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DIVISION OF TRANSPLANT AND OPHTHALMOLOGY PRODUCTS
(DTOP)
SURROGATE ENDPOINTS IN CLINICAL TRIALS OF KIDNEY
TRANSPLANTATION

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Capital Reporting Company

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Surrogate Endpoints for Clinical Trials in Kidney Transplantation 09-28-2015

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1 P R O C E E D I N G S

2 WELCOME, TOPICS AND GOALS

3 DR. ALBRECHT: Good morning, everyone.

4 We're going to get started in a few minutes. So
5 if people could start making it to their seats,
6 thank you. Good morning, everyone. My name is
7 Renata Albrecht. And on behalf of the Division of
8 Transplant and Ophthalmology Products, in the
9 Office of Antimicrobial Products, I'd like to
10 welcome you to today's FDA workshop on surrogate
11 endpoints in kidney transplantation.

12 The meeting and agenda were planned by
13 representatives from AST, ASTS, TTC, ESOP and FDA.
14 We have four session during the course of today's
15 meeting. Each consists of a series of
16 presentations, followed by a question-and-
17 discussion period. To navigate this ambitious
18 agenda, we're going to be using timers and we're
19 going to ask that the audience hold questions
20 until the end of all the presentations within a
21 session to the discussion period. The goals of
22 today's meetings are to have a deliberate dialogue

1 about the unmet medical needs in kidney
2 transplantation, to identify conditions or
3 phenotypes associated with long-term graft loss,
4 to discuss specific candidates that could be used
5 as surrogate endpoints in clinical trials of
6 immunosuppression and to consider the next steps
7 after the workshop.

8 You will note that we are focusing on a
9 number of topics rather than covering the entire
10 topic of transplantation. And that's because we
11 recognize that it's just not possible to cover
12 everything in one day. So notably, for example,
13 we will not be covering death with a functioning
14 graft or how to minimize toxicity.

15 And now, I would like to start
16 introductions. And I was hoping y colleagues who
17 are busy at the front desk would join me. But
18 I'll introduce them probably after the lunch
19 break. Ms. Ramou Pratt and Dr. Eithu Lwin are
20 names that you've seen on a lot of emails. And
21 they've done a lot of work to help us get this
22 meeting ready. So now, let's go ahead and start

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1 with introductions. And, Dr. Velidedeoglu, will

2 you -- oh, we're sharing three mics per person.

3 So I don't know that we have -- you know --

4 DR. VELIDEDEOGLU: Ergun Velidedeoglu,

5 medical officer, FDA.

6 DR. TAMBUR: Anat Tambur, Northwestern

7 HLA Laboratory.

8 DR. JORDAN: Stan Jordan. I'm medical

9 director of kidney transplantation, Cedars-Sinai,

10 in Los Angeles.

11 DR. WOODLE: Steve Woodle. I'm a

12 surgeon from the University of Cincinnati.

13 DR. BELEN: Ozlem Belen, FDA.

14 DR. FLEMING: Thomas Fleming, University

15 of Washington.

16 DR. STEGALL: Mark Stegall. I'm a

17 transplant surgeon at Mayo Clinic in Rochester.

18 DR. WANG: Yan Wang, statistician at the

19 FDA.

20 DR. MORRIS: Randy Morris, Stanford

21 University.

22 DR. NICKERSON: Peter Nickerson,

1 University of Manitoba, Canada.

2 DR. MANNON: Ros Mannon, transplant
3 nephrologist from the University of Alabama at
4 Birmingham.

5 DR. O'CONNELL: Phillip O'Connell,
6 transplant nephrologist from Sydney University,
7 Westmead Hospital.

8 DR. KUYPERS: Dirk Kuypers. I'm also a
9 transplant nephrologist from Leuven, Belgium.

10 DR. ALLOWAY: Rita Alloway, transplant
11 pharmacist, director of clinical research,
12 University of Cincinnati.

13 DR. HARIHARAN: Harry Hariharan,
14 transplant nephrologist, University of Pittsburgh
15 Medical Center.

16 DR. MENGEL: Michael Mengel, transplant
17 nephrologist, University of Alberta, Edmonton,
18 Canada.

19 DR. CAVAILL Marc CavailleFDA.

20 DR. LOUPY: I'm Alex Loupy. I'm a
21 transplant nephrologist in Paris.

22 DR. BAGNASCO: Serena Bagnasco,

1 pathology in Johns Hopkins.

2 DR. BALA: Shukal Bala, FDA.

3 DR. ALBRECHT: Thank you, everyone.

4 Now, if I could ask everyone to please turn your
5 nametags because originally we placed them so you
6 could find the location of the seats. Now, we'd
7 like to be able to have others look. And the
8 clock here says it's 8:16. So we're ahead of
9 schedule, which is great. So if I could invite
10 Dr. Ros Mannon to start the first presentation,
11 that would be great.

12 SESSION 1: UNMET MEDICAL NEEDS IN
13 KIDNEY TRANSPLANTATION

14 UNMET MEDICAL NEED IN KIDNEY TRANSPLANT
15 RECIPIENTS: THE CAUSES OF
16 LONG-TERM GRAFT FAILURE

17 DR. MANNON: So can I add more spots
18 not, or what? I'm just kidding. Thanks for the
19 introduction. And you know, I'm appreciative of
20 the FDA for organizing and being persistent in
21 organizing this meeting and reminding us about
22 doing this meeting. And hopefully, we'll put

1 aside all of our personal agendas and try to come
2 to some unification. I was given the task of
3 trying to give the 35,000 overview -- foot
4 overview of causes of late graft loss today. And
5 I apologize in advance for those of you who I
6 didn't include your slides. We will see your
7 slides because you will be presenting your data.
8 But I just tried to create a thematic message in
9 terms of understanding long-term graft failure
10 intentionally, in 30 minutes couldn't include
11 everything.

12 These are my relationships. I didn't
13 spell consultant right on number six, but didn't
14 spell check. So this is really the issue that we
15 have in transplantation, this improvement, you
16 know, that has been modest over the last 20 years
17 in graft half-lives for adult kidney transplant
18 recipients, demonstrating the really significant
19 improvements that have occurred over time that
20 have not matched the significant improvements in
21 short-term graft survival, and demonstrating that
22 even if you look at living kidney donors, the

1 half-life that was published this past year is
2 around 13 years, with the very, very dismal
3 outcomes and deceased donation of only about nine-
4 and-a-half years.

5 And again, this is a disparity that is
6 well-known and really a focus when you consider
7 that our patients who should, if they were
8 otherwise healthy, have lifespans out to about 80
9 or 82 years. I heard somebody said 90. I said --
10 but these means that these patients, when they
11 have their transplants, are expecting to have
12 transplant after transplant after transplant,
13 unless we can intervene. This is again SRTR, our
14 data about U.S. transplant patients, looking at
15 deceased donors in the upper panel and living
16 donors in the upper panel, looking at the
17 probability of outcomes in the early post-
18 transplant periods and then later periods. And
19 you can see over time that there have been these
20 improvements in graft failure and death, really in
21 the early post-transplant periods, really six
22 months, a year and three years. But you can see

1 that our work is really still cut out for us
2 because though there has been a modest decline in
3 graft failure or death in this patient population
4 at 10 years, we still have a significant
5 probability of graft loss or graft failure due --
6 you know, either death with a functioning graft or
7 graft loss due to intrinsic graft failure, both in
8 deceased donors and living donors, although the
9 magnitude in living donors, if you look at the
10 vertical axis, is somewhat lower.

11 Indeed, when you try and analyze these
12 registry data, they are a little difficult. You
13 try to sort of figure out if they're particular
14 factors or phenotypes that identify patients that
15 will lose their graft. When we're looking at
16 deceased donors again, this is published SRTTR data
17 from 2013, which was published this past January.
18 Really no significant differences in deceased
19 donation between FCD, our standard criteria, and
20 DCD, donation after cardiac death. And really not
21 a significant demonstration or impact of pre-
22 transplant disease, although I would argue that

1 diabetic patients really have more issues.

2 You do see this disparity. You do see
3 factors related to graft failure come out more
4 with living donation. That is, as time goes on,
5 older donors tend to do more poorly. I won't say
6 what older is because I'm finding out that I'm
7 aging out. So not enough potion from Estee Lauder
8 can help that. That African-American recipients --
9 and I'll talk more about this tomorrow -- tend to
10 do worse. And that the diagnoses of diabetes and
11 whatever heck, hypertension end-stage renal
12 diseases in registry data, those patients tend to
13 do worse. And then, unrelated kidney transplants
14 that are not directly related.

15 So the causes of late graft loss, I will
16 make a couple of comments about death with a
17 functioning graft. This comprises about 50
18 percent of our patient population. I'll mention
19 it only to be inclusive. And I'll focus the vast
20 majority of the remaining time I have for my talk
21 on graft failure. So these are data published by
22 the Mayo Clinic group back in 2009 examining about

1 1,300 patients over a 10-year period. I think it
2 was 1996 to about 2006, looking at the causes of
3 death in their patient population. And it
4 indicated a significant rate of death,
5 particularly in the one- to five-year period after
6 transplantation. Seems sort of remarkable because
7 I think when we were talking to patients about
8 transplant, we recognize that there's a survivable
9 improvement in their graft -- in their lifespan
10 off of dialysis.

11 But there still is really -- I think we
12 tend to forget, particularly in this one- to five-
13 year period, that there's a significant rate of
14 patient death. And the causes typically are
15 cardiovascular disease, as shown here, followed by
16 malignancy in this patient population, infection
17 and a large number that are unknown, I think
18 partly because we don't -- patients, as they get
19 further out from transplants, tend to not notify
20 us or it's hard to track down causes of death when
21 patients are found dead at home.

22 These data are really mirrored by USRDS

1 data. They were published in 2012, again showing
2 the vast majority of deaths are due to
3 cardiovascular disease. The magnitude of
4 malignancy here in this distribution was somewhat
5 lower than the Mayo group. I think that in the
6 U.S., it's probably somewhere in between because
7 here, in these categories, there's a lot of
8 patients that have an unclassified patient death.
9 So that's what I'll say about death with a
10 functioning graft. A significant issue, and I
11 think when we're talking in other meetings about
12 societies and immunosuppression, we really do
13 focus on these issues and the potential for us to
14 have more modified or specific immunosuppressive
15 therapies.

16 In my research work, my focus is on
17 allograft fibrosis, which I characterized here as
18 dysregulated wound healing. And again, as I
19 pointed out previously, there's always an
20 initiation phase. It's either an antigen-
21 dependent insult or an antigen-independent insult,
22 whether this is cellular rejection, antibody-

1 mediated injury or cold ischemic injury, which I
2 think is actually also antigen-dependent in some
3 ways. There's epithelial and endothelial injury
4 and certainly microvascular injury that occurs,
5 not depicted here. This leads to a fibrogenesis
6 phase. This is both a proinflammatory phase and a
7 cytokine storm phase as well. Both cells of both
8 the innate and the adaptive immune system come
9 into these grafts, including macrophages,
10 neutrophils and NKT cells. And a proliferation of
11 cytokines, in particular transforming growth factor
12 beta.

13 This had been a major focus of my
14 research, though when it became linked with
15 regulatory cells, I backed off and tried to look
16 downfield. The association of these cells and
17 inflammatory mediators leads to myofibroblast
18 activation. There was a lot of discussion about
19 whether this was epithelial mesenchymal
20 transition. I think for this group, I think we
21 just need to consider that there are fibroblasts
22 within these grafts that become activated and

1 pericytes in the kidneys may play a role. In
2 other tissues, there may be other contributory
3 cells. Needless to say, in the absence of any
4 other damage or destruction, there would be wound
5 healing and re-epithelization or epithelization.
6 But in transplantation, when grafts fail, there is
7 chronic or repetitive ongoing injury, be it an
8 inflammatory injury or an infectious injury.
9 There's an imbalance between matrix deposition and
10 matrix degradation, ultimately leading to fibrosis
11 in the matrix phase.

12 So when we look at patient graft loss,
13 this is one of the first papers that looked at the
14 cohort study. I referred to this study in my
15 previous slides on death with function. This was
16 about 1,300 patients followed over a 10-year
17 period looking at the cumulative incidences of
18 graft loss over time post- transplant. And you
19 can see that there is a contribution of rejection
20 in late graft failure and so-called medical
21 injury, which I believe was stroke, cardiovascular
22 disease and sepsis.

1 But the vast majority of contributors to
2 graft loss were glomerular injury and a diagnosis
3 of interstitial fibrosis and tubular atrophy.
4 Indeed, when they looked at the biopsies preceding
5 the patients' graft loss, what they found was that
6 a good third or maybe more than a third had
7 recurrent glomerular disease and then, this large
8 group that had fibrosis and atrophy of unspecific
9 etiology, though acute rejection was contributory.
10 And this I think was really not one of the first,
11 but one of the earlier papers highlighting that
12 biopsies are contributory and understanding the
13 differential of what's going on in these late
14 patients is more helpful than just calling them
15 chronic rejection.

16 Indeed, Phil Halloran's group has
17 published their for-cause biopsy cohort of about
18 300, a past couple of years, sort of looking at
19 the causes -- for the for-cause biopsy diagnosis
20 in graft failure over time, kind of indicating
21 that acute inflammatory events are really in the
22 early post-transplant period leading to graft

1 failure. And really, as time goes on over five
2 years, the diagnoses that are more significant
3 appear to be antibody-mediated injury, glomerular
4 injury, some just non-diagnosed atrophy and
5 fibrosis as well as mixed cellular and antibody-
6 mediated rejection. And you could say that this
7 is sort of a hand-picked cohort. It's a single
8 center. It is in a single center. It's in a
9 couple of centers.

10 But it just sort of gives you an idea of
11 the tempo of how things change over time in these
12 transplant patients and whether you call late less
13 or greater than a year or greater than a five
14 years, I think -- I'm not sure how maybe
15 necessarily relevant that is. That may be a
16 discussion point more for tomorrow. But again,
17 highlighting the issues that we see, particularly
18 in the late post-transplant period.

19 One of the key contributing studies in
20 terms of our understanding of late graft failure
21 was by the deterioration of kidney allograft
22 function or the so-called DeKAF study. This is a

1 cross-sectional prospective and also prospective
2 and cross-sectional cohort study, includes nearly
3 4,000 kidney transplant recipients at seven
4 centers. The vast majority were contributed by
5 Minnesota, University of Alabama at Birmingham and
6 Mayo. But the other centers also contributed some
7 patients as well.

8 The cohorts were analyzed by both
9 central pathology and local pathology, central
10 anti-HLA antibody titers by Mike Checka, urine
11 metabolomics by Rush and Nickerson and then a
12 large database and biostatistical core that's
13 housed at Minnesota. This study was not funded in
14 the competitive renewal unfortunately. And so, I
15 don't have a lot of data to share in the
16 prospective cohort. We're now funding that
17 independently. And we do have some data and we'll
18 have some presentations at ATC. But it's taken us
19 nearly 10 years to finally have enough of a robust
20 number of bad events, which may be I guess a good
21 thing but also a difficult thing in terms of
22 trying to show productivity under an NIH-funded

1 study.

2 The cross-sectional cohort of about 440
3 has really been the cohort that we've been able to
4 analyze and utilize and provide information.
5 Again, these were patients that had serum
6 creatinines less than 2 prior to January of 2006.
7 This was the funding period and had to show a
8 deterioration of function, which was characterized
9 by either a 25 percent increase in their baseline
10 serum creatinine or new onset proteinuria and
11 biopsy for cause. So if someone went for a biopsy
12 -- and sometimes, because the timeframe of 2006
13 moving onward, people were collecting DSAs and so
14 forth or had BK and virus which was being
15 monitored, these for-cause biopsies also fell into
16 this definition. And there may not necessarily
17 have been obvious deterioration of function. They
18 had pathology, the mass spec urine and then serum
19 for DSA.

20 Shown here are the characteristics. I'm
21 showing you only partial prospective cohort
22 because I don't have all the data for prospective

1 from the past and the cross-sectional cohort shown
2 here. I just want to point out a couple of
3 features, first and foremost African-Americans.
4 So UAB's transplant population's typically about
5 55 to 60 percent African-American recipients.
6 Because of the large number of patients, we really
7 were not able, though we had quite a number of
8 African-Americans included, the distribution here
9 looks a little bit about the way it is in the
10 United States, maybe a little bit lower. And I
11 think it's probably swamped out by the
12 demographics of the Minnesota programs. But
13 needless to say, the cohort of African-Americans
14 within these studies has really been providing
15 voluminous information in terms of pharmacogenomic
16 studies, work done by Pam Jacobson and Andre
17 Aswani.

18 Really no significant differences in
19 demographics. The time to biopsy in this cross-
20 sectional cohort was about seven years. And a lot
21 of living donors shown here in prospective. I
22 can't remember why I put a dash there. But there

1 were some living donors in that cross-sectional
2 cohort. The event rates are shown here. Again,
3 these are slides from about three years ago. And
4 while there are more events in the prospective
5 cohort, proportionally speaking, the number of
6 events and failures is significantly higher in the
7 cross-sectional cohort, based on the design of
8 this cohort. And survival after enrollment, graft
9 survival is significantly lower than in the
10 prospective, again, based on the definition that
11 these were failing grafts and those patients were
12 enrolled to be studied.

13 Shown here are the primary and secondary
14 local diagnoses in this cohort. I just
15 highlighted a few things that the most common
16 local diagnosis made, either primary, secondary
17 was so-called allograft nephropathy, that is,
18 IF/TA, I-F-T-A, and calcineurin-inhibitor
19 toxicity. We'll talk about this more next. And
20 transplant glomerulopathy was seen quite
21 frequently and then a distribution of other
22 primary and secondary local diagnoses. Again,

1 these pathologists locally agreed to doing Banff
2 criteria biopsies. But of course, when you do
3 central versus local, you can always find new
4 things.

5 But when we used the cohort analysis and
6 used central versus -- and central -- local
7 diagnosis of either CNI nephrotoxicity and applied
8 a time to graft failure, we were really shocked
9 and surprised to see, that though we were always -
10 - and I trained in that era, that, you know, CNI
11 toxicity was the killer. We actually found that
12 patients with that diagnosis primary secondary at
13 their for-cause biopsy had a less likelihood of
14 graft failure than everybody else. And this was,
15 I think, kind of a surprising finding. And
16 indeed, when we went back and looked at the CNI
17 net toxicity, anybody that had a diagnosis of CNI
18 toxicity, we found that nearly 50 percent had C4d
19 positivity in the biopsy that was not read as AMR.

20 A large number of patients had donor-
21 specific antibody detected by Mike Checka. And
22 putting the two together, you know, nearly two-

1 thirds of these patients, maybe more, had either
2 C4d or donor-specific antibody in their failing
3 grafts. And this became obvious to Bob Gaston,
4 who wrote this paper up, defining how grafts fail,
5 if you define patients by the presence or absence
6 of C4d or donor-specific antibody, not regarding -
7 - I'm sorry. I'm trying to use the mouse so that
8 everybody can see my highlights. But again, if
9 you had the -- if you had C4d with or without
10 donor-specific antibody and classified biopsies
11 based on that, regardless of primary/secondary
12 diagnosis, those grafts had significant graft
13 failure rates, much faster than those with donor-
14 specific antibody or those with -- and no C4d
15 versus those with no C4d and no donor- specific
16 antibody. This is about 500 patients in the
17 cross-sectional cohort.

18 This study also highlighted some of the
19 other issues with some of the Banff
20 classification. And it's not my job here to bash
21 Banff. We're going to be doing that next week in
22 Canada. But to highlight some of the issues, so

1 this is a low power view of a patient of mine with
2 late graft failure whose creatinine went up and
3 had proteinuria, highlighting the vast majority --
4 you know, the substantial inflammatory cell
5 infiltrate, which, when this biopsy was read, was
6 only noticed in the comments but did not reach any
7 of the scoring values.

8 And this is because, in the original
9 Banff schema, the infiltrating cells and areas of
10 atrophy and fibrosis were not counted in the
11 scoring schema. And so, Joe Grande and I took this
12 into consideration. And Joe helped to create a
13 central biopsy score called IATR. This has not
14 caught on in the United States. We'll show you
15 what has. But again, looking specifically and
16 solely of areas of inflammation and areas of
17 atrophy, using a sort of similar Banff schema of
18 zero through three and then plotting and looking
19 at patient survival. What we found in this
20 cross-sectional cohort is that as this IATR score,
21 this inflammation in these areas of atrophy, which
22 is normally not reported, the more severe the

1 inflammation in these areas, the shorter the
2 length of time to graft failure. And this
3 prognostic feature was independent of the
4 interstitial inflammatory score. It was
5 independent of acute rejection. And it was
6 independent of the fixed amount of interstitial
7 fibrosis. So again, inflammation in these
8 biopsies is obviously a difficult issue. And Mike
9 Mengel really took this a step further and
10 actually got this adopted by using the so-called
11 total inflammation score, the ti- score, which we
12 do score our biopsies on. Really is an excellent
13 predictor of outcome, probably better than his
14 gene expression studies. Again, here he's
15 comparing the standard i, interstitial
16 inflammation score, to a total-i-score in the
17 biopsy. The total-i includes everything, areas of
18 non-scarred stuff, areas of fibrosis, perivascular
19 infiltrates, subcapsular infiltrates, which are
20 normally not scored. And showing here that the i-
21 score is a better predictor of graft failure,
22 whether it's in all allografts or in allografts

1 that have significant interstitial fibrosis fixed,
2 much more so than just inflammation in the graft.

3 So there's been a lot of correlations
4 between active inflammation and graft fibrosis.
5 I've authored a couple of these papers. But other
6 of my colleagues have, including there's a paper
7 here in lung transplantation and airway
8 inflammation. And then, really -- and I didn't
9 put these in order in terms of when they were
10 published but more in what they show, the
11 developing understanding of inflammation, be it
12 innate inflammation or global inflammation and the
13 role of protocol biopsies in detecting
14 inflammation in failing grafts. Indeed, this is
15 now 10 years since these data were first published
16 and these studies were actually executed by a
17 number of my colleagues, some of whom are in this
18 room, indicating that, you know, just fixed
19 atrophy and fibrosis is not necessarily the whole
20 story. But when you're doing surveillance biopsy
21 and you see the presence of interstitial fibrosis
22 and the presence of subclinical rejection in many

1 of these cases were borderline rejection, which is
2 below the threshold of a 1A, there's a significant
3 rate of graft failure over time.

4 And this has been repeated in other
5 cohorts and other parts of the country and also in
6 pediatrics. [Inaudible] from the Mayo data looked
7 at some of the risk factors in these patients and
8 they include acute cellular rejection, the
9 presence of it. The number of rejection episodes
10 is more frequently associated with inflammation.
11 And I guess that's not necessarily unexpected.
12 And also an association with BK polyomavirus
13 nephropathy, again, a viral infection that has a
14 strong pro-inflammatory and cytotoxic T cell
15 infiltrate.

16 These data have been looked at in a
17 different way at Mayo. This is again Park's data.
18 And this was really looking at one-year protocol
19 biopsies. There's a whole gene expression
20 component piece to this. But again, I highlight
21 these data because if you look at individuals who
22 had interstitial fibrosis and tubular atrophy

1 alone, those patients and their change in GFR from
2 baseline really remains relatively constant over
3 about a four-year period. But it's the
4 individuals that had detected interstitial
5 inflammation with fibrosis at one year that has
6 this sort of constant steady decline and
7 glomerular inflammation rate and also in death-
8 censored graft loss.

9 So DeKAF tried to also find some other
10 phenotypes that they could utilize in terms of
11 creating either new studies or sort of optimizing
12 current studies and created computerized clusters
13 based on selected Banff scores showed here. And
14 you've seen these clocks years ago. They really
15 have not caught on because I think they're just --
16 you know, I can sort of see them because I've
17 looked at them like a thousand times.

18 But essentially when you put the
19 variables on the outside and then the computer
20 generates these figures and puts all the patients
21 in as best they can, the distance, the spoke is
22 related to the percent of individuals with that

1 finding. And then, the thickness of the line, not
2 the color, is related to the severity of the Banff
3 score. So the dotted is Banff 1 and the solid is
4 Banff 3. And you can pictorially see that whoever
5 -- you know, that there's a group of patients that
6 have mainly fibrosis and atrophy and that there's
7 a group of patients here that have significant
8 infiltrates, high T scores, i.e., rejection, and
9 then these other three groups that have a lot of
10 fixed -- you know, so-called fixed injury or
11 matrix deposition, inflammation, peritubular
12 capillaritis, particularly in five and in three.

13 And when you just take these clusters,
14 regardless of their central or local pathology
15 diagnosis, you can actually see graft survival
16 based on this clustering, with the worst
17 individuals being I those clusters with a lot of
18 inflammation, atrophy and fibrosis, particularly
19 peritubular capillaritis and deposition, whereas
20 just simple -- a little bit of atrophy and
21 fibrosis is not the death knell for the graft
22 loss. Indeed, this looks at some of the

1 computerized -- some of the features of these
2 patients. And it's kind of hard to look at. But
3 I just wanted to point out that when you -- that
4 these clusters sort of cross over our usual
5 histopathologic features.

6 So cluster two and five has the vast
7 majority of individuals with acute cellular
8 rejection. You see quite a bit of transplant
9 glomerulopathy in three, four and five -- again,
10 the groups that tended to do worse. But if you
11 look at, you know, the presence of C4d that was
12 distributed predominately in the so- called
13 cellular rejection group. DSA was distributed
14 throughout the cohort, not so much in the patients
15 that did well. Proteinuria was a more common
16 feature when you associate it with transplant
17 glomerulopathy. So again, the idea here was to
18 generate and use Banff scoring in a computerized
19 model to try to create phenotypes that might be
20 amenable to clinical trials.

21 I'll switch gears just a tiny bit.
22 We'll hear more about this later. I think this

1 slide kind of summarizes the impact of donor
2 antibody. I already indicated that in the DeKAF
3 group, the vast majority of patients had
4 detectable donor antibody, really done at the time
5 of biopsy or required by the time of biopsy.
6 Maybe now clinical practice is substantially
7 different. Again, this is the Winnipeg group's
8 massive amount of data that has gone in here and
9 following these patients. I put these numbers up
10 because I think they're important in our
11 discussions is that, you know, de novo DSA, this
12 is a low risk patient population, flow cross-match
13 negative.

14 About a 2 percent per year developed a
15 de novo, donor-specific antibody. And the
16 individuals that do worse are individuals that
17 have clinical DSA, meaning graft dysfunction and
18 proteinuria with a graft half-life that is
19 substantially lower than individuals that have so-
20 called subclinical DSA. It's detected without any
21 functional impairment versus other individuals
22 that do well. so again, the detection of de novo

1 donor-specific antibody is a bad prognostic
2 feature in our patient population. And if there's
3 clinical dysfunction, is associated with poor
4 outcome.

5 Some other examples of this, and I don't
6 have time to do the Clq data. But that's an
7 example where detection of Clq, a complement-
8 binding antibody, is present. But this de novo
9 anti-endothelial cell antibody paper, which was
10 published a few years ago, again shows that de
11 novo, but not preexisting anti-endothelial cell
12 antibodies, are associated with worse transplant
13 outcomes. They're all the lower line shown here,
14 again whether it's graft dysfunction or graft
15 survival. What I don't understand is why
16 preexisting doesn't matter. But certainly this is
17 a negative prognostic feature if you have evidence
18 that there's endothelial cell injury with antibody
19 formation.

20 This is not a test commonly used in the
21 United States in most labs. This is the real
22 killer that we see a lot that's just kind of

1 depressing because we don't know what to tell
2 patients, other than they're going to have graft
3 failure, is chronic antibody-mediated injury. The
4 pathologists in the room already know this. But
5 it's, again, glomerular double contours,
6 peritubular capillary layering associated with
7 fibrosis and atrophy frequently. Typically, it
8 can be C4d-positive, doesn't have to be. Can have
9 DSA. Sometimes you can't find it. This has led
10 to a lot of controversy and debate.

11 But within Banff criteria now, there is
12 some flexibility in this diagnosis. And when our
13 pathologists were not sure, they say suspicious,
14 which makes you read the comment and actually go
15 to the pathologists and look at the biopsy, which
16 is such a novel concept these days, but -- and
17 that's being facetious. And peritubular
18 capillaritis is really -- I think it has been an
19 underappreciated association with this, the
20 microvascular injury. And there'll be some --
21 there'll be another paper that will be presented
22 today I think where microvascular injury, G score,

1 glomerulonephritis and peritubular capillaritis
2 are forerunners. And that indeed -- and the other
3 critical feature of Banff scoring is really the
4 ultrastructural detection of these lesions, that
5 there is clearly detectable electron microscopic
6 evidence of some of this endothelial cell injury
7 that we have -- you know, we really don't see on
8 light microscopy. And so, there is an
9 incorporated Banff schema to look at
10 ultrastructural features. And in fact, in our
11 center, when we suspect glomerular injury, we do
12 send tissue off for electron microscopy.

13 A couple of other papers that have, you
14 know, looked at transplant glomerulopathy and
15 associated features, this is the Paris cohort.
16 I'm sure we'll hear this data later today, 1,300
17 patients. Just to remember that these are CDC
18 cross-matched negative transplants, not flow. So
19 the prevalence here is maybe a little bit
20 different. But just to point out that in their
21 one-year biopsies for surveillance, about 14
22 percent of individuals had detected subclinical

1 antibody-mediated rejection. This was associated
2 with microvascular inflammation and transplant
3 glomerulopathy as significant clinical phenotypic
4 features histologically.

5 It was also associated with a
6 significant rate of graft failure, 56 percent
7 graft survival at eight years compared to things
8 like subclinical rejection, where there was an 88
9 percent graft survival over in the long term. So
10 again, these features of antibody-mediated injury
11 that are detected on surveillance are really quite
12 potent. And indeed, these kinds of papers have
13 led even large programs like our own to
14 incorporate the use of surveillance biopsies in
15 our patients to provide them with some hopefully
16 prognostic features in the long term.

17 And finally, a very nice paper from the
18 group in Belgium looking at indication biopsies.
19 And I point this out to sort of weave back the
20 theme of transplant glomerulopathy, detecting
21 transplant glomerulopathy histologically, as we
22 all know, is really a poor prognostic feature

1 here. And you can see that the grafts in those
2 individuals technically show a significant and
3 dramatic decline in graft survival, as well as
4 some other chronic injuries such as arteriolar
5 hyalinosis. Maybe of you that work in this
6 patient population, this and chronic vascular
7 injury here are associated with poor outcome.
8 Whereas you see sort of the similar decline in the
9 strength of interstitial fibrosis and even
10 inflammation, just general total I, not in areas
11 of atrophy, don't seem to have the same kind of
12 diagnostic features as transplant GN and other
13 chronic injury features.

14 Just two words about BK, because we
15 probably won't talk about it today. Really nice
16 review by the Penn group summarizing a lot of
17 information. I'm not going to go through this
18 slide, other than to point out that, you know,
19 consistent detection of viruria and viremia has
20 been noted across U.S. and international cohorts.
21 Most centers do now monitor for this disease.
22 Interestingly, in their survey of all of these

1 studies, they noted a very low rate of graft
2 failure. And again, I'm not sure if that's
3 related to a lack of reporting from these studies.
4 But I have certainly seen grafts fail that I
5 attribute to BK. And it may be a classification
6 issue because we don't have any direct antiviral
7 therapy for BK other than reducing
8 immunosuppression. And as this group has
9 previously published earlier this year, that's
10 associated with donor-specific antibodies as an
11 unintentional consequence of the immunosuppressive
12 reduction.

13 And finally, recurrent disease. My
14 hat's off to Fernando. If I didn't put this slide
15 in, I think he would mentally be executing me.
16 But again, reminding everyone that this was
17 responsible for nearly 40 percent of the graft
18 loss in the Mayo study. I don't know if there's
19 been an impact in surveillance biopsy, to be
20 honest, in my literature review. This table
21 though, it looks new, is really a repeat of the
22 table from 2002. And I'm not aware of any real

1 new data indicating some of the diseases that
2 occur quite frequently, like focal segmental and
3 IgA nephropathy and the rates of graft loss. FSGS
4 detection, anti-B7 antibody, anti-suPAR doesn't
5 seem to have had any effect in these patients.
6 These patients are typically excluded from major
7 drug trials because of the avoidance and concerns
8 about early graft loss, even though it's very hard
9 to predict who will repeat. And then, membranous
10 GN and the role of anti-PLA2 antibody as used as a
11 predictor of graft loss as well.

12 I think one of my biggest problems, and
13 I will be talking again tomorrow, but for you all
14 to think about, and this is just my random scheme
15 of thinking, is what is high immune risk patients.
16 And the INTAC study, which was an Astellas -funded
17 study to compare Campath induction versus standard
18 therapy, which either was rabbit ATG or
19 basiliximab back in 2010, defined it as African-
20 American race, a re-transplant or panel-reactive
21 antibody greater than 20. But I have other ways
22 of thinking about it. I do deal with patients of

1 African ancestry all the time. And I don't know if
2 everybody is doomed or just people with a double
3 mutant of APOL1 or there's some other feature.

4 We'll hear next about lack of adherence
5 -- the subject of lack of adherence issues,
6 whether it's that our levels are subtherapeutic.
7 There's insufficient therapy for that particular
8 patient, or as in teens and transitioners, there's
9 an intentional absence of taking therapy. And
10 this may be a problem more so in the United States
11 than you realize because I'm in a state that
12 doesn't have great exchanges and people can't
13 afford medications. And after the three years,
14 they tend to really minimize their own therapy in
15 order to survive. Our recurrent rejecters, they -
16 - you know, is that a subset of nonadherence? I
17 don't know. But we see patients that keep
18 rejecting.

19 What is high PRA? You know, I think
20 there's multiple subgroups. We see high PRA that
21 are DSA and flow crossmatch-negative. And we
22 transplant people out to this cohort who are DSA-

1 positive, flow crossmatch- positive. And there's
2 a difference in variation of who does well and how
3 they're followed. As I've shown you, de novo DSA
4 development is a critical feature and a bad
5 prognostic feature. Subclinical inflammation,
6 subclinical rejection typically antibody with
7 IF/TA is a negative feature. And then, of course
8 what's the impact of a marginal donor kidney with
9 or without delayed graft function. And can any of
10 these things help? Can any other assays, genomics
11 of the biopsy, of the peripheral blood help us?

12 So to summarize, and on time, long-term
13 graft survival has been addressed incrementally
14 over really the last 20 years. And in spite of
15 all our knowledge, we really have no specific
16 therapies. We don't have targeted plans for
17 management in these large programs. We do
18 surveillance biopsies, viral PCR, drug levels,
19 drug DSA monitoring. I think I've shown you
20 multiple studies and theory about inflammation as
21 a persistent stimulator of matrix deposition and
22 how it -- and its etiology at a cellular level is

1 really under study, and continued study and
2 mitigating that as well. And then, identification
3 of risk for graft failure is associated with
4 modification of induction and maintenance therapy.
5 But I'll point out that antibody's an issue. Late
6 cellular rejection is an issue. And BK becomes an
7 issue perhaps as a precursor to DSA or its
8 intrinsic pro-fibrotic effects because of a lack
9 of effective antiviral treatment.

10 DR. ALBRECHT: Thank you.

11 DR. MANNON: And with that, I'll end on
12 time. Five seconds over.

13 DR. ALBRECHT: Thank you, Dr. Mannon.

14 DR. MANNON: Thank you.

15 DR. ALBRECHT: The next presentation
16 will be given by Dr. Rita Alloway. And it's
17 titled "Suboptimal Immunosuppression and the
18 Impact on Long-Term Graft Loss".

19 UNMET MEDICAL NEED TOPIC #1:

20 SUBOPTIMAL IMMUNOSUPPRESSION AND
21 THE IMPACT ON LONG-TERM GRAFT

22 LOSS

1 DR. ALLOWAY: Today, I'm going to focus
2 on suboptimal immunosuppression and the impact of
3 long-term graft loss. Here's a slide that
4 represents my disclosures, and they're also
5 available in your packet. The objectives that I
6 want to focus on are the cause and effects of
7 suboptimal immunosuppression in graft and patient
8 survival and outcomes, specifically treated to
9 iatrogenic immunosuppressive reductions and
10 nonadherence with the prescribed regimens. Also,
11 I want us to evaluate alternative surrogate
12 markers for clinical endpoints, which could be
13 related to drug toxicity and potentially to
14 tacrolimus variability. And then, also identify
15 strategies to improve nonadherence.

16 So choosing immunosuppressive regimen,
17 as Dr. Mannon just referred to, includes a variety
18 of factors which may be immunologic donor factors,
19 patient comorbidities, side effect profiles and
20 really primarily, unfortunately, it's probably our
21 personal experience. When you compare and
22 contrast the immunosuppressive regimens after a

1 kidney transplant in the SRTTR data, you see that
2 80 percent of the patients are, as we know, are
3 taking a tacrolimus/MMF regimen with approximately
4 one-third of the patients being steroid-free and
5 80 percent of the patients receiving induction
6 antibody therapy, whether it be primarily with
7 two-thirds of the patients receiving T cell
8 depleting induction and another third of the
9 patients receiving interleukin 2 receptor
10 antibody.

11 However, as you can see here, when you
12 look at the mTOR data, you can see that a low
13 number of patients are receiving mTORs at the time
14 of transplant and what is interesting as well is
15 when you look at the data one-year post-
16 transplant, we are not seeing individualization of
17 immunosuppressive regimens, despite the number of
18 studies that have been done in this area. So the
19 observations from this data shows that the most
20 common immunosuppressive regimen after transplant
21 has really not changed over the past 10 years.
22 It's actually not labeled for use in kidney

1 transplant. And there's very little
2 individualization of immunosuppression at one year
3 with a variety of other agents, despite the dismal
4 outcomes that Dr. Mannon has described.

5 T cell depleting induction with the two
6 agents of anti-thymocyte globulin and alemtuzumab
7 have no indication for use as an induction agent.
8 A third of the patients are steroid-free initially
9 and at one year. And again, the lack of FDA
10 approval of the most common regimen is difficult
11 for development within the field. When you look
12 at potential Phase III studies, you're essentially
13 stuck with a non-inferiority design with a regimen
14 that's only used in less than 25 percent of the
15 kidney transplant recipients. And subsequently,
16 you have increased Phase IV cost of testing these
17 regimens that may get approval in Phase III
18 against the standard of care, which most of us are
19 using.

20 Current regimens, as we all know, are
21 suboptimal in promoting long-term graft and
22 patient survival. The current challenges that are

1 associated with these regimens are the
2 metabolic/cardiovascular complications that result
3 in death with a functioning graft, which attempted
4 to be addressed with a steroid withdrawal
5 regimens. The calcineurin-inhibitor toxicity,
6 primarily nephrotoxicity regimens that we've tried
7 to develop in terms of minimization, avoidance and
8 conversion regimens. And then, really we lack our
9 ability to adjust the immunosuppressive profile as
10 a result of the long-term impact of
11 immunosuppression.

12 Again, it's overall immunosuppression.
13 But I think many of us in this room have been
14 stuck filling out the serious adverse event forms
15 when we're dealing with any of our investigational
16 studies. And we really -- it's difficult to
17 delineate between what's an effect of the
18 individual agent or what is just a result of the
19 overall immunosuppression, when we really have no
20 marker of this for us to use in clinical practice.

21 Now, in 2003, as was alluded to, there
22 was a significant study that really focused on the

1 amount of calcineurin-inhibitor toxicity that were
2 visible on the biopsies. And it really affected
3 our practice over the years. In this study you'll
4 see at two years, 50 percent of the patients had
5 calcineurin- inhibitor nephrotoxicity while at 10
6 years virtually a hundred percent of the patients
7 experienced this toxicity, associated with what
8 was documented then as a decline in immune-
9 mediated responses. And from this, we pursued
10 quite vigorously calcineurin-inhibitor avoidance
11 regimens, whether it be immunization, elimination
12 or calcineurin-inhibitor avoidance.

13 And most of these regimens contained an
14 mTOR arm and were pursued for this consequence.
15 However, what we have found in these regimens is
16 the efficacy and safety was not -- it was not a
17 complete success for all patients. The effective
18 and safety of the regimen was in a category of
19 patients. The effect on renal function in the
20 earlier conversion studies may have been optimal.
21 But with late CNI withdrawal, the debates were --
22 the benefits were debatable. The clinical

1 benefits truly of these small improvements in
2 renal function were also questioned. And with the
3 more recent studies with belatacept and this
4 agent, we began to see the larger incremental
5 improvements in the renal function markers that
6 were attempting to achieve. However, these
7 regimens are difficult to obtain.

8 There's unfortunately a high
9 discontinuation rate probably primarily related to
10 adverse events in some of the mTOR studies. And
11 what is unfortunate, as we began to see as we were
12 minimizing these regimens, an increase of donor-
13 specific antibody production, of which its impact
14 on late-graft loss is now becoming more and more
15 evident.

16 With our iatrogenic immunosuppression
17 minimization, tacrolimus, mycophenolate and
18 steroids have excellent short-term outcomes with
19 our current endpoints. But as we've seen,
20 negative impacts long-term. We have an inability
21 or an unwillingness, whatever it happens to be, to
22 individualize these immunosuppression long-term.

1 And maybe if it's a source of our unwillingness,
2 why are we unwilling. Is it a lack of a
3 mechanistic approach for us to determine which
4 agents we need to minimize? Is it a lack of
5 mechanistic approach to actually treat a rejection
6 or treat a donor-specific antibody when and if it
7 does occur?

8 Really, our lower limits of threshold to
9 minimize are unknown. And currently, they present
10 only after a damage is occurring as we know it,
11 whether it be development of a donor-specific
12 antibody or actually biopsy- proven rejection. In
13 the context of all of these minimization regimens,
14 I mean, why do we really want to do it? We're
15 really attempting to address a toxicity component.
16 And unfortunately, when you look into drug
17 toxicity, drug toxicity occurs primarily from two
18 mechanism, from an on-target effect, which is
19 actually an exaggeration of the desired
20 pharmacological action, or off-target effects,
21 which occur when drugs interact with unintended
22 targets.

1 Unfortunately, the drug toxicities that
2 we're dealing with, with the current
3 immunosuppressants, are primarily on-target
4 effects. And you have limited options to minimize
5 toxicity when the toxicity is an on-target effect.
6 For a while, there was a belief that some of the
7 nephrotoxicity related to tacrolimus and the CNIs
8 were potentially an off-target toxicity. But as
9 more and more is known about this process and the
10 other actions of the CNI inhibitors, it's probably
11 now moved over to the toxicity category of on-
12 target. And as we do this, it's difficult for us
13 to provide the efficacy that were needed to see
14 the substantial benefits in the one-year outcomes
15 that we're used to with minimizing toxicity
16 profiles. However, I think it should be our goal.

17 So when you look at toxicity as a
18 clinical endpoint, could we consider that
19 immunosuppressive toxicity actually encourages our
20 minimization strategies? I think it does? I
21 think that there's also evidence that it impacts
22 non-adherence, and which I'll refer to later as

1 patient minimization. Can toxicity be reliably
2 quantitative as an endpoint that would meet the
3 rigor of that? I don't know. I think that we can
4 look into this more in the future. And I think as
5 drug companies are beginning to develop their
6 agents and they're characterizing their toxicity
7 profile, potentially a quantifiable [sic] measure
8 of toxicity that goes along with it could be a
9 potential endpoint in some of these trials.

10 The other thing that's difficult to
11 differentiate toxicities from -- as a comorbid
12 conditions that occur in our sick patient
13 population and also the overall immunosuppressive
14 regimen that we are giving. But in terms of
15 considering toxicity as the clinical endpoint, I
16 look at the definition of a clinical endpoint as a
17 characteristic or variable that reflects how the
18 patient feels, functions and survives.

19 And I think that if you -- if you go
20 into clinic on the days and you look and you think
21 about the possibility of a non-GI-toxic regimen in
22 a transplant patient population, that would be a

1 dramatic improvement, or if we were able to go
2 into our clinics and actually, for once in a
3 while, not see the chronic creatinine creep that
4 we see over time as a relationship to the loss of
5 graft function, albeit from a variety of different
6 causes. This would certainly impact survival and
7 the way patient feels. So I would like to request
8 you to kind of change your frame of thought when
9 you think about clinical endpoints in terms of
10 could we consider quantitating a toxicity as a
11 clinical endpoint to improve the outcomes of the
12 patients that we serve.

13 Now, focusing in what is probably one of
14 the most important drivers of immunosuppressive
15 minimization, and I'm going to refer to this as
16 patient-driven immunosuppressive minimization, or
17 non-adherence. And I think the American College
18 of Preventative Medicine focused on five
19 dimensions of adherence. Those were the
20 socioeconomic factors, therapy- related factors,
21 patient-related factors, condition-related factors
22 and health system-related factors. And in a

1 recent study in Transplantation, in 2007, New
2 pointed out specifically what these factors were
3 in relationship to transplant recipients.

4 The socioeconomic factors were younger
5 patient, male gender, non-Caucasian, non-U.S.
6 resident, poor social support, poor transportation
7 and literacy. Therapy-related factors included
8 those of complex medical regimens. And I think
9 that if you look at our medication regimens,
10 between the immunosuppressive regimens and the
11 regimens that are treated for comorbid conditions,
12 we probably have the most complex medical regimens
13 that are out there arguably. Our medication
14 regimens also have higher medication toxicity.

15 And I think it's important to
16 differentiate that as we talk about medication
17 toxicity and related to CNI toxicity and things
18 that we can measure with a labor value, the
19 patients are looking at the medication toxicity as
20 the factors of which they can feel and see. As
21 I've alluded to, the gastrointestinal toxicity or
22 the side effects of steroids that are very

1 patient-specific that they want to alleviate. In
2 addition, the lack of pillbox medication education
3 or pillbox reminder systems.

4 When you look at patient-related
5 factors, there's history of non- adherence,
6 adolescence, depression, cognitive impairment,
7 substance abuse and negative beliefs in
8 medications. Also, condition factors of high
9 symptoms distress, development of new-onset
10 diabetes, which is very, very important in a
11 patient who comes into transplantation and has
12 previously not been diabetic, and the increase in
13 time post-transplant that occur. And then, the
14 health care system factors that focus on
15 medication cost, poor access to medication, poor
16 aftercare planning, poor physician/patient
17 relationship or poor physician communication.

18 Now, I think when you look at this and
19 your differentiate these factors, there are
20 several factors that I have struck through here
21 that we essentially could have no impact on.
22 However, there are several factors that we can.

1 There are significant programmatic changes that we
2 could put in place in terms of aftercare planning
3 and provider/patient relationships and provider
4 communication. In addition to addressing the
5 negative beliefs that people may have with
6 medications, especially when they're taking so
7 many. And really, there is a wealth of
8 information that is coming out now regarding
9 medication education and various reminder systems
10 that can hopefully improve the impact that we have
11 overall on medication nonadherence.

12 And then, there's industry changes that
13 could occur. Medication cost and poor access to
14 medication continues to be an issue, despite our
15 efforts long-term. But then, together, and
16 hopefully today as we're here together,
17 clinicians, industry and regulatory -- regulators
18 together can focus on potential therapeutics that
19 are less complex medication regimens that can have
20 fewer medication toxicities and potentially, in
21 particular, look at the development of freedom of
22 no data as a potential endpoint in some of our

1 future clinical trials.

2 And this slide was previously referred
3 to by Dr. Mannon in looking at the individual
4 causes of kidney allograft failure. But I want to
5 point out the information that they highlighted
6 relate to antibody-mediated rejection and
7 nonadherence. And it's why you'll see here our
8 focus has changed away from CNI toxicity. Now
9 we're seeing a full 64 percent of the patients
10 for-cause biopsies to include antibody-mediate
11 rejection or a mixed rejection component. However,
12 in this, the authors of this paper were quick to
13 recognize that if they looked back just at the
14 notes of the patients' charts where nonadherence
15 was documented, almost 50 percent of the patients
16 were known to be nonadherent, that resulted in
17 potentially having an impact on this antibody-
18 mediated rejection component.

19 And so, as we begin to spend a lot of
20 time talking about IF/TA, talking about chronic
21 allograft nephropathy and talking about the
22 formation of donor-specific antibodies, I just

1 want to try to, for one second, compare and
2 contrast what we're taking so much effort to
3 define and yet how comparable it is to
4 nonadherence. When you look at the incidence at
5 one-year post- transplant, IF/TA is approximately
6 13 percent. And there's a variety but a similar
7 factor of 25 percent of nonadherence that occurs
8 in transplant patients. Both of these conditions
9 are poorly understood. Both have multifactorial
10 causes and both have no specific treatment.

11 But what is interesting is the odds of
12 graft failure are roughly a fourfold increase in
13 those with IF/TA whereas a variety of studies have
14 reported up to a sevenfold increase in odds of
15 graft failure when it's associated with
16 nonadherence. So we fully recognize that a major
17 challenge facing transplant is IF/TA and donor-
18 specific antibody formation, et cetera. But have
19 we fully appreciated or recognized as a major
20 challenge of nonadherence related to transplant?

21 And then, I just want to ask, because
22 something as obvious as adherence be the

1 intervention that most statistically improves our
2 long-term post-transplant outcomes? And I want to
3 encourage the industry representatives here to
4 develop strategies that are able to allow you to
5 address nonadherence in your clinical trials
6 because if this is not addressed fundamentally,
7 it's going to be difficult to ascertain what is an
8 effective product and what is a reflection of
9 nonadherence that can occur.

10 The problem, however, with nonadherence
11 is how can we quantify it. Okay. This is
12 debatable. In this study, this looked at a group
13 of Pinsky, et al., and they essentially created
14 what was called a medication possession ratio.
15 They called it MPR. And what they did was assess
16 all of the pharmacy claims data from Medicare to
17 make a determination did the patient actually
18 possess the medication in their hand as a
19 surrogate of them potentially being adherent. And
20 when this medication possession regimen ratio was
21 determined at one year, the patients were divided
22 into quartiles of poor, fair, good and excellent

1 in terms of this ratio. And what you can see here
2 is in the subsequent two years following the one-
3 year assessment, the patients have a 60 percent
4 greater risk of graft loss in the patients -- in
5 the patients that were categorized as poor and
6 fair.

7 In a more recent publication, it was --
8 the focus of nonadherence was shown to be
9 synergistic in -- excuse me -- had a synergistic
10 effect of the -- when comparing it to the class
11 two epitope mismatch. So in this study, basically
12 patients were monitored for their adherence to
13 their antiproliferative, whether it be belatacept,
14 sirolimus, azathioprine, et cetera. And they were
15 evaluated -- their adherence was evaluated by MEMS
16 caps over the first two months post- transplant.

17 And the patients were determined to be
18 nonadherent if they were -- had 80 percent rate of
19 nonadherence within the first month or their
20 adherence was decreasing over the first two months
21 post-transplant. And when you look at this in
22 comparison to patients that were categorized as

1 nonadherent with a DQ epitope mismatch, these
2 patients were threefold more likely to have
3 rejection and lose their graft. And when you look
4 at this in the context of DR mismatch, while it
5 wasn't significant related to rejection, you can
6 see a twofold increase in allograft failure in the
7 patients that were nonadherent and experienced
8 this epitope mismatch.

9 This group, Borra, et al., basically I
10 think visually represented the impact of
11 tacrolimus variability on the impact of graft
12 failure and compared it against something that we
13 all recognize as a very significant negative
14 prognostic indicator as biopsy-proven acute
15 rejection. And in this study looking at graft
16 failure, it was defined as biopsy-proven acute
17 rejection, graft loss, biopsy-proven chronic
18 allograft nephropathy or doubling of serum
19 creatinine. And as you can see in this study,
20 they were comparing the variability, which I'll
21 describe in a second. But the patients who had
22 tacrolimus variability that was categorized as

1 high had the same effect on graft survival as
2 patients who were noted to have a biopsy-proven
3 acute rejection within the first year post-
4 transplant. So again, we are very respective of
5 the endpoint of biopsy-proven acute rejection.
6 But how respectful are we of the variability of
7 tacrolimus or other markers of potentially
8 nonadherence on the impact of graft survival.

9 So again, in this study, the tacrolimus
10 level variability was calculated based upon trough
11 levels that were measured between 6 and 12 months
12 post-transplant. So this was past the time of the
13 variety of dose adjustment period that goes on
14 early post-transplant. Just of note, this group
15 did try to assess the MMF trough level
16 variability. And it was not correlated with graft
17 survival. But when you looked at the median
18 variability in this study of 14.9 percent, the
19 patients were divided into two groups, a group
20 with high variability and a group with low
21 variability.

22 And when you looked at the instance of

1 graft failure, 70 percent of the patients with
2 high variability experience graft failure compared
3 to 29 percent of those with low variability. When
4 the factors were analyzed and the variety of
5 factors that we look into at risk for graft
6 failure and biopsy-proven acute rejection, the
7 factors that fell out in the variable analysis
8 were tacrolimus variability, biopsy-proven acute
9 rejection and recipient age. And when these
10 factors were incorporated into the multivariate
11 analysis model, you can see again that tacrolimus
12 variability, when adjusting for all other factors,
13 still had a threefold increase in hazard ratio of
14 graft failure in this patient population.

15 Dr. Kim's group in Toronto took a
16 different approach to look at tacrolimus
17 variability and its impact on late outcomes. In
18 this study, there were two composite endpoints.
19 The composite endpoint in first analysis was late
20 acute rejection, TG and total graft loss. And in
21 the second endpoint analysis, they actually
22 excluded patients with death with a functioning

1 graft. And you can see these Kaplan-Meier curves
2 here. So essentially what happened in this study,
3 tacrolimus variability was assessed only during
4 stable periods and the doses of immunosuppression
5 up to one-year post-transplant.

6 So it was a very sophisticated analysis
7 that manipulated the variability calculation so
8 that it was precise in focusing on when the doses
9 were stable. And after the one-year post-
10 transplant, the tacrolimus standard deviations
11 tested included breaks at 1.5 deviation, 2, 2.5
12 and 3. And with every breakpoint in standard
13 deviation, the hazard ratio increased by 27
14 percent with each unit in terms of showing the
15 correlation between the composite endpoint. And as
16 you look here, when you look at the standard
17 deviation of cutoff of 0.25 and also of 3, you see
18 a statistically significant differences in the
19 probability of graft failure in these two groups
20 out to five years post-transplant. And this
21 observation was maintained when they excluded
22 death with a functioning graft. And there were no

1 significant changes in these observations when
2 they adjusted for age, sex, EGFR or acute
3 rejection at one year.

4 DR. ALBRECHT: Twenty seconds.

5 DR. ALLOWAY: So in terms of tacrolimus
6 level variability as a clinical endpoint, it is a
7 predictor of outcomes, regardless of cause.
8 Nonadherence is primarily responsible for this.
9 Tacrolimus variability can be reliably
10 quantitated. But ask yourself, if 80 percent of
11 our patient populations are taking a tacrolimus-
12 based regimen, can it be used as a viable clinical
13 endpoint as a surrogate or biological marker.

14 So in closing, I want us to think about
15 strategies that impact nonadherence and really the
16 impact that it could have on long-term survival.
17 So decreasing the frequency of menstruation, some
18 would argue that we already have a once-daily
19 regimen, tacrolimus, azithromycin and prednisone.
20 But it does have inferior efficacy. Now, there
21 are once-daily preparations of tacrolimus that are
22 available on the market, Astagraf and Envarsus is

1 coming. And there's been several studies that have
2 shown that the lower variability, improved
3 adherence and attempts to quantitate the economic
4 impact of these agents in the context of today's
5 world where we have generic immunosuppressants to
6 see if they have an economic benefit.

7 What I'd like to -- the most common
8 method to address nonadherence and the most
9 aggressive is actually observed in menstruation.
10 We do now have an immunosuppressive agent where we
11 can observe in menstruation with a monthly
12 belatacept infusions where we actually avoid the
13 tacrolimus variability altogether. But I'd like
14 to encourage the development of novel clinical
15 agents with an adherence component.

16 DR. ALBRECHT: Thank you, Dr. Alloway.

17 DR. ALLOWAY: Thank you.

18 DR. ALBRECHT: The next presentation
19 will be given by Dr. Mark Stegall, and it's on
20 patients with subclinical injury and inflammation
21 to the kidney and long-term graft loss. There you
22 go.

1 UNMET MEDICAL NEED TOPIC #2:

2 PATIENTS WITH SUBCLINICAL INJURY

3 (INFLAMMATION) TO THE KIDNEY AND

4 LONG-TERM GRAFT LOSS

5 DR. STEGALL: There you go. Don't cut
6 into my time, now. Talk fast. All right. So
7 this little piece of paper, actually you should
8 look at it. So this workshop's supposed to be on
9 surrogate endpoints, right? So I'm going to try
10 to be specific talking about surrogate endpoints.
11 And there's actually a series of questions, or at
12 least goals. And at the bottom, there's a series
13 of questions for questions and discussion. So
14 actually, grade my presentation on those as you go
15 through because I think that's what I really tried
16 to do is tailor it to that.

17 So my talk is really about subclinical
18 inflammation to the kidney. And as you can see,
19 there's a lot of people at Mayo who worked on this
20 throughout, probably since about 1998. And on a
21 certain level, this talk is really not about
22 subclinical inflammation. it's about this

1 surrogate endpoint question, which accelerated
2 approval may be using subpart H as one process.
3 And it's actually about consensus. And I think
4 that people in transplant should look this worked
5 up in the dictionary because I don't know if we've
6 ever actually tried to employ it. But consensus
7 using evidence-based medicine.

8 And I think it's very good because
9 people like the FDA are trying to hold us to a
10 standard of evidence-based medicine that maybe it
11 seems like we've been doing this. But maybe it's
12 not. And I think inflammation is really used as
13 an example of a surrogate endpoint that might or
14 might not gain traction. And I love this quote,
15 that biology is the science of naming things. And
16 certainly, we've given a lot of names to this
17 entity. And the patients are heterogeneous. I've
18 really found out there are no two transplant
19 patients who are exactly alike. And we're trying
20 to categorize them so that we can actually treat
21 them.

22 So we call it subclinical acute cellular

1 rejection and depends on the day of the week,
2 Cosio writes a different paper based on different
3 terminology. It's borderline rejection, which is
4 I think borderline personality, just doesn't sit
5 well with me. There's subclinical inflammation,
6 which is kind of what we started out studying in
7 1998 and when people told you that you couldn't do
8 a long-term study and it was ridiculous. So we
9 did it anyway. And then, interstitial fibrosis
10 plus inflammation, which made it a lot more
11 complicated than it needed to be.

12 Inflammation of areas of fibrosis -- we
13 don't have a lot of fibrosis in these one-year
14 protocol biopsies, just to say this. And then,
15 there's microvascular inflammation, which is
16 probably the CG kind of area too. And really,
17 when you look at it by gene expression, all
18 kidneys are inflamed. So what we're looking at is
19 light microscopy findings. So that's important.
20 It's a spectrum.

21 So we're looking at some sort of
22 threshold that actually is important for outcomes

1 because every kidney gets ischemia reperfusion
2 injury and something else. And we've published
3 this in obscure medical journals and papers that
4 are no longer read. But the central issue I think
5 that was given us as the goal of this section is,
6 is there a condition. I was asked are there
7 patients who could benefit from alternative
8 therapy. Are people on the right
9 immunosuppression that they should be changed?
10 And what are these patients? Who are these
11 patients? And how do we identify them? What's
12 the incidence of this? What's the natural
13 history? And basically, all of this needs to be
14 validated.

15 That's a big FDA word and everybody's
16 looking at this now. And basically, that means, I
17 think, that if we can agree on things using
18 published data and also we have to be able to
19 reconcile disparate data because the biology
20 really is the same here as it is in Winnipeg, as
21 it is in Paris. It's just a matter of figuring
22 out what the biology we have -- or in Sydney,

1 excuse me. But, so the idea about this is there is
2 difficulties in improving this because it really
3 is a lack of consensus regarding the diagnostic
4 criteria.

5 So who do we actually include in a
6 study? There's lack of consensus regarding the
7 timing of the biopsy. Do we use a three-month
8 biopsy, a six-month biopsy, a one-year biopsy, a
9 two-year biopsy, whatever, right? There's lack of
10 data regarding the impact on graft loss. Let me
11 say that again. There's lack of data about graft
12 loss. And I believe the FDA wants graft survival
13 to be the final endpoint for drug approval.

14 So fibrosis is not one, even, you know,
15 a slight kind of eGFR, you name it. It's not what
16 we're really looking at. We have to look at graft
17 loss. It's also very possible that we just don't
18 have a drug that will work, even in compliant
19 patients. It's a heterogeneous process. There's
20 a lot of information that's not probably
21 immunologic. And the numbers, and again, as they
22 say, the optics aren't good. These are going to

1 be very difficult studies to do.

2 Now, I think there is a fact. Let me
3 ask you this. There is growing consensus that
4 subclinical inflammation of some type is one of
5 the major identifiable and possible treated causes
6 of graft loss in the first five years after kidney
7 transplant. Is this -- does anybody believe this
8 -- I'll raise my hand. Who believes this to be
9 true? Even Mengel believes it's true. Okay. So
10 we've established one thing in consensus.

11 Actually, Renata told me this morning that we
12 weren't going to get any consensus today. We're
13 just going to start discussing issues.

14 Well, she was wrong. We got one thing.
15 People think this is a problem. And actually this
16 is a change from 2002 when we wrote the first
17 paper on tacrolimus being subclinical is they said
18 these were t-regulatory cells because the kidneys
19 are doing so well, right? And, whatever. And so,
20 the central issues are there patients who could
21 benefit from therapy. I think subclinical
22 inflammation is a group of patients. It's

1 probably the largest percentage. Who are those
2 patients? That's probably going to be discussed
3 today. Kind of everything is still on the table.
4 We throw this out as -- I think it's conventional
5 patients who have a negative crossmatch, who don't
6 have a lot of DSA. And this is at one year. And
7 maybe they don't have BK or they don't have
8 recurrent disease, right? And if you can't
9 diagnose BK or recurrent disease or DSA, this may
10 not be the forum for you to work in.

11 So the diagnostic criteria that we use,
12 I throw out a one-year protocol biopsy as good.
13 The reason we use one year is because a lot of
14 things happen before one year. By the time they
15 get to one year, people have decided sort of
16 whether they'll take the immunosuppression and
17 whether they'll come to clinic and all the rest.
18 And then, we've used unexplained IF + i and
19 obviously I think the biggest mantra I'm going to
20 talk about is histologic criteria need to be
21 validated.

22 So when you looked at our Mayo Clinic

1 protocol biopsies, we looked at this recently,
2 1,430 one-year biopsies. A lot of work that is.
3 A hundred and ninety-two of them had subclinical
4 inflammation. A hundred and forty-five had
5 unexplained -- 47 actually had something that we
6 could really say was really attributable to
7 something else, which is BK nephropathy. I think
8 can we diagnose BK nephropathy in a kidney?
9 Things like antibody-mediated reject, CMV, pyelo,
10 recurrent diseases. So I think that you need to
11 get rid of some of those diseases.

12 Otherwise, you'll be treating the wrong
13 disease with the wrong -- with the wrong medicine.
14 And then, the diagnosis of this doesn't always fit
15 Banff criteria. There's subclinical, acute
16 clinical rejection, borderline. There's even
17 people who have i-scores and nothing else. So we
18 call that subclinical inflammation. And when we
19 looked at graft loss in the various and sundry
20 groups, so you take the 117 people. Twenty-six of
21 them had subclinical acute cell rejection.
22 Sixteen percent -- at one year. By five years, 16

1 percent had lost their grafts. With the
2 borderlines, 10 percent had lost their grafts.
3 And this chronic inflammation that didn't fit
4 anything, 14 percent.

5 So those were the graft losses. If you
6 had -- and again, this unexplained with no's -- if
7 I can see this right -- is people who didn't have
8 fibrosis. And we've written about this, that
9 patients who have inflammation without fibrosis at
10 one year tend not to lose their grafts by five
11 years. Now, this is just our data. But the idea
12 is if it's not causing fibrosis by one year, we're
13 not seeing a lot of graft loss. So again, if you
14 include those patients in a study, you're kind of
15 diluting out your endpoint if your endpoint's
16 going to be graft loss. And I think that's
17 important as you -- that's an enrichment strategy
18 right there. So we would think that there is an
19 association between unexplained subclinical
20 inflammation and graft loss.

21 Now, we really need to think this
22 through and reach a consensus about what kind of

1 inflammation we're talking about. I think we need
2 to exclude polyoma, whether it's active or a
3 history of polyoma in that first year. And then, I
4 think that we need to find out whether you could
5 really differentiate peritubular capillaritis in
6 the absence of any interstitial inflammation and
7 say that is primarily a glomerular problem. So we
8 go through the next one. The incidence was a
9 question. At our institution, it was 11 percent
10 in 2002. It's about 10 or 11 percent now. It
11 really hasn't changed when we exclude all other
12 causes. And I think this is important for study
13 calculations. And it may also be important in
14 predicting outcomes in response to therapy.

15 If you start getting higher incidences
16 of this in other patient populations, I'm not sure
17 what that means for the graft survival, because we
18 just don't have that data, right? It could be the
19 same. It could be worse. It could be better. I
20 don't know. And again, I think that I understand,
21 having read this and written about it some, and no
22 one sent me a nastygram, that the Subpart H, the

1 final endpoint in this area needs to be graft
2 survival, or at least a very strong decline in
3 GFR. And an interim endpoint has to be associated
4 with graft survival. And I think that Tom is
5 going to tell us something about that. Tom must be
6 pretty good because he's just told me he was at
7 Mayo at one point in his career.

8 And so, and it's best if it's actually
9 part of the pathologic process, right? I mean,
10 it's -- I guess I read this. And Randy's been
11 trying to teach me this over the last couple of
12 years. And so, yes, we do have some outcomes data
13 with this fibrosis plus inflammation. And we were
14 very happy to do the p value for outcomes became
15 statistically significant. But it was just
16 because of the number of patients you really need
17 to get this endpoint. And so, this was that. And
18 then, in this one here, we have outcomes.

19 Remember, we actually treat most of our
20 subclinical inflammations with steroids. So it's
21 actually something that we have set out to do.
22 And I kind of wonder myself why we haven't done a

1 clinical trial of some treatment. And then, I
2 remind myself, because you just need so many
3 patients, that we need 4,000 transplants. And you
4 know, I've done a couple of thousand. But I'm
5 still enrolling patients. And doing a randomized
6 trial in that session -- in that setting is really
7 tough.

8 So the natural history at Mayo is if you
9 have subclinical inflammation of unknown etiology
10 at one year, your five-year graft survival is 85
11 percent. Now, if you don't have it, it's like 97
12 percent. So it's a six times increase in graft
13 loss. But 85 percent graft survival at five years
14 is still really good. So powering that study is
15 going to be relatively difficult. And I guess
16 it's the reason we haven't done it.

17 Now, the graft survival data I'm going
18 to harp on a little bit because most of it is from
19 the cyclosporine era. It's not the current
20 tacrolimus era. There is quite a bit of data on
21 the development of fibrosis. But I don't think
22 that's a clinical endpoint that is going to be

1 acceptable. There's a lot of unpublished data
2 from the recent era, which I'm very happy to see
3 because other people are going to be glomming onto
4 this bandwagon. And then again, there's a lot of
5 this subclinical rejection, general kind of a
6 thing. But I'm really not sure what the biopsies
7 really showed and I'm interested in those. And
8 then, there's really not a lot of data on high
9 risk groups and I'm not really sure what that is.
10 I look at Harry, who has some ideas. And he's
11 going to tell us this afternoon about that. And I
12 think I'm looking forward to the afternoon session
13 because of that.

14 So I'm actually jumping forward to the
15 10:40 so I can go over time because we don't have
16 to talk about this at 10:40, because the
17 intervention trial is to do a one-year protocol
18 biopsy and then to randomized their drug access
19 and standard of care. If, for example, at Mayo,
20 that could be corticosteroids treatment of
21 subclinical rejection. Then, I think that what we
22 would probably be thinking about doing is re-

1 biopsying to see if we had some sort of impact on
2 outcome. Otherwise, we wouldn't have a surrogate
3 endpoint, right?

4 So re-biopsy. And if the inflammation
5 is decreased or resolved, then the drug might be
6 approved because it got rid of subclinical
7 inflammation. It had like a 50 percent reduction
8 in tumor volume or something similar to that,
9 right, in cancer? Then there's a follow-up. This
10 is the hard part. You have to follow the patients
11 up for four years. You have to actually call
12 them, have them come back and be seen, and to show
13 an increased combined endpoint. And I'm
14 suggesting that it is graft survival. And also
15 we've used at Mayo a 50 percent decline in graft
16 loss between one and five years which is actually
17 a lot of those patients continue to go on and lose
18 their graft.

19 And again, one of the issues is if this
20 inflammation is decreased or resolved, then
21 approve the drug. We don't have any data at Mayo
22 that anything kind of decreases or resolves or

1 that's just not -- we just don't have the data.
2 We don't say that it does or it doesn't. It's
3 just not randomized so we can say that you can
4 even quantify that. And I think it's kind of hard
5 to actually go from, you know, this to that
6 actually over time. And so, an intervention trial
7 would be this. If you have 11 percent incidence
8 at one year, graft survival is 85.

9 The power calculations is you need quite
10 a few patients in each arm to show a 50 percent
11 reduction with an 80 percent power. So you
12 probably need about 500 patients or something in
13 that -- Jesse, is that close enough? Okay, to show
14 that considering dropout loss, the follow-up death
15 with function and a few other things that these
16 patients are going to have. I think 500 patients
17 is actually doable. If you do a de novo study,
18 you basically need about 4,000 patients to get 500
19 patients at one year, which truly, even in this
20 study, you'd need 4,000 transplants to get the 500
21 patients. But you just don't have to enroll all
22 4,000 patients in a clinical trial. So you can

1 sort of pick your poison. It's a lot. Four
2 thousand kidney transplants is a lot, right?
3 See, pessimists, I actually had here
4 that -- and I still don't know what big pharma
5 does and how it makes decisions. And that's
6 probably a good thing because it's hard enough
7 figuring out what my group at Mayo -- how we make
8 decisions. And I think that what we really are
9 trying to do is just to provide a path forward
10 that would provide a mechanism for drug approval.
11 But the Mayo Clinic uses this a lot and I think
12 that clinical studies really should focus on
13 what's really wrong with the patient and not the
14 needs of pharma and FDA, the transplant community
15 and all the rest.

16 So what is needed, I think I'm
17 suggesting, is we truly need a methods trial to
18 validate the histology. The question is what
19 Michael Mengel called a subclinical rejection the
20 same as what Joe Grande and Lynn Cornell and
21 everyone else? I'm sure he doesn't. But they do.
22 And so, the idea is I think it really needs to be

1 a validation piece as a fairly banal retrospective
2 study, same biopsies read by different
3 pathologists at different times. And I think we
4 have to correlate these lesions with graft
5 survival and maybe even show that we can determine
6 a 50 percent reduction in inflammation. We've
7 never really said we can do that. I think you can
8 hypothesize a lot of different things. And all
9 studies have risk.

10 But I think the idea is to correlate
11 that. And I think that there needs to be an
12 acceptance of this combined endpoint because you
13 do get another about 30 percent of patients if you
14 use a 50 percent decline in GFR. And again, these
15 are serial -- these are probably about four or
16 five GFRs every six months in a trial to show that
17 you can get a serial decline in GFR. And of
18 course, it'd be nice if we had a drug that
19 actually works beyond all of that. But that's
20 probably not for today.

21 So the overall path forward is that the
22 future trials are going to take more time. We

1 figured that out I think a long time ago. I do
2 think the intervention trials would be easier to
3 show an effect, although maybe harder to get the
4 right drug, but just from a pure design point of
5 view. And I do think what we're talking about now
6 finally is that specific mechanisms need to be
7 targeted if we're going to get an improvement of
8 outcomes in these patients. Thank you.

9 DR. ALBRECHT: Thank you, Dr. Stegall.
10 The next presentation will be by Dr. Peter
11 Nickerson on patients with de novo donor-specific
12 antibodies and ABMR.

13 UNMET MEDICAL NEED TOPIC #3:
14 PATIENTS WITH DE NOVO DONOR-
15 SPECIFIC ANTIBODIES AND ABMR

16 DR. NICKERSON: Thanks very much. So
17 I'm going to try and talk about prevalence, risk
18 factors and natural course around DSAs. And later
19 on this afternoon, we're going to talk about DSAs
20 as a surrogate. So you've already seen this
21 slide. The main point here is that this is a
22 consecutive cohort of patients, 500, that we

1 followed over a number of years. And I think the
2 main emphasis I want to give off at the beginning
3 is that three-quarters of these patients actually
4 do well. So what we're really talking about is
5 the quarter that don't do well. And of that, 13
6 percent have some form of de novo DSA associated
7 with their poor graft outcome. And the other part
8 that we saw where was that, yes, recurrent
9 disease, GN IF/TA was a major problem in our
10 cohort and that isolated TCMR with IF/TA was
11 actually still at 2 percent. So not everything
12 that's allo has antibodies.

13 We did see death with function in this
14 cohort, 10 percent overall. And most of those were
15 in the stable graft patients. So in fact, if we
16 are going to focus on diminishing death with
17 function, it's probably because we're dealing with
18 over immunosuppression in a single cohort.
19 Evolution of de novo DSA, well, it depends on what
20 paper you read. There's this paper in
21 Transplantation that says that there's 20 percent
22 incidence at first year and then 5 percent per

1 year thereafter, out to five years, which is
2 fairly high prevalence. But in our own cohort, we
3 saw that the annual incidence was only 2 percent
4 per year. So this is a big range. And if you
5 look at the literature, you'll see that there's
6 various ranges, anywhere from the 2 percent that
7 we saw, to this paper by Cooper where they, at one
8 year, had 27 percent in the first year.

9 I think what's more informative is
10 actually to look at what's the incidence in the
11 first month. And here, you can see this ranges
12 from zero in Winnipeg to almost 15 percent in
13 Cooper's study. And the question is why the big
14 range in the first month. Whenever I see anything
15 in the first month as de novo DSA, I have to ask
16 the question is this something that was just
17 missed at the time of transplant or is this truly
18 something that's promoting DSA within the first
19 month of the transplant.

20 And so, there's a couple of points here.
21 One is the definition of how you ruled out a DSA
22 before you did the transplant. And you can see

1 that the MFI values that different groups used was
2 actually increasing as you go up towards the
3 Cooper study where flow crossmatch was the only
4 thing to rule out a DSA at the time of transplant
5 and not some MFI cutoff on the solid phase assay.
6 And there seems to be a correlation between the
7 gradation of threshold and the incidence within
8 the first month. The other thing I'd point out is
9 that induction depletion therapy is seen to be
10 associated with the higher rates in the first
11 month. And whether this is causal or not is
12 unclear. But we do know that you have heterotopic
13 repopulation of memory cells in these patients
14 when you do depletion therapy. So you actually
15 may be favoring a memory response with repletion.

16 Now, there's a lot of different
17 correlates in the various studies with de novo
18 DSA. But the most important thing I want to
19 highlight in this slide is that the dominant de
20 novo DSA is class 2 with them predominantly being
21 DQ versus DR and very few DP in the first -- in de
22 novo transplants. One of the areas that is to

1 think about the HLA molecule, and what we've
2 classically done as transplanters is we say you
3 have a single antigen mismatch at a given loci.
4 So we have a DR mismatch or a DQ mismatch. But
5 that's actually not true in terms of how we should
6 be thinking about donor-recipient compatibility
7 because what the antibody sees is not the whole
8 molecule. It actually sees the polymorphic amino
9 acid that its affinity -- has high affinity for.
10 And I'm representing that here in the one cartoon
11 as a single amino acid. The binding site of that
12 polymorphic amino acid is probably the highest
13 affinity binding of the antibody.

14 And that, Rene Duquesnoy has called the
15 functional epitope, or eplet. It's within a three
16 angstrom radius of the polymorphic amino acid.
17 And then, there's the whole structural epitope
18 where the entire binding surface of the antibody
19 sees at the level of the HLA molecule.

20 Now, if for a single DR mismatch,
21 depending upon the donor and recipient
22 combination, there can be many different

1 polymorphic epitopes on the surface of that HLA
2 molecule so that for a given individual, it can be
3 as few as one or two or as many as 60. And so,
4 what we tried to do in this study was to look at
5 the degree of polymorphism between the donor and
6 the recipient for a given DR or a given DQ
7 mismatch and asked the question whether that had
8 more predictability of who was going to form a DSA
9 post-transplant. And indeed, when we did our
10 receiver operator characteristics, we could
11 identify that the threshold of 10 or the threshold
12 of 17 for DQ had a higher increased risk of
13 forming a DR or DQ donor-specific antibodies in
14 the post-transplant period. So the degree of
15 mismatch is beyond just a single mismatch or a
16 conceptualization I think is the finding that we
17 need to get to in our thinking.

18 The other big correlate that's come out
19 with the formation of de novo DSA is early T cell-
20 mediated rejection. And there's a number of
21 papers now from various groups showing that early
22 clinical T cell-mediation rejection within the

1 first year is a predictor or link to the
2 subsequent development of de novo DSA or ABMR.
3 And more importantly, we see that subclinical
4 tubulointerstitial inflammation is also associated
5 with the formation of chronic antibody-mediated
6 rejection. And this has been shown in the Spanish
7 group here but also by our own group and by the
8 group in Mayo Clinic.

9 I'm going to skip this slide just for
10 time. It's in your deck. Nonadherence, as we've
11 already heard about, is a major risk factor for de
12 novo DSA such that by 12 years post-transplant, 72
13 percent of our nonadherent group had formed an
14 antibody, compared to only 19 percent of those who
15 were deemed adherent. So that clearly is playing
16 a major role. And when we put it all together in
17 a multivariate for what's the risk factors for DSA
18 formation, for DR, it's nonadherence. It's DR
19 epitope mismatch load. It's early clinical T
20 cell-mediated rejections. And for DQ, it's
21 nonadherence DQ epitope mismatch load and a
22 younger recipient age so that the younger you are,

1 the higher the risk you're at. And this is
2 independent of adherence. So it may be related to
3 the quality of their immunologic response.

4 Now, once you have an antibody, if you
5 do a biopsy, as we did in this case series, at the
6 time of de novo DSA detection, 76 percent had a
7 diagnosis, according to Banff 2013 criteria, of
8 ABMR. At the same time, 18 percent did not have
9 any T cell-mediated rejection or ABMR. So just
10 because you have a DSA doesn't mean you always
11 have inflammation in the graft, assuming that
12 there's not a variation in sampling error. And
13 when you do see -- when you do do the biopsies,
14 what you do see is TCMR, again, using the Banff
15 criteria, is common. So when you do see a TCMR,
16 it's usually associated with a diagnosis of ABMR
17 in 91 percent of the cases. And when it is
18 present, it's 32 percent of the time borderline
19 and 29 percent of the time grade 1 or higher.

20 At the time of de novo DSA, transplant
21 glomerulopathy is uncommon, and I'll come back to
22 this point later. But IF/TA is very common at the

1 time of a de novo DSA being detected. When we
2 look at a time to graft loss from the time of
3 onset of the de novo DSA, we see that even in
4 subclinical de novo DSA, there is a progression in
5 graft failure, with a t half of about 8.3 years
6 compared to those that have concurrent graft
7 dysfunction and de novo DSA with a t half of 3.3
8 years. So while the process is slower in
9 subclinical, these grafts are still failing. And
10 so, they're a cohort that we have to pay attention
11 to.

12 Now, if we look at the rate of graft
13 dysfunction, what we see in stable patients --
14 remember, 76 percent of our patients are stable --
15 the rate of decline of GFR was -0.43 ml/min/year
16 as compared to those who have de novo DSA
17 preceding the onset of the de novo DSA. They
18 already had a higher rate of graft dysfunction at
19 -1.76 ml/year. And then, after the onset of the
20 de novo DSA, those patients with a de novo DSA had
21 an acceleration in the rate of graft dysfunction.
22 So a group that's already losing function higher

1 than the stable cohort and it accelerates after
2 the onset of de novo DSA.

3 Now, if we compare that to healthy men,
4 various age groups, you can see that our stable
5 group was in fact with a single kidney declining
6 at the rate that you would expect in normal
7 individual, suggesting that maybe CNI toxicity
8 maybe isn't as big of a problem as we think and
9 that the -- that a stable graft actually is
10 behaving much more like a healthy individual with
11 two kidneys. Now, you could ask the question,
12 well, if you have subclinical or clinical de novo
13 DSA, does that differentiate rates of graft
14 dysfunction. You can see that those who had
15 subclinical or clinical, they had identical rates
16 of eGFR decline, both pre- and post-de novo DSA.
17 The only thing that separates the clinical from
18 the subclinical is at the time of DSA detection,
19 there's a stepwise drop in eGFR in those with
20 clinical de novo DSA. So we'll come back to that.

21 Now, for each mil decrease in eGFR at
22 three years post- subclinical de novo DSA onset,

1 the risk of graft loss increased proportionately
2 with a hazard ratio of 1.06. The clinical
3 predictors for graft loss at de novo DSA onset
4 only turned out in a multivariate to be three
5 things: delayed graft function, which is always
6 interesting because it's suggesting that there's
7 something that's going on at the time of
8 transplant that's initiated that persists in
9 affecting that graft for the life of the graft;
10 medication nonadherence should be no surprise.
11 And then, I put in quotes here DSA titer. And
12 then, Anat will talk about what real titer is
13 later on this afternoon. But this was using a
14 cumulative MFI sum. But this was a poor predictor
15 with a hazard ration of only 1.02 percent.

16 In terms of the pathology at the time of
17 de novo DSA onset predicting graft outcome, there
18 is two major factors. One, did you have
19 tubulitis, which I think is interesting, and we'll
20 come back to discuss that later. But tubulitis was
21 a very common finding at the time of the de novo
22 DSA onset. And it was the strongest multivariate

1 predictor for subsequent graft loss. And CG was
2 rare. It was only present in 13 percent of the
3 biopsies. But when it was present, it was a
4 strong predictor for subsequent graft loss at the
5 time of DSA onset. Now, it shouldn't be a
6 surprise that there's not much CG at the time of
7 de novo DSA onset, if CG is largely dependent upon
8 de novo DSA. So I'll leave that there for you and
9 we'll come back to that.

10 So when we looked at independent
11 predictors of Banff chronic score, what we see is
12 that in a multivariate model looking at either
13 different cut points of CG of 1, CG of 2 or CG of
14 3, as you went up in your severity of CG, the only
15 independent predictors of the CG score were the
16 time post-transplant. So there seems to be a time
17 factor here which has been described by a number
18 of groups. And the presence of de novo DSA
19 development. So if you have a de novo DSA, at
20 different levels you have increasing thresholds of
21 CG. And then, for CI or CT, what we saw in the
22 multivariate was that it was early cellular

1 rejections within the first 12 months' time post-
2 transplant and then nonadherence. DSA had no
3 impact on, I put i or t. And what was interesting
4 then is why is nonadherence having an impact on i
5 or t. And I would think that that is suggesting
6 to us that this is a T cell-mediated process in
7 driving this outcome. We just didn't have
8 multiple T cell events to look at in terms of
9 pathology.

10 Now, in terms of the rate of increase in
11 the CG score, what we saw is that after the onset
12 of de novo DSA, it increased by one grade per
13 there years. So this became a predictable --
14 something that we could potentially model later
15 on. And that leads me overall then to this
16 working model for kidney allograft loss. And this
17 is really what I want to work off of for the talk
18 later on today. We can think about lots of inputs
19 going into graft loss. And some of the common
20 inputs we've been talking about, CNI toxicity
21 leading to IF/TA. We can -- what we haven't
22 talked about is what brain death does in terms of

1 its catecholamine storm and turning on of a pro-
2 inflammatory environment or ischemia reperfusion
3 injury.

4 Both of these can lead to delayed graft
5 function. I think we experience that all the
6 time. Both brain death and ischemia reperfusion
7 injury certainly set the stage of inflammation
8 that can then set up allorecognition and turn on
9 risk for TCMR, both clinical or subclinical. And
10 certainly HLA mismatch is the driving factor for
11 both T cell-mediated rejection and de novo DSA
12 development. And within that class too are
13 epitope mismatch loads. And what's probably more
14 important to really get to at some point is
15 talking about what are the immunodominant epitopes
16 that are actually driving risk for antibody
17 formation. These can ultimately lead to de novo
18 DSA.

19 So we have CNI toxicity, delayed graft
20 function reflecting brain death or ischemia
21 reperfusion injury and TCMR, whether it's clinical
22 or subclinical, all of which are driving into

1 IF/TA. And the data we have would suggest, and
2 what is in the literature is that TCMR, whether
3 it's clinical or subclinical, with again the
4 degree of HLA mismatch, is driving the formation
5 of de novo DSA. That leads to ABMR, whether it's
6 clinical or subclinical. And ultimately I think
7 that's linked to CG. And these two things
8 together, IF/TA and CG, is really what's
9 manifesting as the alloimmune response leading to
10 graft loss.

11 If we talk about under-
12 immunosuppression, whether it's nonadherence or
13 physician-guided minimization, as Rita was talking
14 about, this is the break on the system. And what
15 we're doing by under- immunosuppression by any
16 manner is taking essentially the brakes off of the
17 immune system. We're allowing allorecognition.
18 It's allowing TCMR or de novo DSA formation. And
19 that's going to accelerate the process overall.

20 So we can think about it in terms of
21 overall graft survival. For the most part, we
22 have stable grafts. We can see a gradual decline

1 in a stable graft in terms of eGFR over time. We
2 see in those patients who are going to go on and
3 develop de novo DSA, they already have an
4 increased rate of eGFR decline. And it accelerates
5 after the onset of de novo DSA, whether it's
6 subclinical, as a gradual decline, or a step
7 decline in clinical DSA. And both of these
8 subclinical and clinical DSAs are largely
9 characterized by mixed rejection. This concept of
10 pure I think is fairly limited. And again, we see
11 an increased rate of proteinuria after the onset
12 of DSA. And with that, I'll stop.

13 DR. ALBRECHT: Thank you, Dr. Nickerson.
14 And I want to thank the speakers for keeping us on
15 schedule. We will now take a 15-minute break and
16 we'll return at about three minutes after 10
17 o'clock, at which point we will resume
18 presentations. Thank you.

19 (Whereupon, the foregoing went off the
20 record at 9:45 a.m., and went back on
21 the record at 10:02 a.m.)

22 DR. ALBRECHT: -- go ahead and continue

1 with the presentations. And our next speaker will
2 be Dr. Stanley Jordan, who will talk about
3 desensitization. Dr. Jordan, if you could come to
4 the mic? Oops, our speaker's not here.

5 UNMET MEDICAL NEED #4:

6 DESENSITIZATION IN HIGHLY
7 SENSITIZED PATIENTS

8 DR. JORDAN: Okay. Good morning,
9 everybody. I'm Dr. Jordan, from Cedars-Sinai.
10 I'm going to talk about unmet needs in kidney
11 transplantation desensitization. What I'd like to
12 do today is discuss the current desensitization
13 therapies as a means to improve transplantation of
14 highly HLA- sensitized patients, clinically
15 relevant points that allow successful
16 transplantation to occur and potential surrogate
17 endpoints that we could talk about later, both in
18 adult and pediatric transplants, and then the
19 unmet needs that are there.

20 The purpose of desensitization is to
21 accomplish antibody reduction DSAs to an
22 acceptable level that allows the transplant to go

1 forward. We don't need to eliminate all of the
2 antibodies, and this probably would not be
3 desirable. Just get them to a threshold where
4 they are not causing complement activation and
5 injury.

6 DR. ALBRECHT: Dr. Stanley, could you
7 speak into the mic?

8 DR. JORDAN: Okay. There we go. Sorry.
9 I'd like to start out with a case report for
10 pediatrics. This is a young lady that we -- it's
11 our youngest patient that we've desensitized. She
12 was two-and-a-half at the time, Asian female, with
13 renal female secondary to congenital obstructive
14 uropathy. So had had one failed deceased donor,
15 age one, became sensitized. Her mother wanted to
16 donate to her but had these strong antibodies.
17 And she had a very strong score, what we call DSA
18 RIS, a relative intensity score, looking at the
19 sum and the strength of all the antibodies. They
20 were a crossmatch, you can see. So what would you
21 do? Would you have the child remain on dialysis,
22 do a paired exchange or attempt desensitization?

1 Well, the mother was very eager to
2 donate to this young child. So we did desensitize
3 her with our standard PLEX, IVIG, ritux. It
4 wasn't working, or didn't work as well as we liked
5 -- or excuse me, we did IVIG, ritux first and then
6 added PLEX to it about six months later. We got
7 an acceptable crossmatch. She received induction
8 with Campath 1H, was maintained on prednisone,
9 tacro and MMF. At one-month post-transplant, the
10 only DSA present was a weak DQ7 and that has
11 subsequently disappeared. She had a biopsy in
12 2014 with no evidence of ABMR. She's now five-
13 and-a-half years post- transplant. She has no TG
14 on biopsy and she's in second grade, doing well.

15 More importantly, this is the mother and
16 the child. They were selected to be on the Donate
17 Life float at the Rose Bowl Parade about three
18 years ago and we're very proud that they were able
19 to do that.

20 Just briefly, desensitization has been
21 started many years ago. We did work in the 1990s
22 looking at IVIG and found it to be useful to

1 improve rates of transplantation, to lower
2 antibodies. This was subsequently followed up
3 with a study on rituximab. I won't spend much
4 time on this. But both showed improvements in
5 rates of transplantation. Now, this is our
6 current transplant, or desensitization protocol
7 using IVIG and rituximab. And important down here
8 is the -- excuse me, whoops -- going back -- is
9 this area here, looking at the UNet listings that
10 we do where we list unavoidable, or avoids,
11 excuse me, which are Clq antibodies and very
12 strong antibodies. So we would not consider
13 those, and try to desensitize to the lower
14 antibodies. We would then - - if we're not
15 successful within six months, we would then repeat
16 this and we may do PLEX as well.

17 And we'll look at this. So I'm going to
18 look at our patients at pediatrics at first. You
19 saw the patient I mentioned earlier. We have 16
20 patients that we've now desensitized and
21 transplanted. And this is a picture of their DSA
22 scores or their strength of the antibody. And you

1 can see what the relative intensity scale means
2 below, looking at the DSAs. Most have done very
3 well and lose antibodies afterwards. Some have
4 rebounded post-transplant. We can see here that on
5 the horizontal axis, this is pre-transplant, at
6 transplant and then afterwards out to two years.
7 This is the mean antibodies. You can see here
8 over time they do go down. There is some rise at
9 around 15 months due primarily to one patient who
10 had antibody rejection with rebound. The freedom
11 from graft loss is very good. The dotted line is
12 the patients that are highly sensitized compared
13 to 34 normals. Freedom from any type of
14 rejection, you can see is significantly better in
15 those that are non-sensitized.

16 This is freedom from ABMR. Not quite
17 significant, but there were four events in the
18 highly sensitized patients out to three years and
19 then three events in the non-sensitized, four in
20 the sensitized. A very important consideration
21 here is the -- are these protocols causing
22 infection risks. They do not. You can see that

1 the patients' EBV status, especially a problem in
2 pediatrics, is basically none in people treated
3 with rituximab protocol compared to standard
4 patients. BK viremia and CMV viremia are the
5 same.

6 Here are the creatinines going out to 24
7 months. You can see they're pretty good in both
8 highly sensitized and non-highly sensitized
9 patients that were transplanted in peds. Now, one
10 of the things that I just mentioned, looking at
11 donor-specific antibodies, we wanted to -- you
12 know, one of the most important things for the
13 success of desensitization is navigating these
14 antibodies to avoid the very strong ones which can
15 cause severe rejection.

16 And at our place, we've developed an
17 algorithm for doing this, thanks to Dr. Nancy
18 Reinsmoen. We would avoid CDC crossmatches. We
19 will take a flow positive crossmatch at a level of
20 around 225 to allow successful transplant. And
21 DSAs, of course, will be present but at lower
22 levels, as previously mentioned. And you can see

1 here, this is some early data where we looked at
2 230 patients that were desensitized. We
3 transplanted 143. This is 62 percent transplant
4 rate compared to 6.5 percent predicted by UNOS for
5 this greater than 80 percent CPRA group.

6 Subsequently, we've looked at this
7 again. Excuse me. We did 345 patients. A
8 hundred and ninety-four were no DSAs, 151 with
9 DSAs. You can see that 20 were zero mismatches.
10 They were excluded from analysis. A hundred and
11 thirty-one had no C1q DSAs, negative CDC at
12 transplant. The ABMR rate were 21 patients, 16
13 percent compared to 84 percent with no ABMR. So
14 this, we think, is a pretty good way to go
15 forward.

16 What predicts antibody rejection in
17 these patients? Well, there's a couple of things.
18 This is a very important slide, we think, because
19 we look at this score, RIS score that I mentioned
20 earlier -- published this last year. You can see
21 on the left side, on my left side is the -- if the
22 scores are greater than 17, there's a -- excuse

1 me, the people that have antibody rejection have a
2 statistically higher score at transplant. And
3 this, on the right side, the receiver- operator
4 curve, 91 percent correlation with risk for
5 antibody rejection, if we do a score more than 17.
6 So we use this now.

7 In addition, when we look at patients
8 that had antibody- mediated rejection post-
9 transplant, you can see here that their risk of
10 graft loss is higher. Treatments are pretty
11 ineffective in these severe ones because this
12 shows that people that got IVIG plus rituximab for
13 treatment actually did better than PLEX. That
14 doesn't mean that PLEX or plasma exchange is bad.
15 What it means is that it's -- these, we selected
16 the worst cases for this. So we do need other
17 therapies for antibody rejection. And down here,
18 most important I think, are people who fail
19 treatments die very rapidly on the waitlist, going
20 back.

21 Orandi and ours also showed this, if you
22 transplant people that are CDC-positive, after

1 desensitization, not good outcomes. We don't want
2 to do that. We want to stick with a flow and DSA-
3 positive only, which are similar to normal -- more
4 similar, I should say. This is mortality is also
5 increased. Now, one of the things that we've also
6 seen with desensitization -- and I think this is
7 something that could also be an endpoint for some
8 clinical trials -- is that we can really rapidly
9 reduce the wait times these patients have going
10 forward to transplantation. On the left is time
11 on the waitlist prior to desensitization for our
12 patients. It's about a hundred months before they
13 were desensitized. And it takes about four to six
14 months afterwards to transplant them.

15 And this is for the adult group. You
16 can see greater than 80 percent, living and
17 deceased donor patient survival, graft survivals
18 are very good. And most importantly, I think if
19 you look at patient survival compared to the
20 options, which is dialysis -- and this was looked
21 at with three cohorts of patients who were started
22 dialysis on UNOS. And there's about 3,000 or

1 4,000 patients I think in these groups. In 2006,
2 '04, '05 and '06, we followed them for three years
3 and compared them to our desensitized and
4 transplanted patients, all greater than PRA of 80
5 and similar disease characteristics.

6 The death rate after three years is
7 about 22 percent for those remaining on dialysis
8 versus 3 percent for those who received
9 transplants after desensitization. Bob Montgomery
10 has also shown the same thing, that if you look at
11 patients who had been desensitized and
12 transplanted, that their long- term graft -- or
13 patient survival is very good compared to those on
14 dialysis only. One of the things we are also
15 interested in has been looking at what the
16 constituents of our desensitization protocol and
17 what's best. And we did the IVIG alone for a long
18 time.

19 But what you can see here, when we went
20 back and compared this to the IVIG rituximab
21 protocol, that we saw a statistically significant
22 benefit in graft survival with added rituximab.

1 So we did conduct a study, and I'll talk more
2 about this, this afternoon, where we looked at a
3 placebo controlled trial of IVIG -- a placebo or
4 IVIG and rituximab. And what we found was we had
5 the stop the study after about 15 people were
6 entered because we had severe adverse events. And
7 the adverse events were antibody rejection. You
8 can see that as sort of the first -- excuse me, if
9 I can get this thing to move right here -- that
10 this is a typical rebounding up and who lost his
11 graft after transplant. These are the patients who
12 received rituximab, much less rebound and then a
13 tendency for them to go away over time.

14 When we've looked at our total
15 experience at Cedars -- not our total experience,
16 but since 2007 -- we've desensitized 514 patients
17 with this protocol. And you can see the doses of
18 rituximab required for the group of patients.
19 Overall, we've transplanted 514 of these patients,
20 or 80.5 percent. And of the ones not transplanted,
21 10 expired, 16 were delisted and 75 are still
22 waiting. So current status of desensitization in

1 transplantation, desensitization combines --
2 combined with an avoidance of the C1q or
3 complement-activating DSAs can be quite successful
4 with ABMR rates less than 20 percent and graft
5 survival rates comparable to non-sensitized
6 patients.

7 Patient survival is quite superior for
8 patients desensitized and transplanted versus
9 those who remain on dialysis. Current DSA
10 monitoring techniques are problematic in that
11 efficacy of desensitization sometimes cannot be
12 discerned by assessment of CPRA values. This is
13 something we've seen. I didn't talk about it.
14 But looking solely at CPRA, you don't see very
15 much. You have to pair it with the cellular
16 assays to really come up with what is a good
17 kidney for these patients. Pediatric
18 desensitization appears to yield good results,
19 similar to those for adults, and give these kids a
20 good chance at a life.

21 I think the unmet needs from my
22 standpoint are as follows, that there's the

1 recognition -- there needs to be a recognition by
2 the SRTR at centers performing desensitization are
3 serving a higher risk population than non-
4 sensitized patients and appropriate risk
5 adjustments should be granted because it is very
6 difficult to take care of these patients. There's
7 a need for increased biotech and transplant center
8 collaboration to improve implementation of novel
9 therapies aimed at modifying antibodies, B cells,
10 plasma cells and complement. These appear to be
11 our best targets today. And current DSA
12 monitoring techniques are problematic in that
13 efficacy of desensitization cannot be discerned by
14 assessment of CPRA values.

15 Again, cellular assays are essential
16 before we proceed to transplantation and we need a
17 lot of innovative thinking here, how are we going
18 to use the different assays too, and I know Anat
19 is going to talk about that later. And I think
20 pediatric patients represent a growing and
21 underserved population of sensitized patients that
22 should be included in clinical trials. We have

1 some patients who are near death, who are having
2 to get an emergency IMD to try and treat them with
3 some of our drugs because they're not eligible to
4 enter these trials. So I hope that that's
5 something that we can do in the future. Thank you
6 for your attention. Picture of the Blue Ridge
7 Mountains here, so thank you very much.

8 DR. ALBRECHT: Thank you very much, Dr.
9 Jordan. And the final presentation of the
10 morning, first morning session, will be by Dr.
11 Steve Woodle, also discussing desensitization.

12 DR. WOODLE: These are my conflicts of
13 interest. So to put the importance of
14 desensitization into perspective, I borrowed this
15 data from the SRTR kidney committee. Actually,
16 not the SRTR but the UNOS kidney committee, using
17 USRDS data. And in the blue is expected lifetime
18 on dialysis. And in the red is the increased like
19 expectancy that you get when you get a kidney
20 transplant. If you look on the left in the
21 column, using this data, we calculated annual
22 mortality rates on dialysis. And it's important

1 for agency to understand this because these
2 mortality rates rival those that we see in
3 oncology. Yet when you see drug development in
4 oncology, you see a willingness of agency to
5 accept more expedited pathways than we do in
6 transplantation.

7 For example, if you'll take a patient
8 between the age of 45 and 49, that patient has a
9 6.8 percent per year mortality on dialysis. Over
10 five years, that's 34 percent. That means a third
11 of these patients that we're talking about, that
12 Stan just talked about and that I'm going to talk
13 about, are going to be dead within five years. So
14 it's really crucial to get these patients off
15 dialysis. The approaches that we have now are much
16 better than they were a decade ago. A lot of
17 programs are getting better at identifying
18 additional living donors. We have viable, active,
19 very efficient kidney exchange programs.

20 And importantly, recently, the increased
21 allocation priority with exponential points being
22 given for more extreme PRA sensitization in a

1 kidney allocation system as resulted in
2 transplantation in a lot of these patients.
3 That's largely been at the expense of children. I
4 don't expect that to last very long. And so, that
5 positive effect is going to be a transient one.
6 That leaves us with a final option, which is
7 desensitization.

8 Our approach is a little different than
9 that of Stan and other people who have used IVIG.
10 Rather than trying to circumvent the antibodies
11 and try to dampen the inflammatory response, we've
12 gone after trying to eliminate the DSAs using
13 plasma cell-targeted and B cell-targeted
14 therapies. Sort of our rationale is that complete
15 and durable elimination of DSAs is optimal. The
16 absence of a detectable DSA in the serum does not
17 imply an absence of DSA deposition in the graft,
18 and I'll show you some data for that.

19 Long-term reductions in global HLA
20 antibodies on the order of 70 percent in the trial
21 that's noted above there, for up to one year were
22 not associated with an increased infectious risk.

1 It's a little bit beyond the scope of this to talk
2 about that. But when one deletes just the plasma
3 cells, one leaves a relatively small hole in the
4 immune repertoire. And also, congenital
5 hypogammaglobulinemia is a state where there's
6 little to no antibody production is managed very
7 effectively with passive antibody replacement.

8 There are three basic mechanisms by
9 which an antibody can cause injury. On the left,
10 on the far side, is a direct signaling through
11 receptors on the endothelial cell. In the middle
12 demonstrates complement activation. Importantly,
13 sublytic membrane attack complex levels. That is,
14 deposition at levels that aren't sufficient to
15 actually lyse the cell can initiate a number of
16 injurious and deleterious signaling pathways.
17 Jordan Poher at Yale has shown that the non-
18 canonical NF-kappaB signaling pathways may be
19 predominant in this. And finally, on the right-
20 hand side, you have cellular interactions with
21 cells that enter the graft as a result of
22 cytokines and/or chemokine interactions or via FC

1 receptor interactions.

2 This is a picture that's fairly
3 classical for when you do desensitization and you
4 don't deplete antibody. As you can see, there's a
5 short period of IVIG treatment here. The
6 antibodies decrease a little bit, but not
7 substantially. Then, when the transplant is
8 performed, the antibodies go away. The reason they
9 go away is they're soaked up by the graft. This
10 is an example of a patient that we had that was
11 transplanted. Here's all of his antibodies prior
12 to transplant up here in a pre-transplant sera.
13 And these are the antibodies that we eluded out of
14 the kidney less than 24 hours after he was
15 transplanted. Not only were those antibodies
16 present there, but over the next two weeks, the
17 kidney eluates on day 14 showed an even greater
18 degree of absorption of those antibodies. So
19 those antibodies aren't going away. They're being
20 deposited in the graft.

21 This is electron micrographs from that
22 patient showing endothelial cell activation and in

1 some places beginning of the separation of the
2 endothelial cells from the underlying basement
3 membrane. It also shows microvilli projections in
4 a human. And these are very, very similar to what
5 Wink Baldwin has shown in a murine model where
6 there is endothelial -- when he gave passive anti-
7 MHC antibodies into a mouse and then did electron
8 microscopy on the endothelium and you see the same
9 exact types of lesions.

10 So with desensitization, we need to
11 separate and talk about living donor
12 desensitization and deceased donor desensitization
13 because they're fundamentally different. The
14 endpoints differ markedly. In living donor
15 transplantation, you have a donor that's
16 available. So transplantation rate is a
17 reasonable marker and it's a clinically meaningful
18 benefit. In deceased donors, you don't have a
19 donor that's readily available. And depending on
20 physician acceptability, the availability of
21 organs within your particular region, that may
22 induce a level of variability that makes

1 transplant rates a nonviable endpoint for deceased
2 donor transplantation. So then we have to go to a
3 surrogate, which is traditionally a PRA. Stan
4 Jordan has told you that CPRA is problematic.
5 We've developed a solution to this problem.
6 That'll be the focus of my talk this afternoon.

7 So with living donor desensitization,
8 you've heard from Stan that the best data that's
9 out there about how that affects outcome is from
10 Bob Montgomery's group. These were in living
11 donors. This is using alternate day phoresis with
12 low dose IVIG. As you can see, desensitization
13 resulted in significant increases in long-term
14 survival. When this was broken down into three
15 different levels of incompatibility, there were
16 important observations. The first level is the
17 lowest level of antibody which is a negative flow
18 but detectable DSA. And this was about 58 of
19 these patients.

20 Really, we sort of view this as a
21 relatively trivial issue. I'm not sure whether
22 this should be called desensitization or not. But

1 because you're lowering antibody levels prior to
2 transplant, it is. It's not associated with a
3 huge increase in the risk of AMR, only a couple of
4 percent above patients without DSA. But when you
5 get into higher levels, the levels where MFI may
6 vary from 5,000 to 8,000. These are moderate
7 levels of antibodies that give you a positive
8 flow. But the cytotoxic crossmatch is negative.
9 These can be associated with 10 to 20 percent
10 rates of AMR at one year and still, despite that,
11 desensitization provided improvements in survival.

12 The third group is those with the
13 highest levels of antibodies. For example, a
14 correlative to MFI with a DSA greater than 8,000
15 or a cytotoxic- positive crossmatch. When you
16 look at that group a little more closely, you can
17 see here at one year there's about a 15 to 18
18 percent patient death rate. This has resulted in
19 a lot of programs abandoning this. There have
20 been programs that have been flagged by CMS
21 because they did too many of these. And so, this
22 is an area that transplant programs are moving

1 away from. So we believe in living donor
2 transplantation that cytotoxic-positive crossmatch
3 living donor desensitization is an unmet medical
4 need. There is no viable therapy. There are
5 patient death rates of 10 to 15 percent or higher
6 at one year, AMR rates of 30 to 70 percent,
7 increased infection risk. And I don't know if
8 it's largely been abandoned, but we don't do many
9 of these. And I don't know many people that do.

10 With deceased donor desensitization,
11 this is basically a field that's been really
12 championed and dominated by Stan Jordan and his
13 group. And you heard about that earlier. They
14 mainly use IVIG and rituximab. More recently,
15 we've used some proteasome inhibitor-based
16 regimens. Currently, a we've heard from Stan, he
17 avoids antigens in these patients where the DSA
18 are greater than 10,000 or they're C1q-positive.
19 And pretty much, that's the same thing. C1q is
20 only positive when you have high level antibodies
21 of 8,000 to 10,000 or higher. Almost all patients
22 have an IgG1. They don't have much IgG2 to

1 interfere. So most of these are Clq-positive by
2 definition.

3 So as I mentioned, our approach is a
4 little bit different. We want to delete or
5 inhibit the function of selected B cell and plasma
6 cell populations. We target the long-lived bone
7 marrow niche resident plasma cells, which are the
8 source of long-term serologic memory. And we also
9 need to eliminate memory B cells because they can
10 give rise to a new plasmablast population. We
11 want to provide HLA antibody elimination that is
12 extensive, reliable and durable.

13 This is an example of a patient. All of
14 these antibodies from here across are above 10,000
15 MFI. These are the -- this is the window that
16 Stan Jordan would have to transplant this patient.
17 Now, this is not all patients. But there's a
18 substantial proportion of them that have this
19 level of sensitization. In our study with the
20 proteasome inhibitors published back in January,
21 we looked at the level of the titer of the
22 antibody. These beads are all saturated. Anat

1 Tambur is going to talk about this later. All of
2 these are saturated. So one of the surrogates
3 that we used was to look at the titer of the
4 highest level antibody. We've defined that
5 antibody as an immunodominant antibody. And this
6 gives you the distribution of patients that had
7 bead saturation. Out of 38 patients with class 1
8 antibodies in this, 12 of them were saturated.
9 That meant that two-thirds of these antibodies had
10 levels that are higher than 10,000 MFI. All of
11 those antibodies would have -- those patients with
12 that level of antibodies, most of those antibodies
13 are avoided with the IVIG-based approach.

14 This is a slide that we put together
15 using that type of data. On the left is the
16 proportion of patients that have a certain single-
17 antigen bead titer for class 1 and this is class 2
18 over here. So these patients, at 10,000 MFI or
19 lower, that have -- that need sera, their beads
20 are not saturated, all of those antibodies in all
21 of those patients are treatable by IVIG.
22 Everything above that, some of the antibodies or

1 at least some of them need to be reduced. Now,
2 using the proteasome inhibitor-based regimens,
3 we're able to get 87 percent depletion of those
4 antibodies with the regimens that we published
5 back in January. Now, we're approaching levels up
6 in here with more modern and second generation
7 types of approaches. That still leaves these
8 patients here and these patients here, from these
9 levels and above, that have no therapy whatsoever
10 right now that can treat those levels and get
11 those patients transplanted. That meets the
12 definition of an unmet medical need.

13 So in conclusion, cytotoxic-positive
14 living donor transplantation is an unmet medical
15 need. Deceased donor transplantation patients
16 with HLA antibodies greater than 8,000 MFI, that
17 is, their beads are saturated. And there's also
18 no therapy with deceased donor desensitization
19 that can reliably provide long-term antibody
20 suppression beyond four weeks without ongoing and
21 repeated treatments. We can do some of those
22 patients with proteasome inhibitors, but not all.

1 And we cannot predict who's going to respond.

2 Other unmet medical needs. For living
3 donor transplantation, we need methods to provide
4 substantial, reliable and durable DSA elimination.

5 When you phorese on alternate days, you get low
6 dose IVIG. If you don't transplant the patient
7 within 48 hours, the antibody levels are back to
8 where they were beforehand within about 72 hours.

9 So it's just a transient suppression. We need to
10 provide lower antibody-mediated rejection rates.
11 We need techniques that will provide comparable
12 long-term graft survival. And we need to provide
13 rates of transplant glomerulopathy that are less
14 than 10 percent.

15 In terms of deceased donor kidney
16 transplantation, we need to reliably and durably
17 eliminate a substantial proportion of HLA
18 antibodies. We need to be able to eliminate HLA
19 antibodies at levels that are beyond fourfold
20 single antigen bead saturation. We need to be
21 able to provide patient survival that is
22 comparable to non- desensitized patients. We need

1 to get AMR rates down to less than 15 percent at
2 one year, provide long-term graft survival and low
3 rates of transplant glomerulopathy.

4 What should agency do? Number one,
5 appreciate that dialysis survival may be worse
6 than for some cancers. Embrace expedited pathways
7 for drug development and desensitization and other
8 antihumoral therapies for antibody-mediated
9 rejection. Accept non-randomized trials when no
10 FDA- approved drugs exist for the proposed
11 indication. That is, historical controls need to
12 be accepted.

13 Provide support mechanisms, user fee-
14 based support, the types of user fees that have
15 been used to support trials in other areas should
16 be considered for use for trials to support trials
17 for desensitization and endpoint development.
18 Encourage drug development in desensitization and
19 AMR therapy by providing incentives to pharma,
20 extension of patent protection, establish specific
21 orphan drug programs in transplantation that have
22 substantive funding.

1 What else? We know of preliminary
2 meetings between pharma and FDA when pharma walked
3 away and said there's no way we can do this. There
4 needs to be encouragement of these companies and
5 it requires a transition towards what is being
6 done more frequently in oncology. They need to
7 communicate to pharma that FDA is willing to allow
8 development of endpoints during the conduct of
9 Phase II and Phase III registration trials and
10 accept expedited pathways, including nonrandomized
11 trials where current therapies have been
12 abandoned. Thank you very much.

13 QUESTIONS & DISCUSSION

14 DR. ALBRECHT: Thank you very much, Dr.
15 Woodle. So that concludes the presentations for
16 this session. And now, we have time for
17 discussion. And I'd like to invite everyone to
18 participate, including the audience. There are
19 microphones at the front of the room for members
20 of the audience to ask questions. I neglected to
21 mention, we do have Wi-Fi in the room, and there's
22 a sheet telling you the instructions on how to

1 access Wi-Fi at the audiovisual desk in the back
2 of the room.

3 So let me go ahead and start off the
4 discussion section. And we have some -- well,
5 actually, let me pause. Are there any comments or
6 questions either from the table or from the
7 audience to either the speakers or general?

8 DR. CHANDRAKER: Yeah, hi.

9 DR. ALBRECHT: And would you please
10 introduce yourself for the transcriptionist?
11 Thank you.

12 DR. CHANDRAKER: Sure. Anil Chandraker,
13 Brigham and Women's Hospital. So, I mean, I think
14 there is a -- is it on?

15 DR. ALBRECHT: Can we get the mic on,
16 please? The floor mics?

17 DR. CHANDRAKER: Is that better? No.
18 Okay. Anil Chandraker, Brigham and Women's
19 Hospital. So I think everybody agrees that
20 there's an unmet need. One point I just did want
21 to bring up, and I think Dr. Mannon alluded to
22 this right at the beginning, is that death with a

1 functioning allograft is a major cause of graft
2 loss. I think it's one thing that we really have
3 to consider is that, you know, if we do prolonged
4 graft survival, are we just pushing those patients
5 into that category of death with a functioning
6 allograft. And so, I think we have to be very
7 cognizant about what are the causes that's
8 underlying this. And though we have some very
9 broad categories of cardiovascular disease and
10 malignancy, it really does require a lot more
11 investigation. And I'd like comments from the
12 speakers on that.

13 DR. ALBRECHT: Thank you, Dr.
14 Chandraker. So the suggested questions for
15 discussion are which of these conditions that
16 we've heard about in the morning session have
17 enough information on etiology, biology,
18 pathophysiology and/or what additional information
19 is needed to identify the risk of graft failure
20 associated with these conditions, other prognostic
21 factors, patient enrollment criteria or enrichment
22 strategies.

1 DR. MORRIS: Yeah, Rita, Randy Morris.
2 I'd just like to congratulate the speakers on some
3 very substantive presentations. I think it would
4 be helpful for me and the audience, especially for
5 the speakers, Dr. Stegall, Dr. Nickerson, Dr.
6 Mannon, to describe for the audience the case mix
7 of their donors and recipients in Mayo, Winnipeg
8 and Alabama, especially with regard to the risk
9 factors that they believe are important for graft
10 failure, such as their centers' incidence of
11 delayed graft function, their centers' percent of
12 living donor versus deceased donor, their centers'
13 use of black American recipients, other risk
14 factors because I think these do influence the
15 incidence of the -- not only the risk factors but
16 subclinical rejections, inflammation, DSA, et
17 cetera.

18 DR. MANNON: So, from -- I think it's
19 probably just easiest for me to go first. Our
20 center averages about 250 kidney transplants a
21 year in adults and 25 to 30 kids. And the kids,
22 honestly Stan, I have no idea what goes on over

1 there. So they haven't been flagged. Our
2 recipient mix is predominately African-American,
3 probably about 55 to 60 percent. Our population
4 used to be more deceased donor, probably about 65
5 percent, 35 percent living donor. But now that
6 Jayme Locke's been up and running for two years,
7 we have a very active living donor program. And
8 so, it's probably more like 50/50. We do do
9 desensitization. We don't do CDC crossmatch
10 positive. We do flow positive, DSA positive. We
11 also do ABO incompatible. That probably makes up
12 less than 20 percent of our program. And we do
13 active outcomes follow-up.

14 So we incorporate our data in our
15 outcomes center and provide real-time follow-up so
16 that we don't get dinged. Probably maybe 10 or
17 12, 15 percent of our patients are in active
18 clinical drug trials, whether they're
19 investigator-initiated or NIH-funded. I mean, is
20 that helpful? And we do surveillance biopsy. But
21 I don't have enough data yet to tell you because
22 we only incorporated that -- we only incorporated

1 that this past year. And so, we're now starting
2 to see the outcomes of that. I can assure you
3 that there is a lot more inflammation than we
4 expected. Our base immunosuppressive therapy,
5 that's the other key question, is Campath
6 induction. We're steroid avoidance if possible,
7 using tacrolimus and mycophenolate, with
8 variations depending on whether you're hep C, HIV-
9 positive or have had prior transplant. Our DGF
10 rate used to be 20 percent. We pump all our
11 kidneys. It's up to about 40 percent since the
12 allocation scheme switch.

13 DR. MORRIS: Your ti-score, incidence?

14 DR. MANNON: It's not infrequent to see
15 a 1 to a 2. And this -- the faculty struggle in
16 the meaning of what that is because they don't see
17 a threshold. They'll see a borderline with TI.
18 And since we have so many biopsies going on all
19 the time, it's difficult to know. I mean, some of
20 us, like me, try to enhance levels. And I thought
21 Rita's point about the GI toxicity is substantial.
22 I mean, I think it's rare to see someone -- well,

1 first of all, African-Americans are never a 1.5
2 Q12. Because they're on Prograf I think is one.
3 But two, people just don't tolerate the drug very
4 well. That's not a ding to any company. And we
5 try to run our Prograf levels early, 8 to 10.
6 Sometimes that happens. Sometimes it doesn't.
7 And we do have a high Medicaid and charity case
8 population. They don't start as charity, but
9 they're Medicaid.

10 DR. NICKERSON: Okay. So Winnipeg is
11 50/50 living/deceased donation. We transplant
12 across -- well, we do predominately flow
13 crossmatch- negative. Occasionally we'll do some
14 DSA. But some of -- the data I showed you today
15 was all flow crossmatch-negative, DSA-negative by
16 solid phase. We're 65 to 60 percent Caucasian.
17 The rest are Asian and we have a 1 percent
18 African-American. We have about a 13 percent
19 indigenous aboriginal population. Our DGF rate is
20 about 20 to 30 percent. And our meds are largely
21 tacrolimus, CellCept and working down to five a
22 day of prednisone. We target early on 10 in the

1 first few months and then 8 by six months. And we
2 run chronically at around six as our trough
3 levels.

4 CellCept is a gram b.i.d., unless GI not
5 tolerated, which seems to be common. So we're
6 probably running between 500 and 750 b.i.d., in a
7 lot of our patients. And, oh, induction therapy,
8 it's only for zero mismatch, or zero match organs
9 that we're routinely giving thymo induction. For
10 the most part, we're not using induction therapy.
11 And occasionally, we're using basiliximab,
12 although we've had to fight to get that on our
13 formulary. So we don't really have easy access to
14 it. So largely, it's triple therapy with very
15 little induction therapy as a routine. What else
16 did you want, Randy? Is that it?

17 DR. MANNON: I think he's trying to get
18 us to say that there's different rates, that your
19 findings may be different than mine, that my rates
20 of inflammation and so forth may be higher and
21 even higher than in the Mayo population, where
22 there's a lot of --

1 DR. STEGALL: Yeah, I mean, the crux
2 really is are there any differences in these
3 surrogate markers based on the patient population,
4 right? That's the question that's out there. And
5 I don't know -- we don't know the answer to that
6 question. That's the main -- I mean, there's data
7 kind of all over. But the patient population, the
8 incidence may be different. And also, the
9 prognosis may be different, depending on the
10 patient population. And there's a lot of
11 variables, right, as you -- again, no two patients
12 are actually the same.

13 I do think that it's a bit premature to
14 start jumping to the conclusions that there's
15 going to be a huge difference based on the
16 population. I would say that because when we --
17 when Mayo Clinic Arizona, which has a very
18 different population than ours, looked at their
19 incidence of subclinical inflammation at one year,
20 it was 18 percent in the Campath arm, which was a
21 few patients. And it was 11 percent in the thymo
22 arm of their study. And so, that was kind of

1 validation. I think that it's interesting that,
2 yeah, in compliant patients, there's more
3 rejection -- in noncompliant patients, there's
4 more rejection. I got that part too. There's a
5 lot of ways that people get to that endpoint at
6 one year. And they're going to have a lot of ways
7 of getting to the endpoint at five years also.

8 But I do think that also -- so, but what
9 I kind of made the point, is we don't know
10 outcomes data in very many groups, right? So you
11 know, don't hate us because we do 80 percent
12 living donor and 90 percent Caucasians and follow
13 the patients and because -- but that's the only
14 data we have. That's the five-year data we have.
15 We don't have it yet from Pittsburgh and the rest.
16 And you have to be a little bit cautious about
17 trying to power studies based on higher incidences
18 of it when you enroll patients and you don't
19 enroll those patients.

20 DR. NICKERSON: I think maybe just to
21 make the point, you know, there's been studies
22 looking at trying to enroll patients, for example,

1 with de novo DSA and there's a multicenter UK
2 study now doing that. And the big problem they've
3 had is a lower incidence than they actually
4 expected because, in fact, once they started
5 screening routinely everybody, they realized that
6 it wasn't as high as they thought it was going to
7 be.

8 DR. STEGALL: And that's the reason I
9 made the big point about polyoma virus and all
10 these other etiologies. You know, like Kevin
11 Laffey used to talk about intellectual puberty
12 people go through, you know, and they figure out,
13 yeah, I used to think that too. But when you
14 start ruling out a lot of these other etiologies,
15 the incidence of unexplained, maybe immunologic
16 causes of injury starts going down and down and
17 down. And it is a -- obviously the incidence of a
18 lot of things depend on how you manage the
19 patient. So whatever standard of care is, is of
20 critical importance in this area.

21 DR. MORRIS: I think the incidence will
22 vary depending on patient mix. I mean, there's no

1 question about that. But I think that the three
2 talks by Dr. Stegall, Dr. Nickerson and Dr. Mannon
3 all seem to indicate that IF/TA inflammation,
4 fibrosis were pretty prognostic of a failed graft,
5 especially when you include decreased GFR. That's
6 a sick kidney and that's going to go on to fail.
7 And I think that that data is very important for
8 us to know and to understand because the actual
9 cellular and biochemical means by which this
10 happens may be a little bit confusing. But we now
11 have enough data to show that the pathologic and
12 functional parameters do predict eventual late-
13 graft failure.

14 DR. ALBRECHT: Is there a question from
15 the floor?

16 DR. LEVEY: Yeah. Hi. My name's Luke
17 Levey. I'm from GSK. My question is how robust
18 do you think the data is that delayed graft
19 function follows through into increased levels of
20 inflammation and fibrosis and then onto reduced
21 graft survival? And how do you reconcile that
22 with one of the Kaplan- Meier charts that somebody

1 showed this morning showing that DCD and DBD
2 transplant lifetimes were very similar? And so,
3 we've talked about DGF rates as being, you know,
4 one of the factors that might play into this
5 subclinical inflammation. I just am really
6 interested to hear the thoughts of the panel on
7 that point.

8 DR. HARIHARAN: Yeah. Harry Hariharan,
9 from Pittsburgh. I will be showing some data on
10 delayed graft function and its impact on short-
11 term and one-year renal function. I think if you
12 go into the literature, delayed graft function is
13 an important variable which is associated with a
14 lower graft survival. We know that. And coupling
15 delayed graft function with a de novo DSA or
16 patients with T cell rejection, it's really a risk
17 factor. I'll show some data. I think the most
18 interesting part of the delayed graft function,
19 which is very similar to the native kidney
20 disease, acute kidney injury and rapid fibrosis.

21 So we have some data to show when
22 patients have delayed graft function, if you do a

1 biopsy around the time the inflammation's code is
2 there but the fibrosis code is not much. But when
3 you biopsy them again in a few months, I'm talking
4 about three months, you have a progression to
5 chronicity which is very rapid. So there is a
6 problem and there is also an opportunity what we
7 can do for that subset of patients.

8 With the current organ allocation, I
9 think Dr. Mannon already alluded to increased
10 delayed graft function. It's not a problem. It's
11 an epidemic. We have kidneys flowing from Houston
12 or California to Pittsburgh or vice versa. It's a
13 huge problem. And we can tackle and talk about
14 more about delayed graft function later. Thank
15 you.

16 DR. NICKERSON: Yeah. I mean, I think
17 this is just a comment about DGF, the absolute
18 effect of the biological mechanism by which it's
19 leading to an impact on long-term graft outcome.
20 I don't think we really understand that, that
21 well. However, it's a consistent finding across
22 many different databases, that if you have that

1 event, it does strongly correlate with long-term
2 graft function. Now, possible mechanisms, I think
3 as harry just said, that it could be leading to
4 accelerated fibrosis. And that may be even more
5 true when you start looking at things like donor
6 age and how that's factoring into it. The older
7 kidneys seem to be doing poorer, sustaining that
8 kind of injury.

9 And then, there's some nice studies,
10 starting to link in the whole concept of
11 allorecognition through the innate immune system
12 and whether ischemia reperfusion injury or
13 inflammation associated with brain death can be
14 leading to alloactivation within the innate immune
15 system leading to starting to stimulate the
16 adaptive immune system. But again, these are more
17 speculative as opposed to demonstrative.

18 DR. MANNON: I mean, there's a lot of
19 older data. Ojo [ph] published a study in '98
20 that shows the combination of acute cellular
21 rejection, which frequently comes hand in hand
22 with DGF. And the main reason we find it is

1 because you have persistent graft dysfunction and
2 the surgeon says is this rejection. And often,
3 you find it is because maybe you were reluctant
4 with their Prograf.

5 Maybe there is -- I do agree that
6 there's an innate immune response that does
7 crosstalk into adaptive. I do think that if you
8 come in with a kidney that's not the best kidney
9 and your basal -- and your baseline GFR when the
10 injury resolves and you have a GFR below 30,
11 you're not going to do well. And I think that, you
12 know, attacking that problem -- you know, I think
13 the way the current clinical trials are going is
14 just looking really at the immediate effect, much
15 like a lot of the animal studies do, is your
16 creatinine back by day seven down and they don't
17 look out a year. I don't think that's
18 unreasonable right now, for now. But that
19 certainly is an issue. You know, and I see a lot
20 of people at the mics. I'll shut up because I
21 know the European cohort has -- European groups
22 have done a lot in terms of looking at pumping and

1 graft preservation, brain death.

2 DR. STEGALL: My thought about DGF as a

3 surrogate is that its connection to graft

4 survival, it's pretty remote. And so, using this

5 as, you know, a concept, I don't know what the

6 power calculations would be. It's probably pretty

7 daunting to show, you know -- so you have less DGF

8 and a drug gets approved because it's less DGF.

9 And then, you actually then have to go on and show

10 that as increased graft survival in the lower DGF

11 arm. And I don't know if the connection is enough

12 to really make me want to go down that pathway

13 very -- you know, with a lot.

14 I think that you could include DGF

15 patients in subclinical inflammation studies. I

16 would say that would be okay to do, with some

17 trepidation, not knowing what the outcome would be

18 in those patients if in fact you got rid of the

19 inflammation. There could still be other

20 processes going on that could cause graft loss

21 that you could not necessarily -- may not even be

22 impacting. I always kind of think of the unusual

1 pathways which always seem to occur when we don't
2 know the answer completely.

3 DR. ALBRECHT: Let's go ahead to another
4 question. Oh, go ahead.

5 DR. HARIHARAN: (Off mic.) Sorry. The
6 question for the whole group is we are now -- are
7 we here to identify newer endpoints? Endpoints
8 are very definite: graft loss, patient death. Or
9 are we here to look for an alternative surrogate
10 marker or a newer surrogate marker which can
11 potentially correlate with the graft --
12 significant graft dysfunction, as you mentioned,
13 or graft failure. I think that's an important --
14 we need to focus on, in my opinion, an alternative
15 surrogate marker.

16 DR. ALBRECHT: Floor mic?

17 DR. KLUPP: Thank you very much. Jochen
18 Klupp. Novartis, in Basel. It was great to hear
19 all the presentation and the summary, and
20 congratulation to this. It's also good to see
21 that we basically focused on a central issue, the
22 subclinical infiltration, which is a phenotype.

1 And the etiology was very variable and there are
2 many underlying reasons.

3 So my question here to the panel is what
4 do we want to focus on and what do we want to
5 solve? Do we want to improve patient care
6 individually or are there some areas, maybe like
7 the last two presentations, but certainly also
8 others. Are there other areas where we want to
9 change medicine for the overall population on
10 that?

11 DR. O'CONNELL: I'll just say from the
12 clinical perspective, I think in the big picture
13 because it's sort of a big picture question, is
14 that if, in 20 years' time, we want to be using
15 tacrolimus, mycophenolate and prednisone, then we
16 should continue what we're doing because there's
17 no conceivable way that we're going to get better
18 one-year graft survivals than what we've got and
19 the non-inferiority studies is not going to cut it
20 financially in the modern economic world. So it's
21 not big brother pharmaceutical companies. It's
22 just not going to work. So what we want to do,

1 and we all say that, that no one's worried about
2 whether or not we can get a graft to survive a
3 year. It's whether we can get a graft to survive
4 five years or 10 years, to be honest.

5 And that's the hard endpoint, that can
6 we get better 10-year graft survival, five-year
7 graft survival for our patients. And therefore,
8 what we're trying to do is do we take a subgroup
9 of patients, which I think we're all certainly
10 saying we can't just take -- everyone's not the
11 same. People have got different risk factors and
12 we need to identify what those are. And what
13 markers can you measure at one year that's going
14 to accurately predict a better outcome, a hard
15 outcome long-term because you can -- if it looks
16 good and it has less fibrosis and a better GFR,
17 but if we don't have a better hard outcome, then I
18 think that's not going to pass muster with the
19 regulatory authority. So that's thinking as a
20 clinician.

21 So the question I have after that is
22 what hard outcome -- what are the hard outcomes

1 we're willing to accept ourselves. Is it five-
2 year or 10- year graft survival or composite
3 survivals? What's the composite hard outcome
4 we're willing to take? And what surrogate --
5 what's the patient population that we're doing and
6 what's the surrogate for that patient population?
7 So I think in my head, if I think of it that way,
8 then that's what we're trying to change, is how we
9 get to better -- you know, a better clinical trial
10 design.

11 DR. NICKERSON: You know, I think you
12 have to get to five years before you can get to 10
13 years. That's usually what I always say. And so,
14 the real nut of the question I think you're asking
15 is what's -- maybe what's the path forward, right?
16 What do patients really need? And I think that if
17 there was just one instance where we got a drug
18 approved for a Subpart H, that would be a victory.
19 And that's a mechanism that needs to be in place.
20 And I think that's kind of the conversation we're
21 trying to have. Whether or not pharma then would
22 find it in their armamentarium to find a drug that

1 would actually work is probably another piece.
2 And whether a billion dollars was worth it and you
3 had it instead of \$20 billion, that was another
4 question that we had for you.

5 But, and then the transplant community
6 has to speak, I think -- work together to move
7 toward that consensus of what we actually think
8 the problems really are that we can fix. And
9 yeah, sometimes the 10-year problems, you're not
10 going to intervene at two weeks. I kind of think
11 that's probably not going to happen. I would
12 think that as the problems arise, you might find
13 solutions for them as they -- you know, at an
14 appropriate earlier time point. So that would --
15 so I'm thinking is that -- does that help at all?
16 Is that what you're thinking? Or maybe I missed
17 the question.

18 DR. KLUPP: Well, my question is
19 basically what do we want to fix. I understand
20 the holistic view and where we want to go on this
21 one. But what is the biological entity we want to
22 solve? So if we don't prioritize in a certain way

1 that maybe it's nonadherence. Maybe this is
2 something which will make a big difference. Maybe
3 it's another reason for the deterioration of the
4 graft function. But I believe we need to have a
5 biological focus on something where we can work
6 towards and where we can develop because
7 otherwise, if it's holistic, and if we basically
8 say we want to improve for those 15 percent of the
9 patients the outcome, then it may easily become a
10 fishing expedition. And then, the likelihood that
11 we can support it is -- or that we can move
12 forward and solve it is just getting lower.

13 DR. ALBRECHT: Thank you. Perhaps we
14 can revisit that question later. Can we take one
15 last question? And then, we have three more
16 discussion sessions during the meeting. So for
17 those that didn't have a chance to ask now, please
18 come back at the next session. Dr. Budde?

19 DR. BUDDE: So we thought that this
20 problem starts at one year. And we heard that
21 maybe there's under-immunosuppression. But we
22 heard also there's speakers that always use

1 different levels and different drug levels. So the
2 question is, what is the right immunosuppression
3 at one year of our maintenance patients and do we
4 have sufficient data to support this to start
5 with? The second question would be to the
6 desensitization people. Okay, now we see that
7 desensitization doesn't really give good results.
8 The question is would it be an alternative to
9 improve the quality of the dialysis in the United
10 States to levels we see in Japan. And then, of
11 course, we have much better survival for all
12 patients.

13 DR. ALBRECHT: Thank you.

14 DR. NICKERSON: So maybe I'll make a
15 comment and to the first part, which is I don't
16 think we know what the right amount of
17 immunosuppression is. And I would argue it from
18 two points of view. There's no clinical trial
19 that's really talked about good drug levels beyond
20 a year, with any data that's robust. We -- and
21 so, I think that's a major unmet need, is
22 understanding what is good maintenance

1 immunosuppression, not for a year but actually for
2 the next 15, 20 years, if that's our real goal, to
3 get a graft to last that long.

4 And we saw -- and as I showed you, that
5 the 75 percent are going to do well. But of that
6 group, there's a group that's going to be over-
7 immunosuppressed in that group. And so, what we
8 really would like to do is target or personalize
9 our immunosuppression. And I don't think we know
10 how to do that at this point in time because if we
11 overdo it, we're going to get bad outcomes. If we
12 underdo it, we also know that we're dealing with
13 the alloimmune system and we're going to get bad
14 outcomes. And I think that's the real tension of
15 what we're dealing with. And we don't have a clue
16 beyond -- you know, we know how we do for a year.
17 But we have no idea beyond a year what is
18 optimized immunosuppression.

19 DR. ALBRECHT: Dr. Jordan, last comment?

20 DR. JORDAN: Yeah. I'd just like to
21 comment on the -- on your question about improving
22 dialysis. Certainly, we love that and welcome it.

1 But under the best of circumstances, dialysis has
2 been characterized as a very expensive therapy
3 with poor outcomes. And it's about \$95,000 per
4 year to maintain a patient on dialysis in the
5 United States, under the best of circumstances.
6 So I think anything we can do to improve
7 transplant rates and longevity of our patients
8 would be well-advised.

9 DR. ALBRECHT: Thank you. Now, I'd like
10 to introduce Dr. Ozlem Belen, who will introduce
11 the speakers in session two.

12 SESSION 2: SURROGATE ENDPOINTS AND
13 BIOMARKER EXAMPLES FROM OTHER
14 THERAPEUTIC AREAS

15 DR. BELEN: Hello. So this is session
16 two. We're going to discuss surrogate endpoints
17 and biomarker examples from other therapeutic
18 areas. Our first presenter is Dr. Tom Fleming.
19 And he's going to discuss traditional and
20 surrogate endpoints, principles and examples.

21 TRADITIONAL AND SURROGATE
22 ENDPOINTS: PRINCIPLES AND EXAMPLES

1 DR. FLEMING: Can you pull up the
2 slides? So, let me get started while we're
3 pulling up the slides. This has been a great
4 discussion. In this session, we're going to try
5 to draw on some experiences that we have had in
6 other clinical settings about traditional
7 endpoints and replacement endpoints and successes
8 and failures and being able to try to streamline
9 drug development by, in essence, using replacement
10 endpoints or surrogate endpoints. So my key focus
11 here is going to be on four principles for us to
12 consider as we try to identify surrogate
13 endpoints.

14 So as we know here, our goal is we've
15 got important endpoints here. We've got patient
16 survival. We've got graft survival. We have
17 acute rejection. We've talked about wanting to
18 understand how to improve that in 5 and 10 years.
19 But we don't want to take 5 and 10 years. We want
20 one and two- year trials. We want feasible sample
21 sizes. We've heard a lot, and we're going to hear
22 a lot more about potential candidates that we have

1 for replacement endpoints, histologic measures,
2 fibrosis, inflammation, DSAs, GFRs, and everybody
3 liked the concept also of looking at combinations.

4 So in essence, when I think about
5 choosing an endpoint in a registrational trial, I
6 think of several criteria. It would be preferable
7 for these to be easily measurable and not to have
8 an invasive measurement in order to be user-
9 friendly to the patients and to now have laws to
10 follow-up. Sensitivity is key. Measures should
11 be well-defined and reliable.

12 If we're looking at an antibiotic in
13 pneumonia, if we approach the patient 10 days
14 after finishing the course of antibiotics and we
15 say, do you feel better, well, it seems like a
16 good thing to feel better. But is it because the
17 radiologic exam has improved? Is it because their
18 temperature has gone down? Or what it really --
19 what we really want, have we addressed their
20 symptoms, their breathlessness, their coughing,
21 their chest pain, their prolongation and survival.

22 The key is we want a clinically

1 important measure to the patient. Feels, functions
2 and survives, or an alternative replacement
3 endpoint that reliably captures that. I could use
4 any disease rea. I'll use pulmonary arterial
5 hypertension to illustrate this concept. Feels,
6 symptoms, symptoms pain. That comes from the
7 patient. Therefore, we need patient-reported
8 outcomes. A great guidance document from FDA on
9 basically identifying patient-reported outcomes
10 and validating them. Functions, that's not
11 physiologic functions. That's the ability for the
12 patient to carry out normal activities, to be able
13 to engage in recreation, self-care, et cetera.

14 Not much controversy, I hope, that this
15 is about the patient. We want them to feel
16 better, function better and live longer. But in
17 any disease area, and certainly in ours, we're
18 looking for study endpoints that will allow us to
19 do trials in a shorter timeframe and a smaller
20 sample size. Hemodynamic measures is what we try
21 to use in PAH. We use pulmonary arterial
22 pressures, cardiac output, or the ratio of that,

1 which is pulmonary vascular resistance index.

2 A great document by IOM that's really a
3 core document for this meeting, and that is what
4 do we need to do scientifically to validate
5 biomarkers as replacement endpoints. Biomarkers,
6 as they define them here, are very broad and do
7 include all of what we're talking about here,
8 histologic measures, measures of inflammation,
9 DSAs, GFR.

10 This slide is an attempt by several of
11 us to put in a single slide the essence of the
12 kinds of endpoints that we encounter across
13 disease areas. Over here on the left are the
14 direct measures of feels, functions, survives.
15 Feels, the patient. Chest pain, dyspnea, fatigue,
16 dizziness, function -- or the clinical, clinical
17 global measures. The observer, seizures, stroke,
18 death.

19 Over on the right-hand side are the
20 indirect measures that can streamline drug
21 development. In the middle are proximal measures.
22 In PAH, we've used six-minute walk. We've

1 registered on six-minute walk. But the fact is
2 how much further do you have to walk in six
3 minutes to know that I can cross the street before
4 the light changes, that I can carry out normal
5 activities, that I can go shopping. It's an
6 indirect measure. Even more indirect are
7 biomarkers. Every disease area has them. I'm
8 mentioning PAH.

9 PVRI, so what's the typical approach to
10 validate one of these measures? We find a measure
11 like PVRI and we show that it's correlated with
12 what people care about over here on the left.
13 It's correlated with direct measures of feels,
14 functions, survives. Then we show we have an
15 effect on PVRI. We show that we increase PVRI.
16 We improve PVRI. And then, we make the leap of
17 faith that hopefully that means that we're
18 improving outpatients' feels, functions, survives.

19 A little bit of logic. It's post hoc
20 ergo propter hoc, or for those who don't know
21 Latin, after this, therefore because of this.
22 Well, often that fails. So in essence, if you

1 have a biomarker that's correlated, you do know
2 something important if you have an effect on that.
3 You know it's biologically active. But it's not
4 necessarily evidence directly that you've improved
5 how patients feels, functions, survives or a
6 correlate does not a surrogate make.

7 So in essence, how do we explain this
8 paradox. There are four key principles. The
9 first is a disease may causally influence the
10 biomarker and causally influence feels, functions,
11 survives. Not surprisingly. They're correlated.
12 But if that biomarker isn't in the
13 pathophysiological pathway by which the disease
14 process influences a clinical endpoint, an effect
15 on the biomarker won't predict an effect on feels,
16 functions, survives.

17 Mother-child transmission of HIV. You
18 have a pregnant woman infected with HIV. Her CD4
19 count is incredibly correlated with transmission
20 of HIV to her infant. Lower her CD4 count, more
21 likely transmit. Well, we can give her IL-2 in
22 the eighth and ninth month of her pregnancy, spike

1 her CD4 count 100 to 200 cells. What will that do
2 for the clinical endpoint? Nothing. We tried it.
3 What we need it to do was suppress her viral load
4 two or three logs. That would have made a big
5 difference. We'll talk in a little bit about
6 viral load as a validated surrogate.

7 In cancer studies, we use CEA in ovarian
8 cancer. PSA, men monitor their PSA. It's
9 correlated with prostate cancer symptoms and
10 death. But it's not the causal reason why you have
11 prostate cancer symptoms and death. So as a
12 correlate, it's perfectly useful for diagnosis and
13 prognosis. It's not useful as a replacement
14 endpoint as a surrogate.

15 Now, second issue. Suppose that you do
16 have the biomarker on the causal pathway. Suppose
17 this green arrow exists. Second problem, there
18 are multiple pathways that the disease process can
19 use to influence the endpoints. This has been a
20 great discussion today about understanding these
21 issues in our setting. If the biomarker on this
22 green pathway isn't the only pathway, if there's

1 another principal yellow causal pathway not
2 captured by the biomarker, you can get on the top
3 false positives or on the bottom false negative
4 conclusions. Example of the bottom, chronic
5 granulomatous disease. Children with a compromised
6 immune system. Thought was give them gamma
7 interferon, stimulate the immune system. We don't
8 want to do a placebo- controlled trial for years
9 in little children. Let's just look at the effect
10 of bacteria killing and superoxide production.

11 Well, the issue was, yes, that would
12 make the trial smaller and shorter. But we may
13 not get reliable results. I was the chair of the
14 monitoring committee. The study was done with the
15 clinical endpoint of recurrent serious infections.
16 We terminated the trial early with impressive
17 results of a 70 percent reduction in recurrent
18 serious infections. What was the effect on the
19 biomarkers? No detectable effect. If we had
20 taken the shortcut, these kids would have missed a
21 very significant important advance. At the bottom
22 here, gamma does work on recurrent serious

1 infections, not detectable by bacterial killing.
2 Either it did through that mechanism but wasn't
3 detected or maybe it was antibiotic uptake or some
4 other mechanism.

5 At the top, what about false positive
6 conclusions? Throughout the '90s, I served on the
7 Vaccines and Related Biological Products Advisory
8 Committee for FDA. During that time, we had I
9 think four applications for a cellular pertussis
10 vaccines. One of the key studies was a 10,000-
11 person study. Sweden 11, where a third of the kids
12 were given DT control, a third had the SmithKline
13 pertussis vaccine added to it and a third had an
14 Aventis Pasteur added to it.

15 The key measure that we all wanted, we
16 wanted to stimulate the immune system. We wanted
17 FHA and PT antibody responses. That would allow
18 the studies to be much smaller. SmithKline was
19 superior in those antibody responses. Yet when
20 you looked at what patients cared about, which was
21 the actual rate of pertussis, the SmithKline was
22 58 percent protective. The Aventis Pasteur, 85

1 percent protective. The Aventis Pasteur had other
2 mechanisms on the yellow pathway. Plus, there's
3 the issue of durability and magnitude of effect.

4 That brings us to the third critical
5 principle. Even if you have the right pathway,
6 what's the magnitude and direction of effect that
7 you have to have? Classic example, if you have an
8 MI, you need a thrombolytic, clot-buster to
9 restore TIMI blood flow, normal blood flow for the
10 clinical benefit of reducing 30-day mortality.

11 TPA was standard. RPA came along. We did a small
12 trial called RAPID 2. RPA beat TPA on 60 and 90-
13 minute blood flow.

14 That should be good enough, right? FDA
15 came back and said, nope, we want a direct study.
16 FDA's pretty wise. Fifteen thousand people it
17 took. That direct study, GUSTO-III, said, you
18 know what, TPA is better. So we went back and
19 looked at RAPID 2, went back and looked at RAPID
20 2. Yeah, TPA was better than RPA at 30 minutes.
21 So even if you have -- and we do know in this
22 setting the correct causal pathway. How do you

1 know the magnitude and duration of effect you have
2 to have to translate to clinical benefit?

3 Fourth principle, and maybe the most
4 important. If a treatment does what you want,
5 those white dotted lines, it's awfully optimistic
6 to think that it won't have off-target pathways
7 that affect the endpoint, the orange pathways that
8 aren't captured by the biomarker. We could spend
9 all day talking about those examples. One
10 classic, if you have an MI and you have a
11 ventricular arrhythmia, you are at greatly
12 increased risk of sudden death. We can do
13 something about that. We can give you anti-
14 arrhythmic drugs that suppresses those
15 arrhythmias. That's a pretty compelling argument.

16 We had hundreds of thousands of people
17 in this country receiving encainide and flecainide
18 to suppress arrhythmias because that's a risk
19 factor for sudden death. Well, finally we did a
20 placebo-controlled trial, 2,000 patients, shocking
21 cardiologists. Yes, we suppressed the
22 arrhythmias. We're tripling the death rate. So

1 yes, we did suppress arrhythmias. It's a good
2 thing causally impacting survival. But what about
3 the orange pathway? Just recently, all of these
4 bold examples are recent examples of off-target
5 effects for interventions that did what we wanted
6 them to do, but the net effect on irreversible
7 morbidity and mortality was in the opposite
8 direction.

9 So how do we validate replacement
10 endpoints? We validate them by having sufficient
11 evidence that the net effect of the intervention
12 on that replacement endpoint reliably predicts the
13 net effect on feels, functions, survives, or for
14 Subpart H, reasonably likely. So in essence, what
15 do we need? We need -- this is -- the discussion
16 has been absolutely on target so far and will be
17 in the third session as well. We need to
18 understand the causal pathways of a disease
19 process and the interventions of intended and
20 unintended effects. Let me illustrate this with
21 torcetrapib. Major success had been statins.
22 Statins in acute coronary syndrome that affect

1 LDL, that affect your lipids and have the
2 clinically important benefit of reducing MI and
3 death rate.

4 Okay. Interest was let's add
5 torcetrapib to atorvastatin and have further
6 benefit. That was the concept. What the endpoint
7 was in principle was let's -- well, statins are
8 good in lowering LDL. Let's raise HDL. So what
9 actually happened? In the trial, torcetrapib had
10 a marvelously positive intended effect on raising
11 HDL. It was even better in combination than
12 atorvastatin in lowering LDL. And the data
13 monitoring committee terminated the trial early
14 because we had increased death. Well, we hadn't
15 factored in the orange. We didn't factor in that
16 it activated the renin-angiotensin system,
17 increasing blood pressures, which you don't want
18 to do. And that was more potent than what we
19 wanted to do. And the net effect was negative.

20 So even if we know the white pathways
21 and we do what we want, the biomarkers are
22 measuring what we want. It's the patient that we

1 care about, which experiences the totality of the
2 effect, including the orange, off-target effects.
3 So in essence, what do we need? It's not enough
4 to show that we have measures that are correlated
5 on a patient-specific basis. We need to
6 understand what are the principal causal pathways.
7 Is this biomarker on the principal causal pathway
8 of the disease process? And we need to understand
9 the net effect. There are a lot of insights that
10 can get us toward that goal. But that's a huge
11 task. Scientific statistical evidence from meta-
12 analyses are often invaluable as additional
13 evidence.

14 So let's talk about the antihypertensive
15 study to illustrate this. I was on cardiorenal
16 advisory committee in June of 2005. We were asked
17 the question similar to what we're asking today.
18 Do we have to do large-scale trials to validate
19 the effect of these agents on stroke and other
20 clinical measures? Can we just use blood pressure?
21 Here's the data that we were presented. Along the
22 x axis is the effect on blood pressure. How many

1 mm/Hg increase do we have. The y axis is the
2 clinical endpoint. The key here is each dot is
3 not a patient. We don't get at surrogacy by
4 patient-specific correlations.

5 We talk about this in oncology all the
6 time. Suppose you folks over here have tumor
7 shrinkage. Suppose you don't have tumor
8 shrinkage. And suppose you guys live longer than
9 you do. Well, that's wonderful. That means we
10 don't have to do a survival trial in cancer. We
11 just have to look at improving the fraction with
12 tumor shrinkage. Well, wait a minute. We don't
13 know from that correlation the direction of
14 causality. You may have lived longer mediated
15 through your tumor response.

16 On the other hand, your immune system
17 may have been more intact, which was the causal
18 reason you lived longer and also the causal reason
19 why you responded to therapy. All I was doing
20 with therapy was putting a label on those who
21 would have survived longer anyway. So these
22 points here are not patients. Each dot here is a

1 mega-patient clinical trial. And what this
2 analysis showed is the net effect of treatment on
3 blood pressure, x axis, predicted the net effect
4 of treatment on the clinical endpoint.

5 Now, we're not going to do this. But
6 they did this in 500,000 patients. Why so many
7 patients? Well, they did a separate validation of
8 the relationship of net effect for net effect on
9 low-dose diuretics, beta blockers, ACE inhibitors,
10 calcium channel blockers and ARBs because each
11 class of agents could have different orange off-
12 target effects. Interestingly blood pressure was
13 correlated in patient-specific correlations with
14 all of those endpoints at the bottom. Yet the
15 effect on blood pressure did predict the effect on
16 stroke. Only moderately MI and cardiovascular
17 death. Not so well mortality and terribly on
18 heart failure.

19 Another example, in the cancer setting,
20 if you have -- and colon cancer is highly curable.
21 If the surgeon does a complete excision of your
22 colon cancer and the margins are clear but the

1 tissue that's removed has positive nodes, you've
2 got a 50 percent chance of recurrence and death
3 within five years due to undetected microscopic
4 residual disease. So we give adjuvant therapy.
5 The question is in that setting, same as ours, we
6 have like a five-year endpoint. We have the same
7 kinds of mortality risks as you're talking about
8 here. Do we need to do longer, large-scale
9 trials? Same challenge. Or, can we use shorter
10 endpoints? The endpoint that was proposed there
11 was recurrence, the recurrence of detection of
12 disease post-surgery. And it works beautifully
13 when you look at this plot. We had 18 pairwise
14 comparisons. Started with a lot of work at Mayo
15 on five of view [ph] potentiated interventions
16 that shows that the effect on recurrence-free
17 survival predicts the effects on survival. A
18 validated surrogate.

19 But I often say surrogates work best
20 where you need them the least. In essence, what
21 do I mean? I'm treating here. The goal is
22 survival. The surrogate, recurrence-free

1 survival, so the same as survival in patients who
2 don't recur. And in those who recur and die soon
3 after, it's very close. What I want, what we want
4 here is a treatment with a short-term biomarker
5 that's going to predict a long-term endpoint.
6 That experience across history, that is an
7 extraordinarily difficult achievement, to be able
8 to have a short-term biomarker we can use at 18
9 months or 12 months to predict an effect at five
10 years and 10 years.

11 The IOM document said critically
12 evidentiary assessments. We need not just
13 patient-specific correlations. We need data sets
14 that tell us the net effect of these interventions
15 on our proposed biomarker predicts the net effect
16 on the clinical endpoint. And they also said
17 context of use matters. What do they mean by
18 that? A replacement endpoint cannot be deemed as
19 a genetic surrogate for a particular disease. For
20 example, Q coronary syndrome, I mentioned it.
21 Statins, we 've approved them now based on LDL.
22 So now you have a new non-statin intervention.

1 Can I use LDL? Seems like you should be able to.
2 We use them for statins. IOM is saying, but wait
3 a minute, maybe the statin affected other pathways
4 like HDL and all and your new agent doesn't or the
5 statin has a large and robust effect on LDL and
6 yours doesn't or yours activates the renin-
7 angiotensin system, causing blood pressure
8 increases and the statin didn't.

9 IOM is saying to FDA, FDA thought IOM
10 was going to come back and say make more robust
11 use of biomarkers to reduce the size of trials and
12 duration. IOM came back and said the opposite.
13 FDA, be responsible to ensure that we're
14 protecting the public if we're allowing agents to
15 be assessed purely on biomarkers. Basically, do
16 we need them? We know why we need them. We want
17 timely answers to give patients a choice. But
18 wait a minute. We want reliable and timely
19 answers. It's not about giving patients a choice.
20 It's about giving them an informed choice.

21 So correlates. We will discover a lot
22 of correlates. They are invaluable. Correlates

1 can be used to help us diagnose the disease,
2 assess who to transplant, assess the prognosis of
3 patients who've been transplanted. They can be
4 used as measures of biologic activity to establish
5 plausibility of effects, to validate whether we
6 should go on to Phase III trials. But the real
7 clinical utility of biomarkers are as replacement
8 endpoints, as I've just mentioned, and in
9 enrichment. We talk about this in oncology all
10 the time, using genetic signatures to tailor and
11 to identify the right patients for the right
12 treatments. In oncology, for example, eGFR
13 inhibitors are used in third-line colorectal
14 cancer to moderate benefit until we discovered
15 that the genetic characterization KRAS
16 distinguishes the sensitive benefited patients,
17 the wild-type patients from the mutant patients
18 who don't benefit.

19 Now, the issue is you can't do that by
20 just treating everybody with your eGFR inhibitor
21 and seeing who survives longer because that's just
22 a prognostic factor. That could be true in the

1 untreated patient. I need randomized controlled
2 trials that allow me to see whether the treatment
3 effect over control is better in the wild-type
4 patients than in the mutant patient. Or in simple
5 terms, a correlate or a prognostic factor dose not
6 an effect modifier or predictor make, just as in
7 the top, a correlate does not a surrogate make.

8 So biomarkers have many uses as IOM
9 said. The ones of greatest utility, and the one
10 at the top is the one that we're talking about
11 today, are incredibly complex in terms of being
12 able to understand what is necessary to ensure
13 that if we're moving away from showing what is
14 actually the consequence in patient survival and
15 graft survival and acute rejection, that we are
16 actually not leading the public astray in how we
17 intervene.

18 So what did you -- what did we do in
19 PAH? What we did in PAH was essentially look
20 globally. We looked at a wide array of measures.
21 The hemodynamic measures didn't serve us well.
22 With a pediatric written request, requested again

1 by the wisdom of FDA, we found that if you give
2 children higher and higher doses of sildenafil,
3 Revatio, Viagra, same agent, the higher the dose,
4 you get the better hemodynamics. And the higher
5 the death rate. And so, in essence, we have gone
6 to clinical endpoints. As I mentioned, six-
7 minute walk. But that's indirect.

8 So what we've actually gone to now is
9 this array of measures. Some are based on
10 observer-reported outcomes, death, syncope, days
11 of school missed. Some are based on clinical
12 measures, six-minute walk, New York Heart
13 Association, clinical global scores, the camphor.
14 And some are passed on PROs, SF-36, dyspnea and
15 pain measures. We have also gone to composite
16 endpoints. I'm delighted we're going to talk about
17 that this afternoon, the option of composite
18 endpoints. In PAH, we did death. We add lung
19 transplantation. That's still irreversible
20 morbidity and mortality. We add PH
21 hospitalization. That's still compelling endpoint.
22 Then we add worsening and New York Heart

1 Association six-minute walk. That gives us more
2 events.

3 But now, a chain is as strong as the
4 weakest link. Now it's a much weaker endpoint.
5 We need to think about that as we choose
6 composites. My favorite composites in acute
7 coronary syndrome, cardiovascular death, stroke,
8 MI. Every component is irreversible mortality and
9 morbidity. And then, we can also look at
10 composites.

11 The foundation for NIH is working to
12 help guide FDA in pneumonia for the development of
13 new antibodies for pneumonia, looking at a
14 composite of symptoms based on cough, pain,
15 dyspnea and sputum production. So we're thinking
16 about that now as a similar approach, a composite
17 of symptoms in PAH based on dyspnea, chest pain
18 and fatigue. So there are lots of creative ways
19 that we can go in thinking about the totality of
20 what we're doing for the patient and looking at
21 how composite endpoints could make a difference.

22 So bottom line here is, and I've loved

1 what I've heard so far, there is a great need at a
2 meeting like this and in future meetings to really
3 understand what are the actual causal pathways.
4 Not what are the correlates, not what are the CD4s
5 that are correlated with mother-child
6 transmission. But what are the viral loads?
7 What's the essence of what is in fact causing the
8 consequences to patients? Understanding those
9 principal causal pathways and the biomarkers then
10 from that understanding will flow. And then, of
11 course, we also need to be confident that we're
12 not just assessing outcomes based on what we
13 intend to do. But we have to look at the net
14 effect. Thanks.

15 DR. BELEN: Thank you, Dr. Fleming.
16 Next presenter is Dr. Cavaill He is going to talk
17 about surrogate endpoints, examples from HIV.

18 SURROGATE ENDPOINTS, EXAMPLES FROM
19 HIV: FROM CLINICAL ENDPOINTS
20 TO VIRAL LOAD

21 DR. CAVAILL I can probably give my
22 presentation without the slides. But I think this

1 will be better. Well, while I'm waiting for my
2 slides to appear, I was going to give you a talk
3 about how we've progressed from clinical endpoints
4 in HIV drug development to the use of viral load.
5 I'll be using slides courtesy of Dr. Jeff Murray,
6 from the Division of Antiviral Drug Products.

7 Okay. These are my disclosures. Very
8 well. Clinical endpoints in AIDS really consisted
9 of AIDS-defining opportunistic infections and
10 other conditions, infections, viral, fungal,
11 bacterial, parasitic and mycobacterial, as well as
12 syndromes such as wasting syndromes and
13 malignancies. These standard definitions were
14 established by criteria often made by collective
15 groups such as the AIDS clinical trial group.
16 Usually, the first occurrence was only counted.
17 And the events were weighted equally, even if they
18 occurred at different levels of immune function
19 deficiency. This is illustrated in this slide
20 here where you see a spectrum of clinical
21 endpoints in AIDS with the corresponding CD4 cell
22 counts that are associated with these, 20, 200,

1 250, knowing that normal CD4 counts are 500 to
2 1,500.

3 This slide shows the evolution of
4 surrogate endpoints for HIV drug approval, going
5 early on from CD4 cell counts. We just heard
6 about p24 antigenemia and then eventually the
7 adoption of HIV RNA viral load, which the message
8 is that with time, increasing number of drugs were
9 approved with the development of this surrogate
10 endpoint. 1996 proved to be an important year in
11 this development. These are some of the clinical
12 practices -- the clinical practice of the use of
13 HIV viral load in 1996. There were several assays
14 available. There was an idea of what a
15 significant change would be, two standard
16 deviations. The HIV viral load was considered a
17 prognostic indicator of disease progression,
18 meaning that adults proceeded to CD4 cell count
19 decreases, although CD4 cell counts were probably
20 a better measure than net degree of
21 immunosuppression and maybe still used as a
22 criteria for starting treatment.

1 HIV viral load was also used for
2 assessing the response to therapy. In particular,
3 a viral rebound associated with drug resistance
4 signifies the need to change regimen. Therefore,
5 in 1996, a collaborative group was for us to look
6 at surrogate markers. It was created with
7 industry and academia and the government.
8 Sponsors FDA and NIH analyzed data to assess
9 correlations between viral load and clinical
10 outcome as well as correlations between short-
11 term viral load suppression and durability of
12 viral load response. Meta-analyses were presented
13 to a July, 1997 advisory committee. These are
14 some of the analyses that were used. Five
15 analyses in 1996 encompassed more than 5,000
16 patients, representing all kinds of -- all
17 spectrums of HIV infection with respect to CD4
18 cell counts -- for example, on the right side, 20
19 to 200 -- different types of regimens in the third
20 column.

21 The next few slides will speak about the
22 association of viral load reduction and clinical

1 benefit as measured by looking at the magnitude of
2 reduction, the nadir of reduction and the duration
3 of reduction. In a pooled ACTG study with a
4 thousand patients, we have on the y axis the
5 adjusted relative risk of disease progression, and
6 on the x axis, the week 24 HIV RNA reduction. The
7 message is really that the greater the reduction,
8 the greater the -- well, the greater the
9 reduction, the less the progression. This looks
10 at viral load nadir. On the y axis, we have the
11 incidence of AIDS-defining diagnoses per hundred
12 patient years. And on the x axis, we have the
13 viral load nadir in four categorical groups. And
14 basically, the message here is that the lower the
15 nadir, the lower the risk or the incidence of
16 disease progression.

17 And finally here we have an analysis
18 looking at hazard ratio of progression by looking
19 -- by duration of reduction. We see in the first
20 column we have the response duration by five
21 quintiles. And in the middle, we have the hazard
22 ratio that is associated with progression compared

1 to a non- responder group. And basically, the
2 greater the duration of the reduction, the lower
3 your risk of progression. So in summary, there's
4 a lower risk of clinical progression associated
5 with HIV RNA decreases greater than 0.5 log,
6 greater reductions in HIV RNA and more sustained
7 reductions of 8 to 12 weeks.

8 Suppression of HIV RNA below assay
9 quantification is also associated furthermore with
10 longer duration of virological suppression and
11 less emergence of HIV-resistance. These data were
12 presented to the advisory committee in 1997. And
13 the committee concurred that HIV RNA is a suitable
14 endpoint for accelerated approval at 24 weeks and
15 that durability of such a response, a favorable
16 response, up to 48 weeks would be acceptable for
17 traditional approval. They also expected there
18 should be a concordance in the changes of other
19 markers such as CD4 counts that would be
20 consistent with the effect on HIV viral load. And
21 they cited the precedent for using other
22 laboratory endpoints such as cholesterol LDL or

1 hemoglobin A1c in diabetes mellitus as precedents
2 for using the laboratory marker as a surrogate
3 marker.

4 So many of these conclusions, I think,
5 would apply also to transplantation, meaning that
6 validated surrogate endpoints can substantially
7 facilitate drug development. Multiple trials,
8 large databases and other types of supporting data
9 are needed to validate a surrogate. In addition,
10 a hundred percent correlation of a surrogate and
11 clinical endpoint is not likely. Our clinical
12 endpoints are not perfectly gold -- perfect gold
13 standards. At the risk of sounding a little bit
14 judgmental, I think there still is room for
15 improvement in enrolling and treating greater
16 numbers of transplant patients under clinical
17 protocols where these data can be collected.

18 These are the selected references. I'd
19 like -- most of the slides I presented to you came
20 from the 1999 paper by Jeff Murray and his
21 colleagues. And there's also the 2002 FDA guidance
22 for industry on antiretroviral drugs using plasma

1 HIV RNA measurements, clinical considerations for
2 accelerated and traditional approval. Thank you
3 for your attention.

4 DR. BELEN: Thank you, Dr. Cavaill Next
5 is Dr. Shukal Bala. And she's going to talk about
6 FDA experience with biomarker qualification and
7 galactomannan patient selection.

8 FDA EXPERIENCE WITH BIOMARKER
9 QUALIFICATION (USE OF
10 GALACTOMANNAN IN PATIENT SELECTION)

11 DR. BALA: Thank you, Dr. Belen. These
12 are my disclaimers. I discuss the biomarker
13 qualification for an example using galactomannan
14 for fungal infections invasive aspergillosis. By
15 way of background, aspergillus is a fungal organism
16 which colonizes the respiratory tract. However,
17 in susceptible hosts, it can lead to symptomatic
18 disease and a full-blown invasive aspergillosis
19 with tissue damage and high mortality without
20 treatment. Clinical trials for invasive
21 aspergillosis have relied upon positive fungal
22 culture findings. However, the sensitivity of

1 culture is low. There's a desire to have an
2 easier, less invasive biomarker, which would be
3 perfect for use in the context of used to identify
4 patients with invasive aspergillosis.

5 The candidate biomarker, galactomannan,
6 is a polysaccharide complement which is released
7 by fungal hyphae during growth. There is also an
8 FDA-cleared test, which is Platelia aspergillus
9 enzyme immunoassay. The indication for use in the
10 package insert for the test is that the test
11 results should be used in conjunction with other
12 diagnostic procedures such as microbiological
13 culture and histological examination. By culture
14 or histology, one identifies the hyphae whereas
15 the Platelia assay detects the biomarker, which in
16 this case is galactomannan. The question one may
17 ask is if the test is cleared, do we need to go
18 through this biomarker qualification process. The
19 answer is yes. The purpose of qualification is to
20 determine whether the galactomannan biomarker,
21 measured by the cleared test, is appropriate for
22 the context of use or effect for use. In this

1 case, the question is to serve as a sole
2 microbiological criteria to diagnose patients as
3 having probably aspergillosis without having to do
4 culture or histology.

5 In the next few slides, I'll go over the
6 process and steps which were taken for biomarker
7 qualification for galactomannan. Generally, the
8 biomarker qualification starts when there is a
9 request. In this case, the submitter was mycoses
10 study group and the European Organization for
11 Research and Treatment of Cancer. The process
12 started with a letter of intent. And that was
13 followed by a submission which was based on
14 multiple publications on the Platelia assay.
15 There was a summary report which included
16 background, as well as the submitters' analysis
17 and all individual references were included.

18 The proposal for the context of use was
19 to use the Platelia assay positive results from
20 testing of serum or bronchoalveolar lavage fluid
21 to be used as a sole microbiological criteria for
22 the diagnosis of probable invasive aspergillosis.

1 In the context of patients with hematologic
2 malignancies or hematopoietic stem cell
3 transplants and specific CT findings. A review
4 team was formed which consisted for FDA medical
5 officers, microbiologists and statisticians from
6 Center for Drug Evaluation and Research as well as
7 Center for Devices and Radiological Health. The
8 review process consisted of critically reviewing
9 the available data, not only the one which was
10 submitted by the submitter. The FDA review did
11 independent literature search. Any case report
12 forms, any review papers, any study which did not
13 testing based on the Platelia assay were excluded.
14 The goal was to look for quantitative evidence of
15 correlation between the test and the outcome and
16 the context of use.

17 This is a busy slide. I'll just use it
18 to make a few points. This shows the findings
19 based on testing of galactomannan in serum.
20 Starting on the left here, these are the
21 galactomannan index or the cutoffs, which were on
22 the basis of its results were expressed. Next to

1 it are the number of samples which were tested,
2 whether single or consecutive, the number of
3 studies for which different parameters which were
4 thought to be important for evaluating the
5 results, sensitivity, specificity, positive
6 predictive value and negative predictive value.

7 The number of studies varied from six to
8 nine for these different parameters. The number
9 of patients which were tested varied and are shown
10 in red. They varied from about a hundred to less
11 than 2,000. Based on analysis, these are the
12 thresholds which were -- sorry -- which were
13 thought to be useful or appropriate for clinical
14 diagnosis. And similarly, for testing of
15 galactomannan in bronchoalveolar lavage fluid,
16 there were six studies available for the relevant
17 patient population. The number of patients was
18 less than we saw -- I showed you for the serum.
19 And these are the cutoffs which were thought to be
20 appropriate. The message I want to give from
21 these two slides is that we looked at all
22 available data to correlate biomarker with

1 clinical diagnosis for patient selection.

2 Based on our review, the draft guidance
3 was published. And here, I have listed those
4 headings and subheadings of the draft guidance
5 document. There is a use statement and conditions
6 for use. The Platelia assay, I've already talked
7 about. The patient population I've also
8 mentioned. What I have not mentioned is the
9 limitations of use of the Platelia assay. The
10 assay showed cross-reactivity with other pathogens
11 as well besides aspergillus. So other pathogens
12 were showing positive findings. A Plasmalyte
13 which is used for preparation collection of
14 bronchoalveolar lavage fluid also shows false
15 positive results in this assay.

16 So those kind of limitations were
17 pointed out in the guidance document. Under the
18 supportive information, there is a clarifying
19 statement that the findings -- the cutoffs which
20 have been -- are recommended for patient selection
21 are different from that in the FDA-cleared test.
22 And those are for clinical practice and these are

1 for research use only. There are links to the
2 CDRH website with their decision summaries are
3 posted for the Platelia assay. So here we are
4 qualifying the biomarker and not the test. But if
5 somebody else wants to measure this analyte using
6 another assay, then a comparison can be made based
7 on the performance of the assay.

8 The information I presented to you is
9 available on the FDA website if one uses the term
10 search as galactomannan reviews or galactomannan
11 guidance. I've provided a brief overview of the
12 process and components which were needed to
13 qualify a biomarker using the FDA-cleared Platelia
14 assay in the context of diagnosing probable
15 invasive aspergillosis for patient selection or
16 enrichment. That's my last slide. And with that,
17 I'll stop. Thank you for your attention.

18 DR. BELEN: Thank you, Dr. Bala. Next
19 is Dr. Yan Wang. And she's going to present
20 highlights of FDA guidances which relate to drug
21 development tools, enrichment strategies and
22 companion diagnostic devices.

1 HIGHLIGHTS OF FDA GUIDANCE: DRUG
2 DEVELOPMENT TOOLS, ENRICHMENT
3 STRATEGIES AND COMPANION DIAGNOSTIC
4 DEVICES

5 DR. WANG: Thank you, Dr. Belen. Good
6 morning. Thank you. In my talk today, I'm going
7 to highlight three FDA guidance document. For the
8 first guidance, I will focus on biomarker
9 qualification. For the second guidance, I will
10 describe the prognostic and predictive enrichment
11 strategies. For the third guidance, I will
12 briefly introduce the concept of companion
13 diagnostic devices for patient selection to
14 increase efficacy and safety.

15 The first guidance is titled
16 "Qualification Process for Drug Development
17 Tools." Three type of drug development tools were
18 covered in the guidance. they are biomarkers,
19 clinical outcome assessments and animal models.
20 In my talk, in the next few slides, I will focus
21 on biomarker qualification. Here is the
22 definition of biomarkers. A biomarker is defined

1 as the characteristic that is objectively measured
2 and evaluated as an indicator of normal biologic
3 or pathological processes or biological responses
4 to a therapeutic intervention.

5 Biomarkers are typically classified into
6 four categories. Diagnostic biomarkers categorize
7 patients by the presence or absence of a
8 particular disease. Prognostic biomarkers provide
9 information on the likely cause of disease in
10 untreated individual. Predictive biomarkers
11 categorized patients by their likelihood of
12 response to a particular treatment relative to no
13 treatment. Response biomarkers show a biological
14 response in patients after receiving a treatment
15 intervention.

16 Note that a biomarker can fit into more
17 than one category. For example, HIV viral load is
18 a diagnostic biomarker as well as response
19 biomarker, depending on the content of use. Here
20 is the concept of biomarker qualification.
21 Qualification is defined as the conclusion that
22 within the stated content of use, a biomarker can

1 behave a specific interpretation and application
2 in drug development. As illustrated in this
3 diagram, the first step in qualification is to
4 define the intended content of use, the manner and
5 the purpose of the use of the biomarker. The
6 second step in qualification is to determine the
7 level of evidence required for qualification. The
8 required evidence is driven by the intended
9 content of use.

10 Here are some examples of potential
11 content of use of biomarkers. As is the case of
12 galactomannan, diagnostic biomarkers -- diagnostic
13 biomarkers can be used for patient selection in
14 clinical trials. Prognostic biomarkers can be used
15 to enrich trials with patients who are likely to
16 have disease or worsening condition. Predictive
17 biomarkers can be used to enrich trials with
18 patients who are likely to respond to a new
19 intervention. Response biomarkers can be used as
20 an indicator of intended drug activity or a
21 monitor for toxicity or a surrogate for clinical
22 endpoint. As you may have -- you just heard from

1 the talk earlier, there are many biomarkers,
2 including HIV viral load, blood pressure have been
3 used as a surrogate endpoint in clinical trials.

4 With regard to the level of evidence
5 required for qualification, the guidance states
6 that robust scientific evidence is needed to
7 qualify a biomarker for use as a surrogate
8 endpoint. However, it does not define the
9 evidentiary standards for qualification.

10 Evidentiary considerations are described in a
11 recent publication by FDA on biomarker
12 qualification, building a multiple stakeholder
13 framework for biomarker development. Some of
14 those considerations from this publication are
15 presented in the next slide.

16 For assay considerations, analytically
17 validated method is required to obtain reliable
18 and accurate measurement. Type of data available
19 to assess the strengths of association of the
20 biomarker with its proposed clinical outcome.
21 They can be retrospective or prospective, registry
22 data and/or randomized clinical trial data.

1 Reproducibility of the data is needed. They can
2 come from multiple studies or a single large study
3 consisting of test dataset or and confirmatory
4 dataset. Finally, the use of appropriate pre-
5 specified statistical methods is important to
6 demonstrate the hypothesized relationship for the
7 content of use.

8 Recently, three biomarkers have been
9 qualified. They were submitted by either a study
10 group or consortium and involved substantial
11 collaborative efforts. As presented earlier by
12 Dr. Bala, galactomannan was qualified for patient
13 selection and enrichment of clinical trials in
14 invasive aspergillosis. Total kidney volume, an
15 image biomarker, was qualified for enrichment of
16 clinical trials in autosomal dominant polycystic
17 kidney disease. Fibrinogen, a plasma biomarker,
18 was qualified for enrichment of clinical trials in
19 chronic obstructive pulmonary disease. The
20 content of use of these three biomarkers were all
21 involved with enrichment strategies. This is the
22 topic of the second guidance, "Enrichment Strategy

1 for Clinical Trials to Support Approval of Drugs."

2 As you may already know that, enrichment
3 strategies are used in many clinical trials to
4 increase study power. Enrichment is defined as
5 the prospective use of any patient characteristic
6 to select a study population in which detection of
7 a drug is more likely than it would be in an
8 unselected population. Enrichment may also refer
9 to the analysis population with the enrichment
10 factor in the study of a broader population.

11 Prognostic enrichment strategies refer to
12 selecting high-risk patients, patients who are
13 more likely to have the outcome events or
14 worsening condition. Predictive enrichment
15 strategies refer to selecting likely responders to
16 a new intervention.

17 These slides present two clinical trials
18 of enalapril in patients with congestive heart
19 failure. They illustrated that clinical trials
20 enriched with high-risk patients need a smaller
21 sample size and a shorter study duration to
22 demonstrate efficacy. The first trial,

1 CONSENSUS, was a trial enriched with high-risk
2 patients. It enrolled 253 very ill CHF patients.
3 The patients were followed up for seven months on
4 average. And enalapril reduced the mortality rate
5 by 27 percent. As noted in that part on the top,
6 there was a large separation between the mortality
7 curve of the two treatment groups.

8 By comparison, the second trial was a
9 large and long-term trial. It enrolled more than
10 2,500 less ill CHF patients. And patients were
11 followed up for 41 months on average. And
12 enalapril reduced mortality rate by 13 percent. As
13 shown in the part on the bottom, there was a very
14 small separation in the mortality curve.

15 These slides show the example of
16 gefitinib. It illustrated that use of predictive
17 enrichment strategy can enhance risk-benefit
18 relationship by avoiding potential toxicity in
19 patients who cannot benefit from the drug.
20 Gefitinib was originally approved in 2003 based on
21 the results of a surrogate endpoint in patients
22 with advanced lung cancer and who cannot benefit

1 from chemotherapies. in 2005, FDA withdrew
2 approval because the post-marketing commitment
3 studies failed to demonstrate clinical benefit in
4 overall survival. In 2009, the result of new
5 trial were published. This was an active
6 controlled trial. It enrolled more than 1,200
7 patients with lung cancer. It demonstrated
8 superiority of gefitinib over chemotherapy in the
9 primary endpoint of progression-free survival.
10 The hazard ratio was 0.74. however, the treatment
11 effect was not consistent, as noted in the part.
12 The survival curve crossed over around month five.
13 Prior to month five, gefitinib was doing worse
14 than the control.

15 These inconsistent results were due to
16 the interaction between treatment and epidermal
17 growth factor receptor, eGFR, mutation, as shown
18 in the next slides. The part on the left were the
19 survival curve for patients with eGFR mutations.
20 For this group of patients, gefitinib performed
21 better than the control over the whole study
22 entire course. On the other hand, the part on the

1 right showed the result for the people, for the
2 patient without the eGFR mutation.

3 For these patients, gefitinib performed
4 worse than the control. Based on this finding, a
5 small pivotal enrichment trials were conducted.
6 It enrolled only patients with eGFR mutations and
7 demonstrated treatment benefit. And gefitinib was
8 approved in July, in 2015 for patients whose tumor
9 have eGFR mutations. As stated here in the drug
10 label, the eGFR mutations are detected by an FDA-
11 approved test. This test is an example of
12 companion diagnostic devices and this is the topic
13 of third guidance, "Individual Companion
14 Diagnostic Devices."

15 Companion diagnostic devices provide
16 information essential for the safe and effective
17 use of a corresponding therapeutic product. They
18 are often used to select the right patients for
19 increased efficacy and safety, as shown in the
20 example of gefitinib. And they should be
21 developed contemporaneously and they should get
22 FDA approval or clear prior to marketing. And

1 their information should be included in the drug
2 label.

3 For kidney transplantations, potential
4 future examples of companion diagnostic devices
5 may include quantitative tests for HLA antibody,
6 mean fluorescence intensity. In summary,
7 substantial and collaborative efforts are needed
8 to develop biomarkers and surrogate endpoints.
9 Use of enrichment strategies in clinical trials
10 can increase efficiency of drug development and
11 enhance risk-benefit relationship. However,
12 determination of appropriate enrichment
13 characteristic to predict response is a big
14 challenge. Thank you for your attention.

15 QUESTIONS & DISCUSSION

16 DR. BELEN: Thank you, Dr. Wang. So we
17 are going to go ahead and take questions. Please
18 state your names clearly for the transcript when
19 you do so.

20 DR. MORRIS: Randy Morris. I have a
21 question for Dr. Fleming. I was interested in
22 your education for us about the acceptance of

1 surrogate endpoints for oncology trials and drugs.
2 We didn't have a chance. We tried to get somebody
3 from the oncology division to speak here. But we
4 couldn't do that. But I'm aware that there have
5 been several surrogate endpoints that have been
6 accepted and can you tell us why and how that was
7 done?

8 DR. FLEMING: Oncology, in my view, has
9 really tried to take an evidence-based strategy to
10 this. They have some opportunities that are
11 greater than we have. Unfortunately, cancer is
12 even more prevalent than our clinical condition
13 here. But that at least gives them an opportunity
14 to develop significant evidence-based insights.
15 So it's been very specific to the indication.
16 Hematological malignancies that have very long-
17 term survival, they have accepted using complete
18 eradication on an extended basis as a measure for
19 approval. I mentioned in the adjuvant setting
20 they have validated recurrence- free survival.

21 The biggest controversy there has been
22 in the advanced disease setting where they have

1 attempted to use an evidence-based approach
2 between continuing to use overall survival or
3 using a PRO versus progression- free survival
4 which is basically their classic biomarker of
5 showing a delay in the advancing tumor burden.
6 And that is clearly getting at the causal pathway
7 in that setting. Of course, the problem is what's
8 the magnitude and duration of effect. So there
9 are still many settings in oncology where
10 patient's survival is still the endpoint.
11 Pancreas cancer, lung cancer, prostate cancer.
12 And in fact, with immune-based therapies, in
13 prostate cancer, if you use PFS, you would miss
14 effective therapies because you have early
15 advancement of the tumor. And yet, the immune
16 effect over the long-term is controlling the tumor
17 burden and improving survival. So they're very
18 much in a position where I think they're trying to
19 be very evidence-based.

20 I'll mention cardiology has the most
21 failed surrogates. But it's not because
22 cardiologists are the most ignorant. I think

1 they're the most critical. They do largescale
2 trials to establish whether or not their
3 biomarkers are valid. And in most cases, to their
4 surprise, they're not. And the last point just
5 quickly, while I have the mic, the experience that
6 we've had that our colleagues from FDA presented
7 in the HIV arena are very enlightening. We have
8 accelerated approval. Thank you to the AIDS
9 activist community that worked with NIH and FDA in
10 the late '80s and early '90s to push for
11 streamlined drug development. We did however in
12 those settings, we did clinical endpoint studies.

13 We didn't start with viral load as a
14 surrogate. We did an array of clinical endpoint
15 studies from 1985 to 1997. I was on the data
16 monitoring committee for 20 years that monitored
17 50 NIH-sponsored trials by ACDG and CPCRA, working
18 with the AIDS activists, working with industry and
19 NIH. We did those studies. CD4 failed. Viral
20 load eventually succeeded, as we saw in '97. But
21 industry collaborated together from '93 to '97,
22 after Subpart H came in and they worked together

1 to pool their information, share their information
2 on working toward the success in viral load,
3 although I'll mention context of use matters. If
4 we use viral load for a prevention trial, you give
5 a vaccine to prevent transmission of HIV and you
6 assess its efficacy by seeing whether or not you
7 eliminate susceptibility. You may miss the effect
8 of the vaccine, which is actually not to prevent
9 infection but to mount the immune system and
10 prevent the sequelae which is how a measles
11 vaccine works. So context matters.

12 DR. BORIE: All right. So it's always
13 tough to beat Randy to the mic. But, so my name
14 is Dominic Borie. I'm from Genentech, San
15 Francisco. And I wanted to go back briefly to the
16 first discussion that we had and maybe address one
17 point that we didn't have time to address that was
18 when we are looking at the population of patients
19 who are hypersensitized, I wanted to ask the panel
20 if they are aware, you know, of criteria for in
21 those patients that aside from measuring
22 sensitization that could help us inform on the

1 prognosis, you know. I'm thinking are there
2 things aside from the fact that they have been
3 already sensitized by the transplant. You know,
4 are there other factors that should be considered
5 and maybe used to better characterize the
6 population and potentially stratify the population
7 in clinical trials.

8 DR. ALBRECHT: Dr. Jordan?

9 DR. JORDAN: Yeah. From our standpoint,
10 and looking at risk for antibody rejection, one
11 thing that stands out is patients -- re-transplant
12 as the cause for sensitization. Even in those
13 patients, if they have no antibody at the time
14 that we assess them, they're at very high risk for
15 antibody rejection recall. And so, we desensitize
16 them as a matter of principle because we've had
17 very bad outcomes in patients where we've not done
18 that and the patients do not respond to standard
19 immunosuppression. So I think re-transplantation
20 is a very high risk group that one would have to
21 consider would be more at risk even if they don't
22 have antibodies at the time we assess them.

1 DR. WOODLE: So I don't know if these
2 assays are going to work out. But if you look at
3 the patients that get into trouble, it's the
4 patients that have a big plasmablast response
5 early after transplantation. And that's a
6 function of the memory B cell population. There
7 are starting to be developed assays to quantitate
8 memory B cell populations in the peripheral blood.
9 They're at very early stages. But I think those
10 are the types of markers that ought to be included
11 in your trial that are developed as potential
12 surrogates in the context of a trial. But that's
13 probably I think the most promising marker that is
14 out there right now. It's biological. The
15 problem is it's looking in the peripheral blood is
16 not looking where the action is, which is in the
17 secondary lymphoid organs. But I think it's the
18 most promising marker that's out there for any
19 upcoming trial.

20 DR. BORIE: Okay. Thank you.

21 DR. BELEN: We'll get the next question
22 from the floor.

1 DR. STOCK: Peter Stock, from the
2 University of California, San Francisco. Thank
3 you for this wonderful set of presentations. With
4 regards to the sort of combining both the unmet
5 needs and surrogate markers, Dr. Alloway, you
6 mentioned -- briefly alluded to NODAT, the new
7 onset of diabetes. And I would -- I'm just -- I'd
8 like to hear from the panel about the potential
9 use of glucose insufficiency, glucose intolerance,
10 I'm sorry, and new onset diabetes as a marker, as
11 an early marker. It certainly is an unmet need in
12 terms of our patients. They continue to suffer
13 from the development of new onset diabetes after
14 transplantation. It has been shown in study after
15 study to be correlated with death of a functioning
16 graft. So I'm -- and it certainly is a population
17 where we know the risk factors. And we could
18 enrich for them. So I'd like to hear whether that
19 -- your thoughts about that as a surrogate
20 endpoint.

21 DR. NICKERSON: So Peter, I think the
22 big problem with NODAT is definition. And that

1 you need a definition that can -- that's
2 quantitative. There's as many definitions of new
3 onset diabetes after transplant -- there's
4 multiple definitions. There's a couple of review
5 papers that have come out. One was by Roy First
6 looking at NODAT in populations of patients in
7 Astellas studies. The other one is the extensive
8 analysis done in the Astellas double-blind
9 steroid withdrawal trial. And I think those two
10 are fairly instructive as to the relative values
11 of the multiple definitions of NODAT.

12 DR. MORRIS: Yeah. Peter, I'm glad you
13 brought that up. As you know, we didn't have time
14 when we organized the workshop to include safety
15 endpoints. But it seems to me that in our
16 patients, NODAT would qualify for the way the
17 patient feels, functions, survives. So it could
18 be a primary endpoint, not surrogate.

19 MR. FOWLER: Hi. Excuse me. My name is
20 Kevin Fowler. I'm a kidney transplant recipient,
21 11 years and 1 month. And I just have one comment
22 and then two questions. I just want to say thanks

1 to Dr. Alloway for your presentation on adherence.
2 To me, it's like the elephant in the room that no
3 one really wants to address. And to that end, I'm
4 just curious what is being done, at least in the
5 short-term, to provide incentives for adherence.
6 I think they're sorely needed. I think we need to
7 provide that. I think you'll see changes in
8 behavior.

9 And then, the second is that, you know,
10 since quality of life is such a large component of
11 transplant and since there are people like me that
12 have a very good experience, others do not, I'm
13 just surprised, and maybe I've missed something.
14 But I don't see any patient-reported outcomes
15 studies, and which is, you know, curious if I'm
16 missing something. So thank you.

17 DR. ALLOWAY: That's fine. That's fine.
18 So I think I'll start with your second question
19 first. I think the opportunity for maximizing the
20 use of patient-reported outcomes in transplant
21 trials is potentially a missed opportunity. But
22 unfortunately, it's been a missed opportunity for

1 the spectrum of medicine. I think that developing
2 these outcomes cost effectively, in a way that can
3 be broadly applied has been very, very expensive.
4 And really, I guess people have been averse to
5 attempting to go down that path. But I think I
6 still would want to encourage it in our
7 collaborations with the regulatory bodies,
8 especially in relationship to this, to find a more
9 realistic approach to developing a PRO in a
10 transplant population would be hugely beneficial.

11 In regards to the elephant in the room
12 with nonadherence, we don't have a mechanistic
13 pathway. It's not sexy. It's not exciting.
14 There's not a quick test to order. However, I
15 would like to say that the cost of doing a
16 protocol biopsy, or the cost of ordering a DSA
17 minimizes the cost associated with resources to
18 impact adherence. I agree that adherence is
19 multifactorial. But I think that there are now
20 mechanisms in which we can develop reminder
21 systems to all patients and mechanism of which the
22 providers can provide follow-up care based upon

1 those interventions to a specific patient.

2 And I believe that we can individualize
3 a patient adherence regimen today more efficiently
4 than we can individualize an immunosuppressive
5 regimen. I think that when we talk about
6 combining potential databases, there are a lot of
7 databases that are out there that are available
8 now that could potentially look at tacrolimus
9 variability and its long- term impact on survival.

10 Now, granted, when you start to pull up the
11 industry- sponsored studies, many a time the drug
12 is provided during those studies, which, you know,
13 removes a big impactor of adherence.

14 But I think that there's some definite
15 progress that could be made by looking at the
16 large databases addressing adherence. The final
17 point that I'd make about that is using adherence
18 for enrichment. And I kind of didn't get to that.
19 But I mean, when we're developing these new drugs,
20 if we are not - - if we are not controlling for
21 adherence, or at least defining it in these new
22 pathways, it's such a significant portion that

1 with these minimal benefits that we may be seeing,
2 we may cloud it without our ability to define
3 adherence.

4 MR. FOWLER: Thank you. And I just --
5 one suggestion too. If CMS is not here, I would
6 just suggest in the future that we have CMS at
7 these meetings because they're part and parcel of
8 defining solutions. So anyway, thanks.

9 DR. NICKERSON: Just one more comment
10 for you. I think the other issue is that it's,
11 you know, talking about NODAT or adherence, it's
12 really why are patient nonadherent. And I think
13 they do want to minimize their drugs. And we're
14 not doing clinical trials around minimization
15 either, which is I think the other piece that we
16 really need to be thinking about. How do we do a
17 well- designed minimization trial that will allow
18 us to maybe minimize nonadherence at the same
19 time?

20 MR. FOWLER: Thank you very much.

21 DR. STEGALL: Can I just -- I have a
22 question actually. Maybe what I'm sort of hearing

1 is that other fields have made progress in this
2 area. They probably were at this table at one
3 point in their lives, right? They were at this
4 point where they didn't really know. They had a
5 few ideas maybe 30 years ago. It seems to be a
6 long time ago. And I guess the question I would
7 have for -- first off, actually from Marc,
8 because one of your slides says you need multiple
9 slides, large databases, other types of supporting
10 data. And that's good. And then, a hundred
11 percent correlation of a surrogate in clinical
12 endpoint is not likely.

13 And then, I see actually there are some
14 endpoints that were actually even suggested, like
15 size of kidneys for PKD. And I don't know how you
16 can validate that because you can't actually --
17 there's no therapy that alters it. So I guess the
18 question is what's -- where we are now, what is
19 the next step forward. Is it retrospective
20 studies? I mean, data for data's sake is a good
21 idea. But I think more of a focused data mining is
22 always a better way to approach this. So we have

1 some data. And then, what are the -- you know,
2 when we talk about specific things, that's what
3 I'm kind of getting at.

4 What do I need to go back and mine out
5 of our data to help us out for the next phase,
6 knowing full well that it may fail? That seems to
7 be the track record for a lot of these things
8 anyway. Marc?

9 DR. CAVAILL Well, first I'd like to
10 qualify the statement about a hundred percent
11 correlation between clinical endpoints and
12 surrogate endpoints. And I think this came out of
13 the discussion with my colleagues on antivirals,
14 where using viral load as -- looking at treatment
15 effect of viral load and looking at a prediction
16 of long-term outcome at the same time that people
17 are using viral load to make treatment decisions.
18 You have somebody who's meeting the endpoint of
19 change and increasing their viral load out to week
20 24. But they're going to have their regimen
21 change. So in many -- and now they have many
22 other opportunities, many other combinations there

1 too. So if you're going to be trying to look for
2 a correlation between that treatment effect and
3 today at a viral load at 24 weeks -- I mean, 24
4 weeks, with long-term patient outcome, it's going
5 to be very difficult.

6 The other point is that as we've
7 mentioned earlier today, if you can't prevent
8 rejection due to immune-related functions and so
9 forth, well, patients are going to live long
10 enough to have a heart attack or to have a stroke.
11 So if you're going to try to correlate your
12 treatment effect on some surrogate endpoint with
13 patient death where half of your death is not
14 related to transplant, those are difficult.
15 That's why I was speaking about the difficulty in
16 100 percent correlation. I did say though that,
17 yes, we do have clinical studies. We do have
18 databases there. But I'm not sure how many of
19 them really talk to each other, if they have the
20 same data standards. I think we're trying to at
21 least try and unify some data standards that would
22 allow us to do these types of meta-analyses that

1 were done. And maybe Dr. Fleming can speak a
2 little bit more about that. But this was a lot of
3 work and a lot of studies were done to get this
4 type of information and people were treating all
5 their patients under clinical protocols at the
6 time.

7 DR. STEGALL: So just to clarify that
8 point. So somewhat of a fatherly advice to us
9 then would be to try and get as much of these
10 databases that may exist in transplant to talk
11 together so that we could be mining them for
12 things we're not even sure exist right now, such
13 as high risk patient outcomes, et cetera. Again,
14 that might be -- I'm not just saying the word.
15 We're not going to go down that way. But that
16 might be a good idea, right?

17 DR. MANNON: Yeah. I need a
18 clarification. Are we talking about everybody's
19 EMR? Are we talking about datasets from
20 previously run clinical trials where companies
21 have oodles of data? Like a company I know has a
22 drug that apparently is effective against DSA

1 development. But they've not released those data
2 yet. And we keep talking about them, you know, in
3 our heads. But is that what you're talking about?
4 Because it's going to be a substantial overhaul in
5 the field to try and, you know -- with our small
6 patient population, to try to unite every EMR.
7 Maybe we could do it because there's mainly two.
8 But I'm not sure if I'm understanding that
9 concretely.

10 DR. CAVAILL Well, I think Dr. Fleming
11 can speak more about this. But I think that what
12 -- the story that I told you really -- there was
13 one of my slides that showed the multiple studies
14 that were involved, number of companies. This is
15 better described in detail in the reference
16 provided by Dr. Murray, where he explains all the
17 collaborations that happened with the different
18 drug companies that did share their data. But
19 this allowed this to happen.

20 DR. FLEMING: Yes. So both sources are
21 important. So registries are sufficient for
22 defining and validating a PRO. The validation of

1 a surrogate replacement endpoint is ideally done
2 though with randomized trials that show the effect
3 on the clinical endpoint and the effect on the
4 biomarker. Really quickly, 10 seconds each on
5 three great issues that came up. I completely
6 agree with the comment that PROs offer us an
7 option here of -- and this is what has been done
8 in PAH. If we struggle with being able to get
9 long-term results, but we care about what's
10 happening to the patient over time, we can get
11 those results in a proximal way with validated
12 PROs.

13 Second point. We've heard about the
14 importance of adherence. Absolutely, it is
15 important. In other disease settings, we're using
16 this for enrichment, for looking -- when we look
17 at interventions for antihypertensives that take a
18 long time for therapy. We want to screen people
19 in who are going to be adherent. When we're
20 looking at approaches to prevent transmission of
21 HIV, with pre-exposure prophylaxis or
22 microbicides, critical there is adherence. We're

1 using them for enrichment. We're not using
2 adherence as the endpoint. We're using it to
3 refine the design and improve the strategies to
4 give us better results.

5 And the last comment, I completely agree
6 that off-target effects can lead to really
7 clinically tangible things. One of them could be
8 the induction of diabetes. The problem that we
9 have in diabetes prevention trials is, as my
10 colleague said, defining it. If the definition is
11 based on glucose, that's a surrogate still, folks.
12 The consequence of diabetes is
13 microvascular/macrovascular complications. So
14 it's a challenge to be able to use this very
15 relevant off-target effect as part of our
16 composite, unless we have a feels, functions,
17 survives way to define it.

18 DR. ALBRECHT: I will try to keep us on
19 schedule. This is a wonderful discussion. Let's
20 continue it after lunch. Boxed lunches are
21 available in the hall. And there are hotel staff
22 available to direct folks to the other

1 restaurants. We will see you back promptly at 1
2 p.m., at which time we will resume our meeting.

3 (Whereupon, the foregoing went off the
4 record at 12:18 p.m., and went back on
5 the record at 1:04 p.m.)

6 DR. ALBRECHT: We're going to go ahead
7 and get started. My apologies. The food service
8 was fairly slow and I think some people are still
9 waiting to be served. But if you'll indulge us,
10 we'll continue. And the moderator for this
11 portion will be Dr. Ergun Velidedeoglu of FDA.

12 SESSION 3: POTENTIAL SURROGATE
13 ENDPOINTS IN KIDNEY TRANSPLANTATION

14 DR. VELIDEDEOGLU: Good afternoon,
15 everybody. Now, we have come to the third session
16 of this workshop. And we will be discussing
17 potential surrogate endpoints in kidney
18 transplantation. The third session has three
19 parts. The first part is about donor-specific
20 antibodies as a potential surrogate. And the
21 second part is about histology, kidney histology
22 findings as a potential surrogate endpoint. And

1 during the third part, we will be discussing
2 possible composite endpoints. So from here, Dr.
3 Peter Nickerson is going to be our first speaker.
4 And he will be presenting de novo donor-specific
5 antibodies and antibody-mediated rejection.

6 DE NOVO DONOR-SPECIFIC ANTIBODIES
7 AND ANTIBODY-MEDIATED REJECTION

8 DR. NICKERSON: Thanks very much. So I
9 want to build on what I had this morning as sort
10 of the framework and now talk about DSA as a
11 surrogate endpoint. And then, I'm going to also
12 talk about DSA as maybe a launching point for
13 clinical trial as well. So I think there's two
14 major points that I want to make, is I think there
15 are enrichment strategies to increase the endpoint
16 frequency of de novo DSA. And the prognostic
17 biomarker that I would use in this regard is what
18 I referred to earlier around class 2 HLA epitope
19 mismatch. And as we've been talking about, I
20 think the confounder to control for is medication
21 nonadherence. And it really requires what I would
22 argue is an objective measure to know what is

1 going on with regard to nonadherence.

2 So just an example of how it might be
3 used as an endpoint in a clinical trial, this was
4 an NIH-sponsored clinical trial, the CTOT-09
5 trial, where we had the hypothesis that in
6 patients who clinically were pristine at six
7 months, this potentially could be a low risk group
8 that we could withdraw a CNI. Given that we knew
9 that we had patients on the old days on Imuran and
10 prednisone alone, maybe this was the sub-cohort
11 that we could identify based on clinical course.
12 So these were primarily living donor transplants.
13 They had pre-transplant -- no pre-transplant
14 antibody by -- no DSA, PRA less than 30 percent.
15 They got quadruple therapy as standard of care.
16 And out to six months, they had to have a perfect
17 clinical course, no rejection, normal histology
18 and no DSA. And they were randomized two to one
19 to CNI withdrawal.

20 And essentially, the DSMB stopped the
21 trial after the first 21 patients were enrolled
22 because in the tacrolimus withdrawal arm, we had

1 acute cellular rejection in three, DSA with no
2 cellular rejection in two. They were all against
3 class 2. And we had DSA and acute cellular
4 rejection in another three. So basically, we had
5 way too many events in the withdrawal arm as
6 compared to the standard therapy arm that the DSMB
7 said you had to stop. And so, essentially, de
8 novo DSA was one of the composites in the endpoint
9 in this study in terms of a stopping rule.

10 So what predicted DSA was also an
11 interesting point. And when we looked at this,
12 what we saw was those patients developing DSA all
13 had DQ epitope mismatches above what had been a
14 predefined threshold. And those without DSA in
15 the tacrolimus withdrawal arm, one that was above
16 the threshold on a longer follow-up went on and
17 developed a DSA. One of the patients had a TCMR
18 and was restarted on CNI. So that may be why they
19 didn't develop a DSA. So basically only one
20 patient above the threshold didn't develop a DSA
21 in the tacrolimus withdrawal arm, suggesting that
22 this could be an enrichment strategy by looking at

1 epitope mismatches.

2 And the second point I want to make
3 around medication nonadherence is how to
4 objectively measure it. And this is using what
5 was already mentioned by Rita, the MEMS event
6 monitoring system. This is a trial done in
7 Minnesota where 195 patients were enrolled into
8 the trial. They were told while they were in the
9 trial to monitor for nonadherence. And despite
10 that, 22 percent had decreased adherence by 7
11 percent or more at month two. So clearly just
12 being told you're being monitored for nonadherence
13 isn't sufficient to make you take your pills. I
14 think life gets in the way.

15 But what was interesting is that these
16 patients had an increased rate of late acute
17 rejection and early graft loss. And this
18 manifested not within a few months but actually
19 within a few years. So the late acute rejections
20 largely occurred between six months and two years
21 and graft loss in this group was really starting
22 at three years to four years. So there's a

1 delayed impact of the behavior of nonadherence.

2 And I think that's another major point to take
3 into account.

4 And then, the other point that was
5 already made by Rita is we went back and looked at
6 the interaction between nonadherence and epitope
7 mismatching, showing that the worst outcome was in
8 those patients that had both nonadherence and a
9 high epitope mismatch load, suggesting an at-risk
10 group when looking at poor outcomes. Not only is
11 the epitope mismatch load correlated with antibody
12 late rejections and poor outcomes, but in this
13 study out of Toronto, they correlated it very
14 closely with thresholds that we had used with the
15 development of transplant glomerulopathy, which
16 I've already told you correlates very strongly
17 with de novo DSA formation.

18 So de novo DSA as a surrogate endpoint,
19 I think there's a few caveats in thinking about
20 study design. I think, as I made the point this
21 morning, you have to be strict in ruling out
22 preexisting DSA. And to do that, you probably

1 have to set a reasonably low threshold for MFI. I
2 would argue that we should be assessing more than
3 one pre-transplant sera because a lot of the
4 studies just look at one sera instead of maybe a
5 history of a few sera. And we know antibodies can
6 fluctuate up and down. And as already mentioned
7 by one of the other individuals here, we are
8 getting into more functional B cell assays to look
9 at immunologic memory for B cells. And maybe
10 that's also going to be a good way of making sure
11 somebody doesn't have memory before you go ahead
12 and do the transplant.

13 And then, controlling for MNA I think is
14 really an important point. It may require MEMS
15 monitoring. But you know, as I showed you in the
16 study out of Minnesota, they only needed two
17 months of monitoring to define the behavior
18 subtype that existed within the group. And then,
19 I think you could be enriching for at-risk
20 patients if that's what you want to do by
21 targeting high epitope mismatch load patients.
22 And just to give a sense of that, in the Manitoba

1 cohort, where we had an unselected population, the
2 epitope mismatch load that was below the threshold
3 for both DQ and DR was 37 percent of our
4 population.

5 So if you include those patients in your
6 study design, where you're going to use DSA as a
7 readout, those patients are unlikely to develop
8 antibody. And therefore, you're going to dilute
9 out your readout effect. Now, a lot of us
10 typically exclude zero A, B, DR mismatches as a
11 way of enriching for at-risk patients. But when
12 you do that within our cohort, still a full 30
13 percent of the cohort are below the thresholds for
14 DR and DQ epitope mismatching, suggesting that
15 that again is still going to wash out your effect
16 if you're using de novo DSA as your readout.

17 On the other hand, de novo DSA as a
18 surrogate endpoint actually may have its greatest
19 utility in clinical trials where you're looking at
20 MNA intervention studies where you know that the
21 patients who have MNA are at high risk to
22 developing an antibody. And if you randomize them

1 to an intervention, maybe de novo DSA going down
2 is actually going to put you at -- you'll see a
3 decrease in the rate of de novo DSA. So that's
4 one way of thinking about it. And then if you're
5 doing physician-guided minimization studies, like
6 we did in CTOT, clearly that de novo DSA may have
7 a better utility at that point. Otherwise, the big
8 issue is how long do you have to wait for DSA to
9 show up, which on average is quite long.

10 The second way of doing this is to do
11 what Dr. Stegall suggested around IF/TA and I,
12 where you might look at randomizing patients who
13 developed de novo DSA into a clinical trial. And
14 here, you can start thinking about enrichment
15 strategies again using prognostic biomarkers. De
16 novo DSA titer might be something, and Anat will
17 talk about that. Medication nonadherence, again.
18 Tubulitis, as I showed you, is one of the
19 predictors and Banff CG scores. And then, the
20 endpoints for that kind of trial might be graft
21 loss. And we'll talk about what that might look
22 like, or eGFR or Banff CG scores are the other two

1 surrogates that I would propose.

2 So the prognostic biomarkers, I think
3 there's a few caveats to keep in mind about the
4 DSA MFI. It's not an FDA-approved quantitative
5 assay. It may not be linearly related to outcome.
6 It's a weak correlative outcome in our study. And
7 a change in MFI may be a surrogate endpoint. But
8 it needs a prospective study demonstrating that a
9 drop in MFI correlates with improved graft
10 survival. And I think that's one of the points
11 that Dr. Fleming was trying to make in his talk.

12 In terms of MNA caveats, I think we have
13 to ideally objectively define it. I would suggest
14 using something like a MEMS cap system. Without a
15 strategy to improve adherence in clinical trials,
16 which include these patients, it may be futile, as
17 MNA may persist. So if you have a large cohort of
18 medication nonadherence and you're a randomized
19 controlled trial and you haven't done something to
20 mitigate that nonadherent behavior, then you may
21 show that your drug is useless. But that may not
22 be because it's useless. It may be because the

1 patients aren't taking the drugs in the first
2 place, right? And then, focusing on adherent
3 patients to avoid the error of a trial reporting
4 negative effect due to MNA will increase the
5 sample size.

6 So what about prognostic biomarkers
7 using microvascular inflammation? Well, what we
8 saw was MVI was present in the majority of those
9 who progress. But the grade of MVI, microvascular
10 inflammation, does not predict the risk for graft
11 loss. And this was what we had in one of our
12 supplemental pictures in our publication, that as
13 you went up to g + ptc of 1 to 2 or g + ptc
14 greater than or equal to 3, it really made no
15 difference on the graft outcome.

16 And that's in distinction to this paper
17 that came out in AJT in 2013 from the de Kort
18 study which suggested that the grade of
19 microvascular inflammation indeed did predict who
20 was going to progress to graft failure. But
21 there's differences in the studies in that we use
22 quadruple therapy with some thymo induction and

1 that onset of DSA, on average, was at 49 months
2 compared to the other study by de Kort where in
3 fact the onset of DSA on average was 3.8 months,
4 on average was 3.8 months. And they were using 90
5 percent depletion with Campath with tac
6 monotherapy with no CellCept and no prednisone.
7 So I think there's two different studies.

8 And the other problem with this study by
9 de Kort is that many of these patients, no matter
10 what the grade of MVI, actually had coexistent T
11 cell- mediated rejection either grade one or
12 higher or suspicious in the majority of the
13 patients who had the worst outcome. So I don't
14 know what made them worse, the microvascular
15 inflammation or the concomitant T cell-mediated
16 rejection that was occurring or both in these
17 grafts. And C4d did not predict graft loss
18 whereas again it was suggested in the de Kort
19 study that it might. But we actually saw no
20 benefit at all and I think may be related to the
21 same issues.

22 So what about graft survival? Well, if

1 we want to do a de novo DSA clinical trial with a
2 five-year graft survival as an endpoint, we looked
3 at sample size calculation based on our data. If
4 we took all comers of de novo DSA, an expected
5 mean graft survival would be 60 percent and to go
6 for different levels of risk reduction, you'd have
7 to enroll a fair number of patients with an 80
8 percent power and 10 percent dropout with an alpha
9 of 0.05.

10 Now, you could subdivide that into
11 clinical or subclinical de novo DSA and you would
12 obviously get a much smaller trial design required
13 in the clinical de novo DSA compared to the
14 subclinical. However, I remind you that 90
15 percent of the clinical de novo DSA patients were
16 determined to be nonadherent in our study. So
17 essentially you're looking at randomizing patients
18 who are nonadherent. And I think, as I told you,
19 randomizing nonadherent patients to a study design
20 without an intervention for adherence may be
21 futile in and of itself. So really we're talking
22 about a subclinical de novo DSA clinical trial

1 that's required. And that's clearly going to have
2 a lot more patients required in the enrollment
3 strategy.

4 Now, what about eGFR? Well, clearly the
5 FDA and CKD trials will accept eGFR as a surrogate
6 endpoint, a doubling of serum creatinine, or a 57
7 percent decline in eGFR is accepted by the FDA.
8 And in a recent position paper on AJKD, there was
9 a whole series of reports looking at using a 40
10 percent decline over two years, assuming a
11 baseline of about 50 ml/min. Now, that's
12 something we could think about in transplant
13 because most of our patients start out at about 50
14 to 60 ml/min in their eGFR. So maybe a 40 percent
15 decline. And even in this paper, they were
16 accepting at sometimes even a 30 percent decline.

17 Well, from our study, what we saw was
18 that for every 1 ml/min decrease in eGFR at three
19 years post subclinical de novo DSA onset, the risk
20 of graft loss increased by 1.06. so we looked at
21 having a subclinical de novo DSA clinical trial
22 with eGFR as a surrogate endpoint and we could

1 power it to two years or three years and looking
2 at a decline expected of 7 to 10. And then, if we
3 wanted to have a 50 or 70 percent risk reduction
4 in that eGFR decline, you can see how many
5 patients you'd require there. And so, you'd be
6 really looking at probably the 70 percent level.
7 And at three years, that would take 251 patients,
8 which would equate to about a 35 percent risk
9 reduction in graft loss at the end of the day. So
10 I think that's something that might be doable.

11 The other surrogate endpoint that I
12 think we should talk about is CG and we'll
13 probably hear more about that. And the rationale
14 for CG is it correlates strongly with de novo DSA.
15 It's infrequent at the onset of de novo DSA. It
16 increases in grade after the onset of de novo DSA.
17 And what we saw was one grade per three years
18 using the Banff schema. And it's a prognostic
19 biomarker of graft loss and that's been well-
20 accepted in the literature. The caveat is that we
21 still need a validation, as we heard about, that
22 preventing the development of progression and

1 response to treatment correlates with improved
2 graft survival. And that's what we're missing to
3 date.

4 And a key consideration, and I think Ros
5 mentioned this earlier as well, is that electron
6 microscopy in Phil's group in Westmead showed this
7 a number of years ago, may be a very useful tool
8 to detect changes with more sensitivity than
9 earlier with light microscopy. And so, I think we
10 should be thinking about if we're going to use CG,
11 using EM as a way of looking at progression of
12 these lesions around CG.

13 So potential surrogate endpoints, I
14 think de novo DSA could be a potential surrogate
15 endpoint. I think it would be most useful in
16 nonadherent studies or physician-guided
17 minimization studies. We could do enrichment
18 strategies around class two epitope mismatching to
19 try and increase the frequency of the outcome.
20 And I think we could also consider de novo DSA
21 clinical trials where the surrogate endpoints,
22 apart from five-year graft loss, we might be able

1 to shorten it up to maybe two years at earliest,
2 but likely three years is more reasonable, looking
3 at CG or eGFR changes over that time period as a
4 way of getting to a clinical trial design. And
5 I'm a minute early. So I'll stop.

6 DR. VELIDEDEOGLU: Thank you, Dr.
7 Nickerson, for this nice presentation. Our next
8 speaker is Dr. Anat Tambur, from Northwestern
9 University. And she will give a presentation
10 about the challenges in the de novo DSA
11 measurement and the hypersensitized patient.

12 DONOR-SPECIFIC HLA ANTIBODIES AND
13 HIGHLY SENSITIZED PATIENTS

14 DR. TAMBUR: Okay. So just to make sure
15 everyone knows, I'm a lad rat. I'm not a
16 practicing M.D. So I will focus on my
17 presentation about the solid-phase assays in the
18 HLA antibodies. And I want to talk about two
19 things that I think we can generate using the
20 currently available reagents that we have, that
21 we're really not taking advantage of that I think
22 can be very useful as we go.

1 The first one I'm going to go through
2 very, very quickly and it pertains to an opinion
3 paper that was published at AJT a couple of months
4 ago that kind of generated a rebuttal editorial.
5 And what I'm showing you here is the response to
6 that letter. And sometimes we need to challenge
7 our existing paradigms as we're looking at things.
8 So I want to talk a little bit about high
9 resolution, or allele level resolution typing
10 versus low resolution, or antigen resolution
11 typing. And just to make sure we're all on the
12 same page, when we're talking about HLA antigens,
13 we're talking about a family, say the Jones
14 family. And we can have antibodies to the Jones
15 family and we will kill pretty much everyone in
16 the Jones family. But the Jones family have
17 several members A Jones, B Jones, C Jones. And we
18 can have antibodies to one of them and not the
19 others. And I think appreciating that is going to
20 be really important.

21 The important thing to remember is that
22 the solid-phase assay actually provide us the

1 antibodies at the high resolution level. The
2 manufacturer provide us this information. And
3 what we do in HLA lab is we take the data and
4 condense it into the family name, into the low
5 resolution typing because this is how UNOS allow
6 us to put the data and this is how a lot of the
7 studies are being organized. And why is that
8 important? I'm going to briefly go through two
9 cases. Let's assume our donor is typed as HLA
10 DQ2. And you can see the single antigen bead
11 assay. You have MFI values here. And the little
12 things that you cannot read here are the alleles
13 that are the reagents that are provided within
14 this assay.

15 And you can see that we have five
16 different beads here that recognize alleles of the
17 DQ2. Two of them are really positive. Three of
18 them are negative. And if we don't have the high
19 resolution information on the donor, we cannot
20 derive information whether we have donor-specific
21 antibodies or not. And this is just another
22 example just to show you that this is a real

1 problem. It's significantly more prominent when
2 we're talking about HLA DQ. But it pertains to
3 the rest of the HLA antigens. So something that I
4 think will be very easy to implement if we pay
5 attention to this moving on.

6 But really where I want to focus the
7 vast majority of my talk is assessing antibody
8 strength. And I'm going to walk you very slowly
9 through this slide because I think it's going to
10 be really important to appreciate what I'm talking
11 about. That was published a few months ago in
12 AJT. And it's a work where we compared different
13 ways to assess antibody strength. So you can see
14 here the neat MFI values. This is the results
15 that we get from the regular Luminex single-
16 antigen assay. You can see the results that we're
17 getting for Clq. EDTA is a permutation of the
18 assay where we're trying to remove inhibitory
19 factors in the assay. And I'll come to this in a
20 second.

21 And what I want you to pay attention to
22 is what I talk -- what I call titration studies.

1 So we actually take the serum and dilute it in
2 doubling dilutions and we run each of them and
3 record the MFI values. So all of the results that
4 I'm going to superimpose on this particular slide
5 are coming from -- sorry -- one serum sample.
6 these are 10 analytes that are all together in one
7 tube, one patient, one serum, one run. And it's
8 important to remember because we're going to see
9 very different patterns. What we will see when
10 we're looking at dilution studies or what we
11 expect to see is kind of what we're seeing here.

12 We are starting from a higher MFI --
13 sorry -- and as we keep diluting the serum
14 samples, the MFI values will go down. And you can
15 see that the Clq kind of gives you similar results
16 to what we're seeing higher antibodies, lower
17 antibodies and the EDTA shows you something very
18 similar. But here are some other things that we
19 can see as we look at this serum sample. We can
20 see what we call prozone or inhibitory effect,
21 which means when we run the regular titer, we see
22 low MFI. But really the antibody is much, much

1 stronger.

2 Now, granted the Clq will show you that
3 information. The EDTA will pick it up here. But
4 you can see -- I think the importance of what we
5 see, and hopefully I can convince you as we go
6 along and I'm running ahead of myself, is that
7 what are we looking at. The neat IgG, the Clq,
8 the EDTA. We get a stationary, one-time point
9 piece of information. And as we're looking at
10 titration and how the serum dilutes, we get
11 something that is way more dynamic. And we can
12 therefore get significantly more information.

13 So here are two more beads within that
14 particular serum sample. And you can see that they
15 start kind of close to each other but really
16 titrate very, very differently. And you can see
17 that the EDTA -- sorry, the EDTA is maybe picking
18 it up. They tell us that they have antibodies.
19 But I'm not sure about how to determine strength.
20 And for some reason, the Clq shows that this
21 antibody is fairly positive. Keeping -- adding
22 more information again, extremely strong prozone.

1 We would have missed that information early on.
2 Clq picks it up beautifully. EDTA I guess
3 starting to get exhausted and this is just to
4 finish the rest of this particular slide.

5 So I think what we can get from
6 titration study is, yes, we can get a titer and
7 that's where I'm going to focus a lot later on.
8 But as we look at the patterns as the antibodies
9 are moving, I think we can get some assessment of
10 how strongly the antibody actually binds to the
11 bead. Now, granted, this is the bead. This is
12 not the patient. And all the results I'm going to
13 show you are all methodological. I don't have any
14 actual correlation to outcomes. But I think -- I
15 think that we can do much more as we're looking at
16 titration studies.

17 Following this particular work, we
18 decided to desert EDTA and just focus on neat MFI,
19 peak MFI, which will be the highest point that we
20 can get no matter how -- what is the dilution that
21 we're looking at. So that would be the peak here
22 and obviously those will be the peak here and the

1 Clq assay. And we had about 2,600 and 4,400 data
2 points for class 1 and class 2. And we compared
3 the Clq MFI with the neat MFI. And you can see
4 our values are not that great.

5 But when we took the same data and
6 compared it to the peak MFI, it correlates to each
7 of those. The R value is much, much better. You
8 can see that a lot of what was considered IgG-
9 negative Clq-positive earlier is actually a
10 prozone effect. And as we are diluting the serum
11 samples, we are masking this. The nice thing that
12 I think we show from that study is that the Clq
13 correlates very, very nicely with the titers. So
14 really with the Clq, we all know this, Clq will
15 pick the stronger antibodies. But we see a really
16 nice correlation. Yes, there are outliers. But
17 overall, I think our R values are really, really
18 nice. Something else though to take from this
19 slide is that the Clq will completely miss the
20 lower titer antibodies. In my mind, I think this
21 is a very important piece of information. And we
22 cannot assume that if the Clq is negative but the

1 IgG is fairly low, that these are not clinically
2 relevant antibodies. Those can definitely
3 represent potential memory response being awakened
4 later on.

5 So just to kind of get you a sense of
6 how we were determining serum titers in the lab,
7 I've listed here, again, these are just the
8 different antigens, or the alleles, I should say.
9 The names are really irrelevant. You can see the
10 neat MFI values and they're sorted from the
11 highest to the lowest. The different MFI values
12 as we go with titration. This is actually how we
13 call the titer. But I want you to pay attention
14 to how the antibodies behave through the
15 titration. And just for comparison, I put the
16 Clq.

17 And I want to focus your attention on
18 two pairs of beads. This is again one patient,
19 all the serum samples coming from one tube. And
20 we can have two pairs here with really, really
21 similar MFI values. And if we will try to design
22 treatment approach, for example, based on this

1 information only, we would assume that we're
2 dealing with the same type of antibodies.
3 Granted, Clq will give you more information about
4 this. But if you can look at the response of how
5 the antibody is being tittered for the top versus
6 the lowest bead in each of those studies, you can
7 see that the dynamics is very, very different.
8 Hence, the titer becomes very different. And I
9 can tell you that at least at Northwestern, my
10 nephrologists can look at a titer and decide how
11 many cycles of plasmapheresis he's going to use in
12 order to desensitize prior to living donor
13 transplant.

14 This is another patient case that was
15 actually published earlier. And we're looking here
16 at a heart transplant recipient that received
17 rituximab treatment. And you can see now I'm
18 looking at Clq MFI values versus the titer. And if
19 you focus at the Clq, I've highlighted a group of
20 antibodies that were really strong MFI by Clq
21 prior to transplant. And then you can see at the
22 end of the first cycle of rituximab, before and

1 after. And then, at follow-up, the patient was
2 actually transplanted at this point. Fairly low
3 Clq antibodies. And again, I'm highlighting three
4 pairs here for you. And you know, I didn't
5 believe when I saw those results. These are
6 perfect slides, as you see them coming up as raw
7 data. But again, the MFI values are really,
8 really clear and very, very close. And when you
9 look at this, you would assume their responses to
10 treatment will be very similar. And as you can
11 see, in each of those pairs, the top bead barely
12 responded. Or you can see some response over
13 time.

14 But at least if you are looking at the
15 end of this second treatment, you can see that the
16 top bead barely responded. The lower bead
17 responded very, very beautifully. And I can tell
18 you that actually as we were treating that
19 patient, I was able to tell the clinician I can
20 predict which of those antibodies will respond to
21 treatment and which is not because I had done at
22 the same time the titer information for those.

1 And you can see that up front, before the
2 treatment we were able to say these are much lower
3 titer antibodies. Therefore, they're way more
4 likely to respond to treatment.

5 The data that I'm going to share with
6 you right now are just underway to the journal.
7 So hopefully they will appear in a manuscript
8 format. But they have not gone through peer review
9 process, just as a disclaimer right here. But
10 what we've done here is we looked at 40 patients.
11 Twenty-five of them were undergoing
12 desensitization prior to living donor transplant.
13 Fifteen of them were treatment with AMR. All of
14 them had received that protocol with minor
15 permutation, whether they were descent [ph] or AMR
16 treatment. And I'm sure you've seen figures like
17 this.

18 So we took the immediately pretreatment
19 serum sample and we took the immediately, or
20 within 24 hours, posttreatment serum sample and
21 reran all of them just recently. So all of them
22 were run with the same -- a lot of beads with the

1 same tech at the same time going through all of
2 the technical hurdles that you want. And again,
3 this is what we usually see when we're talking
4 about desensitization. We ran the C1q in
5 comparison to this. And here's what you see when
6 you run the titers. All the antibodies had shown
7 a trend down. And it's fairly equivalent, fairly
8 uniform for all the beads.

9 Very quickly, two additional patients.
10 One way to look at their results is to look at
11 what we call the delta reduction. So if we take
12 the MFI value or the titer prior to treatment and
13 the one posttreatment, we can get the delta
14 reduction. And we can convert this into
15 percentages. So we will be able to compare
16 between the three different ways of assessing
17 antibodies. And this is what we see. So again,
18 this is one patient looking at the range of
19 responses between the different beads or the
20 different antibodies. And you can see that the
21 delta titer is way tighter, way more uniform for
22 all of them. And again, the two additional

1 patients.

2 This is when we plot all the 40 patients
3 that actually equates to 58 serum samples that
4 were -- or 58 -- yeah, serum samples that were
5 followed from before and after treatment. And
6 again, you see that the percent CVs for following
7 the patients by titers are significantly more
8 uniform versus the huge ranges that we see by the
9 single point, either IgG or Clq assays. I'm going
10 to skip -- this is just to show you the standard
11 errors or deviation for those assays.

12 I'm going to skip the next two slides
13 because I want to make sure that I'll say
14 everything that I want to say. But those are in
15 the packets. And we just looked within a
16 particular treatment, like five cycles of
17 plasmapheresis, how the different strength MFI
18 behaved over time. But what I want to make sure
19 that I have time to put in, I think what we need
20 to remember when we're using the solid-phase
21 assays -- and I know for a long time we bashed the
22 vendors for not giving us the perfect reagents --

1 that there actually are a lot of issues that are
2 serum-specific, that it doesn't matter how great
3 the reagents are. But there are factors within
4 the serum that we need to find ways to overcome.

5 So inhibition, for example, or prozone
6 effect, it's a serum- inherited issues. No
7 reagents would allow us to solve that issue. And
8 I think by doing titrations, we can remove this.
9 Yes, we can do it with EDTA for the vast majority
10 with a lot of success. But I think titration
11 allows us to do this, plus gives us some
12 information about the binding strength. And
13 again, I'm very well- aware this is binding
14 strength in vitro, not in vivo. We need to do
15 many more.

16 DR. ALBRECHT: Could you please wrap up?

17 DR. TAMBUR: I'm wrapping up. And the
18 last thing is oversaturation. And Stephen talked
19 a lot about this. And as we keep on diluting the
20 serum, obviously we get beyond that point. So I
21 was I think very enthusiastic saying solid-phase
22 antibody testing can be used as a reliable

1 endpoint surrogate marker. I'm going to say maybe
2 as a tool, following the talks that we heard
3 earlier. But I really think that if we know how
4 to use those tools a little better than what we
5 have right now, we can get a little more
6 information.

7 DR. VELIDEDEOGLU: Thank you, Dr.
8 Tambur, for your presentation. Our next speaker
9 is Dr. Stanley Jordan, from Cedars-Sinai. The
10 title of his talk is "Desensitization".

11 DESENSITIZATION

12 DR. JORDAN: Let me find this. I'm a
13 Mac guy, so. Okay. What I wanted to try to do in
14 this talk this afternoon is talk about donor-
15 specific antibodies, a new problem for transplant
16 physicians, sort of in a context of how I see it
17 and cover some other issues we didn't talk about
18 this morning. We've already gone over this. I
19 won't spend too much time. But there are a number
20 of factors that do impact de novo DSA generation
21 that ultimately becomes problems for those who
22 have to re-transplant these patients. Among them

1 are inadequate immunosuppression and medication
2 nonadherence, as you've heard already.

3 I wanted to give you a case that we had
4 earlier this year that I saw on a Friday
5 afternoon. It's a patient that we didn't know
6 about. It's a 22- year-old Hispanic female that
7 was transferred to Cedars, had a creatinine of 4.7
8 after being stable at 0.7 milligrams for two-and-
9 a-half years. She had received a living donor
10 transplant from her mother in 2012, without
11 complications. She was eventually transferred
12 from Children's Hospital Los Angeles to a private
13 sector nephrologist and was not being followed up
14 as much as she had been at the other place. Her
15 local nephrologist indicated that she was
16 compliant with meds. But when I asked about her
17 Prograf level, it was unmeasurable. And a renal
18 biopsy showed this. I think we're all familiar
19 with these features of antibody-mediated
20 rejection, including C4d staining and
21 glomerulonephritis, capillary thrombi, excuse me.
22 And then, you can see the arrows indicate all the

1 DSAs.

2 Now, what is the aftermath of this?

3 Well, we tried to treat her. She got pole steroids
4 [ph], PLEX, IVIG, ritux. Her insurance refused to
5 let us use the eculizumab because I guess they
6 felt it was financially toxic. And she's now
7 returned to dialysis. So just looking at this, I
8 think from, again, a perspective -- I think from a
9 societal perspective, we estimated that the
10 allograft failure cost about \$200,000 for the
11 first year, then \$95,000 per year after that for
12 dialysis. The cost of treating the ABMR is around
13 \$90,000, if we gave all those agents. The human
14 cost, of course, is very important. The patient
15 lost her graft and the family have an enormous
16 burden now. The mother donated the kidney and
17 this young woman will likely return to dialysis,
18 which she did, highly sensitized with limited
19 prospects for future transplant. This will likely
20 result in a reduced lifespan and lower quality of
21 life for her.

22 So ultimately, the most expensive

1 medication we use, or in this instance, is the one
2 that is never taken. So I think what Rita did
3 this morning really pointed this out. This is a
4 very important issue. But it does focus our
5 attention now on the problem of sort of a
6 transition or, as the old '90s term, paradigm
7 shift, I think, that where we felt everything was
8 a T cell-centric issue in terms of allograft
9 rejection. But now we know that certainly the
10 humoral arm is very, very important and that this
11 is progressively superseding the historical dogma
12 that allograft losses are caused by T cell
13 rejection and CNI toxicity.

14 You've seen this already. And I just
15 wanted to focus a bit on, if I can find the little
16 thing here -- there we are -- how antibody injures
17 the allograft. And this is from Bob Colvin's
18 paper a few years ago. We know there can be three
19 types of injury, primarily one that antibodies can
20 directly simulate, proliferation and fibrosis,
21 obliterative vasculopathy. Complement is
22 certainly exceedingly important, as you've seen

1 already with detecting complement in these
2 patients' biopsy. And complement with its lytic
3 factors and C3a and C5a anaphylatoxic reducing
4 also recruit cellular elements to the graft
5 endothelium and also activates the coagulation
6 pathway. The C5b through C9 membrane attack
7 complex causes injury as well. And over on the
8 far right side, another probably important issue
9 for capillaritis and glomerulitis would be the
10 ADCC pathway, or antibody-dependent cellular
11 cytotoxicity where macrophages encase cells and
12 polys are involved in releasing lytic enzymes and
13 doing -- and killing these cells by lytic enzyme
14 digestion.

15 So the most important thing here, at
16 least that we've seen and talked about today, is
17 that here's implementation of several new advances
18 in the past decade that have helped us understand
19 this better. As Anat just showed you with all the
20 anti-HLA antibody detection methods, how important
21 they are. Improved comprehension of graft
22 pathology through the Banff and then growing

1 implementation of molecular approaches that we'll
2 hear about later this afternoon.

3 We talked a little bit about this, this
4 morning, factors that predict risk for antibody
5 rejection. And one thing that for us has been
6 very good is looking at this DSA score where we
7 can -- and we use this in patients coming to
8 transplantation after desensitization if they're -
9 - what we found, if they have a score of greater
10 than 17, that those who -- that they fell into
11 this area where they would develop antibody
12 rejection. Over here, you can see it's a 91
13 percent positive predictive value for antibody
14 rejection. So we feel this is really helpful in
15 making a decision when to go forward with a kidney
16 or not. And again, of course I mentioned other
17 independent factors such as re-transplantation are
18 also very important, regardless of antibody
19 status.

20 I think everybody's see this a lot.
21 Alex Loupy, who's right here in the audience with
22 us today, whose study from France showed that the

1 importance of complement-activating capacity for
2 DSAs, and not only in increasing graft loss but
3 also in inflicting much more harm to the allograft
4 through the different microvascular inflammation,
5 C4d graft deposits and TG scores. Now, we looked
6 at a drug just recently, this was just published
7 this year, called C1-inhibitor. And this is a C1
8 esterase-inhibitor. It's a normal plasma protein
9 that has the ability to inactivate the assemblage
10 of C1qrs.

11 So it's a much more proximal inhibitor
12 of complement than eculizumab. And we did a
13 placebo controlled trial to look at this,
14 primarily for safety but then also to assess the
15 ability of this to prevent rejection. We found
16 several interesting things, which I've tried to
17 summarize on this slide. At the very top --
18 excuse me. Up here at this level you can see that
19 C4 levels were higher in the drug-treated group
20 compared to placebo group over the period of the
21 study. And down below, these -- as you know, I
22 told you we don't do C1qs. But we did have

1 patients who had Clq non-DSAs and when we looked
2 at them with Adriana Zeevi at university of
3 Pittsburgh in a completely blinded way, we found
4 that patients who had these antibodies, they were
5 completely inhibited by the C1 inhibitor after
6 treatment. And this was not seen in the placebo
7 group. So this drug appears to have the ability to
8 disarm the Clq activating capacity of these
9 antibodies. And one might predict also help
10 prevent some of the more serious types of antibody
11 rejection. So we were very excited about that.

12 Adriana also did some in vitro studies
13 with this drug. And you can see that around 0.1
14 unit per well, that it completely inhibits CDC
15 cytotoxicity. So this is an interesting way to go
16 too. However, we have to be careful because, you
17 know, from Marc's studies with the eculizumab,
18 Lynn Cornell has shown that despite complement
19 inhibition, you can still get TG. And I think
20 that makes sense, right, because you still have
21 other mechanisms. You have the NDAP [ph]
22 mechanisms and you also have the ADCC in patients

1 who have maintained antibodies. So antibody
2 reduction is still an important aspect of what we
3 do. So and this is a paper also I wrote an
4 editorial about that Carmen Lefaucheur and
5 Alexandra did where they looked at other aspects
6 of antibodies that may cause harm. And this is
7 looking at subclass, IgG subclasses. Three were
8 associated with inflammatory lesions and C1q
9 activation and graft loss. But surprisingly, IgG4
10 subclasses seemed to be more associated with the
11 interstitial fibrosis lesions. And this may also
12 help us understand how to treat these patients.
13 IgG4 is very susceptible to rituximab, for
14 example, in the patients with IgG4-related
15 disease. So this will be helpful in the future to
16 understand. So we've got a lot of things to think
17 about here.

18 Now, there's a few other things that I
19 want to talk about in terms of factors that do
20 impact de novo DSA development. And as you can
21 see here, there are two things that I've sort of
22 boxed in. First up here is viral infections and

1 then autoimmunity. And I'll talk briefly about
2 that. This is a study that we did many, many
3 years ago in a heart transplant patient at Cedars.
4 And we were looking endothelial cells, or IKA
5 [ph], anti-endothelial cell antibodies in patients
6 who had received heart transplantation and the
7 two-year graft survival. Now, what is very
8 interesting that we also found in this study is
9 down below here. And this -- these are Western
10 blots looking at proteins from endothelial cells
11 and the binding. And over here is -- you can see
12 this guy looked okay until right about here.

13 And it's sort of like the old -- the
14 drug advertisement thing. You know, this is your
15 brain and this is your brain on CMV. So this is
16 your endothelium on CMV infection. You're just
17 lighting up a lot of targets and causing
18 antibodies to be developed there. And these are
19 on the other side other patients. So CMV induces
20 a lot of antibodies. And one might understand how
21 this could be a proclivity factor for DSA
22 development in other antibodies. The other thing,

1 very -- I mean, the more you're around, the more
2 stuff you see. And I know the pathologists here
3 will love this.

4 This is one of our patients who had end-
5 stage renal disease secondary to polycystic kidney
6 disease and presented with proteinuria and a
7 rising creatinine. Many years after transplant.
8 His biopsy showed that he has transplant
9 glomerulopathy with tubulitis. Got antibody
10 rejection, right? Well, he does but it's a
11 different antibody. This is an anti-GBM antibody,
12 your antibody to maybe a protein component. We
13 don't -- I have no idea what it is. He had no DSAs
14 that we could detect. So one has to assume that
15 this is an auto-antibody developing to an epitope
16 in an uninjured kidney that is causing the same
17 phenotype of injury. This is also -- we've
18 reported this several years ago, Dr. Reinsmoen at
19 our place and at the angiotensin-1 receptor
20 antibody, which is -- we see in quite a large
21 number of our sensitized patients. It's also
22 important in mediating allograft rejection in DSA-

1 negative patients. And this has been further
2 characterized by the Terasaki group.

3 So Alex and I did this paper a few years
4 ago just looking at the impact of antibodies in
5 late-allograft failure. And I think everybody's
6 seen these types of schema before. We know that
7 certainly development of antibody early on
8 activates C4d, does the NDAP stuff, peritubular
9 capillaritis and eventually you have loss of graft
10 function. What can we do with it? You know, we
11 know this is sort of -- is it a fait accompli? We
12 know the natural history of antibodies. I think
13 the work that Alex and others have done has really
14 outlined the natural history of antibodies. We
15 know that they're bad. We know that they cause a
16 lot of problems. We know that people that develop
17 them don't do well.

18 Well, this is a paper from Tanabe's
19 group in Tokyo looking at ABO incompatible
20 patients, comparing them to ABO-compatible. And
21 what I want you to look at is down here. If you
22 look at de novo DSAs in patients right here that

1 received rituximab at about five years, 1.7
2 percent compared to the ABO- compatible, 18
3 percent. Chronic ABMR here you can see, much
4 higher rates. And here, de novo DSAs just do not
5 develop in these patients compared to those that
6 were compatible.

7 So what is happening here? B cell
8 depletion in the early phase may affect chronic
9 antibody development and may also be very
10 important in preventing long-term graft loss. I
11 don't have a slide to show you of Jeff Plant's
12 work that he presented not long ago looking at
13 patients -- following patients who were DSA-
14 negative at transplant but developed fibroblasts
15 from the donor and recipient pairs. And he showed
16 that B cell immunity to these cells was very rapid
17 after transplant with standard immunosuppression.

18 This paper was also very important. It
19 was a controlled trial of rituximab for just
20 normal transplant patients. What they showed was
21 that in the placebo controlled format, in high
22 risk patients that were DSA-positive or re-

1 transplant, there was a much lower rate of
2 rejection. I'm going to skip this and just go to
3 the final here and just say that in conclusion,
4 cryptic B cell responses to allograft occur early
5 and often. Emergence of DSA is a sentinel event,
6 indicating intense and significant sensitization
7 to the allograft. And major causes, as we know,
8 are lack of immunosuppression.

9 Unmet needs, all DSAs are pathogenic.
10 Are they? No, probably not because some of them
11 are okay and people don't do too bad. We do need
12 a better way of measuring that. Non-HLA DSAs are
13 also important, as we mentioned, and appear to be
14 quite important to the AT1 receptor does. And
15 future development of newer methods to assess
16 allosensitization at the cellular level and
17 molecular will be desirable. Thank you for your
18 attention.

19 DR. VELIDEDEOGLU: Thank you, Dr.
20 Jordan, for your presentation. Our next speaker
21 is Dr. Steve Woodle, from the University of
22 Cincinnati.

1 DR. WOODLE: So I want to speak on
2 endpoint development for desensitization trials.
3 Same conflicts of interest as this morning. They
4 haven't changed. And again, I want to flavor this
5 with our perspective on desensitization. And so,
6 it's just our way of viewing the problem. So
7 since sensitization refers to development of an
8 antibody response to HLA antigens. Desensitization
9 therefore to us implies a deconstruction of this
10 antibody response with HLA antibody elimination.
11 We develop plasma cell-targeted therapies with an
12 intent to inhibit or delete plasma cell and memory
13 B cell function and possibly more immature B cell
14 populations, resulting in marked reductions or
15 elimination of HLA antibody levels. These
16 properties distinguish these approaches from
17 others.

18 In living donor transplantation, the
19 endpoint's pretty simple. You have a ready donor.
20 It's a transplantation rate. It's clinically
21 meaningful. It's a viable primary endpoint. But
22 one thing that needs to be done in these trials is

1 you have to define how much incompatibility exists
2 before you treat them and then how much you've got
3 to lower that before you allow them to go on to be
4 transplanted and those both need to be objectively
5 measured. And then, you can have common primary
6 and secondary endpoints such as rejection rate,
7 graft survival, proteinuria or TG.

8 In deceased donor transplantation, as
9 was mentioned earlier, it's more complicated. The
10 transplantation rate, in my opinion, is a
11 nonviable endpoint. It's compromised by
12 variabilities in organ availability, therefore
13 waiting times, and variability in organ acceptance
14 practices between centers. You could remove all
15 the antibody in a hundred percent of the patients
16 and not transplant anyone because of the
17 availability of organs. And so, it's a problem.
18 Therefore, the enhancement of transplantability is
19 a potential surrogate. It's traditionally been
20 assessed by PRA methods, historically cytotoxic or
21 CDC PRAs.

22 The problem with those is

1 standardization between labs and the frequency of
2 use of this assay is declining. It's largely
3 being replaced by calculated PRA. It's important
4 to understand that when you talk about a
5 calculated PRA, you've got to define what the
6 level of cutoff is for the antibodies that you're
7 measuring. This is going to vary from one lab.
8 In our lab, we look at a CPRA at 1,500, 4,000 and
9 8,000 because that's what correlates with -- 4,000
10 correlates with a positive flow cytometry
11 crossmatch. 8,000 MFI antibody correlates with a
12 cytotoxic crossmatch. Therefore, a CPRA of 8,000
13 is comparable to a CDC PRA.

14 So when we were developing plasma cell-
15 targeted therapies, we had a hierarchical
16 approach. We first wanted to look at how much we
17 reduced the HLA antibody levels. That's important
18 to understand that you've got a therapeutic
19 response and you're actually doing what you want
20 to do. The amount of plasma cell population that
21 you actually delete or deplete should be directly
22 correlated with how much you reduce the HLA

1 antibody levels. And we view solid-phase assays
2 as a readout. The other way -- the second order
3 in this hierarchy is looking at the effect on
4 populations of antibodies and how that correlates
5 with transplantability which has traditionally
6 been measured by PRA.

7 This is a patient that we talked about
8 earlier this morning. As you can see, this
9 patient -- all of these antibodies from this level
10 across are saturating levels on the beads.
11 Therefore, these are going to be the first
12 antibodies -- when you deplete populations, these
13 are going to be the first to disappear and these
14 will disappear later. So when we went to conduct
15 this first trial of desensitization, and the
16 reason we were particularly interested in this is
17 we're targeting plasma cells that are in the bone
18 marrow niche. So they're long-lived plasma cells
19 resident in the bone marrow. And these are the
20 plasma cells that are going to be with patients
21 long-term.

22 And so, this gave us an approach to deal

1 with that long-term memory. We looked at
2 immunodominant antibody levels. And so, that
3 level is defined as this antibody over here.
4 Usually it's the highest level of the highest
5 antibody. Anat has some issues about prozone.
6 When you have prozone, it may not be this
7 antibody. It may be another one. But that's the
8 immunodominant antibody. And as you can see here
9 in this study, that antibody was dropped almost 85
10 to 90 percent elimination, early on, at the peak
11 response of therapy. And 65 percent -- six months
12 later, 65 percent reduction. This is the first
13 time really that in a group of patients that a
14 therapy's been shown to be stopped and you can
15 have prolonged, long-term suppression of
16 antibodies without putting a graft in.

17 We also looked at high level antibodies,
18 moderate level antibodies and low level antibodies
19 separately. So you can see the reductions here in
20 the high level antibodies were on the order of
21 about 55 percent with this amount of variation in
22 the population. And we had greater levels of

1 reduction with moderate level antibodies and low
2 level antibodies. And that's something that we
3 see consistently. The highest titer, or the
4 highest level antibodies are less responsive to
5 therapy and more difficult to treat. We also
6 looked at these antibodies using various CPRA
7 cutoffs.

8 As you can see, at a CPRA of 1,500, that
9 means we count every antibody that's above 1,500
10 MFI goes into the CPRA calculator. Twenty-six
11 percent of patients were responders by this
12 definition. Seventy-three percent were non-
13 responders. At 4,000, you had 44.7 percent
14 responders. At 8,000 PRA, you had 50 percent
15 responders. And that was fairly similar to what
16 we saw with the CDC PRA. So where you use your
17 cutoff and where you apply your cutoff affects the
18 sensitivity of the potential endpoint. The
19 lessons we learned was that traditional and newer
20 methods were needed. The older methods were
21 inadequate. And even the newer methods were
22 somewhat inadequate. We needed newer approaches.

1 Now, what I want to talk to you is about
2 the newer approaches that we've used. CPRA as an
3 endpoint is limited. It has a lack of
4 sensitivity. You can have highly sensitized
5 patients with a very large number of antigens,
6 remove a lot of them and not have the CPRA budge.
7 There's problems -- and that derives largely from
8 the problems with the UNOS/OPTN CPRA calculator.
9 Once the CPRA hits 99.5 percent, it's
10 automatically rounded up to a hundred percent. So
11 patients with a hundred percent CPRA that's
12 calculated with the UNOS calculator may actually
13 be 99.5 percent or they may be 99.999 percent. A
14 patient with a 99.5 percent CPRA has a 1 in 200
15 chance of finding a donor. A patient with a
16 99.999 percent has a one in a million chance of
17 finding a donor.

18 So we went back to our favorite patient.
19 And we used the UNOS CPRA calculator and
20 progressively removed each one of the 85
21 specificities that the patient had. And as you
22 can see, you can remove 31 antibodies and hardly

1 see a budget in the CPRA. Clearly, anything
2 giving you this effect is very effective. So CPRA
3 is ineffective as a potential way to measure the
4 effects on a population of antibodies in a
5 waitlisted patient. And what we did was we
6 actually looked and we took 19 of our patients
7 that were desensitized that showed a response in
8 the trial that we published using proteasome
9 inhibitors. And using a CPRA -- we calculated
10 changes in CPRA at 1,500, 4,000, 8,000. I'm just
11 going to show you 1,500. We defined arbitrarily a
12 reasonable response is a 25 percent change in the
13 CPRA. Only 15.8 percent of patients in this study
14 met this criterion.

15 Part of the problem is that antibodies
16 shift. Antibodies don't just go away. They go
17 from one bucket to the next bucket. As you can
18 see here, a high level antibody may actually go
19 into the midlevel. It may shift down to the low
20 level or it may shift and disappear. The only
21 bucket in which new antibodies don't come into the
22 bucket is the CPRA thousand. So there's nothing

1 feeding into that bucket. So we developed a
2 concept called enabled PRA. We've not published
3 this. The paper's in preparation. So it's a new
4 concept.

5 We defined it as a CPRA determined for
6 HLA antigens that are reduced below a defined
7 threshold by desensitization. So in other words,
8 if you use an MFI of 1,500 as a cutoff, any
9 antibody above that that's then reduced below that
10 gets put into a PRA calculator. And so, you
11 calculate the proportion of the population that is
12 reactive with the antibodies that are removed. So
13 this should provide a highly sensitive means for
14 assessing the impact of desensitization. It may
15 be that it may be too sensitive. It may not
16 reflect the overall impact on transplantability.

17 So we took the same patients and
18 calculated an EPRA at 1,500, 4,000 and 8,000. And
19 this is the data. Using a cutoff of 25 percent,
20 meaning we think that if you remove antibodies
21 that react with 25 percent of the population, if
22 we do more than that, then it should be effective.

1 Seventy-eight point nine percent of the patients
2 in this study met that primary endpoint. So it
3 appears to be much more sensitive than CPRA. We
4 then went and did another thing. We then came up
5 and decided to use a high precision CPRA
6 calculator where basically the CPRA is not rounded
7 up. It's actually calculated out to six decimal
8 places. And we collaborated with Marcelo Pando
9 Rigal, who's in Scottsdale, at the Mayo Clinic.
10 He did these calculations for us.

11 And so, we used the same group of
12 patients again. And on the bottom is a high
13 precision PRA calculator removing each one of the
14 antibodies, the exact same antibodies that were
15 removed in the top as in the bottom. And as what
16 you can see is a consistent, almost linear decline
17 -- well, I'm sorry. Let me explain this. This is
18 the actual chances of finding a donor. So the
19 patient starts out with all 85 antibodies in place
20 with about a one in a million chance of matching.
21 And when you plot this on a logarithmic function,
22 it's linear over time. Almost each antibody shows

1 an effect over time.

2 So when you put that in, we assumed and
3 made the arbitrary distinction that a 50 percent
4 increase in the transplantability rate using a
5 high precision PRA calculator would be
6 significant. When we looked at that, our patient
7 population, 73.7 percent of patients met that
8 endpoint. We also, as we mentioned, looked at
9 change in iAb as a marker of a response to
10 therapy. And we've already talked about -- in the
11 presence of saturation, this required dilutional
12 analysis. And so, if we said that a percent
13 decrease in HLA -- in the immunodominant antibody
14 of 75 percent was a marker of effective therapy,
15 we had 63.2 percent of patients that met that
16 criterion.

17 We then correlated and asked the
18 question how do these different definitions of
19 responses to these antibody populations correlate
20 with each other. The change in CPRA versus
21 extended -- versus enabled PRSA calculated a
22 little bit. At 1,500, there was no correlation,

1 0.32 was the R value for at 4,000 cutoff. At an
2 8,000 cutoff, the R value was 0.47. So that's
3 fairly reasonable. The enabled PRA correlated
4 with a change in PRA fairly well. And this is I
5 think the reason why it's 8,000 is better is
6 that's the bucket where antibodies are going out
7 and they're not coming in. We looked at the CPRA
8 versus the precision-calculated PRA and got no
9 correlation.

10 And what's really got us excited is when
11 we calculated the enabled PRA versus the
12 reciprocal of the precision-calculated PRA and
13 used a logarithmic function, we had a correlation
14 at 1,500 of 0.81. At 4,000 -- I'm sorry. I'm
15 sorry. Let me move down. At 0.81 at 1,500. At
16 4,000, the R value was 0.74. and at 8,000, it was
17 0.43. So this is a means that tells you that the
18 number of antibodies that you remove in the
19 proportion of the population that they respond or
20 react with correlates with the estimates of
21 transplantability when a high-precision PRA is
22 calculated.

1 So in conclusion, published waitlist
2 desensitization trials have been designed largely
3 without predefined primary endpoints. We looked
4 at about 12 of them of the 20-some-odd that were
5 published. And we stopped looking because none of
6 them had a predefined primary endpoint. CPRA is a
7 poor endpoint for waitlist desensitization because
8 of its lack of sensitivity. We believe that EPRA
9 and high-precision PRA are more sensitive
10 parameters of desensitization. And these initial
11 analyses support further development of precision-
12 calculated PRA as an endpoint for waitlist
13 desensitization. Thank you.

14 DR. CAVAILL Thank you. Now, we'll
15 switch to the potential for histology in surrogate
16 endpoints, clinical transplantation. Our first
17 speaker is Dr. Michael Mengel, for Edmonton, who
18 will speak about portable biopsies revisited.

19 PROTOCOL BIOPSIES REVISITED

20 DR. MENGEL: Thank you. So please
21 ignore your handout. I used the morning listening
22 to all talks and changed my talk completely.

1 Okay. It's probably down here. Here it is.
2 Okay. So I'm a pathologist, and accordingly, my
3 disclosure list is short. Nobody wants to work
4 with me. What I was tasked with is reviewing
5 protocol biopsies and especially what
6 histopathological lesions we see in those, provide
7 some molecular insights on four studies done on
8 protocol biopsies and in particular set the stage
9 to discuss with the uncertainties around the
10 lesions we see in biopsies and how they could be
11 used as surrogate endpoints or endpoints in
12 general for trials and what more work is needed in
13 that regard.

14 So first, I would start with
15 terminology, which is I think sometimes confusing.
16 There is biopsies for cause, where clinical
17 indication moved the clinician to put a long
18 needle into a patient. And protocol biopsies are
19 usually taken at predefined time points. But it
20 can be at donation. It can be from a stable
21 graft. That is when the time point was set on a
22 day when the creatinine is up. Is that still a

1 protocol biopsy? What is it if you use a more
2 sensitive biomarker like inflammatory markers in
3 the urine or DSA to trigger a biopsy? is that
4 still protocol biopsy, when the DSA is suddenly
5 positive but the creatinine is stable? So some
6 people nod, others shake your heads. I think we
7 have consensus.

8 So I cite this landmark paper from
9 Winnipeg which really gave a lot of emphasis to
10 protocol biopsies. It was to me probably the only
11 randomized trial on protocol biopsy and
12 intervention. Protocol biopsies were done at
13 preset times, six months and 12 months. And one
14 group had biopsies and was treated for subclinical
15 pathology and rejection. The other group had no
16 biopsies. And then, after follow-up, those who
17 had biopsies and were treated for subclinical
18 rejection had better allograft function after 24
19 months. However, the Winnipeg group redid the same
20 trial essentially as a multicenter trial in
21 Canada. And under current and very effective
22 immunosuppression with MMF and tacrolimus, the

1 differences were not significant anymore, mainly
2 due to the fact that subclinical rejection in a
3 compliant patient taking the right drugs is a rare
4 event.

5 We learned this morning that
6 inflammation is bad. Inflammation, especially in
7 combination with interstitial fibrosis and tubular
8 atrophy. But these data from the Mayo Clinic are
9 very important in that regard, that even
10 inflammation below the Banff threshold seem to be
11 associated with inferior outcome. The study I did
12 in Hanover is showing that the more biopsies a
13 patient has, and those biopsies showing
14 inflammation, the worse is your kidney function.
15 So don't get a biopsy is not the conclusion from
16 those data. But it says that there is a cumulative
17 burden of inflammation over time which underlies
18 the outcome.

19 So how do pathologists score
20 inflammation? This is where you will all fall
21 asleep and where I really get activated. So the
22 Banff rules are the international consensus

1 platform how pathologists should assess transplant
2 biopsies. Rejection is based on the so-called
3 Banff i-score, where the rule says you score in a
4 relative fashion the inflammation non-scarred
5 cortical areas. You ignore infiltrates around
6 blood vessels and in nodular shape and you do not
7 score for rejection for the Banff i-score
8 inflammation and fibrosis. I will focus on how
9 inflammation is scored. I will not focus on
10 microcirculation inflammation, capillaritis and
11 glomerulitis, which definitely is critical and
12 crucial for patients with DSA. But I think my
13 colleague, Dr. Bagnasco, will allude to that
14 later.

15 When you look at a large series of
16 around a thousand protocol biopsies, which were
17 all done very early, three months -- between three
18 and six months post-transplantation, you see that
19 these different types of infiltrates, diffuse or
20 nodular infiltrates or in natural thick areas,
21 increase with time but also increase whether there
22 is a clinical indication for a biopsy or not. So

1 when there is a rise in creatinine and you do a
2 biopsy, you have more inflammation than you do in
3 a stable, compliant patient. The surprising
4 finding was also that less than 20 percent of all
5 allografts never had an infiltrate.

6 So inflammation is a common feature. I
7 think, mark, you mentioned it before. And we all
8 know allografts will be rejected if you do not
9 give enough immunosuppression. It's a function.
10 It's an inverse relationship between
11 immunosuppression and immune response. And that
12 is what you see and most of our grafts are just at
13 that level not to have significant inflammation.
14 When you ask pathologists at the Banff meeting how
15 do you score inflammation in regard to these
16 different compartments which are supposed to be
17 scored by Banff rules and which are not supposed
18 to be scored, one-third says certain infiltrates -
19 - and this is inflammation and fibrosis -- I do
20 ignore, as Banff tells me. One-third says I do
21 consider them. And one-third says it depends.

22 So it depends. Yeah, you would think

1 those guys, why do they get paid. Actually we
2 then investigated the data further and it was the
3 group of the most senior and the most experienced
4 pathologists who said it depends. The junior
5 people follow the rules. They obey. And they
6 apply them. But the more senior they are, they
7 said I have my own opinion because I know
8 sometimes rules might be flawed. And remember,
9 Banff is consensus. It's not truly evidence-
10 based. 1991 in Banff, 11 people, a threshold of
11 25 percent was a sunny day, Banff, Alberta. Could
12 have been 30. It was 25.

13 And the rationale to exclude certain
14 infiltrates at the time was they were seen in all
15 kidney biopsies and not only in transplants, as a
16 nonspecific, non-rejection-specific lesion. So
17 the point I tried to make is Banff was designed to
18 be diagnostic. And we talked the whole morning
19 about prognosis and prediction. But we used the
20 same Banff lesions. They were never assessed for
21 that or designed for that, the scoring system. We
22 talked a lot about inflammation areas of fibrosis

1 and the prognostic relevance. And I think that's
2 very strongly supported by evidence.

3 We did a study with the Banff group of
4 how do people score fibrosis. We compared against
5 the gold standard, computer-sensed measurement by
6 image analysis. And what we found is there's two
7 ways to score fibrosis. You assess the area of
8 abnormal cortex or you function like a computer
9 and actually assess the percent volume of space.
10 And interestingly, half the pathologists do it one
11 way and the other half does it the other way. And
12 when you then line up whether fibrosis correlates
13 with function, which is what it does, but with a
14 computer standard, you see that there are
15 pathologists who are constantly over-scoring and
16 there are pathologists who are constantly
17 underscoring. So you'd better know your
18 pathologist.

19 What do you do for a clinical trial to
20 get around this variance? You regionally put self-
21 declared expert in one room and they are blinded
22 or blind. Some of my colleagues, as you don't

1 know what you do. And then, you let them generate
2 consensus on specific cases to take our variants.
3 So there is a way around this. But we have to
4 remember that all the data we reviewed are coming
5 from different settings in different styles, under
6 different treatment and different populations.

7 Back to fibrosis and tubular atrophy, I
8 think I can skip that. There is real evidence
9 that when you have this type of fibrosis, which is
10 ignored by most Banff reads, you have a prognostic
11 association. But the extent of inflammation and
12 fibrosis depends on how much fibrosis you have.
13 So when you have no fibrosis, you cannot score
14 inflammation and fibrosis. And fibrosis in
15 allograft is a function of time. These are the
16 different compartments. Inflammation without
17 fibrosis, inflammation with fibrosis and the
18 longer you're out post-transplant, the more you
19 have of that.

20 We could show that there is a difference
21 between uninflamed and inflamed areas. So when
22 inflammation and fibrosis are in the same area and

1 there is something going on which drives inferior
2 outcome, the DeKAF study confirmed this in a much
3 larger series of cases. So again, time post-
4 transplant shows you or correlates with how big
5 this compartment is and how big this compartment
6 is.

7 And Banff, as addressed, is now what you
8 have the opportunity to give in your report or see
9 the so-called total i-score how much inflammation
10 is in all cortex and when you have an i-score and
11 total i-score, you can calculate how much
12 inflammation is in the scarred area. So you get
13 the inflammation or at least you have the option.
14 But Banff has not generated consensus what the
15 total i-score means, whether that's diagnostic or
16 prognostic. It will just be reported. It's not
17 part of making any diagnostic decisions.

18 When you look about total inflammation
19 or the i-score, it was Banff's original intention
20 or it's only where inflammation is used is for
21 diagnosing T cell-mediated rejection. But it is
22 present in all different diseases, especially

1 inflammation and fibrosis. It's not
2 diagnostically specific. But it has even
3 independent of the underlying disease a very
4 strong prognostic factor. The area under the curve
5 for total i-score in this cohort in Edmonton was
6 greater than other diagnostic categories. So
7 don't mix the diagnostic component with the
8 prognostication if you look for endpoints.

9 And especially again Edmonton data in
10 late biopsies, inflammation -- increased
11 inflammation is a prognostic value, not in early
12 biopsies. Why is this? I will try to give an
13 answer. The question really is then for outcome
14 again what causes the inflammation. So the
15 hypothesis I pose is when you have a certain
16 disease and you have a certain amount of
17 inflammation and you have a different disease with
18 the same amount of inflammation, the prognosis
19 will be different because depends on what the
20 disease is. Some are amenable to treatment.
21 Others are not a lot or at all. Some have a more
22 benign biology. Others have a way more aggressive

1 biology. So we have to come back to some
2 granularity of phenotypes and then we can use this
3 universal histological feature as a prognosticator
4 because what drives outcome in equal classes of
5 inflammation are the underlying disease in this
6 multivariate analysis.

7 I can skip this. Peter talked about
8 that extensively, the relationship between
9 inflammation and DSA. So quickly about molecules.
10 These are six-week protocol biopsies with gene
11 micro-area testing. So whole genome studies.
12 Three classes or pathways is increased
13 inflammation, increased injury and repair and loss
14 of function in nephrons. And the association
15 between early inflammation, subclinical
16 inflammation is with -- mainly with inflammation
17 and injury. Before six weeks the variables, there
18 is a very strong association between molecular
19 changes and prior injury, i.e., delayed graft
20 function. And this is then here reflected that
21 diseased donors with DGF essentially if the
22 highest gene expression compared to those with DGF

1 overall or living donors without DGF have the
2 lowest inflammation, as you see.

3 So injury -- extent to injury at
4 transplantation translates to an inflammatory
5 signature even six weeks post-transplantation.
6 And in the long term, this inflammatory signature
7 -- not in all patients -- either resolved or
8 translated into ongoing damage. Treatment of
9 subclinical rejection did not affect the outcome
10 in this context and this cohort. This is a study
11 from Australia from Sydney, Brian Nankivell's
12 group, looking at sequential protocol biopsies
13 also with gene expression micro-arrays. And what
14 you see here when you look at the black bars is
15 that's the fibrosing remodeling or injury response
16 at those with the similar transcripts. It goes up
17 and it does down. There is some healing. So
18 donation, brain death, transplantation causes
19 injury. But it heals and it heals with some
20 scarring and some inflammation. But it is
21 probably not the inflammation you see later on.

22 These are data from Minnie Sarwal's

1 group is when you do six- month protocol biopsies
2 and look 24 months in terms of outcome, the
3 inflammatory burden has an association with later
4 outcome. Is this the same inflammation that we
5 measured at, say, six weeks? I would postulate
6 probably not because the Mayo Clinic did an
7 elegant study where they tried to subtract this
8 background injury from the novel inflammation due
9 to a rejection. And you could see that there is a
10 difference in inflammatory processes, although a
11 lot of the transcripts are overlapping.

12 So I tried to summarize in this figure
13 time post-transplant matters. The context you do
14 the protocol biopsy matters. Are you pre-
15 sensitized or are you not pre-sensitized? You will
16 see different lesions at different timing. And
17 therefore, when you design your trial, this is
18 critical where you enroll and what will the
19 disease be driving the underlying or the
20 underlying cause for the inflammation.

21 Okay. I can quickly summarize. There
22 is early types of inflammation due to early

1 injury. This does not relentlessly go one way
2 down to fibrosis forever. New disease processes
3 come in, also cause inflammation which looks
4 similar in the microscope. No way to specify
5 that. And therefore, I think we need some more
6 thought of when we do a biopsy and what we call
7 it. Thank you.

8 DR. CAVAILL Thank you, Dr. Mengel. Our
9 next speaker is Sundaram Hariharan. He will be
10 speaking about clinical and subclinical acute
11 rejection.

12 CLINICAL AND SUBCLINICAL ACUTE
13 REJECTION

14 DR. HARIHARAN: Good afternoon. I've
15 been in Pittsburgh for little over three-and-a-
16 half years. So one of my good friends told me
17 when I moved to Pittsburgh, he said two principles
18 here to follow. Listen to others and don't quote
19 the good qualities of your previous center. It is
20 like telling your second wife the good qualities
21 of your first wife. It won't go well. So as a
22 transplant nephrologist, my work -- my job has

1 been just to listen to others. I listen to the
2 patients, most important. Obviously the surgeons,
3 and hear them out. Listen to the pathologists a
4 lot. We need them every day. Listen to the
5 tissue typers, all the researchers, all the
6 coordinators. So put that all together, I've been
7 in kind of a hibernation period and collecting
8 data. So I'm going to show some data which has
9 not been presented before.

10 But I'm going to show a couple of old
11 papers, which many of you may have seen. I'm
12 going to show the paper again in terms of kidney
13 transplant half-life in patients without rejection
14 and in patients with rejection, which we published
15 about 15 years back. Subsequent to that, we
16 published a paper on a kidney transplant survival
17 based on renal function and the survival in the
18 related hazard for graft failure, which is
19 expressed in y axis and the stable creatinine at
20 the end of one year and various lines showing the
21 delta creatinine showing increment in the
22 creatinine and increment in the delta creatinine

1 is associated with graft failure.

2 Ideally speaking, we should not be
3 quoting this paper anymore. Why? This is
4 published in 2000. This is published in 2001.
5 Immunosuppressions are different. We did not have
6 an MMF. We did not have tacrolimus. But
7 unfortunately, we are still citing this paper.
8 I'm not citing this paper anymore. We are still
9 citing this paper because it raised clinical
10 trial, we are still using BPAR, biopsy-proven
11 acute rejection as an endpoint, which was a theme
12 in the first paper. And the secondary endpoint is
13 renal function, which is a theme in the second
14 slide. I think it's time to go forward.

15 With that background, I will show you we
16 have been preaching about transplant protocol
17 biopsies or magnet biopsies. Let's look at how
18 many centers do biopsies. We did a survey
19 recently which has not been published yet -- we
20 are analyzing the whole data. We looked at the
21 national survey. We sent the information to about
22 200 centers, little over 200. They have to do

1 some threshold or number of transplant. We got a
2 response from half of them, which is not bad. But
3 essentially, 63 percent of them, they don't do
4 protocol biopsies. We may preach whatever we want.
5 Most of the centers are not doing it and some
6 centers are doing it on a select basis, whatever
7 the reason may be. But that's the information
8 that we have. So if we think it's important, we
9 have to [inaudible] this pie graph into a
10 different picture, a different number.

11 Well, this is the data I'm presenting.
12 As I said, it's not been presented before. We are
13 collecting information and see where we are and
14 look at the roadmap. Many of you have done that
15 very well. I am doing it for a short period here.
16 We have done about 295 transplants, both living
17 donor and deceased donor, in the period of 18
18 months, January, 2013 to 2014. All patients
19 treated -- most of them were treated with
20 thymoglobulin, with MPA, with rapid withdrawal of
21 steroids.

22 We excluded eight patients. They either

1 lost the graft or died within a month or two after
2 transplant. So we analyzed 287 patients
3 prospectively. All of them we are still
4 following. And we performed three- and twelve-
5 month protocol biopsy and our compliance for
6 protocol biopsies at the end of three months was
7 72 percent. We did not biopsy patients who were
8 on anticoagulation, obesity, patients on Plavix
9 and so on, okay?

10 So 72 percent of the patients underwent
11 a protocol biopsy in this group. And if you look
12 at the 12-month biopsy, which has just completed
13 in terms of analysis, 81 percent of the patients
14 who underwent treatment protocol biopsy had a 12-
15 month biopsy, which is reasonable. What are the
16 results? Within four months or three-and-a-half
17 months after transplant, approximately 10.8
18 percent of the patients had a clinical acute
19 rejection, which means there was a prompt for
20 doing the biopsy because of renal dysfunction and
21 documented with the expert pathologist giving us
22 the information this is rejection. Borderline

1 rejections are not included in that. And about
2 18.2 percent of the patients had subclinical
3 rejection at the end of three months. This does
4 not include borderline biopsy. The 18.2 percent,
5 we are to be careful in terms of the
6 interpretation. We did not include the
7 denominator and patient did not undergo biopsy
8 because I don't know the real story in that.

9 What about the risk variables? We did a
10 univariate analysis. We had just completed the
11 multivariate analysis which I have not the slide
12 for. Most important risk factor for our analysis
13 the delayed graft function, patient with clinical
14 acute rejection, patient with subclinical acute
15 rejection. There's a proportionately more number
16 of patients with delayed graft function in that
17 group. DSA is also important. And the
18 multivariate analysis comes sort of the same
19 factor, combination of DGF and DSA with important
20 risk factors for acute clinical rejection and
21 subclinical rejection.

22 What happened to these patients? What

1 about renal function? I'm going to show you a
2 slide here only on the creatinine, not on the GFR.
3 Patients were divided into three groups based on
4 the three-month biopsy. Three-month biopsy can be
5 normal or no rejection or patients who had a
6 clinical acute rejection within three-and-a-half
7 or four months after transplant or patients who
8 had a subclinical rejection. As the slide -- as
9 expected, the normal histology of those renal
10 function was excellent and it remained excellent
11 up to one-year follow-up. If you look at patients
12 who got a subclinical rejection, they did respond
13 to some extent and at the end of one year, the
14 creatinine slightly is increasing, not
15 drastically. Obviously patients with an acute
16 cellular rejection or a clinical rejection, their
17 creatinine remained elevated. Most of these
18 patients, over 90 to 95 percent of them, are
19 treated with steroids.

20 What about the i-scores and t-scores?
21 The top panel is the i- score. The bottom panel
22 are t-scores. The blue represents the three-month

1 protocol biopsy results and the red represents --
2 red bar represents the 12- month protocol biopsy.
3 And the first group of patients particularly shown
4 here is patients who had an acute clinical
5 rejection. The t-scores and i-scores were
6 elevated obviously. And more importantly, between
7 three months and 12 months, the t- and i-scores
8 are still elevated. But it was not much
9 difference. So what about the treatment the
10 physicians gave? In my opinion, was not
11 sufficient.

12 If you look at the borderline -- not
13 borderline, the subclinical rejection, the t- and
14 i-scores were elevated at three months and that
15 did improve substantially at the 12-month protocol
16 biopsy. And if you look at patients who got a so-
17 called normal biopsy, the inflammation scores are
18 very minimal. And at 12 months, there was some
19 increment. Reason being, there were some patients
20 who developed subclinical rejection at 12 months
21 but did not have a rejection at three-month
22 protocol biopsy.

1 What about the chronicity score? We
2 calculated the chronicity score, the chronic
3 composite score as well as IF and i-score. Once
4 again, the same division. If you look at patients
5 with an acute cellular rejection, clinical acute
6 cellular rejection within three months, their
7 chronicity score did go up from three months to 12
8 months, but not substantially in patients with a
9 subclinical rejection. And even in patients who
10 had a so-called normal biopsy, there was an
11 increment in the chronicity score and we have to
12 do some further analysis. But essentially, the p
13 value is significant because of the large number
14 of patients we studied. There were 140 patients
15 in that particular group.

16 More importantly, let's look at the
17 concurrence. What happened to the biopsy at 12
18 months in patients who had a biopsy at three
19 months? At the end of three months, we divided
20 patients into three groups: acute cellular
21 rejection, subclinical rejection and normal
22 biopsy. What proportion of them had a persistent

1 rejection even later? So in this group, one-third
2 of the patients who had an acute clinical
3 rejection, they had a persistent subclinical
4 rejection at 12 months. I don't know whether it's
5 the labs or persistent. We did not biopsy many of
6 them in between. But the inflammation persisted
7 in patients with acute cellular rejection as well
8 as subclinical rejection and proportionately it
9 was much, much smaller in patients who had normal
10 biopsy at three months. I think this is an
11 important thing here to keep in mind because those
12 are the patients -- I don't think we're treating
13 them effectively.

14 Sorry. What about the delayed graft
15 function? I said delayed graft function was an
16 important feature. We had 49 patients who had a
17 delayed graft function. If you look at the renal
18 function in patients with delayed graft function
19 and patients without delayed graft function,
20 obviously patients without delayed graft function
21 had a better renal function comparing to patients
22 with delayed graft function. So we need some

1 subsequent analysis to divide the delayed graft
2 function or primary graft function and separate it
3 because most of the living donor transplants were
4 included in the primary graft function. You see
5 the same pattern, patients who had an excellent
6 renal function immediately after transplant,
7 whether living or deceased, they had an excellent
8 function. But the other group with delayed graft
9 function had an elevated creatinine throughout.

10 Many patients who had delayed graft
11 function, we also biopsied them around day 14
12 because they had a persistent renal dysfunction,
13 not all of them. So if you look at the
14 inflammation score, it was not very high at 14
15 days. But beyond that, it was definitely a little
16 bit high. More importantly, let's concentrate on
17 the chronic scores. Patients who had a biopsy at
18 14 days post- transplant who had a persistent
19 delayed graft function, the chronicity was not
20 bad. But same patients when they are biopsied at
21 three months, the chronicity went up. So the
22 chronicity went up from 14 days to three months

1 and persisted at the end of one year after
2 transplantation which is a real problem. So there
3 are events occurring very early after
4 transplantation, especially in the subgroup of
5 patients with delayed graft function. We have to
6 think about intervening.

7 Once again, I am dividing this into
8 three-month protocol biopsy and one-year protocol
9 biopsy and looking at the t-scores. T-scores were
10 definitely elevated in patients with delayed graft
11 function, same as the i-score, same as the
12 chronicity score, especially at three months and
13 they were not substantially different at the end
14 of one year of the number of patients definitely
15 small and hopefully we'll be accumulating more
16 data into this dataset.

17 I'm going to skip this slide and for
18 discussion. We have seen a lot of power analysis
19 this morning on various levels. So I did some
20 power analyses to come out how many patients we
21 need if you are to do an intervention trial. Let's
22 take the presumption that our clinical rejection

1 is approximately 10 percent. It could be 12 or
2 15, or if it's 15 percent, if you reduce the
3 clinical rejection by 20 percent or 25 percent or
4 30 percent, you might need anywhere between 3,500
5 patients to a little over 1,000 patients in the
6 study.

7 But if you are to incorporate acute
8 clinical rejection to the subclinical rejection,
9 our number goes from 10 or 15 percent to 25
10 percent. The number of patients required for the
11 interventional trial will be much, much lower or
12 if it goes to 30 percent, it can even be lower.
13 So I'm going to summarize the findings, what we
14 have derived from these 287 patients. I don't
15 have a very long-term follow-up. Only one-third
16 of the centers do protocol biopsy. So we have to
17 keep that in mind. Not all centers are doing it.
18 DGF is an important risk factor for acute cellular
19 rejection as well as subclinical rejection. Renal
20 dysfunction is the problem. Even in the patients
21 with acute clinical rejection or subclinical
22 rejection, creatinine remains elevated even at the

1 end of one year after transplant. And that is
2 especially true in patients who had a DGF and
3 combination of DGF patients who had a subclinical
4 rejection.

5 Histological score was definitely high
6 in patients with DGF. Histological score at the
7 end of 12 months, one-third of the patients who
8 had rejection before, they had a persistent
9 inflammation that is definitely a problem. And
10 recipients who had DGF, they progressed very
11 quickly from day 14 to three months after
12 transplant and that has to be kept in mind. And I
13 strongly feel that we have to include -- we should
14 not be depending upon only clinical rejection.
15 It's time to include -- go beyond clinical
16 rejection, go beyond renal function and also
17 include subclinical rejection as a kind of a
18 meaningful endpoint for our future interventional
19 trial.

20 So my conclusion, ACR and SCR are
21 important immunological events after kidney
22 transplantation. DGF is an important factor. In

1 our deceased donor transplant, one-fourth of them
2 have DGF and large number, 35 percent of them
3 develop acute either subclinical rejection or
4 clinical rejection within one year. And patients
5 who have allograft rejection at three months,
6 clinical or subclinical, they have a persistent
7 inflammatory process going on at 12 months. So
8 there is an opportunity for intervention. And as
9 you already mentioned, SCR and ACR should be
10 implemented for future clinical trials.

11 So we can consider clinical trials for
12 all de novo patients. That means you are going to
13 expose patients who are doing very well, 40, 50,
14 60 percent of them, with new immunosuppression.
15 Then we are going to push them to higher risk for
16 various complications. And instead, we can look
17 at intervention for high-risk patients, which I
18 feel is either the DGF or de novo DSA or African-
19 Americans for an interventional trial. I think
20 that's doable. The treatment of ACR for a
21 complete resolution is another way of intervening
22 in the trial -- intervening to improve the

1 outcome.

2 All of us in this room, including
3 myself, have written articles saying one-year
4 survival is improved. We cannot do anything. Our
5 death rate is so low, we cannot improve. That is
6 not true. If you measure the graft survival and
7 the patient outcome, we cannot improve. There are
8 events occurring within the one year after
9 transplant when patients are really under our
10 surveillance and we have an opportunity to
11 identify. There are so many events occurring,
12 whether it's DGF, DGF with subclinical or clinical
13 rejection. We have an opportunity --

14 DR. ALBRECHT: Would you be so kind to
15 wrap up?

16 DR. HARIHARAN: -- to modify those
17 patients and improve. Thank you very much. There
18 are a lot of collaborators, a lot of people who
19 have done an excellent job in this. Thank you.

20 DR. CAVAILL Thank you, Dr. Hariharan.
21 Our next speaker is Dr. Philip O'Connell who will
22 speak to us on i-IF/TA and surrogate -- as a

1 surrogate marker for renal graft loss. Thank you.

2 i-IF/TA AS A SURROGATE MARKER FOR RENAL
3 GRAFT LOSS

4 DR. O'CONNELL: Thank you. Okay. So
5 thank you very much. So I guess I'm a bit in a
6 theme. So most of my talk here will be looking at
7 what i- IF/TA and its correlation with renal graft
8 loss and most of this has been recently analyzed
9 predominately by Brian Nankivell and has not been
10 published as of yet. So I guess you would say the
11 aim of what I'm trying to do today is to see if i-
12 IF/TA is predictive of graft loss and then to also
13 identify the histological and clinical events that
14 lead to i-IF/TA at 12 months. And the patient
15 cohort we're doing is a patient cohort we've done
16 a fair bit of study and which is a group of
17 simultaneous kidney/pancreas transplant
18 recipients. And when we did this, we've had --
19 these patients have protocol biopsies at 0, 1, 3,
20 12, 36 and 60 months post-transplant. And that
21 group of patients have been published together.

22 So the thing I just want to start off is

1 i-IF/TA, as Marc pointed out, isn't sort of a
2 Banff criteria per se, though people seem to talk
3 about it. So I thought I'd just say what we mean
4 by that and I guess we're talking about a
5 mononuclear cell infiltrate in areas of tubular
6 atrophy and interstitial fibrosis. And we gave it
7 a semi-quantitative assessment which is consistent
8 with others here, which is scoring it like the i-
9 scores where it's inflammation within areas of
10 fibrosis, if it's between 10 and 25 percent, then
11 it's given a score of one, between 26 and 52 and
12 greater than 50 percent of the damage core
13 effects, it's -- hang on, where'd I go here.
14 Yeah, so it's three.

15 So this is, I guess, what we mean by
16 that, is these areas of fibrosis where there's a
17 mononuclear infiltrate, not looking at the
18 interstitial infiltration with around viable
19 tubules. And our papers, this is I think from the
20 Mayo saying that if you've got inflammation with
21 areas of fibrosis, that you have worse outcomes.
22 So the patient cohort we looked at were 301

1 simultaneous kidney/pancreas patients. And the
2 advantage of that group is that they're
3 homogenous. So they've all got the same disease.
4 You don't have problems of disease recurrence.
5 They're generally young. And then, they generally
6 get good grafts. The downside is that they do get
7 good grafts. So you don't get a lot of graft
8 loss. So you don't get a lot of events to measure
9 when you're looking at for hard endpoints such as
10 graft loss.

11 And on the left here, you can see this
12 is our incidence of overall graft survival. So at
13 five years, the incidence of graft survival, not
14 for the 300 but for our cohort in general, which
15 would be roughly the same. It's around 92 percent
16 and it's 87 percent at 10 years. And overall,
17 it's 87 and 73 percent. And if we're looking at
18 this in a broader kidney transplant population,
19 this is our five- year graft survival, overall
20 graft survival at Westmead which is around about
21 88 to 90 percent. So still at five years, there's
22 limited events when you're thinking about

1 developing a clinical trial.

2 So what we have done here is when we
3 scored i-IF/TA in these biopsies, and then we
4 correlated it with chronic scores. And what we
5 did is looked at two things. So one is we looked
6 at biopsy pairs. So we looked at one biopsy. And
7 if they had i-IF/TA and then looked at a
8 subsequent biopsy further down the track. So if
9 you looked in the blue bars, it's the i-IF/TA
10 score. And you can see that there were -- if you
11 had a higher i-IF/TA score, then you had chronic
12 interstitial fibrosis or correlated with that,
13 though that didn't change. But if you had an i-
14 IF/TA score and then looked at the subsequent
15 biopsy, that there was a delta change in CI.

16 So in other words, you had worse
17 fibrosis further down the track. So you could --
18 had i-IF/TA, you're going to predict that things
19 are going to get worse the further down you looked
20 at it. The other thing we then looked at was we
21 looked at all the time points and then did a
22 univariate analysis to predict graft loss at any

1 time. So we got an average follow-up of around
2 about 10 years for this group of patients. And in
3 a univariate analysis, it came close. But two
4 things we wanted to find to that were which was a
5 good time to do a biopsy that was going to predict
6 graft loss, if that's what you wanted to do and
7 what scores picked things up.

8 So what we have found, a few things that
9 were interesting was that i-score came close to
10 being significant at one year but was -- if you
11 had inflammation at three years or five years,
12 that was bad. C4d didn't seem to predict graft
13 loss in this cohort early on but did if you got it
14 late, which we suspect is noncompliance. And if
15 you looked at the chronic scores, that the most
16 predictive of that was the CV score, suggesting
17 severe prior acute vascular rejection. And i-IF/TA
18 at one year was close to being significant or
19 predictive of graft loss in a univariate analysis.
20 When we looked at -- of this score, function per
21 se wasn't predictive of graft loss at any time
22 point except at five years. So then if we put

1 this into a multivariate -- so what we did then
2 was we said we'd concentrate at one year.

3 We felt that that was in combination, if
4 you're thinking about designing a clinical trial,
5 it being a time point where you can have an
6 endpoint. If it's a prevention trial, or it's a
7 good point to do an intervention if you're doing
8 intervention study. We then did a multivariate
9 analysis at the one-year histopathology and the
10 three things that were predictive were CV, i-IF/TA
11 and CG. So as you can see that CV being sort of
12 being a predictive -- what I would say could be a
13 marker of acute vascular rejection. And it was
14 highly predictive. But there weren't many event
15 rates. i-IF/TA was in a multivariate analysis was
16 predictive of graft loss where it wasn't quite
17 significant in a univariate analysis. And CG
18 suggestion of an event from antibody-mediated
19 rejection was also present.

20 So the other important thing about,
21 well, if you looked at the one-year biopsies, what
22 was the -- I'm trying to get the thing to come on

1 -- but what was the prevalent rate of i-IF/TA. So
2 in other words, in these 300 patients, how many
3 people actually had i-IF/TA. So there was about
4 roughly a third. So there was quite a lot who had
5 grade one. There were very few who had grade
6 three or grade two biopsies. But if we scored i-
7 IF/TA yes/no, so any grade encountered, it was
8 still predictive. So if you looked at that, those
9 three events, then you could see that basically i-
10 IF/TA was present in roughly 30 percent. And this
11 is again looking at if you had no i-IF/TA, there
12 was about a 6.6 percent of grafts were lost over
13 time whereas that was close to 20 percent if you
14 had i-

15 IF/TA.

16 If you had CG, that was also about 20
17 percent of those grafts were loss. But you only
18 had very small numbers that actually had that. So
19 it's a problem we had if we were recruiting people
20 to a study with that. We weren't going to get
21 many events that were going to be people recruited
22 into that. There were slightly more with CV. But

1 certainly, i-IF/TA was something that we saw a lot
2 of and had the same sort of proportion of graft
3 loss as the other pathological events.

4 So the other thing we then looked back,
5 that's sort of looking forward. If you've got i-
6 IF/TA, what's the future hold. The other one is
7 then to take i-IF/TA and then look back to say,
8 well okay, what type of events did this look for,
9 did this correlate with. So if you're going to
10 have a surrogate marker, then it should correlate
11 with clinical -- prior clinical -- early clinical
12 events that would be consistent with what you're
13 trying to treat. And also, if you're going to do
14 an intervention, that you had some pathological
15 process you're going to intervene with. And so,
16 what we found here that if you looked here on the
17 x axis at i-IF/TA, that if you looked at early at
18 one-month and three-month i- scores, that that
19 correlated pretty well.

20 So people that had early inflammation
21 were very likely to have i- IF/TA at one year,
22 both on their one-month and three-month biopsies.

1 The other thing again was whether you'd had prior
2 rejections. So in other words, if you'd had one
3 or two prior acute cellular rejections, then that
4 was very lucky, very likely to correlate with i-
5 IF/TA and was also very, very likely to correlate
6 with having interstitial fibrosis at one year.

7 The next thing we looked at, this was
8 not our controlled trial. This was really looking
9 at an era when we had different immunosuppression
10 and looked at cyclosporine and patients who'd been
11 on cyclosporine and tacrolimus. And there were
12 different event rates. So certainly the era and
13 the immunosuppression was able to modify the
14 histological events with these events being far
15 more prevalent in patients with cyclosporine than
16 in those with tacrolimus and also with the chronic
17 score. So you're more likely to get interstitial
18 fibrosis and tubular atrophy if you'd been on the
19 era when we were using cyclosporine compared to
20 those with those who are on tacrolimus.

21 So basically, what we found was that i-
22 IF/TA was predictive of graft loss. It was

1 associated with early clinical events that would
2 be consistent with the histopathological events
3 and it seemed to be modifiable by immune
4 suppression, which means it would be a pretty good
5 surrogate endpoint you'd think for having a
6 clinical trial. So I think we're going to
7 revalidate this in a kidney group rather than a
8 kidney/pancreas group. I think there's a few
9 things we need to think about in this meeting
10 we're having here, like if we're doing protocol
11 biopsies, how many patients, going to have to get
12 that.

13 If you're doing -- if that's going to be
14 the endpoint, how many people cannot get that
15 biopsy and still have a trial be valid. I think
16 there are events like that. I'd be keen to hear.
17 I hope Jesse might be looking at some of those
18 things or can give us some off-the-cuff advice
19 about that statistical perspective for missing
20 data points. So thank you. That's all I have
21 here.

22 DR. CAVAILL Thank you, Dr. O'Connell.

1 Our next speaker is Dirk Kuypers, who will be
2 speaking to us about early predictors of five-year
3 fibrosis (ci) and protocol biopsies. Thank you.

4 EARLY PREDICTORS OF 5-YEAR FIBROSIS (ci) IN
5 PROTOCOL BIOPSIES FROM SOC-

6 TREATED PATIENTS

7 DR. KUYPERS: Thank you. I wanted to
8 share some data which we are looking at, at the
9 moment, at our center which are related to
10 effective fibrosis and grafts in the long-term, if
11 there are actually any predictors in that and
12 predictors that we are examining now in our lab.
13 I'll give you just a background why we are doing
14 this analysis. We know that fibrosis is a final
15 common pathway of all the injuries that the graft
16 sustains early on, ischemia reperfusion, biopsy-
17 proven acute rejection but also DSAs and patients
18 who are highly sensitized. The final common
19 pathway of fibrosis is maybe less well-
20 understood. It's complex in any way. And we have
21 taken an interest in a sort of reverse manner.

22 What we have done is we've been running

1 a transplant protocol biopsy program since 2004.
2 And we have looked at our biopsies in a sense that
3 what we have tried to do is take it from the
4 biopsies, from individual donors, the proximal
5 tubular cells and immortalize them and grow them
6 in the lab. The idea is that we can then expose
7 these cells to different drugs that patients are
8 on and see how these proximal tubular cells react
9 or responds to a dose increment in the different
10 drugs that we use in clinic. And I usually am
11 going to talk about standard of care, meaning
12 tacrolimus, MMF and steroids.

13 Now, what we have seen is that the cells
14 react differently responding to the standard of
15 care immunosuppressive drug, depending on, amongst
16 other things, the genotype of the donor. And so,
17 what we do now is when patients come up from our
18 protocol biopsy or biobank with a specific
19 genotype, then we can take out these cells, grow
20 them in the lab and see how they individually
21 respond to the drugs. And that's why we were
22 interested in what happens to fibrosis in these

1 patients because we now have identified a panel of
2 about nine molecules which are involved in the
3 fibrosis process. And we're going to test these
4 molecules in a prospective study and in a clinical
5 trial.

6 What I want to show you is that we took
7 one of these markers as an example just to see how
8 much information such a marker, which comes from a
9 response in the lab, what that would add to the
10 clinical practice in terms of measuring this
11 marker in the urine and maybe also staining for it
12 in biopsies. So what I'm showing you is patients
13 who had a biopsy at three months, which is about
14 370 patients which are followed up for five years
15 and about 200 of these patients had also a five-
16 year follow-up biopsy. There is a smaller cohort
17 of patients who we were specifically interested
18 in, in the fibrosis process, and that was patients
19 with a protocol biopsy at three months, which came
20 back with an interstitial fibrosis score of zero.

21 So as you can see, these are patients
22 all treated on a tac, MMF and steroid regimen.

1 There's a mix of different types of donors in this
2 cohort. What we see if we look at the scores of
3 pathology, then we see that we have an increase in
4 scoring overall. It seems to be that we're
5 dealing with a low risk population in the sense
6 that we do not see a lot of CG, for instance. If
7 we follow these up, these patients for five years,
8 we don't actually see a significant increase in CG
9 score. And if we look for a part of these
10 patients that the development of DSA were about 2
11 to 3 percent per year after transplantation.

12 You can also notice that the graft loss
13 is fairly low in this specific cohort. We had 30
14 patient deaths. But we had only eight grafts lost
15 that were adjusted for death with a functioning
16 graft. Now, when we looked at three months
17 predictors, classical clinical predictors but also
18 histological predictors, for what we're going to
19 see in the five-year follow-up biopsies of these
20 patients, and we also correlated with not only the
21 chronic scores but also with the GFR at 60 months.
22 Then you see that overall donor age always comes

1 up as the most important predictor, the most
2 persistent predictor in these trials.

3 Early on graft function already reflects
4 later graft function and acute rejection does the
5 same. However, none of the immediate Banff
6 qualifiers that were present at three months was
7 predictive of what happened in later stages and
8 definitely not in terms of what happened with
9 graft function. When you did the same in
10 multivariate analysis at 12 months, again, donor
11 age was persistent. GFR at 12 months was also
12 predictive of course of what happened later on.
13 And biopsy-proven acute rejection also.

14 Proteinuria came out as a risk factor here. I
15 will show you this later on. This was not the
16 case in our further analysis.

17 Now, at this stage of 12 months, if you
18 substituted ci score at 12 months with the total
19 chronicity score, it didn't make a difference, as
20 I said, in our low risk population. And again, if
21 you looked at the interstitial fibrosis combined
22 with inflammation, it did also not improve the

1 model. When we then split these patients up in
2 those who declined renal function and we took a 10
3 milliliter decrease in GFR over the five years
4 when the biopsies followed each other up as a
5 significant decrease, we had 99 decliners. And
6 for multivariate analysis, all the risk factors
7 that were associated with decline, you can
8 identify and you recognize them from clinical
9 practice. GFR, 12 months, proteinuria, donor age
10 and patients who had a re-transplant. Again, when
11 we did that between three months and five years,
12 we had 96 decliners and the same risk factors came
13 up in terms of predicting decline of more than 10
14 ml/min.

15 Now, as I said, the biopsies that
16 interested us the most from the information which
17 we gained from the cell model, the proximal
18 tubular cell model, were the biopsies which had a
19 ci score of zero, came back from our pathologist
20 at three months and that were 225 biopsies the
21 case. In this group, graft loss was even lower
22 and patient death was also lowered where 18

1 patients who died in this specific cohort of 225
2 patients. We also identified here patients who
3 had functional loss. So decliners versus patients
4 who did not decline more than 10 ml/min. Then
5 again, the same classical risk factors as in the
6 previous cohort, the total cohort came forward as
7 predictors of declining GFR. As you can
8 appreciate when we used chronicity score together
9 with the eGFR and the donor age, also that was a
10 risk factor for further decline.

11 Now, one of the factors that we looked
12 at and that came back also from the cells which
13 were exposed to immunosuppressive drugs, which
14 connective tissue growth factor, which is a
15 molecule which is slightly simpler than TGF better
16 because that's far less post-translational
17 modifications. And we have previously shown in
18 another cohort of patients that patients who
19 developed actually interstitial fibrosis in a
20 cross-sectional way that degree of interstitial
21 fibrosis correlates with the CTGF that they
22 excrete in the urine. And this was corrected for

1 alpha-1-microglobulin. So it's not just a marker
2 of tubular injury. It's independent of alpha-1-
3 microglobulin concentrations in the urine. And the
4 CTGF in the urine predicted this together,
5 adjusted for age. Again, donor age as predictor
6 and also eGFR.

7 What triggered our interest was actually
8 when we looked at the three month biopsies again
9 in these patients who had no ci score at three
10 months and we then progressively looked at the
11 two-year protocol biopsies in these patients, we
12 could identify those who developed interstitial
13 fibrosis and those who did not. Well, actually,
14 the excretion of the CTGF in the urine at three
15 months was higher in patients who subsequently
16 developed any score of ci later on at two years.
17 So that's why we combined the urine excretion of
18 CTGF with the staining in the biopsies in the
19 cohort I just illustrated at 225 patients to see
20 if excretion from this pro-fibrotic molecule
21 together with staining which was then also
22 confirmed by in situ desensitization and to semi-

1 quantify that score, if that would add to the
2 predictive power.

3 Well, as you can see here, in
4 multivariate analysis, donor age again comes out
5 as a predictor of fibrosis at five years. But
6 CTGF positivity in the graft as well. So
7 increasing degrees of interstitial fibrosis at
8 five years are correlated with CTGF positivity
9 earlier on, early after transplantation. There
10 was no functional correlate for all clarity, donor
11 age, renal function at three months and BPAR at
12 three months were still the only predictors in
13 multivariate analysis for renal function at five
14 years.

15 Now, in multivariate analysis, when we
16 looked at those patients who had a pristine biopsy
17 in terms of ci score at three months but who
18 progressed over five years to develop any degree
19 of ci score, and that was 81 of the patients, so
20 64 percent of all patients. And we looked at
21 predictors of three months, again, donor age,
22 urinary CTGF and CTGF staining were predictive of

1 this process. This seems to be of value. But if
2 you compare that then to the predictive power and
3 that's on the right lower level there, if you see
4 the predictive power, it doesn't really increase
5 dramatically and definitely not in a clinically
6 significant way if you add that to preexisting
7 classical risk factors for progression.

8 Again, interstitial fibrosis at any time
9 cross-sectional correlates which function. But
10 what was also interesting from our point of view
11 and with our interest in how fibrosis takes place
12 in the patients who progressed or who did not
13 progress between three months and five-year
14 biopsies in terms of fibrosis, this was not
15 noticeable in terms of functional decline. So in
16 five years' time, the development of any degree of
17 interstitial fibrosis does not translate in loss
18 of renal function, not in five years at least.

19 So in conclusion, donor age is still the
20 single strongest classical determinant in the
21 sense that it is persistent for fibrosis at five
22 years after transplantation as assessed by

1 protocol biopsies in our low immunological risk
2 cohort. At five years, it's still determined by
3 the classical risk factors, which we have all
4 known to be associated with graft. We did the
5 interstitial fibrosis and graft function at five
6 years. What we did observe was that patients that
7 developed any degree of fibrosis that was
8 associated with donor age but also with this
9 interstitial staining of CTGF.

10 While in patients without fibrosis early
11 in the biopsy, development of that fibrosis was
12 again related not only with staining but also with
13 urinary secretion. It shows us however that one
14 single marker does not add to the clinical value.
15 So adding one of these potential pro-fibrotic
16 markers in a classical clinical model does not
17 actually help clinicians. And we are convinced
18 that we need to do more simultaneous or combined -
19 - combining these markers in order to get more
20 information that will be of clinical value. And
21 that I think concludes my talk. Thank you.

22 DR. CAVAILL Thank you, Dr. Kuypers. Our

1 next speaker is mark Stegall, who will speak to us
2 about accelerated approval, Subpart H and
3 surrogate endpoints for graft loss.

4 ACCELERATED APPROVAL (SUBPART H)
5 AND SURROGATE ENDPOINT FOR GRAFT
6 LOSS

7 DR. STEGALL: All right. It's very
8 clear to me that there's nothing that I can say
9 that would actually interest you at this point in
10 the day. Let's be real. I taught a year of high
11 school. And the worst class was the sophomores
12 right after lunch. I mean, they were bright kids,
13 nice kids. But they were animals at 1 o'clock.
14 They all wanted to go to sleep, just like you
15 people do right now. And actually, I'm not that
16 far away from you.

17 So how many kidney transplants do we do
18 in the United States every year? About 16,000,
19 17,000, right? There you go. See it's really --
20 it's a pretty smart group. I mean, they got into
21 medical school at one point in their life. They
22 just stopped thinking after that. How many are

1 living donors of the 16,000? Eleven thousand.
2 All right. There's about 5,000 deceased donors.
3 Okay. What is the five-year death-censored graft
4 loss rate in the deceased donor group? These are
5 getting harder. There you go. You can't call a
6 friend. Seventeen, eighteen percent. It's
7 actually in the paper we wrote. You should -- you
8 know, it's good. It's 17, 18 percent of the
9 death-censored graft survival.

10 So really, about 82 percent of those
11 kidneys are still working. I mean, the graft
12 survival is really good. And for living donor, I
13 think it's about 90 percent, 89 percent or
14 something like that. It's -- so a year graft
15 survival is what a lot of people are seeing,
16 right? We're putting -- obviously you can find --
17 if you put a really bad kidney into a patient
18 who's noncompliant, yeah, if you can really just
19 set it up, it won't work. But most patients
20 actually do quite well. And I think that -- and I
21 think that a lot of patients actually are trying.
22 That's the other thing.

1 And we talked about this before about
2 what do I tell a person who's actually compliant
3 and really trying and yet something happens. And
4 I think that that's kind of where we are. What I
5 learned today actually is if we design something
6 and it fails, we'll be in very good company,
7 right, that people have been doing this for a long
8 time. But I do think that there's enough data
9 that we can start to at least walk down this road
10 about putting things together. Again, I think the
11 graft survival is still important to people,
12 right? Don't you think? It's still the endpoint
13 that we're kind of interested in. And I think
14 that that would be definitely down the road to
15 what we want to do. We want to improve graft
16 survival. There's multiple ways of doing that.

17 But I think there are people who have
18 received a transplant who are doing sort of okay
19 and but they still have problems along the way.
20 And those are the patients we need to focus on.
21 If 10 percent of the patients have subclinical
22 inflammation at one year, that's still 1,600

1 kidney transplants every single year.

2 Now, the other thing that was brought up
3 is I don't think people should do protocol
4 biopsies. I don't think people should. First
5 off, if 30 percent of people do protocol biopsies,
6 that's more than actually I think than people who
7 actually follow their patients. You have to have
8 a patient back and see them in clinic to have
9 protocol biopsies done. And some people don't
10 have the infrastructure to do them and should not
11 do them, just like they shouldn't do a positive
12 crossmatch kidney transplant. And also, it's
13 harder to justify doing a protocol biopsy when
14 there's really no treatment for it. So it's
15 definitely a learning process. At some point, if
16 there was actually a treatment for it, we actually
17 probably people would start doing it more. People
18 would actually come back if they were told there
19 was something that would actually affect their
20 outcome.

21 So I think that that's kind of where we
22 are today is that we are learning about this.

1 We're stepping down a pathway. And I think that
2 again, having beat my head against a wall for
3 many, many years thinking about this, subclinical
4 inflammation is just, in my opinion, the simplest
5 step forward in this area if you're going to
6 improve graft survival. It has the highest
7 incidence. And I'm talking about subclinical
8 inflammation of unknown etiology. It was
9 mentioned, well, we should learn the causes of
10 subclinical inflammation. That would be nice.
11 But we don't know. And it probably is a
12 heterogeneous group. And they're probably all not
13 going to respond to some new therapy. I got that
14 part too. It's an adult world. You don't always
15 get everything you want to turn out the way that
16 you want it too. But again, if you get half of
17 what you want, you know, you're a lot better off.
18 And I think that, again, we saw this afternoon
19 that probably a lot of this data is sort of
20 reconcilable.

21 And the real question I think is whether
22 we can develop some sort of consensus. And I look

1 directly at Dr. Mengel because I think the
2 pathologists are the key to this if we're going to
3 use histology, right? They have got to do a study
4 that I think would exclude polyoma. Can we
5 diagnose polyoma? Okay. And I think we can
6 exclude possibly peritubular capillaritis, unless
7 we find -- I think the other thing is when we
8 finally figure out what subclinical inflammation
9 does, we probably should start then looking at
10 targets that might be affected to change the
11 outcome, right? And maybe that's where genomics
12 does come in, or immunohistochemistry or something
13 of that nature.

14 And I think that what I learned this
15 afternoon, which was kind of a little bit of what
16 I was hoping to learn as I came in, was that the
17 pulling together of disparate databases might
18 really be helpful in some of the learning about
19 this and reassuring people that what we see in
20 Rochester, Minnesota is similar to what's seen in
21 Sydney, is similar to what's seen in Pittsburgh.
22 It's just a different -- maybe a little bit

1 different incidence. But in general, it's the
2 same histologic findings that we see, and that the
3 patients who have it have similar kind of
4 outcomes, within an order of magnitude. I mean,
5 not every patient does the same. And maybe type 1
6 diabetics have a little bit different, all this
7 kind of stuff. And I think it's important to say,
8 you know, you don't treat renal carcinoma with
9 tamoxifen.

10 So the idea is you should really not
11 treat polyoma virus with some sort of increased
12 immunosuppression. Most patients aren't going to
13 do as well. So again, we went through this
14 before. And I think that I'm just repeating
15 myself by saying that it looks as if that there is
16 some need for a methods trial to validate the
17 histology around this area. And I think that to
18 sit down and go through each step, and maybe
19 that's what we can do in the next couple of days,
20 and do that. And then, definitely we need
21 outcomes data. I think graft survival would be
22 the best outcomes data that we have. And

1 obviously step down the road here, and I think
2 that the other thing that I'm interested in are
3 combined endpoints. And I'm kind of open-minded,
4 not just looking at graft survival, but other
5 things that might also hinge on some of these same
6 processes. And I think I got that from that.

7 It's sort of a downstream effect for
8 being on certain types of immunosuppression. And
9 maybe there are certain types of patients that are
10 in this category and I don't really know what's
11 really wrong with them except that I have a biopsy
12 that has subclinical inflammation. But maybe that
13 patient has other issues surrounding their whole
14 immunologic/immunosuppressive regimen. DGF is a
15 good example. It does definitely beg the question
16 is it a patient management issue that we have,
17 right? Is that really the difference between
18 living donor and deceased donor? I can tell you
19 one of the things is follow-up is important.
20 Patients who don't come back for follow-up at the
21 Mayo Clinic have a lower graft survival than those
22 who do come back for follow- up.

1 And so, maybe just making that a bigger
2 deal is a way to improve outcomes in patients.
3 And we get CMS here and they give us big bucks to
4 pay for it and everybody would be happy. And
5 finally, I think that, you know, if we can get our
6 act together within the transplant community and
7 can have a nice dialogue with FDA, that pharma
8 will hopefully chime in also. Questions,
9 thoughts? I know. I'm sure I do. Thanks, guys.

10 DR. ALBRECHT: So, thank you, Dr.
11 Stegall, for getting us ahead of scheduled so we
12 can now take a 15-minute break and come back for
13 the next session. Thank you.

14 (Whereupon, the foregoing went off the
15 record at 3:13 p.m., and went back on
16 the record at 3:30 p.m.)

17 DR. BALA: The next talk will be by Dr.
18 Serena Bagnasco on learning from kidney allograft
19 biopsies in highly sensitized patients.

20 LEARNING FROM KIDNEY ALLOGRAFT
21 BIOPSIES IN HIGHLY SENSITIZED PATIENTS

22 DR. BAGNASCO: Thank you. I decided to

1 talk about highly sensitized patients because
2 these are patients that are at very high risk of
3 losing their graft and so could be the one that
4 most would benefit for a new type of intervention.
5 And also, since they represent in a way the worst-
6 case scenario, we have an opportunity to study
7 perhaps better than in other group the evolution
8 and progression of graft damage in these patients.

9 This is briefly the scheme that we use
10 for our incompatible kidney transplant program to
11 desensitize ABO and HLA-incompatible patient,
12 which essentially consist of plasmapheresis, IVIG
13 and then depending on the type of patients,
14 sometimes we use other agents as well. Recently
15 there have been some patients in whom we have also
16 used newer agents like eculizumab. Here is a brief
17 summary of the characteristic of our patients.

18 This is a slide that Dr. Krauss provided. This
19 was basically compiled in an analysis of patients
20 who were transplanted from '98 to 2010 and
21 included 318 patients of whom 69 were ABO-
22 incompatible, 249 HLA-incompatible and 26 were a

1 mix.

2 As you can see from the demographics, we
3 have a predominance of females, which is not
4 unexpected. And also, our program has a
5 predominately white prevalence of individuals. If
6 we move to immunologic status, as expected, a lot
7 of these patients, more than half were HLA-
8 incompatible group have had previous
9 transplantations. And the mean cPRA for these
10 patients is very high, about 83 percent. As far
11 as how good graft survival is, as in other
12 centers, the survival of the graft in HLA-
13 incompatible individuals is not as good as in ABO-
14 incompatible individuals as far as one year. We
15 have about 5 percent graft loss. On the -- on the
16 -- oops.

17 On the right panel, I summarize the
18 graft survival in this group of patients that was
19 described in different study and correlate to
20 specific study cited. And we can see that for a
21 relatively good survival at one and three years,
22 there is a significant decrease as we progress to

1 five and eight years post- transplant. So we
2 definitely need to do better for these patients.
3 We tried to analyze the graft function at one year
4 compared to standard living donor. This was done
5 in 2011. And we saw that looking at the ABO-
6 incompatible, the percentage of patients who had
7 eGFR above 60 was similar to the general living
8 donor population. But it was decreased to 41
9 percent in HLA-incompatible patients. If we go
10 beyond one year, we see that fortunately there is
11 a trend to a decreased function in HLA-
12 incompatible patients as we go on.

13 So we need to identify the factors that
14 leads to this progression of disease and try to
15 find remedies to this decline of function. So
16 now, I will spend some time describing the finding
17 of a study that we did and published in 2014 in
18 which we analyzed the histologic injury of 745
19 kidney graft biopsies and 129 patients who were
20 transplanted with positive crossmatch HLA-
21 incompatible kidney between 2000 and 2010. And
22 the follow-up for this study was about from one to

1 nine years. At our institution, we do protocol
2 biopsies in the incompatible patient at one,
3 three, six and twelve months.

4 But in this study, we included both
5 protocol biopsies as well as indication biopsies.
6 And the inclusion requirement for this study was
7 essentially to have two protocol biopsies at
8 least, one covering the early time from one to
9 three months post-transplant and another later on
10 between 6 and 12 months post-transplant. What we
11 wanted to do was analyze repeated measurement in
12 the same patient over time, looking at the graft
13 biopsy as well as the graft function in order to
14 capture early and late changes in individual
15 patients.

16 So looking first at how many patients
17 had rejection, we had about 70 percent of patients
18 who experienced rejection during the entire
19 follow-up. About 25 percent patients experienced
20 a clinical rejection. And 39 patients -- 39
21 percent of all rejection detected in biopsies were
22 subclinical, which is a proportion that was

1 similar to other studies on this group of
2 patients. As far as the proportion of subclinical
3 rejection that we saw in subclinical rejection, it
4 was about 36 percent within the first year and
5 less for the antibody-mediated rejection, about
6 13 percent.

7 We then started to look at several
8 histologic parameters of graft injuries, starting
9 with tubular interstitial scarring. Here I show
10 on the graph a sum of ci and ct meaning combined
11 tubular interstitial fibrosis and atrophy over the
12 first year and then afterwards. You can see that
13 there is a progressive increase over time which is
14 significant among different time point even within
15 the first year. And then, tend to increase
16 afterwards. We had the 41 percent of patients who
17 had tubular interstitial scarring combined score
18 more than one and 71 with a score more than one at
19 one year.

20 And looking at this patient, there was a
21 small but significant inverse correlation between
22 the degree of tubulointerstitial scarring at the

1 last follow-up and the last known eGFR value in
2 individual recipient. And we found that episode
3 of cell-mediated rejection in the first year did
4 not result in a higher degree of
5 tubulointerstitial scarring at 12 months and we're
6 not really associated with decreased graph
7 function compared to the whole group. Looking at
8 microvascular inflammation, we generally look at
9 the microvascular inflammation in glomeruli as a G
10 above one and peritubular capillaritis, PTC, more
11 than or equal to one.

12 We had glomerulitis detected in a total
13 of 434 biopsies, approximately 72 percent of
14 patients during the entire follow-up. And there
15 was a good correlation between glomerulitis and
16 inflammation in the peritubular capillaries which
17 was significant and there was also good
18 correlation between capillaritis and interstitial
19 fibrosis. This is a bar graph showing the number
20 of patients who exceeded glomerulitis in the first
21 year and, as you can see, significant proportion
22 was detected by a protocol biopsy. In general,

1 the first appearance of glomerulitis in the
2 individual patient was within the first three
3 months, specifically the median time of appearance
4 was 1.2 months and the average was 3.8 months. So
5 this is an earlier rejection -- an earlier lesion
6 in this group of patients. And also we noticed
7 that the patients who had the glomerulitis
8 detected in biopsies at one month tended to have a
9 lower eGFR at six months as 12 months compared to
10 patients who didn't have glomerulitis at one
11 month.

12 Moving on to transplant glomerulopathy,
13 which was the finding of cg above one, we observed
14 this lesion in about 47 percent of patient. And
15 the cg score overall appeared to be progressively
16 increasing from -- even from the early portion of
17 post-transplant course and later on in up to four
18 years. At that time, for that study, we didn't --
19 we considered only transplant glomerulopathy that
20 was evident in light microscopy.

21 There was no significant difference in
22 the 12 months eGFR between patients with or

1 without transplant glomerulopathy. But there was
2 a moderate but significant inverse correlation
3 between the degree of transplant glomerulopathy
4 and the last known eGFR in individual patients.
5 We then wanted to look at the time appearance of
6 first detection for individual parameter
7 glomerulitis and transplant glomerulopathy to see
8 whether and how many time we could say that
9 glomerulitis was a precursor of transplant
10 glomerulopathy.

11 So in this graph here, we saw individual
12 point representing the first appearance of
13 glomerulitis in the patients who developed that
14 change. And you can see that this is an early
15 lesion. And again, the median, most of the
16 patients tended to show that in the first month
17 post-transplant. And now, we look at the first
18 appearance of transplant glomerulopathy. And
19 here, the median lesion was 12 months, with an
20 average of 17 months. But you can see that there
21 is a disturbing proportion of patients who showed
22 this lesion even within the first year. So we

1 have even for these lesions that is considered to
2 be chronic, you could say that we have a
3 stratification of patients composed by early
4 progressor and late progressor. Of 61 patients
5 who developed transplant glomerulopathy, 95
6 percent had previous evidence of glomerulitis in
7 their biopsy. So we wanted to use these subgroups
8 to try to determine on average what was the time
9 that was passing between the first detection of
10 glomerulitis and detection of transplant
11 glomerulopathy.

12 So this is shown in this second graph
13 here. And you can see that between detection of
14 glomerulitis and first appearance of transplant
15 glomerulopathy, the median time was 12 months,
16 which not a lot of time. And the average of the
17 group was 15 months. Also we found that another
18 factor that was associated with the increased
19 rates of transplant glomerulopathy by year two was
20 the presence of detectable donor-specific antibody
21 after transplantation.

22 The fact that transplant glomerulopathy

1 is a bad thing to have in these patients was also
2 reinforced by another study from our group where
3 we looked at these graft survival in patients who
4 had transplant glomerulopathy at one year. And
5 you can see that those who have this lesion as a
6 significant lower graft survival compared to those
7 who don't. And also, there were other published
8 works recently showing that glomerulitis was an
9 important factor associated with the risk of graft
10 failure. Here is a recent work by Nabokov in
11 Transplantation, although this was done in
12 patients who were not incompatible. And also again
13 in patients who were not incompatible, it was
14 found that diffuse peritubular capillaritis was
15 associated with greater GFR decline after three
16 years.

17 So we need to do more for these patients
18 and improve the outcomes. But there are some
19 barriers to it. And as had been evident from
20 talks of different people at this symposium, there
21 are a lot of difference among U.S. and
22 international transplant centers, as far as

1 definition, technologies, criteria for pre-
2 transplant and post-transplant management. These
3 differences have not been systemically analyzed
4 and that should be done to identify best evidence-
5 based approaches to the care of these patient,
6 also for design of meaningful multicenter large
7 trials.

8 So I am part of a working group for the
9 Banff transplant conference focusing on highly
10 sensitized patients. And we would like to
11 determine the definition and practices of various
12 types of people who are dealing with these
13 patients, namely HLA-typing laboratories,
14 pathologists and clinicians who manage these
15 patients on a regular basis. And eventually, the
16 goal of our group, and I guess of everybody
17 dealing with these patients, is to develop
18 evidence-based recommendation for evaluation and
19 transplantation of these patients who have broad
20 sensitization and high-titer donor-specific
21 antibodies.

22 So we decided to do three questionnaires

1 for tissue-typing laboratories, nephrologists and
2 surgeons and pathologists. And here are some of
3 the questions that we posed during this survey.
4 And we hope we will have some response for HLA,
5 clinical and pathologists. And I will stop here
6 because I'm out of time. Thank you.

7 DR. BALA: Our next speaker is Dr.
8 Alexandre Loupy. He will be talking about
9 defining endpoints in transplantation, an
10 integrative multidimensional approach.

11 DEFINING ENDPOINTS IN TRANSPLANTATION:
12 AN INTEGRATIVE

13 MULTIDIMENSIONAL APPROACH

14 DR. LOUPY: Thank you very much. I'm
15 going to present you an integrative approach for
16 defining an endpoint in transplantation which we
17 called the iBox. And let me start with the good
18 news for the industry and drug market development.
19 So the transplant universe is about 1 million
20 people, two-thirds being kidney transplants. And
21 guess what? Those people need immunosuppressive
22 drugs. I read recently that the number of

1 turnaround patients worldwide is probably equal to
2 the number of living donors dying after surgery.
3 So it's not a large number. And I think there is
4 room now for immunosuppressive drugs. So it's
5 120,000 new organ transplants per year. And the
6 estimated number of organ transplants that fail
7 each year is over 50,000 organs.

8 So the unmet need is for optimizing
9 selection of patients for clinical trials. And
10 you've seen that clinical trials are lacking in
11 this field. We need to achieve more personalized
12 care. And there is lack of consensus on staging
13 system aiming to predict the key allograft
14 survival risk profile, which leads to potentially
15 an appropriate patient management and also
16 confusion in results development. So what are the
17 milestones in transplantation? So we need to
18 improve discrimination for predicting allograft
19 survival. We need to better stratify patients for
20 various treatment options. We need to ensure that
21 the groups are well-balanced in clinical trials.
22 It's very important. We need to better optimize

1 the studies' design and also spare time. It's now
2 you have to wait for eight years before seeing
3 differences in terms of graft outcome.

4 So we need very proximal upstream
5 surrogate endpoints for predicting long-term
6 failure. And we need to improve patient health-
7 related quality of life and treatment cost
8 effectiveness ratio. So what was the mistake? The
9 mistake maybe was to start for treatment and we
10 did not have the basis. So the basis really is to
11 reassess using the complementary tools that are in
12 this activity stage and to better identify re-
13 stratification. And then, we will include the
14 right patient and the right protocol and we will
15 evaluate this risk and the surrogate endpoint for
16 those clinical trials.

17 So why did we fail? There are a lot of
18 issues in transplantation. There is an important
19 heterogeneity in this disease among kidney
20 allograft patients. And also regarding the
21 allograft survival risk profiles. So the current
22 state of the art is leaded by missed diagnosed,

1 incorrect classification of disease, absence of
2 connections between specialties and lack of
3 cutting-edge technologies applied prospectively in
4 large cohort. So what we need, we need
5 multidimensional transplant assessment. And
6 prognoses are important. We are already moving
7 our days to precision medicine. So how can we
8 provide concrete answers to the unmet need for
9 refining surrogate endpoints in the field of
10 transplantation?

11 So our results strategy is the
12 prospective multicenter cohort of unselected
13 patients. All patients included in these studies
14 are extensively phenotyped. We do precision
15 diagnosis. We have three pathologists reading the
16 biopsies, blinded for a lot of clinical elements.
17 We are performing protocol biopsies universally,
18 not only in patients doing well or doing bad.
19 They all have a protocol biopsy at three months
20 and one year. All patients have DSA assessment,
21 multiple time points using the same platform,
22 cutting edge technologies, MFI. And we have

1 kinetics. We have timelines. We know what the
2 diseases are and we have eight years' follow-up in
3 this cohort now. And we have a large number of
4 events.

5 So having said that, we can apply the
6 tools in the iBox strategy, smart data,
7 performance calibration, validation, artificial
8 neural network, decision trees and machine
9 learning. So this is what we have. And the iBox
10 strategy, I'm going to be defining now. We have
11 patients and we have been prospectively collecting
12 all donor characteristics, including days over
13 biopsies, many variables as you can see, recipient
14 characteristic at transplantation and also
15 transplantation characteristics, ischemic timing,
16 et cetera, et cetera. And days DSA using Luminex
17 single-antigen technology.

18 So we have all these baseline
19 assessments. And we move to one year. One year
20 is a very important endpoint in transplantation.
21 And we have including the validation cohort now
22 more than 2,000 patients extensively phenotyped

1 and at one year we do a protocol biopsy. They all
2 have a biopsy and we measure GFR, proteinuria,
3 histology, Banff scoring and anti-HLA and DSA.
4 And of course we also integrate what has happened
5 in the first year. It's very important to know
6 whether patients experience before this biopsy BK
7 virus, nephropathy or had evidence for CNI
8 toxicity in a biopsy for cause or rejection TCMR
9 or ABMR or recurrent disease is very important.
10 And we also integrate in the first year not only
11 the biopsy but the DSA assessment.

12 So it takes a lot of efforts and also a
13 lot of money. But we can follow these patients.
14 And we are looking at graft loss. It's very
15 important to look at graft loss two, five and
16 eight years post-transplant. And we also need to
17 know whether what happens after one year. So
18 since we have all this information about all the
19 biopsy for cause performed after one year with DSA
20 assessments simultaneously, we can also evaluate
21 the performance of the score after one year and
22 how it performs.

1 We integrate all of these in
2 mathematical equations, including the world
3 spectrum of graft injury. And of course these
4 models have to be fully validated. They have to
5 be externally validated to look at the
6 exportability of the data. It's very important.
7 They have to be internally validated using
8 bootstrap resampling, cross-validation. I'm not
9 going through this in detail because I don't have
10 enough time. So the models need to have high
11 accuracy. Performance calibration, discrimination,
12 c-statistics, NRI, IDI have to be performed in
13 this cohort. The models need to take into account
14 multiple entries, collinearities independency.
15 It's very important to do complementary approach
16 not only do to the classical cox model but also to
17 run the model and see how they perform using
18 decision tree, random forest and all artificial
19 neural network or integrative nomograms.

20 As we have multiple entries with
21 collinearities between variables, we need to know
22 whether there are real independency across the

1 cohort. And the models need to be dynamic, not
2 only one time point. It needs to include time.
3 It needs to be simple and it needs to quantify the
4 amplitude of the effect. We are not here to find
5 the new biomarkers. But we need to have robust
6 biomarkers simple to use, including graft
7 histology function and quantify these
8 independently and the amplitude of these effects.
9 And last, the models need to be biologically
10 meaningful.

11 So this is the global strategy I'm
12 summering here. So the iBox is just concentrating
13 all these data in a robust epidemiological model
14 including histology, clinical biological factor,
15 immunology and integrative and highly dimension
16 analysis. So this is summary of what you can get
17 in these cohorts. And you see the Kaplan-Meier
18 curves derived from the model integrating those
19 parameters, identifying four groups with these 10
20 prognosis.

21 We are eight years after the evaluation,
22 which means seven years -- eight years post-

1 transplant. And you can see here a group with a
2 very low risk of failure, a second group with a
3 low risk of failure, a group with intermediate and
4 a group with a very high risk of failure. So this
5 is what the model gives. It's one of the models
6 is to segregate for distinct, highly distinct
7 group with highly distinct prognosis. It's very
8 important that the curves have to be different.

9 So I won't go through all the models and
10 the validation in detail. But there are 33 entries
11 in the model. And this is the way you end up with
12 these parameters. First, scarring, if the Banff
13 score. Second parameters are injury,
14 microcirculation injury and the Banff score,
15 complement for the allograft deposition, anti-HLA
16 DSA, allograft function, of course, GFR at the
17 time of biopsy and also proteinuria which is a
18 strong biomarker associated with failure. So the
19 iBox gives us a c-statistic of 0.87. So the c-
20 statistic says that if you are over 0.7, it's
21 pretty fair. If you are over 0.8, it's a very
22 good discrimination of your model. So many

1 nomograms used also in the cancer field have 0.7
2 c- statistic. So I think it's pretty good
3 accuracy of this model in this cohort.
4 So I was talking about calibration. The
5 model needs to be calibrated. So you have to
6 compare the predicted allograft survival as
7 compared to what is really measured. Predicted
8 versus observed. So you can see here the
9 calibration curves regarding three years survival,
10 five years and also seven years graft survival.
11 And this is the nomogram. So you end up with a
12 nomogram.
13 So the nomogram runs the parameters I
14 was talking about. And each parameter has upon
15 direction -- it has all been -- including
16 ponderation of the variables. So you have DSA.
17 You have the IF/TA score, GPDC and C4d deposition,
18 eGFR and finally, proteinuria. So each parameter
19 gives you a score and some of the score projects
20 you in the total points regarding your allograft
21 survival probability. So let me show you an
22 example of the iBox, if I have access here to

1 this.

2 Okay. So this is a French Google. So
3 you have the baguette here. But okay, let me just
4 -- okay. So it's a complete collapse of the
5 presentation now. Thank you, Steve Jobs. Okay.
6 I will -- yeah, it's Bill Gates. That's Bill
7 Gates. You're right. So I won't show you that.
8 But we have a software in which you can integrate
9 these parameters and you can just enter the data
10 and then you will get the predicted probability of
11 failure at three, five and seven years post-
12 transplant.

13 So can I go further? Okay. So I will
14 be concluding with the iBox approach. Though this
15 is an integrative model established with a full
16 spectrum of allograft parameters. It's a unique
17 cohort with a high level of detail, long- term
18 follow-up, kinetics, DSA assessment and not only
19 DSA but all parameters that may encounter for
20 allograft outcomes. We developed a prognostic
21 nomogram that precisely and accurately predicted
22 the individual long-term graft survival

1 probability. The iBox is validated. It's a
2 multi-centric, validated in two external
3 independent centers in France. It's exportable
4 and it's dynamic because we validated the iBox
5 equations after one year using ROC -- time-
6 dependent ROC curves as well.

7 So the iBox could be useful for patient
8 selection in clinical trials and/or as a
9 stratification factor for randomization into
10 clinical trials to reduce the variability within
11 arms. It's very important. And it's robust and
12 it's also an early surrogate endpoint. Now, if we
13 are looking at graft survival we cannot wait
14 anymore eight years to see the differences. And I
15 think the industry is really looking for a while
16 very early surrogate endpoints. We can't predict
17 the future. I'm just classifying you in one of
18 the four strata of allograft outcomes. So it may
19 be also important for guiding clinical management
20 of patients, spare time and also spare money. I
21 would like to thank you for your attention.

22 DR. BALA: Thank you, Dr. Loupy. The

1 next speaker is Dr. Lihui Zhao, will be talking
2 about composite graft prediction index.

3 COMPOSITE GRAFT PREDICTION INDEX
4 (CGPI)

5 DR. ZHAO: I appreciate the opportunity
6 to speak here on behalf of my co-authors on this
7 project. So basically we are trying to develop a
8 composite graft predictive index for graft
9 survival and then I'm going to present how we
10 abstract the data and the procedure we built our
11 risk model and then some results for assessing the
12 discrimination and prediction performance. And
13 then, I will share the results with some
14 conclusion.

15 So the CGPI was conceived as a clinical
16 question framed by Dr. Bruce Kaplan, Bing Ho and
17 Anton Skaro. And they probably will be the better
18 person to present the results. Unfortunately,
19 they are all not available. So I have no clinical
20 experience and I'm a statistician. So just
21 letting you know. So if you have any clinical
22 questions, you can refer to the three doctors.

1 And the result here considers preliminary and have
2 not been submitted yet. We are still getting more
3 data. So the results may change.

4 So here's the introduction. As you all
5 know well, the SRTR adopted patient graft survival
6 with outcome and the patient graft survival has
7 been increased over the past years. So I guess
8 that's motivation why we're now interested in a
9 surrogate endpoint trying to assess the endpoint
10 rather than graft survival to conduct well-run
11 trials. So here's just a table showing the
12 results that the creatinine and protein are very
13 predictive for kidney failure. As we can see in
14 this table, if you have a decreasing eGFR and the
15 relative risk increases very dramatically.

16 So come back to the problem we are
17 interested in is trying to build the best possible
18 prediction model for grafts and the patient
19 survival following kidney transplant and the
20 predictor we are trying to use is to use the lab
21 and pathology data collected after
22 transplantation. Specifically, we're going to use

1 just the biopsy result at one year after
2 transplant as well as the associated lab data. So
3 the method here is this is a single center
4 experience at a Northwestern Comprehensive
5 Transplant Center. All those transplant kidney
6 biopsy results were read by a single renal
7 pathologist. So the reading is pretty consistent
8 across all the data we have. And we used the
9 Banff 2007 scoring system.

10 We have a total of over 1,500 biopsies
11 that have been abstract up to date. But for this
12 preliminary result, we only have about 751 persons
13 with biopsies included. So although we have lots
14 of repeated lab data between the transplant date
15 and the one-year biopsy date, mostly is repeated
16 measure of creatinine. We have over 300,000
17 observations. So for the data of transplant, days
18 of follow-up, patient death and graft survival as
19 well as donor-recipient variables, we were
20 abstracted from the UNOS and SRTR data. So as I
21 mentioned earlier, for this initial analysis, we
22 used the 751 patients that we claimed with

1 biopsies done approximately one year following
2 transplant and their associated lab values.

3 For the statistical analysis, we used
4 the Kaplan-Meier estimates for the survival
5 probabilities and we ran a Cox regression model
6 with stepwise variable selection procedures to
7 build a multivariate model using creatinine
8 protein and the individual biopsy results, namely
9 the Banff 2007 sub-scores at one year after a
10 kidney transplant. So those included the
11 antibody-mediate rejection, the C4d and the Banff
12 sub-scores like GIVT, ci, cv, ct and AH and MM.
13 Those are the potential predictors we started in
14 the model. And so, then, after we build this
15 model, we examined the added value of biopsy
16 results in the discrimination for long-term graft
17 survival prediction using c-statistics. We also
18 examined the added value in risk prediction as
19 well, as we know the c-statistics sometimes is not
20 very sensitive if we got already a pretty
21 reasonable c-statistics.

22 And the metric we used for assessing the

1 added value in risk prediction is based on this
2 UNOS statistical medicine paper. This table is
3 just a baseline characteristic of the
4 participants. We included -- as we can see, our
5 center did a lot of living donor transplant. We
6 have about 40 living donor transplantation. The
7 mean time in this cohort was four years with
8 extended vision two years. And here's the graft
9 survival over the follow-up was about 90 percent.

10 So this -- I'm just showing you Kaplan-
11 Meier estimates for the graft survival and the
12 patient survival for the cohort that we have. So
13 from here, it seems that we can estimate -- well,
14 for the prediction, we can do it pretty long-term,
15 for example, of six years of survival. So that
16 would be the time point that we're going to use
17 for estimate of c-statistics. So as we mentioned
18 earlier, we used the Cox regression model with
19 stepwise regression, stepwise variable selection
20 procedure, starting with from the variables I
21 mentioned earlier. And this is the model we ended
22 up with. So including serum creatinine and

1 protein. The protein, we have three categories
2 here, inactive, trace or greater than 300. And
3 then, there are two biopsy sub-scores remaining in
4 the model were antibody-mediated rejection and
5 interstitial inflammation.

6 So this plot showing the ROC curves with
7 the creatinine and the protein predictive model as
8 well by adding the biopsy results with the
9 previous multivariate model we ended up with. So
10 we can see the c-statistics were by using only
11 creatinine and protein was 0.745 by adding biopsy,
12 we increased it to 0.77. The incremental value in
13 c-statistics is about 0.03. And we got a
14 creatinine of -.01 to a 0.06 which was not
15 statistically significant. But it's promising.
16 We are going to gather more data. So maybe we
17 will increase the power. And as I mentioned
18 earlier, we know the c-statistics is not sensitive
19 to -- its' not sensitive to address the added
20 value of an added biomarker if we already got a
21 pretty reasonable c-statistics.

22 And also, the c-statistics is just for

1 discrimination. It does not take into account the
2 prediction accuracy. So we used the UNOS approach
3 to try to figure out whether there's added value
4 in risk prediction by adding the biopsy result.
5 And here's the graph we got. I'm going to go
6 through this graph here. So we have a P1 hat and
7 a P2 hat. The P1 hat here will be the predicted
8 six-year graft failure risk if we just use the
9 creatinine and the protein. This too predicts.

10 And then, this P2 hat will be the --
11 what will be the predicted graft failure risk at
12 six years if we add the two biopsy results that
13 were selected in this model. So we have the two
14 predicted risks for graft failure at six years and
15 then we take the difference of the one predicted
16 by the multivariate model, including biopsy and
17 the model without the biopsy. And so, thus we got
18 this D hat which is the difference between the two
19 risk predictions. So if there's no added value of
20 the biopsy result, then this P2 hat and P2 hat
21 would be pretty much tangled together and this D
22 hat would be -- would be sort of random and has

1 the same distribution for the people who had the
2 graft fail in the first year and the graft did not
3 fail before six year.

4 So if we recall those people with graft
5 failure before six years, the cases and the people
6 who did not have a failed graft at six years, the
7 controls, then now we can look at the distribution
8 of this \hat{D} that which was the difference in the risk
9 prediction of six-year graft failure between these
10 two models and we can look at the distribution of
11 that, this \hat{D} among the cases and among the
12 controls. So this F and G essentially will be the
13 CDF or the distortion function of this \hat{D} among
14 cases and the controls.

15 If there's no added value of the biopsy
16 result, then we would expect these two
17 distributions would be pretty much identical. So
18 then on this curve here what we get is we see we
19 have a thicker CDF empirical CDF -- not really
20 empirical CDF, but estimate of the distribution of
21 this F. So we have the thick curve and a thinner
22 curve. So the thicker curve would be

1 corresponding to estimate of F and the thinner
2 curve would be estimate of G. So then now we can
3 use different metric to quantify how different
4 these two curves are. If they are significantly
5 different, then that means adding the biopsy
6 result, it's making a difference.

7 And specifically, for example, if we
8 look at this here, this value of zero here,
9 meaning the probability of $D \leq 0$ for the cases, we would then expect the
10 zero for the cases, we would then expect the
11 probability of this score, less than or equal to
12 zero for the cases to be small because for the
13 cases we would expect that the predicted risk from
14 the biopsy would be higher than the predicted risk
15 from only the creatinine and the protein. So that
16 means this D tends to be positive for the
17 cases and on the other hand tends to be negative
18 for the controls because for the controls, if the
19 model is better than creatinine and protein only,
20 then it should predict that person who is a
21 control has less risk of graft failure at six
22 months. So that means for --

1 DR. ALBRECHT: Dr. Zhao, less than a
2 minute, please. You're almost out of time.

3 DR. ZHAO: That means for this zero, we
4 would imagine this plot should be higher for the
5 thinner curve and lower for the thicker curve. So
6 this difference between these two plots naturally
7 quantify the difference in the probability that
8 the added variable of biopsy would classify that
9 person at a higher risk than if is a control
10 person than it will have the person in the lower
11 risk for the control person. And then, we also
12 have the area under this curve --

13 DR. ALBRECHT: Dr. Zhao, if you could be
14 so kind as to wrap up.

15 DR. ZHAO: And yeah, so the thinner
16 curve would have higher risk -- would have higher
17 area under the curve. So here, this table showing
18 the result for the three metrics and we see that
19 for mostly we show the significant difference for
20 by adding the biopsy result. So then we can do
21 risk stratification by using the index we created,
22 the prediction index using the -- adding the

1 biopsy result and then we call that the index into
2 two tertiles.

3 Here show the three groups and we can
4 see there are very nicely separated for the graft
5 survival and the p value based on logarithmic
6 testing is highly significant and also the two
7 tertiles had much higher risk than the first
8 tertile. And similarly, for the patient survival.
9 So finally, we are getting more data and we are
10 going to use the more longitudinal measure of
11 creatinine and protein to increase the power of
12 this study. So in conclusion, adding the biopsy
13 result might provide a better prediction model by
14 using only creatinine and protein and also it may
15 improve risk stratification. Thank you.

16 DR. BALA: Thank you, Dr. Zhao. Our
17 last speaker for this session is Dr. Jesse Schold,
18 who will be talking about composite endpoints
19 registry data.

20 COMPOSITE ENDPOINTS: REGISTRY DATA

21 DR. SCHOLD: Good afternoon. I don't
22 have any disclaimers to announce prior to the

1 conversation, other than most of what I'm going to
2 mention here has been covered at different levels
3 during the session and I'm not as nimble as Dr.
4 Mengel to adapt my slides along the way. But
5 hopefully, just reinforce a few of the important
6 concepts here. So when we talk about composite
7 endpoints, first off, I think there's a lot of
8 potential value. There's a lot of reasons I think
9 it's applicable for transplantation.

10 But there are a lot of devil's in the
11 details in how to logistically pull it off and
12 figure out what those endpoints are that would be
13 applicable in different scenarios. When we talk
14 about just in general the use of surrogate
15 endpoints, which have been, again, talked about in
16 detail, we think about one way to think about
17 whether the value of them, or to use the classic
18 Prentice criteria in thinking about how a
19 surrogate is related to a primary endpoint and
20 what the treatment of intervention, relationship
21 between those are, you've heard this morning from
22 Dr. Fleming many classic examples of when those

1 purported surrogates do not necessarily manifest
2 themselves and the outcomes that we desire.

3 And so, we need to think about this
4 critically. Typically, the most difficult of
5 these criteria to satisfy are the third, that the
6 association of surrogate endpoint and the true
7 endpoint must be consistent between treatment and
8 intervention. So is the effect of acute rejection
9 or changes in renal function consistent between,
10 say, a standard of care and a new intervention.
11 And that's something that's very difficult to
12 ascertain prognostically.

13 And you've seen slides that look like
14 this, depictions of ways in which surrogate
15 endpoints may not be in the direct causal pathway
16 between a condition and a true endpoint. And in
17 my simplified view of the utility of a composite
18 endpoint, I think about in replacing the surrogate
19 endpoint, sort of broadening the impact on these
20 diagrams, so picking up some of these pathways
21 which a single entity might not. So whether you
22 can intervene and include elements in that

1 surrogate which can sort of break some of those
2 pathways which aren't picked up for more specific
3 markers and sort of the very generalized
4 representation of how a composite might work.

5 So again, we've heard about what the
6 potential values of different endpoints are and
7 specifically talking about composite endpoints,
8 typically it's to increase statistical power,
9 limit resources necessary for therapies likely to
10 have similar effects. And I say likely to have
11 similar effects on all of the elements of the
12 composite endpoint. And that certainly is
13 unlikely to happen in exact proportion. But it's
14 something that have to consider in terms of what
15 the elements of that composite might be.
16 Obviously incorporating multiple clinically
17 relevant events, which may be ignored with a
18 single endpoint.

19 And we've heard a number of people talk
20 about different potentially important clinically
21 relevant events and trying to incorporate them all
22 in a single endpoint is challenging, but again has

1 the benefit of not missing something which is
2 clearly relevant to patient outcomes, also
3 allowing for reporting of individual components
4 along the way, which may be hypothesis- generating
5 prospectively. But more specifically, not
6 ignoring primary endpoints of interest. So we
7 might be interested in very specific biomarkers
8 that are clearly well-vetted in the literature in
9 terms of being in the pathway of injury for
10 subsequent graft failure. But we don't want to
11 ignore obvious things that are important to
12 incorporate in some manner when evaluating the
13 efficacy of a specific intervention.

14 And then, there is also without having a
15 composite endpoint, the concern of competing risk.
16 The reason somebody doesn't develop DSA is because
17 they'd get hit by a bus, obviously any -- if they
18 have a cardiac event or something like that that
19 is independent of that pathway, you want to
20 incorporate that in some way intuitively. So how
21 can you do that from a methodological standpoint?
22 What are the limitations of composite endpoints?

1 Well, they may combine events with highly
2 differential impact on patient outcomes and how do
3 you reconcile the fact that different elements of
4 them might be much more severe than others.

5 And as mentioned, and I think very
6 important to the conversation here, those
7 different perceptions about what that impact is
8 might be very different from a trial that's based
9 on empirical evidence as opposed to patient,
10 patient-reported outcomes. So even more complex,
11 how do you put those together and reconcile them
12 in development of how this composite endpoint
13 would look. You do have the concern that,
14 depending on the selection of endpoints, you may
15 be overpowered by some specific endpoint which
16 happens in greater frequency than others, but may
17 or may not be as severe as others. And it also
18 may dilute effects if it's fairly equally
19 distributed between interventions.

20 Primary endpoints may have incidence in
21 direction opposite of composite endpoint. This
22 has happened, I think we mentioned cardiology

1 trials quite a bit where you see a composite
2 endpoint, have a positive finding in one
3 direction. But you may see mortality go in the
4 direction opposite the primary endpoint. And how
5 do you reconcile that and interpret that when you
6 say your endpoint might be good, as long as you
7 don't die at the end of the day. What are the
8 potential difficulties -- and there's also
9 potential difficulties with the interpretation of
10 composite endpoints. When you combine a lot of
11 diffuse things, many different pathways, how do
12 you disseminate that? How do you sort of
13 reconcile what the underlying mechanisms are that
14 is less specific than some of the other points
15 that we've talked about today.

16 So you know, I bring up results of one
17 very large trial in renal transplantation, which
18 certainly had value. But it's a depiction of many
19 of the different types of endpoints that we think
20 about. And the fact here, the primary endpoint
21 being treatment failure, incorporated many
22 different clinical endpoints. And a few things to

1 point out, which is obvious to those participants
2 in the room, they were in a context in which graft
3 loss and death rates as 12 months are very low.

4 So hence, the challenge and why we're
5 here and why we're talking about the need for
6 other biomarkers and surrogate endpoints also in
7 this case. You can see acute rejection rates are
8 fairly low. But this also depicts a case where
9 the biggest, most frequent events included those
10 of loss of follow- up, withdrew consent which may
11 be very relevant in the context of this study but
12 is also something that when you try to reconcile
13 those as counting as much as a graft loss or
14 death, it's hard to sort of reconcile that that
15 truly may be the case. And in some contexts, this
16 may overpower what we consider really to be the
17 most important from the patient's perspective.

18 So one alternative to that, which you've
19 seen very elegantly in a couple of the previous
20 presentations, are is there a way to potentially
21 weight those composite endpoints. And I think
22 there is a lot of potential for this. There has

1 been a lot implemented in other health care
2 contexts and it's something that I think we have
3 to think critically about. Certainly the benefit
4 is to apply appropriate value on a clinical event.

5 And obviously a death or a graft loss
6 might be more important for what we're trying to
7 learn than something like lost to follow-up. You
8 may -- however, you may decrease power from all
9 caused positive endpoints, depending on how it's
10 necessarily derived. But you can reduce the
11 variation and treatment effects. Big question is
12 often how you weight those and how do you weight
13 those in a way that's going to apply equally by
14 different -- theoretically by different therapies,
15 different populations and so forth. And there,
16 again, we get to the devil's in the details. But
17 I think conceptually, again, there's a lot of
18 value.

19 So just to get very basic case examples
20 and data derived from our national registries, as
21 most people in the room know, we are in a unique
22 circumstance in transplantation which we know

1 information from every transplant candidate, every
2 transplant recipient in the United States and can
3 we leverage this data in some way and can we
4 borrow some of the information from that to
5 include in some capacity in how we might develop a
6 composite endpoint.

7 And just an example of some of the
8 information that is collected, certainly it
9 doesn't have the granularity nor does it have some
10 of the endpoints that we've been talking about
11 today. So there are certainly weaknesses in some
12 of these data. The value, though, being that
13 they're collected in a large population, they're
14 collected in the same way in a large population,
15 for the most part, and we can assess things like
16 heterogeneity between centers, between regions,
17 between populations. So we can get some depiction
18 and theoretically think about how that might
19 manifest itself in a trial.

20 Also not only are transplant databases,
21 but we also have a lot of claims databases to pick
22 up things like cardiac events, as was mentioned

1 earlier, new onset diabetes, ways we can
2 incorporate that type of information, which
3 clearly has important clinical notifications. If
4 we just think about the incidence of some of these
5 events and not really concentrating on the
6 specific endpoints in this case but the types of
7 things that might happen, and even in this case
8 when we talk about things like acute rejection, of
9 course it's very heterogeneous. When we talk
10 about things like hospitalization, which may be
11 very diffuse and have a lot of different etiology,
12 but it's something that also may have some
13 important clinical long-term outcomes.

14 And then, we talk about what the
15 association might be for something which we may
16 perceive to be the true endpoint. So the value in
17 this data also is we have the longer term follow-
18 up and we actually know the -- we can simulate
19 what the five-year mortality might be and the
20 association of these specific events that might
21 help guide us, think about how we can
22 prospectively weight them. And if we put those in

1 a very simple multivariable model, we can see that
2 they, as one would expect, have a very different
3 association at one year with the five-year
4 adjusted hazard for mortality if we were to
5 consider that a true endpoint. Certainly there's
6 nothing magical about five-year mortality. You
7 could think about other endpoints as well.

8 And then, I think the other point just
9 to make, and it's something that has come up in a
10 number of the discussions, and I think it's very
11 salient in our population, given the relatively
12 small population size, and that is how does
13 participate historically in research and
14 transplantation. We know there are systematic
15 differences just in general in health care in who
16 participates. And how we use that information to
17 guide prospective development and should we think
18 about that systematically.

19 So we've talked about enrichment of
20 trials. We've talked about having patients in
21 trials that are more likely to conduct an event
22 for -- to manifest an event based on resources.

1 Also, we have the potential to put patients in
2 certain disease groups and look at them
3 individually where they might have a more
4 homogenous disease pathway. So I think we need to
5 think critically about how we want to include
6 patients, whether we want to do that in a
7 systematic manner that may allow us to evaluate
8 endpoints in a more rapid manner.

9 So in summary and conclusion, I think
10 composite endpoints should be considered for
11 trials in transplantation, given potential
12 improved efficiencies, incorporate multiple
13 pathways with therapeutic effects. Weighted
14 composite endpoints may further advance the
15 specificity of evaluating interventions and these
16 national data can be helped to use informed trial
17 development. Careful consideration obviously of
18 the external generalizability of effects based on
19 patient participation and then thinking about
20 selectively including patients more likely to
21 incur events to improve efficiencies. Thank you
22 for your attention. Hopefully I got us back on

1 schedule.

2 DR. BALA: Thank you, Dr. Schold. So I
3 think we can open for questions now from the
4 audience or from the panel here.

5 QUESTIONS & DISCUSSION

6 DR. ALBRECHT: I think everyone's still
7 taking all the information in. To try to start
8 some of the discussion, we were proposing the
9 question of what additional research is needed to
10 look at some of the surrogates that we've heard
11 about and the related long-term graft loss. And
12 if I -- okay, Kevin?

13 MR. FOWLER: Yeah, hi. I'm Kevin -- can
14 you hear me okay? Good. I won't use this then.
15 So the -- I guess my feedback is in two
16 categories. One is looking at research in terms of
17 other health care systems, looking at Europe and
18 Australia which seem to have better long-term
19 outcomes. And then, the other area I would
20 recommend is just again going back to the point
21 about adherence. But what can we do in the short-
22 term to provide incentives to reimburse them to

1 drive positive patient population change.

2 So just looking at short-term

3 incentives, let's say for example with adherence,

4 what can we do to help make the case for that in

5 terms of getting reimbursement? And then, the

6 second category is I was talking -- I had lunch

7 with Dr. Harris today. And -- or Dr. Morris, I'm

8 sorry. I apologize. And he asked me, he said

9 what would be the one area that you would like to

10 see as a patient. And so, I could just put in the

11 category of personalized treatment. And to

12 achieve that end, my suggestion is really three

13 areas specifically.

14 Patient-reported outcomes. I mean, I

15 really am surprised that there hasn't been

16 anything in that area. The second part is there

17 are companies and diagnostic area. Full

18 disclosure, I've consulted for one of them for a

19 year. But I'm just surprised that they're not here

20 in this conversation. And then third, I would

21 just say is the role of self-care management where

22 patients are assuming more responsibility because

1 of transplant centers are under so much stress and
2 duress. So those are my thoughts.

3 DR. STEGALL: I have a question for
4 Jesse. So give me some examples of composite
5 endpoints that would work, let's say, if we were
6 doing a study on subclinical rejection, de novo
7 DSA. Maybe that's a composite endpoint. What
8 would that look like?

9 DR. SCHOLD: So you're asking me to
10 design a trial now?

11 DR. STEGALL: Well, just -- I mean, just
12 elaborate. I mean, honestly --

13 DR. SCHOLD: I mean, I think at the very
14 least, it'd be -- even if we were looking at very
15 specific results of pathology and so forth, at the
16 very least it'd be important to incorporate clear,
17 strong clinical events, graft loss, death within
18 that month. So that's a composite endpoint,
19 right? We want to put those together. We don't
20 want to ignore that all together because if in a
21 randomized controlled trial those were
22 systematically different, if they were different

1 between the groups and they were ignored or
2 censored in the trial, that could very easily
3 affect the interpretation of the results. So at
4 some level, I think it's almost obligatory to
5 include them for the most important clinical
6 endpoints. Now, where you draw the line, how far
7 down you get into that in complications really
8 comes down to what you think you're covering all
9 of those pathways. And you can sort of hedge your
10 bets by including more of them. But you may argue
11 that you're including too much noise if you have a
12 wide variety as well.

13 So I think there's a balance there. And
14 it's not -- there may be some value in developing
15 that differently for different questions. It's
16 not to say that there's one weighted composite
17 endpoint that would work for all trials. I doubt
18 that's the case. I think it would depend more on
19 the biology. It would depend more on what the
20 hypothesized mechanism of effect would be. And
21 so, that can look different ways. I mean, I don't
22 think it has to be a single design.

1 DR. GILL: Hi. John Gill, from
2 University of British Columbia. This question is
3 for Dr. Mengel or anybody who talked about
4 protocol biopsies or biopsies. Might the issue of
5 the -- you mentioned the importance of implant.
6 But I don't think too many of the talks discussed
7 heterogeneity at time zero. And the second issue
8 is sampling bias. So if you could comment on
9 those two issues, I think they're important, if we
10 think of pathology as a surrogate.

11 DR. MENGEL: In regard to implant
12 biopsies, the morphology data are not very good.
13 Still, everything is dominated by age strongly.
14 And but it is having an implant biopsy is a good
15 point zero to see what's the delta when you talk
16 about --

17 DR. GILL: That's what I meant.

18 DR. MENGEL: Yeah, when you talk about
19 composite endpoints, you want to know where you
20 start, especially where donor age still comes up
21 also for long-term survival. The old garbage
22 in/garbage out, a very injured kidney already at

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1 implantation will probably require or show a
2 different delta in certain surrogate endpoints.
3 So it is -- when you try to treat an early disease
4 that's relevant, I don't know how relevant it is
5 when you try to treat or intervene with disease
6 which present five years out.

7 And what was the second question?

8 Sampling error. Oh, sampling error. Yeah. That
9 has been -- I don't understand it. But clinicians
10 are reluctant to send the whole transplant to
11 pathology. Then we could go around sampling
12 error. But that's something we have to live with.
13 Phil Harrold always claims that when you do
14 molecular -- and I support him in that -- when you
15 do molecular testing, the molecular phenotype is
16 probably more diffuse and less prone to sampling
17 error when you compare it to very specific and
18 very focal histology lesions like endothelialitis,
19 which has a significant impact but can be very
20 focal. It's definitely a problem. But there is
21 no absolute way around it.

22 DR. BUDDE: I would like to follow up on

1 this, on the disease. So I think that maybe it's
2 important to consider the context of the biopsy.
3 So is this a pre-transplant or a biopsy in the
4 early period, as Michael just pointed out, or late
5 biopsy, a patient with preexisting antibodies or a
6 patient with de novo antibodies 10 years after
7 transplantation. And you see the same picture in
8 peritubular capillaritis. Is it the same disease
9 or is it maybe a different disease? And maybe the
10 panel might comment on this so that we have the
11 same histology but different disease entities.

12 DR. MENGEL: So I totally agree with
13 that point. My question, building on that, to
14 Alex and Jesse is can you use large registry data
15 and identify these four or five subpopulations and
16 simulate in a subpopulation a composite- weighted
17 endpoint. As you said, Jesse, it will be in pre-
18 sensitized patients probably microcirculation
19 inflammation, TG, MFI. And when you do this
20 across a full population, it loses effectiveness,
21 I would assume. So can you go back to registries
22 and try to build a model which tells us which is

1 the best weighted endpoint for a certain question
2 in a certain population.

3 DR. LOUPY: Yeah. So the first part of
4 the questions, I think that a composite endpoint
5 has to take into account the variability of the
6 diseases that might be in both transplants.
7 That's the reason why you are using the world
8 cohort and its variability as the strains to build
9 the models. For the present diagnosis of disease
10 and the similitude and discrepancies between PDC
11 in the early and late period, we are doing a study
12 comparing type 1 and type 2 ABMR, for example,
13 using the molecular microscope. And it shows that
14 actually it's not kind of the same disease. You
15 have more in type 1, more augmented response, more
16 MK response, more endothelial injury and less
17 scarring transcripts than in the late period. So
18 I mean, the disease is spectrum and the time is
19 very important. And time at which you make your
20 evaluation should also be important. That's the
21 reason why it has to be incorporated in the model,
22 I think.

1 DR. SCHOLD: I mean, I think that's the
2 ideal, what you just described. I think Alex's
3 database might have more than some of the U.S.
4 registry databases based on some of the
5 biopsy information and so forth. But I think
6 that's the concept and it's sort of a balance
7 between internal and external validity. You could
8 have one endpoint which you try to incorporate
9 everything for the whole population. But you're
10 likely to be a little bit diffuse. If you can
11 design it more specifically tailored to certain
12 disease processes, I think you have a greater
13 likelihood of finding endpoints. And then, see if
14 it may extrapolate in terms of its interpretation
15 to other populations.

16 DR. LOUPY: So if I can add something,
17 when you have a scarring to grade thing like
18 histology, C4d, DSA, GFR and proteinuria, you have
19 so much information inside that, that if you are
20 aiming really to predict failure, it works very
21 well and it gives you high c-statistics, whatever
22 the time point you are applying the score, which

1 is the advantage of a composite score. But the
2 score is not here to decipher the underlying
3 disease and the pathology. That's the reason why
4 in this score they are only Banff scoring and not
5 diagnosis. It's adjusted on diagnosis but at the
6 end it's just scarring that enter into the score.
7 But GFR and proteinuria in themselves carry so
8 much information that it's in itself accurate, so.

9 DR. HARIHARAN: Mark, the question to
10 you is if you are to improve the long-term
11 survival, that's the pretext. We want to improve
12 the long-term survival or enhance the survival.
13 What events would you like to reduce at the end of
14 one year after transplantation and what kind of
15 intervention -- potential intervention that could
16 have an impact on reducing some of those events at
17 the end of one year? I mean, there are a variety
18 of scenarios you could --

19 DR. STEGALL: Sorry. When you looked at
20 -- you know, when we looked at the causes of graft
21 loss based on events in the first year. And I
22 think that there onesies and twosies. They all

1 add up kind of a thing. Unfortunate, right?
2 That's the problem in transplant patients, I
3 think. So to put them into discrete category, I
4 think that the subclinical inflammation still
5 comes back to me and always has as one of the few
6 that seems to have enough patients that will
7 actually move the needle forward at all. And I
8 think that de novo DSA actually is not one of
9 those right now. Now, in the first five years, if
10 you captured everybody in five years, that starts
11 to get to the same number of patients. So the
12 inclusion criteria for that may be de novo DSA as
13 a marker and then maybe a biopsy that shows
14 peritubular capillaritis as the surrogate
15 endpoint. But also, I would say in a true
16 disclaimer, I think that we're very early in this
17 thought process. And it could be that subclinical
18 inflammation is very heterogeneous in its etiology
19 and its response to therapy. But that's just
20 where we are. So I would say that, again, if I
21 were going to put any of my retirement money in
22 anything that might show some efficacy in changing

1 the absolute numerical, it's subclinical
2 inflammation. If you look at it numerically,
3 people with normal biopsies actually also make up
4 a large numerical number of graft losses. But I
5 don't know which of those people are going to lose
6 their graft. So the ones that have a marker that
7 I can possibly intervene on, it's the biopsy
8 still. And you can -- I guess you could take this
9 in multiple other markers. But that's just a
10 number. It's just not the new patients.

11 DR. MENGEL: So I put something out, an
12 analogy to cancer. I would say interstitial
13 inflammation and fibrosis is like lymph node
14 metastasis. Most tumors metastasize at a certain
15 point into lymph nodes and it's a bad prognostic
16 sign. But the major recent breakthrough in cancer
17 care was not treating with across-the-board
18 chemotherapy based on staging for lymph nodes and
19 primary tumor size for targeted treatment in a
20 certain biological process.

21 Even a metastasis or a fully advanced
22 malignant melanoma, which has a BRAF mutation goes

1 into remission with the right treatment. And when
2 we look now for treatment, we have in antibody-
3 mediated rejection, that's very specific and
4 targeted to antibody-mediated tissue injury. So I
5 think general inflammation might not be a
6 surrogate in that anymore because you are beyond
7 the crude polymodal chemotherapy of advanced tumor
8 metastasis where you only inhibit proliferation
9 across the board and people lose their hair and
10 everything. No, you target it for what makes this
11 tumor this disease- specific. And I think
12 especially in antibody-mediated rejection, we are
13 more advanced and we can -- we have to look in
14 that category for people having the druggable
15 target.

16 DR. ALBRECHT: Can we take a question
17 from the floor?

18 DR. DEVEY: Sure. Sorry to hold us up.
19 One last thing about biopsies, which is we've
20 heard a lot about biopsies. There's a huge amount
21 of data about biopsy. But clearly the compliance
22 with them in a clinical trial is only about 70

1 percent did I hear somebody say earlier on. We
2 also heard about CTGF being highly predictive of
3 interstitial fibrosis. We also saw Dr. Zhao's
4 talk where he was talking about non-additive data
5 from biopsy. So it's an invasive thing to do.
6 Should we be using biomarkers of fibrosis,
7 cytokine panels to look for subclinical
8 inflammation or if we haven't got the right
9 markers yet, is that not a direction we should be
10 pursuing for future clinical studies?

11 DR. STEGALL: For the future, yes. For
12 the future.

13 DR. MENGEL: So with -- I think the
14 problem with noninvasive tests is, again, what is
15 the question you're asking. So what do you want
16 to detect? Because we -- a lot of diagnoses, we
17 can't even render accurately in the biopsy. So
18 there is no true diagnostic gold standard. And
19 whatever noninvasive test you have, what are you
20 validating it against? When you look for
21 something in general, kidney disturbance, your
22 current gold standard is creatinine. And you can

1 see whether there is something more sensitive.

2 And I think the Winnipeg group has very, very
3 convincing data. You can detect inflammation in
4 the graft and the urine. So it really depends on
5 the area of application.

6 DR. DEVEY: So I mean, just interstitial
7 fibrosis, subclinical inflammation, that would do
8 me. But is there not -- should we not be focusing
9 on these other ways of getting that data since the
10 compliance rate with biopsy is so low?

11 DR. MENGEL: Sure. If I would have a
12 choice between a needle like that and peeing in a
13 pot, I think compliance clearly is an argument.

14 DR. STEGALL: Well, I think it depends
15 on the study design. Obviously if you have to have
16 a biopsy to get into the study, I think that's a
17 different study for sure. And I mean, again, in
18 the spectrum of steps forward, we just have more
19 data on biopsies now than we do on anything else.
20 And that would be the most logical place to start.
21 But I would say yeah, very supportive of any
22 technology that would obviate the need for a

1 protocol biopsy. I'm not married to it. I just
2 do a lot of it. So he's married to it, but I'm
3 not.

4 DR. HARIHARAN: One terminology issue.
5 I would like to change the protocol biopsy as a
6 management biopsy. It is not a protocol biopsy we
7 are doing and looking for thing. We are changing
8 the management depending upon what we find in the
9 biopsy. It's a little change in the word. But it
10 does make a big difference for a variety of
11 reasons. I mean, even some insurance companies
12 may not agree or approve our payment for a
13 protocol biopsy. But that's not the case with
14 management biopsy.

15 DR. O'CONNELL: But do we -- but do we
16 have data to support this hypothesis, Hariharan?

17 DR. HARIHARAN: I'm sorry?

18 DR. O'CONNELL: Do we have data to
19 support this?

20 DR. MANNON: Well, you could change the
21 name to surveillance. I think everybody would be
22 happy.

1 DR. : Motion to approve --

2 DR. HARIHARAN: Data to support -- I'm
3 sorry. I didn't --

4 DR. O'CONNELL: Call it a management
5 biopsy.

6 DR. MANNON: Surveying. We're looking
7 for things.

8 DR. O'CONNELL: So how many --
9 mic]. So how many - what compliance do you need
10 with a biopsy for it to be acceptable for a trial?
11 So there's two things. I'm trying to think of a
12 trial where the biopsy histology was the primary
13 endpoint. I've been in a lot of studies where
14 they do it. But it's sort of an add-on extra for
15 point one.

16 The other thing is that a lot of, say,
17 pharmaceutical-driven trials have had a philosophy
18 of getting a lot of centers to put in a few
19 patients. I think that sort of covers both the
20 marketing initiative as well as the trial
21 initiative. And maybe if you're doing a protocol
22 biopsy study, you need a few centers that do them

1 rather than centers that -- enrolling a center in
2 a study that doesn't do surveillance biopsies or
3 do a lot of biopsies in that way and then hoping
4 they're going to get a 95 percent compliance with
5 that may not be a good way to design that study.

6 DR. MANNON: I mean, I think that's a
7 good point. I mean, the success of GOPAR [ph]
8 with that NIH-funded study was that the centers
9 that were under the aegis of Barbara Murphy were
10 centers that did surveillance and they had very,
11 very good follow-up of the patients. Now, I'm
12 still looking for the Scholds paper on who signs
13 up for a research study. But these patients were
14 very diverse. I mean, they came from all over the
15 world and they had good compliance.

16 I only know of one study where the
17 primary endpoint -- it's a small NIH investigator-
18 initiated study where they're looking at the
19 changes in i- and t-score after a cellular
20 infusion. But they're using quantitative
21 morphometrics as well. And as a secondary
22 endpoint, they're looking at the CREM [ph] or

1 whatever the immune core panel is just to look at
2 that, plus other clinical characteristics.

3 DR. HARIHARAN: You know, this is a very
4 important point. If you look at the pre-
5 cyclosporine era, biopsy was not done routinely.
6 It is all rejection, okay? Even in the tacrolimus
7 trial and the MMF trial, there was a lot of
8 problem in convincing centers or physicians and
9 surgeons that we need to do a biopsy when it was
10 clinically indicated. But today, that's the norm.
11 Everyone does a biopsy naturally to find out
12 what's going on. Help us to differentiate, you
13 know, what kind or what severity and modify the
14 treatment. The same thing should be extended for
15 the subclinical rejection. If you had to do a
16 trial, we should request centers to participate or
17 compliant with at least 90 to 85 percent of
18 protocol biopsies. That's what I would recommend.

19 DR. O'CONNELL: Yeah. So does anyone
20 have data that where you -- what would the FDA --
21 have they got a view on how many you'd need or is
22 there a statistical point on this? So if you've

1 got 90 percent compliance with the biopsy at the
2 endpoint, is that going to be acceptable? Do we
3 need better than that?

4 DR. ALBRECHT: So maybe that's a
5 question that the statisticians could address
6 because they have to deal with all that missing
7 data.

8 DR. O'CONNELL: Yeah. So is there one
9 who's willing to do that without notice or do they
10 want to go ahead and think about that?

11 DR. STEGALL: I think the one thing that
12 you could do is like for the subclinical
13 inflammation idea is that one arm would get
14 steroids and that's an intervention. And the
15 other arm might get, you know, conversion to
16 something else. And then, both might need
17 biopsies to, you know, maybe some further
18 interventions that might be happening. So I was
19 thinking about -- because I did kind of think
20 about what's a control arm. They get a biopsy.
21 They don't want to get a repeat biopsy for no
22 reason whatsoever. And so, I mean, it's some

1 methodological issues and stuff that would have to
2 be addressed.

3 DR. ALBRECHT: It reminds me of Dr.
4 Bala's presentation about looking for the
5 galactomannan so people wouldn't have to biopsy
6 invasive aspergillus patients. So probably
7 looking for a biomarker.

8 DR. FLEMING: Whatever endpoints we
9 choose, we have to assess them. We have to assess
10 them consistently. The first point I made in
11 choosing an endpoint is that it should be readily
12 measurable. And in pseudo- medicine [ph] in a
13 separate document from their document on the
14 importance of caution about biomarkers, they had a
15 document they sent to FDA in 2011 on missingness.
16 They said there's only one way to effectiveness
17 address missingness, which is -- right, not to
18 have it. Statisticians don't have any magical
19 imputation methods to take care of that.

20 DR. MURPHY: Just a comment. I agree
21 with Michael on the issue around biopsies and the
22 lack of consistency. But it is actually currently

1 the gold standard. And one of the concerns I have
2 with one of the remarks, I've agreed with nearly
3 everything you've said except one comment where
4 we're talking about the use of differential gene
5 expression, genomics, et cetera and the difficulty
6 of moving ahead with that because it's compared to
7 biopsy when biopsy isn't the gold standard. And
8 so, how do you develop a methodology with genomics
9 if you're comparing it to biopsy.

10 But we're not going to move ahead unless
11 we question it and try. And it is the one
12 potential way to have an objective look and a
13 quantitative look as opposed to the more
14 subjective approach of biopsy. And my concern
15 about a lot of the discussion here, and I know we
16 have to have the discussion around biopsy. But we
17 need to move away from it because it is so
18 subjective. So how do you -- if you --

19 DR. MENGEL: No, I'm not disagreeing
20 with what you said. The problem is what -- with
21 noninvasive tests were they were starting with
22 very broad diagnostic claims. So I can have all

1 rejection. They were not discriminating between T
2 cell-mediated and antibody-mediated rejection. So
3 I think what you say is we have to start and
4 refine it further. It's all about stratifying
5 your patient cohort and not contaminating your
6 study essentially. But I agree. It will then be
7 possible. There is a signature in urine and/or
8 blood.

9 DR. MURPHY: So we agree -- [off mic].

10 DR. STEGALL: Well, I think though it's
11 just a matter of having the outcomes data too. I
12 mean, that's what you really need.

13 DR. MENGEL: Yeah.

14 DR. STEGALL: I mean, if you had great
15 outcomes data on urinary whatever, SuPAR and that
16 really correlated with something, then you could
17 just give a drug and treat that and reverse it and
18 you'd be okay with it. The problem is we just
19 don't have that data.

20 DR. MENGEL: Well, you could think about
21 it so that a noninvasive urine test, you would
22 just publish paper in urine for the chemokines.

1 You identified clearly or discriminate clearly
2 kidneys which are not inflamed at all from some
3 which are inflamed. So you can stratify already a
4 protocol biopsy by not biopsying the more
5 inflamed. It gives you more resource to do more
6 biopsy or more intervention in the inflamed one.
7 And I think that would be very helpful as a
8 composite stratification model.

9 DR. MORRIS: Michael, correct me if I'm
10 wrong. But although our field has differing
11 opinions among pathologists on biopsy findings and
12 that they're not exactly the best concordance
13 rate, am I not correct in what I've heard about
14 staging solid tumors, that pathologists also have
15 a lot of non- concordance when they study solid
16 tumors? And these stages are part of clinical
17 trials.

18 DR. MENGEL: Oh, of course the tumor
19 pathologists are worse than the transplant
20 pathologists. But no, this is why recent
21 molecular technologies in tumor assessment,
22 especially next-generation sequencing, had such a

1 dramatic impact where you had a druggable target
2 you could identify and you have a drug. So
3 currently, most transplantation or what we do is
4 we are really at the polymodal global
5 chemotherapy. Just inhibit T cell proliferation.
6 And I think we're now at the transition,
7 especially in antibody-mediated rejection,
8 towards a more targeted treatment. And that
9 changed cancer dramatically, melanoma, lung cancer
10 and colon cancer. There is really survival in
11 melanoma was from six months a couple of years ago
12 to now years in average and some people who take
13 the drugs and do not get a new mutation forever
14 probably. So that is where we want to be. And I
15 think we can accomplish it at least in some areas.

16 DR. MORRIS: I'm not sure that DSA is
17 the best way to go because the cancers you refer
18 to -- and there have been very many successes.
19 These are cancers through signal mutations. Of
20 course, most cancers have many mutations and they
21 keep mutating. And so, it's the cancers where we
22 have one mutation, one target, one drug where we

1 do very well. Most cancers unfortunately are not
2 like that.

3 DR. MENGEL: No. This strategy is
4 changing. You sequence your melanoma and you get
5 400 mutations. But now, empirically from outcomes
6 studies you know which 10 are driver mutations and
7 390 are passenger mutations. Then you look at the
8 10 driver mutations, where is a drug available.
9 And then, your first line drug. Then you get your
10 relapse. You sequence again and you look for the
11 driver mutations. Is there a new drug available?

12 So it's not one magic bullet. But there
13 is a strategy to understand the biological process
14 driving the disease. And I think that is today
15 what we reviewed here and understand that even in
16 transplants you have large disease groups driving
17 progression of interstitial fibrosis and
18 inflammation. And we have drug classes available.
19 You would not treat probably BK with a C5-
20 inhibitor or is that a trial somebody's
21 considering today? No. So therefore, you should
22 not have BK cases in your complement inhibition

1 trial, I would argue, as a simple example.

2 DR. MORRIS: I agree. I think we are at
3 a stage in our field where we know enough about
4 the biology to begin to stratify, to begin to
5 enrich for molecular or cellular phenotypes so the
6 trials that we do can be more focused. The other
7 advantage we have over cancer is we don't have
8 drug resistance.

9 DR. MENGEL: Yeah, or not that we know
10 of.

11 DR. O'CONNELL: Well, I think you're
12 being too pessimistic there, Michael. There's a
13 lot of drugs out there in immunology that if you
14 look at autoimmune diseases, there's a huge number
15 of drugs, some of which would have Phase II
16 clinical trials in transplantation. The companies
17 just abandon it, even though the drug trial was
18 effective and everyone in those trials felt that
19 they should go to Phase III.

20 So I think there's a lot of agents out
21 there that we could trial, as in oncology, that
22 you're right that the diagnosis of, you know, like

1 a pancreatic cancer no longer holds in some drug
2 that may not be designed for that is not effective
3 in some genotypes. But you know, that's a
4 relatively new iteration in oncology, whereas it
5 was histology-driven and they have had a lot of
6 drugs. I think if you think outside the square,
7 that if we can either enrich populations, look for
8 conditions where we think we have an understanding
9 of the biology, that there are things we can try.
10 And you look at antibody-mediated rejection, the
11 bortezomib and all those drugs, none of those were
12 designed for transplantation. Yet people, or
13 rituximab, they're all oncology drugs that we're
14 repurposing here.

15 So there's a lot on that in
16 autoimmunity. So I think if we're thinking rather
17 than being pessimistic about the clear gaps which
18 we all acknowledge we have, I think there's a lot
19 of information, of which the genomics is now
20 adding to that, that it would be a good time to
21 design a focused trial where we were -- where
22 we're more keen on understanding what the endpoint

1 of having a surrogate endpoint that meant
2 something, not just function, and maybe trying
3 something new that's been developed for rheumatoid
4 arthritis. That's just another way of looking at
5 the same problem.

6 DR. ALBRECHT: So on that optimistic
7 note, can we go ahead and transition to session
8 four and then continue the discussion after the
9 presentations? The moderators for this session,
10 Dr. Ros Mannon and Dr. Philip O'Connell.

11 SESSION 4: FUTURE DIRECTIONS IN
12 KIDNEY TRANSPLANTATION

13 DR. O'CONNELL: So it's really easy that
14 I'll just ask Renata to give her talk on the FDA
15 experience with surrogate endpoints and drug
16 development and other therapeutic areas. So I
17 think this will be a really important talk.
18 Thanks, Renata.

19 FDA EXPERIENCE WITH SURROGATE
20 ENDPOINTS AND DRUG DEVELOPMENT IN

21 OTHER THERAPEUTIC AREAS

22 DR. ALBRECHT: Thank you. Okay. So

1 thank you very much. All righty. So now we're in
2 the future directions session. But sometimes it's
3 useful to go back and look at history to learn
4 from experiences of others. And so, today I'll be
5 giving you some historical perspectives from
6 infectious diseases and oncology to help us talk
7 about future directions in transplantation. This
8 is my disclosure slide.

9 So as Randy mentioned, we invited people
10 from these areas.

11 They had conflicts. So they courteously
12 provided me with slides that I will use to
13 summarize a few key points. Dr. Kluetz of
14 oncology provided the following slides. So the
15 first, there's been discussion about approval
16 pathways. And I wanted to mention there are two
17 FDA uses: one, regular approval on the left- hand
18 side of this screen; two, accelerated approval on
19 the right side of the screen. And let me talk
20 about the similarities and differences.

21 So for regular approval, and my
22 presentation's going to be focused on the text in

1 the red rectangles. For regular approvals, well-
2 controlled study, generally two, are needed. And
3 in these studies, what is measured is direct
4 patient benefit, as Dr. Fleming and many others
5 already spoke about. This can be prolonged
6 survival or this can be how a patient feels or
7 functions. By comparison, for accelerated
8 approval, which also requires well-controlled
9 clinical studies, the product must show a
10 meaningful therapeutic benefit over existing
11 therapies. And this can be done by showing an
12 effect on a surrogate endpoint that is reasonably
13 likely to predict clinical benefit.

14 So because of the uncertainty around a
15 surrogate endpoint, post- marketing clinical
16 trials are required, which are then designed to
17 confirm the predicted clinical benefit. So
18 accelerated approval has both benefits and risks.
19 The benefit, you could use an unestablished
20 surrogate endpoint which usually provides for
21 early events and smaller, quicker trials. On the
22 risk side, one must demonstrate that the product

1 is better than existing therapy in a serious life-
2 threatening condition and also one must complete
3 the post-marketing studies to confirm the
4 clinically meaningful benefit. As we heard from
5 Dr. Fleming, the oncology office has used this
6 approach in quite a number of therapeutic
7 products. And they report that for 10 percent of
8 accelerated approvals in oncology, approval had to
9 be withdrawn because the confirmatory study failed
10 to confirm a clinical benefit. The oncology
11 office doesn't consider this a failure of the
12 program. Rather, they actually expect this kind
13 of uncertainty and a failure to verify a benefit
14 because of the use of un-validated surrogates
15 early in the process.

16 A little comment about endpoints again.
17 So as we heard, direct measure of clinical
18 benefit, how a patient feels, functions and
19 survives, does provide certain -- relatively high
20 degree of certainty about patient benefit and
21 supports regular approval. Established
22 surrogates, as we heard about, LDL, HIV RNA and

1 blood pressure, started as surrogates but now are
2 used for regular approval as well. And in the
3 rectangle, unestablished surrogates of clinical
4 benefit, I think that's the discussion that we're
5 having. These are surrogates that have limited
6 existing data, lack of regulatory precedence. But
7 if they are believed to predict clinical benefit,
8 can be used in clinical trials to support
9 accelerated approval.

10 A summary of the oncology experience.
11 On the left-hand side, surrogate endpoints measure
12 response rates. There's a lower certainty that
13 they will in fact confirm clinical benefit. They
14 do support accelerated approval and treatment can
15 sometimes be approved earlier in the drug
16 development process. On the right-hand, by
17 comparison, a measurement of direct clinical
18 benefit to the patient such as overall survival,
19 reduction of symptoms or improvement in function
20 of daily life has a higher certainty and supports
21 regular approval.

22 Now, let me turn to the second example

1 in the area of antimicrobial products. And these
2 slides are courtesy of Dr. John Rex, who was the
3 keynote speaker at the 2014 International
4 Conference on Antimicrobial Agents and
5 Chemotherapy. The challenge in antimicrobial
6 products was not dissimilar to what we face.
7 There was declining antimicrobial development and
8 the Infectious Disease Society of America called
9 it the bad bugs, no drugs dilemma.

10 As you can see on the left side in the
11 graph, the rate of new antimicrobials was
12 declining over the past 30 years so that in the
13 timeframe of 2008 to 2012, there were only two
14 antimicrobials approved. In that same timeframe,
15 in transplant, we approved Zortress and Nulojix,
16 two products as well. On the right side of the
17 screen, licenses for new drugs. It's hard to
18 discover new antibiotics. It's hard to develop
19 new antibiotics and the economic value of new
20 antibiotics to a developer can be close to zero.
21 Much of this also applies to transplantation one
22 might say.

1 There's a second challenge with clinical
2 trials. Superiority-based approaches that work
3 for other areas do not offer a long-term path to a
4 diverse pipeline. And therefore, thoughts of
5 using non-inferiority trials must be considered
6 because untreated infections are lethal and, for
7 comparators, successful pathogens, modern
8 comparators at full doses are very effective. Much
9 the same can be said about transplant. The early
10 drugs were approved based on superiority studies.
11 More recent ones based on non-inferiority studies.
12 We cannot use an effective control regimens and
13 withholding immunosuppressants from a transplant
14 recipient is unethical. And by comparison to
15 susceptible pathogens, one could say that in
16 transplant, for quite a few patients, especially
17 if they're adherent, the currently available
18 transplant immunosuppressants when used at
19 effective doses, are effective.

20 So what did the antimicrobial group do
21 to address the problem? First, there was global
22 involvement, global leadership. Dr. Rex has put

1 together a partial list. It starts with the 2003
2 initiative by the Infectious Disease Society
3 facing the bad bugs/no drugs dilemma and includes
4 other initiatives by both the European Union as
5 well as the U.S. in collaboration with industry,
6 academia and regulators.

7 These collaborations included public-
8 private partnerships such as in the U.S., the
9 NIAID and the BARDA collaboration, and in the
10 European Union, the IMI's new drugs for bad bugs
11 program. In addition, the IDSA put forth the 10
12 by '20 initiative, meaning that 10 new
13 antimicrobials will be developed by 2020. To
14 date, four have been developed. And a few words
15 about the economic side of drug development and
16 tracking the net present value model. So in the
17 anti-infective area, they've put together -- put
18 forth two economic ideas. One is refundable tax
19 credits and a second is insurance-based
20 approaches. In addition, on the bottom right, the
21 infectious disease community is rethinking value
22 and business models. And let me also add that

1 there have been some additional -- there's been
2 additional legislation in this area.

3 So the Generating Antibiotic Incentives
4 Now Act, the QIDP designation and additional
5 exclusivity have actually been added to the 2012
6 FDASIA legislation. So in summary, how does this
7 apply to transplantation? Well, there are quite a
8 few parallels. Effective therapy is available for
9 many transplant patients, analogous to the
10 susceptible pathogen example. However, new
11 therapies are needed to address unmet medical
12 needs. Superiority and non-inferiority trials can
13 be challenging. Ineffective comparator regimens
14 are not acceptable. Withholding treatment is
15 unethical.

16 Additional primary endpoints are needed
17 beyond acute rejection. These can either be a
18 measure of direct patient benefit or a measure of
19 an unestablished surrogate endpoint. In this
20 area, just as in others, regular approval and
21 accelerated approval are both available options.
22 But for the latter, we need to identify

1 unestablished surrogate endpoints and keep in mind
2 the risks and benefits of surrogates that we heard
3 in oncology. Orphan indications, which is what
4 transplant indications are, make patient
5 enrollment a challenge. We need to use rapid
6 diagnostics more and include them in clinical
7 trials. And finally, I think we recognize that
8 the drug development has stalled and we need to
9 start to dialogue to address that challenge.
10 Thank you.

11 DR. O'CONNELL: Thank you. Thank you,
12 Renata. Randy, you're next. Then it will be open
13 up for final --

14 DR. MORRIS: The first and last.

15 DR. ALBRECHT: You're first and last
16 forever.

17 A FUTURE DIRECTION IN TRANSPLANTATION:
18 SURROGATE ENDPOINTS IN

19 CLINICAL TRIALS OF
20 IMMUNOSUPPRESSION IN RENAL TRANSPLANT RECIPIENTS

21 DR. MORRIS: I've got to make sure I
22 select the right -- there we go. Well, thank you

1 all for coming. I learned from Dr. Mark Stegall
2 this was the, quote, "best day of his life." So
3 I've learned that -- I've learned that FDA
4 workshops improve the way patients feel. So
5 that's a plus. What I intend to do in the next
6 hour or two is actually wake all you people up and
7 have some fun with you because this is the last
8 talk. I'm going to try to remind you why we're
9 here. I'm going to try to remind you how the
10 transplant community, industry and FDA can work
11 together to meet the goals for why we are here.

12 I was given the first -- the first title
13 I was given on the agenda was future directions.
14 That's a big talk. So I put some boundaries on it
15 and put one future direction would be for
16 accelerated approval of immunosuppressants using
17 surrogate endpoints. That's really the focus of
18 our meeting. And the question is can a surrogate
19 endpoint allow accelerated approval. And I'm
20 quoting Cicero to the Roman Senate. He said, "It
21 seems to me there no soothsayers should be able to
22 look at another soothsayer without laughing." So

1 even they were a little skeptical about
2 predictability. Disclosures, the usual stock
3 options. This presentation is the nth revision.
4 It contains some minor revisions. And I will
5 disclose that I've been heavily influenced by Dr.
6 Thomas Fleming's writings, which is a positive.

7 Now, in industry, sometimes there's this
8 sort of feeling. I'm from the FDA. But mommy,
9 I'm scared of the government. But in actual
10 effect, don't be scared. Remember, the FDA
11 initiated this, sponsored this, organized it. So
12 we owe the FDA a gratitude of thanks. This
13 workshop has been a lot work, a lot of telephone
14 conferences, which many of you participated in,
15 and many, many drafts of the program agenda. I
16 think so far the day has been a huge success. I
17 also want to thank all the presenters for their
18 work, moderators, the discussion and the audience
19 for staying here. Just stay awake for another 20
20 minutes and the discussion to follow will answer
21 all your questions. The final discussion will be
22 the key to the meeting.

1 So we realize that our field is a work
2 in progress. And the future for our field
3 obviously is decreased immune graft failure. We
4 all agree with that. And we all agree that we
5 want immunosuppression better than the standard of
6 care, safer, more effective. Better understanding
7 of the mechanisms and improved adherence, as Rita
8 said. The next slide is for Rita. California, we
9 don't have to worry about adherence because we
10 have people to remind the patients to take their
11 drugs.

12 To reach the goal, we need new trial
13 designs. And that's what we've been discussing
14 today. We need more sensitive endpoints to prove
15 efficacy or superiority. And for trials,
16 acceptable duration, slashed cost and of course
17 collaboration among the FDA, transplant community,
18 C-Path and ACMS and others.

19 Why is it important to decrease immune
20 transplant failure? I mean, I'm going to again
21 remind you of why we're here. Transplantation is
22 life- saving, no doubt about it. This is an

1 interesting study published this year which shows
2 that when compared to dialysis, the number of
3 life-years saved by transplant is over 2 million
4 versus about 1 million for dialysis. Transplant
5 does include the way people feel, function and
6 survive and we should all be very proud to be
7 members of this community.

8 Why else do we need to improve? Can
9 estimates of death- censored graft failure. You
10 know the data. I'll just remind, the living
11 donor, half the people lose the graft at 16 years.
12 Deceased, half lose at 13. And with the more and
13 more expanded, half lose in nine years. Non-
14 transplant half-lives are even worse, all about
15 five years and tested less. Death rates after you
16 lose a graft and go back on dialysis are horrible.
17 Overall just the death rate three times higher
18 after a functional transplant. Seventy-eight
19 percent greater versus transplant candidates and
20 mortality, HR 2.7 in the Canadian registry. These
21 are all published. Now, in Australia, when
22 patients were queried about what their priorities

1 were after transplant, the number one priority
2 wasn't CNI toxicity. It wasn't GI toxicity. It
3 was not going back dialysis. And then, kidney
4 function, damage to other organs. Death or
5 survival is actually number four.

6 We know there are many causes of renal
7 failure. We've been focusing on the immune
8 factors. And I think we do know a lot about these
9 immune factors, enough so that we can begin to
10 phenotype the patients, stratify them and enroll
11 them in enriched trials. This is a 2015 paper
12 which again shows you the schematic ways that
13 grafts are rejected in acute and even use the word
14 chronic rejection, showed DSA. But DSA, as you'll
15 note on the schematic, is not alone. It
16 incorporates cellular components with it. So it's
17 a mixed problem.

18 This is an interesting slide from
19 another field. But it shows basically the
20 disorder -- I put transplant dysfunction. And in
21 simple fields, you may have three etiologies than
22 one very stereotypical mechanism leading to the

1 disorder. In our field, we have many etiologies,
2 many cellular mechanisms leading to disorder. But
3 I think we're learning more and more about how to
4 distinguish these so that we can devise more
5 appropriate trials. This 2015 paper also lists a
6 number of approved and new interventions for
7 transplantation. But they did not dress what
8 we're addressing here today and that is how to get
9 from approved and show superiority.

10 We discussed today the problems of
11 short-term results. All caused graft failure is
12 low. Death is low. These are all primarily FDA
13 endpoints. And biopsy-proven rejection is not one
14 you're very low but we feel they detect a lot of
15 things going on in the first year which later on
16 cause problems. I did a quick look at
17 ClinicalTrials.gov and looked at these following
18 search terms for trials and only found nine trials
19 listed for recruiting interventional trials in our
20 field, which is pretty bad.

21 Three years ago, I spoke at the workshop
22 at the FDA on barriers to progress. And I noted

1 that Subpart H may offer an opportunity at that
2 time to overcome the barriers. And since 2012,
3 I've been really focused and bugging a lot of
4 people on surrogate endpoints. I've learned a
5 lot. Let's see how the FDA has done from '05 to
6 2012. This is a 2014 paper. They've approved 188
7 novel drugs, for cancer. Interestingly, 16.5
8 percent for orphan status, which our field
9 qualifies for, and also interestingly, if you look
10 at surrogate endpoints, primarily endpoint for 49
11 percent of trials. And of course, 95 percent of
12 those are accelerated approvals. Not yet for
13 transplant. But it shows that the FDA does do it.
14 So we're in good company.

15 You all remember Rapunzel and this
16 cartoon says my dad decided to make me more
17 accessible. So we hope that surrogate endpoints
18 for accelerated trials will help make our patients
19 more accessible for newer therapies. I won't go
20 through all these definitions. I went through
21 this before. But I will comment that this is a
22 very good paper to read about biomarkers.

1 Several people have mentioned, including
2 Dr. Fleming, the Institute of Medicine article
3 which is available which is very good and which
4 talks about analytical validation being required,
5 qualification being required, utilization -- that
6 is, what's the context in which the biomarker is
7 being used. And Dr. Fleming mentioned the
8 biomarker hierarchy going from most desirable to
9 most reasonable. And these are the ones that are
10 the ones that are the most reasonable to obtain.

11 There was a report to the president on
12 propelling innovation and direct discovery in
13 2012. And this report recommended that the FDA
14 accelerate approvals, expand its use to more
15 indications, transplantation. It presented a
16 clear guidance and active engagement of medical
17 communities. That's what the recommended to the
18 FDA. Then of course the FDA Safety and Innovation
19 Act was written into law in 2012. This was a very
20 important new innovation. It expanded the use of
21 accelerated approval for life-threatening disease.
22 We've already talked about it required the FDA

1 program to develop new SEPs biomarkers and to
2 provide guidance.

3 The FDA wrote a white paper this July,
4 targeted drug development where many institutes
5 are lagging behind. And it noticed there should
6 be a focus on orphan disease. Again, transplant
7 is qualified for that. Fifty to sixty percent of
8 orphan drug approvals were based on SEPs,
9 accelerated approval not ready for transplant.
10 Recommended flexible trial design and actually 66
11 trials were approved for a single trial.

12 This is slides from Dr. McShane in the
13 National Cancer Institute talking about
14 biomarkers. And she brought up the point that
15 some biomarkers are not sensitive. Others are not
16 specific. We won't go through these. But this
17 slide is interesting. If you look at the
18 biomarkers here, two biomarkers. This biomarker
19 does respond to treatment. This biomarker does
20 not. And here, you can't read the slide very
21 well, but this is a part biomarker which is
22 positive. It did not respond to treatment. This

1 biomarker did, showing that the treatment was
2 predictive. And Dr. McShane also mentioned data
3 from the cancer literature where she was talking
4 about predictability in renal cell cancer. If you
5 look here at the placebo group, IL-6 levels did
6 predict outcome, progression-free survival. And
7 if you look at this group here, the treatment
8 group here predicted longer progression-free
9 survival versus the control group.

10 How to do a trial was suggested by Dr.
11 McShane and her trial design is more of an
12 enrichment trial. But we could use this as an
13 example for our areas for an intentional or
14 prevention trial where you take a look at the
15 marker -- patients who are marker-positive,
16 certain endpoint-positive but get the new agent or
17 the controlled therapy. And then, they would be
18 reassessed for the effect of that therapy on that
19 surrogate marker. If you really want to be very
20 rigid, you would do this and treat the patients
21 who did not show the surrogate marker. We can
22 talk about that later.

1 The last part of the talk is really
2 about a wonderful paper published by the FDA. I
3 highly recommended it, published again in July,
4 which tells you in the academic community and
5 industry really gives you a roadmap of how to deal
6 with the FDA in getting your biomarkers and
7 surrogate endpoints accepted. And mainly it
8 encourages you to work as a group rather than a
9 single sponsor, as a consortium to go through the
10 processes needed for acceptance of a marker. This
11 FDA paper does subdivide the biomarkers into the
12 same groups that Dr. Wang talked about earlier.
13 And you can read this for yourself. It discusses
14 predictive, prognostic, response biomarkers which
15 can be used for enrichment or surrogate endpoints
16 for trial and accelerated approval.

17 That paper also talks about the stages
18 of biomarker qualification, letter of intent. I
19 won't go through the details. But it's a good way
20 for you to be able to learn about what the FDA
21 wants you to show them. They want you to deal
22 with considerations for your biomarkers. What re

1 they used for? SEP. What's the rationale? We
2 talked about that, disease pathway. Relationship
3 between biomarker and outcomes, validation. Here,
4 we have to really be careful because a lot of the
5 assays we've been discussing, especially antibody
6 assays, need a lot of work. More evidentiary
7 considerations regarding the strength of the
8 biomarker, data reproducibility, statistics and
9 the strength of the evidence.

10 And this gets to the next slide, also in
11 that paper. This slide shows you the perceived
12 risk of accepting a biomarker versus the level of
13 regulatory scrutiny the FDA will apply. As the
14 risk for approving a biomarker increases, you've
15 got more scrutiny and this would be a decisional
16 biomarker. This is explanatory. And there's an
17 interesting typo in this paper. If you look very
18 carefully, it says agnostic, not diagnostic. But
19 I wonder if that's a Freidan slip. I'm not sure
20 they really believe what we want to do here.

21 Anyway, so the level of scrutiny may be
22 very high, depending on what you want to do.

1 Consideration is a very complex area and they
2 admit that more clarification is required. You
3 need to show the biomarker changes caused by
4 treatment, predicted outcome. And the more
5 difficult one is the meta- analysis, which may not
6 be necessary.

7 Today we really talked about three areas
8 for surrogate endpoints, histopathology and donor
9 antibody, combination of biomarkers. I think that
10 when we planned the workshop, we were wise to
11 focus it on these three areas. There are more.
12 But I think we've had a very in-depth discussion
13 of these and it's been very worthwhile. Life is
14 short. The art is long. Opportunity fleeting,
15 according to Hippocrates. I just want to show you
16 a slide from Aesop, from the Medical University of
17 Vienna. Eighty sixty is a positive patients.
18 These people had no ABMR, even though they are
19 positive. The ones that had ABMR had a whole
20 heterogeneous group of causes. That's a
21 challenge, I think, for our field.

22 Now, I have a series of questions which

1 I will run through that could be the basis for
2 what we discuss in the last discussion period of
3 this meeting, which I hope will be a discussion
4 period where we decide what we know, what we don't
5 know and what we're going to do next in concrete
6 form. So there may be more questions. But these
7 are the ones I've come up with. What's the
8 surrogate evidence for prognostic biomarkers? Of
9 course, today we've really been talking about
10 prognostic; that is, biomarkers which tend to
11 predict the patient course, not treatment. But
12 that's where we are today.

13 For which of the biomarkers are
14 measurement methods validated? And I'm showing
15 you a whole list of things we need to do. For
16 which of the biomarkers are combination -- is
17 existing evidence stronger or weakest for
18 predicting injury progression and failure? And we
19 need to answer these questions during the
20 discussion. Again, prognostic biomarkers. For
21 which of the biomarkers does evidence support the
22 use of enrichment trials because prognostic

1 biomarkers can be used to select phenotypes to
2 enroll. And can these biomarkers identify
3 specific donor-specific phenotypes to enrich our
4 enrollment. Again with prognostic biomarkers, for
5 which of these is more evidence required to
6 predict transplant failure, to enrich trials. An
7 the key question is what additional evidence do we
8 need, how, when and by whom it be required. I
9 really would like to get that question answered by
10 the group during the discussion period.

11 Predictive biomarkers, these are the
12 biomarkers where you're looking for a treatment
13 effect rather than just prognosis. Which of them
14 measure method again could be validated? Are the
15 incidence of these biomarkers, SEPs and the
16 clinical outcomes high enough for acceptably
17 powered trial, accept the number of subjects. You
18 don't want a biomarker or SEP that has such a low
19 incidence that it's going to be hard to do a
20 trial. And you don't want one with low incidence
21 of graft failure either.

22 Predictive biomarkers, which biomarkers

1 is the evidence strongest or weakest to detect
2 treatment effects? Again, based on the 11
3 criteria. Which of those for predictive is more
4 evidence required? And again, the critical
5 question, if we know what the evidence is needed,
6 how will we get it, who will get it, when will we
7 get it. So I'm going to end with the admonition
8 that the journey is going to be exciting. Be
9 bold. Be courageous. This is when I'm on my
10 summer vacation here. Just to refer you to the
11 backup slides, if you want citations for papers
12 written on transplant biomarkers, interest let's
13 SEPs from 2014 to '03. You can see it in the
14 back. So thank you very much for your attention.
15 I enjoyed being the very last speaker.

16 DR. MANNON: Randy wants us to get all
17 this answered by tonight.

18 QUESTIONS & DISCUSSION

19 DR. JORDAN: Yeah. Thank you. Renata,
20 I wanted to ask you a question. I noticed in my
21 thinking maybe less statistically, but one of the
22 endpoints that you had -- potential endpoint would

1 be a direct benefit to the patient. And then what
2 we're doing today or what we've tried to do, and I
3 mean, in our work and I think in our groups is to
4 improve people's lives by transplantation. And
5 people who have an immunologic barrier to this, it
6 seems to me if one could remove that and have
7 statistical improvements in transplant rates over
8 those seem for a group of comparably sensitized
9 patients who remain on dialysis, that that would
10 be an important endpoint to think about.

11 DR. ALBRECHT: So something that
12 directly benefits a patient, how they function,
13 feel, survive is an endpoint that supports regular
14 approval. I guess the question would be what
15 exactly would define that particular endpoint and
16 how would it be measured. You know, it's easier
17 when you're talking about like headache trials,
18 which are placebo-controlled and use a Likert
19 scale to say my headache was this and now it's
20 this. I don't know what specifically would
21 translate, for example, in those patients.

22 DR. JORDAN: Well, I think, you know,

1 it's length of life, quality of life, measures
2 that were talked about for dialysis versus kidney
3 transplantation that one would say you're more
4 likely to add years to your life and more quality
5 with a transplant than with remaining on dialysis.

6 DR. ALBRECHT: So if we had trials
7 measuring duration of survival, that's a clear
8 direct benefit. Quality of life, the challenge
9 there is what Rita said from the beginning and
10 we've kind of heard. Patient-reported outcomes,
11 there's actually a very comprehensive FDA guidance
12 on how to put those together. But it is a
13 lengthy, probably costly process. And very few
14 PROs get validated, if that makes sense. So it is
15 something. If there's a patient-reported outcome,
16 rather an outcome that the patient has which can
17 be measured by the clinician, that's another
18 approach. But the challenge is that when we talk
19 about quality of life, the importance is --
20 there's again a context of use. It's for those
21 patients, based on their conditions and measured
22 in parameters that are both defined and

1 quantitated.

2 MALE: [Off mic.] So I guess maybe
3 that's the larger issue. [Off mic.]

4 DR. ALBRECHT: So how would you design a
5 controlled trial? Would you make the patient their
6 own control? Would you have --

7 DR. BUDDE: I just would like to comment
8 that it's not only about to increase transplant.
9 It's about to increase successful transplants. We
10 don't have to have a revolving door phenomenon
11 where we do a lot of resources in transplanting
12 and transplanting and transplanting and coming
13 back to dialysis and then dialysis and dialysis.
14 So we need successful transplant as an outcome,
15 not a transplant only.

16 DR. JORDAN: I think one way that I
17 would think about it is you could look at a
18 database, the UNOS database cohort of highly
19 sensitized patients who are not undergoing
20 desensitization and to follow them for a
21 comparable period of time during treatment, assess
22 mortality, assess -- which I think would be a very

1 important endpoint over a period of time compared
2 to those who get transplanted. And certainly,
3 everyone agrees. I don't think -- I mean, those
4 of us who have been in the desensitization
5 business know we can't have a therapy where we're
6 rotating people back on the dialysis list. And I
7 think most of the selection criteria we talked
8 about today and how the drugs we have at least now
9 allow us to be pretty well if we can avoid
10 rejection, allograft rejection early. They do
11 quite well for a long term. That would be my
12 comment.

13 DR. WOODLE: Well, I think Bob
14 Montgomery's paper is quite instructive, isn't it?

15 DR. JORDAN: Yeah.

16 DR. WOODLE: I mean, very clearly
17 patients who undergo desensitization have much
18 better long-term survival. And it can be
19 predicted. If you've got a functioning graft
20 after desensitization after one year, you're very
21 likely to go on and survive for seven years. The
22 other point I would make is even in the cytotoxic

1 crossmatch group, despite a 10 to 15 percent death
2 rate in the first year, the long-term outcomes
3 were substantially better.

4 And so, what happens is we have a short
5 come outcome driving a sister agency with DHHS,
6 that is CMS, that is restricting us from even
7 being able to transplant those patients. And what
8 appears to me is that we need a partnership where
9 we have multiple agencies working together that
10 knock down the barriers to us being able to move
11 this field forward.

12 So the question I would have is there's
13 four recent examples of major impetuses put forth
14 in terms of hundreds of millions of dollars to
15 advance drug development in specific fields. And
16 I'm talking about the advancing medicines
17 partnership in RA, lupus, diabetes and I would ask
18 the FDA what is the role of FDA in that. I know
19 it's a partnership primarily between NIH and the
20 pharma. But I would ask does the FDA have a role
21 in those four AMP programs.

22 DR. ALBRECHT: So generally FDA's role

1 during the development of any program is advisory.
2 There is an importance in keeping separate the
3 review work of the FDA from the decisions made
4 going into drug development. Basically, the way
5 it's articulated is we can't create the protocols
6 and then to review our work of the protocols that
7 we created. So the partnership is that FDA works
8 with whoever the sponsors are, be they academia,
9 be they industry, be it another government agency
10 like NIH and helps in designing protocols that are
11 likely to meet the objective of the protocols so
12 that when the results are reviewed, they can lead
13 to a positive recommendation.

14 DR. WOODLE: I mean, I think that, you
15 know, as we're sitting here looking at this, you
16 threw up 50 antimicrobials that have been approved
17 in the last 30 years. We counted them up and
18 there have been 10 in transplant. There's been one
19 in the last 10 years. So we're way behind, way
20 behind. And I really think that what
21 transplantation needs is something on the order of
22 an advancing medicines partnership, a major

1 investment, multiple cooperation between multiple
2 federal regulatory agencies and industry to move
3 this forward. The FDA alone can't do it. They
4 can be a partner in it. But that's what it's
5 going to take to move this field forward, I think.

6 DR. BUDDE: When I heard Randy's talk
7 and thinking about potential surrogate endpoints,
8 so histology won't make it for several reasons.
9 Donor-specific antibodies is difficult. You have
10 to standardize. But it will come. But they are
11 infrequent if you have good immunosuppression. So
12 it's difficult. But it's made enrichment factor.
13 But what about the most obvious ones, renal
14 function and proteinuria? We have seen basically
15 renal function and proteinuria predicts outcome,
16 histology only adds a little bit eventually in
17 this complicated analysis.

18 So what about renal function and
19 proteinuria as surrogate endpoints? They can be
20 measured. They can be validated. We have tons of
21 data. We use them in kidney disease every day,
22 diabetes, diabetic nephropathy. So why not use

1 proteinuria and kidney function as surrogate
2 endpoints? And I think you can show superiority.
3 Belatacept clearly has shown that you have
4 superiority of kidney function, despite the fact
5 that you have more histologic lesions, whatever
6 that means. But you have better long-term
7 outcomes after seven years. So please, I would
8 ask the panel to discuss five minutes on kidney
9 function and proteinuria.

10 DR. MANNON: Didn't we do that in 2012?

11 [Off mic.]

12 DR. MORRIS: One of the problems of
13 renal function is that the actual pathways in a
14 transplant patient causing renal function are very
15 heterogeneous. And if you go by Dr. Fleming's
16 diagrams, you may have a therapeutic which affects
17 one pathway, leading to decreased renal function.
18 But it does not affect the others. So if you're
19 able to enroll patients where you knew the actual
20 causal pathway for that cause of renal function
21 and those patients had a drug which
22 mechanistically affected that pathway, you could

1 probably do it. I think the histology actually is
2 a better bet because you're dealing with a clearly
3 diseased kidney, which is diagnosed. And you do
4 have some pathological evidence that this is
5 ongoing. And that combined as a composite
6 endpoint with renal function may be the best way
7 to go.

8 DR. STEGALL: I think that it's too
9 simple just to talk about endpoints because,
10 depending on the inclusion criteria, who you put
11 in the study, like if you have recurrent FSGS and
12 you want to be able to treat that, then
13 proteinuria would be a pretty good endpoint. You
14 know, it really would. So but it depends on the
15 patients you start with, what the endpoint is.
16 But if you want to start with low renal function
17 at one year as an inclusion criteria, I wouldn't
18 know how to -- what drug to give those people
19 except, you know, I don't know, you know, ACE
20 inhibitor and whatever we used to do for these
21 people, fish oil, back in the day. And I think
22 that's the limitation of that approach.

1 DR. FLEMING: I'd like to take maybe two
2 minutes to follow up. Dr. Morris laid out what I
3 thought were critical issues. And I wanted to
4 make four points based on what I take away from
5 this meeting in terms of action items for the
6 future. So the first is the work that's been done
7 by Dr. Loupy, Dr. Zhao and others has very
8 significant utility in addressing some of these
9 questions that Dr. Morris mentioned. These kinds
10 of efforts give us important insights about use of
11 biomarkers for prognosis, for diagnosis, for risk
12 stratification, for event rates that help guide us
13 in understanding the size of the trial, who to
14 target in the trials, what's the variability of
15 the population and also for counseling patients
16 about prognosis.

17 Those are all very important. They do
18 not tell us two critical things. They do not tell
19 us whether they're valid surrogate endpoints
20 because once you intervene with your experimental
21 therapy, you are changing how those covariants are
22 predictive of outcomes. And you can only assess

1 the extent to which you are by having randomized
2 trials. And they're also not telling us about
3 enrichment. So the slides that Dr. Morris had
4 from Lisa McShane, please read them again because
5 it tells -- she is getting exactly the distinction
6 between prognostic factors and predictive factors.
7 Prognostic factors is what you get out of these
8 kinds of studies. Predictive factors is telling
9 you whether the experimental therapy will work
10 differentially across those. You need to have
11 randomized trials. She told you how. She showed
12 you -- you showed the slide. You need to have
13 randomized biomarker-stratified trials to get that
14 kind of data.

15 Second point, my sense is you're well on
16 your way toward important insights about whether
17 we can use biomarkers for regulatory purposes. I
18 don't know the answer yet. But I'm very impressed
19 with the insights that came about today in
20 understanding the factors and whether they are
21 integral as causal -- as the principal causal
22 pathways by which the disease process leads to

1 these outcomes, leads to patient failure and graft
2 failure. So creatinine, GFR, the biopsy, the
3 kidney biopsies with fibrosis, the subclinical
4 inflammation, the donor-specific HLA antibodies,
5 these all, I'm impressed, matter.

6 But what we need, second action item, we
7 need to have these built into our prospective
8 trials where we're looking at results on feels,
9 functions, survives endpoints and results on these
10 biomarker endpoints. And that's the evidence-
11 based source that we're going to have in the
12 future. Surely that's necessary to use these
13 biomarkers for full approval. But even to be able
14 to do some of the formal analyses to use these for
15 accelerated approval.

16 Third point, we are not going to have to
17 wait, though, for that second step to be done. We
18 have the potential to do many clinical endpoints
19 as we speak. Either, and I definitely agree with
20 Jesse's talk, there are pros and cons to composite
21 endpoints. So I'm not saying whether we should
22 make these as composites or not. But we should be

1 looking globally at what matters in feels,
2 functions, survives. So we have patient. We have
3 deaths. We have graft loss. We have acute
4 rejection, short-term and long-term. But we also
5 have the potential to be developing patient-
6 reported outcomes, CLIN ROS and ODD ROS [ph] for
7 how patients feel and function.

8 And they are not as daunting as we might
9 make it sound. You don't even need randomized
10 trials for setting up those PROs. You need
11 registries. Hospitalization, dialysis, other
12 things that are tangible and matter to patients.
13 We also heard today about the off-target effects
14 and how we could be assessing, we said diabetes.
15 I put that as sustained use of insulin injections,
16 severe infections, malignancies. We can compare
17 therapies on any of these measures. And they are
18 all feels, functions, survives. There's no
19 controversy about what they mean.

20 And then, the last point is, yes, we can
21 also think carefully about ways of using adherence
22 insights to improve how we target which patients

1 get into trials and to maximize the effect of how
2 an intervention works. For retention, I say I
3 want everybody. For adherence, I don't. I want
4 best real- world achievable. But what are ways
5 that we can maximize best real-world achievable of
6 adherence to these interventions to increase their
7 benefit? So to me, there are multiple steps that
8 come out of this meeting that can move us forward
9 from where we are in constructive ways to getting
10 at more effective therapies to patients. But
11 again, it's not about getting more therapies.
12 It's about getting more evidence-based
13 justification, that we have therapies that are
14 effective and safe.

15 DR. MORRIS: Could I make a comment?
16 Maybe we're further along than we think we regard
17 to predictive surrogate endpoints. Maybe if we
18 are able to get industry to partner with us to
19 look at their controlled -- randomized controlled
20 trials, where their primary endpoints were
21 rejection, death, graft loss, within those trials,
22 they may have captured histology, DSA and may have

1 captured a treatment effect or not on a secondary
2 endpoint which could be a surrogate endpoint if
3 the treatment effect affected that surrogate and
4 improved the clinical benefit whereas in the
5 control it did not.

6 So I see Dr. Klupp at the microphone and
7 I hope he and other industry partners will be
8 willing to go back into their trial and look for
9 the evidence that we already have information
10 showing treatment effect on biomarkers.

11 DR. O'CONNELL: So to back that up, I
12 think we've had discussions earlier, Jochen and
13 Mark will be next, but that there's a lot of data
14 done by a lot of companies in transplantation
15 where they've been. The trials are very well
16 setup. You've got, you know, well-controlled
17 clinical trials, that there may not be a primary
18 endpoint. But you've got histology data that's
19 not been reported or we've not looked at i-IF/TA
20 or we've just looked at acute rejection but not
21 looked at chronic change.

22 And there may be the opportunity that

1 within that data to answer some of the questions
2 about the validity of a biomarker already within
3 and how predictive it is within that. So I guess
4 the question is do you think that if we reached
5 out to industry, that that would be likely that we
6 could -- that people who had valid questions could
7 come and ask --

8 DR. FLEMING: Those are exactly the
9 kinds of information that we need to understand
10 more effectively the use of biomarkers as
11 replacement endpoints and for enrichment is to
12 have an aggregation of evidence from randomized
13 controlled trials. Now, the extrapolation of
14 enrichment is of some question because new
15 interventions that come forward with new
16 mechanisms may have different interactions.

17 But this is -- and that was Lisa
18 McShane's point is as we do prospective trials, we
19 should be stratifying on biomarkers that will
20 allow us to test the principal hypothesis but also
21 to learn about the extent to which biomarkers are
22 telling us who will benefit.

1 DR. MANNON: So I just have to
2 interrupt. Is the representative from Critical
3 Path here? Do you know, Renata?

4 DR. ALBRECHT: I think they --

5 DR. MANNON: Because one of the suggest
6 products by Critical Path, to the societies was to
7 sort of do a unification of all data. And I think
8 it's a lot as an individual to say, well, we're
9 just going to extract all this data. But we
10 certainly have experts. And from what I'm
11 hearing, this is a step forward would be to try to
12 unify that data through a third party, i.e.,
13 Critical Path. But I don't know if they're here
14 or not.

15 DR. ALBRECHT: I think they might have
16 been watching it on the streaming --

17 DR. MANNON: By the streaming, okay.

18 DR. ALBRECHT: But I think that's
19 something. We should follow up on that.

20 DR. O'CONNELL: So would you like to
21 respond to that?

22 DR. BUDDE: Well, I had a question. But

1 I also would like to respond because it's somehow
2 related. Pooling data sounds easy and obvious and
3 getting it all together. If you actually try it
4 and you want to get it together for whoever tried
5 it before was getting too hard pretty soon. On
6 the other hand, we are making progress.
7 Specialists are making progress in a new way on
8 data assessment and bringing various databases
9 together where this may be a path forward. And as
10 there are so much progress, I agree that this is a
11 sensible way to move forward.

12 That brings me back to my question also
13 to Dr. Loupy. And we discussed today -- and I'm
14 focusing on prognostic biomarkers not on
15 predictive markers. For prognostic markers, we
16 focused on many different singular markers and we
17 realized the limitation of many of those, whether
18 these are on the histology, on renal function,
19 maybe on the DSA we are making more progress. But
20 we may come to a situation where we don't get on a
21 single marker that we can move forward.

22 If I then listen to such an amazing

1 presentation as from Dr. Loupy and we put
2 everything into an iBox, this may be an excellent
3 path forward. But intuitively there may be only
4 very few people who are able to understand it. My
5 question here to the community is would we be
6 willing actually, if we have an algorithm
7 developed by experts, which may not be medical
8 experts or it may be a combination between medical
9 and informatics experts, and creating some kind of
10 a scoring system, iBox or so, in enriching a
11 population where we can then at least go in the
12 population where we can study easier because we
13 trust those markers.

14 They are validated as an iBox and
15 working on this one as the next development step.
16 So I'm curious about the feedback from the panel
17 for someone who wants to volunteer.

18 DR. MENGEL: I volunteer. No. My
19 question is to that. These tools are not
20 regulated by anybody. So how do we know whether
21 his equation is better than his equation or his
22 equation? But I think the advantage is that you

1 can evaluate them in retrospective well-annotated
2 data sets. But how will they be regulated and
3 then used by the community? Is it an online tool?
4 Everybody can upload their enrollment criteria for
5 a trial?

6 I think questions like this come to my
7 mind. I don't know whether that is the direction
8 you were asking. But it's a new field. It's like
9 validating a diagnostic assay platform, these
10 equations. To me, it's the same. It needs
11 quality control, quality assurance when you want
12 to stratify patients on that. But it's doable.

13 DR. O'CONNELL: But is the question is
14 this better than yours or mine? But is the
15 question rather does his work, regardless of
16 whether yours is better? So because it's a
17 surrogate, also the hard endpoints are still going
18 to be the same at the end, so --

19 DR. MENGEL: Not necessarily.

20 DR. O'CONNELL: No, the hard endpoint's
21 going to be death or graft loss.

22 DR. MENGEL: Right.

1 DR. O'CONNELL: So in other words --

2 DR. MENGEL: But I think the whole point
3 is when a surrogate, you don't want to wait for
4 that.

5 DR. O'CONNELL: Yeah, but --

6 DR. MENGEL: So how does when the
7 strategies and calculated variables for death and
8 graft loss retrospectively, that doesn't mean when
9 you apply to a different population or in a
10 different equation system, you have identical
11 values.

12 DR. O'CONNELL: No. But we're all in
13 that boat. So in the end, it's just if you like
14 it and you try and it works, then that's fine.
15 But I guess you'd have to --

16 DR. MENGEL: -- the process --

17 DR. O'CONNELL: But no one's going to
18 find out until we try something. Is that --

19 DR. MENGEL: Sure.

20 DR. O'CONNELL: So I don't think -- I
21 think if there's three things being trialed,
22 that's not a bad thing. It's just that we've come

1 to a point where there's enough data for people to
2 come on and give it a go.

3 DR. MENGEL: So my analog would be
4 imagine the MMF or tacrolimus trials with three
5 different histology classifications. Not one
6 Banff system but three different classifications
7 and three different trials. So that is the
8 dilemma when you use analytical tools. They all
9 of course go for biopsy- proven rejection. But
10 one classification calls for rejection this way,
11 the other one this way and the other this way.

12 DR. STEGALL: It actually --I think
13 that, for example, we revalidated this so-called
14 Birmingham model that was used and the problem I
15 had with that -- I mean, it's a fine model. It
16 does -- it does put people in higher risk groups
17 is what it really does. And it's -- some of the
18 risk factors are African- American. They're
19 people who have albumin or creatinine ratios that
20 are elevated at one year, the usual suspects kind
21 of thing. The problem is I have with those kinds
22 of systems -- and it may identify high risk

1 groups.

2 But it may not differentiate which
3 groups they fall into. It's one of the one-size-
4 fits-all kind of a thing because that's the reason
5 it predicts all graft losses. But I think that
6 using a combination, which we already do already,
7 people with delayed graft function, people who
8 have DSA pre-transplant or whatever, those are
9 already risk models in certain ways.

10 And a more robust risk model would
11 probably be more predictive and therefore may be
12 of utility to try and identify patients to go into
13 clinical trials or what their outcome should be.
14 And I don't think -- so the flavor is not really
15 three different forms of antibody-mediated
16 rejection. You have to look into the details of
17 each of the model systems. Some of them rely on
18 other features. But they all end up with point A
19 being the c-statistic, by the way.

20 DR. LOUPY: Yeah. So I think -- I think
21 that one of the goals and there are many papers in
22 biostatistics and bio management who -- which

1 focus on the fact that the prospective assessment
2 in a heterogeneous cohort, which is well-
3 annotated, can provide you a large portal for
4 delivering composite endpoints. And when you look
5 at the -- one of my colleagues has presented --
6 you can achieve like 0.9 c-statistics, meaning
7 that a one-year measurement, using whatever
8 variable you want to use, can predict with a 90
9 percent accuracy what will happen eight years
10 after this measure, which I think is a pretty good
11 way to start, you know, as a composite endpoint.

12 So it's not like randomized validated.
13 But it's a prospective, well- annotated,
14 heterogeneous taking pre-sensitized and non-pre-
15 sensitized donors, all that criteria, living
16 donors and everything, integrating the variables
17 inside, which can end up with a model which you
18 have GFR which is highly very strong in the model,
19 proteinuria, which is very strong, histology,
20 which is dependence, carrying injury, complement
21 and also DSA, which is a very good biomarker. So
22 I think that I would see that more as a strength

1 than a limitation to start with a composite
2 endpoint.

3 DR. NICKERSON: So my only comment to
4 that would be if I have a bad GFR at one year and
5 I have proteinuria at one year, that's a bad
6 outcome, right? I mean, those patients are not
7 that prevalent, unless they had a preexisting DSA
8 or gave them a really bad graft to start with.
9 Most of our patients at one year are actually
10 doing really well and don't have significant
11 proteinuria. And yet, their attrition rate, as we
12 saw from the half-life data, by 10 years is
13 progressively significant.

14 So the problem I have with a surrogate
15 at one year that's looking at function and
16 proteinuria, and even if they have a DSA at that
17 point, because I think most of the data you're
18 showing us with DSA is preexisting DSA, is that
19 that is really some of the worst transplants that
20 we've done, for whatever reason. And I think
21 that's not the vast majority of the transplants
22 we're doing. So I think we have to ask the

1 question what is the more subtle injury to the
2 graft that is going to rumble along and lead to
3 graft failure. And I think that's likely to be a
4 composition of is it pathology, because it's
5 subclinical. It's not clinical. And as your own
6 data is showing, it's subclinical that's more
7 prognostic than clinical.

8 And I would actually back up even
9 further and say what's the enrichment strategy
10 that's going to be key. And we're really not
11 talking a lot about that, I don't think at this
12 meeting. And some of the key enrichment
13 strategies, I would actually argue, and I'm an HLA
14 guy, so I'm going to argue HLA. But you know, we
15 still talk very -- in a very -- in the same way we
16 talk about thinking what we know about surrogates
17 might be. HLA, we have no real good assessment of
18 compatibility of HLA when we do our transplant.
19 The whole antigen match thing is so crude in our
20 thinking that we have to refine that.

21 So if you want an area ripe for
22 research, let's start asking how mismatched is an

1 individual. And if we ever want to get to
2 minimization studies, we'd better get rid of the
3 driver of the immune response in the first place,
4 which is how disparate are two recipient and donor
5 combinations. And I think that's an area we
6 really have ignored at this meeting largely in our
7 understanding. So I would argue that really bad
8 outcomes by a year, yeah, we know they're back and
9 they're probably bad because we did a transplant
10 that had a marginal kidney in the first place
11 because we're not really looking at slope of eGFR
12 at a year.

13 We're looking at absolute value of eGFR
14 at a year. If you have significant proteinuria by
15 a year, well, that's probably there for a big
16 reason, right? So I think badness at a year
17 that's overt is really I think the minority of
18 what we're dealing with, not the majority.

19 DR. LOUPY: yeah. So if I just can make
20 a comment on that, the score is not only good and
21 bad. It has like four strata inside. And GFR is
22 not good and bad. It's a continuous variable in

1 the process. Proteinuria is not presence or
2 absence. It's a quantification in gram per gram
3 of creatinine and proteinuria. So it means that
4 you're not measuring like and only looking at the
5 bad, bad guys at one year, which I agree with you
6 are not that many.

7 But you are looking at five different
8 strata of risk, starting from no risk, low risk,
9 intermediate and high. And that's the way you
10 split your cohort in one year, even if you have
11 like 50 ml/min GFR and DSA. And of course, of
12 course it's important to notice that in the score,
13 the histology and the inflammation is independent
14 of the GFR and proteinuria. It gives an
15 additional prediction. And so, I think that if we
16 want to have too many refinements and also in
17 terms of HLA in the composite endpoints, we will
18 never succeed.

19 We will never get an endpoint and we
20 will look at the different subtypes and epitopes
21 and everything, which are important. But now what
22 is needed is a simple, robust and something that

1 predicts with a high accuracy at eight year. And
2 I think we are -- we can be -- we are pretty
3 close.

4 DR. NICKERSON: Right. I guess what I
5 would say back though, Alex, is if I have a -- I,
6 as a clinician, I think we all know as the GFR
7 goes down, the graft is going to fail sooner,
8 right? That's just what we know in nephrology in
9 general. The lower your GFR to start. The
10 problem is what's going to progress. And I think
11 you discussed this in 2012. You can have a GFR
12 that sits at 25 for years or you can have a GFR
13 that is going to progress, right?

14 DR. LOUPY: Yeah.

15 DR. NICKERSON: And so, that's where I
16 would argue that pathology and inflammation is
17 going to tell us a lot more than ultimately --

18 DR. LOUPY: Yeah. Yeah, but they are
19 not --

20 DR. NICKERSON: And I'm not disagreeing
21 with the iBox idea of a composite, right? I'm not
22 disagreeing with that. I'm just saying these

1 things that we're picking out, when they're
2 progressively worse, and I think, you know,
3 proteinuria over a hundred milligrams or even 50
4 milligrams probably the higher it goes, the worse
5 we know it's going to be.

6 DR. LOUPY: Yeah. But you need to
7 compete your histology assessment and injury with
8 those strong biomarkers to show independency and
9 not to bring an additive value. Otherwise, the
10 score has no meaning if you just insert like
11 histology and inflammation inside.

12 DR. MANNON: We're already over. Harry
13 and those guys and then we can like go out into
14 the hallway. I mean, because we can't be here all
15 night. I think this is a valuable discussion.
16 But we also have some action items from Renata.
17 So Harry, boom, boom. John, if you're going to
18 the mic -- no, you're just listening? You're just
19 strolling? Okay.

20 DR. HARIHARAN: You know, when any drug
21 gets approved, ultimately there is a label there.
22 So and so combination therapies are approved for

1 the prevention of whatever, acute rejection after
2 renal transplantation, de novo renal
3 transplantation. My question to FDA is what
4 additional information or data you would require
5 to consider subclinical rejection along with
6 clinical rejection as a potential short-term
7 surrogate marker for transplant, you know,
8 interventional trial for transplantation. Perhaps
9 a loaded question, but --

10 DR. ALBRECHT: It's a loaded question.
11 But I think I'll answer it by saying I think
12 during today's presentations, particularly from
13 the FDA, you saw examples of how biomarkers were
14 qualified and how surrogate endpoints were
15 developed. We did not go into a great deal of
16 detail but did provide some search words to go and
17 look these up.

18 But I think some of the common themes
19 are looking at data from studies, multiple studies
20 using clear definitions, as others have said, of
21 what I the proposed marker, biomarker, surrogate
22 endpoint and what is the data that links it to the

1 ultimate point of -- or rather the clinically
2 meaningful endpoint for the patient.

3 And the stronger that information, the
4 more the data support it from study to study,
5 center to center. It doesn't always have to be
6 controlled data. It can be, as you heard,
7 retrospective, prospective registry data. But the
8 stronger that information and then if that can be
9 put together in a document with a summary and the
10 individual studies, that starts the process.

11 DR. HARIHARAN: Thank you.

12 DR. MANNON: Kevin?

13 MR. FOWLER: Yeah. I just wanted to
14 make a suggestion. You know, the Kidney Health
15 Initiative that's being -- which I'm a member of
16 and I'm representing transplant. They formed a
17 patient-family partnership council. It's very
18 early right now. But I mention it for two
19 reasons. One is that the whole Kidney Health
20 Initiative is another possible collaborator that I
21 don't think is really being tapped into. So
22 that's one recommendation is greater engagement

1 there. I'm happy to help facilitate that.

2 And then, the second thing related to
3 that is, is that there's a clear recognition
4 within the renal community that if they're going
5 to find new clinical trials, that patients have to
6 be engaged and the patients have not been engaged
7 in that community. And I think that if we're
8 looking at the issues that we have here, they're
9 not insurmountable. But I think we have to be
10 honest with ourselves. Look at rare diseases.
11 Look at cancer. Look at all these other areas.
12 They all have very strong patient advocacy. And
13 so, I mention that and I also mention a point too.
14 I'm willing to help make that better here. But I
15 think that is a critical path to bring this
16 forward, so.

17 DR. MANNON: So Kevin, I appreciate your
18 comment. You know, I guess I can speak for the
19 AST, even though I'm not the president or involved
20 anymore. I do know the society is specifically
21 looking at engaging patient groups and recently
22 had a transplant roundtable summit where patient

1 groups were invited. And there are a lot of small
2 disease groups of rare diseases like cystinosis
3 and oxaluria where the development of renal
4 failure is almost a hundred percent. And now,
5 even though it's not in children, it's delayed
6 into adolescence and later. So I know that's
7 important.

8 With regard to the Kidney Health
9 Initiative, that was really one of the first
10 groups that I was engaged in before I came up with
11 the concept of transplant therapeutics. Rita
12 Alloway and I have been tapped in to do a project
13 with C-disk to sort of create a uniform way of
14 assessing the outcome variables in all clinical
15 trials. The project is supposed to start
16 Thursday, right -- no, in a few days, maybe next
17 week. This would really be a test project. And
18 it's a transplant-specific project. One of the
19 difficulties with KHI is, as successful as it is,
20 it is focused on renal disease.

21 And in my lofty ideas, I was always
22 thinking that this was solid organ and had -- and

1 it was hard to engage when I engaged the
2 leadership. But be that as it may, it is an open
3 opportunity. The quality -- the quantity of this
4 project of extracting information from multiple
5 clinical trials will be held up by the fact that
6 every variable is coded very differently. So even
7 though I want renal function in the Opticept trial
8 may be as eGFR and serum creatinine or creat
9 (md/dl), you know they're going to be coded
10 differently. And so, it seems almost, you know --
11 mentally to me, it's almost insurmountable. But I
12 do think it's achievable.

13 And I think one of our action items that
14 Randy said we have to have action items is that
15 the leadership of each society really needs to go
16 back and talk to the leadership if they're no in
17 charge and to say that this is valuable and that
18 we buy in. And I can already sense that, you
19 know, AST, ASTS, ESOT, TTS, you know, are very
20 engaged. And one of the reasons we're having this
21 meeting is because we did reach out to FDA three
22 years ago. Translational medicine encouraged us

1 to get together. We met and one of our many
2 meetings, but last October Renata reminded us that
3 we really needed to have this meeting and ask the
4 public to get engaged and decide what the focus
5 is. So I do appreciate your comments --

6 MR. FOWLER: But I'm going to be
7 unrelenting in my comments.

8 DR. MANNON: Sure.

9 MR. FOWLER: Just because I'm the only
10 one here, I'm not going to let up because I just
11 think it is such an issue. And I think it's the
12 fact that we need to have patients from --

13 DR. MANNON: Sure. No, absolutely. You
14 wouldn't hear an argument from me.

15 MR. FOWLER: I mean, in terms of
16 scholarship. So just FYI.

17 DR. MANNON: Yeah. I'm a total patient
18 advocate. And certainly engaging them in trials
19 is complicated. Barbara?

20 DR. MURPHY: I want to get back to Steve
21 Woodle's comment about there's only been one drug
22 approved in transplant in the last 10 years and

1 point out that although it's very important, our
2 discussion around endpoints is incredibly
3 important. But changing endpoints wouldn't have
4 change any of that. Unless we actually learn from
5 cancer and learn how to immunologically risk
6 stratify our patients from the get-go and move
7 away from the idea that every drug has to suit
8 every patient, we're never going to -- the
9 endpoints won't really matter.

10 DR. MANNON: John Gill?

11 DR. GILL: That's a great point. Hard
12 to follow Barbara. I just want to come back to
13 Dr. Fleming's point about the fact that we need to
14 do trials and prospectively validate these
15 outcomes. I just -- let's go back to the benefit
16 trial. The reason we were so uncomfortable about
17 it is because the co-composites went in a
18 different direction. But we learned a ton from
19 that. And I don't think we should be lost on
20 that. I think it's viewed in a failure in some
21 regards by people. But the bottom line is now
22 we're seeing long-term outcomes and we're learning

1 a lot more about this field, about costimulatory
2 blockade.

3 So I would say that, you know, we need
4 to look back on what we've done and say why did it
5 not go the way -- what are we uncomfortable about
6 it. But we actually are learning a ton from it.
7 So I think that's an incredibly important point.
8 What I'm really saying is we do need to be bold.
9 Even if we make mistakes along the way, there's a
10 ton to be learned along the way. So thanks for
11 that comment.

12 DR. MENGEL: Just on that note, John,
13 I'm not aware of a single robustly designed drug
14 trial, randomized drug trial which includes a
15 composite diagnostic in transplantation, a new,
16 novel tool like they did in cancer.

17 DR. MANNON: I'm not sure industry would
18 even remark. And I won't use it because I've
19 signed a million CDAs. I know of at least two
20 Phase IIs where samples were collected. I've
21 never seen those mechanistic --

22 DR. MENGEL: Published data, okay?

1 DR. MANNON: Yeah.

2 DR. MENGEL: So --

3 DR. MANNON: I've never seen those
4 mechanistic data. I know they're collected. But
5 again, it's another issue. I mean, I've had
6 patients do quality of life measures for some of
7 the major trials, never seen any of that data.
8 It's disappeared. Obviously it's a low hanging
9 piece of fruit that companies may want to release
10 and say, you know, maybe it isn't great that I'm
11 pooping five times a day. I mean, these are
12 general examples of label trials where we're -- I
13 mean, we fill out tons of paperwork on each
14 enrolled patient and that hasn't been brought up.
15 But there are studies that have employed
16 mechanistic markers. There's a proposed study
17 from another company that wants to test one of the
18 other markers that's for sale out in the community
19 as well.

20 DR> MENGEL: That's not what I meant,
21 Ros. I meant the design we saw in the slide where
22 you randomize into biomarker yes/no and then

1 within each arm treatment --

2 DR. MANNON: No. That has not been
3 done.

4 DR. MENGEL: That's a robust composite
5 diagnostic trial design and that hasn't been done.

6 DR. MANNON: No. It has not been done.

7 DR. MENGEL: And what I think what the
8 opportunity is that the technologies evolved so
9 dramatically over the last couple of years, that
10 probably is it now feasible to do this because it
11 advanced. It is cost-effective. It can be done
12 in a reasonable setting. So maybe that's just
13 another opportunity.

14 DR. MANNON: Well, we could discuss it
15 tomorrow in our trial design. I mean, right?

16 DR. MENGEL: Yeah. So --

17 DR. O'CONNELL: So I think we're at the
18 point where we need to stop going around in
19 circles, looking at our surrogate markers and
20 albeit prospective or predictive and be bold. Go
21 out and design something and trial it. Maybe if we
22 can, look retrospectively at studies that might

1 have that data, see if that's illustrative to us.

2 But I don't think that us talking about it

3 anymore, what's that going to do.

4 And I think -- personally, I think

5 looking at that data we've seen out here, a lot of

6 people put a lot of thought into this. And I

7 think -- you know, I don't think there's going to

8 be one strategy that's going to come out like a

9 beam of light. I think there might be three or

10 four things we ought to as a community go out and

11 try. But I think we've got to try something and I

12 think we've got enough data that you could put

13 forward an argument that could get you funded

14 either academically to -- you know, to try

15 something. That's what I think.

16 So I hope that people felt that. You

17 know, we all have different things that we want to

18 look at. But I think there's enough out there

19 that we could really do things differently and

20 really incorporate biomarkers, incorporate

21 enrichment strategies. Just as a general sign

22 off. And I'd like to hand over to Renata to give

1 us our homework.

2 DR. ALBRECHT: Okay. Thank you. So I
3 think today was extremely valuable. And I'll
4 borrow Dr. Fleming's phrase, that I think we've
5 reached an insight. I think the other thing is
6 that I hope we're going to continue a deliberate
7 and systematic dialogue on the surrogates. I
8 agree with Dr. O'Connell. I don't think we know
9 the answers. I don't think we know what
10 surrogates will pan out. I don't know what
11 additional clinical endpoints, such as function,
12 survival for patients. We can identify the
13 example of desensitization that Dr. Jordan and
14 Woodle just mentioned earlier.

15 Regulators have a role. We have
16 guidances. We can give you examples from before.
17 We can guide. We can't do the validation of the
18 surrogates. We can review it. And Marc Cavaill
19 gave a presentation. He showed you what was done
20 in the HIV arena. Industry working with academia
21 working with investigators and then holding an
22 advisory committee before the FDA, which before an

1 advisory committee, FDA reviews that information.
2 Sometimes it can take a few months. But then,
3 having a public discussion of the science, the
4 evidence and how to move it forward.

5 So I would like to encourage all of us
6 to stay engaged. I hope tomorrow and the day
7 after are fruitful. I will say that when the
8 funding is available, FDA is very happy to do
9 these workshops. It dried up after 2012. We got
10 it again and I hear maybe we'll have it in 2016.
11 So you know, we're going to continue the
12 workshops. And with that, I guess, you know, good
13 luck. And I hope to see everybody at whatever
14 next public meeting where we continue this
15 discussion. And thank you, again, very, very much
16 for everybody coming and spending all day here.

17 (Whereupon, the foregoing concluded at
18 6:18 p.m.)

19

20

21

22

1 CERTIFICATE OF NOTARY PUBLIC

2 I, JEN METCALF, the officer before whom the
3 foregoing proceeding was taken, do hereby certify
4 that the proceedings were recorded by me and
5 thereafter reduced to typewriting under my
6 direction; that said proceedings are a true and
7 accurate record to the best of my knowledge,
8 skills, and ability; that I am neither counsel
9 for, related to, nor employed by any of the
10 parties to the action in which this was taken;
11 and, further, that I am not a relative or employee
12 of any counsel or attorney employed by the parties
13 hereto, nor financially or otherwise interested in
14 the outcome of this action.



Jenifer A. Metcalf

18
19 JEN METCALF
20 Notary Public in and for the
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1 CERTIFICATE OF TRANSCRIPTION

2

3

4 I, BENJAMIN GRAHAM, hereby certify that I am not

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9 is a true, correct, and complete transcription of

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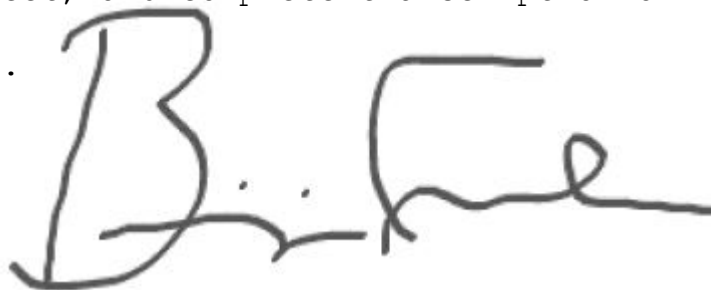
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A handwritten signature in dark ink, appearing to read 'B. Graham', is written over the signature line.

BENJAMIN GRAHAM
Transcriptionist

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