ENDPOINTS IN CLINICAL TRIALS OF KIDNEY TRANSPLANTATION

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1 A G E N D A

2 PAGE

3

4 WELCOME 10

5

6 SESSION 6: RENAL FUNCTION AS AN ENDPOINT IN

7 KIDNEY TRANSPLANTATION 10

8

9 Topic #1: Assessment of Kidney Function:

10 Measured vs. Estimated GFR by Different

11 Formulas

12 Speaker #1: Emilio Poggio, MD 11

13

14 Topic #2: Effect of Procurement and

15 Preservation on Quality and Function after

16 Kidney Transplantation

17 Speaker #2: Rutger J. Ploeg, MD, PhD, FRCS 26

18

19 Topic #3: GFR and Long-Term Outcomes:

20 The Mayo Experience

21 Speaker #3: Walter D. Park, BS 39

22

1 Topic #4: Stability of GFR Over Time as a
2 Clinical Outcome
3 Speaker #4: Robert S. Gaston, MD 53
4
5 Topic #5: Hyperfiltration Nephropathy,
6 Proteinuria, and Inflammation as Contributing
7 Factors to Chronic Allograft Injury:
8 Implications for Biomarker Discovery and Therapy
9 Speaker #5: Matthew R. Weir, MD 70
10
11 Topic #6: Is Higher GFR at Two Years Better?
12 Speaker #6: Ergun Velidedeoglu, MD (FDA)
13 80
14
15 Question and Answer Period (Panel and Audience)/
16 Public Comment Discussion of Suggested Questions
17 (to be introduced by the moderator(s)) 93
18
19 SESSION 7: NEW WAYS FOR CONSIDERING EFFICACY/
20 SAFETY ENDPOINTS TO DEMONSTRATE SUCCESSFUL
21 OUTCOME IN PATIENTS 143
22

1 Topic #1: Protocol vs. Prescribed vs. Actual
2 Immunosuppressive Regimens: Are Efficacy and
3 Toxicity Rates Known?
4 Speaker #1: Rita R. Alloway, PharmD, FCCP 144
5
6 Topic #2: Metabolic Complications
7 Speaker #2: George W. Burke III, MD 162
8
9 Topic #3: Redefining Renal Transplantation:
10 Cardiovascular Complications
11 Speaker #3: Alan G. Jardine, BSc,
12 MBChB, MD, FRCP 175
13
14 Topic #4: Infectious Disease Complications
15 Speaker #4: Camille N. Kotton, MD 188
16
17 Topic #5: Development of Malignancy
18 Speaker #5: E. Steve Woodle, MD, FACS 200
19
20 Topic #6: Balancing Efficacy with Toxicity
21 to Improve Long-Term Outcome
22 Speaker #6: Flavio Vincenti, MD 214

1 Topic #7: Scaling Issues with Current Endpoints:
2 Can Effectiveness Rather than Efficacy Offer
3 Some Solution?
4 Speaker #7: Bruce Kaplan, MD 228
5
6 Topic #8: Successful Outcome: Proposed Approach
7 Speaker #8: John S. Gill, MD, MS 241
8
9 Question and Answer Period (Panel and Audience)/
10 Public Comment Discussion of Suggested Questions
11 (to be introduced by the moderator(s)) 255
12
13 Summary Day 2 273
14
15 Adjourn Day 2 277
16
17
18
19
20
21
22

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

2 Welcome

3 DR. SALOMON: If people could find their way

4 to the tables and sit down, that would be very much

5 appreciated. Session 6: Renal Function as an Endpoint

6 in Kidney Transplantation

7 Moderators: Daniel R. Salomon, MD, Reshma

8 Kewalramani, MD, FASN, Frank Hurst, MD (FDA), and Ergun

9 Velidedeoglu, MD (FDA)

10 DR. ALBRECHT: So if everyone could come to

11 their seats, Session 6 is "Renal Function as an

12 Endpoint in Kidney Transplantation." The moderators

13 are Dr. Dan Salomon, Dr. Frank Hurst, and Dr. Ergun

14 Velidedeoglu.

15 DR. HURST: Okay, good morning. I would like

16 to introduce our first speaker for Session 6, who is

17 Dr. Poggio, who is going to speak about "Assessment of

18 Kidney

19 Function: Measured Versus Estimated GFR by

20 Different Formulas."

21

22 Topic #1: Assessment of Kidney Function: Measured vs.

1 Estimated GFR by Different Formulas
2 Speaker #1: Emilio Poggio, MD
3 DR. POGGIO: Good morning, everybody. First
4 I would like to thank the organizers for
5 giving me the opportunity to present in this workshop.
6 I am going to be talking about "Assessment of Kidney
7 Function: Measured and Estimated GFR." My talk is
8 going to be rather simple and less technical. The
9 challenge will be for the next speakers to discuss how
10 to use this information.
11 So I have disclosures, as shown in this
12 slide.
13 The first thing is that GFR, as we all know,
14 is considered the best overall index of kidney
15 function, and that's its application in clinical
16 medicine. In fact, we are looking for alternatives to
17 assess the kidney, and for the last 100 years, this has
18 been the way to go. So GFR is the clearance by the
19 kidney, of a marker, either endogenous, like
20 creatinine, or exogenous, in plasma, expressed as the
21 volume of plasma completely cleared of the marker per
22 unit time. So we have several components here, and as

1 you can see, here you have the marker is on the
2 numerator and denominator of the formula. One is in
3 the urine there, and one is in the plasma. And based
4 on this formula, which is the basis for any measurement
5 of kidney function, either creatinine clearance or
6 iothalamate or inulin, you are using the inverse of the
7 serum creatinine.
8 So the ideal filtration marker should be
9 freely filtered by the kidneys, excreted only by
10 glomerular filtration, should be inert, the rate of
11 generation should equal the rate of elimination so you
12 achieve a stable plasma level, its circulating levels
13 should not be altered by any other physiological
14 factors, and then it should not be affected by any drug
15 commonly used in clinical transplantation.
16 There are several filtration markers. As you
17 will know, the creatinine -- actually the first one to
18 be available clinically back in 1910 was urea, blood
19 urea, and then in 1937, creatinine became clinically
20 available. Cystatin C, something more recent, is a new
21 marker that has been recently incorporated and has been
22 now reported in several studies that could be used as a

1 marker of kidney function. And then a newer marker
2 that needs further investigation is beta-trace protein.
3 As you will know, inulin is the gold standard for GFR
4 measurement when we talk about exogenous markers. There
5 are different tracers that are labeled with
6 radioisotopes. Iothalamate is more commonly used in
7 the U.S; EDTA is most commonly used in Northern Europe;
8 DTPA is used around the world. And then we have the
9 so-called "cold" iothalamates which are newer
10 techniques in which basically you are using a tracer
11 with no isotope label on it. And then you measure the
12 level through different techniques, either capillary
13 electrophoresis or HPLC like you do for tacrolimus, for
14 example. Iohexol is a commonly available marker, and
15 that can also be used.
16 So, as you will know, the simple thing to do
17 is to check a serum creatinine, which is the most
18 inexpensive, it's only $6 to $10 maybe, for research it
19 could be $3, $4. It's convenient, it's widely
20 available, you can use the inverse of the creatinine,
21 this has been used in many studies, or the doubling of
22 the creatinine, as a marker or as an endpoint in

1 clinical trials. You can calculate creatinine
2 clearance from Cockcroft-Gault, you can measure
3 creatinine clearance, you are increasing complexity,
4 you are getting more information, you are getting to
5 more costly methodologies, but you gain on one side and
6 you lose on the other. Estimated GFR has been the
7 proposed way to go in the last 10 years. Measured GFR
8 remains the gold standard, and inulin clearance is the
9 gold standard, although rarely done in the U.S.
10 anymore.
11 So if you think about measuring GFR, you can
12 go with hot, it's called "hot" because of the
13 radioisotope attached to the marker, or cold. And
14 there are different labs doing different techniques. I
15 think nowadays we are all moving to cold methodologies.
16 In both of them you need to do a clearance. So it
17 doesn't really matter, they are both equally labor
18 intensive in that respect. You collect the urine
19 clearances for a few hours, and then you just average
20 them.
21 When you use an isotope attached to the
22 marker, you use much less iodine, so it's easier to do

1 a hot iothalamate GFR in a patient who has an allergy
2 to iodine. When you use a cold marker, then you need
3 to use much more iodine. It is also contraindicated in
4 pregnancy. The intensity of the preparation of the
5 patient and everything is the same. The cost is higher
6 when you use an isotope label marker, but then you lose
7 on that side, but then you gain on the analytical cost
8 and the labor intensity analysis of the research.
9 However, newer technologies like tandem mass
10 spectroscopy, HPLC. Tandem mass spectroscopy permits
11 the reading of many more GFRs at a very low cost and a
12 very high throughput manner.
13 But we all think, we all claim, that's an
14 expensive test, so let's look at other tests that we do
15 in clinical practice and how much we think about the
16 prices. So these are costs not charged to patients but
17 actually what the institutions charge, and not what
18 they get reimbursed. So an electrocardiogram is $224,
19 spirometry, $300, echocardiogram, that is incorrect,
20 but it's about $1,000, renal ultrasound, $900, CT of
21 the abdomen, $3,000. We don't think too much when we
22 order all those tests. When you do iothalamate GFR,

1 you can get it for 100, 200 bucks. So if you can spend
2 $2,000 measuring the heart function and nobody
3 questions it, I don't know sometimes why we question
4 measuring kidney function for a hundred bucks or two
5 hundred.
6 But this is the trick here when we think
7 about estimation of GFR. There is a fundamental
8 difference between the two approaches. When you
9 measure GFR, you are measuring everything. So you are
10 leaving little room for error. The error you are
11 leaving in is a technical error from the person doing
12 the GFR or the patient missing the urine sample, et
13 cetera.
14 However, when you estimate GFR, the only
15 thing you are measuring is the creatinine, and there is
16 a big potential source of bias here, too. Everything
17 else on the numerator above the equation you are
18 modeling it based on demographic and other information,
19 so you are leaving much more room for error. That's
20 why estimating GFR hasn't been easy. In fact, if you
21 look back in the literature, you can go back to 1959
22 when people started to come up with new equations, and

1 I haven't listed here all the ones that in the last 10
2 years people have come up with, but I highlighted here
3 the most commonly used, Cockcroft-Gault, the first in
4 the equation, which I didn't know this for 2 years
5 until the National Kidney Foundation recommended to use
6 it, and then this was modified a little bit, and then
7 it was reexpressed when calibration of the creatinine
8 was completed, and now we are dealing with the CKD-EPI
9 equation, which was published in 2009.
10 So when you think about estimating equations,
11 you think about two sources of potential error, some
12 related to creatinine-dependent factors, and the main
13 one is systematic error or calibration bias. The
14 measurement error or imprecision of the assay now is
15 minimal, coefficient variability is like less than 3
16 percent, but this was a big issue in the past. That's
17 because everybody had to run their serum creatinines in
18 the Cleveland Clinic Lab, because we did the MDRD
19 study, and we run all the GFRs there, and the reason
20 was simply to calibrate. We were talking about this
21 yesterday for antibodies, this is the same thing here.
22 The nice thing is that this has been solved and has

1 helped a lot.
2 Let me give you an example of how important
3 calibration is. The bias is a systematic error
4 resulting from calibration differences among various
5 labs, creatinine in the main lab here. You can see that
6 if you have a systematic error throughout a whole range
7 of GFR -- creatinine, I'm sorry -- it has a much lower
8 impact on higher creatinine levels than lower
9 creatinine levels. This has been addressed and now we
10 can use the reexpressed MDRD equation. You can get one
11 of these samples from the NKDEP and you can calibrate
12 your assays, but now you don't even have to worry about
13 that because all the new analyzers come up already
14 calibrated, so you can actually buy everything
15 calibrated, and there is no more need to cross-
16 calibrate your creatinines.
17 The other big issue that determines the
18 performance of the equation is the population from
19 which the equations have been developed because the
20 characteristics of the region of population determines
21 the strength of the biological associations between
22 variables in the equations and the measured GFR. And

1 these equations, remember they used a fixed factor to
2 model this relationship, so if you change the setting,
3 you are complicating the performance of the equation.
4 We all know that the relationship between creatinine
5 and creatinine clearance is a nonlinear inverse
6 relationship; that's why we use one over serum
7 creatinine. And when they developed the MDRD equation,
8 basically you are dealing with a GFR between 20 and 60,
9 so you are modeling this into this equation, and then
10 when you apply to a CKD population, you can see that it
11 fits pretty well.
12 When you change the setting, then you are
13 dealing with this relationship, which is not the same
14 as this one, and therefore the equation cannot do its
15 job because you are changing the setup. So because of
16 this, when many authors or investigators look at the
17 performance of these equations in the setting of kidney
18 transplantation, you come up with very wide or
19 heterogeneous type of results, and everybody says, "It
20 works," "It doesn't work for me," "It works," "It
21 doesn't work," et cetera, but it's all because of
22 methodological issues on one side. On the side, it's

1 because the equation hasn't been developed for
2 different setups.
3 So this is actually a nice review by
4 Christine White looking at all the published studies up
5 to 2008 and how they all provided different -- you
6 know, they have different performances, and you can see
7 some -- this is a group from Germany, he published two
8 papers differently. There is a calibration issue in
9 their study. Every time they do any study to perform,
10 the equation is off, et cetera.
11 So in order to address this, the Chronic
12 Kidney Disease Epidemiologic Calibration Study, which
13 was sponsored by the NIH, came up with a set of
14 equations. This is an NIH-sponsored study, U01 study,
15 that used different GFR databases across the country.
16 The gold standard was iothalamate GFR. And basically
17 what they tried to do was to come up with different
18 equations where you can add factors such as
19 hypertension, diabetes, transplantation, et cetera, to
20 see if you can improve the performance of the equation.
21 As you can see, they pulled a lot of data. We
22 had a development dataset 10 studies across the U.S.

1 mostly, 5,000 GFR measurements for
2 development, internal validation of one-third of the
3 total, and then they came up with an external
4 validation cohort to externally validate the data. You
5 can see that from the initial Category 1 studies that
6 developed internal validation, only 4 percent of the
7 patients were transplant patients, and they were not
8 kidney transplant patients, they were liver, kidney,
9 heart, et cetera. And then the external validation,
10 they said 30 percent of the patients were transplant
11 patients, mostly kidney. The difference between the
12 CKD-EPI, and then the MDRD is now you have still
13 gender, you have creatinine, you have age and race, but
14 now it differentiates where the modeling factor is
15 different were the creatinine was less or more than
16 0.7.
17 So when they apply this new formula to just a
18 cohort of patients with chronic kidney disease, this is
19 the measure minus estimated GFR, so if you have
20 positive values underestimation. It is set up the other
21 way around, but it's underestimation, and then you have
22 the range of GFR. You can see that within the MDRD

1 equation you underestimated GFR, especially at the high
2 GFR levels, but then with the CKD-EPI equation you
3 minimize that by still underestimating GFR to a much
4 lower degree, though. And the precision and accuracy,
5 which is a spread of the measurement, remains an issue.
6 So it hasn't been resolved.
7 So using this dataset, we tried to come up
8 with an equation that permitted us to include factors
9 to modify the result based on whether the patient was a
10 diabetic, obese, or transplanted patient. In blue you
11 see the performance of the MDRD equation. Again, this
12 is measured minus estimated, so positive values are
13 underestimation of GFR. You can see that where you
14 have diabetes, the diabetes affected the performance of
15 the equation -- okay? -- of the new equation, the MDRD
16 equation. Transplantation is the same thing. You have
17 a little bit less of an effect. And then in BMI, it
18 didn't really matter much on this, if you had a BMI of
19 more than 30.
20 With the new equation, the CKD-EPI equation,
21 you minimize all the biases here to a certain degree,
22 so you carry down significantly except for patients who

1 had a very low BMI.
2 When the modified CKD-EPI equation, which
3 permits it to enter where the patient has diabetes,
4 transplantation, or the weight of the patient, the
5 performance of the equation improved to a certain
6 degree in comparison to the MDRD, but not to the CKD-
7 EPI. So the CKD-EPI group recommended that we continue
8 to use the CKD-EPI equation for transplantations, but
9 remember that a lot of these data used in this equation
10 didn't come from kidney transplant recipients but from
11 liver transplant recipients or other organs.
12 So in summary, the CKD-EPI equation has less
13 bias on the GFR, more than 60, but similar performance
14 when the GFR is less than 60, poor precision and
15 accuracy remains an issue. When you add the transplant
16 modifier, it does not significantly improve the
17 equation, and it's acceptable to use in the setting of
18 chronic kidney disease pre- and post-transplant care if
19 the GFR is on the lower side.
20 This is the last slide. The only study that
21 looked at and compared, in transplantation, measured
22 GFR by estimated GFR was a study, the BENEFIT study.

1 Although the data hasn't been reported in the papers,
2 I'm sure here some people may know more about this. In
3 the first publication they measured GFR at 3 months, 6
4 months, and 1 year, I believe, or 1 month, 6 months,
5 and 1 year, on estimated GFR and the MDRD equation in
6 comparison to the other equations, Nankivell, which is
7 a transplant-dedicated equation, Cockcroft-Gault, and
8 Jellife equations performed better than any of their
9 equations. So MDRD provided the best correlation, but
10 I don't know the statistics of it. And then in the
11 follow- up study, the mean GFR difference at 12 months
12 between the intervention groups -- this is just text
13 from the paper -- and control group was 13 to 15 mLs
14 per minute versus 15, so it seems to be that the bias
15 is similar.
16 So it seems that this is the only study that
17 they have head-to-head comparison in GFR measurement
18 and estimation.
19 So with this, I'm going to finish the
20 presentation. I have a summary here. Measured GFR by
21 using a non-radiolabel tracer remains the gold
22 standard. The estimation of GFR by either of these

1 equations is acceptable. Central laboratory creatinine
2 assays using IDMS-traceable sample and calibrated
3 instrument are paramount, and a well-collected and
4 assayed sample will permit the application of any
5 creatinine-based GFR equation that's developed in the
6 future. So the key is the creatinine. Gender doesn't
7 change, race doesn't change, and age, in these very
8 short clinical trials that we are doing with age, that
9 simply is a significant role in the estimation. So we
10 could say, well, let's just use the creatinine change
11 over time.
12 So the key is to store samples, properly
13 store, so we can always go back, calibrate different
14 creatinines, assay different markers, et cetera, and
15 apply in the future.
16 One thing I am not discussing, but we can
17 leave it for discussion after that is how to use this
18 information -- how to analyze this information in the
19 state of transplantation? Should we go by changing
20 creatinine from baseline? changing GFR from baseline?
21 looking at estimated GFR into different
22 models? et cetera? We can leave it for discussion.

1 Thank you very much.
2 (Applause.)
3 DR. SALOMON: The second topic of this
4 morning is the "Effect of Procurement and Preservation
5 on Quality and Function after Kidney Transplantation,"
6 and for that, it will be Dr. Rutger Ploeg.
7
8 Topic #2: Effect of Procurement and Preservation on
9 Quality and Function after Kidney Transplantation
10 Rutger J. Ploeg, MD, PhD, FRCS
11 DR. PLOEG: Thank you very much, Dan. And,
12 Renata, thank you very much for inviting me to come
13 over here. My task was to give you in the next 15
14 minutes some data on what is the effect of procuring
15 and preservation of the quality of the donor kidney.
16 My disclosure I voiced yesterday.
17 This estimation obviously is accompanied and
18 affiliated with a serious cascade of injury, which
19 obviously not just starts in the donor, it already
20 starts in the patient, however, after donation,
21 obviously it becomes very obvious, and donor management
22 as well as organ retrieval and preservation will have

1 their effect on quality in graft function.
2 Obviously, before we go into deceased
3 donation, we have to go to the benchmark, which is
4 living donation, and that really takes two to Tango,
5 however, and not everybody has this kind of living
6 donor partner. Obviously, in the benchmark, we have
7 optimal selected patients, actually they're not even
8 patients because they're clients, there is a remaining
9 kidney in the donor which will have only minimal injury
10 and function before and response after donation can be
11 measured. In the donated kidney then, of course, there
12 will be surgical trauma and cold ischemia time and then
13 functional recovery in a hostile environment.
14 Going back to what was just said in the
15 previous talk is we checked, for example, in our
16 sequence of living donors renal function before and
17 after living donation, and as you can see, we have done
18 the measured one using the (inaudible) since 1968 in
19 (inaudible) and the measured shows actually that you
20 recover very well after donation as a living donor. It
21 also shows what was just said by Emilio that the
22 equations many times underestimate the actual function

1 if you compare it to the measured GFR, which, if you
2 don't really watch that, can mean that you can decline
3 up to 30 percent of your living donors using the
4 equations instead of the measured GFR. So I think
5 that's a very important remark to be made.
6 Now, we all know that GFR declines by age in
7 healthy subjects, and all the donors have lower pre-
8 donation GFRs. Fortunately, however, we also see that
9 effects of age on long-term adaptation of renal
10 perfusion and function after donation are very well. As
11 you can see here, you're looking at the GFR and ERPF
12 (sic), in older donors, less than 55, and over 55
13 years, which follows basically the same line with the
14 follow-up line until 6 years. So it appears here that
15 on long-term follow-up, the adaptive rise in perfusion
16 and function of the remaining kidney is adequate in the
17 older donor.
18 Of course, the most relevant question is
19 then, well, can we achieve the same kind of good
20 results as the remaining native partner kidney with the
21 donated kidney? And that has been shown very elegantly
22 by Mark Stegall's group where he basically showed that

1 if we exclude, let's say, the events you don't want to
2 be happening -- like, for example, rejection -- you can
3 actually achieve in the partner kidney, which is now
4 transplanted, a very similar quality and function after
5 transplantation.
6 Unfortunately, we don't have enough living
7 donors, as we know, so we kind of depend not only just
8 on conditioning the recipient, as we've heard
9 yesterday, but also on better preservation and on what
10 can we do actually to the donor, and that is something
11 which we really have to focus on in the next years
12 because I feel that that is very much an Achilles' heel
13 in transplantation.
14 Obviously, the deceased donor and also the
15 standard criteria donor is a donor after brain death.
16 Cerebral injury will be caused and then brain death
17 will become evident. There is an extended period of
18 donor management where the donor is being manipulated
19 and the organs are affected by the management. Then
20 there is the retrieval operation, there is preservation
21 with both warm and cold ischemic injury, there is
22 reperfusion injury, and then finally again the

1 functional recovery in a let's call it hostile
2 environment.
3 And we know that following actually cerebral
4 injury and brain death, there is an enormous cytokine
5 storm which is not just an epiphenomenon but is also
6 followed by an influx into the tissues of PMNs and CAM
7 activation. It will affect already during the donor
8 management, the function obviously being more profound
9 when there is hemodynamic instability, and as we've
10 seen in very much standardized animal models, whether
11 it's kidney or liver or lung transplantation, there
12 will be an inferior result after transplantation when
13 brain death was invoked.
14 And, of course, it has become very important
15 in the last so many years to kind of find out what kind
16 of genes are involved and also what kind of proteome is
17 involved if we want to kind of see whether we can
18 improve the quality of the donor organ.
19 Now, some things we cannot change, and donor
20 age is one of those, and whether it's now in DBD or in
21 DCD, as you can see on this slide, there is a
22 significant effect on delayed graft function and also

1 in graft survival with older age. So older age means
2 more DGF and lower graft survival.
3 When we did the trial to see with machine
4 preservation whether we could actually salvage some of
5 those kidneys and improve function after
6 transplantation, it also gave us a very protocolized
7 nice way to look at the risk factors in general in
8 standard criteria, ECDs, and DCDs, and I would like to
9 show you some of the results here.
10 Now, these are the independent risk factors
11 for DGF, defined now very crude and I think very
12 insufficient as dialysis at least once in the first
13 week. Now, we excluded all those so-called
14 ultrafiltrations for a little bit too much fluid, which
15 were like on their own, and we also looked at where it
16 was a so-called hyperkalemia dialysis because obviously
17 those are not the DGFs, but still you see that
18 preservation had significant effect. Donor age was a
19 risk factor, cold ischemia time, duration of pre-
20 transplant dialysis, and DBD versus DCD.
21 And if you looked at the little bit better
22 functional DGF, which I think is something we should

1 consider, functional DGF being defined as a reduction
2 with at least 10 percent per day in 3 consecutive days
3 in the first week after transplantation, which is kind
4 of more subtle than that one dialysis in the first
5 week, we actually saw that it's more refined, that
6 there was a significant effect. Prior renal function
7 did not reach significance because of the numbers, and
8 there was the duration of DGF.
9 What we also saw, and did not expect, was a
10 significant effect on graft survival overall,
11 especially in the cold storage group, as you can see,
12 with a difference between 80 percent and 60 percent,
13 and that kind of lasted longer out until 3 years post-
14 transplant.
15 Here you see the factors which were important
16 for this graft loss, being the machine preservation as
17 a method of preservation. There was the recipient age
18 and the donor age.
19 Yesterday we talked a little bit about
20 predictive and diagnostic markers. We also tried to
21 see whether we could predict delayed graft function,
22 and it is possible to say with the renal resistance

1 that there will be delayed graft function. However,
2 there is no cutoff point, so it is not a marker which
3 can be used to discard kidneys. The same thing for a
4 whole lot of biomarkers which we tested, and of those,
5 about 15 or 16 biomarkers being very promising in the
6 literature. In this kind of clinical trial, only two
7 made it to really predict DGF, which were GSD and
8 fatty-acid binding protein of the heart-type. However,
9 again, in these numbers, not being able to have a real
10 algorithm to say when it is over that, you will have a
11 higher chance, and thus don't use that kidney. So we're
12 still stuck there with those biomarkers.
13 Well, extended criteria donor is the next
14 thing, and I think there was a very elegant study by
15 Jesse Schold and his group to kind of compare now a
16 left versus right and see what the difference is in
17 longer cold ischemia times as far as outcome after
18 transplantation. You see here that in this paired
19 kidney analysis there was a significant increase in DGF
20 when there was longer cold storage time going from very
21 short to more than 15 hours between left and right
22 differences. However, in his study he was not able to

1 see any effect of this kind of difference in DGF on
2 outcome of the transplantation, so no effect there as
3 far as survival is concerned, which is a little bit in
4 contrast to the study we did when we did the RCT for
5 the ECDs where indeed apart from that, there was a
6 significant difference in DGF as far as machine versus
7 cold storage, although it was only a trend in the
8 numbers. Cold ischemia time did affect DGF as well as
9 mismatches, duration, and retransplantation.
10 And as far as graft survival, the fit was
11 even very significant, as you can see here. If there
12 is no DGF, there is no difference between the two
13 groups in the trial. However, if there is DGF, there
14 is a significant difference, both are reduced
15 significantly versus non- DGF, but also you can see
16 here that the cold storage group had a 1-year graft
17 survival, about 40 percent, versus 80 percent when the
18 kidneys had been machine preserved, so that is another
19 outcome compared to the previous study.
20 Now, when we go to deceased donation, then
21 again for the DCD donor, it's either the combination of
22 cerebral injury with withdrawal of support and warm

1 ischemia or the unsuccessful resuscitation, which is
2 the Type II Maastricht DCD donor, and all these donors
3 will have had a profound agonal phase, the retrieval,
4 warm and cold ischemia time, reperfusion injury, and
5 then the functional recovery. What we saw in the study
6 is that the risk factors for DGF in DCDs were again
7 very much cold ischemia time as well as the
8 preservation strategy and recipient age.
9 Very unexpected, but very obvious, you can
10 see while there was a significant effect on graft
11 survival in these groups for DBD, we did not see effect
12 on graft survival with the DCD group, which in a way
13 tells us that despite a reduction in DGF and a higher
14 incidence of DGF in DCD, it did not affect graft
15 survival. And in the end an outcome, as you can see
16 from this slide, after 3 years in all DCDs was quite
17 good, and there was, for example, no difference between
18 the preservation strategies.
19 Finally, then, what about the length of the
20 so- called agonal phase? which we now have like a
21 stand-down time after 1 hour because then many times
22 different teams will say, "Well, we don't want to use

1 the kidneys," some will maybe go to 2 hours, but there
2 is a certain cutoff point.
3 And there was a very interesting experiment
4 done by the Cambridge group where they actually made a
5 scoring system using some markers, which you can see
6 here, and using the scoring system, they tried then to
7 predict whether a kidney would, yes or no, have delayed
8 graft function or better function after transplantation
9 and effect in graft survival, and the interesting thing
10 is actually that using our actually even times two of
11 warm ischemia times up to 4 hours and even sometimes
12 more, there was a longer agonal phase with indeed more
13 donor instability, but surprisingly no effect on
14 outcome. Three-month but not 12-month GFR were affected
15 by donor age and cold ischemia time, but in the end,
16 the outcome after transplantation was very equivalent,
17 meaning that this extra donor resource is very likely
18 to be used, and up to 4 hours quite safe. So, in
19 effect, it is actually an extension of the so-called
20 agonal phase we always kind of feared about, and up to
21 4 hours they did not see in their relevant numbers of
22 about 200 kidney transplants no detrimental effect.

1 So, indeed, we do have a problem, but we also
2 have an opportunity. And one of the things we haven't
3 done, we have always kind of looked very much at single
4 center analysis, and what we try now in the U.K., at
5 least to solve part of this, is get a better handle on
6 the quality in organ donation. We formed a national
7 consortium where all the retrieval zones and major
8 transplant centers are involved, including a
9 bioresource, and we're trying to kind of have this so-
10 called quality in organ donation concept where we try
11 to match on a national basis, donor management, with a
12 clinical informatics system, the bioresource, and
13 molecular diagnostics to better, with large samples
14 sizes, identify and validate pathways as well as
15 markers.
16 And obviously the other thing to do with this
17 consortium is something which I think is very
18 important, is to start interventions at any level
19 during donation after brain death, during retrieval,
20 and during preservation.
21 Finally, another opportunity we will have
22 embarked on is a European consortium. We just were

1 awarded the EU Framework 7 Grant, which will allow us
2 to test the modalities during preservation and see what
3 kind of combinations are probably better to achieve
4 better function after transplantation with what kind of
5 donor and what kind of situation.
6 So finally, and my last slide, is that I
7 think that with future borderline donors and more
8 complex recipients there is a definite need to increase
9 the quality of organs, and I think, as we already told
10 each other yesterday, and will probably today as well,
11 we have to have more sophisticated definitions of
12 outcome, and I think the GFR is one of those, and I
13 think functional DGF is probably better than the plain
14 one dialysis in the first week, but we are still
15 lacking better refined molecular models.
16 We also, I think, have to really embark on
17 improving the donor quality with smart studies with
18 protective agents, and those will be smaller studies,
19 those won't be pills which will be taken for like so
20 many years after transplantation but just needed during
21 a very short time to basically increase the quality.
22 And, of course, it will be very important that our

1 partners in industry are also helping us with those
2 studies.
3 Pre-treatment and conditioning obviously
4 becomes very important, and I think as important as
5 we've discussed yesterday, the post-transplant
6 immunosuppressive regimen. And I think the use of
7 molecular diagnostics and bioinformatics, as already
8 alluded to yesterday, is very critical.
9 So I think it's an exciting time. The race
10 is on, and I think it's quite exciting.
11 Thank you very much.
12 (Applause.)
13 DR. HURST: Thank you, Dr. Ploeg.
14 Our next speaker is Walter Park, and his
15 topic is "GFR and Long-Term Outcomes: The Mayo Clinic
16 Experience."
17
18 Topic #3: GFR and Long-Term Outcomes: The Mayo Clinic
19 Experience Walter D. Park, BS
20 DR. PARK: Like everyone else has done, I
21 would like to thank the organizers for the opportunity
22 to present our work in this area of GFR long-term

1 outcomes, our experience, as well as published
2 experience from other groups.
3 I have nothing to disclose.
4 I wanted to begin with a brief overview, talk
5 about potential trial designs for long-term studies,
6 and then discuss in detail single and multiple
7 measurements as an endpoint, and I was specifically
8 asked to talk about selecting an appropriate baseline
9 for multiple measures studies, so I'll talk about that
10 as well.
11 So our overall goal for everyone here is to
12 obviously improve long-term graft survival, and there
13 are a couple of different potential trial endpoints
14 that would involve GFR, both single and multiple.
15 From a single perspective, you could give a
16 treatment which would decrease the frequency of
17 patients with low GFR, say at some time point, like at
18 1 year. The data I'll show today shows that nearly half
19 of the grafts that we lose, at Mayo anyway, and
20 elsewhere actually, at 5 years actually have good
21 function at 1 year.
22 Another option would be that treatment would

1 increase the overall function of a group. Using
2 standard protocols, the data will show that most grafts
3 actually do well. At Mayo, our graft survival is above
4 85 percent at 5 years. And also it's really unclear if
5 increasing the mean GFR actually changes the outcome of
6 those patients. Does it really change the underlying
7 biology, DSA, for example, or subclinical rejection?
8 Under the multiple category, does the
9 treatment decrease the proportion of grafts that are
10 experiencing a progressive decline of function? And
11 the data I'll show today suggests that this is likely a
12 suitable endpoint. And it's actually best when used in
13 combination with a single-time approach.
14 So Dr. Poggio already talked about this. This
15 is just to emphasize that we are using in our studies
16 mostly MDRD equations; we get a lot of data from that.
17 But we also do iothalamates at Mayo.
18 So as all of you are aware, there have been a
19 number of studies that have looked at correlating GFR
20 values in the first post-transplant year with graft
21 failure. I just pulled three here of interest. I'll
22 direct your attention to this one from a group in

1 Poland that was published in 2009. And what they did
2 was they looked at 332 deceased donor grafts and then
3 they used the 6-month EGFR measurement to stratify
4 patients into a low group, they have a renal function
5 of less than 40 at 6 months, and a high group, and they
6 had greater than 40.
7 They followed the patients out a mean of 7
8 years, and perhaps not surprising, the group with the
9 low GFR at 6 months, they had the lowest graft
10 survival, at 77 percent. But the majority of graft
11 failures were actually in the high EGFR group.
12 What is the Mayo Clinic Rochester experience?
13 To conduct this study, I looked at all the conventional
14 renal transplants done from 2000 to 2005 at our center
15 and was able to find 1-year EGFR data on 896 of them.
16 This is a plot of the graft survival versus
17 the 1-year EGFR. We looked at all of the deciles less
18 than 40 and compared them to a control group where the
19 renal function was greater than 60 at 1 year. And
20 perhaps not surprising, the graft survival was
21 significantly lower for those grafts that had renal
22 function less than 20, 20 to 29, and 30 to 39. However,

1 when we looked at all of the deciles greater than 40
2 and compared them to our control group, we did not find
3 any significant difference.
4 So we summarized the data with this figure,
5 which shows that if you have a high or greater than 40-
6 mL-per-minute EGFR at 1 year, you have better survival
7 than if you're a low person.
8 The next thing we looked at was, when do the
9 failures occur? And to do this, we broke the data into
10 three intervals: those grafts that fail from 1 to 2-
11 1/2 years, 2-1/2 to 5 years, and then greater than 5
12 years. And what we found is that 80 percent of the
13 failures between 1 and 2-1/2 years have an EGFR at 1
14 year of less than 40, but 65 percent of the failures
15 that occur after 2-1/2 years occur in the group with an
16 EGFR greater than 40 at 1 year. And that is such a
17 dominant number that actually by the end of the study
18 or the follow-up that we have done, 49 percent of the
19 failures actually occurred in the greater than 40
20 group. And therefore we conclude that the single
21 measure of renal function is unlikely to be a suitable
22 endpoint.

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1 Now I'll focus on multiple EGFR measures.
2 As I said at the beginning, I was asked
3 specifically to talk about what baseline is the best,
4 and I tried to come up with a good way to have data to
5 articulate this. Obviously, everyone would like to
6 take the baseline when the graft is stable, but, of
7 course, it's not that simple to just, "What is stable?"
8 Most long-term studies use a baseline during the first
9 post- transplant year. And so I thought a good way to
10 look at this would be to determine the mean monthly
11 EGFR during the first transplant year. So on this
12 chart, the X axis is just each month, and on the Y axis
13 is the renal function.
14 And I looked at 1,300 adult conventional
15 transplants done at Mayo. This involves 70,000
16 creatinine measurements. And you can see that by month
17 3 the eGFR, the mean eGFR, is relatively stable from
18 that point forward. But it's an important caveat, is
19 that there is obviously a large spectrum of eGFR at
20 each month post-transplant, and that's what's depicted
21 here on the right chart. The values, each one of these
22 black dots is an individual patient's eGFR measurement,

1 so there is a lot of spread even though the mean stays
2 relatively constant after the third month.
3 There are also a number of potential
4 influences to the baseline selection that I thought
5 would be interesting to look at. The first is the type
6 of donor. If you receive a deceased donor graft, your
7 course is a little bit different. Obviously, deceased
8 donors have the issue of delayed graft function, so
9 their first month eGFR is often quite a bit lower as a
10 group than it is for the living donor grafts, but
11 again, both groups by month 3 or so have a relatively
12 stable course.
13 I then looked at patients that had had a
14 first year complication. These are overt complications
15 like BK, acute rejection, or delayed graft function.
16 And it's interesting here the mean value stays low,
17 lower in the group that has the complication in the
18 first year, but it actually is relatively stable,
19 again, after 3 months it seems to stabilize.
20 So the third group I looked at were those
21 grafts that failed early, so they failed less than 2.5
22 years post-transplant. And you can see that -- and

1 this is why means are a little bit of a challenge
2 sometimes, the patients that don't fail, they have a
3 good, nice stable course, but those people that are
4 failing, their mean is decreasing over time, so by
5 using a mean value, we're missing the subset of
6 patients that are actually doing poorly.
7 This is also a summary of means. So I
8 thought it would be good to look at what's the
9 variation for individual grafts in the first year post-
10 transplant. And to do this, I determined the mean eGFR
11 from 3 to 12 months for every graft, and I consider
12 that the reference value, and then I have this really
13 nice colorful chart. I calculated the deviation from
14 the reference for each month, this is for each graft,
15 and the take-home is that after 3 months greater than
16 70 percent of the grafts, any month, their eGFR value
17 is within 10 percent of the mean or the reference
18 within that first year. And if you go out to 20
19 percent, plus or minus 20 percent, it's actually more
20 than 90 percent of the grafts.
21 And I conclude with this, that for the
22 majority of grafts, a monthly baseline after 3 months

1 really should be similar to the overall eGFR from 3 to
2 12 months.
3 The other thing that from a baseline
4 perspective or selection of a baseline, is: What other
5 clinical data is being collected at the same time? And
6 at Mayo, as we heard a little bit yesterday, 1 year is
7 the takeoff point for many of our studies. There are a
8 number of reasons for this. The majority of kidneys
9 reach 1 year, the majority of patients come back for a
10 1-year visit, and then at Mayo Rochester we do a number
11 of standard of care tests that help us understand the
12 graft and the status of the graft. We do a protocol
13 biopsy, and we and other groups -- again we heard about
14 this yesterday -- but we and other groups have shown
15 correlations with histology and graft survival. We
16 also do a number of labs at the 1-year time point. We
17 look at renal function both with iothalamate and with
18 serum creatinine. We test for donor-specific antibody,
19 24-hour urine protein, and BK virus, and we, at our
20 institution, have shown all of these things to
21 correlate with poor outcomes. So selecting the 1-year
22 time point for us is not just on the basis of the

1 measure of eGFR, it's also on these other clinical
2 values.
3 Now, there also have been a number of studies
4 that have looked at multiple GFR measurements. Going
5 back all the way to 2002 in this brief list, a couple I
6 wanted to highlight, one by Dr. Gill in JASN in 2003,
7 and this was a USRDS study. They looked at the rate of
8 functional decline in about 32,000 grafts surviving at
9 2 years. They required a median of five data points,
10 or had a median of five data points, and they looked at
11 the annual change in GFR calculated with a least linear
12 squares regression. And the take-home that I had from
13 this paper, they had a mean follow-up of 5.7 years, and
14 I think one of the most interesting things is that 50
15 percent or so of the recipients had no change or an
16 improvement in eGFR during that study.
17 The second study was by Wu, et al., in
18 Clinical Transplantation and they actually were doing
19 something we were doing at the same time, they just got
20 it published faster, and they combined the 1-year data
21 and a slope concept just between 3 and 12 months, and
22 hazard ratio, if they used just the single measurement,

1 was 2.6, but when they combined the 1-year measurement
2 and the slope measurement, the hazard ratio became 7.4,
3 so it almost tripled.
4 And, again, what is the Mayo Clinic Rochester
5 experience? So we take our original cohort of 896
6 grafts. We then set an additional filter criteria that
7 the graft had to last 2-1/2 years. That left us with
8 788 grafts that we stratified on the basis of their 1-
9 year eGFR into a low group and a high group. And
10 notice that it's important here, there were 675 grafts
11 in the high group, but actually they represent the
12 majority of graft losses; 48 out of the 70 graft losses
13 occurred in this group. So they had good function, but
14 this represents the largest number of grafts. So we
15 focused on them and looked at trends in their renal
16 function.
17 To measure their slope, or to assess their
18 slope, we used the mean eGFR during 6-month intervals
19 from 1 to 5 years post-transplant. We required a
20 minimum of 5 intervals, we did a linear regression to
21 determine the slope, and then we divided the grafts
22 into quintiles based on that slope. We're talking

1 about a lot of data. This is 675 patients, 25,000 eGFR
2 measurements.
3 This is one of the ways that we chose to
4 visualize the data because it's a lot of data, is this
5 chart, and this just shows kind of the vectors of all
6 five of the quintiles. The top three quintiles are
7 shown here. Group 1 has an average slope of an
8 increase of 7.4 percent. There are no graft failures
9 in the first 5 years in this group of patients,
10 probably not surprising. Quintile 2 has an increased
11 slope of 2.5 percent, again no less than 5-year graft
12 failures. And quintile 3 has a very stable slope of -
13 0.01 and only one graft failure in that cohort.
14 Quintile 4 had an average decline of 3.4 percent, and
15 there were no graft failures in that group of patients.
16 It isn't until we get to quintile 5 where the mean
17 slope is -15 percent, and 27 out of the 28 less than 5-
18 year graft failures fall into this category.
19 I don't want to spend a lot of time on it,
20 but we also plotted the low GFR patients. Their slope
21 actually is a slight increase, but it's a little more
22 muddy in that group of patients where 10 of those

1 patients actually reached failure.
2 With this quintile number 5 group, we thought
3 that wasn't the best way to describe them, so we
4 described them, called them a term "high progressors."
5 These people have a good 1-year renal function, they
6 have a declining slope greater than 6.2 percent, they
7 have at least one eGFR value that's less than 60, and
8 they have a greater than 20-percent reduction in eGFR
9 over time. That leaves us with 122 progressors, or high
10 progressors, and 553 non-progressors.
11 This is just to go back to the kind of
12 beginning approach. If we had used just a single
13 measurement, could we have differentiated these
14 patients? And this is a plot of the 1-year eGFR of the
15 progressors and the non- progressors, and there is no
16 difference between them.
17 If we combine the single and the multiple
18 measurement, we get this survival plot. There is 1
19 percent of graft failures in the non-progressor group,
20 whereas there are 34 percent of the high progressors
21 have failed. So it's a very big difference.
22 Well, I'll conclude then by just saying that

1 the single-time approaches are likely to correlate only
2 with short-term risk, but they do have value in that
3 they can be used to stratify grafts into low and high
4 baseline function and distinguish those grafts that are
5 at increased risk in the short term.
6 The multiple time approach, it is important
7 to select a proper baseline. And, again, any month
8 within that first year, you should get fairly close as
9 long as the graft is stable, you should get fairly
10 close to the mean of that year for that patient.
11 The slope approach is more likely to identify
12 grafts that are at risk for future loss, but there are
13 definitely some caveats, I didn't spend much time on
14 them today. You do want a high capture rate of data,
15 you want to collect the data over a lengthy period of
16 time so you get an accurate assessment, and in our
17 case, because we used the 6-month mean approach, we
18 also did other analysis looking at the individual data
19 as well as other formulas and our iothalamate data to
20 see how close the data was, and there was very good
21 overlap with all of the approaches we used.
22 And finally, the Mayo Clinic Rochester

1 results, we identified kind of, as others have, that 40
2 to 60 percent of all kidney transplant recipients who
3 achieve good early function will maintain it for a
4 prolonged period of time. And then a combination of
5 early and repeated estimates of GFR can be used to
6 identify grafts at high risk for failure up to 7 years
7 post-transplant.
8 And I will just end with thanking the large
9 research team we have at Mayo.
10 Thank you.
11 (Applause.)
12 DR. SALOMON: Topic 4: "Stability of GFR
13 Over Time as a Clinical Outcome," and that will be
14 delivered by Dr. Robert Gaston.
15
16 Topic #4: Stability of GFR Over Time as a Clinical
17 Outcome Robert S. Gaston, MD
18 DR. GASTON: Thanks very much again to the
19 organizers for allowing me to participate and not just
20 speak. There has been a great deal of important
21 interchange in the last 24 hours, and we would like,
22 speaking a little bit for AST, like to thank the FDA

1 for arranging this. And hopefully at the end of the
2 day we'll have a productive time. I always think it's
3 nice when people who prepare presentations have lots of
4 overlap from different points of view that is really
5 confirmatory of each other; that sort of suggests that
6 there may be some validity there, and so you will see
7 some of that here.
8 I do have some disclosures, none of which are
9 relevant to this presentation, though.
10 And just to change the dynamic a little bit,
11 this is from our friend Hallvard Holdaas in Oslo. These
12 are the first five cases, first five transplants, done
13 in Oslo in the late '50s and early '60s, and for those
14 of you who say things have not gotten better, they have
15 gotten better. My Norwegian is not very good, but I
16 think all of those X's are poor outcomes in the
17 patients, so that we have to keep in mind where we've
18 come from, and we've come a long way.
19 So, much like Professor Ploeg, this talk will
20 start with what happens in a solitary kidney in terms
21 of GFR over time, and this was very well described in
22 the living donors of the very first twin transplants in

1 the '50s. There is compensatory hypertrophy,
2 hyperfiltration with stability or increasing GFR over
3 time, and you could see that in the '50s, you can see
4 it perhaps a bit better graphically in this very recent
5 update of the Swedish living donor follow-up
6 experience, and this is median eGFR and this is
7 measured GFR, you can see they're quite similar, a
8 little bit of variation. This is from the 50- year-old
9 donors, these are 30-year-old donors, and if you look
10 at the timeline, what you see here is basically 10
11 years since the time of donation, and regardless of the
12 age or how you measure it, there may be a little bit of
13 flip here, but during this time, GFR seems to increase.
14 And this is the time period in our clinical trials at
15 which we're really following GFR in the patients so
16 that GFR during the course of the clinical trials that
17 we're doing in transplant recipients, there is no
18 reason why this shouldn't mimic this, as was pointed
19 out very well in the paper about a decade ago from the
20 Mayo Clinic, that this is what we should be striving
21 for, this is how a solitary kidney behaves.
22 So what happens in a transplanted kidney? And

1 I don't know that it's been spelled out this precisely.
2 I'll try to do it, is there are basically two phases
3 that we think about of GFR in the transplanted kidney,
4 and that's baseline and slope. This was spelled out
5 very well in a paper from Sita Gourishankar and Larry
6 Hunsicker published again about a decade ago looking at
7 the Edmonton experience, and they chose the creatinine
8 or the GFR at 6 months as baseline, and you can choose
9 whatever time you wish as a baseline. Some of the data
10 I'll show you chooses a baseline of renal function at 1
11 year. In the DeKAF study, we chose baseline at 3
12 months, but there is some time at which the patient has
13 gotten over all the insults that you've heard about in
14 the previous talks and establishes a baseline GFR for
15 that patient.
16 The factors that influence a baseline GFR
17 were delineated in this trial, things basically that
18 are present at the time of transplant, older donor age,
19 female donor, female recipient, very early rejection
20 with less effect if it's mild to moderate versus
21 severe, older recipient age, and retransplantation, and
22 you can see the effect of donor age on baseline GFR

1 here, the older the donor, the lower the baseline GFR,
2 and again they chose 6 months.
3 There is validity and meaning of baseline
4 GFR, that's been shown in numerous studies. This is
5 one from Ulf Meier-Kriesche and Bruce Kaplan that shows
6 the relationship of a baseline GFR, in this case at 12
7 months post-transplant, with 10 years of cardiovascular
8 outcomes, and you can see that if your creatinine, your
9 baseline creatinine, is above, say, 1.3, 1.4, there is
10 substantially increased risk of cardiovascular
11 mortality. The similar concept in this paper, I think,
12 this paper was really the seminal one that influenced
13 the design of a lot of clinical trials focused on GFR
14 as an endpoint, and this was the Harry Hariharan study
15 published in KI that shows again the effect of a
16 creatinine at 1 year on long-term graft survival, and
17 you can see that with a creatinine of above 1.6, there
18 is a substantial effect of the baseline creatinine on
19 long-term outcome. This was said to predict, and that
20 was the term used in the paper, and we'll come back to
21 that in a minute, what predict means or doesn't mean,
22 and you've already heard a hint of that in the Mayo

1 data.
2 You then look, once you establish the
3 baseline GFR, pick your time point, then you have
4 progression of GFR over time. What happens in that
5 would be the slope of GFR, and what you see here is
6 while donor age exerted a fairly profound effect on the
7 baseline GFR, it exerted no effect at all on what
8 happens over time on the slope of GFR, the change in
9 GFR over time, and this is a very different list, the
10 variables that influence slope, from the ones that
11 influence how you establish your baseline GFR, again
12 rejection, and in this case, rejection after 6 months.
13 The year of transplantation -- we'll talk
14 about that again in a minute -- hypertension, and
15 female recipient being major variables influencing
16 slope over time.
17 And one of the things that has come out, and
18 I'll show you data from the DeKAF preliminary study in
19 a minute in this regard as well, is that the decline in
20 renal function or the negative slope over time of GFR
21 seems to have changed. Now, what changed here in
22 Edmonton was a shift from cyclosporine to tacrolimus,

1 and what you see is the kidney behaving more and more
2 like the living donor kidney over time with actually a
3 positive slope occurring after 1998, at least in this
4 series, so that a negative downward slope is not a
5 necessary parameter accompanying the life of a
6 transplant, and you've sort of seen that again in the
7 Mayo data.
8 So with that as background, we come to the
9 question: Is stability of GFR desirable? And you've
10 already heard the answer to that, the answer is very,
11 very much so. It is desirable. It is associated with
12 a very good outcome. You can see that from lots of
13 different datasets.
14 Again we go back to Harry's data with the
15 relationship of baseline GFR to graft survival. When
16 you then add a correction for what happens over time,
17 what they called in this study delta creatinine, what
18 you can see is the risk associated with the baseline
19 creatinine on this line, but if you have increasing
20 change or downward slope in the creatinine, that
21 dramatically alters the risk, and the values are quite
22 similar to what you guys showed from Mayo, so that it's

1 not just the baseline risk that you have, but it's also
2 what happens to that baseline over a course of time, so
3 that again stability is a very strong positive factor.
4 And this is preliminary data from the DeKAF
5 study published -- Bert Kasiske did the analyses -- and
6 these data are from five centers -- again we showed
7 this timeline. We chose as an endpoint greater than 25
8 percent decline in GFR at any point whether it was
9 reversible or not. Anyone who had a 25-percent
10 increase in serum creatinine and decline in GFR was the
11 endpoint of that study, and you can see that between
12 '84-'89, '90-'94, '95-'98, and then '99 to 2002, over
13 time the risk of that happening in the population
14 declined, confirming that we've become much better at
15 preserving GFR over time even in the presence of
16 calcineurin inhibitors.
17 You can see that early acute rejection was
18 associated with increased risk of death-censored graft
19 failure. Late rejection, the risk confirmed a much
20 stronger risk. Baseline GFR, even though it was
21 statistically significant, was not associated with
22 really an altered significant effect on risk, but

1 patients who experienced a greater than 25-percent
2 decline in GFR had a sevenfold increased risk of death-
3 censored graft failure, again the phenomenon that was
4 described by Walter Park in the last talk.
5 From those preliminary data, we designed what
6 is termed as the DeKAF study, and you've already heard
7 data from this, other places in this. This is a study
8 of long-term deterioration of kidney allograft
9 function. Our goal was to identify modifiable variables
10 that cause late allograft failure, and we arbitrarily
11 define "late" as beyond 3 months. It involves the
12 centers that you see here with some of the laboratory
13 work also occurring with Mike Cecka at UCLA. Yesterday
14 you saw largely data from the cross-sectional cohort.
15 Today what I'll show you is data from the prospective
16 cohort that we begin enrolling in October of 2005.
17 The key in our study was what we call the
18 index biopsy, and that was the first clinically
19 indicated biopsy beyond 90 days post-transplant, so
20 even though we recorded it, we weren't interested in
21 graft losses in the first 90 days, we were interested
22 in what happened beyond establishment of the baseline.

1 We agreed across the centers that a greater than 25-
2 percent increase in serum creatinine would trigger a
3 biopsy or new onset proteinuria. The biopsy results
4 that I'll show you are largely triggered by a change in
5 GFR. Clinical care was based on local biopsy reading
6 and local preference, although the biopsies were
7 subsequently read by a blinded pathologist -- there's
8 that term -- and then we collected a lot of other
9 things to analyze at the time of these events.
10 In this analysis, we looked at 25 baseline
11 and early post-transplant risk factors along with the
12 index biopsy as an indicator of new onset late graft
13 function on the risk of death-censored graft failure,
14 and the median time to index biopsy was about 10 months
15 post- transplant in this.
16 And this is what we found in the multivariate
17 analysis. Age, the younger you were, the more likely
18 you were to undergo death-censored graft failure. The
19 more time you spent on dialysis, it was nice to see
20 that confirmed. PRA greater than 20 percent was not
21 statistically significant, and these are data from
22 2,700 patients. Induction surprisingly was with

1 polyclonal as the standard, IL2 antagonist a bit more.
2 Early acute rejection, if you experience acute
3 rejection before 90 days, there was a slight numerical
4 increased risk of death-censored graft failure, but
5 that was not statistically significant. Your baseline
6 creatinine, serum creatinine, at 90 days, the higher
7 the serum creatinine, the greater the risk that was
8 significant, but basically an episode, loss of
9 stability of GFR, a greater than 25-percent increase in
10 your serum creatinine was associated with a twenty-
11 sixfold risk of death- censored graft failure, so that
12 loss of stability was the single most, by a wide
13 variable, predictor of whether or not the patient was
14 destined to lose their graft.
15 That then begs the issue of what triggered
16 the biopsy or could you identify patients who did or
17 did not have biopsies? And again about 2,700 patients
18 from the cohort, 460 had had an index biopsy, 2,300 had
19 not. If you were younger, but it's hard to sort
20 between 50- and 46-year-olds, I can't look around the
21 room and do that, but if you were younger, you were
22 more likely to have had the biopsy. Gender made a

1 little bit of a difference. Ethnicity as well. PRA
2 made no difference. Serum creatinine, baseline serum
3 creatinine, at 90 days, there was no difference between
4 the two groups, very much what was said by Professor
5 Park in the last talk, that it was hard to look at
6 these people on the front end and tell what was going
7 to happen to them. DGF and early acute rejection were
8 variables that influenced outcome, but again this means
9 that 91 percent of the patients without a biopsy had no
10 DGF, and 86 percent with a biopsy did, and then similar
11 with rejection. So it's hard for these, even though
12 they're statistically significant to be clinically
13 predictive of what happens. Stability is good; loss of
14 stability is bad.
15 So is it desirable? Yes. Is it a reasonable
16 endpoint for clinical trials? Well, this is a very
17 impressive dataset from the BENEFIT trial. It was
18 impressive here, more impressive after 2 years, and
19 extremely impressive after 3 years. You can see that
20 the slope of GFR in the overall cohort of those
21 receiving cyclosporine was what had been seen in
22 previous times, as we've shown you, with a much better

1 preservation of GFR in the two belatacept groups, and
2 this despite a bit more early rejection in these
3 patients. So stability of GFR as an endpoint looked
4 quite nice here, but there are issues.
5 This is unpublished data again from the DeKAF
6 group, this is from the preliminary analyses, and this
7 would appear to be reassuring and again it confirms
8 exactly what came from the Mayo group as well. What we
9 were interested in really in this analysis was, were
10 the people who died, was their death a reflection of a
11 declining GFR? Because as you've seen here, half of
12 graft failures are due to the death of the patient
13 roughly, and what this suggested is, no, that the
14 people who died, died with basically stable kidney
15 function, the people who were alive with grafts did
16 quite well, the people who ultimately lost the grafts
17 had relatively rapid decline, and this is, as you can
18 see here, again confirming what was said from the Mayo
19 experience as well.
20 The other reason, going back to, "Does
21 baseline GFR predict outcomes?" it goes back to very
22 important work from Bruce Kaplan -- and we're glad to

1 see you made it, Bruce, here today -- but it basically
2 says that there is a strong association between GFR and
3 outcome, but it's not predictive. And this is an ROC
4 curve looking at the serum creatinine at 1 year and how
5 it impacts survival at 2 years, and you can see that
6 it's only slightly better than flipping a coin, and
7 many would say the reason why it doesn't predict is
8 that graft is random, what happens is random. The
9 easiest way to think about it is work that we did in
10 the '90s, that the Edmonton group has done in more
11 recent years, showing the impact of non-adherence on
12 outcome. If your creatinine is 1 and you stop taking
13 your drugs, you're probably just as likely to lose your
14 graft as if your creatinine is 2 and you stop taking
15 your drugs.
16 So that the things that lead to graft loss,
17 whether it's rejection, whether it's infection, whether
18 it's non-adherence, tend to be random events that are
19 not really predicted by what your serum creatinine is,
20 but it does show up in the change of creatinine over
21 time, as we were talking about earlier.
22 Back to the wonderful paper by John Gill that

1 has already been alluded to as well, that what happens
2 in that mean serum creatinine is not the same in all
3 patients, and this is again looking at what happens.
4 You had in this large cohort -- and I believe this was
5 over a 5-year period -- you had roughly 20 or 30
6 percent of patients in whom it didn't change at all,
7 you had 20 percent in whom it actually increased, and
8 then you had 30 or 40 percent in which GFR decreased
9 over time. So it's not a homogenous effect even though
10 the means are homogenous and you see the same effect
11 there in that graft.
12 And then back to the work of my mentor, John
13 Curtis, this simple thing that we, as nephrologists,
14 know how to manipulate GFR. We can infuse amino acids
15 if we want to increase the GFR, we can hydrate the
16 patient. The patient's creatinine goes up, their GFR
17 drops, you tell them to go drink fluids, it alters
18 things. You can take them off calcineurin inhibitors.
19 This is someone who appeared to have a failing graft,
20 decline in GFR, taken off calcineurin inhibitors and
21 then over 10 years the GFR is back where it was. GFR
22 is a very dynamic measurement that when you think about

1 it as an endpoint may not necessarily serve the purpose
2 that you want it to serve.
3 And then this was another landmark study, and
4 I would have sworn that GFR got much better than this
5 when the patients were taken off cyclosporine. Mean
6 arterial pressure dropped, renal vascular resistance
7 dropped, ERPF dropped, serum creatinine didn't really
8 change a whole lot, and this was people who were beyond
9 a year post- transplant on cyclosporine, it just showed
10 the effect of taking them off cyclosporine. There are
11 other studies in which serum creatinine also dropped,
12 as you would expect here.
13 Finally, using GFR as an endpoint is very
14 interesting, but these are 15-year data from a study
15 done testing calcineurin inhibitor versus no
16 calcineurin inhibitor versus conversion off calcineurin
17 inhibitor, and the bottom line is the group that did
18 best was the group that was on calcineurin inhibitor a
19 while and then came off. This is looking at GFR, and
20 the issue that I wanted to make from this is it becomes
21 very difficult to interpret the data, and at what time
22 point are you looking at it?

1 GFR again is a dynamic measure, and you can
2 see that even more recently in what was called the
3 ASCERTAIN trial, this was taken randomizing patients to
4 stay on CNI, minimize CNI, or eliminate CNI. The
5 percentage of patients that were eliminate CNI was
6 fairly low. There was really no difference in GFR at
7 baseline, no difference at 24 months, but there were
8 subgroups of patients that seemed to gain benefit so
9 that again the idea that GFR or even stability of GFR
10 has this very heterogeneous component to it.
11 So to conclude, a solitary kidney
12 demonstrates stability or an increasing GFR over the
13 duration of which most clinical trials are performed.
14 That should be the norm for what happens in a well-
15 functioning transplanted kidney. Baseline and slope of
16 GFR reflect the impact of different variables.
17 Stability is quite desirable. And a greater than 25-
18 percent increase in serum creatinine is associated with
19 a very high risk of graft failure. Change in GFR is a
20 much stronger risk factor than absolute or baseline
21 GFR.
22 There is a limitation, though, and the

1 limitation is really in the dynamism associated with
2 the measurement. There is a variability in GFR that
3 may not reflect the effect of the therapy that you're
4 trying to study.
5 Thank you very much.
6 (Applause.)
7 DR. HURST: Thank you. Our next speaker is
8 Dr. Weir, and his topic is "Hyperfiltration
9 Nephropathy, Proteinuria, and Inflammation as
10 Contributing Factors to
11 Chronic Allograft Injury: Implications for
12 Biomarker Discovery and Therapy."
13
14 Topic #5: Hyperfiltration Nephropathy, Proteinuria,
15 and Inflammation as Contributing Factors to
16 Chronic Allograft Injury: Implications for
17 Biomarker Discovery and Therapy Matthew R. Weir, MD
18 DR. WEIR: Good morning. Much of what we've
19 been discussing troubles us both with native kidney
20 disease progression, but also obviously with much more
21 variable changes in renal function over time that we
22 see in the transplanted kidney. Much of the arguments

1 that need to be focused on address the issue of: What
2 are the opportunities for better prediction and then
3 treatment strategies?
4 None of my disclosures here have any
5 influence on my presentation.
6 I'll briefly provide some background and then
7 go through the list of points that are in my title.
8 Obviously, we've all discussed the issues
9 that longer term outcomes have not improved quite as
10 much as the short-term outcomes, and there are a lot of
11 different reasons for this. A lot of it may be related
12 to the effects of immunosuppression either over or
13 under, and obviously differential issues related to
14 attrition factors over time. And we've already touched
15 on issues surrounding non-compliance and
16 immunosuppression minimization.
17 But I think we need to conceptualize some of
18 our thoughts when we look at this type of picture.
19 Obviously, on the vertical axis is our nephron dosing,
20 and the slope change -- obviously in arbitrary units --
21 the flatter the slope, the better. But the
22 appreciation we have to have is that accelerated slope

1 may be the biggest problem we face regardless of where
2 your nephron dosing is, and obviously if you have a
3 flatter slope, even with a lower dose of nephrons,
4 you're going to be better off than with a better kidney
5 with a more accelerated slope of decay.
6 And obviously there are many factors here,
7 and which ones are in play in an individual patient is
8 obviously our major concern and how best to identify
9 them.
10 Some of these are modifiable, some aren't.
11 That's not what I would like to focus on now, but
12 really to address the issues surrounding what we have
13 to do next. And, of course, the magnitude of the
14 problem is in the U.S., it's the fourth leading cause
15 of endstage renal disease.
16 So that's why what I would like to do is to
17 now touch on briefly some of the topics here, which
18 will be obviously fodder for future conversation.
19 We've already touched on some of the issues
20 surrounding the donor graft itself and the age and its
21 characteristics. I would take the argument that we
22 really don't have good evidence of hyperfiltration

1 nephropathy, and we do have to appreciate there are
2 many factors that are involved here, both in terms of
3 the age of the kidney itself, but obviously also, too,
4 the impact of the various influences surrounding it.
5 We've already seen this data from the
6 Edmonton group earlier, where we know that older donor
7 age is associated with a reduced 6-month estimated GFR,
8 but that does not appear to influence slope of change
9 over time. And loss of GFR is not increased at low GFR.
10 This, I think, is a pretty good argument that the
11 hyperfiltration process, although possibly involved in
12 some kidney graft failures, is not an overwhelming
13 problem for us.
14 Another issue we've also touched on is the
15 issue of proteinuria. We know it's a prognostic factor
16 both in native and in transplanted kidneys, but I think
17 what's more important is to determine the phenotype and
18 features of graft dysfunction that are associated with
19 the proteinuria because that will guide your treatment
20 strategy.
21 I think there are a lot of questions about
22 the causality. Is the presence of the proteinuria or

1 albuminuria just an association, like a biomarker, or
2 is it an immediate endpoint, a biomarker on the causal
3 pathway? Or is it a surrogate endpoint, evidence that
4 the variable is causally related to the outcome, and
5 modification results in a proportionate change in
6 outcome? And certainly studies in native kidney
7 disease have started to address this issue. But we're
8 realizing more and more it's not the be-all and end-
9 all.
10 The temporality of the association is also
11 important. The prevalent hypothesis is that the
12 albuminuria or proteinuria may also reflect vascular
13 disease in the body, and would therefore precede
14 clinical renal disease. And obviously we know that
15 people with progressive kidney dysfunction do not all
16 have albuminuria, so there obviously must be other
17 processes involved. And, of course, we also have to
18 question the mechanistic link for this association.
19 Again, is it a marker for vascular damage or is it
20 causative?
21 We do know that the reclamation of urine
22 proteins in the kidney is proinflammatory. Does this

1 lead to systemic vascular inflammation or increased
2 production of atherogenetic lipoproteins, as some have
3 suggested? And does improvement of the albuminuria
4 persist after the withdrawal of treatment, perhaps
5 indicating a beneficial effect on structure? So again
6 the issue of proteinuria remains problematic.
7 I think central to much of the conversation
8 with loss of GFR is the central consideration of
9 inflammation and whether this is related to immune
10 responses or other pathways. I think we're all
11 becoming aware of a new generation of therapeutic
12 strategies designed to attenuate oxidative stress and
13 inflammation and whether or not they particularly may
14 influence progression of kidney disease, whether this
15 is native kidney disease or even kidney disease in
16 recipients of allografts.
17 But I think the bottom line is there is much
18 that needs to be learned here, and this may also
19 explain the link between kidney disease and
20 cardiovascular disease. Oxidative stress and
21 inflammation are constant features and major mediators
22 of progressive CKD and CVD, and there may be issues

1 surrounding reactive oxygen species and impaired
2 antioxidant capacity, which may be important
3 therapeutic targets in the future.
4 I list just a few of the many relationships
5 here which may prove to be important. Many of these
6 have been discussed before, but obviously many here
7 listed are future opportunities for biomarker discovery
8 and treatment strategies for the future.
9 We're also aware of many factors contributing
10 to antioxidant depletion, and again I listed many of
11 these shown here. There are newer drugs in development
12 which may be important in this particular regard, and
13 there are also many older generic drugs which could
14 potentially be repurposed for treatment strategies
15 here. In fact, the NIH NIDDK just put out a U01
16 contract RFP specifically to look at designing clinical
17 trials to repurpose old generic drugs for use as a
18 strategy to delay progression of kidney disease. So
19 many more opportunities for us here in the future.
20 But I think this may very well be an
21 important area; it will be for repurposing older drugs
22 and obviously developing newer drugs, to look at

1 opportunities for targeting oxidative stress and
2 inflammation.
3 Lastly, I'll touch on implications for
4 biomarker discovery and therapy with some perspective
5 from where we have been and where we hope to go in the
6 future.
7 Obviously, there are several well-identified
8 factors that are associated with kidney deterioration.
9 Most of these population factors we're all familiar
10 with, and I will not belabor them, but I think within
11 these subgroups we have to appreciate there is
12 tremendous variability that we've discussed earlier,
13 and obviously what we need to find out is what is going
14 on in the graft now and not necessarily what happened
15 in the past. I think the real focus of the future is
16 looking at slope. We've already touched on that. The
17 relationship between a preset baseline GFR, whether
18 that at 6 month or a year, may be helpful in
19 prognosticating, but obviously it is the slope of
20 change over time which may be the most important.
21 Clearly, we know that there is a potential
22 for hypertrophy if we give the kidney that best

1 opportunity, but we also have to remember we have many
2 of these population factors which also need to be
3 brought into consideration, plus long-term intercurrent
4 metabolic hazards such as diabetes, dyslipidemia, and
5 then the influence of the human factor and
6 noncompliance.
7 So that's why I think it's critical as we go
8 forward with our discussion today is to consider the
9 difference between correlation and prediction.
10 Population parameters that correlate with kidney
11 transplant outcome are powerful but are of low
12 predictive value, and that's why I think it's much more
13 important when we start considering whether GFR
14 estimates correlate with subsequent graft survival but
15 not patient survival. Again, we've already identified
16 that low GFR estimates correlate with increased risk of
17 graft loss because there is less reserve if damage
18 occur. However, many people with low GFR have stable
19 kidney function indefinitely.
20 So I think really what we need to address is
21 what's going on now and that obviously many parameters
22 would correlate with increased probability of graft

1 loss do not predict graft loss for the individual,
2 maybe as a whole group, and this may be the tyranny of
3 generalizing and using mean data to extrapolate to
4 individual patients.
5 So I would submit to you that we have many
6 unmet needs. The identification of appropriate
7 serological and pathological biomarkers, early
8 diagnosis. I suspect that our biggest opportunity may
9 be the specific targeting of donor-specific antibody. I
10 think the development of novel anti-inflammatory
11 therapies that I touched on. And, of course,
12 identification of optimal blood pressure, cholesterol,
13 and glucose goals in the treatments of our kidney
14 transplant patients.
15 Thank you very much for your attention.
16 (Applause.)
17 DR. SALOMON: And the ultimate presentation
18 of this morning, Topic 6, "Is Higher GFR at 2 Years
19 Better?" and this will be delivered by Dr. Ergun
20 Velidedeoglu, of the FDA. Topic #6: Is Higher GFR at
21 Two Years Better? Ergun Velidedeoglu, MD (FDA)
22 DR. VELIDEDEOGLU: Good morning, everybody.

1 So as you see, the title of my talk is, "Is Higher GFR
2 at Two Years Better?" So I will try to put this into
3 context. It's a provocative title. What we really
4 mean is that within the context of a clinical trial,
5 like a 2- , 3-year long trial, when one arm is
6 receiving a CNI- based regimen and the other arm is
7 receiving a non-CNI- based regimen, so that's the
8 context of what I'm talking about. And I will be
9 trying to draw parallels between a marathon, which is a
10 26-mile race, I believe, and long- term kidney graft
11 survival, which we all hope that will survive longer
12 than 26 years under ideal conditions.
13 And otherwise, as we have already seen, if
14 you look at registry data or institutional database
15 where everybody is receiving CNIs or more or less
16 similar antihypertensive therapy, et cetera, probably
17 most of us will agree that a good GFR at any time point
18 will probably correlate with better long-term outcome.
19 I have no conflicts to disclose, and I won't
20 be discussing any off-label use.
21 So the purpose of the presentation is there
22 is an interest in using GFR as an efficacy endpoint in

1 clinical trials, and the assumption is that a higher
2 GFR is associated with improved graft survival while a
3 lower GFR is associated with a lower graft survival.
4 And the counterhypothesis to this may be lower GFR, in
5 other words, suppression of the compensatory
6 hyperfiltration may be associated with improved long-
7 term survival.
8 So this counterhypothesis is based on the
9 data coming from CKD patients in general, and so what I
10 want to state in the beginning is that most of my talk
11 will be based on different hypotheses, so we will be
12 exploring any similarities between CKD patients, living
13 donors, and the transplant patients.
14 So as we all know, in CKD patients, ACE
15 inhibitors and angiotensin receptor blockers slow the
16 progression of chronic kidney disease, and it's among
17 their approved indications, by reducing blood pressure,
18 by reducing proteinuria, and a variety of other
19 mechanisms, but this benefit is usually accompanied by
20 a reduction in GFR, and this reduction may be
21 sustained. And more importantly, in experimental
22 animals, ACE inhibitors and angiotensin receptor

1 blockers reduce the intraglomerular pressure, which has
2 been claimed to be the crux of this benefit, it's still
3 being debated, but people have been publishing about
4 the effects of increased intraglomerular pressures.
5 So these findings are supportive, or at least
6 partially supportive, of the hypothesis of the
7 hyperfiltration injury in CKD patients.
8 So this graph is from a recent editorial by
9 Dr. Matt Weir, he is among us now. And by the way,
10 this editorial is written for CKD patients, not for
11 transplant patients. And this was based on another
12 publication, which includes a reanalysis of the data
13 from the famous RENAAL trial, and I will not go into
14 the details in the interest of time. So we see drug A,
15 which initially increases the GFR, but later followed
16 by a steep decline; and we see drug B, in blue circles,
17 which initially decreases the GFR, but later on draws a
18 flat line. So it's obvious that in the long term drug
19 B is probably more beneficial despite the fact that it
20 initially decreases the GFR.
21 And I call drug A a fast runner just because
22 of the fact that it increases the GFR initially, if we

1 make an analogy to the marathon, and in the editorial,
2 calcium channel blockers are given as a hypothetical
3 example for drug A, and I take it one step further and
4 say maybe the non-CNI regimens, because of the known
5 effects of the CNIs, may be considered in this group.
6 And drug B, I call it the slow runner because
7 it initially decreases the GFR, and in the editorial,
8 ACE inhibitors are given as an example, and I take it
9 one step further and I say maybe the CNIs fall into
10 this group.
11 So this is New York Times' advice for
12 marathon runners: don't go out too fast, you will be
13 tempted, resist, don't do it. You will. Almost every
14 marathoner does it, especially in New York. "The
15 trick," he added, "is not to use what you can." So we
16 don't know if this advice of not using what you can is
17 applicable to transplant patients or not, but we will
18 keep reviewing the data.
19 So can we extrapolate CKD data to transplant
20 patients? Are we going to see the same associations
21 that we have been seeing in CKD patients between the
22 slope of GFR and the long-term outcome? We don't know.

1 What is the importance or what is the place of
2 hyperfiltration injury in transplant patients? Still
3 unknown. But what we probably know is that glomeruli
4 in the transplant kidneys are stressed, and that is due
5 to the fact that all transplant kidneys are
6 hyperfiltrating because of the compensatory
7 hyperfiltration and the driving need for increased
8 metabolic demand.
9 And one of the important missing links is
10 probably the natural course of long-term GFR is not
11 fully known. What I mean by "the natural course" is
12 that there is a typical course over like 10 years, 15
13 years, not just 3 or 5 years probably.
14 And this is from another editorial. Here we
15 see another hypothetical course of GFR, mainly in
16 diabetic kidney patients, and the author is arguing
17 that probably this course of GFR should be applicable
18 to other types of kidney disease like kidney disease
19 due to hypertension, et cetera. And at the bottom we
20 see the rising albumin over the course of time, the
21 albumin excretion ratio. So we don't know, of course,
22 if this is applicable to transplant patients, but if it

1 is applicable, it may have some important implications.
2 As we see, the most prominent thing is the
3 hump in the middle, the hyperfiltration phase, so if we
4 don't look at other parameters, you see the 150 mL
5 line, so it will be very difficult to say for somebody
6 who has a GFR of 150 -- this could have been 60
7 depending on the nature -- if he is in the beginning of
8 the hump or at the end of the hump.
9 And the second important thing is probably
10 the accelerated slope. What I mean by "accelerated" is
11 the exponential decrease of GFR, which we see on the
12 right side of the decline phase of the curve.
13 So what we know in transplant patients --
14 this is from Dr. Gill and colleagues' article mentioned
15 several times during this workshop -- what we see is
16 that the slope of decline may change over time. Here
17 we see an initial decline of .33 mLs per year, and
18 during the following 2 years it goes up to -2.6 mLs. So
19 the decline may actually increase over time.
20 The role of hyperfiltration injury in the
21 progression of chronic allograft injury in kidney
22 transplant recipients has been suggested in several

1 publications. And due to the difficulty of measuring
2 the intraglomerular hemodynamics, mainly the
3 intraglomerular pressure in patients, probably we need
4 to rely on indirect evidence if we are to search for
5 any evidence of hyperfiltration injury in transplant
6 patients, just like they have been doing in CKD
7 patients.
8 Some data from kidney transplant patients
9 suggest that functional nephron mass relative to the
10 recipient body size may be critical for long-term
11 survival. So this raises the question of possible
12 hyperfiltration injury.
13 This is again from the famous paper by Dr.
14 Kasiske and colleagues, and this is an analysis of UNOS
15 database. As we see, large-size and medium-size
16 recipients of small-size kidneys have an increased risk
17 for graft failure which was statistically significant.
18 And this is another very interesting study
19 from France. Here instead of using BSA as a surrogate
20 for the nephron mass, they actually weighed the kidneys
21 right after donor nephrectomy, and they looked at the
22 ratio of the kidney weight to the recipient body

1 weight, and if that ratio was below a certain amount --
2 here you see it's 2.3 grams per kilogram -- they called
3 these kidneys, kidneys with functional overload, and
4 the other group of kidneys were called kidneys with
5 less functional overload. As we see, there is a
6 survival difference which becomes apparent after 2
7 years. The functionally overloaded group has worse
8 survival, and that is statistically significant.
9 And this is again we are continuing with the
10 same article. This shows the GFR curves in the exact
11 same populations. Initially, we see the compensatory
12 hyperfiltration, as we see here, right after
13 transplant. Within the first 6 months we see a rise in
14 the order of probably 11 mLs, and we see the same
15 compensatory hyperfiltration in the less burdened
16 group. The overburdened group continues drawing a
17 plateau with a slight upward slope while the other one
18 shows a slight decline.
19 But things change by year 7. By year 7, we
20 see a much steeper decline in the functionally
21 overloaded group compared to a less steep decline in
22 the less functionally overloaded group, so that by year

1 10 or 11 the curves cross and the less functionally
2 overloaded group shows a better survival afterwards.
3 And this may be even more important. Here we
4 see the effect of acute rejection, this time, on the
5 course of GFR in the same two groups. Here again
6 initially we see the same compensatory hyperfiltration
7 within initial the 3 to 6 months, and in the case of
8 acute rejection, we see a big dip in the functionally
9 overloaded group, which is probably in the order of 11
10 mLs. We see a smaller dip in the less functionally
11 overloaded group, which is around 5 mLs, and again
12 followed by the plateau phase, again a little upward
13 slope in the functionally overloaded, a little downward
14 slope in the less functionally overloaded, and the
15 turning point here around 7 years, and we see again a
16 steeper decline in the functionally overloaded and a
17 less steep decline in the less functionally overloaded.
18 So in the case of acute rejection, not only
19 the early course of GFR is affected, but it also seems
20 to affect the long-term course, and the curves cross at
21 an earlier time point.
22 So as we all know, living donors are

1 resistant to hyperfiltration injury. Hyperfiltration
2 after donor nephrectomy is considered to be
3 compensatory, and long- term outcome is comparable to
4 the general population. Except probably for a little
5 incidence of proteinuria and a little rise in blood
6 pressure, there is no evidence that these patients are
7 developing a higher incidence of endstage renal
8 disease.
9 So once we start looking into different
10 subsets of living donors, we may start seeing a
11 slightly different outcome. This is another study from
12 the University of Maryland, and 36 of these living
13 donors, which they performed the analysis on, with a
14 mean follow-up of 7 years. Almost half of these donors
15 displayed GFR values below 60, and in the author's
16 conclusion, this raised concern for hyperfiltration
17 injury.
18 So kidney recipients, coming back to kidney
19 recipients, why should it be a concern? Why would
20 hyperfiltration injury be a concern in kidney
21 recipients when it's not a concern for living donors?
22 For a number of reasons probably. Kidney grafts have

1 less nephron mass, as stated earlier, than a native
2 kidney in a living donor due to ischemia reperfusion
3 injury, acute rejections, the events related to brain
4 death, and antibody-mediated injury, et cetera, et
5 cetera.
6 And they are also denervated. And from the
7 animal experimentation, we know that denervation causes
8 impaired autoregulation of renal blood flow, and there
9 is evidence that there is never complete nerve
10 regeneration in transplant patients. And I don't have
11 time to go into details.
12 And probably, as a third factor, kidney
13 recipients have higher levels of RAAS activation
14 compared to living donors for a number of reasons,
15 which may be an additional factor in raising the
16 intraglomerular pressure.
17 So within this context, can there be any
18 possible benefits of calcineurin inhibitors in the
19 mitigation of hyperfiltration injury. As we all know,
20 CNIs are known to be nephrotoxic, but at the same time,
21 CNIs may reduce intraglomerular pressure mainly due to
22 the afferent arteriole constriction. And CNIs may also

1 decrease proteinuria through this mechanism and
2 probably through other mechanisms.
3 So this is rat data. And as you see, in two
4 different groups of rats exposed to cyclosporine versus
5 no exposure to cyclosporine, under three different
6 conditions. Under conditions of euvolemia,
7 hypervolemia, or hypervolemia plus angiotensin II,
8 these rats, the group of rats exposed to cyclosporine,
9 displayed lower single nephron GFR, and, more
10 importantly, lower intraglomerular pressures. And, of
11 course, this is animal data. The applicability to
12 humans may not be always possible.
13 And this is again another rat data from
14 another published paper, and here we see that increased
15 exposure to cyclosporine -- this is, by the way, an
16 extensive renal ablation model in rats -- with
17 increased levels of exposure to cyclosporine, the rats
18 displayed smaller amounts of proteinuria, decreased
19 amounts of proteinuria, and here we see the control
20 arm. Again this is animal data. The applicability may
21 be discussed. But we also have other types of human
22 diseases that we have been using CNIs for the purpose

1 of decreasing proteinuria and for similar reasons.
2 So in the end, instead of conclusions, we are
3 left with questions. Should hyperfiltration injury be
4 a concern in kidney transplant recipients, especially
5 in states with further reduced nephron mass? I call it
6 "further" because they already have reduced
7 nephron mass, but in extended criteria donors or
8 especially in the case of failing grafts, which already
9 sustained a good deal of alloimmune injury. And the
10 following question can be: Can there be a benefit in
11 maintaining a lower GFR in kidney recipients? for the
12 reasons that I already discussed.
13 And thank you for your attention.
14 (Applause.)
15 DR. SALOMON: Okay. So we discuss things,
16 and Renata made a great suggestion that we take a 15-
17 minute break right now since most of us have been
18 sitting here almost 2 hours, and that would make us
19 return, unless my watch is wrong, at 10:00.
20 (Recess from 9:47 a.m. to 10:04 a.m.)
21 DR. SALOMON: Okay, if we can come back to
22 our places at the table, we can get started with the

1 discussion. I'll give everyone another minute to
2 settle down.
3
4 Question and Answer Period (Panel and Audience)/ Public
5 Comment Discussion of Suggested Questions (to be
6 introduced by the moderator(s))
7 DR. SALOMON: Okay, so I would like to
8 welcome everybody back from the break and initiate this
9 discussion, for which we'll have 1 hour. It's a few
10 minutes after 10:00 right now, so my partners and I,
11 Frank and Ergun and Renata, will watch what's going on.
12 So I would like, just to get started, but
13 everyone should do as we had done yesterday, just speak
14 up. So I jotted down a couple questions, but one was
15 to Dr. Ploeg, before he walks away.
16 (Laughter.)
17 DR. SALOMON: So, Rutger, I have a question.
18 So you made a very nice presentation of the importance
19 of preservation and all these different methods. So
20 given in the context of thinking about endpoints in
21 clinical trials, I was thinking to myself, okay, can
22 you think of a way -- so if you did a multicenter

1 clinical trial of a drug and you were looking at a
2 factor like survival or outcomes or GFR or whatever,
3 all of these would be very much affected by differences
4 in the centers in your multicenter trial in the way
5 they approach preservation as well as perhaps in
6 variability in the donor procurement organizations, for
7 example, that serve these centers and the kind of
8 kidneys, the kind of donors, they had.
9 So taking that all into consideration, would
10 there be a way to integrate some sort of a correction
11 to weight, for example, these different elements so
12 that you could say, okay, I did these multiple centers,
13 but center A, I multiplied by .8 or something in terms
14 of the GFR because they had poor preservation whereas
15 center B is all machine perfused, and so I multiplied
16 by 1.2?
17 DR. PLOEG: Well, thanks for this challenging
18 question. The bottom line is I haven't gotten the
19 model in the last 2 seconds for you ready, but I think
20 it would be very, very, very difficult. For one thing
21 is if we look at a lot of, let's say, donor and
22 preservation- related factors, they are very much

1 affecting the function immediately after
2 transplantation. And we have also looked at the
3 relevance, for example, outcome measures like GFR in
4 the first so many days after transplantation in
5 previous studies, and obviously at that point GFR is
6 not a validated marker because you're not at a stable
7 state, and it may vary very much, so outcome right
8 after transplantation and GFR are not good. So I think
9 the first point where we actually were able to see and
10 discriminate thoroughly with GFR following those
11 studies was at 1 month.
12 Now, coming back to your original question,
13 whether for a drug study you have to correct for
14 confounding factors like preservation or whatever, and
15 I think there is only one way. If you do such a study,
16 you have to make sure people adhere to the right
17 protocol because otherwise you're in zombie land and it
18 becomes very difficult. And do you see a way to
19 correct for all these factors?
20 DR. SALOMON: That's why I asked. I mean, I
21 have one suggestion I'll make in one second. The
22 problem in the U.S. -- and people can say they don't

1 agree with me on this one -- but the problem in the
2 U.S. is that everybody is very independent, you know,
3 we have guns, we have freedom --
4 (Laughter.)
5 DR. SALOMON: -- and basically everybody
6 wants to do what they want to do on something like
7 that. I mean, we can all agree on a 25-percent
8 increase in creatinine is a signal for a biopsy, that's
9 progress, but the idea of telling programs in New York,
10 Chicago, and Los Angeles that their organ procurement
11 organization has to follow a certain protocol of, let's
12 say, pumping kidneys, for example, I don't know, good
13 luck with that.
14 So the question --
15 DR. PLOEG: So sorry to interrupt, but you
16 just asked me in the context of a study. Now, I'm not
17 saying -- see, if people go out like we used to do in
18 Wisconsin, you've got your organs, you transplant
19 everything yourself, you're very much like on an
20 island, and you do it yourself, you don't even share
21 too much, unless it's mandatory, right? But if you do
22 a study, then you're bound to the protocol, and even

1 then all those free Americans have to stick to the
2 study protocol; correct?
3 (Laughter.)
4 DR. SALOMON: I'll just leave that at that.
5 We can --
6 (Laughter.)
7 DR. PLOEG: Well, there's a big laugh.
8 (Laughter.)
9 DR. SALOMON: No, and people should comment
10 on that. I guess one thing you could say, Rutger, is
11 correct, is that you're saying if we agree that these
12 sorts of preservation methods are critical influences
13 of an outcome parameter, then the value of what you
14 presented could be interpreted as saying, yes, then
15 that has to just spill over into the protocol.
16 The problem is, is that for a transplant
17 program to join a study that would also implicate the
18 OPO that served the transplant program and otherwise
19 four other transplant programs in the same area, that
20 they would have to change the way they normally manage
21 organs, that would then get incredibly complex.
22 So I was wondering whether there would be a

1 way -- so in genomics what we do frequently is
2 normalize data. Does anybody normalize data in a
3 multicenter trial? We look for center effects, but I
4 don't think I -- and I again look to correction, it's
5 just all part of the discussion -- but I don't think
6 I've ever seen anybody take a six-center multicenter
7 trial and normalize the results for each of the centers
8 like we would normalize datasets across arrays and then
9 combine the data so that you would remove center-
10 specific changes like, let's say, the behavior of the
11 OPO or differences in the donor populations. I don't
12 know, I'm just throwing that out.
13 DR. SCHOLD: Dan, I mean, I'm sorry,
14 technically the one way you would handle a significant
15 confounding factor like that in a randomized controlled
16 trial is you stratify at a central level, so if
17 randomization isn't going to take care of itself at a
18 patient level, you would stratify centers, say, for
19 those who pump and those who don't pump, and that would
20 be sort of the next step in a more complex than a
21 simple randomized controlled trial design. So that's
22 probably something along the lines. Whether you would

1 have to get more complex than that is less typical, but
2 if there was something that would be a major concern
3 for the measurement, I think that would be the next
4 step in the design.
5 DR. HURST: Dr. Gill had a comment?
6 DR. GILL: I was just going to say the same
7 thing. I mean, you can do various -- you can do
8 cluster trial designs or block randomization, but
9 that's usually how that's going to be handled.
10 DR. KAPLAN: Then the only thing I worry
11 about, normalizing multicenter study design or results,
12 would be that sometimes a lot of the information is in
13 the variability and in the distribution, and by
14 normalizing, you fit it back into -- I often see this
15 with log normalization and other things, some things
16 are fat- tailed, some things are not normally
17 distributed, and when you force it back into that,
18 maybe all the information is in the variability, and
19 it's just something to be cognizant of, and I'm not
20 saying right or wrong, but just something to remember,
21 that sometimes the variability is what is the question.
22 DR. STEGALL: Well, I think it's pertinent to

1 this discussion of GFR actually, normalization of data
2 over time and the variability of the data, and that's
3 the reason I think that a declining GFR, a delta GFR,
4 actually can be normalized even if there may be certain
5 variations in GFR measurements. And just to reiterate,
6 we would say that a single mean GFR as a study endpoint
7 is not really the best way to look at study
8 populations, that an iothalamate would be best, but
9 given the fact that we do multiple, multiple GFRs --
10 70,000 or something can be calculated -- and the range
11 that we are looking at is most transplant patients have
12 GFRs up to 60, so we've looked at that, no matter what
13 estimate we use, it's pretty good, but it really is the
14 change in GFR that determines patients over time, and
15 they're not subtle changes either, we're not looking at
16 1 or 2 point differences.
17 And the other thing I would say just
18 parenthetically because it got into this last talk is I
19 want to say very clearly that we're not talking about
20 delta GFR as a CNI toxicity issue. The differences
21 between tacrolimus and cyclosporine and subclinical
22 rejection have been published by more than one group,

1 and so I would still think that the major difference in
2 those patients at 1 year is that the patients who have
3 a declining GFR have an immunologic process going on
4 that is not recognized by the biopsy or by anything
5 else, sometimes by DSA, but that's probably going to go
6 less over time as we get better at doing this, but
7 transplant patients have immunologic processes going
8 on. And you could actually design a study trial that
9 looked at 20 percent of the patients actually had a
10 decline in GFR between 1 and 4 years. So GFR is a very
11 important measurement; in fact, that's all that matters
12 in a kidney transplant recipient, is their GFR, but
13 it's just how you apply that. I mean, if they don't
14 have GFR, they're on dialysis.
15 (Laughter.)
16 DR. STEGALL: So that's what I'm kind of
17 getting at. So delta GFR, it's actually -- and you're
18 looking at this, it's a concept that's catching on, but
19 just taking the entire population and bumping up their
20 GFR doesn't mean you're going to get better 5-year
21 graft survival, I can agree with that 100 percent, but
22 the mechanism really probably isn't these other

1 hyperfiltration injuries and all the rest. I mean, I
2 don't have the data exactly yet, but it's there.
3 DR. HURST: Dr. Jardine and then Dr.
4 Vincenti.
5 DR. JARDINE: So I have a simple question. I
6 think that the problem with endpoints is that we've
7 worked on counting out the things we don't want. We
8 don't want the patient to die, we don't want the graft
9 to fail, and we don't want acute rejection, but these
10 things have become so infrequent that it's almost
11 impossible to do a trial within the time scale that
12 we've got, and cellular rejection is probably not the
13 risk factor it was. So we're left with death, graft
14 loss, and perhaps antibody-mediated rejection.
15 So my question to the panel is: Which of the
16 GFR variables could we add into this endpoint? We've
17 heard the median or the mean GFR probably isn't a
18 useful endpoint for a clinical trial, but there are
19 some levels of GFR that are as bad as a graft failure.
20 I mean, a creatinine of 5 or above, the graft is
21 probably finished. So could we add to the endpoint a
22 creatinine of 5 or above, or a creatinine of so much

1 that increases over time, or a creatinine of X with
2 proteinuria? Are these hard endpoints that we could
3 include in a composite endpoint?
4 DR. STEGALL: I want just to say that we know
5 that a low GFR is not a good thing, but the point we're
6 trying to make is if you want to improve long-term
7 graft survival, you have to identify people who are
8 going to lose their grafts, and the majority of people
9 who actually will lose their grafts by 5 years have
10 good function at 1 year. So it does not help you
11 necessarily just to do one little study and say we're
12 going to say -- we already know those people with GFR
13 of 22 are -- most of them are out -- they're going to
14 lose their grafts, but if you really want to improve
15 the slope of the Lamb paper, you have to go back and
16 find those people who are going to go from either the
17 noncompliant patients or whatever. So that's what I
18 would say, there is no number in that regard. There is
19 a change in GFR, that's what we would say, and the
20 change in GFR is important, and there may be other
21 surrogate markers that one could use that would tell
22 you what the biological process is.

1 DR. JARDINE: So we are constrained by time.
2 We have to do our trial within 1 year, say.
3 DR. STEGALL: No, I don't think that's true.
4 I would disagree with that. I think if you were going
5 to do that, then you shouldn't do a long-term study at
6 this stage today because we just don't have enough
7 surrogate markers to tell you that this marker is going
8 to tell you what's going to happen 5 years down the
9 road. You know, if you want to do a 1-year trial,
10 that's fine, but then you won't have the data. The
11 better data you have, the less controversy there will
12 be at the end of the day of what to do.
13 DR. HURST: Okay. Dr. Vincenti.
14 DR. VINCENTI: So, Mark, I don't understand
15 what you are saying. If you have a patient who has a
16 high GFR at 12 months, had a good GFR at 6 months, the
17 slope is either neutral or positive, they had a normal
18 biopsy, and they don't have DSA, this patient is
19 destined to have an excellent outcome. The patient
20 could have a random event, like any patient, they could
21 be hit by a bus, or they lose a kidney because 40
22 percent of patients who lose their kidney, they die

1 prematurely, but there is not going to be some unknown
2 immunological problem in the background that's going to
3 surface.
4 DR. STEGALL: Yeah, there is. I didn't think
5 that either. I thought that these people who had
6 normal renal function at a year did something wrong
7 later on, but our data, as we look at the biopsies and
8 follow the patients long term, the data is forming our
9 opinions, it's not that I just came up with this off
10 the wall, it's kind of an unusual opinion.
11 Twenty percent of those patients probably
12 have an immunologic process going on that we don't call
13 on their biopsy, and it's because it's light
14 microscopy, it's anodized (ph), you know, there are
15 macrophages in those grafts that we don't look at, and
16 that's I think what happens. And 60 percent of the
17 patients actually have stable renal function and
18 increase, but there are 20 percent of the patients, and
19 maybe belatacept would be a drug that would get rid of
20 that underlying immunologic process and you wouldn't
21 see it in that patient population, and that would be
22 the drug then they should be on. Do you see what I'm

1 getting at?
2 But these patients aren't the -- this is what
3 happens, that little finger graph that Walt showed on
4 page 9 here is really the natural history of GFR
5 between 1 and 5 years after kidney transplants. Just
6 taking all comers, that's what happens to them.
7 DR. GILL: I just want to make a comment
8 about kidney function and differentiating it out, and
9 if we just go back how we struggled with kidney
10 function at the time when we were thinking about it as
11 a surrogate or an intermediate outcome in trials, we
12 had all the issues about standardization and so forth
13 and what was the best prediction equation, which I
14 think distracted us a lot, and then, rightly so, I
15 think Bruce's paper that showed us that the predictive
16 value of this is limited.
17 But we do have to say some simple truths
18 here:
19 it's the function of the organ. And I just
20 want to draw a parallel with the heart. No one is
21 going to say that left ventricular ejection fraction is
22 not a good outcome because it's the function of the

1 organ. If the guy has an MI the next day and now his
2 LVF plummets and he dies, so be it.
3 But I think that we do have to recognize the
4 intrinsic aspect of GFR, which differentiates it from
5 some of the other intermediate outcomes that we say,
6 notwithstanding the importance of what Mark said, that
7 we do know that patients at 1 year subsequently do
8 well, but it, in itself, is an intrinsically valuable
9 outcome, which I think we do it a bit of disservice in
10 terms of its value by lumping it and saying that it has
11 limited predictive value, and I just want to say that.
12 I think we have to say some simple things about what we
13 value clinically. There is no question GFR stands out
14 amongst all the other players as an outcome.
15 DR. HURST: Dr. Lorber?
16 DR. LORBER: So I sort of feel like I'm being
17 the contrarian, but I am going to be the contrarian. So
18 are you saying that since GFR doesn't have predictive
19 value and we shouldn't use it as a clinical trial
20 endpoint therefore, then we're back -- let's start from
21 our beginning discussion yesterday, requirements to
22 develop a drug in the transplant space right now

1 translate into larger and larger patient numbers if
2 we're going to use the traditional endpoints that have
3 been used over the years in order to get
4 discrimination, and even then we're not sure what the
5 benefit is that we're showing. So if not GFR, if not
6 kidney function, in a kidney transplant indication,
7 maybe could somebody start to talk about what we could
8 use?
9 DR. STEGALL: Can I say that we actually
10 advocate GFR measurements, we just don't advocate one
11 single GFR measurement and that's going to tell you
12 everything you need to know over time.
13 DR. LORBER: That's not the question I'm
14 asking.
15 DR. STEGALL: No, but you said the GFR was
16 not predictive, and I think that it --
17 DR. LORBER: No, that's what I'm hearing what
18 people are -- well, it's they're not --
19 DR. STEGALL: I just said GFR is predictive.
20 DR. LORBER: Okay.
21 DR. STEGALL: A change in GFR is predictive,
22 so don't put words into my mouth because I don't think

1 that that's -- we're really very clear that we're not
2 saying that GFR should be thrown out. In fact, a
3 change in GFR is the endpoint that we are advocating.
4 DR. LORBER: Okay. Thank you. That's what I
5 was trying to become clarified because this discussion
6 is not at least leaving me with the impression that
7 that's what you were saying. Okay? And that's great,
8 that's great.
9 DR. SALOMON: Mark, can I follow up? Yeah,
10 hang on. Can I just follow up? There is a specific
11 question, and then, Eli, you'll be next.
12 So this would be to Bruce. So all the data
13 that I saw this morning said to me that if you take an
14 individual patient and you look at delta GFR, that it's
15 predictive, and that's what I think Marc just responded
16 to you on.
17 Now, the one piece of data that suggested it
18 was not predictive was done -- and it's a little
19 different, but I would like -- it was your data, Bruce,
20 so could you please explain how you view this?
21 DR. KAPLAN: Well, first of all, from our
22 data and going back to Harry's data, I mean, it's a

1 given that if you take a large group of patients and
2 you have a Y intercept, and you have a lot of patients,
3 further injury is going to be randomized dispersed. So
4 if both have the same slope, the group that's at 70 is
5 going to hit 10 later than the group that has 50.
6 That's really all that was saying. And if you take it
7 to the patient level, it almost becomes a stochastic
8 process of who is going to get that injury, if you're
9 looking at a registry.
10 DR. SALOMON: So was your concern, Bruce,
11 when you did that study -- because it may be that
12 really your study wasn't quite quoted correctly because
13 it seems to me that all the data that we saw was that
14 if you calculated a delta GFR, a change in GFR, as a
15 function of time -- and I think Walter's data was very
16 clear, but so was others -- that that was very
17 predictive of bad outcomes.
18 DR. KAPLAN: I think when you do -- and again
19 I turn to Mark as well -- that I think the question is
20 no one would doubt that the slope of GFR -- well, the
21 intercept obviously will make a difference -- but the
22 slope of GFR, by definition, of course, is going to be

1 related to the loss of graft function. I mean, it's a
2 given, it's a mathematic given.
3 My question for Mark and everybody in the
4 audience is we're under the constraints of a calendar,
5 that we measure at 1 year, we measure at 15 months, we
6 have to have a trial that goes 18 months. So whenever
7 that injury occurs, we may not catch it. So --
8 DR. STEGALL: Well, it's a test, first and
9 foremost. It may not be a stochastic event. All
10 right? And it's a testable hypothesis. All right?
11 That's what we want to do. So 20 percent of patients
12 have a decline in GFR between 1 and 5 years, that's the
13 number we use.
14 It's actually 40 percent, some have less GFR
15 decline than others. But one thing that's for sure is
16 they do not all develop CNI toxicity; that's one thing
17 I think that data shows: chronic allograft
18 nephropathy does not depend on having a really high GFR
19 at 1 year and then you just have more money in the bank
20 and it takes more time for you to go broke. All right?
21 But that's important. That actually, when our reviews
22 got back, that was one of the things that people sort

1 of pushed back in there. That's not the case.
2 But maybe the event isn't random, maybe the
3 event is something else. Maybe the event is that 20
4 percent of the patients have subclinical allorejection
5 going on. That's not a random event, that actually
6 would be a diagnosable event, maybe even a treatable
7 event, and you could move forward with treatment for
8 that, and that would take care of some of the decline
9 in GFR that we see between 1 and 5 years.
10 DR. KAPLAN: Mark, I don't disagree with you.
11 And when I use that --
12 DR. STEGALL: That's testable.
13 DR. KAPLAN: -- when I use that word
14 "random," obviously if we had all the information in
15 the world, nothing would be random. I'm saying just
16 given the information we have now, it's seemingly
17 random, not that it is random. Of course, we go to the
18 point where we want to take the randomness out.
19 So I'm not disagreeing with you at all, Mark,
20 I'm saying we have to search for the time period, and
21 maybe we have to get away from the calendar and we have
22 to look -- you know, we have studies that end at a

1 year, we have studies that end at 3 years, but biology
2 probably doesn't go at 1 year or 3 years.
3 DR. KATZ: Yeah, that's why, Mark, I wanted
4 to ask you a specific question. Accepting everything
5 you're saying, 20 percent of patients develop some
6 deterioration of GFR between 1 and 5 years. I'm a drug
7 developer. I'm come to you and ask you how you
8 recommend me to implement what you just said in a
9 clinical trial of a new drug? If you ask me to follow
10 the patient for 5 years, it's a no go for me as a drug
11 developer, I have no time for that, no money for that.
12 So if we're saying that the only way to use GFR as a
13 clinical endpoint is to look at time period between 1
14 and 5 years and look at the slope and the change
15 between 1 and 5 years, this is a no go for drug
16 development, and we have a problem here. So what is
17 your answer to that?
18 DR. STEGALL: Then we have a no go on a
19 certain level because I don't think that really the
20 data that you can generate right now -- I mean, I may
21 have a surrogate marker in a year that could tell me
22 what to do. You could say I'm going to go 2-1/2 years,

1 and we can negotiate somewhere in the middle, but I do
2 think that, again, the chronic studies that are going
3 to improve long-term graft survival may not fit the
4 timeframe of some people. I'm --
5 DR. KATZ: Some people.
6 (Laughter.)
7 DR. STEGALL: Right, and I'm not talking who
8 those people are, but it may fit other people's
9 timeframe. I mean, I'm just really looking at what
10 really might actually happen in the real world.
11 DR. KATZ: Okay. That's important.
12 DR. STEGALL: Because net present value may
13 not correspond with chronic allograft nephropathy.
14 Those are two entities. The biology will dictate at
15 the end of the day what happens anyway.
16 DR. KATZ: So if today I have a new
17 immunosuppressant drug and I want to show any benefit
18 in clinical function using GFR, we're actually talking
19 about long-term studies. I think it's important, as
20 you said, to be realistic and understand where we are,
21 and I think this is part of the thing I would like to
22 hear more today from this discussion. If you introduce

1 GFR as an endpoint, when and how to do it, and then we
2 need to go back and think, you know, can we do it and
3 what is the consequences?
4 DR. SALOMON: Eli, I've got down here a
5 couple different people, I've got in order, I have
6 Fernando, Jane, Marc Lorber, and Randy and Rutger. I
7 mean, this is great, this is what we want, but if
8 everybody can just kind of keep their remarks a little
9 briefer, we'll be able to continue this dialogue.
10 DR. COSIO: I agree with most of the
11 comments. It certainly is inevitable that GFR slope is
12 going to correlate with survival, but we make two
13 assumptions here. The first one is that the GFR slope
14 is uniform, and the data is that this is incorrect. In
15 most grafts, they have a stable GFR over a long period
16 of time and then suddenly they lose function. So, of
17 course, the time issue is the problem that you have. So
18 the question is, can a GFR slope over a brief period of
19 time, say from 1 to 2 years, predict the future? And
20 the answer from DeKAF and from Bert Kasiske will say
21 that it's not, it does not. You have to get the
22 closest to the end to make a prediction. Well, that's

1 too late for me, as a clinician.
2 In regards to the GFR, I agree completely
3 with Mark. A single measurement of GFR at 1 year
4 doesn't tell you very much. If it is very low, of
5 course it tells you a lot, if it is higher, it tells
6 you that it's higher, because you can have a GFR that
7 is perfectly good, but you have some proteinuria, that
8 patient will do very poorly. Or you can have a GFR
9 that is perfectly good and you have a biopsy that is
10 inflamed, that kidney will do very poorly. So we need
11 to interpret GFR but in context with all the parameters
12 of GFR or kidney structure because a low GFR with no
13 proteinuria and with a normal structure of the kidney,
14 that kidney will do very well.
15 So I think it's a wonderful endpoint, if we
16 put it together with all the parameters of kidney
17 function. We shouldn't ignore the other ones. And
18 proteinuria is a big one that we haven't talked very
19 much about.
20 So I think that would be an excellent
21 endpoint. You know, GFR, plus proteinuria, plus
22 structure of the kidney.

1 DR. SALOMON: Yeah, which is good, composite
2 endpoints, a very good point to make.
3 Okay, Jane.
4 DR. TAN: I agree with Fernando. I also want
5 to bring this back to lessons learned from clinical
6 trials in native kidney disease, and again we're using
7 composite endpoints in these large trials. And in
8 native kidney disease, 15 percent of individuals have
9 stable allograft -- well, stable kidney function over 2
10 years, and 85 percent has a decline. This is in
11 contrast to what you are saying, Mark, that 20 percent
12 actually have this decline in GFR, and that's part of
13 the problem, that you have a lower population of
14 individuals within transplant that actually have this
15 real change in delta GFR.
16 And one of the questions I have is even in
17 the CKD population, the slope of the GFR really didn't
18 pan out as a great surrogate marker, it's only when you
19 use something like a doubling of the serum creatinine,
20 which they took as a marker of chronic irreversible
21 damage, that there was a large enough event rate to
22 have significance. So I wanted to throw that out --

1 DR. STEGALL: Well, the paper is actually 40
2 percent of the people, 40 percent of the kidney
3 transplant population has a declining GFR between 1 and
4 5 years.
5 DR. TAN: Okay. But that is still
6 significantly lower than 85 percent in the CKD
7 population. But that's part of the problem --
8 DR. STEGALL: I think it's different
9 biological processes that are going on there. I
10 hearken back to that, that it's different. I think
11 that kidney transplant patients don't all have
12 recurrent disease, and especially between 1 and 5
13 years. And, again, I would also just say -- so that's
14 the difference. I don't think that there is that many
15 things that happen in kidney transplants that can be
16 correlated back to chronic kidney disease on a one-to-
17 one basis. It's a very difficult analogy to make. It's
18 kind of like making the marathon analogy because think
19 that 5 years is really good. We don't have any data
20 beyond 5 years. I'm not even going to try to talk
21 about that, but if you can't run 13 miles, you can't
22 run 26 miles.

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1 DR. SALOMON: Randy.
2 DR. MORRIS: Yeah. I've certainly enjoyed
3 the discussion, but I think there are three cultures
4 here which tend to be speaking past one another. There
5 is the pharma culture, which wants an endpoint at 1
6 year or approximately 1 year, which would be a
7 surrogate biomarker which would be reasonably
8 predictive of late clinical outcomes, say at 5 years.
9 And if the FDA agreed, they would get approval,
10 conditional approval, at 1 year, be able to market the
11 drug, have the obligation to follow those patients for
12 several years to prove there actually is a clinical
13 benefit.
14 So the question that I'm not hearing answered
15 either yesterday or today very definitively is what are
16 possible early accelerated review surrogate endpoints
17 or biomarkers at 1 year. And then we have the
18 clinicians, the academic groups, that get sort of in
19 the weeds about all the different issues with regard to
20 GFR and genomics and all that. So can we get some
21 people to suggest some endpoint or composite endpoints,
22 as Fernando just did, which was GFR, biopsy,

1 proteinuria? Is that an endpoint, surrogate endpoint,
2 that might be considered debated at 1 year which might
3 predict 5-year outcomes, or are there other endpoints
4 that we should be discussing from yesterday, such as
5 biopsy plus DSA? This is the sort of thing I'm
6 missing, is the synthesis and the delineation of what
7 endpoints might be useful.
8 DR. SALOMON: There are a couple of people
9 that still want to talk, and so I'll keep this brief,
10 but I do want to keep the focus here a little bit. This
11 is on GFR. And one of the things that Eli brings up is
12 -- and
13 Mark responded with the idea, well, you have
14 to go 5 years. So let me put this out to the group: Is
15 the message that this group wants to give the FDA and
16 anyone else listening, is that in order -- we all
17 agreed, I think, with little nuance, that a progressive
18 decline in GFR is a good predictor of a bad outcome,
19 and Fernando added some other parameters, which are
20 good, maybe we'll come back to that. But then the
21 question is, Eli says, okay, do you mean that I have to
22 do that over 5 years?

1 So what is the shortest period of time that a
2 decline in GFR measured by the things that Emilio so
3 nicely reviewed this morning, what's the minimal period
4 of time that you would buy that as correlative with
5 outcomes? Because if you do it at 12 months, then Eli
6 and Mark are happy, and we're using GFR.
7 DR. LORBER: Could I just make, Dan, just one
8 very brief clarification, and I don't have more to say
9 because I think the discussion is exactly where I was
10 hoping we would go, okay? But I think it's important
11 to understand that from the drug development decision-
12 making perspective, a year is probably an outside
13 limit. Okay? I mean, it's not a year or two or three
14 or four. A year is a long time given the pressures
15 within the decision- making bodies at the sponsors.
16 Okay? So, I mean, I just think it's important to keep
17 that timeline in perspective as we have this
18 discussion.
19 DR. SALOMON: Okay. So the question -- yes,
20 Bob, you are on the list. No.
21 (Laughter.)
22 DR. SALOMON: So the question is: Can we do

1 this at a year? Is a change in GFR over the first year
2 per patient measurable and accurate as a predictor or
3 not?
4 DR. GASTON: The answer is no, and my comment
5 was going to be, why does time zero have to be the time
6 of transplant? That's the bottom line of what we're
7 discussing here, and most other -- you know, I asked
8 the question yesterday about, how different is
9 transplant?
10 Well, most other drug development starts in
11 treating patients with a disease: you have a
12 diagnosis, you do this, then you enter the patient into
13 the trial. In our field, we enter patients at time
14 zero. The transplant is not the disease, and that's
15 basically what we're talking around. Time zero is not
16 the disease.
17 DR. KATZ: We're using immunosuppression,
18 developing immunosuppression, so we must start the day
19 of transplant to show that actually efficacy as far as
20 rejection has met the standard of care, or at least
21 better or equivalent standard of care.
22 DR. GASTON: That's the way things have been.

1 All I'm saying is it's a different time because we can
2 get from time zero to 1 year in almost everyone.
3 DR. KATZ: Yeah, but what I'm saying, if
4 we're talking about developing immunosuppression, if we
5 develop other drugs that intervene in the deterioration
6 of kidney after transplantation, this is another thing,
7 but if we develop an immunosuppressive drug, then we
8 must -- the requirement -- and I think everybody agree
9 -- is to show first that it's actually effective as
10 immunosuppressive drug and maintain low rejection rate
11 compared to standard of care. So we must start at
12 transplantation.
13 DR. SALOMON: Okay. So I'm just trying to be
14 a good chair here.
15 (Laughter.)
16 DR. SALOMON: So that's key, but that's
17 another question.
18 So, Rutger.
19 DR. PLOEG: I think we've gone around in
20 circles. Coming back to the major issue, I think we
21 all agree that GFR is good, and then some of us say,
22 but it takes too long. And Mark says, well, you just

1 have to stick to it because otherwise -- and then we
2 start to talk strategies.
3 Another idea -- and I don't have the solution
4 -- could be also -- and maybe Bruce knows about that --
5 mathematical modeling. And Tarasenko in Oxford has
6 done noise modeling. If you have enough events, for
7 example, in ICU -- he did it actually with Rolls Royce
8 aircraft machines, engines, he can predict from the
9 noise modeling when the machine is going to fail; he is
10 now applying it also to intensive care. So if we would
11 have together with the GFR confounding surrounding
12 noises which are patterns, we would be able in maybe
13 less than a year to say when the delta change would
14 occur.
15 DR. SALOMON: Flavio?
16 DR. VINCENTI: Well, I want to go back to the
17 points I made just before Dr. Cosio, and I agree with
18 him. I think the GFR 6 and 12 months are very useful.
19 I think they have to be coupled with a biopsy. I think
20 proteinuria is important to rule out the additional
21 events that can affect the kidney, for example,
22 recurrent disease. I don't think you need to wait 5

1 years, I think you can do good short-term trials, but
2 you have to have a combination of these endpoints. And
3 I think if you marry the biopsy with the GFR, you rule
4 out, of course, the presence of proteinuria, that that
5 graft is going to survive much better long term.
6 DR. SALOMON: Okay. Emilio?
7 DR. POGGIO: Well, Flavio just came before
8 me, but I echo Fernando's point. If you choose GFR
9 stability from 3 -- whatever time you want, up to 1
10 year coupled with donor-specific antibody, pristine
11 biopsy, no proteinuria, those patients will be unlikely
12 to have progression of disease unless something
13 happens, which everybody can have. You cannot predict
14 what's going to happen tomorrow. But there is no
15 underlying recognizable disease at that point. And you
16 will lose 20 percent, yes, I do, someone --
17 DR. STEGALL: Walt, is that the case? We're
18 talking more biopsies that do not -- these are normal
19 biopsies, they don't have DSA, they don't have
20 recurrent disease, and I'm telling you, those -- I wish
21 it were different, too, but numerically, that's where
22 most of the graft losses are occurring, between 1 and 5

1 years after kidney transplant. Again, that's what the
2 data shows. It's going to be out in publication, and so
3 read it and then tell me what we're seeing wrong. But
4 there really are patients who between 1 and 5 years
5 look really good at 1 year and then go on to develop a
6 decline in GFR.
7 DR. POGGIO: But the same is true for any
8 disease in medicine.
9 DR. STEGALL: Right, but this is the medicine
10 I want to --
11 DR. POGGIO: If you get any more, if GFR
12 drops, the patient dies.
13 DR. STEGALL: I think that those patients
14 actually are fixable, that's my hypothesis.
15 DR. VINCENT: Well, they stop taking their
16 medication.
17 DR. STEGALL: I think that there are -- well,
18 some do, but some don't. Half don't. Half of them
19 have genetic --
20 MALE SPEAKER: But half do.
21 DR. STEGALL: -- half of them have genetic
22 variability to immune responses to the graft. There is

1 genetic variability in the response to the
2 immunosuppressive medicines. Maybe they're just not on
3 the right immunosuppressive medicine. That's a
4 hypothesis.
5 DR. SALOMON: Okay. Bruce and then Matt, and
6 then there are a couple other people's comments.
7 DR. KAPLAN: I just wanted to go back to
8 Rutger's point, and also to Mark. There is something
9 that we're not talking about too much, and that's the N
10 that's needed to show the effect. Obviously, if we had
11 unlimited N, we probably could show an effect of slope
12 of GFR, but one way around -- and Rutger is correct --
13 would be we would have to -- I don't know what the N we
14 would need, but if we could get some level of decrease
15 in GFR that's well above two standard deviations above
16 noise, and it was irreversible within a year, that's a
17 bad event. If X intervention prevented that, reverses
18 Y intervention, that's a good drug regardless of what
19 else happens, graft loss 10 years later. If you can
20 prevent an injury that won't go away that's well above
21 any kind of noise that you would expect in the random
22 variability of the population, and you could prove that

1 on the causal pathway X was the reason for that versus
2 Y within a year, let's say it's slope of GFR, then you
3 would be fine.
4 The question is: How could you model that,
5 get the N that you would need from pharmaceutical
6 development to actually make it feasible from a utility
7 standpoint? I think it's possible, and I think it's a
8 different way of thinking, and I think we should think
9 about it that way, and I think it may be a way of
10 coming together of all these issues. I'm not saying it
11 could be done, but at least a thought.
12 DR. SALOMON: Matt?
13 DR. WEIR: Yeah, I was just going to comment
14 that what everyone is dancing around and basically
15 trying to say is, sure, we probably can use GFR at a
16 specific time coupled with slope, but the real issue is
17 to standardize as best we can the type of expected
18 change in renal function over time. For example, if
19 you took a 1- year time point, for example, to start a
20 study that could last a year or two, basically what you
21 could try to do would be to standardize those patients
22 at 1 year with inclusion and exclusion criteria to

1 include whether or not they have diabetes or
2 hypertension or DSA or albuminuria.
3 I mean, you're going to have to go through
4 the motions because we know that each and every one of
5 these variables will influence the likelihood for
6 intercurrent changes in kidney function.
7 And again just to draw some analogies from
8 what we have done in native kidney disease, for
9 example, the African American study of kidney disease
10 and hypertension, we tried, as best possible, to use
11 biopsy- proven hypertensive nephrosclerosis, we tried,
12 and we got some results based on that, even though not
13 everybody had a kidney biopsy. The same thing in
14 people with diabetic kidney disease, preferentially
15 using Type 2 diabetes, because in these patients we
16 feel there is a greater possibility that we could look
17 at a more homogeneous group and then modify that slope
18 of change over time.
19 So I think in transplant we have to take some
20 lessons from the past. I think we do have to try to
21 design clinical trials where we can hopefully have a
22 more homogenous change over time. And, again, we can

1 debate how best to do that, who to include, who to
2 exclude, but I think the greater the effort we have to
3 have a more homogenous expected change in renal
4 function over time will provide a better opportunity
5 for us to make sense of newer immunomodulatory therapy
6 or other therapies that modify oxidative stress or some
7 of the other repurposing of older medications that I
8 mentioned earlier.
9 DR. SALOMON: At the back table?
10 DR. EVERLY: So, yeah, I agree with Dr.
11 Gaston. You've got to start with something that's an
12 event, so the biologic event, before you look at delta
13 GFR post that. I mean, if you say DSA -- we looked at
14 our data, if you look at 20-percent increase in GFR
15 post the DSA entry point, then they do, do poorly, but
16 if you just look at post-transplant, most people don't
17 even have events. I mean, if you look at DSA, for
18 instance, as I was talking about surrogate endpoints,
19 most people don't ever have DSA post-transplant, so
20 they're not at the same risk as everybody else. I
21 think risk stratification and knowing that population
22 that's at highest risk as your entry criteria is more

1 important and looking then afterwards.
2 DR. SALOMON: Bob?
3 DR. GASTON: Yeah, we learned this the hard
4 way in the DeKAF, that we thought massive numbers of
5 patients, but in the prospective study, even with an N
6 of 4,000 patients, it took years before things started
7 happening to these patients, and that's sort of part of
8 what's underlying my remarks that -- anyway.
9 DR. SALOMON: Thanks, Bob.
10 Fernando?
11 DR. COSIO: Yeah. In regards to proteinuria
12 -- and thank you, Flavio, for your comments -- it
13 certainly identifies glomerular disease, but the
14 majority of patients with low-grade proteinuria do not
15 have glomerular disease and then it becomes really an
16 interesting predictor. Low levels of proteinuria are
17 highly predictive of grafts losses long period of time,
18 you know, in the 200 milligrams a day of proteinuria.
19 DR. STEGALL: But the problem with that is
20 that most of the people who develop graft loss between
21 1 and 5 years don't have proteinuria, they have a
22 different process going on. And I guess getting back

1 to the thing, if you really want to change the slope of
2 the Lamb paper, we're getting to the point that there
3 is a possibility that we could go back and look and see
4 maybe at 1 or 2 years after that initial endpoint there
5 actually might be enough of a demarcation, you might be
6 able to see those patients, but then just the caveat is
7 that that's a heterogeneous group, too. They may not
8 have all the same biologic processes going on. Some
9 will have protein, some won't.
10 DR. SALOMON: Bill?
11 DR. HARMON: Yeah. I wanted to second what
12 Bob has said, or maybe third it or fourth it, if those
13 are appropriate verbs, insofar as our mindset in
14 transplantation has been to start with an
15 immunosuppression regimen and stick to it forever, and,
16 indeed, now we're looking at a lot of conversion
17 trials. The reality is we've improved 1-year graft
18 survival to the point where it probably can't get much
19 better, and, indeed, why bother to try to do that if in
20 fact we found a way to do it?
21 So I think Bob is absolutely right, that we
22 should pick out those patients who are not going to do

1 well and start experimenting on them, and when we make
2 the change is indeed time zero. So we need a different
3 mindset in transplantation. In oncology, you don't use
4 Stage 3 drugs when you've got Stage 1 tumors. You
5 know, you stage things and then you go up and you do
6 different things based upon what that patient is.
7 So I think that's where we have to start
8 thinking about it. Now, I don't know if that's going
9 to be attractive to the pharmaceutical companies
10 because it's a smaller market, but, indeed, I think
11 that's the reality of what we're dealing with.
12 DR. SALOMON: So I think this has been a
13 terrific discussion. I was going to try and see if we
14 could summarize a few things. Is there anyone that
15 wanted to talk -- I mean, it got very lively, which is
16 fantastic. Did someone have something they wanted to
17 say that didn't come out?
18 DR. MORRIS: I'll just say that I think that
19 the concept that Bob raised with regard to treating
20 disease rather than preventing graft loss late is a
21 worthwhile endeavor, and selecting subpopulations at
22 risk for graft loss and treating them with a new

1 therapy is perfectly acceptable, and I think reasonable
2 and would be a great value to everybody.
3 DR. SALOMON: Marc?
4 DR. LORBER: Just one thing that I would like
5 to at least have this discussion consider because I
6 think that it could in some ways get the longer term
7 questions as well. I think there would be a fairly
8 substantial appetite within the sponsor group that if
9 we were to be able to find a short-term approval with a
10 commitment to do the longer term studies, I don't think
11 that that would a problem at all. That, I'm guessing,
12 would be accepted enthusiastically. It's about making
13 an upfront investment that's going to take many, many
14 years before you even know the answer, "Do you have a
15 drug?" That's where the real problem is, and so I
16 think that that should be considered within the context
17 of this discussion as well.
18 DR. SALOMON: All right, so just in terms of
19 summarizing, so if I say something that you don't agree
20 with, then this is a great time, we have time to talk
21 still.
22 So one thing I hear is that if we choose a

1 time for a disease to start, whether that be time zero,
2 at the time of transplantation, which would be the
3 objective, let's say, of a new drug that was just
4 supposed to be global immunosuppression, be a better
5 drug, or we say that the objective of the study in this
6 time zero is when you develop blank, you know,
7 proteinuria, a falling GFR, DSA, whatever.
8 I think that what we're saying, however, all
9 of us, and maybe with, again, nuances typical of a big
10 group like this, but with nuances that at that point,
11 one year from that point, there are now pretty -- even
12 if you add a little bit of composite variables, as
13 Fernando suggests, GFR is still a very good marker. If
14 the GFR is declining, that's a bad thing. If you stop
15 the decline of the GFR with whatever intervention one
16 makes, that's a good thing, and it can all be done
17 within a year, and I think Bob's excellent point is it
18 just depends on when that year starts, and that has to
19 do with the trial design and the objective.
20 The second thing I hear -- and I've heard
21 that for 2 days now -- is that maybe the field has
22 matured to the point where we're saying, "You know, our

1 1-year graft survival with the drugs we have is pretty
2 good." There are things we don't like that occur in
3 the first year or two, but a lot of the issues that we
4 wake up and worry about in clinic every day are
5 occurring at 5 and 10 years, and I think that came out,
6 a lot of people talked on that, Walter and Mark and
7 others. So maybe what we need to do is say, what kinds
8 of new therapies can impact on these things that we're
9 really worrying about and it's not 1-year graft
10 survival anymore?
11 But to say if a company comes along with a
12 brand-new global immunosuppressive, I didn't hear
13 anyone in here really say anything that would say, you
14 know what, if they do as well equivalently at 1 year as
15 you would -- that we don't have to hold that new drug
16 accountable for all this other stuff, like recurrent
17 glomerulonephritis and what's occurring at 5 and 10
18 years, and gosh forbid, noncompliance. I mean, it's
19 great if the new drug solves all noncompliance, but why
20 would you hold drug companies to that?
21 So I think maybe part of this is a maturation
22 of a field in which our expectations of what we expect

1 for approval and for these drugs ought to be coached
2 with a lot more nuance than we probably have been in
3 the past. I don't think the idea that I'm hearing from
4 everyone is that suddenly you have to introduce a new
5 drug today and you have to solve every single problem
6 that a kidney transplant is ever going to have for the
7 next decade.
8 So how many people around here would agree
9 that we can do this, just to give a final sort of real
10 clear message, that if you define the start of the
11 trial at whatever time you wanted to, picking up on
12 Bob's point, 1 year, with the current variables that we
13 have, would be good enough?
14 DR. MORRIS: Well, 1 year with accelerated
15 approval, which means if the FDA agrees to give you
16 approval from the 1-year data, you're obligated to
17 follow those patients for another 4 years to get
18 traditional approval. So, please, let's make sure that
19 we understand that --
20 DR. SALOMON: Perfect. Yeah.
21 DR. MORRIS: Okay.
22 DR. SALOMON: Yeah, no, I was basically just

1 throwing it out for people to say, "I disagree
2 completely," or something to that.
3 DR. STEGALL: I disagree that we know that it
4 would work or not. The possibility is that it would,
5 but I think the probability is not 100 percent, and
6 then I worry that I don't want to oversell something
7 that then will get people to thinking that transplant
8 is just crazy and you can never get anything done
9 because there is a history now of drugs not making it
10 through that could have helped transplant patients if
11 the trials had been designed differently, if the
12 expectations had been different.
13 And I think that the change in GFR to a year
14 was one thing that I was on, talked about, and I said I
15 don't think it's a very good endpoint, it's not going
16 to be a very good endpoint, but people really were
17 wedded to that concept.
18 So I just think that the caveat should be is
19 there are ways of improving long-term graft survival. I
20 think that new immunosuppressive medicines may be a key
21 to improving long-term graft survival, but to say that
22 it's going to start at a year and by 2 years you're

1 going to have the data no matter what the FDA gives you
2 biologically, that may or may not happen.
3 DR. KAPLAN: Dan, the only fear I would have
4 -- and Bob's idea is obviously a great idea, of
5 starting with the disease -- is we're starting at zero
6 again and we're kind of going, "How long do you have to
7 treat? What size effect do you need?" Not everybody
8 has the same disease. We know there are a multitude of
9 diseases that can occur, there is non-adherence, there
10 is AMR, there is DSA, there is interstitial fibrosis
11 that Mark can't even figure out why they got it, you
12 know, there are all sorts of things that are going on.
13 So even from the pharmaceutical development
14 side of things, which we're partly here, is a year
15 enough? What's the effect size that you need that's
16 going to be adequate to say that you're going to reach
17 that endpoint? Are we going to be here in 3 years
18 saying, is that really a surrogate or is that just
19 another correlation?
20 So I think we have to go back and think
21 whatever thing we raise here, we're starting from the
22 beginning again, and there is going to be a lot of

1 thought that's going to have to go into these trials.
2 DR. SALOMON: Eli?
3 DR. KATZ: I just wanted to raise another
4 point to you, that the accelerated approval and the 1-
5 year approval and then follow-up, I think it's a great
6 idea. However, we need to understand also some of the
7 consideration when you develop a new drug, let's say a
8 new immunosuppressive drug. Let's assume we get
9 accelerated approval at 1 year, and then we continue to
10 do whatever we need to do, which is a great idea
11 because it gives the company the financial basis to
12 move forward. However, one of the concerns is, of
13 course, why are you, all the clinicians here, going to
14 start using a new drug?
15 If we're just going to show in 1 year that a
16 new drug has the same graft survival, patient survival,
17 and ACR, which are the accepted endpoints, and we
18 cannot differentiate it in any other way from the other
19 drugs, like kidney function or diabetes or
20 hypertension, et cetera, then none of you are going to
21 use the drug because we have tacrolimus, we have
22 belatacept. I mean, why do we need another drug?

1 So the challenge now for the pharmaceutical
2 industry and a new immunosuppressive is actually to
3 develop a drug that can stand different than other
4 drugs, and different is not graft survival, patient
5 survival, and ACR. So that's a challenge that still we
6 didn't solve it even if we go to accelerated approval.
7 DR. SALOMON: Yeah, I think that's -- why
8 don't we hold comments on that only because that's
9 actually Session 7, that will be just coming up in a
10 minute, and it's a nice segue, so for that the FDA is
11 appreciative.
12 Flavio?
13 DR. VINCENTI: I mean, one of the challenges
14 in intervening when you have the disease process is
15 that the pharma then is faced with two issues: one,
16 whether the drug works, two, whether the process can be
17 reversed. When you use an immunosuppressant from the
18 beginning, you have one, "Is my drug working?" But if
19 you, for example, went to treat transplant
20 glomerulopathy, do you know that you can reverse it? I
21 have no idea.
22 So here they're not facing only whether the

1 drug is effective, they're facing whether in fact the
2 disease process can be treated, and so you're going to
3 add more to the uncertainties in terms of what they
4 want to do. I mean, we know, for example, in the
5 conversion trial of sirolimus that if you get a GFR of
6 40 when you have disease, or 40 or below, that in fact
7 you don't improve outcome, and therefore there is a
8 certain inflection point where you can't really change
9 the course of the disease.
10 And so these are the complexities, although
11 it's a nice concept, but I think it can be pretty
12 challenging for a drug company.
13 DR. SALOMON: Well, I think that is very well
14 said, Flavio, and that is, we can't solve every problem
15 that's possible, but what we can be, however, is a
16 clear message -- right? -- to what the thresholds are,
17 what the bar is, and then that is what drug companies
18 get paid the big bucks to decide, you know, whether --
19 Roy, what was it? Net present value, right? I really
20 like that.
21 So if we make it clear, as a field, what the
22 bar is, what the tools they have for it is, so if they

1 choose to try and reverse transplant glomerulopathy,
2 you and I will give them our opinion -- right? -- and
3 we'll charge them for it, and basically they can agree
4 or not agree that they can reverse it, fine, let them
5 try, but then what we've told them in clear terms is if
6 their proteinuria gets less, if their interstitial
7 inflammation decreases, if their slope of GFR changes,
8 that those are good surrogates. At least we're giving
9 them the tools that they need to make their own
10 decisions on net present value and go forward or not go
11 forward. So I think that's a positive. Does everyone
12 agree with that?
13 (No audible response.)
14 DR. SALOMON: Okay.
15 DR. ALBRECHT: Thank you, Dr. Salomon, I
16 think that was a wonderful discussion, and now we're
17 going to turn to Session 7, with my co-moderators, Dr.
18 Rutger Ploeg and Dr. Mark Stegall, who will introduce
19 the first speakers.
20
21 Session #7: New Ways for Considering Efficacy/Safety
22 Endpoints to Demonstrate Successful Outcome in Patients

1 Moderators: Mark Stegall, MD; Rutger Ploeg,
2 MD, PhD, FRCS; Renata Albrecht, MD (FDA)
3 DR. PLOEG: Right. So after this summary
4 then, thank you very much, we move to the first speaker
5 of this session, which will go on until 12:00, and then
6 we'll go for lunch -- correct? -- which will be
7 "Protocol vs. Prescribed vs. Actual Immunosuppressive
8 Regimens: Are Efficacy and Toxicity Rates
9 Known?" by Rita Alloway.
10
11 Topic #1: Protocol vs. Prescribed vs. Actual
12 Immunosuppressive Regimens: Are Efficacy and
13 Toxicity Rates Known? Rita R. Alloway, PharmD, FCCP
14 DR. ALLOWAY: I would like to thank the FDA
15 and others for assembling us here together today. I
16 think that we've had a lot of innovative discussion,
17 but I hope to bring up some of the potential ways that
18 we can try to see each other's net present value, and
19 the ones that we have from different perspectives and
20 try to come together to a solution for some of these
21 issues that we've been discussing.
22 In terms of disclosure, I have a financial

1 relationships within the last 12 months with several
2 pharmaceutical companies in relationship to grant
3 support, and I am going to not be discussing any off-
4 label use in this presentation.
5 The objectives that I have are to discuss the
6 implications of analyzing randomized controlled trials
7 by "intention-to-treat" versus "per protocol" basis to
8 quantitate efficacy and toxicity. Also, discuss the
9 impact of non-adherence on long-term outcomes, and
10 evaluate drug development and other disease states to
11 sustain the advancement in renal transplantation drug
12 development for the future.
13 In the context of randomized controlled
14 trials, RCTs are the preferred design for clinical
15 trials to evaluate efficacy. However, they do suffer
16 from many limitations of which are very common within
17 our transplant trials. Two of the major limitations
18 are missing data points and noncompliance with the
19 protocol.
20 And in an attempt to differentiate
21 noncompliance versus non-adherence, as we're referring
22 to noncompliance with a protocol here, we're talking

1 about the American investigators, I guess, that maybe
2 can't stick to the design of the trial or actually the
3 patients and various things that change the
4 responsibility that we have, as investigators, to make
5 the best choice that we can for the patients in terms
6 of physician discretion. So I think it's important to
7 understand these limitations.
8 Intent-to-treat analysis is a statistical
9 concept -- all right? -- and it attempts to address
10 these limitations. Intent-to-treat analysis includes
11 anything after randomization, and so you have to keep
12 in your mind "once randomized, always analyzed" and
13 basically whether the patient underwent a protocol
14 deviation, the patient withdrew, the patient was
15 noncompliant, or the physicians with the protocol
16 regimens, they're included in the intent-to-treat
17 analysis.
18 It's also important to understand that the
19 intent-to-treat estimate of a treatment effect is very,
20 very conservative, and with it being conservative in an
21 area in which we are trying to see such small changes
22 in improvement, there may be alternative methods of

1 analysis that will allow us to get away from a
2 conservative approach to become a little more granular
3 in seeing the effects that we want to see.
4 Randomized controlled trials, as we've all
5 discussed, highlight mean differences in the treatment
6 response and actually blur the individual differences
7 in the responses that we're wanting to see. And I
8 think that as our 1-year rates of, I guess, positive
9 outcomes in renal transplants have improved, we're
10 still unable to find the individuals that are really
11 going to benefit from the potential treatment effects.
12 So what are the pros to intent-to-treat
13 analysis? Basically, you have to look at it as a
14 complete trial strategy that includes design, conduct,
15 and analysis; it's not just the analysis portion alone.
16 It does provide an unbiased impact on treatment effect;
17 thus, it is the primary analysis mechanism in
18 superiority trials. It preserves the sample size of
19 the trial. I think that all of us know that a lot of
20 time is spent on determining what the margins of a
21 treatment effect is going to be and attempting to
22 predict what the sample size of a study is going to be

1 to have power to show a difference.
2 What is concerning is that in transplant
3 right now, when we're taking all of the patients that
4 come to transplant, we still have a hard time getting a
5 sample size to show the effect. So there are value to
6 intent- to-treat analysis that preserves a sample size,
7 and, thus, statistical power.
8 There are limits. The inference of the
9 arbitrary subgroups do occur, but it allows for more
10 generalizability of the results. So keep in mind
11 you're looking at generalizable results to an entire
12 run-of-the- mill transplant patient. The cons,
13 however, includes the fact that subjects that do not
14 receive treatment at all are included in the analysis.
15 Also, it includes noncompliant subjects that dilute the
16 treatment effect, and the endpoint data differs
17 remarkably among noncompliant subjects, subjects who
18 have dropped out or subjects who cross over, especially
19 in the context with the trials in transplantation
20 today, is many of the crossovers that occur actually go
21 to the treatment group of which it's being compared.
22 To minimize missing data points, some data

1 must be imputed. I think there are a lot of different
2 strategies that go into deciding how data is imputed,
3 and if we don't fully understand what those strategies
4 are, it may interfere with our ability to interpret the
5 final results. And also it requires that subjects lost
6 to follow-up be included in the endpoint. I think
7 we're relatively lucky in transplantation that most of
8 our patients are not lost to follow-up per se, so this
9 does not represent a high percentage, but it is still
10 part of the final endpoint analysis.
11 Now, if you switch from intent-to-treat
12 analysis to two "per protocol" analysis, it includes a
13 subset of the intent-to-treat patients who completed
14 the study without any major protocol deviations. So
15 obviously careful control to defining what these major
16 protocol deviations is very important.
17 Granted, when we look at "per protocol"
18 analyses, we don't necessarily exclude any potential
19 negative outcomes that may have happened and resulted
20 in major protocol deviations, but "per protocol"
21 analysis does allow us to define what the treatment
22 effect is of the regimen that we're attempting to

1 research.
2 Again, "per protocol" analysis are only
3 considered supportive analyses in superiority trials.
4 However, analysis of intent-to-treat and "per protocol"
5 have equal importance when you're looking in non-
6 inferiority trials.
7 So what are the implications for renal
8 transplants randomized controlled trials? Our
9 randomized controlled trials, the gold standard for
10 transplantation today, when the control arm does not
11 even represent the standard of care.
12 The next thing is: What is the appropriate
13 control arm in renal transplant studies? As Dr. Gaston
14 has mentioned, transplantation is not the disease. And,
15 granted, some people may view this as a step forward,
16 but is our appropriate control arm potentially
17 dialysis? I know that's a little outside of the scope,
18 but really thinking about how we evaluate these
19 treatments to what the other options are for a patient
20 is important.
21 Do intention-to-treat analyses provide
22 meaningful measures of efficacy and toxicity when only

1 60 to 70 percent of the Phase 3 trials that have been
2 submitted to the FDA -- in our area actually the
3 subjects were maintained on the designed protocol.
4 Okay, that's relatively alarming when you're sitting
5 and you're looking at the ability to define really what
6 the acute rejection rates are, what the GFR is, or what
7 the toxicity profile may be.
8 Other implications in renal transplant trials
9 include, how can innovative data analysis options be
10 explored as an alternative to the rigid data analysis
11 strategies that will actually still meet the regulatory
12 standards that the FDA is under for data analysis?
13 I certainly can't answer these questions, but
14 I hope that many of the statisticians in the room may
15 be able to provide us some insight in regards to this.
16 Also, how can innovative trial designs and
17 enriched populations be explored without limiting the
18 indication of a drug label or further compound the
19 problems of off-label treatment and subsequent
20 reimbursement? So, for example, if we were to start a
21 transplant study at, say, 1 year post-transplant, and
22 you basically stated that only 20 to 40 percent of the

1 patients have the endpoint that would allow us to put
2 the patient in that trial, do we have the N to actually
3 show the power that we need to do the study?
4 The second thing is we all agree that we want
5 to do longer clinical trials. However, I want to pose
6 to you that longer clinical trials do not necessarily
7 have to be done with the same intensity of trial design
8 as we are used to in maybe Phase 2 trials or the 1-year
9 post- transplant trials, and we'll talk about some of
10 those things later.
11 As we begin to talk about enriched patient
12 populations, I think that that's a very novel concept
13 and it's something that we should do, but, however, I
14 think that as clinicians, we must understand that when
15 we do these trials in enriched patient populations,
16 we're basically going to narrow the indication or the
17 label that the drug company is going to be able to
18 receive, and that's been all fine and good historically
19 in transplantation, but the things that are changing
20 today is as we've moved further and further to off-
21 label treatment, we are being exposed to regulatory
22 risk and we're also exposing ourselves to subsequent

1 reimbursement issues as we begin to use more and more
2 drugs off-label.
3 What was briefly discussed yesterday, too,
4 are the PROs, patient-reported outcomes, studies to
5 target drug development pathways for agents with
6 different toxicity profiles. I think that as we begin
7 to individualize and personalize immunosuppressive
8 regimens, that we are giving our patients -- we are
9 really beginning to differentiate them in the context
10 of the toxicity profiles they obtain.
11 Now, if we do have a positive patient-
12 reported outcome that we can include in the label for a
13 drug, does that really impact the indication or the
14 reasons that we use the drug? I think it's yet to be
15 determined, but hopefully we'll be getting more
16 information on that in the future in terms of really
17 how the patient-reported outcomes may actually drive
18 what the clinicians prescribe.
19 I think another important thing to discuss in
20 the context of some of the other things we've been
21 discussing is conversion trials, in terms of enrollment
22 and long-term follow-up have been relatively

1 unsuccessful because a lot of times the patients and
2 the clinicians feel like everything is fine, just as
3 you say, because the GFR is, quote/unquote, acceptable,
4 and most of the times the clinicians and the patients
5 are averse to change, you know, "If it's not broke,
6 let's not fix it." I think that it's going to really
7 require a change in the way of all of us look at this
8 situation and see that as we've talked about a lot, the
9 eGFR at 1 year does not necessarily always mean that
10 everything is okay.
11 So non-adherence, I personally think that
12 non- adherence is the white elephant that's been in the
13 room today. Addressing the issue of non-adherence is
14 not sexy, it's not going to allow us to give this new
15 innovative drug that we're going to make a lot of money
16 on, it's not going to be a quick test that we can get a
17 lot of NIH funding to support our studies for; however,
18 it, in my opinion, may be one of the ways that we can
19 most single-handedly impact the long-term graft
20 survival that we have in transplantation.
21 It's estimated that up to 67 percent of
22 kidney transplant recipients do not take their

1 medications as prescribed, and I think that we all know
2 how you define that compliance rate, or the definitions
3 of compliance impacts the percentage of compliant
4 patients that you report.
5 The rate of non-adherence is highest among
6 kidney transplant recipients compared to all other
7 types of organ transplants that have been reviewed. The
8 reasons for non-adherence are multifactorial, as we all
9 know, but the research does prove that adherence
10 decreases over time. All right? The adherence to a
11 prescribed medication regimen decreases over time. I
12 challenge you that if I were to throw Dr. Rush's slide
13 that he presented yesterday that looked at the gradual
14 increase of DSAs over time, or maybe if I were to put
15 the decline in slope of GFR over time, I could almost
16 overlay that with non-adherence that we're dealing with
17 the patient population that we're reviewing.
18 Also, non-adherence is our inability to show
19 a significant effect in long-term outcomes and part a
20 reflection of non-adherence. Again, is DSA monitoring
21 a predictor of non-adherence? I think a lot of us
22 agree with that. However, can health care providers

1 recoup the costs that are associated with medication
2 adherence improvement strategies? It's a lot easier to
3 order an FK level or order a new drug or order a test
4 than it is to spend 5 to 10 to 15 minutes talking about
5 a patient about non-adherence when they come into the
6 clinic, et cetera.
7 And some of the frustrations in us doing this
8 is our concern is, can we really impact the outcome?
9 Despite how much we talk about it, can we
10 really improve the adherence with a medication regimen?
11 And I think that we would be naive to say
12 that the financial and industry developments are not
13 driving the development of transplantation, so it begs
14 to ask the question: How can industry be incentivized
15 to develop tools that actually improve patient
16 adherence?
17 So what about a change in paradigm as we look
18 at transplant trials? We can always start from scratch
19 and try to come up with this perfect way on our own,
20 but I think that it's going to require a lot of
21 agreement around a lot of different people at the
22 table, and it's going to take a while. Or we could

1 look at other groups and see what have succeeded and
2 what have failed in their attempts to improve the
3 ongoing clinical research in their specialties.
4 So the American Society of Clinical Oncology
5 developed what they called a Blueprint for Transforming
6 Clinical and Translational Cancer Research. Their
7 goals were to prioritize trials with greatest potential
8 benefit for patients, address unmet needs, shift away
9 from trials promising only marginal improvements. Their
10 goal was also to develop shared standards for flexible
11 trial design to focus on trials with smaller numbers of
12 patients and also select a trial participant based upon
13 molecular characteristics.
14 So how did they do this? They are in the
15 process of creating expert working groups which include
16 patient advocates, industry, investigators, insurers,
17 the FDA, and the NIH to develop consensus to define
18 what a meaningful patient outcome is. And again, going
19 back to the net present value, I think that we've used
20 it as a joke as it relates to industry and what the net
21 present value is with industry, but in reality, every
22 single one of us has defined our own net present value,

1 and what the importance is to the things that we're
2 doing. And it's important to understand if we are
3 going to attempt to come and put these working groups
4 and these consensuses together, that we have to
5 understand the value for each of the individual
6 contributors.
7 Also, this group has major proposals in terms
8 of streamlining the regulatory processes. Again, I
9 don't know exactly what the FDA limitations are, but I
10 do think that it begs to question how we can improve
11 and streamline the regulatory process within
12 transplantation. There are changes in the regulatory
13 process that are happening in other disciplines and in
14 other areas. I do think we need to step back from our
15 own little cocoon for one second and see what is
16 happening in other areas so that we can really question
17 the dogma of the things that we've continued to do just
18 because we've always done it that way.
19 Also, working with the FDA and industry to
20 streamline data reporting and building a safety data
21 that already exists for treatments from a variety of
22 randomized controlled trials conducted in transplant.

1 Again, maybe this would require a control group that
2 that would not necessarily have to be repeated in a
3 future trial.
4 Also streamlining the logistical process to
5 focus on data collection that is directly relevant to
6 clinical decision-making. I propose to you that we
7 spend over 50 percent of our time doing a clinical
8 trial, collecting data, and verifying data that nobody
9 in this room will ever look at or ever see. We collect
10 all the con-meds, we collect the exact start date, the
11 exact stop date, we collect all the lab values, not
12 necessarily the lab values at the time points of the
13 study, but any lab value that happened to occur within
14 the year post- transplant that is abnormal and totally
15 irrelevant to the actual endpoints that we're looking
16 at. However, we spend a lot of resources collecting
17 this data that is totally irrelevant.
18 Again, I'm not saying that we should
19 disregard any safety signals that we would see from
20 this, but I think we need to go back to the table and
21 reassess the resources that we are putting into this
22 strategies and try to allocate those resources to one

1 of the end goals that we want to achieve.
2 And also I think it is very important to
3 encourage and train transplant health care providers to
4 conduct clinical research as an integral part or
5 component of patient care with a particular focus on
6 team-oriented research, and I actually want to offer to
7 you is just because a person has been a PI on a
8 clinical trial does not make them trained to do
9 clinical research and understand everything that goes
10 along with it. And if we, as a group of transplanters,
11 would improve our understanding of how to conduct
12 clinical research and what industry is looking for and
13 understand the value components that everybody is
14 bringing to the table, we may be able to facilitate the
15 process.
16 Now, what are the challenges? Can
17 transplantation learn from oncology and begin
18 incremental steps toward innovation in clinical
19 research? I want to think that we can. I personally
20 think that study in oncology they have been using
21 Bayesian design methods to decrease the sample size and
22 target on the specific appropriate dose of these new

1 agents for a while now, and they've had a lot of
2 success with that. I think that, especially in the
3 field of transplantation as it relates to delayed graft
4 function, that is a perfect, perfect model of which we
5 could incorporate Bayesian design, to decrease the time
6 that it costs to do the study and decrease the exposure
7 of the patients to an ineffective drug regimen that's
8 not going to have the result that we need.
9 When we have approached these things before,
10 some of the comments are, "We've never had a Bayesian
11 design study in transplant before." I don't understand
12 why we can't. And there are some mechanisms of success
13 that we should look at to see if it would be proper to
14 implement that within our regulatory realms.
15 Also, the challenges are to implement
16 personalized medicine in transplantation. To do that,
17 the therapies must have three of these following
18 criteria: treatment options with heterogeneous
19 responses, clinical biomarkers, and differing
20 biological mechanisms. I have to say that I don't
21 believe that we're as far along as oncology in terms of
22 defining differing biological mechanisms for some of

1 the endpoints that we are looking at. Certainly, we
2 don't have the receptors, per se, to measure that can
3 direct treatment to very specific types of cancers with
4 certain receptors. However, it is important for us to
5 understand what will allow us in the future to
6 implement some of these personalized medicine
7 strategies that will allow us to focus in on the
8 patient that is going to do poorly in the future.
9 And then last, development of comparative
10 effectiveness research to improve the value of
11 transplantation is going to be huge. I think that
12 improving the value of transplantation, not only to the
13 drug companies but to society, is something that we
14 need to address, and we need to open our eyes to some
15 of the other research strategy that may allow us to
16 provide this value in the future.
17 Thank you very much.
18 (Applause.)
19 DR. STEGALL: Thank you. Our next speaker is
20 going to be George Burke, who is going to talk about
21 metabolic complications as new ways to consider
22 efficacy and safety endpoints.

1

2 Topic #2: Metabolic Complications George W. Burke III,

3 MD

4 DR. BURKE: Well, for starters, I would like

5 to thank the FDA and the organizers of this meeting for

6 allowing me the opportunity to speak.

7 So I was asked to speak about the metabolic

8 complications of kidney transplantation. So these are

9 something that everybody in this audience is familiar

10 with. So starting with dysregulated glycemic control,

11 so that's anywhere from in here, glucose control to

12 Type 2 diabetes. And secondly, hyperlipidemia.

13 Thirdly, hypertension. Fourth, obesity. And finally

14 metabolic syndrome.

15 So now I'm halfway through my talk.

16 (Laughter.)

17 DR. BURKE: I'll try to catch up.

18 So I said this yesterday. None of these

19 conflicts should interfere with my presentation.

20 This was the first slide I just gave.

21 So risk factors for new onset diabetes after

22 kidney transplant, which is sometimes referred to as

1 NODAT, include those that are fixed, so increased age,
2 race, ethnicity, which is higher in African Americans
3 and Hispanics, the question of whether gender and male
4 is more likely to be associated than females, still not
5 entirely clear, and family history of diabetes also not
6 entirely clear. Then which of these might be
7 modifiable? Well, there are a number. So there is the
8 issue of physical activity, lifestyle modification,
9 diet, the change in kidney function, reduced GFR over
10 time, which was discussed at length this morning,
11 inflammation or different molecules that may lead to
12 inflammation, proteinuria, immunosuppression, acute
13 rejection or not, various antihypertensive agents, and
14 even dyslipidemia.
15 So diabetes post-transplant is associated
16 with increased age, is associated with insulin
17 resistance as well as diabetes mellitus with insulin
18 dependence. It's associated with increased weight. And
19 diabetes post- kidney transplant is associated with
20 reduced patient and kidney allograft survival, and this
21 is actually a very key issue because all of these
22 metabolic complications can be associated with reduced

1 kidney allograft survival, and the bottom line is that
2 kidney allograft survival is the driver here. The
3 metabolic complications are important but it's your
4 kidney survival and your kidney function that are the
5 major impact on your longevity.
6 So the screening for new onset diabetes is
7 clear and has been supplied for us by the KDOQI people
8 and so it includes looking a weekly hemoglobin A1c,
9 oral glucose tolerance test, hemoglobin A1c every 3
10 months for a year and annually thereafter, and then if
11 there is any change in immunosuppression -- so, for
12 example, increase in CNIs, mTORs, or corticosteroids --
13 then it's important to also continue to look for NODAT.
14 Secondly is dyslipidemia, and one of the
15 landmark trials was the ALERT trial in 2003 and 2005
16 update. And this was fluvastatin versus placebo, which
17 was noted to be associated with reduction in both total
18 and LDL cholesterol, reduction in risk of
19 cardiovascular disease, reduction in cardiac death,
20 reduction in non- fatal MI, and negligible clinically
21 significant Rhabdo.
22 Importantly, along with the ALERT trial was a

1 spin-off that again emphasized the issue of kidney
2 function and the importance of renal dysfunction or
3 allograft loss, which is a strong and independent risk
4 factor for mortality and cardiovascular complications
5 following kidney transplantation. And I also mention
6 this because this concept again was just recently
7 updated in the FAVORITE trial that just came out in the
8 most recent AJT, and that is in stable kidney
9 transplant recipients, lower eGFR, and particularly
10 less than 45, is independently associated with adverse
11 events suggesting that reduced kidney function itself,
12 rather than previous comorbidity, may lead to
13 cardiovascular disease.
14 And the definitions and the therapies for
15 dyslipidemia are all present in AJT 2009, and you can
16 refer to that.
17 Thirdly is hypertension, and quite simply,
18 two of the landmark papers from Opelz. First,
19 hypertension or poorly controlled hypertension
20 contributes to graft loss. And then just as
21 importantly, or more importantly, better control is
22 associated with better results. And hypertension is

1 generally regarded as systolic pressure over 140,
2 diastolic over 90, and the targets are less than 130
3 over 80. And again the same guidelines are put forth
4 by KDOQI.
5 So the next issue is obesity, and obesity or
6 weight gain pre-transplant, a BMI over 30 is associated
7 with an increased risk of diabetes, hypertension,
8 cardiovascular disease, increased graft loss, and
9 increased cardiovascular disease.
10 Post-transplant, weight gain is common,
11 particularly in woman, African Americans, those with
12 low income and/or low education, and it's associated
13 with increased surgical wound infections. Importantly,
14 there is a benefit of exercise or behavior
15 modification. And the KDOQI suggestions are to measure
16 height and weight with each visit, calculate BMI, and
17 measure waist circumference and to offer a weight
18 reduction program.
19 Now, for immunosuppression, the calcineurin
20 inhibitors are well known to have nephrotoxicity and
21 neurotoxicity, but from a metabolic standpoint,
22 tacrolimus is associated with insulin resistance and

1 new onset diabetes and dyslipidemia. Cyclosporine has
2 been associated with increased hypertension and
3 increased dyslipidemia. Rapamycin well known to
4 increase dyslipidemia or make that worse and is
5 associated with insulin resistance in new onset
6 diabetes as well as proteinuria.
7 Steroids are associated with everything:
8 hypertension, dyslipidemia, dysregulated
9 glucose metabolism, and increased weight and appetite.
10 Perhaps a benefit is that there is reduced risk of
11 acute rejection with steroids.
12 And so I thought I would take advantage of
13 this opportunity to show a demonstration of insulin
14 resistance related to rapamycin. So this is coming out
15 of one of our group's papers that's a 10-year
16 randomized prospective trial comparing rapa to MMF in
17 the context of low-dose tacrolimus and steroids, and
18 over the course of 10 years, there is no difference, P
19 value of .62 in levels of C-peptide.
20 Now, when we look at hemoglobin A1c, there is
21 a striking difference throughout the entire study, the
22 entire 10-year course. So the hemoglobin A1c in the

1 patients treated with CellCept is always better than
2 patients on rapa despite the fact that C-peptide,
3 fasting C-peptide, levels are the same throughout the
4 study. So this is one of the better demonstrations of
5 insulin resistance associated with rapa. But one other
6 point is that these both are normal hemoglobin A1c's,
7 so despite the use of rapa and the issue of insulin
8 resistance, they still have normal hemoglobin A1c's.
9 And along a similar note, looking at total
10 cholesterol and comparing rapa versus MMF over a 10-
11 year period, the levels of total cholesterol are lower,
12 the area under the curve is less, than with MMF versus
13 rapa. However, the values are still normal throughout
14 the course, and similarly for triglycerides, a similar
15 story, where the area under the curve for MMF, or
16 levels of triglycerides with MMF are lower throughout
17 the time course than they are with rapa, but still they
18 were all within normal limits.
19 So the last is the metabolic syndrome, which
20 is, as you know, a combination of all the above, and
21 there are a number of different ways to define it, but
22 basically they all include some element of central

1 obesity measured in different ways, either by waist
2 circumference or other means; hypertension, and
3 generally according to the same guidelines that we've
4 just discussed; glucose dysregulation, and there are
5 slight differences among definitions of what is glucose
6 dysregulation; and then dyslipidemia, generally HDL
7 less than 40 in men, less than 50 in women, and
8 triglycerides greater than 150.
9 And so what's the problem with metabolic
10 syndrome? Well, for the general population, there is
11 an increased risk of overt diabetes and cardiovascular
12 disease as well as proteinuria and reduced GFR. The
13 prevalence of the metabolic syndrome before and after
14 kidney transplantation, in the U.S., almost 60 percent
15 of kidney transplant recipients have the metabolic
16 syndrome pre-transplant, and of these 31 percent,
17 develop new onset diabetes within 1 year of kidney
18 transplant. So patients with metabolic syndrome and
19 low HDL are more likely to develop NODAT, and NODAT is
20 ultimately going to be associated with reduced
21 allograft survival, et cetera.
22 Now, in Europe, they're a little bit thinner,

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1 32 percent of kidney transplant recipients with stable
2 renal function at 1 year have the metabolic syndrome,
3 although this increased by 38 percent as they became
4 more American-like by 18 months and had an adverse
5 effect on allograft survival; again, the issue of
6 decreasing allograft survival, which ultimately has to
7 be the driver, your kidney transplant has to work.
8 And then 32 percent of kidney transplant
9 recipients with metabolic syndrome at 1 year after
10 kidney transplantation, and again worse outcome with
11 increased risk of atherosclerotic events.
12 And then finally now we're up to American
13 standards, 63 percent of kidney transplant recipients -
14 - increasing numbers in each one of these studies --
15 with the metabolic syndrome by an median of 6 years
16 post- transplant, and again this is associated with
17 impaired kidney transplant function beyond 1 year post-
18 kidney transplantation.
19 So the next three slides are the same
20 pattern. These are overall kidney transplant patient
21 results, and this is the percentage of freedom from
22 NODAT. And so in patients with the metabolic syndrome

1 identified at 12 months, they are much less likely to
2 be free from NODAT or much more likely to have diabetes
3 post-transplant.
4 In a similar fashion, those patients with
5 metabolic syndrome identified at 12 months, 1 year,
6 post- transplant are more likely to have coronary heart
7 disease. And then finally, as the theme that has been
8 alluded to for most of this talk, those patients with
9 the metabolic syndrome at a year are much more likely
10 to have loss of allograft survival.
11 So there are five things that we can do about
12 this in addition to maintaining kidney transplant
13 function. We can push for therapeutic lifestyle
14 changes with diet and exercise. We can do something to
15 impact the glycemic control. We can do something to
16 impact the level of hypertension, restoring it to
17 normalcy. We can impact the dyslipidemia. And we can
18 do something about the hypercoagulable state that many
19 of these patients have with some form of
20 anticoagulation.
21 And I just thought I would bring this home
22 with an example of a patient and the effect of diet,

1 exercise, and medications on metabolic complications
2 after kidney transplantation. And the story is a
3 patient who is a 60- year-old Caucasian diagnosed with
4 Type 1 diabetes at the age of 31, C-peptide of less
5 than .1 nanogram per mL, peritoneal dialysis starting
6 April 1999, cardiac history with stents the same year,
7 poor exercise tolerance, and he weighed 215 pounds, and
8 he had a kidney-pancreas transplant in 2001.
9 So now in 2012, here are his labs. So his
10 hematocrit is 41, so that tells you his kidney is
11 probably working pretty well. In addition, his BUN and
12 creatinine are in a nice range and very stable.
13 Hemoglobin A1c of 5.4 with a C-peptide fasting of 2.1.
14 The lipid profile is really extraordinary:
15 total cholesterol 100, triglycerides 43, HDL
16 77, and an LDL of 14. This is not a misprint, he's
17 been gradually heading down towards 14. I have been
18 discussing this with our endocrinologist to look at, is
19 there a downside to an LDL that's less than 100 or 70
20 or I'm told 30 by our endocrinologist? But if there is
21 no evidence of Vitamin E deficiency, then nobody is
22 sure if this is a good thing or a bad thing, but it

1 certainly is an interesting thing. Serum albumin of
2 4.2. Vital signs include a weight of 174, so he's down
3 40 pounds over 10 years. That almost never happens in
4 America, maybe in Europe, but not here. Blood pressure
5 is normal, 130 over 80. Heart rate of 55.
6 Now, this is due to a number of different
7 things. He's on Prograf, CellCept, good doses,
8 prednisone 5 milligrams, he's on Toprol, Vytorin,
9 Bactrim, Plavix, and Pepcid. And he exercises five
10 times a week, and he is extremely attentive to his
11 diet, and this is what he looks like. So a 60-year-old
12 who used to weigh 215 pounds, had cardiac intervention,
13 and would certainly have died given the statistics of
14 this kind of patient on dialysis, but this is also what
15 can happen if somebody is motivated enough to exercise
16 and diet and overcome the various metabolic issues that
17 we know are associated with the meds but can in fact be
18 overcome with meds without necessarily changing or
19 adapting the medications that we know will allow long-
20 term graft function.
21 So thank you very much.
22 (Applause.)

1 DR. PLOEG: Thank you very much. The next
2 talk will be given by Alan Jardine, from University of
3 Glasgow, with the title of "Redefining Renal
4 Transplantation: Cardiovascular
5 Complications." Alan.
6
7 Topic #3: Redefining Renal Transplantation:
8 Cardiovascular Complications Alan G. Jardine, BSc,
9 MBChB, MD, FRCP
10 DR. JARDINE: Thank you very much. It is a
11 privilege to have been involved in this meeting, I
12 think for myself and also on behalf of ESOT. So those
13 of you who have been to Glasgow will recognize a
14 Photoshop sky.
15 (Laughter.)
16 DR. JARDINE: I have been slightly
17 apprehensive about listing my conflicts of interest
18 because there have been so many saintly people who have
19 none of them. I was reminded of Mark Pescovitz, who
20 used to start these talks with saying, "If your name is
21 not on that list, can you see me afterwards?"
22 (Laughter.)

1 DR. JARDINE: So I'm not going to use all the
2 slides that are in the slide deck, you'll be pleased to
3 hear, just a few. And I'm going to concentrate really
4 following on nicely from George's talk on
5 cardiovascular disease in transplant recipients.
6 So if there is one truism, it is that the
7 most effective way to prevent cardiovascular disease in
8 dialysis patients is to transplant them, but despite
9 that, they still have a very high incidence of
10 cardiovascular complications. It's worse immediately
11 after transplantation, and it settles down, but the
12 cardiovascular mortality rate is around 2 to 3 percent
13 per annum thereafter.
14 In the ALERT trial that's been alluded to, we
15 started off looking at cardiovascular disease. It
16 accounts for approximately half of the all-cause
17 mortality in transplant recipients, but it's not just
18 as simple as you might think, it's not all coronary
19 disease. And the study that's also been shown earlier,
20 the FAVORITE study, broke down the events, and you can
21 see this is quite different from the ALERT study
22 because things have changed over the last 15 years, but

1 when you look at cardiovascular events following
2 transplantation, myocardial infarction makes up part of
3 it, cardiac death is at least an equal proportion, and
4 then there is coronary interventions, which
5 increasingly is an endpoint and an event which we
6 accumulate.
7 So what are the risk factors for
8 cardiovascular disease in transplant recipients? You'll
9 have seen this slide often. This is Bert Kasiske's
10 study that has rolled on over the years, and when he
11 first started looking for cardiovascular markers in
12 transplant recipients, it was remarkably difficult to
13 find any of the conventional ones. In the ALERT study
14 where we had independently validated events, we were
15 able to look at the risk factors for myocardial
16 infarction independently of those for cardiac death.
17 And I show this slide because it illustrates that when
18 you look for independent factors for myocardial
19 infarction, it includes preexisting coronary disease,
20 LDL cholesterol and, indeed, the other cholesterol
21 subfractions, cigarette smoking, diabetes, and age.
22 But when you look at cardiac death, sudden cardiac

1 death, presumed arrhythmic or due to intractable heart
2 failure, then there are a whole lot of other risk
3 factors, and the LDL nor any of the other lipid
4 subfractions didn't reach statistical significance, but
5 blood pressure, pulse pressure, left ventricular
6 hypertrophy, and left ventricular strain on an ECG are
7 markers.
8 So there are two types of cardiac death; the
9 FAVORITE study has confirmed this -- sorry, of cardiac
10 event or coronary events, and there is cardiac death
11 that's probably driven by left ventricular structural
12 changes, mostly a consequence of time spent on
13 dialysis.
14 So the FAVORITE study analyzed the
15 cardiovascular risk in the post hoc analysis that's in
16 this month's AJT and showed, just as we have, that
17 blood pressure is important. LDL cholesterol wasn't a
18 statistically significant factor, and that may reflect
19 the fact that myocardial infarction, which is dependant
20 on cholesterol, was a lesser component of the composite
21 endpoint or that the patients were on statins that had
22 reversed this element of the composite cardiac

1 endpoint. And, in fact, lumping together a composite --
2 and there is probably a lesson for transplantation here
3 -- is only a useful thing if all the components of the
4 composite are driven by the same kind of pathogenic
5 mechanism.
6 And then you've seen these data shown in
7 another way. One of the major problems with
8 cardiovascular disease in transplantation is that most
9 of the drugs we use alter conventional and proven
10 cardiovascular risk factors. So a transplant may
11 improve cardiac risk, but it interferes with a whole
12 lot of cardiovascular risk factors, and the drugs,
13 until belatacept came along anyway, the drugs that we
14 had that had neutral effects weren't utilizable on
15 their own.
16 So just a couple of slides on lipids. Again,
17 George has shown you some slides on lipids. This is a
18 study that I was involved in many years ago where
19 patients were given cyclosporine, azathioprine, or MMF
20 and steroids, and it shows what we were all aware of,
21 which is that immediately after transplantation, LDL
22 cholesterol goes up by about 1 millimole per liter, but

1 40 milligrams per deciliter, and the same is true for
2 all cholesterol subfractions, including triglyceride.
3 It's probably largely driven by steroids.
4 And when you look at the influence of
5 elevated cholesterol on cardiac endpoints, this is a
6 mixture of individual cardiac endpoints from the ALERT
7 trial. The dotted line here in purple is myocardial
8 infarction, and myocardial infarction is dependent on
9 cholesterol-driven coronary disease and is the major
10 endpoint that's dependent on lipids.
11 If we look at hypertension, this is from the
12 Opelz study, is associated with cardiovascular disease
13 death. So this is blood pressure years out from
14 transplantation, and even within the normal range,
15 there is an impact of hypertension on cardiovascular
16 events. And Opelz has done this kind of analysis for
17 all sorts of endpoints. Blood pressure at 1 year is
18 associated with graft outcome, it's not a completely
19 independent effect, it's clearly dependent on graft
20 dysfunction.
21 Again, in the ALERT study, when we looked at
22 the impact of blood pressure, then this yellow dotted

1 line here is the thing that is most dependent on blood
2 pressure, and this is stroke. And along the bottom
3 here, the purple dotted line, which is myocardial
4 infarction, high blood pressure has very little effect
5 on that. So there are two types of cardiovascular
6 endpoints: the lipid-driven coronary events,
7 myocardial infarction; and there are events like stroke
8 and cardiac death are more driven by blood pressure and
9 structural changes to the heart.
10 If we look at graft function and its impact
11 on cardiovascular events, this is from Meier-Kriesche
12 showing that the higher serum creatinine at 1 year, the
13 smaller the number of patients who remain free of
14 cardiovascular events. So whereas there has been
15 debate earlier on about the impact of serum creatinine
16 on long- term graft function, it does seem to have an
17 effect on cardiovascular events which, in the overall
18 scale of things, is something that's probably
19 worthwhile preventing.
20 And again when we looked in the ALERT study
21 at serum creatinine, what component of the
22 cardiovascular disease that these patients get was

1 dependent on serum creatinine, it wasn't myocardial
2 infarction or stroke, but it was more cardiac death. So
3 different risk factors are more associated with
4 different cardiovascular endpoints. And, again, the
5 post hoc analysis of the FAVORITE study has shown the
6 same thing. When you look at the impact of GFR here,
7 the greatest effect is on cardiac death rather than
8 myocardial infarction.
9 Dr. Burke talked about new onset diabetes
10 after transplantation. We used to think of it as a
11 nuisance, but now we know that it's associated with
12 mortality and also with cardiovascular events. So this
13 is a study from Joran Hjelmesaeth in Norway, a small
14 study, but these data have been confirmed by other
15 groups, including Bert Kasiske, showing that diabetes,
16 at least as a discrete entity, probably has the
17 greatest effect on cardiovascular endpoints of any of
18 the conventional risk factors.
19 So the drugs we use interfere with
20 cardiovascular risk factors; cardiovascular risk
21 factors are associated with adverse outcomes after
22 transplantation. It seems a difficult to reconcile. So

1 how have we done with it over the years or how are we
2 doing? And the answer is that we are doing much better
3 than you might have expected. In the same way that the
4 composite endpoint for transplantation we've used is
5 imperfect, and yet we seem to have made things better,
6 when it comes to cardiovascular disease.
7 These are data from Helen Pilmore and the ANZ
8 data, the Australia and New Zealand's registry, as you
9 go along across the eras here from 1980 to 2006, the
10 cardiovascular mortality rate is falling, malignancy
11 isn't, infection is, and overall, outcomes are
12 improving, but the greatest effect has been in
13 cardiovascular disease.
14 And this just shows cardiovascular disease
15 death rates per 100 patient-years and time from
16 transplantation again showing that each of these
17 points, if you look at individual eras, the outcomes
18 are improving, and they're improving for each of the
19 age groups that she looked at.
20 And how are we doing this? Well, again, this
21 in now from the PORT study and Helen Pilmore again,
22 it's probably because where long-term grafts or early

1 graft outcomes at least are improving, we are using
2 immunosuppressive agents more efficiently perhaps, but
3 we're also adding in all sorts of cardiovascular risk
4 medications. These are statins, beta blockers,
5 angiotensin blockers, et cetera. And the rates of
6 these have gone up following transplantation. You
7 still see that less than half the patients got statins
8 despite the fact that we know they have some effect.
9 And again she looked at eras and the use of
10 these agents and with different eras, the use of
11 individual cardiovascular risk medications are going
12 up.
13 One of the frustrations, if you like -- we
14 know that cardiovascular disease is important, we know
15 it's important for transplant recipients, and in fact
16 it's a major complication of transplantation -- one of
17 the frustrations is that we don't really record it well
18 in trials. This is the SYMPHONY study, which, as you
19 know, is probably the single trial that has had the
20 biggest effect on day-to-day management of transplant
21 patients, at least in Europe, but when you go looking
22 for the cardiovascular events, they're down in Table 4

1 and the safety endpoints, and they're reported by
2 investigators, they are not quantified or characterized
3 in any particular way.
4 So a clearer reporting of cardiovascular
5 complications would be a useful thing, I think.
6 Can we predict them? And one of the things
7 that we've been doing recently is to try and use
8 cardiovascular risk data to produce a calculator. We
9 know that the Framingham calculator is not particularly
10 good for transplant patients or for dialysis patients
11 or, indeed, for other renal groups, so we used the data
12 we had in the ALERT study to create a calculator. This
13 is Inga Soveri, who has done the modeling for this, and
14 the parameters that we identified that we put into the
15 model were age, preexisting disease, smoking status,
16 renal function, diabetes, LDL cholesterol, and a number
17 of transplants. And using this, we found that we were
18 able to predict the observed MACE, major adverse
19 cardiac event, rate, and we did this by using two-
20 thirds of the ALERT study to derive the model, and then
21 testing out in the other third. We've gone on to test
22 out on the PORT dataset and also to use it to try and

1 predict the long- term or the potential long-term
2 benefits of patients treated with belatacept in the
3 BENEFIT and BENEFIT- EXTENDED studies. So this shows
4 the validation against the PORT dataset, and this shows
5 the predicted 7-year cardiovascular event rates and the
6 BENEFIT and BENEFIT- EXTENDED patient datasets. And
7 the red bars here are what we would predict for the
8 cyclosporine-treated control group. And the green bar
9 is what we would predict for the belatacept-treated
10 patients. It remains to be seen whether that pans out
11 in real life. And this isn't published yet, although
12 it has had very favorable reviews and is in the
13 process.
14 And then finally -- this is my last slide --
15 and I thought my naive approach to this has been the
16 endpoints that we use for trials have become less
17 frequent, and one of the problems we have is that we
18 don't have enough rejections, graft losses, and deaths,
19 we need huge datasets or huge study sizes. So why
20 don't we add in other things?
21 So in our own dataset in Glasgow, I added in
22 the cardiovascular events. So I took the patient

1 population here with the standard FDA endpoint of acute
2 rejection, graft loss death, and loss to follow-up, in
3 two patient groups divided by the number of transplants
4 they had had prior to getting the transplant, the index
5 transplant, and then I added cardiovascular events, and
6 certainly there are more events when you add
7 cardiovascular events than there are in patients who
8 are having graft loss and cardiovascular events, so
9 from my naive viewpoint, adding these in will at least
10 give you more numbers to play with statistically.
11 So to conclude, cardiovascular disease is
12 common following transplantation. I think we have a
13 much better understanding of the risk factor event
14 relationships than we did when Bert Kasiske started out
15 in the early 1990s. There are two types of major
16 cardiovascular complications and they have different
17 determinants.
18 When it comes to trial design and how we
19 might incorporate these endpoints, I think, at the very
20 least, we need improved reporting of cardiovascular
21 events. We could perhaps use the risk factors that
22 were recorded in clinical trials to predict long-term

1 cardiovascular outcomes. And, finally, I think it's
2 worth considering anyway the inclusion of
3 cardiovascular events in a composite endpoint.
4 Thank you very much.
5 (Applause.)
6 DR. SALOMON: All right. The last talk of
7 the morning will be from Camille Kotton on "Infectious
8 Disease Complications" to be considered as efficacy
9 safety endpoints.
10
11 Topic #4: Infectious Disease Complication Camille N.
12 Kotton, MD
13 DR. KOTTON: Good morning. I would like to
14 thank the FDA for inviting me to talk. I'm the only
15 infectious disease specialist here today.
16 My disclosures are the same as yesterday.
17 Unfortunately, my spouse has no significant financial
18 disclosures, but I wish he would work on that.
19 (Laughter.)
20 DR. KOTTON: So I will talk briefly about the
21 scope of infectious disease in transplant.
22 Unfortunately, it's really never a primary endpoint in

1 trials, so it is kind of a common wrinkle and something
2 to think about, but usually not an endpoint.
3 I'm a big advocate for better screening for
4 infection both in the pre-transplant period, which I
5 think is a really important opportunity, and also after
6 transplant. And then I think there are a lot of ways
7 in which we have really improved safety in the past
8 decade especially, including with the use of
9 guidelines.
10 So I think you're all familiar with the
11 timeline of infectious disease after transplant. This
12 was nicely summarized initially by Bob Rubin and Jay
13 Fishman in the original New England Journal paper in
14 the '90s and subsequently in 2007. We know that in the
15 first month it's usually donor-derived or nosocomial
16 infection, and then in the first 1 to 6 months after
17 transplant, we think a lot more about the opportunistic
18 infections. The biggest -- and this is usually a long
19 laundry list of infection, as we know, which makes
20 things like clinical trials difficult in some ways, but
21 one thing we do know is that appropriate use of
22 prophylaxis, including Pneumocystis, which includes

1 often antibacterial coverage and toxo coverage as well
2 as antiviral prophylaxis, really can change outcomes,
3 and I think that that's been something that we've
4 learned and really many institutions have implemented,
5 and I would encourage it to be part of clinical studies
6 as well. Usually more than 6 months out we tend to
7 think about the more routine infections.
8 The sources of infection can be tricky in
9 that they can come from the recipient, including
10 reactivation and colonization. They can also come from
11 the donor, and that's an area that's been really
12 increased in the past 5 years, including all the
13 efforts by DTAC from UNOS. Nosocomial infection occurs,
14 and then de novo infections, emerging infections, and
15 the advent of novel or geographic infections as well.
16 Probably one of the more recent trials that
17 defined the infectious risk particularly well was the
18 belatacept trials. So attention was paid to infectious
19 disease risk due to unanticipated infectious outcomes,
20 and they looked at the three main studies, including
21 the Phase 2 study as well as the two BENEFIT trials.
22 And they looked at the more intensive and less

1 intensive belatacept dosing along with cyclosporine
2 controls, and in these trials all patients received at
3 least 3 months of CMV prophylaxis, and I think, as
4 almost everybody here knows, they saw significantly
5 higher rates in the EBV seronegative recipients,
6 especially in the higher dose belatacept at 11.6
7 percent versus 4 percent in the lower dose, and then
8 1.8 percent in the cyclosporine arm.
9 The nice thing about this trial is that they
10 really had to focus on infectious disease, and so it
11 was really well defined as far as the overall risk of
12 all infections, including serious infections, CMV,
13 polyoma, herpes, and tuberculosis. I would just argue
14 that perhaps somewhat in hindsight, some of these
15 infections are preventable. You know, better
16 tuberculosis screening, better screening for
17 polyomavirus, and perhaps optimization of CMV
18 prevention could really even result in lower infectious
19 disease outcomes overall.
20 And as you know, the lesser intensity regimen
21 was FDA-approved, and there is now a black box warning
22 against the use of belatacept in EBV seronegative or

1 unknown recipients. And they do recommend the use of
2 CMV prophylaxis for 3 months. And then there is a REMS
3 involved to help decrease the risk of further
4 complications.
5 Another nice example, although this isn't in
6 the transplant world, but of infectious disease having
7 an impact on immunosuppressive regimens was PML that
8 was caused by JC virus. It was seen primarily with
9 natalizumab, or Tysabri, that many of you are familiar
10 with. We also see it with rituximab, alemtuzumab,
11 efalizumab, which was withdrawn from the market, but it
12 is kind of one of the worst infectious disease
13 complications we see in immunocompromised hosts.
14 There have been 58 cases of PML since the
15 remarketing of natalizumab in June 2006 among 67,000
16 treated patients, and overall the risks seemed to
17 increase with the number of doses given. So it was
18 close to 1 in 1,000 for all exposed individuals, and
19 that increased with 12 and then over 24 infusions. So
20 really a concerning area. It was pulled off the market
21 and reput on the market due to a lot of advocacy for
22 it. And there has been a lot of interesting work done

1 trying to figure out how to mitigate the risk of
2 something that's really potentially quite devastating.
3 And unfortunately, there really aren't good predictors
4 yet that can tell us who is at risk for PML, but it is
5 sort of a word of caution, and things like that are
6 what we dread in clinical trials and then post-trial
7 obviously.
8 I'm a big advocate for pre-transplant
9 screening, and it's something that I think could be
10 incorporated a little better into clinical trials. At
11 this point, as I'm largely a clinician and I'm actually
12 seeing the majority of patients at the Massachusetts
13 General Hospital who are listed for all organ
14 transplants.
15 We do, as most of you do, routine screening.
16 We also include focused screening, and we've enhanced
17 our TB screening in recent years. We see a lot of
18 people who are born in a variety of places throughout
19 the world, and so we do a lot more screening for
20 various demographic illnesses including Chagas,
21 strongyloides, and whatnot, and we take that
22 opportunity to do better vaccine administration, which

1 I think is something that could potentially enhance
2 trials as well. That pre-transplant period is a time
3 when there may be a better immunologic response to
4 vaccination and provide better protection rather than
5 post-transplant. And it's also a time to develop good
6 regimens for chemoprophylaxis, including against
7 tuberculosis, hepatitis B, strongyloides, and others.
8 And I would just say a lot of people, it
9 depends where you live in the country and what your
10 rates of immigrants are. I talk to Shelly Morris, who
11 is in Miami, and we kind of share a lot of patients, or
12 at least the concepts of better screening of these
13 patients, it sort of depends where you live, but I
14 would just say that there are a lot of immigrants from
15 all over the world, and it's good to know who they are,
16 what their latent diseases are, and what to watch out
17 for, because every year there are deaths that really
18 could have been prevented through better screening.
19 As far as tuberculosis, we know that with the
20 TNF inhibitors, there were higher rates of TB reported
21 roughly a decade ago. And with good screening, we were
22 actually able to decrease the rates of tuberculosis,

1 and I think that that's a good take-home, so screening
2 does work and really results in overall better
3 outcomes. Similarly, for hepatitis B, we know that good
4 screening can really enhance outcomes as well.
5 Post-transplant, it's a good time to do
6 monitoring and optimize prophylaxis. I think that in
7 the modern era most programs are screening for BK, and
8 I would say that that could be included in clinical
9 trials. EBV monitoring I think is not done by all
10 institutions but something that is really worthwhile
11 considering especially in the D plus or minus or even
12 in the reverse situation where we've seen several cases
13 of PTLD in the past year. CMV monitoring is done by
14 some, although others use prophylaxis. And hepatitis B
15 monitoring as well. And then antiviral prophylaxis I
16 think is standard at many institutions and I would
17 recommend be standardized in trials as well. And then
18 anti- pneumocystis coverage usually with Bactrim, but
19 again things that really save lives and overall greatly
20 enhance outcomes.
21 And I would just say that there have been a
22 variety of guidelines that have been published in

1 recent times. There was the paper on BK and then there
2 are subsequent guidelines that sort of recommend
3 routine screening. There were the CMV guidelines that
4 came out several years ago and which are being updated
5 at a meeting this year that really I think enhanced and
6 standardized prevention of CMV and overall management.
7 There is also a new international standard
8 for CMV viral load testing that will make clinical
9 trials easier in that the diagnosis of CMV has been
10 fraught with some technical testing issues, but
11 hopefully the new international standard will help
12 smooth that out.
13 And Stan Martin had a recent paper in AJT
14 that looked at screening of EBV mismatched patients and
15 overall showed good outcomes, or better outcomes, with
16 routine screening and lower risk of complications.
17 Atul Humar and Marian Michaels, on behalf of
18 the ASTID community of practice had a nice paper in
19 2006 that could be used to help apply a standard of
20 care across clinical trials but sort of uses standard
21 definitions of infections, guidelines for laboratory
22 monitoring, and then better documentation of infectious

1 disease complications.
2 I would also say that in the AJT December
3 2009 Supplement, there were actually over 30 different
4 guideline documents published on a variety of different
5 infectious disease topics, and that's being updated
6 again this year, but that may actually help as well as
7 a reference standard for developing trials.
8 One thing I wanted to emphasize, which is
9 sort of a post-marketing issue, but I often talk about
10 infectious disease complications especially with the
11 use of the biologics, and when I ask an audience, "How
12 many people have seen infectious complications from
13 biologic agents?" most people raise their hand. And
14 then I say, "And how many of you have reported those
15 complications?" and pretty much nobody raises their
16 hand.
17 And I think that that's one of the biggest
18 issues, is we're talking now about clinical trials, but
19 I would say very few clinicians that I speak to
20 actually know about how important it is to do post-
21 marketing reporting either to the FDA or to the
22 companies. And so I think that that's a really good

1 educational point to emphasize. I would say that the
2 times that I've reported, paperwork is a real nightmare
3 and it actually doesn't encourage me to report, to be
4 honest, to report in the future, and so the question I
5 would have is, could that process be minimized? But,
6 again, as much education as possible should be given.
7 From an infectious disease perspective for
8 clinical trials, my dream would be to have more
9 screening either pre-transplant or post-transplant and
10 then to have things like prevention and prophylaxis as
11 a standard part of protocols, often guideline based,
12 and then also to be open-minded about possible
13 complications either during the course of the clinical
14 trial or after the clinical trial in the post-marketing
15 phase. And I think we've learned some good lessons
16 about EBV and PML and then Neisseria with things like
17 eculizumab.
18 But we also have to be realistic, and it's
19 hard, and in putting together this talk, I struggled a
20 bit because we all know about the higher risk things,
21 CMV and BK and whatnot, but how do we deal with so many
22 of the outliers that we see, you know, the

1 Cryptococcus, the nocardia, the atypical things, and so
2 how do we focus on the most important ones? It's
3 harder to focus on the "zebras," as we call them, or
4 the opportunistic infections.
5 And endpoints do need to be precise, and so I
6 would say pick the top most common infections for
7 clinical trials, but don't forget about the importance
8 of the other ones as well.
9 Thanks a lot for your attention.
10 (Applause.)
11 DR. PLOEG: Thank you very much, Camille. I
12 suggest that we now adjourn for an hour and get back
13 here at 10 after 1:00, and then we will take these 10
14 minutes out of the discussion time so that we can still
15 close in time. Thank you very much.
16 (Lunch recess from 12:10 p.m. to 1:15 p.m.)
17 DR. STEGALL: Okay, we're going to get
18 started. What we're going to do is we're going to have
19 four talks and then we're going to have some
20 discussion. We may have to cut the discussion short a
21 little bit to get people going.
22 DR. ALBRECHT: Quick, we have an emergency

1 announcement. If anyone in the room owns Toyota Camry,
2 North Carolina tags ZRE3770, your lights are on.
3 DR. STEGALL: I have to go.
4 (Laughter.)
5 DR. STEGALL: The keys are in it. That's
6 good.
7 So Steve Woodle is going to talk about the
8 development of malignancy as a new safety and efficacy
9 endpoint.
10
11 Topic #5 Development of Malignancy E. Steve Woodle, MD,
12 FACS
13 DR. WOODLE: Just to put malignancy as a
14 safety endpoint into perspective, it's important to
15 realize that despite the fact that that is a major risk
16 in terms of survival, the overall benefit of
17 transplantation that mainly consists of cardiovascular
18 risk reduction translates into a major improvement in
19 survival, and as sort of a corollary to some of the
20 discussions we had the other day, this data basically
21 shows what the expected remaining lifetimes are for
22 wait listed patients that stay on dialysis versus being

1 transplanted. This is data from the USRDS, and it was
2 prepared as a request for the UNOS Kidney Committee by
3 the SRTR.
4 A 25-year-old in the United States on wait
5 list has a 12-year life expectancy if he stays on
6 dialysis. That means he has a 50-percent chance of
7 living 12 years, a 4-percent mortality rate per year.
8 if he is transplanted, you can add 20 years
9 plus to his life expectancy, meaning that he has a 50-
10 50 chance of reaching the age of 60 rather than the age
11 of 40 if he lives on dialysis.
12 So transplantation has an effect to restore
13 life expectancy; in some patients, it exceeds that of
14 many cancer therapies. And this is why I think that
15 it's important for the FDA to consider these trials of
16 some of the innovations we have much in the way that
17 they're considering those in a very progressive fashion
18 in the cancer field.
19 So we're going to talk about malignancy
20 endpoints. Traditionally, these have largely been
21 safety endpoints, which has really been dominated by
22 PTLD. We'll talk about some recent data on efficacy

1 endpoints, primarily with non-melanoma skin cancers.
2 And we'll also talk about some future approaches.
3 When one talks about post-transplant
4 malignancies, you're talking almost exclusively about
5 solid organ tumors, and of these, 90 percent of these
6 post-transplant malignancies are non-melanoma skin
7 cancers. PTLD is the second most common solid organ
8 malignancy. And then if you want to develop -- there
9 is no real third most common that really sticks out,
10 but if you combine all of the papillomavirus-driven
11 cancers, this would then be the third most common
12 group. No one has ever, to my knowledge, in the
13 context of a clinical trial grouped these together, but
14 I think that is a reasonable approach as a future
15 approach, which we'll talk about a little bit later.
16 PTLD is occasionally a defined secondary
17 endpoint. It has traditionally been a part of the
18 predefined safety data collection element, is now a
19 universal one. The issues with PTLD as an endpoint is
20 that one must recognize that this is a heterogeneous
21 disease, it represents a spectrum from primary
22 infections to benign tumors to malignant tumors. And

1 also, very importantly, it has a bimodal distribution.
2 Really what's relevant to registration trials are the
3 early ones that occur within the first 1 to 2 to 3
4 years, and these lesions are actually different than
5 the late PTLDs that occur several years later, which
6 tend to more closely resemble the traditional types of
7 lymphomas that occur in the general population.
8 So this is really probably an
9 immunosuppressive- related effect that's largely and
10 predominantly virally driven.
11 As a safety signal, skin cancers have largely
12 been ignored as a predefined endpoint in registration
13 studies. The data, therefore, derives largely from AE
14 reporting, and these are usually AEs and not SAEs.
15 Their clinical importance is diminished by the fact
16 that the great majority of these are effectively
17 treated or cured with surgery alone, and these can
18 often be missed by a research coordinator. You can
19 imagine a patient who is several months out, they get
20 an excision of a skin lesion on their back, and the
21 coordinator never knows about it.
22 There are high-risk non-melanoma skin cancer

1 populations that do confer SAE types of risks. These
2 are more relevant as an endpoint. This would include
3 subpopulations that have multiple recurrent non-
4 melanoma skin cancers, particularly when they're
5 temporally clustered, for example, three non-melanoma
6 skin cancers within 12 months. These are the patients
7 that are at risk for getting nodal dissemination and
8 have a tumor that may result in death.
9 Of all the agents that have been looked at
10 before, all of these have been shown to increase risk
11 of PTLD, and many of them other cancers, including
12 steroids and skin cancers, and so there is no
13 individual agent that is free of these types of risks
14 to my knowledge except possibly the IL-2 receptor
15 blockers, which, as you notice, were not on this slide.
16 As a starting point, I thought that we would
17 put out the PTLD rates that have been observed in
18 registration trials in the individual limbs. Here you
19 can see with mycophenolate mofetil between zero percent
20 and up to about 1.2 percent in these studies, zero
21 percent here with azathioprine. Tacrolimus multicenter
22 trial, these are the highest rates that have been out

1 there in registration trials. As you can see,
2 tacrolimus here at 2.4 percent, cyclosporine at 2.9
3 percent. As I'll show you in a few slides, all of the
4 attention that was placed on belatacept was with
5 frequencies that are about half of this range with
6 tacrolimus.
7 Daclizumab, zero, 1.6 percent. Basiliximab,
8 zero to 0.5 percent. Sirolimus, on the neighborhood --
9 here's one at the 5 milligram in the Global Multicenter
10 Trial, it was 2.3 percent. And here are the belatacept
11 numbers. As you notice, this is a drug that was
12 approved in 2011. Not only were these lower numbers of
13 PTLD thought to be significant, but they resulted in a
14 significant REMS program that was required by the FDA.
15 So the field has changed. Back when the
16 tacrolimus levels of 2.9 percent or 2.4 percent, and
17 those trials resulted in no major effects or
18 recommendations from the regulatory agency. Now with
19 rates of 1 percent or less, these are resulting in REMS
20 programs.
21 PTLD risk factors for consideration in
22 clinical trial design, of course, the type of

1 induction, particularly T cell depleting induction, EBV
2 positive to seronegative recipients. As you know, the
3 label for belatacept now excludes these, and there's a
4 black box for that. Pediatric recipients, we've
5 already made the point about early PTLD and late PTLD.
6 We would note that there is evidence and a
7 trail in the literature that PTLD rates have
8 traditionally been higher in earlier reported
9 experiences and that reductions in PTLD rates are
10 observed when optimal dosing regimens are actually
11 established and developed, and this has been shown for
12 a number of drugs, most obviously were the rates with
13 cyclosporine with early rates of PTLD at 10 percent in
14 the earliest experiences to where now today it's around
15 1 percent. The same thing happened with tacrolimus.
16 And these are the data, for example, early
17 studies with Roy Calne, this was not registration, but
18 as you can see, there were 10 percent of patients who
19 developed PTLD, and once they actually found out how to
20 dose it, not at this dose, but at the doses more
21 similar to what we give today, these rates went down.
22 Let's talk a little bit about non-melanoma

1 skin cancers. The incidence is between 65 and 250
2 times that in the general population. The incidence of
3 non- melanoma skin cancers increases with the duration
4 of immunosuppression, and is essentially linear over
5 time. The slope of that actual incidence curve varies
6 based on geographic factors and also genetic factors,
7 and this is evidenced by data from Queensland,
8 Australia, where the rate at 1 year was 7 percent and
9 rises to 82 percent at 20 years. So the population in
10 that portion of the world has a non-melanoma skin
11 cancer rate that is substantially greater from another
12 population of patients who are in a different climate
13 at 0.2 percent at 1 year. And in Japan, these rates are
14 actually extremely rare.
15 So the other point I want to make is
16 eventually 50 percent or more of Caucasian transplant
17 recipients will wind up with a non-melanoma skin
18 cancer.
19 Important for trial design -- and I'm going
20 to show you a couple of trials that have been conducted
21 with non-melanoma skin cancer as a primary endpoint --
22 is the interval between transplantation and diagnosis

1 is actually shorter for elderly patients than it is for
2 patients who are younger.
3 Recurrent non-melanoma skin cancers, once you
4 have one non-melanoma skin cancer, you have a
5 significant risk of getting a second one. Twenty-five
6 percent of patients with a first one will have a second
7 one within 13 months, and 50 percent will actually have
8 a second non-melanoma skin cancer within about 3-1/2
9 years. So the interval, once you get a second or
10 third, they start to accumulate, 15 months between the
11 first and second, and 11 months between the second and
12 third non-melanoma skin cancer. So once you develop
13 one, you're at substantial risk to develop a second
14 one, and once you develop a second one, you're at
15 higher risk to develop a third one.
16 So in non-melanoma skin cancers, there are
17 actually two potential trial designs. One is a primary
18 prevention. To my knowledge, there are no studies to
19 date in kidney transplantation. A secondary prevention
20 is once you develop the first one, you then go on to
21 prevention strategy to develop a second one.
22 There have been two randomized trials

1 reported in this year, one I termed the ANZ-USA
2 randomized study, it's led by Graeme Russ, and it
3 originated out of Australia. And then there is the
4 TUMORAPA Study Group, which largely is a European
5 trial.
6 This is the report from the ANZ-USA study. As
7 you can see, it was in AJT of this year. Seventeen
8 participating centers in Australia, New Zealand, and
9 the U.S. Open-label randomized study, patients
10 randomized 1:1 to either CNI continuation or conversion
11 to sirolimus-based immunosuppression. The patients
12 were actually stratified based on the number of new
13 lesions, five or less, or more than five.
14 A primary endpoint in this trial was the
15 number of new biopsy confirmed non-melanoma skin cancer
16 lesions per patient per year, and these are the
17 inclusion/exclusion criteria, just as a point of how
18 you look at it. They needed to be on stable
19 immunosuppression, on a CNI. These were for the
20 sirolimus conversion, GFR, and proteinuria
21 restrictions. No other cancers. In patients with bad
22 non-melanoma skin cancers with previous metastatic

1 disease or more than 20 per year, those were excluded.
2 And also they controlled for the type of therapy the
3 patient had had, an important point in assuring
4 homogeneity in the study population. Eighty-seven
5 patients in this study, and as you can see, completion
6 is about 35 to 40 patients in each limb.
7 Now, again, this is a multicenter study,
8 enrollment was at least a couple of years, and this is
9 the most common solid tumor that's out there, and you
10 wind up with 30 to 40 patients in each limb. It's
11 difficult studies to do.
12 They had some issues with study follow-up,
13 and a blinded review of the data performed 7 months
14 after the last patient was randomized. Because of low
15 enrollment and high early discontinuation rate, there
16 were significant discontinuation rates with sirolimus,
17 which, as we know, is characteristic for that
18 particular drug, they cut the observational period from
19 2 years to 1 year.
20 And this is the primary endpoint expressed in
21 a table, and the intent-to-treat analysis revealed that
22 the rate of biopsy-confirmed new lesions in terms of

1 number per patient per year was substantially
2 statistically significantly reduced with sirolimus, so
3 they achieved what they hoped they would do despite the
4 fact they changed follow-up. And these are the actual
5 time-to- event curves for new non-melanoma skin
6 cancers. As you can see, freedom from a new non-
7 melanoma skin cancer is better once these patients
8 converted to sirolimus.
9 This is the second trial, the TUMORAPA group.
10 Ten centers, France, Belgium, Switzerland, and Spain.
11 Same type of a design, 1:1, remain on CNI or convert to
12 sirolimus. The primary endpoint here was survival-free
13 of new squamous-cell cancer at 2 years.
14 Over a 5-year period, 129 patients were
15 enrolled. So about 20 patients per year, again
16 outlining the fact that even though this is the most
17 common malignancy that you see in a transplant patient,
18 you're talking about multicenter trial, small patient
19 populations being enrolled. And then here at the
20 analysis, again, almost 40 patients are in each limb to
21 be available for the analysis.
22 The other thing that this study did was they

1 actually analyzed different skin types, eye colors, and
2 hair colors, known factors that influence the risk of
3 non-melanoma skin cancer, so this assured that the two
4 groups were reasonably comparable with those respects.
5 And again you see curves here that are very
6 similar to what we're seeing in the other study, and I
7 think the real strength of these two studies is that
8 the results are very similar and they show that despite
9 the discontinuation rates with sirolimus, you still see
10 an observable and beneficial effect.
11 So novel approaches, one of the things that
12 we did was actually looked to see if there were other
13 patient populations. This is Eric Engels' paper where
14 he combined SIR data with UNOS data to identify -- or
15 SRTR data to identify more specifically and with
16 greater precision identify the risk rates of individual
17 cancers. When one goes and takes the papillomavirus-
18 derived cancers and looks at the incidence per 100,000
19 patient- years and the excess rate above the general
20 population over 100,000 years, you can see here are the
21 rates. And so there are about 59.1 cases. When you
22 put this into context and compare it to lymphomas, it

1 is about a fourth that of non-Hodgkin's lymphoma. So
2 if you take this as the third most common solid organ
3 malignancy and combine all of these cancers together --
4 cervix, vulva, penile -- they're about a fourth what
5 they were with the Hodgkin's disease, with the EBVs.
6 And so these are even much less common than are the
7 skin cancers, and it gives you an idea of the
8 possibility of using even a combined group of tumors
9 that have a common sort of etiology and the possibility
10 of doing such a trial.
11 So in conclusion, malignancies have been
12 primarily safety endpoints. However, there have been
13 two recent non-melanoma skin cancer trials that have
14 been the first to use malignancy as an efficacy
15 endpoint. And these two trials have demonstrated the
16 feasibility of doing these trials, but they have to be
17 done with significant enrollment periods and also as a
18 multicenter effort.
19 PTLD rates are probably high enough to make
20 efficacy trials potentially feasible, but you need to
21 identify high-risk populations; for example, EBV
22 positive or negative or those that are high immunologic

1 risk, that is, that they are likely to require T cell
2 depleting therapy, but you will need a large number of
3 centers. And we actually think that the papillomavirus-
4 associated malignancies may be a group that may have
5 potential to combine as a safety endpoint.
6 And with that, I will just leave you with
7 this slide to remind you of how big an effect
8 transplantation has over dialysis.
9 (Applause.)
10 DR. PLOEG: Thank you very much. We proceed
11 with the next speaker, who is Flavio Vincenti. The
12 title of his talk is "Improving Long Term Outcome:
13 Balancing Efficacy with Toxicities."
14 Flavio.
15
16 Topic #6: Balancing Efficacy with Toxicity to Improve
17 Long-Term Outcome Flavio Vincenti, MD
18 DR. VINCENTI: Thank you. I would like to,
19 of course, thank the FDA for inviting me to this really
20 very exciting symposium. Well, the interesting thing
21 is that every slide I have has been shown more than
22 once.

1 (Laughter.)
2 DR. VINCENTI: Except for three slides.
3 DR. PLOEG: We should start the discussion
4 then?
5 (Laughter.)
6 DR. VINCENTI: Yeah, almost.
7 So except for three slides, which has
8 cartoons or pictures. The first one, nobody has shown
9 the Golden Gate Bridge yet, so that's one.
10 (Laughter.)
11 DR. VINCENTI: This slide shows my conflicts,
12 mostly research grants made to the UC Regents of
13 California.
14 So the question here is: How do we improve
15 long-term outcome? Do we do it with more intense
16 immunosuppression or with minimization of
17 immunosuppression to decrease toxicities? And the
18 issue is: How do we define efficacy? Classically,
19 historically, we defined it only by the reduction of
20 acute rejection rate. But is this relevant? And
21 should we maybe look at one group of rejection, a
22 subgroup, while many rejections many not have impact on

1 long-term outcome? So we may have to rethink what
2 efficacy means.
3 And how do we define toxicities? Of course,
4 if a drug produces a lot of PTLD, I think we understand
5 that, but do we define it by the rate of diabetes,
6 cardiovascular disease, hypertension? I always give
7 the example to my fellows that if a patient comes in
8 with a rising creatinine because they have a rejection,
9 it's an emergency, we admit them to the hospital,
10 biopsy them and do all kinds of things. A patient
11 comes in with new onset hyperglycemia, well, we take it
12 as, well, it's another little complication, we'll start
13 the patient on insulin or hypoglycemic agents, yet they
14 may have the same impact long-term on the patient and
15 graft survival.
16 And I want to ask the third question a bit
17 differently, not have we achieved, but actually can we
18 achieve a proper balance between efficacy and toxicity
19 in CNI-based regimen? And, frankly, I don't think
20 there is such a balance. I think either we go one way
21 or the other, but I think it's very hard to reach that
22 balance.

1 Now, historically, we've always thought that
2 the more potent the immunosuppression, the better it
3 is, but, you know, there are unintended consequences,
4 and I want to give you an example. Our kidney-pancreas
5 group years ago were not happy with the rejection rate
6 and the 20 percent or so, so we had the protocol of
7 Thymo, TAC, MP, and steroids. They said, well, let's
8 add sirolimus to this regimen, and withdraw prednisone,
9 and maybe this way we'll have less rejection.
10 And you know what happened? They were right.
11 Rejection rates went down to single digit, but you know
12 what increased to double digit? BK nephropathy. So
13 what do they end up? They decreased an event that
14 could be treated and potentially reversed, and they end
15 up with a new disease that's untreatable and has a
16 pretty bad course. So I don't think we need more
17 intense immunosuppression, we need better or smarter
18 immunosuppressive agents.
19 And we've achieved what we wanted. I mean,
20 rejection rates these days are quite low, and possibly
21 one could make the argument that acute rejection rates
22 may be too low and we're paying indirectly some price

1 for that.
2 So one of the first papers that was published
3 after the revolution of the great agents that were
4 introduced in the 1990s was from Bruce Kaplan and
5 Meier- Kriesche, and, of course, as we expected, after
6 the introduction of these drugs, rejection rates came
7 down quite a bit, and our expectation, because there is
8 a good association between rejection and graft loss,
9 that the relative risk of graft loss would be
10 decreased, and, lo and behold, when they looked at the
11 same time period following the reduction of
12 immunosuppression, the relative risk of graft loss at 3
13 years did not get lower; in fact, it seemed to be going
14 higher, and it didn't get better even in patients who
15 received living donor transplants.
16 Now, this was back in 2004, and the issue was
17 things may have changed now because very frequently you
18 hear people say -- actually, every center tends to say
19 -- "Well, our long-term outcome has improved," yet when
20 we put all the data together, it doesn't seem to be the
21 case.
22 So this is again another nice study which you

1 have seen earlier today showing that in fact the
2 cumulative graft failure, the attrition rate, in the
3 first year after transplant has decreased a lot, about
4 14 percentage points, but the 1 to 3 years, 3 to 5, and
5 5 to 10, neither in patients who received deceased
6 donor kidneys or living donors has not really improved.
7 So we're pushing a lot of people, which is great, up to
8 1 years with functioning grafts, but once they reach
9 that, the rate of attrition of the graft has remained
10 pretty stable, maybe a tiny bit of improvement, but
11 really not a whole lot.
12 So what is the problem with immunosuppression
13 that has resulted in this lack of major improvement
14 long term? Well, more intense regimens may not address
15 the main causes of why these people are losing kidneys
16 and are dying. The nephrotoxicity and metabolic
17 abnormalities may be unavoidable with our current
18 agents.
19 Now, Dr. Matas made a very good argument,
20 that nephrotoxicity, in the current regimen, the way we
21 manage them, may not be an important cause of graft
22 loss, but however, CNI are nephrotoxic, but because

1 we're managing CNI with minimization, then we're
2 allowing maybe the development of more alloimmune
3 responses. And minimization regimen, as I said, are
4 unlikely to benefit patients longer term because
5 primarily we are then allowing them to have more
6 immunologic injury.
7 Now, we spent a lot of time about which
8 combination is better, et cetera. I always like to
9 show this slide. I don't know understand it, and I've
10 asked Gerhard about this slide. This is an outcome at
11 5 years on 52,000 people from Gerhard Opelz's registry
12 showing that independent of the CNI and adjunct
13 therapy, at 5 year graft outcome is the same. So we're
14 spending a lot of energy about rearranging chairs here
15 and there and so on, but at least in this database it
16 doesn't seem like we're making a whole lot of progress.
17 On the other hand, there are some issues that
18 we still cannot tackle very well. For example, new
19 onset diabetes mellitus, and this is a study presented
20 here from Kasiske showing that at least 25 percent of
21 patients by 3 years develop NODAT and that it is
22 associated independently with a risk of graft loss and,

1 of course, a risk of death. Yet there is little that
2 we can do about diabetes other than treat the patients.
3 And, again, this slide, you've seen it, the
4 relationship of renal function with graft loss, and
5 maybe more importantly, the fact that renal function is
6 associated with cardiovascular death. So renal
7 function really plays a role. I think if you end up at
8 1 year with great renal function with a good slope,
9 either neutral or positive, you may decrease your
10 cardiovascular risk, you may improve your long-term
11 outcome, as long as beyond that point you continue to
12 have effective immunosuppression and I think this is a
13 problem that we deal with, that to maintain these
14 benefits, we're doing it at the expense of proper
15 immunosuppression.
16 And hypertension, over 80 percent of patients
17 are hypertensive. And, again, you've seen this slide
18 before, showing that in fact it is an independent risk
19 factor for graft loss.
20 I'm showing this study again by Phil Halloran
21 just to show you that this is a detailed study of over
22 300 patients whereby both histologically and by other

1 techniques, they made sure to separate patients who had
2 T cell rejection versus those who did not have, and
3 look at their outcome, and they found that patients who
4 have pure early T cell-mediated rejection had no impact
5 on outcome.
6 So we focus a lot of attention, our primary
7 endpoints is always acute rejection, and so on, but if
8 it doesn't affect outcome, why are we overemphasizing
9 it?
10 Now, none of us like rejection, and clearly
11 there are unintended problems with rejection because we
12 treat it, we have to give high-dose steroids,
13 occasionally we have to give depleting agents, but I
14 think we have to balance this single endpoint of
15 efficacy with everything else that may be important to
16 the outcome of the kidney. And I think it is no
17 surprise that long- term outcome hasn't improved when
18 one examines why two patients lose their kidneys. So
19 death with function is still a predominant cause of
20 graft loss, and most of this is cardiovascular disease.
21 So we could have zero rejection rate and this is not
22 going to change. I think there is little we can do at

1 this point on recurrent disease. And CAN, which
2 actually it's a term I like, I mean, it came out of
3 failure, and so occasionally it feels like it's not
4 politically correct, because people have associated CAN
5 with a specific disease or phenotype while it's a
6 clinical centromic diagnosis that has several
7 pathogenic mechanisms. So the DeKAF group will say CAN
8 is mostly antibody-mediated rejection. Jeremy Chapman
9 will say CAN is mostly CNI nephrotoxicity. The truth
10 may be somewhere in between, although I think
11 immunologic injury appears to be the more predominant
12 cause in my mind.
13 So the other issue is that nowadays we find
14 that innocent looking interstitial infiltrate with
15 fibrosis has a poor prognosis, so maybe when we want to
16 have endpoints, just looking at clinical acute
17 rejection may not be adequate. Maybe we want to look
18 at antibody- mediated rejection as a more important
19 indicator of severe rejection or something that Bruce
20 Kaplan published many years ago, that the rejections
21 that after therapy where the renal function after
22 therapy doesn't go back to baseline, those are the ones

1 that have progressive renal failure.
2 And so this could be another endpoint that
3 could be added to improve our assessment of efficacy.
4 And clearly this has to be validated by other studies
5 also, although there are a couple of other publications
6 suggesting again that the presence of an inflammatory
7 infiltrate tends to foreshadow a decline in renal
8 function.
9 And I think a lot has been said about the
10 presence of de novo HLA antibodies. This is a study
11 from Terasaki showing again patients who convert to
12 antibody- positive have in the subsequent 2 years a
13 rate of graft loss of 2, 2-1/2 times greater than those
14 who remain negative.
15 So we have these tangible endpoints that we
16 could add, we could refine them, and not just rely on
17 that single endpoint that we have been using all these
18 years.
19 So I think, as has been said here for a long
20 time, we thought that nephrotoxicity was the main
21 culprit of progression of renal failure, and then the
22 DeKAF people did a beautiful study. And this is a

1 slide that I like because it shows that those patients
2 who had been stamped as having nephrotoxicity did
3 better than those who did not, and there are many ways
4 to interpret this. My interpretation is that if you
5 give a lot of CNI, enough to produce nephrotoxicity,
6 you are probably pretty well immunosuppressed and
7 you're less likely to have chronic immunologic
8 rejection. And so clearly the majority of patients in
9 this study at least appear to have an antibody-
10 mediated-driven progression of renal dysfunction.
11 So we come to the SYMPHONY study, and this
12 question is, you know, SYMPHONY, when came up with the
13 name, is that it was all melodic, you know, low cyclo,
14 low Prograf, low sirolimus, compared to the full dose
15 of cyclosporine. So this is a study that may have had
16 unintended consequence meaning that at first year
17 everything looks good, by 3 years all the arms seem to
18 have the same GFR, and then maybe after that -- we
19 don't have a follow-up -- but maybe we're doing the
20 wrong thing, where we're using immunosuppression when
21 we should not be using immunosuppression. If the major
22 cause that's driving these kidneys slowly to renal

1 failure is chronic rejection and chronic alloimmune
2 responses, so can we afford to have high CNI throughout
3 the period when the kidney is present? Probably not.
4 And that's why frankly I think the future clearly
5 belongs to the non-CNI agents. And so what are the
6 agents? And then we think about the endpoints if we
7 want to use as we develop them.
8 Clearly, we want something non-nephrotoxic so
9 that we can give it in high dosage or at the same level
10 over the period of time when the graft is in place. We
11 don't want the agents that produce diabetes or
12 hypertension, hyperlipidemia, clearly associated with
13 increased cardiovascular-related deaths. And as Steve
14 Woodle just reported, the incidence of malignancy with
15 time increases, and, of course, we would like agents
16 that do not directly promote metastasis as the CNI have
17 been reported to do.
18 So a new paradigm in immunosuppression is
19 needed to preserve renal function because I think that
20 is the key for long-term improvement in renal function.
21 Decreased cardiovascular toxicities, because that's the
22 main cause of death of patients with functioning

1 grafts.
2 So the agents should suppress both T and B
3 cells. It looks like our regimens are doing a great
4 job or a pretty good job with T cells, but as you see,
5 a lot of late graft loss is due to antibody-mediated
6 rejection. We're not doing as well a job with
7 suppressing the humoral component. They should lack
8 nephrotoxicity, not aggravate cardiovascular risk
9 factors, not affect glucose metabolism, and from
10 several of the studies reported -- and we haven't
11 spoken too much about that today -- is quality of life.
12 I think we do not put enough emphasis on some
13 of the CNS toxicity of our regimens. I think
14 occasionally this is driven home by a patient who gets
15 converted away from a CNI and they feel dramatically
16 better. And so if compliance is a major problem, and,
17 of course, it has a multifactorial cause -- but if it's
18 driven by not feeling well, by having CNS issues,
19 cosmetic, et cetera, then an agent that avoids these
20 should contribute to long-term outcome.
21 So in conclusion, clinical trials with new
22 agents need to place greater emphasis on factors that

1 affect long-term outcome. Further decreasing acute
2 rejection may not have a meaningful effect on graft
3 outcome, and I don't think it should be emphasized as
4 the only important endpoint; it should be as part of a
5 number of other factors that we need to assess. And
6 endpoints for evaluating toxicities need a better
7 balance with efficacy, which itself needs maybe a
8 redefinition and maybe Bruce Kaplan will discuss that
9 in his presentation.
10 Thank you.
11 (Applause.)
12 DR. STEGALL: Our next speaker is Bruce
13 Kaplan. He is going to talk about "Scaling Issues with
14 Current
15 Endpoints: Can Effectiveness Rather than
16 Efficacy Offer Some Solution?"
17
18 Topic #7: Scaling Issues with Current Endpoints: Can
19 Effectiveness Rather than Efficacy Offer Some Solution?
20 Bruce Kaplan, MD
21 DR. KAPLAN: Thank you very much. Flavio,
22 thank you for the tests that I can't do.

1 Anyway, I decided it was such a broad topic
2 that I was going to talk about, I really wanted to talk
3 about one issue, and there are going to be a whole
4 bunch of equations and statistics, all that, if I can
5 only get one point across, is the idea of internal
6 versus external validity in terms of the studies that
7 we do. And as a preface, when I say "internal
8 validity," I'm talking about the standard causal
9 deductive study that we try to do, our trials. What we
10 try to do is show there was a causal link between
11 intervention A versus intervention B and the endpoint
12 of Z. That's a deductive causal study. That's how you
13 get funded, that's how all our studies are done.
14 But what I would like to point out in this
15 talk -- and I won't go through every equation, I
16 promise -- is that internal validity is always at
17 tension with external validity. How can you use the
18 data from that study to the population as a whole? But
19 also, what are the requirements of an endpoint to be a
20 good endpoint for a causal deductive study to have
21 internal validity versus the characteristics of an
22 endpoint that's good for an entire sick population? And

1 actually, surprisingly, they're a little bit different,
2 and I'll have to stop there, I don't know how to go
3 forward.
4 No one wants me. I have no conflicts of
5 interest.
6 We've already talked about the issues here,
7 that the difficulties with current endpoints that we
8 have in terms of the hard endpoints we're talking about
9 are really that the event size is small. It's not that
10 we can't do any kind of study, but the fact is if we
11 want to do a superiority trial, which is what we all
12 want to do, a two-sided test, that the amount of
13 patients we would need or the time that we need to do
14 it is just prohibitive from a resource utilization
15 standpoint, to do the standard causal study with these
16 kinds of endpoints. And even if we could, if patient
17 survival were 95 percent and we could show a difference
18 to 95.8 percent, would it really even make a
19 difference?
20 So I'm just reiterating what everybody has
21 talked about before, that with the current endpoints,
22 we're really at a standstill in terms of the first year

1 studies.
2 So the first thing we do when we try to
3 design a study when you're using the endpoint, you
4 power the study, you want to know: How many patients
5 do I have to use in the study? What's the N? And
6 obviously from a resource standpoint, we want to use
7 the smallest N possible. To execute the above, we try
8 and identify an endpoint that has small inherent
9 variability, that doesn't have a lot of noise, that
10 allows you to discriminate that the effect is truly an
11 effect of the intervention and not just random noise
12 around it. So we try to get very little variability so
13 we can show that the treatment arm was the effect, was
14 the cause of the difference between the two groups, so
15 we want very little variability.
16 So in terms of an RTC, we're trying to show
17 deductive causality, we're not trying to show that it
18 works in everybody, we're not trying to show this is a
19 universal phenomenon, we're just trying to show that
20 the intervention caused the endpoint, so we try to get
21 rid of as many confounders as we can, we try to make
22 the study as homogeneous as possible, and we want that

1 endpoint to be very small in its inherent noise or
2 variability.
3 So in doing so, we take an entire sick
4 population, we make it a smaller population. We take
5 an endpoint that doesn't have a broad band around it,
6 and thus we have good internal validity, we have a good
7 causal trial. That's what we do when we design our
8 studies. There is nothing wrong with that. We have to
9 go there, and, if anything, a plea here is not to say
10 that we have to do one or the other, that a causal
11 study is the beginning, that's good enough, that should
12 be good enough to approve the drug. The next step, of
13 external validity, takes time, but that doesn't mean it
14 has to hold up the approval process.
15 A statistician that I work with did a little
16 modeling here of a kind of paradox, that if we look at
17 the entire population, it turns out that it's the exact
18 opposite. If you want to look at the risk in the
19 entire population, the smaller the variability of that
20 endpoint, the more patients you need. The exact
21 opposite of the endpoint you would want to use for an
22 RCT.

1 And I tried to think through this, and the
2 best way I could think of it is if you take the entire
3 population, let's take GFR, if the inherent variability
4 in the population were 60 plus -.01, but a clinical
5 difference was 65 versus 55, well, to get two standard
6 deviations out, let's say you had 10,000 patients, to
7 get 2,000 patients in, you would have a difference of
8 60.1 versus 59.9. You would have to go 10 standard
9 deviations out either end to see a difference to
10 eliminate that noise, but yet that would be the best
11 endpoint to use for your internal validity.
12 So I don't think we can combine these two; we
13 have to view these as separate issues. I'm going to
14 show you some statistical approaches that can get
15 around the issue, but they are distinct, they're always
16 at tension with each other.
17 And everybody is supposed to memorize this
18 equation, and there is a test at the end. Just to
19 show, this goes back to 1983. Schoenfeld first looked
20 at this inherent tension between internal and external
21 validity. It's actually just now beginning to show up
22 in more current statistical texts and statistical

1 treaties of trials. I know the FDA is trying a lot of
2 innovative trials to try to get at the idea of external
3 validity, Bayesian types of studies, that allow you to
4 get past the initial conditional probabilities that we
5 put to broaden out those conditions. A lot of ways
6 around it, but I would argue that maybe there's an
7 inherent tension.
8 This is -- and Steve Woodle pointed this out
9 to me -- Steve, you're incredible with detail. The
10 standard deviation should be .5. And actually, we
11 looked at GFR. We used GFR. So this is a standard
12 deviation of 5 mLs, 10 mLs, and 15 mLs, and what the
13 number of patients you would need in the population to
14 show that there was an effect. And if the standard
15 deviation were 15 mLs, you would need about 800
16 patients. If the standard deviation were 5 mLs, just
17 like we talked about, if you imagine that bell curve,
18 we don't transplant enough patients to see a
19 difference; yet for internal causality, again -- I'm
20 always told to repeat it three times -- it's the exact
21 opposite. There's an inherent tension.
22 So, again, we always have this tension

1 between internal validity and external validity. One
2 is classic science, deductive causality, and we have to
3 use that as our first step. That's the scientific
4 method. We can approve drugs based on that, but that
5 doesn't mean that it will be generalizable to the
6 population. That's a whole different ballgame, and we
7 shouldn't expect that of the studies that are well
8 designed as randomized controlled trials. We try --
9 like I said, a well- designed trial tries to show that
10 the intervention, whether it was belatacept, whether it
11 was low-dose TAC, actually caused that change in GFR.
12 When you take it out into that whole population,
13 though, it gets a lot more muddy, the waters. But to
14 approve a drug, we need not say that the randomized
15 trial has to have that external validity, my opinion.
16 One of the keys of this is random selection
17 from a population. It's just not feasible. What we
18 actually do is we do random assignment to protocol
19 arms. I'll go further and we also choose what
20 assumptions we wish to make and what endpoints we
21 choose. So we try to stack the deck by not doing
22 random selection, which we would never get to our

1 causal endpoint, and we try to keep the variability of
2 our endpoint low enough so we can actually show that
3 causal relationship, but in doing so, we make the
4 population a tiny portion of the entire sick
5 population.
6 Now, there are other threats to external
7 validity that we know about other than just mathematic.
8 Obviously, a study is different than taking it out into
9 the real world. I think we're all aware of this. I
10 think the only point I'm going to really stress here is
11 the lack of random selection. And there's a big
12 difference between randomization and random selection
13 of the population.
14 So one possibility to get around that, there
15 is a growing field called randomization statistical
16 tests, which is essentially our permutation statistics
17 which allow you to look at all possibilities within the
18 population and actually say, "If I see that there is a
19 statistical difference in the potential possibilities
20 that could occur, then that gives me some external
21 validity." It's possible we should be looking at that
22 in terms of our RCTs, not as the be-all and end-all,

1 but as at least a part of at least getting at external
2 validity. I don't think it lets us off the hook of
3 letting it see how it really works in the real world,
4 but it's a part that we can at least consider.
5 Now, one question in basic science would be:
6 Do you need external validity? A basic scientist in
7 the audience should be saying, "The hell with external
8 validity." You know, strictly from a Karl Popper or
9 John Stuart Mill point of view, external validity is
10 nonsense because basic science, you can repeat a study
11 -- you know, if Einstein came around and did
12 relativity, and 12 other people did it again, it
13 wouldn't prove that it was more right, but when the
14 "God particle" comes and refutes it, that proves it. So
15 we have hypotheses that only can be refuted. Proving it
16 over and over again doesn't make it more robust, it
17 just proves it over and over again, it's not actually,
18 from the internal causal point of view, doesn't make it
19 more robust, so we don't get around it that way.
20 I would argue, though, we do need external
21 validity because we don't live in a world of physical
22 science where we can wait 200 years to see if that

1 study can fit my patient; we have to make decisions
2 now, so we have to deal with idea of external validity.
3 Whenever we look at a study, we have to say, "Does that
4 fit my patient? Does that fit my patient population?"
5 So we don't have the luxury of the physical sciences
6 and some of the other sciences to be strict scientists.
7 It was funny, in looking it up, the most
8 cited scientists, no one even close, is Fisher. Among
9 others, he is cited for the P value, T tests, all the
10 Fisher tests you know, Cox tests, all sorts of tests he
11 is cited for. One of his papers was cited 600,000
12 times. He was the first one to do permutation
13 statistics, and you can just read through how this
14 would work. And he took of some Charles Darwin data
15 and looked at the possible permutations that could have
16 occurred and came up with a result of an internally
17 valid study to show if it had external validity.
18 So it can be done, again, carefully, with the
19 right assumptions, because you can go wrong, because
20 randomization tests, the main thing I'll say here is
21 that they require independence of the subjects and
22 independence of each permutation. In the real world,

1 and particularly when we deal in transplant, that's
2 probably not true, but there is a lot of
3 interdependence of the possible combinations that we
4 use, so probably we would get false tests by this way,
5 and that's why I'm stressing the idea that maybe our
6 only way out is to accept the fact that we'll do our
7 RCTs, get approval, and learn later about the external
8 validity.
9 This is just another example where you can go
10 wrong with randomization tests, a lack of independence.
11 It's in the handout, I won't go through the statistics.
12 Now, one place -- and Flavio did touch on
13 this, and actually this is one of the reasons for
14 comparative effectiveness research, was the search for
15 external validity. Now, again, it allows us to
16 liberalize our protocols a little bit, but it also
17 allows us -- imagine you had a study where somebody had
18 one intervention and 99 percent graft survival, no
19 rejection, same GFR, but the person had a terrible
20 stomachache every day, and other group, the same exact
21 results, but the person felt great, as a matter of
22 fact, felt 10 times better than they did before the

1 intervention, are you really going to say they're the
2 same?
3 Now, what comparative effectiveness research
4 does, by loosening up, by allowing you to use some of
5 this, not only allows you to differentiate in your
6 studies and use those ends and show causal
7 relationship, but it actually does increase external
8 validity. So while I'm not a total proponent of
9 comparative effectiveness research, it has its place,
10 and there are obvious places where it comes up. And I
11 think if you were to power those into your study, you
12 could show a causal relationship and gain external
13 validity. It would also do patients better.
14 Again, the definition of efficacy refers to
15 effectiveness, and we have to strike a balance between
16 efficacy and effectiveness: efficacy being, does the
17 intervention cause result?; effectiveness, to what
18 extent does the intervention achieve the objectives
19 that you want in the population?
20 So in summary, variability is a double-edged
21 sword. It's a critical component in power
22 calculations, but it underlines the difficulties of

1 reconciling our randomized controlled trials causal
2 studies and extrapolating to external validity. We are
3 in the habit of not thinking about external validity,
4 yet it has become more and more important to see all
5 the RFAs and other things out there for comparative
6 effectiveness research.
7 Some possible solutions are randomization
8 statistical analyses, loosening up Bayesian statistical
9 analyses, Bayesian trial designs, allowing quality of
10 life, other metrics to come in, or simply allowing the
11 fact that these are two distinct entities and dealing
12 with both of them for what they are, and allowing
13 approval based on causal studies, and then working on
14 external validity next.
15 And really thank you for your attention.
16 (Applause.)
17 DR. PLOEG: Thank you very much, Bruce. We
18 move to our last speaker of this session, which is John
19 Gill, with the topic, "Successful Outcome: A
20 Proposed Approach."
21
22 Topic #8: Successful Outcome: Proposed Approach John

1 Gill, MD, MS
2 DR. GILL: Thanks very much. I want to thank
3 the organizers.
4 That's a touch act to follow, Bruce.
5 You can tell by my title, I've been given
6 some leeway here, "Proposed Approach," so I am going to
7 touch on some of the themes that we've heard about
8 already that Jesse started us on 2 days ago, I think,
9 or a day and a half ago.
10 Those are my disclosures.
11 I'm going to start with a simple statement,
12 that everything should be made as simple as possible,
13 but not one bit simpler, and hopefully you'll feel that
14 way at the end of this talk.
15 So one of our problems is we've got a
16 successful therapy, and because of that, we can offer
17 it to not only the best patients but a whole swath of
18 patients who have a number of different challenges. And
19 so when we think about success, we need to think about
20 the variability of our patients and one size might not
21 fit all.
22 Now, this is a picture from, I think,

1 Suffolk, England, although Alan might correct me, and
2 it's an artist's conception, and basically I put it up
3 there to mimic what we do in clinical trials. This is
4 a conglomerate. The person in the middle is not a real
5 person, it's a conglomerate of 2,000 photos
6 superimposed to represent what a generic individual in
7 this town of 2,000 would look like, and I put it up
8 there because that's what, in fact, our clinical trials
9 do.
10 We give an average effect in a clinical
11 trial, and that's what we take home from a study. And
12 the question, of course, is: How does that apply to
13 that variable group of patients that I showed you in
14 the previous picture?
15 So we all know this, the average results of
16 RCTs often don't apply to all or even most individuals
17 in a clinical trial since a small group of patients who
18 receive substantial benefit can heavily influence the
19 overall average benefit.
20 And I'll remind you that it's not just
21 treatment heterogeneity that sorts out the outcomes in
22 our patients or determines our outcomes of our

1 patients, but it's also their risk/side effect for
2 different therapies that we may offer them, and it's
3 also the presence of competing risks. So when we put a
4 patient on a given therapy, we need to consider all of
5 these factors in terms of whether we actually recognize
6 an improvement in outcome in that patient.
7 And just to bring home this issue of
8 competing risk, this is some data from Angela Webster,
9 and what's she's looking at here is risk factors for
10 cancer in kidney transplant recipients. At the very
11 bottom of the slide you can see that patients who have
12 diabetes are actually protected from cancer, and, of
13 course, I'm alluding to the fact that they obviously
14 have a huge competing risk which never lets them get
15 that endpoint.
16 Now, just to make sure that we're all
17 starting from the same point, I want to just go through
18 this simple graph, which I think makes some of the
19 points clear about the issue of treatment heterogeneity
20 in trials. So at the top we have the baseline outcome,
21 risk of the outcome of interest, it could be whatever,
22 let's say graft survival. What this curve is, is the

1 known distribution of that risk in our patients, and we
2 don't know that, that's our Achilles' heel, that we
3 often can't predict that, but as you can see, probably
4 most of our trials, it's skewed towards the lower end
5 of lower risk patients, and then we've got a few
6 patients out here.
7 Now, in the second panel, what you see is, is
8 what happens to those patients in terms of outcome,
9 along the Y axis here, if they got placebo and what
10 happens to those patients with a treatment. Now,
11 importantly, the treatment has a bit of a side effect
12 profile which puts the lower risk patients actually at
13 higher risk of the adverse outcome but is beneficial in
14 the higher risk patients. So when we look at the
15 overall population, we may not measure an effect, but
16 we may be missing an effect in different groups of
17 patients.
18 Just to bring that home, this was a study
19 that I think Bert is the senior author on this, but it
20 was published in AJT, and what they did here is they
21 divided a population into low, moderate, and high risk
22 groups for rejection, this is a theoretical study, and

1 then the overall effect. Treatment A is in black, and
2 treatment B is effective for preventing acute
3 rejection, it causes about a 40-percent reduction in
4 the outcome of acute rejection. And then you can see
5 that overall when we see this, we see this difference
6 in acute rejection. When we look at that in terms of a
7 surrogate of function GFR, you can see that because the
8 highest risk group is at the highest risk for
9 rejection, the biggest difference in GFR is recognized
10 in that group.
11 If, however, now in Panel C, we assume that
12 this treatment also is associated with a 10-mL
13 decrement in GFR, so the hash lines are actually
14 bringing down the GFR in treatment Group B in each of
15 these things, when you look at it at the end of the
16 day, overall we measure no impact of this therapy.
17 However, it is clearly beneficial in our patients who
18 are at high risk for rejection but detrimental in our
19 patients who are at low risk for rejection.
20 So I don't mean to be "Epidemiology 101," but
21 I think these are really basic important points for us
22 to glop onto.

1 So where does this take us to? Well, what we
2 need to do is to be able to determine the baseline risk
3 for relevant outcome of patients of different flavor
4 that we want to treat and that are included in our
5 clinical trials to variable degrees. Now, that may
6 sound like a daunting task, and again I'm trying to
7 keep this simple, but at the time of transplantation
8 when we look at individual patients, we all have a
9 "gestalt" of what's going to happen to that person, we
10 don't necessarily know when, but I bet you we can lay
11 down 20 bucks and say this person is likely to die with
12 a functioning graft or this person is likely to return
13 to dialysis. And what I'm going to submit is, is that
14 identification of the most relevant risks for
15 individual patient groups should allow us to define
16 unique definitions of success in these individual
17 subgroups of patients.
18 And I couldn't resist this. You know, we can
19 put these two fellows up there and we can all ask:
20 Which do we think each of these patients who have had
21 transplants is going to exit with, death with a
22 functioning graft -- forget that he's had a heart

1 transplant -- or a death-censored graft loss? So on a
2 basic level, we shouldn't get rid of that. And we've
3 heard about Bayesian, but we do have a preconceived
4 idea of what our patients will end up with.
5 Now, what I'm going to take you through is a
6 different approach to clinical trial design, which is
7 talked about in cardiovascular disease and increasingly
8 in cancer, and this is a risk-stratified approach or
9 score. And basically what we're trying to do is trying
10 to identify where our treatment will have the most
11 impact, where you can see in the first panel, the
12 clinical trial, we don't really have a good way of
13 differentiating that. When we do what we all loathe,
14 which is subgroup analysis, you can see we're quite
15 limited in sorting out which patients in blue, who will
16 benefit, versus those in red, who will not benefit, but
17 this risk-stratified approach is something that can
18 help us determine individual subgroups of patients
19 where our therapies might have the most efficacy.
20 So a bit about this is it's a multivariate
21 risk stratified approach that's not really the
22 application of multivariate analysis post hoc to

1 clinical trial data. What you're doing is you're
2 developing a risk stratification or a risk score from
3 an external source that is validated and that you are
4 now applying to let you determine risk within your
5 population set. And so the multivariate risk
6 production tools can be used to calculate for each
7 study patient their predicted risks and benefits from
8 individual treatments.
9 Now, just to make the point clear that we're
10 not talking about subgroup analysis here, this is
11 different than that, and so when we're combining
12 predictors of net benefit, similar to what I think Roy
13 was alluding to a day ago now, into a single production
14 tool that can greatly increase our degree of risk
15 stratification, importantly, these prediction tools
16 often give us continuous estimates of risk, not just
17 this person is at risk, this one is not, and it avoids
18 multiple comparisons, which is one of the big problems
19 with subgroup analyses.
20 And this slide, which is in BMC Research,
21 just shows you a couple of important points about this.
22 The first is that statistical power is enhanced by

1 combining risk factors. What you've got here is a
2 different baseline risk of the outcome from 1.5 percent
3 to 9 percent, and here what you have is the power to be
4 able to detect heterogeneity in the treatment effect
5 with just a subgroup analysis or one risk factor or a
6 risk score that incorporates four risk factors, in this
7 case, I think each of which with an odds ratio of 2 for
8 the outcome.
9 And the two points here are, first of all,
10 that all the power is higher on this side where the
11 multivariate risk analysis, and the other thing that's
12 interesting is that your power is higher in lower risk
13 patient populations, so it wouldn't mean that you could
14 only apply this to a super high-risk group of patients.
15 Now, the important thing of this is the crux
16 of this is we need an external risk score to be able to
17 apply this in clinical trials, and that's where our
18 challenge is. I have already alluded to we can guess
19 who is going to die with a functioning graft or who's
20 having death-censored graft loss, but that's not really
21 good enough. What we need is what mechanism by which
22 they get these outcomes, and for that, we need to do

1 some work.
2 So to start at that and how might we then get
3 at producing a risk score, I think Arthur has left, and
4 I didn't talk to him at all this meaning, so I thought
5 I would put up a quote up from him. So Arthur defined
6 in this study what success was, and he called it,
7 "Long-term survival, with continuing transplant
8 function, that is equivalent to that in the general
9 population."
10 And so we've seen on the one hand a number of
11 people have compared our outcomes to dialysis patients,
12 on the other extreme, we should compare them to people
13 who never had disease in the first place. And there is
14 this study in Transplantation which attempts to do that
15 where they simply layer out individual transplant
16 recipient subgroups by age and the type of donor type,
17 and you can see that we fall short, particularly in
18 older age groups and people who receive deceased donor
19 transplants.
20 The key to this is that in order to develop
21 these risk scores, where we might within a subgroup
22 say, "Who have the best outcomes in that subgroup?" and

1 use that as our playing surface to assign a risk score,
2 the first thing then we need is we need to develop
3 these risk indices. And I think this work has started
4 to be done. Bert Kasiske put together a group of people
5 in the PORT, investigators, where they tried to get
6 more robust risk scores.
7 So our Achilles' heel here is that our large
8 observational datasets or our registry data don't have
9 the granularity of detail that we need to really get
10 robust risk sets. Where we do have the granularity --
11 i.e., in our clinical trial databases -- we don't have
12 long-term outcomes. So I think one of the things we
13 need to think about going future is: How do we link
14 those two things, and is it inconceivable that we might
15 be able to follow long-term outcomes in patients who
16 were actually in trials at one point in time?
17 Now, in terms of getting these risk scores, I
18 want to take you back to that survival gap concept
19 where we're comparing our patients to people who never
20 had disease. I would submit that that's probably not a
21 fruitful way for us to go about developing these risk
22 scores in transplantation because, of course, our

1 patients have other ailments or comorbidities that are
2 nothing related to transplantation itself necessarily.
3 And so I think a better way to do that again would be
4 to define subgroups of patients -- for example,
5 patients who are at risk of death with a functioning
6 graft -- and among those people who share a simple set
7 of risk factors -- i.e., diabetes, age -- say among
8 those, "Who do the best and who do poorly?" and try to
9 develop risk sets within those subgroups.
10 The other rub with this is that we still need
11 effective surrogates. Right? So what I'm proposing is
12 a more individualized approach to clinical trials, but
13 still need to be able to have an intermediate or early
14 fencepost by which we can predict that long-term
15 outcome which is relevant to our specific patient
16 group. And I would submit, however, that if we did
17 take this stratified approach, we might be able to be
18 more successful at identifying surrogates because
19 presumably the mechanisms of disease are similar with
20 people within certain subgroups.
21 This is my last slide, and I'm just going to
22 sum up here. So what I've hopefully taken you through

1 is that to define a success, we need to start thinking
2 about an individualized approach. I think a number of
3 people have touched on that. We need to develop risks
4 for specific outcomes that are relevant to specific
5 subgroups of patients.
6 And the next part of that is we need to
7 identify surrogates for those outcomes. Therapeutic
8 success can then be defined by optimization of that
9 surrogate or combination of surrogates. So success
10 would be specific for a patient group and for the
11 outcome that was most relevant to those patients.
12 And I've just given you some examples here to
13 get some of this esoteric thought down to how this
14 might work. So for our overall average transplant
15 patient, this almost certainly, in my mind, will
16 include some combination of GFR and biopsy, plus or
17 minus DSAs, depending upon the immunological risk of
18 the patient, and we've heard that floated here before.
19 For a person like Mark described in his
20 trials, a person who was desensitized to get a
21 transplant, as Mark outlined, I would agree, success
22 may be defined by projected freedom from death-censored

1 graft loss, which could be measured at an early time
2 point -- i.e., 1 year -- by surrogates such as the GFR,
3 the absence of TG or DSA, and freedom from infection or
4 rejection.
5 And then finally, most provocatively in that
6 patient that is the sort of nebulous patient that is
7 probably not going to do as good as we would like, the
8 diabetic male over 60 transplanted with an ECD kidney,
9 success here might be defined as projected freedom from
10 the outcome of death with a functioning graft due to
11 cardiovascular disease. And how would you predict that
12 at an early time point? Well, by a good GFR, the
13 control of hypertension, absence of diabetes,
14 minimizing post- transplant weight gain, or maybe just
15 feeling well enough to go out and take a walk.
16 I'll stop there. Thanks.
17
18 Question and Answer Period (Panel and Audience)/ Public
19 Comment Discussion of Suggested Questions (to be
20 introduced by the moderator(s))
21 DR. STEGALL: That was a lot of topics to
22 cover, and I don't know exactly how we would start this

1 discussion, but I thought I would throw out a few ideas
2 maybe just for comment, and one of those is, I guess,
3 what is the actual incidence of some of these ones and
4 twos complications, and maybe the question is: What
5 changes in immunosuppression would actually lead to
6 some modification of their incidence and outcome? And
7 maybe it's just to follow up on what Eli Katz talked
8 about earlier this morning, is, is it really enough --
9 because we're not doing it now very often -- that you
10 would change the practice because something happened
11 like this to a patient? We already are doing steroid-
12 free immunosuppression in some patients because somehow
13 we got out externally validated that in some sort of
14 non- Bayesian way, but the question is also, then if
15 that was the case, then would that ever lead to an
16 indication? I guess. Would it be enough to say we're
17 going to decrease post-transplant diabetes, and this is
18 the immunosuppressive regimen that's going to do it,
19 whether it's a subset or whatever?
20 So I think those are kind of the issues
21 around these. Are there really maybe critical, so
22 critical now in transplant, so important, or are these

1 the leftover issues that are still the most important
2 to fix? What kind of indication would you get and
3 where would we be going with that? And, I guess, is it
4 a combination of things or is it one at a time?
5 DR. GILL: I mean, the simplest thing is the
6 health of the graft has to be the first aspect of that.
7 So you'll notice that I put GFR in all of those things.
8 Everything else you add on into those subsequent
9 subgroup types analyses I think are things that we're
10 hoping that we can target to improve future outcome,
11 but the crux of it all has to be allograft function, at
12 least in my mind.
13 DR. STEGALL: And cardiovascular disease is a
14 big one.
15 DR. JARDINE: Well, I think NODAT is probably
16 the best, to find one where there has been a study with
17 that as the primary endpoint. We know the instance
18 over the first year. We know the implications after 1
19 year are worse for the patient than acute rejection, I
20 mean, it carries a mortality risk and greater than
21 acute rejection does, and we know a strategy that would
22 minimize that, we just don't use it. So perhaps Flavio

1 would like to say something of his trial.
2 DR. VINCENTI: Well, I mean, the point that I
3 wanted to make is that we have to shift the emphasis
4 from just looking at rejection as the all-important
5 endpoint. I mean, graft survival and patient survival
6 are clearly the gold bar. I mean, nobody is going to
7 touch that. Every drug has to produce similar results,
8 I mean, no question about it, we can't afford to
9 compromise on those. But can we afford to compromise
10 on some rejection if we get no diabetes, if we get no
11 hypertension, if the cardiovascular risk factors are
12 markedly decreased? So that's an issue. It could be
13 that a new drug, a new antibody, could target as all
14 the endpoints being renal function, diabetes,
15 hypertension, and only as secondary endpoints, acute
16 rejection and maybe antibody-mediated rejection, you
17 know, the bad rejection. And it's a question of
18 emphasis and balance I think that we ought to
19 reconsider in the way we design our trials.
20 DR. GILL: I think Jesse touched on that as
21 well. How we weight those things that Flavio just
22 listed off, and the only point I think I'm adding is

1 that that weighting might actually be individualized
2 based on the biggest risk for the type of patient or
3 subgroup of patients that we're looking at. So a
4 patient who is high immunological risk, those other
5 things that Flavio listed would be lower down on the
6 list or weighted less, but in a patient where
7 cardiovascular disease is probably the mechanism that
8 they're going to lose their graft through, you would
9 weight them higher.
10 DR. SCHOLD: I would agree with that. The
11 caveat is these weighted outcomes may not necessarily
12 resolve the issues that we're discussing. In a lot of
13 contexts, you might have these components go in
14 opposite directions, if we take the BENEFIT trial, for
15 example, you might have less power to detect outcomes
16 if certain endpoints go in different directions. So I
17 think it's an attractive option and something we can
18 explore, but it's not necessarily a cure-all either,
19 and it also is dependent on us coming up with agreed
20 upon indices and weights for these respective outcomes,
21 which, as has been described, often can be
22 heterogeneous in and of themselves. So I think it's

1 something to explore but not necessarily to take
2 lightly in how to implement it. The devil is sort of
3 in the details.
4 DR. GILL: No, just briefly, I agree with
5 that, Jesse, but the fact that these things might go in
6 opposite directions might be the case because you're
7 looking at the entire study population as a whole, they
8 might walk together in certain types of patients and
9 only diverge in -- you know, I think that's the whole
10 issue of the heterogeneity of the people in the trial.
11 DR. SCHOLD: And I agree with your concept
12 and I agree with that thought, and I think it's
13 important to take those different endpoints into
14 consideration, so I'm not discounting the use of that,
15 I think that's actually very valuable to know, I'm just
16 saying with respect to making our studies more powered
17 and dealing with the issues that we're talking about in
18 terms of fewer endpoints, it may not necessarily
19 resolve it in the direction that we hope for.
20 DR. STEGALL: Randy, then Flavio.
21 DR. MORRIS: Yeah, I would like to ask Alan
22 and George to help us out a little bit with a trial

1 where the design of the trial is not to show non-
2 inferiority for the efficacy of the drug but perhaps
3 superiority at 1 year with a surrogate endpoint of,
4 say, creatinine or GFR, in Alan's case, or NODAT, in
5 George's case, for risk of cardiac death 5 years down
6 the line. Is that sort of surrogate endpoint at 1 year
7 predictive enough to be reasonably comfortable that a
8 certain value for renal function, in Alan's case, and
9 NODAT, in George's case, can predict cardiac death? And
10 if so, do you have any numbers?
11 DR. JARDINE: I'm not sure I can answer that.
12 I think --
13 DR. MORRIS: Yes or no would be all right.
14 (Laughter.)
15 DR. JARDINE: I think yes, as a way forward,
16 and we have to find to a way forward. We have to
17 restructure this so that we can do trials in a
18 functional timeframe and move forward. And if you
19 like, at the end of 1 year, if you have the
20 cardiovascular risk factors, you can predict -- perhaps
21 better than you can predict graft outcomes, you can
22 predict human outcomes.

1 With regard to the size of the study, I
2 really don't know.
3 DR. MORRIS: No, what I'm getting at, Alan,
4 is, what sort of level of decreased renal function, no
5 matter how you measure it, is going to be predictive of
6 cardiac death? You showed data, and there are lots of
7 data from Fellstrom and Holdaas and those guys --
8 DR. JARDINE: My favorites. I mean, the
9 lower the eGFR, I think the greater the increase in the
10 -- I mean, it's a huge increase for the GFR --
11 DR. MORRIS: How low?
12 DR. JARDINE: I think something like 5 mLs
13 per minute as a difference --
14 DR. MORRIS: Okay, that's worth -- I'm not
15 holding you to that, but I just wanted to try to get
16 some specificity here.
17 DR. BURKE: Well, you can take that from the
18 FAVORITE trial, that the 5 mLs made a difference as it
19 was a stage below 45. I think, first of all, I would
20 say yes as well, and that the study could be designed
21 with those endpoints in mind.
22 DR. VINCENTI: And just maybe to add further,

1 you know, I think there is enough data that we can get
2 from registry data to have a risk predictive model that
3 is validated that could be used at 1 year for the
4 cardiovascular risk factors and cardiovascular risk
5 events. You know, I think if we look at the various
6 studies that have involved these risk predictive models
7 and we can revalidate them from database and then use
8 them for clinical trials as maybe the important
9 endpoint. I don't see why this is not feasible. And I
10 think it would facilitate a lot of tasks in terms of
11 designing trials that could have long-term impact but
12 short-term follow-up.
13 DR. STEGALL: Because we kind of do this
14 already, I think people do this already in clinical
15 practice anyway. I think that they have different
16 immunosuppressive regimens for people who are 65 than
17 people who are 25, and I think that there is not a lot
18 of data other than, you know, "I know what works," kind
19 of approach to things, but I do have sort of a soft
20 spot in my heart for this kind of approach, for the
21 quality of life and -- I'm not sure we're going to make
22 every 65- year-old type 2 diabetic live 25 years, but

1 you could actually add 5 years of life as a big
2 percentage increase.
3 Eli Katz, who is the next one.
4 DR. KATZ: Yeah. I think, based on what
5 Randy asked and what the discussion is going on, I
6 think the challenge here, we're sitting in front of the
7 Agency, and we are here because the Agency
8 called us to be here. I think we need to understand
9 that if we think today: What kind of a drug do we need
10 to develop or we would like to develop in
11 transplantation? What do we need to develop? What new
12 drugs, as a drug developer, I need to think that I want
13 to bring to the market? In what area?
14 So any immunosuppressive drug, as a global
15 immunosuppressive, as we said this morning, if I just
16 show that there is the same graft survival, patient
17 survival, and rejection rate, nobody will buy it, so
18 why should I develop it? So I need to show
19 differentiation in other areas, like diabetes,
20 cardiovascular, or GFR, but to do that, the Agency need
21 to accept study, a protocol, that the endpoints are
22 cardiovascular, diabetes, or GFR, and not coming back

1 to us and saying, "No, GFR is not a good one because A,
2 B, C, D, and E. You go back and do graft survival,
3 patient survival, and rejection rate."
4 Now, if we talk about other type of drugs,
5 let's say drugs that are supposed to improve DGF or
6 drugs that are supposed to address antibody-mediated
7 rejection, overall antibody issue, then okay, so then
8 we need also new endpoints to develop these drugs,
9 because if I'm going to develop a drug for DGF, I want
10 to do a study which is 3 months duration and actually
11 related directly to the issue of DGF and not to go back
12 to -- you know, I don't want to repeat again and again,
13 graft survival, patient survival, and ACR.
14 So I think all of us agree here is that the
15 issue now in 2012, the issues that we face in
16 transplantation are different than we faced before, and
17 in order to develop drug to address these new
18 challenges, we need new endpoints that are actually
19 going to be accepted by the community, academic, and
20 science, and by the Agency, and I think this is the
21 challenge that we have, and I'm sure, and maybe we are,
22 coming today from this discussion with better ability

1 at least to start doing that because I think that's
2 what we need to do.
3 DR. STEGALL: Thank you, Dr. Katz.
4 Bruce.
5 DR. KAPLAN: Just one cautionary note. Using
6 the registry data and relative risks and hazard ratios
7 in terms of assuming that if we change it -- remember,
8 when we look at registries, we're looking backwards and
9 saying, everything else being the same, if you change
10 that, you'll have an increased risk. We're here, all
11 sitting here, agreeing that acute rejection may not be
12 the best outcome, yet I'll tell you from a registry
13 standpoint, it has the highest relative risk. Now,
14 maybe there are other collinear confounders that are
15 not part of the capture in the database, it may be a
16 marker for other things.
17 The only thing I would want to be -- I'm not
18 negating it, it's just a cautionary note that anything
19 we generate from retrospective associative studies,
20 it's not necessarily going to be on the causal pathway
21 nor if we change it will we change the outcome. I
22 think that needs to be proven as opposed to taking it

1 as a given from a registry study.
2 DR. PLOEG: Okay, another point which was
3 voiced several times was numbers. We say, well, of
4 course, depending on the assumption, we go from 100 to
5 400 to 1,000 or to multiple thousands. Some of the
6 developments have voiced to go from a conventionally
7 powered study design to sequential design, and I would
8 like to have the opinion -- maybe Jesse can comment on
9 that, or maybe Bruce has an opinion -- is that an
10 alternative which earlier will detect the validity or
11 not.
12 DR. STEGALL: Jesse?
13 DR. SCHOLD: So I think the idea of utilizing
14 adaptive designs, as they're framed in some of the
15 recent literature, has caught a lot of momentum and I
16 think has a lot of potential. So the basic concept,
17 for those of you who are not familiar with it, is that
18 as the trial goes along, at some point, typically at
19 one or two points, the study is reanalyzed to evaluate
20 if it's meeting the a priori assumptions of the trial,
21 and if it is not, to essentially adapt the design so
22 that you're not having a longstanding trial that is

1 underpowered or not meeting these assumptions that
2 ultimately is going to lead to something that is very
3 difficult to interpret. So, in theory, I think there
4 are a lot of attractive elements of that.
5 There are a lot of practical limitations of
6 those. They're hard to pull off. There are a lot of
7 logistics involved in having to change along the way.
8 You do pay some penalty statistically when you look at
9 the data, so there are things to trade off in
10 determining that. These were traditionally used in
11 dose finding in Phase 1/Phase 2 but have been utilized
12 more and more now in further clinical trials.
13 I think there is some utility and I do think
14 there is some potential utility in using Bayesian
15 methods, in taking information from a priori studies,
16 the caution there also, though, is that there are a lot
17 of assumptions embedded there in utilizing Bayesian
18 methods and that the a priori assumptions are going to
19 be met in the prospective trial, and failure to have
20 concordant assumptions can actually lead to more
21 conservatism in a Bayesian trial than would be in a
22 Frequentist trial.

1 So all of these I think are things that we
2 should think about, all of these have potential to
3 enhance the situation in which we're struggling with
4 sample size and are attractive options, but we have to
5 pay, of course, special attention to the caveats that
6 come with all of these, as there are tradeoffs, as you
7 would expect.
8 DR. PLOEG: Thank you. Bruce and then Marc.
9 DR. KAPLAN: Yeah, the only thing I would say
10 is I agree with Jesse, and using these conditional
11 probabilities actually started with game theory, and
12 anyone who knows the Monty Hall paradox will understand
13 this, that as you gain information, you're almost
14 obligated to change your choice. I won't go into it.
15 Nonetheless, the problem with that is it is so
16 counterintuitive and it's so difficult to calculate,
17 I'm not sure we would be able to carry it off, yet from
18 a probabilistic standpoint, trying to design -- that
19 would be the best way to design a study if you could
20 pull it off, if you go back to actually game theory.
21 DR. LORBER: So my comment is related to the
22 issue of trying to apply adaptive design to the kinds

1 of trials that we talk about, especially in a field
2 like transplantation, because we've struggled with this
3 the whole time that I've been on this side, and I'm not
4 a statistician, and I'm not going to speak statistics,
5 but the reality is that by the time you get to a point
6 where you would make a decision on the adaptive
7 pathway, you've enrolled 95 percent of the patients in
8 each of the arms that you've already set out to enroll
9 in, and so it becomes kind of moot.
10 MALE SPEAKER: That's not true.
11 DR. SCHOLD: Well, that may or may not be the
12 case.
13 DR. LORBER: It works for dose finding, don't
14 get me wrong, it works in that setting, but when you're
15 talking about larger confirmatory trials, it just
16 doesn't -- we've not been able to make it work.
17 DR. SCHOLD: And I agree, there are a lot of
18 logistical challenges of those, but on the other hand,
19 it's much better to know 3 months into a trial if
20 things are headed in a direction in which patients are
21 being enrolled in a trial where you're not going to be
22 able to learn anything and prove anything definitely

1 either way, save a lot of resources in following up
2 from 3 months to 12 months and potentially be able to
3 adapt the trial so you can find something out at that
4 point and enroll more patients or change what the
5 enrollment criteria are at that point. So in theory,
6 in theory, there is a lot of utility for doing that.
7 Now, I agree, there are a lot of logistical impediments
8 in pulling that off, but if done correctly, I think
9 it's something to consider.
10 DR. LORBER: Yeah. The idea comes up every
11 time that you start to try to design a trial, and then
12 sort of reality sets in, and we just haven't been smart
13 enough to figure out a way to make it happen. That's
14 what I'm trying to say.
15 DR. PLOEG: Well, the reason I actually
16 brought it up is because of a recent trial which was
17 done that way by Cambridge looking at DCD and pumping
18 as an outcome DGF, and after 43 donor passed, had to
19 stop because they hadn't fulfilled the adaptive
20 criteria while at the same time we were doing without a
21 conventionally powered design including 188 two-sided
22 test, and so forth, the same kind of thing.

1 So the question then was, is it the
2 methodology adaption which made the difference because
3 they couldn't see a difference, and we did see a
4 significant difference, or was it more the material of
5 the trial?
6 So what we did then is we simulated with our
7 trial set, which was a complete trial set, whether we
8 also would have been forced to stop following their
9 sequential adapted trial design, and we were not. And
10 also with a sequential design, we would have shown the
11 same outcome as with our conventional powered. So it
12 was the material included in the study in England. But
13 it brought kind of to my mind the question whether it
14 would be a valid alternative or not.
15 I saw another hand then.
16 DR. ALLOWAY: I think that you basically made
17 the comment, but I think when you look at adaptive
18 trial design related to what Dr. Lorber was saying, you
19 have to look at the timing of your endpoint. Again, if
20 we have a 300-patient study and we're looking at acute
21 rejection rate at 1 year, it's not going to work, but
22 maybe if we are looking at the incidence of DGF where

1 we define it as dialysis within the first 7 days, it
2 should.
3 DR. JARDINE: We haven't made much of
4 noncompliance, or as much as we might, and in fact if a
5 study is a year long, the proportion of patients who
6 are taking the drug at the end of year tells you a
7 whole lot, it tells you a whole lot about tolerability,
8 it tells you about efficacy because you often change
9 drugs for efficacy failure. Should that be included as
10 a component of primary endpoint?
11 DR. HARLER: Hi. At the risk of sort of
12 complicating the discussion at nearly the end of the
13 meeting, I was wondering if we could take just a moment
14 to talk about comparative efficacy and assignment of
15 controls, getting to the point around the dynamic
16 tension between results that are clinically informative
17 versus those that pass regulatory muster; right? And
18 how do we come up with a feasible study that can be
19 conducted within a reasonable period of time with
20 realistic treatment effect that can be projected in
21 today's environment? I think the belatacept program
22 may be a very good example, you know, comparison

1 against standard of care 7 to 10 years ago, but, lo and
2 behold, at the time of approval, one could argue that
3 these results are less than clinically relevant. And
4 this is certainly not unique to belatacept, this has
5 been a challenge for every drug approved in this space,
6 but I think as we talk about specific patient
7 populations with significant unmet need -- a la Marc's
8 comments and other's comments -- are there any
9 allowances that can be made, frankly, to enable use of
10 standard of care regimens in order to address these
11 unmet needs? Perhaps we need to think a little bit out
12 of the box given appropriate safeguards. Summary Day 2
13 DR. ALBRECHT: So I think we're coming to the
14 close of this 2-day workshop, and I think to follow up
15 on the idea of thinking out of the box, I want to
16 actually thank and acknowledge all of the excellent
17 presentations and especially all the thought-provoking
18 discussion where I think we've all been trying to think
19 out of the box. I think we did acknowledge that in
20 2012 we know the history of the drug development in
21 transplantation, the importance of patient and graft
22 survival and our historical use of acute rejection, but

1 I think we've also during the past 2 days made
2 comments, and I think taken the first steps in perhaps
3 a new direction in addition to not forgetting how we
4 got here historically because we still need to be
5 paying attention to patient and graft survival.
6 I think we've had a lot of questions asked
7 and not as many answers, but I think the answers are,
8 as someone said, what we need to work on: that is the
9 challenge facing us.
10 I think we heard discussion about acute
11 rejection but also about thinking about it in a
12 different way, maybe not all acute rejections have to
13 be taken as an absolute failure, but we need to balance
14 them against other possible benefits.
15 I think we've heard some discussion about
16 whether we can look at other endpoints that haven't
17 been conventionally the ones we've used. Well, first
18 we do need to agree on some basis of efficacy. I think
19 this was the point made in one of the early
20 presentations. We need to persuade ourselves that a
21 product is effective, but as was said, maybe our
22 definition of efficacy is one that we can revisit. What

1 do we really mean by a product being effective as an
2 immunosuppressant?
3 I think we also heard about looking at new
4 designs. We recognized all the challenges of powering
5 by the old endpoints, but then the thought was perhaps
6 we can look at new designs. Although the word was not
7 used, it sounded like an enrichment trial design where
8 we would look for patients in whom were likely to
9 demonstrate an effect. Much of that discussion was
10 about treating patients who currently break through
11 their immunosuppression and get into difficulty with
12 rejections, whether they're DSA related or chronic
13 rejection and other analogous terminology. But along
14 the same lines, we could even be looking at preventing
15 the development of untoward events such as antibody-
16 mediated rejection be it acute or chronic.
17 I think we also heard some discussion about
18 new statistical methodologies, normalizing adaptive
19 trial design, Bayesian trial design. So all of these
20 ideas are ones that I think we heard a little bit about
21 but need to be worked through a little more.
22 I think there was mention of other

1 therapeutic areas, so can we learn anything from those
2 therapeutic areas? I think all of us can independently
3 go and try to identify a little bit of: What have
4 other therapeutic areas done and how applicable is that
5 to the area of transplantation? I think some may be,
6 some may not, but again that is the challenge that
7 faces us.
8 And I think we are acknowledging that
9 this is a difficult undertaking, but I think we also
10 heard, for example, about the possibility of PRO, and
11 then we heard our patient representative, who talked
12 about knowing what her creatinine is for the past 20
13 years. Well, at FDA we don't think of creatinine as a
14 PRO, but perhaps we have to think differently. And I
15 was struck when she talked about her labs as a report
16 card because
17 I think there is a connotation to what a
18 report card means, it means: How well are you doing?
19 So again I think thinking out of the box and
20 thinking of new study designs, new endpoints, is
21 something that I hope we embark on together. And I
22 look at this as either a beginning or a continuing

1 dialogue, and I think we need to continue this dialogue
2 because I think in the long run we saw the graph where
3 patients are doing better, but they still could do
4 better, and I think that's really the goal of
5 developing new therapies to allow patients to do even
6 better than what they are already doing, and what's
7 already happening is, of course, a testament to all the
8 hard work that has preceded us. Adjourn
9 DR. ALBRECHT: So thank you again. Thank you
10 to all the speakers. Thank you to all the moderators,
11 all the discussants, and safe trips back.
12 (Applause.)
13 (Whereupon, at 2:45 p.m., Day Two
14 of the "FDA Workshop: Endpoints in
15 Clinical Trials of Kidney Transplantation"
16 was adjourned.)
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1 CERTIFICATE OF NOTARY PUBLIC

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11 interest in this proceeding.

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19 NATALIA THOMAS

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01 233:4

1

1 6:9,12 8:1,4 10:22 11:2 21:5 24:4,5 35:21 40:18,21 42:19 43:6,10,13,16 47:6,9 49:8,19 50:7 51:18 56:10 57:16 66:4,12 93:9 95:11 100:16 101:2,10 103:10 104:2 106:5 107:7 111:5,12,19 112:9 113:2,6,13,15 115:19 116:3 118:3,12 119:5,6,10,17 120:2 123:2 125:9,22 126:4,5 128:19,22 131:21 132:4 133:4 136:14 137:12,14 140:4,9,15 144:11 151:21 154:9 170:17 171:2,9,17 172:5 173:4,5 179:22 180:17 181:12 189:16 192:18 203:3 205:19 206:15 207:8,13 210:19 219:4,8 221:8 255:2 257:18 261:3,6,19 263:3 272:21
1,000 192:18 267:5
1,300 44:14
1.2 94:16 204:20
1.3 57:9
1.4 57:9
1.5 250:2
1.6 57:17 205:7
1.8 191:8
1/2 43:11
1/Phase 268:11
1:00 199:13
1:1 209:10 211:11
1:15 199:16
10 6:4,7 14:7 17:1 20:22 32:2 46:17 50:22 55:10 57:7 62:14 67:21 84:12 88:1 110:5 127:19 136:5,17 156:4 168:18 169:10 174:3 199:13 206:13,18 219:5 233:8 234:12 239:22 274:1
10,000 233:6
10:00 92:19 93:10
10:04 92:20
100 11:17 16:1 101:21 138:5 173:15,19 183:15 267:4
100,000 212:18,20
101 246:20
10-mL 246:12
10-year 168:15,22
11 1:9 6:12 87:14 88:1,9 208:11
11.6 191:6
12 24:11 46:11 47:2 48:21 57:6 104:16 121:5 124:18 145:1 172:1,5 192:19 201:7 204:6 237:12 271:2
12:00 144:5
12:10 199:16
122 51:9
129 211:14
12-month 36:14
12-year 201:5
13 24:13 118:21 208:7
130 167:2 174:5
14 173:16,17 219:4
140 167:1
143 7:21
144 8:4
15 24:13,14 26:13 33:5,21 50:17 84:12 92:16 111:5 117:8 156:4 176:22 208:10 234:12,15
150 85:4,6 170:8
15-year 68:14
16 33:5
162 8:7
174 174:2
175 8:12
18 111:6 171:4
188 8:15 271:21
1910 12:18
1937 12:19
1959 16:21
1968 27:18
1980 183:9
1983 233:19
1990s 187:15 218:4
1998 59:3
1999 173:6
1-year 34:16 42:15,17 47:10,16,21 48:20 49:1 51:5,14 104:9 132:17 136:1,9 137:16 147:8 152:8

2

2 6:14,17 8:6,7 9:13,15 17:4

26:8 36:1 43:10 48:9 50:10 64:18 66:5,14 79:18 80:5 85:18 87:6 92:18 94:19 100:16 115:19 117:9 129:15 132:4 135:21 138:22 152:8 163:2,12 176:12 190:21 203:3 210:19 211:13 224:12,13 242:8 250:7 263:22 268:11 274:12 275:1

2,000 233:7 243:5,7

2,300 63:18

2,700 62:22 63:17

2.1 173:13

2.3 87:2 205:10

2.4 205:2,16

2.5 45:21 50:11

2.6 49:1 85:18

2.9 205:2,16

2:45 278:13

20 19:8 42:22 46:18,19 62:20 67:5,7 101:9 105:18 111:11 112:3 113:5 117:11 125:16 151:22 201:8 207:9 210:1 211:15 217:6 247:11 277:12

200 8:18 16:1 36:22 131:18 237:22

2000 42:14

2001 173:8

2002 48:5 60:12

2003 48:6 165:15

2004 218:16

2005 42:14 61:16 165:15

2006 183:9 192:15 196:19

2007 189:14

2008 20:5

2009 17:9 42:1 166:15 197:3

2011 205:12

2012 1:9 173:9 265:15 274:20

2015 279:22

20-percent 51:8 130:14

21 279:22

2-1/2 43:11,13,15 49:7 113:22 224:13

214 8:22

215 173:7 174:12

22 103:13

228 9:4

24 53:21 69:7 192:19

241 9:7

24-hour 47:19

25 60:7 62:1,10 69:17 220:20 263:17,22

25,000 50:1

250 207:1

255 9:11

25-percent 60:9 61:1 63:9 96:7

25-year-old 201:4

26 6:17 80:12 118:22

26-mile 80:10

27 50:17

273 9:13

277 9:15

28 50:17

29 42:22

2-day 274:14

3

3 6:19,21 8:9,11 17:15 24:3 32:2,13 35:16 39:18 44:17 45:11,19 46:11,15,22 47:1 48:21 50:12 56:11 61:11 64:19 84:13 88:7 113:1,2 125:9 133:4 139:17 151:1 165:9 175:7 176:12 191:3 192:2 203:3 218:12 219:4 220:21 225:17 265:10 270:19 271:2

3.4 50:14

3:00 1:11

30 21:10 22:19 28:3 42:22 67:5,8 167:6 173:20 197:3 210:10

300 221:22

300-patient 272:20

30-year-old 55:9

31 170:16 173:4

3-1/2 208:8

32 171:1,8

32,000 48:8

33 85:17

332 42:2

34 51:20

35 210:6

36 89:12

38 171:3

39 6:21 42:22

3-year 80:5

4

4 7:1,3 8:14,15 21:6 36:11,18,21 50:14 53:12,16 101:10 137:17 184:22 188:11 191:7

4,000 131:6

4.2 174:2

40 34:17 42:5,6,18 43:1,5,14,16,19 53:1 67:8 104:21 111:14 118:1,2 142:6 151:22 170:7 174:3 180:1 201:11 210:6,10 211:20

400 267:5

40-percent 246:3

41 173:10

43 173:15 271:18
45 166:10 262:19
460 63:18
46-year-olds 63:20
48 49:12
49 43:18
4-percent 201:7

5

5 7:5,9 8:17,18 40:20 41:4 43:11 49:19,20 50:9,16,17 51:2 70:14 84:13 88:11 102:20,22 103:9 104:8 106:5 111:12 112:9 113:6,10,14,15 118:4,12,19,20 119:8 120:14,22 124:22 125:22 126:4 131:21 136:5,17 156:4 174:8 190:12 200:11 205:9 219:4,5 220:11,13 234:10,12,16 261:5 262:12,18 264:1
5,000 21:1
5.4 173:13
5.7 48:13
50 48:14 55:8 63:20 110:5 159:7 170:7 201:9,10 207:16 208:7
50-percent 201:6
50s 54:13 55:1,3
52,000 220:11
53 7:3
55 28:12 174:5 233:5
553 51:10
58 192:14
59.1 212:21
59.9 233:8
5-year 50:11 67:5 101:20 120:3 211:14

6

6 6:6 7:11,12 8:20,22 10:5,11,16 24:3,4 28:14 42:5,9 56:8 57:2 58:12 77:18 79:18,20 87:13 88:7 104:16 124:18 171:15 189:16 190:6 214:16
6.2 51:6
60 19:8 23:13,14 32:12 42:19 51:7 53:2 85:6 89:15 100:12 105:16 151:1 170:14 173:3 201:10 233:4 255:8
60.1 233:8
600,000 238:11
60s 54:13
60-year-old 174:11
62 168:19
63 171:13
65 43:14 207:1 233:5 263:16,22
67 154:21
67,000 192:15
675 49:10 50:1
6-month 42:3 49:18 52:17 73:7

7

7 7:19 9:1,4 38:1 42:7 53:6 87:19 88:15 89:14 141:9 143:17,21 207:8 210:13 228:18 273:1 274:1
7.4 49:2 50:8
70 7:9 46:16 49:12 110:4 151:1 173:19
70,000 44:15 100:10
77 42:10 173:16
788 49:8
7-year 186:5

8

8 9:6,7 94:13 241:22
8:00 1:11
80 7:13 32:12 34:17 43:12 167:3 174:5 221:16
800 234:15
82 207:9
84-'89 60:12
85 41:4 117:10 118:6
86 64:10
8777 1:15
896 42:15 49:5

9

9 106:4 250:3
9:47 92:20
90 46:20 61:19,21 63:3,6 64:3 167:2 202:5
90-'94 60:12
90s 66:10 189:14
91 64:9
93 7:17
95 230:17 270:7
95.8 230:18
95-'98 60:12
99 60:12 239:18

A

a.m 1:11 92:20
A1c 165:8,9 168:20,22 173:13
A1c's 169:6,8
abdomen 15:21
ability 149:4 151:5 265:22
ablation 91:16
able 33:9,22 42:15 95:9 115:9 119:10 124:12 132:6 134:9 151:15 152:17 160:14 177:15

185:18 194:22 247:2 250:4,16 252:15 253:13,17 269:17 270:16,22 271:2

abnormal 159:14

abnormalities 219:17

absence 255:3,13

absolute 69:20 275:13

absolutely 132:21

academic 119:18 265:19

accelerated 71:22 72:5 85:10 119:16 137:14 140:4,9 141:6

accept 239:6 264:21

acceptable 23:17 25:1 134:1 154:3

accepted 134:12 140:17 265:19

Accepting 113:4

accompanied 26:17 81:19

accompanying 59:5

according 170:3

accountable 136:16

accounts 176:16

accumulate 177:6 208:10

accuracy 22:4 23:15

accurate 52:16 122:2 279:7

ACE 81:14,22 83:8

achieve 12:12 28:19 29:3 38:3 53:3 160:1 216:18 240:18

achieved 211:3 216:17 217:19

Achilles 29:12 245:2 252:7

acids 67:14

acknowledge 274:16,19

acknowledging 277:8

ACR 140:17 141:5 265:13

across 20:15,22 62:1 98:8 183:9 196:20 229:5

act 242:4

activation 30:7 90:13

activity 164:8

actual 8:1 27:22 144:7,11 159:15 207:5 211:4 256:3

actually 12:17 15:17 18:14 20:3 27:7,19 29:3,10 30:3 31:4 32:5 36:4,10,19 40:20 41:3,5,12 42:11 43:17,19 45:18 46:6,19 48:18 49:11 50:21 51:1 59:2 67:7 85:19 86:20 95:9 100:1,4 101:8,9,17 103:9 105:17 108:9 111:14,21 112:5 114:10,18 117:12,14 118:1 119:12 122:19 123:9 124:7 126:14 128:6 132:5 141:2,9 146:2 147:6 148:20 151:2,11 152:2 153:17 156:15 160:6 164:21 193:11 194:22 197:3,6,20 198:3 203:4 206:10,19 207:14 208:1,7,17 209:12 212:1,12 214:3 216:17 218:18 223:2 230:1 233:21 234:10 235:11,18 236:2,18 237:17 239:13 240:7 244:5,12 245:12 246:13 252:16 256:5 259:1 260:15 264:1 265:10,18 268:20 269:11,20 271:15 274:16

acute 45:15 60:17 63:2 64:7 88:4,8,18 90:3 102:9 151:6 164:12 168:11 187:1 215:20 217:21 222:7 223:16 228:1 246:2,4,6 257:19,21 258:15 266:11 272:20 274:22 275:10,12 276:16

adapt 267:21 271:3

adaptation 28:9

adapted 272:9

adapting 174:19

adaption 272:2

adaptive 28:15 267:14 269:22 270:6 271:19 272:17 276:18

add 20:18 23:15 59:16 102:16,21 135:12 142:3 186:20 187:6 201:8 217:8 224:16 257:8 262:22 264:1

added 83:15 120:19 186:21 187:5 224:3

adding 184:3 187:9 258:22

addition 172:12 173:11 275:3

additional 49:6 90:15 124:20

address 20:11 71:1 72:12 74:7 78:20 146:9 157:8 162:14 219:14 265:6,17 274:10

addressed 18:9

Addressing

154:13
adequate 28:16 139:16 223:17
adhere 95:16
adherence 154:12 155:9,10 156:2,10,16
adjourn 9:15 199:12 278:8
adjourned 278:16
adjunct 220:12
administration 1:7 193:22
admit 216:9
adult 44:14
advancement 145:11
advantage 168:12
advent 190:15
adverse 166:10 171:4 182:21 185:18 245:13
advice 83:11,16
advocacy 192:21
advocate 108:10 189:3 193:8
advocates 157:16
advocating 109:3
AE 203:13
AEs 203:14
affect 30:7 34:8 35:14 88:20 124:21 222:8 227:9 228:1
affected 12:14 22:14 29:19 36:14 88:19 94:3
affecting 95:1
afferent 90:22
affiliated 26:18
afford 226:2 258:8,9
African 129:9 164:2 167:11
afterwards 88:2 131:1 175:21
against 186:4 191:22 194:6 274:1 275:14
age 21:13 25:7,8 28:6,9 30:20 31:1,18 32:17,18 35:8 36:15 55:12 56:18,21,22 58:6 62:17 72:20 73:3,7 164:1,16 173:4 177:21 183:19 185:15 201:10 251:16,18 253:7
agency 205:18 264:7,20 265:20
agent 204:13 227:19
agents 38:18 153:5 161:1 164:13 184:2,10 197:13 204:9 216:13 217:18 218:3 219:18 222:13 226:5,6,11,15 227:2,22
aggravate 227:8
ago 55:19 56:6 179:18 194:21 196:4 217:5 223:20 242:8,9 249:13 274:1
agonal 35:3,20 36:12,20
agreed 62:1 119:9 120:17 259:19
agreeing 266:11
agreement 156:21
ailments 253:1
aircraft 124:8
AJT 166:8,15 178:16 196:13 197:2 209:7 245:20
al 48:17
Alan 3:13 8:11 175:2,5,8 243:1 260:21 262:3
Alan's 261:4,8
alarming 151:4
Albrecht 2:3 10:10 143:15 144:2 199:22 274:13 278:9
albumin 84:20,21 174:1
albuminuria 74:1,12,16 75:3 129:2
alemtuzumab 192:10
ALERT 165:15,22 176:14,21 177:13 180:6,21 181:20 185:12,20
algorithm 33:10
alive 65:15
all-cause 176:16
allergy 15:1
all-important 258:4
allocate 159:22
allograft 7:7 61:8,10 70:11,16 85:21 111:17 114:13 117:9 164:20 165:1,2 166:3 170:21 171:5,6 172:10 257:11
allografts 75:16
alloimmune 92:9 220:2 226:1
allorejection 112:4
allow 38:1 147:1 149:21 152:1 154:14 162:5,7,15 174:19 234:3 236:17 247:15 278:5
allowances 274:9
Alloway 2:5 8:4 144:9,13,14 272:16
allowing 53:19 163:6 220:2,5 240:4 241:9,10,12
allows 148:9 231:10 239:15,17 240:5
alluded 39:8 67:1 172:8 176:14 250:18
alluding 244:13 249:13
alone 147:15

203:17
ALPHABETICAL 2:1 3:1 4:1 5:1
already 18:13 26:19 30:7 38:9 39:7 41:14 57:22 59:10 61:6 67:1 71:14 72:19 73:5 77:16 78:15 80:13 92:6,8,12 103:12 158:21 206:5 230:6 242:8 250:18 256:11 263:14 270:8 278:6,7
alter 179:9
altered 12:13 60:22
alternative 146:22 151:10 267:10 272:14
alternatives 11:16
alters 59:21 67:17
am 11:6 25:16 107:17 145:3 242:6 279:8 280:3
America 174:4
American 129:9 146:1 157:4 171:12
American-like 171:4
Americans 97:1 164:2 167:11
amino 67:14
among 18:4 81:16 82:9 148:17 155:5 170:5 192:15 238:8 253:6,7
amongst 107:14
amount 87:1 230:12
amounts 91:18,19
AMR 139:10
analogies 129:7
analogous 276:13
analogy 83:1 118:17,18
analyses 60:5 65:6 149:18 150:3,21 241:8,9 249:19 257:9
analysis 15:8 33:19 37:4 52:18 62:10,17 65:9 86:14 89:13 146:8,10,17 147:1,13,15,17 148:6,14 149:10,12,21 150:2,4 151:9,10,12 178:15 180:16 182:5 210:21 211:20,21 248:14,22 249:10 250:5,11
analytical 15:7
analyze 25:18 62:9
analyzed 146:12 178:14 212:1
analyzers 18:13
analyzing 145:6
and/or 167:12
Angela 244:8
Angeles 96:10
angiotensin 81:15,22 91:7 184:5
animal 30:10 90:7 91:11,20
animals 81:22
announcement 200:1
annual 48:11
annually 165:10
annum 176:13
anodized 105:14
answer 7:15 9:9 59:10 93:4 113:17 115:20 122:4 134:14 151:13 183:2 255:18 261:11
answered 119:14
answers 275:7
antagonist 63:1
anti 195:18
antibacterial 190:1
antibodies 17:21 224:10
antibody 47:18 79:9 125:10 223:18 224:12 225:9 258:13 265:7 276:15
antibody-mediated 90:4 102:14 223:8 227:5 258:16 265:6
anticoagulation 172:20
antihypertensive 80:16 164:13
anti-inflammatory 79:10
antioxidant 76:2,10
antiviral 190:2 195:15
anybody 98:2,6
anymore 14:10 136:10
anyone 60:9 120:16 133:14 136:13 200:1 269:12
anything 101:4 136:13 138:8 146:11 232:9 266:18 270:22 277:1
anyway 40:19 114:15 131:8 179:13 188:2 229:1 263:15
anywhere 163:11
ANZ 183:7
ANZ-USA 209:1,6
apart 34:5
apparent 87:6
appear 65:7 73:8 225:9
appeared 67:19
appears 28:14 223:11
appetite 134:8 168:9
Applause 26:2

39:12 53:11 70:6 79:16 92:14 162:18 174:22 188:5 199:10 214:9 228:11 241:16 278:12

applicability 91:11,20

applicable 83:17 84:17,22 85:1 277:4

application 11:15 25:4 248:22

apply 19:10 21:17 25:15 101:13 196:19 243:12,16 250:14,17 269:22

applying 124:10 249:4

appreciate 73:1 77:11

appreciated 10:5

appreciation 71:22

appreciative 141:11

apprehensive 175:17

approach 9:6 41:13 51:12 52:6,11,17 94:5 147:2 186:15 202:14,15 241:20,22 242:6 248:6,8,17,21 253:12,17 254:2 263:19,20

approached 161:9

approaches 16:8 52:1,21 202:2 212:11 233:14

appropriate 40:8 79:6 132:13 150:12,16 160:22 189:21 274:12

approval 119:9,10 134:9 137:1,15,16,18 140:4,5,9 141:6 232:14 239:7 241:13 274:2

approve 232:12 235:4,14

approved 81:17 205:12 274:5

approximately 119:6 176:16

April 173:6

arbitrarily 61:10

arbitrary 71:20 148:9

ARBOGAST 280:3,15

area 2:20 39:22 76:21 97:19 146:21 151:2 169:12,15 190:11 192:20 264:13 277:5

areas 158:14,16 264:19 277:1,2,4

aren't 72:10 106:2 193:3

argue 191:13 234:6 237:20 274:2

arguing 84:16

argument 72:21 73:10 217:21 219:19

arguments 70:22

arm 80:5,6 91:20 150:10,13,16 191:8 231:13

arms 225:17 235:19 270:8

arranging 54:1

arrays 98:8

arrhythmic 178:1

arterial 68:6

arteriole 90:22

Arthur 3:21 251:3,5

article 85:14 87:10

articulate 44:5

artist's 243:2

ASCERTAIN 69:3

aspect 107:4 257:6

assay 17:14 25:14

assayed 25:4

assays 18:12 25:2

assembling 144:15

assess 11:17 49:17 228:5

assessment 6:9 10:17,22 11:6 52:16 224:3

assign 252:1

assignment 235:18 273:14

Associate 4:7

associated 59:11,18 60:18,21 63:10 69:18 70:1 73:7,18 77:8 81:2,3,6 156:1 164:4,15,16,18,19,22 165:17 166:10,22 167:6,12,22 168:2,5,7 169:5 170:20 171:16 174:17 180:12,18 182:3,11,21 214:4 220:22 221:6 223:4 226:12 246:12

association 66:2 74:1,10,18 218:8

associations 18:21 83:20

associative 266:19

assume 140:8 246:11

assuming 266:7

assumption 81:1 267:4

assumptions 115:13 235:20 238:19 267:20 268:1,17,18,20

assured 212:3

assuring 210:3

AST 53:22

Astellas 2:21

ASTID 196:18

atherogenetic 75:2

atherosclerotic

171:11
attached 14:13,21
attempt 145:20 158:3
attempting 147:21 149:22
attempts 146:9 157:2 251:14
attention 41:22 79:15 92:13 190:18 199:9 205:4 222:6 241:15 269:5 275:5
attentive 174:10
attenuate 75:12
attractive 133:9 259:17 268:4 269:4
attrition 71:14 219:2,9
Atul 196:17
atypical 199:1
audible 143:13
audience 7:15 9:9 93:4 111:4 163:9 197:11 237:7 255:18
Australia 183:8 207:8 209:3,8
author 84:16 245:19
authors 19:16
author's 89:15
autoregulation 90:8
available 12:18,20 13:14,20 211:21
Avenue 1:15
average 14:19 50:7,14 243:10,15,19 254:14
averse 154:5
avoids 227:19 249:17
awarded 38:1
aware 41:18 75:11 76:9 179:20 236:9
away 93:15 112:21 127:20 147:1 157:8 227:15
axis 44:12 71:19 245:9
azathioprine 179:19 204:21

B

Baan 2:7
background 59:8 71:6 105:2
backwards 266:8
Bactrim 174:9 195:18
bad 64:14 102:19 110:17 120:18 127:17 135:14 173:22 209:21 217:16 258:17
Bala 2:9
balance 216:18,20,22 222:14 228:7 240:15 258:18 275:13
Balancing 8:20 214:13,16
ballgame 235:6
band 232:5
bank 111:19
bar 142:17,22 186:8 258:6
bars 186:7
based 12:3 16:18 22:9 49:22 62:5 80:6,7 81:8,11 82:11 129:12 133:6 157:12 198:11 207:6 209:12 235:4 241:13 259:2 264:4
Basel 3:17
baseline 25:20 40:8 44:3,6,8 45:4 46:22 47:3,4 52:4,7 56:4,8,9,10,11,14,16,22 57:1,3,6,9,18 58:3,7,11 59:15,18 60:1,2,20 61:22 62:10 63:5 64:2 65:21 69:7,15,20 77:17 223:22 244:20 247:2 250:2
basic 237:5,6,10 246:21 248:2 267:16
basically 13:10 19:8 20:16 28:13,22 38:21 55:10 56:2,17 63:8 65:14 66:1 96:5 122:15 128:14,20 137:22 143:3 146:13 147:13 151:22 152:16 169:22 200:20 243:2 248:9 272:16
Basiliximab 205:7
basis 12:4 37:11 47:22 49:8 118:17 140:11 145:7 275:18
Bayesian 160:21 161:5,10 234:3 241:8,9 248:3 256:14 268:14,17,21 276:19
be-all 74:8 236:22
beautiful 224:22
became 12:19 49:2 171:3
become 29:17 30:14 60:14 102:10 109:5 147:2 186:16 241:4
becomes 26:21 39:4 68:20 87:6 95:18 110:7 131:15 270:9
becoming 75:11
begin 40:4 61:16 152:11 153:1,6 160:17
beginning 44:2 51:12 81:10 85:7 107:21 139:22 141:18 153:9 232:11 233:21

277:22
begs 63:15 156:13 158:10
behalf 175:12 196:17
behaves 55:21
behaving 59:1
behavior 98:10 167:14
behold 218:10 274:2
belabor 77:10
belatacept 65:1 105:19 140:22 179:13 186:2 190:18 191:1,6,22 205:4,10 206:3 235:10 273:21 274:4
belatacept-treated 186:9
Belen 2:11
Belgium 211:10
believe 24:4 67:4 80:10 161:21
bell 234:17
belongs 226:5
benchmark 27:3,6
beneficial 75:5 82:19 212:10 245:13 246:17
benefit 23:22 64:17 69:8 81:19 82:2 92:10 108:5 114:17 119:13 147:11 157:8 167:14 168:10 186:3,6 190:21 200:16 220:4 243:18,19 248:16 249:12 259:14
benefits 90:18 186:2 221:14 249:7 275:14
benign 202:22
Bert 60:5 115:20 177:9 182:15 187:14 245:19 252:4
best 11:14 24:9 41:12 44:3 51:3 68:18 72:8 77:22 100:7,8 106:13 128:17 129:10 130:1 146:5 233:2,10 242:17 251:22 253:8 257:16 266:12 269:19
bet 247:10
beta 184:4
beta-trace 13:2
Beth 3:5
better 7:11 24:8 29:9 31:21 36:8 37:5,13 38:3,4,13,15 43:6 54:14,15 55:4 60:14 64:22 66:6 68:4 71:2,21 72:4 79:19,21 80:2,18 88:2 101:6,20 104:11 122:21 125:5 130:4 132:19 135:4 166:21,22 169:1,4 183:2,5 187:13 189:3 191:15,16 193:10,22 194:3,4,12,18 195:2 196:15,22 211:7 217:2,17 218:14 220:8 225:3 227:16 228:6 239:22 240:13 253:3 261:21 265:22 270:19 278:3,4,6
beyond 61:11,19,22 68:8 118:20 171:17 221:11
bias 16:16 17:13 18:3 23:13 24:14
biases 22:21
biggest 72:1 79:8 184:20 189:18 197:17 246:9 259:2
Bill 132:10
bimodal 203:1
binding 33:8
bioinformatics 39:7
biologic 130:12 132:8 197:13
biological 18:21 103:22 118:9 161:20,22
biologically 139:2
biologics 197:11
biology 4:9 41:7 113:1 114:14
biomarker 7:8 70:12,17 74:1,2 76:7 77:4 119:7
biomarkers 33:4,5,12 79:7 119:17 161:19
biopsies 62:6 63:17 105:7 125:18,19
biopsy 47:13 61:18,19 62:3,5,12,14 63:16,18,22 64:9,10 96:8 101:4 104:18 105:13 116:9 119:22 120:5 124:19 125:3,11 129:11,13 209:15 216:10 254:16
biopsy-confirmed 210:22
bioresource 37:9,12
bit 17:6 22:17 31:14,21 32:19 34:3 45:7,9 46:1 47:6 53:22 54:10 55:4,8,12 63:1 64:1 65:2 107:9 120:10 135:12 170:22 198:20 199:21 202:15 206:22 216:16 218:7 219:10 230:1 239:16 242:13 245:11 248:20 260:22 274:11 276:20 277:3
BK 45:15 47:19 195:7 196:1 198:21 217:12
black 44:22

191:21 206:4 246:1
blank 135:6
blinded 62:7 210:13
block 99:8
blockers 81:15 82:1 83:2 184:4,5 204:15
blood 12:18 79:12 81:17 89:5 90:8 174:4 178:5,17 180:13,17,22 181:1,4,8
blue 22:10 82:16 248:15
Blueprint 157:5
blur 147:6
BMC 249:20
BMI 22:17,18 23:1 167:6,16
Bob 121:20 131:2,9 132:12,21 133:19 189:12
Bob's 135:17 137:12 139:4
bodies 121:15
body 74:13 86:10,22
borderline 38:7
born 193:18
Boston 3:7
bother 132:19
bottom 68:17 75:17 84:19 94:18 122:6 165:1 181:2 244:11
bound 96:22
box 191:21 206:4 274:12,15,19 277:19
brain 29:15,16 30:4,13 37:19 90:3
brand-new 136:12
break 92:17 93:8 276:10
Bridge 215:9
brief 40:4 48:5 115:18 120:9 121:8
briefer 115:9
briefly 71:6 72:17 153:3 188:20 260:4
bring 117:5 144:17 172:21 244:7 245:18 264:13
bringing 160:14 246:14
brings 120:11
Bristol-Myers 3:5,15
British 3:4
broad 229:1 232:5
broaden 234:5
broke 43:9 111:20 154:5 176:20
brought 78:3 271:16 272:13
Bruce 9:4 57:5 65:22 66:1 109:12,19 110:10 124:4 127:5 218:4 223:19 228:8,12,20 241:17 242:4 266:4 267:9 269:8
Bruce's 106:15
BS 6:21 39:19
BSA 86:19
BSc 8:11 175:8
bucks 16:1,4 142:18 247:11
building 158:20
bumping 101:19
BUN 173:11
bunch 229:4
burdened 87:15
Burke 2:13 8:7 162:20 163:2,4,17 182:9 262:17
bus 104:21
buy 18:14 121:4 264:17

C

calcineurin 60:16 67:18,20 68:15,16,18 90:18 167:19
calcium 83:2
calculate 14:1 167:16 249:6 269:16
calculated 46:13 48:11 100:10 110:14
calculations 240:22
calculator 185:8,9,12
calendar 111:4 112:21
calibrate 17:20 18:11,16 25:13
calibrated 18:14,15 25:2
calibration 17:7,13 18:3,4 20:8,12
California 5:6 215:13
Calne 206:17
CAM 30:6
Cambridge 36:4 271:17
Camille 3:18 8:15 188:7,11 199:11
Camry 200:1
Canada 3:4 4:14
cancer 157:6 201:14,18 203:22 207:11,18,21 208:4,8,12 209:15 211:7,13 212:3 213:13 244:10,12 248:8
cancers 162:3 202:1,7,11 203:11 204:4,6,11,12 207:1,3 208:3,16 209:21,22 211:6 212:17,18 213:3,7

capacity 76:2
capillary 13:12
Capital 1:20
capture 52:14 266:15
card 277:16,18
cardiac 165:19 173:6 174:12 177:3,16,22 178:8,9,10,22 179:11 180:5,6 181:8 182:2,7 185:19 261:5,9 262:6
Cardiothoracic 4:5
cardiovascular 8:10 57:7,10 75:20 165:19 166:4,13 167:8,9 170:11 175:4,8 176:5,7,10,12,15 177:1,8,11 178:15 179:8,10,12 180:12,15 181:5,11,14,17,22 182:4,12,17,20 183:6,10,13,14 184:3,11,14,22 185:4,8 186:5,22 187:5,7,8,11,16,20 188:1,3 200:17 216:6 221:6,10 222:20 226:21 227:8 248:7 255:11 257:13 258:11 259:7 261:20 263:4 264:20,22
cardiovascular-related 226:13
care 23:18 47:11 62:5 98:17 112:8 122:20,21 123:11 124:10 150:11 155:22 160:3,5 196:20 274:1,10
careful 149:15
carefully 238:18
Carla 2:7
Carolina 200:2
carries 257:20
carry 22:22 269:17
cartoons 215:8
cascade 26:18
case 52:17 57:6 58:12 88:7,18 92:8 112:1 125:17 218:21 250:7 256:15 260:6 261:4,5,8,9 270:12
cases 54:12 192:14 195:12 212:21
catch 111:7 163:17
catching 101:18
category 21:5 41:8 50:18
Caucasian 173:3 207:16
caught 267:15
causal 74:2 128:1 229:8,10,12,20 230:15 232:7,10 236:1,3 237:18 240:6,12 241:1,13 266:20
causality 73:22 231:17 234:19 235:2
causally 74:4
causative 74:20
cause 61:10 72:14 219:21 222:19 223:12 225:22 226:22 227:17 231:14 240:17
caused 29:16 192:8 231:20 235:11
causes 90:7 219:15 246:3
caution 193:5 268:16
cautionary 266:5,18
Cavaille-Coll 2:16
caveat 44:18 132:6 138:18 259:11
caveats 52:13 269:5
Cecka 61:13
cell 206:1 214:1 222:2
CellCept 169:1 174:7
cell-mediated 222:4
cells 227:3,4
cellular 102:12
censored 61:3 63:11
center 2:8 3:12 37:4 42:14 94:13,15 98:3,9 218:18
centers 37:8 60:6 61:12 62:1 94:4,7,12 98:7,18 209:8 211:10 214:3
central 25:1 75:7,8 98:16 169:22
centromic 223:6
cerebral 29:16 30:3 34:22
certain 22:21 23:5 36:2 87:1 96:11 100:4 113:19 142:8 162:4 253:20 259:16 260:8 261:8
certainly 74:6 115:11 119:2 131:13 151:13 162:1 174:1,13 187:6 254:15 274:4
CERTIFICATE 279:1 280:1
certify 279:4 280:3
cervix 213:4
cetera 16:13 19:21 20:10,19 21:9 25:14,22 80:16 84:19 90:4,5 140:20 156:6 170:21 184:5 220:8 227:19
Chagas 193:20
chair 123:14
chairs 220:14
challenge 11:9 46:1 141:1,5 155:12 250:18

264:6 265:21 274:5 275:9 277:6

challenges 141:13 160:16 161:15 242:18 265:18 270:18 276:4

challenging 94:17 142:12

chance 33:11 201:6,10

change 19:2,12 25:7,10 30:19 41:6 48:11,15 54:10 58:8 59:20 62:4 66:20 67:6 68:8 69:19 71:20 73:8 74:5 77:20 85:16 87:19 97:20 100:14 103:19,20 108:21 109:3 110:14 113:14 117:15 122:1 124:13 128:18 129:18,22 130:3 132:1 133:2 138:13 142:8 146:3 154:5,7 156:17 164:9 165:11 190:2 222:22 235:11 256:10 266:7,9,21 268:7 269:14 271:4 273:8

changed 58:21 176:22 205:15 211:4 218:17

changes 41:5 70:21 98:10 100:15 129:6 143:7 146:21 158:12 172:14 178:12 181:9 256:5

changing 19:15 25:19,20 152:19 174:18

channel 83:2

Chapman 223:8

characteristic 210:17

characteristics 18:20 72:21 157:13 229:21

characterized 185:2

charge 15:17 143:3

charged 15:16

Charles 238:14

Charlotte 3:14

chart 44:12,21 46:13 50:5

check 13:17

checked 27:15

chemoprophylaxis 194:6

Chicago 96:10

Chief 2:14

Children's 3:8

choice 146:5 269:14

cholesterol 79:12 165:18 169:10,11 173:15 177:20 178:17,20 179:22 180:2,5 185:16

cholesterol-driven 180:9

choose 56:8 125:8 134:22 143:1 235:19,21

chooses 56:10

chose 50:3 56:7,11 57:2 60:7

Christine 20:4

chronic 7:7 20:11 21:18 23:18 70:11,16 81:16 85:21 111:17 114:2,13 117:20 118:16 225:7 226:1 276:12,16

cigarette 177:21

Cincinnati 2:6 5:9

circles 82:16 123:20

circulating 12:12

circumference 167:17 170:2

cited 238:8,9,11

CKD 19:10 23:6 75:22 81:9,12,14 82:7,10 83:19,21 86:6 117:17 118:6

CKD-EPI 17:8 21:12 22:2,20 23:2,7,8,12

claim 15:13

claimed 82:2

clarification 121:8

clarified 109:5

classic 235:2

Classically 215:18

clear 109:1 110:16 137:10 142:16,21 143:5 164:5,6 165:7 244:19 249:9

clearance 11:18 12:5 14:2,3,8,16 19:5

clearances 14:19

cleared 11:21

clearer 185:4

clearly 77:21 100:19 180:19 222:10 224:4 225:8 226:4,8,12 246:17 258:6

Cleveland 4:12,18 17:18

clients 27:8

climate 207:12

clinic 2:18 4:8,12,19,21 17:18 39:15,18 42:12 49:4 52:22 55:20 136:4 156:6

clinical 1:3 3:14,18 7:2 11:15 12:15 14:1 15:15 25:8 33:6 37:12 47:5 48:1,18 53:13,16 55:14,16 57:13 62:5 64:16 69:13 74:14 76:16 80:4 81:1 93:21 94:1 102:18 107:19 113:9,13 114:18 117:5 119:8,12 129:21 145:14 152:5,6

157:3,4,6 159:6,7 160:4,8,9,12,18 161:19 187:22 189:20 190:5 193:6,10 195:8 196:8,20 197:18 198:8,13,14 199:7 202:13 203:15 205:22 223:6,16 227:21 233:4 243:3,8,10,17 247:5 248:6,12 249:1 250:17 252:11 253:12 263:8,14 268:12 278:15

clinically 12:18,19 61:18 64:12 107:13 165:20 273:16 274:3

clinician 116:1 193:11

clinicians 119:18 140:13 152:14 153:18 154:2,4 197:19

close 52:8,10,20 192:18 199:15 238:8 274:14

closely 203:6

closest 115:22

cluster 99:8

clustered 204:5

CMV 191:3,12,17 192:2 195:13 196:3,6,8,9 198:21

CNI 69:4,5 80:6 100:20 111:16 209:10,19 211:11 219:22 220:1,12 223:9 225:5 226:2,16 227:15

CNI-based 216:19

CNIs 80:15 83:5,9 90:20,21,22 91:22 165:12

CNS 227:13,18

coached 137:1

Cockcroft-Gault 14:2 17:3 24:7

cocoon 158:15

coefficient 17:15

cognizant 99:19

cohort 21:4,18 49:5 50:13 61:14,16 63:18 64:20 67:4

coin 66:6

cold 13:9 14:13,15 15:2 27:12 29:21 31:19 32:11 33:17,20 34:7,8,16 35:4,7 36:15

colleagues 85:14 86:14

collect 14:18 52:15 159:9,10,11

collected 47:5 62:8

collecting 159:8,16

collection 159:5 202:18

collinear 266:14

colonization 190:10

colorful 46:13

colors 212:1,2

Columbia 3:4

combination 34:21 41:13 53:4 125:2 169:20 220:8 254:9,16 257:4

combinations 38:3 239:3

combine 51:17 98:9 202:10 213:3 214:5 233:12

combined 48:20 49:1 212:14 213:8

combining 249:11 250:1

comers 106:6

comes 136:11 183:6 187:18 216:7,11 237:14 240:10 271:10

comfortable 261:7

coming 81:9 89:18 95:12 123:20 128:10 141:9 168:14 259:19 264:22 265:22 274:13

comment 7:16 9:10 93:5 97:9 99:5 106:7 122:4 128:13 255:19 256:2 267:8 269:21 272:17

comments 115:11 127:6 131:12 141:8 161:10 274:8 275:2

Commission 279:22

commitment 134:10

Committee 201:2

common 145:16 167:10 187:12 189:1 199:6 202:7,9,11 210:9 211:17 213:2,6,9

commonly 12:15 13:6,7,14 17:3

community 196:18 265:19

co-moderators 143:17

comorbidities 253:1

comorbidity 166:12

companies 133:9 136:20 142:17 145:2 162:13 197:22

company 1:20 136:11 140:11 142:12 152:17

comparable 89:3 212:4

comparative 162:9 239:14 240:3,9 241:5 273:14

compare 28:1 33:15 212:22 251:12

compared 23:21 34:19 42:18 43:2 87:21 90:14 123:11 148:21 155:6 225:14

251:11
comparing 168:16 169:10 252:19
comparison 23:6 24:6,17 273:22
comparisons 249:18
compensatory 55:1 81:5 84:6 87:11,15 88:6 89:3
competing 244:3,8,14
complete 90:9 147:14 272:7 280:8
completed 17:8 149:13
completely 11:21 116:2 138:2 180:18
completion 210:5
complex 38:8 97:21 98:20 99:1
complexities 142:10
complexity 14:3
compliance 155:2,3 227:16
compliant 155:3
complicating 19:3 273:12
complication 45:14,17 184:16 188:11 216:12
complications 8:6,10,14 45:14 162:21 163:2,8 164:22 165:3 166:4 173:1 175:5,8 176:10 185:5 187:16 188:8 192:4,13 196:16 197:1,10,12,15 198:13 256:4
component 69:10 160:5 178:20 181:21 227:7 240:21 273:10
components 11:22 160:13 179:3 259:13
composite 103:3 117:1,7 119:21 135:12 178:20,22 179:1,4 183:4 188:3
compound 151:18
compromise 258:9
concentrate 176:3
concept 37:10 48:21 57:11 101:18 133:19 138:17 142:11 146:9 152:12 166:6 252:18 260:11 267:16
conception 243:2
concepts 194:12
conceptualize 71:17
concern 72:8 89:16,19,20,21 92:4 99:2 110:10 156:8
concerned 34:3
concerning 148:2 192:20
concerns 140:12
conclude 43:20 46:21 51:22 69:11 187:11
conclusion 89:16 213:11 227:21
conclusions 92:2
concordant 268:20
conditional 119:10 234:4 269:10
conditioning 29:8 39:3
conditions 80:12 91:6 234:5
conduct 42:13 147:14 160:4,11
conducted 158:22 207:20 273:19
confer 204:1
confirmatory 54:5 270:15
confirmed 60:19 62:20 178:9 182:14 209:15
confirming 60:14 65:18
confirms 65:7
conflicts 80:19 163:19 175:17 215:11 230:4
confounders 231:21 266:14
confounding 95:14 98:15 124:11
conglomerate 243:4,5
con-meds 159:10
connotation 277:17
cons 148:12
consecutive 32:2
consensus 157:17
consensuses 158:4
consequence 178:12 225:16
consequences 115:3 217:3
conservatism 268:21
conservative 146:20 147:2
consider 32:1 46:11 78:8 134:5 162:21 201:15 237:4 244:4 271:9
consideration 75:8 78:3 94:9 140:7 205:21 260:14
considered 11:14 83:5 89:2 120:2 134:16 150:3 188:8
considering 7:19 78:13 143:21 188:2 195:11 201:17
consists 200:17
consortium 37:7,17,22
constant 45:2 75:21
constrained 104:1
constraints 111:4

constriction 90:22
Consultant 4:6,10
context 80:3,4,8 90:17 93:20 96:16 116:11 134:16 145:13 148:19 153:9,20 168:17 202:13 212:22
contexts 259:13
continuation 209:10
continue 23:7 115:9 140:9 165:13 221:11 278:1
continued 3:2 4:2 5:2 158:17
continues 87:16
continuing 87:9 251:7 277:22
continuous 249:16
contract 76:16
contraindicated 15:3
contrarian 107:17
contrast 34:4 117:11
contribute 227:20
contributes 166:20
contributing 7:6 70:10,15 76:9
contributors 158:6
control 24:13 42:18 43:2 91:19 149:15 150:10,13,16 159:1 163:10,11 166:21 172:15 186:8 255:13
controlled 98:15,21 145:6,13 147:4 150:8,9 158:22 166:19 210:2 235:8 241:1
controls 191:2 273:15
controversy 104:11
convenient 13:19
conventional 42:13 44:14 177:13 179:9 182:18 272:11
conventionally 267:6 271:21 275:17
conversation 72:18 75:7
conversion 68:16 132:16 142:5 153:21 209:10,20
convert 211:11 224:11
converted 211:8 227:15
coordinator 203:18,21
corollary 200:19
coronary 172:6 176:18 177:4,19 178:10 180:9 181:6
Corporation 3:20
correct 95:13,19 97:2,11 127:12 144:6 223:4 243:1 280:8
correction 59:16 94:10 98:4
correctly 110:12 271:8
correlate 47:21 52:1 78:10,14,16,22 80:18 115:12
correlated 118:16
correlating 41:19
correlation 24:9 78:9 139:19
correlations 47:15
correlative 121:4
correspond 114:13
corticosteroids 165:12
Cosio 2:18 115:10 124:17 131:11
cosmetic 227:19
cost 15:5,7,11
costly 14:5
costs 15:16 156:1 161:6
counsel 279:8
counterhypothesis 81:4,8
counterintuitive 269:16
counting 102:7
country 20:15 194:9
couple 40:13 48:5 93:14 115:5 120:8 127:6 179:16 207:20 210:8 224:5 249:21
coupled 124:19 125:10 128:16
course 27:11 28:18 30:14 38:22 44:7 45:7,12 46:3 55:16 60:2 72:13 74:17 79:11 84:10,11,12,15,17,20,21 88:5,19,20 91:11 110:22 112:17 115:17 116:5 125:4 140:13 142:9 168:18,22 169:14,17 198:13 205:22 214:19 216:3 217:16 218:5 221:1 226:15 227:17 243:12 244:13 252:22 267:4 269:5 278:7
Court 280:4,6
cover 255:22
coverage 190:1 195:18
Cox 238:10
C-peptide 168:19 169:2,3 173:4,13
crazy 138:8
create 185:12
creating 157:15
creatinine 11:20 12:5,7,17,19 13:17,20,22 14:1,3 16:15

17:7 18:5,7,8,9 19:4,5,7 21:13,15 25:1,6,10,20 44:16 47:18 56:7 57:8,9,16,17,18 59:17,19,20 60:10 62:2 63:6,7,10 64:2,3 66:4,12,14,19,20 67:2,16 68:7,11 69:18 96:8 102:20,22 103:1 117:19 173:12 181:12,15,21 182:1 216:8 261:4 277:12,13

creatinine-based 25:5

creatinine-dependent 17:12

creatinines 17:17 18:16 25:14

criteria 29:15 31:8 33:13 49:6 92:7 128:22 130:22 161:18 209:17 271:5,20

critical 39:8 78:7 86:10 97:12 240:21 256:21,22

cross 18:15 88:1,20 148:18

crossovers 148:20

cross-sectional 61:14

crude 31:11

crux 82:2 250:15 257:11

Cryptococcus 199:1

CT 15:20

culprit 224:21

culture 119:5

cultures 119:3

cumulative 219:2

cure-all 259:18

cured 203:17

current 9:1 137:12 219:17,20 228:14,18 230:7,21 233:22

currently 276:10

Curtis 67:13

curve 66:4 85:12 169:12,15 207:5 234:17 244:22

curves 87:10 88:1,20 211:5 212:5

cut 199:20 210:18

cutoff 33:2 36:2

CVD 75:22

cyclo 225:13

cyclosporine 58:22 64:21 68:5,9,10 91:4,5,8,15,17 100:21 168:1 179:19 191:1,8 205:2 206:13 225:15

cyclosporine-treated 186:8

Cystatin 12:20

cytokine 30:4

D

Daclizumab 205:7

damage 74:19 78:17 117:21

Dan 10:13 26:11 98:13 121:7 139:3

dancing 128:14

Daniel 4:15 10:7

Darwin 238:14

data 20:21 21:4 23:9 24:1 26:14 40:18 41:2,11,16 42:15 43:4,9 44:4 47:5 48:9,10,20 50:1,4 52:14,15,18,19,20 56:9 58:1,18 59:7,14 60:4,6 61:5,7,14,15 62:21 65:5 68:14,21 73:5 79:3 80:14 81:9 82:12 83:18,19 86:8 91:3,11,13,20 98:2,9 100:1,2 102:2 104:10,11 105:7,8 109:12,17,19,22 110:13,15 111:17 113:20 115:14 118:19 126:2 130:14 137:16 139:1 145:18 148:16,22 149:2 151:9,10,12 158:20 159:5,8,17 179:6 182:14 183:7,8 185:8,11 200:20 201:1,22 202:18 203:13 206:16 207:7 210:13 212:14,15 218:20 229:18 238:14 244:8 249:1 252:8 262:6,7 263:1,2,18 266:6 268:9

database 80:14 86:15 220:15 263:7 266:15

databases 20:15 252:11

dataset 20:22 22:7 64:17 185:22 186:4,21

datasets 59:13 98:8 186:6,19 252:8

date 159:10,11 208:19 280:15

daunting 247:6

David 4:13

day 9:13,15 32:2 54:2 104:12 107:1 114:15 122:18 131:18 136:4 200:20 239:20 242:9 246:16 249:13 274:12 278:13

days 32:2 61:19,21 63:3,6 64:3 95:4 135:21 217:20 242:8 273:1 275:1

day-to-day 184:20

DBD 30:20 31:20

35:11
DCD 30:21 31:20 34:21 35:2,12,14 271:17
DCDs 31:8 35:6,16
de 190:14 224:10
deal 53:20 92:9 198:21 221:13 238:2 239:1
dealing 17:8 19:8,13 133:11 155:16 241:11 260:17
death 29:15,16 30:4,13 37:19 61:2 63:11 65:10,12 90:4 102:13 165:19 177:3,16,22 178:1,8,10 180:13 181:8 182:2,7 183:15 187:2 204:8 221:1,6 222:19 226:22 247:21 253:5 255:10 261:5,9 262:6
death-censored 60:18 62:13,18 63:4 248:1 250:20 254:22
deaths 186:18 194:17 226:13
debate 130:1 181:15
debated 82:3 120:2
DEBORAH 280:3,15
decade 55:19 56:6 137:7 189:8 194:21
decay 72:5
deceased 27:2 29:14 34:20 42:2 45:6,7 219:5 251:18
December 197:2 279:22
decide 142:18
decided 229:1
deciding 149:2
deciles 42:17 43:1
deciliter 180:1
decision 121:11,15 270:6
decision-making 159:6
decisions 143:10 238:1
deck 176:2 235:21
decline 28:2 41:10 48:8 50:14 58:19 60:8,10 61:2 65:17 67:20 82:16 85:12,16,17,19 87:18,20,21 88:16,17 101:10 111:12,15 112:8 117:10,12 120:18 121:2 126:6 135:15 155:15 224:7
declined 60:14
declines 28:6
declining 51:6 65:11 100:3 101:3 118:3 135:14
decrease 40:16 41:9 85:11 91:1 127:14 160:21 161:5,6 192:3 194:22 215:17 221:9 256:17
decreased 67:8 91:18 217:13 218:10 219:3 226:21 258:12 262:4
decreases 82:17,20 83:7 143:7 155:10,11
decreasing 46:4 92:1 171:6 228:1
decrement 246:13
deductive 229:9,12,20 231:17 235:2
deficiency 173:21
define 61:11 137:10 149:21 151:5 155:2 157:17 169:21 215:18 216:3,5 247:15 253:4 254:1 273:1
defined 31:11 32:1 157:22 190:17 191:11 202:16 215:19 251:5 254:8,22 255:9
defining 149:15 161:22
definite 38:8
definitely 52:13 270:22
definition 110:22 240:14 275:22
definitions 38:11 155:2 166:14 170:5 196:21 247:16
definitively 119:15
degree 22:4,21 23:6 249:14
degrees 247:5
DeKAF 56:11 58:18 60:4 61:6 65:5 115:20 131:4 223:7 224:22
delay 76:18
delayed 30:22 32:21 33:1 36:7 45:8,15 161:3
delineated 56:17
delineation 120:6
delivered 53:14 79:19
delta 59:17 100:3,20 101:17 109:14 110:14 117:15 124:13 130:12
demand 84:8
demarcation 132:5
demographic 16:18 193:20
demonstrate 7:20 143:22 276:9
demonstrated 213:15
demonstrates 69:12

demonstration 168:13
demonstrations 169:4
denervated 90:6
denervation 90:7
denominator 12:2
Department 3:10 4:15
depend 29:7 111:18
dependant 178:19
dependence 164:18
dependent 180:8,10,19 181:1 182:1 259:19
depending 85:7 254:17 267:4
depends 135:18 194:9,13
depicted 44:20
depleting 206:1 214:2 222:13
depletion 76:10
Deputy 2:11
derive 185:20
derived 212:18
derives 203:13
describe 51:3
described 51:4 54:21 61:4 254:19 259:21
desensitized 254:20
design 57:13 98:21 99:4,11 101:8 129:21 135:19 145:14 146:2 147:14 152:7 157:11 160:21 161:5,11 187:18 205:22 207:19 211:11 231:3 232:7 248:6 258:19 261:1 267:7,21 269:18,19,22 271:11,21 272:9,10,18 276:7,19
designed 61:5 75:12 138:11 151:3 235:8,9 262:20
designing 76:16 263:11
designs 40:5 99:8 151:16 208:17 241:9 267:14 276:4,6 277:20
desirable 59:9,11 64:15 69:17
despite 35:13 65:2 82:19 156:9 169:2,7 176:8 184:8 200:15 211:3 212:8
destined 63:14 104:19
detail 40:6 234:9 252:9
detailed 221:21
details 82:14 90:11 260:3
detect 250:4 259:15 267:10
deterioration 61:8 77:8 113:6 123:5
determinants 187:17
determine 44:10 49:21 73:17 247:2 248:18 249:4
determined 46:10 153:15
determines 18:17,20 100:14 243:22
determining 147:20 268:10
detrimental 36:22 246:18
devastating 193:2
develop 107:22 111:16 113:5 123:5,7 126:5 131:20 135:6 140:7 141:3 156:15 157:10,17 170:17,19 194:5 202:8 208:12,13,14,15, 20,21 220:21 226:7 251:20 252:2 253:9 254:3 264:10,11,18 265:8,9,17
developed 18:19 19:7 20:1 21:6 25:5 157:5 206:11,19
developer 113:7,11 264:12
developing 76:22 89:7 122:18 123:4 197:7 249:2 252:21 278:5
development 2:21 3:5,14,17 8:17 20:22 21:2 76:11 79:10 113:16 121:11 122:10 128:6 139:13 145:10,12 153:5 156:13 162:9 200:8,11 220:2 274:20 276:15
developments 156:12 267:6
deviation 46:13 146:14 234:10,12,15,16
deviations 127:15 149:14,16,20 233:6,9
Devices 3:12
devil 260:2
DGF 31:2,11,22 32:1,8 33:7,19 34:1,6,8,12,13,1 5 35:6,13,14 38:13 64:7,10 265:5,9,11 271:18 272:22
DGFs 31:17
diabetes 20:19 22:14 23:3 78:4 129:1,15 140:19 163:12,21 164:5,15,17,19 165:6 167:7 168:1,6 170:11,17 172:2 173:4 177:21 182:9,15 185:16

216:5 220:19 221:2 226:11 244:12 253:7 255:13 256:17 258:10,14 264:19,22

diabetic 22:10 84:16 129:14 255:8 263:22

diagnosable 112:6

diagnosed 173:3

diagnosis 79:8 122:12 196:9 207:22 223:6

diagnostic 32:20

diagnostics 37:13 39:7

dialogue 115:9 278:1

dialysis 31:12,16,20 32:4 38:14 62:19 101:14 150:17 173:5 174:14 176:8 178:13 185:10 200:22 201:6,11 214:8 247:13 251:11 273:1

diastolic 167:2

dictate 114:14

die 102:8 104:22 247:11 250:19

died 65:10,14 174:13

dies 107:2 126:12

diet 164:9 172:14,22 174:11,16

difference 16:8 21:11 24:11 32:12 33:16 34:1,6,12,14 35:17 43:3 51:16,21 64:1,2,3 69:6,7 78:9 87:6 101:1 110:21 118:14 148:1 168:18,21 230:17,19 231:14 233:5,7,9 234:19 236:12,19 246:5,9 262:13,18 272:2,3,4

differences 18:4 33:22 94:3 98:11 100:16,20 147:5,6 170:5

different 6:10 10:20 11:1 13:5,12 14:14 20:2,5,6,15,17 21:15 25:13,14,21 35:22 40:13 45:7 54:4 58:9 59:13 69:16 71:11 81:11 89:9,11 91:4,5 93:19 94:11 109:19 115:5 118:8,10 119:19 122:8 123:1 125:21 128:8 131:22 133:2,6 138:12 141:3,4 144:19 149:1 153:6 156:21 164:11 169:21 170:1 174:6 176:21 182:3,4 184:10 187:16 197:3,4 203:4 207:12 212:1 230:1 235:6 236:8 242:18 244:2 245:16 247:3 248:6 249:11 250:2 259:16 260:13 263:15 265:16 275:12

differential 71:13

differentiate 140:18 145:20 153:9 240:5

differentiated 51:13

differentiates 21:14 107:4

differentiating 106:8 248:13

differentiation 264:19

differently 20:8 138:11 216:17 277:14

differing 161:19,22

differs 148:16

difficult 68:21 85:5 94:20 95:18 118:17 177:12 182:22 189:20 210:11 268:3 269:16 277:9

difficulties 230:7 240:22

difficulty 86:1 276:11

digit 217:11,12

dilute 148:15

diminished 203:15

dip 88:8,10

direct 41:22 162:3

direction 260:19 270:20 275:3 279:7

directions 259:14,16 260:6

directly 159:5 226:16 265:11

Director 2:11 3:18 4:11

disagree 104:4 112:10 138:1,3

disagreeing 112:19

discard 33:3

disciplines 158:13

disclose 40:3 80:19

disclosure 26:16 144:22

disclosures 11:11 54:8 71:4 188:16,18 242:10

discontinuation 210:15,16 212:9

discounting 260:14

discovery 7:8 70:12,17 76:7 77:4

discrete 182:16

discretion 146:6

discriminate 95:10 231:10

discrimination 108:4

discuss 11:9 40:6 92:15 145:5,8 153:19 228:8

discussants 278:11

discussed 39:5 71:8 76:6 77:12 91:21 92:12 147:5 153:3 164:10 170:4

discussing 25:16 70:19 80:20 120:4 122:7 144:21 145:3 153:21 173:18 259:12

discussion 7:16 9:10 25:17,22 78:8 93:1,5,9 98:5 100:1 107:21 109:5 114:22 119:3 121:9,18 133:13 134:5,17 143:16 144:16 199:14,20 215:3 255:19 256:1 264:5 265:22 273:12 274:18 275:10,15 276:9,17

discussions 200:20

disease 3:19 8:14 20:12 21:18 23:18 70:20 72:15 74:7,13,14 75:14,15,19,20 76:18 81:16 84:18 89:8 117:6,8 118:12,16 122:11,14,16 124:22 125:12,15,20 126:8 129:8,9,14 131:13,15 133:20 135:1 139:5,8 141:14 142:2,6,9 145:10 150:14 165:19 166:13 167:8,9 170:12 172:7 176:5,7,15,19 177:8,19 179:8 180:9,12 181:22 183:6,13,14 184:14 185:15 187:11 188:8,11,15,21 189:11 190:19 191:10,19 192:6,12 197:1,5,10 198:7 202:21 210:1 213:5 216:6 217:15 222:20 223:1,5 248:7 251:13 252:20 253:19 255:11 257:13 259:7

diseases 91:22 139:9 194:16

dispersed 110:3

displayed 89:15 91:9,18

disregard 159:19

dissemination 204:7

disservice 107:9

distinct 233:15 241:11

distinguish 52:4

distracted 106:14

distributed 99:17

distribution 99:13 203:1 245:1

diverge 260:9

divided 49:21 187:3 245:21

Division 2:3,9,11,16 4:3 5:4

documentation 196:22

documents 197:4

dogma 158:17

dominant 43:17

dominated 201:21

donated 27:11 28:21

donation 26:20 27:3,4,10,17,20 28:8,10 34:20 37:6,10,19 55:11

done 14:9 27:17 36:4 37:3 39:20 42:14 43:18 44:15 54:12 66:10 68:15 93:13 109:18 124:6 128:11 129:8 135:16 138:8 152:7 158:18 180:16 183:1 185:13 192:22 195:9,13 213:17 229:13 238:18 252:4 271:8,17 277:4

donor 26:15,19,21 27:6,9,20 28:17 29:10,14,15,18 30:7,18,19 31:18 32:18 33:13 34:21 35:2 36:13,15,17 37:11 38:5,17 42:2 45:6,10 55:5 56:18,19,22 57:1 58:6 59:2 72:20 73:6 86:21 89:2 90:2 94:6,21 98:11 190:11 218:15 219:6 251:16,18 271:18

donor-derived 189:15

donors 27:16 28:3,7,12 29:7 35:2 38:7 45:8 54:22 55:9 81:13 88:22 89:10,13,14,21 90:14 92:7 94:8 219:6

donor-specific 47:18 79:9 125:10

dosage 226:9

dose 72:3 160:22 191:6,7 206:20 225:14 268:11 270:13

doses 174:7 192:17 206:20

dosing 71:19 72:2 191:1 206:10

dots 44:22

dotted 180:7,22 181:3

double 217:12

double-edged

240:20
doubling 13:21 117:19
doubt 110:20
downside 173:19
downward 59:4,20 88:13
Dr 10:3,10,13,15,17 11:3 26:3,6,11 39:13,20 41:14 48:6 53:12,14,18 70:7,8,18 79:17,19,22 82:9 85:14 86:13 92:15,21 93:7,15,17 94:17 95:20 96:5,15 97:4,7,9 98:13 99:5,6,10,22 101:16 102:3,5 103:4 104:1,3,13,14 105:4 106:7 107:15,16 108:9,13,15,17,19,20,21 109:4,9,21 110:10,18 111:8 112:10,12,13 113:3,18 114:5,7,11,12,16 115:4,10 117:1,4 118:1,5,8 119:1,2 120:8 121:7,19,22 122:4,17,22 123:3,13,16,19 124:15,16,17 125:6,7,17 126:7,9,11,13,15,17,21 127:5,7 128:12,13 130:9,10 131:2,3,9,11,19 132:10,11 133:12,18 134:3,4,18 137:14,20,21,22 138:3 139:3 140:2,3 141:7,13 142:13 143:14,15,17,18 144:3,14 150:13 155:12 162:19 163:4,17 175:1,10,16 176:1 182:9 188:6,13,20 199:11,17,22 200:3,5,13 214:10,18 215:2,3,6,11 219:19 228:12,21 241:17 242:2 255:21 257:5,13,15 258:2,20 259:10 260:4,11,20,21 261:11,13,15 262:3,8,11,12,14,17,22 263:13 264:4 266:3,5 267:2,12,13 269:8,9,21 270:11,13,17 271:10,15 272:16,18 273:3,11 274:13 278:9
dramatically 59:21 227:15
draw 80:9 106:20 129:7
drawing 87:16
draws 82:17
dread 193:6
dream 198:8
drink 67:17
drive 153:17
driven 178:11 179:4 180:3 181:8 203:10 227:14,18
driver 165:2 171:7
driving 84:7 156:13 225:22
dropped 68:6,7,11 148:18
drops 67:17 126:12
drug 1:7 12:14 82:14,16,18,21 83:3,6 94:1 95:13 105:19,22 107:22 113:6,9,10,15 114:17 119:11 121:11 122:10 123:7,10 127:18 134:15 135:3,5 136:15,19,20 137:5 140:7,8,14,16,21,22 141:3,16,18 142:1,12,17 145:10,11 151:18 152:17 153:5,13,14 154:15 156:3 161:7 162:13 205:11 210:18 216:4 232:12 235:14 258:7,13 261:2 264:9,12,14 265:9,17 273:6 274:5,20
drugs 66:13,15 76:11,13,17,21,22 123:5 133:4 136:1 137:1 138:9 140:19 141:4 153:2 179:9,12,13 182:19 206:12 218:6 235:4 264:12 265:4,5,6,8 273:9
DSA 41:7 101:5 104:18 120:5 125:19 129:2 130:13,15,17,19 135:7 139:10 155:20 255:3 276:12
DSAs 155:14 254:17
DTAC 190:13
DTPA 13:8
due 65:12 84:4,19 86:1 90:2,21 174:6 178:1 190:19 192:21 227:5 255:10
duration 31:19 32:8 34:9 69:13 207:3 265:10
during 30:7 37:19,20 38:2,20 44:8,11 48:16 49:18 55:13,16 85:15,18 198:13 275:1
dying 219:16
dynamic 54:10

67:22 69:1 273:15
dynamism 70:1
dysfunction 73:18 74:15 166:2 180:20 225:10
dyslipidemia 78:4 164:14 165:14 166:15 168:1,3,4,8 170:6 172:17
dysregulated 163:10 168:8
dysregulation 170:4,6

E

earlier 66:21 73:6 77:12 88:21 90:1 130:8 176:19 181:15 206:8 219:1 256:8 267:10
earliest 206:14
early 45:21 53:3,5 54:13 56:19 60:17 62:11 63:2 64:7 65:2 79:7 88:19 119:16 183:22 187:15 203:3 206:5,13,16 210:15 222:4 253:13 255:1,12 275:19
easier 14:22 156:2 196:9
easiest 66:9
easy 16:20
EBV 191:5,22 195:9 196:14 198:16 206:1 213:21
EBVs 213:5
ECD 255:8
ECDs 31:8 34:5
ECG 178:6
echo 125:8
echocardiogram 15:19
eculizumab 198:17
editorial 82:8,10 83:1,7 84:14
Edmonton 56:7 58:22 66:10 73:6
EDTA 13:7
education 167:12 198:6
educational 198:1
efalizumab 192:11
effect 6:14 22:17 26:4,8,14 27:1 30:22 31:18 32:6,10 34:1,2 35:10,11 36:9,13,19,22 56:20,22 57:15,18 58:6,7 60:22 67:9,10 68:10 70:3 75:5 88:4 127:10,11 139:7,15 146:19 147:16,21 148:5,16 149:22 155:19 171:5 172:22 180:19 181:4,17 182:7,17 183:12 184:8,20 201:12 203:9 212:10 214:7 228:2 231:10,11,13 234:14 243:10 244:1 245:11,15,16 246:1 250:4 273:20 276:9
effective 123:9 142:1 176:7 221:12 246:2 253:11 275:21 276:1
effectively 203:16
effectiveness 9:2 162:10 228:15,19 239:14 240:3,9,15,16,17 241:6
effects 28:9 71:12 82:4 83:5 98:3 147:3,11 179:14 205:17
efficacy 7:19 8:2,20 9:2 80:22 122:19 144:8,12 145:8,15 150:22 162:22 188:8 200:8 201:22 213:14,20 214:13,16 215:18 216:2,18 222:15 224:3 228:7,16,19 240:14,16 248:19 261:2 273:8,9,14 275:18,22
Efficacy/Safety 143:21
efficiently 184:2
effort 130:2 213:18
efforts 190:13
eGFR 42:3,11,15,17 43:6,13,16 44:1,11,17,19,22 45:9 46:10,16 47:1 48:1,16 49:9,18 50:1 51:7,8,14 55:6 154:9 166:9 262:9
Eighty-seven 210:4
Einstein 237:11
either 11:19 12:5 13:12 24:22 34:21 71:12 100:15 103:16 104:17 105:5 119:15 170:1 197:21 198:9,13 209:10 216:20 221:9 233:9 259:18 271:1 277:22
ejection 106:21
elderly 208:1
electrocardiogram 15:18
electrophoresis 13:13
elegant 33:14
elegantly 28:21
element 169:22 178:22 202:18
elements 94:11 268:4

elephant 154:12
elevated 180:5
Eli 109:11 115:4 120:11,21 121:5 140:2 256:7 264:3
Eliezer 3:16
eliminate 69:4,5 233:10
elimination 12:11
else 16:17 39:20 101:5 112:3 120:16 127:19 130:20 222:15 257:8 266:9
elsewhere 40:20
embark 38:16 277:21
embarked 37:22
embedded 268:17
emergency 199:22 216:9
emerging 190:14
Emeritus 4:5
Emilio 4:11 6:12 11:2 27:21 121:2 125:6
emphasis 227:12,22 258:3,18
emphasize 41:15 197:8 198:1
emphasized 166:1 228:3
employed 279:9
enable 274:9
encourage 160:3 190:5 198:3
end-all 236:22
endeavor 133:21
endocrinologist 173:18,20
endogenous 11:19
endpoint 6:6 10:5,12 13:22 40:7 41:12 43:22 57:14 60:7,11 64:16 65:3 68:1,13 74:2,3 80:22 100:6 102:16,18,21 103:3 107:20 109:3 113:13 115:1 116:15,21 119:5,21 120:1 132:4 138:15,16 139:17 148:16 149:6,10 152:1 177:5 178:21 179:1 180:10 183:4 187:1 188:3,22 189:2 200:9,14 202:17,19 203:12 204:2 207:21 209:14 210:20 211:12 213:15 214:5 222:14 224:2,17 228:4 229:11,19,20,22 231:3,8,20 232:1,5,20,21 233:11 236:1,2 244:15 257:17 258:5 261:3,6 263:9 272:19 273:10
endpoints 1:3 7:20 9:1 40:13 93:20 102:6 103:2 108:2 117:2,7 119:16,21 120:3,7 125:2 130:18 140:17 143:22 159:15 162:1,22 180:5,6,17 181:6 182:4,17 185:1 186:16 187:19 188:9 199:5 201:20,21 202:1 213:12 222:7 223:16 224:15 226:6 228:6,15,18 230:7,8,16,21 235:20 258:14,15 259:16 260:13,18 262:21 264:21 265:8,18 275:16 276:5 277:20 278:14
endstage 72:15 89:7
energy 220:14
Engels 212:13
engines 124:8
England 189:13 243:1 272:12
enhance 194:1 195:4,20 269:3
enhanced 193:16 196:5 249:22
enjoyed 119:2
enormous 30:4
enriched 151:17 152:11,15
enrichment 276:7
enroll 270:8 271:4
enrolled 211:15,19 270:7,21
enrolling 61:16
enrollment 153:21 210:8,15 213:17 271:5
enter 23:3 122:12,13
enthusiastically 134:12
entire 101:19 148:11 168:21,22 229:22 232:3,17,19 233:2 236:4 260:7
entirely 164:5,6
entities 114:14 241:11
entity 182:16
entry 130:15,22
environment 27:13 30:2 273:21
EPI 23:7
Epidemiologic 20:12
Epidemiologist 4:18
Epidemiology 246:20
epiphenomenon 30:5
episode 63:8
equal 12:11 150:5

177:3
equally 14:17
equation 16:17 17:4,9 18:10,18 19:3,7,9,14 20:1,10,20 22:1,2,8,11,15,16,20 23:2,5,8,9,12,17 24:5,7 25:5 106:13 229:15 233:18
equations 16:22 17:10 18:19,22 19:1,17 20:14,18 24:6,8,9 25:1 27:22 28:4 41:16 229:4
equivalent 36:16 122:21 251:8
equivalently 136:14
era 195:7
eras 183:9,17 184:9,10
Erasmus 2:7
Ergun 5:4 7:12 10:8,13 79:19,21 93:11
Eric 212:13
ERPF 28:11 68:7
error 16:10,11,19 17:11,13,14 18:3,6
ESOT 175:12
esoteric 254:13
especially 22:1 32:11 83:14 92:4,8 118:12 148:18 161:2 189:8 191:6 195:11 197:10 270:1 274:17
essentially 207:4 236:16 267:21
establish 58:2,11
established 206:11
establishes 56:14
establishment 61:22
estimate 16:14 100:13 146:19
estimated 6:10 10:19 11:1,7 14:6 21:19 22:12 23:22 24:5 25:21 73:7 154:21
estimates 53:5 78:14,16 249:16
estimating 16:20 17:10
estimation 16:7 24:18,22 25:9 26:17
et 16:12 19:21 20:10,19 21:9 25:14,22 48:17 80:16 84:19 90:4 140:20 156:6 170:21 184:5 220:8 227:19
ethnicity 64:1 164:2
etiology 213:9
EU 38:1
Europe 13:7 170:22 174:4 184:21
European 37:22 209:4
euvolemia 91:6
evaluate 145:10,15 150:18 267:19
evaluating 228:6
event 104:20 111:9 112:2,3,5,6,7 117:21 127:17 130:12 177:5 178:10 185:19 186:5 187:13 211:5 217:13 230:9
events 29:1 62:9 66:18 90:3 124:6,21 130:17 166:11 171:11 176:20 177:1,14 178:10 180:16 181:6,7,11,14,17 182:12 184:22 186:22 187:5,6,7,8,21 188:3 263:5 276:15
eventually 207:16
Everly 2:19 130:10
everybody 11:3 17:17 19:19 27:5 79:22 80:15 93:8 96:2,5 111:3 115:8 123:8 125:13 129:13 130:20 134:2 139:7 160:13 163:9 191:4 230:20 231:18 233:17
everyone 10:10 39:20 40:11 44:5 93:1,13 123:2 128:14 137:4 143:11
everything 15:5 16:9,16 18:14 96:19 108:12 113:4 154:2,10 160:9 168:7 222:15 225:17 242:12 257:8 266:9
evidence 72:22 74:3 86:4,5 89:6 90:9 173:21 206:6
evidenced 207:7
evident 29:17
exact 87:10 159:10,11 232:17,20 234:20 239:20
exactly 65:8 102:2 121:9 158:9 255:22
examines 222:18
example 13:14 18:2 27:15 29:2 35:17 41:7 83:3,8 94:7,11 95:3 96:12 124:7,21 128:18,19 129:9 141:19 142:4 151:20 165:12 172:22 192:5 204:5 206:16 213:21 216:7 217:4 220:18 239:9 253:4 259:15 273:22 277:10

examples 254:12
exceeds 201:13
excellent 104:19 116:20 135:17 274:16
except 22:22 89:4 204:14 215:2,7
excess 212:19
excision 203:20
exciting 39:9,10 214:20
exclude 29:1 130:2 149:18
excluded 31:13 210:1
excludes 206:3
exclusion 128:22
exclusively 202:4
excreted 12:9
excretion 84:21
execute 231:7
exercise 167:14 172:14 173:1,7 174:15
exercises 174:9
exerted 58:6,7
exists 158:21
exit 247:21
exogenous 11:20 13:4
expect 32:9 68:12 127:21 136:22 235:7 269:7
expectancy 201:5,9,13
expectation 218:7
expectations 136:22 138:12
expected 128:17 130:3 183:3 200:21 218:5
expense 221:14
expensive 15:14
experience 6:20 39:16,19 40:1,2 42:12 49:5 55:6 56:7 63:2 65:19
experienced 61:1
experiences 206:9,14
experiencing 41:10
experiment 36:3
experimental 4:16 81:21
experimentation 90:7
experimenting 133:1
expert 157:15
Expires 279:22
explain 75:19 109:20
explore 259:18 260:1
explored 151:10,17
exploring 81:12
exponential 85:11
exposed 91:4,8 152:21 192:18
exposing 152:22
exposure 91:5,15,17 161:6
expressed 11:20 210:20
extended 29:17 33:13 92:7 186:3,6
extension 36:19
extensive 91:16
extent 240:18
external 21:3,9 229:6,17 232:13 233:20 234:2 235:1,15 236:6,20 237:1,6,7,9,20 238:2,17 239:7,15 240:7,12 241:2,3,14 249:3 250:16
externally 21:4 256:13
extra 36:17
extraordinary 173:14
extrapolate 79:3 83:19
extrapolating 241:2
extreme 251:12
extremely 64:19 174:10 207:14
eye 212:1
eyes 162:14

F

face 72:1 265:15
faced 141:15 265:16
faces 277:7
facilitate 160:14 263:10
facing 141:22 142:1 275:9
FACS 8:18 200:12
fact 11:16 16:20 76:15 82:19,22 84:5 100:9 101:11 109:2 132:20 142:1,6 148:13 169:2 174:17 178:19 179:1 184:8,15 200:15 203:15 211:4,16 218:13 219:1 221:5,18 230:10 239:6,22 241:11 243:8 244:13 260:5 273:4
factor 19:1 21:14 31:19 60:3 69:20 73:15 78:5 90:12,15 94:2 98:15 102:13 166:4 178:18 187:13 221:19 250:5
factors 7:7 12:14 17:12 20:18 22:8 31:7,10 32:15 35:6 56:16 62:11 70:10,15 71:14 72:6 73:2 76:9 77:8,9 78:2 94:22 95:14,19 163:21 177:7,15,18 178:3 179:10,12 182:3,18,20,21

187:21 205:21 207:6 212:2 227:9,22 228:5 244:5,9 250:1,6 253:7 258:11 261:20 263:4

fail 43:10 46:2 102:9 124:9

failed 45:21 51:21 157:2

failing 46:4 67:19 92:8

failure 41:21 50:13 51:1 53:6 60:19 61:3,10 62:13,18 63:4,11 69:19 86:17 102:19 178:2 219:2 223:3 224:1,21 226:1 268:19 273:9 275:13

failures 42:11 43:9,13,14,19 50:8,12,15,18 51:19 65:12 73:12

fairly 52:8,9 58:6 69:6 134:7

fall 50:18 83:9 251:17

falling 135:7 183:10

false 239:4

familiar 77:9 163:9 189:10 192:9 267:17

family 164:5

famous 82:13 86:13

fantastic 133:16

fashion 172:4 201:17

FASN 10:8

fast 82:21 83:12

faster 48:20

fasting 169:3 173:13

fat 99:16

fatal 165:20

fatty-acid 33:8

favorable 186:12

FAVORITE 166:7 176:20 178:9,14 182:5 262:18

favorites 262:8

FCCP 8:4 144:13

FDA 1:7 2:4,10,12,17 3:12 4:4 5:5 7:12 10:8,9 53:22 79:20,21 119:9 120:15 137:15 139:1 141:10 144:2,14 151:2,12 157:17 158:9,19 163:5 187:1 188:14 197:21 201:15 205:14 214:19 234:1 277:13 278:14

FDA-approved 191:21

fear 139:3

feared 36:20

feasibility 213:16

feasible 128:6

213:20 235:17 263:9 273:18

features 73:18 75:21

feel 29:12 107:16 129:16 154:2 227:15 242:13

feeling 227:18 255:15

feels 223:3

fellows 216:7 247:19

Fellstrom 262:7

felt 239:21,22

female 56:19 58:15

females 164:4

fencepost 253:14

Fernando 2:18 115:6 117:4 119:22 120:19 131:10 135:13

Fernando's 125:8

fewer 260:18

fibrosis 139:10 223:15

field 122:13 135:21 136:22 142:21 161:3 201:18 205:15 236:15 270:1

figure 43:4 139:11 193:1 271:13

filter 49:6

filtered 12:9

filtration 12:8,10,16

final 137:9

149:5,10

finally 29:22 35:19 37:21 38:6 52:22 68:13 163:13 171:12 172:7 186:14 188:1 255:5

financial 140:11 144:22 156:12 188:17 279:10

finding 268:11 270:13

findings 82:5

fine 104:10 128:3 143:4 152:18 154:2

finger 106:3

finish 24:19

finished 102:21

first 2:20 10:16 11:3,13 12:17 17:3 24:3 31:12 32:3,4 38:14 41:20 44:8,11 45:5,9,14,18 46:9,18 50:9 52:8 54:12,22 61:18,21 87:13 95:4,9 109:21 111:8 115:13 122:1 123:9 136:3 143:19 144:4 163:20 166:18 177:11 189:15,16 203:3 208:6,11,20 213:14 215:8 218:2 219:3 225:16 230:22 231:2 233:19 235:3 238:12 248:11 249:22

250:9 251:13 252:2 257:6,18 262:19 273:1 275:2,17

Fisher 238:8,10

Fishman 189:13

fit 34:10 99:14 114:3,8 238:1,4 242:21

fits 19:11

five 48:9,10 50:6 54:12 60:6 172:11 174:9 209:13

fix 154:6 257:2

fixable 126:14

fixed 19:1 164:1

FK 156:3

flat 82:18

flatter 71:21 72:3

Flavio 5:6 8:22 124:15 125:7 131:12 141:12 142:14 214:11,14,17 228:21 239:12 257:22 258:21 259:5 260:20

flavor 247:3

flexible 157:10

flip 55:13

flipping 66:6

floated 254:18

flow 90:8

fluid 31:14

fluids 67:17

fluvastatin 165:16

focus 29:11 44:1 72:11 77:15 120:10 157:11 159:5 160:5 162:7 191:10 199:2,3 222:6

focused 49:15 57:13 71:1 193:16

fodder 72:18

follow-up 28:14,15 43:18 48:13 55:5 89:14 140:5 149:6,8 153:22 187:2 210:12 211:4 225:19 263:12

Food 1:7

forbid 136:18

force 99:17

forced 272:8

foregoing 279:4

foregoing/ attached 280:7

foremost 111:9

foreshadow 224:7

forever 132:15

forget 199:7 247:22

forgetting 275:3

form 172:19

formed 37:6

forming 105:8

formula 12:2,4 21:17

formulas 6:11 10:20 11:1 52:19

forth 106:12 167:3 271:22

Fortunately 28:8

forward 44:18 78:8 112:7 140:12 143:10,11 150:15 230:3 261:15,16,18

Foundation 2:19 17:5

fourth 72:14 132:12 163:13 213:1,4

fraction 106:21

framed 267:14

Framework 38:1

Framingham 185:9

France 86:19 211:10

Francisco 5:7

Frank 3:12 10:8,13 93:11

frankly 216:19 226:4 274:9

fraught 196:10

FRCP 8:12 175:9

FRCS 6:17 26:10 144:2

free 97:1 172:2 181:13 204:13 256:12

freedom 96:3 171:21 211:6 254:22 255:3,9

freely 12:9

frequencies 205:5

frequency 40:16

frequent 186:17

Frequentist 268:22

frequently 98:1 218:17

friend 54:11

front 64:6 264:6

fruitful 252:21

frustrations 156:7 184:13,17

fulfilled 271:19

full 225:14

fully 84:11 149:3

function 6:6,9,15 10:5,11,19,22 11:7,15 12:5 13:1 16:2,4 26:5,9 27:1,10,16,22 28:10,16 29:4 30:8,22 31:5 32:6,21 33:1 36:8 38:4 40:21 41:1,10 42:4,19,22 43:21 44:13 45:8,15 47:17 49:13,16 51:5 52:4 53:3 56:10 58:20 61:9 62:13 65:15 70:21 78:19 95:1 103:10 105:6,17 106:8,10,19,22 108:6 110:15 111:1 114:18 115:16 116:17 117:9 128:18 129:6 130:4 140:19 161:4 164:9 165:4

166:2,11 171:2,17 172:13 174:20 181:10,16 185:16 221:4,5,7,8 222:19 223:21 224:8 226:19,20 246:7 251:8 257:11 258:14 261:8 262:4

functional 27:13 30:1 31:22 32:1 35:5 38:13 48:8 86:9 87:3,5 261:18

functionally 87:7,20,22 88:1,8,10,13,14,16,17

functioning 69:15 219:8 226:22 247:12,22 250:19 253:5 255:10

fundamental 16:7

funded 229:13

funding 154:17

funny 238:7

future 25:6,15 38:7 52:12 72:18 76:3,7,8,19 77:6,15 115:19 145:12 153:16 159:3 162:5,8,16 198:4 202:2,14 226:4 252:13 257:10

G

gain 14:5 15:7 69:8 167:6,10 240:12 255:14 269:13

game 269:11,20

gap 252:18

Gaston 7:3 53:14,17,18 122:4,22 130:11 131:3 150:13

Gate 215:9

gender 21:13 25:6 63:22 164:3

general 3:19 31:7 81:9 89:4 170:10 193:13 203:7 207:2 212:19 251:8

generalizability 148:10

generalizable 148:11 235:5

generalizing 79:3

generally 167:1 170:3,6

generate 113:20 266:19

generation 12:11 75:11

generic 76:13,17 243:6

genes 30:16

genetic 126:19,21 127:1 207:6

genomics 98:1 119:20

geographic 190:15 207:6

George 2:13 8:7 162:20 163:2 179:17 260:22

George's 176:4 261:5,9

Georgia 1:15

Gerhard 220:10,11

Germany 20:7

gestalt 247:9

gets 143:6 227:14 235:13

getting 14:4 101:17 106:1 131:22 132:2 148:4 153:15 187:4 204:7 208:5 237:1 252:17 262:3 273:15

GFR 6:10,19 7:1,11 10:19 11:1,7,13,18 13:3 14:6,7,11 15:1,22 16:7,9,12,14,20 18:7,22 19:8 20:15,16 21:1,19,22 22:1,2,3,13 23:13,14,19,22 24:3,5,11,17,20,22 25:5,20,21 28:1,4,6,11 36:14 38:12 39:15,18,22 40:14,17 41:5,19 42:9 48:4,11 50:20 53:5,12,16 54:21 55:2,7,13,15,16 56:3,8,14,16,22 57:1,4,6,13 58:3,4,5,7,8,9,11,20 59:9,15 60:8,10,15,20 61:2 62:5 63:9 64:20 65:1,3,11,21 66:2 67:8,14,15,16,20,21 68:4,13,19 69:1,6,9,12,16,19,21 70:2 73:7,9 75:8 77:17 78:13,16,18 79:18,20 80:1,17,22 81:2,3,4,20 82:15,17,20,22 83:7,22 84:10,15,17 85:6,11 87:10 88:5,19 89:15 91:9 92:11 94:2,14 95:3,5,8,10 100:1,3,5,6,14,20 101:3,10,12,14,17,20 102:16,17,19 103:5,12,19,20 104:16 106:4 107:4,13,18 108:5,10,11,15,19,21 109:2,3,14 110:14,20,22 111:12,14,18 112:9 113:6,12 114:18 115:1,11,13,15,18 116:2,3,6,8,11,12,21 117:12,15,17 118:3 119:20,22 120:11,18 121:2,6 122:1

123:21 124:11,18 125:3,8 126:6,11 127:12,15 128:2,15 130:13,14 135:7,13,14,15 138:13 142:5 143:7 151:6 154:3 155:15 164:9 170:12 182:6 209:20 225:18 233:3 234:11 235:11 239:19 246:7,9,13,14 254:16 255:2,12 257:7 261:4 262:10 264:20,22 265:1

GFRs 15:11 17:19 28:8 100:9,12

Gill 3:3 9:7 48:6 66:22 85:14 99:5,6 106:7 241:19 242:1,2 257:5 258:20 260:4

given 83:2,8 93:20 100:9 110:1 111:2 112:16 121:14 174:13 175:2 179:19 192:17 198:6 242:5 244:4 254:12 267:1 274:12

gives 139:1 140:11 213:7 236:20

giving 11:5 143:8 153:8

glad 65:22

Glasgow 3:13 175:3,13 186:21

global 2:21 3:5,14,17 135:4 136:12 205:9 264:14

glomerular 12:10 131:13,15

glomeruli 84:3

glomerulonephritis 136:17

glomerulopathy 141:20 143:1

glop 246:22

glucose 79:13 163:11 165:9 168:9 170:4,5 227:9

glycemic 163:10 172:15

goal 40:11 61:9 157:10 278:4

goals 79:13 157:7 160:1

God 237:14

gold 13:3 14:8,9 20:16 24:21 150:9 258:6

Golden 215:9

gone 123:19 184:6 185:21

gosh 136:18

gotten 54:14,15 56:13 94:18

Gourishankar 56:5

gradual 155:13

gradually 173:17

Graeme 209:2

graft 27:1 30:22 31:1,2 32:10,16,21 33:1 34:10,16 35:10,12,14 36:8,9 40:12 41:3,20 42:9,10,16,20 44:6 45:6,8,15 46:11,14 47:12,15 49:7,12 50:8,11,13,15,18 51:19 52:9 57:16 59:15 60:18 61:3,21 62:12,13,18 63:4,11,14 65:12 66:8,14,16 67:11,19 69:19 72:20 73:12,18 77:14 78:14,17,22 79:1 80:10 81:2,3 86:17 101:21 102:8,13,19,20 103:7 111:1 114:3 125:5,22 126:22 127:19 131:20 132:17 133:20,22 136:1,9 138:19,21 140:16 141:4 154:19 161:3 166:20 167:8 174:20 180:18,19 181:10,16 184:1 186:18 187:2,8 216:15 218:8,9,12 219:2,9,21 220:13,22 221:4,19 222:20 224:13 226:10 227:5 228:2 239:18 244:22 247:12,22 248:1 250:19,20 253:6 255:1,10 257:6 258:5 259:8 261:21 264:16 265:2,13 274:21 275:5

grafts 40:19 41:2,9 42:2,21 43:10 45:10,21 46:9,16,20,22 48:8 49:6,8,10,14,21 52:3,4,12 53:6 65:15,16 89:22 92:8 103:8,9,14 105:15 115:15 131:17 183:22 219:8 227:1

grams 87:2

grant 38:1 145:2

granted 149:17 150:15

grants 215:12

granular 147:2

granularity 252:9,10

graph 82:8 106:3 244:18 278:2

graphically 55:4

great 53:20 92:16 109:7,8 115:7 117:18 134:2,20 136:19 139:4 140:5,10 203:16 218:3 219:7 221:8 227:3

239:21
greater 42:6,19 43:1,5,11,16,19 46:15 51:6,8 60:7 61:1 62:1,20 63:7,9 69:17 129:16 130:2 170:8 207:11 212:16 224:13 227:22 257:20 262:9
greatest 157:7 182:7,17 183:12
greatly 195:19 249:14
green 186:8
group 20:7 23:7 24:13 28:22 32:11 33:15 34:16 35:12 36:4 41:1,22 42:4,5,8,11,18 43:2,15,20 45:10,17,20 49:9,11,13 50:7,9,15,22 51:2,19 65:6,8 66:10 68:17,18 73:6 79:2 83:5,10 87:4,7,16,21,22 88:2,9,11 91:8 100:22 110:1,4,5 120:14,15 129:17 132:7 134:8 135:10 148:21 158:7 159:1 160:10 186:8 202:12 209:4 211:9 213:8 214:4 215:21 217:5 223:7 239:20 243:13,17 246:8,10,14 250:14 252:4 253:16 254:10
grouped 202:13
groups 24:12 34:13 35:11 40:2 45:11 47:13,14 64:4 65:1 88:5 91:4 119:18 157:1,15 158:3 182:15 183:19 185:11 187:3 212:4 231:14 245:16,22 247:15 251:18
group's 168:15
growing 236:15
GSD 33:7
guess 97:10 131:22 146:1 147:8 250:18 256:2,16 257:3
guessing 134:11
guide 73:19
guideline 197:4 198:11
guidelines 167:3 170:3 189:9 195:22 196:2,3,21
guns 96:3
guy 107:1
guys 59:22 262:7

H

habit 241:3
hair 212:2
half 40:18 65:11 89:14 126:18,20,21 176:16 184:7 205:5 242:9
halfway 163:15
Hall 269:12
Halloran 221:20
Hallvard 54:11
hand 197:13,16 220:17 251:10 270:18 272:15
handle 37:5 98:14
handled 99:9
handout 239:11
hang 109:10
happen 64:7 104:8 114:10 118:15 125:14 139:2 174:15 247:9 271:13
happened 61:22 77:14 149:19 159:13 206:15 217:10 256:10
happens 54:20 55:22 58:4,8 59:16 60:2 64:13 66:8 67:1,3 69:14 105:16 106:3,6 114:15 125:13 127:19 174:3 245:8,10
happy 121:6 217:5
hard 63:19 64:5,11 103:2 131:3 148:4 198:19 216:21 230:8 268:6 278:8
harder 199:3
Hariharan 57:14
Harler 3:5 273:11
Harmon 3:7 132:11
Harry 57:14
Harry's 59:14 109:22
Hartwell 3:9
Harvard 3:8
hash 246:13
haven't 17:1 37:2 94:18 116:18 227:10 271:12 273:3 275:16
having 111:18 187:8 192:6 225:2 227:18 250:20 267:22 268:7
hazard 48:22 49:2 266:6
hazards 78:4
HDL 170:6,19 173:15
Head 2:20 3:21
headed 270:20
heading 173:17
head-to-head 24:17
health 155:22 160:3 257:6
healthy 28:7
hear 114:22 134:22 135:20 136:12 176:3 218:18

heard 29:8 47:6,13 56:13 57:22 59:10 61:6 102:17 135:20 242:7 248:3 254:18 275:10,15 276:3,17,20 277:10,11

hearing 108:17 119:14 137:3

hearken 118:10

heart 16:2 21:9 106:20 172:6 174:5 178:1 181:9 247:22 263:20

heart-type 33:8

heavily 243:18

Heeger 3:10

heel 29:12 245:2 252:7

Heidi 4:17

height 167:16

Helen 183:7,21

hell 237:7

help 47:11 103:10 192:3 196:11,19 197:6 248:18 260:22

helped 18:1 138:10

helpful 77:18

helping 39:1

hematocrit 173:10

hemodynamic 30:9

hemodynamics 86:2

hemoglobin 165:8,9 168:20,22 169:6,8 173:13

hepatitis 194:7 195:3,14

hereby 279:4 280:3

here's 205:9

herpes 191:13

he's 173:16 174:2,7,8 247:22

heterogeneity 243:21 244:19 250:4 260:10

heterogeneous 19:19 69:10 132:7 161:18 202:20 259:22

Hi 273:11

high 15:12 22:1 42:5,11 43:5 49:9,11 51:4,9,20 52:3,14 53:6 69:19 104:16 111:18 149:9 176:9 181:4 210:15 213:19,22 226:2,9 245:21 246:18 259:4

high-dose 222:12

higher 7:11 15:5 18:8 33:11 35:13 63:6 79:18,20 80:1 81:1 89:7 90:13 116:5,6 164:2 181:12 191:5,6 194:20 198:20 206:8 208:15 218:14 245:13,14 250:10,12 259:9

highest 130:22 155:5 204:22 246:8 266:13

highlight 48:6 147:5

highlighted 17:2

highly 131:17

high-risk 203:22 213:21 250:14

hindsight 191:14

hint 57:22

Hispanics 164:3

histologically 221:22

histology 47:15

historical 274:22

historically 152:18 215:19 217:1 275:4

history 106:4 138:9 164:5 173:6 274:20

hit 104:21 110:5

Hjelmesaeth 182:13

HLA 224:10

hoc 178:15 182:5 248:22

Hodgkin's 213:5

hold 136:15,20 141:8 232:14

Holdaas 54:11 262:7

holding 262:15

home 172:21 227:14 243:11 244:7 245:18

homogeneity 210:4

homogeneous 129:17 231:22

homogenous 67:9,10 129:22 130:3

honest 198:4

hook 237:2

hope 77:5 80:11 144:17 151:14 260:19 277:21

hoped 211:3

hopefully 54:1 129:21 153:15 196:11 242:13 253:22

hoping 121:10 257:10

hospital 3:8,19 193:13 216:9

hostile 27:13 30:1

hosts 192:13

hot 14:12 15:1

Hotel 1:14

hour 35:21 93:9 199:12

hours 14:19 33:21 36:1,11,18,21 53:21 92:18

HPLC 13:13 15:10

huge 162:11 186:19 244:14

262:10
human 78:5 91:21 261:22
humans 91:12
Humar 196:17
humoral 227:7
hump 85:3,8
hundred 16:4,5
Hunsicker 56:6
Hurst 3:12 10:8,13,15 39:13 70:7 99:5 102:3 104:13 107:15
hydrate 67:15
hypercoagulable 172:18
hyperfiltrating 84:6
hyperfiltration 7:5 55:2 70:8,14 72:22 73:11 81:6 82:7 84:2,7 85:3,20 86:5,12 87:12,15 88:6 89:1,16,20 90:19 92:3 102:1
hyperglycemia 216:11
hyperkalemia 31:16
hyperlipidemia 163:12 226:12
hypertension 20:19 58:14 84:19 129:2,10 140:20 163:13 166:17,19,22 167:7 168:2,8 170:2 172:16 180:11,15 216:6 221:16 226:12 255:13 258:11,15
hypertensive 129:11 221:17
hypertrophy 55:1 77:22 178:6
hypervolemia 91:7
hypoglycemic 216:13
hypotheses 81:11 237:15
hypothesis 74:11 82:6 111:10 126:14 127:4
hypothetical 83:2 84:15

I

i.e 252:11 253:7 255:2
ICU 124:7
idea 69:9 96:9 120:13 124:3 137:3 139:4 140:6,10 141:21 213:7 229:5 234:2 238:2 239:5 248:4 267:13 271:10 274:15
ideal 12:8 80:12
ideas 256:1 276:20
identification 79:6,12 247:14
identified 53:1 78:15 172:1,5 185:14
identifies 131:13
identify 37:14 52:11 53:6 61:9 63:16 72:8 103:7 212:14,15,16 213:21 231:8 248:10 254:7 277:3
identifying 253:18
IDMS-traceable 25:2
ignore 116:17
ignored 203:12
II 35:2 91:7
III 8:7 163:2
IL2 63:1
IL-2 204:14
I'll 40:9,18 41:11,21 44:1 51:22 56:2,10 58:18 61:15 62:4 71:6 77:3 93:1 95:21 97:4 120:9 133:18 163:17 205:3 230:2 235:19 238:20 243:20 255:16 266:12
illnesses 193:20
illustrates 177:17
I'm 18:7 24:2,19 80:8 96:16 98:12,13 99:19 101:16 105:22 107:16 108:13,17 112:15,19,20 113:6,7,22 114:4,7,9 118:20 119:14 120:5 123:1,3,13 125:20 128:10 134:11 137:3 159:18 163:15 173:20 176:1,3 188:14 189:3 193:8,11 207:19 221:20 229:8 230:20 233:13 234:19 236:10 239:5 240:8 242:11 244:13 247:6,13 248:5 253:11,21 258:22 260:14,15 261:11 262:3,14 263:21 265:9,21 266:17 269:17 270:3,4 271:14
imagine 203:19 234:17 239:17
immediate 74:2
immediately 95:1 176:10 179:21
immigrants 194:10,14
immune 75:9 126:22
immunocomprom ised 192:13
immunologic 101:3,7 105:12,20 194:3 213:22 220:6 223:11 225:7
immunological 105:2 254:17 259:4
Immunologist 2:7
immunomodulato

ry 130:5

immunosuppressant 114:17 141:17 276:2

immunosuppressed 225:6

immunosuppression 71:12,16 122:17,18 123:4 132:15 135:4 164:12 165:11 167:19 207:4 209:11,19 215:16,17 217:2,17 218:12 219:12 221:12,15 225:20,21 226:18 256:5,12 276:11

immunosuppressive 8:2 39:6 123:7,10 127:2,3 136:12 138:20 140:8 141:2 144:7,12 153:7 184:2 192:7 203:9 217:18 256:18 263:16 264:14,15

impact 18:8 66:11 69:16 73:4 136:8 145:9 147:16 153:13 154:19 156:8 165:5 172:15,16,17 180:15,22 181:10,15 182:6 192:7 215:22 216:14 222:4 246:16 248:11 263:11

impacts 66:5 155:3

impaired 76:1 90:8 171:17

impediments 271:7

imperfect 183:5

implement 113:8 161:14,15 162:6 260:2

implemented 190:4

implicate 97:17

implications 7:8 70:11,16 77:3 85:1 145:6 150:7 151:8 257:18

importance 84:1 93:18 107:6 150:5 158:1 166:2 199:7 203:15 274:21

important 18:2 28:5 30:14 32:15 37:18 38:22 39:4 44:18 49:10 52:6 53:20 65:22 73:17 74:11 76:2,5,12,21 77:20 78:13 84:9 85:1,9 88:3 101:11 103:20 111:21 114:11,19 121:10,16 124:20 131:1 146:6,18 149:16 150:20 153:19 158:2 160:2 162:4 165:3,13 178:17 184:14,15 189:5 197:20 199:2 200:14 201:15 207:19 210:3 219:21 222:15 223:18 228:4 241:4 246:21 249:21 250:15 256:22 257:1 260:13 263:8

importantly 81:21 91:10 165:22 166:21 167:13 203:1 221:5 245:11 249:15

impossible 102:11

imprecision 17:14

impression 109:6

impressive 64:17,18,19

improve 8:21 20:20 23:16 30:18 31:5 40:12 103:6,14 114:3 142:7 156:10,15 157:2 158:10 160:11 162:10 179:11 214:16 215:14 221:10 224:3 257:10 265:5

improved 23:5 71:9 81:2,6 132:17 147:9 187:20 189:7 218:19 219:6 222:17

improvement 48:16 75:3 146:22 156:2 200:18 219:10,13 226:20 244:6

improvements 157:9

improving 38:17 138:19,21 162:12 183:12,18 184:1 214:12

imputed 149:1,2

inability 155:18

inaudible 27:18,19

incentivized 156:14

incidence 35:14 89:5,7 176:9 207:1,2,5 212:18 226:14 256:3,6 272:22

include 22:8 103:3 129:1 130:1 151:9 153:12 157:15 164:1 169:22 174:2 193:16 204:2 254:16

included 146:16 148:14 149:6 195:8 247:4 272:12 273:9

includes 82:12 146:10 147:14 148:13,15 149:12 165:8 177:19 189:22

including 37:8 180:2 182:15 189:8,22 190:9,12,20 191:12 193:20 194:6 204:11 271:21

inclusion 128:22

188:2
inclusion/ exclusion 209:17
income 167:12
inconceivable 252:14
incorporate 161:5 187:19
incorporated 12:21 193:10
incorporates 250:6
incorrect 15:19 115:14
increase 33:19 38:8,21 41:1 50:8,21 55:13 60:10 62:2 63:9 67:15 69:18 85:19 96:8 105:18 130:14 155:14 165:12 168:4 192:17 204:10 240:7 249:14 262:9,10 264:2
increased 50:10 52:5 57:10 60:18 61:2 63:4 67:7 73:9 75:1 78:16,22 82:4 84:7 86:16 91:14,17 164:1,16,18 167:7,8,9,13 168:2,3,9 170:11 171:3,11 190:12 192:19 217:12 226:13 266:10
increases 82:15,22 103:1 207:3 226:15
increasing 14:3 41:5 55:2 59:19 69:12 171:14
increasingly 177:5 248:7
incredible 234:9
incredibly 97:21
incremental 160:18
indeed 34:5 36:12 37:1 132:16,19 133:2,10 177:20 185:11
indefinitely 78:19
independence 238:21,22 239:10
independent 31:10 96:2 166:3 177:18 180:19 220:12 221:18
independently 166:10 177:14,16 220:22 277:2
index 11:14 61:18 62:12,14 63:18 187:4
indicated 61:19
indicating 75:5
indication 108:6 151:18 152:16 153:13 256:16 257:2
indications 81:17
indicator 62:12 223:19
indices 252:3 259:20
indirect 86:4
indirectly 217:22
individual 44:22 46:9 52:18 72:7 79:1,4 109:14 147:6 158:5 180:6 183:17 184:11 204:13,18 212:16 243:6 247:8,15,16 248:18 249:8 251:15
individualize 153:7
individualized 253:12 254:2 259:1
individuals 117:8,14 147:10 192:18 243:16
induction 62:22 206:1
industry 39:1 141:2 156:12,14 157:16,20,21 158:19 160:12
ineffective 161:7
inert 12:10
inevitable 115:11
inexpensive 13:18
infarction 177:2,16,19 178:19 180:8 181:4,7 182:2,8
infection 66:17 183:11 189:4,16,19 190:8,13 255:3
infections 167:13 189:18 190:7,14,15 191:12,15 196:21 199:4,6 202:22
infectious 3:19 8:14 188:7,11,15,21 189:11 190:17,18,19 191:10,18 192:6,12 196:22 197:5,10,12 198:7
inference 148:8
inferior 30:12
inferiority 150:6 261:2
infiltrate 223:14 224:7
inflamed 116:10
inflammation 7:6 70:9,15 75:1,9,13,21 77:2 143:7 164:11,12
inflammatory 224:6
inflection 142:8
influence 56:16 58:10,11 71:5 73:8 75:14 78:5 129:5 180:4 212:2 243:18
influenced 57:12 64:8
influences 45:4 73:4 97:12

influencing 58:15
influx 30:6
informatics 37:12
information 11:10 14:4 16:18 25:18 99:12,18 112:14,16 153:16 268:15 269:13
informative 273:16
infrequent 102:10
infuse 67:14
infusions 192:19
Inga 185:13
inherent 231:8 232:1 233:3,20 234:7,21
inhibitor 68:15,16,17,18
inhibitors 60:16 67:18,20 81:15,22 83:8 90:18 167:20 194:20
initial 21:5 85:17 88:7 132:4 234:4
initially 82:15,17,20,22 83:7 87:11 88:6 189:12
initiate 93:8
injuries 102:1
injury 7:7 26:18 27:9 29:16,21,22 30:4 34:22 35:4 70:11,16 82:7 84:2 85:20,21 86:5,12 89:1,17,20 90:3,4,19 92:3,9 110:3,8 111:7 127:20 220:6 223:11
innocent 223:14
innovation 160:18
innovations 201:16
innovative 144:16 151:9,16 154:15 234:2
insight 151:15
insofar 132:13
instability 30:9 36:13
instance 130:18 257:17
instead 28:4 86:19 92:2
Institute 4:16
institution 47:20
institutional 80:14
institutions 15:17 190:4 195:10,16
instrument 25:3
insufficient 31:12
insulin 164:16,17 167:22 168:5,13 169:5,7 216:13
insults 56:13
insurers 157:16
integral 160:4
integrate 94:10
intense 215:15 217:17 219:14
intensity 15:4,8 152:7 191:20
intensive 14:18 124:10 190:22 191:1
intent 148:6
intention-to-treat 145:7 150:21
intent-to-treat 146:8,10,16,19 147:12 149:11,13 150:4 210:21
intercept 110:2,21
interchange 53:21
intercurrent 78:3 129:6
interdependence 239:3
interest 41:21 80:22 82:14 175:17 230:5 244:21 279:11
interested 61:20,21 65:9
interesting 36:3,9 45:5,16 48:14 68:14 86:18 131:16 174:1 192:22 214:20 250:12
interfere 149:4 163:19 182:19
interferes 179:11
intermediate 106:11 107:5 253:13
internal 21:2,6 229:5,7,16,21 232:6 233:11,20 234:19 235:1 237:18
internally 238:16
international 196:7,11
interpret 68:21 116:11 149:4 225:4 268:3
interpretation 225:4
interpreted 97:14
interrupt 96:15
interstitial 139:10 143:6 223:14
interval 207:22 208:9
intervals 43:10 49:18,20
intervene 123:5
intervening 141:14
intervention 24:12 127:17,18 135:15 174:12 229:11 231:11,20 235:10 239:18 240:1,17,18
interventions 37:18 177:4
intractable 178:1
intraglomerular 82:1,4 86:2,3 90:16,21 91:10
intrinsic 107:4
intrinsically 107:8
introduce 10:16 114:22 137:4

143:18
introduced 7:17 9:11 93:6 218:4 255:20
introduction 218:6
inulin 12:6 13:3 14:8
inverse 12:6 13:20 19:5
investigation 13:2
investigators 19:16 146:1,4 157:16 185:2 252:5
investment 134:13
inviting 26:12 188:14 214:19
invoked 30:13
involve 40:14
involved 30:16,17 37:8 73:2,11 74:17 175:11 179:18 192:3 263:6 268:7
involves 44:15 61:11
iodine 14:22 15:2,3
Iohexol 13:14
iothalamate 12:6 13:6 15:1,22 20:16 47:17 52:19 100:8
iothalamates 13:9 41:17
irrelevant 159:15,17
irreversible 117:20 127:16
ischemia 27:12 31:19 33:17 34:8 35:1,4,7 36:11,15 90:2
ischemic 29:21
island 96:20
isn't 50:16 98:17 101:22 102:17 112:2 183:11 186:11 192:5
isotope 13:11 14:21 15:6
issue 17:16 18:17 20:8 22:5 23:15 45:8 63:15 68:20 71:1 73:14,15 74:7 75:6 100:20 115:17 123:20 128:16 154:13 164:8,21 166:1 167:5 169:7 171:5 197:9 215:18 218:16 223:13 229:3 233:15 244:7,19 258:12 260:10 265:7,11,15 269:22
issues 9:1 19:22 65:4 71:8,13,15 72:12,19 75:22 106:12 119:19 128:10 136:3 141:15 144:21 153:1 174:16 196:10 197:18 202:19 210:12 220:17 227:18 228:13,18 230:6 233:13 256:20 257:1 259:12 260:17 265:15
it's 13:18,19 14:12,22 15:20 19:21,22 21:21 23:17 30:11,20 32:5 34:21 39:9,10 41:4,12 44:7,18 45:16 46:19 48:1 49:10 50:4,21 51:21 54:2 56:1,20 59:22 60:1 63:19 64:11 66:3,6,17,18 67:9 72:14 73:15 74:8 78:7,12 80:3 81:16 82:2,18 87:2 89:21 93:9 96:21 98:4 99:19,22 100:13 101:13,17,18 102:2,10 105:9,10,13,14 106:19,22 108:18 109:14,18,22 111:1,2,8,10,14 112:16 113:10 114:19 115:21 116:6,15 117:18 118:8,10,17 121:10,13,16 123:1,9 126:2 128:2,7 133:10 134:12 136:9,18 138:15,22 140:5 141:10 142:11 146:6,18 147:15 148:21 152:13 153:14 154:5,6,14,16,21 156:2,20,22 158:2 164:18 165:3,13 167:12 176:10,17,18 180:3,18,19 182:11 183:22 184:15,16 188:1,22 189:15 193:9 194:5,15 195:5 198:18 199:2 200:14 201:15 206:14 209:2 210:10 216:9,12,21 223:2,3,5 227:17 230:9 232:17 233:21 234:20 235:17 236:21 237:4,17 239:11 240:21 243:2,5,20 244:1,2 245:4 248:20 256:7,19 258:17 259:17,18,22 260:12 262:10 266:18,20 267:20 269:16 270:19 271:9 272:21
I've 98:6 115:4,5 119:2 135:20 198:2 220:9 242:5 253:22 254:12 270:3

J

Jane 5:3 115:6 117:3
Japan 207:13
Jardine 3:13 8:11 102:3,5 104:1 175:2,8,10,16 176:1 257:15

261:11,15 262:8,12 273:3

JASN 48:6

Jay 189:12

JC 192:8

Jellife 24:8

Jeremy 223:8

Jesse 4:18 33:15 242:8 258:20 260:5 267:8,12 269:10

job 19:15 227:4,6

Jochen 3:17

Joette 4:3

John 3:3 9:7 66:22 67:12 237:9 241:18,22

join 97:17

joke 157:20

Jones-Burton 3:14

Joran 182:13

jotted 93:14

Journal 189:13

June 192:15

K

Kaplan 9:4 57:5 65:22 99:10 109:21 110:18 112:10,13 127:7 139:3 218:4 223:20 228:8,13,20,21 266:5 269:9

Karl 237:8

Kasiske 60:5 86:14 115:20 182:15 187:14 220:20 252:4

Kasiske's 177:9

Katz 3:16 113:3 114:5,11,16 122:17 123:3 140:3 256:7 264:3,4 266:3

KDOQI 165:7 167:4,15

Kewalramani 10:8

key 25:6,12 61:17 123:16 138:20 164:21 226:20 251:20

keys 200:5 235:16

KI 57:15

kidney 1:4 2:14 3:21 4:11 6:7,9,16 10:6,12,18,22 11:6,14,17,19 12:5 13:1 16:4 17:5 19:17 20:12 21:8,11,18 23:10,18 26:5,9,15 27:9,11 28:16,20,21 29:3 30:11 33:11,19 36:7,22 53:2 54:20 55:21,22 56:3 59:1,2 61:8 65:14 69:11,15 70:19,22 72:4 73:3,12 74:6,15,22 75:14,15,19 76:18 77:8,22 78:10,19 79:13 80:10 81:16 84:16,18 85:21 86:8,22 89:18,20,22 90:2,12 92:4,11 101:12 104:21,22 106:5,8,9 108:6 116:10,12,13,14, 16,22 117:6,8,9 118:2,11,15,16 123:6 124:21 126:1 129:6,8,9,13,14 137:6 140:19 154:22 155:6 163:8,22 164:9,19,20 165:1,2,4 166:1,5,8,11 170:14,15,17 171:1,7,8,10,13, 17,18,20 172:12 173:2,10 201:2 208:19 222:16 226:3 244:10 255:8 278:15

kidney-pancreas 173:8 217:4

kidneys 12:9 31:5 33:3 34:18 36:1 47:8 73:16 84:4,5 86:16,20 87:3,4 94:8 96:12 219:6,15 222:18 225:22

kilogram 87:2

kinds 136:7 216:10 230:16 269:22

Klupp 3:17

knowledge 202:12 204:14 208:18

known 8:3 83:4 84:11 90:20 144:9,13 167:20 168:3 212:2 245:1

Kotton 3:18 8:15 188:7,12,13,20

Kriesche 218:5

L

la 274:7

lab 17:18 18:5 159:11,12,13

label 13:11 15:6 145:4 151:18 152:17,21 153:12 206:3

labeled 13:5

labor 14:17 15:8

laboratory 25:1 61:12 196:21

labs 14:14 18:5 47:16 173:9 277:15

lack 219:13 227:7 236:11 239:10

lacking 38:15

Lamb 103:15 132:2

land 95:17

landmark 68:3 165:15 166:18

large 37:13 44:19 53:8 67:4 110:1 117:7,21 214:2 252:7

largely 61:14 62:4 180:3 193:11 201:20 203:9,11,13 209:4

larger 108:1 270:15
large-size 86:15
largest 49:14
Larry 56:5
last 11:17 14:7 17:1 23:20 30:15 38:6 49:7 53:21 61:4 64:5 94:19 100:18 128:20 145:1 162:9 169:19 176:22 186:14 188:6 210:14 241:18 253:21
lasted 32:13
Lastly 77:3
late 54:13 60:19 61:10,11 62:12 116:1 119:8 133:20 203:5 206:5 227:5
latent 194:16
later 82:15,17 105:7 110:5 127:19 152:10 202:15 203:5 239:7
laugh 97:7
Laughter 93:16 96:4 97:3,6,8 101:15 114:6 121:21 123:15 163:16 175:15,22 188:19 200:4 215:1,5,10 261:14
laundry 189:19
lay 247:10
layer 251:15
LDL 165:18 173:16,19 177:20 178:3,17 179:21 185:16
lead 66:16 75:1 164:11 166:12 256:5,15 268:2,20
leading 72:14
learn 160:17 239:7 270:22 277:1
learned 75:18 117:5 131:3 190:4 198:15
least 31:12 32:2 37:5 48:11 51:7 59:3 82:5 109:6 122:20 128:11 134:5 143:8 177:3 182:16 184:1,21 187:9,20 191:3 194:12 210:8 220:15,20 225:9 237:1,4 257:12 266:1
leave 25:17,22 97:4 214:6
leaves 51:9
leaving 16:10,11,19 109:6
led 209:2
leeway 242:6
leftover 257:1
length 35:19 164:10
lengthy 52:15
lesion 203:20
lesions 203:4 209:13,16 210:22
less 11:8 14:22 17:15 21:15 22:17 23:12,14 28:12 42:5,17,22 43:14 45:21 50:11,17 51:7 56:20 78:17 80:15 87:5,15,21,22 88:1,10,14,17 90:1 99:1 101:6 104:11 111:14 124:13 143:6 166:10 167:2 169:12 170:7 172:1 173:4,19 184:7 186:16 190:22 205:19 209:13 213:6 217:9 225:7 259:6,15 274:3
lesser 178:20 191:20
lesson 179:2
lessons 117:5 129:20 198:15
lets 237:2 244:14
let's 15:14 25:10 29:1 30:1 94:21 96:11 98:10 107:20 128:2 135:3 137:18 140:7,8 154:6 206:22 217:7 233:3,6 244:22 265:5
letting 237:3
level 12:12 13:12 37:18 98:16,18 110:7 113:19 127:14 156:3 172:16 226:9 248:2 262:4
levels 12:12 18:8,9 22:2 90:13 91:17 102:19 131:16 168:19 169:3,11,16 205:16
liberalize 239:16
life 59:5 186:11 201:5,9,13 227:11 241:10 263:21 264:1
lifestyle 164:8 172:13
lifetimes 200:21
light 105:13
lightly 260:2
lights 200:2
likelihood 129:5
likely 36:17 41:11 52:1,11 62:17 63:22 66:13 164:4 170:19 172:1,2,6,9 214:1 225:7 247:11,12 276:8
limb 210:6,10 211:20
limbs 204:18
limit 121:13
limitation 69:22 70:1
limitations 145:16,17 146:7,10 158:9

268:5
limited 106:16 107:11 248:15
limiting 151:17
limits 148:8 169:18
line 28:13,14 59:19 68:17 75:17 82:18 85:5 94:18 122:6 165:1 180:7 181:1,3 261:6
linear 48:11 49:20 207:4
lines 98:22 246:13 276:14
link 74:18 75:19 229:10 252:13
links 84:9
lipid 173:14 178:3
lipid-driven 181:6
lipids 179:16,17 180:10
lipoproteins 75:2
list 48:5 58:9 71:7 76:4 121:20 175:21 189:19 201:5 259:6
listed 17:1 76:7,10 193:13 200:22 258:22 259:5
listening 120:16
listing 2:1 3:1 4:1 5:1 175:17
liter 179:22
literature 16:21 33:6 206:7 267:15
little 16:10 17:6 22:17 31:14,21 32:19 34:3 45:7 46:1 47:6 50:21 53:22 54:10 55:8,12 64:1 88:12,13 89:4,5 103:11 106:3 109:18 115:8 120:10,17 135:12 147:2 150:17 158:15 170:22 181:4 193:10 199:21 202:15 206:22 216:12 221:1 222:22 230:1 231:12,15 232:15 239:16 260:22 274:11 276:20,21 277:3
live 194:9,13 237:21 263:22
lively 133:15
liver 21:8 23:11 30:11
lives 195:19 201:11
living 27:4,5,16,17,20 28:3 29:6 45:10 54:22 55:5 59:2 81:12 88:22 89:10,12,21 90:2,14 201:7 218:15 219:6
lo 218:10 274:1
load 196:8
loathe 248:13
local 62:5,6
log 99:15
logistical 159:4 270:18 271:7
logistics 268:7
long 52:9 54:18 80:5,10 81:6 82:18 89:3 105:8 115:15 121:14 123:22 125:5 131:17 139:6 174:19 181:16 186:1 189:18 214:12 219:14 221:11 222:17 224:19 273:5 278:2
longer 32:13 33:17,20 36:12 71:9 80:11 134:6,10 152:5,6 220:4
longevity 165:5
longstanding 267:22
long-term 6:19 8:21 28:9,15 39:15,18,22 40:5,12 44:8 57:16,19 61:8 78:3 80:18 83:22 84:10 86:10 88:20 103:6 104:5 114:3,19 138:19,21 145:9 153:22 154:19 155:19 183:22 186:1 187:22 214:17 215:15 216:1,14 218:19 221:10 226:20 227:20 228:1 251:7 252:12,15 253:14 263:11
loosening 240:4 241:8
Lorber 3:20 107:15,16 108:13,17,20 109:4 115:6 121:7 134:4 269:21 270:13 271:10 272:18
Lori 3:9
Los 96:10
lose 14:6 15:6 40:19 63:14 66:13 103:8,9,14 104:21,22 115:16 125:16 222:18 259:8
losing 219:15
loss 32:16 52:12 63:8,12 64:13 66:16 73:9 75:8 78:17 79:1 102:14 111:1 127:19 131:20 133:20,22 166:3,20 167:8 172:10 187:2,8 218:8,9,12 219:22 220:22 221:4,19 222:20 224:13 227:5 248:1 250:20 255:1
losses 49:12 61:21 125:22 131:17 186:18
lost 65:16 149:5,8
lot 18:1 20:21 23:9 33:4 41:16 45:1 50:1,4,19 57:13 62:8 68:8 71:10,11 73:21

94:21 99:12 106:14 110:2 116:5 132:16 136:3,6 137:2 139:22 144:16 147:19 149:1 154:1,8,15,17 155:21 156:2,20,21 159:16 161:1 178:2 179:12 189:6,17 192:21,22 193:17,19 194:8,11,14 199:9 216:4 219:3,7,11 220:7,14,16 222:6 224:9 225:5 227:5 231:9 234:1,5 235:13 239:2 255:21 259:12 263:10,17 267:15,16 268:4,5,6,16 270:17 271:1,6,7 273:7 275:6

lots 54:3 59:12 262:6

low 15:11 23:1 40:17 42:4,9 43:7 45:16 49:9 50:20 52:3 69:6 73:9 78:11,16,18 103:5 116:4,12 123:10 131:16 167:12 170:19 210:14 217:20,22 225:13,14 236:2 245:21 246:19 262:11

low-dose 168:17 235:11

lower 18:7,8 22:4 23:19 28:7 31:2 42:21 45:9,17 57:1 72:3 81:3,4 91:9,10 92:11 117:13 118:6 166:9 169:11,16 191:7,18 196:16 205:12 218:13 245:4,5,12 250:12 259:5 262:9

lowest 42:9

low-grade 131:14

luck 96:13

lucky 149:7

lumping 107:10 179:1

lunch 144:6 199:16

lung 30:11

luxury 238:5

LVF 107:2

lymphoma 213:1

lymphomas 203:7 212:22

M

Maastricht 35:2

MACE 185:18

machine 31:3 32:16 34:6,18 94:15 124:9

machines 124:8

macrophages 105:15

magnitude 72:13

main 17:12 18:5 190:20 219:15 224:20 226:22 238:20

mainly 84:15 86:2 90:21 200:17

maintain 53:3 123:10 221:13

maintained 151:3

maintaining 92:11 172:12

major 37:7 58:15 72:8 75:21 99:2 101:1 123:20 145:17 149:14,15,20 158:7 165:5 179:7 180:9 184:16 185:18 187:15 200:15,18 205:17 219:13 225:21 227:16

majority 42:10 46:22 47:8,9 49:12 103:8 131:14 193:12 203:16 225:8

male 126:20 164:3 255:8 270:10

malignancies 202:4,6 213:11 214:4

malignancy 8:17 183:10 200:8,11,13 201:19 202:8 211:17 213:3,14 226:14

malignant 202:22

manage 97:20 219:21

management 26:21 29:18,19 30:8 37:11 184:20 196:6

managing 220:1

mandatory 96:21

manipulate 67:14

manipulated 29:18

Manitoba 4:13,14

manner 15:12

marathon 80:9 83:1,12 118:18

marathoner 83:14

Marc 2:16 3:20 109:15 115:6 134:3 269:8

Marc's 274:7

marginal 157:9

margins 147:20

Marian 196:17

Mark 4:21 28:22 104:14 107:6 109:9 110:19 111:3 112:10,19 113:3 116:3 117:11 120:13 121:6 123:22 127:8 136:6 139:11 143:18 144:1 175:19 254:19,21

markedly 258:12

marker 11:19,21 12:1,8,21 13:1,14,22 14:13,22 15:2,6 33:2 74:19 95:6

104:7 113:21 117:18,20 135:13 266:16

markers 12:16 13:4 25:14 32:20 36:5 37:15 103:21 104:7 177:11 178:7

market 119:10 133:10 192:11,20,21 264:13

marketing 197:21

marry 125:3

Martin 196:13

Mary 3:5

Maryland 89:12 279:21

mass 15:9,10 86:9,20 90:1 92:5,7

Massachusetts 3:19 193:12

massive 131:4

Matas 3:21 219:19

match 37:11

material 272:4,12

mathematic 111:2 236:7

mathematical 124:5

Matt 82:9 127:5 128:12

matter 14:17 22:18 100:12 139:1 239:21 262:5

matters 101:11

Matthew 2:19 7:9 70:17

maturation 136:21

matured 135:22

may 24:2 54:6 55:12 68:1 70:3 71:11 72:1 74:12 75:13,18,22 76:2,5,12,20 77:18,20 79:2,8 81:4,6,20 83:5 85:1,16,19 86:10 88:3 89:10 90:15,21,22 91:12,20 95:7 100:4 103:20 110:11 111:7,9 113:20 114:3,8,12 128:9 132:7 138:20 139:2 146:22 149:4,19 150:15 151:7,14 153:17 154:18 160:14 162:15 164:11 166:12 178:18 179:10 194:3 197:6 199:20 204:8 214:4 216:1,14 217:22 218:17 219:14,17,21 221:9,10 222:15 223:10,17 225:15 228:2 244:2 245:15,16 247:5 254:22 259:11 260:18 266:11,15 270:11 273:22 277:5,6

maybe 13:18 36:1 79:2 83:4,9 99:18 105:19 108:7 112:2,3,6,21 120:20 124:4,12 127:2 132:4,12 135:9,21 136:7,21 146:1 152:8 155:14 159:1 174:4 215:21 217:9 219:10 220:2 221:5 223:15,17 225:18,19 228:7,8 234:6 239:5 255:14 256:2,4,7,21 258:16 262:22 263:8 265:21 266:14 267:8,9 272:22 275:12,21

Mayo 2:18 4:7,21 6:20 39:15,18 40:19 41:3,17 42:12 44:15 47:6,10 49:4 52:22 53:9 55:20 57:22 59:7,22 65:8,18

MBChB 8:12 175:9

MD 1:16 6:12,17 7:3,9,12 8:7,12,15,18,22 9:4,7 10:7,8,9 11:2 26:10 53:17 70:17 79:21 144:1,2 163:3 175:9 188:12 200:11 214:17 228:20 242:1

MDRD 17:18 18:10 19:7 21:12,22 22:11,15 23:6 24:5,9 41:16

mean 24:11 28:2 41:5 42:7 44:10,17 45:1,16 46:4,5,10,17 48:13 49:18 50:16 52:10,17 57:21 67:2 68:5 79:3 80:4 84:11 85:10 89:14 95:20 96:7 98:13 99:7 100:6 101:13,20 102:1,17,20 109:22 111:1 113:20 114:9 115:7 120:21 121:13,16 129:3 130:13,17 133:15 136:18 140:22 141:13 142:4 147:5 154:9 217:19 223:2 232:13 235:5 246:20 250:13 257:5,20 258:2,5,6,8 262:8,10 276:1

meaning 36:17 57:3 201:9 225:16 251:4

meaningful 150:22 157:18 228:2

means 31:1 46:1,7 57:21 64:8 67:10 137:15 170:2 201:6 216:2 277:18

measurable 122:2

measure 13:11

14:2 16:9 21:19 43:21 48:1 49:17 55:12 69:1 111:5 162:2 167:15,17 245:15 246:16 262:5

measured 6:10 10:19,22 11:7 14:7 18:22 22:12 23:21 24:3,20 27:11,18,19 28:1,4 55:7 121:2 170:1 255:1

measurement 12:4 13:4 17:14 22:5 24:17 42:3 44:22 48:22 49:1,2 51:13,18 67:22 70:2 99:3 101:11 108:11 116:3

measurements 21:1 40:7 44:16 48:4 50:2 100:5 108:10

measures 40:9 44:1 95:3 150:22

measuring 14:11 16:2,4,9,15 86:1

mechanism 91:1 101:22 147:17 179:5 250:21 259:7

mechanisms 81:19 91:2 161:12,20,22 223:7 253:19

mechanistic 74:18

median 48:9,10 55:6 62:14 102:17 171:15

mediated 223:18 276:16

mediated-driven 225:10

mediators 75:21

Medical 2:3,8,16 3:8,12 4:11 5:4

medication 126:16 155:11 156:1,10

medications 130:7 155:1 173:1 174:19 184:4,11

medicine 2:14 3:10,11 4:16 11:16 126:8,9 127:3 161:16 162:6

medicines 127:2 138:20

medium-size 86:15

meds 174:17,18

meet 151:11

meeting 163:5 175:11 196:5 267:20 268:1 273:13

Meier 218:5

Meier-Kriesche 57:5 181:11

melanoma 204:4 207:3 211:7

mellitus 164:17 220:19

melodic 225:13

memorize 233:17

men 170:7

mention 166:5 276:22

mentioned 85:14 130:8 150:14

mentor 67:12

message 120:15 137:10 142:16

met 122:20 268:19

metabolic 8:6 78:4 84:8 162:21 163:2,7,14 164:22 165:3 167:21 169:19 170:9,13,15,18 171:2,9,15,22 172:5,9 173:1 174:16 219:16

metabolism 168:9 227:9

metastasis 226:16

metastatic 209:22

method 32:17 235:4

methodological 19:22

methodologies 14:5,15 276:18

methodology 272:2

methods 93:19 97:12 146:22 160:21 268:15,18

metrics 241:10

Meyer 4:3

MI 107:1 165:20

Miami 2:14 194:11

Michaels 196:17

microscopy 105:14

middle 85:3 114:1 243:4

Mike 61:13

mild 56:20

miles 118:21,22

mill 148:12 237:9

Miller 2:14

milligram 205:9

milligrams 131:18 174:8 180:1

millimole 179:22

mimic 55:18 243:3

mind 54:17 146:12 148:10 223:12 254:15 257:12 262:21 272:13

mindset 132:13 133:3

minimal 17:15 27:9 121:3

minimization 71:16 215:16 220:1,3

minimize 22:3,21 69:4 148:22 257:22

minimized 198:5

minimizing 255:14

minimum 49:20

Minnesota 3:22 4:22

minus 21:19 22:12 46:19 195:11 254:17

minute 24:14

57:21 58:14,19 92:17 93:1 141:10 262:13
minutes 26:14 93:10 156:4 199:14
mismatched 196:14
mismatches 34:9
misprint 173:16
missed 203:18
missing 16:12 46:5 84:9 120:6 145:18 148:22 245:16
mitigate 193:1
mitigation 90:19
mixture 180:6
mL 85:4 173:5
mL-per-minute 43:6
mLs 24:13 85:17,18 87:14 88:10,11 234:12,15,16 262:12,18
MMF 168:16 169:10,12,15,16 179:19
modalities 38:2
model 19:2 91:16 94:19 128:4 161:4 185:15,20 263:2
modeling 16:18 19:9 21:14 124:5,6,9 185:13 232:16
models 25:22 30:10 38:15 263:6
moderate 56:20 245:21
moderator(s 7:17 9:11 93:6 255:20
moderators 10:7,12 144:1 278:10
modern 195:7
modifiable 61:9 72:10 164:7
modification 74:5 164:8 167:15 256:6
modified 17:6 23:2
modifier 23:16
modify 22:9 129:17 130:6
mofetil 204:19
molecular 4:15 37:13 38:15 39:7 157:13
molecules 164:11
moment 273:13
momentum 267:15
money 111:19 113:11 154:15
monitoring 155:20 195:6,9,13,15 196:22
month 24:4 44:12,16,20 45:2,9,11 46:14,16 52:7 77:18 95:11 189:15
monthly 44:10 46:22
months 24:3,4,11 42:5,9 45:19 46:11,15,22 47:2 48:21 56:8,12 57:2,7 58:12 61:11 62:14 69:7 87:13 88:7 104:16 111:5,6 121:5 124:18 145:1 165:10 171:4 172:1,5 189:16 190:6 191:3 192:2 203:19 204:6 208:7,10,11 210:13 265:10 270:19 271:2
month's 178:16
Monty 269:12
moot 270:9
morning 10:15 11:3 26:4 70:18 79:18,22 109:13 121:3 164:10 188:7,13 256:8 264:15
Morris 4:5 119:2 133:18 137:14,21 194:10 260:21 261:13 262:3,11,14
mortality 57:11 166:4 176:12,17 182:12 183:10 201:7 257:20
mostly 21:1,11 41:16 178:12 215:12 223:8,9
motions 129:4
motivated 174:15
Mount 3:10
mouth 108:22
move 112:7 140:12 144:4 241:18 261:18
moved 152:20
moving 14:15
MP 217:7
mTORs 165:12
muddy 50:22 235:13
multicenter 93:22 94:4 98:3,6 99:11 204:21 205:9 210:7 211:18 213:18
multifactorial 155:8 227:17
multiple 40:6,9,14 41:8 44:1 48:4 51:17 52:6 94:12 100:9 204:3 249:18 267:5
multiplied 94:13,15
multitude 139:8
multivariate 62:16 248:20,22 249:5 250:11
muster 273:17
mycophenolate 204:19
myocardial 177:2,15,18 178:19 180:7,8 181:3,7 182:1,8

myself 93:21 175:12

N

naive 156:11 186:15 187:9
Nankivell 24:6
nanogram 173:5
narrow 152:16
Natalia 1:19 279:3,19
natalizumab 192:9,15
national 17:5 37:6,11
native 28:20 70:19 73:16 74:6 75:15 90:1 117:6,8 129:8
natural 84:10,11 106:4
nature 85:7
nearly 40:18 273:12
nebulous 255:6
necessarily 68:1 77:14 103:11 149:18 152:6 154:9 159:2,12 174:18 247:10 253:2 259:11,18 260:1,18 266:20
necessary 59:5
negating 266:18
negative 58:20 59:4 149:19 213:22 224:14
negligible 165:20
negotiate 114:1
neighborhood 205:8
Neisseria 198:16
neither 219:5 279:8
nephrectomy 86:21 89:2
Nephrologist 3:3,7,13 4:17 5:3
nephrologists 67:13
Nephrology 2:18
nephron 71:19 72:2 86:9,20 90:1 91:9 92:5,7
nephrons 72:3
nephropathy 7:5 70:9,14 73:1 111:18 114:13 217:12
nephrosclerosis 129:11
nephrotoxic 90:20 219:22
nephrotoxicity 167:20 219:16,20 223:9 224:20 225:2,5 227:8
nerve 90:9
net 114:12 142:19 143:10 144:18 157:19,20,22 249:12
Netherlands 2:8
Network 3:9
neurotoxicity 167:21
neutral 104:17 179:14 221:9
newer 13:1,9 15:9 76:11,22 130:5
nice 17:22 20:3 31:7 46:3,13 54:3 62:19 65:4 93:18 141:10 142:11 173:12 191:9 192:5 196:18 218:22
nicely 121:3 176:4 189:12
NIDDK 76:15
nightmare 198:2
NIH 20:13 76:15 154:17 157:17
NIH-sponsored 20:14
NKDEP 18:11
nobody 16:2 159:8 173:21 197:15 215:8 258:6 264:17
nocardia 199:1
nodal 204:7
NODAT 164:1 165:13 170:19 171:22 172:2 220:21 257:15 261:4,9
noise 124:6,9 127:16,21 231:9,11 232:1 233:10
noises 124:12
non 34:15 51:15 150:5 154:12 165:20 204:3 207:3 211:6 256:14 261:1
non-adherence 66:11,18 139:9 145:9,21 154:11,13 155:5,8,16,18,20,21 156:5
non-CNI 80:7 83:4 226:5
noncompliance 78:6 136:18,19 145:18,21,22 273:4
non-compliance 71:15
noncompliant 103:17 146:15 148:15,17
none 54:8 71:4 140:20 163:18 175:19 222:10
Nonetheless 269:15
non-Hodgkin's 213:1
nonlinear 19:5
non-melanoma 202:1,6 203:22 204:5 206:22 207:10,17,21 208:3,4,8,12,16 209:15,22 211:5 212:3 213:13
non-nephrotoxic 226:8
non-progressor 51:19
non-progressors

51:10
non-radiolabel 24:21
nonsense 237:10
nor 178:3 266:21 279:9
norm 69:14
normal 104:17 105:6 116:13 125:18 169:6,8,13,18 174:5 180:14
normalcy 172:17
normalization 99:15 100:1
normalize 98:2,7,8
normalized 100:4
normalizing 99:11,14 276:18
normally 97:20 99:16
North 200:2
Northern 13:7
Norway 182:13
Norwegian 54:15
nosocomial 189:15 190:13
Notary 279:1,20
note 169:9 206:6 266:5,18
noted 165:17
notes 280:6
nothing 40:3 112:15 232:8 253:2
notice 49:10 204:15 205:11 257:7
notwithstanding 107:6
Novartis 3:17
novel 79:10 152:12 190:15 212:11
novo 190:14 224:10
nowadays 14:15 223:13
nuance 120:17 137:2
nuances 135:9,10
nuisance 182:11
numerator 12:2 16:17
numerical 63:3
numerically 125:21
numerous 57:4

O

obese 22:10
obesity 163:13 167:5 170:1
objective 135:3,5,19
objectives 145:5 240:18
obligated 137:16 269:14
obligation 119:11
observable 212:10
observational 210:18 252:8
obtain 153:10
obvious 26:21 35:9 82:18 240:10
obviously 26:17,19,21 27:2,6 29:14 30:8 31:16 37:16 39:3 40:12 44:5,19 45:7 70:20 71:8,13,19,20 72:2,6,8,18 73:3 74:14,16 76:6,22 77:7,13,19 78:21 95:5 110:21 112:14 127:10 139:4 149:15 193:7 206:12 231:6 236:8 244:13
occasionally 202:16 222:13 223:3 227:14
occur 43:9,15 78:18 124:14 136:2 139:9 148:9,20 159:13 203:3,5,7 236:20
occurred 43:19 49:13 238:16
occurring 59:3 61:13 125:22 136:5,17
occurs 111:7 190:13
October 61:16
odds 250:7
offer 9:2 160:6 167:17 228:16,19 242:16 244:2
officer 2:3,16 3:12 5:4 279:3
off-label 80:20 151:19 153:2
okay 10:15 22:15 92:15,21 93:7,21 94:12 104:13 108:20 109:4,7 114:11 117:3 118:5 120:21 121:10,13,16,19 123:13 125:6 127:5 137:21 143:14 151:4 154:10 199:17 262:14 265:7 267:2
old 76:17 276:5
older 28:12,17 31:1 56:18,21 57:1 73:6 76:13,21 130:7 251:18
oncology 133:3 157:4 160:17,20 161:21
ones 17:1 58:10 72:7 116:17 144:19 177:13 199:2,8 203:3 223:22 256:3 275:17 276:20
one-third 21:2
one-to 118:16
ongoing 157:3
onset 62:3,12 163:21 165:6 168:1,5 170:17 182:9 216:11 220:19
onto 246:22
Opelz 166:18

180:12,16
Opelz's 220:11
open 162:14
Open-label 209:9
open-minded 198:12
operation 29:20
Ophthalmology 2:4,10,12,17 4:3 5:5
opinion 105:10 143:2 154:18 235:15 267:8,9
opinions 105:9
OPO 97:18 98:11
opportunistic 189:17 199:4
opportunities 71:2 76:7,19 77:1
opportunity 11:5 37:2,21 39:21 78:1 79:8 130:4 163:6 168:13 189:5 193:22
opposed 266:22
opposite 232:18,21 234:21 259:14 260:6
optimal 27:7 79:12 206:10
optimization 191:17 254:8
optimize 195:6
option 40:22 259:17
options 150:19 151:9 161:18 269:4
oral 165:9
order 15:22 20:11 87:14 88:9 108:3 115:5 120:16 156:3 251:20 265:17 274:10
organ 26:22 30:18 37:6,10 96:10 106:19 107:1 155:7 193:13 202:5,7 213:2
organization 96:11
organizations 94:6
organizers 11:4 39:21 53:19 163:5 242:3
organs 23:11 29:19 38:9 96:18 97:21
original 49:5 95:12 189:13
originated 209:3
Oslo 54:11,13
others 53:1 110:16 111:15 136:7 144:15 194:7 195:14 238:9
other's 144:18 274:8
otherwise 80:13 95:17 97:18 124:1
ought 137:1 258:18
ourselves 152:22 275:20
outcome 7:2,21 8:21 9:6 33:17 34:2,19 35:15 36:14,16 38:12 41:5 53:13,17 57:19 59:12 64:8 66:3,12 74:4,6 78:11 80:18 83:22 89:3,11 95:3,7 97:13 104:19 106:11,22 107:9,14 120:18 142:7 143:22 153:12 156:8 157:18 171:10 180:18 214:12,17 215:15 216:1 218:19 220:10,13 221:11 222:3,5,8,16,17 227:20 228:1,3 241:19,22 244:6,20,21 245:8,13 246:4 247:3 250:2,8 253:15 254:11 255:10 256:6 257:10 266:12,21 271:18 272:11
outcomes 6:19 39:15,18 40:1 47:21 54:16 57:8 65:21 71:9,10 94:2 107:5 110:17 119:8 120:3 121:5 145:9 147:9 149:19 153:4,17 155:19 182:21 183:11,17 184:1 188:1 190:2,19 191:19 195:3,4,20 196:15 243:21,22 250:22 251:11,22 252:12,15 254:4,7 259:11,15,20 261:21,22
outliers 198:22
outlined 254:21
outlining 211:16
outside 121:12 150:17
overall 11:14 32:10 40:11 41:1 47:1 64:20 171:20 181:17 183:11 191:11,19 192:16 195:2,19 196:6,15 200:16 243:19 245:15 246:1,5,16 254:14 265:7
overburdened 87:16
overcome 174:16,18
overemphasizing 222:8
overlap 52:21 54:4
overlay 155:16
overload 87:3,5
overloaded 87:7,21,22 88:2,9,11,13,14,16,17
oversell 138:6

overt 45:14 170:11
overview 40:4
overwhelming 73:12
owns 200:1
Oxford 4:10 124:5
oxidative 75:12,20 77:1 130:6
oxygen 76:1
Ozlem 2:11

P

p.m 1:11 199:16 278:13
page 6:2 106:4
paid 142:18 190:18
paired 33:18
pan 117:18
Pancreas 2:15 4:11
panel 7:15 9:9 93:4 102:15 245:7 246:11 248:11 255:18
pans 186:10
paper 24:13 48:13 55:19 56:5 57:11,12,20 66:22 86:13 91:14 103:15 106:15 118:1 132:2 189:13 196:1,13,18 212:13
papers 20:8 24:1 166:18 168:15 218:2 238:11
paperwork 198:2
papillomavirus 212:17 214:3
papillomavirus-driven 202:10
paradigm 156:17 226:18
paradox 232:16 269:12
parallel 106:20
parallels 80:9
parameter 59:5 97:13
parameters 78:10,21 85:4 116:11,16 120:19 185:14
paramount 25:3
parenthetically 100:18
Park 4:7 6:21 39:14,19,20 61:4 64:5
partially 82:6
participant 157:12
PARTICIPANTS 2:1 3:1 4:1 5:1
participate 53:19
participating 209:8
particle 237:14
particular 76:12 160:5 185:3 210:18
particularly 75:13 166:9 167:11 185:9 190:17 204:4 206:1 239:1 251:17
parties 279:9
partly 139:14
partner 27:6 28:20 29:3
partners 39:1 93:10
pass 273:17
passed 271:18
past 17:16 77:15 119:4 129:20 137:3 189:7 190:12 195:13 234:4 275:1 277:12
pathogenic 179:4 223:7
pathological 79:7
pathologist 62:7
pathway 74:3 128:1 266:20 270:7
pathways 37:14 75:10 153:5
patient 15:1,5 16:12 22:9,10 23:3,4 26:20 52:10 56:12,15 63:13 65:12 67:16 72:7 78:15 98:18 102:8 104:15,18,19,20 105:21 108:1 109:14 110:7 113:10 116:8 122:2,12 126:12 133:6 140:16 141:4 146:13,14 148:12 150:19 152:2,11,15 153:11 155:17 156:5,15 157:16,18 160:5 162:8 164:20 171:20 172:22 173:3 174:14 186:6,22 187:3 203:19 209:16 210:3,14 211:1,17,18 212:13,19 216:7,10,13,14 227:14 230:16 238:1,4 244:4,6 247:15 249:7 250:13 253:15 254:10,15,18 255:6 256:11 257:19 258:5 259:2,4,6 264:16 265:3,13 274:6,21 275:5 277:11
patient-reported 153:4,17
patients 15:16 21:7,8,10,11,18 22:22 27:7,8 40:17 41:6 42:4,7 45:13 46:2,6 47:9 50:1,9,15,20,22 51:1,14 54:17 55:15 61:1 62:22 63:16,17 64:9 65:3 67:3,6 68:5 69:3,5,8 79:4,14 81:9,12,13,14 82:7,10,11 83:17,20,21 84:2,16,22 85:13 86:3,6,7,8 89:6 90:10 100:11,14 101:2,7,9 103:17

104:22 105:8,11,17,18 106:2 107:7 110:1,2 111:11 112:4 113:5 118:11 119:11 122:11,13 125:11 126:4,13 128:21 129:15 131:5,6,7,14 132:6,22 137:17 138:10 146:3,5 148:3 149:8,13 152:1 153:8 154:1,4 155:4 157:8,12 161:7 169:1,2 170:18 171:22 172:4,8,19 176:8 178:21 179:19 181:13,22 184:7,21 185:10 186:2,10 187:7 191:2 192:16 193:12 194:11,13 196:14 200:22 201:13 204:6 206:18 207:12 208:1,2,6 209:9,11,21 210:5,6,10 211:7,14,15,20 218:14 219:5 220:4,21 221:2,16,22 222:1,3,18 224:11 225:1,8 226:22 230:13 231:4 232:20 233:6,7 234:13,16,18 240:13 242:17,18,20 243:13,17,22 244:1,11 245:1,5,6,8,10,12,14,17 246:17,19 247:3,8,17,20 248:4,15,18 250:14 251:11 252:15,19 253:1,4,5 254:5,11 256:12 259:3 260:8 270:7,20 271:4 273:5 276:8,10 278:3,5

patient's 44:22 67:16

Patients 7:21 143:22

patient-years 183:15

pattern 171:20

patterns 124:12

pay 268:8 269:5

paying 217:22 275:5

Pediatric 3:7 206:4

penalty 268:8

penile 213:4

people 10:3 16:22 17:2 24:2 46:3 51:5 54:3 64:6 65:10,14,15,16 68:8 74:15 78:18 82:3 95:16,22 96:17 97:9 103:7,8,12,16 105:5 108:18 111:22 114:4,5,8 115:5 118:2 119:21 120:8 129:14 130:16,19 131:20 136:6 137:8 138:1,7,16 150:15 156:21 165:7 175:18 193:18 194:8 197:12,13 199:21 218:18 219:7,15 220:11 223:4 224:22 237:12 251:11,12,18 252:4,19 253:6,20 254:3 260:10 263:14,16,17

people's 114:8 127:6

Pepcid 174:9

per 11:21 24:14 32:2 85:17 87:2 122:2 145:7 149:8,12,17,20 150:2,4 162:2 173:5 176:13 179:22 180:1 183:15 201:7 209:16 210:1 211:1,15 212:18 262:13

percent 17:16 21:6,10 28:3 32:2,12 34:17 41:4 42:10 43:12,14,18 46:16,17,19,20 48:15 50:8,11,14,17 51:6,19,20 53:2 60:8 62:2,20 64:9,10 67:6,7,8 69:18 101:9,21 104:22 105:11,16,18 111:11,14 112:4 113:5 117:8,10,11 118:2,6 125:16 138:5 151:1,22 154:21 159:7 170:14,16 171:1,3,8,13 176:12 191:7,8 202:5 204:19,20,21 205:2,3,7,8,10,16,19 206:13,15,18 207:8,9,13,16 208:6,7 217:6 220:20 221:16 230:17,18 239:18 250:2,3 270:7

percentage 69:5 149:9 155:3 171:21 219:4 264:2

perfect 137:20 156:19 161:4

perfectly 116:7,9 134:1

perform 20:9

performance 18:18 19:3,17 20:20 22:11,14 23:5,13

performances 20:6

performed 24:8 69:13 89:13 210:13

perfused 94:15

perfusion 28:10,15
perhaps 42:8,20 55:4 75:4 94:5 102:14 168:10 184:2 187:21 191:14,17 257:22 261:2,20 274:11 275:2 276:5 277:14
period 7:15 9:9 29:17 52:15 53:4 55:14 67:5 93:4 112:20 113:13 115:15,18 121:1,3 131:17 169:11 189:4 194:2 210:18 211:14 218:11 226:3,10 255:18 273:19
periods 213:17
peritoneal 173:5
permit 25:4
permits 15:10 23:3
permitted 22:8
permutation 236:16 238:12,22
permutations 238:15
persist 75:4
person 16:11 43:7 160:7 239:19,21 243:4,5 247:9,11,12 249:17 254:19,20
personalize 153:7
personalized 161:16 162:6
personally 154:11 160:19
perspective 40:15 47:4 77:4 121:12,17 198:7 200:14
perspectives 144:19
persuade 275:20
pertinent 99:22
Pescovitz 175:19
Peter 3:10
Pfizer 3:16 4:20
ph 105:14
pharma 2:21 119:5 141:15
pharmaceutical 128:5 133:9 139:13 141:1 145:2
Pharmacist 2:5
PharmD 8:4 144:13
phase 35:3,20 36:12,20 85:3,12 88:12 151:1 152:8 190:21 198:15 268:11
phases 56:2
PhD 6:17 26:10 144:2
phenomenon 61:3 231:19
phenotype 73:17 223:5
Phil 221:20
photos 243:5
Photoshop 175:14
physical 164:8 237:21 238:5
physician 4:13 146:6
physicians 146:15
physiological 12:13
PI 160:7
pick 58:3 132:22 199:6
picking 137:11
picture 71:18 242:22 243:14
pictures 215:8
piece 109:17
pills 38:19
Pilmore 183:7,21
placebo 165:16 245:9
placed 205:4
places 61:7 92:22 193:18 240:10
plain 38:13
plasma 11:20,21 12:3,12
plateau 87:17 88:12
Plavix 174:9
play 72:7 187:10
players 107:14
playing 252:1
plays 221:7
plea 232:9
please 109:20 137:18
pleased 176:2
Ploeg 4:9 6:17 26:6,10,11 39:13 54:19 93:15 94:17 96:15 97:7 123:19 143:18 144:1,3 175:1 199:11 214:10 215:3 241:17 267:2 269:8 271:15
plot 42:16 51:14,18
plotted 50:20
plummets 107:2
plus 46:19 78:3 91:7 116:21 120:5 195:11 201:9 233:4 254:16
PML 192:7,14 193:4 198:16
PMNs 30:6
pneumocystis 189:22 195:18
Poggio 4:11 6:12 10:17 11:2,3 41:14 125:7 126:7,11
point 33:2 36:2 40:17 44:18 47:7,16,22 58:3 60:8 68:22 80:17 88:15,21 95:5,9 100:16 103:5 112:18 117:2 125:8,15 127:8 128:19 130:15 132:2,18 135:10,11,17,22 137:12 140:4

142:8 169:6 193:11 198:1 204:16 206:5 207:15 209:17 210:3 221:11 223:1 229:5,14 236:10 237:9,18 244:17 249:9 252:16 255:2,12 258:2,22 267:2,18 270:5 271:4,5 273:15 275:19

pointed 55:18 234:8

points 48:9,10 54:4 71:7 124:17 145:18 148:22 159:12 183:17 219:4 244:19 246:21 249:21 250:9 267:19

Poland 42:1

politically 223:4

polyclonal 63:1

polyoma 191:13

polyomavirus 191:17

poor 23:14 47:21 54:16 94:14 173:7 223:15

poorly 46:6 116:8,10 130:15 162:8 166:19 253:8

Popper 237:8

population 18:18,20 19:10 60:13 77:9 78:2,10 89:4 101:19 105:21 117:13,17 118:3,7 127:22 130:21 155:17 170:10 187:1 203:7 207:2,9,12 210:4 212:20 229:18,22 232:4,17,19 233:3,4 234:13 235:6,12,17 236:4,5,13,18 238:4 240:19 245:15,21 249:5 251:9 260:7

populations 87:11 98:11 100:8 151:17 152:12,15 204:1 211:19 212:13 213:21 250:13 274:7

PORT 183:21 185:22 186:4 252:5

portion 147:15 207:10 236:4

pose 152:5

positive 21:20 22:12 59:3 60:3 104:17 143:11 147:8 153:11 206:2 213:22 221:9 224:12

possibilities 236:17,19

possibility 129:16 132:3 138:4 213:8,9 236:14 277:10

possible 32:22 86:11 90:18 91:12 119:16 128:7 129:10 142:15 198:6,12 231:7,22 236:21 238:15 239:3 241:7 242:12 275:14

possibly 73:11 204:14 217:20

post 32:13 44:9 46:9 62:15 68:9 130:13,15 152:9 159:14 164:19 171:16,17 172:6 178:15 182:5 197:20 248:22 255:14

post-marketing 197:9 198:14

post-transplant 23:18 39:5 41:20 44:20 45:22 49:19 53:7 57:7 61:19 62:11 130:16,19 151:21 164:15 167:10 172:3 194:5 195:5 198:9 202:3,6 256:17

post-trial 193:6

potent 217:2

potential 16:16 17:11 40:5,13 45:3 77:21 144:17 147:11 149:18 157:7 186:1 208:17 214:5 236:19 267:16 268:14 269:2

potentially 76:14 150:16 193:2 194:1 213:20 217:14 271:2

pounds 173:7 174:3,12

power 148:1,7 152:3 231:4 240:11,21 249:22 250:3,10,12 259:15

powered 260:16 267:7 271:21 272:11

powerful 78:11

powering 276:4

PRA 62:20 64:1

practical 268:5

practice 15:15 196:18 256:10 263:15

pre 23:18 28:7 31:19

precede 74:13

preceded 278:8

precise 199:5

precisely 56:1

precision 22:4 23:14 212:16

preconceived 248:3

predefined 202:18 203:12

predict 32:21 33:7 36:7 57:19,21 65:21 66:7 79:1 115:19 120:3 124:8 125:13 147:22 185:6,18 186:1,7,9 187:22

245:3 253:14 255:11 261:9,20,21,22

predicted 66:19 186:5 249:7

prediction 71:2 78:9 106:13 115:22 249:15

predictive 32:20 64:13 66:3 78:12 106:15 107:11,18 108:16,19,21 109:15,18 110:17 119:8 131:17 261:7 262:5 263:2,6

predictor 63:13 120:18 122:2 131:16 155:21

predictors 193:3 249:12

prednisone 174:8 217:8

predominant 222:19 223:11

predominantly 203:10

preexisting 177:19 185:15

preface 229:7

preference 62:6

preferentially 129:14

preferred 145:14

pregnancy 15:4

preliminary 58:18 60:4 61:5 65:6

prematurely 105:1

preparation 15:4

prepare 54:3

prepared 201:2

prescribe 153:18

prescribed 8:1 144:7,11 155:1,11

presence 60:15 73:22 125:4 224:6,10 244:3

present 11:5 39:22 56:18 114:12 142:19 143:10 144:18 157:19,21,22 166:15 226:3

presentation 24:20 54:9 71:5 79:17 80:21 93:18 145:4 163:19 228:9

presentations 54:3 274:17 275:20

presented 97:14 155:13 220:19

preservation 6:15 26:4,8,15,22 29:9,20 31:4,18 32:16,17 35:8,18 37:20 38:2 65:1 93:19 94:5,14,22 95:14 97:12

preserve 226:19

preserved 34:18

preserves 147:18 148:6

preserving 60:15

preset 77:17

pressure 68:6 79:12 81:17 82:1 86:3 89:6 90:16,21 167:1 174:4 178:5,17 180:13,17,22 181:2,4,8

pressures 82:4 91:10 121:14

presumably 253:19

presumed 178:1

pre-transplant 167:6 170:16 189:4 193:8 194:2 198:9

Pre-treatment 39:3

pretty 19:11 73:10 100:13 135:11 136:1 142:11 173:11 197:15 217:16 219:10 225:6 227:4

prevalence 170:13

prevalent 74:11

prevent 127:20 176:7

preventable 191:15

prevented 127:17 194:18

preventing 133:20 181:19 246:2 276:14

prevention 191:18 196:6 198:10 208:18,19,21

previous 27:15 34:19 56:14 64:22 95:5 166:12 209:22 243:14

price 217:22

prices 15:16

primarily 192:8 202:1 213:12 220:5

primary 147:17 188:22 202:21 207:21 208:17 209:14 210:20 211:12 222:6 257:17 273:10

prior 32:6 187:4

priori 267:20 268:15,18

prioritize 157:7

pristine 125:10

privilege 175:11

PRO 277:10,14

probabilistic 269:18

probabilities 234:4 269:11

probability 78:22 138:5

probably 38:3,10,13 50:10 66:13 80:16,18 82:19 84:3,10,13,17 85:9 86:3 87:14 88:9 89:4,22 90:12 91:2 98:22 101:5,22 102:12,17,21 105:11 113:2 121:12 127:11 128:15 132:18 137:2 173:11

178:11 179:2 180:3 181:18 182:16 183:22 184:19 190:16 203:8 213:19 225:6 226:3 239:2,4 245:3 252:20 255:7 257:15 259:7

problem 37:1 72:1,14 73:13 95:22 96:1 97:16 102:6 105:2 113:16 115:17 117:13 118:7 131:19 134:11,15 137:5 142:14 170:9 219:12 221:13 227:16 269:15

problematic 75:6

problems 151:19 179:7 186:17 222:11 242:15 249:18

proceed 214:10

proceeding 279:4,5,8,10,11 280:5,6,9

process 73:11 101:3 103:22 105:12,20 110:8 131:22 141:14,16 142:2 157:15 158:11,13 159:4 160:15 186:13 198:5 232:14

processes 74:17 101:7 118:9 132:8 158:8

procurement 6:14 26:4,8 94:6 96:10

procuring 26:14

produce 185:8 225:5 226:11 258:7

produces 216:4

producing 251:3

product 275:21 276:1

production 75:2 249:6,13

productive 54:2

Products 2:4,10,12,17 4:4 5:5

Professor 2:13 4:5,9 54:19 64:4

profile 151:7 173:14 245:12

profiles 153:6,10

profound 30:8 35:3 58:6

prognosis 223:15

prognostic 73:15

prognosticating 77:19

Prograf 174:7 225:14

program 97:17,18 167:18 205:14 273:21

programs 96:9 97:19 195:7 205:20

progress 96:9 220:16

progression 58:4 70:20 75:14 76:18 81:16 85:21 125:12 224:21 225:10

progressive 41:10 74:15 75:22 120:17 201:17 224:1

progressors 51:4,9,10,15,20

prohibitive 230:14

proinflammatory 74:22

projected 254:22 255:9 273:20

prolonged 53:4

prominent 85:2

promise 229:16

promising 33:5 157:9

promote 226:16

proper 52:7 161:13 216:18 221:14

properly 25:12

prophylaxis 189:22 190:2 191:3 192:2 195:6,14,15 198:10

proponent 240:8

proportion 41:9 177:3 273:5

proportionate 74:5

proposals 158:7

propose 159:6

proposed 9:6 14:7 241:20,22 242:6

proposing 253:11

pros 147:12 153:4

prospective 61:15 131:5 168:16 268:19

protected 244:12

protection 194:4

protective 38:18

protein 13:2 33:8 47:19 132:9

proteins 74:22

proteinuria 7:6 62:3 70:9,14 73:15,19,22 74:12 75:6 81:18 89:5 91:1,18,19 92:1 103:2 116:7,13,18,21 120:1 124:20 125:4,11 131:11,14,16,18, 21 135:7 143:6 164:12 168:6 170:12 209:20

proteome 30:16

protocol 8:1 47:12 95:17 96:11,22 97:2,15 144:7,11 145:7,19,22 146:13,15 149:12,14,16,17, 20 150:2,4 151:3 217:6 235:18 264:21

protocolized 31:6

protocols 41:2 198:11 239:16

prove 76:5 119:12 127:22 155:9

237:13 270:22
proven 129:11 179:9 266:22
proves 237:14,17
provide 71:6 130:4 147:16 150:21 151:15 162:16 194:4
provided 20:5 24:9
providers 155:22 160:3
Proving 237:15
provocative 80:3
provocatively 255:5
PTLD 195:13 201:22 202:7,16,19 204:11,17 205:13,21 206:5,7,9,13,19 213:19 216:4
PTLDs 203:5
Public 1:6 7:16 9:10 93:4 255:18 279:1,20
publication 24:3 82:12 126:2
publications 86:1 224:5
published 17:9 20:4,7 40:1 42:1 48:20 56:6 57:15 60:5 91:14 100:22 186:11 195:22 197:4 218:2 223:20 245:20
publishing 82:3
pull 268:6 269:20
pulled 20:21 41:21 192:20
pulling 271:8
pulse 178:5
pump 98:19
pumping 96:12 271:17
pure 222:4
purple 180:7 181:3
purpose 68:1 80:21 91:22
push 172:13
pushed 112:1
pushing 219:7
puts 245:12
putting 159:21 198:19

Q

quality 6:15 26:5,9,15 27:1 29:4 30:18 37:6,10 38:9,17,21 227:11 241:9 263:21
quantified 185:2
quantitate 145:8
Queensland 207:7
question 7:15 9:9 16:3 28:18 59:9 74:18 86:11 92:10 93:4,17 94:18 95:12 96:14 99:21 102:5,15 107:13 108:13 109:11 110:19 111:3 113:4 115:18 119:14 120:21 121:19,22 122:8 123:17 128:4 156:14 158:10,16 164:3 198:4 215:14 216:16 225:12 237:5 243:12 255:18 256:4,14 258:8,17 272:1,13
questions 7:16 9:10 16:3 73:21 92:3 93:5,14 117:16 134:7 151:13 255:19 275:6
quick 154:16 199:22
quintile 50:10,12,14,16 51:2
quintiles 49:22 50:6
quite 35:16 36:18 39:10 45:9 55:7 59:21 65:4,16 69:17 71:9 110:12 166:17 176:21 193:2 217:20 218:7 248:14
quote 251:5
quote/unquote 154:3
quoted 110:12

R

RAAS 90:13
race 21:13 25:7 39:9 80:10 164:2
radioisotope 14:13
radioisotopes 13:6
raise 139:21 140:3 197:13
raised 89:16 133:19
raises 86:11 197:15
raising 90:15
Randall 4:5
random 66:8,18 104:20 112:2,5,14,15,17 127:21 231:11 235:16,18,22 236:11,12
randomization 98:17 99:8 146:11 236:12,15 238:20 239:10 241:7
randomized 98:15,21 110:3 145:6,13 146:12 147:4 150:8,9 158:22 168:16 208:22 209:2,9,10 210:14 235:8,14 241:1
randomizing 69:3
randomness 112:18
Randy 115:6 119:1 260:20

264:5
range 18:6 21:22 100:10 173:12 180:14 205:5
rapa 168:16 169:2,5,7,10,13,17
rapamycin 168:3,14
rapid 65:17
rare 207:14
rarely 14:9
rat 91:3,13
rate 12:10,11 48:7 52:14 117:21 123:10 155:2,5 174:5 176:12 183:10 185:19 201:7 207:8,11 210:15,22 212:19 215:20 216:5 217:5 219:2,9 222:21 224:13 264:17 265:3 272:21
rates 8:3 144:8,13 147:8 151:6 183:15 184:5 186:5 191:5 194:10,20,22 204:17,22 205:19 206:7,9,12,13,21 207:13 210:16 212:9,16,21 213:19 217:11,20,21 218:6
rather 9:2 11:8 133:20 166:12 182:7 194:4 201:10 228:15,19
ratio 48:22 49:2 84:21 86:22 87:1 250:7
ratios 266:6
rats 91:4,8,16,17
RCT 34:4 232:22
RCTs 145:14 236:22 239:7 243:16
reach 32:7 47:9 139:16 178:4 216:21 219:8
reached 51:1
reaching 201:10
reactivation 190:10
reactive 76:1
reading 15:11 62:5
ready 94:19
real 33:9 77:15 114:10 117:15 128:16 134:15 137:9 186:11 198:2 202:9 212:7 236:9 237:3 238:22 243:4
realistic 114:20 198:18 273:20
reality 132:17 133:11 157:21 270:5 271:12
realize 200:15
realizing 74:8
really 14:17 22:18 27:4 28:2 29:11 33:7 38:16 41:4,6 46:12 47:1 54:4 55:15 57:12 60:22 65:9 66:19 68:7 69:6 70:1 72:12,22 78:20 80:3 100:7,13 101:22 103:14 106:4 109:1 110:6,12 111:18 113:19 114:9,10 117:17 118:19 126:4,5 131:15 132:1 136:9,13 138:16 139:18 142:8,19 147:10 150:18 151:5 153:9,13,16 154:6 156:8,10 158:16 173:14 176:3 184:17 188:22 189:5,7 190:2,4,11 191:10,11,18 192:20 193:2,3 194:17 195:2,4,10,19 196:5 197:22 201:21 202:9 203:2,8 214:19 219:6,11 221:7 229:2 230:9,18,22 236:10 237:3 240:1 241:15 246:21 248:12,21 250:20 252:9 256:8,21 262:2 276:1 278:4
realms 161:14
reanalysis 82:12
reanalyzed 267:19
rearranging 220:14
reason 17:19 55:18 65:20 66:7 100:3 128:1 271:15
reasonable 64:15 134:1 202:14 273:19
reasonably 119:7 212:4 261:7
reasons 47:8 71:11 89:22 90:14 92:1,12 153:14 155:8 239:13
reassess 159:21
reassuring 65:7
receive 45:6 148:14 152:18 243:18 251:18
received 191:2 218:15 219:5
receiving 64:21 80:6,7,15
recent 12:20 55:4 66:11 82:8 166:8 190:16 193:17 196:1,13 201:22 213:13 267:15 271:16
recently 12:21 69:2 166:6 185:7
receptor 81:15,22 204:14
receptors 162:2,4
recess 92:20 199:16
recipient 29:8

32:17 35:8 56:19,21 58:15 86:10,22 101:12 190:9 251:16

recipients 23:10,11 38:8 48:15 53:2 55:17 75:16 85:22 86:16 89:18,19,21 90:13 92:4,11 154:22 155:6 166:9 170:15 171:1,9,13 176:5,17 177:8,12 184:15 191:5 192:1 206:2,4 207:17 244:10

reclamation 74:21

recognizable 125:15

recognize 107:3 175:13 202:20 244:5

recognized 101:4 246:9 276:4

recommend 113:8 192:1 195:17 196:2

recommendations 205:18

recommended 17:5 23:7

reconcile 182:22

reconciling 241:1

reconsider 258:19

record 184:17 279:8

recorded 61:20 187:22 279:5

recordings 280:7

recoup 156:1

recover 27:20

recovery 27:13 30:1 35:5

recurrent 118:12 124:22 125:20 136:16 204:3 208:3 223:1

red 186:7 248:16

Redefining 8:9 175:3,7

redefinition 228:8

reduce 82:1 90:21

reduced 34:14 73:7 92:5,6 164:9,20,22 166:11 168:10 170:12,20 211:2 279:6

reducing 81:17,18

reduction 32:1 35:13 51:8 81:20 165:17,18,19,20 167:18 200:18 215:19 218:11 246:3

reductions 206:9

reexpressed 17:7 18:10

refer 166:16

reference 46:12,14,17 197:7

referred 163:22

referring 145:21

refers 240:14

refine 224:16

refined 32:5 38:15

reflect 69:16 70:3 74:12 178:18

reflection 65:10 155:20

refuted 237:15

refutes 237:14

regard 58:19 76:12 103:18 119:19 133:19 262:1

regarded 167:1

regardless 55:11 72:1 127:18

regards 116:2 131:11 151:15

regeneration 90:10

Regents 215:12

regimen 39:6 80:6,7 132:15 149:22 155:11 156:10 161:7 191:20 216:19 217:8 219:20 220:3 256:18

regimens 8:2 83:4 144:8,12 146:16 153:8 192:7 194:6 206:10 219:14 227:3,13 263:16 274:10

region 18:20

registration 203:2,12 204:18 205:1 206:17

registries 266:8

registry 80:14 110:9 183:8 220:11 252:8 263:2 266:6,12 267:1

regression 48:12 49:20

regulatory 151:11 152:21 158:8,11,12 161:14 205:18 273:17

reimbursed 15:18

reimbursement 151:20 153:1

reiterate 100:5

reiterating 230:20

rejection 29:2 41:7 45:15 56:19 58:12 60:17,19 63:2,3 64:7,11 65:2 66:17 88:4,8,18 100:22 102:9,12,14 122:20 123:10 151:6 164:13 168:11 187:2 215:20,21 216:8 217:5,9,11,20,21 218:6,8 222:2,4,7,10,11,21 223:8,17,18,19 225:8 226:1 227:6 228:2 239:19 245:22 246:3,4,6,9,18,19 255:4 257:19,21 258:4,10,16,17 264:17 265:3,7 266:11 272:21 274:22 275:11

276:13,16
rejections 90:3 186:18 215:22 223:20 275:12 276:12
related 17:12 71:11,13 74:4 75:9 90:3 94:22 111:1 168:14 203:9 253:2 265:11 269:21 272:18 276:12 279:9
relates 157:20 161:3
relationship 19:2,4,6,13 57:6 59:15 77:17 145:2 221:4 236:3 240:7,12
relationships 76:4 145:1 187:14
relative 86:9 218:9,12 266:6,13
relatively 44:17 45:2,11,18 65:17 149:7 151:4 153:22
relativity 237:12
relevance 95:3
relevant 28:18 36:21 54:9 159:5 203:2 204:2 215:20 247:3,14 253:15 254:4,11 274:3
rely 86:4 224:16
remain 181:13 211:11 224:14
remained 219:9
remaining 27:8 28:16,20 200:21
remains 14:8 22:5 23:15 24:21 75:6 186:10
remark 28:5
remarkably 148:17 177:12
remarketing 192:15
remarks 115:8 131:8
remember 19:1 23:9 78:1 99:20 266:7
remind 214:7 243:20
reminded 175:19
remove 98:9
REMS 192:2 205:14,19
RENAAL 82:13
renal 3:9 6:6 8:9 10:5,11 15:20 27:16 28:9 32:6,22 42:4,14,19,21 43:21 44:13 47:17 49:15 51:5 56:10 58:20 68:6 70:21 72:15 74:14 89:7 90:8 91:16 105:6,17 128:18 130:3 145:11 147:9 150:7,13 151:8 166:2 171:2 175:3,7 185:11,16 221:4,5,6,8 223:21 224:1,7,21 225:10,22 226:19,20 258:14 261:8 262:4
Renata 2:3 26:12 92:16 93:11 144:2
repeat 234:20 237:10 265:12
repeated 53:5 159:2
reperfusion 29:22 35:4 90:2
report 155:4 198:3,4 209:6 277:15,18
reported 1:19 12:22 24:1 153:12 185:1 194:20 197:14 198:2 206:8 209:1 226:14,17 227:10 280:4
Reporter 280:4
Reporter's 280:6
reporting 1:20 158:20 185:4 187:20 197:21 203:14
represent 49:11 149:9 150:11 243:6
representative 277:11
represents 49:14 202:21
repurpose 76:17
repurposed 76:14
repurposing 76:21 130:7
reput 192:21
request 201:2
require 154:7 156:20 159:1 214:1 238:21
required 48:9 49:19 205:14
requirement 123:8
requirements 107:21 229:19
requires 149:5
research 4:7,16 13:18 15:8 53:9 150:1 155:9 157:3,6 160:4,6,9,12,19 162:10,15 203:18 215:12 239:14 240:3,9 241:6 249:20
resemble 203:6
reserve 78:17
Reshma 10:7
resist 83:13 247:18
resistance 32:22 68:6 164:17 167:22 168:5,14 169:5,8
resistant 89:1
resolve 259:12 260:19
resolved 22:6
resource 36:17 230:14 231:6
resources

159:16,21,22 271:1
respect 14:18 260:16
respective 259:20
respects 212:4
responded 109:15 120:13
response 27:10 127:1 143:13 147:6 194:3
responses 75:10 126:22 147:7 161:19 220:3 226:2
responsibility 146:4
rest 102:1
restore 201:12
restoring 172:16
restrictions 209:21
restructure 261:17
result 22:9 30:12 161:8 191:18 204:8 238:16 240:17
resulted 149:19 205:13,17 219:13
resulting 18:4 205:19
results 19:19 28:20 31:9 53:1 62:3 74:5 98:7 99:11 129:12 148:10,11 149:5 166:22 171:21 195:2 212:8 239:21 243:15 258:7 273:16 274:3
resuscitation 35:1
rethink 216:1
retransplantation 34:9 56:21
retrieval 26:22 29:20 35:3 37:7,19
retrospective 266:19
return 92:19 247:12
revalidate 263:7
revealed 210:21
reverse 141:20 143:1,4 195:12
reversed 141:17 178:22 217:14
reverses 127:17
reversible 60:9
review 20:3 119:16 210:13
reviewed 121:3 155:7
reviewing 83:18 155:17
reviews 111:21 186:12
revisit 275:22
revolution 218:3
RFAs 241:5
RFP 76:16
Rhabdo 165:21
rid 105:19 231:21 248:2
rightly 106:14
rigid 151:10
rise 28:15 87:13 89:5
rises 207:9
rising 84:20 216:8
risk 31:7,10,19 35:6 52:2,5,12 53:6 57:10 59:18,21 60:1,13,18,19,20,22 61:2 62:11,13 63:4,7,11 69:19,20 78:16 86:16 102:13 130:20,21,22 133:22 152:22 163:21 165:18 166:3 167:7 168:10 170:11 171:11 177:7,15 178:2,15 179:10,11,12 182:3,18,20 184:3,11 185:8 187:13,21 190:17,19 191:11 192:3 193:1,4 196:16 198:20 200:15,18 204:7,10 205:21 208:5,13,15 212:2,16 214:1 218:9,12 220:22 221:1,10,18 227:8 232:18 244:8,9,14,21 245:1,5,12,13,14,21 246:8,18,19 247:2 248:21 249:2,4,5,14,16,17 250:1,2,5,6,11,12,16 251:3,21 252:1,3,6,10,17,21 253:5,7,9 254:17 257:20 258:11 259:2,4 261:5,20 263:2,4,6 266:10,13 273:11
risk/side 244:1
risks 192:16 204:1,13 244:3 247:14 249:7 254:3 266:6
risk-stratified 248:8,17
Rita 2:5 8:4 144:9,13
rituximab 192:10
road 104:9
Robert 7:3 53:14,17
robust 237:16,19 252:6,10
ROC 66:3
Rochester 4:8,22 42:12 47:10 49:4 52:22
role 25:9 85:20 221:7
rolled 177:10
Rolls 124:7
room 16:10,19 63:21 151:14 154:13 159:9 200:1
Rotterdam 2:8

roughly 65:13 67:5 194:21
routine 190:7 193:15 196:3,16
Roy 2:20 142:19 206:17 249:12
Royce 124:7
RTC 231:16
rub 253:10
Rubin 189:12
rule 124:20 125:3
run 17:17,19 118:21,22 278:2
runner 82:21 83:6
runners 83:12
run-of-the 148:12
Rush 4:13
Rush's 155:12
Russ 209:2
Rutger 4:9 6:17 26:6,10 93:17 97:10 115:6 123:18 127:12 143:18 144:1
Rutger's 127:8

S

SAE 204:1
SAEs 203:14
safe 36:18 278:11
safeguards 274:12
safety 2:11 7:20 158:20 159:19 162:22 185:1 188:9 189:7 200:8,14 201:21 202:18 203:11 213:12 214:5
saintly 175:18
Salomon 4:15 10:3,7,13 26:3 53:12 79:17 92:15,21 93:7,17 95:20 96:5 97:4,9 109:9 110:10 115:4 117:1 119:1 120:8 121:19,22 123:13,16 124:15 125:6 127:5 128:12 130:9 131:2,9 132:10 133:12 134:3,18 137:20,22 140:2 141:7 142:13 143:14,15 188:6
salvage 31:4
sample 16:12 25:2,4 147:18,22 148:5,6 160:21 269:4
samples 18:11 25:12 37:13
San 5:6
save 195:19 271:1
saw 32:5,9 35:5 61:14 109:13 110:13 191:4 272:15 278:2
scale 102:11 181:18
Scaling 9:1 228:13,18
Schaefer 4:17
Schoenfeld 233:19
Schold 4:18 33:15 98:13 259:10 260:11 267:13 270:11,17
School 2:14 3:8,11
Schulman 4:20
science 235:2 237:5,10,22 265:20
sciences 238:5,6
scientific 235:3
scientist 237:6
scientists 238:6,8
scope 150:17 188:21
score 248:9 249:2 250:6,16 251:3 252:1
scores 251:21 252:6,17,22
scoring 36:5,6
scratch 156:18
screening 165:6 189:3 191:16 193:9,15,16,17,19 194:12,18,21 195:1,4,7 196:3,14,16 198:9
Scripps 4:16
se 149:8 162:2
search 86:4 112:20 239:14
seats 10:11
second 26:3 48:17 85:9 95:21 132:11 135:20 152:4 158:15 202:7 208:5,6,8,9,11,13,14,21 211:9 245:7
secondary 202:16 208:19 258:15
secondly 163:12 165:14
seconds 94:19
seeing 83:21 89:10 126:3 147:3 193:12 212:6
seem 181:16 183:5 218:20 220:16 225:17
seemed 69:8 192:16 218:13
seemingly 112:16
seems 24:14,16 45:19 55:13 58:21 88:19 110:13 182:22
seen 30:10 59:6 64:21 65:11 73:5 80:13 98:6 177:9 179:6 186:10 192:8 195:12 197:12 219:1 221:3,17 251:10
segue 141:10
select 52:7 157:12
selected 27:7
selecting 40:8 47:21 133:21
selection 45:4 47:4 235:16,22 236:11,12
Self-Employed 4:6
seminal 57:12

senior 245:19
sense 130:5
separate 222:1 233:13
September 1:9
sequence 27:16
sequential 267:7 272:9,10
series 59:4
serious 26:18 191:12
serological 79:7
seronegative 191:5,22 206:2
serum 12:7 13:17 17:17 19:6 47:18 60:10 62:2 63:6,7,10 64:2 66:4,19 67:2 68:7,11 69:18 117:19 174:1 181:12,15,21 182:1
serve 68:1,2 94:7
served 97:18
session 6:6 7:19 10:5,11,16 141:9 143:17,21 144:5 241:18
Seth 4:20
sets 252:10 253:9 271:12
setting 19:2,12,17 23:17 270:14
settle 93:2
settles 176:11
setup 19:15
setups 20:2
sevenfold 61:2
Seventeen 209:7
several 11:22 12:16,22 77:7 85:15,22 119:12 145:1 195:12 196:4 203:5,19 223:6 227:10 267:3
severe 56:21 223:19
sexy 154:14
share 96:20 194:11 253:6
shared 157:10
Shelly 194:10
Sheraton 1:14
she's 244:9
shift 58:22 157:8 258:3
short 25:8 33:21 38:21 52:5 199:20 251:17
shorter 208:1
shortest 121:1
short-term 52:2 71:10 125:1 134:9 263:12
showed 28:22 59:22 60:6 68:9 106:3,15 178:16 196:15 243:13 262:6
showing 66:11 108:5 181:12 182:15 183:16 219:1 220:12,20 221:18,20 224:11
shown 11:11 28:21 47:14,20 50:7 57:4 64:22 76:11 176:19 179:6,17 182:5 204:10 206:11 214:21 215:8 272:10
shows 27:19,21 40:18 43:5 50:5 57:5,15 87:10,18 88:2 111:17 126:2 179:20 183:14 186:3,4 200:21 215:11 225:1 249:21
Shukal 2:9
sic 28:12
sick 229:22 232:3 236:4
signal 96:8 203:11
signals 159:19
significance 32:7 117:22 178:4
significant 25:9 30:22 31:18 32:6,10 33:19 34:6,11,14 35:10 43:3 60:21,22 62:21 63:5,8 64:12 86:17 87:8 98:14 155:19 165:21 178:18 188:17 205:13,14 208:5 210:16 213:17 272:4 274:7
significantly 22:22 23:16 34:15 42:21 118:6 191:4 211:2
signs 174:2
Silver 1:14,16
similar 23:13 24:15 29:4 47:1 55:7 57:11 59:22 64:10 80:16 92:1 169:9,14 172:4 206:21 212:6,8 249:12 253:19 258:7
similarities 81:12
similarly 169:14 195:3
simple 11:8 13:16 44:7 67:13 98:21 102:5 106:17 107:12 176:18 242:11,12 244:18 247:7 253:6
simpler 242:13
simplest 257:5
simply 17:20 25:9 166:17 241:10 251:15
simulated 272:6
Sinai 3:10
single 37:3 40:6,14,15 43:20 48:22 51:12,17 63:12 91:9 100:6 108:11 116:3 137:5 157:22 184:19 217:11 222:14 224:17 249:13
single-handedly 154:19
single-time 41:13 52:1

SIR 212:14
sirolimus 142:5 205:8 209:20 210:16 211:2,8,12 212:9 217:8 225:14
sirolimus-based 209:11
sit 10:4
Sita 56:5
sitting 92:18 151:4 264:6 266:11
situation 38:5 154:8 195:12 269:3
six-center 98:6
sixfold 63:11
size 86:10 139:7,15 147:18,22 148:5,6 160:21 230:9 242:20 262:1 269:4
sizes 37:14 186:19
skewed 245:4
skin 202:1,6 203:11,20,22 204:4,6,12 207:1,3,10,17,21 208:3,4,8,12,16 209:15,22 211:5,7 212:1,3 213:7,13
sky 175:14
slide 11:12 23:20 30:21 35:16 38:6 155:12 163:20 176:2 177:9,17 186:14 204:15 214:7,21 215:11 220:9,10 221:3,17 225:1 244:11 249:20 253:21
slides 171:19 176:2 179:16,17 205:3 215:2,7
slight 50:21 63:3 87:17,18 170:5
slightly 66:6 89:11 175:16
slope 48:21 49:2,17,18,21,22 50:7,11,12,17,20 51:6 52:11 56:4 58:5,8,10,16,20 59:3,4,20 64:20 69:15 71:20,21,22 72:3,5 73:8 77:16,19 83:22 85:10,16 87:17 88:13,14 103:15 104:17 110:4,20,22 113:14 115:11,13,18 117:17 127:11 128:2,16 129:17 132:1 143:7 155:15 207:5 221:8
slow 81:15 83:6
slowly 225:22
small 146:21 182:13 211:18 230:9 231:8 232:1 243:17
smaller 38:18 88:10 91:18 133:10 157:11 181:13 232:4,19
smallest 231:7
small-size 86:16
smart 38:17 271:12
smarter 217:17
smoking 177:21 185:15
smooth 196:12
so-called 13:9 31:13,16 36:19
society 157:4 162:13
soft 263:19
solid 202:5,7 210:9 213:2
solitary 54:20 55:21 69:11
solution 9:3 124:3 144:20 228:16,19
solutions 241:7
solve 37:5 137:5 141:6 142:14
solved 17:22
solves 136:19
somebody 85:5 108:7 174:15 239:17
somehow 256:12
someone 67:19 125:16 133:16 275:8
somewhat 191:14
somewhere 114:1 223:10
sophisticated 38:11
sorry 18:7 96:15 98:13 178:9
sort 54:5 59:6 63:19 94:10 98:20 107:16 111:22 119:18 120:5 131:7 137:9 193:5 194:13 196:2,20 197:9 200:19 213:9 255:6 256:13 260:2 261:6 262:4 263:19 271:12 273:11
sorting 248:15
sorts 97:12 139:12 180:17 184:3 238:10 243:21
sound 247:6
sounded 276:7
source 16:16 249:3
sources 17:11 190:8
Soveri 185:13
space 107:22 274:5
Spain 211:10
speak 10:17 53:20 93:13 163:6,7 197:19 270:4
speaker 6:12,17,21 7:3,9,12 8:4,7,11,15,18,22 9:4,7 10:16 11:2 39:14 70:7 126:20 144:4 162:19 214:11 228:12 241:18 270:10

speakers 2:1 3:1 4:1 5:1 11:9 143:19 278:10
speaking 53:22 119:4
special 269:5
specialist 188:15
specialties 157:3
species 76:1
specific 79:9 98:10 109:10 113:4 128:16 160:22 162:3 223:5 253:15 254:4,10 274:6
specifically 40:7 44:3 76:16 212:15
specificity 262:16
spectroscopy 15:10
spectrum 44:19 202:21
spelled 56:1,4
spend 16:1 50:19 52:13 156:4 159:7,16
spending 220:14
spent 62:19 147:20 178:12 220:7
spill 97:15
spin-off 166:1
spirometry 15:19
spoken 227:11
sponsor 134:8
sponsored 1:6 20:13
sponsors 121:15
spot 263:20
spouse 188:17
spread 22:5 45:1
Spring 1:14,16
squamous-cell 211:13
squares 48:12
Squibb 3:6,15
SRTR 201:3 212:15
stability 7:1 53:12,16 55:2 59:9 60:3 63:9,12 64:13,14 65:3 69:9,12,17 125:9
stabilize 45:19
stable 12:12 44:6,7,17 45:12,18 46:3 50:12 52:9 65:14 78:18 95:6 105:17 115:15 117:9 166:8 171:1 173:12 209:18 219:10
stack 235:21
stage 104:6 133:4,5 262:19
stamped 225:2
Stan 196:13
stand 141:3
standard 13:3 14:8,9 20:16 24:22 29:15 31:8 41:2 47:11 63:1 122:20,21 123:11 127:15 150:9,11 187:1 195:16 196:7,11,19,20 197:7 198:11 229:8 230:15 233:5,8 234:10,11,14,16 274:1,10
standardization 106:12
standardize 128:17,21
standardized 30:10 195:17 196:6
standards 151:12 157:10 171:13
stand-down 35:21
standpoint 128:7 167:21 230:15 231:6 266:13 269:18
stands 107:13
standstill 230:22
Stanford 4:6 5:3
start 37:18 54:20 78:13 89:9,10 107:20 108:7 122:18 123:11 124:2 128:19 130:11 132:14 133:1,7 135:1 137:10 138:22 140:14 151:20 156:18 159:10 175:20 208:10 215:3 216:12 242:11 251:2 254:1 255:22 266:1 271:11
started 16:22 74:7 92:22 93:12 131:6 176:15 177:11 187:14 199:18 242:8 252:3 269:11
starters 163:4
starting 139:5,21 163:10 173:5 204:16 244:17
starts 26:19,20 122:10 135:18
state 25:19 81:10 95:7 172:18 279:21
stated 90:1 151:22
statement 242:11
states 92:5 145:10 201:4
statins 178:21 184:4,7
statistical 146:8 148:7 178:4 233:14,22 236:15,19 241:8 249:22 276:18
statistically 60:21 62:21 63:5 64:12 86:17 87:8 178:18 187:10 211:2 268:8
statistician 4:18 232:15 270:4
statisticians 151:14
statistics 24:10 174:13 229:4 236:16 238:13 239:11 270:4
status 47:12

185:15
stay 69:4 200:22
stays 45:1,16 201:5
steep 82:16 87:21 88:17
steeper 87:20 88:16
Stegall 4:21 99:22 101:16 103:4 104:3 105:4 108:9,15,19,21 111:8 112:12 113:18 114:7,12 118:1,8 125:17 126:9,13,17,21 131:19 138:3 143:18 144:1 162:19 199:17 200:3,5 228:12 255:21 257:13 260:20 263:13 266:3 267:12
Stegall's 28:22
stents 173:6
step 83:3,9 98:20 99:4 150:15 158:14 232:12 235:3
steps 160:18 275:2
steroid 256:11
steroids 168:7,11,17 179:20 180:3 204:12 217:7 222:12
Steve 5:8 8:18 200:7,11 226:13 234:8,9
stick 97:1 124:1 132:15 146:2
sticks 202:9
stochastic 110:7 111:9
stomachache 239:20
stop 66:12,14 126:15 135:14 159:11 230:2 255:16 271:19 272:8
storage 32:11 33:20 34:7,16
store 25:12,13
storm 30:5
story 169:15 173:2
strain 178:6
strategies 35:18 71:3 75:12 76:8,14 124:2 149:2,3 151:11 156:2 159:22 162:7
strategy 35:8 73:20 76:18 147:14 162:15 208:21 257:21
stratification 130:21 249:2,15
stratified 49:8 209:12 248:21 253:17
stratify 42:3 52:3 98:16,18
streamline 158:11,20
streamlining 158:8 159:4
strength 18:21 212:7
stress 75:12,20 77:1 130:6 236:10
stressed 84:4
stressing 239:5
strict 238:6
strictly 237:8
strike 240:15
striking 168:21
striving 55:20
stroke 181:2,7 182:2
strong 60:3 66:2 166:3
stronger 60:20 69:20
strongyloides 193:21 194:7
struck 277:15
structural 178:11 181:9
structure 75:5 116:12,13,22
struggled 106:9 198:19 270:2
struggling 269:3
Stuart 237:9
stuck 33:12
studies 12:22 13:21 20:4,22 21:5 38:17,18 39:2 40:5,9 41:15,19 44:8 47:7 48:3 57:4 68:11 74:6 95:5,11 112:22 113:1 114:2,19 134:10 150:13 153:4 154:17 171:14 186:3 190:5,20 203:13 204:20 206:17 208:18 210:11 212:7 224:4 227:10 229:6,13 231:1 232:8 234:3 235:7 240:6 241:2,13 260:16 263:6 266:19 268:15
stuff 136:16
subclinical 41:7 100:21 112:4
subfractions 177:21 178:4 180:2
subgroup 215:22 248:14 249:10,19 250:5 251:21,22 257:9 259:3
subgroups 69:8 77:11 148:9 247:17 248:18 251:16 253:4,9,20 254:5
subjects 28:7 148:13,15,17,18 149:5 151:3 238:21
submit 79:5 247:13 252:20 253:16
submitted 151:2
subpopulations 133:21 204:3
subsequent 78:14 151:19 152:22

196:2 224:12 257:8
subsequently 62:7 107:7 189:14
subset 46:5 149:13 256:19
subsets 89:10
substantial 57:18 134:8 208:13 243:18
substantially 57:10 207:11 211:1
subtle 32:4 100:15
succeeded 157:1
success 161:2,12 242:19 247:16 251:6 254:1,8,9,21 255:9
successful 7:20 9:6 143:22 241:19,22 242:16 253:18
sudden 177:22
suddenly 115:16 137:4
suffer 145:15
Suffolk 243:1
suggest 86:9 119:21 199:12
suggested 7:16 9:10 65:13 75:3 85:22 93:5 109:17 255:19
suggesting 166:11 224:6
suggestion 92:16 95:21
suggestions 167:15
suggests 41:11 54:5 135:13
suitable 41:12 43:21
sum 253:22
summarize 133:14
summarized 43:4 189:12
summarizing 134:19
summary 9:13 23:12 24:20 46:7 144:3 240:20 274:12
super 250:14
superimposed 243:6
superiority 147:18 150:3 230:11 261:3
Supplement 197:3
supplied 165:7
support 3:9 34:22 145:3 154:17
supportive 82:5,6 150:3
supposed 135:4 233:17 265:5,6
suppress 227:2
suppressing 227:7
suppression 81:5
sure 24:2 95:16 108:4 111:15 128:15 137:18 173:22 222:1 244:16 261:11 263:21 265:21 269:17
surface 105:3 252:1
Surgeon 4:10,21 5:8
surgery 2:13 4:6 203:17
surgical 27:12 167:13
surprise 222:17
surprising 42:8,20 50:10
surprisingly 36:13 62:22 230:1
surrogate 74:3 86:19 103:21 104:7 106:11 113:21 117:18 119:7,16 120:1 130:18 139:18 246:7 254:9 261:3,6
surrogates 143:8 253:11,18 254:7,9 255:2
surrounding 71:15 72:12,20 73:4 76:1 124:11
survival 31:1,2 32:10 34:3,10,17 35:11,12,15 36:9 40:12 41:3 42:10,16,20 43:6 47:15 51:18 57:16 59:15 66:5 78:14,15 80:11 81:2,3,7 86:11 87:6,8 88:2 94:2 101:21 103:7 114:3 115:12 132:18 136:1,10 138:19,21 140:16 141:4,5 154:20 164:20 165:1,2,4 170:21 171:5,6 172:10 200:16,19 216:15 230:17 239:18 244:22 251:7 252:18 258:5 264:16,17 265:2,3,13 274:22 275:5
survival-free 211:12
survive 80:11 125:5
surviving 48:8
suspect 79:8
sustain 145:11
sustained 81:21 92:9
swath 242:17
Swedish 55:5
switch 149:11
Switzerland 211:10
sword 240:21
sworn 68:4
SYMPHONY 184:18 225:11,12
symposium 214:20
syndrome 163:14 169:19 170:10,13,16,18 171:2,9,15,22 172:5,9

synthesis 120:6
system 36:5,6 37:12
systematic 17:13 18:3,6
systemic 75:1
systolic 167:1

T

table 92:22 130:9 156:22 159:20 160:14 184:22 210:21
tables 10:4
TAC 217:7 235:11
tackle 220:18
tacrolimus 13:13 58:22 100:21 140:21 167:22 168:17 204:21 205:2,6,16 206:15
tags 200:2
tailed 99:16
take-home 46:15 48:12 195:1
takeoff 47:7
taking 66:12,14 68:10 94:9 101:19 106:6 126:15 148:3 236:8 266:22 268:15 273:6
talk 11:7 13:4 27:15 40:4,8,9 44:3 54:19 58:13 61:4 64:5 80:1 81:10 100:18 108:7 118:20 120:9 124:2 133:15 134:20 152:9,11 156:9 162:20 163:15 172:8 175:2 176:4 188:6,14,20 194:10 197:9 198:19 200:7 201:19,22 202:2,15 206:22 214:12 228:13 229:2,15 242:14 251:4 265:4 270:1 273:14 274:6
talked 32:19 41:14 116:18 136:6 138:14 154:8 182:9 230:6,21 234:17 248:7 256:7 277:11,15
talking 11:6 17:20 49:22 66:21 80:8 100:19 114:7,18 122:15 123:4 125:18 127:9 130:18 145:22 156:4 197:18 202:4 211:18 229:8 230:8 249:10 260:17 270:15
talks 56:14 175:20 199:19 202:3
Tan 5:3 117:4 118:5
tandem 15:9,10
tangible 224:15
Tango 27:4
Tarasenko 124:5
target 153:5 160:22 257:10 258:13
targeting 77:1 79:9
targets 76:3 167:2
task 26:13 247:6
tasks 263:10
TB 193:17 194:20
team 53:9
team-oriented 160:6
teams 35:22
technical 11:8 16:11 196:10
technically 98:14
techniques 13:10,12 14:14 222:1
technologies 15:9
temporality 74:10
temporally 204:5
tempted 83:13
Ten 211:10
tend 66:18 119:4 190:6 203:6
tends 218:18 224:7
tension 229:17 233:16,20 234:7,21,22 273:16
Terasaki 2:19 224:11
term 51:4 52:5 57:20 62:8 71:9 80:10 81:7 82:18 89:3 105:8 125:5 134:6,10 174:20 181:16 186:1 214:12 219:14 220:4 222:17 223:2
termed 61:6 209:1
terminology 276:13
terms 54:20 73:2 94:13 107:10 134:18 142:3 143:5 144:22 146:5 153:16,21 158:7 161:21 200:16 210:22 229:6 230:8,22 231:16 236:22 244:5 245:8 246:6 252:17 260:18 263:10 266:7
terrible 239:19
terrific 133:13
test 15:14 38:2 47:18 111:8 154:16 156:3 165:9 185:21 230:12 233:18 271:22
testable 111:10 112:12
testament 278:7
tested 33:4
testing 68:15 185:21 196:8,10
tests 15:14,22 47:11 228:22 236:16 238:9,10,20 239:4,10
text 24:12

texts 233:22

TG 255:3

thank 11:4 26:1,11,12 39:11,13,21 53:10,22 70:5,7 79:15 92:13 109:4 131:12 143:15 144:4,14 162:17,19 163:5 174:21 175:1,10 188:4,14 199:11,15 214:10,18,19 228:10,21,22 241:15,17 242:2 266:3 269:8 274:16 278:9,10

thanking 53:8

thanks 53:18 94:17 131:9 199:9 242:2 255:16

that's 11:15 15:13 16:19 17:16 19:6 25:5 28:5 44:20 51:7 56:4 57:4 72:11,16 78:7,12 80:7 95:20 96:8 98:21 99:9 100:2 101:5,11,16,18 103:17,19 104:3,10 105:2,16 106:6 108:11,13,17 109:1,4,7,8,15 110:4,6 111:11,12,15,16, 21 112:1,5,12 113:3 114:11 115:22 117:12 118:7,13 122:6,14,22 123:16 125:21 126:1,14 127:3,9,10,15,16 ,18,20 130:11,22 131:7 132:7 133:7,8,11 134:13,15 135:14,16 139:15 140:1 141:5,7,8 142:15 143:11 150:17 151:4 152:12,18 154:12 161:7 163:11 168:15 173:19 176:14,19 178:11,15 180:10 181:18 190:3,11 193:2 195:1 197:5,17,22 200:5 203:9 210:9 215:9 217:15 225:22 226:4,21 229:12,13,22 232:7,11 235:3,6 239:1,5 242:4 243:8,11 245:2 248:21 250:11,17,20 252:20 256:18 258:12 260:9,15 262:14 266:1 270:10 271:13 278:4

theme 172:7

themes 242:7

themselves 259:22

theoretical 245:22

theory 268:3 269:11,20 271:5,6

therapeutic 2:20 75:11 76:3 172:13 254:7 277:1,2,4

Therapeutics 3:20

therapies 79:11 130:6 136:8 161:17 166:14 201:14 244:2 248:19 278:5

therapy 7:8 70:3,12,17 77:4 80:16 130:5 134:1 210:2 214:2 220:13 223:21,22 242:16 244:4 246:16

thereafter 165:10 176:13 279:6

therefore 19:14 43:20 74:13 107:20 142:7 203:13

there's 62:7 97:7 206:3 234:6,21 236:11

they're 27:7,8 55:7 64:12 100:15 101:14 103:13 108:18 127:2 130:20 141:22 142:1 146:16 170:22 183:18 184:22 185:1 201:17 204:4 213:4 230:1 233:15 240:1 259:8 267:14 268:6 276:12

they've 161:1

thinner 170:22

third 45:2,20 90:12 132:12 185:21 202:9,11 208:10,12,15 213:2 216:16

Thirdly 163:13 166:17

thirds 185:20

Thomas 1:19 279:3,19

thoroughly 95:10

thought-provoking 274:17

thoughts 71:18

thousands 267:5

threats 236:6

Three-month 36:14

thresholds 142:16

throughout 18:6 168:21 169:3,13,16 193:18 226:2

throughput 15:12

throw 117:22 155:12 256:1

throwing 98:12 138:1

thrown 109:2

thus 33:11 147:17 148:7 232:6

Thymo 217:7

timeframe 114:4,9 261:18

timeline 55:10 60:7 121:17

189:11
time-to 211:5
tiny 219:10 236:4
tissues 30:6
title 71:7 80:1,3 175:3 214:12 242:5
TNF 194:20
today 38:10 40:18 41:11 52:14 61:15 66:1 78:8 104:6 114:16,22 119:15 137:5 144:15 148:20 150:10 152:20 154:13 188:15 206:14,21 219:1 227:11 264:9 265:22
today's 273:21
tolerability 273:7
tolerance 165:9 173:7
tomorrow 125:14
tool 249:14
tools 142:22 143:9 156:15 249:6,15
top 50:6 199:6 244:20
topic 6:9,14,19 7:1,5,11 8:1,6,9,14,17,20 9:1,6 10:22 26:3,8 39:15,18 53:12,16 70:8,14 79:18,20 144:11 163:2 175:7 188:11 200:11 214:16 228:18 229:1 241:19,22
topics 72:17 197:5 255:21
Toprol 174:8
total 21:3 165:17 169:9,11 173:15 240:8
totally 159:14,17
to-treat 148:6
touch 72:17 77:3 239:12 242:4,7 258:7
touched 71:14 72:19 73:14 77:16 79:11 254:3 258:20
toward 160:18
towards 173:17 245:4
town 243:7
toxicities 214:13 215:17 216:3 226:21 228:6
toxicity 8:3,20 100:20 111:16 144:8,13 145:8 150:22 151:7 153:6,10 214:16 216:18 227:13
toxo 190:1
Toyota 200:1
tracer 13:10 24:21
tracers 13:5
trade 268:9
tradeoffs 269:6
traditional 108:2 137:18 203:6
traditionally 201:20 202:17 206:8 268:10
trail 206:7
train 160:3
trained 160:8
transcript 279:7 280:5,7
transcription 280:1,8
Transcriptionist 280:16
Transforming 157:5
translate 108:1
translates 200:18
Translational 157:6
transplant 2:4,5,7,9,12,17 3:3,18,21 4:3,7,9,21 5:3,5,8 21:7,8,10 23:10,11,15 31:20 32:14 37:8 44:9,11 46:10 53:2 55:17 56:18 59:6 62:15 68:9 78:11 79:14 81:13 82:11 83:17,19 84:2,4,5,22 85:13,22 86:5,8 87:13 90:10 92:4 96:18 97:16,18,19 100:11 101:7,12 107:22 108:6 117:14 118:3,11 122:6,9,14,19 126:1 129:19 137:6 138:7,10 141:19 143:1 145:17 148:2,4,12 150:13 151:8,21 152:9 154:22 155:6 156:18 158:22 159:14 160:3 161:11 163:22 164:19 166:9 170:15,18 171:1,7,8,13,16, 17,20 172:6,12 173:8 176:5,8,17 177:8,12 179:10 184:15,20 185:10 187:4,5 188:21 189:6,11,17 192:6 207:16 211:17 219:3 234:18 239:1 244:10 248:1 251:7,15 254:14,21 255:14 256:22
transplantation 1:4 2:15,20 3:16 4:12,20 6:7,16 8:9 10:6,12 12:15 19:18 20:19 22:16 23:4,21 25:19 26:5,9 29:5,13 30:11,12 31:6 32:3 33:18 34:2 36:8,16 38:4,20 48:18 58:13 95:2,4,8 123:6,12 132:14 133:3 135:2 145:11 148:19 149:7 150:10,14 152:19 154:20 156:13 158:12

160:17 161:3,16 162:11,12 163:8 166:5 170:14 171:10,18 173:2 175:4,7 176:11 177:2 179:2,8,21 180:14 182:10,22 183:4,16 184:6,16 187:12 200:17 201:12 207:22 208:19 214:8 247:7 251:14 252:22 253:2 264:11 265:16 270:2 274:21 277:5 278:15

transplantations 23:8

transplant-dedicated 24:7

transplanted 22:10 29:4 55:22 56:3 69:15 70:22 73:16 201:1,8 255:8

transplanters 160:10

transplants 36:22 42:14 44:15 54:12,22 106:5 118:15 147:9 150:8 155:7 185:17 187:3 193:14 218:15 247:21 251:19

trauma 27:12

treat 139:7 141:19 221:2 222:12 247:4

treatable 112:6

treated 142:2 169:1 186:2 192:16 203:17 217:14

treaties 234:1

treating 122:11 133:19,22 276:10

treatment 40:16,22 41:9 71:3 73:19 75:4 76:8,14 112:7 146:19 147:5,11,16,21 148:14,16,21 149:21 151:19 152:21 161:18 162:3 231:13 243:21 244:19 245:10,11 246:1,2,12,14 248:10 250:4 273:20

treatments 79:13 150:19 158:21 249:8

tremendous 77:12

trend 34:7

trends 49:15

trial 31:3 33:6 34:13 40:5,13 56:17 64:17 69:3 80:4,5 82:13 94:1,4 98:3,7,16,21 99:8 101:8 102:11,18 104:2,9 107:19 111:6 113:9 122:13 135:19 137:11 142:5 146:2 147:14,19 151:16 152:2,7 157:11,12 159:3,8 160:8 165:15,22 166:7 168:16 176:14 180:7 184:19 187:18 191:9 198:14 202:13 204:22 205:10,22 207:19 208:17 209:5,14 211:9,18 213:10 230:11 232:7 235:9,15 241:9 243:11,17 248:6,12 249:1 252:11 258:1 259:14 260:10,22 261:1 262:18 267:18,20,22 268:19,21,22 270:19,21 271:3,11,16 272:5,7,9,18 276:7,19

trials 1:3 14:1 25:8 55:14,16 57:13 64:16 69:13 76:17 81:1 93:21 106:11 117:6,7 125:1 129:21 132:17 138:11 140:1 145:6,14,15,17 147:4,18 148:19 150:3,6,8,9 151:1,8 152:5,6,8,9,15 153:21 156:18 157:7,9,11 158:22 165:15 184:18 186:16 187:22 189:1,20 190:16,18,21 191:2 193:6,10 194:2 195:9,17 196:9,20 197:7,18 198:8 199:7 201:15 203:2 204:18 205:1,17 207:20 208:22 213:13,15,16,20 227:21 229:9 234:1,2 235:8 241:1 243:3,8 244:20 245:4 247:5 250:17 252:16 253:12 254:20 258:19 261:17 263:8,11 268:12 270:1,15 278:15

trick 16:6 83:15

tricky 190:8

tried 20:17 22:7 32:20 36:6 44:4 129:10,11 233:1 252:5

tries 235:9

trigger 62:2

triggered 62:4 63:15

triglyceride 180:2

triglycerides 169:14,16 170:8 173:15

tripled 49:3

trips 278:11

troubles 70:19

true 104:3 126:7 180:1 239:2

270:10 279:7 280:8
truism 176:6
truly 231:10
truth 223:9
truths 106:17
try 37:4,10 56:2 80:2 118:20 128:21 129:20 132:19 133:13 143:1,5 144:18,20 156:19 159:22 163:17 185:7,22 229:9,10 231:2,7,12,20,21 234:2 235:8,21 236:1 253:8 262:15 271:11 277:3
trying 37:9 70:4 80:9 103:6 109:5 123:13 128:15 146:21 193:1 231:16,17,18,19 234:1 247:6 248:9 269:18,22 271:14 274:18
tuberculosis 191:13,16 194:7,19,22
Tuesday 1:9
tumor 204:8 210:9
TUMORAPA 209:4 211:9
tumors 133:4 202:5,22 213:8
turn 110:19 143:17
turning 88:15
turns 232:17
twenty 63:10 105:11
Twenty-five 208:5
twin 54:22
twos 256:4
two-sided 230:12 271:21
type 19:19 35:2 45:5 71:18 128:17 129:15 163:12 173:4 205:22 210:2 211:11 251:16 259:2 263:22 265:4
typed 280:5
types 84:18 91:21 155:7 162:3 178:8 181:5 187:15 203:6 204:1,13 212:1 234:3 257:9 260:8
typewriting 279:6
typical 84:12 99:1 135:9
typically 267:18
tyranny 79:2
Tysabri 192:9

U

U.K 4:10 37:4
U.S 13:7 14:9 20:22 72:14 95:22 96:2 170:14 209:9
U01 20:14 76:15
UC 215:12
UCLA 61:13
Ulf 57:5
ultimate 79:17
ultimately 65:16 170:20 171:6 268:2
ultrafiltrations 31:14
ultrasound 15:20
unable 147:10
unanticipated 190:19
unavoidable 219:17
unbiased 147:16
uncertainties 142:3
unclear 41:4
underestimate 27:22
underestimated 22:1
underestimating 22:3
underestimation 21:20,21 22:13
undergo 62:18
underlines 240:22
underlying 41:6 105:20 125:15 131:8
underpowered 268:1
understand 47:11 104:14 114:20 121:11 137:19 140:6 146:7,18 149:3 152:14 158:2,5 160:9,13 161:11 162:5 216:4 220:9 264:8 269:12
understanding 160:11 187:13
undertaking 277:9
underwent 146:13
unexpected 35:9
unfortunately 29:6 188:17,22 193:3
uniform 115:14
unintended 217:3 222:11 225:16
unique 247:16 274:4
unit 11:22
United 3:20 201:4
units 71:20
universal 202:19 231:19
University 2:5,13 3:3,13,21 4:13,17 5:3,6,8 89:12 175:2
unknown 84:3 105:1 192:1
unless 92:19 96:21 125:12
unlikely 43:21 125:11 220:4
unlimited 127:11
unmet 79:6 157:8 274:7,11
UNOS 86:14

190:13 201:2 212:14
unpublished 65:5
unsuccessful 35:1 154:1
untoward 276:15
untreatable 217:15
unusual 105:10
update 55:5 165:16
updated 166:7 196:4 197:5
upfront 134:13
upon 133:6 157:12 254:17 259:20
upward 87:17 88:12
urea 12:18,19
urine 12:3 14:18 16:12 47:19 74:21
useful 102:18 120:7 124:18 179:3 185:5
USRDS 48:7 201:1
usually 81:19 99:9 189:2,15,18 190:6 195:18 203:14
utility 128:6 268:13,14 271:6
utilizable 179:14
utilization 230:14
utilized 268:11
utilizing 267:13 268:17

V

vaccination 194:4
vaccine 193:22
valid 238:17 272:14
validate 21:4 37:14
validated 95:6 177:14 224:4 249:3 256:13 263:3
validation 21:2,4,6,9 186:4
validity 54:6 57:3 229:6,8,16,17,21 232:6,13 233:11,21 234:3 235:1,15 236:7,21 237:2,6,8,9,21 238:2,17 239:8,15 240:8,13 241:2,3,14 267:10
valuable 107:8 260:15
value 45:16 46:5,12,16 51:7 52:2 78:12 97:13 106:16 107:10,11,13,19 114:12 134:2 142:19 143:10 144:18 148:5 157:19,21,22 158:5 159:13 160:13 162:10,12,16 168:19 238:9 261:8
values 21:20 22:12 41:20 44:21 48:2 59:21 89:15 159:11,12 169:13
Vancouver 3:4
Vanderbilt 4:17
variability 17:15 70:2 77:12 94:6 99:13,18,21 100:2 126:22 127:1,22 231:9,12,15 232:2,19 233:3 236:1 240:20 242:20
variable 63:13 70:21 74:4 243:13 247:5
variables 18:22 58:10,15 61:9 64:8 69:16 102:16 129:5 135:12 137:12
variation 46:9 55:8
variations 100:5
varies 207:5
variety 81:18 158:21 193:18 195:22 197:4
various 18:4 73:4 99:7 146:3 164:13 174:16 193:20 263:5
vary 95:7
vascular 68:6 74:12,19 75:1
vectors 50:5
Velidedeoglu 5:4 7:12 10:9,14 79:20,21,22
ventricular 106:21 178:5,6,11
verbs 132:13
verifying 159:8
versus 10:19 24:14 31:20 33:16 34:6,15,17 42:16 56:20 68:15,16 91:4 128:1 145:7,21 165:16 169:10,12 191:7 200:22 222:2 229:6,11,21 233:5,8 248:16 273:17
vertical 71:19
view 54:4 109:20 150:15 233:13 237:9,18
viewpoint 187:9
VINCENT 126:15
Vincenti 5:6 8:22 102:4 104:13,14 124:16 141:13 214:11,17,18 215:2,6,11 258:2 262:22
viral 196:8
virally 203:10
virus 47:19 192:8
visit 47:10 167:16
visualize 50:4
Vital 174:2
Vitamin 173:21
voiced 26:16 267:3,6

volume 11:21
vs 6:10 8:1 10:22 144:7,11
vulva 213:4
Vytorin 174:8

W

waist 167:17 170:1
wait 124:22 200:22 201:4 237:22
wake 136:4
walk 255:15 260:8
walks 93:15
wall 105:10
Walt 106:3 125:17
Walter 4:7 6:21 39:14,19 61:4 136:6
Walter's 110:15
warm 29:21 34:22 35:4 36:11
warning 191:21
wasn't 51:3 110:12 178:17 182:1
watch 28:2 92:19 93:11 194:16
waters 235:13
ways 7:19 50:3 134:6 138:19 143:21 144:17 154:18 162:21 169:21 170:1 189:6,20 225:3 234:5
Webster 244:8
wedded 138:17
weeds 119:19
week 31:13 32:3,5 38:14 174:10
weekly 165:8
weigh 174:12
weighed 86:20 173:7
weight 23:4 86:22 87:1 94:11 164:18 167:6,10,16,17 168:9 174:2 255:14 258:21 259:9
weighted 259:6,11
weighting 259:1
weights 259:20
Weir 7:9 70:8,17,18 82:9 128:13
welcome 6:4 10:2 93:8
we'll 54:2 57:20 58:13 93:9 115:9 120:20 143:3 144:6 152:9 153:15 201:22 202:2,15 216:12 217:9 239:6
well-collected 25:3
well-identified 77:7
we're 33:11 37:9 46:5 49:22 55:15,17 65:22 74:7 75:10 76:9 77:9 100:15,19 102:13 103:5,11 107:20 108:2,4,5 109:1 111:4 113:12 114:18 117:6 121:6 122:6,15,17 123:4 125:17 126:3 127:9 132:2,16 133:11 135:8,22 136:8 139:5,6,14,21 140:15 143:8,16 145:21,22 147:7,9 148:3 149:7,22 152:16,22 154:15 155:16,17 158:1 159:15 161:21 171:12 184:3 197:18 199:17,18,19 201:19 212:6 217:22 219:7 220:1,13,16 221:14 225:19,20 227:6 230:8,22 231:16,17,18,19 236:9 244:16 248:9,14 249:9,11 252:19 256:9,16 257:9 259:3,12 260:17 263:21 264:6 266:8,10 269:3 272:20 274:13
we've 29:8 30:9 39:5 54:17,18 60:14 64:22 70:18 71:8,14 72:19 73:5,14 77:12,16 78:15 100:12 102:6,12,16 123:19 132:17 143:5 144:16,21 147:4 152:20 153:20 154:8 157:19 158:17,18 161:10 170:3 183:4 185:7,21 190:3 193:16 195:12 198:15 206:4 217:1,19 230:6 242:7,15 245:5 248:2 251:10 254:18 270:2,16 274:18 275:1,6,15,17
whatever 56:9 94:2 95:14 103:17 125:9 135:7,15 137:11 139:21 140:10 244:21 256:19
whatnot 193:21 198:21
whenever 111:6 238:3
whereas 51:20 94:14 181:14
whereby 221:22
Whereupon 278:13
whether 22:9 30:10,17,20 31:4 32:21 36:7 60:8 63:13 66:17 75:9,13,14 77:17 78:13 95:13 97:22 98:22 129:1 135:1 141:16,22 142:1,18 146:13 164:3 186:10 235:10 244:5 256:19 272:7,13

275:16 276:12
white 20:4 154:12
whole 18:6 33:4 68:8 79:2 178:2 179:11 219:11 220:16 229:3,18 235:6,12 242:17 260:7,9 270:3 273:7
whom 67:6,7 276:8 279:3
who's 250:19
wide 19:18 63:12
widely 13:19
William 3:7
wind 207:17 210:10
Winnipeg 4:14
Wisconsin 96:18
wish 56:9 125:20 188:18 235:20
withdraw 217:8
withdrawal 34:22 75:4
withdrawn 192:11
withdrew 146:14
woman 167:11
women 170:7
wonderful 66:22 116:15 143:16
wondering 97:22 273:13
Woodle 5:8 8:18 200:7,11,13 226:14 234:8
work 19:20,21 39:22 61:13 65:22 66:9 67:12 138:4 171:7 188:18 192:22 195:2 232:15 238:14 251:1 252:3 254:14 270:16 272:21 275:8 278:8
worked 102:7 276:21
working 141:18 157:15 158:3,19 173:11 241:13
works 19:20 141:16 231:18 237:3 263:18 270:13,14
workshop 1:6 11:5 85:15 274:14 278:14
world 13:8 112:15 114:10 192:6 193:19 194:15 207:10 236:9 237:3,21 238:22
worry 18:12 99:10 136:4 138:6
worrying 136:9
worse 87:7 168:4 171:10 176:10 257:19
worst 192:12
worth 188:2 262:14
worthwhile 133:21 181:19 195:10
wound 167:13
wrinkle 189:1
written 82:10
wrong 92:19 99:20 105:6 126:3 225:20 232:8 238:19 239:10 270:14
Wu 48:17

X

X's 54:16

Y

year-old 55:8 173:3 263:22
yellow 180:22
yesterday 17:21 26:16 29:9 32:19 38:10 39:5,8 47:6,14 61:13 93:13 107:21 119:15 120:4 122:8 153:3 155:13 163:18 188:16
yet 102:2 153:14 183:5 186:11 193:4 215:9 216:13 218:19 221:1 233:10 234:19 241:4 266:12 269:17
York 83:11,14 96:9
you'll 109:11 176:2 177:8 242:13 257:7 266:10
younger 62:17 63:19,21 208:2
yourself 96:19,20
you've 56:13 57:22 59:6,9 61:6 65:11 96:18 130:11 133:4 179:6 221:3,17 250:1 270:7,8

Z

Zealand 209:8
Zealand's 183:8
zebras 199:3
zero 122:5,14,15 123:2 133:2 135:1,6 139:5 204:19,20 205:7,8 222:21
zombie 95:17
zones 37:7
ZRE3770 200:2