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U.S. FOOD & DRUG ADMINISTRATION
PUBLIC MEETING ON PATIENT-FOCUSED DRUG DEVELOPMENT FOR
PATIENTS WHO HAVE RECEIVED AN ORGAN TRANSPLANT

September 27, 2016

9:02 A.M. - 4:59 P.M.

Food and Drug Administration
White Oak Campus
10903 New Hampshire Avenue
Silver Spring, Maryland

Reported by: Erick McNair,
Capital Reporting Company

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

2 MS. CHALASANI: Good morning, everyone.
3 Good morning. My name is Meghana Chalasani, and I'm
4 from the office of strategic programs within the
5 Center for Drug Evaluation and Research here at FDA.
6 My colleague Sara asked me to start off with a little
7 joke about the Beltway and traffic, but I don't drive.
8 And most of you guys apparently didn't have a horrible
9 commute. So, you should give us FDAers some tips,
10 because it's hard to get here in the morning every
11 day. I will be co-facilitating the discussion today
12 with my colleague Sara Eggers.

13 Today's meeting, conducted as part of the
14 agency's patient-focused drug development initiative,
15 is focused on hearing from patients who have received
16 an organ transplant. Later this afternoon, we will be
17 having a more scientific discussion with patients,
18 patient advocacy organizations, health care providers,
19 academic experts, and industry on various aspects of
20 clinical drug development intended for patients who
21 have received organ transplants, including medication
22 adherence and experience with intervention.

1 Dr. Edward Cox will be providing some
2 opening remarks in a few minutes. But first, let me
3 start by asking my colleagues sitting here in the
4 front to state their names and their role within the
5 agency.

6 DR. COX: Good morning. I'm Ed Cox,
7 director of the office of antimicrobial products
8 within the office of new drugs in CDER, FDA.

9 DR. ALBRECHT: Hello. My name is Renata
10 Albrecht. I'm the director of the division of
11 transplant and ophthalmology products within the
12 office of antimicrobial products and OND, FDA.

13 DR. BELEN: Hello. Good morning. My name
14 is Ozlem Belen. I am a deputy director for safety in
15 the same review division as Dr. Albrecht.

16 MR. VELDIDALA: Good morning. Ergun
17 Veldidala (ph), medical officer in the same division.

18 DR. CAVAILLE-COLL: Good morning. I am Marc
19 Cavaille-Coll, medical officer in the division of
20 transplant and ophthalmology products at CDER. Thank
21 you.

22 DR. MULLIN: Hello. I'm Theresa Mullin. I

1 direct the office of strategic programs, and I'll say
2 a little more later. Thanks.

3 DR. CAMPBELL: Good morning. I am Michelle
4 Campbell. I'm a reviewer in the clinical outcome
5 assessment staff in the office of new drugs, CDER.

6 MR. VAIDYA: Good morning. I'm Pujita
7 Vaidya, from the office of strategic programs.

8 MS. EGGERS: And I'm Sara Eggers, from the
9 office of strategic programs.

10 MS. CHALASANI: And we also have Graham
11 Thompson, from our office, as well as Shannon
12 Woodward, who are helping us today.

13 Now, to give you all a brief overview of the
14 agenda -- it's a busy one. We will first spend a bit
15 of time providing background on our patient focused
16 drug development initiative, and on organ
17 transplantation and available post-transplant
18 treatment options. And then we'll hear how the
19 information we learn at our PFDD meetings, like
20 today's, is and can be used.

21 Then we will move into our discussion with
22 patients and patient representatives. Our two main

1 topics are life after receiving an organ transplant,
2 and post-transplant treatment regimen. Sara will be
3 providing some more details about the format at the
4 start of those discussions. We have time set aside
5 later today for open public comment. While the
6 primary discussion this morning is focused dialogue
7 with patients and patient representatives, the open
8 public comment will give anyone in the audience the
9 opportunity to make a comment. To participate in
10 that, you will need to sign up at the registration
11 table. Participation is first come, first serve.
12 We'll close that sign-up sheet later, at the end of
13 our first break, which is around 10:45. The time
14 allowed for each speaker will depend on the number of
15 participants who express interest -- likely one to two
16 minutes each.

17 For a few logistical and housekeeping
18 points, there is a kiosk right outside where you can
19 get food and beverages. There is an option to
20 preorder lunch. Restrooms are located behind the
21 kiosk. At any point, if you need to get up for any
22 reason please feel free to do so. As I mentioned, we

1 will be taking a 15 minute break around 10:45. Lunch
2 is from 12:30 to 1:15, and then we have another 15
3 minute break this afternoon, around 2:50.

4 I do want to ask at this time that you all
5 silence your cell phones. This meeting is being
6 transcribed, and a live webcast is being recorded --
7 both of which will be archived on our website. With
8 that, I'd like to welcome Ed for opening remarks.

9 DR. COX: Great. Thanks. Well, good
10 morning and welcome, everyone, to this meeting on
11 patient-focused drug development for patients who have
12 received organ transplants. I've introduced myself,
13 but I'm Ed Cox. I'm the director of the office of
14 antimicrobial products, and Renata and I work
15 together. Our office reviews the drugs that prevent
16 rejection in organ transplant recipients.

17 I want to thank you all for joining us here
18 today. We're happy to see so many folks here --
19 patients, caregivers and advocates in the audience. I
20 understand we also have a number of people, too, on
21 the web who will be joining in and listening in to the
22 meeting. So, I think that's great. So, there are a

1 lot of folks in the room, but there's also a lot of
2 folks out there on the web that are watching us too.
3 And we appreciate your willingness to be part of the
4 meeting, and sharing your experiences with us. It
5 really is what provides, in essence, the value to the
6 meeting. So, we're very grateful for that.

7 We're excited for the opportunity to engage
8 directly with you, and to learn about the symptoms
9 that matter most to you, the impact that organ
10 transplantation has on your daily lives, and what
11 factors you take into account when selecting a post-
12 transplant regimen, and, you know, just quite simply
13 the things that you like and that you don't like about
14 your transplant medications.

15 In our discussion today, we'll be focusing
16 on various types of experiences that are present among
17 organ transplant recipients, and we'll delve into
18 changes into your post-transplantation therapy
19 regimen, and what aspects of your care have changed
20 over time. Marc Cavaille-Coll, from the division of
21 special -- special transplant and immunologic products
22 -- or, ophthalmologic products -- will provide more

1 background on organ transplantation and will also talk
2 about available treatment options in just a few
3 minutes.

4 We understand that organ transplantation is
5 a life-altering experience, with physical, emotional
6 and social impacts, and that there is an unmet need
7 for patients. It's the FDA's responsibility to ensure
8 that the benefits of a drug outweigh its risks.
9 Therefore, having this kind of dialogue is extremely
10 valuable for us, because hearing what patients care
11 about can help us lead the way in figuring out how to
12 best facilitate drug development post-organ
13 transplantation, and understand how patients view the
14 benefits and risks of various drug products in this
15 complex area. For example, what we hear today from
16 you can help us understand how to develop better
17 endpoints, to measure the aspects of post-organ
18 transplantation management that are important to
19 patients.

20 I know we also have representation from
21 industry, academia and other government partners in
22 the room and on the web, and while FDA plays a

1 critical role in drug development we are just one part
2 of the process, and I'm glad to see a high level of
3 interest from folks from the various different parts
4 that play a role in drug development.

5 FDA protects and promotes public health by
6 evaluating the safety and effectiveness and quality of
7 new drugs, but important to keep in mind that we
8 aren't the ones that actually do the clinical trials.
9 The drug companies, typically working with patients
10 and research -- with the research community -- are the
11 ones who actually conduct the clinical trials and
12 submit the applications for new drugs to FDA. It's
13 then FDA's responsibility to evaluate this information
14 and to evaluate whether the benefits of a drug
15 outweigh its risk. The benefit/risk decision-making
16 is an integral part of our review process, and we look
17 forward to incorporating what we learn here today from
18 the patient's perspective into thinking and how we
19 evaluate our evaluation of benefit and risk as we look
20 at treatments for managing organ transplantation. So,
21 once again, we're here today to hear the voice of the
22 patient. So, thank you for your participation. Thank

1 you for joining us today. You are, in essence, what
2 makes this meeting what it is, and I think that's
3 great. We're grateful to each of you for being here,
4 and your willingness to share your experiences with
5 us. It really helps us to understand and appreciate
6 your perspective on these issues.

7 And just so that folks know, this morning is
8 really the patient focused session. We also have a
9 scientific session in the afternoon, and we welcome
10 and would help that many of you could stay so that we
11 can also have the patient perspective as we move to
12 talk about the scientific aspects in the afternoon.
13 So, with that I'll turn the podium over to Theresa
14 Mullin, who will provide some background on FDA's
15 patient-focused drug development effort. So, Theresa,
16 the podium is yours.

17 DR. MULLIN: Okay.

18 DR. COX: Thank you.

19 DR. MULLIN: Thank you, Ed. So, as Ed said,
20 I'm going to take just a few minutes to tell you about
21 this patient-focused drug development initiative.
22 This is the context and the initiative that we -- has

1 been the vehicle for our scheduling and planning this
2 meeting, and others that we have done so far, in the
3 last few years, and will do a few more next year.

4 And it got started -- this idea of having a
5 meeting focused on only hearing from patients and
6 their caregivers, where their caregivers have input to
7 give us as well, back in 2010, when we were having
8 discussions about this. We recognized that we had
9 this benefit/risk assessment framework that we were
10 developing, but we realized that patients are really
11 uniquely positioned to tell us about the benefits that
12 would be most meaningful to them and the things that
13 would bother them, and really their perspective on
14 their disease. And this was sort of missing as an
15 overarching source of input for us, because we had
16 only at that time the patient representative program,
17 where you have an individual patient who would be
18 asked to join discussions and maybe weigh in on what
19 we call in the government a particular matter -- which
20 is to say, about a particular drug and decision-making
21 around that, and that, of course, means we also have
22 to put that person through conflict of interest

1 screening, and this tends to really narrow the
2 possibilities and the timing and our flexibility in
3 trying to get the input of the community. And so, we
4 didn't really have a mechanism at that time.

5 We only were able to have one person help us
6 think through the patient's perspective. Sometimes
7 those people didn't have a disease that we were
8 thinking about t that time either. And so, this is a
9 more systematic way to gather that information and get
10 the patient's perspective, to have these meetings
11 where we try to bring everyone that we can into the
12 process. We work with the advocacy groups, and with a
13 care provider community to try to help us let patients
14 know about it. And I want to also welcome the people
15 on the webcast. Thank you for joining us on the
16 webcast, as well. That's a key feature of these
17 meetings, because it helps us to enable more people to
18 participate in the process. And you'll see our
19 facilitators bring them into the discussion as well.
20 And so, this helps us to really get that larger
21 community involved. And we made a commitment to do
22 this as part of our reauthorization of the

1 Prescription Drug User Fee Act in 2012.

2 We can -- we said we would do at least 20 of
3 these meetings. And guess what? This is the 20th
4 meeting. But they're so popular among the review
5 divisions that we actually have more coming next year.
6 We're going to exceed that number. But this is what
7 we've set up to systematically get this input. And at
8 the time we made that commitment we thought 20 sounded
9 like a big number. But, we were quickly told by a lot
10 of patient groups that that was way too few meetings,
11 and that they were concerned that we might not be able
12 to get to their condition and their concerns.

13 And so, we went through a process where we
14 asked the review divisions to help us identify what
15 diseases they could think of and conditions where they
16 would really like to -- they think it would really
17 help them in particular to hear more from the patient
18 community. And that produced about 40 diseases that
19 were like the top 40 in their minds, and we published
20 that in the federal register to get comment. We got
21 about 4,500 comments about that list. We had to then
22 go back and do the very hard thing of trying to winnow

1 it down to more like the 20 that we were going to be
2 able to do. As a result, we're going to do 24, and
3 we've come up with another mechanism called externally
4 led meetings to try to help us to hear from other
5 groups as well, because these meetings patients have
6 really enjoyed having the opportunity to speak at
7 these meetings. They've been useful. So, we have
8 this other process as well.

9 And here's just a quick overview of the
10 diseases and the conditions that we have focused on in
11 the past few years. And you can see where we are
12 today. And there's quite a range. I mean, we wanted
13 to find conditions that were chronic in general, had
14 an important symptomatic or a loss of functioning that
15 might be -- an effect on functioning that was
16 important to patients, and affected a wide range of
17 ages. And that's not a whole lot of -- those criteria
18 are met by many diseases. And you can see that range
19 here. And here we are today, with our meeting focused
20 on patients who have had an organ transplant and what
21 your experience is, including with your -- the
22 medications you take after the transplant.

1 Now, each of these meetings is tailored to
2 the condition that we're exploring and listening to
3 and hearing from you all about. A very diverse group
4 of patients from different disease advocacy groups
5 came to us to hear how we were going to run this
6 process, because they were very interested. And they
7 actually helped us come up with what they thought were
8 good basic questions that they thought resonated with
9 all of them. And so we have some of those in the mix
10 of what we will -- or, Meghana and Sara will be asking
11 and talking about today.

12 And we have also tailored and brought in
13 other questions that the review divisions have
14 particular interest in, and want to hear more about as
15 well. And they will be asking you questions as they
16 feel the need to, in the course of the discussion, if
17 they hear something that maybe -- we heard sometimes
18 that -- from the division that they hear things in
19 these meetings that they've never heard before, that
20 are not reported in the literature. It's a very
21 unique opportunity for them to learn and, in some
22 ways, almost start problem solving around things that

1 they're hearing. So, it's very exciting. And so,
2 we'll also talk about what topics are currently of
3 concern. And we've learned, as I said, a great deal
4 from these -- the input of these meetings.

5 One of the most concrete and near term
6 outputs of these meetings is what's called a voice of
7 the patient report. We keep a docket open so that
8 those on the webcast and those in the room, and
9 others, can submit other information that you may have
10 that you think is relevant to what you've heard today,
11 or you want us to know. And so, we leave that open
12 for a little while after the meeting, so people have
13 time to submit information that they might want us to
14 know about. And after that's closed, we analyze very
15 carefully what comes in that docket. As you heard, we
16 are doing a transcript of this meeting. We analyze
17 the transcript to try to really capture what's been
18 said. And we try to make these documents one that
19 reflect very faithfully what we hear from you, in the
20 words of the patients as they are conveyed to us. So,
21 we think this has been a useful reference tool for us.
22 We also have heard from patients who have been in

1 these meetings and felt the reports were very useful
2 to them, as well. So, that's just the first step.
3 And we're really building on what we've learned here
4 in our next five year plans for trying to further sort
5 of capture the information from patients more
6 systematically, as well, in clinical trials and in
7 other ways, to build even more -- build it even more
8 into our decision-making. So, with that -- I think
9 that's my last slide. Yes. I'll turn it over to
10 Marc. Thank you.

11 DR. CAVAILLE-COLL: Good morning. I'd like
12 to present to you an overview of organ transplantation
13 and available post-transplant treatment options in the
14 United States. Organ donation and transplantation to
15 treat end-stage organ disease is lifesaving,
16 transformative and restorative for patients with a
17 serious condition. The number of donated organs --
18 or, donors recovered, represented in blue below, and
19 the number of transplanted patients annually,
20 represented in green, has not kept up with the
21 increasing number of patients on the waiting list,
22 represented in yellow.

1 Organ allocation in the United States. The
2 National Organ Transplantation Act of 1984 established
3 the organ procurement and transplantation network
4 which maintains the organ registry and ensures
5 equitable allocation of organs in the United States.
6 Regional organ procurement organizations identify
7 equitable -- identify suitable donors and collect
8 donated organs. The united network of organ sharing
9 operates the OPTN and allocates the organs from the
10 OPOs. The scientific registry of transplant
11 recipients, also created by NOTA, conducts ongoing
12 evaluation of the clinical and scientific status of
13 transplantation in the United States. Much of the
14 data that will be presented here comes from their
15 annual reports.

16 The types of organs transplanted annually in
17 the United States include kidney, liver, pancreas and
18 intestine, as well as heart, lung and heart/lung. The
19 majority of the organs are recovered from deceased
20 donors, but with a substantial contribution of living
21 donors in kidney and, to a lesser extent, in liver
22 transplantation.

1 Here are presented the number of patients
2 active on the waiting list on the left, and total
3 transplants on the right for the decade of 2004 to
4 2014. Approximately 17,000 kidney transplants are
5 performed per year, with an increasing number of
6 patients on the waiting list, in excess of 60,000.
7 About 7,000 liver transplants are performed, and about
8 2,600 heart transplants are performed. Only in lung
9 transplantation has the number of transplantations
10 increased and number of patients on the waiting list
11 decreased.

12 Polypharmacy is the rule in solid organ
13 transplantation, with all the challenges of managing
14 drug interaction and complex daily regimens. There
15 are medications to prevent and treat rejection,
16 including induction immunosuppression with intensive
17 combination regimens, maintenance immunosuppression
18 with less intensive combination regimens, and
19 additional medications for treatment of acute
20 rejection. Thus, the need for medications to prevent
21 and treat viral, bacterial, fungal and other
22 opportunistic infections, as well -- there's also the

1 need for medications for treating the existing or
2 preexisting underlying medical conditions, such as
3 hypertension, diabetes, and hepatitis C that led to
4 the organ failure. And there are also need for
5 medications to treat the emerging complications of the
6 immunosuppressive regimens, including hypertension and
7 new onset of diabetes.

8 Let's look at some of the treatment options
9 for immunosuppression use in transplantation. There
10 are agents used for induction treatment, lymphocyte
11 depleting agents, polyclonal IgG antibodies derived
12 from horse or rabbit, Interleukin-2 receptor
13 antagonists, monoclonal antibodies modified to be
14 humanized or chimeric that bind to the alpha chain of
15 the interleukin 2 receptors and inhibit cell
16 proliferation. There is a high dose of other agents
17 used in maintenance also, round out the induction
18 immunosuppression.

19 Maintenance immunosuppression usually uses a
20 combination of two to three agents, below.
21 Glucocorticoids are used for both induction and
22 maintenance immunosuppression as well as for treatment

1 of rejection. Calcineurin inhibitors, namely
2 cyclosporine and tacrolimus, are the agents around
3 which additional agents are added to complete the
4 immunosuppressive regimen. Purine antagonists include
5 azathioprine, mycophenolate mofetil, that inhibit cell
6 proliferation. The inhibitors of mammalian target of
7 rapamycin, modulate mTORi, and also impair cell
8 proliferation. And there is at least one
9 costimulation blockade that blocks CD-80 costimulation
10 of T lymphocytes.

11 Here are represented the immunosuppression
12 used in adult kidney transplant recipients per year,
13 from the SRTR. The majority of kidney
14 transplantations receive a regime of tacrolimus and
15 mycophenolate, and about two-thirds are receiving
16 steroids at transplantation and one year post-
17 transplantation. The vast majority receive some form
18 of induction agents, two-thirds receiving T cell
19 depleting agents and about one-quarter receiving
20 interleukin-2 receptor antagonists.

21 In liver transplantations, similar to kidney
22 transplantation, the majority received tacrolimus and

1 mycophenolate. 80 percent received steroids at
2 transplantation, and still 40 percent are receiving
3 steroids at one year post-transplant. There is an
4 increasing use of induction agents in liver
5 transplantation as more patients come to liver
6 transplantation with impaired renal function.

7 Similarly, in heart transplantation
8 tacrolimus and mycophenolate is the regimen used in
9 the majority of the patients, the majority receiving
10 corticosteroids. About 50 percent are receiving
11 induction immunosuppression. Let's take a look at
12 some of the outcomes. Again, five year graft survival
13 in kidney transplantation is about 74 percent of
14 deceased donor recipients, and 86 percent for living
15 donors.

16 In liver transplantation, five year overall
17 graft survival is about 70 percent, and there are more
18 than -- now more than 72,000 liver transplant
19 recipients that are alive with a functioning graft,
20 with many more pediatric recipients reaching adulthood
21 every year.

22 In heart transplantation, five year graft

1 survival is about 76 percent, and there are more than
2 28,000 heart transplant recipients surviving with a
3 functioning graft. Most of them had undergone
4 transplantation after the age of 50.

5 There were about 2,000 lung transplants
6 performed in 2014, and the five year survival is about
7 55 percent in that population. Graft survival in
8 intestine transplantation has improved over the past
9 decade, and the number of functioning -- patients with
10 functioning intestinal grafts has steadily increased
11 from 2003 to more than a thousand in 2014. 42 percent
12 are pediatric intestinal liver transplant recipients.
13 The number of pancreas transplants has declined since
14 2004.

15 Future challenges. New approaches are
16 needed to increase organ donation procurement and
17 decrease discard of procured organs, to prevent and
18 treat delayed graft function, to prevent or treat
19 antibody-mediated rejection, to individualize
20 treatment using biomarkers, genomics and systems
21 biology, to induce durable and stable immune
22 tolerance, still the holy grail, to minimize adverse

1 reactions associated with the IS regimens and to
2 integrate the use of novel concomitant agents and
3 manage drug interactions. Above all, the risk/benefit
4 of new/old approaches and interventions need to be
5 assessed from a patient's perspective.

6 Thank you for your attention. And now, I'll
7 turn the podium over to Michelle Campbell.

8 DR. CAMPBELL: Good morning. My name is
9 Michelle Campbell, and I am with the clinical outcome
10 assessments staff. The clinical outcome assessments
11 staff advises the clinical review divisions in the
12 office of new drugs, upon request, regarding clinical
13 outcome assessments, which include physician or
14 clinician reported outcomes and, most importantly,
15 patient questionnaires that are commonly referred to
16 as patient reported outcomes. We review these
17 questionnaires to ensure that they are measuring the
18 most important and bothersome symptoms and impacts to
19 patients, and that they are measuring these concepts
20 in an accurate and reliable measure. Today, we'll
21 briefly present on how we utilize the information from
22 the patient-focused drug development program and

1 meetings, and how we aim to incorporate patient input
2 into clinical study endpoints.

3 You may be wondering how is this information
4 we use in the PFDD meetings, and what do we do with
5 what we hear from our patients -- we have these
6 meetings, but where do we go from here. How do we
7 take this valuable information and generate clinically
8 relevant patient-focused endpoints to a place in
9 clinical studies. So, I hope the next few slides I
10 can answer some of these questions for you.

11 One of the main advantages to having these
12 PFDD meetings is that it gives all stakeholders the
13 opportunity to listen to the patient voice. We find
14 it very useful to hear the patient experience,
15 particularly to hear what is important from their
16 perspective, and how you describe your symptoms and
17 impacts in your own words. We hope it helps give drug
18 sponsors ideas about what are important symptoms and
19 impacts to measure in clinical studies, and later make
20 the investment to develop or select questionnaires to
21 measure these important concepts, as well as engage in
22 future FDA discussion. The information from these

1 meetings also helps inform how we at the FDA review
2 patient questionnaires and drug applications, to see
3 if they adequately are assessing the patient's
4 perspective of their medical condition.

5 While the PFDD meetings provide initial
6 input, we also strongly recommend that drug sponsors
7 or other researchers who are developing these
8 questionnaires engage with additional patients who are
9 -- or, to using qualitative research, either through
10 focus group interviews or one on one interview
11 interactions, as well as gather input from other
12 experts, such as physicians or caregivers. The goal
13 of this is to confirm that the questionnaires include
14 important yet relevant information, to ensure that the
15 questions and instructions in these questionnaires are
16 clear and understandable to patients.

17 Another advantage of these meetings is that
18 it helps us to think about clinical study endpoints.
19 So, what is an endpoint? In the case of a patient
20 questionnaire, the study endpoint would be how the
21 questionnaire's score is going to be measured and
22 analyzed in a clinical study. For example, if

1 patients reporting that the most important treatment
2 benefit to them is symptom improvement, then we would
3 encourage that the drug sponsor to develop or select a
4 symptom questionnaire using good measurement
5 principles and meeting regulatory standards. The
6 study endpoint could possibly be changed in the
7 questionnaire's score during the clinical study, which
8 would measure the amount of symptom improvement. One
9 key consideration is that there are many things that
10 are important to patients that are discussed during
11 PFDD meetings and/or in patient focus groups or
12 interviews. However, not all of these things lent
13 themselves to be measured in clinical studies for drug
14 approval, as they may not be impacted by treatment,
15 making it difficult to interpret its results.

16 Here at the FDA, we focus on efficacy and
17 safety. So, for example, financial well-being may be
18 an important concept for patients, but may be
19 minimally or not at all impacted by treatment in a
20 clinical study setting. So, encouraging drug sponsors
21 to consider selecting important concepts that can
22 measure treatment effect as key study endpoints.

1 Financial wellbeing and other important concepts that
2 are unrelated to treatment can still be measured, but
3 perhaps in exploratory purposes. For organ
4 transplantation, study endpoints that include patient
5 questionnaires will be helpful to provide additional
6 supportive evidence of benefit.

7 At the FDA, we have to uphold laws and
8 regulations. Within these regulations, there are
9 regulatory standards for assessments like patient
10 questionnaires that require methods of assessments of
11 subjects' responses to be called well-defined and
12 reliable. Thus, when we describe these findings of
13 these assessments in labeling, those statements are
14 not potentially false or misleading. So, not only do
15 we recommend drug sponsors to engage with patients to
16 develop questionnaires using qualitative research, we
17 also recommend that they perform appropriate
18 quantitative research or statistical testing that show
19 that the questionnaire is well-defined and reliable.
20 Both qualitative and quantitative research can tell us
21 whether the patients can understand and respond as
22 intended to these questionnaires. Additionally, these

1 tests can provide an estimate of what a meaningful
2 change or improvement is on the questionnaire.
3 Patient involvement also is extremely important in
4 determining how to interpret what a meaningful change
5 or improvement is.

6 We recommend that drug sponsors seek input
7 from the FDA as early and often as possible in their
8 drug development programs. In some cases, if a
9 patient questionnaire does not exist then existing
10 questionnaires may be modified, or a new one
11 developed. It is important for drug sponsors to start
12 the process of selecting or developing these
13 questionnaires early, and use them early and often in
14 clinical development to gain experience with them
15 before using them in a phase 3 clinical trial to
16 confirm clinical benefit.

17 So, we have two pathways to provide advice
18 to those interested in using patient questionnaire or
19 patient reported outcomes or other clinical outcome
20 assessments in clinical trials. First is within the
21 context of the individual drug development program.
22 This is where we encourage drug sponsors to begin

1 discussions as early as possible, preferably in the
2 pre-IND stage. So that if any work is needed that
3 needs to be done, we can go ahead and have those
4 discussions early.

5 The second pathway is outside of the
6 individual drug development program. This is through
7 our drug development tool or DDT qualification
8 process. In this program, we can work with
9 questionnaire developers, patient advocacy groups,
10 sponsors, researchers to develop and qualify
11 questionnaires for use across multiple drug
12 development programs. We work with many stakeholders,
13 including consortia, patient groups, individual
14 academic investigators, and drug developers within
15 this program. Once qualified, this tool becomes
16 public available for use.

17 So, key takeaways is that our PFDD meetings
18 are the starting point for developing patient focused
19 outcome measures and endpoints. The outcomes of these
20 meetings will support and guide the FDA's risk/benefit
21 assessment and drug reviews, and patients' input
22 ultimately helps determine what is measured to provide

1 the evidence for treatment benefit, how best to
2 measure the concepts in a trial, and what is
3 meaningful improvement.

4 At this time, I would like to turn it over
5 to Sara so we can begin our discussions.

6 MS. EGGERS: Good morning, everyone. I hope
7 that you gain appreciation of the complicated that
8 FDA, our colleagues, have to think about every day
9 when they come to work. And now it's time to turn it
10 over and think about and hear from you about what you
11 think about. And if I don't have to make a joke about
12 the Beltway and the traffic, then we are having a good
13 day. We're getting off to a good start. I'd also
14 like to say before we get started that we've done 20
15 meetings now, and the energy in the room today -- we
16 always have great energy in the room, but it's
17 particularly strong, positive and constructive in
18 today. So, I think that's also a good sign that we're
19 going to have a great discussion. If you are a
20 patient or patient representative, if you are someone
21 with an organ transplant or care for and advocate for,
22 and you are sitting in the back, we strongly encourage

1 you to -- if there's room at a round table, to join
2 and we can see you better, if you want to join in our
3 conversation.

4 I'm going to give a bit of overview about
5 our discussion today. As Meghana mentioned, we have
6 the two topics for discussion. And we're going to go
7 through those in two different sessions. It's all in
8 your agenda. But, to boil it down, what topic one is
9 talking about what are the most significant changes in
10 your health since you received your transplanted organ
11 or organs; what are the symptoms and post-transplant
12 health effects that have the most significant impact
13 on your life; and what worries you most about your
14 health post-transplant.

15 And then the second discussion, we will
16 focus -- drill down more into treatment regimens,
17 looking at what you're doing currently to manage your
18 health post-transplant, both the medications that we
19 talked about -- that Marc talked about today, and
20 other things that you may be doing, and how well those
21 treatments helping you manage your most significant
22 symptoms and your health effects; what are the

1 downsides to those treatments; and, if you could craft
2 an ideal treatment what would it look like -- what
3 would be some of the features of that treatment.

4 So, for each of those two topics we're going
5 to have a panel of people living with an organ
6 transplant to go through some comments and tell their
7 story, very succinctly, to set the context. And I'm
8 going to ask the topic one panelists to come up now,
9 if you can, and just take a seat up here. Make your
10 way to the front. We have -- you'll see we've -- have
11 a wide range of ages, and we've identified several
12 organs to really, we hope, give a rounded idea of what
13 life is like.

14 And then we're going to broaden the
15 discussion. We're going to come out -- Meghana and I
16 will come out in front, and we have microphones that
17 will come to you, so that you can build on what we
18 hear from the panelists. We're going to ask that you
19 state your name -- first name only is fine. But state
20 your name before answering, so that we can capture it
21 in our notes. And state also what organs that -- what
22 organ or organs you have had transplanted. That's

1 important to set the context. We will be moving
2 around. We're not going to be focusing on kidney and
3 then liver. It is an open discussion, and we're
4 trying to find the common themes throughout. So, you
5 know, if we've heard a lot from kidney and you have a
6 liver organ, you know, raise your hand and we'll round
7 out that way. Okay.

8 You'll also have a chance to answer polling
9 questions, and that is for those in the room today and
10 also on the web. And I want to give a shout-out to
11 the web participants. You are very important, because
12 not everyone can make it around the Beltway in
13 Washington, D.C., to get here. And we often find that
14 the perspectives of those on the web is somewhat
15 different than the perspectives shared in the room.
16 So, please participate through the comment boxes. We
17 will have a chance, we hope, to go to the phone lines
18 in the topic two discussion, to get a person or two on
19 the phone. So, please participate as often and as
20 much as you want to over the web.

21 For the polling questions, both on the web
22 and in person, it's really a discussion aid. Please

1 don't look at this as a scientific polling or survey
2 result, and please don't report on it in that way.

3 It's really to see who do we have in the room and what
4 perspectives are you sharing -- what are you thinking
5 about.

6 We're going to hand out clickers. I think
7 those can be handed out now. So, we'll -- they'll be
8 distributed, and it should be self-explanatory.
9 You'll click whatever letter corresponds to the choice
10 that you see up when the polling question comes.
11 We're going to ask that patients or parents of
12 patients only participate. Okay.

13 And as Theresa mentioned, the conversation
14 doesn't end today. We very much value your continued
15 dialogue, through the public docket, as she mentioned,
16 which is our vehicle to engage in dialogue with our
17 constituency. It will be open until November 27. You
18 can share your experiences. If you didn't get a
19 chance to fully participate, as much as you wanted to
20 today -- I think most people would say that, by the
21 end of the day, that there's more that they wanted to
22 say -- please send it along. Reference if you're in

1 the room or participating on the webcast -- that you
2 participated, please, and that you're building on.
3 But, if you know people who were not able to join
4 today or have not -- maybe didn't know about the
5 meeting in your dialogue with them, encourage them to
6 submit responses to those questions that we asked you
7 today and share their story. It's very important to
8 us. Anyone can comment. So, if you're, if you're
9 someone other than a patient, or a patient advocate or
10 caregiver, you can send along comments as well.

11 We have other resources. Anyone in our
12 office of strategic programs, that -- we introduced
13 ourselves today -- come find us. But we also have an
14 office of health and constituent affairs. They run
15 the patient representative program. Is there anyone
16 here from OHCA, as we call them? Okay. I think
17 they're on the website -- on the web link today. But,
18 you can reach out to them if you have follow-up
19 questions or if this excites you, to participate in
20 this way, and you want to participate more broadly in
21 other ways.

22 We also have our professional affairs and

1 stakeholder engagement, or PASE, and -- is Chris in
2 the room today? He might also be participating on the
3 webcast. They also facilitate communication and
4 collaboration between the center for drugs and patient
5 health care stakeholders. So, you can reach out to
6 anyone -- if we're sitting up here or if we're -- if
7 their name is mentioned, please reach out.

8 A few ground rules, to make sure that our
9 discussion is as effective and respectful as possible.
10 We encourage patients -- people living with an organ
11 transplant -- to contribute to the dialogue. And
12 caregivers and advocates are welcome too. FDA is here
13 to listen. My colleagues will help Meghana and I with
14 some detailed questions, as you see fit. Please feel
15 free. We may not be able to answer all the questions
16 that you have today. Send those in the docket, if you
17 have a question -- a burning question and it hasn't
18 been addressed today. Also, similarly, the industry
19 representatives and the academics and researchers in
20 the audience -- they are primarily here in listening
21 mode too, but if you have thoughts please share those
22 through the docket comment as well. We also have the

1 open public comment period that Meghana described
2 earlier this morning. If there's something that's
3 outside of the topics of health effects and treatments
4 that you want to discuss, then open public comment.

5 We really -- this will be a very organic
6 discussion today. We do have some topics that we want
7 to make sure that we get through. So Meghana and I --
8 we have to play the timekeepers, and we will move
9 along as we have to. And so, we hope that the docket
10 you can expand. Remember that the views expressed
11 today are personal opinions. They're very personal,
12 and often very sensitive. So, respect for one another
13 is paramount. I don't -- I think I'm preaching to a
14 choir here, so -- we just want to make sure that we're
15 all on the same page. And really, let us know how the
16 meeting went today and how it's going. Find us during
17 breaks. But also, at the end, please fill out an
18 evaluation form. It does help us. Even though we've
19 done 20 meetings, we still learn something each and
20 every time about how we can improve. Okay.

21 With that, we can start some polling
22 questions. It's both a practice and gives us a good

1 sense of some of the characteristics of the folks in
2 the room. So, if you'd get your clickers -- anyone
3 need a clicker? Okay. We have a couple more clickers
4 needed here.

5 FEMALE SPEAKER: Sara. Sara.

6 MS. EGGERS: Yes.

7 FEMALE SPEAKER: Our CDRH colleague has
8 joined us.

9 MS. EGGERS: Okay.

10 FEMALE SPEAKER: Can you allow him to
11 introduce himself?

12 MS. EGGERS: Yes. Arturo, would you like to
13 introduce yourself?

14 MR. HERNANDEZ: Yes.

15 MS. EGGERS: Oh, and turn your --

16 MR. HERNANDEZ: Hi. My name is Arturo
17 Hernandez. I'm a medical reviewer for devices in
18 organ transplantation, for organ preservation -- solid
19 organ transplant.

20 MS. EGGERS: Thank you, Arturo.

21 DR. MULLIN: Sara.

22 MS. EGGERS: Great. Okay.

1 DR. MULLIN: Sara.

2 DR. MULLIN: Yes, Theresa.

3 DR. MULLIN: I think it would help if people
4 could keep their hand up, if they don't have a
5 clicker, so Shannon can see them.

6 MS. EGGERS: Yeah. Anyone still need a
7 clicker?

8 DR. MULLIN: If you need a clicker, just so
9 she can -- knows you need one.

10 MS. EGGERS: Okay. In the back there.
11 Okay. So, where do you live? You click A if you're
12 within the Washington, D.C., metro area, or B if
13 you're outside of the metro area. Okay. All right.
14 Okay.

15 This is typical. We typically have about
16 two-thirds of participants who are traveling, and we
17 give a special shout-out to you. You had to probably
18 fly or drive or take a train, and then get around the
19 Beltway. So, thank you.

20 Have you received an organ transplant?
21 Okay. So, it -- we have quite a few -- we have about
22 -- let me do some math. Approximately 20 folks in the

1 room who have had an organ transplant. And we are
2 going to ask now the remainder of the polling
3 questions that it's answered by you, or, if you are
4 here representing someone who is not able to answer or
5 is not here today, then do the polling questions.
6 Okay.

7 Let's move on to the next one. What is you
8 or your loved one's age? If you're on behalf of
9 someone else. Okay. Let's see. So, we will be
10 discussing primarily the adult perspective today. We
11 have a wide range of adult ages. I'm going to put a
12 special shout-out for pediatric perspectives. If
13 you're on the web -- can we have the web numbers,
14 please?

15 MR. THOMPSON: We're got 5 percent from 18
16 to 34, 21 percent 35 to 49, and 47 percent 50 to 64
17 and 26 percent 65 or older.

18 MS. EGGERS: Okay. Great. So, again, a
19 shout-out for the pediatric perspectives. They often
20 differ. We will get as much as we can out today, but
21 I think this is a place where the docket comment is
22 going to be extremely helpful.

1 Do you identify as male, A -- B, female?

2 Okay. So, we have -- oh, this looks funny. It's a
3 good thing I read the numbers and not just look at the
4 height of the bars. I'm going to take the numbers,
5 that we have a pretty even mix of men and women here,
6 in person, and on the web?

7 MR. THOMPSON: Thirty-nine percent male and
8 61 percent female.

9 MS. EGGERS: We squeeze the most that we can
10 out of the technology we have here at FDA. Okay.

11 What type of organ transplant have you
12 received? And if you have multiple -- I think this is
13 a check one only. So, if you have multiple just click
14 F. Okay. So, reflecting, I think, the statistics of
15 who has organ transplants, we do have -- half of you
16 in here are kidney -- have a kidney organ. And
17 multiple -- I think some of the multiples have kidney
18 as well. Followed by lung. Okay. So, a little bit
19 less representation of heart and liver. We will
20 squeeze all we can out of that today. But, again, if
21 you are on the web -- can we have the web numbers?

22 MR. THOMPSON: Forty-five percent kidney

1 transplant. 20 percent liver. 20 percent lung. And
2 15 percent multiple.

3 MS. EGGERS: Okay. So, encourage all of you
4 to participate on the web, particularly the heart and
5 liver -- by the web or the docket -- as well. So, we
6 can get as much as we can. And pancreas also. I'm
7 sorry.

8 Okay. What is the length of time since you
9 received an organ transplant? Okay. Okay. So, we
10 have several who have lived a long time with their
11 organ -- with their transplanted organ or organs.
12 But, we also have a -- several in here, in person, who
13 have -- are really new to this. Your perspectives may
14 be a lot different. If you are one of those people
15 who have -- are new to this, let us know in your
16 comment, so that we make sure we can tease out. On
17 the web?

18 MR. THOMPSON: Four percent less than one
19 year ago. 19 percent for one to two, three to five
20 and six to ten years ago. And 38 percent for greater
21 than ten years ago.

22 MS. EGGERS: Great. Thank you. Okay. Have

1 you received more than one organ transplant, or
2 received a retransplant? Okay. So, two-thirds of you
3 here have done this multiple times.

4 Did you receive your organ transplant from a
5 living or deceased donor? If you don't know, press C.
6 Okay. Okay. So, most -- two-thirds of you here today
7 have received an organ from a deceased donor.

8 Have you experienced organ rejection? A
9 yes, B no. Okay. About half. Okay. We'll get into
10 some of the issues with that today. Okay. On the
11 web?

12 MR. THOMPSON: We had 39 percent saying they
13 had experienced organ rejection, and 61 percent saying
14 they had not.

15 MS. EGGERS: Okay. Great. Then, we're
16 about ready to move on to our discussion. And we'll
17 go down, starting with Jim. We didn't actually meet
18 in person. Hi, Jim. But before we get started, I'm
19 going to ask you when it's your turn to -- and I just
20 want to say that we received many, many comments from
21 people who expressed interest in providing comments as
22 part of the panel, and they were so informative. We

1 encourage you to submit those to the docket as well,
2 so that we can take all we can from what -- the
3 comments that you've sent in. So, I want to thank
4 you. Thank the panelists for preparing their remarks,
5 but also thank you, who have -- who submitted your
6 comments. It was very, very helpful to us in
7 planning.

8 And with that, we'll start with Jim.

9 MR. GLEASON: First, on behalf of myself and
10 some of the others that I represent from various
11 transplant organizations I lead, thank you for all you
12 do to make our lives better and safer.

13 (Applause).

14 MR. GLEASON: Yes. When people ask how has
15 a heart transplant changed my life, I respond my most
16 significant change is that I'm still alive and active.
17 At the age of 50, given just two years life expectancy
18 from a virus-induced cardiomyopathy, back in 1992, the
19 heart transplant in '94 has allowed me to live a
20 fulfilled and active life for 22 years now, living to
21 see seven grandchildren born. The earliest two are
22 now in college. With no prior health issues -- not

1 even taking aspirin -- my heart was attacked by an
2 unknown virus -- idiopathic cardiomyopathy --
3 requiring hospitalization and a heart transplant, I
4 now take 30 plus pills a day, both prescription and
5 over-the-counter. Very expensive brand name and
6 generic drugs that prevent rejection and keep me
7 otherwise healthy.

8 I've dealt with the typical post-transplant
9 issues, including various cancers -- prostate cancer
10 in 2000, many skin cancer, kidney cancer in 2012 --
11 and living with Type 2 diabetes for the past ten years
12 now, a common side effect of the specific drugs that I
13 take today. I live a fully functional life in
14 retirement today, having returned to full-time
15 employment just three months post-transplant for 12
16 years, until reaching normal retirement these past ten
17 years now.

18 Most of my life challenges can be attributed
19 to the immunosuppressant drugs and advancing age, as I
20 am now 73 years old. Specifically, the cancers --
21 especially the many skin cancers -- are well-known to
22 be high risk for patients with organ transplant, both

1 with growing years after transplant and with normal
2 aging. The meds taken in the early post-transplant
3 years were toxic to the kidneys, and when the kidneys
4 began showing damage due to those meds new drugs had
5 come on the market that were a substitute for the
6 cyclosporine, with tacrolimus as a less toxic med but
7 still with its own side effects -- that diabetes I
8 came down with in 2006.

9 The only worry I live with is the concern
10 for those cancer risks, and personal finances as I
11 age, given the heavy cost of the meds, even with
12 Medicare and gap insurance support. Each day is a
13 gifted extension to the life that was threatened those
14 many years ago, now living with a strong heart gifted
15 by a 38-year-old stranger in their dying.

16 What's changed over time? With a heart
17 transplant, you begin with heavy doses of those meds
18 and weekly heart cath biopsies. Both tapered down
19 over time, with the invasive heart cath less frequent,
20 finally stopping at the five year point, and the meds
21 at a long-term standard dose much lower than those
22 first six months. My current regimen seemed to be

1 working perfectly, with semiannual clinic visits and
2 testing, we catch issues early and treat them with
3 minimal pain or damage. Overall, I have experienced
4 ideal treatment with a great transplant team and the
5 other doctors, for all those 22 years, which I will
6 happily celebrate this October 19th, again. Thanks
7 again for a unique opportunity to share this amazing
8 heart-filled life adventure with you.

9 (Applause).

10 MS. EGGERS: Thank you, Jim. And now we'll
11 have Jeff.

12 MR. GOLDSTEIN: So, I too would like to
13 thank you for this unique opportunity to share my
14 perspective on a double lung transplant, 13 years July
15 of 2003. So, we did see some slides. Some of you may
16 not be aware, but a lung transplant has some of the
17 worst long-term outcomes of all solid organ
18 transplants. And none of the medications I take were
19 designed for lung transplant. So, I often say that
20 lung transplant, and that means all transplant as
21 well, is just exchanging one set of problems for
22 others.

1 I'm very fortunate to have effectively
2 avoided major rejection issues. My lungs have been
3 mostly stable. My pretransplant disease and my need
4 to take immunosuppressants has put me at risk for skin
5 cancers, which I deal with daily -- and as you can
6 see, has affected my Hollywood good looks. All
7 transplant recipients are at risk for kidney failure,
8 as a result of long-term anti-rejection meds. And in
9 addition, it has been suggested that my loss of
10 hearing is a result of prescribed antibiotics.

11 Managing drug side effects -- fear, anxiety
12 and feeling different every day is a real challenge,
13 along with fatigue. It is the most frequent issue I
14 manage, as I tire easily, while sleep is restless and
15 mostly incomplete. Other than regular changes of
16 anti-rejection meds and the addition of skin cancer
17 reduction medications, my therapies have remained
18 mostly constant. But these issues do impact my daily
19 life. I often struggle with staying focused and
20 managing my time, and energy levels can vary widely.
21 There are bad days and good days, but still it beats
22 the alternative. I am very fortunate, as on the best

1 days my symptoms are manageable and tolerable, and I
2 try not to let them dictate my lifestyle. When they
3 are at their worst, I listen to my body and respond
4 accordingly. I have -- on occasions where I was
5 unable to do something I planned or hoped to, I
6 accommodate the inconvenience. My motto has been get
7 busy living.

8 So, what has changed? I avoid the sun as
9 much as possible, and no longer fish the waters of
10 Florida Keys, trying to reduce my skin cancers. I
11 worry daily about bronchial obliterations disease, cancer
12 rejection and leaving my wife widowed, in that order.
13 I would like to take this opportunity to encourage the
14 FDA and pharmaceutical companies to consider
15 developing treatments that make the lives of all post-
16 lung transplant recipients better, safer and thus more
17 rewarding. And I'd like to -- I'm known for leaving
18 everybody with a quote, and I hope you'll find this
19 one interesting. Our scars are a reminder that the
20 past was real. Hannibal Lecter.

21 (Applause).

22 MS. EGGERS: Thanks, Jeff. He warned me

1 there would be a chuckle or two. Now, we'll go with
2 Leilah.

3 MS. SAMPSON: Right. Now I have to follow
4 that. I don't have any jokes. I'm a newbie. My name
5 is Leilah, like the Eric Clapton song if anyone has
6 heard of it. And I'm truly blessed for this amazing
7 opportunity to be here and share my experience. I'm
8 only nine months out from a kidney transplant, and
9 this is a completely new life for me. The last time I
10 was healthy I was 19. I am now 28, as of last week
11 was my birthday. First birthday with my kidney.

12 I was diagnosed with SFGS, which is scarring
13 of the kidneys, that progressed to renal failure. And
14 I spent five years on dialysis, and the deceased donor
15 list. However, I acknowledge I will always be a renal
16 patient, which still means paying extra close
17 attention to my health. And many believe that you get
18 a transplant, it's a cakewalk, and you're healed
19 forever. Surprise, it's not. Post-transplant wasn't
20 a day at the beach for me. Sure, I'm very grateful,
21 but you have to fight for your organ the same way that
22 you fought to receive it. A couple of days after my

1 transplant surgery, I experienced a drop in my
2 hemoglobin and platelet levels. Initially, we thought
3 my disease, FSGS, was recurring and attacking my
4 kidney. However, after plasmaforesis, which is
5 exchanging of donor plasma, to wash out antibodies,
6 two blood transfusions and multiple biopsies, we found
7 that it wasn't reoccurrence but just not the right
8 combination of immunosuppressants for me. So, once I
9 was switched from prograf to cyclosporine, coupled
10 with prednisone and cellcept, everything turned around
11 immediately.

12 I simultaneously experienced a serious bout
13 of pneumonia from lack of movement and deep breathing
14 due to pain. So, use those spirometers. They
15 actually work. From there, the next few months would
16 be trial and error with water intake, even being
17 readmitted due to severe dehydration. But, I tested
18 the limits and I learned from it. Luckily, I only
19 needed a couple of days of IV fluids and I was back on
20 the right track. I worry about losing my kidney due
21 to dehydration, because on dialysis we were so fluid
22 restricted and now it's hard to immediately adjust

1 back to drinking more water.

2 I also started back exercising, and that's
3 still in a trial and error phase. I think that's
4 going to be a lifelong trial and error phase for me.
5 But I was trying to reignite my old 19-year-old
6 healthy athletic self. But I found myself spiking my
7 creatinine levels. Now, I listen to my body and I
8 start with walking, biking and yoga for short periods
9 of time. I'm also finding that if you had anxiety and
10 depression prior to transplant -- guess what? You
11 still have it. But I've been with a therapist for
12 over four years, and continue to do the work on myself
13 while adjusting to life post-transplant. And it
14 definitely takes some adjusting, too. But, I'm
15 honoring the process.

16 Now, for example, seeing this stubborn acne
17 on my face caused by steroids and hormones brings me
18 some anxiety about just how immunocompromised I was
19 told that I would be. However, I haven't been sick or
20 had any infections. But, we'll see after the plane
21 ride home. So, when I put it into perspective, I
22 think I could live with the acne. Maybe I'm not as

1 immunocompromised as I thought. When everyone got
2 sick at work, I washed my hands frequently, carried
3 Lysol -- and they thought I was rude because I said
4 stay away from me -- but it's necessary. You have to
5 take care of yourself.

6 Also, I found by living a more stress-free
7 and meditative life helps reduce both anxiety and
8 depression. I send my kidney and myself unconditional
9 love, gratitude and self-compassion, to try out
10 different things until we find a balance. My kidney,
11 Phil, obviously is a trooper to put up with me. But
12 he knows I love him and we will continue to thrive. I
13 encourage you all to give yourself a little bit of
14 love, self-compassion and honor your process, whatever
15 it may be. Thank you.

16 (Applause).

17 MS. EGGERS: Thank you, Leilah. And now
18 Michael.

19 MR. GARRETT: Good morning. My name is
20 Michael Garrett, and I'm in my 62nd year. I was
21 diagnosed with Type 1 diabetes when I was five, and my
22 first transplant occurred in 1990, when I was 35, and

1 that was a very early -- at least in the transplant
2 game -- kidney pancreas, done here locally. I also
3 had a living related kidney transplant, also in 1990,
4 because you can't keep a good immune system down. And
5 I had a second pancreas only transplant in 1990.

6 My biggest or my best answer to question
7 number one is that I'm still here. I had a -- I
8 checked once with insurance tables, in 1960, and male
9 diagnosed at age of five with Type 1 diabetes in 1960
10 had a life expectancy of approximately 31 years. I've
11 now doubled that, so I guess something is working.

12 The second question about post-transplant
13 effect and symptoms, I can say my wallet is a little
14 lighter. But at least I have a wallet. Physically,
15 there are affects from transplant, and most assuredly
16 the drug therapies. I have muscle aches, outbreaks of
17 cancer, skin and otherwise, and less resistance to
18 viruses and infections. I sometimes wonder, though,
19 if some of these are due to my advanced age.

20 Question three about what I don't do now,
21 because of transplant therapies -- the answer is not
22 much. But I am not as active as I once was

1 physically. But again, how much is transplant related
2 and how much is age related. I'm losing my vision,
3 and you can probably tell from this. But this seems
4 to be the fault of long-term Type 1, and not the fault
5 of the therapies. On good days, I plow through and on
6 bad days I take a break.

7 My experience with transplant organs has
8 changed over time. I have received four organs in
9 transplants, and have rejected or lost three of them.
10 The first two were due to acute rejection, and the
11 third -- well, I was told ten years on a pancreas was
12 about all I could expect. So, I'm definitely looking
13 for therapies to protect transplant organs for a
14 lifetime. And of course, on a -- as a side note, I
15 realize that the scientific community has pretty much
16 decided that Type 1 diabetes is an autoimmune disease.
17 And so, I never thought that getting a pancreas
18 transplant was a cure for Type 1 diabetes. It's
19 merely another form of therapy. And logically
20 speaking, at least in my small brain, if it's going to
21 attack a natural pancreas it's going to attack the
22 transplanted ones also. So, probably what's going to

1 be happening from my own point of view is that
2 pancreas transplants are doomed to failure until we
3 figure out how to cure Type 1 diabetes.

4 As far as most worrisome, probably organ failure
5 first, followed by cancer and major infections or
6 illnesses. But I've stayed relatively healthy over
7 the past 26 plus years, despite being so sick. Thank
8 you.

9 (Applause).

10 MS. EGGERS: Thank you, Michael. And now
11 we'll have the Lindsey.

12 MS. LINDSEY DUQUETTE: Hello. My name is
13 Lindsey, and I'm 14 years old. I received my kidney
14 transplant from my dad in 2012, when I was ten. I'm
15 so grateful to him and everyone directly involved in
16 my care, including the doctors, nurses, and child
17 life. But very importantly, I am also thankful for
18 the people who helped me who didn't even know me.
19 Specifically, I mean the researchers and other
20 transplant patients whose efforts in the years before
21 my journey helped me to get where I am today.

22 To understand my gratitude, I will tell you

1 a little bit about my eight year battle with
2 idiopathic SFGS. Over the course of eight years,
3 starting when I was two and a half, I endured 172
4 hospitalizations, 22 surgeries, hemodialysis,
5 peritoneal dialysis, countless medications, including
6 steroids that compressed my backbones and left me in a
7 wheelchair, and one black box drug administered 13
8 times over a year and a half. I missed my entire
9 first and third grade years. I was sick, sad and lost
10 my childhood.

11 How has life been since my transplant?
12 Awesome. It's been a huge difference. I grew five
13 inches in the first year after my transplant. I'm
14 only taking seven pills twice a day, instead of 21
15 pills twice a day. I have no -- I have had no
16 recurrence of SFGS. I have more energy. I don't have
17 any pain. I can eat normally -- no more gross renal
18 diet. I can go to school. I can have sleepovers and
19 spend time with my friends, and I have a life.

20 It's not perfect, though. I have some
21 unique challenges for me as opposed to other students
22 at my school. I have some orthostatic blood pressure

1 issues, not due to renal insufficiency, and daily
2 morning fatigue. I tend to feel nauseous every
3 morning, and need to stand up slowly. I can't
4 exercise as much as I would like to. I don't have
5 much stamina in gym class. I lost all of my childhood
6 vaccine tethers during the course of my disease. This
7 is going to be tough, because I am not supposed to get
8 sick. But, of course, I will always be immune
9 suppressed. I have to drink 85 ounces of fluids
10 daily, and this can be hard when you're running from
11 class to class all day. I used to overload my body
12 with fluids when I got home from school, just to get
13 my required amount in before the end of the day. It
14 was not good for my body, and worse with my morning
15 nausea problem. It's becoming a little easier to
16 drink now, now that I am in high school.

17 Personally, I do not have any adherence
18 issues but I do understand where other teenage
19 transplant patients might. It is hard to remember to
20 take your meds every 12 -- 12 hours exactly. It's
21 hard to drink as much as we have to. And it's hard to
22 keep away from infectious people. I know I'm going to

1 need at least one more transplant in my lifetime. I
2 know that I'm going to be on these potentially toxic
3 anti-rejection meds for the rest of my life, and I
4 understand that I will always have to be so careful
5 not to get sick.

6 Here are some items on my post-transplant
7 wish list. How about a transplanted kidney that will
8 last the rest of my life? Fear of toxic medications
9 and it would be great if meds could be taken just once
10 a day. Rituximab and all my other meds carry the huge
11 risk of cancers over my lifetime. That's pretty
12 scary. Monthly blood work to check my tacrolimus
13 levels is annoying, and it's worse if I get sick.
14 Then I end up getting labs every two days until I get
15 better. Will constant sticks in my vein cause me
16 access issues later in life? Will it be hard for me
17 to find another kidney someday, due to increased
18 antigen sensitivity. What if I want to become a mom
19 someday? Can we make it so that pregnancies will not
20 increase my PRA? I wish I wasn't so susceptible to
21 sicknesses due to my immune suppression. I would love
22 to have to drink less. It would free up some time. I

1 know I'm not the only one wishing that. Will I be
2 able to get health insurance on my own someday? What
3 will happen to me when I start showing signs of ESRD
4 again, and need a new kidney? Will I lose my job?
5 Those are my thoughts and concerns. Thank you for
6 listening.

7 (Applause).

8 MS. EGGERS: Thank you all -- very much to
9 all of the panelists, who provided a -- what we hope
10 is a reflective set of comments sharing your
11 perspectives and experiences. We always start by
12 asking did you hear yourself, your thoughts, your
13 experiences in at least one of those panelists up
14 there? Okay. That's what we hope, and that's what
15 you guys have provided. So, thank you very much.

16 Is there anyone with a liver -- we didn't
17 have liver on the panel, I don't believe. Anyone with
18 a liver -- who wants to briefly share, your
19 experience, if it -- especially if it's a little
20 different.

21 FEMALE SPEAKER JEAN: I don't know how
22 different it is. I have primary biliary cirrhosis,

1 and required a liver transplant. It came on rather
2 suddenly. I thought I had the flu. And then I
3 started bleeding internally. So, that's the onset.
4 Prior to that, general childhood and adolescence and
5 young adulthood, I had no diseases. My basic concerns
6 are -- have been reflected. I'm -- I had a heart
7 attack, and it was otherwise unprecedented. And I now
8 have diabetes, and this I believe is from the drugs.

9 One of the things that you had asked about
10 was an ideal or a preferable treatment. And I don't
11 know where the research is on this, but what I would
12 hope for is a mechanism or a method for pretransplant
13 suppression, such that when this transplant occurs it
14 is not a foreign body to the human and that subsequent
15 to that they -- it may be for a short time, but would
16 not need lifetime drug therapy.

17 MS. EGGERS: Thank you very much, Jean.

18 FEMALE SPEAKER JEAN: Yes.

19 MS. EGGERS: Is there anything on the web?
20 Is anyone putting comments in yet?

21 MR. THOMPSON: There are a few questions
22 related to treatment, but not much on symptoms yet.

1 MS. EGGERS: Okay. So, I'll take this as a
2 reminder to those of you on the web -- I don't know if
3 you can see us or the people in the audience. But
4 please contribute your thoughts during the course of
5 this meeting, and we will summarize them periodically.

6 So, what we noticed in our team as we were
7 going through the panel comments that came in, as we
8 were talking to the panelists, is the overall
9 gratitude, that has been heartwarming. The gratitude
10 for you to be here today, and be able to be here
11 today. It is very helpful to have this big picture,
12 and I think you've said it strongly. So, as we
13 continue and as we go through the day we encourage you
14 to voice the significant impacts or downsides. Don't
15 be afraid to tell us what the downsides are. We know
16 of your gratitude for having the transplanted organ.
17 In the spirit of continual improvement, we're going to
18 be focusing primarily on challenges that you face, and
19 what you would like to see in making drugs better.
20 So, I think we've never heard such gratitude in our
21 meetings before, and so it really is heartwarming.

22 So, now, I will get off my emotional state.

1 It really -- it does -- it's emotional. You have made
2 it such. Well, let's do a polling question, then.
3 That will bring us back. So -- oh, this is a hard
4 one. What comorbid conditions -- and you can check
5 all that apply -- have you experienced post-
6 transplant, if any? I'm not going to read through the
7 list. I'll let you read through it. If you have not
8 had any comorbid conditions that you're aware of, then
9 you would click I?

10 MALE SPEAKER: All of them?

11 MS. EGGERS: Yeah. You can do all of them,
12 if they all --

13 FEMALE SPEAKER JEAN: If cancer, is that --

14 MS. EGGERS: It would include all cancers.

15 MALE SPEAKER: (Inaudible).

16 MS. EGGERS: Things that you acquired,
17 things that you acquired post-transplant.

18 MALE SPEAKER: Okay. Only post-transplant.

19 MS. EGGERS: Uh-huh. Okay. So, the
20 infections of A and F are -- we've heard -- we heard
21 about those. You're concerned about infections, and
22 you've experienced infections. We might dig into that

1 a little bit. Followed by D, the depression or
2 anxiety, as we heard Leilah say before. I will let
3 the panel -- if there's any that you would like to
4 follow up on, in particular -- if something surprises
5 you. And while you're thinking about that, let's talk
6 about infections, just for a few minutes. We're going
7 to be bouncing to many, many different topics. We'll
8 only spend a few minutes on this. We heard about the
9 risk of infection, and worrying about it. Let's talk
10 about your experience with infection -- anything that
11 surprised you about an experience with infection,
12 post-transplant. We'll go here to Dan, and then back
13 there. And again, state your name and your organ,
14 please.

15 MR. BONNER: Hi. Good morning. My name is
16 Dan Bonner. I'm a liver transplant patient. And I
17 think what has surprised me with infections --
18 particularly EBV -- is how over time my EBV levels
19 would start out very low, you know, around 200, and
20 then work their way up to over 2,000. But then with
21 no sort of medical intervention at all, my numbers
22 seem to come back down to below 200. And I find that

1 to be odd, because during that time my
2 immunosuppressant levels weren't changed at all, in
3 any way. But, at one point, at the same time having
4 kidney enzymes that -- or, a creatinine level of 2.8,
5 around there, is the same time EBV was going up. And
6 then magically, my numbers came back down. So that,
7 to me, was a little bit surprising, considering the
8 lack of medical intervention.

9 MS. EGGERS: Okay. And then back there.

10 MR. LENNON: Good morning. My name is Jack
11 Lennon. I had a three time kidney transplant
12 recipient. So, most probably surprising -- and I'm
13 sure most of the others in the room have experienced
14 this -- it's not just that we are more susceptible to
15 the viral infections that the doctors will check on a
16 regular basis, but it's also the -- you know, the
17 seasonal flus and the infections that you would catch
18 at school or at work. And the worst part about those
19 is that, A, you're more likely to catch them because
20 of your, you know, decreased immune system. But also
21 the fact that you can't kick it. Right. It's -- I
22 want a super antibiotic, because, you know, I -- my

1 brother will get better in two days. I'm out for a
2 week, right. Or sometimes even worse, it really lays
3 you on your back and you have to be admitted for
4 something, you know, somebody else is just going to be
5 able to, you know, normally function throughout the
6 day with. And so, you know, it's that concern about
7 really the impact of the infection and what it can
8 have on your daily life.

9 MS. EGGERS: Uh-huh. Right. We saw a lot
10 of heads nodding -- a point that resonates. Okay.
11 Let's -- anything else on infection? Okay. One more.

12 MR. FOWLER: Yes. My name is Kevin Fowler,
13 12 year kidney transplant recipient. I think the
14 whole aspect about infections is -- the question is is
15 that what's really happening in terms of my concern is
16 the cancer risk. And then I think it underscores the
17 need to have tailored therapy, the need for
18 diagnostic, yada, yada, yada. But that's the larger
19 issue, right.

20 Am I on too much medication, or am I right enough?
21 Besides the inconvenience that it results in too.

22 And then the other thing, too, is just to

1 point out is that there's a lot of people that are
2 losing their organs due to those hospitalizations,
3 because of the fact of the cumulative effect of all
4 the antibiotic use, and the fact that sometimes
5 patients don't take it serious.

6 MS. EGGERS: Okay. All right. Thank you,
7 Kevin. Okay. We heard about diabetes from a couple
8 of you on the panel. Is there any perspective on the
9 onset of diabetes that has surprised you? Anyone else
10 want to -- okay, we'll come here to Jean.

11 FEMALE SPEAKER JEAN: Just one quick thing.
12 My endocrinologist is of the belief that there is a
13 difference between normal weight diabetes and
14 metabolic syndrome. I'm not obese currently, nor have
15 I ever been. Nor have -- do I have a profile of
16 really high sugar intake. I mean, I like sweets too,
17 but -- so, he's -- his belief and his -- he says the
18 status of the research now is they're looking at
19 normal weight diabetes as being something different.
20 And I don't know what the status of that is, or how
21 well accepted that is, but it would be interesting to
22 find out.

1 MS. EGGERS: Thank you, Jean. Our
2 colleagues have indicated that they would like to hear
3 a little bit more about depression or anxiety. We
4 heard Leilah -- oh. Okay. Go ahead, Jeff.

5 MR. GOLDSTEIN: I just wanted to say
6 something about the diabetes issue. So, I don't know
7 if this is the case for all solid organ transplants,
8 but in the lung transplant world it's not unusual to
9 get diabetes post-transplant. And for some of us, it
10 goes away once our medications are stabilized.

11 MS. EGGERS: Okay. Okay. Thank you for
12 making the point. Okay. So, now, thinking about
13 depression and anxiety, as Leilah pointed out if you
14 had it before it doesn't go away. Any other thoughts
15 on your experience with depression or anxiety that
16 you'd like to share? Okay. Go ahead, Kevin. And on
17 the web, please, too, write in your comments.

18 MR. FOWLER: I think this kind of goes back
19 to that this is a huge issue, right. And I think that
20 -- kudos to the agenda this afternoon. They're going
21 to deal about that with adherence or nonadherence,
22 which is a byproduct. But, I go back to my first year

1 and a half transplant. I had it easy, in comparison
2 to many people. But that whole psychological
3 adjustment -- most physicians don't understand it. In
4 that first year and a half, I struggled tremendously.
5 So, I think it's a large issue because of a lot of
6 different reasons. But, if you're looking to improve
7 it for patients is now how do you improve the patient
8 journey by really understanding the emotional side for
9 the patient.

10 MS. EGGERS: Uh-huh. Okay.

11 MR. FOWLER: That is a huge issue.

12 MS. EGGERS: Okay. So, that's raised
13 another thought here. And then we'll go --

14 MS. JEFFERSON: Hi. My name is Nicole
15 Jefferson. Kidney transplant, 2008. One thing I
16 wanted to discuss with the depression issue is
17 although I had my transplant in 2008 right now it's in
18 the process of failing, so I'm going through trying to
19 get listed again. And that's one of the things that's
20 come up, is the depression -- the anxiety, the
21 feelings of disappointing my donor. Although
22 deceased, the process of her dying again now that I'm

1 losing this one. And although I see a therapist,
2 that's something that I didn't think about in the
3 beginning. I didn't think I would -- I was told it
4 would last four to six years. However, I never
5 understood that the time would come and how I would
6 feel, and that it would put me in an anxiety mode or
7 depression mode.

8 MS. EGGERS: Okay. I'm sorry. We have
9 someone on the -- something on the web, and then we'll
10 come here.

11 MR. THOMPSON: We've heard a few symptoms on
12 the webcast, including tremors, GI issues including
13 diarrhea, broken or restless sleep. One person
14 specifically was talking about how her chronic sinus
15 issues have been surprisingly limiting to her, because
16 she is restricted from taking medications that might
17 help with them. So, they linger much longer than
18 normal. And a few other experiences like that.

19 MS. EGGERS: Thank you. And we'll come
20 here.

21 FEMALE SPEAKER HEATHER: So, my name is
22 Heather. I have a lung transplant, and I had one 10

1 years ago -- now 11 -- and it lasted one year. And
2 then my native lung came back somehow, even though I
3 had IPF. And now I have a new one last October, and
4 it's fantastic. But one thing that my husband and I
5 discuss a lot, especially in this first year, is the
6 feeling that we truly have PTSD.

7 MS. EGGERS: Uh-huh.

8 FEMALE SPEAKER HEATHER: And I think -- I
9 don't, you know, I don't say that lightly. But, it's
10 -- you have a sneeze, and you freak out. And, I mean,
11 and what that causes is your body reacts. And we have
12 a lot going on. We have to, we have to heal. You
13 know, we have to calm down. You know, your body has
14 to have time. And I -- our doctors don't -- you know,
15 there's always a social worker involved. But really,
16 they're not giving you the things you need.

17 And I -- you know, most of us don't want to
18 take another medication. I fortunately meditated. I
19 learned to do that. I calm myself down that way.
20 It's helped with pain, all kinds of things. But, it
21 just -- even with all of that -- and for a little bit,
22 I was on celexa. But, you know, it was decided, you

1 know, it was going to cause some more issues with my
2 medication and if I could be away from it, try and be
3 away from it. So, you know, it -- but I think this is
4 just such a common thing that even our caregivers go
5 through and -- you know, it's quality of life, you
6 know. And that's what we're trying to do our best
7 with. So, if that could be somehow part of the
8 protocol, whether it's medicated -- but with, you
9 know, figuring out that -- those medications that
10 won't hurt us as much as they will help us. I think
11 that's something that --

12 MS. EGGERS: Uh-huh. Uh-huh. Thank you to
13 you, Heather. And what was your name, in blue?
14 Nicole. Nicole. Make really great points, I think,
15 that we will probably hear again, about the trauma of
16 when the challenges sets in and when the worry sets
17 in. So, thank you for that.

18 There is one more polling question that we
19 will have here, about the comorbidity. For our
20 understanding, if you could get your clickers out.
21 Which statement best categorizes the source of your
22 comorbidity? As best you can. We know this is

1 sometimes hard to know or to differentiate. But one
2 of these that best categorizes it. You didn't know
3 there would be a quiz, when you came today. Yes. Oh,
4 okay.

5 Can you -- what other -- the other health
6 effects that you've had that you have experienced
7 post-transplant that you could reasonably think could
8 be because of your transplant. How did you, how did
9 you -- to the best of your knowledge, how did you
10 acquire that? Was it -- do you know if it was
11 transmitted from the donor of the organ? Did you get
12 it when you got the organ? Was it prior to your organ
13 transplantation? That would be B. C, was it
14 acquired, you know, in the community because of
15 immunosuppression or infection. Or, was it acquired,
16 as you could best guess, as an adverse event effect of
17 a treatment that you were on. Yes.

18 FEMALE SPEAKER: (Inaudible) is not listed
19 up there is Barre syndrome, from (inaudible).

20 MS. EGGERS: Okay. So, Barre syndrome from?

21 FEMALE SPEAKER: I don't know if this
22 applies to anyone else, but I've developed Barre

1 syndrome, from -- possibly from the repeated
2 endoscopies that have been required. And I don't know
3 if that's unique, or if that's -- but it's not a
4 category. It's a post-transplant surgical
5 intervention that wasn't listed.

6 MS. EGGERS: Thank you. Okay. Let's see
7 what the responses are. But, I think what we'll take
8 away from this, maybe even more than the responses, is
9 the difficulty in answering this type of question and
10 understanding how your -- how all the pieces fit
11 together and where you might have acquired it. It's
12 easy for us to come up with the question, and we don't
13 always appreciate how it might be to answer the
14 question. But with that said, we have someone in the
15 back.

16 MS. COHEN: Hi. I'm Ellen Cohen -- well,
17 Ellen Griffith for purposes of my transplant. My
18 kidney's name is Ben.

19 MS. EGGERS: Hi, Ben.

20 MS. COHEN: But, anyway -- for my brother,
21 who was my donor. The issue of comorbidities -- I
22 don't know how much research there is being -- has

1 been done on differences in hospital post-transplant
2 protocols. When I had my transplant -- I have a long
3 history, genetic history, going back generations of
4 depression. And I was terrified of -- I knew that
5 some medications -- post-transplant medications made
6 depression worse.

7 My transplant center, you virtually -- well,
8 they generally, as a practice, do not give you
9 prednisone after you leave the hospital. Other
10 transplant centers that I know of from being on web
11 groups routinely put people on long-term prednisone.
12 So, that -- it seems to me that this issue of
13 comorbidities, somewhere there is a side issue of what
14 are the hospital protocols and how do they compare --
15 how do they affect the comorbidities.

16 I also -- I had my transplant in January --
17 kidney in January, in the middle of that incredible
18 flu season where several types of flus were going
19 around. I never caught anything. And most recently,
20 I did catch a cold that has disabled people for weeks,
21 and I'm over it. I caught it last week. It's gone.
22 Why are immune systems different? Why am I somehow

1 almost as healthy and almost as immune as I was before
2 my transplant?

3 MS. EGGERS: I can see the envy in Jack's
4 eyes as he -- as you hear about how healthy -- thank
5 you for raising those questions. And now, we're going
6 to move on to -- oh, yes, go ahead. Leilah.

7 MS. SAMPSON: Okay. I have something to
8 add.

9 MS. EGGERS: Uh-huh.

10 MS. SAMPSON: My situation is quite unique,
11 because when you think of something being transmitted
12 from a donor we typically think of infections or
13 viruses. And my donor actually committed suicide
14 while in jail. And so, he was a high risk donor. And
15 throughout multiple testing, I didn't get any
16 infections from him, no HIV, no viruses. However,
17 since I did already struggle with depression, post-
18 transplant I felt the depths of his depression. And
19 it's interesting, because I've talked to other
20 transplant recipients and they will say, like, if they
21 got an organ from a woman who is in menopause, they
22 will feel the sweating.

1 MS. EGGERS: Uh-huh.

2 MS. SAMPSON: You know, they'll take on some
3 of those symptoms. I mean, why wouldn't you, if that
4 organ has been with this person all of their life
5 through all of their experiences. And I knew my
6 depression was under control, and it was days I would
7 just lay in the hospital in the dark. I would have
8 horrible thoughts. I would just -- I would sink to
9 such a -- like, a low that I've never experienced
10 before. I knew it wasn't mine.

11 And, of course, with the help of an amazing
12 therapist she helped me to just decipher, you know,
13 you have to just send him love and let him know that
14 this is going to be different this time, you know. I
15 always let my kidney know that he'll never experience
16 those depths of depression that he did, to take his
17 own life. And I think that's something we don't
18 typically look at, because it's not tangible. It's
19 not something you can measure. But, it was very real
20 for me.

21 MS. EGGERS: That's a profound point, about
22 the reality that you have another being that you have

1 acquired, that you're sharing with. So, thank you
2 very much.

3 So, we'll move on to another polling
4 question. Yes.

5 MS. CHALASANI: So, I think the topic one
6 panelists really set up how life after transplant
7 changes, after -- as Leilah said, it's not just
8 perfect. You have to find that balance. And so,
9 there's a lot of lifestyle changes. So, if we can
10 start with this polling question. Which aspects of
11 your personal care have changed most significantly?
12 Skin care, hair care, dental care -- D is eye care, E
13 is dietary needs, and F is other areas not mentioned.

14 MALE SPEAKER: (Inaudible).

15 MS. CHALASANI: Yes. You may check all that
16 apply. Okay. So, 72 percent skin care, which goes
17 back to the skin cancer risk that everyone has kind of
18 been mentioning this morning. We have 68 percent with
19 dietary needs, and then a variety for all the other.
20 Let's talk about -- so, we've talked about the risk of
21 cancer but we haven't really talked about some ways
22 that you guys have changed your lifestyle to manage

1 some of those risks. Does anyone want to kind of tell
2 us how they avoid the sun and so forth?

3 MALE SPEAKER: Avoid the sun.

4 MALE SPEAKER: I'm sorry. I thought someone
5 was speaking for me there a second. I think just the
6 thing about the skin is that -- I mean, basically,
7 it's trying to cover my body as much as possible.
8 But, I think the issue is a lot of times it was kind
9 of unreported as an issue at the time of transplant.
10 As well as overall -- a lot of these other issues that
11 are being listed here, many of these issues were
12 really not counseled upon 12 years ago. So --

13 MS. CHALASANI: Okay. Anyone else? I think
14 Nicole --

15 MS. JEFFERSON: Hi. I think one of my
16 biggest issues is C, dental care.

17 MS. CHALASANI: Okay.

18 MS. JEFFERSON: I didn't realize with the
19 transplant and the medications that I would be on that
20 my dental care would have to be so intensive. The
21 bone loss in my -- and the gum pain, also in addition
22 -- and I guess this goes into it with the dental, the

1 bone loss in my teeth. Also with my legs. I had
2 severe bone problems, and I actually broke a hip
3 pretty early on onto it. And that would be my biggest
4 thing.

5 MS. CHALASANI: Okay. What about dietary
6 needs? I don't think we've really heard much about
7 that.

8 MS. EGGERS: The dietary --

9 MS. CHALASANI: Changes due to constipation,
10 diarrhea, weight gain or weight loss.

11 FEMALE SPEAKER: All right. Well, mine just
12 simply relates to the diabetes. It's, you know, it's
13 a struggle to keep that A1C in line and when I don't
14 it's very depressing, because my appetite really
15 hasn't changed. So, that's been significant for me.

16 MS. PIERCE: I'm Mary Pierce (ph). I am a
17 double lung transplant, 23 years out, which makes me a
18 bit of an outlier. The dietary needs -- with all the
19 drugs that we're taking, particularly the antibiotics,
20 I think we all deal with diarrhea, irritable bowel,
21 those kinds of issues. And it takes a good balancing
22 act to make sure that we do everything we can to

1 maintain that. Weight gain is a huge issue for most
2 of us. We've got to watch everything we do,
3 everything we take in. And the additional challenge
4 for all of us, I think, is watching the -- what we eat
5 -- the cleanliness of what we're eating. Make sure we
6 wash things, stay off a salad bar, don't eat anything
7 that's prepared for us that we're not sure of its
8 origins.

9 And then, in my situation, I've had eye
10 problems and a problem with veins and cataracts. And
11 I would imagine that many of us have -- well, you can
12 see the cataract tissue is very visible. And then
13 hearing loss -- I'd be curious to ask that specific
14 question, how many of us have had hearing loss due to
15 the side effects of the drugs.

16 MS. CHALASANI: Raise -- at any point, you
17 can feel comfortable to raise your hand. So, thank
18 you for the question. Hearing loss?

19 FEMALE SPEAKER: Here I am. I'm a ten year
20 heart transplant patient. And, yes, the dietary needs
21 -- I mean, I can check off everything. But the
22 dietary needs are particularly challenging at the

1 moment. In fact, it nearly got in the way of my
2 joining you, because I cannot heal from diverticulitis
3 since April. And it's painful and dreadful. The
4 constipation or the diarrhea, you never know what
5 you're going to have one day to the next. But, it is
6 chronic and it gets in the way of a normal schedule,
7 and nearly interfered with my being able to come. My
8 doctors only gave me permission on Friday.

9 MS. EGGERS: I think Michael had one
10 comment.

11 MR. GARRETT: Well, when this -- I got into
12 this game as a Type 1 diabetic, so I was used to
13 watching my diet. But, most everybody that I was
14 friends with back in the early days -- the prednisone
15 therapy was quite prevalent, and everybody would blame
16 their overweight on taking all that prednisone. Of
17 course, I did have one doctor that told me that my
18 problem was an overactive fork.

19 MS. COHEN: On the lighter side -- I'm still
20 Ellen Griffith Cohen, and I'm still a kidney
21 transplant recipient. My biggest fear for infections
22 is that I am a lifelong -- not only nail biter but

1 biting the cuticles and the skin around my nails, all
2 of which is, I thought, a very good source for
3 infection. And so, one of my post-transplant changes
4 has been going for a manicure every two weeks. I
5 recommend it.

6 MS. EGGERS: I think we have one more.

7 FEMALE SPEAKER MARY JANE: Jane. I am a
8 kidney transplant, 21 years. And my biggest challenge
9 is the dietary needs, but not of those conditions up
10 there. It's the sodium intake. I struggle every day
11 to figure out what to eat when I'm not at my house.
12 The sodium intake at a restaurant -- I can't tell --
13 if I want to order a grilled chicken and then go look
14 it up online, it has so much sodium in it and I am
15 very, very sensitive to that, especially with the
16 medications that I'm on. So, for me the dietary
17 needs. And I would love to see the restaurants
18 instead of putting the fat, the calories, put the
19 sodium intake in there. Put the other stuff in there
20 that people who have transplants can choose healthier
21 options, so that we know how to eat better.

22 MS. EGGERS: Thank you, Mary Jane. Graham,

1 anything from the web?

2 MR. THOMPSON: So, we've been getting a lot
3 of stuff on the web. Thank you very much for
4 participating. A few symptoms that people have been
5 mentioning -- several people mentioned blurred vision.
6 Again, we heard about tremors and restless sleep.
7 Joint and bone pain. Damage to the lower GI and GI
8 issues. Various skin cancer issues. Losing hair. A
9 few people mentioned hearing loss.
10 Hypoparathyroidism, and in terms of depression or
11 anxiety three people mentioned that they had disease
12 reoccurrence, which may prevent them from getting
13 another transplant, which is a scary thought for them.
14 And also, people worried about having to live the rest
15 of their lives on dialysis.

16 MS. CHALASANI: There's a lot, as far as
17 lifestyle changes and management. So, please feel
18 free to expand upon all of what you've heard here, and
19 anything that we may not have gotten to in our public
20 docket. We read through all of the comments, and
21 they're all part of the public record.

22 MS. EGGERS: And, Meghana, so, I'm looking

1 at the clock. And we -- we're going to dip into the
2 break, for a -- five minutes. So, we'll shift it all
3 back. So --

4 MS. CHALASANI: Okay. Great. More time to
5 talk.

6 MS. EGGERS: I'm the one who got to make
7 those calls, and I will make that call.

8 MS. CHALASANI: So, I kind of want to ask
9 everyone in the room right now what has surprised you
10 the most about your health, post-transplant? As far
11 as, like, impacts on daily life. The most surprising.

12 MS. PROUT: It was being alive afterwards.
13 So, that's all I have to say.

14 MS. CHALASANI: Yeah.

15 MS. PROUT: I'm Jean Prout. I'm 12 years
16 out from a single lung transplant.

17 MS. CHALASANI: We have Jack --

18 MR. LENNON: I think -- so, Jack Lennon
19 again, three time kidney transplant recipient. I
20 think the thing that surprised me the most is that
21 even though you're stable, how much the consideration
22 of having a transplant comes into daily decision-

1 making. For example, you get hired on at a company
2 and they offer you additional supplemental life or
3 supplement disability. Right. I'm 28 years old.
4 Normal 28-year-old male, I don't need that, you know.
5 But, me thinking, you know what, I've been in
6 dialysis. I know what that's like. I should probably
7 get that. You know, same thing with just, you know,
8 any type of going to, you know -- I haven't been
9 feeling very well recently, should I go in and get my
10 labs checked. It's just this sort of simmering worry,
11 and then every once in a while you're like, oh, I got
12 -- I do have to make the consideration for this,
13 either for today or planning long-term.

14 MS. CHALASANI: Let me narrow the question a
15 little bit. So, what negative health effect post-
16 transplant has surprised you the most? Anyone? I
17 think we have.

18 MR. LEE: Hello. My name is Austin Lee, and
19 I've had two kidney transplants. I had one that
20 lasted 14 years, and one now that's doing great. It's
21 been six years since I had it. And they're both from
22 living donors. And negative is that -- it's kind of

1 funny, because I'm a two-year-old teacher. I work
2 with toddlers. So, getting sick. Like, you know,
3 colds and flus and -- but actually, in my first year
4 of working in childcare I really got sick a lot. I
5 worked around infants. But as time went on, I guess
6 like my immune system got better. Because I really
7 haven't had much, you know, issues with flus or colds.
8 But that's pretty much -- and it probably speaks for a
9 lot of people who have had organ transplants. It's
10 just, you know, just getting sick and your immune
11 system. But, that's pretty much it for me.

12 MS. CHALASANI: We're going to let -- Marty
13 has your --

14 MR. MARIN: Hello. My name is Marty Marin.
15 I'm a liver transplant, six and a half years ago. I
16 think the thing that surprised me the most is I do
17 have a lot of trouble with my eyesight nowadays, and
18 hearing. The good news is, however, I started off
19 with about 20 hairs on the top of my head and look at
20 this gorgeous head of hair now.

21 MS. CHALASANI: Thank you very much, Marty.
22 I do kind of want to see -- I know we have a couple of

1 folks in the room who may have received their
2 transplant as a pediatric patient. I know we have
3 Lindsey, who is currently a pediatric patient. But,
4 was anything strikingly different as far as health
5 impacts post-transplant? Do we have anyone?

6 MS. EGGERS: And if you're on the web,
7 please contribute.

8 MS. CHALASANI: Yes. On the web as well.

9 MS. EGGERS: If you're a caretaker or a
10 teenager.

11 MS. SCHWARTZ: Hi. My name is Lindsay
12 Schwartz. I have a five-year-old son who received a
13 kidney transplant when he was two and a half. So,
14 he's about three years post-transplant. And it's been
15 an incredible change in his life and our life. He was
16 born in renal failure, so he spent two and a half
17 years on peritoneal dialysis at home every night, for
18 12 hours. So, his kidney transplant has dramatically
19 changed his life -- it's given him life. And it's
20 given us parents -- it's given us our lives back.
21 It's -- there's only a very few negative things. He's
22 in kindergarten. He's there today, spending the whole

1 day at school drinking his water. He still has a
2 feeding tube to give him his medications. We're
3 trying to wean him. But it's difficult as a pediatric
4 patient, because -- I'd like to get him on pills, but
5 to get him on pills he needs to be at specific doses.
6 And we can't make the changes -- the little miniscule
7 .1 amount changes to his doses on pills.

8 So, we're kind of stuck in this no man's
9 land of wanting to push him off his feeding tube, to
10 give him even more of a normal childhood -- not at the
11 nurse's office multiple times every single day,
12 changing dressings and those kinds of things. But we
13 just aren't able to get to that place. And he's not
14 able to drink the two liters of water, you know, as a
15 five-year-old. He's doing great, but he's not there
16 yet.

17 So, it would be great if we could make some
18 changes to compounded medications or, you know, pills
19 in different dosages.

20 MS. EGGERS: Okay. Great.

21 MS. CHALASANI: We have one more comment,
22 over here.

1 MR. MIDDLEMAN: Hi. My name is Michael
2 Middleman. Three time transplant recipient, two from
3 cadaver, one from living. My first transplant was
4 when I was six. So, the things that I see as very
5 different is, one, when I was a pediatric patient --
6 that was from a cadaver -- the care in the hospital
7 and post was very different. I'm treated, I don't
8 think, as well as an adult patient as I was when I was
9 a child. I -- that's very true.

10 But I also think that afterwards sort of the
11 way my body has rebounded has been very different.
12 And then also, I think a third thing has been sort of
13 the care protocols. After my first two transplants,
14 there was a lot of restriction around -- you know,
15 wearing the mask and doing all these things
16 afterwards. And the third one was in 2001, and there
17 was like no restriction. So, no premeds before going
18 to the dentist, no wearing a mask and going to matinee
19 movies and -- you know, none of that stuff. So, the
20 restrictions have gone way down. Maybe that's also a
21 lax in care, as well.

22 MS. CHALASANI: Okay. Thank you, Michael.

1 Let's tease apart some of these daily impacts a little
2 bit more. I think we have another polling question.
3 What are the most bothersome impacts of your organ
4 transplantation on your daily life? Please choose up
5 to three impacts. A, ability to participate in or
6 perform activities; B, ability to fall asleep at
7 night; C, ability to sleep through the night; D,
8 ability to concentrate or stay focused; E, ability to
9 care for self, family and others; F, impacts on sexual
10 intimacy; G, emotional impacts; and H, other impacts
11 not mentioned.

12 Okay. So, half of you -- D, ability to
13 concentrate or stay focused. Cognitive. Okay.
14 Nearly 50 percent, ability to sleep through the night.
15 And then a little of everything else as well. Other
16 impacts not mentioned, first off. Would someone mind
17 sharing with us what those impacts might be? Anyone?
18 22 percent. No? Okay.

19 Ability to concentrate or stay focused. Can
20 someone expand on that? Is that at work? A time of
21 the day? Is there something that triggers that
22 possibly?

1 MS. JEFFERSON: First, I want to go back to
2 other impacts.

3 MS. CHALASANI: Okay.

4 MS. JEFFERSON: I think one of the impacts
5 that's not listed up there is the social aspect of
6 things. The kidney failure, the transplant --
7 invisible disease. So, people see me and they don't
8 see a person who doesn't feel well, a person who has
9 issues and can't walk that far. So, people will say
10 well, come on -- especially at work. When I changed
11 departments, they may not know my situation so they
12 don't understand why I can't walk to the other end of
13 the building. Because my legs give out or I'm tired
14 or I don't feel good. So, I think social impacts
15 would be a big one.

16 Also, if I park in the handicapped people
17 look at me funny, because I get out and they don't
18 understand why I am walking what looks to be okay, but
19 I'm really not okay. But the ability to perform
20 activities such as work -- work is an issue.
21 Sometimes I'll wake up and there will be issues from
22 the night before, where I couldn't fall asleep, or

1 just the medicine may make me feel sick, depending on
2 when I take my prednisone or different things like
3 that. So, that's an issue that I have with both of
4 those.

5 MS. CHALASANI: Great. Thank you, Nicole.
6 I think Lindsey was going to add something.

7 MS. DUQUETTE: Staying, like, concentrated
8 isn't a problem for me, because when I take tests and
9 unit tests I tend to rush. But then I try to slow
10 myself down by looking at stuff in the room, but then
11 I can't regain that focus. I just -- I don't know. I
12 kind of go off into another world. And my tremors,
13 they kind of affect my handwriting. And that affects
14 it as well.

15 MS. CHALASANI: Thank you, Lindsey.

16 MS. EGGERS: We'll have time for a few more.
17 We knew we wouldn't be able to get into all of these.
18 But this gives us a sense. And we'll probably be
19 revisiting some of these themes --

20 MS. CHALASANI: Throughout.

21 MS. EGGERS: -- in the topic too, and in the
22 afternoon.

1 MR. GLEASON: Can I just add to the question
2 on H? Something that didn't get mentioned, I'm sort
3 of surprised, that -- is the bothersome regimen of
4 taking pills on a timely basis every single day. And
5 the coordination of those pills, some of which have an
6 impact on each other.

7 MS. EGGERS: Yes, we will get into that in
8 the topic two discussion, in some depth.

9 MS. CHALASANI: Yes.

10 MS. EGGERS: I just -- I'm keeping an -- I
11 think we're going to need to go to a break.

12 MS. CHALASANI: Sara is playing bad cop
13 today.

14 MS. EGGERS: So, we'll take a couple more.
15 Yes.

16 MR. MIDDLEMAN: Hi. This is Michael again.
17 I was just talking, sorry. One thing that's been
18 particular bothersome for me, which may seem like a
19 small thing, is being on the job market. I have a lot
20 of things in my background and for a resume related to
21 kidney world and transplant world, and I get
22 questioned about it a lot. And I'm pretty sure I've

1 been discriminated against because of that, and
2 employers that look at you and say is this person
3 going to be out again for -- you know, be out for six
4 months. So, I'm -- it's always a struggle to kind of
5 -- how do you answer that and how do you talk about
6 that. I have no good answer for it, except that it's
7 happened and it's hard to deal with.

8 MS. CHALASANI: Thank you, Michael. I was
9 going to say please expand on the docket comments.
10 Like I said, we read all of them. The link is on the
11 agenda, as well as on the slides, and we will email it
12 to you guys as well. We'd love to hear a little bit
13 more detail and more insight on all of these issues.
14 We originally had a 15 minute break. Should we make
15 it --

16 MS. EGGERS: I think we can -- I think topic
17 two is just going to be building on this. So, we will
18 take a 15 minute break.

19 MS. CHALASANI: Okay.

20 MS. EGGERS: And please come back at 11:10,
21 and we'll get started promptly. Topic two panelists,
22 if you could just make your way up to the front when

1 you come back in.

2 MS. CHALASANI: Thank you, everyone.

3 MS. EGGERS: Thanks.

4 (Off the record at 10:55 a.m.)

5 (On the record at 11:11 a.m.)

6 MS. CHALASANI: I'm going to start calling
7 out people's names, if you guys don't start getting
8 seated. I memorized them during topic one. So, just
9 a couple of quick logistic reminders. I think we may
10 have some folks that may have joined us for this
11 topic. And so, if you are a patient or a caregiver
12 and you don't have a clicker, would you mind raising
13 your hand so that we can help you get a clicker? I
14 think we have one right there. Okay.

15 I would also like to remind everyone that
16 after this topic we do have lunch. But then after
17 that we have an afternoon session. And while we're
18 calling it a scientific workshop, it's -- and it's a
19 little bit more technical, there is definitely a lot
20 of interaction with the patients and the patient
21 community. So, we really encourage you guys to stay
22 for the afternoon session, if you're able to.

1 So, topic two is where we want to hear your
2 experiences with current approaches to managing your
3 condition, a little bit more specific and a little bit
4 more on the complexity than topic one. And including,
5 like, what ways are they most effective and in what
6 ways are they not effective, and any other downsides.
7 And similar to topic one, we're going to have five
8 panelists share their comments to kind of set the
9 context. So, Piper?

10 MS. BEATTY WELSH: Hi. My name is Piper
11 Beatty Welsh, and I am a two time double lung
12 transplant recipient, due to a genetic disease called
13 cystic fibrosis, or CF. Just a little bit of
14 background. CF is a recessive inherited disease that
15 really affects the entire body, but is most commonly
16 thought of in terms of the lungs and digestive
17 systems, where it causes a very thick mucus to build
18 up, leading to progressive organ damage. I was
19 diagnosed with CF in infancy, and have therefore spent
20 my entire life dealing with the realities of
21 complicated chronic illness.

22 I received my first double lung transplant

1 in 2010, at the age of 28. And my second in 2013,
2 after a brief but intense struggle with chronic
3 allograft rejection. I am currently 34, coming up on
4 three years post-transplant with my second set of
5 lungs. I am also a staff member at the cystic
6 fibrosis foundation, but I'm here today to talk about
7 my personal experience as a lung transplant recipient.

8 One of the things I would like to focus on
9 today is the interplay between my routine to protect
10 my lungs post-transplant and the rest of my body,
11 which still suffers from complications relating to CF.
12 I remember hearing a surgeon say, and we actually -- I
13 think Jeff touched on this -- but, I remember hearing
14 a surgeon say that lung transplant should not be
15 considered a cure, that it's actually trading one set
16 of problems for another. In my case, I traded one
17 part of my original disease -- the lung disease, which
18 is often fatal -- for post-transplant life. But I
19 still maintain all the other aspects of my original
20 disease.

21 Cystic fibrosis creates difficulties in
22 absorbing certain nutrients and vitamins, and can also

1 create difficulties in digestion that make it really
2 tough to maintain steady drug levels. This has been a
3 challenge for me personally, especially in relating to
4 immunosuppression drugs and particularly tacrolimus.
5 My doctors and I have tried several solutions, ranging
6 from adjusting my digestive enzyme therapy to
7 sublingual dosing of the tacrolimus, to actually
8 adding on additional drugs to try to increase and
9 stabilize the amount of the drug in my bloodstream.
10 Especially after having gone through chronic allograft
11 rejection once, I am acutely aware of the need for
12 stable immunosuppression levels. This continued CF-
13 related complication also means that my CF care center
14 team remains an integral part of my care post-
15 transplant.

16 Another struggle for me is the ongoing
17 steroid therapy required for maintaining my lung
18 transplant. Because CF impacts the pancreas, it makes
19 us naturally more susceptible to a form of diabetes
20 known as CF-related diabetes. The steroids have
21 definitely heightened the risk for me of diabetes-
22 related complications, particularly because, as

1 someone with CF, I also have to maintain a very high
2 calorie diet. This is particularly frustrating when
3 combined with ongoing steroid use, and the potential
4 for these drugs to cause things like calcium loss in
5 the bones, which is also a big concern for me as a
6 woman living with CF.

7 In an ideal treatment world, I would love to
8 see mechanisms of drug delivery that really target the
9 lungs specifically, through nebulizer or other direct
10 delivery, in order to help alleviate some of the
11 problems with systemic steroid use or poor absorption
12 issues. Additionally, working to make the post-
13 transplant routine steroid free and a concentrated
14 effort on reducing the side effects and systemic
15 damage to other systems caused by immunosuppression
16 drugs is important, not just to make post-transplant
17 life easier to manage but also to improve the overall
18 health and longevity of people post-transplant.

19 And one other issue I'd like to just touch
20 on quickly is emotional care post-transplant. We've
21 been talking a lot about that today. And the
22 importance of mental health. Managing a transplanted

1 organ means dealing with a wide variety of effects
2 from drugs and other changes in the body, and we as
3 people, not just as patients, need support and
4 attention paid to that part of the process. I was
5 fortunate enough to have a team that recognized this
6 challenge, even in patients like me who are very much
7 used to complicated medical routines and appointments.
8 I started on an antidepressant to help me manage my
9 anxiety around caring for my new organ and adjusting
10 to the new normal after surgery. In the now almost
11 three years since my second transplant, I have been
12 able to find a number of effective ways to manage this
13 additional stress, and have decreased the dose of my
14 antidepressant accordingly. However, I am extremely
15 grateful to my doctors for proactively helping me to
16 manage the emotional impact of the complicated medical
17 experience of lung transplant.

18 MS. CHALASANI: Thank you, Piper.

19 (Applause).

20 MS. CHALASANI: Dan?

21 MR. BONNER: Hi. Good morning. Again, my
22 name is Dan Bonner. I'm currently 43 years old. I'm

1 a liver transplant recipient, class of 2005. I had a
2 liver transplant due to a disease called primary
3 sclerosing cholangitis, which is basically a disease
4 where the bile ducts in the liver will continue to
5 close until the patient experiences liver failure, and
6 would eventually die without the use of transplant for
7 that condition.

8 I'm going to go a little bit off topic from
9 my scripted comments, because my scripted comments
10 echo a lot of what has been already said. So, I'm
11 going to try to incorporate other things in here from
12 a more scientific perspective, to the best of my
13 ability, in the hopes that it would add greater value.
14 But just like many others, I'm coming at this from a
15 perspective of immeasurable gratitude and humility for
16 the second chance. So, I'm sure that that's already
17 taken into consideration.

18 Immediately following my transplant, my
19 post-transplant immunosuppression include prednisone,
20 tacrolimus and cellcept. However, I had found out
21 that my liver donor was CMV positive while I was CMV
22 negative. This presented an interesting scenario,

1 because it required me to have a different medication,
2 called cyclosporine, for a hundred days after I was
3 transplanted. To the best of my knowledge, I didn't
4 think that there was any sort of negative impact to
5 cyclosporine, other than it just allowed me to
6 continue to have a CMV positive liver when I myself
7 was CMV negative. However, also in the hospital I
8 experienced a severe bout of rejection, at which time
9 I was treated with a thousand milligrams of Solu-
10 Medrol, as the initial protocol, which proved not to
11 work.

12 And then I was upgraded to a medication
13 called OKT3. OKT3 has since been removed as a
14 prescribed medication for rejection, due to its level
15 of toxicity that it presents to the patient. And just
16 to sort of give a sort of quick synopsis of how toxic
17 is it, I had met a woman in my transplant travels who
18 had rejected multiple times and they wanted to give
19 her a third round of OKT3 and she refused and passed
20 away several days later. So, the level of toxicity of
21 OKT3 was just -- is just too great, and not used
22 anymore. But what makes it sort of important for me

1 about OKT3 is when you look at ten years plus down the
2 road now for someone like me, there are studies that
3 are being done around OKT3 and the use of cyclosporine
4 that will predict things like PFC recurrence, graft
5 survival and patient survival, which is something I
6 think that at the time the medical community was
7 unaware of, of how these drugs affected not just the
8 immediacy of the situation but also the five and ten
9 year out time frames that someone like me has had the
10 benefit to live long enough to figure out.

11 So, when we're talking about drug
12 development it's interesting to me to think, you know,
13 I would like for some consideration to be given into
14 not just treating that disease or that particular
15 situation but what are the impacts five, ten years
16 down the road that we -- that may not come up in those
17 initial discussions, for that medication, but may come
18 up down the road later on. In terms of my own
19 medication treatments, though, I've been given
20 tacrolimus, cellcept, and prednisone, as I said. My
21 tac levels have been adjusted accordingly, depending
22 on my situation. I would say the biggest concern now

1 I have is cancer, like many of you. I had mentioned
2 before my EBV levels have fluctuated greatly recently,
3 resulting in an enlarged lump node in my lung, and
4 I've been being looked at for PTLD, which is post-
5 transplant lymphoproliferative disorder, which was --
6 EBV is an indicator of that. So, these are the types
7 of things that I've personally experienced that I
8 wanted to add that hopefully would have some value to
9 this.

10 And then lastly, just to talk about what I
11 think my ideal treatment would be -- my ideal
12 treatment would be one where, like many of others, I
13 don't have to take as many pills, I don't have to take
14 them every 12 hours, that I would get back some energy
15 levels that I don't currently have, I would be able to
16 spend some time in the sun and, as silly as it may
17 sound, I'd love to be able to drink socially again,
18 because as a liver transplant guy alcohol is a big no-
19 no. So, I'm looking forward to someone who can create
20 a medication that would allow me to drink socially
21 again, or make non-alcoholic gin. I would prefer
22 either one. So, thank you.

1 (Applause).

2 MS. CHALASANI: Thank you, Dan. Deborah?

3 MS. HEFFERNAN: My name is Deborah Daw
4 Heffernan, and almost to the day I'm celebrating ten
5 years with my new heart, from Massachusetts General
6 Hospital in Boston. Prior to my heart transplant, I
7 suffered nine years of heart failure following two
8 massive heart attacks, each caused by a shocking
9 spontaneous coronary artery dissection and requiring
10 open heart surgery. After almost 20 years with heart
11 disease, despite no family history, being thin, fit
12 and having perfect health habits, like all of you I'm
13 very glad to be here, in all its meanings.

14 Two disclosures. My husband is a retired
15 founding officer of a biotechnical company. Also, I
16 am the author of a book featured on the 2002 Oprah
17 show about young women having heart attacks. The next
18 book on my transplantation experience will be out in
19 about a year.

20 The FDA has asked me to focus specifically
21 on what am I doing to maintain my life with a
22 transplanted heart, and all I can think of is that

1 Emily Dickinson could have been writing about all of
2 us, and in my case definitely it's been my experience
3 that life is so astonishing it takes -- you have
4 little time for -- to do anything else. My transplant
5 cardiologist, Mark Simergrand (ph), prepared Jack and
6 me by saying you will not be restored to the health
7 you enjoyed before you got sick. You are exchanging
8 one set of problems for another.

9 While others may breeze out the door in the
10 morning, I am already preoccupied with preventing
11 rejection, infection and cancer, the heart transplant
12 graduate's main causes of illness and death -- not
13 heart disease, interestingly enough. This is the
14 paradox of cardiac transplantation. The very
15 operations, procedures and daily medications that give
16 us life also make us sick. The main culprit --
17 immunosuppressants. From life, my daily preoccupation
18 begins with the prevention of infection. Face masks
19 and hand sanitizer are with me everywhere. Every
20 cough in a crowd is a gunshot. Even a little cold can
21 become deadly. It's taken years to establish systems
22 and protocols for cooking, cleaning, socializing, and

1 basic affection. Days begin with double-checking,
2 ingesting, digesting, monitoring, managing side
3 effects of my meds. Plus, ordering, confirming and
4 sorting them. I have spent hours scheduling,
5 preparing for, enduring, and recovering from daily,
6 weekly, monthly, quarterly and annual checkups, tests
7 and horrible procedures -- all of which you know all
8 about. My life depends on these drugs and procedures
9 -- a heart transplant graduate's primary therapies.

10 But, my life also depends on
11 counterbalancing therapies that I've cobbled together
12 through time-consuming trial and error, always with
13 the permission of Mass General. My discipline begins
14 with eating well and exercising every day, even if all
15 I can do is twirl my ankles in the air from my
16 sickbed. I use supplements, psychotherapy, and body
17 therapies to help clear toxins and blockages in both
18 body and mind, and to ease contortions and pain from
19 multiple operations, as well as the meds.

20 But I've had no rejection episodes during
21 the first five years of highest rejection risk, and I
22 like to think I participated in that result. And no

1 rejection episodes during the second five years, of
2 vascular damage risk. And now I'm more than ten years
3 out, because I'm just a month later.

4 I've had to let go of many aspects of normal
5 life, including people who do not respect a fragile
6 immune system. I hope specifically for better
7 approaches to immunosuppression that target organ
8 specific response. Because I think we may be further
9 along, maybe, in that than regenerative cell biology.
10 Excuse me, generative cell biology. But, living
11 consciously is the best way I know to honor my donor,
12 clinicians, husband and family. And if you're
13 interested, I can go into more of these details during
14 a discussion period.

15 (Applause).

16 MR. LENNON: Good morning, everybody.
17 Thanks for the opportunity to participate, first of
18 all. You guys heard me in the topic one. My name is
19 Jack Lennon. And I was born with posterior urethral
20 valves, which is a blockage of the urinary tract in
21 the womb. Which causes the amniotic fluid at the time
22 the fetus's urine to back up into the bladder, up

1 through the urethras and then just sit in the kidneys,
2 until you're born. So, literally had kidney disease
3 all my life. So, not exactly sure what normal is,
4 necessarily.

5 So -- but, I received my first kidney
6 transplant at the age of seven, from my father. But,
7 after 14 years of the chronic changes from a couple of
8 rejection episodes, as well as the damage from the
9 immunosuppression meds, that kidney failed and I had
10 to go back -- I had to go on dialysis for the first
11 time. Luckily, that was a short-lived period of time,
12 and received a kidney from my mom in 2008.

13 Unfortunately, that never really took. The kidney
14 never functioned as well as what the doctors, as well
15 as myself and family, had hoped. And despite adequate
16 drug levels, via the laboratory monitoring, I came
17 down with antibody-mediated rejection. So, a little
18 bit of a cautious optimism with the medications. So,
19 that kidney transplant from mom only lasted five
20 years, as a result of that antibody-mediated
21 rejection, and I had to go on dialysis for the second
22 time, this time for a much longer period of time,

1 before receiving a perfectly matched kidney from my
2 older brother, which I am now two and a half years out
3 from and doing extremely well, knock on wood.

4 (Applause).

5 MR. LENNON: Thank you. And it better last
6 a long time. I'm running out of family members. So,
7 if I've really learned one thing from listening today,
8 as well as my own experiences, there's no such thing
9 as a simple transplant patient, and -- medically,
10 socially, emotionally, et cetera. And so trying to
11 craft a medical or treatment regimen to those
12 individual patients is extremely difficult.
13 Especially when I like to think of it in the framework
14 of what I like to call the holy trinity, which is
15 longevity -- how long the organ will last, want it to
16 maximize the life -- the health of myself, as the
17 patient, and then the quality of life associated with
18 the longevity and health, and the treatment regimens
19 that you have to undergo. So, currently, I'm on seven
20 pills, in addition to a monthly infusion called
21 belatacept, which is the main immunosuppressant, which
22 is fantastic, as it has significantly decreased the

1 worry of missing that medication dose once or twice
2 during the week or during the month, and I -- it's
3 very easy for me to make the one hour appointment
4 every month, instead of getting caught up with friends
5 and -- oh, man, I forgot my meds, I got to go back
6 home, et cetera.

7 So, you know, one of the other things I'll
8 mention that we got into in the first topic is
9 managing it as a pediatric patient, there was a lot of
10 caregivers that had to participate in my care as I
11 grew older. And my mom still nags me and calls me
12 just about every week -- have you missed any
13 medication doses this week. And I know -- thinking
14 ahead, you know, I've had three. I -- hopefully this
15 one lasts for quite a while. But I know that it may
16 not. It might not last until my time is up, per se.
17 And so the need for more kidneys -- you know, another
18 kidney transplant down the road is inevitable, and
19 having caregivers at the end of -- you know, when --
20 are you able to maintain that treatment regimen
21 yourself, and I'm sure we've all had experiences in
22 the hospital when you can't self-advocate, and you're

1 really at the mercy of the drugs and the treatments
2 and the providers who are giving you those drugs and
3 treatments.

4 And lo and behold, I have worked, now, at
5 Cincinnati Children's Hospital in the kidney
6 transplant program, and the doctors and nurses don't
7 always know what they're doing. Medicine is an art
8 and a science. And so, it is a little bit of trial
9 and error, as I'm sure we've all experienced, and so
10 the last piece -- and I think this is -- really sums
11 up kidney transplant, and all transplant really, is
12 the rosebush analysis -- or, analogy, which is, you
13 know, from the sidewalk of the casual observer, you
14 know, a rosebush is really pretty. You know, it's
15 really nice, and that's the gift of transplant. Oh,
16 you got your kidney. You look so much healthier. You
17 can do all the things -- you know, you can -- you're
18 back to normal. But, there's a whole lot of work
19 behind the scenes and a lot of thorns and a lot of
20 scrapes and scratches, that it really takes to make
21 that rosebush bloom and be successful. So, thank you.

22 MS. CHALASANI: Thanks, Jack.

1 (Applause).

2 MS. WAGER: Hi. Thanks, Jack. My name is
3 Bobbi. I'm a two time kidney transplant recipient.
4 My first transplant -- my primary -- the primary
5 disease was pyelonephritis. I had my first transplant
6 in January of 1983. Due to their protocol back then,
7 I had my spleen taken out, helping with the
8 immunosuppression. My drugs at that time just
9 consisted of imuran and prednisone.

10 However, with these medications I was in and
11 out of the hospital each year at least twice a year,
12 for acute rejection episodes. My husband -- his
13 favorite thing was to pick me up at the hospital,
14 because he wanted to see how much hair growth I had on
15 my face, did I have the acne come back, did I have the
16 buffalo hump. But, he also was not sure what person
17 he would pick up at that time, because of the mood
18 changes. So, my nickname is Sybil.

19 Okay. The second transplant -- my first
20 transplant lasted 15 ½ years. My second transplant
21 has now lasted over 18 years. My drugs -- my drug
22 treatment regimen has changed. I am still on

1 prednisone. I've added prograf and cellcept. Due to
2 the side effects of these medications, my treatment
3 regime also now include blood pressure meds -- diovan
4 and metoprolol. I take nexium for the gastro reflux
5 -- gastro esophageal reflux disease, lovaza and
6 crestor for cholesterol and triglyceride management.

7 I also take several medications on an as-
8 needed basis. Valacylovir, because I have suffered
9 several bouts of CMV, and with my spleen missing my
10 nephrologists trusts me to be able to take that
11 medication when I feel I need it. Otherwise, I end up
12 in the hospital. I also take neurontin, due to a
13 degenerative bone disease caused -- of course, we
14 blame everything on the steroids -- of my spine. My
15 new treatment regimen includes now getting an
16 injection of avastin, which is off label, in my right
17 eye due to the retinal disease.

18 The medications on my current regimen
19 totally -- today, totally help manage the most
20 significant symptoms I've experienced for transplant.
21 For instance, if I don't take my nexium I can't eat or
22 I can't swallow. If I don't get the shot of avastin

1 every four to six weeks, my eyesight in the right eye
2 becomes distorted and I'm able to drive -- I'm unable
3 to drive and carry out every day activities. My post-
4 transplant regime has changed from the first
5 transplant to the second, all dictated, as we all
6 know, by the medications. Due to the 33 years of
7 steroids, I see a retinal specialist, as you know, on
8 a regular basis, a gastroenterologist, due to treating
9 irritable bowel syndrome and GIRD, a urologist to
10 treat the increased episodes of UTI, and a
11 dermatologist.

12 Keeping a structured treatment regime has so
13 improved my ability to do specific activities in my
14 daily life. Because of this, I can continue to
15 practice as a nephrology nurse, and practice, of
16 course, a wife -- which I'm not perfect -- and a
17 mother. My current treatment regime is such a small
18 commitment to the benefits that I reap. I honestly do
19 not think there are any downsides to the current
20 treatment regimen. Sure, it does get difficult,
21 annoying and frustrating keeping up with all the
22 multiple physical appointments and the multiple

1 medications. But, reality is if I don't do it I lose
2 a kidney and I'm back on dialysis, as we all know, and
3 my quality of life would suffer. And adhering to a
4 strict treatment, to me, is easy and it's a win-win
5 situation. Because of transplant, I've been able to
6 live a life that has enabled me to dream, that I
7 thought at 23 years old I wouldn't live to middle age.

8 In my opinion, the ideal treatment for a
9 patient -- a transplant patient -- would be to take a
10 medication only once a day. And I know you all have
11 heard that. But being a nurse -- a nephrology nurse
12 in the field and working with patients in the CKD
13 realm, I see recurring patients that are losing their
14 transplants because of not taking the medication. I
15 wish there was more data -- more studies for the
16 patients that have had their transplants for over ten
17 years, because I believe that's when the noncompliance
18 or the nonadherence starts.

19 I want to thank again, as we all do, the FDA
20 for putting this together. If there was a change, I
21 would like very much that you get a drug that has, of
22 course, less side effects, but get us to where we're

1 not taking as much steroids. I don't mind taking the
2 other drugs. But the steroids over time, as we all
3 know, cause so many problems. So, thank you very
4 much.

5 (Applause).

6 MS. CHALASANI: Bobbi. I want to thank all
7 of our topic two panelists. I think you guys really
8 provided us with rich detail on the complexities of
9 your treatment regimens, and it's going to be a great
10 foundation to kick off the rest of the discussion. I
11 saw a lot of head nods. So, I think what we heard
12 here -- at least one of their stories definitely
13 resonated with all the patients and the caregivers in
14 the audience. Is that about right? Yeah. Okay.

15 I think we have a polling question. Thank
16 you. So, let's see, have you ever used any of the
17 following drug therapies to manage your organ
18 transplantation. I'm not quite as skilled as Bobbi
19 here with pronunciation. So, I'm just going to give
20 you the brief. A, calcineurin inhibitors; B,
21 glucocorticoids; C, purine antagonist; D, mammalian
22 target of rapamycin inhibitors; E, antidepressant

1 drugs; F, opioid pain medicines; G, other drug
2 therapies not mentioned; and H, I'm not taking any
3 drug therapies. You guys can check all that apply.

4 MS. EGGERS: And does anyone need a clicker?

5 MS. CHALASANI: Oh, we need one more. Okay.
6 Nearly all of you guys have taken a calcineurin
7 inhibitor. Nearly all of you guys have taken
8 glucocorticoids. 73 percent with the purine
9 antagonist. Nearly 50 percent other drug therapies
10 not mentioned. What are some of these other drug
11 therapies not mentioned? I do want to point to that
12 we do have a follow-up polling question that we'll
13 talk a little bit about the nondrug therapies, as
14 well. So, just the drug therapies. Would someone
15 mind letting us know some of the others, particularly?

16 MALE SPEAKER JAMES: Yeah, I've added
17 valacyclovir to my regimen. I've had a couple of
18 occurrences of the shingles, and I can't take the
19 vaccine, since it's a live virus, as an organ
20 recipient.

21 MS. CHALASANI: Thank you, James. Anyone
22 else? Oh, yes, Lindsey.

1 MS. LINDSEY DUQUETTE: Rituximab, pre and
2 post-transplant.

3 MS. CHALASANI: Okay. Thank you, Lindsey.

4 FEMALE SPEAKER: I have taken the valcyte --
5 the noxafil, which I guess is -- like -- I never
6 remember the big long names. So --

7 MS. CHALASANI: You're in good company.

8 FEMALE SPEAKER: And I'm trying to -- there
9 were other viral -- or, antifungals, I think, that
10 aren't mentioned.

11 MS. CHALASANI: Okay. Okay. Okay. So,
12 what are some of the biggest downsides that you guys
13 have seen with these treatments? Maybe the side
14 effects -- the most significant side effects. Nicole?

15 MS. JEFFERSON: I saw immediately after
16 transplant was the weight gain with prednisone. I
17 probably gained 40 pounds in a month. So, that was
18 the biggest one for me.

19 MS. CHALASANI: I see a lot of head nods
20 with that.

21 MS. SCHWARTZ: Hi. My son -- my five-year-
22 old -- had the kidney transplant. The biggest issue

1 we've had is the mycophenolate, the cellcept. He
2 became so neutropenic post-transplant, about three
3 months. It just kept going down, down, down, until he
4 basically had nothing left, and at that point then
5 picked up a blood infection, which then, you know,
6 sends him to a whole other set of issues. But, the
7 cellcept has given him issues since the very
8 beginning. And his team -- thankfully, they took him
9 off the cellcept, and he did pretty well without the
10 cellcept. But, it's not a long-term therapy for him.
11 So, we're back on the cellcept and it's a constant
12 issue and concern that it's not going to work.

13 MS. CHALASANI: Thank you.

14 MR. MIDDLEMAN: Cellcept, I am on it now but
15 I would urge the FDA and the folks on this panel to
16 study it more in pediatric patients. And the person
17 that just spoke, I lost my second kidney because of
18 mycophenolate. And at St. Christopher's Hospital for
19 Children, the transplant program pretty much fell
20 apart in the late nineties. I want to say almost 80
21 percent of the kids lost their livers, kidneys, hearts
22 because of mycophenolate. And particularly on the

1 hemoglobin side, and our hematocrits dropped down to,
2 like -- mine dropped to 4 and 5. So, I'm very
3 hesitant. I take it now, but for the mother who just
4 spoke I would be very hesitant -- I'll tell the FDA
5 people -- to keep your kid on mycophenolate. I don't
6 think you guys have properly tested it on pediatric
7 patients.

8 MS. CHALASANI: Thank you. Any other
9 comments?

10 MR. GLEASON: Jim Gleason. The prednisone,
11 what a great roller coaster ride that was in the
12 beginning, huh? But in our program -- I got off that
13 in three months. And as I hear some of the long-term
14 effects of that, I truly am blessed 22 years later not
15 to have any of those issues anymore. Cyclosporine was
16 the saving grace back in the early nineties,
17 especially. And so when that got toxic to the
18 kidneys, it was great to find that there were now some
19 new medications on the program they could move over to
20 -- tacrolimus. Of course, the negative of that is
21 while I thought everybody that complained about
22 diabetes -- how could that be, not everybody gets

1 diabetes -- well, guess what. Now I have diabetes for
2 the past ten years, and I understand that even better.
3 So, the negative of that is the diabetes.

4 MS. CHALASANI: Thank you. So, how many
5 folks in the room are -- have concerns about
6 effectiveness with these treatments? Is effectiveness
7 a concern? Maybe a show of hands. I've got 10 to 15,
8 for those on the web, if you can't see. Can you talk
9 to us a little about some of those concerns?

10 MS. SAMPSON: Again, my name is Leilah. And
11 maybe because I'm a newbie, I have a much different
12 perspective. I'm doing well on my immunosuppressants,
13 and prednisone. I was even on a 200 milligram taper
14 initially, after transplant, because of the thickening
15 of the wall of my urethra. And I didn't gain much
16 weight. I'm still on prednisone, and I'm nine months
17 out. And I've been on prednisone all my life, due to
18 asthma. And I tolerate it well. And besides the
19 prograf issue initially I had after transplant, that
20 dropped my hemoglobin and platelets, other than that I
21 feel like the cyclosporine and the cellcept I'm on
22 have been doing very well, and I have very minimal

1 side effects. So, while, you know, it's important to
2 hear about the negatives, I think it's also
3 encouraging for the researchers to continue to do the
4 research and hear from the patients that are doing
5 very well on these drugs.

6 MS. CHALASANI: We have -- that whole table
7 is very active.

8 MR. LEE: Thank you. Again, my name is
9 Austin Lee. I've had two kidney transplants. And I
10 just want to say for the cellcept, as far as like the
11 negative I had -- because I had only took it for maybe
12 about a month when I had my second transplant.
13 Because it gave me like leg cramps, and then, like,
14 they -- my nephrologist from Children's Hospital, she
15 automatically switched me to a medication called
16 myfortic. You guys probably heard about it. And I've
17 been doing fine on that. And actually, I mean, it was
18 kind of interesting. Because I used to take
19 cyclosporine but I take -- well, I took cyclosporine
20 with my first transplant and now I take tacrolimus, or
21 I didn't really understand that. But that was just
22 about it.

1 MS. CHALASANI: Thank you. We can take one
2 more, maybe. I think we have Kevin.

3 MR. FOWLER: Yes. This is Kevin Fowler. I
4 guess my question is not so much directed toward the
5 side effects of these medications, or effectiveness,
6 but just the general comment that there are really not
7 a lot of options available for patients and
8 physicians. So, that's my two cents. And then,
9 related to that, then, too, is that, you know, I'm on
10 a regimen of prograf for 12 years. But is that really
11 the best regimen. Would belatacept be a better
12 regimen for me at this point? The doctors really
13 don't know.

14 MS. CHALASANI: Thank you, Kevin. So, one
15 of the main topics of discussion for our scientific
16 discussion this afternoon is going to be medical
17 adherence. But, we would like to touch upon that a
18 little bit right now, with all of you. What are some
19 of the biggest challenges you guys have in
20 maintaining, you know, your adherence to some of these
21 treatments and your treatment regimen overall? Any
22 significant challenges? Oh, yes. Bobbi.

1 MS. WAGER: I think the big thing -- I don't
2 know how you guys feel about -- is taking these
3 medications at the same time every day. Especially
4 that -- the prograf. And I don't know if any of you
5 guys do it, but I stay on brand. I don't -- my doctor
6 -- I do not want generic. So, I stay on brand --
7 prograf and cellcept.

8 MS. CHALASANI: Okay. Anyone else? We have
9 Nicole and Kevin.

10 MS. JEFFERSON: One of the things that Bobbi
11 brought up about prograf and cellcept staying on brand
12 -- and this also goes into what he was discussing
13 about the mycophenolate -- I was at Baylor transplant
14 center last week in Dallas, and they brought up a good
15 point that I had never considered. And this is a
16 question, I guess, maybe for the FDA also. There was
17 one gentleman who lost his transplant after 19 years
18 because the pharmacy that he was made to go to changed
19 the vendor of the generic brand every four months.
20 Whoever had the lowest bid. So, because the generic
21 was changed -- and I almost believe that that was
22 mycophenolate, because I've noticed that once I

1 changed from cellcept to mycophenolate now my kidney
2 is 90 percent scarred. Are there -- again, I believe
3 maybe the research was not done properly with
4 mycophenolate. And what are you doing about making
5 sure that there are protocols to say you cannot
6 continue to change generic vendors to these pharmacies
7 and things like that.

8 MS. EGGERS: Well, we will -- I think you
9 are raising an excellent broader question, that is
10 very much noted, even if we can't discuss it today.
11 But bringing out your concern about the -- I'm going
12 to say the interchangeability of these medications, as
13 well as their just study, in general, and the
14 protocols for that. So, we will definitely note that
15 as a concern that you have and we had a lot of head
16 nods here. So, thank you for raising it.

17 MS. CHALASANI: Thank you, Nicole. I think
18 we have one.

19 FEMALE SPEAKER: In regards to the last
20 question, I think something -- the broader issue is
21 how much alike are generics. Because my understanding
22 was that a generic was supposed to be the exact same

1 formulation, with the same standards as the name
2 brand. But in regards to timing, I find getting it
3 coordinated with food, especially for the diabetic
4 medication, is the challenge.

5 MS. CHALASANI: Okay. Thank you. I'd like
6 to follow up with a pediatric perspective. Any
7 striking differences as far as medical adherence?

8 MR. LENNON: Yes. Yeah, actually. So, like
9 mentioned I work at Cincinnati Children's Hospital as
10 the program manager. And so, what we're finding in
11 particular is that children want to be normal. They
12 don't want to be seen as different. And so, part of
13 it is the psychological I'm different, I have to take
14 medications. The other big piece is there's no
15 immediate sensation of the medicine working, right.
16 You take a Tylenol or an ibuprofen for a headache.
17 Your, typically, headache will go away. Right. Or,
18 you take a medication and it's supposed to, you know,
19 make you feel good. There's none of that. And so by
20 the time you start feeling cruddy, to -- you know,
21 it's already too late. So, at least that's what some
22 of the stuff we found. And again, in pediatrics,

1 you're depending a lot on the caregiver to be able to
2 help manage that with the patient, while also building
3 capability within the patient to be able to manage it
4 long-term throughout transition into adulthood, and
5 long-term.

6 MS. EGGERS: Can I ask a follow-up question,
7 Jack?

8 MS. CHALASANI: Of course.

9 MS. EGGERS: Because it was raised here
10 earlier. Briefly, if you can go back to your child
11 self and say here's the one thing that I wish you knew
12 then about this, that you now know and you wish you
13 knew then. Oh, putting you on the spot for a top of
14 mind --

15 MR. LENNON: I do think -- the balance of --
16 which I now do because I've had to learn to do it, is
17 the balance of now versus future. Right. So, the
18 benefit -- again, going back to that whole -- what I
19 refer to as the holy trinity, the longevity of the
20 organ, the health that I'm able to maintain and the
21 quality of life that I have as through managing my
22 kidney transplant. There's the consideration of all

1 of that now, and then there's also the consideration I
2 have to look at in the future, five, ten -- way down
3 the road, and do I really want to -- you know, when
4 they put me on belatacept, there's no long-term
5 outcomes yet. But, in terms of my ability to adhere
6 to a once a month infusion, compared to twice month
7 meds -- or, twice daily meds -- I don't know. I mean,
8 we'll see. And that's sort of where the cautious
9 optimism and faith -- cautious faith in some of these
10 treatments and the providers providing them really
11 come into place.

12 MS. EGGERS: All right. Thanks, Jack. So,
13 I put Jack on the spot. But, the -- for those of you
14 here, and on the web and in the room, those of you
15 that have had transplants in childhood or in young
16 adulthood and have worked your way and now you're in
17 your mid-life, or -- I'll even -- you're closer to my
18 age -- and thinking back on your transition, please
19 put that in the docket. Because it's really -- it was
20 asked by a researcher who wants to really understand
21 what goes on in your head, and what you wish you would
22 have known then. So --

1 MS. CHALASANI: Definitely. Graham, do we
2 have any web comments?

3 MR. THOMPSON: So, we've been getting a lot
4 of input on the web again. So, thank you for
5 providing some inputs. On side effects, a few things
6 mentioned. Developing hernias after physical therapy,
7 developing stress fractures after taking steroids, or
8 needing hip replacement. Cataract surgery as well.
9 Problems with attention, and staying focused. Several
10 people also mentioned weight gain, side effect from
11 prednisone specifically. Also, acid reflux. Other
12 people mentioned nausea more generally. Hair loss
13 with prograf, and also diarrhea and other drug
14 interactions. Mood swings, vascular necrosis,
15 diabetes, swelling, damage over time, things like
16 that.

17 For adherence, we heard things about
18 difficulty with regular use at the proper time, with
19 coverage issues again, uncertainty over generics, and
20 a few other specific drugs were mentioned, and some
21 non-drug therapies.

22 MS. CHALASANI: Thank you, Graham. I think

1 we have time for one more comment.

2 MS. PIERCE: Thank you. I'd like to go back
3 to adherence for just a moment, and I think it relates
4 to the elephant in the room. We haven't talked about
5 cost, as yet. I've lost friends and known people that
6 have skipped doses because they can't afford to buy
7 all of them. We actually -- the Alpha-1 foundation
8 did a survey of our patients. We had a note from one
9 of our patients who indicated that Medicare had taken
10 cellcept off his list of drugs that he could have,
11 because it was not approved for lung transplant. And
12 his Blue Cross plan then went along with that. So,
13 lots of issues. And I'm sure we're going to talk
14 about it at some point today, in terms of being able
15 to pay for the drugs and the cost of insurance and
16 finding insurance and all that. But --

17 MS. CHALASANI: Thank you, Mary. I think --
18 okay, maybe one more.

19 MS. COHEN: Hi. This is Ellen Griffith
20 Cohen again. And one of the -- as I'm listening to
21 this, when I got my transplant in January -- now,
22 first of all, I should say I got it from my brother.

1 He was HLA identical to me, and I had not yet gone on
2 dialysis. It was preemptive. So, I was in great
3 shape except for my kidneys failing. You know,
4 whenever I would see something saying how is your
5 health -- great, except my EGFR is way down.

6 But, I've -- you know, one of the things we
7 talked about is the anxiety post-transplant. Now, my
8 first anxiety was that they hadn't sewed it in
9 properly, and it was going to acute reject like across
10 the room -- there it would go, you know. And it took
11 me a long time to trust that it was really sewn in
12 there. But, I -- one of the things, as we mentioned
13 several times, is this -- you know, 12 hours exactly
14 on time all the time. When I got home, I sort of
15 looked at it and I said, okay, I have all these things
16 that can freak me out and I'm going to assume -- and
17 then I cleared it with my clinic -- that this 12 hours
18 exactly on time really means actually relatively
19 exactly on time, and I really kind of target about an
20 hour of leeway. And again, I've cleared this with my
21 clinic. My labs are absolutely stable. And I'm not
22 putting the pressure on myself to do it perfectly

1 every single day.

2 I do carry -- I always carry in my purse my
3 evening meds, so that -- because my first foul-up
4 after my transplant was I went out to dinner at
5 someone's house, and then realized I hadn't -- didn't
6 have my meds with me. And I had to eat and run. But,
7 I always have my evening meds with me. I always
8 separate my prograf out on the day that I'm going to
9 do lab work, so that I don't take it with my morning
10 meds.

11 But, the terror that is put into patients
12 about compliance -- and especially once you find -- if
13 you go to the hospital, compliance goes out the window
14 because -- and that's true, by the way. And I don't
15 know whether that's in the FDA or the Medicare area.
16 But, when patients are managing a chronic disease at
17 home, whether it's dialysis, or whether it's -- there
18 are a lot of -- not -- there are ten percent of
19 patients dialyze at home. Or, whether it's post-
20 transplant -- once you go into the hospital, you lose
21 all control over your own disease. And one of the
22 things that some of us are pushing for now is that the

1 treatment needs to follow the patient into residential
2 settings. If I am doing home dialysis, I should be
3 able to do it when I go into the hospital. If I'm
4 doing my medications at home and managing my
5 medications at home, I should be able to manage them
6 when I'm in the hospital, and not have to have my care
7 affected by other people's noncompliance.

8 MS. CHALASANI: Thank you. Thank you. So,
9 both our topic two panelists and all of our topic one
10 panelists really talked about the whole management of
11 post-transplant life. And while the treatment
12 regimens played one part, we also had a lot of drug --
13 non-drug therapies mentioned as well. So, let's talk
14 about those a little. I think we have one polling
15 question, to set up the discussion. Besides the
16 therapies mentioned previously, what are you doing to
17 manage any symptoms you have experienced because of
18 your organ transplantation. A, dietary and herbal
19 supplements; B, diet modifications and behavioral
20 changes; C, complementary or alternative therapies; D,
21 physical or occupational therapy; E, exercise and
22 other physical activities; F, over-the-counter

1 products; G, other therapies not mentioned; H, I am
2 not doing or taking any therapies to treat symptoms.
3 Okay. So, we have nearly 80 percent diet
4 modifications and behavioral changes. I think we
5 touched upon that a little bit during our topic one
6 discussion. E, we have exercise and other physical
7 activities. 56 percent dietary and herbal
8 supplements, and then nearly 50 percent for over-the-
9 counter products. So --

10 MS. EGGERS: On the -- can we just -- on the
11 web, can we get?

12 MS. CHALASANI: Oh, sure.

13 MR. THOMPSON: 66 percent for dietary and
14 herbal supplements. 80 percent for diet
15 modifications. 24 percent for complementary or
16 alternative therapies, or physical therapy. 68
17 percent for exercise. 45 percent for over-the-counter
18 products, and 18 percent for others not mentioned.

19 MS. CHALASANI: Very similar.

20 MS. EGGERS: Okay. So, tracking very
21 closely.

22 MS. CHALASANI: Yeah. Very similar. So, by

1 a show of hands, how many would say that collectively
2 the non-drug therapies or lifestyle changes give you
3 as much or more overall benefit as your medications?
4 Okay. Let's count. My goodness. I'm going to say
5 that was around 15 hands. Maybe 20.

6 How many would say that your non-drug
7 therapies are important, but they can't match the
8 benefit of your medications? More hands than the
9 first one. Okay. Maybe we'll say 25 -- maybe 30.
10 Okay. How many -- one more, show of hands. Thinking
11 about all of your therapies together, how many feel
12 that you are managing your condition well right now?
13 A lot of hands. Okay. So, for you guys that have
14 raised your hands, how do you define being managed
15 well. In your definition, what does managed well
16 mean.

17 MS. EGGERS: So, just -- for the web, he's
18 out -- you're saying you're out 26 and a half years.
19 You're still living. Uh-huh. Okay.

20 FEMALE SPEAKER: I'm out 17 years, but my
21 basic parameter is the results of blood testing. When
22 I actually go into the doctor, you know, I'm the same

1 as I'm sitting here. It's only when we get those
2 blood results back that there's any kind of real
3 discussion. So --

4 MS. CHALASANI: Okay. Other folks?

5 MALE SPEAKER: Defined it as, one, not being
6 on dialysis. I don't view that as an alternative.
7 And then second, I'm working. That's how I measure
8 success.

9 MS. CHALASANI: Okay. Great.

10 MS. SAMPSON: Hi. I'm Leilah. I would say
11 a lot of trial and error. And initially, after I got
12 my transplant I was up on a treadmill like a few weeks
13 after transplant. I was in the gym. I'm like, oh,
14 I'm healthy again, I have all this energy. But then
15 I'd get my blood work back, and my creatinine would
16 spike. So, I think, you know, just even with the meds
17 and eating right and living a stress-free life, I
18 think it all plays a major role in how you view your
19 outcomes of your medications. I know that when I'm
20 eating better and I'm exercising and I'm feeling
21 better, I feel more compelled to take my medicine,
22 because I see an outcome and I see a hopeful life and

1 future for myself.

2 MS. CHALASANI: All right.

3 FEMALE SPEAKER: I think for lung
4 transplants it's, you know, your spirometries are
5 continuing to be good, or your biopsy -- there's no
6 rejection. That's -- you know, there's always bumps
7 and -- and few hospitalizations, I guess, is the
8 other.

9 MS. CHALASANI: Okay.

10 MS. EGGERS: You said acute -- okay, go
11 ahead. Acute hospitalization? Fewer. Fewer. Fewer.
12 Sure.

13 MS. CHALASANI: I think we have -- Dan, you
14 want to go first.

15 MR. BONNER: I think when we talk about
16 success, though, in terms of nontherapies, whether it
17 be exercising or meditation, the -- by and large, I
18 think that comes down to the individual. There hasn't
19 been a doctor who has come to me that has said have
20 you ever tried meditation, having you tried
21 exercising. There's just an innate desire that says I
22 want to live longer. And, you know, traditional

1 studies will say, well, if you eat right and exercise
2 then that will happen. So, I think that that's -- so,
3 when we talk about success, I think you do have
4 therapeutic success.

5 And then I think you have non-therapeutic
6 success, but I think the non-therapeutic success is
7 much more difficult to quantify or qualify, because it
8 really comes down to each individual and how much time
9 and effort they put in to do that. And I say the
10 differentiation, because I've never been -- no doctor
11 or institution has come to me and say let me put you
12 in touch with an exercise therapist, let me put you in
13 touch with a dietician, let me put you in touch with,
14 you know, a physical therapist that we think would
15 contribute to the overall longevity of your organ,
16 your health, your life, whatever it may be.

17 So, I do think that when we're talking about
18 these success factors, you -- it now becomes very
19 individualized. And I think that you have to be sort
20 of very specific to each individual, of how much time
21 and effort they put in and how much success they're
22 getting out of it.

1 MS. CHALASANI: Okay. I think we're --

2 FEMALE SPEAKER: Yes. I just wanted to say
3 that you really have to look at management under two
4 different conditions. One, I've known people who go
5 through chronic and acute rejection all the time, and
6 never ever do well. And that, to me, would be you're
7 not managing -- you know, the drugs are not managing
8 your transplant.

9 But dealing with side effects from the drugs
10 that you take, that you knew were going to happen
11 anyway, I think that's a matter of acceptance. You
12 know these things are going to happen. It's part of
13 it. And that's it. But, there's a huge difference
14 between acute and chronic rejection type things versus
15 side effects from medications.

16 MS. CHALASANI: Okay. I think, Bobbi, you
17 wanted to --

18 MS. WAGER: I have to agree with Kevin in
19 regards to -- I think we all have to define what
20 success is to us. And I -- after my first transplant,
21 I set goals. The kidney was working. I took my
22 medication. I was doing fine. But I set goals. It

1 was like, you know, I want to become a nurse. I want
2 to advocate for myself. I went to school. I think
3 stuff like that, to me, is a success. That I'm able
4 to complete the goals. But yet my health still stays
5 good. And I can work, which I couldn't before.

6 MS. CHALASANI: Okay. Let's take -- yeah.

7 MS. FELIX: Hi. My name is Latifyah Felix.
8 I'm 15 months transplanted. I think that when we talk
9 about managing -- kidney, by the way. When we talk
10 about managing, it started long before our
11 transplants. It started during the onset of our need
12 for any kind of transplant. So, I think it's
13 continuous. I think that this is where the anxiety,
14 the stressors come in. It's continuous. For those of
15 us that are kidney patients, even if a high-risk donor
16 was involved, there was still some maintenance -- some
17 management that you did in order to qualify.

18 It is quantitative in its effects on you,
19 whether you're setting personal goals to manage that.
20 Indeed, scientifically your labs will show whether or
21 not your body is in compliance. Again, keeping in
22 mind also the mindset. Although you're not being

1 referred to a dietician, maybe you should be. Because
2 we know that all together things that work good for
3 our new bodies, to maintain our old vessel. So, I
4 thank you for the opportunity to comment.

5 MS. CHALASANI: Thank you. So, I know most
6 of you guys raised your hand saying that you believe
7 that your condition is being managed well. Was there
8 anyone that believed that they're not being managed
9 well right now? Maybe what aspects of your condition
10 these therapies are not managing well, specifically.
11 Kevin?

12 MR. FOWLER: The whole point is what do we
13 really have to compare? Right. So, I mean, that
14 question is -- there has to be another category in
15 there, what's the comparison. I mean, there's
16 essentially one gold standard right now in the
17 marketplace. And unless you have other options for
18 patients and physicians, it's very difficult to answer
19 that question.

20 MS. CHALASANI: Okay. I think we have one
21 more.

22 MS. EGGERS: On the web, if you, if you can

1 comment. Often in these meetings it's the folks who
2 are pretty well managed who are able to come and
3 attend and join us in person. And at -- when we're
4 talking about things that are not well managed, we
5 draw -- we need to draw heavily from the web, from
6 those of you on the web. Or, contributions to the
7 docket. If you can share the stories of someone you
8 know who has not been well managed, or encourage them
9 to put their comments in.

10 MR. THOMPSON: I'll just add real quick that
11 we've had a -- several people on the web wondering
12 that exact question, on whether or not the webcast has
13 a difference in terms of conditions being well managed
14 or not. And several people have said that their
15 adherence issues or symptoms seem to be somewhat more
16 severe on a relative scale.

17 MS. EGGERS: Okay. Thank you. And keep
18 those comments coming.

19 MS. HEFFERNAN: May I pop in for a minute?
20 About the maintenance regime. My experience is that
21 most doctors have no clue how to take care of
22 themselves, in terms of basic health, and the medical

1 schools and that training has encouraged that. This
2 is changing, thank heavens. But when it comes to
3 you've been transplanted, this is great, we're
4 focusing on all your biochemistry reactions, the mix
5 of drugs -- time to go home. And so we go home, and
6 we're faced with pills of drugs, how do you get them
7 organized. And I think simple assistance with systems
8 would help patients tremendously. I'll never forget
9 when my husband said let's just make this card table
10 for all the drugs, and that began my system of having
11 a separate place to deal with my transplanted life.
12 And therefore, to psychologically separate my real
13 life from the life of someone who is chronically ill.

14 But, in terms of the additional weight on
15 our time of taking care of ourselves despite the
16 medications and the procedures, that's all on the
17 patient. Nothing is documented. We're out there on
18 our own. We're figuring it out. I see the most
19 terrifying things on chat rooms, and I think that this
20 is an area that needs to be developed. You're home,
21 now how do you manage it, how do you explore things
22 that will help you without hurting you, that come from

1 a complementary world.

2 MS. CHALASANI: Okay. Thank you. I think
3 we have one more here.

4 MS. COHEN: Hi. I'm Ellen Griffith Cohen,
5 again. I probably didn't get reflected in the 19
6 percent with other therapies not mentioned, because I
7 hit the button just about the time you were tabulating
8 it. But, both in the pretransplant area and in the
9 transplant area, I think -- and this doesn't go to
10 your drug development, but it goes to understanding
11 the lives of transplant patients. That chronic
12 disease is isolating.

13 Chronic disease, where you need a transplant
14 -- and especially if there's a possibility of living
15 donor transplant -- is incredibly isolating, because
16 particularly people get angry because their friends
17 say they will step up and then they don't, or their
18 families won't step up and they get mad at their
19 families. You become -- you know, every other one of
20 these things is an individual thing.

21 The fact is that maintaining a support
22 system pretransplant and post-transplant is a critical

1 therapy. It reminds me every time I am with my
2 support system that I am important. And when I get
3 low, or I think, you know, I don't want to do this
4 anymore, or whatever -- and I can do that even with my
5 transplant, because of my depression -- the reminder
6 that I am a valued member of this society and that
7 people care about me is a critical -- it's critical to
8 adherence. That you take your drugs not just because
9 of you, but because of the people who love you. My
10 support groups include online groups, but it's also my
11 church. I go to a transplant support group, and in
12 fact tomorrow night we're going to be talking about
13 spirituality and transplants. But, that whole area is
14 so critical.

15 MS. CHALASANI: Oh, thank you. I think I
16 have one more follow-up question. By a show of hands,
17 how many of you had to change or stop medication -- a
18 medication? Okay. I have around 20, 25. A few more
19 went up. Okay. Why did you have to change or stop
20 your medication?

21 MALE SPEAKER: As I said, the cyclosporine
22 initially is toxic to the kidneys. And when the

1 kidneys started showing that, we were fortunate enough
2 to have new medications. This is back in the --
3 around 2000 time frame. And so tacrolimus became the
4 switch. Yes, it's toxic to kidneys but in a different
5 way, or less so.

6 MS. CHALASANI: Okay. Thank you. One more,
7 all the way back there.

8 MR. LONGINO: Kevin Longino. I'm 12 years
9 out from a kidney transplant. I had the same issue.
10 After about six years, cyclosporine (inaudible).

11 MS. CHALASANI: Okay. Thank you. And one
12 more, and then I have a follow-up questions.

13 MR. GARRETT: Mike Garrett. I have -- you
14 know, back in the stone age it was prednisone and
15 cyclosporine and imuran, and then they got the
16 brilliant idea to switch me over to prograf and
17 cellcept. And I actually did better on the cellcept -
18 - or, the cyclosporine and imuran, but it was mostly
19 because the doctors didn't know how to prescribe the
20 prograf, and I got very toxic for about six months
21 because of too much prograf, until I finally found a
22 physician who knew what she was doing and brought the

1 levels down. And, you know, things worked out very
2 well since then.

3 MS. CHALASANI: Thank you, Michael.

4 MS. EGGERS: So, can I ask a follow-up
5 question?

6 MS. CHALASANI: Sure.

7 MS. EGGERS: Those of you who have talked
8 about your switching, or even the -- if you haven't
9 raised your hand, what goes through your mind when it
10 says -- when you hear that your drug is not working
11 the way it should be doing? What are you thinking
12 about at that moment? You hear your drug is not
13 working. If this is a hard -- if I've asked a hard
14 question, change the question around to however makes
15 sense for you.

16 MS. CHALASANI: I think we have some --

17 MR. MIDDLEMAN: Hi. This is Michael
18 Middleman again. Now that I'm an adult, and once I
19 probably turned 15, I started reading pretty much
20 every scientific publication I could on the
21 medications. Because I will never, ever trust one
22 that a physician gives me again, until I see and

1 believe the efficacy for myself, given what happened
2 with the imuran change to cellcept, as a child. So,
3 my feeling is always why change if I'm doing well.
4 Like, don't change my medications at all, and that's
5 my current doctor's thoughts, is everything is doing
6 so well, there's no need to put you on another -- a
7 different one. So, I won't do anything until I see,
8 like, proven results of it on the market.

9 MS. CHALASANI: Okay. Thank you.

10 MR. GAMALITA: I was on -- Tom Gamalita
11 (ph). Heart transplant, 2008. I was on cellcept and
12 I lost all that weight I always wanted to lose on that
13 drug, and they decided to stop it and it's there,
14 well, God, I hope there's another drug that's going to
15 work. I mean, that was the first thought with it.
16 But, one of the things I've heard here, and I feel
17 great empathy for everybody -- I'm a veterinarian, and
18 I think you need a medical degree before you go
19 through this stuff.

20 I mean, the people here that are not --
21 don't have that background, I feel for them because
22 it's such an overwhelming amount of information,

1 understanding the drugs, how they work, what they
2 work, alternative therapies. It's just a huge
3 challenge for people that don't have a sophisticated
4 level of training. And, you know, it's a lot of hard
5 work to understand that.

6 And even if you have the training, it's so
7 specific to the disease. I mean, I'm a generalist as
8 a veterinarian. But, I certainly learned a lot
9 because I had a 40 year warning that I was going to
10 have a problem. So, you know, it was, God, is there
11 another drug that will work.

12 MS. CHALASANI: All right. Thank you. I
13 think we'll take one more, maybe Lindsey. Leilah, I'm
14 so sorry.

15 MS. SAMPSON: No, no. Oh, you're fine. And
16 see, I was going to talk about something else, but now
17 to piggyback off of what he said. Actually, I was in
18 school to be a nurse anesthetist before I was
19 diagnosed with FSGS out of nowhere. And just that
20 background in microbiology and anatomy, that
21 definitely helped me as I could communicate with a lot
22 of my physicians. And I had some knowledge. And I

1 really worry about, you know, what would my life have
2 been like if I hadn't even had the small foundation
3 that I did have to understand.

4 And I find that sometimes health care
5 providers, they kind of undermine your intelligence
6 and what they think you may be able to absorb about
7 these medicines. And I would like to be more educated
8 on why specifically cellcept works the way that it
9 works, differently than prograf, just on a level that
10 a patient can understand. Because I think that will
11 also help us to be more compliant. Because instead of
12 just blindly taking medicine because someone says,
13 hey, this will work, you know, I'd like to know why,
14 specifically, and where does it work.

15 MS. CHALASANI: How about the -- I was going
16 to ask a pediatric perspective.

17 MS. EGGERS: Yes. Of course.

18 MS. CHALASANI: Okay.

19 MS. EGGERS: I was thinking the same thing.

20 MS. CHALASANI: One of our pediatric
21 spokespeople, if anyone wants to volunteer an opinion.
22 Or even the caregivers, maybe. What's running through

1 your mind, when they say that your child might have to
2 change or stop a medication. Okay.

3 MR. LENNON: So, I am maybe -- probably not
4 the only one in here who has been on cyclosporine,
5 rapamune, prograf and now belatacept. That have been
6 on the gamut. In addition to some of the other ones
7 that were mentioned. And it's -- what I've come to
8 realize, and this is how my parents trained me as part
9 of the care team, which is the -- to look at the
10 provider as an advisor of how to manage your care.
11 And so, taking what they say as their advice -- this
12 is what you should change to -- asking those
13 intelligent questions, why should I change to this,
14 what's the data, right, and then taking that back
15 thinking -- you know, reflecting on and thinking about
16 it, and then, you know, moving forward with a
17 decision, you know, with your doctor in collaboration.

18 So, I think a lot of it, you know -- I know
19 we preview the plan on all of our patients the week
20 prior coming in. And we have our standard protocols
21 of what we think people should be on, what these kids
22 should be on. And a lot of times the doctors are

1 like, man, I don't know why that's working but it's
2 working, don't rock the boat. Right. And then
3 there's other times where they're like oh, my gosh,
4 we've tried every single thing that we can possibly
5 imagine, and we still can't get it to work.

6 And so, I -- part of it, I think, is just
7 that open -- the communication between the patient and
8 the providers. I mean, it's, it's hard to hear as a
9 patient, but it's also somewhat reassuring when a
10 physician says I sort of don't know what's going on,
11 and can we try this, right, as an option. Instead of
12 dictating what's going to happen. Can we work
13 together to try to figure out a solution. So, thanks.

14 MS. CHALASANI: Thanks, Jack. Anything from
15 the web, Graham?

16 MR. THOMPSON: We've been hearing a lot of
17 very similar perspectives. Nothing else different.

18 MS. CHALASANI: Okay. Great.

19 MS. EGGERS: At this time, we're going to
20 keep moving forward. We do want to make sure to allow
21 for a few phone calls from people who aren't able to
22 join in person, and who are on the web. And so if --

1 we're going to tee up the phone. We'll open the phone
2 line for two or three callers in about five minutes.
3 And what we really like to ask -- and you guys think
4 about this too -- is what that maybe hasn't been
5 mentioned yet if you could improve treatments what
6 would that ideal treatment -- what's something about
7 treatments that would improve. So -- but, before we
8 do that we want to get a little bit of more wrap up
9 the insight into your treatment decision-making that
10 we've been talking about for the last few minutes.
11 And we have a polling question to do that. We'll move
12 to -- Graham, can you move to the next polling
13 question? Again, another long one.

14 In addition to preventing organ rejection,
15 of the factors that we have listed here which two
16 would you rank as most important to your decisions
17 about using a therapy to manage your organ
18 transplantation. So, you can choose two of the
19 following items. We understand that there are -- we
20 would need five slides to put up all the factors that
21 go into your thoughts. But, these were the ones that
22 FDA wanted to know how you might think about in

1 comparison to one another. So, of the two, A,
2 frequency of administration of the drug, such as twice
3 a day versus once a day or infusion versus; B, the
4 common side effects; C, the possibility of rare, but
5 serious side effects, Such as nerve or liver damage;
6 D, the possibility of interactions with medications
7 for other conditions that you have; E, your access to
8 this treatment -- for example, insurance coverage --
9 or, F, some other consideration that you think is
10 really critical. Okay.

11 So, the most prevalent in the room is the
12 common side effects of the treatment, followed by the
13 possibility of rare but serious side effects. And of
14 course -- and access. Which lower considerations in
15 the room of the frequency, the interactions with other
16 health conditions -- of course, that's dependent on
17 what other health conditions you have, we know.

18 On the web, what are we hearing?

19 MR. THOMPSON: Sixty-one percent say common
20 side effects. 48 percent say possibility of rare and
21 serious side effects. 17 percent say possibility of
22 interactions with medications. 69 percent say access

1 to treatment. 8 percent said other. Oh, and zero
2 percent said frequency.

3 MS. EGGERS: We have covered a lot of these
4 topics today -- I mean, already this morning. And I
5 think we'll be talking about A, the administration
6 issues -- how the drug is taken -- in the afternoon as
7 well. Let me turn to my FDA colleagues. Anything on
8 here that you would like to follow up on or ask.
9 Okay. You guys, this has been such a rich discussion
10 already. It's leaving us speechless. It takes time
11 to absorb all of this.

12 So, then, let's turn to the -- in the room,
13 here, think about, you know, as much time as we can
14 take. We're going to take the hard stop at 12:30.
15 So, you might not be able to talk about your ideal
16 therapies. But we will try to get -- wrap -- work
17 this into the afternoon, as well. But, let's take a
18 few phone calls on this. And I have to say this.
19 Operator, can we open the phone line? Can we take our
20 first caller, please?

21 MALE SPEAKER: Hi there, Vanita, you can go
22 ahead.

1 MALE SPEAKER DANNY: Hi, my name is Danny.
2 I've got a question about the gentleman who talked
3 earlier on the panel about the IV once a month. I was
4 curious about the name of it, and the long-term
5 effects.

6 MR. LENNON: Hi, Danny. This is Jack
7 talking to you. So, the once a month infusion is
8 called belatacept. And --

9 MS. EGGERS: Go ahead.

10 MR. LENNON: Good? Okay. It's also the --
11 which I believe is the sort of street name for it.
12 It's also called nulojix. And so, the side effects,
13 at least initially published -- and again, there's not
14 a whole lot of long-term data on it -- but some of the
15 effects, at least in the first year, is a higher rate
16 of rejection within the first year of post-transplant,
17 and then decreased rates of rejection post. And then
18 you get your somewhat common side effects of an
19 infusion medication, which are mostly tied around to
20 the actual infusion itself. So, you get your
21 headache. You get your swelling at the site of the
22 infusion, et cetera. And if anybody has more

1 information, chime in.

2 MS. EGGERS: I -- well, we don't have to --
3 that doesn't have to be -- the meeting was never
4 focused too much on the technical aspects of drugs.
5 So, we will let that go. I'm going to assume that we
6 -- the question was raised about infusion as a
7 question of -- that -- of exploration, for those of
8 you who have not done that as a possible alternative.
9 Is there another caller?

10 MR. THOMPSON: Phyllis, your line is open.

11 MS. FRYE: Okay. Yes. I had a -- hi, this
12 is Phyllis Frye. I'm a living donor of a recipient
13 who has survived for 16 years post-transplant.
14 Recently rejected. We did our transplant out of
15 state, up near you, at Georgetown. And had to have
16 follow-up here in North Carolina. And I'm going to
17 make a comment as to what we can do to improve
18 treatment, in terms of long-term treatment and what
19 would an ideal treatment plan consist of. I would
20 like to also add that I think we need to do more to
21 facilitate long-term across state lines, because
22 different transplant centers, for especially living

1 donor situations where we've had to go out of state
2 and those donors may live in different states or --
3 the recipient could get treatment locally, and even
4 long-term. As I said, one of the reasons my recipient
5 rejected was simply being able to get local care at a
6 local transplant center was way more difficult, simply
7 because he didn't have the transplant at that
8 institution. So, anything you could do to improve
9 treatment for recipients locally, even if they haven't
10 had the transplant locally, I think should be
11 incorporated into an ideal treatment model.

12 MS. EGGERS: Great.

13 MS. FRYE: I think that should be included.

14 MS. EGGERS: Thank you, Phyllis. And you're
15 reiterating a point that we've heard that has been
16 sort of underlying all of this, is you could have the
17 best drugs but in this case, for the organ transplant,
18 it is the overall care and your ability to access the
19 care and manage the complexity across the whole
20 complicated system you're in. So, thank you, Phyllis,
21 for that.

22 MS. FRYE: Yes. Thank you.

1 MS. EGGERS: Do we have one more caller?

2 MR. THOMPSON: We had somebody who submitted
3 a question earlier who couldn't call in. Specifically
4 about the flu shot, and wondering -- they're a senior,
5 and they're wondering if they're on immunosuppressants
6 whether or not they should get a regular flu shot, the
7 higher strength flu shot, or neither.

8 MS. EGGERS: Well, I -- so, I will just
9 reiterate that we - this is not a forum for giving out
10 medical advice. So, I -- unless my panel -- we will
11 have to leave that as a conversation between your
12 health care provider or a health care provider.

13 But, it does raise -- in each question
14 there's a point to be made, and this one raises a very
15 important point about how do you manage even very
16 simple things. I can just go and get my flu shot.
17 And you have to think a lot more about that. So,
18 we'll take that point out of the question. Any final
19 questions? We're going to continue in the afternoon.
20 Okay. So, let's come here to -- we'll hold this
21 thought, and we'll go to Theresa's question.

22 DR. MULLIN: Well, I didn't think quick

1 enough last time, when Sara asked us. But in looking
2 at the polling results, I would -- and how the common
3 side effects of treatment were -- both on the webcast
4 and here, the highest ranking in terms of most
5 important to your decision -- I wonder if our patients
6 could say more about what common side effects would
7 you most like to avoid, that maybe you have
8 experienced with your current therapy. But if that's
9 the highest ranking one, is there even among those
10 common side effects ones that are particularly high
11 ranking. You'd like to avoid, in a treatment.

12 MS. EGGERS: We're going to go to the
13 lightning round with this. So, no -- not much
14 explanation, just name out the side effects.

15 FEMALE SPEAKER: Nausea.

16 MS. EGGERS: Nausea? Okay.

17 FEMALE SPEAKER: Fatigue.

18 MS. EGGERS: Fatigue. Here

19 FEMALE SPEAKER: Tremors.

20 MS. EGGERS: What is it?

21 FEMALE SPEAKER: Tremors.

22 MS. EGGERS: Tremors. Okay. Thank you,

1 Lindsey.

2 MALE SPEAKER: Diarrhea.

3 MS. EGGERS: Huh?

4 MALE SPEAKER: Diarrhea.

5 MS. EGGERS: Diarrhea. Okay.

6 MALE SPEAKER: Damage to the organ.

7 MS. EGGERS: Damage to the organ.

8 Neurotoxicity, or damage to another organ. Okay.

9 Hey, that lightning round worked. Okay. We have one
10 more person who hasn't had much -- has a topic. So --

11 MR. RUSHACK: Yes. Thank you. My name is
12 Mikolos Rushack. I had a bilateral lung transplant
13 eight months ago, at HUP. And we have not really
14 talked too much about rejections. I experienced two
15 different types of rejections. Fortunately, very low
16 level. Both of them are avon (ph) rejections. But
17 the topic is very important, because the other option
18 is either you die or you get another organ. I like to
19 share my experience because I think it's -- it could
20 be educational for others.

21 The first one I had a so-called HLA/DSA,
22 which really means that it was an HLA type of antibody

1 rejection, which was level after the transplant, and
2 the DSA just stands for, for those who don't know,
3 donor specific antigen. And the -- if this is -- if
4 the B cells which are producing this -- they produce
5 sufficient number, then eventually these HLA
6 antibodies could attack the lung, and this potentially
7 could lead to graft failure.

8 So, I was very happy that where my
9 transplant was done the -- my doctors immediately,
10 even though my rejection level was low, immediately
11 altered the problem. And I received a treatment which
12 is off-label for FDA, but because it is a clinical
13 hospital they were able to use a drug which is
14 approved for several other uses. It is uximab (ph).
15 And this uximab was administered four times during the
16 month, weekly, and did a wonderful job. My level
17 dropped from 38,000 to 2,100 over the course of like
18 six months. And under 3,000 it means that essentially
19 you don't really have any kind of antibody level
20 rejection. But, it keeps going down.

21 So, I hope that this never comes back.
22 Because logically, I sort of read about how it works,

1 and the way how it is supposed to work that
2 essentially the immune system recognizes my donor lung
3 right now as a friend, at least from the point of
4 antibody creation. So, it would no longer generate
5 those antibodies. The B cells which have been
6 destroyed, like about 25 percent were destroyed, and
7 the new B cells apparently are not recognizing the
8 donor lung as an enemy.

9 So, what I like to do is to -- just to make
10 sure that others have access to these kind of
11 therapies. Because I have a feeling that there are so
12 many hospitals which are doing transplants and they
13 are not licensed to do this. If they are not licensed
14 to do this and any other drug is available -- I'm not
15 sure, but this targeted therapy -- I think this is
16 really the future. This is the future in cancer
17 therapy, but it is the future also dealing with these
18 kind of rejection issues.

19 The other rejection I have is like at an
20 avon, but it's a cellular level rejection and the only
21 thing we can do is monitoring. It's just a little
22 annoying that I have to go every couple of months. I

1 have to do bronchoscopy. I mean, that's a pain. If
2 somebody could invent some other ways of monitoring,
3 it would be great.

4 MS. EGGERS: Thank you.

5 MR. RUSHACK: Thank you.

6 MS. EGGERS: We've got a number of
7 discussions that we weren't able to get (inaudible)
8 about the challenges, and the opportunities
9 (inaudible), and off-label products. We will make a
10 note of that. We'll take one more quick one quick
11 one, because you haven't had too much of a chance, and
12 then we're going to stop for lunch. So --

13 MR. GHANDI: Thank you. My name is Mital
14 Ghandi. I have -- I had a transplant six and a half
15 years ago. A kidney -- sorry, I forgot where I am.
16 We're talking about kidneys and hearts and lungs.
17 It's so great to be here. So, thank you for having
18 us. But, the one other thing I did want to mention --
19 in one of your questions, I know you had several, is
20 other type of drug developments. It's not really a
21 drug development but I have Googled it to no end but
22 I'd love a portable creatinine monitor. And so, at

1 one point they are out there. And I know that the FDA
2 has something called like a waived list of different
3 tests that are, quote unquote, waived. I don't know
4 what that means. But, you know, for the consumer or
5 for me as a patient, I would love a portable
6 creatinine monitor. At one point -- not only are they
7 out there, but they wouldn't sell it to me because I
8 wasn't, you know, a health care facility, either.
9 Which I -- you know, which is ridiculous, you know
10 what I mean. I would pay for it, or if not me maybe
11 Blue Cross Blue Shield would pay for it. But, that's
12 something that would definitely help kidney patients,
13 at least.

14 MS. EGGERS: All right. So, we're ending on
15 a great point. And we are going to end for lunch.
16 Renata, please.

17 DR. ALBRECHT: Maybe you were going to say
18 this, Sara, but even though the morning session is
19 ending I think just to echo what Dr. Cox said during
20 the introductory comments, we seriously hope that
21 everybody can stay for the afternoon scientific
22 session, and we've asked Sara and Meghana if even

1 during the afternoon we have an interactive dialogue.
2 Because I think all of us here at the table, as well
3 as the presenters for the afternoon sessions, really
4 are very, very interested in hearing your comments.
5 They've just been invaluable. You've brought up
6 issues that probably in the back of our minds we knew
7 were there, but you've brought them to the forefront.
8 And for those of you who are willing to stay the rest
9 of the afternoon, both here in the room and on the
10 web, we really welcome you to do so. So, thank you.

11 MS. EGGERS: Great. And with that, we will
12 break for lunch and we'll ask you to be back at around
13 -- it's 1:15. 1:15.

14 (Off the record at 12:38 p.m.)

15 (On the record at 1:23 p.m.)

16 MS. EGGERS: Everyone, we're going to get
17 started now. You can keep eating. In fact, I will be
18 eating as well. It's a short lunch break. And
19 please, another reminder, take bio breaks as you need
20 them. This is a very informal discussion and format
21 here. But, I'm going to turn it over to Ozlem to give
22 a preface to our afternoon's discussion.

1 DR. BELEN: Hello, everyone. Welcome to the
2 afternoon scientific session of the public meeting on
3 patient-focused drug development, which will
4 concentrate on medication adherence and experience
5 with intervention.

6 We want to thank all of the patients, their
7 representatives and afternoon session presenters for
8 their time and effort. We have a very diverse group
9 of presenters today from various backgrounds, and they
10 are very excited about that. The afternoon scientific
11 session will be made up of two sections, with four
12 presenters in each one. And the first session will
13 focus on causes of late allograft loss, and the impact
14 of nonadherence, definitions, terms and background.

15 And the session -- second session will focus
16 on interventions to mitigate on nonadherence. There
17 will be a panel discussion after each session, with a
18 break between the two sessions. And we welcome
19 interactions with the audience during the panel
20 discussion.

21 Our first speaker will be Dr. Peter
22 Nickerson. And he's going to present an overview of

1 late allograft outcomes and risk factors for premature
2 graft loss.

3 DR. NICKERSON: Thank you very much. I want
4 to thank the FDA for a chance to come and to share our
5 -- some of our research that we've been doing. And I
6 want to thank you. I've really enjoyed this morning,
7 hearing the patients' perspective, hearing what are
8 some of the keys issues that you're dealing with, and,
9 in fact, many of the ones that you're dealing with are
10 some of the ones that we're trying to solve. So,
11 again, I want to thank you for your input. And we
12 hope for this afternoon -- I think the panel is
13 looking forward to ongoing input from you and help
14 guiding us in some of our thinking.

15 So, I am going to focus on late allograft
16 outcomes, and what we've been learning. In terms of
17 disclosures, I do have some consulting relationship
18 with Novartis and Astellas. I won't be discussing any
19 off-label drugs.

20 You've seen this slide before, but
21 essentially what it's showing us is over the last
22 decade we've been using a combination of therapies in

1 our immunosuppression. Induction therapy, with T-cell
2 depleting therapies, has become the dominant approach
3 -- about 60 percent of our patients are receiving this
4 in our centers. Calcineurin inhibitors -- tacrolimus
5 has become the dominant CNI that we're using. In
6 terms of anti-metabolite, mycophenolate, and about 90
7 percent of our patients receiving mycophenolate. mTOR
8 inhibitors, rapamycin, for example, had a bit of a
9 presence back in 2003 but it's diminished
10 subsequently. And about two-thirds of programs are
11 trying to go steroid-free, depending upon what type of
12 patient they're dealing with.

13 So, this is where we've been for the last
14 decade, and we really have nothing new to offer very
15 much going forward at this point, in terms of what
16 combinations we have to offer to patients. So, one of
17 the questions is, well, how are patients doing
18 overall. And this is my program in Canada, where we
19 have almost a decade's worth of patients here -- 500
20 patients that we followed. We can see that half are
21 from deceased donor transplants, and half are from
22 living donor transplants. None of these patients had

1 donor specific antibodies pretransplant. We ruled
2 that out with a cross match. And we were seeing acute
3 rejection rates in the first year of about 11 percent.
4 And I think this is pretty typical of most programs
5 nowadays. And when we do death-censored graph
6 survival, at one year 99 percent of our kidneys are
7 surviving and at five years 96 percent of our kidneys
8 are still functioning. So, again, I think this is
9 fairly typical data that are coming from most centers
10 over the last decade.

11 But, what we are seeing is that patients are
12 losing their kidneys or developing dysfunction in
13 their kidneys beyond those first few years. And this
14 is a long-term follow-up in this cohort, where we've
15 looked out as far as 15 years post-transplant. And we
16 actually see three-quarters of our patients -- 75
17 percent -- are actually having very stable function.
18 They're doing well on their immunosuppression. But
19 the other 24 percent have been developing some
20 problems. And I'm going to deal with a few of these
21 causes.

22 Eleven percent are other causes, and those other

1 causes are recurring kidney disease. So, one of the
2 common things we see is recurrent IgA nephropathy in
3 the kidney. We see some isolated T-cell mediated
4 rejections late, in about 2 percent of our patients.
5 IFTA is another way of saying scarring or fibrosis in
6 the kidney. We see that in about 1.6 percent.
7 Infection in the kidney caused by a virus called BK
8 virus, leading to kidney damage -- .4 percent of our
9 patients. And then there's a smattering of others.

10 But the largest thing we've been seeing is
11 that about 13 percent of our patients are developing
12 donor specific antibodies against the mismatched
13 antigens in the donor kidney at some point post-
14 transplant. 4 percent of the time this is showing up
15 with an acute rejection. So, this is graft
16 dysfunction, and we detect an antibody in the blood
17 against the donor. And 9 percent of the time this is
18 occurring subclinically. The kidney is functioning
19 fine, but we find that there is an antibody in the
20 blood when we screen the blood. And these patients
21 subsequently go on to develop dysfunction at some
22 point down the road.

1 We do see death with function. We have 10
2 percent of our cohort in this study that had died with
3 a functioning graft, and most of those patients -- 9
4 percent of them -- had died with a stable functioning
5 graft. Now, we expect and our goal is death with
6 function. We want you to live the rest of your life
7 with a functioning graft. What we don't want is
8 premature death with a functioning graft, and that is
9 some of the issues that we'll talk a little bit about
10 later.

11 In terms of the incidence of donor specific
12 antibodies post-transplant, in our program what we see
13 is that about two percent of our patients have
14 developed a donor specific antibody by a year post-
15 transplant, and by 12 years post about a quarter of
16 the patients have developed this antibody. Now,
17 there's other groups that have shown higher rates --
18 20 percent in the first year and 5 percent per year
19 thereafter. But again, there is some discrepancies
20 here, I think, in how people are defining these
21 antibodies using the diagnostic tools that we have.
22 And I'm not going to go into any deeper detail in

1 that, just to say that the true incidence is probably
2 somewhere between these ranges.

3 In terms of what are the risk factors for
4 developing an antibody after the transplant, it turns
5 out how mismatched you are is one of the driving
6 factors. When we first did transplants -- and this is
7 one of the first transplants in the U.S., done in 1955
8 at the Brigham and Women's Hospital, where they had
9 identical twin transplants, we didn't need any drugs.
10 These were truly identical genetically, at all genes,
11 and so you don't need immunosuppression when you're
12 HLA identical.

13 What we've learned from the UNOS database,
14 even into 2004, was that if you are mismatched at the
15 class 2 region, HLA DR, you're at a higher risk of
16 having graft failure late post-transplant. So, we
17 know that the better you're matched with your donor
18 the better you'll do. The other thing that we've been
19 learning about these antibodies when they're forming
20 is that they're largely against what are called HLA
21 class 2 molecules, the DR or DQ molecule. And HLA
22 class 1 mismatching doesn't seem to dry de novo DSA

1 formation quite so much.

2 The other thing we found out was that T-cell
3 mediated rejection -- so, a cellular rejection early
4 post-transplantation, if you have this kind of a
5 rejection, it seems to put you at higher risk for
6 subsequently developing an antibody somewhere down the
7 line. And that may just be relating to the fact that
8 you're allowing the immune system to turn on, and at
9 some point it turns on enough that it allows an
10 antibody to be generated.

11 And many groups around the world now have
12 shown this association. So, we were showing this back
13 in 2012 in Canada. Groups in Europe, Japan, and in
14 the U.S. have also found this relationship -- that
15 early cellular inflammation in the graft can lead to
16 the subsequent development of these antibodies.

17 One of the things that we've also been
18 trying to do, and I think it's related to a lot of
19 what we've been hearing, is that we want to try and
20 minimize our drug immunosuppression. We want to try
21 and reduce it, so that we can reduce our side effects.
22 So, this was a study that was funded by the NIH. It

1 was a multicenter study in the U.S. and Canada, where
2 we had patients enrolled who had receiving living
3 donor transplants. We made sure that absolutely at
4 the time of transplant they had no evidence of any
5 memory in their immune system towards the donor. So,
6 this is truly going into what we call a naïve immune
7 system. We gave them what is considered standard of
8 care, in terms of immunosuppression. They had thymo
9 as an induction therapy, and then received tacrolimus,
10 cellcept and prednisone. And for the first six
11 months, these patients had absolutely no acute
12 rejection. We did a biopsy at six months to look in
13 the graft to make sure that the kidney was actually
14 doing fine, and the histology here was completely
15 normal. And we tested these patients for antibodies,
16 to make sure that their immune system hadn't started
17 developing an antibody against the mismatched
18 antigens.

19 And then we randomized the patients into
20 coming off of their cellcept -- or, sorry, their
21 tacrolimus over about a three month period. So, we
22 did a slow taper, watching them very closely to see

1 whether they were going to develop rejection or not.
2 And what we found was that as we started withdrawing
3 the tacrolimus, we started having some acute cellular
4 rejections and we started developing some donor
5 specific antibodies.

6 And this was occurring frequently enough
7 that the DSMB, the drug safety monitoring board of
8 this clinical trial, halted the trial. We were
9 supposed to enroll well over 300 patients into this
10 trial, and they halted it after 21 patients, saying
11 this is too frequent an event, you cannot continue
12 this trial. It's not -- we don't feel it's safe to do
13 so. And what that taught us was that just because
14 you're doing well on the immunosuppression that you're
15 on doesn't mean that reducing the immunosuppression is
16 necessarily a safe thing to do. And that's a major
17 message that the community had to learn. And I think
18 -- because we see patients in our clinic and we say,
19 you know, you're doing quite well, why don't we try
20 lowering your immunosuppression a little bit. And I
21 think that's a slippery slope that we can get into,
22 thinking that you're doing well and all of a sudden we

1 get below that level and we see the immune system is
2 capable of mounting a response and getting activated.
3 And that's not what we want to have happen.

4 We look at nonadherence, and we found that
5 this was a major risk factor for developing
6 antibodies. And so, in patients who had reported to
7 us that they had been missing drugs -- that their rate
8 of developing antibodies actually was about 72 percent
9 at 12 years, compared to only 19 percent in patients
10 who were taking their medications as they were being
11 prescribed. So, this is a major risk factor that we
12 had identified.

13 And the other question is well, when does
14 nonadherence occur. And this was an interesting study
15 out of Minnesota, where they had 195 patients start
16 using what are called medication event monitoring
17 systems. So, in the pill cap bottle there was a
18 little microchip, and a time and date stamps when you
19 open the bottle and when you presumably, then, have
20 taken your medication. And this was an informed
21 consent study. They told patients we're doing this to
22 see how well you're taking your medication. And what

1 turned out to be true is that 22 percent of the
2 patients had -- were starting to miss 7 percent or
3 more of their drug doses by two months post-
4 transplant. So, nonadherence and missing drug
5 medication is not something that happens years after
6 the transplant. It actually starts actually early
7 post-transplant. And I think this just tells us a
8 couple of things.

9 One, that missing your drug is a very -- is
10 enmeshed in a very complex world. You're living your
11 life, you're trying to remember to take your
12 medication -- we heard about that earlier -- and life,
13 I think, gets in the way. And it's one of the harder
14 things, and we're going to talk a lot about how we can
15 help try and avoid this.

16 But, what this translated into for these
17 patients was that they started having late rejections
18 -- so, a year to two years later, after the transplant
19 they were having more acute rejections in their
20 transplant. And by three to five years post-
21 transplant, they were starting to lose their grafts
22 more frequently than those patients that were adhering

1 with their medication regime.

2 When we put this all together in a
3 multivariate analysis, where we're trying to look at
4 what are the independent predictors of risk for
5 forming these antibodies against the graft post-
6 transplant, what we found for antibodies that -- HLA
7 DR was that it was nonadherence, how mismatched you
8 were to your donor, and if you had these early
9 cellular rejections preceding the development of
10 antibody. For HLA DQ antibodies, again, it was
11 nonadherence, how much you were mismatched to your
12 donor for HLA, and the recipient age. And what the
13 recipient age here was was that the younger the age,
14 the more likely you were to form these antibodies.
15 And this was independent of nonadherence, because a
16 lot of times younger individuals are always being said
17 well, they -- they're more likely to miss their drugs.
18 That's got nothing to do with their adherence or
19 nonadherence. It's got to do with their younger age.
20 At a younger age, you probably have a more robust
21 immune system and therefore you're more likely to
22 respond to mismatched antigens.

1 When we looked at what was going on when
2 these antibodies were formed -- and I'm not going to
3 drag you through a lot of this in detail, because it's
4 going to get into a lot of what are called histologic
5 grading systems -- but suffice it to say that 76
6 percent or three-quarters of our patients that were
7 forming these antibodies in their blood actually had
8 histologic evidence of rejection in their grafts. So,
9 there was a good correlation between the detection of
10 the antibody and evidence of antibody-mediated
11 rejection inside the graft. There was also evidence
12 in these patients of having T-cell mediated rejection,
13 concurrently. Only 18 percent had no evidence of
14 rejection. So, just because you have an antibody
15 doesn't always mean that you have rejection. But
16 certainly, the majority did. And we started to see
17 that there was some scarring also in these kidneys by
18 the time that we were doing these biopsies. And we
19 think that that was probably related to the immune
20 inflammation going on inside these grafts.

21 Once they form these antibodies, if we look at
22 time zero as the time we first detect these

1 antibodies, if you started out having what's called
2 the subclinical rejection, where the antibody was
3 there but your graft was functioning fine, it took
4 about eight years for half the patients to lose their
5 grafts. And if you had a clinical onset of rejection
6 at the time that antibody first showed up, it took
7 about three and a half years before you would lose
8 your graft. So, this wasn't a sudden process of
9 losing your graft. But, there was a slow progression
10 to graft loss, once these antibodies were forming, in
11 a fair number of these patients.

12 When we looked at what's the strongest
13 predictor of fibrosis and scarring inside the filters
14 of the kidney, we saw that it was the formation of
15 these antibodies. And when we looked at what
16 predicted whether or not you formed scarring in the
17 interstitial compartment, in the tubules of the
18 kidney, we found that that was related to early
19 cellular rejection and, again, to nonadherence. So,
20 again, thinking that nonadherence was leading to
21 inflammation inside the graft.

22 So, this brings me to the summary slide,

1 which is when we do a transplant -- and I'm sorry I
2 don't have a -- well, I guess I do have a pointer --
3 when we do a transplant there's a lot of factors that
4 are going into how long that graft is going to last,
5 or whether or not our patient is ultimately going to
6 pass away with either -- hopefully at a natural
7 lifetime, but we know that premature graft loss can
8 lead to premature death.

9 Scarring inside the graft largely relates to
10 a number of different things, but one of them is
11 certainly rejection -- cellular rejection or antibody-
12 mediated rejection. And the antibody-mediated
13 rejection is preceded by the formation of these
14 antibodies. And the degree of mismatching between the
15 donor and the recipient is really what's driving the
16 immune system to go forward. We try to counteract
17 that by giving immunosuppression, but the
18 immunosuppression itself has some toxicity, as we've
19 been talking about, and it has side effects that put
20 you at increased risk for metabolic problems, like
21 diabetes, infection or tumor. And we can have
22 recurrent disease or infection in the graft, and we

1 have also the comorbidities -- the illnesses that
2 everybody has prior to developing their end organ
3 failure that can be contributing to the outcomes. We
4 know that nonadherence acts, as our inadvertent
5 minimization of immunosuppression, can lead to
6 acceleration of the immune response towards the graft.
7 And so this is why we've been focusing a lot on
8 nonadherence and minimization -- avoiding minimization
9 inappropriately.

10 What are the keys to the future? Well, I
11 think one of the keys is for us to think about how can
12 we match better. When we have an organ available, how
13 we can dial in tissue matching beyond what we're
14 currently doing now, to try and -- if we were to do
15 that, it would decrease the drive for this rejection
16 response, which would mean that we could use less
17 drug. That's one strategy going forward.

18 The other key is how do we actually
19 understand better what is nonadherence, what leads to
20 nonadherence, and how do we help the patient avoid
21 nonadherence.

22 And then the third thing is we need new

1 drugs that have been immunosuppressive profiles with
2 less drug toxicities and side effects, as we've been
3 discussing already today. And with that I'm going to
4 stop. Thank you very much.

5 (Applause).

6 DR. NICKERSON: Our next speaker is Dr. Rita
7 Alloway, who is a research professor of medicine and
8 director of transplant clinical research at the
9 University of Cincinnati. Rita.

10 DR. ALLOWAY: Thank you. First, I would
11 like to take the opportunity to truly thank members of
12 the FDA and the patient community on behalf of the
13 transplant professionals, for the spirit in which you
14 have come today, in allowing us to better recognize
15 the issues that are very, very important to you. And
16 even though we know it, it helps to hear it yet again.
17 I am going to lead in the next discussion in terms of
18 talking about the aspects of nonadherence, focusing on
19 definitions and identification, and also looking at
20 the detection and risk factors.

21 In terms of financial disclosures, within
22 the last 12 months my institution has received several

1 clinical research grants from a variety of sponsors of
2 a variety of studies in transplantation. I'm on the
3 advisory board for Genzyme-Sanofi and on the speaker
4 bureau for Veloxis and Sanofi. This presentation does
5 not include discussion of off-label or investigational
6 use of any drugs.

7 So, the objectives I want to focus on today
8 is to differentiate between medication nonadherence
9 and compliance. I want to identify risk factors for
10 nonadherence in solid organ transplant recipients, and
11 I want to describe the measures to quantitate
12 medication nonadherence. As we all know, medication
13 nonadherence is an age-old problem. Hippocrates was
14 actually credited with a statement in 500 B.C., "Keep
15 watch also on the fault of patients which makes them
16 lie about taking things prescribed." And as not to
17 offend anybody's religious beliefs, I might want to
18 offer -- this may -- noncompliance may have actually
19 started with Adam and Eve, when she took the bite of
20 the apple. But, we won't go there.

21 C. Everett Koop in 1985 went a little step
22 forward, in basically trying to explain the

1 variability that we see in drug responses. Why does
2 the drugs not work the same in all patients? And
3 basically, he said "Drugs don't work if people don't
4 take them."

5 Now, I think that typically nonadherence,
6 especially when we describe this to you as patients,
7 sounds like a very negative connotation. But, I want
8 us to let down those barriers and encourage you to
9 believe that we understand why you are nonadherent
10 sometimes. However, we are still here to try to help
11 you and hopefully develop things in the future that
12 will improve this. And I think what's evident in
13 transplantation is that we can no longer accept the
14 status quo of any nonadherence that is occurring.

15 And to follow up with one of Dr. Nickerson's
16 quotes, as it -- as he has said many times before, is
17 our first shot is our best shot for transplant
18 success. I know many of you here today have talked
19 about having the beautiful medical miracle of multiple
20 transplants. But really, our first shot is our best
21 shot. For biologic reasons, as he discussed, with the
22 formation of antibodies, to the additional

1 comorbidities that come as we begin to add on the
2 stronger immunosuppressants that you take with each
3 transplant. Unfortunately, despite millions of
4 investments -- of dollars in investments, we don't
5 have a magic drug or procedure to render adherence
6 irrelevant that is currently on the horizon. So, what
7 are we going to do for the next generation of
8 transplant recipients?

9 And hopefully, adherence does not continue
10 to be neglected in the therapeutic process, and -- to
11 such an extent that federal mandates may be necessary
12 to properly resource adherence and symptoms. We want
13 to provide the resources to facilitate good medication
14 adherence.

15 Now, there are a variety of terms used to
16 describe taking your medications appropriately. Two
17 of the most common terms are medication adherence and
18 medication compliance. Medication adherence is the
19 extent to which a patient takes medications as
20 prescribed by the health care provider, while
21 compliance is described as more of a passive act of
22 the patient following the provider's orders.

1 In a 2012 publication in the British Journal
2 of Clinical Pharmacology, they have a really good
3 summary article about the taxonomy and definitions of
4 medication nonadherence. And while they fundamentally
5 believe that these two terms are interchangeable, they
6 feel like compliance focuses too much of a passive act
7 of the patient, basically following specific
8 directions that the provider may have given to them,
9 while medication adherence connotes a more
10 collaborative approach, with the patients and the
11 health care providers. And hence, the words
12 medication adherence have now become kind of our go-to
13 terms, at least as present to discuss this concept.

14 And medication adherence is a behavioral
15 process that is influenced by many, many factors, many
16 of which we've heard today. It assumes that the
17 patient has knowledge, motivation, skills and
18 resources to follow the health care provider's
19 prescription. Medication nonadherence can fall in two
20 different categories. There can be intentional
21 medication nonadherence, which is basically an active
22 process by which the patient chooses to deviate from a

1 treatment regimen, or unintentional medical
2 nonadherence, which is more of a passive process where
3 patients may be careless or forget about adhering to
4 their treatment regimen.

5 Now, the World Health Organization defined
6 five dimensions of adherence, and these dimensions
7 included health system or health care team factors,
8 social or economic factors, condition or comorbid
9 disease factors, therapeutic or medication factors,
10 and also patient-related factors.

11 Our next speaker, Mary Amanda Dew, has
12 basically published in 2007 a meta-analysis, which
13 basically reviewed the literature that was available
14 at that time, to look at the specific factors that had
15 been reported in transplant recipients and categorize
16 them in these dimensions. In terms of the social
17 economic factors, younger patients, male gender, non-
18 Caucasian, non-U.S. residents, poor social support,
19 poor transportation and literacy were common factors
20 that were limitations in terms of the social and
21 economic factors.

22 In terms of the therapy or the

1 immunosuppressive factors, complex medication
2 regimens, higher medication toxicity -- as we've
3 clearly heard -- lack of medication education systems,
4 and lack of pillbox or reminder systems were
5 therapeutic-related factors that are common in
6 transplant recipients.

7 Patient-related factors were that a history
8 of nonadherence tended to predict the future
9 nonadherence with the immunosuppressive regimens.
10 Adolescence, psychological disorders -- as many have
11 discussed today, related to depression -- cognitive
12 impairment, substance abuse and negative beliefs of
13 the medications were contributory factors to
14 nonadherence.

15 Condition-related are basically high
16 symptoms of distress. And I think, again, it's a
17 common theme that we've heard today. The new disease
18 that you have of immunosuppression is a stressful
19 disease. And it's something that you must manage.
20 Also, we heard loud and clear development of new onset
21 diabetes, or basically diabetes that occurs in you
22 after you're transplanted that you did not have before

1 transplant. And also, your increased time post-
2 transplant.

3 Health care system factors, such as medication
4 costs, poor access to medication, poor aftercare
5 planning, poor physician patient relationship, and
6 poor physician communication again related to the
7 health care system and health care team factors that
8 led to nonadherence.

9 So, when you -- any time you do a risk
10 assessment analysis, you want to look at all these
11 figures and -- factors, and attempt to differentiate
12 which of these factors are modifiable and which ones
13 are not. Any of these factors in which are
14 modifiable, we want to try to develop a system
15 approach to address these.

16 However, as we're focused today on patient
17 drug development, you have to understand that for us
18 to really have an impact on drug development from an
19 adherence perspective, we've got to be able to measure
20 at least pharmacoadherence -- your adherence to your
21 medication -- in a proper way. When you attempt to
22 measure pharmacoadherence, you have objective

1 measures, which may be direct and provide evidence
2 that medication has actually been taken and consumed.
3 Examples of that are actually direct observation, and
4 we have one drug available in transplantation where we
5 do that routinely.

6 We have indirect measures of adherence, such
7 as providing evidence suggesting that medication is
8 being consumed or taken, such as pill counts,
9 tacrolimus drug levels, pharmacy refill records,
10 medication possession ratio, and then lastly,
11 subjective measures, which provide testimony that the
12 medication has or has not been taken, often by self-
13 reports or assessment of others. So, in terms of
14 direct observations this is -- basically has the
15 advantage of being objective, highly specific and non-
16 invasive. However, there are disadvantages.
17 Feasibility issues, they're very labor intensive,
18 they're not practical, they may be expensive, and
19 they're not actually an option for all transplant
20 recipients.

21 Drug concentration monitoring, which we are
22 very fortunate in transplantation, really since the

1 development of calcineurin inhibitors, to have drug
2 concentration monitoring available to us. The
3 advantages of this are its objective, it's part of our
4 standard of care, and direct assessments of whether
5 the patient has taken the medication, at least during
6 that short period of time, is available for us to
7 review.

8 Disadvantages are that this is really just a
9 snapshot of the behavior of what's going on as we look
10 at these levels. And unfortunately, it can be
11 affected by a variety of factors other than
12 pharmacoadherence, such as the way you metabolize or
13 get rid of a drug, a drug-drug interaction, a drug-
14 food interaction, and poor absorption. And I think
15 that historically, before the broader understanding
16 about all of the factors that impact drug level
17 monitoring, we tended to maybe, quote unquote, assign
18 nonadherence to a lot of the variability that we saw
19 which may be attributable to other factors. And even
20 though it's a very, very good marker and we can
21 understand if the drug is in your system, there are a
22 lot of other factors that we have to consider. It's

1 also costly, and it's an invasive test.

2 However, some more novel approaches have
3 recently been introduced to look at the tacrolimus
4 level variability, instead of just a single snapshot.
5 And without going into the complexities of the study,
6 basically patients that had a higher tacrolimus level
7 variability over time, as measured here by standard
8 deviations, basically were associated with negative
9 risk factors or negative outcomes, such as late acute
10 rejection, transplant glomerulopathy, which is a
11 negative biopsy finding that's previously been
12 described, or total graft loss. And even when we
13 excluded death with function, variability that was
14 associated in the tacrolimus levels that we monitored
15 still predicted these negative long-term outcomes.

16 Another form of monitoring is actually
17 electronic monitoring. It does have advantages of
18 being objective. It can indicate the date and time a
19 bottle or pill box has been opened, providing you a
20 real-time tracker. With this specific information, it
21 also can detect poor pharmacoadherence with the dosing
22 schedule. So, for example, you may do very well with

1 your morning dose but very poorly with your evening
2 dose. And it allows us to get an idea of what is
3 working and what isn't working in regards to your
4 medication regimen.

5 The disadvantages are cost, among other
6 here, and basically it assumes that medications that
7 are removed from the bottle are actually taken.
8 Strategies to impact nonadherence have been
9 incorporated into some recent publications, again
10 focusing on the electronic medication monitor -- the
11 MEMS system that Dr. Nickerson previously described.
12 So, for sake of time I'm going to skip over this.

13 One of the other measures that we have of
14 medication adherence are refill or pharmacy records.
15 When we actually take the records from the pharmacy of
16 the number that was dispensed, the date and time that
17 was dispensed, and the dosage you may be taking to
18 provide objective standardized data to identify
19 patients who may not be adherent, the disadvantages of
20 these systems are possible misinterpretation of the
21 use when making dose changes, which are very common in
22 transplantation, as you know, and that's one of the

1 real limits -- especially with tacrolimus -- of us
2 effectively using these records. It assumes that
3 prescriptions are filled or actually taken. It
4 assumes that all sources of medication are captured.
5 And that there is increased complexity when there is
6 using multiple pharmacy records.

7 This data has actually been translated to a
8 medication possession ratio or proportion of days
9 covered, and basically used this formulas to estimate
10 the adherence to chronic medication. Now, what is
11 very frequently brought up in transplantation is while
12 we tell you you must be a hundred percent compliant
13 all the time, we really don't know what the optimal
14 medication possession ratio is for any of our known
15 immunosuppressants to date. And then there are self-
16 reports, which I'm sure many of you have been asked to
17 fill these out. And these can be, unfortunately,
18 quick and inexpensive but unreliable. But if you
19 think that the self-reports are unreliable, you should
20 even see how worse reliable the clinician reports are
21 that we provide. And we may think it's simple, quick
22 and inexpensive, but it is highly inaccurate.

1 So, in summary, these -- an article --
2 chapter published recently in Clinical Transplants, by
3 Dr. Tiffany Kaiser (ph), summarizes these methods to
4 monitor immunosuppression and focuses on many other
5 aspects of nonadherence. So, in terms of quantitative
6 nonadherence, there are many measures of
7 pharmacoadherence that are applicable to
8 transplantation. However, there is no single perfect
9 measure of pharmacoadherence. Multiple measures of
10 pharmacoadherence are optimal to provide an accurate
11 adherence assessment, and this is going to be
12 necessary for us to introduce it in the future of drug
13 development for transplantation. Okay. Thank you
14 very much.

15 (Applause).

16 DR. ALLOWAY: Our next speaker will be
17 presenting the prevalence of nonadherence after organ
18 transplant, and it's Dr. Mary Amanda Dew. She is
19 professor of psychiatry, psychology, epidemiology,
20 biostats and clinical translational science. She is
21 the director in the clinical epidemiology program at
22 the Western Psychiatric Institute and Clinic at the

1 University of Pittsburgh School of Medicine. Dr. Dew.

2 DR. DEW: Thank you, Rita. Well, I'm really
3 humbled after hearing all of the comments of everyone
4 this morning. So, I hope that what I will tell you
5 will be informative, and I think that actually some of
6 the evidence really supports all of the things that
7 you've said, and you might be pleased to know that
8 some of it has appeared in the scientific literature,
9 so that other health care professionals may have been
10 forced to read it. So, on that note I'll begin. But
11 only if I can make this move. Okay.

12 So, when we look at prevalence we're talking
13 about counting things. And counting can be pretty
14 boring. So, why do we have to count how many people
15 are nonadherent. We need to know exactly how common
16 nonadherence is in order to estimate -- in order to
17 look at the scope of this problem, to estimate how
18 many people are likely to have trouble with various
19 elements of the regimen. And we need know how common
20 the exact prevalence, in order to design and test
21 interventions that are targeted to the right people
22 and are cost-effective. So, adherence is really a

1 bread basket of different activities. It's not just
2 taking medications after transplant. You all have
3 spoken about the various other things that are
4 required after transplant, and there are many things.
5 And that's part of what makes this a complex problem.

6 There are two ways to study adherence. You
7 can look at it from a quantitative perspective, where
8 you ask patients to report on their adherence. You
9 can use biologic measures -- all the approaches that
10 Rita was just describing. Or you can use qualitative
11 measurements, where you rely on patient descriptions
12 of how they manage their problems and what kinds of
13 problems they experience. And in fact, there are many
14 studies within both of these categories, and there
15 have been now several definitive systematic reviews
16 that have tried to summarize all of this evidence so
17 that we can have an overall picture of the nature of
18 this problem. So, I'm going to talk about those
19 reviews today, because there are too many individual
20 studies to make sense of them on their own.

21 So, our group in Pittsburgh did three
22 systematic reviews. We did three meta-analyses, and

1 we focused on post-transplant adherence to all areas
2 of the regimen. We looked across all types of solid
3 organ transplantation, and so we examined adult
4 general transplant samples. We looked at a
5 subpopulation composed of people who are transplanted
6 after histories of substance abuse, which is quite
7 common, for example, in liver transplantation. And we
8 looked at pediatric studies as well.

9 So, this shows for the adult and pediatric
10 studies there were 147 studies of adults, and that's
11 on the left. And you can see that most of them
12 involved kidney recipients, which makes sense because
13 that's the most common type of transplant. And then
14 heart and liver recipient populations were the next
15 most common.

16 In the studies of kids, kidney recipients
17 also were the most common, but liver was the second
18 most common. And these studies came from all over the
19 world, but primarily from North America and Europe.
20 And then the studies that focused on relapse to
21 substance use were mostly in the liver population.
22 So, this slide shows, then, the distribution of areas

1 of nonadherence that were considered in these studies.
2 And the length of the bar means more studies were
3 done. So, the issue of taking medications has been
4 most commonly looked at, and you can see that the bar
5 is about half and half green and blue. The pediatric
6 and adult studies were about equally as common. But,
7 for the other areas of the regimen that you can see
8 down on the left-hand side of the slide, there's been
9 much more study of those problems among adults than
10 among pediatric recipients -- even though many of
11 those areas are equally important for the pediatric
12 groups too.

13 I'm going to walk through this slide because
14 this shows the key results from these meta-analyses.
15 So, you can see on the left the different areas of the
16 regimen. And then these numbers are the estimates
17 across all of the different studies combined. So, if
18 you look, for example, at this first group, if you saw
19 a hundred people during a one year period after
20 transplant -- it might be the first year, it could be
21 the tenth year, whatever -- you would expect to see
22 3.4 percent of them go back to using tobacco during

1 that one year period. With alcohol, it's 3.6 percent
2 who would go back to using alcohol at levels higher
3 than were prescribed. So, these problems -- substance
4 uses of different types and attending clinic
5 appointments -- are relatively low. They're on the
6 left-hand side of the slide. So, not that many
7 patients have trouble in those areas.

8 These ones down at the bottom are the
9 lifestyle kinds of activities. Patients are told they
10 should exercise, follow certain diets, have blood work
11 and tests and so on. These are more common, so up to
12 25 percent of people seen within a 12 month period
13 would have trouble with their diet, for example. And
14 then unfortunately, taking immunosuppressant
15 medications was up in -- among -- it's like the
16 lifestyle things. It's a little bit more common than
17 we would hope. So, about 23 out of every 100 people
18 seen during a year would have trouble taking their
19 medications that would rise to a level where they
20 would be considered nonadherent.

21 Then, adding on the pediatric information --
22 what I just described you was for adults -- described

1 to you was for adults. The pediatric rates, then, are
2 shown in green. And you can see that generally the
3 rates are lower. It's important to note that this
4 includes all age pediatric samples. So, you know, you
5 know that parents have a big role for younger kids.
6 Nonadherence to medications goes up a lot among the
7 adolescent group. So, that's one important
8 distinction here. But overall, the rates tend to be
9 lower in pediatric groups.

10 So, then, what are the risk factors? We
11 tried to look at them across all of the studies in our
12 analyses, and actually we could not look at very many
13 because very few studies have looked at risk factors.
14 They often will report on rates of nonadherence, but
15 then not go very far beyond that. But in our meta-
16 analyses in adults, we found the ones that are shown
17 on the left-hand side of the slide -- for example, for
18 immunosuppressants, nonwhite ethnicity, having poorer
19 social support and poorer perceived health were linked
20 to having nonadherence problems. But the important
21 thing is that those linkages were relatively weak.
22 The size of these effects were small. It's not like

1 they were the major factors that anybody would point
2 to and say, oh, I've solved the problem. Just focus
3 on this factor. The only one that was really
4 important was that people with pretransplant histories
5 of substance abuse are more likely to have problems
6 with that post-transplant. But you would expect that,
7 because that's the nature of addiction. So, that just
8 goes hand in hand with that kind of issue.

9 For kids, we couldn't look at nonadherence
10 by specific areas because there were fewer studies.
11 But we did find that in general factors like the
12 stress of the parents, the behavioral functioning of
13 the child, and the distress of the child were
14 relatively important. But again, the sizes of these
15 effects were relatively modest, which means that we
16 can't point to a single factor and say that's the
17 cause of the problem for everybody.

18 Now, I mentioned initially there's also been
19 qualitative information. And in these qualitative
20 studies, the investigators focus on trying to capture
21 what the recipients tell us in their own words about
22 the medical regimen, as well other areas of

1 transplantation. And if you look up these three
2 papers, at the bottom of the slide the dates should be
3 2009, '11 and '16. So -- in case you're interested in
4 finding those papers. They focused primarily on
5 kidney recipients, and they have looked at adult
6 recipients as well as adolescent recipients.

7 So, in these qualitative systematic reviews,
8 they found that looking across this whole body of
9 qualitative literature, there are quite a few studies
10 that have tried to look at this and get the patients'
11 own words. The first important theme was empowerment
12 -- that patients want to gain a sense of control over
13 the regimen, and many people here today have mentioned
14 that. The importance of being able to manage, being
15 able to organize, how a person can organize, who can
16 help -- so, these are two illustrative quotes. "I
17 discovered the possibility of maintaining control,
18 even if you have to ask for help." So, they didn't
19 have to do it all by themselves, but they could
20 manage. "I'm good at planning ahead. I got this
21 chart, this box I refill once every week."

22 A second theme was fear of the consequences. And

1 you all have also discussed that quite a bit -- fear
2 of graft loss, fear of adverse effects, and defining
3 what is an acceptable risk that they can live with.
4 So, one person said, "I do think we walk on a knife-
5 edge all the time and you can just fall off of it
6 [and lose the transplant]." And this person was
7 talking about the difficulty of trying to have a life
8 and manage all of these things, and the fear that it
9 wasn't going to work.

10 Then another person said, "To find out that
11 I had cancer [due to the medications] would probably
12 be more devastating to me than having kidney failure."
13 So, for that person defining an acceptable risk was
14 that they had an overriding concern about cancer and
15 that concern was greater than their concern about the
16 loss of that graft.

17 A third thing was managing regimen demands -
18 - forgetfulness, side effects, lifestyle disruptions.
19 So, people like you have said things like, "The
20 hardest thing is if you are someplace new or doing
21 something new and remembering to take your
22 medications." Another person said, "I really had to

1 push for a [medicine] change because the doctors
2 didn't think [that hair loss] was kind of a relevant
3 thing to worry about." So, these lifestyle
4 disruptions can be things where the patients do have
5 to push their providers to convince them that this is
6 important to them -- this is part of balancing what it
7 means to have a transplant and go on with their lives.

8 A fourth theme had to do with
9 overmedicalizing life -- fatigue at being a patient or
10 self-management burnout. One person, who was very
11 demoralized, said, "You can't call it living a life.
12 I'm still living like a patient. I can't do the stuff
13 I wanted to. I'm just dead!" So, that person really
14 was burned out at that time.

15 Someone else said, "I was doing really well.
16 I started thinking. I don't need all those pills. I
17 just stopped taking them [little by little]. I was
18 tired of them, they made me feel like a sick person.
19 Then, of course, I went into rejection." So, the
20 person realized that that wasn't the best choice, but
21 they did it because of their other concerns and
22 feelings of distress.

1 The fifth theme was social accountability
2 and motivation. And I think many people have
3 expressed that theme here today, as well. "This
4 kidney was given to me by my wife. I have an
5 obligation to take good care of this kidney." "You
6 can't forget [your meds]. I'd be afraid to face my
7 [doctor] if I did that. They don't say much but it's
8 the way they look at you. You know they are
9 disappointed in you." And all of us have been a
10 patient, and I've said that to my husband -- my doctor
11 is going to be disappointed.

12 So, the authors of those systematic reviews
13 felt that those themes really were then reflected in
14 five different kinds of behaviors that were observed
15 and that patients talked about when they did these
16 interviews. First, on the left, was not taking
17 medications -- just refusing. Sometimes they refused.
18 Sometimes it was inadvertent -- it was forgetfulness.
19 Sometimes it was side effects. But that fell into the
20 nonadherence level of behaviors.

21 On the other side is total adherence, where
22 people are extremely vigilant. And I think many of

1 you who are here today are motivated by your extreme
2 vigilance and by the fact that you've been able to
3 master this and that you're hopeful that you can help
4 other people to rise above some of these problems and
5 maybe address some of the problems so they can master
6 the regimen as well.

7 Then, in the middle is maybe where many
8 patients lie. They want to be completely adherent,
9 but they may be changing doses to minimize side
10 effects. They may forget a dose. Or they may vary
11 the timing of doses inadvertently due to other
12 lifestyle factors. So, in general, then, what can we
13 conclude from all of these reviews of the quantitative
14 and qualitative literature? Nonadherence occurs
15 relatively often. The rates are higher in adults.
16 They are lower in kids, but if you want to look at the
17 areas of greatest problem it's clinic appointment
18 attendance.

19 Nonadherence is modestly associated with
20 psychosocial risk factors -- the things that I showed
21 you on that one slide. But, a limited range of such
22 factors have been considered, and the effects are not

1 large. Patients most commonly voice the need to take
2 control of their regimen but not let it control them,
3 concerns about adverse effects and motivations for
4 following the regimen, and that is what you have said
5 here today. So, that -- it appears in the literature
6 too, and I think that's very important that it's
7 gotten into the literature.

8 And finally, if those of us who are
9 professionals and work in this area would take time, I
10 think, to attend this kind of meeting we could listen
11 and then maybe generate some new ideas for better ways
12 to address this problem. So, thank you.

13 (Applause).

14 DR. DEW: So, I'd like to introduce Robert
15 Ettenger, who is a distinguished professor, emeritus,
16 the department of pediatrics, division of nephrology,
17 at the Mattel Children's Hospital at the David Geffen
18 School of Medicine at UCLA.

19 DR. ETTENGER: Thank you very much, Mary
20 Amanda, and thank you both to the FDA for inviting me
21 -- I'm humbled to be here in the presence of so many,
22 you know, real luminaries in the area. I'm just a

1 pediatric nephrologist. But, I most of all want to
2 honor all of you who are going -- who have really
3 shared with us today a lot of what it really means in
4 transplantation, and something that we physicians
5 really sometimes unfortunately lose a bit of sight of,
6 as to the challenges that you're going through as well
7 as the successes that you've had.

8 I'm going to -- I want you to focus today --
9 I'm going to try to go relatively quickly. So, I'm
10 going to ask that you focus, when you do, on those
11 things that are highlighted in red, because those are
12 the important things that I want you to see about with
13 regard to how adolescence and pediatrics differs from
14 what you've heard so far.

15 Many of you do not know how to define
16 adolescence, and allow me to do it as a pediatric
17 nephrologist. Adolescence is the age at which dad
18 becomes a two syllable word -- where they go, "Dad."
19 So, just thought you'd -- you just might want to know
20 that.

21 Adolescents have the best one year graft
22 outcome. This is data from the NAPRATICS (ph)

1 database. But patients who are transplanted age 11 to
2 17 years of age have the worst five year graft
3 survival. And most have attributed this in large part
4 to the issues of medication nonadherence in
5 adolescence.

6 After the first post-transplant year,
7 adolescents have the highest graft failure of any age
8 group. Now, this is a seminal study by Beth Foster in
9 2011. And what this is showing -- and let me address
10 this specifically to this area right here, because
11 this is the relative risk of losing a kidney allograft
12 at a specific given age. Not when you were
13 transplanted, but at a specific given age. And as you
14 can see on the slide, things start to get bad at age
15 10, 11, 12 years of age, and then continue to go up to
16 where they hit the maximal graft loss in the late
17 teens and early twenties. This is true whether you
18 count or don't count the first year of graft outcome.
19 The point of this is that it's the age at which a
20 patient is that really seems to register with graft
21 failure. So, our patients who were transplanted as
22 adolescents, they will tend to do badly. But,

1 patients who are transplanted as young children we
2 expect will transit through adolescence, and those
3 patients are equally at risk after a period of
4 relative quiescence.

5 The graft failure that we see is most often
6 due, as Peter said, to antibody-mediated rejection,
7 likely secondary to medication nonadherence. And this
8 is important. The donor specific antibodies that
9 Peter discussed that are generated during adolescent
10 graft failure due to noncompliance lead to ultimate
11 prolonged waiting times for a second graft and
12 subsequent poorer retransplant outcome. So, the first
13 kidney is the best kidney, and we really need to pay a
14 lot of attention to patients who are in their
15 adolescents, because this is going to color their
16 experience for the rest of their lives, if in fact
17 they do develop donor specific antibody.

18 The prevalence of medication nonadherence in
19 pediatric transplant recipients is shown here. And
20 you can see that for liver and heart it's in the 30 to
21 32 percent range -- I'm sorry, liver and kidney, 30 to
22 32 percent range. Heart is a bit less. But when you

1 look at the percent of patients -- and this is data
2 that I'm showing you here for renal outcome -- less
3 than ten years of age it's 22 percent. Greater than
4 ten years of age, 43.2 percent -- showing you how much
5 more adolescents are at risk.

6 These are the selected factors associated
7 with medication nonadherence in pediatric, but shown
8 in red are the adolescent transplant recipients. And
9 specifically, there are issues of low self-esteem,
10 patients don't like to carry the medications with them
11 and look different. Adolescents tend to have a busy
12 lifestyle, and are sometimes disorganized in terms of
13 being able -- and forgetful in being able to remember
14 to take their medications. We've heard a lot about
15 the psychological issues this morning, that may
16 afflict patients, and this is certainly true in
17 adolescents. We'll talk a bit more about those
18 psychological issues of depression, PTSD, anger and
19 denial a bit later on. But, poor coping mechanisms
20 can very well be seen in adolescents, who are not
21 particularly good at coping anyway. And then finally,
22 there are issues of social skills -- poor social

1 skills, deficient social support and reluctance to
2 admit to friends or peers that in fact they have a
3 transplant.

4 So, this is an MRI of -- busted. These are
5 the unique psychosocial and developmental aspects of
6 adolescence. You can see, this is the adolescent
7 brain. The love lobe, the rebellion center -- all of
8 you see this. I want to direct your attention to this
9 area right down here -- right over here -- memory for
10 chores, homework. And we have actually mapped
11 nonadherence and meds. We have scientifically mapped
12 this -- not. Thank you for that. Can I get a --
13 okay.

14 (Applause).

15 DR. ETTENGER: So, what are some unique
16 psychosocial and developmental aspects of adolescence
17 that impact nonadherence? Well, three prominent
18 characteristics of adolescent behavior are risk-taking
19 -- just think back to your own adolescence --
20 increased sensation-seeking, and the move away from
21 parents to greater peer affiliation. As I've shown in
22 red, that is an important point that we need to be

1 addressing. With regard to patient's cognitive and
2 emotional neuronal networks, patients -- adolescents
3 develop differently. Their emotional system circuitry
4 develops earlier. The prefrontal lobe circuitry,
5 which is the executive functions, the -- able to
6 abstract -- that develops later. And the prefrontal
7 lobe circuitry is necessary for executive functioning,
8 which means abstraction, long-term planning,
9 attention, response inhibition -- adolescents don't do
10 these things well because they haven't developed the
11 appropriate circuitry yet.

12 Finally, there's the issue with the
13 adolescents -- the need for separation and
14 individuation -- and adolescents will tend to
15 experiment to see which values of patients they will
16 adopt. Adolescents will question authority. And the
17 question always is what happens if meds are missed.
18 If there are no immediate consequences -- as we've
19 heard this morning, well, I can get away with it now,
20 maybe I can get away with it, you know, a bit later.
21 And thus, the medical team -- the docs who say don't
22 miss your medicines, we lose credibility when

1 adolescents are nonadherent without consequences.

2 Shown here is a scale called the barriers to
3 adolescent medication adherence, which is actually
4 quite a useful tool. I've listed four barrier types,
5 but in red I think the important barriers for
6 adolescents -- that I'm showing in this slide -- are,
7 number one, that -- the adolescent reported barriers,
8 almost 30 percent reported forgetfulness. Like not
9 paying attention, I'm completely out.

10 Also, poor planning or poor scheduling. And
11 notice that parents notice this even more than the
12 adolescent -- 68 percent of parents reported that
13 their adolescent transplant recipients had problems
14 with planning, and 58 percent of adolescents reported
15 that.

16 Now, with regard to the barriers of
17 adherence, in the interest of time I'm going to direct
18 you to the area in red. Barriers reflecting
19 disorganization are not planning ahead and the desire
20 to avoid others observing you taking your medications
21 is a major issue. The kids don't want to be found
22 out. This will lead -- is strongly associated with

1 medication nonadherence, and with emotional distress
2 such as -- as I mentioned, anxiety, depression, et
3 cetera. These in turn -- these emotional distressors
4 are correlated with medication nonadherence. So, it's
5 a cycle. And so, the more that these barriers are
6 showing up and we can assess them, perhaps the better
7 we can address them prospectively to keep kids from
8 going on.

9 The barriers tend to remain stable over
10 time, but poor adherence to medication is associated
11 with a series of these barriers that can be measured
12 during the time of transplant, and it's one of the
13 ways now we're using in the clinic to assess how much
14 we have to worry about the kids.

15 What about measuring adherence in
16 adolescents? Directly observed therapy can become
17 cumbersome and contentious between parents and
18 adolescents. The kids don't like taking the medicines
19 in front of their parents. So, directly observed
20 therapy is an issue. Success with indirect measures,
21 such as drug levels, is something I'm going to show
22 you just a little bit, to how we can perhaps pick up

1 nonadherence early.

2 Electronic measurement systems seem like a
3 good idea, but they can be limited if patients don't
4 want to bring a separate electronic container or smart
5 pillbox with them. And finally, self-report
6 instruments are particularly limited in adolescents.

7 This is the results of a liver transplant
8 study by Al Shemesh, et al, called the MALT study.
9 And basically, the point here is that if patients have
10 a -- if children have a large variability in their
11 tacrolimus levels, they're more likely to have liver
12 transplant rejection. So, these are a robust
13 predictor of late allograft rejection, and following
14 this in the clinic can inform our ability to hopefully
15 head off rejection and address the nonadherence.

16 Finally, this is data that we have just
17 published that's still not out in print, but is on the
18 internet. And this slide shows patients with high
19 levels of -- high coefficients of variation for
20 combinations of both tacrolimus and sirolimus shown
21 in the red circle. Those patients that are in this
22 area are patients that have very high variability in

1 both their tacrolimus and their sirolimus levels.
2 Previously, we have also published that high
3 tacrolimus levels in and of themselves predict
4 rejection. But importantly here, what this data shows
5 is that in patients that are on this dual therapy you
6 see that rejection is significantly higher when they
7 have these high coefficients of variation for both tac
8 and sirolimus, that self-reported nonadherence is very
9 high, and most importantly, pursuant to what Peter
10 said, the donor specific antibody is significantly
11 higher in those patients. Those are going to make a
12 problem for long-term outcome and for subsequent
13 grafts.

14 With that, I have hit my time and I want to
15 thank you all for your attention. And I'll turn the
16 podium back to the moderator. Thank you very much.
17 (Applause).

18 MS. EGGERS: Okay. Again, Sara Eggers. I
19 got tasked with continuing on. They liked so much
20 what we did in the morning that they want the same
21 sort of facilitation in the afternoon. But, to
22 everyone here, this is an experiment. But, I think we

1 can do this well.

2 Before getting in, I would like the folks --
3 the presenters -- the panelists up here who did not
4 present, if you could introduce yourselves so that we
5 know -- so -- yeah.

6 DR. CHISHOLM-BURNS: I'm Marie Chisholm-
7 Burns. I'm the dean and professor at the University
8 of Tennessee health science center, at the college of
9 pharmacy in the department of surgery, at the medical
10 school.

11 DR. FITZSIMMONS: I'm Bill Fitzsimmons. I'm
12 with Astellas Pharma, global development.

13 MR. LONGINO: My name is Kevin Longino, and
14 I'm the CEO of the National Kidney Foundation. I'm
15 also a kidney transplant patient for 12 years.

16 MS. EGGERS: Great. We asked Kevin to be up
17 here to serve as a voice representing and reflecting
18 the broader patient community. And so, you can jump
19 in at any point reflecting that. But we also have you
20 here in the audience to provide the individual context
21 of it. If there are any folks still on the web, feel
22 free to pull in comments as well.

1 So, there are three discussion panels. And
2 I understand we get to -- we can go to 3:00 with this.
3 The one person signed up for open public comment. If
4 you can come find me at the break, and we will discuss
5 something. So, we get to go until -- for 30 minutes
6 on this. And we have three questions to get through.
7 And I think how it's going to be best to try to do
8 this is a little bit of that lightning round format
9 that we did at the end of the topic -- the morning
10 discussion, where let's take the first question, how
11 well do we understand the extent of nonadherence in
12 patients post-transplantation.

13 We had four wonderful presentations that, I
14 have to say -- I'm going to speak, I think, for my
15 colleagues as well. They were so well-coordinated.
16 Thank you for that. They really flowed together very
17 nicely.

18 We heard a lot from you about the extent of
19 nonadherence and the type, and I think by type I'm
20 going to interpret this is the whys of nonadherence.
21 Is that a fair interpretation? So -- how much is it
22 happening and why is it happening. And I'm going to

1 ask just the panelists -- maybe we'll start with those
2 of you who hadn't yet spoken.

3 Do -- let's change it -- all the things
4 you've heard or what you're -- in your research, what
5 concerns you the most? And just briefly describe that
6 concern, either about the -- probably about the type
7 of adherence, or how well we understand the extent of
8 adherence. So, for example, it could be the aspect of
9 wanting to live a normal life or other factors that
10 have really resonated with you of concern. And then
11 we can get some discussion going on those factors.
12 Okay. My -- did the experiment sound -- make sense?
13 So, let's start with -- I'm going to put Marie -- if
14 you could, what surprised you -- what concerns you the
15 most when you think of the types of -- why
16 nonadherence is occurring.

17 DR. CHISHOLM-BURNS: I think what concerns
18 me the most, especially at the beginning when I
19 started researching this -- probably about almost 20
20 years ago, now -- is that how complicated it can be
21 and how individualized it really is. And I think that
22 that's what we heard this morning, from the recipients

1 here -- how complicated and how individualized. And
2 with the complication, how much sometimes us in the
3 health care profession -- it's hard for us to pinpoint
4 or even slow down to recognize it, as well as having
5 the time to do it. And how we need a
6 multidisciplinary team to help with that, and how we
7 actually really, really, really need you guys to tell
8 us about that.

9 MS. EGGERS: Okay. All right. William, do
10 you have any thoughts? What concerns you? What's
11 resonated?

12 DR. FITZSIMMONS: Sure. Rita mentioned the
13 difficulty in defining what's the critical level of
14 adherence that's necessary. And I think that's an
15 important component. Because we all say we would like
16 perfect adherence. But, it -- none of us are perfect
17 from that perspective. But, is taking 80 percent, 90
18 percent, 50 percent of your medications -- and this
19 morning someone mentioned it's not always going to be
20 every 12 hours, can I go plus or minus an hour around
21 that -- two hours, three. We don't have answers to
22 those questions and those are really important ones.

1 MS. EGGERS: So, both knowing it and then
2 being able to communicate it back to the people living
3 with the organ transplant, so that they're not making
4 up their own sets of rules about, well, I think I can
5 go -- 90 percent is okay. Maybe it is. Maybe it's
6 not. Uh-huh. Kevin, anything?

7 MR. LONGINO: Well, I -- there were so many
8 good things that were said this morning. It's really
9 hard to add to that. But, I think -- I think the
10 point that was just made is true. I think a lot of
11 patients try to make their own guesses as to what's
12 tolerable and what's not. And it would be important
13 to know those things.

14 I think in terms of compliance, one of the
15 things I haven't heard us talk about -- we talk about
16 medications that have to be taken on the spot at 12
17 hours. But it's not just that. It's oftentimes you
18 have to have an empty stomach for two hours and an
19 empty stomach for one hour afterwards, and then if you
20 make a mistake there then it throws off the rest of
21 your day. And so, what happens if you did have a
22 cookie accidentally and it's now inside of your three

1 hour window -- is that okay? Do you take your
2 medicine at the regular time or do you -- or what?
3 And nobody seems to have answers to that, and yet
4 that's a big factor in the compliance. And adjusting
5 just the logistics of the lifestyle.

6 MS. EGGERS: Okay. Thank you. A rich
7 amount of considerations. So, let me turn it to the
8 audience, and on the web feel free to comment. Take
9 one thing that you've heard, and say let me tell you
10 why that's such a challenge. Or let me tell you why
11 that's not a challenge for me. So, we'll -- and we're
12 not going to be able to take all the comments that we
13 want to, but we'll hope to --

14 MS. JEFFERSON: A really quick thought --
15 thing I thought about earlier.

16 MS. EGGERS: And your name?

17 MS. JEFFERSON: Nicole Jefferson.

18 MS. EGGERS: Nicole.

19 MS. JEFFERSON: Most of us here are here
20 because we're passionate about our organs and we want
21 to keep them. I think a lot of the issues with
22 nonadherence comes from people who don't really think

1 that much about their organs. And those are people
2 who don't have a support system, don't have the
3 family. So, I think the families being a part of the
4 doctor's appointments is a very big part, because if
5 you -- if a family member doesn't understand that it's
6 important for me to take these medications, I may not
7 remember and they may not understand why they're
8 important. So, I think we have a good grasp on taking
9 -- on our meds, and understanding it. But it's the
10 population to there, especially in my community, that
11 doesn't have the support or doesn't realize the
12 importance of taking the medicine.

13 MS. EGGERS: Okay. You raise a very good
14 point that I think we all know, which is that the --
15 you in the room, you are reflective of a patient
16 population but you're not completely representative of
17 the patient -- the entire population of people living
18 with an organ transplant. We know that. So, even as
19 you still -- you still have challenges. And so we
20 still want to hear those as well. But, that is an
21 excellent, excellent point.

22 MALE SPEAKER: I think Dr. Chisholm-Burns,

1 you hit it on the head. It's just -- it's a very
2 complex issue. Right. So, it's not going to be like
3 one little bullet is going to solve this. And to me,
4 I think if you look at, like, for -- if you're kidney
5 recipients, you have a very poor health literacy for
6 CKD. It's one of the lowest health literacy rates out
7 there. So, recognize that from a communications
8 standpoint. Because so much of this comes down to
9 communication. Right. So, how much of it -- and to
10 be frank, is that the doctors are really struggling
11 right now with the time they have. But, it goes back
12 to a message that's appropriate to the audience. And
13 the audiences are not all monolithic. But, to me, it
14 goes back to that. It's about the communication, trust
15 -- all the basics in relationship building.

16 MS. EGGERS: We'll take a couple more.

17 MALE SPEAKER: I would just add that part of
18 the issue is actions are louder than words. And so in
19 the medical profession, for example, you say take your
20 medications on the 12 hours the best you can. And
21 then you go in for a blood draw, and you're not
22 allowed to take your medications and you're made to

1 wait until three hours beyond the 12 hours. Well,
2 then, obviously it's not that critical.

3 Secondly, oh, we're going to do some testing
4 and you can't take anything, including your
5 medication, for 12 hours before. And then you get
6 there, and the next thing you know it's delayed --
7 surgery is delayed, stuff like that, throughout 18
8 hours. And obviously, it's not that critical, then,
9 if we can wait 18 hours.

10 And thirdly, when you're in the hospital
11 forget any timing on your critical medications. I
12 don't care if it's diabetes or it's immune
13 suppressants, you're on their schedule. Not yours.
14 And you can't convince them that this is really
15 important, and by the way this is my 12 hours -- I'm
16 sorry, this is when we give out meds. The actions
17 speak so much louder than the words.

18 MS. EGGERS: Okay. We'll take one more from
19 Piper.

20 MS. BEATTY WELSH: I think that engaging
21 patients in their own care is also a really key part
22 of it. I think that, you know, in my experience as

1 someone who has CF, one of the key components to
2 getting people to take drugs is involving them in
3 understanding how they're going to impact their
4 bodies. Because if the only experience you really
5 have -- the only thing you see the drug doing is
6 causing you muscles, for example, then you're going to
7 assume that that med is bad, you know. And I think
8 it's very important to sort of explain -- especially
9 when there are multiple immunosuppression therapies on
10 the table. You know, why do I have to take prograf
11 and mycophenolate and a steroid. You know, why is it
12 not okay for me to miss any of these. And I think
13 that additional level of empowerment also makes people
14 sort of take control over the medication for
15 themselves. So that, you know, we can stand up to a
16 hospital, for example, that says well, we're in the ER
17 so we can't order your meds and you'll be here for 12
18 hours at least. And you have to be able to say, oh,
19 well, then I brought my own, you know. And that's --
20 you can't do that unless you understand why it's so
21 important.

22 MS. EGGERS: Uh-huh. Thank you, Piper. I

1 think Rita -- you have a question?

2 DR. ALLOWAY: I was going to make a comment
3 before. I think that as a pharmacist I can say this.
4 We're kind of obsessive compulsive. And we want --
5 you know, we're trying to give you all these little
6 details of exactly how to do it perfect. When really
7 and truly, we need to step back and look at the
8 immunosuppressive regimen and ask the patient what
9 about -- what time of the day does an
10 immunosuppression regimen work for you. How do we
11 build it around you. Yes, all of these things that we
12 tell you to do two hours before, one hour later, with
13 food, without food creates the ideal circumstance.
14 But we do, as you said, have ability to adapt that
15 regimen and monitor the drug levels as such that go
16 along with that.

17 However, it requires consistency on the
18 patient's part as well, so we can adapt and adjust to
19 those particular changes. And I think that when we
20 talk about we really don't know the percentage of
21 which patients need to be compliant, I think that just
22 as you do to yourself we say a hundred percent,

1 knowing that it's never going to be a hundred percent.
2 You know, and we're hoping that we minimize the lack
3 of -- the nonadherent times that we can. So, you
4 know, we're learning. But -- and we continue to
5 learn.

6 MS. EGGERS: Okay. Thank you. Any other on
7 the panel, thinking of question one about the whys of
8 nonadherence, that you -- that's a burning question
9 for you or a burning comment you would like to make
10 about that? Go ahead, Mary Amanda.

11 DR. DEW: I was struck by the comment that
12 Jack had made this morning -- I don't know if Jack is
13 still here -- oh, there you are -- about how if a
14 medication is missed there's nothing that you
15 immediately notice, you know. And it can lull a
16 person into thinking, well, if I'm not going to notice
17 anything it can't be all that important. You know,
18 it's important, sure, but it's not that critical --
19 like if you had some immediate issue. And so, I think
20 it gives -- sometimes it can give people a false sense
21 of confidence and without having enough understanding
22 of the real consequences that might not be observable

1 for a while, it becomes a problem.

2 And then the second thing is I'm concerned
3 about all of the people that are not like you all,
4 that are not here. And how they can be reached, that
5 -- because they don't see this as a critical issue.
6 You're here because it's so important to you, and you
7 thought about it a lot. But what about all of those
8 other people that don't think about it a lot. Like
9 how are they managing? How are they figuring out --
10 or maybe they're not figuring it out, and they just
11 don't even realize that it's such a big issue.

12 MS. EGGERS: And Peter?

13 DR. NICKERSON: So, I think one of the other
14 things that comes into what's been discussed and the
15 point you raised, we don't understand how much
16 nonadherence is acceptable or -- in terms of
17 tolerated, and not have a bad outcome, in part because
18 we're treating everybody as if they're the same. And
19 you made the point earlier, what we really need to get
20 to is personalized immunosuppression. And we honestly
21 don't know how to do that yet. Short of what I showed
22 you with the twin transplants, where you don't need

1 any drug, there are some people who don't need as much
2 drug.

3 And we certainly -- I showed you the
4 clinical trial that we did with the NIH, where we
5 withdrew the tacrolimus in a number of patients and we
6 stopped the trial. But we stopped the trial because
7 some people rejected. But there were other people
8 that came off and they were fine coming off, right.
9 So, that's the other problem here, is that there's a
10 biological difference between everybody who is getting
11 their transplant. Some need more drug than others.
12 The problem is I don't have the magic wand that tells
13 me who does and who doesn't. And that was the whole
14 point of the trial, could we predict who could come
15 off one of their drugs and try and get to a
16 personalized immunosuppression regime. And we
17 couldn't do it, because none of the things that we
18 thought were going to predict it predicted it.

19 So, I think that's the other complexity
20 here, is that nonadherence is probably okay in some
21 people. In other words, it gets to some people need
22 less. But we can't predict who that person is. And I

1 think that's some of the challenges that we face, and
2 that the drug industry faces -- is how do we actually
3 identify and move to personalized immunosuppression.
4 Because I think that is part of the solution here, is
5 allowing patients to realize how much they really need
6 for the transplant that they have received.

7 MS. EGGERS: Thank you, Peter. And Robert?

8 DR. ETTENGER: What you're all hearing when
9 you're hearing that the patient needs to take the
10 medications at 12 hours, on an empty stomach, et
11 cetera, what you're really hearing -- and I see
12 transplant patients sort of every day -- what you're
13 hearing is our insecurity as physicians. Because we
14 don't know how much is enough. We also don't know
15 what the difference is between patients, and data that
16 Peter has generated suggests that depending on some
17 very sophisticated sorts of matching -- that we don't
18 do yet well enough, that's coming -- that some
19 patients may be more privileged than others. So,
20 unfortunately, we do have a one size fits all policy,
21 because that's about the best we can do. So, what
22 you're hearing is the insecurity of the physicians.

1 Because we know -- we think we know that perfect
2 adherence is the best that we can hope for. So,
3 that's what we tend to shoot for.

4 The other thing I want to say is that the
5 issue of not having any specific issue when you miss a
6 medicine -- an immunosuppressive medicine -- becomes a
7 major issue in adolescence, to the point where I was
8 thinking of floating to the FDA that we spike all --
9 because it doesn't hurt when you make the medications.
10 So, I was thinking that we spike all of the tacrolimus
11 with heroin, so that if you miss your medication you
12 go into a bad withdrawal response. You'd be surprised
13 -- everybody is laughing and says, you know, what a
14 good idea. I don't think the FDA will go for it, but
15 they're here. And so we can see. No, I -- I take
16 that back.

17 MS. EGGERS: All right. So, Robert, what
18 you're bringing up, I think, is going to tie into the
19 next question. And before we do that, let's hear one
20 more from Kevin.

21 MR. LONGINO: Well, just a general comment.
22 What would it take to start a personalized medicine

1 initiative for transplantation?

2 MS. EGGERS: What would it take to start a
3 personalized medicine --

4 MR. LONGINO: Initiative.

5 MS. EGGERS: -- initiative. Yeah. I think
6 it's a broader question.

7 MALE SPEAKER: (Inaudible).

8 MS. EGGERS: Uh-huh. Okay. So, let's move
9 on and then we can always come back, if we have time.
10 But let's move on to question 2, about the role of
11 health care providers in this. We've talked a lot
12 about health care providers today. But this question,
13 sort of, I think, wraps it up. Are health care
14 providers appropriately involved when it comes to
15 promoting adherence or are they not paying attention,
16 and what improvements would you suggest. And I'm
17 going to start with two of the panel members, and then
18 we'll open it up. So, if we can start with Mary
19 Amanda -- do you have any -- okay, wait --

20 DR. DEW: My view --

21 MS. EGGERS: Okay. Let's --

22 DR. DEW: Start with Peter. Okay.

1 DR. NICKERSON: So, it really comes back to
2 -- I think there's been a really good discussion this
3 morning about individual autonomy, and what are we
4 trying to create. Are we trying to create a situation
5 where patients are relying upon themselves and
6 developing their own systems and strategies to have
7 autonomy, in essence, versus us trying to assume that
8 autonomy. And I think from one perspective I would
9 say that we try to be too much assuming your autonomy,
10 and we need to elicit you being autonomous and working
11 a solution that would then be something that works for
12 you. And I think that that actually would be a better
13 strategy. So, from one perspective I'd say we're
14 maybe too involved, and that may be leading to
15 problems in and of itself. Although I could argue the
16 other side, and maybe -- Mary Amanda, I'm sure she
17 will.

18 DR. DEW: I could probably argue both as
19 well. But, I guess I tend to think that the problem
20 is not that anybody wants the health care provider to
21 hold everybody's hand and hand out their pills all the
22 time, and be in their house. It's that they don't ask

1 enough when patients come back. They don't show
2 enough interest, often. You know, they assume that
3 things are going okay or that there's no issue, if the
4 patient doesn't have any questions. And by not
5 showing interest, I think sometimes patients -- and
6 all of us have been patients -- feel that then the
7 person doesn't care about that issue.

8 And they are given -- I know in our program
9 they're given logs, they're told they have to record
10 certain things, and then after a while the program
11 staff just never ask about that anymore. And the
12 person says why am I doing this, and the staff's view
13 is, well, they're supposed to be doing it for
14 themselves. But, what's the point of endless little
15 pieces of numbers written on a page, if the provider
16 never looks at that and says anything about if it's
17 okay, if it's not okay, is there something that's not
18 being understood. So, in that sense I think there's
19 need to be more involvement in the sense of being
20 committed to talking with the person about how things
21 are doing. Not holding their hand. Talking with
22 them and coming up with new strategies, as needed.

1 MS. EGGERS: Can you hear me now? What if
2 I move over here? Can you -- just kidding. So, let's
3 ask a question this way, to get at -- thinking about
4 what you just heard from Mary Amanda and Peter, I'm
5 going to ask first if -- can someone or a few of you
6 think of the best physician you've had, with regard to
7 the helping you in -- as one of your support -- in
8 your support network, addressing the challenges of
9 adherence. Anyone want to talk? We have Dan, over
10 here. And then we'll go to Leilah. And what was it?
11 What did they do, and how did you feel about it? Were
12 they too -- were they really involved? I guess too is
13 not -- if you liked this, but were they involved?
14 Were they laid back about it?

15 MR. BONNER: So, I actually -- I'm not
16 thrilled with this question, the way it's worded, to
17 be honest.

18 MS. EGGERS: Okay.

19 MR. BONNER: Because health care providers
20 is such a general term. Does my dentist really care
21 about my transplant medication adherence? I'm not so
22 sure that he or she is. But -- so, the question to me

1 is which one of our health care providers are
2 adequately -- are engaged in our medication adherence,
3 and which one of our health care providers -- maybe
4 who should be -- aren't. That's, I think, a more
5 interesting question.

6 But, I come from a transplant program that's
7 large in nature. And I really need to take a moment
8 to credit the post-transplant liver coordinator nurse
9 that I have, and the nursing team. I can't say enough
10 about what they do, in terms of patient engagement,
11 because they are the lifesavers behind the brains and
12 the technicians of the doctors. It is that liver
13 transplant coordinator, Samantha, who is my advocate,
14 who is my person who is checking to make sure that
15 adherence is done to the best of her ability. And
16 because of her, and because of her sort of follow-up
17 skills for me personally, that's what has a huge
18 influence on my adherence.

19 So, if you were to sort of take that a step
20 further you then would have to sort of say, okay, so
21 in order for Samantha to be more effective at her job
22 how big is her patient list. And I believe it's

1 hundreds of patients long. So, how can someone like
2 Samantha be effective across a large pool of people
3 like that? So, what is that right number of patient
4 transplant people that she can engage with? What is
5 that right number to possibly lift adherence to
6 medication and things like that. And then from a
7 suggestion standpoint is, you know, I would say that
8 this here -- the education I got today in adherence
9 and the things that all of you have brought about --
10 is so eye opening. But, I also think we need to find
11 ways to get that to every transplant patient, in terms
12 of suggestion to improve our overall education of how
13 important adherence is. Because, you know, 11 years
14 out it's still a very important topic to someone who
15 is 11 years out or 11 months out. So, those are just,
16 you know, a couple of quick comments that I wanted to
17 make. So, thank you very much for that.

18 MS. EGGERS: Okay. We'll go with Leilah.

19 MS. SAMPSON: Leilah, again. For me, I
20 would say specialty pharmacy at Northwestern Medicine
21 in Chicago. They're on-call, basically 24/7. They
22 call me a week in advance, to make sure I have all my

1 immunosuppressants and my medicines. And I live in
2 two different places right now, nine months out from
3 transplant, working full-time, and there are days
4 where, you know, I have to split up my medication
5 between two different locations. And they've been
6 very instrumental in just being able to coordinate
7 that with me.

8 And then also, Robert Ettenger -- Dr. Robert
9 Ettenger, he really supported what I've been feeling,
10 as far as -- I'm now 28. The last time I was healthy
11 I was 19. You may see that as an adult, but at 19 I
12 was an adolescent. And I was very noncompliant. I'm
13 not going to lie -- like, oh, I was so compliant. No.
14 I was dealing with trying to be normal and not wanting
15 to tell my friends and I want to hang out and I'm in
16 college.

17 And then now, to be healthy again, and the -
18 - I find that issues -- those issues with scheduling
19 and all the things that you deal with as -- at
20 adolescence, because I spent eight years of my life
21 fighting kidney disease -- I haven't fully developed
22 mentally. And now I'm 28, and I'm thrown back into

1 this real world of being healthy. And I'm like what
2 do I do with this. I don't have these skills. I
3 gained a lot of wisdom and skills on dialysis, but now
4 to, you know, be 28 with basically the mindset of a
5 19-year-old, is something that I'm kind of struggling
6 with. So, he really supported that for me. And
7 everything that I've learned here today from everyone
8 helps me to move forward and feel more motivated that
9 I am definitely far more adherent.

10 MS. EGGERS: We're going to take one more
11 here, and then I'll have a show of hands, questions,
12 and then I -- it's important to get a little bit to
13 the last question. So, I'm --

14 MS. PAM DUQUETTE: Pam. Pam Duquette. I'm
15 Lindsey's mom. And something that struck me was a lot
16 has to do with patients not understanding that they
17 can self-advocate. A lot of people -- and it's been
18 touched on before -- where they just -- okay, I'll do
19 what you tell me to do and that's it. I think a lot
20 has to do with the health care providers or the
21 centers.

22 At our center -- and it's a very large

1 center -- every person that we spoke with, and this
2 is over eight years of her course of her disease, and
3 I'm talking from the -- some of the pharmacists I
4 actually would speak with, to the nursing staff, to
5 the prestaff, to the dialysis nurses -- everybody
6 always said are you okay with this, do you understand
7 this, do you have any questions about this, what do
8 you feel -- there was a lot of back and forth, which
9 when I was -- we were both thrown into this, I was
10 petrified. And I just sat there with -- deer in
11 headlights, didn't know what to do.

12 But, it was the constant prodding in a very
13 gentle way. And the fact that they respected my
14 opinion, when -- in advocating on her behalf. That
15 was really important.

16 MS. EGGERS: Okay. So, to wrap this up,
17 we'll do a show of hands and on the -- all -- anyone
18 up here can show -- raise their hands, and in the
19 audience. Who -- now, I know you -- I think you guys
20 were assigned those cases, but who -- what type of --
21 what's the reality for you? Who is making, whether it
22 is the less -- the provider who wants to give you more

1 autonomy, that you're dealing with, or the one where
2 you wish -- they're too much, they're too much in your
3 face about it, if I can use that term. So, how many
4 think that their -- it's too overbearing? That the
5 health care providers -- and let's -- I think we've
6 learned that we need to think of it broadly, across
7 the spectrum of health -- of providers that you're
8 doing, that -- basically, that you agree with Peter.
9 Okay. What about Mary Amanda?

10 FEMALE SPEAKER: He's used to that. He's
11 used to that.

12 MS. EGGERS: Okay.

13 FEMALE SPEAKER: (Inaudible) too overbearing
14 or too --

15 MS. EGGERS: Okay. Too overbearing, that
16 the -- that the providers, collectively, are too
17 overbearing about adherence. Okay. Is underbearing a
18 word? Too passive -- not asking you enough questions
19 about adherence. Raise your hand. Okay.

20 FEMALE SPEAKER: (Inaudible).

21 MS. EGGERS: Well, it could be that it's
22 just a very hard question. I think what we're hearing

1 is that most people would have sided with Mary Amanda
2 in the description, and in terms of what you would
3 like to see. So, we'll leave it, we'll leave it with
4 Robert.

5 DR. ETTENGER: But in the pediatric setting,
6 the adolescents will tell you to a person it's too
7 overbearing. I had a full head of hair before I
8 started taking care of adolescent transplant
9 recipients. And I can tell you that every fellow,
10 every time, every doctor, every nurse makes attempts
11 to make that connection with the adherence, and the
12 kids get tired of hearing it after a while. So, we
13 have to dial exactly how we do it. So, again, it's
14 not one size fits all.

15 MS. EGGERS: Great. Thank you for that
16 point. Renata.

17 DR. ALBRECHT: And that's actually a great
18 segue. Let me try to tackle, I guess, Kevin's
19 question, and then perhaps try to touch on Nicole's
20 comments earlier in the morning. You talk about
21 individualized medicine. And I guess I'll take the
22 liberty to follow Bob's comment about our insecurities

1 -- the clinicians' insecurity knowing the doses. The
2 FDA approved drugs called prograf, cellcept, myfortic,
3 nulojix, et cetera -- they come in certain strength
4 and certain regimens are recommended.

5 But, if you think about it -- I'll sort of
6 venture to say that that personalized medicine is in
7 its baby steps. Because your physician doesn't
8 prescribe you a fixed dose every day, the same dose,
9 and just lets you go. For certain of them, the
10 calcineurin inhibitors, you're getting your levels
11 measured early on after transplant more frequently,
12 later less frequently.

13 Rita talked about medical adherence, which
14 is not a passive act. It's a dialogue between the
15 clinician, be it your primary physician, be it your
16 nurse coordinator, be it whoever is taking care of
17 you. And I guess I've heard also people saying I ask.
18 I ask what's my value. You know, the gentleman said
19 I'd like to know what my creatinine is, can we get a
20 device approved for that. So, I think if you think
21 about the drugs, your interactions with the
22 clinicians, asking about your values, and then hearing

1 how your regimen is getting modified -- we heard -- I
2 don't know if it was James who said, you know, I'm
3 getting belatacept -- doctors are making changes based
4 on the patient's individual course. And I think that
5 in a sort of simplistic way is the beginning of
6 personalized medicine. Hopefully in the future, as we
7 learn more, there will be more of that. But I think
8 the feedback from you in the audience -- the patients
9 who are saying, you know, I want to know more, I want
10 to understand, I want to know why -- someone said I
11 want to know the mechanism of action. Why am I being
12 asked to do this. How does it make a difference to me
13 personally for my organ, for my lung, for my kidney.

14 And then the FDA approves the drugs that I
15 mentioned, but economics came up. So, as you aware,
16 there is -- there are not present today, otherwise I'd
17 ask them to speak, but there is a whole group called
18 the office of generic drug products, and they're
19 responsible for making available to the public generic
20 versions of the products that are -- that start as
21 innovators. The goal of that group is make those
22 products -- I'll use the phrase carbon copies. They

1 should have the same effect, the same efficacy and
2 safety profile, as the innovator, because they really
3 are trying to be carbon copies in terms of their
4 therapeutic activity.

5 Anecdotally, we will hear that patients
6 don't do as well. Can I ask for people who have those
7 experiences -- what Sara said earlier, please share
8 those experiences. Perhaps we can look into that.
9 You know, every so often a drug company will have a
10 problem in the plant -- something goes wrong. The
11 tablet is not full strength. That's a solvable issue.
12 But that's different from, you know, maybe a patient
13 didn't do well because they didn't take it the same
14 way because it didn't taste the same way, or they
15 couldn't swallow it the same way. It's unclear. But
16 the only way we will know is if you find out something
17 or you hear something, you send it to the FDA. And,
18 again, let me make the plea that Sara voiced earlier.
19 Until November 27th, everyone here, everyone on the
20 web, if you have information that you think we would
21 find valuable -- like we have all the discussion that
22 we've had -- please send it in.

1 MS. EGGERS: Thank you, Renata.

2 DR. ALBRECHT: And that may be a segue to
3 your last question.

4 MS. EGGERS: Yeah. At the break, we will
5 put the information on how to get to the docket, which
6 is your way of submitting a comment electronically.
7 So, I think we want to make sure we address the last
8 question quickly. And then we will go into a break.
9 So, we will do it kind of a lightning round. So,
10 first of all, can I have a show of hands how many of
11 you have participated in a clinical trial? Okay.
12 We've had some experience here.

13 Okay. So, unfortunately, I don't think we
14 get to get into what might make it difficult or hard
15 about measuring adherence in the clinical trial. We
16 can -- you can write that in the docket. But, let's
17 get a -- anyone on the panel who wants to address this
18 question briefly, about how critical it is to collect
19 the adherence data. I think we heard from the panels,
20 but any other thoughts on that or perspectives?

21 DR. NICKERSON: So, maybe just -- from the
22 concept that if you're trying to qualify a new drug

1 and you end up showing it doesn't have a benefit, but
2 if the patients weren't taking that drug or adhering
3 to the regime of that new drug, then is it -- you've
4 essentially disqualified a drug. But, it might
5 actually have had an effect, had it been taken
6 appropriately. And that's the risk of a clinical
7 trial, not knowing their adherence activity around
8 that drug. So, you -- ideally, you would know for
9 both arms of the trial what the adherence rates are,
10 and that then you're actually judging the drug on its
11 effects, as opposed to the nonadherence, which may
12 show that it has a negative effect.

13 MS. EGGERS: Okay. Any other thoughts?
14 Yes, William.

15 DR. FITZSIMMONS: And the other side of that
16 is if you're performing a study that is a
17 noninferiority study, rather than failing to show the
18 effect of the drug you may make two drugs look very
19 similar, because they're not -- they're muddling the
20 two arms of the trial. So, there are consequences
21 either way, depending on the design. But, I think
22 it's important to keep in mind the clinical trial

1 setting, particularly in the registration driven
2 trials, is very different than the real world setting.
3 We're already out there having patients sign informed
4 consents, putting them on a specific schedule,
5 counting the medications when they bring them back and
6 when they're dispensed. It's a very different
7 setting. So, we have to be careful in realizing that
8 that's not immediately able to extrapolate that to the
9 on-market real world setting outside of the trial.

10 MS. EGGERS: Okay. Can I show a hands? So,
11 of the number of you that have participated in a
12 clinical trial, was adherence -- the challenges with
13 adherence easier when you were in the clinical trial?
14 Harder when you were in the clinical trial? Anyone --
15 we can take probably two comments on anyone's
16 experience having to be adherent while on a clinical
17 trial, and challenges that you faced. Okay. We're
18 putting you on the spot. So, I think we will take
19 that as a sign that -- I'm going to take it as a sign
20 that it's a break time. So, we will take a break and
21 come back at 3:15, and continue with some more
22 enlightening presentations. So, thank you.

1 (Off the record at 3:03 p.m.)

2 (On the record at 3:15 p.m.)

3 DR. BELEN: So, hello everyone. We're going
4 to go ahead and go ahead with this session 2 of
5 afternoon scientific session, interventions to
6 mitigate nonadherence. Our first presenter is Dr.
7 William Fitzsimmons, of Astellas Pharma, and he is
8 going to discuss pharmaceutical dosage forms to
9 improve adherence.

10 DR. FITZSIMMONS: Good afternoon, and thank
11 you very much. I want to express my appreciation to
12 the FDA for organizing and leading this patient-
13 focused drug development discussion, organ
14 transplantation. I really believe this is a -- is a
15 milestone in our field, an important one. And also,
16 thank all the patients who -- particularly those who
17 have been participating this morning as well as this
18 afternoon. It's really the motivation for people like
19 me, who work in drug development, in this area to hear
20 from you. Because we don't have that opportunity as
21 much our colleagues that are direct health care
22 providers. And it's really motivating to hear that.

1 My disclaimer is I'm an employee of Astellas Pharma, a
2 pharmaceutical company. I've been working there 26
3 years, starting on the development of tacrolimus in
4 1990. But, I'll be expressing opinions today that are
5 my own opinions, even though I've been working at the
6 company for quite a long time. But they shouldn't be
7 considered the opinions of Astellas.

8 What I'd like to stress, and has been
9 touched on in a number of the themes already, that I
10 think will be great because they tie well into my
11 presentation, is that I'm going to focus on
12 pharmaceutical dosage forms that pharmaceutical
13 companies could work on to help improve adherence.
14 But, I think it's important, as we just discussed, to
15 realize this is a very complex multi-faceted issue of
16 adherence. So, I don't want to fool myself or anyone
17 else to think that dosage form development is the
18 answer. There is no magic bullet here.

19 What we need to do is try to work together
20 on all the different aspects of this, and one of the
21 things that the pharmaceutical industry can do is help
22 in terms of regimen complexity, as well as

1 pharmaceutical dosage forms. So, I'll be focusing in
2 there with the big picture that this is one small
3 element of the big -- of trying to address issues in
4 adherence.

5 So, what can we do from the standpoint of
6 dosage form technology and what have we done in the
7 industry to try to improve this. Probably the most
8 fundamental one for oral drug development has been
9 sustained release technologies. And there are a lot
10 of different sustained release approaches, and with
11 the main goal of trying to decrease the frequency of
12 dosing. I'll talk a little bit about some of these,
13 from the standpoint of transplanted, to give you
14 more specifics there. But, if you think about some of
15 the products that are out there that have made a
16 difference already -- outside of transplant -- in
17 sustained release technology, there might be a couple
18 of approaches.

19 We were talking about difficulties with
20 adolescents and adherence. So, attention deficit
21 hyperactivity disorder medications used to be all
22 immediately release, multi dose per day. And

1 sustained release technology came out. It really
2 helped, because those kids then didn't have to try to
3 bring medications to school. Didn't have to go to the
4 nurse or somewhere else to get their ADHD drugs,
5 didn't have to worry about trading those drugs or
6 having someone acquire them while they're at school.

7 So, we don't really think about those things
8 too much but that's a big improvement in the lifestyle
9 for an adolescent with ADHD, that can be helped a lot
10 just by a reduction in the dosing frequency.

11 Another example is improving adverse events
12 if they're associated with a high drug level. A very
13 simple one, if you're taking niacin for the treatment
14 of high triglycerides -- if you take immediate release
15 niacin, there's a very dramatic flushing that lots of
16 people get. And if you just put it into a sustained
17 release, you can dramatically reduce that amount of
18 flushing and make it a tolerable medication for
19 hypertriglyceridemia.

20 The second approach I want to touch on was
21 transdermal patch. We're talked a lot about those in
22 the past. I believe that, honestly, this -- they

1 aren't applied all that frequently. But, if you think
2 about transdermal patches, what they can do is, one,
3 decrease frequency of dosing, because you can put a
4 patch on for potentially days. You can also avoid the
5 issue of the oral route of administration, for people
6 who have difficulty swallowing. So, the -- probably
7 the most common ones you think about are scopolamine
8 patches for people with motion sickness, nicotine
9 patches that you see over-the-counter now for smoking
10 cessation. Those have been very common.

11 Within prescription products, probably the
12 ones that have had the biggest breakthrough are things
13 like opioids, using fentanyl patches for chronic pain
14 control. Also, topically, testosterone. Most of
15 testosterone replacement therapy is done topically,
16 not necessarily in a patch but counting on oral
17 absorption. Because one of the advantages is it --
18 when you put a drug on the skin rather than swallow
19 it, it doesn't go through the liver. Most of the
20 blood flow from the intestines goes initially through
21 the liver. We call it first pass metabolism. And
22 that will greatly affect some drugs, and this is a way

1 of getting around that.

2 Third is melting tablets. Some people call
3 these melt dose or WOW tablets -- without water
4 tablets. It's not used too commonly, but it's another
5 approach that oftentimes people have to run around and
6 worry about where -- if they have a source of water,
7 right, to take all their medications. People have
8 difficulty swallowing them. This is a way of
9 pharmaceutical formulation where it will dissolve very
10 rapidly in the mouth, and reduce your need for water.

11 Long-lasting injections. Most of the time
12 when we have proteins or biologics that can't be
13 absorbed through the GI tract, so they can be put into
14 an injection, hopefully the thing can be dosed at a
15 very infrequent time. But, patients sometimes can do
16 that at home, with self-injections -- particularly
17 subcutaneous injections at home. But, they may need
18 to go to the clinic for their administration. But,
19 hopefully that will be infrequently.

20 And then chewable tablets. I could probably
21 put also sprinkles and granules and liquids into this
22 group as well. All formulated to help make it easier

1 to swallow, particularly in the pediatric populations
2 that have difficulty with solid oral dosage forms and
3 the size of them.

4 And then lastly, fixed dose combinations.
5 The simplest way to think of this is we've taken two
6 drugs and put them into one pill. So, commonly, our
7 -- you might see this in areas like hypertension,
8 diabetes -- I'll show a few of those. It's also used
9 in antiviral therapies. And now you're seeing more
10 and more products come out that combine things like a
11 nonsteroidal anti-inflammatory drug along with a drug
12 to protect the gut, like a proton pump inhibitor or H2
13 blocker, so that you put them both together -- one
14 drug that protects against the side effects and one
15 drug that causes that side effect, all in the same
16 tablet or capsule. Another way of -- and I'll show
17 some of the data on how that effects adherence.

18 So, if we think about overall regimen
19 complexity, one of the -- there's a number of factors
20 to consider. One is simply the number of doses and
21 dose frequency per day. And I'll show data on once,
22 twice, three times, four times a day dosing. But,

1 also, just the total number of pills. It struck me
2 this morning, people were talking about 20, 30 pills a
3 day -- the more the pills, the more complex. Even if
4 they're once or twice a day, simply the number makes a
5 difference. The third is liquids versus solids.
6 Liquids are harder. They're harder for people to
7 carry around, for people to take. So, we want to
8 shoot for solid dosage forms if we can.

9 One thing that was talked about a moment ago
10 was the issue of taking products with food
11 restrictions. So, you go to the pharmacy and you get
12 the little label on the side of your bottle that says
13 take this on an empty stomach, one hour before or two
14 to three hours after a meal. That is actually the
15 most complex. People have the hardest time trying to
16 space drugs with that instruction. That's worse than
17 saying take it with food -- that's easier. And then
18 the easiest, of course, is it doesn't matter whether
19 it's on an empty stomach or with food. So, we have to
20 keep that in mind for the complexity of the regimen.

21 Other things to think about --
22 refrigeration. Patients don't have the ability to

1 keep something on ice and at a low temperature, even
2 though stability for some products is an issue. And
3 then, as I -- with the liquids, the issue of whether
4 you have to reconstitute it. Is it a powder that you
5 then you have to add a liquid to? Again, that step
6 adds to the complexity of the regimen.

7 So, these are all things that we have to
8 consider. A lot of the work on this, actually, came
9 out after the treatments -- the antiretroviral
10 treatments for HIV/AIDS, because they were concerned
11 about all the multidrug regimens and trying to
12 maintain adherence in that setting.

13 So, what's the best? The best situation,
14 when -- and the patients described it this morning,
15 was if you could take one tablet or capsule once a
16 day, regardless of food, and take it in the morning.
17 Right. That's the ideal scenario, if we could
18 accomplish that. That's the rarity, but that should
19 be our goal for oral therapy if we can do that.

20 I'm going to look at some of the data both
21 in and outside of transplant, in regards to adherence,
22 but I want to put forward a couple of assumptions that

1 I'm making. And one is that simplifying the dosing
2 and reducing the complexity of the dosing should
3 improve adherence, even when there are very few
4 studies to show that. It's not -- there's a lot of
5 studies on adherence that you heard about earlier this
6 afternoon. But not so many that really show the
7 impact of just changing the dosage form. But, I
8 believe we have to go through the premise that
9 simplification and reduction in complexity is good,
10 and we should strive for that.

11 The other thing is that we tend to get hung
12 up, sometimes, in our field on saying but has it been
13 studied in transplantations. And so what I'd like to
14 say is that we can extrapolate from other chronic
15 diseases to transplantation. For instance, we know
16 that diabetes, hypertension are very common amongst
17 transplant patients. We've heard about that today.
18 Hypertension is a good example of a fairly silent
19 disease, like preventing rejection, right. Normally,
20 everything is going fine until something big happens.
21 So, I think that these are valid areas to extrapolate
22 to transplantation.

1 So, what do we have in terms of examples of
2 dosage form technology for transplant
3 immunosuppression -- actually, very few, if we focus
4 just on immunosuppression. One that was talked about
5 -- introduced by Jack this morning is nulojix, or
6 belatacept. A once monthly -- when it's in the
7 maintenance phase -- intravenous injection. So,
8 that's an area where if you are able to get to a
9 clinic that can provide that once a month injection,
10 it's a way of ensuring that patients have exposure
11 over a full month with just that one hour injection.

12 Now, you do take other oral
13 immunosuppressants along with it in the regimen. But,
14 it's sort of an all or none, right. If you get your
15 injection, you've got a month's worth of
16 immunosuppression, at least from that agent. So,
17 that's one approach. The other approach that has been
18 used in transplantation is -- with tacrolimus, going
19 from the immediate release twice daily formulation,
20 which is how we originally launched it, to once a day
21 formulations. There's two that are on the market in
22 the U.S., Astagraf XO and Envarsus XR.

1 So, let me start out first to say if you're
2 looking at once a day, does once a day versus multiple
3 doses help. Now, I think it's fairly clear. We
4 already have heard from patients that that's desired.
5 So, I think all this does is validate the opinion that
6 you have. But, it's important to also look at that
7 data.

8 So, this is a group of -- a systematic
9 assessment of studies that used electronic monitoring.
10 Rita talked about different monitoring methods for
11 adherence. This is with electronic monitoring across
12 numerous disease states, starting at the left side
13 with once a day dosing all the way to four times a day
14 dosing at the right. And somewhat intuitive to you,
15 but shown by these studies, you can see that the
16 average adherence rate drops as you go to increased
17 number of doses per day, with four times being much
18 worse than once a day and once a day being the best.
19 Fairly intuitive. You might say does that hold up for
20 a disease like hypertension, where you're not
21 symptomatic. And the answer is yes, it does. It's
22 not as striking the numbers, but once a day in

1 hypertension is definitely better than twice a day and
2 three times a day, in this situation. And this was
3 looking at if you took at least 80 percent of your
4 prescribed meds. If you cut this at 90 percent -- if
5 that's your criteria -- these differences actually
6 even get bigger.

7 The other thing is what about a nonlife-
8 threatening but symptomatic disease, like overactive
9 bladder. Does it hold up there. This is oxybutynin,
10 one of the most commonly used drugs in the U.S. for
11 treating overactive bladder. And once a day ER on the
12 top line, you can see that -- has a much higher
13 percentage of patients staying on therapy than when
14 you go to multiple doses in an immediate release. And
15 you see very low rates of one year persistence. Less
16 than 10 percent of patients stay on twice a day
17 oxybutynin for a year. It's remarkable how long the
18 adherence rate is.

19 Now, I just want to touch on what do we know
20 about transplantation for once a day. There has been
21 some studies done. One of the studies is of 219
22 patients, where they were randomized to once a day

1 versus twice a day tac after kidney transplant, and
2 then followed for six months. And what they found in
3 this study was after a three month running period --
4 and then there's that vertical line through the slide
5 at the point of randomization -- the top line is the
6 once a day group, the bottom line is the twice a day
7 group. And this was looking at the percentage of
8 patients with correct dosing. And they used an
9 electronic system, so every day they could check on
10 the dose. So, that's what -- that's every day you're
11 looking at the compliance. And you see that they
12 separate out. So, once a day in transplant patients
13 you see higher percentage with correct dosing relative
14 to twice a day.

15 The other thing that was interesting about
16 this study, that taught us a little about human
17 nature, was they looked at the day of the week --
18 because they did this every day. And what you can see
19 at each day of the week is that the evening doses
20 there's a higher rate of missed doses -- that's the
21 top line -- than the morning doses. The other thing
22 is the worst time is Saturday night. So, Saturday

1 night -- I guess that's intuitive too -- is the worst
2 time in terms of compliance. Okay.

3 The last thing I wanted to touch on was this
4 idea of fixed dose combination. Fixed dose
5 combination, where you put two drugs into one dosage
6 form, compared to having to take two pills, has been
7 studied in diabetes and shown enhanced adherence
8 rates. It's also been studied in hypertension with
9 ACE inhibitors, along with diuretics. These are the
10 data on lisinopril in single pill versus two, as well
11 as the data on enalapril, along with
12 hydrochlorothiazide. So, there is no doubt that
13 combining, in certain situations, you know, into one
14 dosage form helps over two. There are -- you could
15 extrapolate this, and there's data to say, that even
16 if you package it together in a unit dose package, so
17 that patients get them both together, does help. It's
18 the best to put it in the same pill.

19 So, let me end by saying I think that there
20 is a number of pieces of data -- there is a number of
21 innovations that pharmaceutical companies can help
22 with, in terms of enhancing adherence through dosage

1 form development. But there are some limitations.
2 And as we heard well today, transplant patients are on
3 multidrug regimens just for the immunosuppression, let
4 alone all of the other indications they're taking.
5 So, just going from twice a day to once a day
6 tacrolimus -- but then you have to take twice a day
7 mycophenolate and you have to take all your other
8 medications -- doesn't mean we've solved the issue.

9 Secondly, that when you looked at that list
10 of possibilities a lot of people say, well, you should
11 do all of those things with your drugs. Why aren't
12 you making all those different dosage forms. The
13 reality is we're limited by the science of the
14 chemistry, as well as the pharmacokinetic, or how a
15 drug moves through the body. Those molecules that
16 sometimes make it impossible -- sometimes we can't get
17 it to go into a solution to make a liquid, we can't it
18 go through the skin -- so, we do what we can but it's
19 not -- we don't have the ability to apply it in all
20 circumstances.

21 And lastly, that what we try to do is speed
22 drugs to market, particularly to get it to patients in

1 need, and almost always we don't know everything there
2 is to know about the dosage regimen, nor have the best
3 formulation. We have a good formulation. We know as
4 much as we can to get the drug out on the market.

5 But, there's a lot of work that needs to be
6 done. And so, once the drugs are generic, that some
7 of the -- there's some disincentive for doing some of
8 the work to enhance these formulations. So, we need
9 to work on, together, to make this practical, to do it
10 quicker, less expensive and with less complexity, so
11 that we can get some of these innovations out in terms
12 of new formulations to enhance adherence.

13 Thank you very much. And our next speaker
14 is -- Dr. Dew is coming back, from the University of
15 Pittsburgh.

16 (Applause).

17 DR. DEW: Okay. I'm going to briefly review
18 the evidence that we have about adherence in heart,
19 lung and liver transplant in adults, and then Dr.
20 Chisholm-Burns will cover kidney transplant
21 intervention studies. There are a number of
22 challenges, if you think about what can transplant

1 programs do in order to help their patients maintain
2 adherence or improve adherence to their regimen after
3 a transplant. People go to big centers. They often
4 -- they may live thousands of miles away from the
5 center where they got their transplant. Transplant
6 teams have limited resources, that they're constantly
7 having to justify to their institutions. We've
8 already talked about how adherence to their regimen is
9 really composed of a number of different elements.
10 There haven't been many interventions tested directly
11 in transplantation, and we really don't have powerful
12 interventions from other chronic disease populations.
13 We have some, but they are only modestly effective.
14 So, the key issues are when, where and how to
15 intervene with transplant recipients.

16 This is adapted from a review that was
17 focused on hypertension, and in this review they
18 pointed out that adherence problems can develop
19 anywhere from shortly after the onset of treatment or
20 care all the way through the very long term. And
21 that's come up in some of the comments today as well.
22 So, over on the left side, if you think about in the

1 transplant case when you have the surgery as the
2 beginning point, then you can think about the period
3 after transplantation as first -- in the first year,
4 dealing with things like maybe trouble initially
5 getting into the routine, low motivation to get into
6 the routine, the onset of intolerable side effects
7 that inhibit adherence, confusion about the regimen.

8 Then, as time goes on and you move over
9 towards the right-hand side here, there may be delayed
10 toxicity that creeps up over time. It may be hard for
11 the person to sustain their motivation to adhere to
12 the regimen. And so, those kinds of problems can
13 develop in the long-term.

14 In terms of where and how to intervene, if
15 you look at the chronic disease literature in general
16 we only have a fixed number of possibilities
17 concerning the mode of offering the intervention. We
18 might do it face to face, at discharge or at clinic
19 visits. It could be done on the telephone, through
20 smart phone apps or through other kinds of internet or
21 web-based applications. And then in terms of what the
22 interventions could be composed of, these are sort of

1 the fixed set of elements that people usually begin
2 with when they try to put together an intervention.
3 Some educational component, or maybe solely education,
4 behavioral aspects, problem solving therapy, for
5 example -- teaching people how to use certain
6 techniques to deal with new problems, focusing on
7 psychological aspects, using motivational interviewing
8 -- which is not interviewing, but trying to bring out
9 the person's motivation -- their own motivation -- for
10 doing something. Technology-based approaches, and
11 then multicomponent strategies that put these things
12 together in novel packages.

13 In chronic disease, we know that the types
14 of interventions that have been used across studies
15 are very heterogeneous. People have tried a lot of
16 different approaches, but in looking across the
17 literature it's the things that are multicomponent
18 that seem to be the most effective. So, you don't
19 just offer education. You offer education plus some
20 kind of problem solving or education plus some
21 psychoeffective kind of element. It can be difficult,
22 then, to say what element of this multicomponent

1 intervention is the thing that's really potent. But,
2 the fact remains that it seems to be the synergy of
3 different elements that matters.

4 We know that effectiveness is increased by
5 tailoring it to the patient needs. So, you don't just
6 use a one size fits all intervention strategy. And
7 also, tailoring it to incorporate dynamic information.
8 Meaning that if you used one of the medication
9 monitoring systems and you got feedback on the times
10 that you were most likely to miss doses, that kind of
11 dynamic information on how you've been doing lately
12 could be really useful for how to improve in the
13 future.

14 We know also from this literature that the
15 degree of impact is variable, but it tends to be small
16 to moderate at best. So, no intervention is hugely
17 effective, but it has resulted in measurable
18 improvements. And whether interventions improve
19 clinical outcomes is a whole other issue. Many
20 intervention studies don't address that issue.
21 Finally, new mobile health strategies appearing
22 promising and are really increasing in terms of

1 visibility in the literature.

2 So, then, what do we know directly in
3 transplant? Well, I'm going to focus on the
4 extrarenal studies, the heart liver and lung studies.
5 There have been descriptive reports with no
6 evaluation. So, we really can't say anything about
7 whether they're helpful or not, except anecdotally
8 sometimes they seem to be helpful. There have only
9 been six trials to date that have actually looked at
10 interventions in heart, liver and lung recipients.
11 Two of them I'm not going to talk about. They were
12 just education and they showed that education alone
13 doesn't work.

14 There have been two others that used
15 electronic platforms, and those were done by our group
16 in Pittsburgh. And then two others that used face to
17 face multicomponent interventions, and both of them
18 were done in Europe. So, these four studies I'm going
19 to talk about, because they did show some evidence of
20 effectiveness.

21 About 10, 12 years ago we did a study
22 focused on heart recipients, and we developed a

1 website that was multicomponent. It had education.
2 It had a question and answer library. It had
3 discussion groups. And it had coping skills workshops
4 that, as you can see here, one focused on managing
5 stress and the other focused on managing the medical
6 regimen. So, it was a short trial and we compared
7 people who used the intervention to historical
8 controls who were the same amount of time post-
9 transplant. And what we found was that their mental
10 health, even in this short four month trial period,
11 improved relative to the controls. Recipient
12 adherence improved in some areas, but it was only
13 among the people that actually used that component of
14 the website. Recipients social functioning and their
15 quality of life in that area improved, and we found a
16 dose response relationship between the frequency of
17 the website use, no matter what component they used,
18 and intervention effects.

19 But the issue is that the sample was small.
20 It wasn't randomized, even though it was a prospective
21 study and it had a short study period. More recently,
22 we focused on a large randomized trial in lung

1 recipients. And we were testing a smart phone app
2 called Pocket PATH. And Pocket PATH gave the user a
3 variety of tools that they could use on their phone to
4 monitor what they were recording. So, rather than
5 using paper and pencil logs, they could record
6 information about their spirometry, their temperature,
7 their blood pressure and so on directly into this app.
8 And they could see both a listing of what they had
9 recorded, but over on the right there at the bottom
10 the most important thing was they could see graphs.
11 They could see how their numbers were trending over
12 time, and it had critical values so that they got an
13 alert if they were going outside of their critical
14 range, or if they were showing good improvements or
15 whatever. And that kind of feedback seemed really
16 important.

17 So, in this trial we randomized patients at
18 discharge and we compared them to a usual care group
19 and we found that those that had the app were more
20 frequent in their self-monitoring, had higher regimen
21 adherence across the board, to all of the elements.
22 They were more likely to report abnormal indicators to

1 the team. We didn't find effects on rehospitalization
2 or first year mortality. So, this just shows
3 graphically the self-monitoring difference for Pocket
4 PATH versus usual care. The higher bars -- the green
5 bars -- for Pocket PATH showed that self-monitoring
6 was higher and adherence was higher, but you can see
7 that for everybody adherence declined over the first
8 year. So, Pocket PATH helped but it didn't prevent
9 what we always see, which is that adherence generally
10 does worsen over time in almost everybody, transplant
11 or not.

12 This study didn't follow people past their
13 first year post-transplant. However, a follow-up
14 report that's just going to come out now -- it was
15 under review when I did these slides, but now it's
16 going to be published -- looked at subsequent years
17 and did find that the people who benefited from Pocket
18 PATH in the first year did show a lower mortality risk
19 in subsequent years, up to about six years post-
20 transplant.

21 And then, we've more recently been testing a
22 version of this for adolescents, called Teen Pocket

1 PATH, which focuses only on medication use. And
2 again, as a smart phone app that helps them to monitor
3 that, to see their trends in taking it and to contact
4 the team as appropriate.

5 The third intervention out of the four that
6 I'll discuss is a face to face pharmacist-led
7 educational and monitoring intervention. It was done
8 in Germany, and involved a very small group of 41
9 liver recipients. But they were randomized, so that
10 was a great strength of the study. It used education
11 as well as quarterly meetings with the pharmacist to
12 review their medications, their lab values, any
13 problems they were having and so on. And this slide,
14 it shows box plots. The point of the slide is that
15 the higher box on the left is showing better dosing
16 compliance. They were more likely to open this
17 electronic pill bottle, with the correct number of
18 openings per day, than the control group, which has a
19 lower box, which was not as good at doing that. So,
20 the intervention was effective from that standpoint.

21 They also found higher target serum levels.
22 They didn't find effects in every area. For example,

1 self-reported adherence didn't change and graft
2 rejections didn't change either. But, the issue,
3 again, is that the follow-up period was short and the
4 sample was small.

5 Lastly, the MAESTRO study, which has just
6 been completed recently in Belgium and is almost
7 accepted as a publication -- it was present at an
8 international meeting in the spring -- is a really
9 nice example that involved heart, lung or liver
10 patients. It had a long follow-up period. All the
11 patients were beyond the first year of post-transplant
12 when they were randomized, and this intervention
13 focused on giving them feedback using electric
14 monitoring. So, it was dynamic information that I
15 mentioned earlier. It helped them with goal-setting
16 and action plans. They had social support and
17 education, and it used motivational interviewing to
18 draw out the motivations for people to want to adhere
19 closely to their regimen. It was also tailored, based
20 on their initial level of difficulty.

21 They looked at adherence outcomes, up to 12
22 months after the baseline, and then they looked at

1 clinical event-free survival over five years. So,
2 they found that they did have an effect on adherence.
3 They had only a marginal effect on clinical event-free
4 survival. So, this is a graph of the adherence
5 effect. You can see the green bar is the intervention
6 group. They had better dosing adherence. It was
7 about the same at baseline, by intervention, and it
8 was clearly better. And notably, they maintained that
9 over the subsequent 12 months, even though they were
10 no longer getting components of the intervention. So,
11 it went beyond Pocket PATH and showed durability.

12 The problem is that it may not be feasible
13 in a given transplant program's practice, because it's
14 a relatively complex labor-intensive intervention, and
15 you might have to have somebody that was dedicated to
16 offering that intervention.

17 So, to conclude, there are very few studies
18 in heart, liver or lung recipients relative to about
19 three or four times as many in kidney recipients.
20 Education alone does not work, even though clinicians,
21 if you ask them what works, they say education, that's
22 what going to work. It doesn't work. Multicomponent

1 strategies can improve adherence, but tailoring is
2 needed, I think, to make them maximally effective.
3 And most studies to date have just short follow-up
4 periods. So, the durability and impact remains not as
5 well understood. Thank you.

6 (Applause).

7 DR. DEW: So, Dr. Chisholm-Burns, who hasn't
8 been introduced before, is the dean and professor,
9 college of pharmacy, professor of surgery, college of
10 medicine, at the University of Tennessee.

11 DR. CHISHOLM-BURNS: Thank you, Mary Amanda.
12 I also want to thank you for inviting me here today.
13 I'm humbled by the experience. I always like to see
14 my fellow colleagues and present with them. We've
15 been presenting over the years on different issues.
16 So, again, thank you for inviting me.

17 I also want to thank you guys out there for
18 reminding me of why we do what we do. And it's
19 because of you. So, again, thanks for allowing me to
20 share this time with you.

21 I'm going to talk to you a little bit about
22 interventions to improve adherence among the adult

1 renal transplant population. And as you recap and
2 think about today, you learned -- or, we talked about
3 many things, all the way from organ donation to
4 polypharmacy therapy to adverse drug events, cost,
5 rejection, whose responsibility is it anyway, in terms
6 of adherence and -- side with Peter on that one. I
7 know it was a hard call. Are we too passive about
8 adherence. We also talked about -- you reminded us
9 about engaging patients, empowering you guys -- what I
10 call self-efficacy. And so what I'm going to try to
11 do is kind of tie all of this together using two
12 studies to do that -- two studies that I have been
13 involved in over my career, looking at adherence. And
14 among the six or seven that I've done that looked at
15 intervention groups, I think these two are the ones
16 that could tie this together the best.

17 The first one was published in The American
18 Journal of Transplantation a couple of years ago. And
19 it looked at improving outcomes of renal transplant
20 recipients with behavioral contracts. You might be
21 thinking, oh, now that's really heavy -- a contract,
22 right. This is like closing on a house or going to

1 make me sign something, now I'm liable and
2 responsible. But, I don't want you to get caught up
3 in that. This is just a mechanism -- a medium, if you
4 will, that we use to make the health care professional
5 and the patient pause to talk about adherence. And
6 you talked about that. Let's pause. Let's make them
7 do it, and talk about adherence.

8 So, let me give you a little bit of
9 background about behavioral contracting. I know this
10 came up in Mary Amanda's talk. All it really is is a
11 behavior modification technique, which is grounded in
12 social cognitive theory in which there is patient-
13 specific written agreements, or contract, if you will,
14 that's developed between an individual, patient and a
15 health care professional. So, it's not a legally
16 binding contract. Okay. It's just a way to pause, to
17 get some thoughts written down on paper, and I have a
18 copy of the contract. It's a one page sort of deal.
19 And what this contract does is identifies a target
20 behavior. In this case, the target behavior is
21 medication adherence, specifically immunosuppressive
22 therapy adherence, and it looks at those factors that

1 influence that behavior, okay. And we talked about a
2 lot of those factors here today -- cost, and I know
3 that's probably the elephant in the room. I had a
4 discussion earlier today with an individual that is
5 pretty high up in one of the pharmacy chains, and I
6 know the question was put forth to the group about
7 changing drug vendors. And a lot of that sometimes is
8 controlled by a lot of other factors, including PBMs
9 and things of that nature.

10 But anyway, it was looking at factors that
11 control that behavior, and proposes strategies to
12 modify the target behavior to achieve a desired
13 outcome. So, all the factors that you talked about,
14 all the factors that we didn't talk about -- because
15 it's very individualized. And so, in this study,
16 again, we looked at adults. So, the study included
17 renal transplant recipients who were 21 years of age
18 or older, who were at least one year post-transplant.
19 So, these were people that -- probably for the most
20 part they were established on a drug therapy. They
21 were prescribed tacrolimus or cyclosporine. They
22 obtained their immunosuppressive therapy from a

1 specialty pharmacy. And I know someone made a comment
2 about that earlier. And they had to be enrolled in a
3 specialty pharmacy for at least one year prior to
4 study enrollment and during the entire study period.

5 Now, participants in the intervention group
6 met with the study pharmacists at baseline to
7 negotiate the behavioral contract, then again at
8 months three, six, nine to review the contract, to
9 discuss progress toward the goal -- which, again, is
10 to achieve the highest possible adherence that we
11 could, to update the contract, and to resign the
12 contract for the next quarterly period. And they met
13 the last time at the 12 months, to terminate the
14 contract.

15 Now, what did the behavioral contract
16 address? Well, it addressed several factors,
17 including the motivations for achieving
18 immunosuppressant therapy adherence. Today I've heard
19 people talk about they want to be adherent because
20 they want to be around for their loved ones, or they
21 want to participate in a particular activity. So, the
22 motivations. Again, done on a very individualized

1 scale. They addressed barriers that interfered with
2 adherence for that particular person. And solutions
3 to these barriers, which could include social support.

4 We also looked at other tools and strategies
5 to help remind the renal transplant recipient of the
6 dosing schedule, and possible consequences of
7 nonadherence. So, tying the whole picture together.
8 Now, participants in the control group received
9 standard or usual care. So, once we applied our
10 criteria to the patients -- we had 286 patients in
11 this particular pharmaceutical pharmacy, that actually
12 met the criteria. I need to tell you that it was a
13 multisite intervention, and it was spread over several
14 states. Most of the states were in the southwestern
15 part of the United States. So, I didn't live all my
16 life in the state of Tennessee. So, I was out in the
17 southwestern part for a little while.

18 And 286 people met the study criteria. 150
19 people were accepted into this study. And at the end,
20 we had 67 individuals in the intervention group and 68
21 individuals in the control group.

22 In terms of results, there were no

1 significant differences between the intervention and
2 the control groups based on patient characteristics.
3 So, for the most part, the patient characteristics --
4 the big global ones -- were the same. I have to tell
5 you, we've seen this throughout many of the talks
6 today -- I know Mary Amanda mentioned it and Peter
7 mentioned it when he looked at Nevins' study of 2014
8 -- that baseline adherence was associated with months
9 post-transplants. Meaning, the further you were out
10 from transplant the lower your adherence rate became
11 in most cases. But no other factors or
12 characteristics were associated with adherence at
13 baseline.

14 Now, the intervention group had
15 significantly greater adherence compared to the
16 control group at months 6, 9 and 12 months, and over
17 the entire study period. And that's what's really
18 depicted in this graph. So, you have a line graph
19 here. On the Y axis, you have the month post-study
20 enrollment. On the Y axis, you have the compliance
21 rate -- if you multiple that by 100 you get the
22 compliance rate or the percentage. The solid line

1 represents the intervention group. The dotted line
2 represents the control group. And you clearly could
3 see that the lines diverge. However, just like
4 Nevins' study in 2014, you didn't really see this line
5 diverging until after the third month post-study
6 enrollment. And you could see clearly that the
7 intervention group, as I said earlier, had better
8 adherence.

9 Now, I will tell you that we did follow
10 these people after the 12 month study period. We
11 actually followed them out three months after post
12 that period -- so, a total of 15 months. And this
13 study did hold. The intervention still had higher
14 compliance rates or adherence rates, compared to the
15 control group. In terms of cost -- I mean, in terms
16 of cost as we look at health care utilizations, and in
17 particular hospitalizations -- 40 percent of the
18 patients reported hospitalizations during the study.
19 And if you look at the two groups, 57 percent of the
20 control group was hospitalized during that 12 month
21 study period, compared to only 24 percent in the
22 intervention group. And this really boiled down -- if

1 you want to look at the cost again, not to mention all
2 the other things that associated with
3 hospitalizations, like quality of life -- but just
4 looking at the cost alone, the intervention group was
5 78 percent more likely not to be hospitalized, saving
6 \$28,000 a month in health care costs.

7 So, what did we conclude at the end of this
8 study? For us, having multiple sites out there around
9 the country, we concluded that behavioral contracting
10 is a practical and easy to employ adherence strategy
11 that resulted in several significant improvements, one
12 in adherence and the other in decreased health care
13 costs.

14 So, just to recap this study, it was done,
15 again, in multiple sites. So, you, I believe, talked
16 about scalability. This has the scalability
17 potential. Again, you have to stop and pause and
18 engage in the discussion.

19 I want to present to you another study,
20 which was a study that was done at one site. It was
21 in a renal transplant clinic at the Medical College of
22 Georgia. Now that institution has been renamed to

1 Augusta University. But, we looked at the impact of
2 clinical pharmacy services on renal transplant
3 patients compliance with immunosuppressive
4 medications, and again a multicomponent study where we
5 did lots of things to help with adherence. Very
6 individualized, similar to what you saw in the first
7 study.

8 Again, this study involved adult renal
9 transplant recipients. And since it was done in the
10 center, we had some clinic data that we could go to as
11 well. So, everyone who received a renal transplant at
12 the Medical College of Georgia, over a two year time
13 period, was evaluated to see if they met the study
14 criteria. The study criteria included they had to be
15 at least 18 years of age, this had to be their primary
16 transplant -- meaning that they couldn't have any
17 graft loss prior to this -- and they had to receive
18 follow-up care at our institution, and receive their
19 medications from our institution's pharmacy.

20 After receiving informed consent, patients
21 were randomized, just like the other study, into one
22 of two groups -- an intervention or a control group.

1 Patients in the control group received traditional
2 services, which meant no clinical pharmacist
3 interventions, while patients in the intervention
4 group were seen by the clinical pharmacist at each
5 clinic visit, and they interacted with the clinical
6 pharmacist at least on a monthly basis.

7 Now, what were the clinical pharmacies'
8 duties? Well, they included performing medication
9 reviews with an emphasis on preventing or resolving
10 medication-related problems, monitoring therapy,
11 providing medication recommendations and drug
12 information, increasing patient access to medication
13 -- and I note that was one of the things that you guys
14 talked about earlier, the access -- and encouraging
15 patient compliance to medications.

16 This study was a small study. It involved
17 24 patients, 12 in each group. You could see that
18 there were no differences between the two groups in
19 terms of gender, age, whether they received a living
20 related donor kidney transplant or a deceased donor,
21 as well as no differences between race or ethnicity.
22 This graph -- you've seen something similar to it

1 before, but I do want to remind you this study differs
2 from the first study in that the month post-study
3 enrollment is also the month post-transplant. So,
4 these are freshly or new transplants. The other one
5 was out a year. So, they kind of developed some
6 patterns before we got to them.

7 Again, reemphasizing the point that many of
8 my colleagues made, the point that Dr. Nickerson
9 talked about in Dr. Nevins' study, is that you really
10 didn't see a big divergence in adherence until after
11 the fourth month. And then you could see that yellow
12 line which was the intervention group, and that
13 control group, that red line, where you see the
14 decrease in adherence. So, it does happen early on in
15 the post-transplant time period.

16 So, the message here is that the
17 intervention group had a statistically higher
18 intervention -- had a statistically higher compliance
19 rate compared to the control group. Now, since we had
20 clinic data we could triangulate the compliance rate.
21 And so in both of these studies, we looked at refill
22 records. However, with this study we were also able

1 to look at immunosuppressive drug concentrations, and
2 we found that more people in the intervention group
3 were in the desired therapeutic range with their drug
4 concentrations, compared to those individuals in the
5 control group. And that was statistically significant
6 as well.

7 Now, the study wasn't powered to look at
8 graft rejections, but I will tell you that two people
9 in the control group had graft rejections compared to
10 zero people in the intervention group, leading to some
11 of the other things that you guys talked about.

12 In terms of the economics, we didn't see any
13 differences in hospital costs, as well as clinic
14 visits, emergency room visits, or total costs between
15 the intervention and the control group. But, we did
16 see a statistical difference in the cost of the
17 medications, with the intervention group having a
18 lower cost of medications compared to the control
19 group. And that's really, really important. What we
20 found is when we looked back at the interventions that
21 the clinical pharmacist was making, many of them
22 involved discontinuing medications that the patient

1 didn't need to be on. There was a lot of duplications
2 of medications. There was a lot of doses that could
3 be decreased. So, that was something that we keyed in
4 to. And as we looked at -- more and more into the
5 cost of the medications, we found that patients in the
6 intervention group had a mean total cost charge of
7 about \$2,600 less per patient than patients in the
8 control group, and that equaled to about \$68,000 just
9 for the intervention group alone.

10 So, looking at both of these studies we came
11 up with some conclusions in summary. The interventions
12 have been developed that successfully improve IST
13 adherence in transplant recipients. Again, as my
14 colleagues have said, most of these are multicomponent
15 interventions, and they're very individualized
16 interventions. And I believe, as well as my
17 colleagues, that resources should be devoted to
18 implementation of evidence-based interventions on a
19 very scalable or large scale medium. So, with that, I
20 want to thank my funding sources, that include NIH as
21 well as the Carlos and Marguerite Mason Trust Fund. I
22 want to thank all of you here today, and I want to

1 thank you guys for inviting me.

2 With that said, I want to introduce the man
3 who reminded me that my child is in adolescence ever
4 since I met him. And so, if you could come up here --
5 and that's Dr. Robert Ettenger. We know that he's
6 distinguished research professor, emeritus, with the
7 department of pediatrics, division of nephrology, at
8 Mattel Children's Hospital, as well as the school of
9 medicine at UCLA. So, thank you very much.

10 (Applause).

11 DR. ETTENGER: So, I have -- excuse me, but
12 I have only one thing to say to you, and that is Mom.
13 Okay.

14 So, quickly, let's talk about what
15 interventions can improve medication adolescence and
16 outcomes. And I think this is very much of an open
17 question. The first question, of course, is what is a
18 successful intervention. And as I mentioned, we tend
19 to talk about taking adherence, because that's what we
20 know, but what we really want to be able to measure is
21 the absence of adverse biological outcomes, and that's
22 a much more difficult situation because of the human

1 condition and different immune responses and
2 metabolisms, et cetera. In addition, different
3 developmental stages, different barriers and different
4 emotional problems require different approaches. And
5 so, as has been said, one size does not fit all and
6 nothing is really more characteristic in adolescent
7 outcomes than one size does not fit all. We can't
8 have just one intervention, unfortunately. We have to
9 tailor the intervention to the family and to the
10 patient.

11 The inherent problems with adherence in
12 adolescents really revolve around the adolescents
13 being concerned with the here and now. As we talked
14 about, there is no pain due to missed medications. In
15 addition, and something that is very, very important
16 and something that adult centers that are trying to
17 take care of adolescent patients will tend not to pick
18 up on is that adolescents benefit from immediate
19 feedback and from incentives. And I'm going to be
20 coming back to immediate feedback and incentives again
21 and again.

22 So, from my standpoint having done this --

1 and I will say, not immodestly, I have taken -- we've
2 just counted up all the transplants that have been
3 taken care of at UCLA since I got there, and we just
4 passed a thousand. So, I know I look like I'm only 35
5 years old, but that's not quite the case. What are
6 the minimal practical guidelines to which to build a
7 successful adherence in adolescent medicine
8 transplantation?

9 Number one, and quite important, is the
10 medical team's communication with the family. We need
11 an interactional model rather than we and they. The
12 approach needs to be non-judgmental, and we need to
13 avoid selective attribution. I always start when I'm
14 asking about issues with my adolescents, and I'm
15 talking one on one with them -- I'll always say I know
16 it's hard to take the medications routinely every
17 single time. Let's, you know, let's talk about this.
18 You really want to stress a team approach. Kids
19 respond well to teams. So, patient, parents, health
20 care providers represent the team. And in fact,
21 personal chemistry develops better with a nurse
22 coordinator, sometimes, as we've heard before, than

1 with the doctor, so that we utilize different
2 individuals to ferret out the presence or absence of
3 medication nonadherence.

4 What sort of post-transplant interventions
5 do we need to put in routinely, even before we start
6 to do any research in one versus another? What do we
7 need to be doing routinely to intervene and improve
8 adherence?

9 Number one, we need to continually educate
10 with every visit. On an individual basis, medication
11 nonadherent behavior can fluctuate dramatically over
12 time. So, what was right this month is not going to
13 be right six months from now. And so these kids,
14 therefore, need to be seen more frequently to provide
15 continual reinforcement, even years after transplant.
16 That is sometimes a difficult pill, and -- you know, I
17 was really interested in talking about not intrusive
18 versus too intrusive. We are most certainly, in the
19 pediatric transplant arena, regarded as too intrusive.
20 Because we'll bring these kids back every six weeks,
21 two months, if we think that there are any issues at
22 all.

1 What happens all too often, and I just -- I
2 was on call Sunday night, and what happened Sunday
3 night, a kid who was taken care of at another center
4 hadn't been seen in four months, came into UCLA
5 because they weren't feeling very well, and the
6 creatinine, which had been 2.0, was 11. And the kid
7 had not been seen for four months, because he didn't
8 need -- you know, he was long out. He was four years
9 out afterwards and didn't need to be seen, and he had
10 stopped his meds. So, we -- unfortunately, we need to
11 see these kids more frequently.

12 Finally, we need to address parent and
13 patient psychological and social problems promptly,
14 and that goes along with seeing these kids frequently.
15 Now, I'm not going to cover each of these areas
16 because Mary Amanda sort of -- this I took from some
17 of her writing about the different sorts of
18 interventions.

19 But, it's important to highlight a few
20 things. With regard to counseling and behavioral
21 interventions, we want to try to change behavior to
22 empower adolescents to participate in their own care,

1 and to develop new skill sets. And you'll see how at
2 least one controlled trial is doing that. We want to
3 try to be alert the psychological and effective issues
4 of the kids addressing their feelings, emotions, and
5 their social relationships. We tend to perform mixed
6 interventions, because one size does not fit all, and
7 almost everything in the literature now is
8 multicomponent interventions.

9 But again, I want to come to a few issues
10 with the immunobiological. Number one, tolerance
11 induction is something that really needs to be
12 considered, not only in the adults, where it's being
13 tried in some centers, but it needs to be really
14 conceptualized in adolescents, because these are the
15 poster children for nonadherence. And yet, they want
16 to show it in adults first. Well, the big risk in
17 situations is not with the adults not taking their
18 medicines near as much as with the adolescents not
19 taking their medicines.

20 Peter has written about improved matching,
21 so I'm not going to be discussing that too much.

22 But I do want to say something about the

1 last point here, and that's the simplifying the drug
2 regimen or reducing the drug burden. All -- a number
3 of the -- and I'm addressing this to my colleagues and
4 friends on the left. I don't mean the left political
5 spectrum, I mean the left -- my left hand. But, those
6 interventions, like one a day tacro, like belatacept,
7 is available to adult patients. They are not
8 available to my adolescents, because we don't know the
9 pharmacokinetics of the once daily drugs. They
10 haven't been adequately reported, that they're not
11 approved in pediatrics. Belatacept, we don't know the
12 pharmacokinetics because the study is just now being
13 completed, and we're not going to have a control trial
14 to meet FDA requirements until, at the very least,
15 2018. We need to get these drugs into the hands of
16 pediatric nephrologists to help manage these things to
17 help ameliorate the issues of medication nonadherence.

18 I will go -- only briefly mention with
19 regard to the cognitive and educational interventions,
20 is that while educational interventions are important
21 educational interventions alone are insufficient by
22 themselves to improve adherence. However, an area

1 that needs to be targeted if we are going to target
2 adherence improvement in pediatrics is in that middle
3 bar that I showed you -- that I'm showing you --
4 useful intervention have to be targeted during the
5 period of time when patients and families are
6 transferring responsibility from parent-directed care
7 to self-adolescent care.

8 General considerations with regard to
9 intervention adherence, multicomponent adherence
10 probably have the highest effectiveness. But
11 treatment effects are strongest immediately after
12 intervention and dissipate over time. Just as we have
13 heard, and it's very true in adolescents, that late
14 out you see this nonadherence. In fact, in addition,
15 we can put in interventions. They may work for the 12
16 months that we're putting them in, but if we don't
17 follow them up and continue to follow these closely,
18 then all that work that has been done in that year is
19 just not going to be useful. So, interventions that
20 study a specific area of time have to be generalizable
21 for longer periods of time.

22 Finally, and something, again, to remember

1 -- there are few randomized control trials in
2 pediatrics. One randomized control trial, the results
3 of which have not been reported, are the take-it study
4 done by Beth Foster up in Canada, and Mary Amanda has
5 been participating, and they utilize a multi-dose
6 pillbox. They use therapeutic drug level variability
7 monitoring, and they're looking at biological
8 outcomes. And they're identifying the patients by the
9 barriers that I mentioned in my first talk, and trying
10 to develop problem-solving skills and developing
11 concrete contingency plans for specific occasions to
12 develop appropriate strategies, if the kids are in
13 situations where they're not able to take them -- so,
14 to develop the best habits for medication adherence.

15 PTSD -- something that I think may resonate
16 with some of you out there, has been studied by Al
17 Shemesh, and reported back in 2000. PTSD is
18 characterized by reexperiencing of emotions, avoidance
19 and hyper arousal responses from previous trauma. So,
20 they did a PTSD response index in 19 liver transplant
21 kids, and 6 of the 19 had positive scores in all three
22 components of the PTS responsive index. Three of the

1 six patients had documented nonadherence, and the PTSD
2 was treated in these three patients with good
3 subsequent adherence. So, the PTSD that somebody
4 mentioned this morning is in fact maybe an important
5 component of adherence, and has not been addressed in
6 a study since the year 2000. So, this is clearly an
7 area that we need more work on.

8 It's also important -- and I don't know if
9 the mother of the pediatric recipient is here -- but
10 PTSD has also been reported in the parents of
11 pediatric recipients.

12 A word about simplifying the drug regimen.
13 It's been recently reported by an ex-trainee and a
14 colleague of Dr. Nickerson's, Tom Blytd-Hansen, that
15 poor adherence is significantly associated with
16 increased medication frequency in pediatric CKD
17 patients. So, this is true with peds as well as
18 adults.

19 So, one should consider and study forgiving
20 medication regimens, and one hypothesis that I have
21 liked is that a once daily regimen of sirolimus and
22 low-dose tac -- with once daily tac or monthly

1 belatacept -- can be a regimen best suited for
2 adolescents. The problem is, as I said, neither of
3 these are available to me to try right now. One
4 danger, of course, with once a day dosing is missing
5 one dose really means missing two doses, because
6 patients are missing morning and evening because
7 they're missing a whole day of dose. Does this put
8 the patient at some increased risk? In any situation
9 where we're studying adolescents, to look at once
10 daily dosing should probably be answering this
11 question. Nonetheless, the table that -- or, the
12 graph that was shown by Bill Fitzsimmons shows that
13 the evening doses are clearly the problems and we know
14 our kids -- our adolescents like to be out in the
15 evening.

16 A word, very quickly, about transition from
17 pediatric-centered care to adult-centered care. We
18 tend to transfer our kids when we have to, which means
19 transferring them when the law says we have to rather
20 than when they're developmentally able to be
21 transferred, and care in a pediatric center is
22 different than care in an adult center. And we see,

1 as I show in the first bar, transfer to adult center
2 care is associated with worsening clinical outcomes.
3 Single transition clinics may work, and may be
4 helpful, but they are resource heavy and we don't have
5 a lot of them right now. But, this is another area
6 that we really need to aim at.

7 Text messaging -- the last two slides are
8 going to be about new developments, mobile health, et
9 cetera. So, what about text messaging and adolescent
10 adherence? With regard to text messaging, the pros
11 are convenience, it addresses forgetfulness and the
12 possibility of instant feedback. The cons,
13 unfortunately, are costs. There is cell service that
14 has to be maintained by the patient, and can be
15 intermittent at times -- so, the texts may not get
16 through. And the patients may get burned out. And
17 there are actually focus groups asking adolescent
18 groups who have been participating in this why don't
19 they acknowledge the text messages anymore, because,
20 as we know, adolescents will sometimes turn us off.
21 Text messaging has been utilized successfully in liver
22 transplants, when you're transferring care from

1 parent-directed care to adolescent self-care. But,
2 there's likely interventions -- additional
3 interventions are going to be needed, in addition to
4 just the text messaging.

5 Finally, two new provocative developments --
6 and this, literally, I found this headline shown on
7 the left, the Proteus's ingestible sensor system is
8 now being used in pediatric organ transplant patients.
9 I'm not sure how well adolescents are going to adjust
10 -- the way this ingestible sensor works is you take a
11 pill where the -- a small wafer -- a vegetable wafer
12 that sends a very weak cell signal is swallowed, goes
13 to the stomach, goes to the -- the pill goes to the
14 stomach. The sensor sends a message to an abdominal
15 or arm patch, which goes to a phone which sends a
16 message to the doctor you took your medicine. This is
17 -- has been tested in adults, has been -- is being
18 betaed in pediatrics. It's an interesting system. It
19 does have some technical issues, and I don't know how
20 many kids are going to go around wearing a bandage on
21 their arm. But it's one other issue.

22 Directly observed therapy is the best way

1 for us to see the kids have taken medications. It has
2 been tried in front of computer screens with
3 adolescents with sickle cell anemia, using a computer
4 platform, and has been found to be successful in
5 getting kids to take their medications. There's a new
6 platform called AI Cure, which uses facial recognition
7 with a smart phone. Kids take the medications as
8 they're -- or, not kids at this point, but only adults
9 -- are taking their medications. It's used in certain
10 clinical trials. I happened to ask one of our
11 audience and one of the previous panelists would you
12 do this if you were an adolescent, and she no, it's
13 too intrusive. But then I said, well, what if we made
14 it worth your while and gave you some extra message
15 units, you know, and bought you a message plan. She
16 goes I'd have to think about that.

17 So, adolescents are quite a challenging
18 area. We can use new technology, but we're going to
19 have to work with what we've been -- the hands we've
20 been dealt, and the hands we've been dealt with
21 adolescents sometimes require some extra work.
22 Anyway, I want to thank you very much for your

1 attention. I turn it back over to the crew.

2 (Applause).

3 MS. EGGERS: Thank you to all the panelists.
4 As a nonexpert in organ transplant, I can speak that
5 it's very appreciative that you're -- all of the panel
6 presentations were very much -- you could tell that
7 you were keeping the nonexperts in mind when you
8 prepared those, and I found them to be -- and I'm
9 seeing head nods, that it's very much appreciated.
10 So, thank you.

11 We have a lot of question in this session.
12 I think we get to dip into a little time. We're
13 actually going to -- there are a couple open public
14 comment, and we're just going to wrap that up at the
15 end of this session. So, we can go for about a half
16 hour with this conversation. And in looking at the
17 questions, they really boil down to three main topics.
18 One is, of all the things we've heard about to help
19 and promote adherence, what resonates. That's
20 questions 1, 2 and -- I'm sorry, 1, 3 and 4. And then
21 there are some questions about resources and can we
22 develop drugs that can solve some of these problems.

1 So, let's focus first on what has resonated
2 about the efforts to promote adherence. I'm going to
3 first ask -- I'm going to call in Kevin, with your
4 advocate hat on and thinking globally, what of the
5 strategies that you hear speaking -- what resonated
6 with you? What kind of thoughts came through your
7 mind?

8 MR. LONGINO: Well, I think most of it's --
9 to use computer terminology, ease of use. You know,
10 the easier the regimen is -- and we're already talked
11 about it. One pill a day, with or without food, is
12 ideal. And if we -- the closer we move to that, I
13 think the more compliant everyone is going to be.

14 MS. EGGERS: Okay. Okay. In the
15 participants here, anything that really resonated with
16 you about strategies that could help address
17 adherence. Kevin, wait -- with the mic.

18 MR. FOWLER: I think just going back to Dr.
19 Dew, your presentation -- you know, just the whole
20 part, your message is understand your population. You
21 know, develop a strategy that's specific to those
22 people. I don't think there's one size fits all. I

1 think the work you have there proves what my intuition
2 has said. So, I would support that.

3 MS. EGGERS: Okay. Anyone else? Right
4 here.

5 MALE SPEAKER: I was dreaming a little bit
6 when the Astellas representative said something about
7 combining the drugs, right. I mean, then I had this
8 magical -- like, I felt like I just woke up, and I
9 said oh, my God, my prograf and cellcept and
10 everything is combined in one pill, and it's going to
11 be so easy. Right. And I doubt that you'll ever get
12 to genetech and, you know, try to combine a pill and -
13 - because there's so many different doses and there's
14 so many different ways to take it. But, that would be
15 huge. Right. I mean, I'm a chronic patient. But I
16 know everyone here is a chronic patient too. And I am
17 on name -- I am on prograf, by the way. And, I mean,
18 I'm not on generic. So, yeah, if they could do that
19 that would be huge.

20 MS. EGGERS: Okay. Right here.

21 MR. RUSHACK: You use patient established
22 support groups.

1 MS. EGGERS: I'm sorry, use?

2 MR. RUSHACK: Patient established support
3 groups. Again, I can give you examples. At HUP there
4 is a website established -- it's a Facebook.
5 Actually, it's a private Facebook on the internet,
6 established by one patient several years ago. And now
7 there are about 130 members.

8 MS. EGGERS: Okay.

9 MR. RUSHACK: And these members interact.
10 Not even daily -- like hourly, with each other. And
11 lots of topics being discussed, and the members
12 provide support for each other and lots of information
13 exchanged. And I think, especially for adolescents,
14 if somehow a -- like providers could find a couple of
15 young patients who could -- would start a group.

16 MS. EGGERS: Okay.

17 MR. RUSHACK: They may be able to influence
18 their peers, better than the -- in formal settings.

19 MS. EGGERS: Great. So, in case you
20 couldn't hear Mikolos, what he was saying was the
21 patient-directed support groups, and he gave Facebook
22 as an example. Has anyone -- or, is anyone currently

1 or have been a part of those support groups? Okay.
2 Anyone else want to talk about the positive or
3 negative effect that it's had? Heather? And speaking
4 of adherent -- like, adherence.

5 FEMALE SPEAKER HEATHER: Adhering, right.
6 Yeah. I think in a way there's a little more -- I
7 guess you have people discussing how long they've been
8 out and the positive -- you know, and you can ask, you
9 know, well, how did you do that, you know. I mean --
10 in fact, that was one of the things I did. I was
11 like, oh, you know, I need all of the information I
12 can. You know, was it exercise, was it, you know, the
13 -- I mean, I never even assumed people stopped taking
14 their medications, like for good.

15 You know, that never occurred to me. I
16 mean, but that is one of the things you hear, you
17 know. This is -- it's like oh, this medication is
18 causing me so many problems, what have you done. And
19 you'll get 15 replies that are really useful. Others
20 are just I'm praying for you. You know, there's all
21 that. But, it's so informative, because you can at
22 least feel like, oh, I'm not the only one with nausea.

1 And this person took, you know, something to help it
2 or that doctor said this -- so, at least it gives you
3 something to ask your doctor. It gives you more
4 pointed questions. So, I find it's been helpful. But
5 can I mention something? I did have a reply for that
6 one thing --

7 MS. EGGERS: Sure.

8 FEMALE SPEAKER HEATHER: -- because I
9 thought when we were talking -- the interventional
10 studies that you were talking about, if that could
11 become -- if, you know, we can convince our groups
12 that that is something -- because we were talking
13 about the psychological issues and the posttraumatic
14 stress and all that, and I'm wondering, now that you
15 do have some studies out there, where this
16 intervention is so -- is useful, is cost-effective, if
17 that couldn't be a -- something that could be part of
18 the overall care across the board. That just -- it
19 just seems right.

20 MS. EGGERS: Okay. We'll go back here.

21 MR. LENNON: So, regarding your -- the
22 discussion on support groups and how it affects

1 adherence and -- one of the things I'm known at --
2 known as at Cincinnati Children's, among patients and
3 families, is Uncle Jack. We need to bring Uncle Jack
4 in to have a conversation with one of the patients.
5 Right.

6 Because being able to relate to somebody who
7 has been through it before and isn't going to
8 necessarily have that position of authority, right, as
9 the doctor or as a parent, and what are the
10 consequences, right. There's no consequences by
11 talking to somebody who has already been through it
12 and, you know, made mistakes in managing the care for
13 themselves previously. And really sharing that, you
14 know, so that they're not able to -- you know, they
15 don't make those same types of mistakes.

16 MS. EGGERS: Uh-huh. We'll go here with
17 Piper and then Kevin, and then --

18 MALE SPEAKER: You know --

19 MS. EGGERS: We're getting good stuff here,
20 and we're going to keep going, I guess.

21 MALE SPEAKER: Following from Uncle Jack
22 over here -- but I think, and I've had conversations

1 with Dr. Nickerson about this too, but I think the one
2 thing to look at this, too, is that you have an
3 untapped resource with patients. So, when I had my
4 transplant my level of wanting to help that first year
5 was so high, but when I wanted to go reach out to the
6 center and support groups to help, the reception
7 wasn't positive. So, I think that, you know, there's
8 a lot of people that really want to help. It doesn't
9 have to be that difficult. You know, you find some
10 trusted people that you can do, and you've got people
11 who are going to be the ambassadors and get that
12 message, and reinforce right behaviors.

13 MS. EGGERS: Okay.

14 MALE SPEAKER: It's not that hard.

15 MS. EGGERS: With Piper.

16 MS. BEATTY WELSH: Okay. I hope I don't get
17 too much backlash for this one, from other patients.
18 But I do want to say that there's -- there is a little
19 bit of a problem, particularly in lung transplant.
20 There's not a lot of standardization of care across
21 centers. And I think some of the support groups can
22 actually cause difficulties for people, because they

1 hear, for example, oh, my center says it's fine to eat
2 sushi. I mean, I've actually heard that. And then,
3 you know, for most lung transplant centers they'll say
4 no, you can't do that. And it becomes a little
5 difficult, because there might be reasons that doctors
6 are telling one particular patient that they can't do
7 X or Y or Z, whereas other patients can.

8 And I think that sometimes a little bit of
9 defiance against the centers -- for example, my lung
10 transplant center does not allow the use of alcohol at
11 all. Some centers seem to allow that. And then --
12 so, patients sort of see it and they think, oh, well,
13 maybe I can use it sometimes. But then they might not
14 be honest with their doctors, because they know that
15 their doctors don't want them using it. And it just
16 -- it sort of creates this instability, I think, of
17 communication. So, I think working on standardizing
18 -- or, at least getting some consensus on the proper
19 way to care for patients is something that could
20 really help maybe make the benefit of those support
21 groups a little more tangible.

22 MS. EGGERS: Great. Thank you, Piper.

1 Comer here with Leilah.

2 MS. SAMPSON: Yeah. Is the mic on? Okay.
3 I feel as though social media and support groups have
4 really held me to a certain level of accountability,
5 because as I've talked to other patients are coming up
6 behind me or who are dealing with transplants and who
7 are on dialysis, I find myself feeling like, okay, I
8 have to take my medicine now because these people are
9 watching me. And if I'm -- you know, if I've already
10 self-appointed myself as support for them, I do also
11 share the good and the bad. You know, I discuss my
12 process and just certain days where I'm not feeling so
13 happy-go-lucky as I'm supposed to feel, post-
14 transplant. And I think they really value that
15 authenticity.

16 And also working with the peers program,
17 with the National Kidney Foundation, as I talk to my
18 mentees and they have questions about post-transplant
19 or things I went through on dialysis, I can go home
20 and I reflect. And I'm like, okay -- it's humbling
21 for me. I used to be on dialysis. I could be back
22 there. So, let me pull it together. Whatever it is

1 I'm dealing with right now, whatever issues I'm having
2 with this medication, just reaching out to people who
3 are coming up on transplant or in transplant help me
4 to hold myself accountable.

5 MS. EGGERS: I think we're hearing about the
6 power, and maybe some limitations of the support
7 groups. I want to make sure we also touch upon the
8 monitoring -- the reminders and the automatic things
9 that we're also touching on today. Any -- from what
10 you heard, about those types of -- any thoughts that
11 resonate? Yeah, that would be great for me -- no, I
12 don't -- I -- for me, anything of that sort.

13 MR. LENNON: I think it sort of maybe goes
14 without saying for some of us, I think most of -- and
15 we've made this observation before, the reason that
16 we're all here is because we own our disease and we're
17 invested in making something work. That said, I also
18 think that most of us in the room and probably those
19 online and those who didn't know about this meeting,
20 et cetera, don't want to be reminded we're sick. I
21 mean, we're patients, right. We have our own
22 classification, right. There's a reason that you guys

1 are holding this meeting for transplant patients,
2 right. No one really wants to be reminded through
3 whatever system -- and by taking their medications,
4 I'm sick, I'm not normal. Right. And so the more and
5 the faster we can get to some of those
6 transformational changes, I hope, you know, that
7 adherence eventually -- the goal of adherence goes
8 away. We don't need adherence, right, because the
9 need to take a medication isn't there at all. So --

10 MS. EGGERS: And that's what -- and so,
11 that's with all -- that's -- you're talking about
12 reminders sort of globally, no matter how they come at
13 you. Okay.

14 MALE SPEAKER: You know, Doctor, what you
15 were talking about earlier about the incentives for
16 adolescents, I was thinking about my son -- 16 years
17 old. He would respond to that. So -- but I think
18 that, you know, to -- I think, again, when you're
19 looking at incentives to promote an adherence, I think
20 they're not sustainable. I think it goes back to the
21 fact that the transplant population as a whole is not
22 really well understood. And where the -- my

1 recommendation is is that's where the time should be
2 spent, to understand your patients. I don't need to
3 be told what to do. Many times I'll tell my doctor
4 what needs to be done. So, I think that's where the
5 shift needs to go. We're not a monolithic group.
6 There's segments, and if you get to understand that
7 segment of patients and implement strategies
8 accordingly.

9 MS. EGGERS: Okay.

10 MALE SPEAKER: Yes. I work in a community
11 in Alpha-1 antitrypsin deficiency, and many of our --
12 many of the people in the community -- not a great
13 percentage, but there are several that have had either
14 lung and/or liver transplant due to their condition.
15 And the nonprofit organization that I work for is
16 called Alpha Net, which is -- everybody that works for
17 Alpha Net is somebody with Alpha-1 antitrypsin
18 deficiency. And it was really refreshing today to
19 hear all of these different adherence -- you know,
20 different angles to get people to adhere more to their
21 medication regimens and to manage their care well.

22 It was very validating for me, because

1 that's exactly the model that we use. We telephone
2 alphas ever month. We talk to them about are you
3 taking your medications, have you been to your doctor,
4 have you kept your appointments, are you exercising.
5 So, all of the critical components of compliance we
6 cover.

7 And it seems to have great outcomes, with
8 some preliminary in-house studies that we've done in
9 promoting, you know, better quality of life for these
10 people as well as, you know, increasing their quality
11 of life as well as their longevity. And I know our
12 medical director, Dr. Sandy Samhouse -- I don't know
13 if any of you know him, but his most recent studies
14 have shown that together with that personal touch,
15 with checking in on compliance items with people that
16 have a specific condition, as well as -- even for
17 those that have been transplanted, those same kinds of
18 questions -- has really made a difference in their
19 lives. So, again, all of the things that you're doing
20 and the presentations that you've made have really
21 validate for me personally that we're on the right
22 track.

1 MS. EGGERS: All right. Jim, I'm going to
2 tie in to Jack's comment. I'm going to put the spot
3 -- this is the second time now I'm putting the
4 spotlight back on you. Sorry. But what Jim's talking
5 about is a type of reminder I think of as the mixed
6 intervention approach. You have reminders and support
7 coupled in one, because you're calling every time.

8 Take it to what you were talking about,
9 about monitors or reminders that are coming at you.
10 How would you respond to Jim? With the support aspect
11 of it, does it remind you that you're sick or does it
12 help you in any way? Do you have any thoughts
13 following up on that?

14 MR. LENNON: Yeah. So, I'm going to, I'm
15 going to seem like a hypocrite, but I have an alarm on
16 my phone to help me take my meds, right. But every
17 time that goes off, I'm like, oh, yeah, no -- you
18 know, most of the population doesn't have to do this.
19 My brother doesn't have to do this, et cetera. And
20 they're not -- it's not that they're not good
21 interventions, right. But -- and it's not that I
22 haven't recommended them to other patients, techniques

1 that have either worked or not worked for me. But,
2 really -- I don't know, I sort of want to -- I mean,
3 well, just to take it a step forward and think about,
4 you know, how do you minimize the impact on the psyche
5 of the patients. And those reminders and that -- you
6 know, it's just more concentration that you have a
7 disease. And if you can have it minimally invasive
8 within the patient's sort of, you know, routine, those
9 are going to be sort of the best interventions. And
10 obviously, those are going to be individual -- you
11 know, individualized. We talk about individualized
12 medicine. So -- yeah.

13 MS. EGGERS: Uh-huh. Thank you.

14 MR. LENNON: So, not that the techniques or
15 reminders aren't good. It's just --

16 MS. EGGERS: But coupled with something
17 else. Something -- a support or just part of your
18 daily life.

19 MR. LENNON: Right. And mom nagging me.

20 MS. EGGERS: Yeah. We'll go right here, and
21 then I -- we'll go over to you.

22 MALE SPEAKER: I think I was just taking

1 everything in, that you were saying. But I also think
2 it's very individual, you know what I mean. To be
3 quite frank with you, I have a reminder too. I don't
4 listen to my reminders anymore, right. Because it
5 just goes off. But I don't think I'm sick if my
6 reminder goes off, right. I mean, right.

7 I mean, I used to think I was sick because I
8 had so many doctor's appointments. That was my big
9 thing. But that's all individual, right. So, for you
10 it may be something else. For me, it's a different
11 issue. But, I really hope technology -- and I think
12 that some of the presenters were going there. We're
13 not there yet, right.

14 This electronic pillbox, I don't think it's
15 perfected yet, quite -- you know. But we hope that
16 Apple or someone else comes out with a really, really
17 cool thing, right, where it's so easy that you do it.
18 And -- but, I just don't think we're there yet.
19 That's all.

20 MS. EGGERS: Okay. Thanks. Let me turn --
21 okay, I was -- Kevin, please.

22 MR. LONGINO: Well, I had a question. If we

1 had the transplant programs represented here, I wonder
2 if we could ask them the same question. Do they have
3 the right incentives to promote adherence. Do they
4 have the right metrics. I know they have a
5 disincentive. If a graft fails, it impacts their
6 score on their quality measures. But, that's driving
7 some behavior. But, do they have the right metrics or
8 incentives to promote adherence to put these kinds of
9 programs in place that we heard about, where people
10 are doing essentially reviews every 3, 6, 9, 12
11 months.

12 MS. EGGERS: All right. Well, then, is this
13 an answer to the question?

14 MALE SPEAKER: It is exactly an answer to
15 the question. There is a disincentive, frankly, in
16 practice to be dealing with adherence, for the
17 following reasons. Number one, usually if you're
18 going to address it you want to be able to do
19 something about it at that time. That means more
20 personnel. The transplant administration is not going
21 to give you that additional personnel. We used to
22 have a psychologist in our clinic. We don't anymore,

1 because of budget cutbacks.

2 Number two, there's an issue of time. Given
3 the large volume in a lot of the adult transplant
4 centers, there's not sufficient time for them to be
5 dealing in-depth with that. If you have a liver --
6 somebody was mentioning this morning, the liver -- and
7 the transplant nurse coordinators are the best
8 invention ever. But, the fact of the matter is that
9 they -- if they have caseloads of 150, 200 patients,
10 they're not going to be able to spend time or call the
11 patients or whatever. So, in fact, adherence
12 monitoring and everything is disincentivized for those
13 reasons.

14 MS. EGGERS: So, in the interest of time,
15 we'll go -- yes, please. Please, go ahead. And then
16 we'll go with Kevin. And then we'll wrap up the --

17 DR. MANNON: So, I've been keeping my mouth
18 shut because I'm a transplant physician. I'm Ros
19 Mannon, and I'm a transplant nephrologist and clinical
20 investigator at University of Alabama, Birmingham.
21 And appreciate the opportunity to be here. I just
22 wanted to address the question about adherence,

1 because I'm in one of those large adult programs. And
2 I think that we have a limited budget, and we do a lot
3 of transplant and you think we're making money but
4 we're a not-for-profit state hospital.

5 And so, the issues of immune monitoring are
6 very expensive now. And we have pharmacists as
7 outpatients, but recently our budget was cut and
8 junior pharmacists on the inpatient squad quit and we
9 had no inpatient pharmacist, so teaching the
10 predischarge all went to nursing staff, who are
11 already overburdened. I think we want to do it.

12 What our program has tried to do is focus on
13 high-risk groups. I'm in a pretty diverse
14 socioeconomic -- I'm in the Deep South, so we have to
15 focus in the first year and we have weekly calls with
16 the coordinators. And we try to look at levels. And
17 that's what we use. So, it's not that we don't care.
18 I think we are just pushed. And our administrative
19 keeps -- the slot to see patients is like ten minutes.
20 And dude, that is not going to make -- you know, I
21 ask, like, how are you feeling. And you -- that's an
22 open-ended question that may take 15 minutes.

1 I do see the psychosocial stress. I see it
2 in particular in the long-term dialysis patient, who
3 has had a routine for ten years, the same people, the
4 same nurses, and they lose that. All the sudden they
5 have this transplant, and a lot of what they did is
6 gone. They can't get back to work.

7 So, there are, I think, a lot of issues. I
8 think that the centers are trying to work on
9 adherence. I don't think most of them do a good job.
10 I don't think we do. And we do look at once a day
11 medications and alterations. But, I think it also
12 goes back to another unmet need is understanding the
13 sufficiency of immunosuppression, because it's
14 different from organ to organ and it's very different
15 from patient to patient.

16 MS. EGGERS: Thank you. We'll have one more
17 -- Kevin, one more comment. And then we'll wrap up.

18 MR. LONGINO: I think just to support, like,
19 what Dr. Mannon said and Dr. Ettenger, is that I don't
20 think it's like -- no one is operating with any bad
21 intentions at all. But I think the truth -- and this
22 is beyond the scope of this conversation, is the way

1 that transplant is set up right now the quality
2 incentives are one year. And until that changes to
3 three years, you're going to keep having these
4 conversations over and over. So, strategically, that
5 needs to be a bigger conversation, to change that.

6 And then you talk about incentives. Then
7 you'll see adherence education rising. But frankly,
8 until that happens you're going to have a lot of just
9 symptomatic responses. So, my two cents.

10 MS. EGGERS: All right. So, we are -- we've
11 had a long day. We didn't get to the issue of
12 forgiving drugs, but I think that hopefully if you're
13 on the expert panel and have perspective that you can
14 give to the docket that would be great. Or, if you're
15 an expert out there or have thoughts on this, do it as
16 well. But, I think it is -- I think that we are --
17 that we have done all we can do in this amount of
18 time.

19 We have two open public comment -- people
20 who signed up for open public comment, and in fairness
21 we do this all -- we do this for every meeting, a
22 chance to give people a floor to talk about something

1 that may be a little bit off topic. And so, I'm going
2 to -- usually we have this script we read. But I'm
3 just going to say the big things. Please keep your
4 comment brief. And if you have anything to disclose
5 -- a financial affiliation or relationship, that would
6 be useful for us to know. We encourage you to
7 disclose it. You don't have to disclose anything.
8 And we'll just bring the mic to you. So, we have two
9 people. Debbie Drew -- do I have that right? And
10 I'll ask you to keep your comment to two minutes or
11 less. Is Debbie here? What? She -- okay. All
12 right. And how about Mary Pierce? Okay.

13 MS. PIERCE: I'll try not to take all four.
14 We started this program by talking about the benefits
15 and the risks of transplant, and I just want to say
16 that with lung transplants the risk is that we'll only
17 live -- 54 percent chance that we'll live for five
18 years. The benefit is that we have a 54 percent
19 chance of living for five years. So, I work with lung
20 disease. I am an Alpha-1 patient. Alpha-1
21 antitrypsin is a genetic disorder that can cause live
22 and/or lung disease in adults, and liver disease in

1 children. In disclosure, I work currently as an
2 advocate for Doman Life Science Services. We're a
3 specialty pharmacy. But I'm here at the request of
4 the Alpha-1 foundation, and basically to summarize the
5 results of a survey that they did recently. And
6 frankly, most of the results have been covered today,
7 with wonderful correlation with what we discovered.

8 We surveyed 81 patients that were a variety,
9 58 with double lungs, 3 single lungs, 37 liver, and a
10 couple of other various patients. And there were just
11 a few things that we didn't really bring up, that were
12 discovered. The question -- most significant
13 disadvantages or complications of your current
14 treatments. Of the group, 74 percent responded that
15 it was about cost and access. And when I was looking
16 at that, I thought oh, my gosh, I don't even know how
17 much my drugs cost. I'm eligible for Medicare. I'm
18 scared of going on Medicare. I'm under a company
19 plan. I added up the cost of my medications for one
20 month, and they're about \$1,500, with the addition of
21 augmentation therapy -- which for Alpha-1 patients we
22 take it before transplant, and it's a bit

1 controversial whether we do it post-transplant. But,
2 43 percent of our people are using it post-transplant.
3 The cost of that drug is 8 to \$12,000 a month. So, we
4 are a little afraid of what's going on with costs and
5 access.

6 We talked about support groups. 96 percent
7 of our respondents are in a support group, either an
8 Alpha-1 or a transplant support group. And I am going
9 to skip over a lot of this.

10 MS. EGGERS: And I hope, Mary, you submit it
11 -- submit the full thing to our docket. So, we'll
12 have it as well.

13 MS. PIERCE: Okay.

14 MS. EGGERS: So, submit all of your results.

15 MS. PIERCE: Good. And then one other
16 question. What's the ideal treatment going to -- what
17 would you consider the ideal treatment for transplant.
18 And again, make it less expensive. 71 percent of the
19 people said that it needs to be less expensive.

20 And then the positive part. How has your
21 condition changed post-transplant -- 69 percent said
22 their condition is better, and 17 percent there was no

1 change. So, those are both positives. 69 percent had
2 depression.

3 And then finally, we asked whether they
4 would be willing to join a working group to work out
5 the next steps, and 88 percent of them said yes, they
6 would volunteer. And I guess I'd pose that to the
7 rest of the transplant patients still in here, how
8 willing would we be to participate in a working group
9 from here on forward. And from what we heard
10 recently, it sounds like it's up to us as patient
11 groups to begin to take over some of these issues that
12 providers don't have funding or time to do. So, I'll
13 leave you all with that question.

14 MS. EGGERS: Thank you very much, Mary. I
15 suppose if you reflect on Mary's question, you can
16 contact through the docket or through those mechanisms
17 -- through PACE. The slides -- by the way, the slides
18 will all be online in a few days, and you will see in
19 there the contact to our professional affairs and
20 stakeholder engagement staff, who can address that.
21 Or, you can come to our team as well. If an
22 organization is interested we'll connect you with that

1 as well.

2 One other thing that came up -- both
3 Michelle and I were going to mention this, which --
4 there was an issue about CMS and their role in here.
5 And we just wanted to acknowledge that that came up.

6 MS. CAMPBELL: And a similar issue, that
7 Debbie was going to bring up, who is our heart
8 transplant patient, was -- her thinking is that maybe
9 some reasons for adherence concerns and issues is
10 related to access, in terms of refills with specialty
11 pharmacies, and really that frontline staff dealing
12 with trying to get your refills and all the other
13 comorbidities you're dealing with, from your
14 transplant and other diseases, the impact of just
15 dealing with sometimes staff and the turnover or the
16 merging and -- or dismerging of pharmacies. So,
17 access level of drugs. And that was her comment.

18 MS. EGGERS: Okay. And another one that I
19 heard about was the strict timelines of the 30 day
20 supply, and the issues that that can raise about that.
21 So, I'm -- that was Ellen's comment. We don't have --
22 Ellen, do you want to say one --

1 MS. COHEN: Only one more moment, please.

2 MS. EGGERS: Okay. We're going to let Ellen
3 do this, because she came up to me so nicely.

4 MS. COHEN: Well, the -- first of all, I
5 love what the FDA is doing in terms of engaging
6 patients. Let me start with that. The other players
7 in this -- one is CMS, and -- one is CMS. The other
8 is Congress. The whole game at the political end is
9 cutting Medicare spending, and that is one of the
10 stresses that CMS works under all the time. But it
11 means, for instance, when you talk about a one a day
12 pill, or combination pill, anything having to do with
13 making it easier for patients to comply is also going
14 to raise cost questions. And you will get a --
15 patients need to engage with CMS in understanding that
16 this isn't just a matter of convenience. That some of
17 these drugs -- the fact that you have an easier way
18 for patients to manage their care, it's not just
19 convenience. It is really a matter of improved
20 outcomes.

21 MS. EGGERS: Great. So, lots, lots of
22 topics were discussed today. Again, go to the docket.

1 We really do read all those comments. And we
2 appreciate them.

3 Evaluation forms -- please fill them out.
4 There should be some at your table. Please leave the
5 clickers here. They're really not useful outside of
6 this room -- and they're not decorative either, so --
7 and with that -- am I missing anything I need to say?
8 Okay. Then, thank you so much to the panelists.
9 We're going to let Renata give some closing remarks.
10 But, I want to thank the panelists and the audience
11 participants for a very engaging discussion. Thank
12 you.

13 DR. ALBRECHT: So, thank you, Sara.
14 Actually, I think there are a lot of groups here today
15 that deserve a round of applause. Several years ago,
16 Theresa Mullin, who did an introduction this morning,
17 met with our division and she said there's this new
18 initiative about involving patients, and we
19 immediately said oh, we've got a topic, we've got a
20 topic. We'd like patients who have solid organ
21 transplant. And she said, well, we can only do 20
22 topics. And every year when they met I said we really

1 want to have a meeting to talk to patients with solid
2 organ transplants. Because in the transplant field,
3 as you heard from our colleagues here on the right
4 with the scientific perspective, and from industry and
5 from physicians and nurses and doctors, we know about
6 their involvement. But we said we really want to hear
7 from patients.

8 So, it is so gratifying to see that today,
9 on the 27th of September, we actually had this
10 patient-focused drug development meeting on -- with
11 patients who have received a solid organ transplant.
12 So, I need to say that to everybody that I spoke
13 during the course of the day, they are just so happy
14 and so excited and so grateful for this opportunity.

15 And I just want to say that we are all so
16 grateful for you taking the time out of your
17 schedules, making the effort to drive -- not just
18 locally, but from far -- Beltway notwithstanding, and
19 I apologize, you're probably going to run into Beltway
20 traffic -- but, it has just been such a wonderful day
21 and we have just heard so much from you, and really
22 benefited from it. So, I want to thank the patients

1 who spoke in the morning. I want to thank Jim, Jeff,
2 Leilah, Michael and Lindsey for the first panel.
3 Piper, Dan, Debbie, Jack and Roberta for the second
4 panel. And all of you that have just voiced your
5 opinion, shared your comment, shared your perspectives
6 and really told us some really important life stories.

7 I think you've identified a lot of issues.
8 FDA is not going to be able to tackle all of them, but
9 I think there are many people in the audience, and
10 there are people who are on the web, and there are
11 people that the transplant community interacts with.
12 And I think many of the messages that you've shared
13 today are going to get repeated to people outside this
14 room. Because I think we really, in the area of
15 transplant, have had a lot of stakeholders and now we
16 also have the patients as part of the dialogue. So,
17 this has been very important. Again, thank you very
18 much. And in the interest of not prolonging the day,
19 thank you and we really appreciate your input today.

20

21

22

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