials to be a very difficult secondary endpoint.

And then, people have already talked today about histologic endpoints in terms of rejection. The issues with Banff components and the subjectivity. Moving on to the molecular, sort of the simple molecular approaches, such as those used in the molecular microscope with just simple gene expression levels.

And then, I will talk a little bit more about more advanced genomic approaches, where gene signals can be ascribed to individual cell populations using advanced genomic approaches.

Next slide. So DSA is an endpoint. Its significance is -- is that it has a big effect on graft survival. But the problem is, is that it has a

varying intensity of effects on graft survival, based largely on how high the DSA is in the clinical setting in which it occurs. For example, a DSA that develops in the absence of clinical rejection, for example, found on a yearly screen with a negative biopsy at a low level, it may not have much significance.

But if it is a DSA, that's a class 2, at a very high level, and a comment -- component of late, mixed rejection, then this is a significant biomarker that has an indication for high risk of graft loss.

The other -- one of the other problems with DSA effect is that in many of the rejections that are recombinant, cellular rejection that exists, and the ability to separate the effect of the DSA from the effect of the said rejection mechanisms, is -- is a -- is quite a challenge, and really hasn't been done yet to any significant degree to our knowledge.

And then, there's also controversy. There's been considerable controversy amongst people in the HLA field over the ability of the existing

single nBSA to provide quantitative data on DSA. I would argue that if one has a laboratory, and you spend considerable amounts of time and effort, especially, you do the assays robotically, one can actually get coefficients of variation of less than 5 percent. But that requires quite an effort.

This is another concept of DSA that hasn't really been highlighted, today very much. And that is, you need to look -- if you get information, if you look beyond not just what the DSA was at the time of rejection diagnosis, but if you look at what the therapeutic response was.

So in a paper in which we first coined the term "mixed rejection," we looked at DSA reduction in both mixed rejection and antibody mediated rejection, and we saw a very wide variation. As you can see over here on the left-hand side of the screen.

We updated that to include 89 patients treated with a single antibody mediated rejection regimen or produced some inhibitor-based regimen at our -- at our centers of single center data. And we

showed that if you can reduce the level of the immunodominant donor specific antibody by 50 percent within 14 days, that you reduced by 50 percent the rate of graft loss. So not only do you need to look at what the DSA is, when it occurs, what's the setting, what's the level, but what is the therapeutic response to really understand the impact of DSA on graft survival.

Next slide. So rejection as an endpoint has a lot of problems. We've already seen some data today indicating that rejections that occur under different immunosuppression have different implications in terms of endpoints. Specifically, bela passive rejections versus calcineurin inhibitor rejection. We now know that those are fundamentally different biologically.

We know from the clinical trials, the BENEFIT and BENEFIT-EXT, that the rejections under bela were more frequent and more severe by Banff criteria than they were under CNR blockade with cyclosporine. But data from our studies, from the

BEST trials, indicate that overall graft survival may be better with belatacept.

One of the facts that's -- that's missed by a lot of people, and hasn't been mentioned today, in BENEFIT and BENEFIT-EXT, there were 666 patients on belatacept, and from two years to five years, there were zero rejections.

And so what belatacept has is provides superior long-term prevention of late rejection. And it's the late rejections that occur under Tacrolimus, that drive a lot of the graft loss.

So the other point that -- that we would like to make, is important to remind everybody here today, that rejection treatments, steroids, and ATG are 70 years old. They still remain today the primary treatment that the FDA requires a drug company, testing a new drug, to treat the rejections with.

All of the rejections that occur except for Banff 1As, and I'll show you data margins for Banff 1As, are associated with very poor graft

survival and significant risk of graft loss, but not the Banff 1A rejections, particularly if they're early.

So the other thing that we have is that we have -- we have required rejection to be treated the same under Tacrolimus and costimulatory blockade, when that is not supported by currently available data. And we'll show you some of that data later on.

Next slide. These are data from a paper that we generated several years ago, where we actually took -- we use our definition for mixed acute rejection, which is basically rejection meeting both Banff criteria for a second rejection and antibody mediated rejection. And that's early, mixed acute rejection, you can see the MAR there.

This is antibody mediated rejection, this sort of rejection. The difference between early and late is that early occurred in the first six months post-transplant, late occurred beyond six months.

The point I would make to you is look

at an early ACR, here. Ninety percent graft survival at four years, 10 percent graft loss rate in four years in those patients.

Whereas you take a late antibody mediated rejection, you have 100 percent graft loss within three years. I would submit to you that that is -- has a profound effect on a clinical trial. So understanding the nature of the rejection, just based on these six clinical phenotypes, which are very easy to do, can help one better understand the impact rejection under a new immunosuppressive therapy.

Next slide. Okay. And I think it's already been mentioned today is that don't forget about SAO rejection. I think there's Peter Nickerson that said that, and I think fatty lipids has been in the year of a lot of people saying, "Don't forget about SAO rejection," it's not all about the antibody.

These are Banff 1A rejections for just pure ACR that are early, on the left-hand side, and late on the right-hand side. And you can see, once again, that if you have a late rejection that is a lot

worse in terms of graft survival than if you have an early rejection.

But look at the Banff 1A rejections. No effect, no graft loss at five years post-transplant. Yet, if it's a Banff 2b, you have 100 percent graft loss within four years. And you can see a Banff 2A, a late Banff 2A, pure ACR, 100 percent graft loss. So I'd submit to you that there are some rejections for which steroids and anti-lymphocyte globulin do a very poor job.

So we need to be considering moving on beyond those drugs and trying to find better drug support that'll do better, certainly in the context of a new immunosuppressive agents.

Next slide. So I'm going to share with you now, data from a study. This was a study that Dave Hilton and I started eight years ago, working towards where we wanted to understand better the biology of rejection, to understand the clinical phenotypes, and what's driving graph loss.

And this technique basically, is a

genomics-based technique, where you actually take gene expression in each individual cell that's in the graph. So you have to digest the biopsy, and then you run the cells through a single cell genomics platform. So you get the -- the level of expression of thousands of genes that are assigned to thousands of different cells.

The U map on the right is actually a presentation of how the cells clustered together. So you feed all the information into a computer, it's like a principal component analysis under basic transcriptomic techniques, and the cells that have gene expression similar to each other cluster together.

Now, you can notice that all these cells over here, most of the cells over here, are derived from the nef log. Okay. There's about 10 or 12 populations, tubular cells, glomerular cells, endothelial cells. But the remainder of the cells you see mainly in a rejection, and they're CDH-B cells, you can see CD4s, and often different sub-clusters.

Next slide. One can then take these cells and say, "Let's just look at the CD8 positive T-cells." Now, we're interested in a CD8 positive T-cells because these are the cells that drive rejection. They're the primary effector cell, they're the ones that destroy real tubular cells, and attack the endothelium.

On the left is a U map. You can see the individual different types of CD8 cell populations, exhausted, activated, resident memory, and a proliferating cell population out here that's assigned number 8. And here's the level of gene expression within each one of those categories for exhaustion markers, activation markers, and memory markers.

And you can see the numbers of cells. So these little violin plots, each plot, the height of it is the number of -- is the level of gene expression. And the width of it is the number of cells with that gene expressions. You see, there's very powerful data here with thousands of cells and

the level of expression of -- of any gene you want expressed in that.

So using this, we can actually very effectively characterize the entire CD8 positive infiltrate within a graft.

Next slide. So one of the first questions we asked was, we wanted to look just at the -- the CD8s that were expanded. So the other beauty of this technique is, you -- well, let me back up.

For the audience that is not familiar with this, you can literally generate a billion different types of T- cells from the genes that you have, and you were born with. And what -- what defines each unique T-cell is its T-cell receptor.

So you literally have the ability to generate more than a billion different T-cell clones. So each clone will have the very same T-cell receptor.

So in this study, we took patients with rejection under Tacrolimus, belatacept, and basiliximab. And the ones that had the same T-cell receptor, that is they were expanded. So there were

hundreds of these cells, they're shown in color. The T-cells that are not expanded are shown in gray. So you can see that these are these expanded CTAs have different phenotypes under Tacrolimus. But when you look at belatacept, it's dominated primarily by memory T-cells. And when it's basiliximab, it's primarily an exhausted cell population and a proliferating cell population.

What this data shows you is very convincing data that the nature of the rejection as defined by the cells driving the rejection. That is an alloreactive CD8 T-cell, are fundamentally different. To think that we can treat these rejections the same with steroids and anti-lymphocyte globulin, is -- is just beyond ridiculous to me.

So move on, next slide. So this is an example of four successive biopsies in a patient with ongoing rejection that didn't resolve, despite multiple manipulations. We had an ACR 1B rejection in this patient, treated with Tacrolimus and steroids. You can see these are the colored cells, the cells in

color are actually expanded CD8s. So CD8s that are clones, that are expanded. You can see, there's a small number of these; very small number of T-cell clones that are driving this rejection.

We treated them with Tacrolimus, increased the Tacrolimus dosing, and steroids. And you can see, we didn't do any better. We didn't really appear to be affecting the cells that were driving the rejection.

We then added back on mycophenolate. It had been taken off because of a low-level positive BK viral load. And you can see, the -- the rejection went down from 1B to a borderline rejection. The clonal populations actually changed a little bit from an activated profile to an exhausted profiles. And a new clone emerged.

And then, at that point, we didn't want to treat the patient anymore, because we were fearful of potential immunosuppressive complications. So we slowly tapered off the MMF for the next two months. Patient increased their creatinine We biopsied them,

now they've got a completely new set of resident memory clones that are driving this rejection, and the other clones are largely diminished, once again.

So what this shows you is that these cells driving rejections can change their phenotype, based on the drugs that you throw at them. They will still hang around; they won't go away. And then, you can even have new clones emerge that can then turn the rejection into a different picture.

Next slide. Let's see. Go ahead and let's see. We're missing some -- oh, here comes. It's just slow. Yeah. One more, click it one more time.

All right. So this -- what this slide shows you is that despite the fact that our pathologist told us that a rejection was completely resolved, as you can see here on post-transplant day 95, you can still see these clonal cell populations that are still in existence, that we can pull out of the graft.

So what this means is that there may be

a lot of patients out there that we think we completely treated their rejection, but yet the cells that are driving the rejection are still there. Six months later, this patient came back with a rip-roaring rejection, these exact same clones were still there, they were present in huge numbers, and that patient lost their graft.

And so this highlights that what -- what we think is effective rejection therapy may very well not be. And we've seen this in a number of patients with histologic appearance of rejection, with long-term persistence of these alloreactive CD8 clones that are driving rejection.

Next slide. Next. Go ahead and click again. And click again. And click one more time.

So in the basiliximab group here, we asked the question, what is the gene expression of these particular genes. And one of the things we're particularly interested in was the calcineurin inhibitors. The calcineurin phosphatase pathway, or calcium dependent pathways, with T-cell activation.

We found that there was increased markers for the Tacrolimus receptors, and also other genes in the pathway.

We then took this patient and treated them with 30 days of Tacrolimus and found that with a significant improvement of rejection, with resolution of rejection. So this is actually an example of how this approach can be used to develop a personalized therapy that is beyond the usual steroids and anti-lymphocyte globulin.

The beauty of 30 days of Tacrolimus is once you pull it off, their immunosuppression is not increased. Had that patient gotten steroids or anti-lymphocyte globulin, they would have been profoundly immunosuppressed for the several -- next several weeks or next few months. So this is a reverse type of rejection therapy.

In a very similar way, we took the patient with belatacept with these memory cell populations and asked the question about M4 signaling pathways, which we knew is a pathway that these cells

use. And we found there was significant upregulation in comparison to the totals in basiliximab. This patient was treated with an M4 inhibitor, Sirolimus, with significant improvement in the rejection. Not resolution, but significant improvement.

And this is an example of how we're moving towards personalized treatment of rejection and moving away from the old paradigms that are dictated to us by sponsors and FDA, and how we have to treat patients under new immunosuppressive drugs.

Next slide.

DR. HIGGINS: Dr. Woodle.

DR. WOODLE: The other beauty of this --

DR. HIGGINS: Do you mind trying to wrap it up? We're running over.

DR. WOODLE. Okay.

DR. HIGGINS: I'm sorry.

DR. WOODLE: All right. Good. I'll wrap it up in a minute.

These clones are also present in the

urine. You can see that they expand and contract in parallel with what's going on in the graph. We no longer need to use the graph to follow rejection therapy or to diagnose rejection therapy, using these particular approaches.

Next slide. So the -- skip this slide. Let's skip this slide.

So these are points for the FDA to consider based on our experience. Required standard rejection treatment across all limbs of registration trials is not supported by this recent data. Personalized rejection therapy approaches have arrived, and they need to be accommodated in ongoing future trials of new immunosuppressive agents.

Banff 1A SAO rejections should not be included as part of the primary. In our opinion, it could be a secondary endpoint, but not as part of a primary endpoint.

And we believe that FDA should encourage and support sponsors who are developing new maintenance therapies, that should be developed co-

existently with new rejection therapies that are tailored specifically for the type of rejection that arises under the new immunosuppressive therapy. Thank you very much.

DR. BLOOM: Our next speaker for the session is Will Fitzsimmons, who's a Senior Adviser to TTC and CPath.

DR. FITZSIMMONS: Good afternoon. I want to thank Dr. Belen and the FDA, as well as Dr. Nickerson and University of Manitoba, for hosting and sponsoring this workshop and the opportunity to present to you on Safety Endpoints in Kidney Transplant Trials.

This is a shift from everything we've heard today, in terms of the efficacy endpoints that we've been discussing up until this point. But I want to put this in the context of two things. One, look at it as non-inferior when efficacy failure isn't good enough, right. What can we do beyond non-inferiority for efficacy failure?

And secondly, how can we make sure that

that is part of a comparative claim that we can talk about, that we can hypothesis test, that we can put the statistical rigor to for our new immunosuppressants? So that's the context. These are my disclosures.

The first thing I'd like to do is talk about the why. So why should we be discussing safety endpoints in this forum? And I think, first and foremost, most important for all of us is the impact of adverse effects of these safety endpoints on patients and transplant recipients.

We've heard from them throughout the day today. And I think as Dr. Corrigan-Curray referenced this morning, to me, one of the most important and impactful, has been Amy -- the late Amy Silverstein.

Next slide, please. Is there a way we can advance the slides? Thank you.

Amy Silverstein wrote in the New York Times earlier this year and spoke on CBS Good Morning before she passed away. And she spoke about the toxic

triad of immunosuppressive medications are calcineurin inhibitors, antimetabolites, and steroids, that are almost four decades old. Of course, as we heard, MMF and Tacrolimus were approved in the 1990s.

And the secondary diseases and dangerous conditions that she mentioned, specifically diabetes, blood pressure, that's uncontrolled, kidney damage and failure, serious infections, and cancers.

And her plea, was transplantation is no different from lifelong illnesses that need newer, safer, more effective medicines. I think that's why we're here today. Right? How can we -- how can we deliver what Amy requested and what we all believe in?

Second why of why we should look at safety endpoints, is there impact on death and graft loss. I think one of the most comprehensive, recent publications from the Mayo Clinic, the three Mayo Clinic centers, was published last year with 507 -- 5,752 kidney transplants performed across those three centers, where they followed them for up to 14 years post-transplant.

So on the left side of this slide, you can see the cumulative incidents of death, with a functioning graft. That's the red line. Graft failure, the green line, and the overall, a black line.

And as you can see, for the first roughly five years post-transplant, the cumulative incidence of death with a functioning graft and graft failure are almost identical in overlay. But beyond five years, the death continues to rise, and that curve is consistently above the graft failure line.

So death, long-term, is a major reason that we're losing patients and recipients, and we need to address that. And importantly, if we look on the right side, what are the causes of those deaths?

And this is consistent, not only in the Mayo Clinic data, but if you look across the literature, there's always three things that come up. It's cancers, it's infections, and it's cardiovascular disease, right? The only difference is the timing. Infections are early, cancers are late, and

cardiovascular complications continue throughout.

All of those are impacted by the immunosuppression that we use in these patients. So with no doubt, there is an impact on death. Even if we look at graft failures, we heard from Dr. Bloom, alloimmune or rejection related causes are the number one reason for graft failure.

But if you look at the top five causes, you can see renal tubular injury at number three. Meaning the nephrotoxicity of the immunosuppression we're giving. At number five, BK nephropathy, a reflection of the intensity and the combination immunosuppression that we're given. So graft failure is also associated with the immunosuppression that we're giving.

So if we look at the top causes of both death with a functioning graft and that censored graft loss, and I've highlighted in yellow those that are impacted and associated with their immunosuppression. It should be very striking. And I would even argue that rejection is related to toxicity of

immunosuppression, because what do we do when we have toxicity, we minimize, we reduce dose, we change the regimens, patients become less compliant and adherent. All of those things result in rejection and eventually losing their graft.

The third main reason is for focusing on safety endpoints is the incidence of these is high. It impacts patients, it occurs frequently, and I'd say high enough to show improvement.

So we've all talked about how we struggle to show superiority on BPAR or efficacy failure, because the rates are so low. That's not the case with adverse events I've looked at. These are just the three most recent immunosuppressants approved in the U.S. Two of them are new formulations of Tacrolimus, Envarsus XR, and Astagraf XL, both extended-release formulations, as well as belatacept or Nulojix, that we've talked about.

Here are the top, in the first year, adverse events in their package inserts. You can see that the rates range from in the 20s to up to 45

percent. We're not talking about rates that are in the single digits. This is really impacting patients. We can make an impact statistically, here and impact patients as well.

And then finally, innovative, new therapies can be targeted to improve safety, even if we can't show improvement and efficacy failure. And that's can be a stimulus for incentivizing development. So let's get a new immunosuppressant out there, even if we can't beat it, the standard of care on efficacy failure, that's safer in the long-term. We can do that if we actually do it correctly and put our minds to it. That's what I'd like to advocate for today.

So hopefully, I've covered the why. And now I'd like to shift to well, okay, how do we do that? And maybe one of your questions should be, well, you collect adverse events in the trials all along. I just showed you a whole table of those adverse events. Why can't companies already actively promote superiority on safety?

And what I felt was telling is I looked at it again, those same three, most recently approved immunosuppressants for kidney transplant, their labels. All three of them have a near identical statement on the label that says, "The studies were not designed to support comparative claims for the adverse reactions."

So what does that mean? These companies cannot go out and promote that, right. So what we need to do is work on designing the studies so that they can support the comparative claims for these adverse reactions.

So with that, how do we do it? I think the first thing we can look at is hopefully the FDA guidance. And I'm extrapolating, there's an FDA guidance on using multiple endpoints in clinical trials. Most recently came out last year. This guidance is targeted towards efficacy endpoints. But I'd like to take the concepts that they've given for secondary endpoints and see if we can apply them in the safety perspective, because I think it will -- it

will teach us a lot.

So one of the important first things is, that the positive results in secondary endpoints can only be interpreted if we first demonstrate that we've met the primary endpoint. So these are always going to be safety endpoints that are coming after our primary efficacy endpoint, right. So we're not saying we're going to get a drug approved because it's safer if it fails on its primary efficacy endpoint. That won't be the case.

The other thing that's important is, in general, it's desirable to limit the number of secondary endpoints. So we can't try to address all of these, at least from a comparative claim, hypothesis testing approach. We're going to collect all the safety but be very targeted in choosing which are the key secondary endpoints for us to evaluate.

So then, we would move into the operational aspects of it. And again, there's -- we could spend a whole day probably just going through this, but I'll try to click through it in one slide,

quickly. The most important things from my perspective are first, predefine the secondary safety endpoint or endpoints. Again, try to limit those, but we predefined them very rigorously.

Dr. Woodle just mentioned the difficulty with diabetes. One of the difficulties there, I still think is a key endpoint for us, is that you can use fasting blood sugar. Fasting blood sugar will give us all kinds of results in post-transplant patients because of the steroid use for both prevention and treatment of rejection. So their fasting glucoses go all over the place. And we've seen rates as high as 70 percent for diabetes, if you're looking at fasting blood sugar.

Secondly, collect the endpoint rigorously, systematically in all patients. It can't be a we'll spontaneously collect adverse events that are reported, then try to make a claim out of them, right. We need to go into this and design the case report forms and the data collection to get them.

Thirdly, use established definitions

and endpoints from trials and approvals of other therapeutics. In other words, we haven't done this in transplantation, but we have approved therapies to treat these conditions in other areas. There's no reason that it would be any different because those therapies actually treat transplant patients as well. We can't use those same established definitions and endpoints.

And then lastly, be very rigorous in our statistical approach. Again, as I mentioned, we need to make the secondary endpoints so appropriately perform hierarchical testing, so that you're only testing these after you've met the efficacy endpoint. Control for multiplicity and type one error. In other words, you can't have 20 of these, right. And then say if any of them get P less than .05, we have a comparative claim, because something's -- you're going to have a type one error and you're not going to be able to do that. So make sure you're very rigorous in terms of the statistics.

So with that, where can we go with the

safety endpoints? I'm going to propose that there are a whole list of them that are clearly established, and I'll call them ready for primetime, now. And they hit many of the things that we talked about, whether it's diabetes, cardiovascular risk, infections, leukopenia, and anemia. We have endpoints already that are quantitative, hard endpoints used for approval of other therapeutics. We should be applying these now in our studies.

Again, the choice of which ones is really dependent upon the therapeutic you're studying, right. You -- if you have a new agent that's -- that has a significant reduction in diabetes, you may choose that one to compare to attack MMF regimen. But you may not, if you have a different type of therapeutic.

I'd also say that there's what I'm calling a second generation. So I don't think we can stop there, we should stop there. I think there are a number of others that are very close for us. For example, we know that diarrhea, as I showed, is a big

-- is a big is a high incidence adverse event. It impacts the quality of life of transplant recipients. It's related to Prograf and MMF use together in particular.

We can advance our ability to do stool counts and stool forms, there's standardized scales to do this, we've just haven't done it in transplant. Let's move in that direction.

And if I had a third slide here, I'd say we can go beyond even these. We should be getting into things like cognition, tremor, patient reported outcome measures, those are there and we need to advance the science. So I think we have low hanging fruit today; in the previous slide, ones that aren't very far away, and we have a long-term aspirational goal that we should be going after.

So with that, my quick summary here is that I hope I've convinced you that adverse events from immunosuppression are related to both death and graft loss. We already have objective, quantifiable safety endpoints for many of the key areas, diabetes,

hematologic, infectious, and cardiovascular adverse events. It's key that we bring the stakeholders together early to facilitate the incorporation in trials, and that includes patients, and include regulators, sponsors, investigators. That has to be a group discussion over the safety events together before they're incorporated in the trials.

And I think we all agree the reason why we're here is we're trying to figure out ways of bringing new innovation into transplantation. The FDA actually has done a phenomenal job in giving us pathways that are purposely designed to expedite the development of new therapies where there's unmet need for serious and life-threatening conditions. Those pathways include accelerated approval, Fast Track designation, breakthrough therapy designation, and priority review, right. They're laid out in their guidance documents.

What we need to do is find ways in order for us to take advantage of those. As an example, if you look at the criteria for priority

review of an NDA or BLA, substantial improvement in safety is one of the criteria for getting a priority review. If we can demonstrate that, our chances of a priority review go way up, that's very valuable to getting innovative therapies out sooner, valuable to the industry.

If we can get iBox qualified as a reasonable, likely, secondary endpoint, we can use the accelerated approval pathway. So shouldn't our dream be to actually keep the efficacy failure endpoint, perform what we're talking about in terms of tightening up the definitions? Yes, we need to figure out are we going to include borderline, are we going to include 1A, are we going to include subclinical rejections?

We should do that. That's not the answer. It has to be done, then move to accelerate approval based on reasonably likely surrogates for efficacy, so we can improve long term survival and test for superiority on safety endpoints. That's what patients need and want and deserve from us. I think

that we can work together to achieve that. Thank you.

DR. BLOOM: So we'll now open the session to a panel discussion. So if people in the audience have any questions, please, could you go to the microphones? And if you haven't already spoken, please identify yourselves.

DR. HEHENBERGER: Thank you so much. And I just want to applaud the -- the last speaker. I think that was the path, it was a very clear path. There is no -- and twice I've spoken in the past. So in both times, I've had the response, you need to think about safety.

But adding a secondary efficacy endpoint that doesn't impact the primary endpoint has nothing to do with safety. And here we got a path where we're actually also adding very important patient endpoints, meaning the safety ones, that impact adherence, impact quality of life, and impact, you know, everything that patients care about.

So I really, really applaud the -- the last speaker, and I think that is the path going

forward. So thank you.

DR. FITZSIMMONS: Thanks.

DR. BLOOM: So if you remember, when I had a question, it was there was the session ended. So this is what my comment was going to be.

There's actually a -- number one, there's a precedent, the direct study was a randomized control trial, where diabetes was a primary safety endpoint. So that's the one comment I was going to make.

But the second is, there was a drug that was developed in phase two clinical trial for preventing rejection, Valoctrosporin, which showed non-inferiority and had a diabetes safety signal. But the company pulled the development of the drug in transplant because they didn't think that -- that showed anything better with a phase two trial, and it's now been approved in a different indication. But that's exactly the case where this cognitive study design could facilitate, you know, expedited approval.

DR. KUMAR: Thank you, Bill. Excellent

presentation. In Center for Biologics, we receive immunotolerance trials, and several of them look at the impact of the immunosuppression therapy on metabolic complications.

The challenge that we face is we don't have good comparators. The transplant community has for a long time, relied predominantly on OPTN and UNOS data, which do not collect information on metabolic complications. So when we ask sponsors, are there natural history studies, are there real-world evidence, are there observational studies? We get case control studies as references and single center in our data.

So why isn't the transplant community investing in getting, in this day of electronic medical records, good natural history studies, good observational data, or real-world evidence to address this issue, which, as several of the patients have expressed is a big problem. And in one of the studies, they showed that cardiovascular disease accounted for 42 percent of the deaths.

So we need good comparators so that we have good performance thresholds as we review these applications.

MR. FOWLER: Hi, Kevin Fowler. I mean, I agree with Karin's comments, part of them. But just want to ask Bill, the presentation was great, and I agree with Karin. But here's where my concern is, right? So coming out of this meeting, how are we going to prioritize things so that we're not having the same discussions again?

So I guess that's my request. When we leave here, the follow up -- what the follow up plan is, is that there's prioritization. There's been a lot of discussion on the iBox, so is that going to be prioritized? And again, I think it's something important to ask the patient community what's important to them.

But also, this is also something I would just suggest too, is that, you know, to have broader stakeholders at this meeting, social security administration. What do you think employment is the

first year after transplant? Anyone want to take a guess? In the United States, not Canada, up here. Anybody want to guess? Employment first year kidney transplant is 30 percent. That's it. And that was done by the Social Security Administration.

So I think that just having broader stakeholders here, get back to what Bill is alluding to, because all the points you made Bill, are all contributing to suboptimal outcomes.

And the other thing, too, is that when we hear the same narrative, right, many times from AST, is survival's improving, but there's no mention of quality of life. So someone's watching unemployment, the government is.

So I just say is, let's have more stakeholders here that can look at this more broadly. But well done, Bill.

DR. NEWELL: Also directed to Bill. I -- I think that that's exactly where patients want to be, and I think where providers want to get our patients.

My question is, you said earlier or I've heard you say, there are currently no phase three trials of de novo immunosuppressants enrolling or in the late stages of planning. So how do -- and assuming, because I've heard you also say there is not a lot of data around these endpoints right now. How in the foreseeable future do we bring those forward?

Because if it's something, again, that you say, "I can tell you how we'll do it, and we can do it in three years," I think there'll be enthusiasm. If it's something that we can't do for the next decade or two, we should start planning now, but we have to be realistic.

DR. FITZSIMMONS: Thanks, Ken. I think that there are companies that are doing it today and working on it. And I know there -- if you look at which immunosuppressants are in development in the U.S., at least for prevention of rejection and kidney transplant, it includes the Veloxis Anti CD28 antibody, the Eledon CD40, Lygon CD154, and Tonix CD40, Lygon 154. I think those companies, and some of

them are here, could be open to talk about this, are already looking for ways to incorporate these safety endpoints into their study.

So I think we're going to be there in phase two, momentarily. And I think that will lay the groundwork for the phase three of the -- of those new molecules.

DR. HEHENBERGER: Can I just modify? There was one, when I said I'm really impressed with the presentation, I am. I just want to make sure that what I said was clear, was yes, this is a path.

But for a path to be taken, we need to take a first step. And the first step needs to be a secondary endpoint, right. An efficacy endpoint, and then we can add the additional safety endpoints.

As a patient, I care about the safety endpoints, but I first care about additional products in the marketplace. So I just want to clarify my statement; we have a path, we should go for the path, but we need to take a first step.

UNKNOWN SPEAKER 2: So I have a quick

question to maybe Bill and the FDA. So in -- in a safety endpoint, that would, as you're indicating, would be a secondary endpoint. Can that get in the label indication? And -- and if it is in the label indication, is that sufficient for it to get qualified, in the sense, if you know what I'm saying. Could it be a safety endpoint that leads to a single trial, that it's -- you have that much more safety? Your efficacy is the same. You could do a single trial. Is that allowable under the FDA?

DR. BELEN: So one can do one same trial, use the same trial for efficacy claim and the safety claim. The -- I think the hurdle is that most companies, when they're designing the efficacy claim, you know, they're designing the study, they're designing it around efficacy claim, and mostly there's no prospective collection of some of these claims.

And we've been saying this, the one part of it is a prospective collection of these secondary safety claims. And also, what is a meaningful difference for tremor, for glucose. So it

has to be defined, pre-specified before the trial starts, not after the trial ends.

So this has been a little bit of difficulty, but you people don't need two or three trials additional to the initial trial. They just have to plan it so that it can be one and done with the same one or two trials.

MS. MCCARTHY: That was fantastic. Thank you. Again, Molly McCarthy, three-time patient.

I love that you're invoking Amy's words at the start, and again, Amy was a very close friend of mine. I spoke with her just a few hours before she passed. And in fact, she and I met at a transplant related conference, and our bonding moment was actually when one of us kind of expressed like, "I don't feel that great all of a sudden." We both reached in our pockets, because we learned very quickly that we keep Imodium in one pocket, TUMS and Zofran in the other pocket.

And we also then, of course, the conversation progressed. And it was like this is the

life we lead. Yes, we're grateful. But gosh, why do we have to do that? And then, choosing specific handbags for things like that. Anyway, I digress.

So I want to kind of track with Amy's spirit. And she would be thrilled to have her words mentioned here, I think. I was just texting with her husband to make sure it was okay I said this. But I think she would also be incredibly frustrated, in the context of this, this is great.

And I am not a scientist, I am a technologist, however, who spends a lot of time on innovation and exploration. And I'm not clearly -- what are we doing with this, right? Like I have this kind of sense of a fear of there's this aspirational, one stop shop, one size fits all, one, you know, gold ring that we're going after that, it may take decades for us to get there. And as a patient, it's not good enough.

So I don't know that I agree with bringing more people to the table. Because I think when we bring more people to the table, it gets

diluted, and it gets way easier to hide accountability and point at the guy at your left or at your right. Instead, what I might suggest, and this is again, maybe where patients can step forward and lean in to provide some surrounding kind of structure and support. Let's find one or two things that we're going to do.

If it's iBox, great. But that shouldn't be the only pony that we put in the race. Let's put iBox and Xbox, ell, no sorry, not X Box. Actually, maybe. Hashtag now you know where I work. You know, a couple of different iterations and related kinds of, you know, experiments out there. And let's see, let's do something specific, finite, measured, well scoped. Measure the impact, apply that learning in one specific thing.

So I don't mean to get to the close, and I'll probably share a few more thoughts at that point but thank you for that. Amy would be really, really proud. But she'd also give us a nice hot poker, too.

DR. BLOOM: Steve Woodle, are you still with us? Oh, okay. So --

DR. WOODLE: Yes, yes, yes, I'm on.

DR. BLOOM: Thanks. So I have a question for you. You had made the point that -- that, you know, we acknowledged that late rejection is still a major cause of graft loss. And you pointed out that -- that belatacept didn't have any rejection shown between years two and five, versus the comparators.

So this is kind of a leading question, why do you think patients are having late rejection that are not on belatacept, that it's still a major cause of graft loss? And then as a result, since that's a long-term outcome, what kinds of surrogates would you think of employing in designing a study looking at trying to predict late reject late rejection outcome?

DR. WOODLE: Yeah, so I think when you look at late rejection that occurs under CNI therapy, that the estimates in the literature vary. but the

estimates of non-compliance as a cause of late rejection is between 50 and 80 percent.

Now, whether or not -- now, some of that, of course, is on the patient. And as you know, and as people have mentioned, some of that's on the physician because we don't have really good guidelines as to exactly where we should set the immunosuppression and each individual patient. but I think it's under exposure, driving, probably 80 percent or more rejections, late rejections under CNI.

And it just turns out that when you look clinically, and then you also look mechanistically, those are very difficult rejections to treat. They're the ones that really drive a lot of the graft losses. And so I think a number of people made the point, we need to be looking at rejections beyond one year.

The first year, the rejection rate's what, 8 percent? But there is a 1 to 2 percent rate of rejection in the entire population of patients that you follow, ongoing. So that means over a 10-year

period, that you've got 15 to 20 percent of those patients experiencing a late rejection.

Once you have a late rejection, if it's a 2A or 2B, you're going to have that graft for another three years. So there is a huge acceleration in the rate of graft loss with these late rejections. And although it's only 1 to 2 percent of the population per year, that's every year.

So now, what was the second part of your question? How could we predict who's going to be at risk for that?

DR. BLOOM: Yeah. I mean, so basically --

DR. WOODLE: I beg your pardon, Roy? Yeah. Yeah. So what we're really interested in, Roy, as you -- as you see, the urine, these alloreactive expanded CD8 clones, as far as we can tell, they're -- when they're in the graft, they're in the urine.

And so I think the -- the way they get into the urine is they invade the tubules, they cause tubulitis, they destroy the tubule, and they get shed,

along with these dead renal tubular epithelial cells in the urine. So they're markers for a -- rejection.

We -- we think, a very reasonable trial moving forward would be, you know, monitoring of the urine for the appearance of expanded alloreactive CD8 clones. And that's mechanistic, well, the preliminary data strongly supports that. Not only that, but when you have a rejection. If you want to follow what those clones are doing, you could do it non-invasively.

And you know, we already know from those studies, that these CD8s, they appear to be like playing a game of Whack-a-Mole. You hit them with something and if it's a static drug that's not designed to kill the cell, the cell just changes phenotype. It's still there, it just changes its phenotype. When you withdraw the drug, it goes back to be whatever it wants to be.

And so we're actually thinking that the anti-rejection drugs that we need to move toward are the ones that call cell death. It's very analogous to

-- to a urinary tract infection with a bacterium. You throw an antibiotic at it, it develops resistance. You throw a bacteriostatic agent at it, it's going to be there, it's hard to get rid of. But if you throw a bactericidal agent at it, different story.

So that's why we are beginning to think that the direction we need to move in is -- is to test drugs that specifically target proliferating cell populations. So there's a few candidates that we have that are out there. I hope that answers your question.

DR. BLOOM: Thanks.

DR. CHAUDHRI: Well, there's one question in the chat that we may want to take. It's by Elke Helen Tara [ph]. "Do you see any role for quality-of-life measures as secondary safety endpoints?"

DR. BLOOM: Yeah, I'll try to answer that question. I think that falls into under the heading of patient reported outcomes. And I mean, as long as the data is, you know, systematically

collected, pre-specified, and well organized, I think there -- there should be a way for it. It's, I mean, it may, if the data is commencing it, may we make it its way to the labeling.

It's -- it will be patient reported outcomes, the quality-of-life measures. But it needs to be systematically rigorously in a well protocolized manner collected, of course, prospectively specified. And then, it should be possible. Yeah.

DR. MENGEL: Dr. Mengel. I would never dare to correct or challenge Dr. Woodle, but since he's not in the room, I thought I'd take the opportunity.

DR. WOODLE: I'M here, still.

DR. MENGEL: You see? Can -- can we mute him?

The -- I totally agree with the concept of your presentation, Steve, is that we need to target certain cell populations and our drugs, instead of hoping with steroids.

Does anybody in the room actually know

what steroids do mechanistically in detail? Probably not, because I heard -- they -- steroids have a have over 100 different mechanisms and in interactions with cell signaling.

Anyways, these thought that certain cell populations all equal rejection is a different research question. They are seen in biopsies, which we per consensus call having rejection. But we're not clear which cell population has which cell function or in this bigger picture.

And I think when we treat, for example, only effector cells very targetedly, does that translate into the endpoints we discussed earlier today. So again, what -- what are we looking for as an endpoint to measure whether a certain drug reduces the efficacy of a certain cell subpopulation, and we want to test automatically that that interaction effects a long-term endpoint, which is a fairly challenging, I think, trial design.

So -- so it comes back to either we risk stratify, but then the populations get small.

And then we need a surrogate endpoint, because we can probably not recruit enough patients. And -- and we are coming back to the iBox, because earlier Dr. Nickerson said is, "Look, we have all these different endpoints. You can progress in i-IFTA, you can develop a DSA," and that may be different, as Dr. Woodle said is, whether you have a population at a certain stage of this inflammatory pattern of different cell interaction, which makes you more susceptible for a DSA, some make you more susceptible to be profibrotic. I think that's what the spatial resolution data show.

And the iBox put it set together and ways in the individual patient. And maybe then, the question really is, or is it the Xbox or PlayStation 4, right? We can compare those head-to-head, see how they do.

But I think there is no way around other than having multiple variables as endpoints after today, listening to everybody. Because just saying BPAR, or whatever the definition of rejection

is, is probably not doing it anymore.

DR. WOODLE: You know, Michael, this is Steve. I just would comment and say, I think what's really going to move us forward is when we take the studies that we've shown, which were all on the adjusted tissue, and we're able to apply them spatially so that we can put these cells in their actual context in the tissue.

And at that point, I think you see an alloreactive or an expanded CD8, and a population that all share the same TCR. They're concentrated within two rules, causing tubulitis lesions. If they're degranulated and they're showing degranulation markers. And the renal tubular epithelial cells next to them are showing the effects of a perforant lesion, then I think you've really hammered it.

You've really nailed it down that that is an alloreactive cell death in a renal tubular epithelial cell mediated by an expanded CD8 alloreactive clone. And so we're just waiting for spatial. The problem is, as you know, the resolution

was spatial now, now about three cell diameters. It needs to get down to where it's actually at the single cell level.

But we're going to have a lot of answers to these questions with those techniques, that that you pathologists are going to be a leader -- leaders in applying that. But I think that's where we've got to get to, and then we can really hammer it down and say, yup, these are the cells. We get rid of these and we're going to be able to turn off rejection.

DR. CHAUDHRI: Dr. Ihran, did you have any other comments in the audience? There was one in the chat that I'll read.

"Are there any payers that are present at this meeting? A limiting factor for drug development is also what payers are willing to cover. Would an improvement in safety events, i.e. decreased diabetes at similar efficacy mean that patients would need to fail Tacrolimus before being on the new agent? Payers need to also be a part of this conversation to

understand the true unmet need of what they will cover."

DR. MANNON: So I don't know, they may not be willing to show themselves. They may not be physically here, but I did invite the Deputy Director for CMS. And I did invite Tom Duvall of CMMI, because they absolutely should have been invited personally, not from Ros Mannon, and I invited the transplantation branch because they absolutely need to be part.

I appreciate Steve Woodle's very detailed discussion, but I'm a practical person. I love spatial, I'm doing it, it is not ready for primetime. If we're going to wait to develop it back to -- this is a mechanistic piece. We're not talking about mechanism today. We're talking about endpoints to use clinical trials.

And so, Steve, I very much appreciate it, and I'm grateful for your thoughts, because you do change my thinking. So I'll put that aside and say I don't think it's practical for FDA to be considering spatial. I also know that they were not particularly

interested in cell free DNA or molecular diagnostics of biopsies, because they haven't been qualified in the right way, and companies have to pay for it, and as it'll be a secondary.

My other comment is about patient reported outcome measures. When the TTC started in 2018, our second work project was on patient reported outcome measures. And in 2018, one whole day was devoted, and we had the NCI here to talk about CTCAE and the lack of overlap for transplant patients, because the side effects are quite a bit different, and we have a publication of interest.

That was, I think, finally came out. Mark Stegall is one of the co-authors, as am I, in 2021. So I think those are important.

The data collection is problematic, and the harmonization is very huge. And I think we had a number of individuals from CPath, and we had a choose a direction. And we -- the entire steering committee of companies, academic experts, CPath recognized that the iBox, all that kind of integrated, hard data

was -- was really ready for prime time to move forward. And it would take us probably another, I hate to say, five to 10 years to harmonize and get good data, because all we had was some SF36s from one trial.

UNKNOWN SPEAKER 3: You know, payers are very important. I'm going to address one small thing, which is probably beyond the scope of the FDA meeting, here.

Patients go through tremendous issues. I mean, I really think if you really listen to them, they really have a stressful period, not just on the side effect, ability to take the medicine, ability to get the medicine, the financial burden, not having a family support.

So invariably, some patients don't, you know, go into non-compliant, we call them, and result in late rejection. A large component or some component of late rejection is purely from a non-adherence to therapies. I don't think we can completely address this in the FDA trial meeting.

So we have to keep that in mind. I have seen patients who literally cry, we don't have money to buy the medications, one hospitalization is a huge burden.

To convert a side effect from Tacrolimus to belatacept, it can take up to 30 days to get an approval from an insurance company. To convert from CellCept to Myfortic, about quite some time back for GI side effects, it will take a lot of time.

It is not easy as we think. Only when you face patients sit down with them, the burden they go through is beyond. So ultimately, our ultimate goal, maybe 20, 30 years from now, or maybe 20 years from now, is the tolerance. But we are not there yet.

I wanted to put this issue across, so keep that in mind.

DR. HARIHARAN: I just want to make sure, I want to support, and I appreciate you.

DR. BLOOM: So while you're coming to the microphone, there are two comments online. One is a question to the FDA.

"Someone related a path to moving beyond rejection endpoint to a safety endpoint or to combined endpoints, such as the iBox."

And the second just relates to you know, well --

DR. HARIHARAN: I cannot get into the specifics of iBox because that's currently under review. But I can provide a probably a general answer. Secondary endpoints, as long as they are predefined in the protocol and the data is appropriately and systematically collected, will be mentioned in the labeling.

And but there's -- in Section 6 of any labeling, safety data is routinely cited. It's -- but comparative safety claims a different issue. It probably -- it requires a higher level of scrutiny and proof, and it again, it needs to be pre-specified in the protocol and the data.

As Dr. Belen said, prospectively and systematically collected because saying, "My drug is causing less tremor than drug X. My drug is causing

less GI side effects than drug X." That's a different level of claim.

Other than that, you know, nausea, vomiting, diabetes, hemoglobin A1C, everything else is automatically included in the labeling, as long as it's prospectively collected.

MR. FOWLER: I would just like to compliment Dr. Hariharan for saying that, because you get -- you think that -- I don't know if people really understand the full part. I don't talk about it, because I've got a family, I want to set an example. But I've been fortunate.

But think about all the times I've been hospitalized, how many surgeries I've had, how many times I've had to figure it out on my own, to stay on brand medication. And there really is no one out there to stand up for us. And I tell you the truth, and that feeling is you just feel alone. It's a battle you got to fight on your own.

And I appreciate you saying this because you're speaking the truth. But again, I go

back to I hope we have a sense of urgency after this meeting, with tangible actions, follow up, and accountability. Because it's not easy, even though we may make it look easy. But think about the people who are not here today. You're not hearing from them. And those are the ones really suffering. Thank you.

DR. BLOOM: Okay. This will be the last questions.

MS. MCCARTHY: You're going to make me close? So those of you who already know me know this about me. I'm guessing those of you who don't know me are just seeing me or getting a sense of kind of how I roll and operate. So either you're welcome or sorry.

You know, I think this comes from probably the weary wisdom that we get as long-term patients. Now, of course, in the you know, the other option is not necessarily a good option. I'm on the right side of the grass, so I, you know, ultimately I'm winning.

But I do also just realize that, you know, I think patients that go through any major

health crisis, or really any crisis in life, at any stage, I think you very quickly, you either just become, you know, you just take it and you roll over and come to whatever end you may or may not come to, or you choose to step forward and lean in.

And so I think it's with that mindset that, you know, I hear things like, "Well, we should have had insurers here." And I agree, I think that's incredible. But if we have a blocker in the context of insurers, how do we -- how do I remove that dependency so that I'm not dependent on the right person, in the right room, for the right conversation, to say yes to the right thing?

There's so much information, I've seen so much data today. Has there ever been any thought around taking either all of that data, some of that data, and unleashing it to the opensource community? Because by now you figured out I work in technology, I think to myself, like there's incredible development talent that may not have biases, may not have career implications, may not have, you know, 30 years of you

know, our experiences that bias us.

Has there ever been any thought about taking some of this to the opensource community so that we can at least get some initial optics, and learnings, and themes that then become things that we can actually start to formalize?

I'm looking for a yes or no, by the way.

DR. CHAUDHRI: This actually, was one comment in the chat, as well that we "Need to address challenges of data collection if we're ever going to go beyond one in five years."

MS. MCCARTHY: Yes.

DR. CHAUDHRI: "It's a cumbersome process, we need better automated tools that are based on usability with feedback looped to the scientific community."

MS. MCCARTHY: Totally agree. Data interoperability, getting in at the same place, and have the same, you know, language, things like that. You got to get the ingredients in the right kitchen in

order to make dinner, right.

So yes, and but again, I feel like instead of relying on the dependency of the blocker, where can we take back that control and at least start to kind of drive our own canoe, I guess?

DR. CHAUDHRI: If it's a quick comment, and then I think we're going to need to --

DR. KLEIN: I'm happy to answer that question about data collection. Amanda Klein, Transplant Therapeutic Consortium.

And we -- we within CPath, TTC has the largest kidney transplant repository that's been standardized to CDIS, to inform regulatory decision making. The entire process of getting buy in from potential data contributors, executing data sharing agreements, and -- and curating data, and then integrating it, and standardizing it is a lot of work.

And as you all can imagine, you know, everyone's very nervous about sharing data, and what are you going to do with my data, and who's going to own it, and all those questions. But fortunately, the

TDC, the Transplant International Transplant Community, with many here that have contributed data to support our -- our efforts.

So if you do have interest in leveraging data, whether it's from your own transplant center, or RCT data, we have the infrastructure in place to do that, to help with the idea to inform future endpoints, different hypothesis testing, and whatnot.

So I'm glad that the process of data was brought up.

DR. BLOOM: Thanks. And on that note, we're going to adjourn for 15 minutes. The next session will start at 2:45.

(Off the record.)

DR. FITZSIMMONS: Our first presenter is Dr. Peter Heeger.

DR. HEEGER: Great. Let's get that first slide up.

DR. FITZSIMMONS: Green button.

DR. HEEGER: This green button? There

we go. Good.

Thanks to the organizers for having me come and speak today. We're going to -- I'm going to -- we switched the order. And I think it doesn't matter. So I'm going to go first, and Chris is going to go second.

We're talking about Biomarkers as Part Of an Enrichment Strategies for Clinical Trials and Transplantation, and I am hoping to provide another pathway for the group to think about to get to where we need to be. I don't have any disclosures of relevance.

I think everybody here recognizes that our current approach to transplant immunosuppression is largely protocol based. Some of that is dependent on the site you are -- you -- in which you work. But there are some standard clinical pre-transplant risk assessment, like HLA typing and cross matching, and some clinical risk factors, and lots of immunosuppression, including induction therapy, is given at the beginning of the transplant period.

And then slowly, over time, depending on your individual study site, immunosuppression has dropped, and in this fall, you end up with a level of triple immunosuppression in many places, that goes for, you know, six to -- six months to however long you follow.

And of course, we understand that people are heterogeneous, and this is not necessarily the optimal way to take care of patients. And so our goal as -- as the general medical field is moving, our goal is to try to move towards immune individualized therapy. And I think what where we are now is on the left here, empirical medicine, where are these people in different colors to represent heterogeneity, one treatment for all of them.

And I think the next step is can we try to stratify people into one of several risk stratification categories that tell you about risk. And then, you can try to test for treatments for each group that's evidence based and may be biomarker led.

And then ultimately, you'll get to

individualized treatments, which may be more of what Dr. Woodle was discussing, where you can look at individual T-cell clones in a patient. We're not quite there yet. But I think the stratification approach is actually here, and we're -- we're doing it. So I wanted to explain that.

So just to reiterate, one of the problems with current trial design is that you're enrolling large proportions of low-risk patients who do not reach -- who do not reach the progression endpoints, like BPAR, or iBox, or eGFR, because you have heterogeneity.

And if you could design -- define approaches to stratify patients based on risk, then we could pick the high-risk patients and give them potentially, tests that a new drug that might be better at preventing this endpoint, or we have low-risk patients, and we could try to take people off of immunosuppression to reduce the safety profile and make it -- make it better.

And you need to have some sort of

biomarkers or clinical markers to "enrich." So what you want to do is find an enrichment strategy, which might be based on clinical parameters or on a biomarker if you have a good one, to enroll high-risk patients or low-risk patients into a clinical trial, so you're targeting that in an individual group, and you're more likely to identify an effect of the drug because you have power to detect change. Right.

So there are different kinds of biomarkers to think about. A prognostic biomarker, as defined by the FDA, would be one that can stratify people into high or low risk, and so you just identified a subgroup.

If you can identify a subgroup, then you can test a predictive biomarker. And so in that context, because remember, this is sort of the context of use conversation we had earlier, you can say, "Well, is this drug, is this biomarker helpful for defining whether the intervention will be effective or not." And that's a trial design based on an enrichment, based on a biomarker, and then you follow

the clinical outcomes. I will give you an example.

Okay. So two examples that I want to talk about. One is not directly related to the kinds of studies we've been doing already, but it's useful as an illustration. So there are clinical risk factors that we use now as an enrichment strategy in transplantation to study the effects on ischemia reperfusion injury.

So ischemia reperfusion injury is a known crucial driver of poor outcomes observed after transplantation. It is -- can result in delayed graft function, which may in and of itself, have some negative impact. But just having the ischemia reperfusion injury is bad. And we know that because deceased donor transplants do worse than living donor transplants, independent of HLA types.

So who is at risk? Well, clinical parameters suggest that if you have a deceased donor with a long, cold ischemia time, or an elevated serum creatinine at the time of the patient's death, or the donor is older, or there's a need for dialysis prior

to transplant, or the donor -- donors after cardiac death are -- are used. Those are at higher risk. High KDPIs are at higher risk for developing ischemia reperfusion injury.

You would not design an ischemia reperfusion trial with every transplant recipient possible, and no enrichment. You want to pick the people who are at risk, right. So -- so you want to choose the right enrollment criteria, because living and deceased donors would together, would dilute the chances of there being an effect, you would then randomize the enriched population to the experimental versus the control arm, and that would permit you to assess the outcome in the right population.

So building on some preclinical data from mouse models and primate models, there's clear evidence that the complement cascade and complement activation is a key mechanistic driver of ischemia reperfusion injury.

My new colleague, I just moved to Cedar Sinai in Los Angeles from New York, I moved there last

year, my new colleague, Dan Jordan, has -- has tested the impact of one complement inhibitor. So a new drug, right, in a small, not -- not a registration trial. And this drug is the C1 esterase inhibitor on outcomes in patients at high-risk for ischemia reperfusion injury.

And so their enrichment strategy was to pick some of these parameters, deceased donor, high KDPI, long call time, et cetera. And that was our clinical -- his clinical enrichment strategy.

He randomized the patients into two study arms, one got the drug at the time of transplant and a second dose, the other got a placebo injection, 35 per group. And the drug was the C1 esterase inhibitor called Berinert. And induction therapy was not standardized, it was a pilot trial, just to sort of get some information.

And so the most important finding on this, there's some very important findings here. One is that delayed graft function, which is the fact that the graft did not function within the first week post-

transplant, that was not impacted by this therapy. Okay. No effect. There was a trend toward better kidney function at several months post-transplant, but that wasn't affected either.

What was affected, and it was remarkable, is that regardless of whether you had delayed graft function or you didn't, the drug, C1 esterase inhibitor, given for two doses at the time of the transplant, led to better eGFR at six months and a year. Better eGFR, right. So that's -- I think that's remarkable on many levels.

And then, he followed these patients up for three -- for three years. And in fact, when you look at three years, let me just go back here, the eGFRs that you've seen on the right table were positive, and the patient .5 change in eGFR was positive in the people who got the drug, and fell in the people who were in the control arm. That's the slope.

The eGFRs were 20 mils per minute better in the patients who got the drug. And then,

there was not really significant incidence of death or cumulative graft loss. Actually, there was less graft loss in the in the treatment arm.

So I think what's really interesting about this is it's an enrichment trial, right. But it also is a paradigm shift in the way we think, at least from a hypothetical standpoint. We need a bigger trial. But the findings suggest that this drug, right, can improve allograft function independent of developing delayed graft function, right.

And so our thinking about this is that what the drug is doing, is it's not affecting the cell death that happens when you -- when you get ischemia reperfusion injury. It's affecting the cell's ability to recover, which is the kind of cool way to think about things.

And I think this drug, which is FDA approved, needs to be, you know, tested in a larger trial, thinking about all this, to sort of improve long-term outcomes in patients who are at risk for delayed graft function.

But this is a -- so we have to carefully define enrollment criteria, what are the right enrichment criteria that we want to use to pick -- to pick for these patients, because you want people who are at risk, et cetera. So that's a discussion that we're having. And we're actually, you know, putting in a study, a request to do a study. So that's the kind of thing that my group is doing.

So then let's switch to biomarkers. All right. And I think we need to talk about this idea of what's a biomarker and what's an in vitro companion diagnostic device or test.

So biomarkers are anatomic, physiological, biochemical, and molecular parameters that indicate or are associated with an alteration in physiology that are of clinical significance. Right. So that doesn't mean that they're useful just means that they associate with something.

A surrogate marker we've already talked about here. But that can be defined as a biomarker that has a established clinical utility. So if it's a

surrogate marker for an endpoint, then we would replace that endpoint by using this surrogate marker.

Surrogate -- and that's what a surrogate endpoint would be. So biomarkers used in clinical trials to evaluate the safety or effectiveness of the therapy and serve as an alternative to a traditional endpoint. So the discussion about iBox result revolves around this idea of a surrogate endpoint. Okay.

So an in vitro companion diagnostic device or test, is an in vitro diagnostic device or test that provides information that's essential for the safe and effective use of a corresponding therapeutic product.

I think the best example, the easiest one to understand is that if you're going to give an anti -- if you're going to use Herceptin, Trastuzumab as a therapy and block breast cancer, that's an antibody directed at the HER2 molecule that's found on certain breast cancers.

So you need to have a way to test

whether the breast cancer is HER2 positive or not. So there's a test, you know, that that is now FDA approved, that allows you to say this is a breast cancer that expresses that. And so that test is used to define, and originally was used to enrich for the patients who had this type of breast cancer to test whether the drug was effective. Okay.

So is there some way to think about that in the context of transplantation? Well, I think before we quite get to that, you have to understand that the FDA approval is required to use or test a candidate in vitro companion diagnostic device in the context of a clinical trial for a particular context of use.

And information about the planned use of this device, and its use in clinical trials, needs to be included in an investigational submission to the FDA. And this information will then help the FDA understand and provide advice on how this investigational, in vitro companion device will be used to enroll subjects. All right.

So are there any we can use? And the one that you're going to hear a lot about, because Chris Wiebe is going to tell you all the background information, and the one that we're using, and I think is important to understand, is the HLA DR/DQ molecular mismatch.

Now, this is not the HLA mismatch, right? Basically, what you will hear is that this is a way of testing, not are there one HLA DR mismatch, or two, or right. It's how different are the molecules? So and each one has a particular DNA sequence, and we're asking how different are they?

And that difference is quantifiable and turns out that it can stratify kidney transplant recipients into high, intermediate and low risk for developing post-transplant immune events, defined as DSA, ABMR, and TCMR.

Now, most of the data has it comes from ad hoc analysis or retrospective -- retrospective analyses of patient cohorts. And prospective validation is required to further provide evidence

that this approach is a valid, prognostic biomarker.

Nonetheless, there's enough information that this this test has been submitted and accepted into the biomarker qualification program at the FDA.

We showed in an interesting sort of ad hoc analysis of a withdrawal trial called CTOT-19, actually CTOT-09, not 19, that we can identify subjects who are at low-risk for developing immune events during Tacrolimus withdrawal.

So if you take people off TAC, 50 percent of them get rejection and 50 percent are okay. Right. And we wanted to know if that was possible to sort of reduce the off-target effects.

It turns out, we could identify those, retrospectively, based on the fact that they had the -- they fell into the low-risk category of the HLA -- HLA DR/DQ molecular mismatch.

So what's needed is a prospective study that's to test the utility of this molecular mismatch as a predictive biomarker. And so, as I said, it's been submitted as a -- to the qualification program,

and that would permit it to be used as an in vitro companion diagnostic device in clinical trials.

So Peter Nickerson and I have been working on this for a while. And we've put together a new study that's about to start enrolling. It's funded by the National Institutes of Health. It is not a registration trial and it's not testing a new drug, it's trust, I should tell you, it's moving a drug from arthritis into -- into this particular indication, but it's doing it in an enrichment strategy with -- with sort of an interesting way to try to get at some of the questions we've been addressing here today.

So we're, firstly prospectively assessing the prognostic utility of this test in kidney transplantation. And I'll tell you how we do that in a second. And then, we're prospectively testing the predictive utility of this test, and kidney transplantation for the defining a low-risk group in whom we can remove immunosuppression, Tacrolimus, and switch it to another drug,

subcutaneous Abatacept, which is similar to bela.

But it's a subcutaneous drug that the patients can give to themselves, and see if we can do that safely with the idea that we will improve kidney function at two years, because we're moving the TAC and putting them on something else. They won't have rejection during this time period. And importantly, we will test some of the specific safety endpoints that we've been discussing.

So the study design is here. And it's -- it's a big ask. There are a number of people in this room who are involved in helping to get this study going, and I really thank them for their participation.

We have 15 centers that have -- this has been funded, and we're getting the trial going. I'm hoping that will enroll the first patient within the next month or two.

We have, you know, the FDA has gone through the protocol. The funding is all here, the regulatory stuff is ready, so we're basically ready to

start.

We're going to enroll 800 kidney transplant patients, and we're going to start them on standard immunosuppression. And we're going to follow them for six months. And so there's a time period where these 800 patients will be followed, we will know their risk category based on a predefined risk assessment strategy, this molecular mismatch. And we're testing the cut offs, the thresholds for these low, intermediate, and high. And we're going to follow the patients over the course of two years to prospectively determine the utility of this biomarker to prognosticate risk. Right. So we have retrospective data, this is the formal proof.

Then, the next part of this is when the patients reached six months, six months post-transplant, if they are stable, if they haven't had a rejection episode, if their biopsies look clean at six months, if they don't have DSA, if they're on drug, right. If it's the right amount, then those individuals will be looked at in terms of their

molecular mismatch.

We are not going to study the high molecular mismatch people because we want to take a drug away or change it. We could have picked a different trial where we took the people who were high molecular mismatch and treated them with another drug. That's another trial we could do and it's an interesting way to think about how you might do a study, right. Pick the highest risk people and add on a drug.

Our study is we take the low and the intermediate risk individuals and we're going to switch them from Tacrolimus to subcutaneous Abatacept over about a month, and then follow them for two years. And what's -- and so it's a superiority for eGFR, is the primary endpoint.

But notice, the secondary endpoints are superiority for cognition using a specific cognitive test that's well established, that takes a -- takes about 45 minutes to administer the test, and we're going to do it to every patient before they start and

after they've been changed on the drug.

And then, we're also using a patient reported outcome measure to see if they feel better when they're off -- off the Tacrolimus and on the Abatacept. And of course, you know, we're looking for BPAR efficacy failure, because the hope is that we're not going to reach the BPR endpoint, that would be -- that would actually be a safety endpoint if we had a high rate of BPAR during this time period.

And the other point I will make that makes this a novel approach is that we have high, intermediate, and low molecular mismatch. We're taking the intermediate and the low patients and we're doing the switch. So we have a built in, prospectively planned adaptive design. So if there's rejection, and if the rejection is in the intermediate risk individuals, we don't have to stop the study, we stopped that arm, and we follow the rest, and we keep them going in the in the low molecular mismatch.

And so the idea here is that we can try to use a risk stratification approach with reasonable

endpoints. Now, you could argue that maybe we could do the iBox, too. I don't know, we have all that information, we could look at that. I'm looking at safety parameters as -- that -- that are important. And -- and measuring things that are important to patients, the cognition and the patient reported outcome measure, using a drug that's already used for -- for rheumatoid arthritis and shifting it over.

Now, this is not something that the pharmaceutical company is doing, right. We're doing this with NIH money, but they are donating the drug, and they are interested in considering, if this is a positive study, is this something that they want to move toward labeling and they'll talk about that. So I think, you know, I just want people to think about it in that context.

So you know, my -- I guess, I don't really -- so my summary and conclusions are not written here. But I think the point here is that we need to think about new trial designs, enrichment strategies, and using adaptive study designs to

incorporate ways to -- to get the information we need, along with, this is not instead of, this is along with defining the right endpoints and the right approaches that we've been discussing, you know, all day today.

So I want to stop here and thank my collaborators, et cetera. I have to apologize; I actually have to get out of here and get on a plane. And now, Dr. Nickerson and I have the same first name. So if you can't remember who to talk to, just ask Peter the question. He knows the data and he will answer all the questions during the question-and-answer session later. But thank you for your attention.

DR. FITZSIMMONS: Thank you, Peter. The next presentation is by Chris Wiebe.

DR. WEIBE: All right. Thank you very much for the opportunity to talk at this workshop. As mentioned, I'm going to talk about HLA molecular mismatch and how it might help us in many things we've been talking about today, and especially the last talk.

I have no conflicts to disclose. And I'll start by just reminding everyone that when a patient develops a de novo donor specific antibody post-transplant, this is a bad outcome. We know from this meta-analysis by Sharma, et. al., that a new de novo DSA is actually associated with almost a 10-fold increased risk of antibody mediated rejection and a five-fold increased risk in overall graft loss. And one of the unmet needs is to try to understand who are the patients who are at risk of having this.

And in order to get everyone on the same page, understanding what we're talking about, I want you to imagine that you are this recipient on the left, recipient with a DQ8. This is one of the HLA molecules. And I'm using DQ as an example here. As some of you may know, DR and DQ antibodies are the most commonly developed post-transplant.

And you're lucky, you have two donors that come forward offering you a kidney. The first on the top is a DQ5, and the bottom donor has a DQ9. And by our traditional mechanism that we've been using to

match for many decades in transplant, both of these donors would be considered a one antigen mismatch.

However, as was mentioned, HLA is a little more complex. We have over 37,000 genetically defined alleles, and because they're genetically defined, we can actually infer what the amino acid sequence is. And that's what I'm showing you on the bottom of the slide.

You can see for, beside the DQ7, every letter there represents an amino acid. And underneath, if there's a dashed line, that means the amino acids are identical. And if there's a letter, that means there's a substitution in those other molecules.

And a quick glance at this slide shows Using the DQ7, 8, 9 are actually very, very similar to each other. Whereas on the bottom, the DQ5, there's a number of amino acids that have been substituted.

So the question is, how can we use this quantitatively? And one mechanism that was developed by Rene Duquesnoy, some time ago, was to talk about

HLA applet mismatch. And an applet is shown in the bottom right of the slide, that red dot in the middle of the molecule. This is just simply a small cluster of these polymorphic amino acids, that takes into account the three-dimensional nature of these molecules.

And the size of the cluster was chosen because this roughly corresponds to a complementary determining region on an antibody, and the antibody epitope-paratope interface, which you see in the upper left-hand part of the slide.

Importantly, an applet is not the same as an epitope, it can be thought of as the smallest functional unit of the complete epitope for an antibody.

But if you think about this concept, if we can define what all of the different amino acid polymorphisms are, and I just showed you on the previous slide, we can. Then, we can actually come up with a list of what all the different theoretical applets are on any HLA molecule. And this would give

us the opportunity to compare any two molecules.

And this is the big step forward or advancement because in the past, we can just say, "Are the molecules the same, yes or no?" But here we have a way of quantifying that difference.

So if we come back to your two friends, if you accepted a kidney from the DQ5 donor, that would have resulted in 27 applet mismatches, whereas the DQ9 donor, there's only two applet mismatches. So that's a 13-fold difference in the amount of non-self-tissue or targets that you're exposing to the immune system, which would be done totally by chance in the way that we talked about allocation today.

So if we take that idea and now expand it to this cohort of about 600 patients from our own center, here, each dot represents a donor recipient pair. And on the y-axis, we have the number of epilate mismatches. On the x-axis is just our conventional way of mismatching patients.

And so for example, all patients inside this red circle have a one DR mismatch. And you can

see, there's tremendous heterogeneity in the number of applet mismatches within this group. And of course, that's also true for the two DR mismatches, as well as the DQ mismatches.

And probably the most important point in the whole slide is here. For many years, we've been using the population data that tells us that a two DR mismatch, on average, is higher risk than a one DR mismatch. And that is true with population data.

But it's not true, all the time, when we start talking about individual patients. And it's also not true when he talks about small trials that might only have a few 100 or 1000 patients. You really need thousands or even tens of thousands of patients for that to be true on average.

And when we put these two types of data and ask the simple question, how do these numbers actually correlate with antibody development post-transplant, we saw that there was a huge increase in the AUC scores from about 0.54 to 0.58, using the numbers on the bottom, to an AUC score of about 0.72,

using the numbers on the top.

And this got us interested in looking at this in even more detail, which we call the single molecule molecular mismatch. And what this is is looking at the -- the applet mismatch of every individual molecule one at a time. And then just asking a simple question, did these molecules result in antibody development post-transplant, when we were doing serial monitoring for these antibodies. And we looked at over 4700 molecules.

And what we saw is that these scores actually correlated very strongly with antibody development. And this allowed us to then select thresholds which we could bring back to the patient level to help categorize them.

So for example, if all of the patients DR molecules were less than 7, and all of their DQ mismatches were less than 9, we could show that those patients had identical risk to the patients without any mismatches at all. So we could combine the blue and the green lines there to say, okay. About 25

percent of the patients are low-risk. But this still left us with 75 percent of the patients that are in the red line.

So we repeated the receiver operating characteristic curve analysis on just the patients in the red line, and that allowed us to identify a second threshold for DQ, which we could break up the patients again. And this is where the low, intermediate, and high-risk groups came from, 25 percent, 35 percent, and 40 percent.

Now, in the study back in 2019, we showed that this system of categorizing patients, which are called alloimmune risk categorization, correlated not just with antibody development, but also with antibody mediated junction on the bottom left, and T-cell mediated rejection Banff 1a or greater, in the bottom right.

And importantly, although we're not showing you all the tables, this -- these alloimmune risk categories were not just univariate predictors, but also independent multivariate predictors of each

of these outcomes.

A few years later, Dr. Rampersaud, working with myself, published this paper where that was mentioned earlier by Dr. Nickerson, where we looked at the recurrence rate of TCMR after treatment. And we showed that recurrent rejections correlate with death censored and all cause graft loss.

What he didn't mention is those recurrent rejections were also predicted by the molecular mismatch categories. You can see here that patients who had at least one episode of TCMR were already enriched for intermediate and high-risk phenotypes. And those who had greater than two rejection episodes were actually enriched towards the high-risk molecular mismatch.

Similarly, we showed that the most -- the -- the TCMR grade on that first TCMR also correlated with molecular mismatch. Both the borderline and the Banff 1A TCMRs were enriched towards intermediate and high molecular mismatch. And greater than Banff 1As were enriched towards the high-

risk category.

So that's all fine. But of course, we need validation. So that's what I'm going to discuss here next. And I see there's a bit of a problem with the formatting on the slide, so I'll have to talk you through it.

But this was the first slide done in Denver, Colorado. The column starts with 65 percent is the Manitoba group, and 71 percent is the Denver group. And these are ethnicities. The top line is actually the Caucasians. Both groups were predominantly Caucasians.

Underneath that, we saw in Manitoba that if you weren't Caucasian, you were most likely indigenous or Asian. Whereas in Denver, if you're not Caucasian, you're actually most likely African American or Hispanic. And this is important that I'm going to mention this with all the validation studies, because one of the early criticisms we had is that, you know, Manitoba may not be representative of this -- the U.S. population in terms of our ethnic

breakdown.

But you can see that, nevertheless, the AUC scores were very similar. The exact same thresholds were predicted. And in both Manitoba and Denver, there was the same breakdown, almost identical in low, intermediate, and high-risk patients. And in the bottom right, you see that the alloimmune risk categories were extremely strong, independent, multivariate predictors of de novo DSA.

This is the third study to use this method. This is actually from Leuven, Belgium. Although this again appears to be missing on the slide, 926 patients in this study really only need to know the top line. Beside the 98 percent, it should say Caucasian. And this is actually not super uncommon in the European cohorts.

This cohort also allocated using DR matching, and so they're actually enriched for the low-risk patients. As you can see, 40 percent of the Leuven group were low-risk patients. And this correlated also, of course, with a low event rate.

And you can see on the right-hand side, that even the high-risk group here only had about 7 percent de novo DSA development.

But there still was a stratification that was statistically significant, despite this being a low-risk cohort, with a seven-fold difference between high and low-risk.

Lastly, this is a group from Emory and in the red box highlighted by 57 percent, that should say African Americans beside it. And that was pretty unique in this cohort. Despite the fact that there was a big difference in the rate or the percentage of African Americans, you can see in the bottom left that Manitoba, Denver, and Emory all had very similar breakdown in terms of the number of patients that fit into each risk category.

And this was a Tacrolimus, belatacept comparison study, and a propensity matched retrospective study. And you can see the Tacrolimus cohort behaved just like the other three cohorts, which are all Tacrolimus based, with low,

intermediate, and high all statistically stratified.

And then the belatacept cohort, you can see that the high-risk group was significantly different from the other two.

So the other one of the other criticisms we received early on was that, are we really sure that low risk means low risk? In other words, is it possible that some applets might be more important than others? And aren't you concerned that this might actually lead to antibody development?

And so far, what we've seen in these four studies combined, is that we have over 2300 patients, 33 percent of them can be defined as low risk. And so far, the rate of de novo DSA development that's been reported is between zero and 2 percent. And I should point out that two of these studies have more than five years of follow-up.

It's also been true in the living donor cohorts. It's just the slide from the National Kidney Registry Website, where they've been using this exact same method for a couple of years already, to help

allocate living donor transplants. And what they've shown is so far in their one-year data, the low-risk group has a 0 percent rate of de novo DSA, not unlike the other studies I showed you.

So how does this stack up as a useful biomarker? Well, it's fast, it's certainly inexpensive, and widely available. I haven't said this yet, but I'm not the one who developed the software. I'm just one of the users, but it's been free to download ever since its invention by Rene Duquesnoy.

It's fast. We've actually trained our own HLA lab techs to provide this data to us in the middle of the night, in five-minutes time. And all you need is the baseline HLA typing, that we all do at our transplant centers already.

That also makes it, of course, non-invasive. I've showed you that it's statistically quite robust and it does correlate with things that we care about, like T-cell mediated rejection and antibody mediated rejection.

It certainly has biologic plausibility, because we're just looking at differences between the donor and the recipient at the molecular level. And it's available at time zero of the transplant, which I think is an a really important point.

If you compare it to some of the other biomarkers that you've either heard about today or at previous meetings, things like inflammation on a biopsy, or de novo DSA development, or cell free DNA. All of these things are actually measures of alloreactivity or injury of the graft.

But if we want to be able to prevent those things from happening, we have to have a way of stratifying early, post-transplant.

So to summarize what I think I've said so far, HLA molecular mismatch is just a more precise way of evaluating the degree of mismatch between donors and recipients.

I showed you some data to show that molecular mismatch is a prognostic biomarker of de novo DSA development, of TCMR, including borderline

and recurrent or persistent TCMR. And of ABMR.

And that molecular mismatch is independent of recipient age and immunosuppression. I haven't really had time to show you the tables, the multivariate predictors to highlight that. But if you have a chance to read the studies, you'll have a chance to see that.

And so how could we apply that to what we're talking about today? Well, certainly for clinical trials, you just saw an example by Dr. Heeger how this could be used in a stratification and adaptive design trial. And as he mentioned, this could certainly be used in enrichment strategies for either high-risk patients or low-risk patients.

I'll just mention that this could also be used in monitoring. In fact, we just published a study in the last month, where we showed a strategy where we could take this concept and move it forward, and we are moving forward already in Manitoba, to apply what we already know, to try to reduce the intensity of monitoring. Because many of these things

that we monitor for post-transplant, like DSA, or histologic monitoring, or many others, are both expensive and time consuming, and probably should be targeted towards the patients who need them the most.

So with that, I'll say thank you for your time, and I'll answer questions at the end.

DR. VELIDEDEOGLU: This session is open for discussion. And Kevin Fowler has joined us on the panel for this discussion, as well.

DR. BLOOM: My question is, does the strategy for risk stratification to enroll in a trial which the last two talks were about? Change our discussion around the right endpoint?

We were talking the whole morning about what's the right endpoint. So I get it that enrichment is better for your power and everything, but are we still struggling to find the right endpoint?

DR. WEIBE: So how would I answer that? I think it's both. Why wouldn't it be both? I think we need better endpoints, and --

DR. BLOOM: But do we need --

DR. WEIBE: And --

DR. BLOOM: -- different endpoints for different enrichments?

DR. WEIBE: Well, I would say we need good endpoints, depending what your trials trying to achieve, right. But we also need ways of targeting the trials to patients and drugs to patients who actually need the drug. So I think it's both. I wouldn't say it's either or. I think it's both.

We should be -- we should be coming up with new endpoints. Absolutely, Michael. And we should be doing that in the in the trial designs we're developing. But we should also, I think, be trying to move towards some more personalized medicine than what we're doing.

And I think, you know, Peter's study of ischemia reperfusion injury, huge problem, I think in all of our programs, where we need to targeted therapy to block or repair kidneys better, that are going to have that insult to them.

And what was the endpoint? It was eGFR. It's the same endpoint we're talking about. In essence, you can say iBox is an endpoint. iBox is eGFR plus other things.

So I think we need both. We need trial designs that are targeted to patients who are going to benefit specifically from a drug that we're going to use. And we also need endpoints that are going to be better than what we have currently.

DR. BLOOM: So is it that then, a bit of a chicken and egg? Do you first have the drug and you risk stratify for the drug? Or you first risk-stratify, and say, "What drug can I use?" And I think, endpoints, like -- like the iBox has the data available that it works in ABMR, when it's risk stratified, and TCMR when it's risk stratified.

So what -- what -- I'm not disagreeing with you, but what's the sequence here for the path forward? Where do we put the call to action first? Is it we need new compounds, and then we design the enrich trials? Do we have a patient population of

greatest need?

DR. KUMAR: Maybe I can respond from a regulatory perspective. I mean, where does this HLA molecule or based risk stratification fit into the scheme of primary endpoint discussion? I believe that's -- that's the main question.

And my answer to that, from a regulatory perspective is, one of the complaints and one of the limitations in designing trials with the current endpoint is the scarcity of the events in that trial. So this risk stratification-based enrichment has the potential to solve that problem.

If we can enroll higher risk patients into a trial, it is likely that the event numbers rates will increase and making that trial feasible and making that existing endpoint usable again. So that was our point.

MR. FOWLER: Thank you. I just want to make a comment. And I think, obviously, Peter, I think this work is important. But can I also maybe give you a boots on the ground perspective, too, is

that what happens within an innovation in the transplant community, it's not equally accessible. So for example, in the United States, National Kidney Registry controls a lot of that. Many patients aren't even aware of it.

So I would just ask, this goes back to what Dr. Mengel said earlier, too, is I think we have to think about this in terms of how we're going to reach the most people and benefit from this innovation, right. I've just asked you to think about that, because a lot of times that's not covered in these conversations.

And so for example, who's disproportionately impacted by kidney disease? African Americans, right. And so are they going to have access to this? And I'll just tell you this. I've had conversations with many of them, that many of my even acquaintances, African American acquaintances, they have no idea what the National Kidney Registry is.

So I'm just -- just putting out,

another perspective. Thank you.

DR. FITZSIMMONS: Dr. Mannon?

DR. MANNON: I'm going to -- I have a couple of questions. So one is just a knowledge question, Chris and Peter, because you both -- you're the only HLA people in the room, and I couldn't tell online.

So does this applet mismatch require high resolution genotyping? I understand it's very quick to do the matchmaker and my daughter could do it or her boyfriend, you know, whatever. I would say something else, but then it would be inappropriate, so.

But the question is, is do you need high quality match, you know, typing to do this? Because like in that paper that you refer to, my recollection is you did imputation, and then you did some special additional typing. And so if we're going to be talking about a trial and doing this, I presume, and I can't remember because we've been working on this study -- your guys' study for so long. Are you

going to do the high resolution typing on everyone?

DR. WEIBE: So we are doing the high-resolution typing. What I will say is that most labs in the U.S., now have moved to high-resolution typing. And when we looked at the centers that are going to participate in the trial, of the 15, I think 13 or 14 are doing high-res typing, now as their standard of care.

They're doing it largely because they do it for bone marrow, they support bone marrow and solid organ transplants. So in fact, the fields moved to high-resolution typing.

In terms of the ability to imputate, in fact, we've done comparisons of imputation to high-resolution typing with NGS. And if you do it in a -- in a very thoughtful manner, it's actually identical, that doesn't change the data.

So it is a point of lab, like you're talking about in NKR, but actually all labs in the U.S., I would say, have really moved to have this technology available.

DR. MANNON: So I would say that I listened to other HLA colleagues, and I'm not sure they're as unified about this applet mismatch. And I think the FDA needs to be aware.

And to follow up Kevin's point about African Americans, I came from a center where two-thirds of our recipients were African American, and three-quarters of our waiting list are. These individual patients have high levels of molecular mismatch.

And so I don't see how -- I think an enrichment strategy based on low-risk, high-risk, I think it's got potential to be problematic, and to limit access of our African American patient population to trial therapy.

DR. NEWELL: I was just going to follow up on Michael's point. And I think many of you were at a meeting just between the TTC and the FDA, and I can't remember what it was. I'm going to guess '18, '19. It was when we were trying to figure out the context of use, and the FDA pointed out to us that we

were confused.

They said, "Is what you're proposing the iBox for to risk stratify? Or is it as an endpoint?" So I think the two are somewhat different. And it seems to me the greatest use for a tool, like an endpoint, if you were to combine Michael's question and say, "What's the role of an endpoint in risk stratification?" It would be too high.

And what the FDA suggested, if you want to use it for risk stratification, use it to risk stratify high-risk patients, so you can get a year, say, "Who's the high-risk patient because we want to enroll them," and enrich for the event rate, so we don't have to enroll so many subjects who won't have good outcomes already.

So I think, you know, it's confusing. I think that the real, unmet need for us is to identify high risk subjects who we can't treat the same way. If we're going to give more immunosuppression, we should be sure we're giving it to the right people, and the iBox could help with

that. Although I would say that's totally separate from what the TTC is proposing as its primary use. It took us a few years to figure that out.

DR. WEIBE: I do agree with you, Ken. I think we should be stratifying for the high-risk individuals, and actually, given that they'll have higher event rates, and then you can actually very effectively and rapidly determine whether your new agent is going to be effective or not.

DR. NEWELL: So all I was going to say, and we propose something like this once, but then you could take the iBox and say, "Who's predicted to have a poor outcome at five years," and we will randomize them to a therapy with the hope of seeing more events and identifying strategies that prolong graft survival in that population.

DR. KUMAR: Peter, regarding the high-resolution typing, I don't think it's been done with all of the transplant programs, just really for diseased donors. Recipients, it's done very well, because it's not an emergency.

The problem when it comes to the trial is currently with the nautical miles, where at least in United States, 65 percent of the kidneys are being shipped away from the center to a different center. So that will create a problem if it is not uniformly adopted by all the organ procurement agency or the closest transplant program to do high resolution for donors.

Recipients, it's very easy. I think we got to keep that in mind. Or perhaps, do a survey through Archie, make sure that can be implemented to as -- as many centers as possible before we think about the trial.

DR. NEWELL: I'd just like to go back to the point about the African American community and other groups that have been marginalized in kidney care.

Just as we go forward with all this, right, 35 percent of the people that are in dialysis are African American.

Every friend of mine that's African

American has been in dialysis, even though he had good health insurance, prior to transplant.

So when we're thinking it'd be about these innovations, I would just make sure are we thinking about this thoughtfully? Are these innovations going to benefit just people like myself? Or are they going to be more widely distributed?

And -- and I think that's a, you know, I think that's a really important pillar that we have going forward to make sure that everyone benefits from this going forward. And that that stakeholder is around from the beginning. Thanks.

DR. VELIDEDEOGLU: We have one question from the online line audience. We have only one question. I will -- I think it's partially answered during the course of the presentation, but I believe this is in regards to Dr. Heeger's presentation.

And the question says, "Can you explain how risk stratification enable leaner trial designs? Eight-hundred patients in the explained, Dr. Heeger mentioned is a huge trial. Is this because you are

targeting the low-risk and molecular mismatch patients?"

DR. NICKERSON: You know, the 800 was a sample size that was being used to validate the prognostic value of the of the -- of the molecular mismatch. So within the trial design, it's a subset analysis for a portion of the patients that are going to be randomized.

The -- the 800 is required to have the validation set for the biomarker.

DR. FITZSIMMONS: Maybe I could ask one question of our FDA colleagues on this topic. Could you comment for everyone how we would handle the companion diagnostic portion of an application if we had this type of test coupled with a new therapy? And then, how also that would impact labeling if we're only looking at a subset of patients?

DR. VELIDEDEOGLU: I will try to answer this question. It's -- Well, companion diagnostics are -- it's we have a special guidance for that. And the review process for companion diagnostics are

conducted hand in hand with relevant centers.

For example, it's for the development of a drug, a test is needed, or a test is developed, that is reviewed in collaboration with the Center for -- Center for Devices, which is CDRH.

And the equivalent of IND at CDRH is IDE, Investigational Device Exemption. And whether an investigational device exemption is needed for that test, which is also considered to be a device, depends on the risk level; whether it's a non-risk, non-significant risk, or significant risk device. And that is decided in collaboration with the CDRH, with CDER and CDRH collaboration.

And there is also another section, if you look at the guidance, it's under -- if you look for clinical trial essays, there are special provisions. And the bar is somewhat lower for clinical trial essays. And if a test is limited to be used in the trial, and not the all for commercial purposes, the requirements are less stringent.

So I don't know if I have been able to

answer.

DR. FITZSIMMONS: Thank you. Dr. Maldonado.

DR: MALDONADO: Hi, Angela Maldonado. If we use enrichment tools to design a clinical trial to stratify patients into the highest risk, moderate, or low risk, and we demonstrate benefit in the highest risk, would it then just preclude our labeling to just that subset of patients and we couldn't apply it to patients with a lower-risk, such as moderate?

DR. NIKOLOV: This is Dr. Nikolov. So maybe I should start by saying that our expectation is that a drug will be developed for the broad population unless there is a specific reason, scientific reason to narrow the patient population, whether that's based on mechanism of action, or potential risk, which may require, you know, more refractory or severe patients. So in that sense, the expectation would be that it would be the broader population.

Now, if you stratify patients, and you identify a patient population that could potentially

benefit better than the other groups, ultimately, the data that you would generate would inform the benefit risk to decide what will go in the label or not.

So if you studied a more narrow patient population to support the benefit risk in that patient population, this is what will end up in labeling.

Although we would encourage, you know, if a drug has the potential to impact the broader patient population, that that's how it should be developed.

DR. MALDONADO: Thanks. I guess we had the same question.

DR. NICKERSON: The other comment, I would say is, I actually think that we don't do stratification prospectively to allow ourselves to have an adaptive design in our trials.

So while you might start off trying to treat everybody, which is I think what we should be trying to do. But if you stratify, it gives you the option that when you see an event rate that's happening in differential between two groups, that you

can actually continue the trial and the group that's benefiting -- the subgroup that's benefiting. And I think that's laudable for patients.

So the trial that Dr. Heeger talked about, that the NIH had funded, where we were trying to take stable patients and take them off Tacrolimus. We had to stop the trial because they weren't stratified. So everybody stopped, right. And there was patients who were not on TAC, who felt great.

But we had to stop the trial. And had we stratified, we would have actually had the option of stopping the group that was obviously losing efficacy, but continuing on the others that were demonstrating maintaining efficacy. So that was a trial design problem from day one. That actually meant the trial stopped right away.

Which I think if you're thinking about developing a new drug, yes, we're trying to get it to work for everyone. But if you stratify, you actually have the option of winning for a subgroup. And that actually may benefit the subgroup substantially.

And they, actually, you know, then you have a drug that's in the market right now. If you don't do that, then what you end up with if you fail, is you have nothing, right.

DR. FITZSIMMONS: Thank you. We'd like to close the Session 4, in terms of personalized medicine enrichment and move on to Session Five directly, which is the workshop takeaways and wrap up. And there are panelists that will be coming forward and some of us will be stepping down.

DR. NICKERSON: Paul, are you still there, online?

MR. CONWAY: Hello.

DR. NICKERSON: Good, good to see you.

So at this point, I think what we wanted to do was really to have what -- what's the takeaways that the group is hearing today? If they were -- if I was to go around the room and ask the group in the panel, which I think it's a broad -- a broad group, what were you hearing today? And what would you be advising going forward?

Because I think this is really, you know, we've heard a lot of information. There's a lot of been great discussion, great data. But I think what we're trying to hear is, so what would -- what was your takeaways from today?

And maybe I can start with the patient. Molly, you're here.

MS. MCCARTHY: I have notes. How long do I have till?

DR. NICKERSON: Well, we have 40 minutes. So I think we, you know, we said we'd go to 4:25.

MS. MCARTHY: That sounds like an offer, right there.

Just a couple of comments. I think, you know, obviously having had a couple of conversations with other people, both professional as well as the patient lay community, I don't know that we were really clear about what were we going to spend our time on today, and therefore not entirely sure what to expect.

So I think in the absence of that, as we've also gone through the day and had some conversation, we've come up with our own action list. So I don't know if that's exactly in what you're looking for. But just to give you a line of sight into this.

I think, you know, again, having known Amy for quite some time, Amy and I actually spoke at the CIAT event several years ago, which I think is, at least at that point, one of the first times patients were very openly brought into conversations and into the inner sanctum of medicine.

So with that, thank you for letting us come along and tag along. And it'll be interesting to see if we're invited back next time.

But at that time, I think Amy and I really kind of fell into this statement and sentiment around, you know, for patients, gratitude is not permission for the status quo. And I think we have reflected that time and again, in a variety of words, and tones, and gestures at times.

So with that in mind, I think, not really having a sense of what the next steps would be, several of us have kind of come together in recognition of we're feeling a similar kind of call to action. Not just because we want to see progress, but also to kind of carry our part of the water to demonstrate our gratitude to help the professional community.

It's easy to point fingers, but I think anytime you point fingers, you need to back that up with an offer to pitch in.

So with that in mind, I think what we were talking about, and what we have planned to reconnect next week on is, let's identify from the patient point of view, three potential things that we want to explore. Ideas, maybe it's some kind of research, is it some kind of low hanging fruit representative of a crawl, walk, run type of learning opportunity.

And let's put together some kind of a hack, right. Technology is out there, it's readily

available. I would invite any of the team members who are with us today that are here from a university setting that have computer science departments. I know there's a big one in Nebraska, hint -- hint.

Maybe there might be an opportunity that we could reach across the aisle a little bit and think about focusing on three scenarios that we really want a pressure test, do some kind of a hack, inclusive of both the lay community as well -- as well as any other willing participants. Computer science students would love this thing, so happy to bring them along. And let's use that to see what we learn.

We probably aren't going to solve or discover the next big thing, but we'll probably figure something out that becomes actionable. And I think that's part of where, you know, when I do a lot of advocacy work in this context, some of the pushback I get is, "Well, transplant is small. It's a relatively scoped -- well scoped community."

That's true. But I also think that it's a highly complicated field of medicine, that I'm

hopeful that not only can we find a few insights that we can act on, and grow on, and continue to learn on to inform additional research. But I think anything that we can solve in the -- in the context of transplant represents patterns that we can extract to really apply to the National Health System.

So I'm hopeful that anything we invent and investigate now helps that which we're talking about today, but also can set precedent for some new ways that we can rethink how we're running innovation in a space like this.

So again, we can kind of bring back some value to the professional teams that have literally saved our lives. So, for anybody else that had that conversation, feel free to keep me honest and in check if I've over or under indexed on anything.

DR. NICKERSON: Thanks, Molly. Paul.

MR. CONWAY: Well, it's been an interesting discussion and I think it's an important one that we've had.

I think from the standpoint of the

American Association of Kidney Patients, we're intensely focused on an issue that we term "Government determinants of health." And government determinants of health are those things that agencies either do intentionally, or inadvertently to either promote the patient interest, or to somehow forget the true anchor of the patients they serve.

We hope that's not the case. But we believe in the school of trust and verify. So there are a couple of things we're going to be looking for here. And this is not about pointing fingers, to be very clear. This is about accountability and transparency.

So as advocates, and as a community patients, and doctors, and transplant surgeons, and medical societies, and industry have worked very, very carefully for over 15 years to impact national policy and set up a structure for success.

And I think it's been very clear, it's across multiple administrations, it's bipartisan, and it's compelling. You have a President of the United

States, who just -- just a month ago, actually stood at a podium and signed legislation that transformed the American transplant system.

And one of the things he said was this, "Current statistics show that Americans belonging to minority groups make up nearly 60 percent of those waiting for an organ transplant. Although a transplant can be successful, regardless of the race or ethnicity of the donor and recipient, there is a greater chance of longer-term survival for the recipient, if the genetic background of the donor and recipient are closely matched."

There's a reason why I'm bringing this up. It's because you have a President of the United States that just a month ago was focused on long-term outcomes. And that's been true for the past three presidents of the United States. It's true in the Congress with legislation.

And so we go back to the core issue here, of to what end is this meeting? And the focus of this meeting must be how are we reducing America's

waiting lists, and making certain that people who get the gift of life can keep it as long as possible.

And in that intersection of policy, science, and patient interests, is the FDA. And whether or not the FDA is maintaining a barrier or removing a barrier that spurs greater innovation and advances the patient interest, is the question.

And I think after today, we're a little bit unclear. Because it's a fantastic discussion. If this were the first time we were having this kind of a discussion, it'd be fantastic. I mean, honestly, we would do a press release, and we say this is absolutely tremendous. But it's not, it's the fifth meeting in eight years.

And at a certain point, people need to kind of get their act together and decide what is the next step? So let me just put iBox on the table. The American Association of Kidney Patients is formally endorsing the iBox as a step forward. That has great significance.

Our organization encouraged people to

attend the meeting today. For FDA, you should understand if you have hundreds of people that sign up for meetings, including congressional staff, that's a signal that there's traction, and there's organization. So I would carefully deliberate what the merits are and sort out what is noise and what is reality in terms of what got discussed in terms of how it advances the National American goals of reducing transplantation and re-transplantation and getting that list down.

And it's kind of a mixed bag. It's good today that we heard that the unmet needs of patients are being addressed. That's fantastic. What about the needs of the taxpayer? What about the needs of organ donors? What about the needs of dialysis patients who have yet to have the opportunity of a transplant? And what about the needs of transplant recipients?

I say this as somebody who has served under four presidents and four governors. I have a kidney transplant that I've maintained for 26 years.

I've taken over 165,000 pills. The folks I used to come to Washington and advocate with 10 years ago, and five years ago, a lot of them are not here anymore. And the reason why is because of the medicines they take, status quo.

And so in a summary comment, I'd say that today was a missed opportunity, because there's a lack of clarity on what got accomplished and where we're going. And because of that, I think one of the biggest takeaways, really, is for another stakeholder here, which are the elected officials that oversee FDA.

We're going to encourage them to take a closer look at process, and results, and deliberations from the standpoint of their interest as elected officials, and the patients that they represent, their constituents. It's why we went to Capitol Hill on October 19th, because we did not have confidence about where this is headed.

And it's unlike other divisions of the FDA, to be very honest with you. The device side of

the FDA has leaned forward into the patient community, they have created the science of patient insight data. Think about that, a division of the FDA created that, it has been recognized by the WHO, by the EMA.

We don't see that same type of equivalency on the drug side. And quite frankly, we don't see the same sense of urgency. It's not a disparagement of anyone's public service. It's just that the tempo is not keeping pace with national policy. The tempo is not keeping pace with patient interest and where we're organized, and it's keeping pace with the interest of this industry and others to promote innovation.

So I think after this meeting, one of the biggest takeaways from FDA is to go back and think where are we? Where does our activity line up on the national stage with presidents, with the Congress, and with the key constituency that FDA serves, and that's patients. Thanks.

DR. NICKERSON: Thanks, Paul.

I'm going to turn it over to Ros.

DR. MANNON: I have a very simple recommendation. A qualification plan was submitted by the Transplant Therapeutic Consortium to FDA. How many months ago? Two and a half. Two-hundred and thirty-five pages, nearly 1000 references, five or six years of data harmonization, DUAs, analyses. And I think it deserves to be reviewed and to, you know, I don't think there was anything here today that was discussed that would change my mind if I, you know. That's my recommendation.

I think there was a lot of noise, a lot of information, mechanistic studies, things that are prospective that haven't been studied before for enrichment. I think the bottom line is, this exists, and it needs to be reviewed, otherwise, don't invite me back to the next meeting. And in fact, maybe I will retire out and sit on a sunny beach. Well, they won't have beaches.

But in all seriousness, I have to support my patients. I agree with Paul, I've seen too much difficulty. And again, I have to advocate for

the general population on the waiting list that's, you know, not getting access. We're doing all this pie in the sky discussion, and we just need to move this forward. It doesn't -- it takes time to review it. But that's all we're asking, is taking the time to review it and what else do you need from us?

DR. NICKERSON: Ken?

DR. NEWELL: I think what I heard today is a very clear expectation from patients and practitioners that we have to find a way forward. to say it's difficult or to propose things that are interesting, are feasible, but are not implementable in the near future, is no longer acceptable. We've done that for several meetings.

And so I think the next meeting in four years, it should be we identified something, we moved it forward, and this is where we stand with it today.

I think that for too long, we have always fought with each other. Ros will have an idea, and I'll say, "That's good, Ros, that's good. But don't do it now. I've got a little bit better idea."

And it just keeps kicking the can down the road.

I think with the TTC, we spent probably three years just going through saying what do we have enough data to put forward that is a potential tool? And certainly, it's not a perfect tool. It doesn't have to be, it just has to be better than what we have today.

I think Bill and Amanda have made a very clear argument that if we came today, proposing here's the data and support of biopsy proven acute rejection as basically the primary endpoint, right. Because it's not death and graft loss. Those are vanishingly rare. You would say, "There is not enough data to support this as the primary endpoint."

So I think what Ros was also saying is, we're not saying it's unimportant, we're saying it's yes, and biopsy proven acute rejection is important. But it's no longer when you talk about enrichment, a frequent enough event that we can power studies around it.

Which means if a pharmaceutical

company, and I know several that will potentially not develop agents that were mentioned, because there's no regulatory path forward. To develop an agent, spending years, multiple phase two and three studies, and then say, "I can now say I've got an agent that's as good as Tacrolimus," is not going to help.

I think, you know, while I was sitting here, I got something about new combinatorial therapies in melanoma breakthrough. And it's like, are you pouring salt on the wound? They're -- they're inviting me to a webinar about new therapies, because they have new ways of doing it. And then, these new regulatory pathways encourage people to invest in potential agents.

And so I think we're being called to say, it's not good enough to say it's a tough problem, we need to think about it, give us a little time to refine our ideas. And I would suggest that we're sitting here saying, "What do you think, Ken?" "What do you think, Molly?" "What do you think, Ros?"

There were what, I forget, somebody can

correct me, but like 800 people who attended this virtually or whatever. I would say a survey should be sent out to everybody who registered for this meeting, saying, you know, here's some potential unmet needs, how do you rank them? Here's some path forward, you know. Do you, you know, what -- what did you hear that resonated with you? Because it's a shame that all these people spend all day listening to us, they can't really comment. And then we will, in the end, decide what we think the takeaways are.

So and I think either the TTC or the ASTS, I'll speak for them. We'd be happy to help facilitate the survey.

DR. NICKERSON: Thanks, Ken. Michael?

DR. MENGEL: I'm like listening to Paul. I think there is an aspect which we didn't discuss today is, we -- our traditional setting of trials forces us to collect large numbers of patients and enroll them for a long time before we come to a decision that trial failed. And that essentially blocks the cohort we can study and use to approve new

innovation.

And I think something like the iBox as a surrogate would accelerate the timeframe of assessing innovation, whether it works or not.

Industry always tells you when you meet with them, tell us to fail a product early. So -- so there is another aspect to advancing the field and being innovative, is by having tools and setups to make non-promising compounds fail quickly.

And with that, move on and trial the next one, especially when we risk stratify in small cohorts. We need an answer, we need a signal fast.

Because there is limited funds. And that's to me, I think that's a main barrier for to invest in the field to look for innovation, because it is such a mountain to climb, and cost so much, and the risk, and the potential return of investment are then not there anymore.

And -- and why would you go into transplant, when you can trial your anti-immuno-blocking compound and many other diseases with way

larger cohorts?

So I think there is -- there is not only -- we all hope, of course, that the next trial is successful. But there is value in knowing faster that something doesn't work.

DR. NICKERSON: Thanks, Michael. Kevin.

MR. FOWLER: Yeah. So first I want to say thanks for the FDA for the invitation. So thank you very much.

Firstly, want to say is that I go back to the question I had when we had Q&A, the first Q&A. I asked what's changed? Crickets, except for Ros. Right.

So I think that that -- but that that lack of response, of which has not changed or has changed, says at all. Says it all.

And I go back to what, Dr. Mannon, Dr. Newell, you said it very well. Paul. iBox. Let's go forward review. I mean, what type of request is that?

But I do ask this, that the patient

community is involved with this process. That they are a stakeholder are not excluded. And I just go back to what, you know, my dad said to me. I don't put any stock in what people say. All I put stock is what I see.

And so I'm very happy where nephrology is going. So I now have extra energy to focus upon transplant to help change things over here. So I'm happy to help. Thanks.

DR. NICKERSON: Nicolay?

DR. NIKOLOV: Yeah. So I just want to basically talk in support of what has already been said. But I mean, what we've heard over the course of the day is that we have disheartened patients at the lack of progress in our field. And it's obviously has all the, you know, these downstream consequences on not getting other patients transplanted and impacting transplant access.

We as clinicians know that these are not optimal therapies, and they are opportunities to do better. We know that that's really been stale over

the last few years. We know that the sort of maintenance immunosuppression that we have, it has done well, in many ways. But that doesn't mean we have to accept where it is. And we also know that without advancing the field, it's just going to lead to more of the same.

So I also want to make the point that the iBox has been available. You know, there's been a lot of work, and effort, and energy that's been invested in it over the past several years, now.

What I haven't heard today is a good, compelling reason to not use it. And I think we really need to keep that in mind. If this is a potential path forward, used in conjunction with some of the other traditional endpoints, then why not do that? The worst thing that will happen is that we find it doesn't work and we still rely on traditional endpoints.

But I would plead that you would review the dossier that was sent, and that there's some action on this to -- to move forward so that we can

finally get away from what we've been doing for the past two decades.

DR. NICKERSON: Okay. Go ahead. Go ahead.

DR. VELIDEDEOGLU: I just want to clarify a few things about the review process of the -- for the qualification of biomarkers and surrogate endpoints. We, as the transplant -- rheumatology and transplant division, in collaboration with the University of Manitoba, organized and sponsored this workshop.

But we are not the decision makers on biomarker qualification, including iBox. We are among the subject matter experts; we our opinion is as certainty. But there are other subject matter experts. And we do not make the final decision. We make recommendations. And we do not decide on the timeline for the review process.

So I just want to make this clear, so that everybody understands how the process works. Thank you.

DR. NEWELL: But -- but certainly you can speak to the unmet need, right, for new diagnostics, and new drug development tools? If you were to say, "We don't need a new tool, we're well positioned, now," it might discourage their review.

On the other hand, if you said, "There is an unmet need, we'd like you to look at this and see if this helps address that need," that would be helpful, wouldn't it?

My understanding is kind of a two-phase thing. Is there a need? And if there -- maybe you can answer?

DR. NIKOLOV: So this is Nicolay Nicolov again. We understand this as the elephant in the room. But we also want you to understand that at this point, we cannot really comment before we have reviewed this instrument to make a determination.

And the purpose of this workshop was not so much to discuss the iBox itself, but to really hone -- hone down on the scientific aspects of how can we address this unmet needs for long-term graft

survival. And we heard that loud and clear that this is on the front and center for not only patients, but everyone else involved.

And I want to make sure that we're clear that we recognize that, and we are going to consider this, you know, the use of iBox, or any other endpoint in that context.

So again, I think I couldn't be more clear to say this, but we are open to consider the iBox or again, any other endpoint that would help inform this long-term benefit for drug development in that space.

MS. MCCARTHY: Hey, I get that, I think, as a layperson. And I can only imagine the level of complexity that I haven't even seen beyond this.

And with that in mind, I guess, I also kind of want to react to some of the comments around like investing in long-term trials and things like that.

Again, as an outsider, I -- I pattern

match that a little bit to like where can we borrow some practices and lessons learned in the -- in the private sector that might be able to be applicable to this context. Specifically, instead of investing in umpteen long trials that may or may not come to a good end, whether it's iBox or whatever it is, you know, I wonder if there's not places where we can think about some initial kind of research, or sticking our toe in the water, and looking for things like a minimum viable experiment so that we can have a higher degree of confidence that something is going to materialize into a value add to patients, so that we can ultimately speed up, and move faster to get to more patient improvement from a life experience.

I just wonder if that's where, you know, teams like ours, particularly that don't have The MD and the professional experience that so many in this room have, where we can lean in and maybe try some things out.

We don't have the perhaps bureaucracy to deal with or things like that, that then we can

bring back some lessons that might be applicable to back you up and pushing for the patient agenda.

DR. NICKERSON: Bill?

DR. FITZSIMMONS: Dr. Nikolov, I was wondering if you could shed any light on the timeline. I realize that, and maybe everyone doesn't, but it's the BQP program under Dr. Siegel, who is here this morning, who's ultimately responsible for any qualification package, right, for a biomarker. And the division is -- is important subject matter experts that give advice on that.

For those of us who have worked in industry, the timing seems fairly gray and opaque compared to PDUFA timelines where we -- we understand that the pace of the FDA review.

In this situation, it's very hard to tell what's happening and what we can expect. So can you, for the transplant community, give us an idea, just in any of the submissions that we make, what could we expect from the FDA in terms of timing, for the submission, the review, and the response that we

could get?

DR. NIKOLOV: And you're right. This is an opaque process, because it is. It's not dictated by PDUFA negotiated timelines. And these projects are primarily based on, you know, certainly the unmet need, but also the availability of resources. And we recognize both are important.

I cannot give a timeline, particularly for something that, you know, could be under review, currently, you know, what the timeline of that review would be.

But I can assure you that the team is really involved in that review and understands the unmet need and the urgency.

I really do not subscribe to the qualifications that were given today that, you know, we're somewhat disconnected from the reality of the situation.

I don't want -- I don't take that.

DR. NEWELL: So my only other comment, I think there was a lot of support. Is if I reflect

apart from support for iBox. The other area that I think there was strong support was around when Bill gave his talk on secondary safety endpoints.

And so I would really encourage industry as they design their trials, to please put in safety endpoints in a very structured way, so that we can actually get those into label indications, as well. Because I think the clinical community doesn't control that, that's controlled by the pharma companies that are actually designing their trials.

And if you don't build it in as a key endpoint along the way, it will never get recognized in the label, as you've seen from the presentation that Bill gave.

So I think that that's another opportunity. And I think Bill sort of put it all together at the end in terms of the various items that could be considered along with iBox.

The secondary safety endpoints really should be studied formally and with rigor. It would help the community a lot, and the patients a lot,

because I think that's another area that the patients really are wanting to see that being targeted.

MR. FOWLER: I do want to address the issue of equity in this this process. If you're like someone who's on dialysis, and you've been on there for five or six years, do you know how you find someone who has a protocol that gets you off dialysis? It's up to you to figure that out. And that's a small percentage of patients.

So, I guess what I'm trying to say is that the system we have has been dependent upon the individual self-advocacy and that rewards some individuals, and then it helps others.

But kidney disease is a disease that disproportionately impacts African Americans and people of color. That's a stated priority of this White House administration to address equity.

So as you're making this decision, and this has been reviewed, I'd think that the context of equity should be first and foremost to be considered.

If this is really important to the

White House, actions speak louder than words.

DR. NICKERSON: Any other comments from the floor? Yeah, go ahead.

DR. VELIDEDEOGLU: I'm new to the FDA. I'm not too far away from the clinical side. I heard all the presentations today; they were all terrific.

If you look at the kidney transplant allograft failure, it doesn't come from single cause. It can come from antibody mediated rejection, acute or chronic action, T-cell rejection, acute or chronic action, or a combination of both. BK virus, recurrent disease, death with the functioning kidney from infection, cardiovascular problems, and tumors.

So you have a variety of conditions causing allograft failure. We are trying to get an endpoint, or a surrogate marker, or whatever short-term endpoint.

I would also recommend that we need newer molecules or combination of therapies for specific disease entities. We need therapy for recurrent T-cell rejection. We need therapy for

chronic active antibody mediated rejection, or different kinds of recurrent disease, like membranous IGA, or C3G and so on.

Similarly, therapy for specific viral infections like CMV, EBV, and even PTLD, and those conditions, that will help -- potentially it'll help to improve the long-term survival. That's my comment.

DR. NICKERSON: Thanks.

DR. BLOOM: I just want to add one thing that I thought you were going to say is everything that Dr. Hariharan described there is a consequence of our current immunosuppression. That's where we are. And that's, in large part, the main reason we're here.

DR. HARIHARAN: Well, you know, we don't have an immuno meter, is that right? We don't have an immune meter to judge how much, to whom do we give more, whom do we give less. That's a topic by itself for a separate discussion.

I think we can say it's a consequence of immunosuppression. Immunosuppression is a

necessary to maintain our allograft function. And we are finding these issues here. We have to find a way to solve them.

MR. CONWAY: Can I make one comment?

DR. NICKERSON: Go ahead, Paul.

MR. CONWAY: Thank you. You know, the FDA officials there have been absolutely correct in saying that they are not the decision makers. And we understand that. And we appreciate the clarification. I think we all understand that.

You do inform process, though. And I just want to mention a story to you very briefly, from a former FDA official, that was profound. Dr. Carolyn Newland, who worked at CDRH. And about five or six years ago, Dr. Carolyn Newland was with a bunch of kidney patients in Nashville for a conference, and then she went out afterwards toward the city of Nashville, had a great time, had dinner.

And she told us this fascinating story about the impact on her, as a young scientist and researcher, at NIH at the time, in the late 1980s.

When HIV patients were chaining themselves to the fence, and under the threat of arrest, the NIH director correctly intervened and welcome them to the conference table at NIH to have a conversation.

And she told me that the thing that kept her in public service, and kept her in science, and got her engaged in HIV, were the stories that patients told her around that conference table about the burden of their disease, and what they hope for future patients. Because they knew there was a fuse and a limit on their life. They knew they were going to die.

That shaped the trajectory of her career. She stayed in the federal government. We had the honor of giving her our first National Federal Public Service Award from the American Association of Kidney Patients. And that story has never left us.

And so I think what we're saying and communicating as a patient population that knows we're at risk, that bears the cost of the status quo, is this, any meeting that you're in, in any decision that

comes across your desk, just give us the assurance. And we know that, because you have good hearts.

But whenever there's an opportunity to raise the voice of those who are not here, and who advocated and who are no longer alive, if you could, just raise that voice in that perspective, in that moment.

We know you're not the decision makers, but we know you work with those who do. And the disconnect of the agency, I think sometimes, on the drug side, is it appears that it's regimented in process, and opaque. It doesn't mean that people don't care but signaling that you do removes a lot of barriers and restores trust.

It's that simple. And I think that's what you hear from Kevin, that's you from other patients. It's relatively easy to do. But that story of Carolyn Newland, it shaped the career of a person and the impact it had on patients decades later when she told it, was profound.

So appreciate all the hard work that

has gone into today's meeting, and the candor and the collegiality.

Collegiality and candor are not mutually exclusive terms. If they were, we would be living in a polite society that was horribly uninformed. So thank you very much.

DR. NICKERSON: Thanks, Paul. All right. I'm going to turn it over to Dr. Belen, for final comments.

DR. BELEN: In closing, I wanted to thank -- take a moment and thank all everyone who made this workshop possible.

I want to thank everyone who served us as speakers, moderators, panelists today for taking the time and providing their thoughtful comments.

Our special thanks to our co-sponsor, University of Manitoba, and specifically Dr. Peter Nickerson and his group, who helped us organize this workshop, since this -- since its inception about a year ago.

I'm also grateful to be working with

FDA colleagues who are dedicated to finding solutions to our current challenges that they acknowledged today regarding developed drug development in kidney transplantation space.

I would like to also thank our FDA colleagues, Dr. Jeffrey "Jeff" Siegel, Dr. Jacqueline Corrigan-Curray, and Dr. Higgins for attending today's meeting.

And finally, our patient advocates for speaking up and providing us with their insights. And finally, on the support staff who worked tirelessly to make this workshop possible -- possible and incorporating a hybrid workshop that we were able to receive comments from the remote attendees, as well.

We are also very appreciative for all the feedback and the product -- productive discussion today. And I want to say that we listen to every word and heard it all. And thank you, all of you for joining us today. Have a good evening.

(Whereupon, the meeting concluded at 4:22 p.m.)

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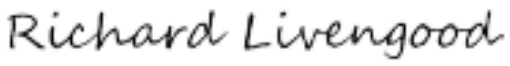

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