MEETING

OF

EVIDENCE-BASED TREATMENT DECISIONS IN TRANSPLANTATION, THE RIGHT DOSE & REGIMEN FOR THE RIGHT PATIENT/INDIVIDUALIZED TREATMENT

Conducted by Renata Albrecht, MD

Thursday, September 27, 2018

8:04 a.m.

Food & Drug Administration

White Oak Campus, Building 31

10903 New Hampshire Avenue

The Great Room Section A

Silver Spring, MD 20993

Reported by: Michael Farkas

Capital Reporting Company

1250 Eye Street, NW, Suite 350

Washington, D.C. 20005

Page 2

APPEARANCES

Renata Albrecht, MD, FDA
Roslyn B. Mannon, MD
University of Alabama at Birmingham
Birmingham, AL
Mark Stegall, MD
Mayo Clinic, Rochester, MN
Ameeta Parekh, PhD, FDA
Inish O'Doherty, PhD, C-Path
Katherine A. Hollinger, DVM, MPH, (DACVPM CAPT, USPHS)
FDA
John Michael Sauer, PhD, C-Path
Gary Steven Friedman, MD, Pfizer
Michael M. Abecassis, MD, MBA
Northwestern Medicine, Chicago, IL
Josef Coresh, MD
Johns Hopkins University
Ulf Meier-Kriesche, MD, FAST
Veloxis Pharmaceuticals - TTC Workgroup Co-Chair
Alexandre Loupy, MD, PhD
CHU Necker, Paris, France

Page 3

Randall Morris, MD, FRCP
Stanford University School of Medicine (Emeritus)
Stanford, CA
Ergun Velidedeoglu, MD, FDA
Peter Nickerson, MD, FRCPC, FCAHS
University of Manitoba, Winnipeg
MB, Canada
Peter Heeger, MD
Icahn School of Medicine at Mount Sinai
New York, NY for the CTOT-09 Consortium
Minnie M. Sarwal, MD, PhD, FRCP, DCH
University of California San Francisco
San Francisco, CA
Ken A. Newell, MD, PhD
Emory University, Atlanta, GA
Kevin Fowler, Kidney Health Initiative
Shukal Bala, PhD, FDA
Barbara Murphy, MD, MB, BAO, BCh, FRCPI
Icahn School of Medicine at Mount Sinai
New York, NY
Alexandre Loupy, MD, PhD, CHU Necker
Paris, France

Page 4

Yan Wang, PhD, FDA
Maria P. Hernandez-Fuentes, MD, PhD
Head of Translation Biology for Immunology
UCB Celltech
Edward Chong, MBChB, MRCP
Chief Medical Officer, Vitaeris
Marc Cavaille-Coll, MD, PhD, FDA
Krista Lentine, MD, PhD
Saint Louis University Hospital
St. Louis, MO
David Axelrod, MD, MBA
Lahey Clinic, Burlington, MA
Margaret Mooney, MD
Chief, Clinical Investigations Branch
Larry
Rhia
Shannon Woodward, PharmD, OPSA, FDA
Robert Woodward

Page 5

Page 5

CONTENTS

SPEAKER	PAGE
Renata Albrecht, MD	7
Roslyn B. Mannon, MD	9
Mark Stegall, MD	23
Ameeta Parekh, PhD	35
Inish O'Doherty, PhD	51
Katherine A. Hollinger, DVM, MPH	54
John Michael Sauer, PhD	55
Gary Steven Friedman, MD	72
Josef Coresh, MD	82
Ulf Meier-Kriesche, MD, FAST	98
Ergun Velidedeoglu, MD	137
Peter Nickerson, MD, FRCPC, FCAHS	138
Peter Heeger, MD	154
Roslyn B. Mannon, MD	246
Shukal Bala, PhD	201
Minnie M. Sarwal, MD, PhD, FRCP, DCH	202
Michael M. Abecassis, MD, MBA	219
Barbara Murphy, MD, MB, BAO, BCh, FRCPI	233
Roslyn Mannon, MD	246

SPEAKER	PAGE
Alexandre Loupy, MD	256
Yan Wang, PhD	299
Ken A. Newell, MD, PhD	300
Maria P. Hernandez-Fuentes, MD, PhD	314
Edward Chong, MBChB, MRCP	328
Marc Cavaille-Coll, MD, PhD	366
Krista Lentine, MD, PhD	367
David A. Axelrod, MD	378
Mark D. Stegall, MD	389
Margaret Mooney, MD	407
Shanon Woodward, PharmD, OPSA	450

P R O C E E D I N G S

DR. ALBRECHT: Let's go ahead and get started. Thank you all for coming. My name is Renata Albrecht. I'm from the Division of Transplant and Ophthalmology Products. To the -- to my right is Dr. Inish O'Doherty, my co-moderator, and also the Executive Director of the Transplant Therapeutics Consortium.

It is our distinct pleasure to welcome all of you to the FDA. And we particularly appreciate your taking the time to participate in what we hope to be one of many milestone meetings in our field.

Unlike or previous FDA workshop, this one was planned by FDA in close collaboration with the recently formed Transplant Therapeutic Consortium and the Critical Path Institute. You'll hear about the history of this public-private partnership from Dr. Ros Mannon, Dr. Mark Stegall, and Dr. Ameeta Parekh at the FDA.

Also, during the day, you'll meet many of the people who are part of this effort in academia, industry, government, and other stakeholders, including our patient guests.

So I'll limit my remarks to say how happy and

honored we are to be able to present this open public workshop on the FDA campus today and thank all of you for attending.

Before we start, a few housekeeping rules. You can order boxed lunches at the kiosk outside the room, and there's snacks and coffee available throughout the day. If you have any questions during the day, there are conference room staff outside, and there will be staff in the room to assist you.

So the focus of the first day is going to be biomarkers. This (inaudible) a series of four sessions. And in the fifth session, we'll talk about transplant center practices.

At or near the close of the first day, we'll have an open public comment period. There's a sign-up sheet at the registration desk for the available time for that session. So please, if you're interested, do sign up. And we know we have a number of folks that already have.

The second day, we'll only do two sessions on the patient-focused drug development. And as moderators during that day, Dr. Everly and I will talk

about the goals of that second day as well.

Finally, a comment on the format of this meeting. Each session will have about three to five formal presentations lasting about 15 minutes, at the end of which we'll have a question-and-discussion period. During that period, there will be questions shown on the slides. And what we ask is that we invite everyone in the audience as well as the panel to participate in that discussions. We find those very beneficial.

So with that, let me go ahead and start our meeting. So I'm going to ask Dr. Ros Mannon to please come to the podium and tell us about the call to action, addressing unmet needs in transplantation.

Dr. Mannon.

DR. MANNON: Thank you, Renata, Inish, members of C-Path that have been instrumental in making this probably one of the most collaborative workshops that I've participated in. And also, you made me very nervous because I have a lot to do.

But anyway, these are my disclosures. So I think that, as a new faculty member and attend --

Page 10

working with Allan Kirk in the NIH in the early 2000s, I was excited about the blossoming transplant pipeline shown on the left that Flavio wrote about -- what's new, what's hot. There were many drugs, many opportunities. And within about six years, that pipeline seemed to be dead. And I mean, how many talks have most of us attended where we've seen a slide that Flavio shows of the graveyard of transplant therapeutics?

And it became clear to me as, through my personal interactions, that there was a lot of biologic therapy as immunosuppressants being used in other fields, but it was not coming to our field anymore. And again, when you think about new drug applications over the last, I don't know, 15 years, the really only novel agent that has been approved was in 2011, was Belatacept, or Nulojix. But the only other approvals have been sort of congeners, or variants of current therapies.

There are also really critical, unmet needs. These are the ones that I think about almost on a daily basis -- increasing the number of organs and improving

Page 11

function of non-ideal organs and new therapies to affect that; improving our patients' long-term outcomes after any type of transplant; improving the function of those grafts; immunosuppression medications that minimize comorbidities and improve the quality of life of the patient; trying to avoid viral diseases and cancer, which are prevalent; and then also thinking about what's going to happen for the really critical areas, specific indications such as antibody-mediated rejection, delayed graft rejection, potentials for tolerance and treatments for recurrent diseases post-kidney transplant.

So I wasn't really familiar with private-public partnerships. I knew a lot about cardiac safety. It had been initiated at Duke. I was at Duke quite a bit of my training in my early years. And it was Rob Califf's launch to look at adverse events in these very large cardiology interventional trials.

But in January 2012, Bob Gaston was unable to attend the dinner at the American Society of Nephrology Board. Ron Falk said I could attend because I was the incoming president. He thought it was okay.

Page 12

And Ron's from UNC. He's chief of nephrology. And he discussed with me this goal of improving kidney disease therapeutic pipeline. And he had this amazing vision where he was going to execute a memory of understanding with FDA through an individual called Patrick Archdeacon, who's known here, who was in, I think, in public policy. And they created what was called the Kidney Health Initiative in October 2012.

This initiative, they were specifically requesting participation by AST, but the depth of the participation and interaction in that initiative of transplantation was not clear. And after discussions with Patrick, it became clear that it would have, really, a very limited scope and not really the vision of transforming our field.

However, I do want to say there was a success story that we created, a series of data standards with CDISC and CFAST and want to thank Dan Brennan and Rita Alloway myself, who served on that group.

Around this time, right before that meeting, we had the famous, or perhaps infamous, 2012 endpoints meeting in downtown Silver Spring. And after watching

Page 13

all the HLA Lab directors throw their shoes at each other, it came clear that there were key themes. One is drug safety and the risk of new therapies and how to transform the field when there's a concern about patient safety.

Thinking about this over the next few months, I participated and requested a presence at a public hearing. This was an FDA public hearing here in February of 2013 presenting transplantations unmet needs. This was a hearing about rapid drug approval, predominantly focused on anti-infectives in special populations.

And I really did feel out of place until one of the breaks when Dr. Cox, who runs the office, came down from the podium of infected -- infectious -- he actually is the office that directs the Transplant Ophthalmologic Division. And he came down. And he said, you know, that was a very compelling argument, and we'll be in touch.

And sure enough, a couple weeks later, I participated in a call with some AST staff. Renata Albrecht was on the call, Patrick Archdeacon

Page 14

representing Kidney Health Initiative and public policy, and then tried to raise the awareness for therapeutic advances. Where would transplant fit into Kidney Health Initiative? It wasn't clear. But it was clear that we needed a position statement. We needed a compelling argument and needed to be supported by data.

So I recruited my colleagues -- Rita Alloway, Tim Schroeder from CTI, and Flavio Vincenti -- to help me draft what we call the Call to Action, the Reviving of the Pipeline of Transplant Therapeutic Agents. And we called it a therapeutic initiative, not consortium, because it was just four of us writing about the field.

We highlighted again that patients following transplantation who returned to dialysis, their five-year survival is not any better than some of the patients with cancers. And when you -- when -- I went into this field not to be taking care of patients that were going to die. I was determined to make a difference, and these data are kind of startling.

We also recognize that we take for granted many of the side effects that impair daily living -- diarrhea, headaches, tremors daily, and difficulty

Page 15

thinking -- and then the comorbidities that develop or worsen after transplantation and, God forbid, the return to dialysis. And there's been some amazing work by Allison Tong looking at standardized outcomes in transplantation through the SONG Network.

In the letter drafted to Renata's office, I provided -- we provided in the document a historical background of the status of transplant and unmet needs, a blueprint for action, harnessing other things like information technology and the regulatory demands on investigators and companies in terms of patient safety, and then a potential approach for therapeutic and device development.

And I mention this -- and this was really the focus of my address in 2013 in Seattle. I reminded everyone that how did we get here. And you talked to one group, and they'd say, oh, it's FDA. You talk to another group, and they say, well, it's industry. And I said the biggest problem is us, that we as physicians and scientists have allowed this to continue. And we -- you know, to see and look at a patient day to day and say, well, this is the best I can do for you, your

Page 16

graft's going to fail, it's unacceptable.

So it took a while after that document was drafted. And we did get a response back. And about a few months later in August 2013, we met here with the Office of Translational Science. This is an office responsible for promoting innovation and drug regulatory review across CDER and was really implemented by the Critical Path Initiative amongst other charges.

And Dr. Buckman-Gardner read the document, had a strategy session. I outlined three potential avenues for us to get to where we are today, recommended an individual named Arthur Holden, who works with the iSAEC, Adverse Events Consortium, meeting with Martha Brumfeld and -- from Critical Path, and also talking to the Biomarker Consortium with Steven Hoffman because it was clear that we needed some biomarkers.

Though I was off, I was no longer president but past president, we had monthly calls, we discussed options, and we spent a tremendous amount of time reaching out to these individuals meeting by phone, but also meeting in person to discuss how they would

Page 17

foresee this kind of opportunity for transplantation. And we would regularly check in with OTS. But to be honest, while they were supportive, they weren't going to tell us what to do. They were hands off, allowing us to make these decisions.

Several months later, we had our first organizational meeting. Arthur Holden then, that CEO of the international consortium, facilitated gratis. There were a few companies that attended. We had a mission statement and goals and discussion of funding.

And this was followed by a second meeting. These were both at AST, a public policy office, Bryan Cave offices downtown. This was co-chaired now by the new joint steering task group for TTC, co-chaired by Mark Stegall and myself. We had much more industry representation. FDA and OTS -- transplant and OTS both attended.

And we came up with two core projects. We wanted to address the barriers to the new therapeutic development almost immediately, typically by a consent -- not a consensus paper, but a white paper, and then identify and evaluate new predictive -- transplant

Page 18

predictive technologies that could effective identify rejection phenotypes earlier and maybe help in developing novel drug -- not -- in other words, drug development tools and transplantation.

It's really hard. It was very slow. And at times, I really almost kind of wanted to give up. And I think it's when you're transforming the field you have this naivete that everyone's going to jump on and understand what you're doing, but people don't.

And despite monthly calls, there was a lot of discussion about which path we were going to take; was an individual going to help us get there? I contacted C-Path again in January of 2015, presented that option to the board, thinking that this was really the way to go, that AST was a small organization. This was an opportunity to take and leverage what they had done.

At that time, Neonatal had just joined them, polycystic kidney disease, TB. I mean, these were opportunities for us, and I thought that they had the bandwidth to do this. And they presented, and I attended the board meeting in May 2015.

Later that fall, we had an exciting and

Page 19

exhilarating endpoints workshop. The outline is shown here of the different directions that we were taking. And this was followed very quickly by an international group of investigators the next morning from the Transplantation Society, led by Philip O'Connell and Dirk Kuypers, where we talked about changing and transforming clinical transplantation studies, again, looking at the notion of surrogate endpoints for approval, looking at how well oncology had advanced and maybe using that as a potential model to advance the field.

Later on, the charge that we had at our second organizational meeting to write about barriers was published in 2016. This is the paper by Mark Stegall where we talked about general barriers and the misconceptions of understanding the state of the field, the regulatory issues that are involved, potential funding issues from the biopharma industry, perspective, and then the transplant community -- no blame, just highlighting the issues.

So things really got started in February 2016. The two societies, AST and ASTS, created a co-steering

Page 20

committee with Anil Chandraker, who was then the incoming president; and Ken Newell sitting here; the immediate past president, Mark Stegall, who's here; and I think I saw Dixon Kaufman as well.

Steve Broadbent then several months later had the third -- or I call it the third organizational meeting. He presented the C-Path overview. And I either -- I credit this to him, but it was somebody in the room who said -- and I wrote this in my notes -- "Theory is easier than practice, consensus takes time, and structure is critical." And he -- you know, it's really true. And so when you hear that, you say, okay, you're impatient, but maybe it does have to take some time.

At that time, there were additional attendees. NIAID actively participated. The KHI/ASN came, and there were multiple additional potential industry partners. And so finally, you know, I use the date April 26, but I think officially it was March 2017. The consortium was created as a private-public partnership through C-Path. These are the current partners most recently updating to include CSL Behring

Page 21

and CareDx, who have recently joined the group. And our FDA liaison is Renata Albrecht.

It makes me very proud to go to the C-Path page and see that we're part of the many consortium of organ diseases and also the thing that this organization can do. And you'll hear more about it shortly.

Lots of feedback.

And then I want to thank the people that aren't in this room -- Susan Nelson, who is our exec of AST; Bill Applegate, our director of public policy. I mean, these two individuals for two and a half years really supported me doing this. It was a tremendous amount of staff time, and they were great.

And another person who I know is in this room, Kim Gifford of ASTS -- you know, it's unusual when an individual from one society crosses to the other asks for help. Kim, you did a marvelous job, and you were really helping at a time when we were undergoing a leadership transition within AST.

My other colleagues, Rita, Randy Morris, Randall -- Randy, Flavio, Tim Schroeder, some of whom

Page 22

are here, and then the FDA for really maintaining this, inspiring us, and continuing us to move forward. And my colleagues in the overseas societies that I maintain close contacts with, particularly Nancy Ascher, who strongly supported the notion of getting in on the ground level with this organization.

And finally, you know, where's my passion? So last week, up in Florence, Alabama, or, actually, west of that. I attended a wedding. And you can see the bride there. She's lovely. And the person of interest is this chickee here, and this is her twin sister. She's also my patient. She allowed me to show you this. And she's really struggling with a failing kidney allograft.

And for me to come into the room every few months and say, well, your kidney function's a little bit worse, and we're going to try this blood pressure medicine, she -- she's very young. I want her to be a bride. And I want her to have a family just like her sister's going to go on to. And so that's the thing -- the kind of things that drive me on a daily basis to move forward.

Page 23

Thank you very much.

(Applause.)

DR. ALBRECHT: Thank you, Dr. Mannon.

Next, we'll have a presentation by Dr. Mark Stegall on the Transplant Therapeutic Consortium current workgroups and undertakings.

DR. STEGALL: All right. So again, thanks for inviting us and allowing us to put this effort together the last few years. So these are my disclosures.

And the main reason I really want to get up here this morning is to thank everyone that's worked on this in the last couple of years. The societies definitely have worked on this, I think, quite closely, which I think is a good thing for the societies to do. And I think that really is the -- one of the main reasons why it has been successful, the aforementioned Kim Gifford in -- on our side; members of the TTC as it continues to grow -- now we're up to 10 industry members of the group, and I think that's a good sign that people are understanding that this actually might turn out to be something; and, certainly, the FDA and C-Path have played an instrumental role in getting us

Page 24

to where we are today.

And so I guess just to go back and -- why do we need the TTC? People could still ask that question. It's been said before, just recently, the transplant's not perfect. There's still many unmet needs. And this sometimes, I think, is still not believed by everyone in the field. And we all believe that we have to improve outcomes. We have to have new therapy.

And so what we decided that had to happen was that a collaborative effort that rethinks the entire drug development process, unmet needs, biomarkers, endpoints, safety is what is really needed. And working all together, I think that we can do this.

But what really became apparent, as was just mentioned, is that the people within transplantation needed help from people who have done this sort of thing outside of transplantation. And that's where we are today. We have C-Path and members of the FDA who have gone through this process before.

How did we get there? Well, we had the history that Ros put together. But also, there was a period where we actually took a pause. And I think Ken

Page 25

was one of the very big proponents of this, is to talk to people outside of transplant and ask them what they think, actually, we should be doing, especially industry. I think there was a good back-and-forth discussion with industry about what would be important for them in getting more interest in developing drugs for transplant patients.

We also decided -- we made some very big decisions early on that set us down the pathway that we are going down today. We decided to start with kidney transplantation. For one, it's the largest number of transplants being done. But also, there is the most data in kidney transplant patients. Most drugs are first approved in kidney transplant patients. But there are a few things that the TTC wants to do, and one of the things that it wants to do is to include other organ transplants as we go down the pathway. And so there is -- there -- what we're going to do now and what we're planning to hopefully be able to do in the future.

From the very beginning, we decided to do the yin and yang of drugs. So there is a -- two

Page 26

workgroups. One is the efficacy in workgroup, which is endpoints and biomarkers. And the other looks at drug safety and profiling and characterization. And we became a public-private partnership with the FDA. And there were some of us that didn't think that that would actually ever happen, and it really did. It was good.

As mentioned, there are now 10 members of this, and this is kind of our -- you'll see this slide many, many times. But the idea is that we can sit now and have discussions in what is termed the "precompetitive space." And I think that that's a very healthy thing to do. We can have back-and-forth discussions with FDA, with members in the transplantation community, and move forward.

The summary here is the current direction that we are going is that we are developing novel drug development tools. And that is a term that may be very familiar to some people in this room and totally unfamiliar to other people in this room. But you're going to hear that a lot.

So what is the TTC doing? We're going to develop basically in the next four years two new drug

Page 27

development tools in transplant. And what we're going to end up with is we're going to have one drug development tool that's going to be a safety, basically, benchmarking tool based on standard of care. And then we'll have another drug development tool that's more of an efficacy tool that basically takes post-transplant data that predicts the likelihood of graft loss. And that post-transplant data is based on things like a biopsy, renal function, proteinuria, DSA, those parameters that, basically, everyone can measure and agree upon that exists. And that has been part of some of the predictive models that people have worked on in the last few years. And the specific one we're looking at employing is the iBox tool.

And so that's really where we are. Potential future directions would be to possibly develop validated biomarkers and PRO measures and expand to other types of organs, all right?

So again, I think we hit this at sort of the right time. The FDA, as I read this, have developed public-private partnerships in other areas. And transplant, you know, is a pretty small field when it

Page 28

comes to moving the needle of healthcare in the United States. It's important to us. But truly, it's not -- 95 percent of the patients in the world don't need a transplant. But it's an important field, and it's important for us. And it's important for us to do drug development right.

And therefore, I think the FDA has agreed with us because we did make the list of public-private partnerships. And actually, when I gave this talk last time, we were at the very bottom. So we're not even the (inaudible) kid on the block. The worldwide innovation network, which is -- it's now below us. So there you go. So we're kind of old kind of school right now.

And I think this is important. I think this is really significant that we're not just off in a corner screaming at -- you know, howling at the Moon that are no new drugs. But we've actually tried to incorporate ourselves into the process of drug development and move within that.

So the industry priorities, how we move this way, industry said they wanted drug development tools

Page 29

that would aid in drug development. And mostly, I think they were talking about efficacy tools. And so we took that into advisement.

And you can see the two workgroups, which a bit now are a bit passe because we've already figured out what we're going to do. But out of those workgroups came the -- those two concepts about drug development tools.

And Workgroup 1, which I believe Ken is -- been chairing, primarily, with Ulf, has -- basically is to develop a tool that looks at -- drug development tool looks at new ways of looking at efficacy of drugs. But basically, as I mentioned, it's looking at post-transplant data that would be predicting long-term graft survival, mostly one-year post-transplant data. And those details of that model that has been looked at are there. And the process that we will be doing -- I will show you -- is the same for both of these drug development tools, how we will develop them.

The other one is a group that I've been working with, with Troy Somerville, who is my co-chair from Sanofi. And it's been very clear to us that

Page 30

transplant patients have a lot of serious adverse events. And that can be something that's hard to quantify, but also could be off-putting to industry and getting involved in transplantation and developing new agents because there's just so many adverse events in transplant patients. But we actually don't have a tool to figure out what those adverse events are and how common they are.

And I think that -- so that's what this is about. And there are -- what was the nice thing about this is, as soon as we were starting to think about this, there are people within C-Path who have worked on drug safety profiling and could take that expertise and rapidly apply it to the data that we have from transplant patients.

So that was the synergy that we were able to work on almost immediately kind of like, you know, I think we should do this. And you know, and he said I -- oh, we can do that. I think -- you know, let me just send you a few slides from Klaus (ph), and he'll work on that. And the -- I think that energy that C-Path brings and the expertise both have been -- really help

Page 31

us a lot.

Yeah. So we wrote yet another white paper. And not -- as Ken says, he doesn't think white papers change the world. They probably don't. But at least they get my mind cleared up about what we should be doing. And so hopefully, this white paper will be in the literature looking at this issue of drug safety. And I believe, also, there will be an FDA letter commentary on the paper, too, to clarify all these issues and, if nothing else, to help us with the terminology.

The TTC, I think, now is really about data. That's what we're going to talk about. In fact, that's the talk about now and talk about in the afternoon. It's about data. And data will allow us to do a lot of things, but it's not the kind of data that is a poster at ATC kind of data. This is going to be data that's going to be much more rigorously collected and gone through than other datasets.

And so what happens in this process and the way that we're going to develop these two drug development tools is that we will develop this

Page 32

integrated database from data that we have collected from multiple datasets. But the primary datasets that we will be looking at are Phase 3 randomized multi-center clinical trials. I believe a lot of that data actually already exists here at the FDA because they were FDA trials. And so I think that that would be data that we can definitely look at validating or, let's say, testing, the iBox first tool, and also looking at serious adverse events, which are actually quite detailed caught by that.

I believe that Mike advocates that your CTOT study is part of the data that was sent. We appreciate that. And then there will be a couple of single-center data that actually fit the profile of iBox. One of them is Paris (ph), obviously -- I hope that fits the profile -- and data from our group here at Mayo, also, because that was part of that.

So the way that this works is you put all the data together, and you can start looking at these different two drug development tools and seeing if they really do turn out to be what we hoped that they would be.

Page 33

And if I'm running out of time, I'll go and say that the Transplant Therapeutics Consortium has actually accomplished a lot in the last couple of years. I would even say in the last year it has really taken form. And we have a very clear idea, I think, of where we are going in the next three to four years. And I don't think we're going to take on any more projects in the next three to four years. But hopefully, at the end of this, we will have those two drug development tools developed and then possibly be able to look forward to more projects in the future.

And the announcement I would like to make is that the -- there has been a broad agency announcement, which is basically a contract between FDA and the TTC, which provides some funding for these endeavors and, also, of course, the membership and the continued funding there. And C-Path has also taken some of their money and put into this, also. So we have enough money. We have some ideas.

And as Ros said, you know, good things take time to get right. I have -- so these are apples, actually, that we just harvested from our yard. It

Page 34

took about five years for the trees to make apples for us. And I don't even like apples. But my wife does, so we have a bunch of apples. So probably give -- some of you may be getting, you know, baskets of apples in the future. Who -- it's a nice gift.

And I know a little bit something about processes that are painful and take a long time. This was the kidney allocation system that was changed in the U.S. I wrote this paper five years into the process, and it still was another five years before it finally got programmed and put into place. And people are still complaining and arguing about that.

So I think that the fact that this started in 2013 and it's only 2018 and we're getting along today, these things do take time to get going forward. And you have to find the right people. And so there are a lot of reinventing of ideas that were good ideas at the beginning, and now they're great ideas -- so very optimistic about the future about this.

Thank you.

(Applause.)

DR. ALBRECHT: Thank you, Dr. Stegall.

Page 35

And the last presenter for the introduction session is Dr. Ameeta Parekh from the Office of Translational Science here at FDA. And she'll talk to us about the role of public-private partnerships in catalyzing the critical path.

DR. PAREKH: Well, good morning, everyone. I do want to thank Renata and Inish for giving me this opportunity to talk to you all.

And I'm from the Center for Drug Evaluation and Research at FDA, CDER. And I'm going to talk about the PPPs, the public-private partnerships.

So it's interesting how Dr. Mannon and Dr. Stegall really laid out the need, the unmet need, for the transplant and the fact that such -- I don't know if I want to call it high-hanging fruit -- but it's within the reach, and it's within reach if we work collectively and collaboratively.

And we at CDER, we have extensive experience now. We have multiple partnerships that are already in place. And thanks to Dr. Stegall and his slide, there are -- he showed the glimpse of about four or five consortia that are listed on our public-private

Page 36

partnership website. He also showed the support that Dr. Woodcock has for these endeavors. And below that list, the four or five that he showed, there are a total of about 40-plus consortia that we are currently collaborating with. And we have considerable experience now, and we've gained this over the years. We've stumbled. We've learned. But we know that it works. And I'm going to give you some examples of the role of public-private partnerships in innovation and drug development.

My disclaimer -- so a general outline, I'm going to talk about the challenges in drug development. So drug development is not new. We've been doing this for many, many years. But we've been learning as we go, and we improve on our previous model as we go.

So what are the challenges that we are facing? And what do we need to do to address these challenges? And how do we address this?

So innovation through collaboration is one of the solutions, and one model for this innovation and collaboration is the public-private partnerships. I would like to share with you some success stories. And

Page 37

the key to this -- the three examples and many, many examples that I want to share and that I would ask you to read about is sharing. And I think that's the message behind the success of collaboration through PPPs.

You've seen this before many, many times. And again, every time I see this slide, I get a different message out of this. But basically, what is the slide telling you about drug development? Many compounds in the pipeline, but they fail. And there are failures throughout. And even late in Phase 1, Phase 2, Phase 3, there are failures.

So what's the issue here? The issue is the uncertainty that we face throughout the drug development pipeline. And we all have seen this in different forms or shapes as either reviewers or drug developers or patients, or what have you. And basically, this is telling us, you know, the standard conventional approach, it works. It's a very strong model. But it's costly, and it may not work for everything. And the challenging questions that we have in this day and age -- maybe we need a different

Page 38

approach. And with the technological advances that are available to us in this day and age, maybe we do need to consider other approaches.

And what am I thinking of in terms of these other approaches? Maybe we need new clinical trial endpoints, maybe novel trial designs, maybe novel and better response predictors. Drug development tools have already been talked about -- biomarkers, for example, as drug development tools for safety and efficacy. And Dr. Stegall already talked about his plan for TTC with two drug development tools to be developed.

All of these things can be done by a single entity. It's -- it takes effort. It takes sharing. It takes sharing in a precompetitive space. And Dr. Stegall mentioned that as well.

So what is needed? One of the models, again, that we have experience in is this consortium model, the innovation through collaboration, and one example being public-private partnerships.

What is public-private partnerships? So I've kind of defined it here, the definition that we have

Page 39

used more recently in our manual of policy and procedures. It's a consortium. It's a collaborative group. It's managed by a convening or coordination organization. It involves multiple stakeholder organizations. It includes at least one nonprofit and at least one for-profit organization. And it takes multiple stakeholders to be at the table to share -- to share their experience, to share their expertise, to share their resources.

And what are the benefits? The benefits are you share the benefits. But you also share the cost. So the cost is you -- one single entity doesn't bear the cost of whatever it takes to get a product through.

And I thought there was a very interesting message in Dr. Mannon's slide, and it really fits very well here. And I made a note of it. "Theory is easier than practice, consensus takes time, and structure is important."

And I think as she was reading that and as I was reading that slide, I thought, oh, my gosh, that's PPPs, and that's the collaborative effort that goes into all of the practical aspects. There is a whole --

Page 40

you know, the guidance, the process that's laid out for PPPs. And I think TTC with Inish has the lead and the Critical Path Institute with their experience in 15 or so consortia I think, hopefully -- I have my fingers crossed -- and we can move forward safely in this arena.

From the FDA side -- again, Dr. Stegall already introduced this -- this is a very strong message from the FDA -- we are very supportive of this. And on this same -- this is a public website for the public-private partnerships and consortia. And it has, again, a list of many consortia that we are collaborating with.

If you go and click on each of these links, the consortia links, you'll see how different they are. One is doing this while the other is addressing a totally different issue. And all of these issues that these consortia are addressing are really unmet needs in product development and drug development.

And one of the things that comes with this that Dr. Woodcock and Dr. Scott Gottlieb have been pushing is, to be able to achieve these unmet needs,

Page 41

there needs to be modernization. And in fact, very recently -- I think August -- Dr. Gottlieb has FDA Voice, a blog calling for organization. And Dr. Janet Woodcock had a similar thing from CDER for modernization of the drug development, the whole strategic drug development process at CDER. And both these documents are on FDA Voice. And they are blogs from our leadership, basically supporting collaboration and working together. So I would encourage you to look for that and see the message that they are driving.

So I mentioned that there are multiple consortia that we are currently partnering with, 40-plus. And this didn't happen overnight. If you recall -- and I think Dr. Stegall mentioned, and I kind of maybe disagree with him on one aspect -- and he mentioned white papers don't get you too far, but they do. And the result of the 2004 Critical Path Initiative, which was a white paper in my mind, led to a lot of partnerships and a lot of juices flowing and a lot of thinking. And that's back in 2004, and that white paper led to a lot of thinking, a lot of collaboration. We need to change our model of our

Page 42

routine drug development. Maybe we need to engage more stakeholders, patients, regulators, academicians, industry. We all need to be at this table to address these unmet needs.

So a result of that white paper was a lot of partnerships, a lot of initiatives. And about a couple years back -- it was 10 years since that white paper, the critical path initiative -- we published. We thought, wait, it's been 10 years. What have we gained from these partnerships? And we talk about 40-plus partnerships today. So we published a couple years back on the consortia the role of public-private partnerships in catalyzing the critical path.

And I'm going to take three examples out. There are many, many examples. And they keep growing. If you go to each of those consortia websites, it's really awesome to see how everyone is working together in advancing this whole collaborate -- collaborative model. And so I'm going to give you three specific examples. And interestingly, there's one common denominator that I see across all of these examples and not just these three -- across all of the initiatives

Page 43

that are going on right now. And that is sharing.

So this one -- the first example that I want to share with you -- and I'm just going to give you a quick glimpse. I -- if you're interested, please go to the website. This one is data sharing, and there's different types of sharing. This one is sharing of data. So this is through the consortium, the Critical Path for Alzheimer's disease consortium, which is also under the Critical Path Institute. Sharing of Alzheimer's disease clinical trials data across the consortia partners and working in this precompetitive space, they were able to develop a quantitative disease drug trial model. And this simulates -- so what's the point of this model, right?

So every drug development tool and that -- you'll hear more and more and more about it throughout today and tomorrow -- every tool that is developed has a context of use. Keep that in mind. You can't just get on this path and say I'm going to develop this and this and this and this. Before you get onto that path, ask yourself what is the context of use, how is it going to be useful because that's -- so -- context of

Page 44

use and that drug development tool is a means to an end. And that means to an end, the end is kind of captured in the context of use. And you'll hear more about it in the biomarker realm and maybe in the COA realm tomorrow.

So this -- so what's the context of use, or COU, if I may call that? It -- what's the COU for this? What's the purpose of this? This simulation tool helps with the design and planning of mild to moderate Alzheimer's disease clinical trials and for every context of use. Whether it's a simulation tool, a biomarker, a COA, anything, you need to have that context of use because you want to have a purpose for addressing the unmet needs to this -- the question. And this disease progression model was submitted. The whole package was submitted to the FDA a few years back, and FDA established it as fit for purpose for -- and a dynamic tool that's -- that went through the regulatory acceptance pathway.

So thank you, C-Path for doing this, and you really paved the path for models and ancillary approaches to addressing complex questions in clinical

Page 45

trials.

Talking about complex questions in clinical trials, I'm going to shift the gears to a very novel approach, the master protocols. We've seen, you know, the standardized, prospectively designed, randomized clinical trials. And some master protocols is a novel trial design approach. It's one overarching protocol designed to answer multiple questions.

And going all the way down to the last bullet on this slide, this master protocol, the -- through the I-SPY 2, it was basically a Phase 2 adaptive design in breast cancer. And it basically used two more biomarkers as a tool, a drug development tool, for screening new treatments. And basically, this I-SPY 2 approach and the master protocol approach evaluated multiple therapies across multiple tumor subtypes. And when there was promising drugs, they moved forward into the next stage of drug development.

The next example that I want to tough on is biomarkers. And the biomarkers -- again, going back, we've talked about biomarkers. Let me give the definition and read it out to you. It's a defined

Page 46

characteristic that's measured as an indicator of normal biological processes, pathogenic processes, or response to an exposure or intervention. And there are many types of biomarkers.

And FDA has a pathway, actually three pathways, for getting -- or integrating biomarkers into drug development. The first two are the conventional pathways that many of you are familiar with, the first one being R&D pathway. It goes individual drug development pathway, and it's through the discussions with the specific division, specific therapeutic product, and the context of specific drug development program.

The second one is the scientifically supported community implementation, examples such as serum creatinine or blood pressure. These are biomarkers that have been used for years because the experts have accepted it. And they are broadly, widely used, and appropriate scientific support exists for their use by experts in the community.

The third one, which is what we were discussing earlier -- and John Michael is going to

Page 47

really expand on it and put a lot of effort into explaining what this entails -- is the FDA's biomarker qualification program. This is relatively new as compared to the other two, but not so new. We've learned over the years. We did a pilot, and we worked over the years. And we experimented with this.

And we are finding that this is a good pathway where a group of consortium, for instance, can review and can pull together the data, share the data, and pull together the evidence that's needed. And the evidence that's needed, again, the -- it pivots on the context of use, and the consortium model really helps to drive this forward.

And one example, a successful example, is that of predictive safety testing consortium. They had the first biomarker qualified back in 2008, and this was a nonclinical qualification. Since then, there have been several qualifications, nonclinical as well as clinical qualifications. And there is a paper, a recent paper and going back to the context of use. What evidence do we need for biomarker qualification? And we have FDA leaders in this field who published this paper. So I

Page 48

would encourage you to go to this paper and check it out.

The principles -- I don't want to spend too much time on it. I know John Michael is going to really, really explain every step. But before you start to construct a biomarker roadmap, our drug development tool roadmap, the need statement, the context of use. What is the benefit of being right? What is the risk of being wrong? And all of those things basically help decide what is the evidence that's needed.

And fortunately, the biomarkers, there can be many types of biomarkers. And two collaborative efforts between NIH and FDA and other groups, other experts, we have come up with this BEST Glossary that defines the different types of biomarkers. And when you think of context of use, you can think, hmm, is it going to be a diagnostic? Is it going to be a monitoring biomarker? Am I going to use it for patient selection? Is it going to be enrichment? Is it going to monitor safety? Is it going to monitor efficacy? So there are different types of biomarkers. And again,

Page 49

I would encourage you to look at the BEST Glossary before you decide where am I headed with these drug development tools.

Just stepping back, biomarker qualification is what we've been talking about and we will talk about later today. And again, there will be examples of the three pathways, the R&D pathway, the acceptance through expertise, and the qualification throughout the day today. There will be examples by different speakers.

But as an example, the biomarker qualification process, it's a multi-step process. It takes several steps of evidence generation, and it requires resources and expertise and collaborative efforts of the things that can facilitate the sharing. And there's different types of sharing, and you learn that as you work with TTC and as you hear John Michael in his talk on what kinds of sharings go into this model.

And the role of consortia really ties it all together. The -- for the -- in this case, for development and qualification of biomarkers, they provide a neutral environment. They have timelines. They have partnering. They have the rules and the

Page 50

agreements that are laid out. And the best thing about these consortia effort that FDA works with is really getting everything out there in the public domain.

And Dr. Janet Woodcock is very supportive of these PPPs, and she is really supporting the collaborative partnerships and through our -- the recent blog that I mentioned earlier, modernization of the drug development processes and the strategies are changing and her approach, the infrastructure, is changing. And I would encourage you to see that blog. It was June 4th blog from Dr. Janet Woodcock and FDA Voices. And she's basically sending the message out that we need to work together to achieve such unmet needs.

Thank you.

(Applause.)

DR. ALBRECHT: Thank you. Thank you very much, Dr. Parekh.

And now we'll move to Session 1. And I'll introduce -- or I'll have Dr. Inish O'Doherty and Dr. Kathy Hollinger, who is from FDA, introduce themselves and take over Session 1.

Page 51

DR. O'DOHERTY: So hello. My name is Inish O'Doherty from the Critical Path Institute. I'm the executive director for the Transplant Therapeutics Consortium.

Thank you again for everyone coming here today. I think it's -- as both Dr. Stegall and Dr. Mannon worked very well to explain, it's taken a long time to get here. These things take time. There's a certain amount of churn. But we're making progress. We do it together. It takes time to have community consensus. So having you all here today is -- you know, it's standing room only in the room is a great achievement for that.

We're going to be going through Session 1. I'll just give a brief overview of how that fits into the course of the day. You know, we're not always saying that Day 1 is biomarkers. And this Session 1 is really focused at giving a level set to the audience and saying, yes, biomarkers exist in the community. We're not doubting that. And they're being used even in clinical decision-making. But how can one make the transition from using a biomarker in clinical

Page 52

considerations and clinical practice to be able to use it for regulatory decision-making in drug development? And these two things don't need to be mutually exclusive. But if you're not aware that there's differences that need to be considered, you're going to miss the mark when you want to be able to incorporate this into a regulatory decision process for drug development.

So you know, and another big thank you goes to the speakers for all these sessions and the planning calls and, you know, taking it on board that we're asking people to think about this a little bit differently than they do on a daily basis, understanding that there's going to be a great body of work done. But how do we translate that into a drug development setting? That's what we're looking to be able to do here today.

So we're not always going to do it exactly right. There might be a misstep in nomenclature, but we're bringing the community forward together, working together on these new principles of how it's going to be applied to drug development, ultimately to get new

Page 53

tools.

So as I said, Session 1 is going to be focused on kind of level-setting with the audience, understanding how to, in this case, qualify a biomarker. And it doesn't mean that every biomarker needs to be qualified. Dr. Ameeta Parekh talked about the idea that there's other pathways. But really, what the first talk's going to look at is how do you create a framework to look at the considerations that one should when examining a biomarker for a regulatory process, so the context of use statement, the unmet need, and the evidence that needs to go in that.

So that's really a theme that we're working on throughout today to try to apply to biomarkers that exist in the community to think about how they can move into drug development.

So at a high level, we're going to work through those, the biomarker presentations, from pre-transplantation. As you'll see in the agenda, it goes to early post and then late post-transplantation. And you'll see that theme we want to carry from the Session 1 throughout that idea of the progression of transplant

Page 54

and how they may be used.

So again, a great pleasure to have you all here today. I'll let Dr. Kathy Hollinger introduce herself as well.

DR. HOLLINGER: Thank you, Inish.

Hi. My name is Kathy Hollinger. I'm a veterinarian and an epidemiologist in the Biomarker Qualification Program. I joined that program a year ago, and biomarkers have been worked on here at FDA for about a decade, if I understand the history correctly, Ameeta. You've been working with them longer. And there may be other people here in the room from FDA who have worked on biomarkers as well.

What I want to say is, in my short tenure in the program, I have worked with some folks on submissions for biomarker qualification. And kind of turning your mindset from a clinical perspective into a regulatory drug development tool perspective is going to help you very, very much. And the more specific your request or your submission is and focused on that drug development aspect, the better we can help you and the more focused our recommendations can be back to you

Page 55

on how to build the evidence that you need to get it to move toward qualification.

So I look forward to the panel discussion, and I look forward to working with many of you in the future.

Thank you.

DR. O'DOHERTY: So without further ado, I'd like to introduce Dr. John Michael Sauer. He's a program officer at the Critical Path Institute and executive director for the Predictive Safety Testing Consortium. And he's going to be talking today about what evidence is required to qualify a biomarker.

DR. SAUER: Great. Thanks a lot for the introduction, Inish. And I'm really happy to be here today. This is going to be a fun talk.

My objective is to really help you understand the biomarker qualification pathway. I'm going to use a lot of the same slides that Ameeta actually used. I'm going to go into a little bit more depth.

And the reason that I'm using those same slides -- it's not by accident -- we need to make sure that we're all on the same page in the words that we

Page 56

use and how we think about this because there is now a codified process by which biomarkers are accepted by the FDA. And so it's best if we follow the process to be successful.

So again, Ameeta already showed you this. What's the definition of a biomarker? I'm not going to read it out loud, but, I mean, it's important that we all understand what this statement means and what it doesn't mean. And many times, what happens is we get into qualifications, and we work with partners. And they begin to think that the assay is being qualified or the assay is the biomarker. That's not right. It's not the assay. It's the actual, you know, molecular, histological, radiographic, or physiological thing that is being measured that's actually the biomarker. And that's an important aspect, right? So we're on the same page there with biomarkers.

Ameeta showed this slide. I'm going to concentrate on the biomarker qualification program. Now, I think when we look at this slide and we look at these different ways of introducing biomarkers, sometimes we're drawn to that community consensus

Page 57

approach. Believe it or not, that's actually a longer approach than actually doing qualification.

What we do in qualification is we basically take the 50 or so years it takes to reach community consensus, and we push that down into 4 or 8 years, right, and do the right science so that we can then convince ourselves as scientists and the regulatory folks that, indeed, these biomarkers do what we say they do.

Again, so what is biomarker qualification? So it's a formal regulatory review and an acceptance process of biomarkers to be used in drug development. So as is on the FDA website, a qualification is a conclusion that, within the stated context of use, the biomarker can be relied upon to have specific interpretation to application and drug development and regulatory review. In other words, we know how the biomarker works, and we're sure that it works that way. We understand the caveats associated with it and when we can and cannot apply that biomarker in drug development.

Again, scientific and -- scientific acceptance

Page 58

and regulatory certainty -- that's what we're looking at, right, so that we can stand up in front of the audience like this and say this is what the biomarker does, these are the conclusions that I'm going to draw from it.

So the exciting part for drug developers is that when they now use a qualified biomarker in drug development, they're going to know what the FDA is thinking and how they're going to interpret that data. Likewise, cut points, clinically significant cut points, those are already being determined, right, and they're predetermined in many cases. Likewise, the quality of the analytics that are required to measure the biomarker have already been accepted.

Now, one thing that's important to remember, and to differentiate from how we think about in vitro diagnostics and other approaches, qualification does not mean that that assay that's being used to measure the biomarker is an in vitro diagnostic, right? It can be, but it doesn't have to be. And likewise, just because you qualify a biomarker, it doesn't automatically give it that status or its assay that

Page 59

status.

I think an important aspect, also, is that qualification just isn't biomarker discovery or clinical validation. They're both a part of it. There's no doubt about it. But it's taking that entire package and being able to then convince the community and to convince regulators how that biomarker works.

And so it's very analogous to drug development in many ways. The documents are very similar. And how they go through the quality, if you will, the biomarker and the data behind that biomarker.

So what is really objective as a qualification? Once a biomarker is qualified, it's available. It's available to the public, right? It's not a proprietary approach, right? And that's important because that's what we're trying to do because we're trying to change drug development overall by introducing these various approaches.

These biomarkers are meant to streamline drug development and speed the review process. A biomarker that's used for regulatory decision-making that's not qualified, basically, you're going to have to prove to

Page 60

that regulatory agency that, indeed, it's performing the way it's performing. But if the biomarker is qualified, that's already been done for you.

Again, the biomarker process, you know, provides a framework -- and that's what I'm going to go into next -- of how, basically, DDTs, these drug development tools, are accepted by the FDA.

So it all starts with a drug development need. So you want to solve a problem. What is that problem? And how are you going to solve it, and how could a biomarker potentially solve that problem for you?

So what you do is you go ahead and you figure out what you want to do with that biomarker very specifically. And that's what the context of use is -- how that biomarker is going to be used within drug development.

Then what comes from there is there's a level of evidence that needs to be met, and that's really a discussion with the agency around what this package is going to look like for the acceptance of the biomarker. Then the actual acceptance happens, and then hopefully that drug development need or gap is then solved.

Page 61

This has all been codified by law by the 21st Century Cures Act. Section 507 actually goes deeply into the qualification of drug development tools. This law was put in place about two years ago, and it really codifies the approach that needs to be used in order to interact with the FDA and to gain approval of these biomarkers or endorsement of these biomarkers.

So here goes the process kind of drawn out, right? It's not graphically drawn out, but I'll show you that later. How to think through the road map, if you will.

So what's the gap? How can you state what the need is? Develop your context of use, which is the concise description of the biomarker's specific use in drug development. Understand the benefit to patients, right, and also the risk associated with the biomarker being wrong because that's all going to then feed into what the evidence that's required. It's a pretty simple map, but the nice part what it does, it creates a conversation piece for requesters, folks trying to qualify biomarkers, to be able to communicate with the FDA and use the same language.

Page 62

So another way to think about this context of use statement, it's like a drug label, right? How is this biomarker going to be applied in drug development? And there's really two elements to any context of use. The first is the class of the biomarker. Is it a diagnostic biomarker, a prognostic biomarker, or is it a clinical trial endpoint?

And this has all been outlined in the BEST Glossary. So if you ever have time, take a look at the BEST Glossary, and it allows you to understand how to characterize these different biomarkers and how they can be used.

The second part of the context of use is really what question is the biomarker intended to address, right? So what is its fit-for-purpose use?

So here are the different classes of biomarkers. I'm not going to go through them one by one, but you can see on these slides that there are a number of different classes that biomarkers can fit into. You know, I think everybody's drawn to the one from the second from the bottom, the reasonably likely surrogate endpoint, but it's the hardest one to get to.

Page 63

And we'll talk a little bit about that with the level of evidence. Probably the easiest one to get to is a diagnostic biomarker, and we can talk a little bit about that.

The next thing, you know, we need to think about is, you know, what is now that biomarker intended to actually address. Why do you want that qualified? Why do you want to use that biomarker? And there's some pretty defined terms out there -- so inclusion, exclusions, right, criteria; you know, stopping a patient in a clinical trial; you know, establishing proof of concept in a given patient population. So there's multiple uses for these biomarkers. So it's very important that we clearly state how we're going to use these biomarkers.

Now, Ameeta showed this slide previously. But really, what it does is it links the different categories, really, to the intended uses. So the nice part, those need to correlate, right? So -- and then that's how you really define then the biomarker category or class that you're going to end up in and then be able to link that then to the use of the biomarker.

Page 64

So again, in the templated guidance documents that are associated with the biomarker qualification and creating a context of use, the -- as I said, there's two important categories to creating a context of use, right -- the category of the biomarker and then its drug development use.

Now, that seems like it's going to be a one-sentence thing. But as you can see from this example from our Polycystic Kidney Disease Outcome Consortium for total kidney volume, you know, it's also very descriptive, right? There's no doubt that it includes those two important pieces -- in this case, a prognostic enrichment biomarker that's to be used for the -- as an enrichment factor in clinical trials.

So -- but what it also does, this context of use, allows users of the biomarker to also then understand how this fits in and how they can apply it to their given trial or their drug development program.

Probably, you know, dealing with consortia, the place where we face the largest amount of anxiety is actually around how much evidence is required in order for be -- for us to be successful. And that's a conversation that can't happen in the absence of the regulators. There has to be alignment around that.

But here's a couple things to think about. This is where qualification differs from drug development. When we think about the level of evidence that's required to register a drug for broad usage, we look at a preponderance of data to support that drug development.

But when we look at biomarker qualification, we're really looking at a correlation. In other words, does the biomarker actually mimic and correlate with the gold standard. It's a really important aspect because it changes your entire statistical approach and how you think about gathering data, et cetera.

The nice part is that, you know, we do have a framework to work from and to drive the conversation with regulators, right? You've seen this before. You've also seen this before from Ameeta. I mean, some people learn graphically; some people like words. I'm a graph guy.

I mean, so you think about it. You know, you

Page 66

have a given statement, a need statement, what you want to do, what you want to solve. You create that context of use. You go ahead then and talk about the benefit, risk. And then from there, you can have a very robust discussion around what the evidence is required to go ahead and then meet qualification.

So one thing to think about is let's say you have a biomarker that you believe could be a surrogate endpoint. But you also know that this is a response biomarker that can be used in clinical trials as an endpoint. Likewise, you know there could be a prognostic biomarker to go ahead and actually use for patient enrichment.

It's a heck of a lot easier to start at the prognostic biomarker point. You don't have as robust of a context of use as you would for a reasonably likely surrogate endpoint. And therefore, the data expectations, the regulatory expectations, the evidentiary expectations are much lower. It's going to be easier to be able to begin to use that biomarker, and they're going to increase as you move towards a response biomarker and then towards a surrogate

Page 67

endpoint.

Now, I realize this is a generalization. But it's going to hold true regardless, right? It's just where the expectations are because, in order to achieve that context of use, you're going to need that much more evidence.

We can break down the evidence component pretty easily. There's two major areas that we need to think about -- first, the analytical validation, the assay that's being used, and the performance characteristics of that assay.

The other side of the coin is really around the clinical validation and whether or not this biomarker actually correlates to the gold standard or not and how well it does, right? Does it do what we want it to do?

We published a paper. I believe last year it came out, and this was around a workshop that was held around defining, really, how we go ahead and codify this process, right, of discussion -- of discussing what evidence is really required to support biomarker qualification.

Page 68

We used safety biomarkers as the example within this publication. And the reason was, was that was the most advanced biomarkers that were moving through the qualification process. And Gary Friedman is actually going to talk a little bit about some kidney safety biomarkers that we've recently qualified and how that was done.

But let me make it more complex for you. Sorry. I have to do this. So if you look at it, when we break down those two features, the clinical validation as well as the analytical validation, we can break it down in the subcategories that need to be met to various degrees, depending on what category of biomarker you choose and what the use of that biomarker is -- in other words, the context of use.

So assay performance -- the validation of the assay is absolutely important, right? You need to make sure that when you measure a given biomarker that you can do that repeatedly, right? Now, we know that most early biomarkers we don't have reference standards, different aspects like that. So you know, sometimes that accuracy aspect will be we can't address all the

Page 69

time. But again, we have ways of dealing with that.

So characterizing the relationship of the biomarker to the clinical outcomes, or whatever that gold standard is, you know, the biological rationale for a biomarker is very important, especially when you're talking to the regulators, right? This is why we think this biomarker is doing what it's doing. Is that always needed? Maybe not. Maybe not. Sometimes it just correlates, and you don't understand why -- but again, an important conversation.

Also, then think about how you're going to achieve your qualification, what datatypes you're actually going to utilize. So in every case, we have to have a prospective analysis, right? But it doesn't have to be prospective data. It could be retrospective data where there's now a new prospective analysis associated with it. So that's something to think about. I mean, do you want to conduct a new trial, or do you want to use data that already exists?

Data reproducibility -- this is a very important aspect of qualification. It's learn and confirm. It's exploratory data followed by

Page 70

confirmatory data. Use the exploratory data to set your cut points and set your hypothesis. Allow that to then be confirmed in a different data set.

Again, comparison to the current standard -- of course, that has to happen. But let's face it. That can sometimes be an issue. If you're having a biomarker that is more sensitive than the current standard, then all of the responses from your new biomarkers are considered false positives. So you sometimes have to reach beyond the current standard and discuss, really, what is the truth that this biomarker is demonstrating.

Pre-specified statistical analysis and then, of course, the strength of the evidence, right? In the end, it's always the strength of the evidence, right? We're scientists. That's what we're driven on.

Here goes just for fun. I put -- very good. Just for fun, I put in two contexts -- I put in a context of use here, and I put in two different possibilities. So in this context of use, we're using some kidney safety biomarkers in individuals with normal renal function. Well, there's a certain base

Page 71

level of evidence. How can we look at where we need more evidence? Well, what if we now apply this to this kidney -- these kidney safety biomarkers now to both individuals with normal renal function, but also individuals with the disease, a chronic disease? Well, of course there's going to have to be more evidence. Your baseline of these biomarkers may be different. The response of these biomarkers to additional insult to the kidney may be different.

A second one is, if you look at this context of use closely, we're using these biomarkers in conjunction with the conventional kidney safety biomarkers -- serum creatinine, BUN, and cystatin C. What if we decide to go ahead and remove those biomarkers and these new biomarkers overtake that? Of course, once again, a higher level of evidence is required. And so that's why it's very important that you craft your context of use such that you're able to obtain that with the data you have or the data that you're looking at generating.

Well, I'll stop there and say thank you.

(Applause.)

Page 72

DR. O'DOHERTY: Thanks, John Michael, for giving a background there, kind of looking at the high-level landscape of, you know, what do we talk about when biomarkers are being considered for drug development, and, also, what do the regulators consider.

So next up, we have Dr. Gary Friedman, who's actually at Pfizer, but a member of the Predictive Safety Testing Consortium. And he's going to be talking about biomarker qualification but with a specific example, working through the process John Michael just worked through, looking at kidney safety biomarkers.

Now, these are biomarkers for drug-induced injury. They're -- you know, we're not saying that these are the biomarkers for transplant. What we're saying is look at the process. This is a worked example of how you navigate that process using this framework.

So Gary, over to you from here.

DR. FRIEDMAN: Inish, thanks very much.

Dr. Albrecht, members of the FDA, we're

Page 73

grateful for your support throughout this long development process. Inish, John Michael, we would not have gotten to where we are without your being good shepherds. So thank you very much.

So without further ado, we're going to take this from the theoretical to the actual. Here are my disclosures. And I've had the good fortune of being part of both the Predictive Safety Testing Consortium based here in the U.S., but also the honor and pleasure of being part of the safer -- well, SAFE-T has a different acronym now. So I'll forgo that one.

But the processes that we have worked through in conjunction with FDA, with EME, and the Critical Path Institute, we could not be here without their guidance, their flexibility. And they're supporting us through some pretty dark days.

And I'm here at this podium speaking. But behind me, actually, are a couple hundred individuals who have been participating in this throughout the EU, throughout the United States, academic centers, pharmaceutical companies, and the like. And I believe we've got everybody on this slide, but I may have left

Page 74

off somebody. So I'll apologize for having left anybody off. But this is an acknowledgement that I'm here as a representative of the Predictive Safety Testing Consortium, and we could not be where we are now without each and every one of these members.

So cutting to the chase in November of 2016, the SAFE-T Consortium achieved this -- the issuance of this letter of support. And this was issued by the FDA as well as a separate letter was issued by the EMA. And I want to share with you that one of the most exciting and amazing aspects was being in the room here in Silver Spring with members of FDA and EMA or being at Westferry Circus in London with members of EMA and FDA all working in concert and, again, with our good shepherds at the Critical Path Institute helping us along.

So here you see the biomarkers that John Michael was referring to just a few moments ago and each of the steps in the process that were required to get to where we are. I'm going to touch on those right now. It's a bit difficult to consolidate all that information concisely in the next 15 minutes.

Page 75

But the piece de resistance was just about six weeks ago where you see this qualification determination letter issued by individuals within -- in the room here. And it is really as we move toward the adjudication of the two prospective studies. And that adjudication process will begin imminently. We expect to be able to deliver that data to FDA and to EMA within the next quarter. And that will be the next step as we move potentially toward full qualification of these biomarkers.

So before you run out of the room screaming, know that everything that was described earlier in terms of the processes -- so the FDA and the EMA, each taking the gaps that they perceive in terms of drug development steps and the ability to move from early preclinical development all the way to drug approval, each of the steps -- and you heard the acronym BEST, biomarkers endpoints testing, each of the learnings and the growth that FDA put together in place before us should take what you see in front of you and potentially contract those timelines.

Going back, however, to 2006 and then moving

Page 76

forward all the way to 2017-'18 are what I'm going to tell you about in summary right now. But each of these steps, as we move through them, we move through them with FDA, with EMA, with Critical Path Institute guiding us every step of the way.

Some of the authors of this publication may or may not be in the room here. But they -- in this publication in 2010, there were 10 articles that were produced -- that provided the roadmap, really, for where we are as of this moment. And the -- this first publication that you see here describes well FDA and EMA perceptions of where the gaps are.

And then on the right side of this slide, it describes the creation of a Critical Path Initiative. And you see incarnate those representatives here to my right. Furthering that publication, the universe of potential biomarkers all the way from the glomerulus, all the way to the collecting duct, you see a smattering of the couple dozen of potential biomarkers that we could consider as we move forward.

You may recognize quite a number of the names there. And you'll notice that, while some of them are

Page 77

from academia, others are clearly from pharma, particularly in this case. Two of the authors are from Novartis. And a number of you in this room have probably interacted with each of these investigators, whether the academic side or the pharma side.

Again, the sharing of data that was emphasized before, you have within the Predictive Safety Testing Consortium, you have for the drug injury -- drug-induced kidney injury work stream, working group. You have members from Pfizer, from Novartis, from -- you name it. They're all present, and they're all sharing information and working closely with ac (ph) admissions who are bringing their acute kidney injury patients or their normal, healthy volunteers to our focus so that we can obtain the requisite samples.

And what was done is, as we move through the approximately 60-plus biomarkers from the glomerulus to the collecting duct, we did the ROC analyses. And those things that fell below the diagonal line were clearly dispensed with. And fortunately, you can see -- - in the upper quadrant, you can see -- without going into the data in specific, you can see the number of

Page 78

biomarkers that exceeded the 50 percent area under the curve. You can see the biomarkers that, if you look closely here, you'll notice that there is a very light -- my wife says I'm color-challenged -- but there is a light mauve curve there. And above that are all of the biomarkers that meet or exceed serum creatinine. And so with this evidence, we move forward in that learn-and-confirm strategy that was referenced earlier.

So what we did was, in terms of within SAFE-T and within PSTC, the preclinical data that were derived from various animal models in animals exposed to cisplatin, aminoglycosides, and other tubular toxins, including cyclosporine and tacrolimus, we began to look at some of those biomarkers that ended up in the urine samples.

And with the preclinical learnings, we then, within the EU at a number of sites -- for instance, in Paris, in Barcelona, and in London and in Dublin -- recruited healthy volunteers as well as individuals with malignancies or with infections and then began to capture those samples that really compose the outputs of the learning phase.

Page 79

From there, we then designed here within the United States two prospective trials where almost 300 subjects have been enrolled. All of their data has now been captured. All the samples have been analyzed, and the data have now been locked. And we will now have an adjudication process by six expert nephrologists who will be independently looking at all of the information.

I'm not going to go into this in detail, but suffice to say, this is our favorite picture, clearly, by the preceding speakers. So in this specific instance, you see the red-highlighted box. So this SAFE-T Consortium, the Predictive Safety Testing Consortium, with the urinary biomarkers all normalize for urinary creatinine. We selected to go with the path of a safety biomarker. And the context of use you can see there as in terms of looking at the presence or the extent of toxicity related to intervention or exposure.

And in a nutshell, there were approximately 150 subjects, either normal, healthy volunteers, or clinical subjects who were exposed to a known

Page 80

nephrotoxin. And you can see that what SAFE-T and what PSTC did, there was some harmonization in terms of the collection points of all of those data. So you can see prior to exposure, during exposure, and after exposure. We can see the rise and fall of each of the biomarkers that ultimately were outlined in that letter of support.

I'm not going to go through this in detail. But suffice to say that, from 2009 to 2018, we've gone from the garnering of preclinical data for each of the biomarkers, done the analysis to see with area under the curve which of those biomarkers we should consider and which we should discard. And subsequently, the letters of support were issued by EMA and FTA.

But really, where we are right now is at this moment. We are about to read out two prospective studies of individuals exposed to cisplatin and individuals exposed to aminoglycoside, and individuals that are matching controls. And those will be read out over the next quarter. And then subsequently, as those individual adjudications are completed and they're completed independently, those data will then be

Page 81

collated and then submitted to FDA and to EMA.

And I'm going to stop right there and really thank you for your time and attention.

(Applause.)

DR. O'DOHERTY: Thanks, Gary, for going through that.

And I think it -- it's nice to be able to see that, you know, certain consortia have really paved the way and have been the vanguard of working through this qualification process with FDA. You know, we've had multiple planning calls to say that qualification is an evolution and -- in its processes within the FDA and EMA. And I think that's clearly evidence through this process.

So a bit of a change of gears on this one. We're going to have Dr. Josef Coresh presenting on GFR decline as an endpoint in clinical trials and CKD. Now, this wasn't a qualification process but, rather, more along the lines of scientific community consensus using a very well-established measure that already existed in the community. So still the same principles of understanding the data that's necessary to garner

Page 82

this endorsement, but a bit of a shift of gears regarding changing from qualification.

DR. CORESH: Thank you. I want to thank you for the opportunity to come, listen, and present and congratulate you on this important undertaking.

So we looked at GFR decline as an endpoint in clinical trials of CKD, and we did this using the CKD Prognosis Consortium and other collaborations that I'll tell you about the next 15 minutes.

In terms of the outline, I wanted to talk for one slide about the criteria for assessing a surrogate outcome in CKD, and you've heard about that already. I wanted to emphasize that our approach was to use data to make progress. And I think you've seen a lot of that, and I think the increased emphasis on data, collaboration, consortia coming together in longstanding undertakings is really important.

I think the other thing that we've contributed is in thinking about surrogates for clinical trials. We realize the data within trials in CKD was limited. So we added data from observational studies and from simulations. And I'll show you that, and I think that

Page 83

helped sort of reach the threshold, which is not a simple threshold to know what thresholds you need.

These, you know, build on the 2012 FDA workshop, and I'll give you the conclusion at the end so you can think about it. And hopefully, you're somewhat familiar with it. It's been published in 2014. And that is that using estimated GFR change as a surrogate outcome, going from a doubling of serum creatinine, which is a 57 percent reduction in estimated GFR, to a lower threshold of 30 to 40 percent reduction is a useful surrogate. And the useful thing is, by looking at data, we could quantify the major caveats, which really related to an acute effect that can nullify the whole paradigm, right? So I think, often, it's both getting to the conclusion and knowing when the conclusion can and cannot be applied.

In terms of related work, we've continued this work sort of, yeah, you're right there award for finishing something in science is you have three new questions, right? And hopefully, you actually get to pursue them thoughtfully. And we finished a related FDA workshop in 2018 on changing in albuminuria and on

Page 84

GFR slopes as a more refined way to look at change in GFR. And I'm happy to discuss that. The papers for that will be presented at the ASN. And then two are going to be published shortly, and two more will be submitted after that.

So I think it's helpful for me in chronic kidney disease to start with the KDIGO guidelines, which define CKD as an abnormality of kidney structure or function present for three or more months. The staging since 2013 is by cause, GFR category, and albuminuria, right? And the colors are sort of a heat map of risk. The lower the GFR, the higher the risk. The higher the albuminuria, the higher the risk. But it's important, especially for this meeting, that cause is important. And within transplantation, you have various nuances of the different pathologic processes going within this cause.

It's also important to note that, when the guidelines were published, progression data were very limited. So we made some statements with limited evidence that decline in GFR category or a drop by 25 percent or rapid progression slope of more than 5 ML

Page 85

permitted per year were, you know, reasonable things to do. But the evidence was limited, and the confidence is dependent on the number of years and number of measures you had. And in terms of albuminuria, we noted that small fluctuations are common, but we didn't have all the evidence to really talk about what level of change was going to be useful.

In terms of assessing a candidate's surrogate endpoint, right -- so now when we get to a biomarker and we want to use it as a surrogate, we really need sort of the highest level of evidence, right? The categories are clear -- so biologic plausibility, strength and consistency of epidemiologic observational data, and, most importantly, prediction of the treatment effects on the clinical outcome from the surrogate. And within that, there are categories in the BEST document which are very useful of a candidate surrogate, a reasonably likely surrogate, and a validated surrogate.

And it's clear that, for the validated surrogate, which would allow drug approval based on the surrogate, you need high evidence, right? But we found

Page 86

it a little bit frustrating that it's not easy to know what is high evidence. And maybe it will never be fully defined, but it's a bit of a challenge to continue to write as people try and, you know, sort of clear that highest obstacle as to what it would be.

So what did we do, right? So this is the summary of a number of years of work. And we were fortunate that we had the CKD Prognosis Consortium, which was born in 2009, out of a controversy. And again, when we succeeded in resolving the controversy, we were given yet another task in forming a consortium. And formally -- fortunately, it builds to progress. The consortium has continued to grow over the last now 10 years. It's amazing. You look back at all these timelines, and you think, oh, we're moving fast. And then, boom, it's a decade. We're moving fast. Boom, it's another decade. But hopefully, we've done something.

And at this point, we've got 70 cohorts that regularly participate. They're allowed to opt in or out into every analysis. So there's no guarantee. They could all disappear tomorrow if they don't like

Page 87

what we do. But basically, almost everybody participates. And with larger datasets and health systems, we've got up to 10 million participants globally.

And I'd like to acknowledge Morgan Grams, who's the co-PI of the consortium; and Andy Levey, who does a lot of the helping, thinking, and editing; Ron Gansevoort in the Netherlands. And this is a group of all the leading investigators we meet annually to pursue the different topics.

This is a list of the investigators and key cohorts. It's just always good to acknowledge that people have done, really, decades of work and then share their data. And it is a tricky balance in that you don't want to just take their data and run with it. You have to sort of really give back something, even if it's just scientific credit, collaboration, and the ability to succeed locally, right, where, often, you really can't pay for any of this stuff.

So what did we do in terms of CKD progression, right? We decided to focus on evidence and on future risk. So observationally, we took the clinical trials

Page 88

perspective, that if you started two patients in an equal starting point, we're going to adjust for the first point. And we -- the question is: Is more rapid CKD progression from Path B compared to Path A associated with higher subsequent risk of ESRD? So we divided it into a baseline period in which we assess the rate of progression or the change, and then we said does that predict the future.

And in many ways, if you look at this, you'll be, like, saying, well, it may be obvious. If their GFR's lower at the beginning of the end of the baseline, of course they'll get the ESRD faster. But that suggests that you believe in GFR being useful, right?

It is important to distinguish that this is different from the diagram on the right, right? That -- - clinicians often see patients at the last measurement because they use all of their data. And they say, given two patients with the same last measurement, is the past slope predictive of future? And it turns out that's a much harder question. We address that as well in papers. But for the surrogacy, it's really the left

Page 89

question that we address.

And we analyze participants in each cohort. In each cohort, we model the percent change in estimated GFR using a spline. We meta-analyzed across cohorts using a random effect meta-analysis. And then we examined the heterogeneity using forest plots and meta regression, right? And the advantage is, if you see both a result and strong consistency across the globe, you are much more confident in terms of concluding that you have something that is really biologically important, consistent, and predictive.

So what did the data show for the observational studies, right? So basically, this is the baseline characteristics and follow-up. And you'll see that we had 19 cohorts with a GFR less than 60, 9 cohorts with a GFR above 60, lots of patients. We looked at one- and two- and three-year baseline periods. We had a number of serum creatinines at two years of about three, and that's the result I'll show you -- lots of ESRD events so we can look at things with precision and about 2.4 years after the two-year baseline period, right? And the mean GFR for below 60

Page 90

was 48 and for above 60 was 90.

This is the risk curve. For a GFR less than 60, we saw that, if you look at percent change in estimated GFR and you use 0 percent as the reference point, then the lower percent change with a doubling of serum creatinine, which was already used by the FDA, the doubling of serum creatinine resulted in a 31-fold greater risk of ESRD subsequently.

And in a way, I was very happy because when we prepared for this meeting, we met with Ed Lewis (ph) and some of the other people who established this surrogate. And it turns out about 30 years ago or so when you establish a surrogate, you know, it's a cab ride to the FDA where the senior statistician and the senior scientist talked and said, so what's a good surrogate? And then they presented something. And if it worked, it worked. And the amount of data available was a lot weaker. It turns out they chose very good reasonable things. And maybe everybody made the right decision and didn't need 10 years of data. I think now we actually need the data to show it.

And the good thing is, I think, in this day

Page 91

and age, we shouldn't take surrogates for granted. We've had some very complicated stories with HDL cholesterol, et cetera.

So the established surrogate worked. And then the question was: Could you back down from that? And what we did was sort of emphasized that, if you looked at a 30 percent decline in GFR, basically, you saw 5-fold subsequent risk of ESRD, which was substantial risk. And it was impressively 6.6-fold at GFR greater than 60, very consistent, right?

We also saw that an increase and a decrease weren't exactly symmetric, so that was important. And then, importantly, the percentage of the population that had an attributable risk was much higher. So in some sense, when you back off to a lesser criterion, you get less or relative risk -- you know, 5-fold rather than 30-fold, but the percentage of the population that experienced this and explained the event was much higher. So the clinical trials with smaller size could actually reach adequate power.

In terms of consistency, it was quite impressive for this outcome, right? I mean, basically,

Page 92

if you look at increased risk, every study showed increased risk -- one wasn't significant, but that was a smaller study -- and higher GFR, a little more heterogeneity, but, still, very impressive consistency for the results.

Then we -- basically, where did we go from there? What we did was we wrote up the result in the cohorts, and that was published shortly after the workshop. We wrote up the results for the observational analysis of clinical trials, the intention to treat analysis of clinical trials. And I'll show you that result briefly. We did simulations, and then Andy Levey drew up a summary of all of this. And then there were commentaries by both the FDA and the EMA about their interpretation of the level of evidence. And then since then, we've been sort of gratified that a number of companies have taken this evidence and built it into their drug development pipeline, right?

I don't think we have a guarantee in a document that this will always work, as in a guidance itself. But instead, we have a body of evidence, a set

Page 93

of publications, and, I think, an understanding of how things work.

This is the data for the clinical trials. And Leslie Inker worked hard on this for a long time to get all the trials. There were 37 randomized trials. But really, data were still limited. Here, they're plotted by drug category, and you can see that, even within the categories of interventions, the standard errors are quite wide.

You also need -- in order to get surrogacy, what you want to see is that a good correlation across studies between the hazard ratio of the alternative outcome really plotted on the X-axis here the surrogate trying to predict the hazard ratio of the established outcome. So if something is very protective on the alternative outcome here, meaning showing less reduction in GFR, it's less likely -- it should also be protective on the definitive outcome, which was end-stage renal disease or doubling of serum creatinine, right? And then drug categories that worked less well on the alternative would work less well on the trial.

You need a range of results, from studies that

Page 94

work very well to studies that work poorly, to get a good correlation. And then you actually have to do some pretty sophisticated tools for all sorts of adjustments for inherent correlations within the studies.

So I think the trials alone were completely consistent, but I don't know they're completely convincing without the observational studies.

We also did simulations. And they, again, supported the use of a 30 to 40 percent decline. That's been published separately. I won't go into the details. But they did nicely point out that, if you have no acute effect, then you really get a Type 1 error (ph) that's success -- acceptable, and the power is improved.

If, on the other hand, you're looking for the long-term effect on GFR, but within the first month or two you actually have an acute hemodynamic effect that changes your GFR by more than a few milliliters, that actually alters your ability to look at the long-term effect, right? So actually, it gave us a major caveat in thinking about this. And it limits the use, but it

Page 95

should limit the use to the appropriate cases where it is useful.

So the summary of the evidence from all the sources, observational studies, trials, and simulations was that, based on a series of metanalyses of the cohorts, clinical trials, and simulations of trial designs and analytic methods, the workshop concluded, including a whole discussion, all the scientists from various stakeholders that confirmed -- so this last endpoint of decline -- it's useful if you repeat it, and it turns out that that increases the power a fair amount -- decline an estimated GFR of 30 percent or 40 percent over 2 to 3 years may be an acceptable surrogate endpoint in some circumstances. But the pattern of treatment effects on GFR must be examined specifically. Acute effect on estimated GFR are an issue. So statements are a little bit nuanced, I guess, in trying to show the example.

And the conclusions are basically that meaningful CKD progression can be understood in the context of its prediction of future risk in surrogacy. And I gave you the conclusion for 30 to 40 percent

Page 96

decline. Within transplant, I think we'll have to look at sort of different acute effects and drugs, different short-term variability, so the actual context for this specific use, right? I said I would give this talk if I presented the data we have, not the data we don't have.

Ongoing work -- so, you know, once we did this, a number of years later, the FDA talked with the National Kidney Foundation. And they said, well, what about slopes and integrating all the different data points. And I actually was a little bit, you know, thinking we already did all this work; we already did a bunch on the slopes; it's all in these 50-page supplements; maybe we don't have to do it. But I was quite interested in albuminuria change, which we hadn't tackled. We tackled a decade before that.

And so we did both topics. And actually, interestingly, the slopes were very powerful. And you'll see some of those results presented, and I'm glad to discuss them in questions.

And finally, surrogacy speaks only to efficacy, not safety, I think, which may be related to

Page 97

off-target effects. So in some sense, if you get a surrogate that's very specific to what you need and you get it to move in the right way, if it's strong, it should predict the clinical outcomes. But the surrogate isn't necessarily likely to capture off-target effects on other pathways, and that's where safety data needs to be assembled in a complementary fashion.

So in closing, I wanted to acknowledge that it really takes a lot of people to do this. The CKD-EPI collaboration -- and this is a picture at the FDA workshop in 2018; the CKD Prognosis Consortium -- and I give you the definition of consortium, which I think is a neat thing. This is our group at Hopkins that does data coordination, and this is the group of investigators for that. And really, the NKF-FDA workshop attendees, international collaborations, co-investigators, it really -- you know, to get to a consensus, it takes a lot of people and listening to everybody.

So thank you.

(Applause.)

Page 98

DR. O'DOHERTY: Thank you for that great presentation. I think it really shows, you know, going after an unmet need through a structured process, although not qualification but still very data-driven, you can see the similarities that really cross-pollinate there.

So in the final presentation, we're going to have Dr. Ulf Meier-Kriesche from Veloxis, who is a co-chair of Workgroup 1 and the TTC, which is a biomarkers and endpoints workgroup. And he'll be talking about clinical biomarkers versus qualified biomarkers for uses, endpoints, and clinical trials of therapeutics.

DR. MEIER-KRIESCHE: Yeah. Thank you so much, Inish.

We have heard now from three different speakers how daunting of a task it can be to get an endpoint, let alone a surrogate endpoint into therapeutic space. Nevertheless, the kidney space has made dramatic progress. And in transplantation, suddenly, we are trying to learn from the other areas of where progress has been made in order to potentially accelerate the timelines we have heard about one

Page 99

decade, two decades, right? We are trying to make something happening a little bit earlier.

But where do we really come from? Why is acute rejection graft loss, death and loss to follow up our endpoint? A lot of people have pointed out that this is really less than ideal. Yes, it is the ultimate verification of whether a therapy works or not. But again, it's very difficult to develop trials for this endpoint.

But if we step back at wherever we are coming from, historically, acute rejection loss actually really important. A lot of patients lost their grafts due to acute rejection in the last century. Graft survival in the beginning was 50 percent at a year. Patient survival was dismal, too. And so the loss to follow-up has always been and will always have to be an assessment just because of potential of bias in the assessments.

But there has been, obviously, a lot of change. From 1950 when transplantation started to now, outcomes have changed dramatically. And with that, the relevance of our endpoint has changed. So now that, I

Page 100

mean, graft and patient survival exceeds 95 percent, now that rejection rates are very low and the impact of rejection certainly has changed over time, our endpoint is really -- I'm not going to say not applicable anymore, but certainly it is something very difficult to measure with the number of patients we have available in our therapeutic space.

So now the burning question is, obviously, why has this endpoint never been updated. We have had that for a long time. We have complained about for -- for a long time. Why hasn't it changed?

To make it very clear, it is not the FDA's mandate to come up with new endpoints. It is really up to the transplant community to drive new endpoints. And while the community has come up with a lot of endpoints which can be clinically useful, we have not really undertaken a concerted effort to drive new endpoints through a biomarker qualification process.

And this is changing now. So with this public-private partnership, we are trying to recognize the steps we have to take to qualify biomarkers which potentially can be used for endpoints in

Page 101

transplantation.

And certainly, there have been very authoritative voices in the field of transplantation pointing out how big of a problem for drug development this is. We all know that we have a fairly dried up drug development pipeline in transplantation, and that is because our population is relatively small. We have a standard of care which produces good one-year results. We have a significant unmet need, but that is in the long term. So again, it's difficult to measure. So how can we bridge all of this?

There is clearly not one specific solution for the transplant community, but we're going to have to start somewhere. Certainly, one would want to be in oncology, right? We would like to have surrogate endpoints, and you have heard how difficult that is. We would like to have clinical trial networks, novel clinical trial designs, adaptive trial designs. These are all things we can explore. But certainly, we have to start somewhere.

So to this end, you have heard the Transplant Therapeutics Consortium was launched in March 2017,

Page 102

first of all, identify the areas where we all agree upon we can make a difference and then trying to drive specifically these initiatives forward.

You have seen this slide. This is how the Transplant Therapeutics Consortium is constructed, importantly, to point out that the societies are really leading the way here. They originally really brought this into our space. Importantly, the FDA and NIH are part of it, but also the industry stakeholders. So it is in the precompetitive space where we can have all discussions and agree on things which make sense for our therapeutic area to improve drug development.

So how can the C-Path model, which obviously has been tried in quite a few instances successfully, be applied to transplantation? As a first step, we identified key challenges. So we set biomarkers and endpoints as clearly one of the key challenges. So we established a workgroup for that. And as Mark explained, although we established another workgroup for drug and safety profiling in transplantation.

Step 2 then is to specifically develop drug development tools. And so we are going to develop one

Page 103

drug development tool to start out with as an endpoint in transplantation and one safety drug development tool.

How to we gain regulatory acceptance? There are different pathways, and I'm not going to belabor this here. We can either go through the regular qualification process, or we can get endorsement through the fit-for-purpose process. Which way we'll ultimately go depends a lot on the data we produce and the ultimately context of use we are seeking.

The structure of the consortium, again, to point out that there's a lot of input from the societies. We have two workgroups which share the data. They are going to bring in a lot of data. That's really where the tactical working part is, to coordinate the data, house the data. And fortunately, for both workgroups we will have similar data needs.

Ken and I are chairing the biomarkers and endpoints workgroup. What we are going to try to do is, as we have heard a lot, we need a context of use. We are going to establish that. We are going to look at the datasets available, predominantly phase III

Page 104

clinical trials in the space. And the basic idea is to take the one-year data from these clinical trials, look at a constructed endpoint, which I'm going to talk a little bit more in a moment, at a year and then see with long-term follow-up data from the public registries what the long-term outcomes of these patients are and see if this candidate endpoint is actually predictive.

We are going to put this into a modeling plan and ultimately get agency feedback. Then we are going to produce all the data, submit the patient-level data, and then hopefully at a certain point get endorsement for the biomarker.

This slide you have already seen. It's just to point out that the process we are proposing for the TTC Workgroup 1 is very -- well-aligned with the general framework for biomarkers within the FDA.

So clearly, the unmet need we have talked about is the drug development process where we need new endpoints. There are other things which, of course, obviously being done. And as I have talked about, we are also going to look at biomarkers. Eventually, we

Page 105

may look at clinical trial designs. But again, the primary objective right now is to find a new endpoint in transplantation.

Specifically, one of the challenges in the endpoints is to have biological plausibility for these endpoints, and we have been really lucky that Alex Loupy in France has been working for many years on the idea to combine clinically meaningful parameters, which most of us in the field actually believe in and try to model them into a composite score. And the reason why that gives us a little bit of a head start -- we do not have to go in and explain why renal function and the measurement of renal function itself is significant -- same for DSAs and proteinuria.

So essentially, the iBox Alex has developed will give us a scoring system at a year after transplantation, and we are going to try to reproduce what he has already shown, that that correlates to long-term outcomes.

To further refine the goals, specifically, we are going to try to predict five-year graft survival. But that's because we probably have that data available

Page 106

for most of the data, we are going to bring in. And certainly, this has to be supplemented with strong mechanistic and epidemiologic rationale.

If this ultimately leads to what we would like to have, which is a reasonably likely surrogate endpoint, this can be instrumental in clinical trials because it could lead to an accelerated approval process, granted, with post-marketing follow-up. If we wanted something which gives us approval without a post-marketing follow-up, then we will need a surrogate endpoint. (inaudible) is really the reason we like the surrogate endpoint. Once a lot of trials are going to be conducted with that, eventually, we may have enough data to seek, really, to obtain a surrogate endpoint.

So the next steps is really to perform the data landscape analysis, and we have already done that, in large part, bring the data in, standardize the data, put them into a data warehouse, and then, again, connect them to the long-term outcomes data developing a modeling plan.

Here are some of the datasets where we are in negotiation with the pharmaceutical companies who have

Page 107

these large datasets. Again, and I have to thank everybody who has worked on this on both sides, on the C-Path side and on the industry side, because this is a lot of work to create data-sharing agreements and create data catalogs. And -- but again, there has been a lot of progress, and we know that there is a lot of data available which will be instrumental in testing the iBox, which has already been modeled by Alex Loupy in France.

So you have seen that there are a lot of different biomarker categories. And in transplantation, we also could think about several different ones. But what we ultimately really would like to get to is a reasonably likely surrogate endpoint because that would allow us to discriminate new therapies, have potentially lower patient numbers needed to show differences, potentially a shorter trial duration. And that will ultimately incentivize industry stakeholders to come in and look at the space more favorably.

So the worker (ph) goal -- obviously, we need to acquire the data we talked about that will support

Page 108

then the quantitative platform and ultimately the submission for regulatory endorsement.

Here's a little bit of the progress we have made. You have heard we have started in 2017. There have been a lot of different meetings which have really driven forward the understanding of us as a limited community, but also the broader community of what we are really doing. And it's really taking very nice shape this year with several presentations at public meetings. We are going to seek advice from the FDA, and that will really guide our path forward in developing the -- this as our hopeful final product of the surrogate endpoint.

And I think, with that, we are up to the end of this session. And we are going to go into the questions. Thank you.

(Applause.)

DR. O'DOHERTY: So as you can see in the agenda, there's a number of questions that are there as guidance on -- to stoke conversation should there not be questions from the floor. But knowing that, you know, the transplant group is always a talkative bunch,

Page 109

I'm sure there will be a few. So we invite folks to come up to the mics and pose questions, but also those that are sitting on the table if they would like to be able to jump and ask any questions on the individual talks or on any of the specific ones that are laid in on the screens at this point in time.

And if there is not an abundance of people to stand up straightaway, maybe I can, you know, ask for perspective from a fellow C-Pather and also for folks who are involved in the Biomarker Qualification Program at the FDA.

I think the first one there, you know, the idea of how do we know when a biomarker is ready to start the qualification process -- John Michael, I know you've dealt a lot with consortia in their fledgling stages to understand how they're thinking about this process, but, you know, kind of giving that perspective from the third-party entity.

DR. SAUER: Yeah, absolutely. Thanks, Inish. That's a really good question.

I mean, what we go through C-Path is a process called regulatory readiness, if you will. And what we

Page 110

try to do is understand around the given biomarker that we want to pursue exactly what data is behind it, so the status, right, because when we're thinking about qualification, we're not thinking about doing biomarker discovery, right? We want to make sure that there's a pretty solid package around that biomarker before we bring it to FDA if we have that opportunity.

So I think that's the important part. When you're thinking about we want to take a biomarker through qualification, where is it actually at? And do a legitimate assessment of that biomarker because that's what the Agency is going to be looking for. That way, you can have a very direct conversation about what else needs to happen along this biomarker pathway.

DR. O'DOHERTY: Thanks, John Michael.

And I know, Kathy, as co-moderator and working the biomarker program, you see a lot of different efforts, not asking to talk about any of those individual particular efforts, but kind of general thematic viewpoints of the Agency when they're looking at these considerations and early submissions.

DR. HOLLINGER: Okay. Thank you, Inish.

Page 111

What I want to get down to is some of the process focus as well because the 21st Century Cures Act mandated a three-step process, or stage process that's starting with a letter of intent and then moving to a qualification package and then to -- or sorry -- plan, and then a full qualification package.

And you know, when you ask the question how do you know when you're ready to start the process, you would be starting that process at the letter of intent stage. And that stage is a pretty light-weight place to start. It's simply asking you what is your biomarker, what's your drug development need, do you have a feasible way to measure it, and what are you proposing as your context of use with knowledge, full knowledge, that context of use can change throughout this qualification process and would change, basically, based on the data that you are providing at the subsequent stages the qualification plan and the full qualification package to reflect what substantiation you have provided for that context of use.

So you're ready to start maybe before you have all of the data that you need because you want to start

Page 112

working with the FDA fairly early so that we can help shape what your plan might look like. And what you get in response to that first stage, the letter of intent stage, is a letter that tells you whether FDA accepts your proposal or your concept into the biomarker qualification program. And in that letter, we provide you with a number of recommendations or suggestions for how to move into your next stage.

So if you come to the table with what might -- you might feel is a fully prepared qualification package and you're starting with an LOI, you might find that FDA has some other thoughts or considerations that might reroute your pathway forward. And so please don't hesitate to start if you know what your biomarker is, if you have a feasible and reliable way to measure that biomarker, and you clearly have a sense of where that will fit in your drug development context of use statement.

And use is basically -- when you look at what your context of use is, you may have started with where is your drug development need. And sometimes your drug development need is where are your biggest problems,

Page 113

where are your roadblocks, where are your challenges.

DR. SAUER: I would like to add one point in that the interactions with FDA for qualification are different than with drug development. It is really a partnership, a scientific partnership, of how to get that biomarker qualified. And so you have to work together.

And what you'll find is that the meetings are a bit more relaxed. I remember when I was in, you know -- in a drug company. I mean, we really didn't have some of those basic scientific discussions that we get to have within the realm of qualification. And so that's an important thing to remember. I mean, it truly is a partnership in trying to get these drug development tools out because everybody wins. FDA wins. The drug developers win. So that's why I think that partnership is that way.

DR. NEWELL: I was going to ask a question I fear I know the answer to, but it's related to procedure.

And so, if I understand from John Michael, there's different types of biomarkers. So there's

Page 114

prognostic. There are those that predict responses to interventions, and there are surrogate endpoints. And they require different levels of evidence. And those would be driven by the context of use, I'm sure.

But so if you said I have -- and as she said, there could be a biomarker or a candidate biomarker that fulfills many of those. So if you say I have something that hits all three of those or some of the others, when you go forward, you're going to say I'm going to propose a reasonably likely surrogate endpoint, and the context of use will be this. If the evidence in the end isn't quite there, is it possible without restarting the process all over to say it doesn't quite meet this bar, but it meets a somewhat lower bar and then to say, okay, and if we get more evidence down the road, we can go back under the same kind of application and have it move up to a, you know, more stringent biomarker?

DR. HOLLINGER: Absolutely. And that's what I mentioned when I was saying that the context of use can evolve throughout this process. And it will be based on what data you've presented to support your context

Page 115

of use. Sometimes we find that, you know, that biomarker needs to be used in conjunction with certain other factors, whether it's a clinical evaluation or whether it's other tests, to be able to be used for a specific context of use. So that's one way you might modify it.

Or you might actually modify the actual use of it. So rather than using it as an endpoint, you might use it as an enrichment factor or for, you know, identifying certain treatment arms or some other way to apply it in drug development. And then you can come back to the table with another qualification effort to get to the place you want to go to when you have -- when you're looking at getting the data that will help support that use.

DR. NEWELL: And you could use the data from the original submission to support the revised submission.

DR. HOLLINGER: Absolutely.

DR. ALBRECHT: Kathy, let me go ahead and ask you -- when you receive a letter of intent, I assume they're not always perfect. So what is your process

Page 116

for interaction -- sorry. I just want to make sure we get sort of the iterative discussion. What is your process with interacting with the person -- or the group that submitted the letter in helping guide them along?

DR. HOLLINGER: So it is a bit of a dialogue. And so the first kind of thing that we do is look at the submission from the requester. And the requester is the person making that submission. And we review and try to understand what the concept is and whether it's well presented and whether they are adding all the elements that people need to look at in their assessment of that letter of intent.

Basically, before we send it to our subject matter experts, we want to make sure that it has an opportunity at success and getting good recommendations from that review division or the various reviewers that will be looking at the submission.

So for example, if I wrote myself a list here, Elements of the Successful Submission, because I think that's very, very helpful. Number one, it's a receptive requester because we will be working with

Page 117

you. And you know, if we say to you, you know, the biomarker description is lacking or the context of use or you didn't give us a good drug development need or we need references in this document, please be receptive to that because the reason we are asking is that, further downstream, someone will have to look at it. And we have many different disciplines reviewing that letter of intent.

So let's say I have a statistician or I have a clinical expert in pulmonary disease or -- you know, they will probably want to go to a certain set of references that might be different from the different discipline.

So if you're making statements in your document, make sure they've been referenced -- they can be referenced with your research; they can be referenced with longstanding research. But make sure you've put your references in there.

Keep it very focused. Sometimes we get submissions that are not focused. They might be promotional and saying this is, you know, the best thing since sliced bread. Not only does it do this,

Page 118

but it does these 10 other things -- excuse me -- does these 10 other things. We realize you work really hard on these, and we realize that this might be step one in the first bite out of the pie. But it doesn't help. It distracts our experts from looking at the specifics and giving you a really good focused set of recommendations. The recommendations can be as all over the map as the submission, and then where do we end up as a group? We don't end up in a good place.

So keep it focused on what is your biomarker, what are your analytics, and what is your context of use. And we really haven't addressed analytics yet. But analytics validation is also a very important piece. And a good part of that occurs in that middle step, that second step during the QP phase.

We want to see that it's feasible and reliable in the LOI phase, but you're going to probably be presenting a lot of data on your analytic in the second stage, the qualification plan because the qualification plan is then going to focus on the clinical validation and making sure that you have all your data together that will allow us to accept the biomarker for that

Page 119

context of use.

Make sure that you define terms in your submissions. So if you're talking graft reduction, what does that mean? How are you defining that in your studies? Or how will you be using your data to demonstrate graft reduction?

And remember, also, that under the 21st Century Cures Act that there is a requirement for transparency. So that letter of intent will be posted on the internet with our decision letter and recommendations. It does also protect confidential commercial trade secret and proprietary information, and those we're suggesting you put in attachments and don't necessarily reference the attachments that you feel are confidential or trade secret in the body of your letter of intent. But certainly mark your attachment. Where you feel it is trade secret, mark it such that it is trade secret or commercial confidential. And we will have a legal review to make sure that we aren't violating the terms of the 21st Century Cures Act by withholding information that could be made public, and we will have a dialogue with you if

Page 120

we ever find the disparity there.

So you know, and those are just some little kind of hints on how to get to where you want to go. And we look forward to working with all of you.

DR. FRIEDMAN: And I would just like to confirm -- and I know there are speakers at the microphones -- but I just want to confirm that this was not a grand inquisition process. This was very much collegial interaction that was a learning process for all of us. And we truly can confirm what you said.

DR. HOLLINGER: Well, I thank you for that.

It feels bad to tell you that -- you know, we now have a little memo sometimes that goes out and says, you know, your submission is not reviewable. Well, that's disappointing. I'm certain that people find that that's disappointing. But I think that if we do that at that stage and then get it to a place where we can get a really good set of recommendations for you -- and sometimes you'll see that not reviewable two or three times. It's happened. And so don't lose faith. We will get there, but that's just part of the process.

DR. O'DOHERTY: So we have a speaker on the

Page 121

floor as well.

UNIDENTIFIED MALE SPEAKER: Yeah. I'm going to introduce a comment, and I would like to get Katherine's and Ameeta's and Renata's reaction.

So it seem -- when you were developing a drug, you started by defining the desired target profiles, and then you -- one-year (ph) plan for preclinical and clinical developments to meet that desired target profile. It seems to me like, in this case, what you're saying is, if you are thinking about a drug development tool, you start by defining your desired context of use. And then you hone in the plan to meet the context of use. So in the end, a statement could be, just as drugs have labels, drug development tools have context of use statements. Would that be a fair representation of the similarities between the two processes?

DR. HOLLINGER: Yes. And I don't want to leave out the drug development need because that's going to define your use and how you apply it. Your biomarker and where it fits in this whole drug development process, whether it's used to enrich a

Page 122

clinical trial or whether it's used as an endpoint, those will be varying levels of evidence and, you know, applications for those tools.

UNIDENTIFIED MALE SPEAKER: Can I ask a question? I'm sorry.

DR. HOLLINGER: Go ahead.

DR. ABECASSIS: So I just wanted to try to clarify something, and I realize that drug development is, you know, front and center. And when I was putting my talk together, which I'll give later, our biomarker has nothing to do with drug development, right? So it was kind of really hard to -- so I guess what I'm asking is: Is there a definition of drug development, A; and if the purpose of the biomarker has nothing to do with drug development, how does it fit into all of the frameworks that you guys have very nicely and kindly provided for us?

DR. HOLLINGER: So very often, we are working with people who work mostly in a clinical realm. And what we need to do, if you're intending it to be qualified, is make sure that we're focused on a drug development use. And I've had one submission where I

Page 123

had to work toward that. And we had to figure out where is the best place to put this, and how can we qualify it to have the greatest versatility and application in the drug development space. So we could work with you to try and figure out how the biomarker will benefit drug development, and that's what we're here for.

DR. STEGALL: So I have a question -- maybe a comment on that is that I think that the way I look at this, the way this works in transplant, we're kind of building this highway, and a lot of things are going to go down it and maybe a subsequent biomarker validation process for something else definitely. But if we don't get this part right, one-year patient and graft survival is not going to allow anything to get -- so I think that's where we're kind of headed with this.

But I have a question for Dr. Coresh, is that -- so you have -- and don't get me wrong. So you have done a million patients, something like that, which we're never going to do, and looked at them very carefully. And it seems like to me that still 30 or 40 percent and still 2 to 3 years. And there's one thing

Page 124

that you're looking at. Maybe you're going to add proteinuria in the mix. And it's good to see that there's something related sort of to kidney. And we're doing kidneys, also, but just in a different context.

And maybe I -- I think when learning this process is what other people have gone through is helpful for us. So how did it get to be, after a million patients, it's still 30 to 40 percent and 2 to 3 years? Because, you know, we're transplant people, so we're going to make it really, you know -- I'm a surgeon, too, so there has to be some sort of, you know, direct kind of input. And where are you kind of in this process then, you know?

DR. CORESH: So I appreciate the question. First of all, when you say you did a million patients, well, I think the distinction is important because that may actually be part of my question to Ulf Meier-Kriesche and the TTC Consortium as to whether they're thinking about the observational data in transplant patients. And I'll expand on that in a bit, but I'll answer my question first.

Right. So first of all, right, not only did I

Page 125

not do it, it isn't even in research studies only, right? So the idea is we've harnessed all of the clinical population. So Geisinger, for example, has followed for over 15 years all of their participants with and without kidney disease and were harnessing all the clinical data in that, right?

Now, when you go to larger health systems, the common denominator of that meat grinder kind of slide that people have shown several times for the data becomes lower, right? So the richness of the data becomes lower.

DR. STEGALL: Okay.

DR. CORESH: But you have that generalizability party, which is actually quite nice. So that's one point.

So it may not be as bad as it seems. And both the million and the decade because you can go a decade backward, right -- and in some sense for epidemiology and data analysis, going backwards is a lot more efficient than going forwards because waiting another decade is a lot worse. I really like getting things done as well.

Page 126

In terms of moving for our 2018 meeting, we looked at slopes. It's interesting. If you look at slopes quantitatively in the clinical trials and you look at even one-, two-, and three-year slopes, on the individual patient, the slopes and change in albuminuria are quite variable and not that informative. But averaged over a group, the slopes, in particular, were highly correlated with the long-term outcomes of the trials, right?

So there actually is quite a bit of hope, more than I had thought about even one- and two-year results, even one-year results, for detailed slopes with this caveat that acute effects can really be an issue. And it's the fact that it's actually kind of amazing that a slope change in one year, really, from minus 5 MLs to minus 4 MLs, of only 1 ML, has been highly predictive of the future outcome when measured in a group precisely. But you can tell. If the drug had an acute effect of one to two ML, it would turn everything on its head. So you have to model that, and we did detail work about that modeling.

So maybe that helps you. I think we still

Page 127

need better biomarkers, better insights, better understanding of pathology, better subsetting of disease subtypes, potentially better understanding of pathophysiology. But it's also useful to have the large common denominators. And sometimes you may need quite a bit of this for the safety data as well, right, because if you get too efficient, you may not know safety as much.

DR. STEGALL: And you used estimated GFR, right --

DR. CORESH: Yes.

DR. STEGALL: Okay.

DR. CORESH: Now, we -- you know, we work a lot on sort of improving the estimates, actually. And some people have criticized that, you know, good enough. The people who said it wasn't good enough now say it's good enough.

And it turns out that it'll depend on whether your drug affects the creatinine itself. But otherwise, I don't know that, by measuring, you're going to get a lot further on the GFR. You may need to look at other domains, as much as I'm a fan of GFR.

Page 128

Okay. Thanks.

DR. STEGALL: Okay. Thanks.

DR. CORESH: But I think I had a question as to -- in terms of the trials, right, in the TTC, is there enough heterogeneity of treatment effects that you think you'll be able to look across trials at the effect on the surrogate and the effect on the trial? Or is it more of an observational analysis of all of these data within trials of one-year outcomes predicting long-term outcomes?

And either way, what do you think about the idea of are there data in observational datasets that might be useful in some way.

DR. MEIER-KRIESCHE: Yeah. So again, we are going to do, obviously, both, right? We are going to, first of all, assess the overall effect, whether the marker at a year is predictive of, let's say, five-year outcomes. But then the next step, as you rightfully point out, will be to assess across drug-treatments, across patient populations. It's this constant.

And we are -- we got a significant head start. And I'm going to punt this a little bit to Alex. I

Page 129

mean, they have done fabulous work in France and in Europe, in general, on validating the iBox in their patient populations and have done all this work to do it across populations, across treatments.

So we have the good fortune that we will be able to use this fact-finding and this preliminary data to now go into a validation phase where we can actually, in an untouched dataset where we take all the clinical trials and link them to long-term outcomes, test what Alex has done in a separate setting. Again, there we're going to look across drug treatments, across populations. And hopefully, that will give us the required evidence.

Now, obviously, there can be always context of uses which come up subsequently which haven't been tested in both trials. You wouldn't be able to cover those. But at least you get a general idea how robust your marker may be. But maybe Alex can expand on that a little bit more.

DR. LOUPY: Yeah. Of course a very important component of validating the models, we're to go inside randomized trials and do some post-work (ph) analysis.

Page 130

So we needed some published randomized clinical trials with sufficient follow-up to the actual events, graft loss, and the capability of having, like, a one-year, or whatever, if it was two-year, rescore evaluation that we could calibrate and compare the assessment of the risk. And the predictive probability of failure was due to actual events observed within these trials.

And it was also important for us, as you mentioned, to study different clinical scenarios -- minimization of treatment, rejection treatment, T cell-mediated rejection, antibody-mediated rejection. That was a very important component, randomized clinical trials. And as you mentioned, also, a very important part of the analysis was to add a lot of heterogeneity in the system to validate the scoring in geographical distant, you know, and different practice across centers in France and U.S. and also South America and other countries.

So it's the -- both are -- we used both approaches because we think they are like providing heterogeneity and also some kind of understanding of how the model can be transported.

Page 131

UNIDENTIFIED MALE SPEAKER: And just to add to that, the approach that we're taking with the -- basing it off of what Alex has done, and to your comment about the structure of the model, what we want to do is turn what Alex has done and turn it into a drug-disease-trial model, which is what Ameeta described as we did for the Alzheimer's effort that we coordinated on C-Path. But then that's going to provide the necessary foundation for the sponsors to be able to adopt the endpoint through the fact that we've quantified the aspects that are (inaudible) about disease progression, the drug effects, and of course the clinical trial realm aspects -- you know, dropouts and allocations and these -- and things like that. So that's kind of the gist of the core of the effort that we want to undertake.

DR. ALBRECHT: So we had a question online as what does it take to get a biomarker ready to be used for clinical decisions. And I think what you've been discussing is the level of evidence and the reiterative evaluation and analysis of the data so that you're confident that it does do what it's purported to do.

Page 132

Thank you.

UNIDENTIFIED MALE SPEAKER: Inish, I had a question -- or a comment. First of all, the speakers in the slides often use the word "qualify" biomarker. And I just want to emphasize for the audience that, as one slide shows, there are two routes to designate a biomarker -- qualification and fit-for-purpose. So when we use the word "qualify," we should understand that, subsumed under that, are the two routes for biomarker designation.

The question I had for was for Gary --

DR. ALBRECHT: I just want to clarify because qualification is a process that was mandated under the 21st Century Cures Act that is the three-step process. The other approach where you go to the review division and have a dialogue and say we want to use this in our drug development program for a particular program, that would be another method, or another approach, for use of a biomarker, but it wouldn't be a qualified biomarker.

The status or designation that is a qualification effort comes after it goes through those

Page 133

three stages and is made public so that anyone can use a qualified biomarker.

So once you have qualification as your status for your biomarker, it's qualified for that particular use, and it's made publicly available so anyone could use it in their drug development program. In the first fit-for-use example, that is for a specific drug development program and dialogue within the review division for that particular project.

And then the third way -- there is a third way, and that's more from a scientific consensus that that's being used, that biomarker is being used, in drug development -- I'm guessing not only in drug development, but it's in clinical use.

DR. MORRIS: And then if Ameeta can also comment on the fit-for-purpose initiative, which is not related to individual drug development submissions, but it's handled by the Office of Clinical Pharmacology specifically for quantitative drug development tools. And you can have a quantitative drug development model that supports the qualification of a biomarker, or you can have the model itself be put through the fit-for-

Page 134

purpose initiative with OCP.
DR. ALBRECHT: Thank you.
DR. PAREKH: And the best part of all this is the transparency that we have currently. So if you do a search for qualification drug development tools FDA, you'll see that you have the list of biomarkers that are qualified. You have seven biomarkers as of yesterday that are listed on that document. There are, I think, four COAs that are listed as qualified clinical outcome assessment tools, qualified. And there's a whole range of submissions that are in the process. I think there were more than 30 that I counted yesterday for COAs. So that's the qualification, two pieces -- the biomarkers and the COAs.
The fit-for-purpose is also on the website. So the fit-for-purpose designation that we are giving as of right now is also for drug development tools, but it's more ancillary tools or methodologies that don't fall under the defined biomarkers and COAs. And currently, we have two fit-for-purpose tools, the Alzheimer's disease ancillary model and the MCP mod,

Page 135

which is a simulation tool that determines dose -- early dose -- or dose determination. So those are the two items that are listed under the formal fit-for-purpose pathway. But they are all through the FDA's regulatory endorsement, the review pathway.
DR. MORRIS: Thank you for that clarification.
I had a question for Gary Friedman. And that is: How applicable are the nephrotoxic biomarkers you described for a wide variety of renal insults? How do we know that data from particular insults you have looked at are applicable to a brand new drug with a mechanism off target that we may never -- can never even anticipate until we see it?
DR. FRIEDMAN: Great question. And I think that going, step-wise, we've looked at the -- these biomarkers which are 8 out of about 65 that we initially looked at in the preclinical space and then moved into the clinical space. As we now look to move into use in patients who have an underlying disease and maybe have normal GFR or have an underlying disease and maybe an abnormal GFR, there -- the data are going to emerge. And there is -- as was referred to earlier,

Page 136

not only is there a discovery of the biomarker and validation, but then there's calibration.
So this is the part that keeps on going that, as we generate more and more data and have data on subsets, whether based on gender, ethnicity, and the like, there is going to be a continuous reevaluation and recalibration of the full changes from baseline.
In specific in transplant, when you consider the variety of transplants that are done, one of the discussions that we've had internally within PSTC as we've thought about transplant but not taken action on it yet, you may actually have "normal, healthy volunteers," meaning, as you look across your clinics, you have patients who have intentionally or unintentionally informed you that they stopped taking their immunosuppression and their creatinine is 1.1. So you have a number with transplant tolerance, whatever that my mean. And so you may have patients with GFRs that are in the normal range on known nephrotoxic drugs. That may be a place to define whether or not these biomarkers that we've seen in normal, healthy volunteers or subjects with normal GFR,

Page 137

that may be one of the translation points in solid organ transplantation.
DR. O'DOHERTY: I think that's a -- maybe we'll just have to pause it there and wrap up the conversation for this session. There will be more Q&A after each other session, but we're going to hit a morning break at this point in time. We'll ask folks to be back in the room by 10:45. And then as well, if you're ordering lunch, still -- it's the last order at the kiosk outside in front to be able to do that.
And thanks again for the discussion. We look forward to welcoming you back after the break.
(Break.)
DR. VELIDEDEOGLU: I think we still have some people out in the hallway. I just want to give a few more minutes before we start the second session of the workshop.
Good morning, everybody. My name is Ergun Velidedeoglu, one of the medical officers here at the FDA. Dr. Ulf Meier-Krieschea and I will be moderating this session, which is the second session of this workshop titled Potential Biomarkers to Identify

Page 138

Alloimmune Risk in Patients Pre-transplantation. Up until now, we heard great presentations regarding the overview of the subject potential biomarker development, and then we have seen one excellent example from CKD patients. Now we are going to start getting into the specifics of the subject.

Our first speaker is Dr. Peter Nickerson from the University of Manitoba, and the title of his talk is HLA molecular Mismatch - A prognostic biomarker for primary alloimmunity.

DR. NICKERSON: Thank you very much. I want to thank the organizers for the kind invitation to come and share our work. And what I'm going to be focusing on is, when I say molecular mismatch, these sub amino acid zones on the whole molecule that are mismatched relative to the recipient and the donor as opposed to the whole entire molecule. And so you'll see this image over and over again.

Disclosures -- I have some consulting in honoraria. I will not talk off label or investigational use.

So the starting premise is that primary

Page 139

alloimmunity is a major cause of allograft loss. And in this publication we put through in 2012, which is a consecutive cohort, and we looked at 10-year median survival. What we saw is that those patients that were developing a de novo HLA donor-specific antibody had a significantly lower graft survival at 10 years compared to those patients that did not develop an antibody.

Now, a de novo donor-specific antibody indicates T and B cell allorecognition for that antibody to develop. In fact, it's a very coordination immunologic response that has to be intact for this antibody to develop as an IgG donor-specific antibody in the serum.

And once we looked at -- and getting into functional aspects, we looked at the estimated EGFR rate of decline in our cohort. We looked at those patients who were stable throughout the entire course. So this group of patients up here in the average rate of decline was minus 0.43 mils per minute per year. And in those patients that were going to develop a de novo DSA as an indicator of primary alloimmunity, they were already losing function at a faster rate before

Page 140

the antibody showed up, and it accelerated in its loss of function after the antibody showed up. And so we took this to indicate that the de novo DSA is really a biomarker of a process that's underway. And you're going to hear more about DSA later in this -- today.

So from there, we were interested in what DSA were specifically important. And what we saw was that Class 2 HLA versus Class 1 HLA allorecognition is a dominant pathway. And if we look at -- this is the graft survival in those patients without an antibody in orange. Those that only developed a de novo Class 1 antibody in red had a graft survival curve that was no different from the patients without antibody. Those with isolated Class 2 or those with Class 1 and Class 2 are the ones that did poorest.

In terms of causality, where HLA mismatching fits in, well, HLA mismatching is really the initiator of the primary immune response leading to allograft loss. And so we conceptualize that this mismatch really is what's driving T cell mediated rejection, whether it's subclinical or clinical. And you'll hear a lot about that later today. And it's also the driver

Page 141

of de novo DSA that leads to ABMR, again, subclinical or clinical. And these can be smoldering processes, ultimately leading to fibrosis and graft loss.

Minimization and nonadherence interacts with the mismatching in the sense that it's really taking the brakes off the immune response and allowing it to progress more rapidly.

From causality, if we can go to the next slide, which it doesn't want to go now -- can you advance the slide? There we go.

The corollary here is that HLA identical transplantation should lead to improved graft survival. And here we have the classic experiment in humans where we take twin transplants, and we didn't need any immunosuppression back then to have excellent graft outcomes.

The more recent data through UNOS and SRTR shows us that if you have a zero mismatched HLA graft, you actually have a graft survival advantage of about five years compared to any degree of mismatching. The problem here is that only 8.5 percent of transplants have a zero mismatch, and 93 percent have one or more

Page 142

mismatches. And so the question becomes how can we grade risk within this 93 percent, and can we get more granular.

And that really leads us to this statement, which is we must now prepare for a second phase in which more sophisticated measures of HLA compatibility should be developed for a more accurate prediction of outcome. And I think that's what we're really talking about when we're talking about biomarkers. And this statement was made only 46 years ago, so we haven't really come a long way in the last 46 years in advancing this concept.

So that really got us to the star working group. And the star working group is a joint AST-ASHE (ph) consensus forum where we're trying to look at immune risk assessment pretransplant for clinical purposes, but really getting it into, ultimately, how do we define this at a mechanistic level. And that could be developed for clinical use.

And so we're focused, and what we recommended was two types of risk assessment -- an immune risk assessment for memory and immune risk assessment for

Page 143

primary alloimmunity, which is what I'm talking about today.

And when we got to primary alloimmunity, we said that, really, molecular mismatching is probably one of the areas that needs to be developed if we're going to think about clinically how to assess primary alloimmune risk.

So taking that, the next step forward, HLA molecular mismatch really induces the B cell receptor allorecognition event as well as a T cell receptor allorecognition event. And the biological basis of this is that you have epitope-paratope structural relationships between an antibody, which is the B cell receptor on a B cell, recognizing the donor HLA molecule. And it does that through a paratope-epitope relationship.

And what's been identified is that there's a core area on the epitope which Rene Dekesnoy (ph) has termed for no other reason to call it an applet (ph). It has no other meaning than Rene liked that term. But it's thought to be that this central amino acid polymorphisms that exist on the donor HLA are the

Page 144

predominant bonding domain of the CDRH3 region on the antibody. And it's felt that this region determines specificity of the antibody, in large.

Now, when you look at comparing donor and recipient HLA molecules -- and he's developed the computational software called HLAMatchmaker to do this -- we can talk about a -- in this example DR beta 10405 (ph) as a 1DR mismatch to this patient's HLA-DR molecule. But if you look at it at the molecular level, the number of surface amino acid differences that exist in this molecule between the donor and the patient, there is up to 11 different areas where you could have potential alloreactivity by an antibody, compared to this HLA-DR beta 1 mismatch where there's only one amino acid difference between the donor and the recipient.

But we treat this, and we've classically treated this as equivalent. This is a 1 DR mismatch. This is another 1 DR mismatch. But they're clearly different at a molecular level in terms of their relatedness between the donor and the recipient. And when you compare this in a whole population, you can

Page 145

say that here's a 1 DR mismatch in our whole cohort. There's a whole range of applet mismatches or molecular mismatches that exist for that 1 DR mismatch in different patients.

So if you were to take two recipients, here's a Recipient A who has a 1 DR mismatch by our traditional whole protein mismatching, and they have very many applet mismatches, compared to Recipient B, who we think of as worse because they have a 2 DR mismatch, who has very few applet mismatches between donor and recipient. So the traditional way of looking at things really has a loss of information as compared to a molecular method of looking at relatedness.

And we put this into a multivariate model and look at DR de novo DSA or DQ de novo DSA as our endpoint and what are the hazard ratios for -- independently for developing these DR DQ DSAs. What we see is that recipient age -- the older you are, the less your risk, but the younger you are, the higher your risk. If you're not taking your meds, well, clearly, that puts you at risk. If you are on cyclosporin versus tacrolimus, you are at a higher

Page 146

risk. And then for every 10 applet mismatches for DR or every 10 applet mismatches for DQ, you are at increased hazard specifically of getting a DR or a DQ de novo DSA.

Now, is applet mismatching and matchmaker the only computational method for doing this? No. Others have developed other methods. So we did a head-to-head comparison of these other HLA molecular mismatch methods to look at whether they were better at predicting HLA immunogenicity.

And we looked at amino acid mismatching or electrostatic mismatching. The first thing we did was we correlated it with applet mismatching. And you can see there's a very tight correlation by any of the three methods in terms of looking at relevant mismatchedness between donor and recipient, if that's a term.

And when you put it into the multivariate models, you find that the same four factors always come up in predicting the outcome. And then the question becomes how can you compare these different models using these different methods. And so we used the AIC

Page 147

scores as a way of comparing the overall quality of that model. And comparing the AIC scores between models, you can get a sense of relative quality of the model. The lower the AIC score, the better the model. And so the applet mismatch had the lowest scores for both DR and for DQ. And whether this translates into clinically improved predictability has not been determined. But at least at a statistical level, the applet one performs well and at least on par with the others if not a little bit better.

Okay. So now we want to try and get to some way of quantifying and categorizing patients into levels of risk. So we look at whole antigen mismatches. And really, apart from zero mismatch, 1 and 2 really has no improvement in terms of predicting a DSA-free survival. And if you look at DQ, in fact, two DQ mismatches perform better than one DQ mismatch.

So again, I think that what we're seeing here is that, if you look at ADCs (ph) and predicting zero versus one or more, the ADCs are quite poor. It's 0.58 and 0.54 with very poor sensitivity. And so we don't want that kind of a biomarker.

Page 148

If we look at the molecular mismatch for DR and DQ, we're able to separate into three different groups -- 0, 1 to 11, and 12 to 41 for DR and similar for DQ. And what we see here is that the AUCs now have improved to 0.73 and 0.72 when we're looking at 1 -- 0 to 11 versus 12 or more. So we're starting to have better resolution of predicting immunogenicity of a given mismatch.

So the context of use of such a prognostic molecular mismatch score would be a prognostic biomarker termed at the time of transplant in conjunction with baseline antibody testing to rule out preformed alloimmunity -- so we're talking about primary alloimmunity -- categorizing kidney transplant recipients as high, intermediate, or low risk for de novo DSA graft rejection or graft failure with categories to be used independently, in pairs, or they could even be used as triplet-risk categories to enrich Phase 2, 3 clinical trials with patients based on risk category in evaluating novel drugs. And so really, it's about prognostic biomarker, categorizing patients, and then using enrichment strategies.

Page 149

The benefit of this is you get improved efficacy in clinical trials versus the current standard of primary alloimmune risk assessment, which, right, today we use low risk being based on PRA. It's only on DR mismatching at the whole antigen level and race. And these criteria are used frequently in inclusion, exclusion, and stratification tools in drug development.

The risk of using this score would be misclassification as high risk. You would have exposure to increased immunosuppression, potentially, when not warranted, or misclassification as low risk where you could expose to inadequate immunosuppression when it's not warranted. And you could be qualifying a drug in only a subpopulation of kidney transplant recipients when, in fact, there's a benefit of the drug to the entire population. So these would be the risks that you would want to take into account.

And in terms of the evidentiary criteria grid, if we think about the assay and analytical validation, what is unique about HLA is it's universally available in accredited clinical laboratory. So this is not

Page 150

limited to one lab, but, in fact, anywhere in the world can do this.

HLA-typing anolytes, HLA-typing devices, and HLA-typing analytic software is all 510(k) FDA-approved at this point. So we're not looking at trying to rederive these aspects. I've called it fit-for-purpose, which is what the evidentiary criteria grid uses as language. The computational analysis for HLA, DR, DQ, and DP matching is -- we've been using a Version 2 of the software, which is a locked version of the software. So I think, in that sense, we're not continually modulating this software as we're using it.

In terms of scientific understanding, I think the biological rationale is present. The causal biological links establishing HLA mismatch and the primary alloimmune response is well established in terms of understanding molecular mechanism. I'd say here there's still some room for improvement. The structural biology of antibody binding to its HLA target is being further refined. And understanding TCMR allorecognition is another area of being further defined.

Page 151

In terms of biological performance expectations, sensitivity to change, it could be -- it is a continuous variable of risk. And consistency of the biomarker response -- I didn't show the data, but we've seen consistent magnitude of effect when adjusting for immunosuppression levels. And in terms of specificity, well, it is donor-specific response. We're looking at an antibody against its target. I don't think you can get much more specific.

In terms of the types of data and samples around establishing qualifications, so far, we've been using a prospective study that's a consecutive cohort. We have a retrospective study as well and a prospective cohort. And we have a small RCT that Dr. Heeger is going to talk a little bit about next, and so I won't go into that.

In terms of statistical considerations, the relationship of the biomarker to clinical outcomes, it's an independent correlative of de novo DSA graft rejection, mariolopathy (ph), and graft loss. And I didn't show you all that data today.

Usefulness of the threshold for decision-

Page 152

making -- well, we've gone from an AUC of 0.45 and 0.58 to 0.72 and 0.73.

Additional considerations -- there's further refinement in the HLA molecular mismatch score that's now in place that we've been developing using the software. Further validation in retrospect of analysis cohorts and RCTs is underway, and we have further validation and prospect of RCTs underway as well.

So where are we at today? Well, in terms of being a prognostic biomarker for primary alloimmunity in kidney transplantation, we're refined our approach. And that's now in submission for publication. But our AUC has now gone up to 0.85 from 0.73 in terms of predicting de novo DR or DQ DSA. And we can stratify low risk, intermediate, and high risk where this represents, actually, 25 percent of all transplants, 35 percent and 45 -- 40 percent, respectively. So you have a nice segregation of the population into different subsets.

Now, DSA is a molecule, but it doesn't translate into rejection. So what about rejection? Well, here's ABMR showing that these three categories

Page 153

give a step-wise gradation of risk for developing ABMR in the first 10 years post-transplant. And in the high-risk group, you're seeing a lot of that in the first five years.

More importantly, it's also stratifying for TCMR in the first year. So this is over the first 12 months of the transplant, and you're able to identify a low-, intermediate-, and high-risk group for developing a T cell mediated rejection, which we've been classically using as one of our clinical endpoints in drug design trials.

So I think this tool could be used as an enrichment tool in clinical trial design to get the smaller ends so that we could actually have more effective and smaller trials.

And that -- I'll stop, and I'll just recognize this is a lot of work. Chris Weeb (ph), Denise Pachenko (ph) in our labs been one of the drivers between the work -- behind the work that I've been showing. We've been collaborating with Vascillis Cosmolioptis (ph) in Cambridge. We've had key collaborations with Peter Heeger in the CTOT Consortia,

Page 154

Arthur Matas in the DCAF (ph) Consortia, and a close collaboration with the STAR Consensus Working Group with Anat Tambur and her leadership in bringing this forward.

Thank you very much.

(Applause.)

DR. MEIER-KRIESCHE: So our next speaker is Peter Heeger from Mount Sinai Medical School. And he is going to talk to us about biomarkers to assess a risk for kidney allograft injury during CNI withdrawal.

DR. HEEGER: Great. Thanks for the opportunity to come here, and thanks for paying attention while there's much more drama down the street in Capitol Hill at the moment. But this is interesting, anyway.

So we'll talk about biomarkers. I don't -- you know, I have a couple of research grants, but nothing that's relevant to this.

So long-term transplant outcomes we now have understood are suboptimal. And what's interesting for those who don't think about this is immunosuppression is basically done by protocol at center-specific

Page 155

practices. Some patients do well and could tolerate less immunosuppression. Others have poor outcomes, despite absence of clinical risk factors. And we're not really making decisions individually. So if we could find ways to individualize, that could improve outcome, and it could also provide a way to enrich for patients to look -- to put into studies, specifically, that are relevant to new drug assessments.

So risk assessment permits at-risk population enrichment that can guide management. Who's most likely to do badly? And we heard something just now from Peter Nickerson. And maybe if we had better biomarkers and better evidence, we could -- I -- put people in the right trials.

Who's most likely to tolerate decreased immunosuppression? And I think that's something we don't always think about. But as was noted earlier today, there are a lot of off-target effects from immunosuppression. So if you could find the low-risk people and then put them into clinical trials, that would be important.

Noninvasive diagnosis of graft injury you're

Page 156

going to hear about later. We'll tough on that a little bit. But that could prevent the morbidity of a biopsy. And if you could detect subclinical or incipient injury, that might be, you know, an important safety net for withdrawal studies and help you get around other morbidities. And again, you're going to hear from my colleagues about that.

You know, we've been doing clinical trials and biomarkers, and we're very interested in validation and standardization. And I think this is just to show that if you're doing a clinical trial, it's important to try to standardize your assay so you can get them out to people, which is sort of a step to getting approval to use them in this -- in the processes that we're talking about today.

So one of the things that we've been interested in now for almost 20 years is studying donor reactive T cell immunity by ELISpot. And this could be a predictive marker for post-transplant risk stratification. This is an assay where we take the recipient cells, test them against the donor cells and then make interferon gamma as a read-out. And it's a

Page 157

measure of memory immunity. So it's a way to sort of say that I have already an immune response against my donor. And that's not something that was studied previously. And again, if you could use this kind of assay to stratify, then maybe you could pick people at higher or lower risk for, you know, drug studies.

So in an initial publication, we showed that if you did not have this assay, if it was negative, the risk of acute rejection was low. And if the -- if you had a positive test, the risk was high. And the kidney function was actually lower at one year in people who had a positive test versus the lower -- a negative test. And that turned out to be independent of all these other -- several other, you know, clinical risk factors.

And although -- and here's just another statement that, independent of delayed graft function or developing acute rejection of this assay, the pretransplant assay was telling us something about what was happening at 12 months in terms of glomerular filtration rate.

Now, we didn't do formal validation initially

Page 158

ourselves, but I think it's important that other people picked up on this assay. And so around the world now, people have tried to do this and have found very similar results that taking this assay can give you some information about post-transplant outcomes, categorize the people as high or low risk.

And here's just another example of a multi-center study that we did through CTOT where the patients had -- who had -- were positive had a higher evidence of acute rejection and a lower EGFR at 12 months.

So you know, the issue here is that there is evidence that this assay could be used to identify transplant patients at an elevated post-transplant risk. We don't know yet, of course, whether altering therapy based on the results if going to improve the outcome. The complexity is that this is a multi-step asset that requires donor cells to assess donor-reactive responses. And as such, it's going to be very difficult, I think, to employ broadly, you know, in the clinic, although it's possible. And it's been standardized, but we haven't gone through this type of

Page 159

approval. And it's, I think, therefore, difficult to commercialize.

And you can imagine if you're doing a deceased donor transplant, how are you going to do this in the middle of the night and get a result? That's not so straight-forward. But nonetheless, I think under certain circumstances there's some evidence that will be important.

We've also been looking at chemokine measurements as a noninvasive diagnostic. We've all heard of chemokine kidney transplant inflammation and rejection. And again, you're going to hear more about these kinds of assays, including molecular assays later. Just for those who don't really know about what chemokines do, interferons release during these immune responses that cause these chemokines to be released that then attract more T cells to come into the area. And so there's a biologic plausibility for using this kind of analysis, particularly in the kidney where you can measure chemokines in the urine. I'm not the first one to do this, but we've been interested in it. And we did a validation study to sort of look at whether

Page 160

one of these chemokines is relevant.

And just to show you a little bit of data, what we're looking at here is can we diagnose acute rejection in a patient who has an elevation in serum creatinine post-transplant. And the data here demonstrate that there's a much higher level of this chemokine, CXCL9, and people who have acute rejection versus those have other causes of injury or even infection. And the area under the curve was really quite reasonable -- 0.856. And the false positives are actually not false positives. They're positives because people have urinary tract infections or BK virus infections which can be detected noninvasively. So actually, you can tell injury here.

Right. So we also noted that the values in these -- this is when the patient had rejection. The values were higher before the rejection, up to 30 days before, which suggests maybe it could be useful as a prognostic or detecting the evidence for rejection before we saw it clinically, right?

So again, there's evidence that these -- from our group and many others that chemokines can detect

Page 161

clinical and subclinical transplant rejection, which I think puts it on a pathway for this kind of validation that we were talking about this morning. It has implications for both clinical care and for trials because you could use this to diagnose -- potentially diagnose rejection subclinically.

There are available kits for research purposes. There aren't really any commercial offerings yet, although there is one company that I know of that has had some IP in this area.

And ideally, the best way I see this as being used is if we could develop a pregnancy test like dipstick, which was -- you could give to the patients and sort of say you could follow this at home and see if that has a clinical utility, not necessary directly relevant to the clinical trials that we're talking about.

So to take -- I want you to see this because we tried to put all these things in context in a study that we did -- it was just alluded -- with the idea we wanted to try to withdraw potentially toxic calcineurin inhibitors in stable kidney transplant recipients and

Page 162

then use the biomarkers to see whether we could predict or diagnose what might happen.

And so our concept was that tacrolimus is good, but maybe it has long-term bad side effects. And so what we did was we took living donors, and we treated them with induction therapy and three drugs -- tacrolimus, MMF, and prednisone. These were low-risk patients by a clinical criteria to begin with, and we let them go for six months on this standard immunosuppression, relatively standard. And if they had no rejection, no DSA, and they had a surveillance biopsy that was absolutely normal, we decided they were at as low a risk as we could detect, right? These were people who were doing great on all these drugs, and we couldn't find anything. And so we decided we would try to randomize them to come off the drug or to stay on calcineurin inhibitors, right?

And so the main lesson of this came out very quickly. And that is that we had to stop the study after we randomized 21 patients. Now, I said -- we actually enrolled 50, but we only got half of them to the randomization standpoint because we had to be so

Page 163

strict. And despite that, we had to stop the study because of the outcomes.

And so this is just to show you that in our patients who had withdrawal, this is when the drug withdrawal started. This is what -- when it was ended. And we could develop DSA or acute rejection in about half the patients right around the time that the drugs were withdrawn. And in the patients who did not have drug withdrawal, they all did fine. Basically, one had a late DSA, and one had a low-level DSA to start with.

So we wanted to understand whether we could tell who was going to get these abnormalities. And we were measuring these chemokines. And when you look at -- and here, we have the same colors, but I want you to know that the rejections are now the red and the CXCL9 positivity in the urine, which we serially measured during this time, came up positive in all of the patients right before they developed the rejection. This is 30 days. This is about a week. This is 3 days. So serially measuring this chemokine over the course of the withdrawal was actually informative. We didn't act on it, but it was informative.

Page 164

There were two patients here who had positive tests once, and when we repeated them and looked for evidence of infection, they had infection. So we didn't do anything, and they didn't have acute rejection. So you know, a small study, it -- so it's proof of principle that this might work.

And then we went back to ask about the pretransplant biomarkers to ask the question maybe our risk stratification pretransplant could tell us what's going to happen to these patients when we withdrew. And so, you know, this is the Peter Nickerson data showing -- reminding me that -- reminding us that this epitope mismatch load can tell you something about who's going to develop DSA, right?

So we applied it to our transplant group with Peter's help. And what we found was that all the people who developed DSA had the high epitope mismatches, and none of the people who had the low epitope mismatches developed DSA, which, you know, further sort of suggests that this pretransplant test is really giving you some indication of risk assessment.

Page 165

And then we also looked at whether or not the patient had pretransplant ELISpot positivity. And also, rejections and the bad outcomes hurt -- happened in the patients who had this pretransplant ELISpot positivity.

So I think it raises some really interesting things about what we could -- what kinds of tests we could use for enriching patients to -- for clinical trials. Those who have these positive tests might be the ones you want to enrich for the highest risk for studying patients who we want to try new drugs in.

From a clinical standpoint, right, we currently sort of give drugs as induction therapy, and we decrease our immunosuppression over time. And we don't really know who's going to develop things. And ideally, what we would do is come up with some sort of a biomarker profile that would tell us who's at the highest risk early, do a series of tests that might include urinary or blood transcriptome analyses over time and try to make decisions to individualized patients that way.

And I think that when I think about doing

Page 166

this, I want to incorporate these biomarkers into clinical trial designs to test whether biomarkers -- biomarker base changes in therapy can detect subclinical injury and improve outcomes. And so you sort of have to do a study where there's a standard of care arm and an arm where you treat or do something different based on biomarker status and ask whether you end up with a better outcome in that group. And I know there's several people in this room who are interested in doing those kinds of things.

So I'm going to stop there, and I'm happy to answer questions later. And this was work done by many colleagues. So thank you.

(Applause.)

DR. MEIER-KRIESCHE: Our third speaker in this session is Dr. Roslyn Mannon from the University of Alabama. And the title of her talk is Genomic single nucleotide polymorphisms - biomarkers of alloimmune risk?

DR. MANNON: Thank you so much and for nominating me to give this talk. This is part of my STAR AAST AASHE (ph) initiative to look at pre-immune

Page 167

risk. And some of you, this is a very broad overview because I have 15 minutes. And even though I can talk fast, I had to cut it down.

These are my disclosures that are not relevant.

So I think the hot topic these days for all patient care in clinical trials is this precision medicine. This is the monograph in the National Academy of Science. It -- if you read the whole report, it really kind of gives you the foundation of what some of the NIH initiatives are in terms of the one -- you know, (inaudible) everybody and also the NIDDK initiative where they're obtaining pathology, linking it to diagnosis, linking that diagnosis to -- potentially to Omix Technologies and developing sort of a very granular database to allow them for patient management. And I think, again, oncology has been sort of a leader in developing this.

But again, we have a really more -- much more complex system. And it would be great to say that the genes of the recipient tells you everything about what's going to happen. This is a figure from a grant,

Page 168

not funded. But I point it out because we were doing all these things to sort of understand what are these plant -- pre- and post-transplant risks. And it's much more complicated than just putting the kidney, and the donor has a significant input to this process.

And so when we're thinking about genome analysis, there are clear pharmacogenomics. And I'm not going to delve deeply because I think Teun van Gelder will do this at a later session, particularly for CNI or calcineurin inhibitor metabolism and also for mycophenolate metabolism that have some important data.

There is recipient genomics. Some of you in the room have looked at immune modification and immune risk of individuals and then the donor genomics, which I really won't describe today.

So just as a flavor about associations with calcineurin inhibitor toxicity, this is a GWA study of tacrolimus concentrations of over 3,000 kidney transplant patients. This was part of work of DCAF genomics and geno 3 (ph), which is an NIAID-funded initiative. This is with University of Minnesota and

Page 169

several transplant centers, including our own.

You can see the Manhattan plot on the left identifies one particular snip in this GWAS. It was associated with tacrolimus trough concentrations. And this was over CYP3A5.

And we've also been able to identify a series of loss of function mutations, which are also present in African-American, although not as commonly as European-Americans. And as shown in the panel on the right, you know, when you look at mean dose-adjusted tap (ph) levels, the number of these loss of function alleles really affect the dose that you need in order to reach your target.

Again, the naysayers will say, well, does genotype dosing affect outcomes. There's been a couple of studies that Teun may bring up. They haven't been conclusive. But certainly, in our research and what we've published is that, if levels are low early, the trend is that they tend to stay low. It really takes effort to get those levels up. And all three variants in the loss of function in clinical factors only account for about half of the variation that we see in

Page 170

tac trough. So there's clearly other factors that are out there.

Nonetheless, the clinical pharmacogenomics implementation consortium has guidelines for CYP3A5 genotype and tac dosing. I only know, like, one center and a half that actually use this. We don't. We wing it. And there's also a tac dosing equation based on the geno 3 data that are published. And so the consideration is maybe this is really a more appropriate way for drug dosing.

There has been data on the genetics associated with mycophenolate hematologic toxicity. The GI toxicity has not been conclusive. But in this study of about 1,000 individuals in the geno 3 DCAF genomics cohort, 23 percent were African American. We used a variety of platforms. We were able to identify SNPs associated with anemia as well as leukopenia.

So we were asked to sort of look at the unmet therapeutic needs. And so I think having a specific dosing strategy to read a therapeutic trough and the shortest and fastest period to minimize activation of alloimmunity is one unmet need, but, also, to identify

Page 171

those at risk for specific PRO (ph) measures, which is part of Workgroup 2, to either provide reduced dose at the onset or avoid that toxicity and may have to switch completely to a different class in terms of maintenance therapy.

In terms of the context of use, the potential for pharmacogenomic SNPs, I think, could be used as safety biomarkers. The -- for the people that like graphs, I put the graph on the right. And the people that like words, the words are on the left. So I thought, rather than being redundant and having two slides, it does sort of give you a sense that the safety is on the bottom shown here, a biomarker. And then the monitoring biomarker is shown at the top, really, sort of to measure and assess the treatment effect. So those are two possibilities.

And if you wanted -- you asked me to draft a context of use statement. So I came up with these, and you can debate them. I'm not here to say this is it. But you could do testing -- pharmacogenomic testing for CYP3A5 as a safety biomarker for patients treated with tacrolimus to assess for under-dosing of

Page 172

immunosuppression and increased risk of acute rejection. And the MPA may not be prime time, but intriguing in terms of PRO measures, such as anemia, leukopenia, that cause us to make therapeutic changes.

Switching to the topic that I was also asked to talk about is immune response SNPs. And this is just a summary of a few studies. Barbara Murphy just left, but she's contributed to this literature. And again, this is in the recipient, whereas different genes alleles are associated with rejection. And you can see a variety of things up at the top -- CTLA4. IL-17 genes have been published. ICAM and vascular cell proteins have been associated in the past.

But also, groups have also looked at other SNPs for immune quiescent things like IL-10, which may have immunosuppress qualities or TGF beta. And then these have not been conclusive. And if you read through the literature, some of this is the patient size or the population and also the platform that was used.

And indeed, other groups have looked at can you determine and associate certain SNPs by GWAS and

Page 173

determine who's going to have allograft function and failure. This is a 326 kidney transplant recipient cohort from Ireland. Inish, I included this for you. But it is good data -- and they are -- again, similarity of ethnicity, so maybe not helpful in defining a very diverse -- ethnically diverse population that exists in the U.S., or at least in the Southeast United States, identifying a number of SNPs in genes that are sort of all -- a little bit all over the place but seem to track closely with graft failure.

In the so-called DCAF cohort, decline in kidney allograft function-funded cohort -- in genomics, this is a paper with Ajay Astrani (ph) that we collaborated with. We were unable to confirm 23 prior SNPs for risks of kidney transplant rejection. So we made an effort to do that. I think we had the patient population. But we also identified 15 new SNPs that are associated with cellular rejection. And those are shown in the table, which you may not read, but my slides are on publically.

And we found a couple things. One, there was a significant-center to center variation in rejection.

Page 174

So this DCAF genomics cohort consists of seven transplant centers. And one center, such as ours, is predominantly a deceased donor population with African Americans, whereas Minnesota's population is more Caucasian, and the opposite two-thirds are living donors.

There also have been something new and intriguing. And in doing my work for STAR, I came -- a couple of publications I thought that I'd share. And one is that of complement polymorphisms. This is a very comprehensive review paper by Michael Senetal (ph) from Utrecht (ph) from -- and published in the American Journal of Transplant in 2017. You can't really read this because you just -- I mean, you need slide and slide.

But the important aspect is that we have to think about complement activation. In its crosstalk with alloimmunity, this is a really significant part of antibody-mediated injury. And again, complement also acts as a co-stimulator. It was this group's recommendation to look at SNPs in CD-46. CD-46 is a co-factor for Factor I and facilitates degradation of

Page 175

complement proteins C3b and C4b, which are important in AMR.

And I also point to you that they have some preliminary data that looks very promising that's on frontiers of immunology that's an online publication -- so, again, not just thinking about T cell mediated rejection, but complement.

And finally, another interesting papers -- series of papers I came across, and that are with SNPs within CD16a at the Fc gamma receptor 3 alpha. Again, the idea here is that maybe gene polymorphisms and IgG effector functions may affect complement activation and antibody-dependent complement cytotoxicity, particularly, in this case, (inaudible) K cells.

Interestingly, there's a paper -- and I forgot to put the reference in for you all, but it's -- you know, there's a genotype-associated response in lymphoma to rituximab. Never thought about looking at that because we use rituximab sometimes quite frequently and sometimes don't see responses. There are preliminary data in kidney transplant patients showing differences in this recipient SNP affecting

Page 176

outcome.

And a very interesting paper that is published in circulation in 2019 -- 2018 is shown here on the right. This is in heart allografts with an association of vasculopathy associated with SNPs. And I won't go through which one is which. But again, it probably needs additional validation.

So the unmet need is defining high immune risk. I think Peter Nickerson shows you sort of the more sophisticated levels, but this is what a lot of us use -- DSA crossmatch negative or positive. In the intact (ph) study, one of the most recent clinical trials published, it was African-American race re-transplant, and it calculated PRA of 20 percent. And I think these are sledgehammers. This is not fine tools. And we need fine tools.

So the context of use, again, a susceptibility risk marker, would be the role for genomic immune response SNPs. And -- or on -- and you can see that graphically on the right -- or as predictive markers to identify individuals who may or more likely experience the undesired effects. So you may be able to define a

Page 177

trial if you believe the validation.

And that's my final point. To date, the results of these analyses have been somewhat ambiguous and controversial. Hence, for me to provide you a definite context of use statement I think is a bit premature. I don't want to say which gene. Rely -- you know, we need reliable validation. And again, is this really too complicated for the transplant field because of this interaction between donor and recipient?

And with that, I'll acknowledge the many -- my lab, who keeps me sustained even when I'm running around like a lunatic; the CTOC Consortia; the DCAF Consortia, which I'm a member of; and also, the STAR initiative by Anat Tambur and Peter Nickerson that have really been helping us define immune risk.

Thank you.

(Applause.)

DR. MEIER-KRIESCHE: Thank you to all our speakers.

It's -- before moving on to the general questions that's going to be shown on the screen

Page 178

shortly, I have a short question to Dr. Mannon or anybody else who wants to tackle.

Dr. Mannon, I've seen that you have briefly mentioned about the CTLA4 SNPs. And this is in follow-up to a discussion -- meeting discussion that took place during last year's AMR workshop. And I remember that there was a discussion that certain patients on Belatacept based regimens do very well, whereas a subgroup of those patients may develop treatment-resistant rejections which don't do as well.

So as far as I looked up in the literature, the CTLA for SNPs have been -- I don't know what the prevalence in the general population, but have been studied in patients who are on tacrolimus-based regiments. So is there any merit in studying or looing into this in Belatacept-treated patients? Or has anybody ever looked into this?

DR. MANNON: So Barbara Murphy is an expert in CTLA4 SNPs. I'm calling her out. But with regards -- so I'll let her answer those first questions. But with regard to Belatacept in our CTOT 10, 15, and 16, these were clinical trials looking at the optimization of use

Page 179

of Belatacept-based regimens and in calcineurin and (inaudible) free regimen, some of which were already published. We did collect that information. The patient populations were too small.

So we did those analyses in our lab and had the independent biostatistician look at them, but we did not see a relationship. And again, it may be because, for example, CTOT 16 only had 69 patients. And though we had a fairly high rate of rejection in the bella (ph) arm because there were three arms, later two arms, it just was not conclusive.

DR. MEIER-KRIESCHE: I see. Thank you.

DR. MANNON: Barbara.

DR. MURPHY: So the SNPs that are related to the (inaudible - off mic) are actually associated with functional (inaudible - off mic) duration as well. So you do actually see a difference between the (inaudible - off mic) when you block the (inaudible - off mic) antibody (inaudible - off mic) the individuals with (inaudible - off mic) so that you can see greater or lesser (inaudible - off mic) depending on the immunosuppression (inaudible - off mic) for those

Page 180

individuals. To my knowledge and in discussions in the past, trying to get people (inaudible - off mic) to look at this, this is (inaudible - off mic).

DR. MEIER-KRIESCHE: Okay. Thank you.

Now we can move on to the general FDA questions. And if there's anybody else in the audience who has a specific question, please ask your question.

UNIDENTIFIED MALE SPEAKER: Yeah. This is for Peter Nickerson. Awesome presentation. I -- it's great to see a fellow clinician think in terms of drug development tools, quantitative models, (inaudible) information criteria. It confirms that I'm not alone. Thank you.

A question for you. Are you thinking of the idea of potentially advancing the models that you've developed that are semi-parametric in nature to turn them into full parametric survival models? Because if you can do that, then, theoretically, through some careful cross validation exercises, we could be looking at potentially simulating clinical trial scenarios for failure based on the biomarker.

DR. NICKERSON: Yeah. So I think that's --

Page 181

we're trying to get to the best version of the biomarker we think we can get to, and then we'd be very interested in pursuing those types of simulation modeling. I think that's sort of the next phase and -- because I think, with that, you can start thinking about then what kind of trial designs do I really need going forward.

UNIDENTIFIED MALE SPEAKER: Cool.

DR. NICKERSON: So absolutely.

UNIDENTIFIED MALE SPEAKER: Awesome.

DR. MEIER-KRIESCHE: Okay. Does anybody from the audience have any specific questions? If not, we are going to move on to the FDA questions.

So the first question is: What are the unmet needs in drug development and clinical practice in the kidney pretransplant setting, and how do these align?

DR. HEEGER: So maybe I'll start with the unmet need in drug development. I think one of the problems -- and I think we recognized this in CTOT-09 - - was what we thought was low risk wasn't low risk. And there is a heterogeneity of risk even within what is traditionally called low risk. So I think that's

Page 182

one of the big problems around drug development, is you're including a lot of patients in trials who don't necessarily need to be in the trial because they're going to dilute out the clinical outcome that you're looking for.

So we really need to drive towards homogeneity in clinical trial design in patient populations to allow the clinical trial design to be more efficient. And I think that's where -- if we can -- and that -- you may say, well, that might get a drug qualified in a restricted population of patients. And yes, that's true. But then you can do subsequent trials to see how broadly applicable it is.

But if you can get a trial done with a much smaller end in a more efficient time frame, then I think you have a real opportunity. And I think we shouldn't be thinking about just one biomarker, but can we do some kind of an enrichment strategy for homogeneity that you can then link to a surrogate endpoint outcome in a clinical trial. And the two together might give you a real efficient trial design to qualify a drug. And then beyond that, you could

Page 183

look at broader utilization of that agent.

So I think the unmet need is precision and risk stratification. And I think you heard three talks about T cell memory, primary memory, SNP as immune responsiveness or safety. And the whole intent was all three of these can be used to get towards homogeneity into maybe a high-risk category if that's the -- to have a higher event rate in your standard of care versus novel agent.

DR. MORRIS: Peter, I noticed in your two slides where you plotted survival and ABMR and TCMR that the slope for decreased survival was steeper earlier in TCMR. So this, to me, indicates that a focus for drug development for primary de novo DSA should still be looking at controlling T cell activation. We know just from basic biology that primary responses are T cell-dependent, and DSA is a signal that we're not controlling the T cells. So I thought that was very instructive.

DR. NICKERSON: And no, I would agree, Randy. I think what we're seeing is that -- and many groups around the world now have shown that TCMR early is a

Page 184

subsequent markers of those at risk to getting DSA late. And when you look at pathologies in ABMR, many of them are mixed. They're not pure ABMR. Alex's group in Paris had a nice paper with -- it was Ojay (ph); I guess it was about a year ago -- that nicely detailed the mixed nature of these rejections.

And so, yes, I think we should be looking at -- you know, and as I showed you, the EGFR was already going down faster in those patients before they developed the DSA. And I think what's going on there is there's probably a subclinical cellular event going on in the graft.

So I believe that we still have to keep the T cell in our sights, and trials focused on TCMR can be very instructive. And I think that's where you'll hear in the next session why subclinical rejection is a really important thing to be able to diagnose as maybe part of your trial design.

(Crosstalk.)

DR. MEIER-KRIESCHE: -- Sarwal has a question or a comment.

DR. SARWAL: So I just wanted to actually, I

Page 185

think, echo what Peter has said. And really, I think the point, the challenge, for us is to really try and stratify which patients should be selecting pretransplant for which drug trials. And I think we have two types of probably drug trials that are going to come in those with equivalency for outcome but with increased safety versus those with increased efficacy dealing with certain things where the safety parameters maybe are more understood.

And so I think what Peter has shown is actually -- you know, really highlights that there is the whole attention that has to be paid between the donor and the recipient.

But I'd like to probably challenge the community and say that I think we probably in the future need to take even one step further because we have access to such deep sequencing tools that the future should lie for us that we are actually developing individual donor recipient (inaudible).

So we should be looking at the recipients' alloimmune recognition response specifically to that donor because, right now, we are doing a pool effect

Page 186

where we are looking at some of this stuff. And I'll talk a little bit about how we can look at other parameters, including doing this kind of sequencing for non-HLA. But I think that's kind of the future. If we could get there, we could really get some of these new drugs and trial them with greater safety and efficacy.

DR. ABECASSIS: Can I make a comment on Peter's?

DR. MEIER-KRIESCHE: Please.

DR. ABECASSIS: So I think what -- first of all, your work is fantastic, really exciting.

But I think there's a danger to doing clinical trials that are so narrow that, you know, by the time you're done, you know, 100 years later, all you can draw is a conclusion about a very specific patient population. And I agree with Minnie. You know, we have the ability to come at data later on and be able to look at -- you know, predictors of failure or, you know, predictors of whatever.

And I've always been of the mind that, you know, you want to just go wide, go big, and then come back and look at data, as opposed to, you know, there's

Page 187

a temptation to do a smaller trial, very focused. But then the outcome is just based on that very narrow population.

DR. NICKERSON: So I think you make a good point, Mike. And I think the other opportunity you have besides enrichment would be a stratification design where, basically, you'd use your markers as stratification tool, and then you could look for is there a differential effect in the different populations of your drug afterwards or as part of your statistical analysis plan of that drug development. And then you could see whether or not -- whether the drug is most efficacious in one subcohort or another. And in fact, that's exactly what they're doing in oncology now, right, with a lot of the targeted drug therapies.

UNIDENTIFIED MALE SPEAKER: And I would also add that there's -- we need to kind of step away from that perception that because if we use a drug development tool that helps us enrich the clinical trial and increase the probability of success, that's really what gets drugs approved. Going too wide just

Page 188

because of a perception that the target population might be wider has not been as successful, and I think history shows that. So that's -- I means, it's striking amounts.

Just because you get a biomarker qualified that can enrich a clinical trial doesn't mean that, first of all, you have to use it every single time. And second, you have to put it into context as to what that means to the individual drug development programs in the pipeline.

DR. SARWAL: Could I just comment on the statement you made that you cannot do trials in a very narrow population? I think times have changed. And the example is the master protocol. And on one of my slides, I gave the reference to a paper last year, I think, with Janet Woodcock and Lisa Lamonge (ph).

And they are using -- so currently, they have -- so the master protocol is multiple therapies, multiple patient subtypes. And they -- recently, I read somewhere that they have approved drugs -- you can't even say a drug -- using the master protocol. You genotype the patient, multiple patients with this

Page 189

test that's approved. And then you can -- based on the outcome of that test, you can treat the patient with one of umpteen drugs. This is all under one trial.

So the concept of one randomized clinical trial prospectively designed to answer one question applies. It's great for certain things. But for complex situations such as what you just mentioned, I think there are options that FDA is looking into and has embarked on.

DR. STEGALL: I have a comment.

DR. MEIER-KRIESCHE: Stegall.

DR. STEGALL: So there's a -- I look around the room, and they -- the pharma that are here, a lot of them are doing studies in post-transplant patient populations where they've identified a problem post-transplant and are doing what I would call rescue therapy. And so I don't know if that's -- it turns out that those studies are pretty hard to enroll, also. They are actually -- their patients already has an identified problem, which is associated with graft loss, right? And (inaudible - technical difficulty) finding more and more of those patients on one-year

Page 190

biopsies and all the rest.

But I think there has to be some sort of discussion around what are the best biomarkers for post-transplant intervention, which is truly an enriched population already. And that truly avoids -- I mean, the easiest patient to enroll is pretransplant, right? And that's an easy transplant population. And yes, there are novel trial designs that might enhance that.

But when you already have a patient post-transplant who has declared themselves a problem patient, which is what iBox does, that's -- I think we need to sort of think more on that way of thinking. And it may be, because there's going to be some more talks about, you know, monitoring patients, but monitoring for DSA or monitoring for peripheral blood assays, but also the histology and what we already kind of -- markers we already know something about very clearly. And I think that seems to me just, also, too, as a person who does these trials, there's a lot of heterogeneity endpoints and inclusion criteria in those studies right now, and it would be really nice to have

Page 191

that -- conversations about trying to get our heads around, like, for example, just clearly post-transplant ABMR. And so -- and that's not, you know, CTOT anything. That's just, unfortunately, what we see.

DR. NEWELL: Just one comment here I want to make is that, I mean, prognostic enrichment in clinical drug trials (inaudible) the legitimate strategy. I mean, if you take the acute rejection example with the current drugs or which -- with the potential drugs which are in the works, it may not -- we may not be able to show a difference for the acute rejection endpoint, just as an example, because the -- if we enroll all comers or low-risk patients as generally has been done in trials.

But if we apply a strategy of prognostic enrichment and enroll patients who are at higher risk for acute rejection, then we may be able to show a difference. So that's one potential hypothetical use for prognostic enrichment.

UNIDENTIFIED MALE SPEAKER: I was going to say. As I try to reconcile the two statements, you're actually trying to achieve very different things. And

Page 192

it's probably the companies who would see it that way.

So I think what Peter is saying is, if you got a very selected population, then you might be able to better risk-adjust and show more meaningful differences for the therapy. But if your marker is so narrow that it only identifies 1 percent of the population and then you go to your context of use statement -- and I think most pharmaceutical companies already say transplant's small -- and if you can now only use the drug in 1 percent of the transplants we do in the country, it would be in some ways helping them, but in some ways hurting them because no one's going to go after that population.

I think what Mike was saying is that it's useful to have studies set up where you can capture more of the population. And so how you transition from, yes, it works in the small subset of patients that's very carefully defined to assessing whether it works in a larger population is, I think, the intersection of what you're talking about.

DR. MEIER-KRIESCHE: I think Dr. Nickerson wants to response.

Page 193

DR. NEWELL: Yeah. So --

DR. MEIER-KRIESCHE: And then Dr. Murphy.

DR. NEWELL: So I think that's the point that I was trying to illustrate on the last slide, which was, in fact, these three risk categories partition 25, 35, and 40 percent of the cohort, right, which is all comers. So in fact, none of the one category is going to really partition you into 1 percent of the population. It's giving you, actually, a big whack of the population.

DR. NICKERSON: I was just saying, rather than as an enrichment strategy, I liked it better as a risk stratification because then you leverage the strength of your tool, but you don't restrict it.

DR. MEIER-KRIESCHE: Dr. Murphy.

DR. MURPHY: Just to follow up on Ken's point, though, the idea of being too restrictive, that's the very way that cancer actually started moving forward. I mean, if you think about how they identified an -- 10 percent of individuals with a certain type of lung cancer and managed to get approval for that drug -- and slowly but surely they started making a difference.

Page 194

And I think we need to be careful about being afraid to be too -- being afraid of being too restrictive.

DR. SARWAL: And I want to give the example of cystic fibrosis drugs. The first one was approved for a sliver and then bigger. And then the concept that you're raising is let's give up before we start. And all the rare diseases -- I mean, there are patients out there, you know. We could be patients at some point. And I think we need to have that consideration. And there are pathways at the FDA, the breakthrough therapies, and, you know, all of that whole area. And it's laid out in the Cures Act, in PDUFA, that we'll work with you on that, and we find ways to get across or get there because these are huge unmet need areas.

DR. MEIER-KRIESCHE: Dr. Mannon.

DR. MANNON: Just to go back to the big versus little studies, I mean, I thought that one of the reasons these have merit is because we could narrow the population numbers we need to find the endpoint that we're mystically looking for. And if we had -- you know, I mean, why do people -- you know, the biggest problem I have with old trials is, like, why did people

Page 195

fail? Why didn't people do well? And we usually can't go back and look.

So I think there is total merit to this because it's obviously more than HLA mismatch. It's obviously more than where you live and how much money you have and whether you have insurance. And so the ability to consolidate many of these factors I think is important moving on. I don't think narrowing the population will affect the sales pitch. I think that you could then use that drug if it's approved, perhaps even in a broader context because if you say I'm taking the high risk and they do well, potentially, we could develop it and expand it to say this is good for all humans with transplants.

DR. MEIER-KRIESCHE: Okay. I think someone in the audience wants to --

MR. FOWLER: Yeah, I --

DR. MEIER-KRIESCHE: Please, go ahead.

MR. FOWLER: I'd just like to add a perspective. My name is Kevin Fowler with the Kidney Health Initiative.

And going back to what Dr. Murphy was saying

Page 196

about look at oncology, I think if you look at what's happening in kidney disease, everyone was looking at diabetic kidney disease. And now they're going to make some progress. But really, where the impact is being made in kidney disease was in rare disease.

And I guess my sense is you can debate going back and forth, but you've got to get someplace to get started to show some success to pharma, to patients, and the larger community. That's just my two cents from my experience in that area.

DR. MEIER-KRIESCHE: So one quick comment to the usefulness of the stratification biomarkers, I think it's very clear from the development prospective they're extremely important. And we are kind of discussing the different (inaudible - technical difficulty), which may apply to individual projects. Whether you use them for enrichment or whether you use them for de-risking (ph) your trial or whether you're go into large, small, it doesn't really matter. It gives you the opportunity to discuss this so you have a more flexible way forward.

And I think Peter's data is actually really

Page 197

amazing because there's a trial which failed which could potentially have succeeded if that stratification variable was available before this trial. And this is exactly the example -- one of the examples where something like this can be useful and then obviously can be useful in terms of increasing the number of events. And obviously, you have to strategically think through how you can make that applicable eventually to the larger population.

But bottom line, having something like that can really prevent you from making missteps. And sitting on the end of really having to try to bring a new therapy into a population, that's really what keeps me up at night, that I may have variability in the population which drives outcomes which I cannot control. So very clearly, in some way, this is going to be extremely helpful, no matter which way we are going to employ this.

UNIDENTIFIED MALE SPEAKER: I think, to echo Ulf's point -- I was going to try and make it, but I think you made it very well -- it's the idea that these are tools, right? These aren't defining the strategy

Page 198

of pharmaceutical organizations. These are tools that can be applied to specific strategies in scenarios which we can't control. We can't control market factors. We can't control all these other things outside of here. But what we can control is developing a toolkit to design and optimize clinical trials such that you have reduced the heterogeneity to have a better shot and goal (ph). And the better you can do that consistently, the more likely you are to succeed.

So it's -- so the specific application and strategy is a great conversation to get into and features into the context of use portion. But clearly being able to reduce the heterogeneity within -- with regard to your patient populations is a great first step in that aspect.

UNIDENTIFIED MALE SPEAKER: I would only say, to beat a dead horse, not reduce the heterogeneity, but account for it.

UNIDENTIFIED MALE SPEAKER: Exactly. Yeah.

DR. MORRIS: I have a comment just generally about drug development. If your drug in a trial fails to meet the endpoint and it's not approved, it's a dead

Page 199

drug. If you do design a trial with the goal of a very broad claim for a large market and large revenue and you win, you win big. But if that trial seeks to fulfill an endpoint with a very broad claim and you fail, then you don't have usually any more chance usually in pharma to recover from that failure.

So I think that there are two factors that are beginning to influence the way we're thinking about designing trials. One is that, if you design a trial with a narrower claim and you succeed in meeting the endpoint, you may have a lower initial revenue. But we all know that drugs are complicated. And once they're in the clinic, you learn how to use the drug. And from that knowledge, you broaden your understanding, and you can do another trial with a broader claim and increase the revenue.

No drug, no money. Small market, some money. Knowledge, bigger market, more money. That's number one.

Number two is the current trajectory toward value-based pricing, meaning that if a drug fails to provide the therapeutic effect in a patient for that

Page 200

disease, then the payor may not have to pay for that drug. It didn't work. It's like getting a -- paying for a car that won't run. Who would pay for that?

So value-based pricing then gets back to narrowing the population in such a way that you're more likely to have a drug that is effective in that population.

DR. MANNON: So following up on Kevin's point, we actually have an online question from someone who writes, "I'm a transplant recipient and rare disease patient. For patients pre- and post-transplant, do you believe that a more specific approach needs to be taken? For patients with particular strong immune systems who have rare diseases, will biomarkers be enough?"

And I know we have limited time, but the question does say pre- and post-transplant. So perhaps in subsequent sessions, we can talk about rare disease and strong immune responses. I don't know if one or two people may want to make comments now, or we can reserve this for the following session, given that we are, I think, getting close to noon.

Page 201

UNIDENTIFIED MALE SPEAKER: The only comment I would say is that it's probably not going to be one biomarker. I think that you need many because there are many different reasons why people have a bad outcome.

And so in the end, you're going to synthesize finding multiple biomarkers to correlate with some surrogate endpoint and individualize based on those results. That is the most likely scenario.

DR. MEIER-KRIESCHE: I mean, the time is 12:00 o'clock. I think we need to close the session here. And we will reconvene sharp at 1:00 p.m. for the next session after the lunch break. Thanks.

(Lunch break.)

DR. BALA: Okay. All right. It's time for the Session 3 now, which is Potential Early Post-Transplant Biomarkers of Alloimmunity or Risk for Graft Loss.

I'm Shukal Bala with the FDA, and my co-moderator is Dr. Peter Nickerson from University of Manitoba, Canada.

Our first speaker for today is Dr. Minnie

Page 202

Sarwal from University of California San Francisco, and her talk is going to be Noninvasive immune monitoring for subacute rejection in kidney transplantation.

DR. SARWAL: Thank you so much. It's actually my pleasure and privilege to talk today about, really, the things -- the kind of thinking that we want to bring together in this room to address what subclinical monitoring -- so sorry -- what monitoring for subclinical rejection and inflammation in the context of graft injury could actually look like.

These are my disclosures with not much relevance to the talk today.

So I wanted to start off with this introductory slide and actually fashion the talk around this in the next 15 minutes. But before I start, I just wanted to actually give you one factoid, which I think is quite startling for the community, is that we -- our reliance on graft injury, our reliance on graft rejection, is based on a transplant biopsy.

But yet if you actually pull a group of transplant pathologists and you take the same slide and you send them -- send it across to them -- and this has

Page 203

been done in the context of Banff meetings; this has been done, actually, by Peter Ferness (ph) in some of his very well-published articles -- the concordance rate for -- across pathologists for that same biopsy slide will range anywhere from about 20 to 30 percent. And we are yet relying on that kind of read for what we are driving the management of our patients.

So I'm not even going to talk about that issue, but it'll come out as to why getting better biomarkers to harness and understand subclinical information and injury in a transplanted organ becomes critical for us to actually look at.

So the kind of management gaps that I'm going to talk about today is really -- I -- understanding the identification of the at-risk population of patients. And I'm going to talk about before transplant because that very transplant period -- before transplant, immediately after transplant -- is really going to impact long-term graft survival. And we have data previously from (inaudible) from the (inaudible) journal that talks about that if you have more than two rejection episodes, you can actually lose something

Page 204

like nine years of allograft life over time. And there's plenty of data around that, so we know that that's a bad thing.

The second part of the talk is going to talk about, really, the post-transplant, noninvasive kind of application of biomarkers. And this is important for us because we want to identify injury before the drift in serum creatinine, which is our current gold standard for noninvasive or minimally invasive monitoring. And we know that that can sometimes rise when more than 60 percent of that allograft is injured, so we really want to move earlier.

Avoiding the late detection of injury -- and that's actually what we're looking at with biopsies that are triggered by clinical graft disfunction, so we really want to address that. And the minimizing invasive biopsies -- so we're trying to address this currently by doing protocol biopsies. But that means we are trying to do protocol biopsies in every patient. And all of us who manage our kidney transplant patients, we know that they are actually not very excited about doing that. And only probably about 20

Page 205

percent of the U.S. transplant programs are doing that. So really, why do we want to do this? Because we want to give the right drug at the right dose to the right patient.

So let's look at the first problem. So I -- and Peter Nickerson gave a fabulous talk about looking at DNA in the context of HLA disparities and then looking at it in a more final microscope and looking at things like applet mismatching. So I'm going to talk about that and say that it -- that is an extremely important focus for us. And for drug trials, looking at the patient prior to transplant and stratifying which patient they're going to select, I think it's extremely important. But can -- but should we even be moving a little beyond HLA?

And so to try and do that, I'm actually just going to give you a concept study that we actually started at Stanford with Mike Snyder over a cup of coffee, and then it actually came to reality and is now funded by the catalyst program at QCSF. They basically help score kind of high-risk, high-gain kind of inventions in academia and try and get them out into

Page 206

commercialization.

So through this kind of proposal, we actually chose to say that, if you look at the concept of the HY mismatch, female recipients who actually get male kidneys do mount an anti-HY response. So there is an immunogenicity for donor-expressed antigens which the recipient lacks.

So in that concept, should we be looking at other non-HLA antigens that the donor is expressing but the recipient lacks? And to do that, we actually did exome sequencing of the donor as well as the recipient. And when we did RNAseq off that donor kidney to make sure that whatever the variant mismatch was, was actually an expressed variant in that donor kidney. We weren't interested if it was present just in spleen or testes, et cetera. So it was really the transplanted organ.

And the concept was that if you had a variant that actually was mismatched between donor and recipient, it could cause a change in the transcription factors, the metalation, et cetera, such that there could be an immune recognition off that antigen because

Page 207

of that variant mismatch. Of course, the question is what does that mean and does it actually correlate with functional outcome.

So to try and do that, this is actually the data. And when we did the whole exome sequencing, of course, we can also look at HLA. And you can see that donor recipient HLA variant mismatches, as we expect, are higher in people who reject. And the red is people who developed antibody-mediated rejection after transplant, T cell mediated rejection after transplant on new rejections. So you can see higher variant mismatches.

But what happens if you look at the rest of the variants in a non-HLA part of the genome? And you can see that, in fact, you can see this actually gets even more enhanced. So we are missing a lot of stuff, that, really, we're looking at the tip of the iceberg here with the HLA. But there's a lot of stuff happening in the non-HLA compartment that we're not even recognizing. And you can see across all these thousands of variants those that are enriched in the kidney are actually much higher here.

Page 208

And so this tells us if we, again, take those HLA variants and we try and cluster our patients across the variants with a color combination still (inaudible) category, you can see again the mismatches that kind of -- if you were to take a pretransplant sample, do the donor-recipient variance on HLA and cluster of (ph) patients, could you have told risk?

Peter is showing that, in large numbers, you can start to see that separation after transplant. But in smaller numbers, you're not being able to see that kind of clean separation. Can you actually see that with the non-HLA variance?

So we have 123 variants that will be mapped, highly expressed in the kidney, highly expressed in immune cells, highly expressed, also, in endothelial -- the compartment. So that's what the bioinformatic algorithm enriched for. You can see it's actually quite nice. You can start separating people who developed AMR, TCMR on this kind of axis. And here are the people who did not reject.

So the reason I put this to you is I think the kind of technologies we have today can harness this

Page 209

kind of information such that focusing on that pretransplant selection of the patient who has maximum risk is really important. But of course we don't want to be doing exome sequencing and spending $2,000 per patient. Can you reduce this to a SNP array? So we actually have generated a fluidigm SNP array customized for the 123 recipients as a four hour turnaround time. Cost of goods is about $250 per sample. And you can actually get pretty good data.

So this is the SNP array now, an independent validation set. And you can see that these are actually the SNPs. So this is a -- if it is red, there is a donor recipient variant mismatch for the SNP; white, there is no variant mismatch. You can see here are the people who actually do -- antibody mediated rejection after transplant, T cell mediated rejection. There are few variants that are actually enriched for people who do not reject, which may be protective.

And you can see here on the Y axis is if you actually got -- the donor was actually related, unrelated, and if there's race, if it's related to African American versus Caucasian, et cetera. But you

Page 210

can see the real prime separation is for the event after transplant.

So I'm not going to present more data on this, but we have actually large-scale validation on about 800 donor recipient pairs. But the idea is that you can take these kind of custom SNPs before. You can combine them with the HLA data that you're getting. You can run the panel on across these non-HLA variants. And these are the most common variants, so, really, the low-hanging fruit. The future, of course, would be is to customize this to each donor recipient pair, which I think is the end of the goal here.

But essentially, if you're getting closure -- included all these variants, you could really select for drug trials which is that patient group that you want to highly enrich that could be having that event after transplant or absence of event.

So we've talked about that. Let's look at the post-transplant patients. So in post-transplant monitoring, this is actually where we're managing our patients today. So we see our patients in clinic. They actually have a change with regards to

Page 211

proteinuria, GFR decline. We could do the iBox over here. We could say how those people are going to respond. But actually, you believe that maybe we are missing stuff.

So what -- as I said, about 20 percent of the programs will do a protocol biopsy. We actually pick up all the subclinical rejection, and we try and treat these patients. There is enough data about that, that if you treat inflammation and you treat inflammation early, you actually can improve outcome with regards to GFR, et cetera.

But here, I'd like to put to you is that more are happening beneath the surface. So rather than just relying on clinical parameters or doing a protocol biopsy, could you actually do something else that will give you the molecular health of the allograft? And why is that important? That is important because if you actually look at the protocol biopsy, when you actually have subclinical inflammation in the graft -- and we've done a lot of this work at Stanford and at QCSF, we've actually found that, about 30 percent of them are actually molecularly active. Seventy percent

Page 212

of them actually could be molecularly quiescent.

So just looking at what the histology shows is sometimes very difficult for us to actually take that and proceed to the right kind of treatment for our patient.

So how do we actually address this? So to go there, we actually propose to actually take a urine specimen over here and look at the molecular health of the allograft as reflected in the urine. I'm just going to present you that data today and not present you new data on blood.

And so why is this important? Because if you actually look at the study of protocol biopsies, these are protocol biopsies and at 0, 6 -- 0, 3, 6, 12, 24, and 36 months as part of an NIH multi-center study across 12 programs in the U.S. You can see that, even in the absence of any donor-specific antibody, these were just the patients selected who had no donor-specific antibody, no clinical acute rejection. You can see if you did multiple protocol biopsies, which is not a reality for our patients, you can see there is a progressive accumulation of injury that's occurring in

Page 213

these allografts. This is injury that we do not recognize because these patients largely have a stable serum creatinine. How are we actually going to figure out this injury? Because we're not going to be biopsying our patients all the time.

So the question is: What do we do? So we did molecular analysis off these biopsies to ask: Is there a difference in people here who actually had a three- or six-month protocol biopsy? Could we have done a molecular analysis here and predicted that they would have got there? So can we take two groups of patients -- patients who got there really fast -- we call them progressors; patients who got there really slowly -- we call them non-progressors? And is there a difference in the molecular profile? And you can see there is. So these are patients who are progressing over -- so you can see these are the non-progressors in blue, and we looked at basically immune signatures that actually drove. See, there's a gene set analysis.

So when we looked at genes involved in T cell, B cell proliferation, natural killer cell, mast cell, so in allo and innate immunity was increased at the

Page 214

six-month protocol biopsy time point when they were histologically normal and not differentiable. And you can see over time these scores increased.

So take-home message is there's more fibrosis occurring. There's more injury occurring. But guess what. There's also more molecular inflammation occurring, and that's what's driving it. And in fact, the take-home message here is that if you actually look at these scores at six-month protocol biopsies here -- again, the progressor, non-progressor -- you can see they're higher. It's -- you can see it's the same signature that's occurring at the time of acute rejection.

So what we are missing today and why we need better biomarkers after transplant is we need to uncover that subclinical injury, which is really a threshold effect of what is happening at acute rejection. If you can pick it up really early and you can pick it up noninvasively, you can treat it, and you can avoid them actually going to a full-blown acute rejection.

So how can you actually do this? And so to

Page 215

try and get to this, we've actually done extensive studies. And these are published papers. I'm not going to go into details. But we looked at solid organ transplants undergoing acute rejection and identified a common hub of genes which we called the common response module. They're all highly kind of co-regulated through STAT1 and NF-kappaB, et cetera. And you can see they've actually reduced this kind of learning down to a urine pellet isolated at the time of the biopsy and actually validated these genes as being able to drive the detection of inflammation in the biopsy but by a urine sample.

And so you -- we've also done a lot of proteomic work, and we've been lucky to have consecutive funding from NIDDK to actually look at deep proteomics in the urine and to try and look at panels of biomarkers that can correlate of this molecular injury in the graft but with a urine sample.

So what does this mean? So we've been able to take these biomarkers and create a gene set score and a protein set score. So this a combination of different biomarkers. And you can see in large datasets they can

Page 216

start to separate at the time of biopsy. We call this set kind of a kidney injury test or kit. And you can see that if we actually look at these biomarkers and we compare them to the current standard of care in urine, which is proteinuria, you can see that it -- the performance is significantly better.

So do we have something better than current standard of care? Yes. But I think it was pointed out earlier. The risk of these kind of biomarkers that are very sensitive and specific for inflammation is that it will give you that false positive, or, should I say, true positive because it'll detect injury when we didn't think there was injury.

So I think the best way to reflex this for monitoring in the context of drug trials may be to look for absence of injury. So quiescence may, in fact, be the most important thing.

So really, this conclusion is that, to evaluate drug efficacy, how do you actually treat this? So I think the take-home message is, just because your graft is clinically stable or histologically stable doesn't mean that it is molecularly stable. So

Page 217

therefore, inclusion of these kind of urine assays or noninvasive assays to quantitate information I think is extremely important. And actually, it's important to recognize that there is this discordance between what you're seeing as a molecular inflammation and what we have not been able to recognize histologically.

And I think, again, in the post-transplant setting, how can we use this? We can use this for monitoring drug efficacy in trials that are actually using novel treatments as well as for quiescence.

And so this is my last slide to show you. We are doing some of this at UCSF. So this is some kind of trials that are being run through NIAID-funded, CTOT-21 trials led by Flavio Vincenti, who is a PI. So we actually got regulatory (ph) T cells that are being infused at the time of subclinical inflammation, as recognized by a six-month protocol biopsy. And we are also trying to give (inaudible) map to block the IL-6 access at the time of subclinical inflammation recognized by a protocol biopsy.

The preliminary data with (inaudible) map suggests that it's very difficult for us to just look

Page 218

at the biopsy and say this is subclinical inflammation. So we are actually combining this with these kind of urinary biomarker studies to actually provide us a better way to assess selection of the patient for that drug and then also to look at efficacy when that noise of what is inflammation is actually very little. And you're going for that very early period post-transplant.

So I think this is just to say that I think this is what we have been wanting to take some of these biomarkers for. I tried to actually put them on this slide and say that, yes, we need assessment. We can do assessment of transplant rejection risk before transplant. We can mainly potentially have, like, a drug that's being used to diminish transplant fibrosis or treat AMR. And we know we have companies here that are interested in bringing these trials forward. We can use the kind of DNA and protein biomarkers to select before as well as to stratify the efficacy of the drug and safety of the drug after transplant.

I'd like to really recognize the many, many people in our community that helped us, funding from

Page 219

all these -- I just put up a picture of the people in my lab who have been integral for a lot or the work that has been shown today.

Thank you so much.

(Applause.)

DR. NICKERSON: Thank you, Minnie.

Our next speaker will be Dr. Michael Abecassis from Northwestern Medicine -- Medical School in Chicago.

Mike.

DR. ABECASSIS: I want to thank the organizing committee for the opportunity to present our work. I'm going to focus today on findings from CTOT-08, which is a NIAID-funded study.

First, disclosures. I'm a co-founder, shareholder, clinical, and scientific advisor to a company called Transplant Genomics Incorporated, which does this test. Also, I shamelessly used a bunch of material provided during the planning sessions from my talk today, as I see most other people did as well.

So the data that I'm going to present today has recently been published. And I want to acknowledge

Page 220

John Friedewald, who is obviously the -- not only the site PI at Northwestern, but the protocol PI for the entire consortium. And I'm only going to present data today from that study that focuses on subclinical acute rejection, which Minnie has done such a wonderful job introducing.

So our definition was histologic evidence of rejection on a protocol or surveillance biopsy. As a matter of fact, greater than 90 percent of our subclinical rejections in this cohort were borderline. And also, stable renal function -- and this was defined as less than 20 percent change compared to the average of the previous 2 to 3 values and a creatinine less than 2.3.

This is a diagram illustrating the study. And the important thing is that all patients underwent surveillance protocol biopsies at either 3 or 6 months, 12 and 24 months and also a serial biomarker monitoring, including at the same time as they got a biopsy. Patients also had for-cause biopsies, et cetera, et cetera. And again, the focus here was subclinical rejection.

Page 221

So this is a busy slide. The left panel shows our algorithm for the analytics of the study. Just to briefly go over this, we first looked at about 3,000 differentially expressed genes. These were mapped using three different softwares and mapped very nicely to genes related to rejection.

We then took these and put them through a random forest model, used Genie for importance and reran them through a random forest model. This allowed us to create our model that had 61 probe sets that mapped to 57 genes. We had a discovery set that included 530 paired samples. These were surveillance biopsies and peripheral blood sample. And then we had a validation cohort, which was from the Northwestern University Biorepository. And we started out with 138 patients who met the criteria of stable and surveillance protocol biopsy and that -- then used 129 that met precisely the definition that was used in the CTOT study.

And so in our discovery set, the AUC was about 85. We purposely identified a threshold that gave us more specificity than sensitivity. And I'll come back

Page 222

to that. And then we locked down the algorithm. We locked down the model. We locked down the threshold. And then we tested each sample as an unknown in the validation study.

And so the table at the bottom shows the performance of the biomarker in both the discovery and the validation cohort and then the subcohort. And the reason for doing those two is one was clinically what we would consider a stable patient, and the other one was what the protocol required to be called a stable patient. As you can see, there weren't many patients that fell out of that second group.

So this was a prevalent population. There were 400 of these had met the definition of no rejection, stable creatinine, and 130 met the definition of stable creatinine and rejection, which was subclinical rejection. We used exactly the same threshold to determine whether the test was positive or negative. And you can see here the MPV on discovery was 88 percent, and it was 78 to 80 percent in the validation cohort. And then the PPV was 61 percent in the discovery and 47 to 51 percent in the validation

Page 223

cohort.

The important other number to consider here is that the test was calling positive approximately the same proportion of patients that had the phenotype. So we didn't way overcall one phenotype or the other.

So in terms of what this all means, we had designed the study to, obviously, capture a whole bunch of clinical data. By the way, this was all reviewed by Roe (ph), which was the DCC, by the NIH, by the steering committee. These data were reviewed by everybody prior to even being allowed to present a single bit of it.

And what this shows -- at least it wasn't a surprise to us, but I think it might be a surprise to some -- that the biomarker -- I'm sorry -- that the clinical phenotype, which is based on the biopsy, if you looked at people that had no episodes or one or greater episodes of subclinical rejection, there was a statistically significant association with a -- both a clinical composite endpoint that consisted of acute rejection, clinical acute rejection, with renal disfunction. It consisted of a delta EGFR greater than

Page 224

10 between 4 and 24 months and Grade 2 or more IFTA on the 24-month biopsy. So we used that as a composite, and we also found a clear association with both Class 1 and Class 2 de novo DSA. And this was a clinical phenotype. So this is no biomarker. This is just a clinical phenotype.

Then we went and looked at the biomarker independent of the clinical phenotype and asked the question: How does the biomarker associate with these exact same endpoints? And again, we found statistical significance with the composite clinical endpoint as well as with de novo DSA almost identical to what we found with the clinical phenotype, even though there wasn't 100 percent concordance, as you saw from the performance of the biomarker between the clinical phenotype and the biomarker.

This was kind of interesting. I thought this was the most interesting part of the study. So I show you the design again because what we asked was that, when a patient had subclinical rejection on a protocol biopsy and whether they were treated or not by the center, we followed that patient with biomarker

Page 225

determination every two weeks. And at eight weeks, we demanded a repeat biopsy. So this was not easy for centers to accept, but the centers that enrolled accepted to do this.

We did say that this was only allowed once per subject. We didn't want subjects to have to do this more than once because, not only were they getting a surveillance biopsy, but they were getting an eight-week repeat surveillance biopsy and only if the serum creatinine remained stable.

And in order to analyze these, we had to have all blood samples in both biopsies. And centers were allowed to treat per their standard of care. And the amazing thing was, first of all, that greater than 50 percent of patients treated for subclinical rejection did not respond histologically at the eight-week biopsy. The biopsy was either persistent or worse.

And when I went around and asked my colleagues at Northwestern to give me a guess, they all said 80 percent would respond, 90 percent would respond. You know, it's subclinical rejection. Of course they're going to respond. It turns out that was not the case.

Page 226

So this was very important.

The second part that was very important -- I don't know what just -- the second part that was very important was that you could predict who was going to respond histologically and who wasn't going to respond histologically based on the biomarker at four and eight weeks. Interestingly enough, at baseline, even though we had 23 patients with a positive biopsy, 13 had a positive test and 12 had a negative test. And of the patients who had a negative test, they all resolved. And of the patients who had a positive test, 75 percent did not resolve.

So we started to think that maybe, you know, the test was giving us more information, which is, I think, what Minnie was alluding to, than the actual biopsy. So this was a really important and surprising result.

So the summary is that, in patients with stable renal function -- and I emphasize that again -- where you think everything's fine, there's nothing going on, right now, the only way to detect subclinical rejection is a surveillance biopsy. So these were all

Page 227

paired samples. We used microarray. We used 3,000 differentially expressed genes that map to relevant pathways, the rejection, and populated the random forest models. I showed you the performance. And we showed a clear association between both the clinical phenotype and independently the biomarker with clinical endpoints known to be associated with poor long-term outcome. And also, as I said, it showed that less than 50 percent of patients treated for subAR demonstrated a histologic response.

Okay. And so now, I tried to take all of this and put it into the framework that we were given and asked to try to reconcile with our data. So you've seen this now, and I'm not going to go over it. So I constructed a context of use statement.

So first, the need statement. I think Minnie just said this. SubAR, or silent rejection, is bad for long-term graft outcomes, which have not improved in decades. The only way to currently diagnose this is through empirically scheduled surveillance biopsies. But 80 to 85 percent of these empirically scheduled surveillance biopsies are negative, which means that

Page 228

the test, this invasive biopsy, was unnecessary and exposed patients to unnecessary risk.

Also, the only way to currently diagnose persistent subclinical rejection following treatment, which we know happens in greater than 50 percent of patients, is to repeat yet another invasive biopsy. Therefore, there is a clear need for noninvasive biomarkers to inform the use of surveillance biopsies in patients with stable renal function following kidney transplants.

So the context of use would be to serially monitor patients following kidney transplant with a blood-based biomarker that can be used in ruling out subAR, identifying patients with adequate exposure to immunosuppressant, immune-quiescent patients, at a lower risk of harboring subclinical rejection, which we all know forms part of the arc of chronic rejection. Therefore, the objective would be to use the biomarkers to guide the stratification or enrichment of patients into a group that might more predictably or prognostically benefit from a surveillance biopsy to detect subclinical rejection or inadequate

Page 229

immunosuppression in order to better individualize the management of kidney transplant.

So again, I stole another figure, and I used it to go through CTOT-08 data and go through the checklist that was provided and put a checkmark next to where we thought -- where I thought we had evidentiary -- or evidence.

So the relationship of the biomarker to clinical outcome -- well, I showed you that that was the case. Biologic rationale for use of the biomarker -- I showed you that that was the case.

The data and study design -- this was an observational study. This was a prevalent population. All samples were paired. I think, as far as design is concerned, you know, for an observational study, it was as well designed as it could have been -- serial samples.

The reproducibility of data was demonstrated through an independent cohort. There's a comparison to the gold standard. Whether we like it or not, the biopsy is the gold standard.

The assay performance I showed you very

Page 230

importantly. When you're doing a performance of an assay, it's essential to have a prevalent population. If you have a phenotype that's 20 percent and it's 50 percent in your validation set, you're going to increase your PPV. And also, prespecify statistical analysis -- so these were off-the-shelf software programs that everybody knows and uses. We did not have best-fit algorithms.

So I also tried to think about this biomarker in the context of BEST. And I found myself struggling a little bit. And so I tried to put a solid circle where I thought that it sort of fit and a dotted circle where I thought that maybe it fit but I wasn't sure. And so when I tried to define what type of biomarker this was, I wasn't really that sure. It seemed to fit into more than one category. And this goes back to my earlier comment that this isn't for drug development. So this is a way to monitor patients. So I wasn't sure, and I'd sure love some help trying to figure out what kind of biomarker this is.

In terms of the level of evidence, it's important to look at potential benefits and risks.

Page 231

Potential benefits -- obviously reducing the number of indiscriminate or empirically scheduled surveillance biopsies that are invasive by stratifying or enriching patients with stable renal function and then stratifying patients into lower or higher risk of harboring subclinical rejection on a protocol biopsy, reducing the number of negative or unnecessary biopsies, and stratifying patients treated for subclinical rejection with stable function who may not -- who may show histologic response or nonresponse to treatment.

Potential risks -- well, you could argue that you could increase the number of surveillance biopsies, especially in programs that do not currently use them. You could increase the risk of monitoring biopsies because no one does them now. And you could over-immunosuppress secondary unmasking of subAR, but we just all finished saying that that's a good thing. But it is a risk.

I wanted to acknowledge Dan Solomon (ph) without whom none of this work would ever have happened. You all know him, and he's here with us

Page 232

right now. And so I wanted his picture to be up there, and I wanted to quote him. "The promise of precision medicine will only be achieved when molecular diagnostics detect actionable differences operating in individual patients that can inform management and change clinical outcomes."

And so to that end, I just wanted to give you a glimpse about a randomized control trial that we are planning. And it's hard to see, but on the left is the standard of care. This would be compared only to patients that get surveillance biopsies, so it would be done at centers where patients get empirically scheduled surveillance biopsies. And then the bottom line is that either a single negative screening, a true graft test -- that's what the test is called -- or two negative tests following a positive test would be required to forego a surveillance biopsy. So the surveillance biopsy is the default, which is what would be done in the standard of care arm.

And if anybody has any questions about this, I'm happy to answer them. And that's it.

So acknowledgments -- I want to acknowledge,

Page 233

as I mentioned, John Friedewald and all the members of the CTOT-08 Consortium. This was a five-center study funded by NIAID date. Roe (ph) was instrumental in all of the data, acquisition, analyses and all the co-authors of the manuscript.

I also want to thank all the transplant coordinators at all the sites -- the research services corps (ph), care providers, et cetera -- and also the steering committee of CTOT, including Dr. Bridges (ph). And as far as funding support, here are the sources -- and Transplant Genomics as well as the Northwestern University Comprehensive Transplant Center.

Thank you very much.

(Applause.)

DR. BALA: Thank you, Dr. Abecassis.

Our next speaker is Dr. Barbara Murphy from Mount Sinai School of Medicine New York. And her talk is going to be on genomic approach to immune stratification.

DR. MURPHY: Thank you very much. I'm delighted to be here today to present our data. And thank you very much to the organizers for, first of

Page 234

all, organizing this and also for inviting me.

So I want to -- my disclosures on several DSMBs. Also, I just want to point out Renalytix, which is a company formed in collaboration with Mount Sinai, which is a licensing agreement with the patents that we have on these studies here.

So the results that I'm presenting today are from the study funded by the NIH, the NIAID, called Genomics of Chronic Allograft Rejection. This is a prospective multi-center study that included five clinical sites -- Mount Sinai, Northwestern at Ann Arbor, Wisconsin, and Sydney Westmead Hospital in collaboration with Brigham and MDH, also.

And this was really -- we enrolled 588 renal transplant patients over a period of three years, following them for two years doing baseline biopsies, baseline blood sampling for RNA, DNA, and then (inaudible) biopsies at 3 months, in some cases 6 months -- 12 month -- and then in all sites 12 months and 24 months. And this really was to look at genomic prefile -- profiling pre- and post-transplantation to determine whether we could predict outcomes or diagnose

Page 235

outcomes in transplantation. And it really is learning set to identify MRNA biomarkers, which would then validate it in multiple independent datasets.

And I'm rushing because what I'm trying to do today is show you three of the assays that we have developed. And what I will do is go quite quickly through them. I'm not giving you all of the data related to them, but I really just want to give you a sense of what we're doing in the lab. And if there's further data that you would like to hear, I can answer any questions or tell you afterwards.

So the first of the assays that we have developed is a pre-transplant assay in recipient blood, which has identified 23 genes. It -- the needs assessment or -- of -- with regards to this is really around the lack of our ability as we've discussed to stratify immunological risk in patients prior to transplantation. And the context of use is risk stratification prior to transplantation and potentially patient selection and clinical trials. I suggest that this biomarker is prognostic and also fits into the risk stratification section for biomarkers.

Page 236

So as I said, this is blood from a recipient before they have seen the transplant. And what we did, we -- a total of 247 patients had RNAseq performed, and 163 of those had biopsies be at -- before six months. Eighty-two had biopsies after six months. So we had clinical indication biopsies as well as protocol biopsies. In the patients with biopsies before six months, we had a discovery set of 81 patients, validation set of 74, and then the second validation was using the later time point for acute rejection.

What we looked at was early acute rejection, i.e., rejection before six months. We eliminated from the analysis initially. When we were developing the gene set, we eliminated BK, and I'll come back to that. And so that reduced the validation set to 74 and 80.

And what you can see here from our -- on the left-hand side form the discovery set was that we were able to -- the 23 -- we identified the 23 genes. And there's an AUC of 0.8 with an MPV of 0.875, PPV of 0.7. And this compares to clinical factors, these clinical factors in this population with an MPV of 0.7 and a PPV of 0.5, so, clearly, outperforming that.

Page 237

When you look at the validation set, so this was all comers. We didn't break them out into looking at patients who had acute rejection versus those who had no acute rejection. This is looked at as a continuum. And you can see here we broke -- they broke out into turtiles (ph).

What we -- I -- what we did find, when you brought in donor variables, the only donor variable that was additive to this recipient risk index was HLA mismatching. So if an individual had five or six antigen mismatches, it improved the AUC to 0.89. If you look down at the bottom here, when you look at these risk score in individuals that had four or less mismatches, you can clearly break out those who have -- ultimately have no acute rejections versus those who are very high risk for acute rejections with a PPV of 75 -- 0.75 and an MPV of 0.1.

Oops. When you look at the risk score, it also identifies individuals at risk for graft loss at a later time point -- and when you -- shown on the left-hand side, and also then looking at AUC for risk of graft loss by two years with an AUC of 0.9, and then in

Page 238

pink the risk for graft loss by five years of 0.82.
This is where you bring everything together. And it's looking at the gene risk score in the top -- the gene expression in the top panel, looking at the continue based on probability, breaking out into turtiles of high, intermediate, and low risk, and then in the bottom panel looking at early acute rejection, late acute rejection, ABMR, de novo DSA, and graft loss. And you can see how, really, I could actually move that line over and break it into two groups, which clearly differentiate those at individual -- those individuals at risk for an event post-transplant versus those who will be extremely unlikely to have an event post-transplant.
What's interesting, when we went back and looked at the individuals that developed BK, they all fell into the lower-intermediate risk, suggesting that if we had avoided induction therapy in these individuals, certainly in the low-risk group, we potentially could have avoided BK.
So when we look at the clinical validity clearly with the training set, the validation set, and

Page 239

then when you look at gene set plus HLA mismatch, the AUC, the PPVs, the MPVs, sensitivities, specificities are all extremely high-performing compared to the clinical factors alone, which we have discussed earlier on as being problematic.
The second assay that we have been developing is similar to the two presenters previous with some variable -- variabilities. Looking to diagnose subclinical acute rejection, it also has been shown to diagnose clinical acute rejection. This is a 17 gene set, really, developed from three month -- by blood in -- both of the baseline and this assay are using RNAseq at -- this is, in this case, at three months post-transplant, the context of use being immune monitoring, diagnosis of subclinical or acute rejection and which are currently things that were not -- that are not feasible clinically as a biomarker. It would suggest it is diagnostic versus an alternative endpoint, though we've also been discussing the idea that we need to -- I'll get back to -- understand how to actually withdraw immunosuppression even in studies where we are using new novel agents. We still are left with the fact that

Page 240

we are tapering our standard immunosuppression at the same rate, and this may be a way of monitoring to guide immunosuppression withdrawal irrespective of whether it's new or old medication that we are using.
So this is a GoCAR cohort again -- 191 patients. The initial discovery set was done with RNAseq and microarray with overlap between those two, so 127 patients, some overlap of about 7 -- 4 -- 17 patients to demonstrate technical (ph) validity between the two platforms. We would then used the 17 genes that we identified to go on and develop a targeted sequencing using MiSEQ or the TREx assay, which is an FDA-approved platform for an assay. There is 113 patients in the training set and 110 patients in the validation set, 64 from GoCAR and 46 from an independent cohort from Belgium.
What we show here is, in the training set in AUC of 0.982 on the 127 patients, a PPV of 0.77, an MPV of 0.967. We validated then three external cohorts. So what's important about these? These are clinical acute rejection, and they are from biopsies taken at multiple time points, which would suggest that this

Page 241

performs over time. And we've also used it at a six-month time point in our cohort in GoCAR.
This is data from the TREx assay showing that we can validate it just with the targeted sequencing of the 17 genes on a third platform. This is the training set for the TREx showing an AUC of 0.83, an MPV of 0.786 and -- a PPV of 0.786, MPV of 0.977, so very high-performing. And again, you see this continuum when you look at it based on probability score.
This is the independent validation set at 3 months on 110 patients. What's really interesting is you look at that intermediate group, and you think look at all these patients that are falling in there. They're not in a high-risk group. What's going on?
There are patients in there with no acute rejection. There are patients with acute rejection. When you look at them, they actually have a higher risk for graft loss than the high-risk group. In fact, what happens is the high-risk group are more likely to go on to develop clinical acute rejection, whereas the intermediate group do not. And I would surmise that they are individuals that get on -- go unnoticed and

Page 242

actually go on. We've shown that they have higher caddy (ph) at a later time point, higher rate of graft loss. And they're individuals that go undiagnosed.

And it's not just skewed by the individuals with acute rejection. Those with no acute rejection perform the same as those with acute rejection and clearly very well able to differentiate individuals with no risk for acute rejection, no underlying rejection.

So I think it's -- we validated this in multiple cohorts, multiple platforms, and currently have developed a TREx assay and validated that. And it's an FDA-approved platform, and we're in the process of doing that for our baseline assay, also.

I think I'm going as fast as I can.

And lastly, this is actually published data. The other two are just submitted. And this is an assay which predicts at -- on a three-month biopsy the likelihood for developing fibrosis at 12 and 24 months and going on to lose your graft in biopsies that look good. Pathologists can't tell who with -- from those people will develop fibrosis. The clinical factors

Page 243

don't differentiate them. The AUC for that is pretty much like flipping a coin.

So these are individuals that we would expect to do well, and they go on to develop fibrosis and lose their kidneys. And this is an assay that identifies those individuals at a time when we could potentially intervene and prevent graft loss. This is -- a learning set was of 101 patients, a validation set of 45, and two publicly available datasets. Context of use is identifying individuals that were high risk for graft loss. And currently, the number of patients required to study or identify an agent that would prevent graft loss or impact graft loss are too large, and this would -- could be used as a potential alternative endpoint.

It's also maybe for risk stratification of individuals within clinical trials. So I suggest that this is, as I said, potentially a surrogate endpoint biomarker or risk stratification biomarker.

This is outlining some of what I mentioned before, outlining the validation cohorts. This is looking at clinical factors for prediction of fibrosis

Page 244

and graft loss both in individuals that had fibrosis versus -- and individuals that did not have fibrosis on their three-month biopsies, basically showing that we do a very poor job of predicting.

This is the training set with an AUC of 1, which is also a little concerning. But we did everything that we were meant to do around overfitting and demonstrated again in a second cohort -- sorry -- second cohort here by PCR with an AUC of 0.99 -- 0.91. And that -- in the paper, we have all the MPVs, PPVs, sensitivities, specificities, et cetera in there. And then we validated this on two publicly available datasets, demonstrating that it also performed well, all of which goes to demonstrate that this is not -- there isn't a problem with (inaudible) overfitting in this.

And when you look at principle component analysis to stratify individuals based on this risk -- gene risk score, we clearly did -- it forms nicely both on the GoCAR cohort and this public data set, so very -- performs highly at stratifying individuals for further risk of -- for risk of graft loss.

Page 245

So what I would suggest is that we have a panel of assays that, A, identify an individual at risk up front, a recipient that is a high-risk individual. And we've actually identified a cellular profile that suggests that this -- that is also identified in individuals who have autoimmunity. And we're working on that at the present.

We clearly -- if we added in the donor factor of HLA typing, high-risk mismatch, I suggest that maybe if we work with Peter around incorporating epitope mismatching, this might be very interesting -- so a recipient risk factor combined with a donor risk factor to identify individuals that are high risk prior to transplantation and then I -- well, a gene risk score that identifies underlying inflammation within the graft, subclinical inflammation, even borderline subclinical inflammation, subsequent risk for -- and subsequent risk for graft loss, and then, as I said, identifying individuals who have good kidneys who are at risk for going on to develop fibrosis and graft loss. So I think the potential for application to drug development in the multiple ways that I point out with

Page 246

regards to classification of biomarkers are potentially interesting.

So thank you very much. I want to thank the GoCAR Consortium and the multiple centers that were involved in that, the principle investigators, Phil O'Connell (ph), Ajay Jamale (ph), Millie Samonego (ph), Lorenzo Gallon (ph), Bob Colvin (ph), and Nader (ph), and all of the transplant teams who were involved in getting all of the biopsies and blood samples that were involved in this really large study and my lab, obviously. So thank you very much.

(Applause.)

DR. NICKERSON: Thank you very much, Dr. Murphy.

Our next speaker will be -- needs no introduction, really -- Dr. Roslyn Mannon talking about protein versus gene expression as a diagnostic biomarker of alloimmunity.

DR. MANNON: So I had actually changed the topic, and I'm presenting on behalf of my colleagues, Karen Keslar and Rob Fairchild (ph). Rob is heading to the AST fellows meeting and could not make a stop in

Page 247

D.C.

So another caveat is that we developed this. This is very early data that has not been published. It's only been discussed in abstract form, and it's based on the Clinical Trials and Organ Transplant, or CTOT, consortia. And this was really from a clinical application perspective. We were not initially developing this as a drug development tool, and it's currently undergoing validation.

These are my disclosures, and Rob has none.

So again, setting the context for immune monitoring, we use allograft biopsy. It's subject to sampling and observer bias. It's -- you know, the histological analysis is quite difficult in some cases, and there's lack of -- there's intra-patient variability. It's invasive. Patients don't like it. There's increased risk. And it's been coupled with, as you heard, transcriptomic analysis to potentially enhance the diagnosis or help us identify or create new phenotypes using that information.

But as a nephrologist, we've always been trained to look at the urine. And about more than a

Page 248

decade ago, Sue Anthron's (ph) lab identified the transcription using quantitative PCR of urinary pellets, identifying gene transcripts such as CXCL9 and CXCL10, granzyme B is being able to distinguish individuals that had rejection on biopsy versus not as (inaudible) being a diagnostic strategy.

But these transcripts (inaudible) regulated in other inflammatory conditions, and it gets difficult to utilize them when you have patients infected with, say, viral nephropathy such as BK polyomavirus.

The other issue with urine is that RNA is not great quantity, and the cells that are in the urine oftentimes can be degenerated and breaking down. And so we decided to try the use of the nanostring technology platform. The advantage here is that you don't do an amplification step. You bind the RNA with gene-specific reporter and capture probes. Those that are hybridized to the RNA fall -- or locked onto a platform, and then that platform is read -- you actually read the platform and actually have counts for the number of genes. And each count is giving you an approximate copy.

Page 249

So we hypothesize that we could use this nanostring platform to look at -- to measure MRNA expression in the urine, look -- looking at individuals that had stable allograft function versus those that had acute rejection and, as I'll show you, also those with BK polyomavirus nephropathy.

Our data set includes RNA urine, pellet RNA isolated from patients in the CTOT-10, 15, and 16 studies. These were studies looking at the optimization of Belatacept. So the control arm had tacrolimus. The Belatacept arm was tacrolimus and CNI and a steroid-free arm. Both trials were stopped for a number of reasons. But for 10, it was a rejection issue and, for 16, similarly, a kidney transplant rejection. 15 is a kidney-pancreas study. And the two samples that are in there are kidney transplant, not pancreas rejection.

We had 29 individuals that had stable function. And we had to actually add an additional BK nephropathy. Our rate of BK nephropathy was not that high.

We used the 795 target genes that are part of

Page 250

the nanostring (inaudible) cancer immunology code set. So we did not have a -- we just used their standard code set. We did not create our own custom.

Shown on the left is the heat map and, on the right, the volcano plot distinguishing acute rejection versus control. There were about 45 upregulated genes, and I think 39 downregulated genes shown there.

And then using this elastic net -- and I won't even pretend to know -- elastic net penalized (inaudible) methodology. A 24 gene set was identified that could distinguish between patients with acute rejection. The genes are shown on the horizontal access, and the extent of expression is shown on the vertical access. The middle panel shows you the box plots showing performance for no injury on the left and then injury on the right.

Now, why did I say injury? Because inadvertently, two patients had BK polyomavirus when we were doing the initial analysis and fell in there. And then we realized that, though the AUC showed good distinguishing from individuals that were stable, we had some contamination of those samples.

Page 251

Be that as it may, we took this initial gene signature and collaborated with Mike Abecassis' and John Friedewald's group as a validation cohort. So in addition to all the sample collection, they had also isolated urine pellet as well. And you can see that our transcription -- this is the heat map. These are no rejection, and these are clinical rejection. Don't ask me what those are because I can't explain it. I know what they are, but I don't want to tell you because I'm just working it out.

And then shown here is the specific assessment of those samples. We went ahead and looked at the samples, randomly pulled samples out to see if we could classify rejection. And indeed, we could.

The -- again, the acute rejections had higher scores with our gene signature, and the box plots are here, identifying the rejection individuals -- and this is true rejection, not BK -- versus nonrejection individuals.

But it's interesting to note that there were a lot of genes expressed by both -- in both T cell mediated rejection shown on the left and also BK. And

Page 252

I had actually demonstrated this in intragraft biopsies probably more than a decade ago. Oftentimes, it's the magnitude of difference. But here, you can see that there are 34 genes upregulated that are shared by both and one downregulated gene.

I just show you these box plots because Karen Keslar provided them to me -- but again, identifying the sort of significant overlap between acute rejection and BK, which are the left two bars here at each box -- at each doplot (ph) and the stable patients. So they look very similar, and they're significantly elevated compared to controls.

But utilizing this data, we have also been able to identify uniquely expressed genes that are unique to both -- to either T cell mediated rejection shown on the left and BK. We were able to identify 21 genes upregulated in acute rejection that are unique with 39 downregulated and about 80 -- 75 or 80 upregulated and about 70 downregulated shown here.

And again, using elastic net regression, we have now developed a new gene set of 55 genes that are predominantly upregulated. But as you can see, some

Page 253

are downregulated and the performance and the training that is shown here comparing acute rejection versus BK with a fairly significant area under the curve.

So we have been able to demonstrate using this as a noninvasive approach. You're comparing patients that are stable compared to those that have T cell mediated rejection or BK nephropathy. I would skip the last part because I don't think we're there yet.

But in terms of what is the unmet therapeutic need, you've heard this repeatedly. We need diagnosis -- diagnostic tools that don't involve an invasive procedure, particularly for patients who are being monitored and, you know, that -- just whether we're doing surveillance or not, it's still kind of a struggle with biopsies. And it's relatively easier than doing a native kidney. But we need a noninvasive, accurate, not expensive, rapid turnaround time procedure. And we need an accurate method to monitor patients, if you've heard. And we've heard different platforms identified here.

When you think about the context of use, if I have to force this into a drug development tool, this

Page 254

could be potentially, if properly validated, be a diagnostic marker measuring disease presence or status to confirm specifically acute rejection or, in cases of BK, the BK diagnosis or use for monitoring to avoid repeated allograft biopsy. I think this is predominantly, in my personal thinking, was a diagnostic strategy.

I was asked to draft conflict -- oh, God -- conflict of you -- you know, got that on my head -- but COU statement examples. So as a diagnostic biomarker, the urine nanostring panel of RNA expression would be used as an alternative method to diagnose acute rejection or BK nephropathy. And then as a monitoring biomarker, the urine nanostring panel of RNA will allow for surveillance of allograft responses to new therapies. Say we have trials where we have withdrawal of agents such as CTOT-09 where we saw significant rejections or, importantly, intolerance trials where we're conditioning and then removing all their drugs.

So moving forward, we clearly need to continue our external validation with the CTOT-08 samples. There are several hundred samples that have been well

Page 255

phenotyped. We needed to perform studies to determine whether -- and because we have serial samples from that cohort, we are determining whether we can actually identify increased upregulation of our 24 gene set prior to the onset. We also have all these subclinical rejection samples that are in the pot as well.

We're excited and considering using different structured code sets to look at antibody-mediated gene expression in the urine of patients. This would be particularly helpful at a center like mine where we do ABO incompatible and HLA incompatible where we are doing rather frequent biopsies and, similarly, trying to develop a profile to develop graft fibrosis and progression.

Obviously, Rob and I want to thank the Clinical Trials and Organ Transplant, an NIAID-funded consortium. But we also have considerable collaboration in this room, including Northwestern, Mount Sinai, University of Maryland, and Emory as well. Thank you.

(Applause.)

DR. BALA: Thank you, Dr. Mannon.

Page 256

Our next speaker is Dr. Alexandre Loupy from Paris, France, and the topic of the talk is going to be risk prediction score for allograft loss in kidney transplant recipients.

DR. LOUPY: Good afternoon, everyone. And thank you very much for the kind invitation. I'm really pleased to share these data with you.

And I will start with this question mark. So in the biomarker world, do we necessarily have to use fancy tools to prognosticate risk of long-term allograft loss? So it's easy to make this statement because I'm the last speaker of the session now. And the thing is that I'm also, and the team, looking into detailing to transcriptogenomics or noninvasive biomarkers. It's not to say it's not useful. It has a very important interest for many components on the way we take care of patients.

But we have to maybe step back and wait and take the lessons for our ancestors. And you know (inaudible). In France, he wrote the (inaudible). And he said that probably sometimes the best is the enemy of good.

Page 257

So today's topic is really to try to understand the fact that, as we need a robust validated integrated system for predicting long-term kidney graft failures, we may already have something good that we could use as the demonstration that it could be actually usable for prognostication.

So we do have probably good biomarkers or good stuff to prognosticate risk of long-term allograft loss, but we do have a lot of issues to overcome. Our task is really difficult because we have to face the low level of detail of transplant registries. They are useful, but they are not primarily designed to address risk stratification and do not contain key prognostic parameters.

Number two is the small number of patients in the more detail cohorts -- the lack of complex integration of data; the lack of generalization (ph) of some scoring system to other transplant systems; the lack of transportability of the scoring system, which is time of assessment; the lack of demonstrated performance in different declinations just because we need readily accessible tools allowing its use in

Page 258

different medical-economic settings and different clinical trials; and last but not least, there is no current system validated in the setting of therapeutic interventions. So you see that we have these big seven steps to overcome.

So what is the iBox strategy started back 15 years ago? And I will just give you some details. We wanted back in 2004 to have a study that could address prognostication. So that was a hypothesis. And this is how we built what we call the Paris Group Multidimensional (inaudible) Database System. And I'm going to spend a little bit of time here because our approach was a very holistic approach. We did not make any assumption that one parameter could be very helpful or not. And it's our multidimensional database system, and the structure is just summarized here. Our goal was to deconstruct the barriers between specialties, and we wanted to have the real transplant life.

So it's an (inaudible) register database. Our database has external audits every year. We have prespecified protocols, curated pipelines that make, you know, automatic import of data within different

Page 259

platforms in our network. This is a very important point. It's a completely unselected cohorts. Any patients who get a kidney transplant will be entering into the database system, and we'll actually stay forever just because, in France, the transplant populations have a (inaudible), meaning that when they get a transplant in the centers, the patient will come over and over again. And we don't have a lot of patients lost to follow up.

So it allows us to have a prospective (ph) assessment of prognostic parameters, to have (inaudible) follow up in events (ph). And not to restrict the prognostic parameters into the pretransplant period or post-transplant period or one year or two years or five years, we have all these data. So the goal is really to have an appraiser with a holistic approach of (inaudible) parameters and just to align them and integrate them in some kind of prognostication system that will assess long-term risk of allograft loss.

So this is the way the database is structured. And of course, when we run the model for assessing

Page 260

risk, we have to test the exportability. So there is a huge validation (ph) cycle that I'm going to be describing later on. And also an important component is how the risk stratification will be interfaced and available for calculating every patient individual profile of allograft loss.

So this is the study design, the iBox risk generation and validation. It's an international study. These are patients who receive a kidney transplant across 11 centers in Europe and North America. You will see that new centers are coming in the process. If you want to have more detail about the inclusion-exclusion criteria in our study design, you can just go onto clinicaltrial.gov because the study registered.

So the participants, as I said, it was very important for us to generate the model in the Paris transplant (inaudible) cohort and test exportability in independent validation cohorts and also to validate our scoring system in three randomized clinical trial covering distant clinical scenario.

So inclusion time was 2000 to 2014, and the

Page 261

median time follow-up was eight years after risk evaluation.

These are the iBox participating centers, and it has been updated just, you know, today. To show you that now the consortium is about 18 centers, 23,000 patients, 150,000 patients (inaudible) for randomized clinical trials. What was important for us was to add as many -- as much heterogeneity as we could. In other words, the goal was to add more and more centers with completely different allocation (ph) system, completely (inaudible) practice pattern, different immunosuppressive regimen to test the robustness of the risk stratification system and probably to be able after a while to adjust it. This is where heterogeneity in such (inaudible) number can be transformed from a weakness to a major strength. And I'm going to show you more details about that.

So of course, this big collaboration needed to have a step-by-step data exchange protocol, manual, dictionary, template, a context of use statement, and also to build some kind of heterogeneity map because, as you guess, not all centers have the same platforms,

Page 262

the same assessment for proteinuria. So we had to take that into account, and that was -- which actually took us many and many years to achieve.

So to make a long story short about the (inaudible) factors, we examined (inaudible), as I said, 42 prognostic parameters from -- starting from day zero, you know, doing a quality, ethnicity, whatever. We have, as I said, (inaudible) database who have treatment, who have injury, who have protocol biopsy, biopsy (inaudible), assessments and (inaudible).

So what we do, it was very important. When you study so many prognostic parameters, you have to (inaudible) for the (inaudible), the independency. We don't want to overfeed the models. So we paid particular attention for performance, discrimination, calibration, validation. We'd use competing (ph) risk approach and the adaptability of our system.

And last but not least, we are not expecting and I'm not going to show you here today a perfect system because you can think about that it's real-life data. So the prognostication system cannot be perfect.

Page 263

That's just impossible.

So then we apply the final model. So importantly, there is no big surprise. But I want to remind you that every single parameter here has been adjusted and the quantification of the amplitude of the independent variables here in this model. And you can see that the first is time from transplant to risk evaluation. It was very important for us to provide a system that can be performed at one year post-transplant, but also three months, six months post-transplant or three years just because we know that the clinical trials would have different endpoints. And we just know that the patient's status can change over time. So you need the system to be adaptable and updatable according to the fact that the patient status will change over time.

EGFR -- we've been talking a lot about EGFR -- it's obviously an important component in the equation; protein-creatinine ratio; and also, as you can see here, some what we call invasive biomarkers, which is basically, again, no real surprise; the degree of interstitial fibrosis and tubular atrophy; injury,

Page 264

which is defined by micro circulation, inflammation, (inaudible) transplant (inaudible); and the presence and (inaudible).

Using that output of the model, again, starting from many prognostic parameters, we kind of think that the most important is the assemblage, the way we assemble these things in the models, and to achieve a very good performance defined by the C-Stat (ph) of 0.83 that you can see here.

Is that enough? Of course not. You have to calibrate the model. In other words, you have to see whether your risk assessment performed after transplant could fit between the predictive probability of failure of your model and the failures observed. So these are the calibration curves that shows that it's a very good feed between what the model measures very early on after transplant and the three, five, and seven years graft failure rate.

Another important aspect was the timeline of risk evaluation and transportability. It was very important for us to make the model dynamic, meaning that you can update the model and recalculate the

Page 265

score, as I said, just because the patient status changes over time.

So this is in the derivation set, the density plots of time of risk evaluation in development cohort. So you can see that most of the risk evaluations were performed within the first year post-transplant. Why the first year? Because this is when, you know, important events can occur, and this is some kind of time point where a lot of centers can perform protocol evaluations. It could be also useful for clinical trials.

So the take-home message of this slide is that the iBox accuracy is confirmed when measured at different time points after transplantation, which permits to a data score based on new events.

An important aspect was also the validation of the score. I do -- I'm not describing here the internal validation procedure like bootstrapping. And I've been focusing on the validation in geographical distant systems, as you can see. And as I said before, it was very important for us to see that the centers are really different from one country to another. But

Page 266

it's some major strengths, I believe, here. And you can see that, in some centers, that the iBox distribution score can vary between the center. But again, not only the score perform well, but also it was well-calibrated in any single validation cohort from the consortium.

Another step which is very important was to quantify whether histology added to the performance of the score irrespectively of the pure functional assessment. So if you ask me, is GFR important? Of course. Is GFR slope important? Of course.

Is the integrative score more important than the simple component of GFR alone or proteinuria alone, of (inaudible) or (inaudible) alone? Yes. You can see here that you can reclassify the patient in term of risk. In other words, when you combine all these things together, it gives you more performance, more power, and a reclassification possibility, which improves your scoring system.

So what about the adaptability now of the system? And we're working the past two years very hard on that. The question was that: How can the iBox be

Page 267

fitted into less-informed (ph) data set and also available clinical trials, so ongoing clinical trials and different (inaudible) system?

First of all, you saw that in the iBox we stuck with the benefit of national classification lesion grading, as we all know is not perfect, but at least we are all speaking the same language when we see about IFTA score or (inaudible). We know what we're talking about.

So when we substitute was the fact that we used the diagnosis instead of the lesion grading. We also at -- made some adaptation of the algorithm for datasets in which this information was lacking on MFI. We also used different algorithm to take into account that, in some centers, they don't have P and C ratio. So we use dipstick gram per liter or gram per 24 hours.

We generated four centers which actually are not performing protocol biopsies, and we would like to follow their patient base on (inaudible) monitoring of GFR, DSA, or proteinuria, a pure functional score that you can see here in this mammogram (ph).

And we also pay particular attention for

Page 268

missing data. This is how we implement some machine learning procedures that can account to missing parameters.

So the last component of the iBox system was, as I said, to test its movements within therapeutic intervention. So we used these three trials that we have on site, which has -- some of treatment of (inaudible); some of get treatment of T cell mediated rejection and patient converted to Belatacept. So three intervention, three different clinical scenario, and this is here, the pre- and post-treatment iBox movement.

So you see that some patients are in blue. It means that they are decreasing their iBox score. It means that they should respond to therapy. But also, you have the red patients who actually are increasing the iBox score. So again, in those three trials, the calibration was very good, meaning that you could assign the patient at the time of treatment the probability of seven years graft failure, which is in the patient -- the patient 83 percent. And you can see that the graft loss probability after treatment here in

Page 269

these patient you can reapply, recalculate the iBox score is 49 percent. And again, the calibration was good.

And last but not least -- and you know, my student -- my PAD (ph) student working on that on the clinical trial spent two years for doing one table. So sometimes you say, Alex, two years for one table; are you kidding me? No. It's just to focus on the fact that, when you gather data from a clinical trial, then you have to update, you have the clean the data, you have to ask the different participating center for updates on histology and everything. It takes a lot of time.

And to make a long story short, it was very important for us induce (ph) randomized clinical trial to do post (inaudible) analysis -- in other words, apply the iBox score very -- at early period or at the time of the therapeutic intervention, and you can see that the C-Stat (ph) again was very good or fair in those clinical trials. And importantly, the projected time that you would have saved for having actually the good assessment of the long-term failures, the time

Page 270

saved was 5.1 years in the (inaudible) trial and 5.3 years in the (inaudible) trial.

So just to conclude, these are some example of the iBox use. You can use these coefficients in the parameters. You can assess a patient at the time of transplant. This patient has an iBox risk assessment and at the time of treatment for possible (inaudible) mediated rejections. So then you have the time post-transplant in years, the estimated allograft survival, and you have a second assessment of your treatment. And you can show the projection of this patient on a long-term run and show that the iBox score after this therapeutic intervention will have translated to an updated survival probability to a certain number.

And this is how some people, you know, started asking us to project their patient in their trail for long-term follow-up. This is the (inaudible) study. And you know, (inaudible) called us and said, okay, I have one-year data for all the patients. So now what would you be able to project every single patient in (inaudible) trial for the seven graft loss? So this is an example where you see that the one-year data will

Page 271

actually translate to iBox code, which will actually translate to seven years allograft survival probability.

So in conclusion, the novelty here in the system, this is a true integrative system, dynamic validating (inaudible) of unselected cohorts in similar independent population in three randomized trials.

The performance of the models are improved when you combine (inaudible) the parameters to traditional functional parameters monitoring. It outperforms currently existing scoring system. And it demonstrated performance in different declination. And last -- and it's a very important task -- it's not perfect. It can be improved with time. We have heard a very nice presentation on emerging predictors and biomarkers that might improve the system.

So I would like to thank you for your attention.

(Applause.)

DR. NICKERSON: All right. That leaves us with about 20 -- just over 20 minutes to have a discussion. There are questions for discussion from

Page 272

the FDA, but we have an open mic as well. So if anybody has any questions they want to raise or address or comments --

DR. MORRIS: Yeah, Peter, I have a question for Minnie.

On your interventional -- where is Minnie? Oh, there she is. On your interventional very small, I know, early trial where you're treating with TREx or tofacitinib (ph) for subacute (ph) rejection, are you including a negative control where you don't treat, and are you including a positive control where you treat with steroids?

DR. SARWAL: Yeah, so that's a good question. We are actually choosing in this trial subclinical inflammation, which currently, by standard of care, is not being treated. So it's not randomized to three arms. The standard of care is do nothing because, these kind of changes, they're really kind of not even Banff-graded kind of -- not a Banff -- it's like really, you know, very subclinical, non-Banff-graded inflammation.

So because that is currently not being

Page 273

managed, by standard of care, it is not being managed. So that's been basically the CTOT-21 application where Flavio's PI was to randomize and have two studies. Both studies would be randomized where you do nothing versus giving TREx or nothing versus giving IL-6 receptor blockade.

And so they -- the -- what we discovered in that is just histological classification of what is subclinical inflammation is very difficult unless you combine it with the molecular assessment that we're doing by the urine testing.

DR. MORRIS: Okay. But at least you have a control arm where you do nothing.

DR. SARWAL: Yes.

DR. MORRIS: Okay.

DR. SARWAL: Yes.

DR. MORRIS: All right.

DR. SARWAL: Yes.

DR. NICKERSON: Ros.

DR. MANNON: Yeah. So you know, I've heard your data, like, a million times, but today it just struck me. Do you weight the subscores for the

Page 274

pathology, or are all of them given equal weight? So is I and T more important than -- do you -- or it just doesn't matter? You just put them all as one score.

DR. LOUPY: No. The -- every single parameter has weighted -- has weight in the equations, of course. I can tell you that if you want to rank the most important parameters from, you know, the less important parameters, you will have to use (inaudible) proteinuria. They are, like, very strongly associated with risk. But still, you have some kind of independency of INT and GPDC (ph) and DSA. That was the -- our goal, is -- was to assign and use the Banff scores, and these are weighted equations.

DR. MANNON: So are any of the Banff subscores more important than the others? Like -- and if you don't -- so if you do --

DR. LOUPY: Yeah.

DR. MANNON: Yeah, I mean, is it micro -- you know, because we hypothesize that. Microvascular injury is most important, blah, blah, blah, than IFTA. But I'm just curious because you've got so many specimens now. And then I kind of wonder for centers

Page 275

like -- I know one large medical center that doesn't use Banff at all. They still use --

DR. LOUPY: Yeah, yeah.

DR. MANNON: -- sort of like --

DR. LOUPY: Yeah, yeah, yeah.

DR. MANNON: -- all a caddy -- not you guys, but it's another big center in the south, not our center -- but that uses that. So I -- they have a lot of data, but I don't know how you would --

DR. LOUPY: So it was very important for us to say, okay, there are, like, three components in the histology part of the score. You have scarring. Actually, scarring is very important for predicting long-term graft loss. You have inflammation, and you have a component of inflammation, which is (inaudible), and the other one which is -- has a T cell mediated component. And you have the CG (ph) lesions. Of course, we know CG is a bad lesion to have and carries a bad prognosis.

So this other ranking of the lesions, you have scarring and activity (ph) and damage. And importantly, if you remove these variables from the

Page 276

equations, you lose some kind of predictive performance in your system.

The simple point is that why did we use the Banff scoring instead of the diagnosis. Just because we wanted to get rid of the interpretation of the lesions, so we used the scoring. But as you said, some centers send their data without Banff scoring, and we use the diagnosis instead of the Banff scoring. BK virus nephropathy, ABMR, TCMR, or CNI toxicity, TMA, whatever, it was really important, as you mentioned, to be able to show that, actually, in those situations, we could validate the system.

DR. BALA: Alex, maybe a couple other questions on iBox. So if you were to try and identify the clinical phenotype of your patient at the time of enrollment or the time of transplant -- in other words, okay, we knew they had a DSA, right, or they didn't have -- or we thought they were naïve or low risk for memory -- how does your -- at what time point do you find that you have a good predictability for prognosticating outcomes? That's one question.

DR. LOUPY: Yeah.

Page 277

DR. BALA: The second question would be you're looking at graft loss, which I am assuming is (inaudible)-censored graft loss. Have you tried to model for all-cause graft loss in your system to -- because, ultimately, in a drug development trial, you would want to have all-cause graft loss as one of your endpoints, right?

DR. LOUPY: So yeah, I will start with (inaudible). Of course it's a very important question, so we validate it in (inaudible). And importantly, we also use competing (ph) risk (ph) approaches for our (inaudible) they may have interfere with the observation of losing the graft. So that was for the second part, your second question.

For the first question, very important, what kind of timeline should we use? And our first study design was to stick with post-transplant parameters, but not to get rid of pretransplant parameters. Why did we stick with post-transplant parameters? Because, actually, in my point of view, day zero, or pretransplant risk scoring system, are helpful for allocation. Be sure that your -- or your arm are

Page 278

balanced. No score generated before transplant actually have a -- has a good performance to predict the future just because we know that, as soon as you put the graft, some stuff will occur.

So it was important for us to have the one-year time frame, but taking into consideration these day zero parameters to adjust the system. It was very important not to exclude them and they be part of some sensitivity analysis, for example. But I think that day zero assessment and post-transplant assessment as some -- are different.

And also, a very important point is that what we wanted was to be also helpful for randomized control trial. And you can see a drug company and say, okay, I do a randomized control trial. I have inclusion-exclusion criteria. I randomized my patient at day zero. So you expect it to group off balance at some point.

But then what happens when you give drug A and drug B? And then that's what I wanted to do. Put yourself at one year and just project the patients and compare the two groups. So it's different questions, I

Page 279

think, but both are interesting.

UNIDENTIFIED MALE SPEAKER: Right. So if you're dealing with an -- what you think is a naïve or relatively what we've always called low-risk population and you -- the question would be: How early could you look to have a prognostic time? And is one year too early? Or is -- or are you better at maybe 18 months or two years? Like, I just don't understand the dynamic of that environment.

DR. LOUPY: The more you get from the timeline, the later you get, the better your prediction will be.

UNIDENTIFIED MALE SPEAKER: Of course.

DR. LOUPY: Of course. So we put it at one year, but also six months, three months, or any time because now the centers participating in the iBox (inaudible) just when you assess risk, whatever, just give the data, and we project and we validate because we want time to be adaptable.

So first of all, the iBox does not work in the first few weeks after transplant just because GFR does not mean anything. You have, you know, recovery and

Page 280

(inaudible).

So I would say that the -- it starts to be good at starting at two and three months after transplant where you are in a kind of steady state. And even (inaudible) cure-all has a (inaudible) rejection, whatever, but then you can calculate the risk. So that's the reason why we stick with the one-year prerogative. Of course, if you move the iBox to two, three, four years, then you're gaining prognosis because you have more, you know, events in your assessment.

DR. BALA: It's --

UNIDENTIFIED MALE SPEAKER: Can I ask a question for Barbara? Just because I think you talked mostly -- or the most about pretransplant risk assessment. And most of us have sort of an inherent guestimate as to high-risk, low-risk. And how does the scoring system, based on the genomics that you came sort of correlate with sort of current clinical judgment? And is that something that you would then -- could see, you know, then categorize in people in terms of induction treatments and that sort of stuff?

Page 281

DR. MURPHY: So the population that we have in GoCAR do not include individuals that are highly sensitized. So they were not included in it. So this is taking a population and using the clinical data from that population, the AUC for prediction of acute rejection within the first six months was 0.5.

UNIDENTIFIED MALE SPEAKER: Right.

DR. MURPHY: And so -- and the interesting thing is, when we look at it, there is actually an immunological phenotype associate, as mentioned, associated with it. So it's not just -- people get nervous when they hear genes. It's like this black box, whatever. But there is actually a clinical phenotype and we're actually seeing the same phenotype in autoimmunity as well. So it's -- it seems to be identifying a high immunological risk individual.

UNIDENTIFIED MALE SPEAKER: Which current -- under current measurement, we probably been --

DR. MURPHY: We have to --

UNIDENTIFIED MALE SPEAKER: -- treat it as a low immunologic risk.

DR. MURPHY: Yeah.

Page 282

UNIDENTIFIED MALE SPEAKER: So I think this is --
DR. MURPHY: Yes.
UNIDENTIFIED MALE SPEAKER: You know, the important thing about the work is that it actually allows intervention, giving current available drugs to better predict those who need more aggressive treatment and potentially the other way around. The people who are being treated --
DR. MURPHY: Yes.
UNIDENTIFIED MALE SPEAKER: -- with more aggressive --
DR. MURPHY: Yes. In fact, the --
UNIDENTIFIED MALE SPEAKER: -- immunosuppression.
DR. MURPHY: -- is even better. So being able to identify an individual who shouldn't get as high immunosuppression actually is even better.
Actually, can I just ask Alex a question?
Alex, have you tested iBox in a low-risk population with good kidneys? And what is the performance? Because --

Page 283

DR. LOUPY: Thank you for the question.
DR. MURPHY: -- the -- as a nephrologist --
DR. LOUPY: Thank you.
DR. MURPHY: -- kind of tell me --
DR. LOUPY: Thank you.
DR. MURPHY: -- you know, albuminuria --
DR. LOUPY: Yeah, yeah.
DR. MURPHY: -- you know, biopsy, et cetera, one year --
DR. LOUPY: Yeah.
DR. MURPHY: -- tells me who's going to lose their kidney. I kind of think I can do that myself, but --
DR. LOUPY: Oh.
DR. MURPHY: But you know, the --
DR. LOUPY: Thank you again. Thank you again.
(Laughter.)
DR. MURPHY: No, but since you -- no, I'm throwing it at you on purpose --
DR. LOUPY: Two very --
DR. MURPHY: -- because you said --
DR. LOUPY: Yeah.

Page 284

DR. MURPHY: -- genomics didn't matter.
DR. LOUPY: Yeah, yeah.
DR. MURPHY: So --
DR. LOUPY: Two very --
DR. MURPHY: -- it's only fair.
DR. LOUPY: Two very important points. So first of all, you know, we are, like, tied as the HLA incompatible --
DR. MURPHY: No.
DR. LOUPY: -- kidney guys --
DR. MURPHY: I understand it. I'm doing --
DR. LOUPY: -- doing --
(Crosstalk.)
DR. LOUPY: That's kind of true. And that's the reason why we paid particular attention to be very careful. First of all, it's an unselected population. So you have patients who are doing really well have compromised kidney --
DR. MURPHY: But have you taken them specifically and tested it?
DR. LOUPY: And so -- and we did sensitivity analysis because we did not want the iBox to give too much power to DSA and microcirculation inflammation and everything. So we applied the score, also, in what you call low-risk patients within our cohort and in the -- also the validation set, and we had a very good conservation of our performance just because I think because it was generated in an unselected populations that actually contains that kind of patients.
So for the second point, it's the subject of an ongoing study because I say you can expect the prognosis. So we --
DR. MURPHY: No, no. I'm just --
DR. LOUPY: No, no.
DR. MURPHY: -- I'm winding you up on purpose.
DR. LOUPY: But I -- we do that as clinician every day. Every day, I see a patient. I patient, and the patient say, okay, you have this -- all of these parameters. He's one year out post-transplant, say, how long will my kidney last? And like, I think --
DR. MURPHY: I know.
DR. LOUPY: -- maybe 14 years. So what we did, we did a study comparing the human assessment, a different label, assistant professor (inaudible) --

Page 286

DR. MURPHY: I actually believe you. I believe you. I totally believe you.
DR. LOUPY: -- (inaudible) professor with the iBox. And I can tell you that when you give to a clinician, including myself -- oh, not myself because I know the coefficient, so I'm a little bit biased.
(Laughter.)
DR. LOUPY: But when you give all these tons of parameters to someone and say, okay, can you model what -- this patient will have this kidney in three, five, seven years or eight years, the AUC of the humans are of 0.52. And the surprise is that the professors are not doing better than the residents. So …
DR. MURPHY: But I think the important point because I was teasing you because you said we don't need genomics, I think it's important to remember that (inaudible) plus genomics and other biomarkers may actually be beneficial. And so we shouldn't throw out genomic -- you shouldn't -- we shouldn't stick in our lanes. We need --
DR. LOUPY: Yeah.
DR. MURPHY: -- to understand that each of

Page 287

these components could enhance each other, and that's going to be critical for us to move forward.
DR. LOUPY: And I agree with your point.
DR. MURPHY: Yeah.
DR. LOUPY: That's the reason why I think that the system can be enhanced. But what I wanted really to stress is that we are -- I think in transplantation we do not have to be shy as compared to the cancer field where prognostic scoring system have been used widely and have poor performance. We already have something which is pretty okay. And of course, we will implement or improve the system and see what will be the new noninvasive biomarkers that will be integrated with some kind of system. And I completely --
DR. MURPHY: Agreed.
DR. LOUPY: -- agree with your point.
DR. NICKERSON: We have a question from the floor.
UNIDENTIFIED MALE SPEAKER: Yeah. This is actually a follow-on to your comment and Dr. Murphy's comment to Dr. Loupy. So I really enjoyed your presentation, so thanks again for coming here.

Page 288

My question kind of goes back to the part about expectations, right? If you establish high expectations with people, right, they may at times hit that. And I'm just wondering because there's a psychosocial dimension of transplant that I don't think is really fully understood because I look at myself. I've done better than my doctor thought, but he set high expectations for me. So I've just met those expectations.
So I'm really curious about the part about the role of exercise, you know, all the other dimensions that could impact graft life. So I just wonder if you can comment if you've done that or, if you haven't, maybe a suggestion.
DR. LOUPY: Yeah. So we have a lot of thing, you know, that we -- we have a lot of things, you know, that are raised, but not what you are talking about. I think it's important. And what is currently lacking in the system is other work, like, the (inaudible) factors that may affect transplant outcomes. And we, unfortunately, cannot control for this aspect, but it's the subject of an ongoing study ancillary to the iBox

Page 289

in my institution. So I think we'll have the answer, but it's very --
UNIDENTIFIED MALE SPEAKER: Good.
DR. LOUPY: -- important.
UNIDENTIFIED MALE SPEAKER: Good. Thank you.
DR. STEGALL: Okay. I have one more comment on what you said -- I -- the -- or the line of thought that you have and, I think in -- as it goes for a TTC progress forward. So it -- there is a movement to have something like this become some sort of drug development tool. And they will have, hopefully, some sort of acceptance of that, more than one year of graft survival and patient survival. But I can see all of these, you know, being then looked at piece by piece. And you can see this is a nice path forward.
And at any time point, if you found a four-month tool that worked better than the one-year tool, as you had mentioned, it was a loud intervention or a specific intervention earlier. I mean, I think that would just be the way -- you know, you can just see how this is the -- adding things on to this might be good. And some of this may turn out to be better for some

Page 290

types of patients than others, right?
I mean, one of the issues I have is that, you know, no matter what, the graft loss rate is pretty low. And so we have to always keep that in mind as we're trying to put these, you know, paths forward, right? We always want to catch the people who have the highest rate of graft loss, include those people in clinical trials and not, you know, do everything else and everyone else is very, very low risk. And most of the times, we're looking at very short-term outcomes anyway, like, maybe five years, right?
So yes, it's -- what do you guys say about these are in evolution always, right -- biomarkers that are an evolutionary thing?
DR. O'DOHERTY: Yeah. I mean, it comes back to that idea that was kind of outlined at the start of the day that -- what's the current regulatory accepted endpoint when you're talking about drug development, right? And you don't take leaps and bounds in regulatory science. You make incremental steps forward.
And you know, one reason why the iBox scoring

Page 291

system kind of percolated to the top with regard to the TTC efforts was because it's not that bit step forward that everyone really wants. It's an incremental step forward based off a lot of very, you know, heterogenous patient-level data that we can aggregate together.
So it doesn't mean that that's the finality of it. It means it's a step forward in that direction. Of course, other groups can keep doing their own things and, ultimately, working together as a community. It's how that coalesces and dovetails in that it's not just one thing being mandated. It's the complements between them. And if there's genetic components that are missing here, does that further refine those -- that model as well? So …
DR. NICKERSON: I think Dr. Albrecht had a comment, and then we'll come to Mike.
DR. ALBRECHT: We had a question from the web. The -- this is a recipient who's had three transplants and is at high risk for ABMR and is asking about the role of biomarkers in switching medications.
And I actually also want to simultaneously say that I think Mike probably does have a drug development

Page 292

tool. We would just have to determine what context to use it in a drug development.
But I guess I would like folks to comment on the biomarkers and the use of them when switching patients between medications or maybe even different doses of medications.
DR. MORRIS: Well, picking up a little bit on that and referring to Mike and, I think, one of the other speakers in the session where they mentioned the context of use as being diagnostic and Mike said, well, it's not a drug development tool, actually, it could well be a drug development tool for identifying patients who have failed current first-line therapy, just as in oncology where they fail first-line therapy and then they're eligible for new second-line therapy. Diagnosis of people who are at risk of losing their grafts based on whatever markers you use could be people who would be identified as subjects would be included in a trial where some are treated with the new drug; the others are on standard of care.
DR. ABECASSIS: Yeah, I agree. So with respect to our biomarker, I want to always have to

Page 293

remind myself and everybody else this has so far only been validated on patients with stable renal functions. So you've got somebody who's in trouble, it may be we haven't tested it. We've got thousands of samples that at some point we'll probably get enough money to test. But you know, this isn't stable patients. So if you're -- if you've got one of these distressed kidneys like the (inaudible) kidneys, what -- we haven't tested or validated these kidneys.
So however, I think that, you know, if you have stable renal function and you're doing well and you get a negative test, your immune-quiescent. You know, you're going to be pretty sure that things are okay. And if you wanted -- or let's say side effects to one medication and you wanted to switch to another medication, you could conceivably, you know, use it to monitor that patient and make sure that you don't have to wait for the creatinine to bump like we usually do. You might want to just monitor that. But I -- it's certainly not a test that's been developed or validated for distressed kidneys.
I had a question about the iBox and something

Page 294

just comes to mind, and I have a question for the whole group, you know. What's the right time? So you know, we've all focused on one year, and then we always talk about long-term outcome. If we really want to look at a number today, 2018, that we would consider a good, long-term outcome versus a bad long-term outcome, you know, I struggle with what's that number.

I mean, you know, kidneys don't last forever in anybody, right? So is it five years? Is it 10 years? Is it 15 years? What is that number? Because I think when you start to look at surrogate endpoints for long-term function, unless you define what long-term function is, you know, it's impossible to identify a surrogate endpoint because, you know, you said something that, I mean, I chuckled at because it makes sense, is, you know, the later you check, the more predictive, you know, you're going to be. Sure. You know, at 9 years, your prediction for 10 years is pretty good.

(Laughter.)

DR. ABECASSIS: But you know, is it -- could it be -- I mean, you know, you want to kind of move

Page 295

both goal posts, right? So you want to say if you have, you know, a kidney at 5 years, can you predict 15 years, which you may not be able to predict at 1 year.

And you know, what are those thresholds? Like, what are we as a community thinking should be, you know, a reasonable long-term outcome of a kidney? And what percent of patients do we expect or do we hope will have good function at that time point? Is that even an answerable question?

DR. NICKERSON: So I think -- I'm going to try, and then Mark can try.

DR. STEGALL: Okay. Go ahead.

DR. NICKERSON: I think it depends on what you're trying to look at. So --

DR. ABECASSIS: It depends on the kidney.

DR. NICKERSON: Yeah. Right. It depends on -- again, if it's a drug development program, you're trying to bring a new drug to market, you're going to have to take it to a clinical outcome to ultimately get long-term qualification. You might get qualified on surrogate, but you're still going to have to take those patients to a long-term outcome to qualify, get it full

Page 296

--

UNIDENTIFIED MALE SPEAKER: (inaudible - off mic).

DR. NICKERSON: Well, that's my point. So the point is the long term will be defined by the number of events. And it's -- and it -- you're going to have to achieve a certain number of events difference between the standard of care and the interventional arm. So you're stuck based on the event rate that you're going to have for your long term, and that may be death or graft loss, right?

So you're stuck on that. And then the question you have to work backwards to is how many event differences would I need to see at this time point to be able to predict that difference at some time point down the road. And then it becomes a viability question for the company. How many years am I willing to invest to follow these patients for those event rates in the long term?

So it's going to really differ, Mike, based on the event rate that you're going to experience --

DR. ABECASSIS: But the reason --

Page 297

(Crosstalk.)

DR. ABECASSIS: The reason I was asking the question, though, is so I think most of the patients in your data set are relatively early post-transplant. I mean, so have you looked at -- we all have patients that are 10, 15 years out, right?

DR. NICKERSON: Yeah.

DR. ABECASSIS: And we all have -- so have you looked at patients, you know, starting at 10 years and then see what happens 10 years late --

DR. NICKERSON: Yeah.

DR. ABECASSIS: -- because we have those patients. They exist, right? So because I get the focus is time zero to whatever, right? But it may be if you haven't modeled it already that it's as important to take patients at five years.

DR. STEGALL: Right. But I don't think that the issues at one year are different. I -- really, the issues at 1 year in a kidney transplant, based on our protocol of biopsy data, are going to be different at 10 years.

DR. ABECASSIS: So --

Page 298

DR. STEGALL: You're going to -- those are going to -- and maybe the iBox will be able to be the same model. But if you have glomerulitis as the major lesion, for example, it's going to be much more common, I would think, in the first five years. And as you go forward -- I mean, again, I may -- minority opinion on this -- so -- but I think that you -- the answer what's long-term graft survival is basically until the patient dies. That's long-term graft survival.

UNIDENTIFIED MALE SPEAKER: So I --

DR. STEGALL: But that -- that's actually a big question.

UNIDENTIFIED MALE SPEAKER: I can --

DR. STEGALL: And I think the think about it is that in -- but in a patient with a high iBox score at one year, five years is long-term graft survival for that patient. And I think that it's -- so that's the reason I said it depends on the kidney. Not everybody ends up with that kind of thing.

But I really do think the goal always is to have the kidneys last forever. But I don't know if some of the issues about antibody and all the rest are

Page 299

going to be the major issue at 10 years for those patients. And I think that -- so --

UNIDENTIFIED MALE SPEAKER: Are or are not?

DR. STEGALL: Are -- they will not be as -- yeah, I think it's --

DR. ALBRECHT: So this is a very important discussion, but we need to switch sessions. And the good news is the next session is late post-transplant biomarkers. And so let's continue this dialogue.

So may I ask Dr. Yan Wang at FDA and Ros Mannon to please moderate the next section?

And sir, can you stand up right after the end of this session, and we'll take your question at that time?

UNIDENTIFIED MALE SPEAKER: Sure.

DR. WANG: Certainly. Okay. Good afternoon. Welcome to Session 4 of the workshop. In this session, we are going to talk about potential late post-transplant biomarkers to identify patients immunological risk.

My name is Yan Wang and (inaudible) at FDA, so (inaudible) transplant product. And Dr. Ros Mannon is

Page 300

the co-moderator for this session. Thank you.

And our first speaker is Dr. Ken Newell from Emory University. He is going to talk about biomarkers of tolerance following kidney transplantation based on the result of the immune tolerance network studies of tolerant kidney transplant recipients.

Thank you.

DR. NEWELL: So I would like to thank the FDA and C-Path for organizing this and inviting me. As I thought about it, I'm invited, as I so often am, because I'm the poster child for what is not a biomarker. And I'm going to show you here why this, I think, doesn't work and how my thought process has evolved over time.

In terms of disclosures, none of these things affect the content of this presentation.

So I'm going to try to outline why we need a biomarker in tolerance studies, evidentiary criteria supporting the association between B cell and B cell phenotypes and the tolerant phenotype, the context of use for a B cell signature of tolerance in kidney transplant recipients as I originally thought it would

Page 301

be, some of the barriers to why it's not, and what it could -- what the current data could support in terms of a context of use and what we need to do to broaden that context of use.

So I think it goes without saying the statement of need is that minimization of immunosuppression, to the extent that it's safe, has the potential to reduce the morbidity of immunosuppressive drugs in our transplant recipients. The problem, though, is that, in the absence of validated biomarkers, this is a purely empiric process where you kind of wean and hope to see nothing bad happen, so it exposes patients to risks.

And there are a couple of papers. There's also a paper from the group ANOT (ph) that is very similar in what it did. But this is Peter's data, so I won't belabor it. But as he said this morning, they took very carefully selected patients under a strict protocol, tried to wean immunosuppression, and 50 percent of them had an outcome that was bad for them. Hence, the study was stopped.

So obviously, if you could use some of the

Page 302

tools he described this morning to guide that so that you went from a 50 percent success rate to a 95 percent success rate, we'd all feel a lot better. Then the same is true when you talk about tolerance, which is simply weaning to the extreme.

So when you talk about is there any evidence to suggest a link between B cells and tolerance, there are a number of papers here. And I'm not going to go through them all, but I am going to hit the high points of a few. I'm going to do it fairly quickly.

So this is the first paper we wrote. It was published in JCI, a companion manuscript, one that Maria might mention, very similar in intent. We took patients who were off immunosuppression for at least a year. They had good renal function. I'll show you what it was. It was near their baseline. And we compared them to patients who were receiving a conventional triple-drug immunosuppressant regimen and tried to say what are the differences.

This is really hard to see here. But what I would tell you is the cohort was a little unusual and that it was predominantly recipients of living donor

Page 303

kidneys. They were really well matched. I don't think I can get the pointer. I -- kind of I can.

The mismatch -- where did it go? Somewhere. Oh, right here. So they were really well matched relative to the comparison group.

They were further out from transplant than the other group. They were about, on average, I want to say, 15 to 20 years out from transplant versus about 5. So that's another, perhaps, significant difference that we'll come back to. But they had good kidney function with creatinines of around one. So these were people who were quite unique in that they were, on average, a decade out from transplant with a creatinine of one who hadn't taken immunosuppression for quite a while, but some important differences.

So this is why you should not be too wed to your hypotheses. If you went back and read my original grant application, it said that tolerance was related to regulatory T cells, and we were going to get samples from patients and prove there were more T cells with a regulatory phenotype and properties, and then we would have a good marker.

Page 304

So we did gene arrays. And what this showed you is -- my first thought is, out of 5,000, roughly, transcripts we looked out, I figured there would be hundreds that were differentially expressed, and it would be impossible to sort it out. And there were only 30 that were really differentially expressed. Of those, about two-thirds were related to B cells. This says B cell-specific. That's probably not correct. It's related to B cells.

So to show you how wrong I was, our original flow cytometry panels didn't even have B cell markers in them. We were so sure that B cells were irrelevant. So then we went back and redid the flow panels and showed that, also, by flow cytometry -- and I'll show some of the data -- there are more B cells, and there are different types of B cells. Their phenotype isn't the same.

This is often overlooked by everybody besides Sue Than (ph), who points it out. And it's in one of his recent reviews. We looked at gene expression in urinary sediment pellet cells. And again, the only gene that was differentially expressed was CD20, a B

Page 305

cell marker. And so it says that not only are there more B cells in the peripheral blood, but there are more B cells in the shed cells from the kidney and, hence, probably in the kidney, which if you believe that, you know, cells should be the site of action to have an effect, then these B cells are in the kidney, perhaps.

This is Maria's paper. I'm not going to belabor it -- a different cohort of patients, slightly different study design, slightly different assays, but still kind of a similar surprising finding.

This is from the group ANOT. They went a little further, and they found more B cells. But they also said these B cells had different surface markers, fitting with the fact that it's not just more of regular B cells, but it might be different numbers of a unique B cell subset.

And they argued in another paper that these are transitional B cells. These B cells produce more IL-10. We'd shown that in our first paper. When you stimulate the maxrebo (ph), why is that important? IL--10 is a potentially immunoregulatory or

Page 306

immunosuppressive cytokine. There was an extensive data that I was totally unaware of from autoimmunity experimental models and then clinical models that there are B cells with regulatory properties.

So when you start talking about is there a biologically plausible reason why having more B cells of this transitional type are good, or could be protective, yes, there is a potential biologic fit for this if they're the right type of cells.

And then they also showed that there was a developmental defect here that prevented terminal differentiation of these B cells. So again, they don't develop into plasma cells. They're not going to produce high amounts of antibody, perhaps. Maybe they produce immunoregulatory cytokines. So it kind of fits as a model.

So the next thing we did is we tried to say, if this signature is going to be relevant, it should be stable over time. If the B cell signature -- and I should say this B signature to go back -- I'm moving kind of quickly -- but it's based on the expression we reduced it to three genes that are all B cell receptor

Page 307

genes. And they're B cell receptor genes that are not very commonly expressed, I'm told, on your average B cell.

So we looked at these three genes, and we tried to say is it stable over time because, if one time they're predicted to be tolerant based on these three genes and another they're not but their clinical phenotype hasn't changed, it's not very useful as a tool, right? Conversely, if their clinical phenotype has changed, then the test continues to predict them with the same phenotype they started with. It's not very useful.

So what this shows you is, over a time period of about three years, the blue, tolerant patients, clinically tolerant by phenotype, maintain about the same B cell expression for the two most predictive genes. What's kind of interesting is that, over time, the control cohort begins to merge with them, suggesting they're acquiring the same type of thing. And this becomes important to say, does this reflect a change in their immune status, or is it just a function of time since transplant? And those are some of the

Page 308

things we can't answer. But certainly, in the liver transplant world, when you look at tolerance, the most powerful predictor of developing tolerance is time from transplant.

This goes into more detail. And this was done by Naki Sans (ph), but more detailed phenotyping. And the biggest difference between the tolerant patients, their B cell repertoires, and the nontolerant has to do with the maturational status. So the naïve and transitional T1 and T2 B cells really distinguished the tolerant from the nontolerant. It wasn't simply that there were just globally more B cells of all types.

This shows it another way. So this is B cell number here. So we rank-ordered all the patients based on how many B cells they had. And this is by the percentage of T1, T2, and naïve. So it's kind of saying, what's more important? The number of B cells or the phenotype of the B cells. And you can't see it, but this is the clustering. And actually, the composition of the repertoire, or the maturational status of your B cell population, predicts tolerance better than just the number of cells -- of B cells.

Page 309

This is more work from the group ANOT. They took six different studies and tried to do a meta-analysis and found out that, although the genes were subtly different, the most commonly differential expressive genes, many of them were related to B cells. So it's, again, just another way of looking and saying it's not one study.

So I'd say that there's a fair amount of evidence that B cells -- and I haven't shown you some of the functional data that the B cells are actually functionally different. They're able to suppress donor-specific responses when you take tolerant -- these regulatory -- or the -- I should say the transitional B cells from tolerant patients can suppress T cells in vitro, arguing that they have some function.

So I've tried to make the argument that there's a fair amount of data supporting this. So what would this tell us? Oh, and then this is also important. This is from the ANOT group. They -- you can't see it, but they tried to take gene expression data and then mix it with clinical, somewhat more like

Page 310

the iBox, you know, where you're trying to put together different types of data to get a predictive model. And as they add things such as age at collection of the sample, age at transplant, and renal function as determined by creatinine, they can increase the predictive power of the model, so moving more towards a drug development tool, perhaps, by adding other types of data.

So then the next study we did, we tried to say, look, if this is only expressed in 1 out of 1,000 patients, even if it's 100 percent accurate, it's worthless. It's got to be in a high enough percentage of patients to be clinically useful as a tool, and yet it's got to -- if it's in 80 percent of patients, I know I can't stop immunosuppression in 80 percent of kidney transplant recipients, so it's probably not useful.

So this was done by NIAID and the ITN together, enrolled 249 patients. And over time, we looked at -- over a three-year period, we said, how many by the two genes we're using now would you predict to be tolerant? To predict -- these are all patients

Page 311

receiving immunosuppression of some sort.

So what you can see is 25 to 30 percent for any given visit had the signature. But then you say, well, remember, it's got to be stable over time. So we took the patients who had it at all three time points versus those who never had it. And that was 17 patients always had it; 71 never had it. So those are the most extreme phenotypes, if you will. And we said, how do those two look?

The most interesting thing is I can't tell you if they're tolerant. We didn't try to wean any immunosuppression. But this is kidney function. Now, what it shows you is, whether you look at creatinine or EGFR, the group that has these B cells has significantly better renal function over time. They start out the same at transplant. But as you go further, they begin to diverge. And I would point out that this is about the same difference in renal function that you see with Belatacept. So it's not a trivial difference, again, arguing that, perhaps, the B cells have a role.

This just says that the signature has

Page 312

different prevalences, depending on your immunosuppression. So if you say what when I first saw this data would I say this meant, I'd say that, as far as the context of use, the ITN B cell signature of tolerance can be used to identify tolerant kidney transplant recipients who can undergo some degree of partial or complete weaning if they meet certain criteria. That's totally wrong.

And I have to wrap up here, so I'll go really quickly now.

But the point is we never attempted weaning. We don't know that the group that doesn't have the signature doesn't contain tolerant patients in it. It's the wrong comparison and control groups.

Maria will talk about this. Immunosuppression is a confounder. And this is just from another group. And it shows you here that immunosuppression has profound effects on B cells. I don't think this is the sole thing because, if you look at tolerance in liver transplant, they get the same drugs, and yet they don't have a B cell signature when you stop their immunosuppression. So I think there are some reasons

Page 313

we can debate later.

But then I tried to say I think -- and I'll conclude with this maybe -- that what you can say from this is patients who are out from transplant doing well without DSA, without rejection, who are taking no immunosuppression, perhaps if they have the signature, you can believe that they will continue to do well without drug. So it might tell you that it's safe to do this, and, that way, it may be -- what's the word I'd want -- it may help diagnose a tolerant state once they exist. It tells you nothing about how you get there. So I think that's the real limitation of this. This is nowhere near a drug development tool, as best I can tell.

And I think I'll just quit there. Thank you.

(Applause.)

DR. WANG: Our next speaker is Dr. Maria Hernandez-Fuentes from UCB Celltech. The title of her talk is Biomarkers of Tolerance in Kidney Transplantation: Are We Predicting Tolerance or Response to Immunosuppressive Treatment?

Thank you.

Page 314

DR. HERNANDEZ-FUENTES: Thank you very much to the FDA for bringing me here and giving me the opportunity to participate in what I think is a very interesting and a very important discussion. And I think it is very important to bring academy and industry and our leaders in the same room and trying to think about how to move this forward.

So I do have a disclosure. I moved into the industry (inaudible) two years ago. But all of the data that I am going to show is -- has been generated in -- as an academic whilst I was in full time in King's College London.

So I am very in the privileged position that Ken Newell has talked before, and he's set the stage of, well, what is it that we're looking. And the idea of the -- when we started was to identify whether we could make sure that we could identify the patients that were not necessarily already in a good position to not be very immunosuppression-dependent.

So I did do the exercise of, if I wanted to use these biomarkers, what is it that we needed. And as -- I agree with Ken. What we need is maybe we could

Page 315

identify patients in (inaudible). We could withdraw or at least decrease immunosuppression. And therefore, we think that has some benefits in the long term.

And this in -- this is contributing to personalizing poor stress plant management. How do we transfer that into a specific drug development programs? It's a complicated issue because the drug development programs in transplantation is not going to be a single drug. It is going to be the (inaudible) drug on the context of all of the other drugs. But that's my side point.

And the context of use is to use them in that context, and that's how we've been thinking about it and developed that program.

Of course, the benefit is, if it is through the patient (inaudible) would control the immunity against the transplant, but there needs a lot less immunosuppression, we would decrease the risk of infection to more nephrotoxicity and cardiovascular disease that immunosuppression brings.

So Ken has mentioned that we did a study which we published (inaudible). We had a set of biomarkers

Page 316

and also, coincidentally, with him, we had a set of genes that were B cell-related. They were different biomarkers, but we used, again, a microarray, and it was a surprise when we initially interchanged information. You know what? The B cells are more important than the D cells.

And I have the same bias in -- we have the same bias in initial design. And we also had some biomarkers that it was flow cytometry and B cell flow -- you know, the percentage of CD19 cells. And briefly, it was important to differentiate the total recipients from the rest of the group that were in the comparator group.

So we did this initial study, and we had a very good sensitivity and a specificity. And importantly, for the discussion afterwards, we had the group of healthy controls both in the test set and the training set. And for the training set, we were really fortunate to interchange sample from the Immune Tolerance Network. And we did (inaudible) the same assays, the flow cytometry, we had a functional assay and (inaudible) and the gene expression, we got very

Page 317

good sensitivity and specificity in that cohort as well.

The statistician thought that it would be a more clinically applicable parameter if we could calculate the probability of being tolerant for each of the patient included in the trials that are in the studies that we were doing. And therefore, she went on and did that. And of course, the differentiation in the training set is very good. And then, importantly, in the validation set, it's also very good.

So we did have some patients with a stable function. That had a cut-off above -- that were similar to those that were identified as operationally intolerant.

So with that, we (inaudible) and did the same validation assay that Ken (inaudible) did with the (inaudible) study because it is very important to identify what is the prevalence of that signature in the stable patients in your population. But also, we needed another ancillary validation of that signature. All of those gene expression was done on microarrays. We needed to do the platform transformation to

Page 318

something that more -- was more close to the point of care, which is RT-PCR.

So we used fluidigm (ph) because we still were looking at a lot of genes. We did do the stability (ph) of signature. If you want, I have the data, but I'm not going to show you.

And we did have a proof of concept group, which were patients that were undergoing a steady withdrawal for clinical reasons, not because they had any biomarkers. And we wanted to see what happened before and after.

This is the cohort. We had 14 completely new total (inaudible) recipients that have not participated in the initial studies. They were a slightly better match, but not as well matched as the other ones. And we have (inaudible) donors there.

We had 190 patients with stable function longer than three years. That's less than 50 percent variation in the creatinine function. And of course, they were on different immunosuppression levels. And we had the group of patients that have had a biopsy that indicated a certain degree of immune damage that

Page 319

was immune-driven. And we call that chronic reaction.

Of course, because it is a retrospective collection, which is the necessity in kidney transplant recipients, all of the -- these are all of the stable patients. We have 17 different treatment groups. And we didn't consider that here because this was -- most of them were five years after transplantation. So we didn't consider the induction protocol, part of that because we didn't have that information in the clinical records, believe it or not.

And so this was the -- (inaudible) is the statistician that did this analysis. She calculated the probability of tolerance that she had done in the other study. You've seen those 10 genes that were identified that had a strong B cell marker. And what happened is that the patients in -- and these are the P (ph) values suggested for the fact that all of the patients are in different treatments. So they are not straight away -- and -- but you have -- you -- what you can see is patients on a -- as a (inaudible) have a much lower probability of being tolerant. The patients that were on prednisone have a lower probability than

Page 320

those that are off prednisone.

Once you adjusted for the other use, cyclosporine and tacrolimus did not seem to have a very strong influence on that probability of being tolerant. Importantly, the patients that were on steroids, when they themselves came off steroids, their probability of being tolerant changed. And we did not see a difference here between the tolerant and the healthy controls.

And as Ken Newell has explained, we were looking at B cells. And here, we already knew about the B cells, so we looked at different subset of B cells. And the general B cells have a (inaudible), the subset that is most affected by the immunosuppressants is the transitional B cells. And these are the high CD -- 38 CD24 subset that I can describe.

Again, so (inaudible) has a very strong effect. Patients on (inaudible) have very low frequency of those B cells. Patients of prednisone have lower than the ones that are out of prednisone. Your CNIs have no effect on the transitional B cells, and the tolerant recipients have the same level of

Page 321

transitional B cells of healthy control. So it's not like they go overboard.

And this is what I think it is more important. The same patients that are -- when they were on steroids, some of these were fairly low, like, two milligrams a day of prednisone. When they came off of steroids, this is six to eight months later. All of them except one increased their percentage of transitional B cells in (inaudible).

So because we wanted to use the signature to select patients to change the immunosuppression, we thought it would rather (inaudible) to have a signature that is dependent on the immunosuppression because if -- - then if you change the immunosuppression, you'll know if that signature has changed just because you changed the immunosuppression or because they are not tolerant anymore. And how do you then handle the clinical follow-up?

So the statistician went back to square one, went back to the instances of tolerance arrays, did a study that -- the (inaudible) is used to control for confounding factors. She did a logistic regression,

Page 322

and she calculated for each one of the genes in the array, the immunosuppressant-independent expression. And you've seen that. She derived the difference between the tolerance and the rest, and she came up with the sets of nine genes that would differentiate between the tolerance and the patients and the healthy controls.

And now the genes are more transcription factor and general uses. It is not that they're not completely B cell-independent. There are two of them that are in the B cells, and then there is one that is quite B cell-specific. This we didn't know when we published, but it is now being described in plasma cells but not in healthy B cells.

So now we have a new set of genes. And then does it matter what the immunosuppression (inaudible)? So we used those same samples. And here you can see a probability of being tolerant using those set of genes in the same patients that I have shown you before. And now you can see that there is no difference of whether you are on (inaudible) or MMF, on CNIs, on prednisone. You have, more or less, the same probability before or

Page 323

after withdrawal, and that's -- the tolerance have a higher probability than the healthy controls. That makes us feel a bit better. Whether that's completely (inaudible) or not is a different matter.

So this is what I think we need to think about. The gene expression of a patient in a certain time point is the consequence of several things that we need to distill. There is some certain biology that is viewed to the immunosuppressant effects or being for years in immunosuppressants. And there is a certain biology that has to be referred to the tolerant (inaudible).

We think that using the strategy that we have used, we have highlighted these versus the other. But it shows the use of the effect.

One of the consequence of not using these, so the -- it's we need robust statistical methods to analyze the gene expression because there is a lot of factors that are influencing the patients. And again, we think that we have this identified. But of course, this is the (inaudible).

What happens if you don't use this? So this

Page 324

is the patients -- the -- all of the stable patients. So if we use the old signature without a control, we identified 25 patients in -- within a 190. That could be identified as tolerance and would be the ones that we would suggest for winning. Using the new one, we identified 20 patients. And then there's only two patients that are the same between one and the other.

And if you can see the -- in the initial signature, there is a higher proportion of patients on tacrolimus. It's interesting. The proportion of patients in (inaudible) is very low, and prednisone is not low. But if we then go and use the immunosuppression-independent, those percentage of patients in -- that are taken in each one of those drugs is different. So we do select different patients. This is an analysis that has been given by Sophia Aristacooney (ph), which is the (inaudible) statistician working in this.

We did take -- we undo (ph) the -- both genes. We took the gene that -- one of the genes of (inaudible). I can't remember why we didn't do the other one. Anyway, the gray bars are the -- this is

Page 325

the percent -- the number of patients that I've selected from the Gambita (ph) study using the expression of that gene that are not on prednisone nor that (inaudible) on prednisone. Gray bars are, if we don't correct for immunosuppression, and the black bars are if we correct for immunosuppression.

So I think the bigger difference (ph) -- and I think you found this as well -- there are quite a few patients on tacrolimus with (inaudible). If we correct for immunosuppression, there are less patients on tacrolimus that we select with those genes.

So I think we need to -- if we are going to use these for patient selection for immunosuppression with (inaudible), I think we would need to do this correction. So the context of use will drive, I think, these decisions.

So the way we were going to do this is, of course, is a clinical trial where you would have patients understand their therapy. And then you would have patients identified that have these tolerant genes. And half of them, you would do partial winning (ph), and half of them should stay on therapy. And we

Page 326

have calculated how many we needed to find differences, and it was -- you know, we needed to screen about 1,000 patients. So it's not a minor trial to be taken into account. This hasn't been done yet. I've asked two or three times for money to do this, and I have been unsuccessful, you know, in getting that.

Okay. So the statement of need and the context of use -- we have talked about it. The benefit to the patients is, in theory, decrease the risk for infection, tumors, nephrology. But the risk is very different in these tests of false positive than a false negative. So a false positive of the test means that you've selected a space (inaudible) to increase their immunosuppression. And then the (inaudible) situation (inaudible) will use the transplant, whereas the false narrative test is the same as we are now. So they will not be (inaudible) on immunosuppression. And I think that has to be taken into account when you calculate the threshold.

And I still think that, of course, it is an intellectual jump to say that patients that have the same signature of patients that have come off the

Page 327

immunosuppression for a while may be suitable to select for lower immunosuppression. That's the demonstration that we neither -- we don't need to do.

I think that they could be identified as a diagnostic of the subset, or as Newell has mentioned, diagnostic of the tolerant recipient. And whether we can use those -- and that's another big jump -- is a likely (inaudible) endpoint in those (inaudible) using trials that are proliferating, that needs also to be demonstrated as well.

And I have to thank a lot of people. So the (inaudible) of Tolerance Network and the Immune Tolerance Network, this was for the initial study. The Gambita Consortium, which is in the last five years, has been included a lot of groups within the UK, but also in Europe. And the two statisticians have had a central point in the analysis of the studies, but there's been a large number of technicians, project managers, research nurses. And these are the funding bodies that have allowed this validation.

Thank you very much.

(Applause.)

Page 328

DR. WANG: Our third speaker is Dr. Edward Chong from Vitaeris. He is going to talk about a backwards approach to identifying a predictive surrogate endpoint for chronical antibody-mediated rejection.

DR. CHONG: Thank you very much. Good afternoon, ladies and gentleman. My name is Eddie Chong. I am the chief medical officer for Vitaeris. And I would like to thank the Transplant Division and the TTC to invite me to speak on behalf of my colleagues.

So let's -- I'm going to change gears slightly. I'm not going to show you any slides of geno array readouts or protein readouts. But what I'd like to do today is to describe the process that we went through and the work that we did for a pivotal trial that we are intending to start early next year.

This slide here summarizes the three pathways that one could under -- could follow to identifying and looking up a surrogate endpoint for clinical trial. So the first bullet is the Biomarker Qualification Program, and you've heard a lot about it already.

Page 329

The second pathway is through an expert consensus. And some of -- the examples of some of the surrogate endpoints are listed here. And these have all been validated through large clinical outcome study. And therefore, you could use this endpoint for a pivotal trial for regular approval.

But what I'd like to discuss is the third route that we took, and this is through the R&D route as part of a drug development process whereby we -- you know, at this point I'd like to take the opportunity to thank the Transplant Division for their help and support and the useful advice they gave us whilst we were working through this process to arrive at this pivotal trial that we -- as -- that I said that we are intending to start next year. And if this trial is positive on the surrogate endpoint, we would hopefully be able to use this as a basis for accelerated approval.

So before I discuss the work we did, a bit about the condition that we tried to develop our therapeutic drug for. And this is for chronic antibody-mediated rejection. As most of you will know,

Page 330

it is now recognized as the leading cause of long-term allograft loss after kidney transplantation. It's recognized to be a rare and serious life-threatening condition with no approved or effective treatment.

And studies, therefore, to demonstrate clinical benefit, this is one of the major problems that we face in transplantation, is that studies requiring to show clinical benefit would be large and would take a long time.

So -- and when you think about the possible surrogate endpoints that one could use for accelerated approval, there are many. And you could think about biopsy data, DSA, proteinuria, or some measure of rental function.

And all of these have been shown to significantly correlate with the risk of allograft loss. But unfortunately, correlation does not make a surrogate endpoint, as we all know, because what we lack is quantitative data to relate the surrogate endpoint with the risk of graft loss, i.e., you need to be able to quantify the change in the surrogate endpoint with the change in the risk of the clinical

Page 331

benefit endpoint, i.e., allograft loss. And without data to show this quantitative relationship, it's very difficult to design a trial and also to convince the FDA that the surrogate endpoint is reasonably likely to predict clinical benefit. Therefore, there is -- there -- up to now, there has not -- no surrogate endpoint has been used for accelerated or full approval by FDA for this condition.

So some -- a couple of slides -- you've seen this slide. I think man of us have seen this slide before. It shows the correlation between DSAs and graft survival or graft loss here. There was people with de novo DSA with clinical renal disfunction have a higher risk, and this is people without de novo DSA and no renal function. So you've seen this. So this here again shows the significant correlation between a potential surrogate endpoint, i.e., DSA and allograft survival.

Again, another slide here, this shows that -- the same thing. You see a significant correlation, statistically significant correlation between DSAs and graft -- and risk of graft loss. And here again, with

Page 332

biopsy data, this is risk of graft loss.

But there is some data in the literature that shows the quantitative relationship between here, the GFR renal function decline and the risk of allograft loss. And this is a publication by Clayton (ph) (inaudible) Group in Australia. It showed the -- it has the -- as the EGFR declined, you get a higher risk of graft loss. But this isn't de novo transplant patients, not in the patients with chronic antibody-mediated rejection.

And the panel on the right here, as you can see, has the decline in EGFR from baseline over -- well, the baseline here is years 1 to 3. The higher the decline in EGFR for -- you get a higher risk of graft failure and also overall patient survival.

So in our study, what we plan to use is EGFR as a predictive surrogate endpoint for our trial. EGFR is an attractive surrogate endpoint that one could use. It's -- the decline in EGFR is the clinical consequence of chronic rejection, antibody-mediated rejection, and on the direct pathway to allograft loss.

So if you can reduce the slope in EGFR by an

Page 333

intervention, this should reflect the beneficial effect of the intervention on the disease process and also on allograft function and, hopefully, allograft survival. Again, it's easy to measure and quantify. As I said earlier, it's not a validated surrogate endpoint for use. It has a basis for full approval except, as was discussed earlier this morning, it has -- it's accepted for CKD for chronic kidney diseases, but not for chronic antibody-mediated rejection. But -- and it's potentially useful as a surrogate endpoint for accelerated approval.

As I mentioned earlier, if we can see a positive effect on the slope of EGFR decline, this should reasonably likely to predict clinical benefit.

The problem, as I mentioned earlier, there is limited data on the quantitative relationship between the slope of EGFR decline and the risk of allograft loss. And in the literature, I -- the only paper I could find is a publication from Peter's group in Manitoba.

So what we did to -- as a workup to supporting and persuading the FDA to -- that -- you know, that

Page 334

EGFR decline can be used as a surrogate endpoint, an interim surrogate endpoint for accelerated approval for a clinical trial, is to do a modeling exercise. This modeling exercise is a noninterventional historical perspective cohort study. And as I mentioned, the primary objective is to validate the functional relationship between the change in EGFR following diagnosis of active ABMR and the risk of allograft loss in the subsequent years.

The inclusion-exclusion criteria that we use to select the patient population reflects the selection criteria that we intend to use in our clinical trial.

So what we -- basically, what we did was we -- patients with active ABMR, using the Banff 2015 criteria, this one-year transplant with a minimum of three-year serial data on (inaudible) and graft status were selected. And thanks to the collaboration from Peter, Dr. Jamale (ph), who's in the audience, and two investigators in Barcelona, we were able to get about 200 patients. They identified patient-level data to do this modeling exercise.

And I'm not a statistician, but the change in

Page 335

EGFR across time was model using a linear mixed-effects model. And the relationship between the change in the EGFR, the slope of decline, and the risk of our allograft loss was examined using this Jung (ph) modeling framework.

And the Jung modeling framework predicted that, you know, there's a -- not surprising, that the baseline EGFR and its rate of decline -- and this is defined as the EGFR slope change per month, following active ABMR, diagnosis, significantly predicted the risk of allograft loss of the -- close (ph) to five years.

And we could then hypothesize the treatment effect of your intervention and ensure what this intervention -- what this treatment effect will have on the clinical meaningful endpoint, which is the reduction of allograft loss over five years. And then looking backwards, you can look at the slopes and see in an earlier time point what the difference in the slopes would be. And then you could also then quantify it as difference in the slope, which is reasonably likely to predict the risk benefit over five years.

Page 336

And with this information, therefore, you will be able then to calculate the sample sizes for the -- for both endpoints, for the early interim surrogate endpoint and also for the final clinical benefit endpoint.

So based on this modeling exercise, the -- I'm -- the FDA has accepted the study design that we plan to initiate next year. And if positive, if we see positive results on the interim EGFR surrogate endpoint -- and hopefully that will be the basis for accelerated approval. And then full, regular approval will then obviously depend on the results of the final analysis on the allograft loss endpoint.

So I think that's the end of my slide. So thank you very much.

(Applause.)

DR. ALBRECHT: So that brings us to the end of this session. And I didn't know if anyone had any questions.

We had a question from the audience that we didn't honor. Perhaps you could start.

UNIDENTIFIED MALE SPEAKER: Thank you.

Page 337

(inaudible - off mic).

DR. ALBRECHT: It may be on.

UNIDENTIFIED MALE SPEAKER: Okay. I'm (inaudible - off mic). The question I wanted to ask at the last transition was prompted by (inaudible - off mic) a question about how long is long term. And then there were several opinions from, I think, the point of view of drug development. Long term for clinical trial for a pivotal trial (inaudible - off mic) long term I would say to two years.

Now, (inaudible - off mic) challenge that. But the logistics of recruiting in big trial or two big trials and then following it up and maintaining (inaudible - off mic) participation and avoiding premature dropouts, the -- they -- just from a practical point of view (inaudible - off mic), et cetera. To go beyond two years is really not (inaudible - off mic) challenge (inaudible - off mic) therapeutic areas, perhaps (inaudible - off mic).

And in terms of long-term allograft survival, two years is not long term at all for (inaudible - off mic). So somehow, in order to apply these same needs

Page 338

(ph), which I'm very impressed (inaudible - off mic), we have to (inaudible - off mic).

DR. ALBRECHT: Here we go.

UNIDENTIFIED MALE SPEAKER: We'd have to find a way --

UNIDENTIFIED MALE SPEAKER: We can hear you better now.

UNIDENTIFIED MALE SPEAKER: Yeah.

(Laughter.)

UNIDENTIFIED MALE SPEAKER: It was in the way.

UNIDENTIFIED MALE SPEAKER: -- we have to find a way to apply these exciting techniques --

DR. ALBRECHT: Yeah.

UNIDENTIFIED MALE SPEAKER: -- in a way that we have a surrogate marker or a surrogate endpoint, preferably of less than two years, but I would say, as a starting point for discussion, more than two years. That's long term to me.

DR. O'DOHERTY: I think maybe just to follow up on the idea as well that, you know, I think Dr. (inaudible) walked through that example of hoping to go through an accelerated approval process so that there

Page 339

are different conduits, I will say. I'm not speaking of the FDA if other folks want to join in -- but to be able to propose different approval processes where you might get with the surrogate a -- to market approval for which you have to define a very specific post-marketing strategy defined with the sponsor and the FDA for that individual therapy in which you are on the market as long as you ultimately meet those hard endpoints, if you will, as well. And then it's kind of a different, you know, novel scenario in which you're able to consider that part.

DR. ALBRECHT: The man at the mic.

UNIDENTIFIED MALE SPEAKER: Thanks. So yeah, I agree with the previous comment in the sense that we need to bring these back to drug development. We need to separate this a little bit from individual patient care. As much as it may be painful to the community, we need to focus this on drug development.

And one of the things that we're saying is we're not necessarily trying to lengthen the duration of the trials, but find the tools that, in the appropriate duration of the trials that are feasible to

Page 340

be executed today, have better prediction of what's going to happen with clinically (inaudible) endpoints farther out in time. That's a -- that might sound like a nuanced concept, but it's critically important if we really want to transform the paradigm for drug development in the transplantation.

Now, the other thing I -- and thank you. That was awesome. Thank you for sharing that.

The concept of joint models is something that FDA is embracing. And it's in PDUFA. It's in the 21st Century Cures Act. It's all about model-informed drug development. Joined models are a conduit to make that happen. We use that same approach for the first imaging clinical biomarker. And this is an example in kidney disease, polycystic kidney disease. That's the effort that Steve led. And that is extremely powerful.

Now, those models are data-hungry. So getting it back to the conversation about this morning, we need to get the data together. So …

DR. ALBRECHT: It goes back to the meat grinder.

Kevin.

Page 341

MR. FOWLER: Yeah. I'd like to go back to Dr. Abecassis' comment about what's long term. So the simple answer is what Dr. Stegall said, right? You live forever with it, and you -- or you die with it, right, simply.

I would just maybe approach this from a -- I think a little more of a complex issue. You know, Dr. Newell and I have had a conversation about there's people like myself that have a transplant, and it's been a great experience. Other people have a transplant, and it's not as great an experience.

And someone here is nodding. And I think you can probably get a lot of information from the patients. Doctor -- or I'm sorry -- Ellison Tom (ph) is doing a paper -- I'm one of the contributing authors -- about life, participation, and transplant. I would encourage you to look at that when it becomes published.

The other thing I would say, too, is that just there's an absence. Like -- and I think if you go back to her work, too, I'm more afraid of dialysis than dying. That's the truth of it.

Page 342

And the truth of it is, too -- and I think -- try to get you to think about this in more of a holistic way is that, you know, I just was involved with a project reviewing a LDO and their education. There's no communication about risk of dialysis. And so I think that's part of the larger picture that this needs to become part of, is understanding that.

And when Dr. Cooper (ph) and I were talking about this earlier, two of the (inaudible) conference, these risk discussions aren't occurring. And I've shared them with the FDA, and they were very surprised of my perspective.

So I think it's a much more richer perspective to look at that -- these different areas. But I was just thinking that the simple thing is I really am afraid more of dialysis than dying, truthfully. Dialysis is death.

DR. NEWELL: So I wanted to comment on that, build on Mike's carry-over from the other, and then ask our last speaker a question as well where I think I don't understand it. But I think when you say how long is long term, it might not be the right question.

Page 343

I think what we need to do as a field is describe what is a successful transplant. That varies depending on the source of the kidney, the age of the recipient, the type of the organ. But I think, as that becomes better defined -- and certainly, survival will become a component of that, but also quality of life and things like that. But then you can still use things like the iBox or any of these other models to say does it impact that -- what is successful.

So I think to think just in terms of long term, I think from a practical standpoint, I'd say right now one year is a whole lot better than -- or I mean five years is a whole lot better than one year. So I like the iBox because I think, you know, if you can't get to five years, it's probably not a good treatment.

So I do think that that's important. But we -- I think that, in five years, we won't be sitting around here saying is three years long enough, is two years, is five years. We'll be talking about a much more complex endpoint that brings in patient-reported outcomes, quality of life, cost, utility.

Page 344

So that's just my perspective. And I know that there are some groups that are taking this on over the next year or so trying to talk about that.

The question I had about using EGFRs and endpoint, when we were discussing this as part of the TTC, there were several people who didn't like that endpoint. They made the simple statement I can convert from a nephrotoxic drug like a CNI to a non-nephrotoxic drug, and all of a sudden, I get a bump in GFR. But does that really equate to a better long-term outcome? And there are confounders. You know, if I have an episode of BK nephropathy, I'm going to take a hit.

And so is it possible to take something that isn't really -- a lot of the studies we've heard about are very specific to studying alloimmunity. Those are the biomarkers. And you say something that's linked to alloimmunity is a good predictor of a treatment to prevent alloimmunity. I understand that. This is a kind of -- something that's linked to kidney injury. It's specific for chronic antibody-mediated rejection. And do you think you'll have so much noise that other things could confound that?

Page 345

DR. CHONG: Yeah. It is a good point you're making. But in the trial that we are planning to do, obviously, we will try and control for the background immunosuppression.

And again, it's important to emphasize that we're looking at the rate of decline in EGFR over time. So these patients coming into the study will have -- will be known to have this slowly progressive decline in renal function. So I think that, you know, hopefully, you know, we would overcome that problem.

UNIDENTIFIED MALE SPEAKER: So I want to -- can I make a quick comment?

So EGFR -- you could have a worse EGFR because you have chronic rejection, or you could have a worse EGFR because you're taking too much calcineurin inhibitor. And the last time I did a little survey, informal, our community was still divided right down the middle as to whether kidneys died because of chronic rejection or because they died -- now, I think it's swinging more and more and more towards what I think is the truth, which is chronic rejection and not, you know, the fact that we're getting them -- so I

Page 346

think in these studies we're testing drugs, and we're using substitutes for what we know to sort of be the best T cell activation drug that we have.

You know, sometimes a bump in EGFR I the right direction may be a great short-term gain for a bad long-term outcome if you're setting somebody up for chronic rejection. And I just kind of ask myself: How far have we swung towards, you know, all of us believing that kidneys die from chronic rejection and not from, you know, using calcineurin inhibitors?

DR. SARWAL: I just --

UNIDENTIFIED FEMALE SPEAKER: (inaudible - off mic).

DR. SARWAL: Yeah, sorry. I just wanted to add to something, actually. I -- I mean, I really agree with, I think speaker from the floor that actually raised this issue. You know, we've become so focused on looking at loss and injury that I think that's become such a paramount endpoint for us, that should we be really thinking about looking at this slightly differently?

I mean, we're looking at cancer-free survival.

Page 347

Why don't we look at injury-free existence? I mean, at what point are we going to say that we should be looking at the day-to-day performance of that allograft in a state of health?

People do like PTT (ph) values because they're trying to optimally dose their patients. We really don't even have a yardstick to be monitoring the efficacy of how we're dosing these drugs so that they stay in that environment of stability. So now that we've learned so much about injury and we got so much -- I mean, we got a little bit better with survival -- should we be trying to look at these -- at selection of drugs and using them on a day-to-day basis by looking at better readouts of daily immune quiescence and inactivity of injury?

DR. MANNON: So that may be -- you guys could continue to argue. But with regards to the trial that he is presenting --

DR. SARWAL: No, that's --

DR. MANNON: -- I think it's actually valuable. I mean, I never imagined that -- when they were proposing to do this, I thought there's no way

Page 348

that the -- that they'll allow them to do this. But if you have a steady level of tac coming into the study, all right -- and again, everybody's a little bit different -- and you have depressed GFR to begin with but not too low because you'll see no effect, I don't think it's unreasonable. FSGS studies have looked at slope of GFR. I mean, I think you have to start somewhere.

But your point is well taken. I mean, you know, nobody wants to -- I agree. I mean, the Song initiative has indicated that patients and caregivers would rather have their (inaudible) rather be dead than go back on dialysis and that dialysis fear. And I think it's tough to manage them. And so maybe being injury-free is the right model.

But I think for this study, I think it's -- I mean --

DR. SARWAL: Yeah, this study --

(Crosstalk.)

DR. SARWAL: So that's different. But I'm just talking about newer drugs that come in. I mean, maybe the focus should be about absence of injury

Page 349

rather than all the time looking at loss and, you know, negative outcomes.

DR. HERNANDEZ-FUENTES: Can I make a comment? One of the problems that I think we have is we do have a marker for kidney function, which his EGFR. And it has all the confounders. What we don't have is (inaudible) marker of level of immunosuppression. And drug doses we know do not reflect the patient individual immunosuppression, and that's a jump that we need to make in all of the drug development studies because we need to do immunosuppression. We think we are, more or less, immunosuppressing the majority of the population, and all of the results are based on population and studies how many acute rejection patients have, but not on individual immunosuppression. How -- we don't have a measure.

And we've tried to do that in some of the assays we've done, the Elispot assay, the -- but it doesn't give you a single -- you know, a single parameter to say that's how much. And that's the term that we all need to (inaudible) and to overcome.

And I agree with you that maybe we need to

Page 350

change. And I don't know what is the step because -- so I know working in the pharmaceutical industry, and when you start talking the people that are signing the trials off, you see an endpoint that nobody has used before. They all go because they think that when you're talking then to the -- you come to discuss with the FDA and the whole regulatory authorities, it's never going to fly because this is an endpoint that nobody has used before. And I don't know how do we change this.

So this is one of the reasons why I'm very happy that we are here together and say how -- I'm asking now the -- how do we change the endpoints?

DR. SARWAL: And we are ignoring two big factors here. When we're only talking about -- we're ignoring the factor that patients are -- can be nonadherent, not Kevin. But, like, there are patients that are nonadherent. And then they're sporadically nonadherent even though they take their drugs at night and they have a good level -- a (inaudible) trough level.

And the second thing is systemic factors.

Page 351

We're dealing with increasing problems with obesity worldwide, and we're dealing with hypocholesteremia and hypertension. And all of those things damage the transplanted kidney just like they damage the native kidney. And so reading out absence of injury kind of may be the most important way for us to go back and manage that patient holistically.

DR. HERNANDEZ-FUENTES: I would agree to try and implement that. And I don't know whether -- you know, I'm asking now the FDA people. Would you want to see it in parallel? Would you want to see unique? Would you accept it as a secondary outcome, some exploratory outcome?

DR. MANNON: So we've heard, like, all of this different kind of technology and assessments. And the question we're asked is can we speculate on which of these biomarkers, or are there other biomarkers that predict long-term graft stability? And I throw that out to the experts because I'm not answering it. I mean, I have my own ideas, but --

DR. O'DOHERTY: And maybe I can add a bit of context as someone who's, you know, new to the

Page 352

transplant community but, you know, working in the space of biomarkers. You know, when we started the TTC effort and that kind of conception of saying how do you make that step forward, how do you overcome this challenge where maybe you want to go from, you know, the kidney function, ultimately, to maybe what you were talking about in your presentation. You had that nice breakdown of, you know, injury, I think morphology and the kind of molecular component.

And you know, with the aspiration to be able to move to that molecular component where maybe you can describe an absence of injury, it goes from how much would it take to move the regulatory science needle in that space, knowing that -- if that is the ultimate goal. And the assessment that we did through some of the effort so the -- prioritizing the idea of the iBox was because it's -- it seems real -- it's going to be straight-forward in a lot of its components, not that it's a full and accurate description of everything by any means.

But I think, you know, the aspirational idea of how you would move that idea forward is an

Page 353

absolutely valid point. And how do you -- knowing if that's the strategy, how do you build it into a regulatory strategy? And what's the right process? Is it qualification, or is it through a sponsor-driven IND submission? And that's really up to the resources that are available and the people who are involved to be able to move that conversation forward.

DR. SARWAL: Absolutely. I think it may take us into an uncomfortable area where we think we're doing really great. And as we start doing more and more molecular analysis, we may realize that our margin of who we think is stable and the creatinines are fine and the slope of the EGFR is fabulous are actually patients that are not actually fine. And you know, we would need to wait for 10 years to see that, yes, they had worse outcome, and they will develop DSAs over time.

So I think we have to -- we may go through an area of discomfort where we will uncover this group -- you know, what may be the burden of molecular injuries. And then the task will be to us what do we do. So if we've got a new drug that's coming in and then we're

Page 354

picking up molecular injury, do we actually dose it differently to actually suppress that appropriately? And that becomes then the new surrogate.

DR. NEWELL: I was going to say it seems to me -- and I struggle with this -- but I used to think that biomarkers endpoints is all kind of related to biomarker (inaudible). But so, like, if you take Peter's example, he shows very clearly the applet mismatching. The degree of applet mismatching is a powerful factor. But if I only have one donor and that's it, it's -- or you know, it's going to predict a worse outcome for me. But it's not really actionable, short of getting a different donor paired exchange, maybe a different immunosuppressive regimen. I don't know.

Then Minnie talks about things that are designed to diagnosis early inflammation under the assumption that that will decrease long-term outcome. Those are both useful. But to me, your context of use would not really have anything to do with guiding therapy to increase long-term graft survival, per se. It would be very hard to show that in the foreseeable

Page 355

future.

I think what I like about the iBox is that's a tool that, today, can be used. And it does respond to therapeutic interventions. So as Inish said, it's closer to being ready.

And so it seems to me that all these are good. It's just how we use them and how quickly we can roll them out. Yours might be the, you know, surrogate endpoint of the future. But I would think that it would have to go through something before that to say I -- just that, you know, you can use it to adjust immunosuppression.

DR. SARWAL: Absolutely. I mean, so we're using things like drug levels. And don't we get a low drug level and adjust the immunosuppressions? I think it's a thinking change. It's like what additional information. And you're absolutely right, of course. What are the stages of validation, and, you know, how do we get it to that point of confidence that you can? But I think that needs to be a plan for the future that we get to that and use that to adjust the drug level, not just the drug level.

Page 356

UNIDENTIFIED MALE SPEAKER: So --

DR. ABECASSIS: Maybe I'm missing --

DR. SARWAL: The two may --

DR. ABECASSIS: -- something.

DR. SARWAL: -- disagree --

DR. ABECASSIS: But isn't a bad biopsy a biomarker of a bad outcome? I mean, Mark, didn't you write a paper that says -- and what am I --

DR. SARWAL: That's --

DR. ABECASSIS: Like, am I just having a moment or …

DR. SARWAL: No, I'm having a moment, too, because you -- I -- what I keep -- feel like we're -- we keep on missing the point that three groups here, and there's several other groups around the world. And we can -- have identified subclinical acute rejection, borderline subclinical acute --

DR. ABECASSIS: On a biopsy.

DR. SARWAL: -- rejection on a biopsy associated --

DR. ABECASSIS: As a biomarker --

DR. SARWAL: -- with long-term --

Page 357

DR. ABECASSIS: -- outcome. What are we missing?

DR. SARWAL: We've been publishing on it since -- for the last 10 years, and we do nothing about it because it's inconvenient to do a biopsy. And --

DR. ABECASSIS: But if you had --

DR. SARWAL: And then we look at the injury --

DR. ABECASSIS: Right.

DR. SARWAL: -- related to the long-term inflammation and say --

DR. ABECASSIS: But to say that you don't have --

DR. SARWAL: -- you do badly.

DR. ABECASSIS: As -- to say that you don't have a surrogate is wrong. You have a -- I'm sorry -- to say you don't have a biomarker is wrong. You do have a biomarker. It's called a biopsy, okay?

So to say you have an invasive biomarker and you need to make it noninvasive would be correct. But it's incorrect to say we don't have a biomarker, right? Or maybe I'm just off.

UNIDENTIFIED MALE SPEAKER: But the question

Page 358

that was raised in the quorum might be also that is -- we have a biomarker for quiescence; do we have a biomarker that projects overimmunosuppression beyond BK virus and the incidence of that, which I think --

UNIDENTIFIED MALE SPEAKER: Biopsy is a biomarker --

DR. ALBRECHT: So if I can jump in --

UNIDENTIFIED MALE SPEAKER: Yes, but the other way around, over --

DR. ALBRECHT: This is sort of foreshadowing tomorrow's day. But we were fortunate to have two meetings in which patients participated. And Ken made a very strong statement that he takes death over dialysis. The patients, when they were hearing about these routine biopsies, one patient said I don't want to be a pin cushion. We would love noninvasive tests. So I think that's the reason to do more because the biopsy, we heard, is also, you know, morbidity, potentially injury, et cetera.

But urine biomarkers, blood biomarkers, I think patients would be very happy with that based on what we heard. And the we have our patients here as

Page 359

well. So I invite you to make comments, if you'd like. We will hear from them tomorrow in more detail.

DR. NICKERSON: So maybe I'll just make one comment to Ken in response. So I agree that we can monitor the grafts with these diagnostic tools that you've heard from multiple groups which will tell you that you have quiescence or you don't have quiescence. And I think that's a major step forward that -- especially if it was noninvasive. And then you can adjust immunosuppression up if it's not quiescent.

What you don't know is can you adjust it down when it's quiescent. And the CTOT-09 study that Peter presented suggested that all of those post-transplant tools held no utility to predict the safety of minimization. They told you that they post-transplant, that they -- that you were losing control because the inflammation started. But they didn't tell you who could go down. And the tests that predicted who could go down were the pretransplant tests, the molecular mismatch. And it may even be in Barbara's type of model with the genomic -- there immune responsiveness.

And so I think that gets to a point that you

Page 360

were making, which can you use that knowledge at the time of transplant to dial in how much drug you need. And in fact, I would argue you may use that to understand that. In fact, you may not need a lot of the aggressiveness that we currently do to everybody.

In the next session, we're going to hear about there is center effect as to who gets what, as opposed to a risk-stratified effect as to who gets what. And so I would argue that the risk stratification at the time of transplant, the hypothesis would be that that could be used to predict how much drug you really need.

DR. NEWELL: I don't understand yet how you'd use it as a drug development tool other than making sure you had the right balance of patients in a study. So you know, if you say how does that lead to drug development, that's the thing I'm blocking on. So …

DR. NICKERSON: Yeah. So I would argue --

(Crosstalk.)

DR. NICKERSON: -- is what stratification is blocked -- (inaudible) -- stratification, as you talked about, and then you could look at is there a response differential across the new drug. Or ultimately, you

Page 361

might be able to use it as a way of saying, okay, I can avoid this. If you do the trial as a drug-dosing trial and say I need this drug dose in this cohort, I need this dose drug in this subcohort of risk, and so you could actually do that trial and use it as a dose-ranging exploratory drug development.

(Crosstalk.)

DR. NEWELL: -- I'm kind of fixated on trying to get it to a reasonably likely surrogate endpoint. And so I think -- I don't see how that works, but we could talk about it --

DR. CHONG: I just want to make a --

(Crosstalk.)

DR. CHONG: I just want to make a --

DR. NEWELL: -- see it as a drug development.

DR. CHONG: I just want to make a point, you know. There is a lot of biomarkers out there, you know, and a lot of people have presented data showing biomarkers. It shows a correlation. But to use that biomarker for drug trial, you need to be able to show a quantitative relationship between that biomarker and your clinical benefit endpoint so that you can then

Page 362

define a change in this biomarker; how does it change the risk of graft loss? So that's the step that is missing from all the discussions that we've had today. So without that information, you can't design a clinical trial using that biomarker.

DR. MANNON: Kevin and then Randy and then -- oh, my gosh. I'm sorry, Maria. I didn't see you because we're going to need to wrap up soon.

MR. FOWLER: Yeah. So just -- I want to amplify what Dr. Albrecht said about the need for a noninvasive monitoring test. I think it just gets to the point like to the conversation with Dr. Stegall, is that you get to the point you're asking yourself what else can I do.

And then I think the -- also, the value that those noninvasive tests have is they also -- it could be also used for adherence and other behavior aspects that could impact outcome. So here, here for noninvasive diagnostics. Bring more to the market. Bring innovation.

DR. MANNON: I've never heard of a patient say, oh, I don't want to pee in the cup. But

Page 363

everybody, they're like, whatever, take it.

MR. FOWLER: Who cares?

DR. MANNON: But you know, certainly. Randy.

DR. MORRIS: Yeah. Certainly, diagnostics are nice. But I think that one of the things I didn't have time to comment on after Alex Loupy's talk was this was an example of a biomarker showing a therapeutic effect and regardless of what you're planning to do -- interventional trials, prevention trials, whatever biomarker you feel is diagnostic or prognostic. Ultimately, you have to show that treating that biomarker then causes a true clinical event later on. And that's the obligation of all the noninvasive people. It's not easy to do.

The last thing I want to do -- there's not enough time -- but it's for Ken and Maria. It's hard enough to develop a drug when you know how the drug -- when you know the actual molecular structure of the drug, you actually know the target, and you think you know how the drug works. I'm curious to know how tolerance really works at a molecular level.

Page 364

DR. HERNANDEZ-FUENTES: So am I …

(Laughter.)

DR. HERNANDEZ-FUENTES: Another point we haven't discussed, and I've --

DR. MORRIS: Don't evade the question there.

DR. HERNANDEZ-FUENTES: No, no, no, no.

So one of the issues when we are developing these biomarker signatures and all of that is when I have the discussion with the statistician how that she select the markers that are a better indicative of the difference between that group and that group. She says that she needs to, A, get rid of all of the markers that are negative in our small group of patients because then she cannot calculate the mathematical algorithm. It doesn't work.

And then she -- we've heard about elastic net. Elastic net selects those markers that are not correlated to each other to give you the better significance.

When I hear this and then I hear people asking is this biologically relevant, I think we -- or at least in my point of view, the markers I have selected

Page 365

are not to explain the biological relevance. If I wanted to understand the biological relevance, I wouldn't ask her to use those markers that correlate to each other and belong to different pathways. And then I can see a picture of what it is. I don't think of (inaudible). So I don't know what tolerance look like.

DR. NEWELL: I think, Randy, when -- and I always struggle with -- so, like, some of the things Maria showed are, like, expressed in spinal cord. And I'm trying to think, is how is a protein expressed only in a spinal cord relevant to tolerance.

I think when you think about mechanisms of tolerance, part of the problem is, at least experimentally, they're very different. And they also change over time. The late Charlies Oros (ph) pointed that out and -- or he hypothesized, and Meghan Sykes (ph) has shown it that, you know, a mechanism that's operative at three months might not be operative at nine months. So it makes it even more complex because your assays may need to evolve over time.

DR. MORRIS: Yeah, but the mechanisms are all phenomenological. They're not molecular. Ask Meghan,

Page 366

molecularly, how one patient is tolerant versus another. What are the actual mechanistic pathways at the molecular level? And if she gives you an answer, I'll pay you $100.

(Laughter.)

DR. NEWELL: Well, what's the mechanism of rejection at the molecular level?

DR. ALBRECHT: All right. All right. On that challenge note, I'm going to let everybody use the restroom, wake up a little, and we resume at 4:15 p.m.

(Break.)

DR. ALBRECHT: Hello. If everybody could take their seat, we're going to go ahead and get started with the next session.

DR. CAVAILLE-COLL: Good afternoon. My name is Marc Cavaille-Coll. I'm a medical officer and reviewer of products for solid organ transplantation. I'll be co-chairing this session with Dr. Randall Morris. And this session is called the Challenges of Developing Data Across Transplant Centers.

Our first speaker is Dr. Krista Lentine from Saint Louis University Hospital, St. Louis, who will be

Page 367

speaking to us about the epidemiology and the variation of both induction and maintenance therapy in kidney and liver transplantation.

Dr. Lentine.

DR. LENTINE: Well, thank you very much. And I'd really like to thank the organizers for the opportunity to join you today.

The data that I have to share is different than a number of the presentations that we've been hearing. It's an epidemiologic framing piece, and I hope that we can use the information in that context.

And specifically, I've been asked to share about work that I've done in partnership with Dr. Axelrod on variation in induction and maintenance, immunosuppression, and national U.S. practice.

And my disclosures -- the most relevant is NIH funding that supported the three studies that we are going to review.

So again, reviewing the -- oh, these slides are not advancing, sir. What do I need to do? There we go. All right. Thank you.

So again, reviewing the problem, scope, and

Page 368

framing, a key theme that we are trying to address again is how to balance efficacy and morbidity and immunosuppression choice. And as we all know, advances in immunosuppression have substantially reduced the risk of early acute rejection in patients undergoing immunologically compatible kidney transplantation such that the current incidence of acute rejection in the first-year post-kidney transplant is now less than about 10 percent. And rejection rates are also quite low in contemporary liver transplant.

But this marked reduction in acute rejection has come at the cost of rising rates of immunosuppression-related complications, including infection, cancer, and cardiovascular disease. And as we know, despite apparently effective immunosuppression, the chronic immunologic injury also limits long-term allograft survival. It's known that immunosuppressive agents vary somewhat in their toxicity profile. But again, how to balance the question of not enough versus too much at the patient level is often elusive.

There are guidelines for kidney transplant

Page 369

immunosuppression practice. For example, 10 years ago, the 2009 KDIGO guideline recommended that all patients receive induction therapy. IL-2 receptor antibodies are advised as first-line, whereas lymphocyte depleting agents were advised for so-called high immunologic-risk patients.

The guideline also offers recommendations on maintenance immunotherapy, favoring use of calcineurin inhibitors, specifically, tacrolimus as first-line and anti-metabolite with mycophenolate as first-line and suggesting that if steroids are discontinued, the discontinuation be conducted within the first week.

Notably, the guideline also suggests tailoring immunosuppression to the patient's risk profile but is not detailed on how to tailor.

And further, the International Liver Transplantation Society issued a very recent statement that -- concluding that current immunosuppression regimens and agents are highly effective in minimizing graft laws due to acute and chronic rejection but can also produce a substantial array of toxicities. And the group noted that utilization of the

Page 370

immunosuppression varies widely and believes that this contributes to the wide disparities in post-transplant outcomes between transplant centers.

So Dr. Axelrod, myself, and our colleagues became interested in describing the national landscape of immunosuppression prescribing. Our approach is grounded on patient-level linkages of the national U.S. transplant registry with other information sources, which combines the value of confirmed patient status, demographic and clinical traits of recipients and donors as recorded in the registry with additional exposure and outcomes information. And specifically, here we use a pharmacy claims linkage as real-world measures of prescribed medications.

We also link Medicare billing claims, which can be used as measures of diagnoses for clinical complications, as Dr. Axelrod will discuss next.

Regarding measures, again, we draw the recipient donor and transplant information from the national SRTR registry. We categorize induction as IL-2 receptor antibodies, thymoglobulin, Alemtuzamab, or no induction. We look at maintenance immunosuppression

Page 371

in periods of 0 to 6 and 7 to 12 months post-transplant and categorize as triple therapy, including tacrolimus, MMF, and steroids, steroid-sparing, anti-metabolite-sparing, mTOR inhibitor-based or cyclosporin-based.

We describe the unadjusted variation in regimen use with stacked bar plots describing use by both transplant center and within UNOS region. And we use hierarchical modeling with patient and donor case factors as Level 1 and center as Level 2. And these models compare each alternative regimen to a referenced regimen.

The empirical Bayesian estimates compare the adjusted proportion of use of a regimen of interest with the reference regimen incorporating the clinical case adjustment from the model. And the interpretation is that, if the 95 percent confidence interval for a centers-adjusted use of a regimen does not include the median national rate of use, then the prescribing pattern is significantly different from the expected use for that regimen.

The heterogeneity measures from the these models include intraclass correlation, which quantifies

Page 372

the proportion of variance in regimen use accounted for by center.

Medians odds ratios is another measure that quantifies the median of the odds that patients with identical characteristics will receive the regimen of interest when two centers are drawn at random. For example, a median odds ratio of two means that a patient with a given set of characteristics has, on average, twice the odds of receiving that regimen of interest at one of the randomly selected centers than at the others. In other words, higher median odds ratios equate with greater variation.

The models also produce adjusted odds ratios describing associations of case factors with each regimen of interest versus the reference accounting for center effect.

So the first study we want to share relates to kidney transplant induction practice. And for induction therapy, there are currently only two approved and accessible choices, as we know -- IL-2 receptor antibodies, specifically, basiliximab versus thymoglobulin. And induction indication for

Page 373

Alemtuzumab is complex, given its manufacturer. And there are no other new induction agents on the immediate horizon.

Notably, the use of induction has been increasing in recent cohorts. More than 80 percent of patients receive induction therapy, including thymoglobulin in 46 percent, IL-2 receptor antibodies in 22 percent, and Alemtuzumab in 13 percent. Use does vary by clinical immunologic risk profile, as defined by that KDIGO, but does not completely follow the KDIGO guideline.

Notably, proportion of the patients receiving induction regimens vary widely across centers from 0 to 100 percent. Accounting for center, there were case factor correlation that make sense. Use of thymoglobulin or Alemtuzumab versus IL-2 receptor antibodies was less common for older patients but more common on with black race and sensitization. Self-pay patients were less likely to receive induction treatment and more likely to receive Alemtuzumab.

Re-transplant, status, sensitization, and receipt of a nonstandard deceased organ were associated

Page 374

with depleting agents versus IL-2 receptor antibodies. And use of depleting agents increased over time, whereas induction-free transplant declined over time in the hierarchical models.

These themes will recur, but this is the quantification of center-level variation. Many centers variation -- varied from the expected use after adjustment for donor and case factors. And this is shown in the so-called caterpillar plots. Each point reflects a center, and we're looking at the 95 percent confidence intervals in relation to the adjusted expectation. Center explained about 60 percent of the variation in regimen choice in these induction models.

The median odds ratios from case factor-adjusted models range from 7.5 to 11, also supporting very large differences in the likelihood of induction choice based specifically on the center, whereas case factors explained a smaller proportion of observed variation.

We applied a similar methodology to assess variation in the use of kidney transplant maintenance immunosuppression. These are data for regimen among 7

Page 375

to 12 post-transplant. Here the center-level variation was not as strong as for induction but still substantial with median odds ratios of 2 to 5. And center explained approximately 15 to 50 percent of the variation in maintenance choice, whereas measured case factors explained 5 percent or less.

Accounting for center, there were case factor correlations that make sense. Minimized regimens were more common in older patients compared to triple therapy, but less common in black patients and prior transplant recipients. And minimized regimens were also less common in sensitized patients, but more common in those using cash pay.

Our most recent study looked at maintenance therapy in liver transplant recipients. And note this article was just highlighted in the Transplant Society Newsletter last month and that, not surprisingly, we found again that liver immunosuppression shifts with time after liver transplant with 42 percent receiving triple therapy in the first six months and then shifting to more common antimetabolite or steroid-sparing regimens for liver patients.

Page 376

Briefly, we again found that center explained more variation than the case factors. But there are also clinical correlations that make sense. For example, a hepatocellular carcinoma as a cause of liver failure, cancer within six months, and a low estimated GFR less than the 30 at six months were associated with mTOR inhibitor use compared with triple immunosuppression.

So regarding what we know now, immunosuppression regimens do vary in potency and side effect profiles in that tailoring immunosuppression regimen balance (ph) the risk of acute and chronic rejection versus toxicity of over immunosuppression may improve long-term patient and graft outcomes and is a recommended goal of chair -- of care and is, in fact, the objective of this workshop.

But at this time, immunosuppressant regimen choice does appear to vary dominantly by center practice. Some patient and donor care -- factors were associated with choice, for example. Factor associated with clinical rejection risk correlate with more potent regiments. However regiments are strongly clustered by

Page 377

center, and center effect is -- explains more variation than case factors. And cost and patient resources may also be a consideration.

What we don't know yet is, really, how to optimally tailor immunosuppression choice. And so the needs include the developing these robust risk stratification and monitoring tools that have been discussed today as well as a need for developing a large clinical trial -- clinical consortia and trials and networks in our field.

And so we -- what we should do now is continue to try -- strive to answer the call and to continue to -- continue efforts to -- continue to define sources of variation, I believe, are useful to help frame the call. And we can build on integrated secondary data analyses through linkages to more granular information, such as laboratory results, pathology, and biomarkers, and also explore the development of a clinical consortia and trials and networks to improve the evidence base for patient-centered treatment choice.

I'd like to thank the collaborators in our research group and now move on to my colleague, Dr.

Page 378

Axelrod, who will discuss the clinical and economic implications of this type of clustered practice.

(Applause.)

DR. AXELROD: So I would also like to thank the moderators for inviting us to participate in this session. And in some ways, I think this session should have been at the beginning and, perhaps, not at the end of today, as it really frames a lot of the discussions that we've had.

I thought I'd spend a few minutes talking about what the implications of what Dr. Lentine just described and why we should care that the variation in practice is significant.

As this audience well knows, effective management of cellular and humoral rejection is the cornerstone of successful solid organ transplantation. Current immunosuppressant protocols vary markedly across centers, as Dr. Lentine has just shown you, and that regimen choice is explained dominantly by center practice rather than clinical and donor factors. And that really reflects the fact that our field continues to evolve and has, you know, been a cottage industry

Page 379

for many, many years. It is, perhaps, remarkable that, you know, in a town like Boston where I was just working, management of the same kidney transplant recipient getting a similar organ can vary, you know, and differ across all seven centers even though we're caring for nearly similar patients.

And it suggests that the choice of immunosuppression is far from uniform nationally, providing, in fact, a national experiment to examine the impact of immunosuppression choice on clinical and economic outcomes while controlling for the variety of factors that we recognize are part of solid organ transplantation, including, as Krista defined as case factors, post-patient and recipient and donor characteristics.

This project is part of immunization optimization project, which aims to develop evidence-based selection of immunosuppression induction and maintenance regimens, which balance patient survival and graft survival with the need to minimize long-term complications for immunosuppression. This requires a rich real-world data set that allows us to deal with

Page 380

the variety of different and markedly impactful differences in the care of our patients.

It's infrequently been answered by the large controlled trials, given the need to balance interpretable conclusion next to -- inclusion criteria and the inherent size limitations. And therefore, we really need systems that balance immunosuppressive complications with benefits of reduction that reflect the real-world practice for our patients.

Finally, I think if clinical outcomes are largely similar, then we have to recognize that we are functioning within a relatively cost-constrained world. And the cost-effective regimen -- that the most cost-effective regimen should be employed.

The impact of regimen selection will be reviewed for its impact on patient and graft outcomes on post-transplant medical complications and, finally, on the cost of transplant and follow-up care.

The analytic methods were largely outlined by Dr. Lentine for the variation in use, the additional data in these analyses, including economic data, we used Medicare payment data, as well as Viseon (ph)

Page 381

health -- county records for transplant programs. Viseon collects data from the majority of the large academic and increasingly nonacademic centers.

Post-transplant complications were defined using Medicare diagnostic claims. All categories required at least one inpatient stay or two outpatient stays for a diagnosis of a specific complication. And the statistical methods included survival analysis, both adjusted and unadjusted, in multi-variate linear regression analysis for cost.

I'll start looking at long-term outcome. As most people are familiar, there are a variation in outcome associated with the use of various induction regimens. You see here there is a graded survival based on the use of immunosuppression induction regimens with campath having a slightly better outcome, perhaps, than IL-2 receptors, although we recognize, A, the differences are small and that there will be potentially differences in the underlying population. These are the unadjusted numbers you see here for graft survival. In fact, it flips on its head where IL-2 receptor unadjusted analyses are slightly better.

Page 382

Again, we recognize that these are generally used in low-risk immunologic patients, which is why you need large studies to be able to adjust for the these confounding factors.

In the adjusted hazard ratio, at three years, you see that the -- compared to IL-2 receptor, which is the reference hazard of 1, you see slightly better outcomes and reduced death in patients who received thymoglobulin, whereas death center graft failure may be a little bit higher, actually, in campath and relatively similar for all-cause graft failure.

If you look at the impact of maintenance regimens on clinical outcomes, again, you see a spread. This is reflected in the patient survival where you see survival of about six -- or about five points less for patients that didn't -- that received -- didn't receive steroids-sparing agents.

The graft survival, again, you see a spread over time. And when you look at the multi-variate analyses, controlling for the differences in donor and recipient factors, you see, in fact, that a steroid-sparing regimen appears to have a lower risk of death

Page 383

compared to some of the other regimens, including CSA-based regimens that have a significantly increased risk of patient death.

When you look at death-censored graft failure, again you see a reduction in death associated with steroid-sparing and perhaps an increase in death associated with CSA-based immunosuppression regimen and, finally, all-cause graft failure with similar patterns.

And I would point out to you that Dr. Lentine showed it relatively quickly, but there are still areas in centers in this country in which the majority of their patients are receiving CSA-based immunosuppression regimens and other that have -- the rarely use steroid reduction protocols. And so we may have evidence-based practice that it suggests that there are opportunities to improve the outcomes of our patients without even the implicate -- the development of new immunosuppression regimens.

But it's important, as we heard from Kevin earlier, to think about outcomes beyond death and graft failure. And while patient and graft failure are of

Page 384

primary interest for patients, the alternative outcomes are also important. And these include the trade-off between immunosuppression and the incidence of complications, including infections, malignancy, and cardiovascular disease.

There is no available transplant registry data set to answer these question. And therefore, we utilize the Medicare claims for patients who had Medicare primary insurance from the point of transplant on.

So you see here that you -- the differences in the incidence of malignancy over time is associated with induction therapy on the left and, similarly, with infection rates over time on the right with various types of rates over time. When you see here summarized, when you combine the impact of induction regimen with maintenance regimen, you see significant differences in the incidence of specific infections -- for example, pneumonia and sepsis, non-melanoma skin cancers, as well as the other viral cancers and NODAT.

When you place this into the multi-variate model, you see, again, that, for example, sirolimus-

Page 385

based regimens have a higher incidence of pneumonia, as do CSA and tac-alone-based regimens with lower rates for steroid-sparing, similar variation in the incidence of sepsis, pyelonephritis, other cancers. And you see here for viral in cancers again, this sirolimus-linked -- this sirolimus therapy seems to have a higher incidence. And the expected association of tacrolimus with new onset diabetes after transplant.

Finally, we consider the economic implications of transplant immunosuppression regimen selection. Choice of induction clearly impacts the cost of care. Thymoglobulin is estimated to be about $14,000 per course, basiliximab about $6,500. And Alemtuzumab, based on the current issues, is free for centers using it. But the economic impact of choice extends beyond these initial pharmaceutical costs, and you see that resources are needed to manage the complications, as we talked about.

The cost analysis differed by time period. The cost of the transplantation itself, again, used the Viseon cost accounting data. And then we used one-year cost data from Medicare claims from 2006 to 2013 to

Page 386

look at the costs after the first period of hospitalization.

Here you see variation in the cost -- differential cost of the transplant care by induction. You see the increased cost of thymoglobulin compared to IL-2 receptor and certainly compared to campath. And you see small variations by induction regimen over the first year.

If you look at attributable costs, it really is thymoglobulin that increased the cost of transplantation by about $10,000. And for those of us that are in the business, we recognize that use of these agents is the best thing for our patients, as we've heard. They clearly reduce the risk of long-term complications. And yet there is no adjustment currently from one of your sister parts of the federal government for people who are getting expensive induction at the time of their transplantation.

Similarly, you see variation in the cost of transplant by maintenance therapy at -- over the first year for Medicare. First, second, and third year, you see the differential by triple therapy compared to

Page 387

steroid-sparing and higher cost for people getting mTOR and CSI-based therapy. Again, attributable cost differences vary markedly according to our choice of immunosuppression regimen after adjustment for baseline donor and transplant factors.

The limitation of this study is its clinical data is limited to the elements that are currently included in the OPTN data set. We lack detailed data on immunosuppression exposure, dose duration, and level. We lack clinical comorbidity capture, including prior malignancy and development of NODAT that we would like to be able to make these analyses richer. And as we've heard this morning, I think we really lack a much better understanding on a molecular level of what the immunosuppression -- the state of immunosuppression and the immunosuppression and rejection risks for these patients are.

However, the post-operative complications are currently captured through administrative data claims and at least provides a real-world experience that allows us to think about alternative outcomes beyond death and graft failure.

Page 388

So in conclusion, induction and maintenance immunosuppression are associated with differential incidents of complications and cost of care during both the kidney transplant and post-kidney transplant period. Higher initial cost savings of some regiments -- for example, thymoglobulin induction appear to be followed by later costs savings likely driving by lower rates of rejection. Additional work is needed to determine the optimal regimen based on the donor and recipient characteristics. And development of a predictive calculator to provide patients and providers with informed choices about immunosuppressant-related outcomes is crucially important and will best be developed by consortium, as you'll hear about from Dr. Stegall.

There's a desperate need for multi-center prospectively collected datasets with richer capture of post-transplant outcomes and, particularly, those beyond just the well-controlled -- randomized controlled trials using the pivotal trials for the immunosuppression.

So I -- again, I appreciate the opportunity to

Page 389

present this work. Thank you.

(Applause.)

DR. CAVAILLE-COLL: Thank you, Dr. Axelrod.

Our next speaker is Mark Stegall from the Mayo Clinic, who's going to be speaking to us towards building a network of clinical centers.

DR. STEGALL: So I'm told that the next speaker may not be here, and so I have, like, an hour.

(Laughter.)

DR. STEGALL: It's going to be awesome because, like, I know, like, a million jokes, and it's going to be that kind of a day, part of the day where -- this is -- Ken knows this. This is the kind of part of the day that I'm gone, right? Usually, by this time, just like Abecassis, blow this off.

So I'm here. You guys are smart, man. Got me.

So building a clinical network, it's -- and I think I'm -- I was supposed to say this; Inish paid me to say this -- it's all about data, right -- collecting data. And collecting data is actually difficult and expensive, and collecting good data is probably nearly

Page 390

impossible. And I would actually say that the current challenges, right, choice of immunosuppression, monitoring protocols (inaudible) by centers where the transplants are formed (ph) and not by patient characteristics are that, actually, people are smart, you know. It's -- when they give you something for free, it's like how bad could it be, right? It's free, you know, so you use it.

But the real issue is I think there's really no clear-cut data that has this -- a compelling reason why you should use this. Not all those centers are using (inaudible) and prednisone as the maintenance immunosuppression. I mean, the field has move forward a little bit.

So my opinion is that it's not really limited types of inductions. There are all sorts of patient-related issues. And I do think -- this is at least my hypothesis. I mean, not everybody will follow compelling data. You've not met my daughter. So -- but I think that it's a good thing.

What kind of data do we have? We have registry data, and I think that that's what the last

Page 391

two talks were about, right -- registry data. And everyone knows that you can get a lot of data from the STAR file, from -- and that's going to be very helpful many times. But the problem is that, with that data, of course, is there's a lot of missing data. It hasn't really been -- there you are -- it hasn't really been validated. And I mean, the people who put in the data, I mean, there is not a clinical research organization that comes back around, looks at data, and makes sure that it is good data. And that's a problem.

Then you have a lot of data from multi-center Phase 3 randomized clinical trials, as we are looking at in the TTC where we really have put a lot of money and effort into developing that patient-level data. And I think that there's a lot of great data. And if you talk about clinical research consortia, there actually are a lot of clinical research consortia that exists in transplants. CTOT has put a lot of consortia together, correct? But I think the real issue is sustaining those consortia.

And also, I think the last thing that I would say is that, as we go through this, it's really not as

Page 392

much real-world data about all types of patients. And for example, you know, Meteor has a study out now looking at HLA-identical living donor kidney transplants. And it turns out that none of those were ever included in any immunosuppressive trial between the rejection rate was so low, so nobody knows anything about those patients. So -- and that seems to be a recurrent theme in just about every trial you want to start.

I guess the folks in Vitaeris had the same issue, too. They had to pay four centers to get data that they -- in order to get a trial -- get the data they needed for a trial. And it's unfortunate that we have to go down this pathway every single time.

And so we need all this type of data. I don't think there's one type of data that is -- that trumps any other data, but I do think that that is really what a research consortium is about.

And most transplant programs individually don't have any long-term data. There's really -- whatever that is -- 5-, 10-year follow-up is actually quite rare in most programs. And it's really hard to

Page 393

collect that data. It was the old unfunded mandate issue. Remember that? But we need to fund this in many ways.

So clinical research consortium defined as a group of medical centers or programs that are organized to conduct clinical trials in a specific space. The way that it's set up -- or I think the classic one in oncology -- classical ones in oncology are -- there are -- there's a centralized organizing group. The members agree to a standard of care and data sharing. It's freestanding and continuous. They're not -- these are not one-and-done consortia, and they are efficient and effective at doing clinical trials. And it's very common in oncology.

And talking to people who are in clinical consortia in oncology or in diabetes, when certain studies come out of a certain consortia, it's got to get a good housekeeping seal of approval, you know. They did it right. They know how to do a clinical trial. And we know that enrollment's such a huge issue in all trials, but especially in transplantation.

And just to say, this was mentioned, I think,

Page 394

by Ken, so I put this up here, that there are many clinical consortia worldwide, but this one is definitely a big one and does a lot of great things. But they have, really, a specific interest in cellular therapy. And so they may not be the group that you would go to find out about HLA-identical living donor kidney transplants.

And I think that the flavor of many consortia in oncology, certainly, there are some disease-specific consortia. But I think they have a little bit of a broader approach to doing that.

So we started something called a multi-center transplant alliance. It's primarily started through the three Mayo sites, which the good thing about that is that there's one bank account and there's one IRB. So it's really helpful to get some trials going. We do a lot of paired donors. We do have a lot of collaboration.

And there also is a convergence of clinical practices. So we actually do use pretty much the same immunosuppressive regimen. It's stratified by certain patient types and all the rest. And if you've ever

Page 395

been to Rochester, Minnesota, this logo is actually kind of fun. I can take a second to explain it.

The IBM logo really looks like the MTA logo. But those birds that are flying in formation are ubiquitous in Rochester, right? It's the Canadian geese, right? And they don't fly very far from Rochester. They stay there all winter.

But when geese fly in formation, they actually use less energy, right? The geese at the front -- the goose at the front takes all the brunt. They -- that's the coordinating center. And everybody else uses less energy. And the idea is that's what a consortia is about. And I think that -- I wanted to give this whole talk why you should never start a research consortium, so I thought that would be the way to do it.

(Laughter.)

DR. STEGALL: Now, that's a little bit over the top, but reality is do not do this. It's not a good idea, right? It will kill everything else that you want to do with your life. It saps a lot of time and energy. There's no question about it.

It will actually only demonstrate to you and

Page 396

your peers, people you know well and you thought respected you, how really inept you are at group leadership. And so if you want to do that, this is perfect.

It's almost impossible to get funded unless there's a single trial. If there's a single trial, that's great. But these kind of consortia that are freestanding, you know, we're starting to -- thinking about studying cancer, actually, because maybe that would help.

Then I think that collaborators are busy. They really are busy. And they're almost -- it's too busy even if they want to help you.

Conference calls are -- there's never a good time. So we try monthly conference calls. And it's kind of we're going to have them whether anyone shows up. And we end up having two, maybe three about the same issue.

I would say parenthetically that, you know, so I got -- let me mention something. Alex actually has a really good research consortia, I think, because it's almost like what France is about, right? You guys

Page 397

share data and all the rest. So that's helpful. We're not that. We're not that. I can tell you that.

It takes a long time to be productive. And I said -- did I say that collecting data is difficult and expensive?

But multi-center research is really important, and it's important for transplantation. And I think it should go beyond just doing Phase 3 clinical trials. It improves diversity and decreases biases in studies. It turned out we wrote a lot of papers at the Mayo Clinic for many years. And people just were not interested in Norwegians who got living donor kidney transplants. Now, I think they're the most fascinating people to study ever. But it just wasn't the number one thing in other people's -- you know, don't knock it if you haven't tried it kind of thing.

So the other thing is that -- I told you I know a million jokes -- resources -- it's a natural history of studies, especially in small subgroups. And Inish, I think, and his group are very interested in the natural history of diseases. And we really don't have a really great handle on the natural history of

Page 398

kidney transplantation. And I can say that at least at 5 and 10 years, that area out there is a bit uncharted territory. We have a pretty good handle the first five years maybe.

Detailed data and specimen collection with a single standard of care is helpful. It's amazing how having specimens biopsy serum cells and all that come in handy when you are answering -- trying to answer new questions, maybe work with other people. Larger populations for faster enrollment, faster study enrollment, is almost an oxymoron. The study part of it makes it hard. It makes studies possible for hard-to-enroll groups.

Antibody-mediated rejection -- I'm going to take a minute to talk about that because there's several studies in that. And actually, it's collective expertise. It turns out we're a lot smarter, you know. We're like a genius when we work all together. And when we work individually, not so much. And I think it's -- probably most people worked in consortia that good ideas come out of just sitting and talking to other people about how things turn out, but it takes a

Page 399

lot of work.

And it -- this -- the reason it really came out of this was not just the Norwegian issue, which was part of the issues. But the other reason is that we had this issue where people would say, oh, our subclinical rejection rate is 30 percent. And these were some of our colleagues. And I would look at it and say it can't be 30 percent.

And so we'd have them get their data, and they would do it. And this is Ray Halmond's (ph) group from -- that does a lot of the deceased donors in Arizona. And it was 14 percent in Alemtuzamab and 9 percent in the ATG group. And that was, like, hundreds of patients. So I think the more you get data -- the other thing is talking to Bob Gaston and Arthur Matas, you know, they were doing biopsies for cause. We were doing protocol biopsies. And at some point, the biology has to kind of merge. There has to be the same thing that happens to a kidney transplant patient.

So I thought we should just really try to get enough programs that would work together on. And this is not necessarily about any one specific research

Page 400

project, but it's try to come up with a standard of care and a way of doing follow-up. And we are partially there.

And so the programs that are now in the MTAK (ph) Consortium I could say some of these programs have moved around because people have moved. And there is also one in pancreas transplantation because a lot of guys about my age thought it was time we should do something about pancreas transplantation before we stop doing it completely.

And then there's -- we do about 1,500 kidney transplants a year, about 300 pancreas transplants a year in these consortiums. And I think the way to look at this is that this is just one model. It's probably just a beginning of maybe something that could be collaborative with a lot of different people. There are a lot of things about -- the studies were opt-in, and we could add other sites if there were people interested in desensitization or other things like that.

And what's happened is that, over the last few years, which would -- we paid for this partly out of

Page 401

some of my money that I have from my professorship, and part of the money is paid for out of some NIH grants and some other things. So we've enrolled 1,000 patients in observational clinical trials over the last few years. And we went from doing 65 percent living donors, which is what we do in Rochester. And they -- now we see -- you can see that Mayo Clinic Florida does 39 percent living donors. So we have much more of a mix of types of transplants.

And if you look at ethnicity, we went from, you know, all the Norwegians to having many different types here. And even though it's only 15 percent, 10 percent of people have no ethnicity. I didn't know that, but what you learn. And -- but even 15 African Americans in clinical trials, not just in people who are transplanted, it's still, you know, a kidney biopsy which have been scanned in our Aperio scanner, biopsy tissues, cells, and serum, allo antibody data on 150 people at one year that could go into iBox, right, Alex?

So what we did is we also got people to work together. So we even got pathologists to work

Page 402

together. So there are two pathologists from Mayo Clinic Rochester, two pathologists from Mayo Clinic Arizona, and two pathologists from Mayo Clinic Florida on this one paper. And that was actually a big deal because reading biopsies is a big thing in what we do. And I think Alex met some of these people when he came to visit us this summer. So it becomes a very collaborative group. And again, they are working hard to make this.

Just the last thing -- I don't know if I'm running out of time, but we want to facilitate enrollment in Phase 3 multi-center trials. Low enrollment is a big problem. I get a lot of phone calls from a lot of companies how the enrollment is going slowly. Why? And I think that it's a big problem when you have data collection.

A big problem, too, when you get a clinical trial is recreating the wheel every single time. Some programs don't have standing up -- don't have a research coordinator doing transplant full time. And so it's really hard to start up again.

And they may only have one person doing it.

Page 403

And then when they quit and they decide they, you know, want to do oncology because there's so many nice studies, they go over there. And then you have nothing.

And then there's this issue about every study seems to be different and even in the same area. And transplant's a pretty complex field to run clinical trials in. And when we ever get anybody else to help us out, they just shake their head how complex they are.

But I just give you an idea about ABMR. You know, I -- it's pretty -- it's a pretty rare event. It's about 1 percent per year. So maybe 5 percent cumulative incidence at 5 years. And there'd be -- there -- you know, you -- like everything else, there are always going to be these patients. Nobody actually meets enrollment criteria for the clinical trial. It's so hard sometimes, especially in these complex patients.

So if you do 5 percent of 100, you need about 2,000 kidney transplants to have been followed. And the center performing 200 transplants will have 10

Page 404

cases in that cohort. So basically, you have to do about 3,000 kidney transplants to get 100 patients, right, in a clinical trial of ABMR. And that's a lot of kidney transplants.

And if you multiply that times the number of drugs that were are trying to use in this area, just the physicality of doing a clinical trial -- and this becomes a big issue -- subclinical rejection was something we've been interested in many years. But doing a clinical trial on subclinical rejection requires about 3 or 400 patients almost in each arm to show an impact on outcome. And so you have to have a bunch of places doing protocol biopsies, and it's hard to do.

And I want to -- I wouldn't go away without mentioning something I think that we should talk about. And I had a conversation this morning with someone from the FDA who was sitting next to me. And I think that we should really consider adaptive trial design in clinical trials and kidney transplantation. It's a way to learn from relatively small numbers of study subjects. In our calculations, you may have as few as

Page 405

eight patients that can be used to decide of therapy is ineffective.

Another aspect at hand is efficiency if there's a single control group, rather than having multiple control groups over and over and over again. And the vast majority of patients then can be assigned to an experimental group. And oncology, of course, beat us to the punch many years before. This is -- you should read these papers and the comments on them about adaptive trial design. This is a Bayesian adaptive trial design. It doesn't have to be exactly like this.

But I think that we should truly think about not when we're thinking about looking at the way we do drug studies. I think that adaptive trial design is something we really need in transplantation, especially if we're talking about subsets of small groups of patients.

So compare oncology to transplantation. A few years ago, they put out an article that there are 23,000 clinical trials going on in the world today, right? I think that, you know, that seems like I do IRBs, and I'm still way behind that. That's a lot of

Page 406

trials. I think 16,000 of them are in oncology.
In transplantation, maybe 20. You think there are that many? Twenty in transplant?
And I think the lessons from oncology is they work together. They have standing clinical research consortia. And again, we are not a great success, but we're trying to do it. And I'd be happy to work with anyone else and try to make this a success in transplantation. They commonly use surrogate endpoints for clinical trials, and they don't give up. There's no question. They're -- they are just persistent, and they will tend to be successful for that.
I really think that the MTA actually is not built for me. It's built for the junior faculty of the place that I work at. And they're probably going to see the most benefit from this long term. And I don't think I'm really worried about how fast it's going to happen.
I think we built some trust. We have some momentum. We're showing some productivity. I would have to thank Matt Everly, also. He's been very active and supporting of what we're trying to do. We're

Page 407

keeping funded, but people are coming along and doing this.
And then the real problem is that when you have this group and it gets to be bigger and bigger, you know, you have to keep -- take care of the people at home, too. And this is a totally -- it's a separate job to do this.
So that's my experience with the clinical research consortia. Maybe in five years I can give you a more rosy update. Thank you.
(Applause.)
DR. CAVAILLE-COLL: Thank you, Dr. Stegall.
Our next speaker is Margaret Mooney from the National Cancer Institute, who's going to address Clinical Trials Networks in Oncology - A Model of Collaboration.
DR. MOONEY: Okay. Well, thank you very much for inviting me here today. And it actually is very nice to listen to the differences in the problems that you have in transplantation and thinking about clinical trials and to realize, even though we may seem like the 100-pound gorilla in the room, even in oncology, we

Page 408

face many of the same issues. And we have to deal with all the same challenges.
So I just want to say I have no financial disclosures. And as a federal employee, any commentary that I might make are my own personal opinions and not those of the National Cancer Institute.
So I was asked to give a very brief history of the NCI-funded (ph) cooperative group program, which is a grant program that was started more than 60 years ago by the NCI to evaluate cancer treatments. So I will try to go through 60 years of history in 6 minutes or less, so I hope you'll bear with me, and then to talk about how we tried to transform that grant program over the past five years into a truly national network program.
And then the last part of my presentation -- I'll just talk about some of the clinical trial designs and challenges in this area of precision medicine that we're encountering in oncology, which leaves us with very few patients in many areas of particular cancer subtypes. And so in that way, we really do have many of the same challenges that you have. I'll also speak

Page 409

a little bit about the way we're designing biomarker-designated trials and using adaptive design features as well.
So we were very fortunate that, in 1955, actually, the U.S. Congress appropriated about $5 million to establish a cancer chemotherapy national service center. And at that time, NCI established a cooperative group model of a resource -- a research consortium to test chemotherapeutic agents. And by 1958, we had 17 cooperative groups. Now, they were small. They were in different cancer areas, and they were really just empirically screening drugs. They weren't really looking at the disease and asking a specific clinical treatment question for that patient population.
And it wasn't until 1966 that we kind of separated that clinical trials activity from a purely sort of empirical drug screening approach to actually an independent evaluation of the cancer and looking beyond just drugs of how we used radiotherapy with drugs, how we used surgery with drugs, and how we combined all three of them to approach the best

Page 410

treatment for cancer patients.
But we still operated on a very independent sort of one-grant-to-each-group model at that time. People would propose trials. They would be reviewed. They would be put into effect.
But we weren't very collaborative at that time. And it wasn't until the early '80s that we changed the paradigm of how we funded those trials and how we worked with those cooperative groups. So it really became a collaboration between the investigators in the academic centers and across the United States that participated in those trials and directly with the physician and physician staff at NCI.
And then in 1983, there was additional funding from Congress to try to expand our research consortium from an academic base into the community. So we started the Community Clinical Oncology Program, or CCOP, now known as an NCOP, was established to ensure that community physicians and their patients could participate in our trials.
And then in 1990, that was extended to provide specific grants to areas and community centers that had

Page 411

a minority base and ethnically diverse populations, again, for the same purpose -- to try to really have a national program that treated all patients in the United States. It also allowed us to advance and look not just at treatment, but also at prevention and control.
But as we found that we got bigger, I wouldn't say our resources always got larger or more substantial. And so we found that, by having so many different groups looking at cancer, there was quite a bit of competition and a lack of efficiency. And the first place we saw that was in pediatric oncology. They actually had four separate national research cooperative groups. Two of them were quite large, one called the Children's Cancer Group, the other the Pediatric Oncology Group. And then they had two smaller, very specific groups, one in Wilms tumor and the other in rhabdomyosarcoma.
But again, they found that, because they were filling up the patient population much more narrowly among the four groups, that they felt it would be much more efficient if they combined into one single group

Page 412

and then approached the whole issue of pediatric oncology in a unifying fashion. And so they did merge into one group in the early 2000s.
And you can see here this is actually a rather dramatic diagram of what happened in terms of the survival of children with acute lymphoblastic leukemia, ALL, who were enrolled in those cooperative group trials between 1968 and 2009. And back in 1968 and 1970, the overall 10-year survival for children who had ALL was about 10 percent. But by consistently, and as Dr. Stegall said, really, never giving up, they tested more and different combinations of multi-agent chemotherapy regimens until the survival in the early 2000s and now in the late 2000s is 90 percent or higher.
So now the focus has shifted as we understand more about the molecular biology of child cancer to focus on trying to understand what the molecular characteristics are that determine which children will have difficulties and will recur with ALL and also to back off of therapy now, particularly for children who we want, hopefully, to live a long normal life and try

Page 413

to have more and less toxic therapy and still have the same equivalent survival.
So as I said, we were very lucky to have that initial support and continued support from the American taxpayers to have a really publicly funded clinical trials system. And it really was rather unique, and it grow -- grew into a very distinctive national system. As I said, we were able to have direct involvement from investigators, not just in academic centers, but also community centers. We're able to expand the types of trials we did, and we have a long history of accomplishments from all the hard work of those initial physicians and those physicians who participate today, but particularly from the patients and their family members who participated in those trials and continued to participate in trials.
Many of our accomplishments are in the area of drug and drug development. But obviously, we also have many trials related to other types of therapeutic approaches like therapeutic -- like radiotherapy and surgery.
At the same time, we've had several reviews

Page 414

and analysis of our program in hopes to make it better. And I've listed just three of these that were done in the -- between 2005 and 2010. And probably the most significant one was the last one on the bottom in 2010 by the Institute of Medicine, who really was given the charge from the NCI director at that time to review our entire program and really recommend how we could make it more efficient and more productive as we entered into an era of precision medicine.

And out of that review by the Institute of Medicine, they did confirm that they really felt that a public clinical trial system was really complementary and had a very important role in patient care and science and that it provided public access for important clinical questions and as well as collecting biospecimens for future research. But it also was important because it would address questions that often in the pharmaceutical and biotechnical industry weren't well addressed.

But they did say that we needed four goals for modernization, and you'll see those listed at the bottom. One is they felt that it had -- we had to

Page 415

speed and run our trials much more efficiently. We had to have more innovative science and trial design. We needed to prioritize the trials that we did. And last but not least, we needed to really incentivize the participation of patients and physicians in these trials.

So at the time in 2010 when the IOM, the Institute of Medicine, did this analysis, we actually had 10 different cooperative groups. There were five that were kind of multi-modality in the sense they cross different modalities of treatment approaches in cancer, but also different diseases. And then we had five that were specialty.

But what was happening, even though they would occasionally collaborate on a trial -- and we had some centralized services such as -- we did have a central IRB that we started at the time. We did have a central portal by which we could put trials they wanted to collaborate on together so they could work together. They still were really operating very independently.

So the question was how did we get to a -- or how could we get to a network program from these

Page 416

individual 10 different cooperative group systems.

And so what the NCI did in July of 2012 was we put out a new RFA for the funding of the program to make it truly a network program. We consolidated it down from 10 different programs to 4 adult groups and 1 pediatric group. So we kind of took that separate infrastructure, consolidated it, and streamlined it.

We also at the same time needed to provide an essential infrastructure that can -- that was standing and that all those groups could use. We tried to put procedures in place to launch the trials more rapidly and to have user-friendly harmonization of the way all of them ran their trials so that everyone could participate in them.

But I think the last and maybe the most important thing that really drove this type of consolidation on the investigator side as well was understanding that we really needed in an area where breast cancer now really was 10 different types of cancer. We were finding out that lung cancer was very different depending on the type of lung cancer you had and the molecular characteristics of your tumor, that

Page 417

we needed to have a functional platform to really perform large-scale testing of increasingly smaller subsets of molecularly defined cancers. And at the same time, we needed to continue to focus on questions that weren't always as well supported in a commercial environment.

So in 2014, we did start the new NCI National Clinical Trials Network. Obviously, it wasn't completely new. It was built on 50-plus years of history and dedication. And all the clinical groups that had participated before actually came in and reorganized themselves and consolidated into the four adult groups and one pediatric group I mentioned.

We continued to have a well-supported community oncology base that participated in our trials. And it did allow us, as you'll see in a few minutes, to continue to do large umbrella trials that screened (inaudible) patients, depending on the characteristics of their tumor. We continued to do multi-modality in non-drug trials when appropriate as well as combination trials with different types of investigational agents combined together when

Page 418

appropriate.
And last but not least, we were able to have some new initiatives where we now, for every completed clinical trial, once the primary results have been published, we're able to take de-identified patient-level data and put it in a public database so researchers can now and into the future use that information and do investigations.
At the same time, we have since the early '60s collected biospecimens on pretty much every clinical trial that was conducted. We now have a reservoir of those biospecimens that weren't ever used for the particular translational science in a trial. And those are now beginning to become publicly available as well for researchers to submit proposals on -- once a trial is completed.
So we have a lot of basic operating principles, which I won't go into here. But I'll just suffice to say that -- and we now make sure that it -- that everyone operates in the network. So if you belong as a particular academic or community institution to one of the groups that participates in a

Page 419

consortium, you can participate in any trial that any other groups put into the network. So this really is open to everyone.
We also have made sure that each one of the separate research consortium or major groups actually uses the same common data management system, the same common data elements, and we really work together to make sure everything is harmonized across the network no matter which particular group is leading a trial.
At the same time, each of those groups has a distinct personality, and they still maintain their individual research characteristics.
So over the last four years, we have put on over 75,000 unique patients onto clinical trials. I've shown here a little bit something that demonstrates, I think, how our trials have changed in the last five years as opposed to a decade before. We have more and more trials now where we initially screened patients for particular patient characteristics, but also molecular characteristics of their tumor so that we can determine which subset patients -- or in which intervention a patient should go into.

Page 420

So we've seen over the last five year -- four to five years that we have more and more trials where that's an essential component of the particular clinical research question that we'll be doing with the intervention.
So I'm now going to shift a little bit and just talk very briefly of some of the recent trials we've done in the era of precision medicine and to give a little bit of examples of adaptive devine -- design features that we use.
On all our trials, we do interim monitoring, and that's because we need to monitor for both efficacy and futility as the trial goes along. That helps us be much more efficient. So if we see that an experimental therapy looks like it is never going to be shown to be better than the control or the standard of care, we end the trial early. And the same thing if we're seeing various distinct and early signal that something is going to be dramatically beneficial.
We also are much more efficient at trying to understand what trials will succeed and what won't so that we end or we modify a trial early if we see we're

Page 421

having accrual problems.
We also put in certain designs like Phase 2, 3 trials. So we'll look for an early signal. And if that early signal meets a certain barrier, we will then move seamlessly into a definitive Phase 3 trial. That also helps us be much more efficient.
There's been a lot of discussion about surrogate endpoints. Those are very challenging to do even in oncology and even with all the resources we have. And we've been misled many times about something that we really thought was going to be a good surrogate for overall survival or for even disease-free survival only to find that that hasn't panned out after we got long-term follow-up.
So we focus much more now on intermediate endpoints. They themselves are obtained, obviously, earlier than the definitive clinical endpoint. They are sometimes and often influenced by the intervention, and they're correlated with a definitive clinical endpoint. But they aren't a pure surrogate.
So that helps us, for example, if we look at something like pathologic complete response of a

Page 422

treatment. We might look at that early on right after neoadjuvant therapy in the surgical specimen. And if that -- we're seeing a high rate of complete pathologic response at a certain level, we would then move on to continue the therapy and evaluate the more definitive endpoint, which is overall survival or even disease-free survival.

The other thing we found were surrogate endpoints. And when we thought they were definitive is when we changed the class of agent that we were using. So when we went from chemotherapy to more targeted agents like anti-angiogenesis agents or even now with immunotherapy, you couldn't necessarily use the same surrogate endpoint. We found that it wasn't -- a surrogate for one class of agents didn't work for another class of agents. It worked in one disease. It didn't work in another disease. It worked in one subtype of patients and not in another.

So it's a very, very challenging area. And obviously, we don't have time to talk today about all the issues related to that. But I think it's changed our approach in some respects in the way we design

Page 423

trials that we're looking more at intermediate endpoints, realizing that many of them really aren't pure surrogates for the primary endpoint of interest.

So I'm very quickly going to give three examples of trials that we've conducted or completed recently in the era of precision medicine. The first one will be early-stage breast cancer where we used a biomarker or an assay to identify a risk level for patients in terms of whether they -- whether the breast cancer recurs or not.

The other is a new umbrella trial for adjuvant therapy in early-stage cancer. And the last is a very challenging signal-thinking, early-phase trial where we try to match all kinds of new agents with distinct targets to patients who have tumors with particular molecular characteristics called match.

So many years ago, we had done a series of cancer clinical trials in breast cancer where, in fact, we also collected biospecimens. And we found over time that women with early-stage what we call ER-positive lymph node negative early-stage breast cancer that was HER2-negative, that they benefited from Tamoxifen

Page 424

therapy. We then found that they also benefited if you used Tamoxifen, which is a hormonal agent, with chemotherapy.

But what we found is we also knew that, although we were treating everyone with hormones in chemotherapy, many patients didn't appear to need chemotherapy. But we didn't know which patients they were.

So biospecimens were taken from many of the trials that were done in the 1980s and 1990s even. And those specimens and the long-term follow-up that we had from those breast cancer patients were used to actually develop a particular biomarker assay on recurrence risk. And so about 250 genes were identified that were thought to be most highly correlated with the risk of breast cancer recurrence. However, with a model building, they then streamlined that down to a 21-gene assay expression model and chose 21 genes. And out of those, they then did a validation study on specimens with long-term outcome that were from a previous trial.

And from that, they developed something from oncotype DX, which is a biomarker that allows us to

Page 425

determine a patient's risk of recurrence when they have early-stage breast cancer. We know that patients who have a low recurrence score have a low risk of developing recurrence and probably only need hormonal treatment. Same thing for those who had a very high score, that they probably needed hormonal therapy and chemotherapy.

But the big question was what to do for the majority of patients, about 70 percent of them, who were in the immediate-risk area where their risk -- excuse me -- recurrent score was somewhere between 16 and 26. Should you give them just hormones? Should you give them hormones plus chemotherapy?

And what we then did is design a very large trial that was done between 2006 and 2010 where over 11,000 breast cancer patients underwent testing of the oncotype DX assay to determine their risk score. If they were immediate risk -- and that meant they had a score between 11 and 25 -- we randomized them to hormones plus or minus chemotherapy. The patients who were in the other two extremes were just treated and followed to see how well they did.

Page 426

And just three months ago, the results of this trial were announced at the annual ASCO meeting in June 2018. The name of the trial was TAILORx. And what we found is that, in fact, patients who were in that intermediate risk category who received hormonal therapy did just as well as those who had hormonal therapy and chemotherapy. And because of that, we are now able to go forward and with a great deal of confidence, based on that risk score, determine which patients need to be treated with hormonal -- or can be treated with hormonal therapy alone and which really need chemotherapy and hormonal therapy.

We're trying to do something slightly different in early-stage lunch cancer. Here we've identified certain types of mutations, EGFR mutations in (inaudible) rearrangements that actually, if a patient has those characteristics in their tumor, we found that, with particular targeted therapies against those targets, they do very well if they have advanced disease.

And what we've designed is a very large trial so that we can screen based on a -- what we call a

Page 427

multiple biomarker randomized enrich design, which is a mouthful. But in any case, what it allows us to do is screen a lot of patients, select the tumors of the patients who have tumors with particular molecular characteristics, and then randomize them to the appropriate therapy.

So we've done that in this trial, umbrella trial, called Alchemist where we select the patients with a particular histology who have either EGFR or an (inaudible) rearrangement and treat them with a particular therapy targeted against that mutation, or we don't give them any further therapy.

At the same time, we've combined it with those patients who don't have those markers, and we treat them with chemotherapy, plus or minus immunotherapy. So that's an ongoing trial that's taking place right now.

And the last big thing that we've been able to do with the new national network is really take that model and use it, actually, in a large national signal-finding trial. So here, what we were trying to do is screen a large number of patients and do complete NGS,

Page 428

next-gen sequencing, of the tumors to determine whether they have particular molecular characteristics that we could then actually match to new experimental drugs.

So this is something that we call a multiple biomarker signal-finding design. And essentially, we picked the marker. And then with the screen of all the patients, regardless of the type of cancer they have. So it's histology agnostic. If they have that molecular characteristic and they have exhausted other areas of therapy, we put them in a clinical trial and see if that particular targeted area -- agent that's actually set up to work with their particular molecular characteristics has an effect or not.

This trial is called Match. It's been very challenging, but, at the same time, very rewarding because in two and a half to three years, we were able to screen over 6,000 patient. We were able to match about -- between 7 to 800 of them to particularly new experimental therapies based on the target of the -- of their particular molecular characteristic. And we also made a focus of the screening to really concentrate on rare cancers as well.

Page 429

So I won't go into the details here, but we were able to, out of those 6,000 patients, just to screen about 62 percent of them who had rare cancers. The rest had more common cancers. We had 40 different treatment arms in that trial. Most of them are still ongoing, but 15 of them have completed treatment. And their results for them have been released.

So we're hopeful that this type of national signal-seeking screening trial will lead us to new discoveries in oncology and new signals for targets and for treatment.

So thank you. That was a whirlwind explanation of what we've done for the last 60 years. But I guess the only caveat I'd like to say is that I think that the model of collaboration has been extremely successful in oncology. It's also been essential. Without that, I don't think we would have made many of the most significant and dramatic changes in therapy that we've been able to do all together. So thank you very much.

(Applause.)

DR. MORRIS: I'd like to thank all the

Page 430

speakers in the session that is now open for questions or comments.

DR. STEGALL: I have a question. So two questions. How do you get two to three pharmaceutical companies to work together on a trial? Because I asked them, and they look at me like I'm crazy. And what percentage of cancer trials are actually in this -- under this format? And is it, like -- is it 20 percent, 80 percent, those kind of things?

DR. MOONEY: Okay. In terms of working with companies, because, you know, going back to the 1950s, I mean, really, initially, there wasn't a biotech industry back then. So in that sense, government did pay -- play an important role in really starting science and research in that area. But because of that, we kind of grew up with the drug development field and with biotech. And so we had many relationships with pharmaceutical companies and biotech companies during that period.

But what we found is that we were able to set up certain types of research agreements with multiple companies where they viewed the government as an honest

Page 431

broker because we didn't have an investment interest in what happened. We had a scientific interest. And so over the last 10 years, we've developed what we call CRADA, which are collaborative research agreements with companies that have certain data-sharing aspects and confidentially -- confidentiality aspects that allow them to go in and combine their two agents together in trials that we run through the research consortium.

At the same time, we've put in IP protection. So that was a significant issue with all the companies and concerns about that. And we've put that in place, too. So it's really to -- a lot of hard work from all the people who work in the regulatory area to set up those kinds of agreements.

DR. STEGALL: And the percentage --

DR. MOONEY: Oh, the percentage I have no idea. I mean, I think what's difficult is, 60 years ago, we could say we were doing most of the clinical trials in oncology. Today, there's been such an explosion, and that's really difficult to say.

We used to say -- and I think we still do -- that we're probably the largest funder of -- public

Page 432

funder of clinical trials. But I think the explosion in investment by biotech and all the number of trials going on, particularly now with immunotherapy, it will be very difficult to categorize.

DR. STEGALL: Okay. Thank you.

DR. MORRIS: I have a question. If you were here earlier, you realize that we're very interested in biomarker surrogate endpoints and drug development tools. And as you mentioned, oncology has spearheaded the area of surrogate endpoints, accelerated approval.

So I was wondering if you could give us a few examples of surrogate endpoints that were endorsed by the FDA and which were used by sponsors to receive accelerated approval and that predicted a true clinical outcome.

DR. MOONEY: So that -- you know, again, that's a different -- difficult question. I think for us in oncology survival itself was always the primary endpoint. So when we began to show differences with certain regimens in progression-free survival in the advanced disease setting and then disease-free survival in the adjuvant setting, which correlated very strongly

Page 433

with chemotherapy to overall survival, the FDA did take progression-free survival in the advanced disease setting, and they did take disease-free survival in the adjuvant setting and did give us accelerated approval on that within waiting for overall survival.

That's where -- in chemotherapy, because we had a long history and a lot of data on those trials, we really could correlate those progression-free survival, disease-free survival with overall survival. As we began to change the class of agents, that didn't become so clear. When we began to realize that some patients were really benefitting when we took everybody together because of molecular characteristics, again, that began to change a little.

But I think, still, if we look, we've moved even earlier in some respects in very advanced and rare cancers where, if we show a dramatic response rate, okay -- so not even progression-free survival, just a response rate -- that they've been very open to using that as an early indicator, maybe not a perfect surrogate, and then waiting for the eventual primary outcome of the end -- of the primary endpoint outcome

Page 434

to get full approval.
DR. MORRIS: So can you -- can an oncologic drug get traditional approval if it shows progression-free survival but not any difference between the comparator in overall survival -- or survival rate?
DR. MOONEY: So --
DR. MORRIS: In other words, the patients don't do any better, but they have progression-free survival. How does that work?
DR. MOONEY: Okay. Well, I'm not from the FDA, so they're the -- they'd be the best one. But I certainly can give an example where, in some cases, they have approved or given full approval based on progression-free survival as long as there's no decrement in overall survival.
So there were some -- and it comes down to the severity of the condition, how, you know, the fatal it is, whether any other alternatives of therapies and what the benefit in that progression you're seeing is. And if the same time they see something very significant clinically and then there's no decrement in over survival, at least in some cases, I believe they

Page 435

have given full approval, even on that.
We've seen a lot more early approvals in terms of accelerated approval waiting for a more definitive endpoint. We've also seen what they call breakthrough approvals.
But to just give one example that they've done in advanced disease setting very recently with immunotherapy in what we call microsatellite instability, so it's probably not worth going into all the details about it. But in any case, immunotherapy across a variety of different cancers in the advanced disease setting seem to be particularly beneficial for patients who had tumors with that characteristic.
So I believe it was, if someone's here from the FDA, one of their first across histology full approvals for use of an agents in that class of disease. Now, again, that was very advanced. People had exhausted other standards of care. But it was based on, really, not long-term outcome, but it was based on seeing a dramatic response in progression-free survival across multiple histologies.
DR. MORRIS: (inaudible - off mic) examples of

Page 436

drugs that have been approved which halt progression of histological stages of disease but don't increase overall survival. In other words, it's another way of looking at progression-free but here at the actual histological level.
DR. MOONEY: Yeah. So I'm not -- are you asking --
DR. MORRIS: Yeah. I'm asking whether there are examples in oncology where a drug prevents progression of a stage of disease assessed by histology but overall the patients in both arms die at the same rate. It's a way of looking at --
DR. MOONEY: Yeah.
DR. MORRIS: -- progression-free --
DR. MOONEY: Yeah.
DR. MORRIS: -- as well but at a histological level.
DR. MOONEY: Yeah. So certainly, most of the trials that we've run up until more recently as we've understood more about the molecular characteristics and targets, we've run within histologies. So there have been many trials where we've seen a difference in

Page 437

progression-free survival that looked quite dramatic, but then there was no difference in overall survival.
Now, sometimes that was because there were alternative therapies available after someone stopped -- tumors stopped responding to that initial therapy. And so there were many examples of that, actually, where we do see a difference in progression-free survival, but overall survival doesn't change.
DR. MORRIS: Drugs were approved --
DR. MOONEY: Well, sometimes they were approved; sometimes they weren't. And they were approved, as I said, where that benefit in progression was quite large. Sometimes they're quite small. There's a difference, but it's not really large. The other thing -- there can be a difference, but if there's a lot of toxicity associated with it, then what are you buying?
So it's a complicated assessment. Nothing seems to be getting easier.
DR. LENTINE: Can I ask a question, Dr. Morris?
So I really wanted to thank Dr. Mooney and Dr.

Page 438

Stegall for those excellent presentations.
And Mark, you began by mentioning some disincentives to consortium, why they're very difficult to build, not just in relation to industry, but other factors. So I just wanted to get your take on what's your vision. How do we advance to become more like what Dr. Mooney describes? And do you envision it's going to take us 50 years, or is it more imminent on the horizon?
DR. STEGALL: (inaudible - off mic). So I think that -- I mean, I'm -- I don't know what the right formula is. We just decided to get started. And I think that was the first thing.
And then we now are in the phase of trying to really get studies going. We'll do kind of whatever. But I -- we submitted, you know, things like NIH grants and things like that. And I think that, at some point, we would like to see -- there has to be like it's happened with NCI. To do something like this, there really has to be money for the infrastructure because you just can't go year to year trying to get money, even grant to grant trying to get money. That's not

Page 439

going to work for a consortia. It's just not.
And so I think at some point, whether we get an endowment, whether societies pull together to do this, whether there's a rich patient at the Mayo Clinic that's willing to give us money, I don't think we need the kind of money NCI does.
We partner with other areas even in our sphere of diseases. I mean, it seems like to me that FDA has kind of moved a little bit out of cancer now, and they're moving in these public-private partnerships are in other areas. And it's great.
So I think the only thing is transplant just needs to be at the table like we are today, be included in the conversation. We've been pretty much early adopters. So I think -- that's my hope.
And then like everything else, it gets better when there's more input. So I'd be happy to talk to anyone in the room about maybe trying to do something bigger. But bigger is not always better. Like you found out, there were a lot of -- I heard about all those horror stories, my friends, you know -- they cut us out, you know. And if you're just not performing,

Page 440

they cut you out.
So there is -- it's -- I think they found that over 60 years -- it may take that long for all those people with the big egos to die.
(Laughter.)
DR. STEGALL: And the collaborators -- and the good thing is the next generation of people that I'm training are collaborative, right? It's not a big deal to them. They're not trying to be as famous as all the rest of the people up here, me included.
DR. LENTINE: And the concept of including not just academic centers, but even moving into the community, do you think that's part of the equation for our field or --
DR. STEGALL: Well, transplant's not. It -- transplant's actually -- it should be really easy, right? It's really 30 -- I think something like 80 percent of the transplants are (inaudible) 30 percent of the programs in the country -- or 30 programs. And I think that -- so one could do really good clinical trials.
You don't need every single -- but I think

Page 441

that cancer may be a little bit different. The only thing about is getting, really, a lot of the limitations, right? I'm sure the way we do a lot more local therapy because people don't want to drive 150 miles every time to get an infusion, right? So there's all those issues about just logistics of doing clinical trials.
It would be great if we could do something more local for patients because people travel a fair ways to get a transplant. Does that answer your question?
DR. LENTINE: Yes. Thank you.
DR. STEGALL: Thank you.
DR. MANNON: I mean, I think one of the differences between oncology that's very stark is the division of the institute support for NIH for the -- for our patients. And there is an implicit or, you know, a well-spoken difference in funding, that NIDDK funds graft failure and graft CKD. And NIAID files immunological outcomes.
And until those two things emerge -- and it's not going to happen any time soon because we just met

Page 442

with them a few weeks ago on behalf of one of the societies -- I think there's no federal mandate. I mean, there's -- we can't even get immunosuppression after three years paid for, Kristine (sic). So I'm not sure that they're going to see this as a hallmark.

I think the public, you know, was responding. The death rates were scary. And almost -- I mean, I think that having a line item in a federal budget is a big difference.

I think communities are really -- you know, I think we can't even get the academic centers to get on board. AST tried this in 2003. I think that was the first year I was on the clinical trials committee with Flavio, and there was tremendous pushback. And we even had members of the -- do you -- I mean, I don't know if you remember. Some of you all may remember that. But people were angry. They were like, well, I'm not going to be included, so I'm not going to be like a blue ribbon.

So I -- you know, I think it's something worth exploring because I don't think that the -- like, first of all, we have CTOT. We have -- you know, and that --

Page 443

it -- I hope there will be an RFA in two more years. And that has really -- there is infrastructure, but we could definitely use more money. And I -- you know, and I'm hoping there's an RFA. I mean, they keep talking about it. But I think that that's one big difference, that we don't have the budget, the funding. And we have smaller patient population.

So it may come from the -- again, why are we here today? Because the societies pushed for this. And it was in -- less threatening, and I think it's worth going back and saying to societies let's try this again.

DR. STEGALL: I'm sure that --

DR. MANNON: And maybe not say blue ribbon -- you know, something more generic like cooperative, you know.

(Laughter.)

DR. MANNON: With junior faculty-- maybe developing their careers that way because that would be more open.

DR. MORRIS: Larry.

LARRY: Yeah. Mark made a comment about what

Page 444

we might call the 80/20 rule. And it's true that 80 percent of the transplants go on in about 20 percent of the centers, more or less.

In a sense, whenever pharma does a multi-center trial, it is establishing a collaborative study group. So there's a lot of -- there's a template for that and a lot of models. One of the real problems, though, is that, even at the "busy centers," recruitment often does not meet expectations. So it's typical, let's say, for a Phase 3 trial in transplant with 6 or 800 patients.

We might have 80 centers, and it takes too long to recruit a trial like that with the BEST efforts because, even the busy centers often don't meet their recruitment targets. So we have --

(Crosstalk.)

LARRY: They're too busy. If you tell us 20 patients in six months, we know that's 10 patients in 12 months.

DR. STEGALL: So I -- but I think that we -- I have a hope that you could probably put together a clinical research trials network. I know -- say it has

Page 445

to be the MTA (ph), that individuals in that network, one of their jobs is to get patients enrolled and to do a good job with this.

LARRY: Right.

DR. STEGALL: And it probably failed the first couple of times. But at some point, you'd probably find someone in there who really wanted to do that and had time to do that. If you paid their salary and some of the infrastructure salary of the people they worked with, I would guarantee you that it would work better than the current system.

LARRY: Well, I absolutely agree. I agree with your model.

(Crosstalk.)

LARRY: But it's just an offering from the real world, you know.

DR. STEGALL: We'd also need tissue banks and all that sort of stuff that -- yeah.

DR. MORRIS: Peter I think is --

UNIDENTIFIED MALE SPEAKER: Peter and Mark, I have the pleasure to work with incredibly talented people at CareDx. I just wanted also to have a

Page 446

positive note because, right now, within six months, we have recruited 27 centers in the United States with our registry study. It's an observational study. But 27 centers in 6 months is quite incredible.

And you know, that's the force of transplantation. We are talking about bringing the village together. And having the ability to recruit 27 centers in any other therapeutic area, that's pretty astonishing, especially when you're thinking about, you know, world-in-class tertiary care centers in the United States.

So just on a positive, there's a lot of force in transplantation, and we should use this because, here around the room, if we hit our recruitment targets, which is a 1,000 patients, within 18 months, that's pretty phenomenal.

So I wanted to thank you for recruiting, but please continue to recruit because it's right, Mark. We need the recruitment targets in order to have the right ends.

Thank you.

DR. HERNANDEZ-FUENTES: So I wanted to comment

Page 447

on the recruitment problem. In the UK, I think we have benefitted from an initiative that the NIH have put together where they were paying the hospitals that included patients in clinical trials that had certain levels of political (ph) criteria.

So for the -- in the -- in not only -- so they were priming (ph) -- investigator led the studies, but also the ones that have public funding like MRC (ph) funding. So now in the UK, the hospitals get funding that support that infrastructure, paired patient included in one of these studies, and (inaudible) observational studies. So they have observational studies, clinical trials. And this is all grant-funded but also commercially funded.

And I think it is an important totally game changer. So in the first study, we could only recruit 70 patients, or something like that, in five years. The second study -- I couldn't cope with the amount of centers that wanted to participate in the study. It was very -- you know, I had the program manager was completely overwhelmed. It changes things.

So I think there are initiatives that the

Page 448

societies and the federal government or the federal funding or -- there are initiatives that are able to change the game in recruitment levels, and that would really accelerate research.

DR. MORRIS: Rhia (ph).

RHIA: Yes. I'd like to make a comment about the clinical trials collaborative and compare it to what's going on in oncology. For those of us that have worked in transplant clinical trials for so long, I think we've learned things that make them work well.

I think, first, is having a clinical research group embedded within your clinical team allows you to identify the patients more quickly and more readily.

The second thing is something that's different about oncology. You get a diagnosis of cancer, and you're not deciding to make a treatment decision that day. There's time that progresses. In transplantation, certainly in the case of a de novo transplant, you really don't have much time to decide that you're going to put them in a de novo trial. And even in the instances of where you have a rejection episode, most people want to implement therapy within

Page 449

24, 48 hours, which we've begun to think is appropriate, and it is.

So having the logistics worked out that it's going -- that -- and understanding the differences in transplantation from some of these other cooperatives is going to be very important. And in my opinion, it has been having the clinical research people embedded within the clinical teams because there's no way that you can have all of the providers knowing exactly what studies are open when and, basically, stopping their decision long enough to say, hey, can we consider enrolling them in a clinical trial. And that's essentially what you have to do in transplantation.

DR. MORRIS: Yeah, Peter.

DR. NICKERSON: I guess I'd like to hear on one other area that could be important, and that's the economics of transplant care. And the economics of transplant care in this country tends to favor very short-term outcomes. And there are many centers. If you take those 80 -- those 20 percent, many of those centers are hesitant to enroll what they might perceive as patients in the higher-risk trials because that

Page 450

could impact their outcomes.
And I think that that's a solvable problem if we, you know, think about how we reimburse. And I just was wondering if that's something people think is relevant.
DR. ALBRECHT: So Peter, thank you for those comments. We should pause for a while because now we need to get to the open public session.
And Shannon Woodward is going to moderate that session. Do we know who the first speaker is, Shannon?
DR. WOODWARD: Hi, everyone. And thank you so much for hanging in there with me.
So right now, I'm just going to go over a couple of things to help facilitate this session for open public comment. So right now, the purpose for this part of the workshop is to allow opportunity for individuals in the audience to add to the dialogue or comment on topics other than the main discussion topics of the workshop.
Keep in mind that neither FDA or Critical Path Institute will be addressing the comments that we hear during this session. But all of the comments are being

Page 451

transcribed, and they will become part of the public record.
We'd also like this to be a transparent process. So we encourage you to note any financial interest that may be relevant to your comment. And if you don't have any, you're welcome to state that for the record as well.
We collected sign-ups before the workshop and also during the breaks as well, and we currently have five speakers signed up.
So as I call your name, you're welcome to approach the microphone here in the middle of the room. And also, there is a two-minute time limit for each speaker.
I don't have one of those Jeopardy-style buzzers, and I won't be screaming at anyone too hard because it's the end of the day. But what I will do is kindly nudge you just to let you know that you're coming towards the end of your time.
And if your name is called and you're no longer interested in sharing your remarks, just let us know, and I'm happy to move on to the next person.

Page 452

So with that, our first speaker is Kevin Fowler. Is Kevin still in the room? Nope.
Okay. In that case, I will move on to Stanley Rose (ph). Stanley Rose?
(Crosstalk.)
DR. WOODWARD: Oh, okay. Next, we have Robert Woodward. Robert Woodward.
MR. WOODWARD: Sorry. I had earlier in the week expressed that we may give a comment, but I decided not to.
DR. WOODWARD: Thank you.
Next, we have Brandon Keeting (ph). Brandon Keeting?
(Crosstalk.)
(Laughter.)
DR. WOODWARD: Oh, wow. Swapna Kakani (ph)? Swapna Kakani? No. Okay.
Well, this is a historically short session.
(Laughter.)
DR. WOODWARD: I think that's proof that our workshop has been very interactive. So thank you all for your time.

Page 453

(Applause.)
DR. ALBRECHT: Thank you, everyone. I think that concludes today's session, and we look forward to seeing you tomorrow morning at 8:00 o'clock to start our patient-focused drug development day. Thank you very much. And thank you to all the speakers and attendees.

Page 454

CERTIFICATE OF NOTARY PUBLIC

I, Michael Farkas, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

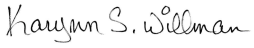
Michael Farkas
Notary Public in and for the
State of Maryland

Page 455

CERTIFICATE OF TRANSCRIBER

I, Karynn Willman, do hereby certify that this transcript was prepared from audio to the best of my ability.

I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of this action.

10/09/2018 
DATE Karynn Willman

&

& 1:5,12

0

0 90:4 148:3,5 212:14,14 371:1 373:13
0.1. 237:17
0.43 139:19
0.45 152:1
0.5 236:22
0.5. 281:6
0.52. 286:12
0.54 147:21
0.58 147:20 152:1
0.7 236:21
0.7. 236:19
0.72 148:5 152:2
0.73 148:5 152:13
0.73. 152:2
0.75 237:17
0.77 240:18
0.786 241:7,7
0.8 236:19
0.82. 238:1
0.83 241:6 264:9
0.85 152:13
0.856. 160:10
0.875 236:19
0.89. 237:11
0.9 237:22
0.91. 244:9
0.967. 240:19
0.977 241:7
0.982 240:18
0.99 244:9
08 219:13 229:4 233:2 254:21
09 3:10 181:19 254:17 359:12

1

1 5:2 29:9 37:11 50:19,22 51:14,17 51:17 53:2,22 94:13 98:9 104:16 126:16 140:8,11 140:14 144:14,18 144:19 145:1,3,6 147:14 148:3,5 192:6,9 193:8 224:3 244:5 295:3 297:19 310:10 332:13 371:9 382:7 403:13 416:5
1,000 170:14 310:10 326:2 401:3 446:15
1,500 400:11
1.1. 136:16
10 5:11 23:18 26:7 42:7,9 76:8 86:14 87:3 90:20 118:1 118:2 139:3,6 146:1,2 153:2 172:15 178:21 193:19 224:1 249:8,13 294:9,18 297:6,9,10,21 299:1 305:20,22 319:14 353:15 357:4 368:9 369:1 392:21 398:2 401:12 403:22 412:9,10 415:9 416:1,5,19 431:3 444:18
10,000 386:11
10/09/2018 455:12
100 186:14 224:14 310:11 366:4 373:14 403:20 404:2 407:22
101 243:8
10405 144:7
10903 1:14
10:45 137:8
11 5:13 144:12 148:3,6 260:10 374:15 425:19
11,000 425:16
110 240:14 241:11
113 240:13
12 5:14 148:3,6 153:6 157:20 158:10 212:14,16 220:18 226:9 234:19,19 242:19 371:1 375:1 444:19
123 208:13 209:7
1250 1:21
127 240:8,18
129 221:17
13 5:15 226:8 373:8
130 222:15
13394 454:16
137 5:16
138 5:17 221:15
14 5:16 285:20 318:12 399:12
14,000 385:12
15 5:17 9:4 10:15 40:3 74:22 82:9 125:4 167:2 173:17 178:21 202:15 249:8,15 258:6 294:10 295:2 297:6 303:8 375:4 401:12,14 429:6
150 79:21 401:18 441:4
150,000 261:6
154 5:18
16 5:18 178:21 179:8 249:8,14 425:11
16,000 406:1
163 236:4
17 5:19 172:12 239:10 240:8,10 241:5 311:6 319:5 409:10
17201 455:12
18 5:20 76:1 261:5 279:7 446:15
19 5:21 89:15
190 318:17 324:3
191 240:5
1950 99:20
1950s 430:11
1955 409:4
1958 409:10
1966 409:16
1968 412:8,8
1970 412:9
1980s 424:10
1983 410:14
1990 410:21
1990s 424:10
1:00 201:12
1dr 144:8

2

2 5:3 37:11 45:11 45:11,14 95:13 102:21 123:22 124:8 140:8,14,14 145:9 147:15 148:19 150:10 171:2 220:13 224:1,4 369:3 370:21 371:9 372:20 373:7,16 374:1 375:3 381:17,21 382:6 386:6 421:2
2,000 209:4 403:21
2.3. 220:14
2.4 89:21
20 5:21 156:17 176:14 203:5

204:22 211:5 220:12 230:3 271:21,21 303:8 324:6 406:2 430:8 444:2,17 449:20
200 334:20 403:22
2000 260:22
20005 1:22
2000s 10:1 412:3 412:14,14
2003 442:12
2004 41:17,20 258:8
2005 414:3
2006 75:22 385:22 425:15
2008 47:16
2009 80:9 86:9 369:2 412:8
201 5:20
2010 76:8 414:3,4 415:7 425:15
2011 10:16
2012 11:19 12:8 12:21 83:3 139:2 416:2
2013 13:9 15:15 16:4 34:14 84:10 385:22
2014 83:7 260:22 417:7
2015 18:13,21 334:14
2016 19:14,21 74:6
2017 20:19 76:1 101:22 108:4 174:13
2018 1:8 34:14 80:9 83:22 97:12 126:1 176:3 294:5 426:3
2019 176:3
202 5:21
20993 1:16
21 5:22 162:20 217:14 252:16 273:2 424:17,18
219 5:21
21st 61:1 111:2 119:7,20 132:14 340:10
22 5:22 373:8
23 5:7 170:15 173:14 226:8 235:14 236:18,18
23,000 261:5 405:20
233 5:22
24 212:14 220:18 224:1,2 234:20 242:19 250:10 255:4 267:16 449:1
246 5:19,22
247 236:3
249 310:19
25 84:21 152:16 193:5 311:2 324:3 425:19
250 209:8 424:14
256 6:2
26 20:19 425:12
27 1:8 446:2,3,7
29 249:18
299 6:3

3

3 5:4 32:3 37:12 95:13 123:22 124:9 148:19 163:19 168:21 170:8,14 175:10 201:16 212:14 220:13,17 234:18 241:10 332:13 391:12 397:8 402:12 404:11 421:2,5 444:10
3,000 168:19 221:3 227:1 404:2
30 83:10 90:12 91:7,17 94:10 95:12,22 123:21 124:8 134:12 160:17 163:19 203:5 211:21 304:6 311:2 376:6 399:6,8 440:17,18 440:19
300 6:4 79:2 400:12
31 1:13 90:7
314 6:5
326 173:2
328 6:6
34 252:4
35 5:8 152:16 193:6
350 1:21
36 212:15
366 6:7
367 6:8
37 93:5
378 6:9
38 320:16
389 6:10
39 250:7 252:18 401:8

4

4 5:5 57:5 126:16 224:1 240:8 299:17 416:5
40 36:4 41:12 42:10 83:10 94:10 95:12,22 123:21 124:8 152:17 193:6 429:4
400 222:14 404:11
407 6:11
41 148:3
42 262:6 375:19
45 152:17 243:9 250:6
450 6:12
46 142:10,11 174:21,21 240:15 373:7
47 222:22
48 90:1 449:1
49 269:2
4:15 366:10
4th 50:11

5

5 5:1,6 84:22 91:7 91:16 126:16 295:2 303:8 375:3 375:6 392:21 398:2 403:13,14 403:20 409:5
5,000 304:2
5.1 270:1
5.3 270:1
50 57:4 78:1 96:13 99:14 162:21 225:14 227:9 228:5 230:3 301:19 302:2 318:18 375:4 417:9 438:8
507 61:2
51 5:9 222:22
510 150:4
530 221:12
54 5:10
55 5:12 252:21
57 83:9 221:11
588 234:14

6

6 5:7 212:14,14 217:18 220:17 234:18 273:5 371:1 408:11 444:11 446:4

6,000 428:17 429:2
6,500 385:13
6.6 91:9
60 77:17 89:15,16 89:22 90:1,3 91:10 204:10 374:12 408:9,11 429:13 431:17 440:3
60s 418:9
61 221:10 222:21
62 429:3
64 240:15
65 135:16 401:5
69 179:8

7

7 5:5,8 240:8 371:1 374:22 428:18
7.5 374:15
70 86:19 252:19 425:9 447:17
71 311:7
72 5:13
74 236:9,15
75 226:11 237:17 252:18
75,000 419:14
78 222:20
795 249:22

8

8 5:9 57:5 135:16
8.5 141:21
80 222:20 225:19 227:21 236:15 252:18,18 310:14 310:15 373:5 430:9 440:17 444:1,12 449:20
80/20 444:1
800 210:5 428:18 444:11
80s 410:7
81 236:8
82 5:14
83 268:21
85 221:21 227:21
88 222:20
8:00 453:4
8:04 1:9

9

9 5:6,10 89:15 294:18 399:12
90 90:1 220:9 225:20 412:14
93 141:22 142:2
95 28:3 100:1 302:2 371:16 374:10
98 5:15

a

a.m. 1:9
aashe 166:22
aast 166:22
abecassis 2:15 5:21 122:7 186:7 186:10 219:7,11 233:15 251:2 292:21 294:21 295:15 296:22 297:2,8,12,22 341:2 356:2,4,6 356:10,18,21 357:1,6,8,11,14 389:15
ability 75:15 87:18 94:20 186:17 195:7 235:16 446:7 454:7 455:4
able 8:1 25:19 30:16 33:11 40:22 43:12 52:1,6,17 59:6 61:21 63:22 66:20 71:18 75:7 81:7 109:4 115:4 128:6 129:6,16 131:9 137:10 148:2 153:7 169:6 170:16 176:22 184:17 186:17 191:11,17 192:3 198:13 208:10 215:10,19 217:6 236:18 242:7 248:4 252:14,16 253:4 261:13 270:20 276:11 282:16 295:3 296:15 298:2 309:11 329:17 330:21 334:19 336:2 339:3,11 352:10 353:7 361:1,20 382:3 387:12 413:8,10 418:2,5 426:8 427:18 428:16,17 429:2,19 430:20 448:2
abmr 141:1 152:22 153:1 183:11 184:2,3 191:3 238:8 276:9 291:19 334:8,14 335:10 403:11 404:3
abnormal 135:21
abnormalities 163:12
abnormality 84:8
abo 255:11
absence 65:2 155:3 210:17 212:17 216:16 301:10 341:20 348:22 351:5 352:12
absolutely 68:17 109:19 114:19 115:19 162:12 181:9 353:1,8 355:13,17 445:12
abstract 247:4
abundance 109:7
ac 77:12
academia 7:19 77:1 205:22
academic 73:20 77:5 314:11 381:3 410:11,16 413:9 418:21 440:12 442:11
academicians 42:2
academy 167:9 314:5
accelerate 98:22 448:4
accelerated 106:7 140:1 329:17 330:11 331:7 333:11 334:2 336:10 338:22 432:10,14 433:4 435:3
accept 118:22 225:3 351:12
acceptable 94:14 95:13
acceptance 44:19 49:7 57:11,22 60:20,21 103:4 289:12
accepted 46:18 56:2 58:14 60:7 225:4 290:17 333:7 336:7
accepts 112:4
access 185:17 217:19 250:13,14 414:14

accessible 257:22 372:20
accident 55:21
accomplished 33:3
accomplishments 413:12,17
account 149:18 169:22 198:18 262:2 267:14 268:2 326:4,18 394:15
accounted 372:1
accounting 372:15 373:14 375:7 385:21
accredited 149:22
accrual 421:1
accumulation 212:22
accuracy 68:22 265:13
accurate 142:7 253:17,18 310:11 352:19 454:6
achieve 40:22 50:13 67:4 69:12 191:22 262:3 264:8 296:7
achieved 74:7 232:3
achievement 51:13
acid 138:15 143:21 144:10,15 146:11
acknowledge 87:5 87:12 97:9 177:11 219:22 231:20 232:22
acknowledgement 74:2
acknowledgments 232:22
acquire 107:22
acquiring 307:19
acquisition 233:4
acronym 73:11 75:17
act 61:2 111:3 119:8,21 132:14 163:22 194:12 340:11
action 9:14 14:9 15:9 136:11 305:5 454:9,13 455:7,9
actionable 232:4 354:12
activation 170:21 174:17 175:12 183:16 346:3
active 211:22 334:8,14 335:10 406:21
actively 20:16
activity 275:21 409:17
acts 174:20
actual 56:13 60:21 73:6 96:3 115:7 130:2,7 226:15 363:19 366:2 436:4
acute 77:13 83:13 94:13,18 95:16 96:2 99:4,11,13 126:13,19 157:9 157:18 158:10 160:3,7 163:6 164:4 172:1 191:8 191:11,17 212:19 214:12,17,20 215:4 220:4 223:20,21 236:10 236:11 237:3,4,15 237:16 238:7,8 239:9,10,15 240:21 241:15,16 241:20 242:5,5,6 242:8 249:5 250:5 250:11 251:15 252:8,17 253:2 254:3,12 281:5 349:14 356:16,17 368:5,7,11 369:20 376:12 412:6
adaptability 262:18 266:20
adaptable 263:14 279:19
adaptation 267:12
adaptive 45:11 101:18 404:19 405:10,10,14 409:2 420:9
adcs 147:19,20
add 113:2 124:1 130:14 131:1 187:18 195:19 249:19 261:7,9 310:3 346:15 351:21 400:18 450:17
added 82:21 245:8 266:8
adding 116:11 289:21 310:7
addition 251:4
additional 20:15 20:17 71:8 152:3 176:7 249:19 355:16 370:11 380:20 388:8 410:14
additive 237:9
address 15:15 17:19 36:17,18 42:3 62:15 63:7 68:22 88:21 89:1 202:7 204:16,17 212:6 257:12 258:8 272:2 368:1 407:14 414:17
addressed 118:12 414:19
addressing 9:14 40:16,18 44:14,22 450:21
adequate 91:20 228:14
adherence 362:17
adjudication 75:5 75:6 79:6
adjudications 80:21
adjust 88:2 192:4 261:14 278:7 355:11,15,21 359:10,11 382:3
adjusted 169:10 263:5 320:2 371:13,17 372:13 374:11,15 381:9 382:5
adjusting 151:6
adjustment 371:15 374:8 386:15 387:4
adjustments 94:4
adjuvant 423:11 432:22 433:4
administration 1:12
administrative 387:19
admissions 77:12
ado 55:7 73:5
adopt 131:9
adopters 439:15
adult 416:5 417:13
advance 19:10 141:10 411:4 438:6
advanced 19:9 68:3 426:19

432:21 433:2,16 435:7,11,17
advances 14:3 38:1 368:3
advancing 42:18 142:12 180:15 367:20
advantage 89:7 141:19 248:15
adverse 11:17 16:14 30:1,5,7 32:9
advice 108:10 329:12
advised 369:4,5
advisement 29:3
advisor 219:16
advocates 32:11
affect 11:2 169:12 169:15 175:12 195:9 288:20 300:16
aforementioned 23:16
afraid 194:1,2 341:21 342:16
african 169:8 170:15 174:3 176:13 209:22 401:14
afternoon 31:14 256:5 299:16 328:7 366:15
age 37:22 38:2 91:1 145:18 310:3 310:4 343:3 400:8
agency 33:13 60:1 60:19 104:10 110:12,20
agenda 53:19 108:19
agent 10:16 183:1 183:9 243:12 412:12 422:10 424:2 428:11
agents 14:10 30:5 239:22 254:17 368:18 369:5,19 373:2 374:1,2 382:17 386:13 409:9 417:22 422:12,12,15,16 423:14 431:7 433:10 435:16
aggregate 291:5
aggressive 282:7 282:12
aggressiveness 360:5
agnostic 428:8
ago 54:9 61:4 74:18 75:2 90:12 142:10 184:5 248:1 252:2 258:7 314:9 369:1 405:19 408:9 423:17 426:1 431:18 442:1
agree 27:11 102:1 102:11 183:20 186:16 287:3,16 292:21 314:22 339:14 346:16 348:10 349:22 351:8 359:4 393:10 445:12,12
agreed 28:7 287:15
agreement 234:5
agreements 50:1 107:4 430:21 431:4,14
ahead 7:2 9:11 60:12 66:3,6,12 67:19 71:14 115:20 122:6 195:18 251:12 295:12 366:13
aic 146:22 147:2,4
aid 29:1
aims 379:17
ajay 173:13 246:6
al 2:6
alabama 2:5 22:8 166:17
albrecht 1:7 2:3 5:5 7:2,3 13:22 21:2 23:3 34:22 50:17 72:22 115:20 131:17 132:12 134:2 291:15,17 299:6 336:17 337:2 338:3,13 339:12 340:20 358:7,10 362:10 366:8,12 450:6 453:2
albuminuria 83:22 84:11,13 85:4 96:15 126:6 283:6
alchemist 427:8
alemtuzamab 370:21 399:12
alemtuzumab 373:1,8,16,20 385:13
alex 105:6,15 107:8 128:22 129:10,18 131:3,5 269:7 276:13 282:19,20 363:7 396:20 401:20 402:6
alex's 184:3
alexandre 2:21 3:21 6:2 256:1
algorithm 208:17 221:2 222:1 267:12,14 364:15
algorithms 230:8
align 181:16 259:18
aligned 104:16
alignment 65:3
allan 10:1
alleles 169:12 172:10
alliance 394:13
allison 15:4
allo 213:22 401:18
allocation 34:8 261:10 277:22
allocations 131:13
allograft 22:14 139:1 140:18 154:10 173:1,12 204:1,11 211:16 212:9 234:9 247:12 249:4 254:5,15 256:3,11 257:8 259:20 260:6 270:9 271:2 330:2,16 331:1,17 332:4,21 333:3,3 333:17 334:8 335:4,11,17 336:13 337:20 347:3 368:17
allografts 176:4 213:1
alloimmune 138:1 143:7 149:3 150:16 166:18 185:21
alloimmunity 138:10 139:1,21 143:1,3 148:13,14 152:10 170:22 174:18 201:17 246:18 344:15,17 344:18
alloreactivity 144:13

allorecognition 139:9 140:8 143:10,11 150:21
allow 31:15 70:2 85:21 107:15 118:22 123:15 167:16 182:8 254:14 348:1 417:16 431:6 450:16
alloway 12:19 14:7
allowed 15:20 22:12 86:20 221:9 223:11 225:5,13 327:20 411:4
allowing 17:4 23:8 141:6 257:22
allows 62:10 64:17 259:10 282:6 379:22 387:21 424:22 427:2 448:12
alluded 161:20
alluding 226:15
alpha 175:10
altering 158:15
alternative 93:12 93:16,21 239:18 243:15 254:12 371:10 384:1 387:21 437:4
alternatives 434:18
alters 94:20
alzheimer's 43:8 43:10 44:10 131:7 134:22
amazing 12:3 15:3 74:11 86:14 126:15 197:1 225:14 398:6
ambiguous 177:3
ameeta 2:9 5:8 7:17 35:2 53:6 54:11 55:18 56:5 56:18 63:16 65:19 131:6 133:15
ameeta's 121:4
america 130:17 260:11
american 11:20 169:8 170:15 174:12 176:13 209:22 413:4
americans 169:9 174:4 401:15
amino 138:14 143:21 144:10,15 146:11
aminoglycoside 80:18
aminoglycosides 78:12
amount 16:20 21:14 51:9 64:21 90:17 95:12 309:8 309:18 447:18
amounts 188:4 306:14
amplification 248:16
amplify 362:10
amplitude 263:5
amr 175:2 178:6 208:19 218:16
analogous 59:8
analyses 77:18 165:19 177:3 179:5 233:4 377:16 380:21 381:22 382:20 387:12
analysis 69:14,16 70:13 80:11 86:21 89:5 92:10,11 106:16 125:19 128:8 129:22 130:14 131:21 150:8 152:6 159:19 168:7 187:11 213:7,10 213:19 230:6 236:13 244:18 247:14,18 250:19 269:16 278:9 284:22 309:3 319:12 324:16 327:17 336:12 353:11 381:8,10 385:19 414:1 415:8
analytic 95:7 118:18 150:4 380:19
analytical 67:9 68:11 149:20
analytics 58:13 118:11,12,13 221:2
analyze 89:2 225:11 323:18
analyzed 79:4 89:4
anat 154:3 177:15
ancestors 256:19
ancillary 44:21 134:19,22 288:22 317:20
andy 87:6 92:13
anemia 170:17 172:3
angiogenesis 422:12
angry 442:17
anil 20:1
animal 78:11
animals 78:11
ann 234:11
announced 426:2
announcement 33:12,13
annual 426:2
annually 87:9
anolytes 150:3
anot 301:15 305:12 309:1,20
answer 45:8 113:19 124:21 166:12 178:20 189:5 232:21 235:10 289:1 298:7 308:1 341:3 366:3 377:12 384:7 398:8 441:10
answerable 295:9
answered 380:3
answering 351:19 398:8
anthron's 248:1
anti 13:11 206:5 369:10 371:3 422:12
antibodies 369:3 370:21 372:21 373:7,17 374:1
antibody 11:9 130:11 139:5,7,8 139:10,12,12 140:1,2,10,12,13 143:13 144:2,3,13 148:12 150:19 151:8 174:19 175:13 179:19 207:9 209:15 212:17,19 255:8 298:22 306:14 328:4 329:22 332:9,20 333:9 344:20 398:14 401:18
anticipate 135:13

antigen 147:13 149:5 206:22 237:11
antigens 206:6,9
antimetabolite 375:21
anxiety 64:21
anybody 74:2 178:2,17 180:6 181:11 232:20 272:2 294:9 403:8
anymore 10:13 100:5 321:17
anyway 9:21 154:15 290:11 324:22
apart 147:14
aperio 401:17
apologize 74:1
apparent 24:14
apparently 368:15
appear 376:18 388:6 424:6
appears 382:22
applause 23:2 34:21 50:16 71:22 81:4 97:22 108:17 154:6 166:14 177:18 219:5 233:14 246:12 255:21 271:19 313:16 327:22 336:16 378:3 389:2 407:11 429:21 453:1
applegate 21:11
apples 33:21 34:1 34:2,3,4
applet 143:19 145:2,8,10 146:1 146:2,5,13 147:5 147:9 205:9 354:8 354:9
applicable 100:4 135:8,11 182:13 197:8 317:4
application 57:16 114:17 123:4 198:10 204:6 245:21 247:7 273:2 303:18
applications 10:14 122:3
applied 52:22 62:3 83:16 102:15 164:15 198:2 285:2 374:20
applies 189:6
apply 30:14 53:14 57:20 64:18 71:2 115:11 121:20 191:15 196:16 263:2 269:17 337:22 338:12
appraiser 259:16
appreciate 7:9 32:12 124:14 388:22
approach 15:12 37:19 38:1 45:4,7 45:15,15 50:9 57:1,2 59:15 61:5 65:14 82:13 131:2 132:15,18 152:11 200:12 233:18 253:5 258:13,13 259:17 262:18 328:3 340:13 341:6 370:6 394:11 409:18,22 422:22 451:12
approached 412:1
approaches 38:3,5 44:22 58:17 59:18 130:20 277:11 413:20 415:11
appropriate 46:19 95:1 170:10 339:22 417:20 418:1 427:6 449:2
appropriated 409:5
appropriately 354:2
approval 13:10 19:9 61:6 75:16 85:21 106:7,9 156:13 159:1 193:21 329:6,18 330:12 331:7 333:6,11 334:2 336:11,11 338:22 339:3,4 393:18 432:10,14 433:4 434:1,3,13 435:1 435:3
approvals 10:17 435:2,5,16
approved 10:16 25:14 150:4 187:22 188:20 189:1 194:4 195:10 198:22 240:13 242:13 330:4 372:20 434:13 436:1 437:9,11,12
approximate 248:22
approximately 77:17 79:20 223:3 375:4
april 20:19
arbor 234:12
arc 228:17
archdeacon 12:6 13:22
area 78:1 80:11 102:12 143:18 150:21 159:17 160:9 161:10 194:11 196:10 253:3 353:9,19 398:2 403:6 404:6 408:18 413:17 416:18 422:19 425:10 428:11 430:15 431:13 432:10 446:8 449:16
areas 11:9 27:21 67:8 98:20 102:1 143:5 144:12 194:14 337:19 342:14 383:11 408:20 409:11 410:22 428:10 439:7,11
arena 40:6
argue 231:12 347:17 360:3,9,17
argued 305:18
arguing 34:12 309:15 311:20
argument 13:18 14:6 309:17
aristacooney 324:17
arizona 399:11 402:3
arm 166:6,6 179:10 232:19 249:10,11,12 273:13 277:22 296:8 404:11
arms 115:10 179:10,11 272:17 429:5 436:11
array 209:5,6,10 322:2 328:14 369:21
arrays 304:1 321:20

arrive 329:13
arthur 16:13 17:7 154:1 399:15
article 375:16 405:19
articles 76:8 203:3
ascher 22:4
asco 426:2
ashe 142:14
asked 170:18 171:17 172:5 224:8,19 225:18 227:13 254:8 326:4 351:16 367:12 408:7 430:5
asking 52:12 110:18 111:11 117:5 122:13 270:16 291:19 297:2 350:13 351:10 362:13 364:20 409:13 436:7,8
asks 21:17
asn 20:16 84:3
aspect 41:15 54:21 56:16 59:2 65:13 68:22 69:21 174:16 198:15 264:19 265:16 288:21 405:3
aspects 39:22 68:21 74:11 131:11,13 139:15 150:6 362:17 431:5,6
aspiration 352:10
aspirational 352:21
assay 56:11,12,13 58:18,22 67:10,11 68:16,17 149:20 156:12,20 157:5,8 157:18,19 158:2,4 158:13 229:22 230:2 235:13 239:6,12 240:12 240:13 241:3 242:12,14,17 243:5 316:21 317:16 349:18 423:8 424:13,18 425:17
assays 159:13,13 190:17 217:1,2 235:5,12 245:2 305:10 316:21 349:18 365:20
assemblage 264:6
assemble 264:7
assembled 97:7
assess 88:6 128:16 128:19 143:6 154:9 158:18 171:15,22 218:4 259:19 270:5 279:17 374:20
assessed 436:10
assessing 82:11 85:8 192:18 259:22
assessment 99:17 110:11 116:13 130:5 134:10 142:16,21,22,22 149:3 155:9 164:22 218:12,13 235:15 251:11 257:20 259:11 262:1 264:12 266:10 269:22 270:6,10 273:10 278:10,10 280:11 280:16 285:21 352:15 437:18
assessments 99:18 155:8 262:10 351:15
asset 158:18
assign 268:19 274:12
assigned 405:6
assist 8:9
assistant 285:22
associate 172:22 224:9 281:10
associated 57:19 61:16 64:3 69:17 88:5 169:4 170:11 170:17 172:10,13 173:18 175:17 176:5 179:15 189:20 227:7 274:9 281:11 356:20 373:22 376:6,20,20 381:13 383:5,7 384:12 388:2 437:16
association 176:4 223:19 224:3 227:5 300:19 385:7
associations 168:17 372:14
assume 115:21
assuming 277:2
assumption 258:14 354:18
ast 12:10 13:21 17:12 18:15 19:22 21:11,20 142:14 246:22 442:12
astonishing 446:9
astrani 173:13
asts 19:22 21:16
atc 31:17
atg 399:13
atlanta 3:15
atrophy 263:22
attachment 119:17
attachments 119:13,14
attempted 312:11
attend 9:22 11:20 11:21
attended 10:7 17:9,17 18:21 22:9
attendees 20:15 97:17 453:7
attending 8:3
attention 81:3 154:13 185:12 262:16 267:22 271:18 284:15
attorney 454:11
attract 159:17
attractive 332:18
attributable 91:14 386:9 387:2
auc 152:1,13 221:20 236:19 237:11,21,22 239:2 240:18 241:6 243:1 244:5 244:9 250:20 281:5 286:11
aucs 148:4
audience 9:8 51:18 53:3 58:3 132:5 180:6 181:12 195:16 334:18 336:20 378:14 450:17
audio 455:3
audits 258:20
august 16:4 41:2
australia 332:6
authoritative 101:3
authorities 350:7

authors 76:6 77:2 233:5 341:15
autoimmunity 245:6 281:15 306:2
automatic 258:22
automatically 58:22
available 8:6,16 38:2 59:14,14 90:17 100:7 103:22 105:22 107:7 133:5 149:21 161:7 197:3 243:9 244:12 260:5 267:2 282:6 353:6 384:6 418:14 437:4
avenue 1:14
avenues 16:11
average 139:18 220:12 303:7,12 307:2 372:9
averaged 126:7
avoid 11:6 171:3 214:20 254:4 361:2
avoided 238:18,20
avoiding 204:13 337:14
avoids 190:5
award 83:18
aware 52:4
awareness 14:2
awesome 42:17 180:9 181:10 340:8 389:10
axelrod 4:11 6:9 367:14 370:4,17 378:1,4 389:3
axis 93:13 208:19 209:19

b

b 2:4 5:6,19 88:4 139:9 143:9,13,14 145:8 213:21 248:4 278:20 300:19,19,21 302:7 304:7,8,9 304:11,12,15,16 304:22 305:2,3,6 305:13,14,16,17 305:19,19 306:4,6 306:12,19,20,22 307:1,2,16 308:8 308:10,12,13,15 308:17,18,21,22 309:5,9,10,14 311:14,20 312:4 312:18,21 316:2,5 316:9 319:15 320:11,12,12,13 320:15,19,21 321:1,9 322:10,11 322:12,14
back 16:3 24:2 25:4 26:12 41:20 42:7,12 44:17 45:20 47:16,20 49:4 54:22 75:22 86:14 87:16 91:5 91:15 99:10 114:16 115:12 137:8,12 141:15 164:7 186:22 194:16 195:2,22 196:7 200:4 221:22 230:16 236:14 238:15 239:20 256:18 258:6,8 288:1 290:15 303:10,17 304:13 306:20 321:19,20 339:15 340:18,20 341:1 341:20 348:13 351:6 391:9 412:8 412:21 430:11,13 443:11
background 15:8 72:2 345:3
backward 125:18
backwards 125:19 296:13 328:3 335:18
bad 120:12 125:16 162:4 165:3 201:4 204:3 227:17 275:18,19 294:6 301:12,20 346:5 356:6,7 390:7
badly 155:11 357:13
bala 3:17 5:20 201:15,19 233:15 255:22 276:13 277:1 280:12
balance 87:14 278:17 360:14 368:2,19 376:12 379:19 380:4,7
balanced 278:1
bandwidth 18:20
banff 203:1 272:19,19,20 274:12,14 275:2 276:4,7,8 334:14
bank 394:15
banks 445:17
bao 3:18 5:22
bar 114:14,15 371:6
barbara 3:18 5:22 172:7 178:18 179:13 233:16 280:14
barbara's 359:20
barcelona 78:18 334:19
barrier 421:4
barriers 17:19 19:13,15 258:17 301:1
bars 252:9 324:22 325:4,5
base 70:22 166:3 267:19 377:20 410:16 411:1 417:15
based 1:4 27:4,8 73:9 85:21 95:5 111:17 114:21 136:5 148:19 149:4 158:16 166:7 170:7 178:8 178:14 179:1 180:21 187:2 189:1 199:21 200:4 201:8 202:19 223:16 226:6 228:13 238:5 241:9 244:18 247:5 265:15 280:18 291:4 292:17 296:9,20 297:19 300:4 306:21 307:6 308:14 336:6 349:13 358:21 371:4,4 374:17 379:18 381:15 383:2,7,13 383:16 385:1,2,14 387:2 388:9 426:9 426:22 428:19 434:13 435:19,20
baseline 71:7 88:6 88:12 89:14,17,22 136:7 148:12 226:7 234:16,17 239:12 242:14 302:16 332:12,13 335:8 387:4

basic 104:1 113:11 183:16 418:17
basically 26:22 27:4,6,10 29:10 29:13 33:14 37:8 37:18 41:8 45:11 45:12,14 48:10 50:12 57:3 59:22 60:6 87:1 89:13 91:7,22 92:6 95:19 111:16 112:19 116:14 154:22 163:9 187:7 205:20 213:18 244:3 263:21 273:2 298:8 334:13 404:1 449:10
basiliximab 372:21 385:13
basing 131:2
basis 10:22 22:21 52:13 143:11 329:17 333:6 336:10 347:13
baskets 34:4
bayesian 371:12 405:10
bch 3:18 5:22
bear 39:12 408:12
beat 198:17 405:8
began 78:13,20 432:19 433:10,11 433:14 438:2
beginning 25:21 34:18 88:11 99:14 199:8 378:7 400:15 418:14
begins 307:18
begun 449:1
behalf 246:20 328:10 442:1
behavior 362:17
behring 20:22
belabor 103:5 301:17 305:9
belatacept 10:17 178:8,16,21 179:1 249:10,11 268:9 311:19
belgium 240:16
believe 24:7 29:9 31:8 32:4,11 57:1 66:8 67:17 73:21 88:13 105:9 177:1 184:13 200:12 211:3 266:1 286:1 286:2,2 305:4 313:7 319:10 377:14 434:22 435:14
believed 24:6
believes 370:1
believing 346:9
bella 179:10
belong 365:4 418:21
benchmarking 27:4
beneath 211:13
beneficial 9:10 286:18 333:1 420:19 435:12
benefit 48:8 61:15 66:3 123:6 149:1 149:16 228:21 267:5 315:15 326:8 330:6,8 331:1,5 333:14 335:22 336:4 361:22 406:16 434:19 437:12
benefited 423:22 424:1
benefits 39:10,10 39:11 230:22 231:1 315:3 380:8 397:8 409:20
benefitted 447:2
benefitting 433:12
best 15:22 48:15 49:1 50:1 56:3 62:8,10 75:17 85:17 117:21 123:2 134:3 161:11 181:1 190:3 216:14 230:8,10 256:21 313:13 346:3 386:13 388:13 409:22 434:11 444:13 454:6 455:3
beta 144:7,14 172:16
better 14:15 38:7 54:21 127:1,1,1,2 127:3 146:9 147:4 147:10,17 148:7 155:12,13 166:8 192:4 193:12 198:8,8 203:9 214:15 216:6,7 218:4 229:1 279:7 279:11 282:7,16 282:18 286:13 288:7 289:17,22 302:3 308:22 311:15 318:14 323:3 338:7 340:1 343:5,12,13 344:10 347:11,14 364:10,18 381:16 381:22 382:7 387:14 414:1 420:16 434:8 439:16,19 445:10
beyond 70:10 182:22 205:15 337:17 358:3 383:21 385:15 387:21 388:19
bias 99:17 247:13 316:7,8
biased 286:6
biases 397:9
big 25:1,8 52:9 101:4 182:1 186:21 193:9 194:16 199:3 258:4 261:18 263:3 275:7 298:12 327:7 337:12,12 350:14 394:3 402:4,5,13 402:15,17 404:8 425:8 427:18 440:4,8 442:9 443:5
bigger 194:5 199:18 325:7 407:4,4 411:7 439:19,19
biggest 15:19 112:22 194:21 308:7
bill 21:11
billing 370:15
bind 248:16
binding 150:19
bioinformatic 208:16
biologic 10:11 85:12 159:18 229:10 306:8
biological 46:2 69:4 105:5 143:11 150:14,15 151:1 365:1,2
biologically 89:11 306:6 364:21
biology 4:3 150:19 183:16 323:8,11 399:18 412:17

biomarker 16:16 44:4,12 47:2,16 47:21 48:6,19 49:4,10 51:22 53:5,5,10,18 54:7 54:16 55:12,17 56:6,12,15,19 57:10,15,18,20 58:3,7,14,19,21 59:3,7,10,11,13 59:20 60:2,4,11 60:13,15,20 61:16 62:3,5,6,6,14 63:3 63:6,8,20 64:1,3,6 64:14,17 65:10,12 66:8,10,12,15,20 66:22 67:14,21 68:14,14,18 69:3 69:5,7 70:7,11 72:10 79:16 85:9 100:18 104:13 107:11 109:10,13 110:1,4,6,9,11,14 110:17 111:12 112:5,14,16 113:6 114:6,6,18 115:2 117:2 118:10,22 121:21 122:10,14 123:5,12 131:18 132:4,7,10,19,20 133:2,4,12,21 136:1 138:3,9 140:4 147:22 148:11,21 151:4 151:18 152:10 165:17 166:3,7 171:13,14,21 180:21 181:2 182:17 188:5 201:3 218:3 220:18 222:6 223:15 224:5,7,9 224:15,16,22 226:6 227:6 228:13 229:8,10 230:9,14,20 235:21 239:17 243:19,19 246:18 254:10,14 256:9 292:22 300:12,18 328:21 340:14 354:7 356:7,21 357:16,17,18,20 358:2,3,6 361:20 361:21 362:1,5 363:8,11,13 364:8 409:1 423:8 424:13,22 427:1 428:5 432:8

biomarker's 61:14

biomarkers 8:11 16:17 24:11 26:2 27:17 38:8 45:13 45:20,20,21 46:4 46:6,16 48:12,13 48:16,22 49:20 51:17,19 53:14 54:9,13 56:2,17 56:21 57:8,12 59:19 61:7,7,21 62:11,17,19 63:13 63:15 68:1,3,6,20 70:9,21 71:3,7,8 71:11,13,15,15 72:4,13,14,16 74:17 75:10,18 76:17,19 77:17 78:1,2,6,14 79:14 80:5,11,12 98:9 98:11,11 100:21 102:16 103:18 104:17,22 113:22 127:1 134:6,7,14 134:20 135:8,16 136:21 137:22 142:9 154:9,16 155:13 156:9 162:1 164:8 166:1 166:2,18 171:8 190:3 196:12 200:14 201:7,17 203:10 204:6 214:15 215:17,20 215:22 216:3,9 218:11,18 228:8 228:18 235:2,22 246:1 256:15 257:7 263:20 271:16 286:17 287:13 290:13 291:20 292:4 299:9,19 300:3 301:11 313:19 314:21 315:22 316:3,9 318:10 344:16 351:17,17 352:2 354:6 358:20,20 361:17 361:19 377:17

biopharma 19:18

biopsies 190:1 204:14,17,18,19 212:13,14,20 213:7 214:9 220:17,20 221:13 225:12 227:20,22 228:8 231:3,8,13 231:15 232:11,13 234:16,18 236:4,5 236:6,7,7 240:21 242:20 244:3 246:9 252:1 253:15 255:12 267:18 358:15 399:16,17 402:5 404:13

biopsy 27:9 156:3 162:12 202:19 203:4 211:6,15,18 213:9 214:1 215:9 215:11 216:1 217:17,20 218:1 220:8,20 221:17 223:16 224:2,21 225:2,8,9,17,17 226:8,16,22 228:1 228:6,21 229:21 231:6 232:17,18 242:18 247:12 248:5 254:5 262:10,10 283:8 297:20 318:21 330:13 332:1 356:6,18,19 357:5 357:17 358:5,18 398:7 401:16,17

biopsying 213:5

biorepository 221:15

biospecimens 414:16 418:10,12 423:19 424:9

biostatistician 179:6

biotech 430:12,17 430:18 432:2

biotechnical 414:18

birds 395:4

birmingham 2:5,6

bit 11:16 22:17 29:5,5 34:6 52:12 55:19 63:1,3 68:5 74:21 81:15 82:1 86:1,3 95:17 96:11 99:2 104:4 105:11 108:3 113:9 116:6 124:20 126:10 127:6 128:22 129:19 147:10 151:15 156:2 160:2 173:9 177:5 186:2 223:12 230:11 258:12 286:6 291:2 292:7

323:3 329:19 339:16 347:11 348:3 351:21 382:10 390:14 394:10 395:17 398:2 409:1 411:11 419:15 420:6,9 439:9 441:1
bite 118:4
bk 160:12 236:14 238:16,20 248:10 249:6,19,20 250:18 251:18,22 252:9,16 253:2,7 254:4,4,13 276:8 344:12 358:3
black 281:12 325:5 373:18 375:10
blah 274:20,20,20
blame 19:20
block 28:11 179:18 217:18
blockade 273:6
blocked 360:20
blocking 360:16
blog 41:3 50:7,10 50:11
blogs 41:7
blood 22:17 46:16 165:19 190:16 212:11 221:13 225:12 228:13 234:17 235:13 236:1 239:11 246:9 305:2 358:20
blossoming 10:2
blow 389:15
blown 214:20
blue 213:17 268:13 307:14 442:18 443:14
blueprint 15:9
board 11:21 18:14 18:21 52:11 442:12
bob 11:19 246:7 399:15
bodies 327:20
body 52:14 92:22 119:15
bonding 144:1
boom 86:16,16
bootstrapping 265:18
borderline 220:10 245:16 356:17
born 86:9
boston 379:2
bottom 28:10 62:21 171:13 197:10 222:5 232:13 237:12 238:7 414:4,22
bounds 290:19
box 79:12 250:14 251:16 252:6,9 281:13
boxed 8:5
brakes 141:6
branch 4:14
brand 135:11
brandon 452:12 452:12
bread 117:22
break 67:7 68:10 68:12 137:7,12,13 201:13,14 237:2 237:14 238:10 366:11
breakdown 352:8
breaking 238:5 248:13
breaks 13:14 451:9
breakthrough 194:10 435:4
breast 45:12 416:19 423:7,9,18 423:21 424:12,16 425:2,16
brennan 12:18
bride 22:10,19
bridge 101:11
bridges 233:9
brief 51:15 408:7
briefly 92:12 178:3 221:3 316:10 376:1 420:7
brigham 234:13
bring 103:14 106:1,17 110:7 169:16 197:12 202:7 238:2 295:18 314:5 339:15 362:19,20
bringing 52:20 77:13 154:3 218:17 314:2 446:6
brings 30:22 315:20 336:17 343:21
broad 33:13 65:7 167:1 199:2,4
broadbent 20:5
broaden 199:14 301:3
broader 108:7 183:1 195:11 199:15 394:11
broadly 46:18 158:20 182:13
broke 237:5,5
broker 431:1
brought 102:7 237:8
brumfeld 16:15
brunt 395:10
bryan 17:12
buckman 16:10
budget 442:8 443:6
build 55:1 83:3 261:21 342:19 353:2 377:15 438:4
building 1:13 123:11 389:6,18 424:17
builds 86:12
built 92:18 258:10 406:14,14,19 417:9
bullet 45:9 328:21
bump 293:18 344:9 346:4
bun 71:13
bunch 34:3 96:13 108:22 219:18 223:7 404:13
burden 353:20
burlington 4:12
burning 100:8
business 386:12
busy 221:1 396:11 396:12,13 444:8 444:14,17
buying 437:17
buzzers 451:16

c

c 2:1,10,13 5:2 7:1 9:17 18:13 20:7 20:21 21:3 23:22 24:18 30:12,21 33:17 44:20 71:13 102:13 107:3 109:9,21 131:7 264:8 267:15 269:19 300:9

c3b 175:1
c4b 175:1
ca 3:3,13
cab 90:13
caddy 242:2 275:6
calcineurin 161:21 162:17 168:10,18 179:1 345:15 346:10 369:8
calculate 280:6 317:5 326:18 336:2 364:14
calculated 176:14 319:12 322:1 326:1
calculating 260:5
calculations 404:22
calculator 388:11
calibrate 130:5 264:11
calibrated 266:5
calibration 136:2 262:17 264:15 268:18 269:2
califf's 11:17
california 3:12 202:1
call 9:13 13:21,22 14:9,9 20:6 35:15 44:7 143:19 189:16 213:12,14 216:1 258:10 263:20 285:3 319:1 377:12,15 423:20 426:22 428:4 431:3 435:4 435:8 444:1 451:11
called 12:5,8 14:11 109:22 144:6 150:6 173:11 181:22 215:5 219:17 222:10 232:15 234:8 270:18 279:4 357:17 366:19 369:5 374:9 394:12 411:15 423:16 427:8 428:14 451:20
calling 41:3 178:19 223:3
calls 16:19 18:10 52:11 81:11 396:14,15 402:14
cambridge 153:21
campath 381:16 382:10 386:6
campus 1:13 8:2
canada 3:7 201:21
canadian 395:5
cancer 11:7 45:12 193:18,21 250:1 287:8 346:22 368:14 376:5 396:9 407:14 408:6,10,20 409:6 409:11,19 410:1 411:10,15 412:17 415:12 416:19,20 416:20,21 423:7 423:10,12,18,18 423:21 424:12,16 425:2,16 426:14 428:7 430:7 439:9 441:1 448:15
cancers 14:16 384:20,20 385:4,5 417:3 428:22 429:3,4 433:17 435:11
candidate 85:17 104:7 114:6
candidate's 85:8
capability 130:3
capital 1:20
capitol 154:14
capt 2:11
capture 78:21 97:5 192:15 223:7 248:17 387:10 388:17
captured 44:3 79:4 387:19
car 200:3
carcinoma 376:4
cardiac 11:14
cardiology 11:18
cardiovascular 315:19 368:14 384:5
care 14:17 27:4 101:8 161:4 166:6 167:7 183:8 216:4 216:8 225:13 232:10,19 233:8 256:17 272:15,17 273:1 292:20 296:8 318:2 339:17 376:15,19 378:12 380:2,18 385:11 386:4 388:3 393:10 398:6 400:2 407:5 414:13 420:16 435:18 446:10 449:17,18
caredx 21:1 445:22
careers 443:19
careful 180:19 194:1 284:16
carefully 123:21 192:18 301:18
caregivers 348:11
cares 363:2
caring 379:6
carries 275:18
carry 53:21 342:19
case 49:19 53:4 64:13 69:13 77:2 121:9 175:14 225:22 229:10,11 239:13 371:8,15 372:14 373:14 374:8,14,17 375:5 375:7 376:2 377:2 379:13 427:2 435:10 448:18 452:3
cases 58:12 95:1 234:18 247:14 254:3 404:1 434:12,22
cash 375:13
catalogs 107:5
catalyst 205:20
catalyzing 35:5 42:13
catch 290:6
categories 63:18 64:5 85:12,16 93:8,20 107:11 148:17,18 152:22 193:5 381:5
categorize 158:6 280:21 370:20 371:2 432:4
categorizing 147:12 148:14,21
category 63:21 64:6 68:13 84:10 84:21 93:7 148:20 183:7 193:7 208:4 230:16 426:5
caterpillar 374:9
caucasian 174:5 209:22
caught 32:10

causal 150:14
causality 140:16 141:8
cause 84:10,14,17 139:1 159:16 172:4 206:20 220:20 277:4,6 330:1 376:4 382:11 383:8 399:16
causes 160:8 363:13
cavaille 4:7 6:7 366:15,16 389:3 407:12
cave 17:13
caveat 94:21 126:13 247:2 429:14
caveats 57:19 83:13
ccop 410:18
cd 174:21,21 320:15
cd16a 175:10
cd19 316:10
cd20 304:22
cd24 320:16
cder 16:7 35:10,18 41:4,6
cdisc 12:18
cdrh3 144:1
cell 130:10 139:9 140:20 143:9,10 143:13,14 153:9 156:18 172:13 175:6 183:4,15,17 184:14 207:10 209:16 213:20,21 213:21,21 251:21 252:15 253:6 268:8 275:16 300:19,19,21 304:8,11 305:1,17 306:19,22 307:1,3 307:16 308:8,13 308:21 312:4,21 316:2,9 319:15 322:10,12 346:3
cells 156:21,21 158:18 159:17 175:14 183:18 208:15 217:15 248:12 302:7 303:19,20 304:7,9 304:12,15,16,21 305:2,3,3,5,6,13 305:14,16,19,19 306:4,6,9,12,13 308:10,12,15,17 308:18,22,22 309:5,9,10,14,15 311:14,21 312:18 316:5,6,10 320:11 320:12,13,13,15 320:19,21 321:1,9 322:11,14,14 398:7 401:18
celltech 4:4 313:18
cellular 173:18 184:11 245:4 378:15 394:4
censored 277:3 383:4
center 8:13 32:4 32:13 35:9 122:9 154:22 158:8 170:5 173:22,22 174:2 212:15 224:22 233:2,12 234:10 255:10 266:3 269:11 275:1,7,8 360:7 371:7,9 372:2,16 373:14 374:6,10 374:12,17 375:1,4 375:7 376:1,18 377:1,1 378:19 382:9 388:16 391:11 394:12 395:11 397:6 402:12 403:22 409:7 444:5
centered 377:20
centers 73:20 130:17 169:1 174:2 225:3,3,12 232:12 246:4 259:7 260:10,11 261:3,5,9,22 265:9,21 266:2 267:15,17 274:22 276:7 279:16 366:20 370:3 371:17 372:6,10 373:13 374:6 378:18 379:5 381:3 383:12 385:14 389:6 390:3,11 392:11 393:5 410:11,22 413:9,10 440:12 442:11 444:3,8,12 444:14 446:2,4,8 446:10 447:19 449:19,21
central 143:21 327:17 415:16,17
centralized 393:9 415:16
cents 196:9
century 61:2 99:13 111:2 119:8 119:21 132:14 340:11
ceo 17:7
certain 51:9 70:22 81:8 104:12 115:2 115:10 117:11 120:15 159:7 172:22 178:7 185:8 189:6 193:20 270:14 296:7 312:7 318:22 323:6,8,10 393:16,17 394:21 421:2,4 422:4 426:15 430:21 431:5 432:20 447:4
certainly 23:21 100:3,5 101:2,14 101:19 106:2 119:16 169:17 238:19 293:20 299:16 308:1 343:5 363:3,5 386:6 394:9 434:12 436:18 448:18
certainty 58:1
certificate 454:1 455:1
certify 454:3 455:2
cetera 65:15 91:3 206:16,21 209:22 211:11 215:7 220:21,21 233:8 244:11 283:8 337:17 358:19
cfast 12:18
cg 275:17,18
chair 2:20 29:21 98:9 376:15
chaired 17:13,14
chairing 29:10 103:18 366:18
challenge 86:3 185:2,14 337:11 337:18 352:5 366:9
challenged 78:4
challenges 36:12 36:16,17 102:16

102:17 105:4 113:1 366:19 390:2 408:2,18,22
challenging 37:21 421:8 422:19 423:13 428:15
chance 199:5
chandraker 20:1
change 31:4 41:22 59:17 81:15 83:7 84:1 85:7 88:7 89:3 90:3,5 96:15 99:20 111:15,16 126:5,15 151:2 206:20 210:22 220:12 232:6 263:13,16 307:21 321:11,14 328:12 330:21,22 334:7 334:22 335:2,9 350:1,10,13 355:16 362:1,1 365:15 433:10,14 437:8 448:3
changed 34:8 99:21,22 100:3,11 188:13 246:19 307:8,10 320:7 321:15,15 410:8 419:16 422:10,21
changer 447:16
changes 65:14 94:19 136:7 166:3 172:4 265:2 272:18 429:18 447:21
changing 19:6 50:9,10 82:2 83:22 100:19
characteristic 46:1 428:9,20 435:13
characteristics 67:11 89:14 372:5 372:8 379:15 388:10 390:5 412:19 416:22 417:19 419:12,19 419:20 423:16 426:17 427:5 428:2,13 433:13 436:20
characterization 26:3
characterize 62:11
characterizing 69:2
charge 19:12 414:6
charges 16:9
charlies 365:15
chase 74:6
check 17:2 48:1 294:16
checklist 229:5
checkmark 229:5
chemokine 159:9 159:11 160:7 163:20
chemokines 159:15,16,20 160:1,22 163:13
chemotherapeutic 409:9
chemotherapy 409:6 412:13 422:11 424:3,6,7 425:7,13,20 426:7 426:12 427:15 433:1,6
chicago 2:16 219:9
chickee 22:11
chief 4:6,14 12:1 328:8
child 300:11 412:17
children 412:6,9 412:19,21
children's 411:15
choice 368:3 374:13,17 375:5 376:18,20 377:5 377:20 378:19 379:7,10 385:11 385:15 387:3 390:2
choices 372:20 388:12
cholesterol 91:3
chong 4:5 6:6 328:2,6,8 345:1 361:12,14,16
choose 68:14
choosing 272:14
chose 90:18 206:3 424:18
chris 153:17
chronic 71:5 84:6 228:17 234:9 319:1 329:21 332:9,20 333:8,9 344:20 345:14,19 345:21 346:7,9 368:16 369:20 376:12
chronical 328:4
chu 2:22 3:21
chuckled 294:15
churn 51:9
circle 230:11,12
circulation 176:3 264:1
circumstances 95:14 159:7
circus 74:13
cisplatin 78:12 80:17
ckd 81:17 82:7,7 82:12,20 84:8 86:8 87:20 88:4 95:20 97:10,12 138:5 333:8 441:19
claim 199:2,4,10 199:15
claims 370:13,15 381:5 384:8 385:22 387:19
clarification 135:6
clarify 31:9 122:8 132:12
class 62:5 63:21 140:8,8,11,14,14 140:14 171:4 224:3,4 422:10,15 422:16 433:10 435:16 446:10
classes 62:16,19
classic 141:13 393:7
classical 393:8
classically 144:17 153:10
classification 246:1 267:5 273:8
classify 251:14
clayton 332:5
clean 208:11 269:10
clear 10:10 12:12 12:13 13:2 14:4,5 16:17 29:22 33:5 85:12,20 86:5 100:12 168:7 196:13 224:3 227:5 228:7 390:10 433:11
cleared 31:5
clearly 63:14 77:1 77:20 79:10 81:13 101:12 102:17 104:18 112:16 144:19 145:21 170:1 190:19

191:2 197:16 198:12 236:22 237:14 238:11,22 242:7 244:19 245:8 254:20 354:8 385:11 386:14
click 40:14
clinic 2:8 4:12 158:21 199:13 210:21 389:5 397:11 401:7 402:2,2,3 439:4
clinical 4:14 19:7 32:4 38:5 43:10 44:10,22 45:2,6 47:18 51:21,22 52:1 54:17 59:4 62:7 63:11 64:15 66:10 67:13 68:10 69:3 79:22 81:17 82:7,19 85:15 87:22 91:19 92:10 92:11 93:3 95:6 97:4 98:11,12 101:17,18 104:1,2 105:1 106:6 115:3 117:10 118:20 121:8 122:1,19 125:3,6 126:3 129:9 130:1,9,12 131:12,19 133:14 133:18 134:10 135:18 140:21 141:2 142:16,19 148:19 149:2,22 151:18 153:10,13 155:3,20 156:8,11 157:14 161:1,4,15 161:16 162:8 165:8,12 166:2 167:7 169:21 170:3 176:12 178:22 180:20 181:15 182:4,7,8 182:20 186:12 187:20 188:6 189:4 191:6 198:6 204:15 211:14 212:19 219:16 223:8,16,20,21 224:4,6,8,11,13 224:15 227:5,6 229:9 232:6 234:11 235:20 236:6,20,20 238:21 239:4,10 240:20 241:20 242:22 243:17,22 247:5,6 251:7 255:16 258:2 260:20,21 261:7 263:12 265:10 267:2,2 268:10 269:6,9,15,20 276:15 280:19 281:4,13 290:8 295:19 306:3 307:7,9 309:22 318:9 319:9 321:17 325:18 328:20 329:4 330:6,8,22 331:5 331:13 332:19 333:14 334:3,12 335:16 336:4 337:8 340:14 361:22 362:5 363:13 370:10,16 371:14 373:9 376:3,21 377:9,9 377:18 378:1,20 379:10 380:10 382:13 387:6,10 389:6,18 391:8,12 391:16,17 393:4,6 393:13,15,19 394:2,19 397:8 401:4,15 402:17 403:7,17 404:3,7 404:10,20 405:20 406:5,10 407:8,15 407:20 408:17 409:14,17 410:17 413:5 414:12,15 417:8,10 418:4,10 419:14 420:4 421:17,19 423:18 428:10 431:18 432:1,14 440:20 441:6 442:13 444:22 447:4,13 448:7,9,11,12 449:7,8,12
clinically 58:10 100:16 105:8 143:6 147:7 160:20 216:21 222:8 239:17 307:15 310:13 317:4 340:2 434:21
clinicaltrial.gov 260:14
clinician 180:10 285:14 286:5
clinicians 88:17
clinics 136:13
close 7:13 8:14 22:4 154:1 200:22 201:11 318:1 335:11
closely 23:13 71:11 77:12 78:3 173:10
closer 355:5
closing 97:9
closure 210:13
cluster 208:2,6
clustered 376:22 378:2
clustering 308:19
cni 154:10 168:10 249:11 276:9 344:8
cnis 320:21 322:21
coa 44:4,12
coalesces 291:10
coas 134:9,13,15 134:20
code 250:1,3 255:8 271:1
codified 56:2 61:1
codifies 61:5
codify 67:19
coefficient 286:6
coefficients 270:4
coffee 8:6 205:19
cohort 89:2,3 139:3,16 145:1 151:12,14 170:15 173:3,11,12 174:1 193:6 220:10 221:14 222:7,21 223:1 229:19 240:5,16 241:2 244:8,9,20 251:3 255:3 260:18 265:4 266:5 285:3 302:21 305:9 307:18 317:1 318:12 334:5 361:3 404:1
cohorts 86:19 87:12 89:5,15,16 92:8 95:6 152:7 240:19 242:11 243:21 257:16 259:2 260:19 271:6 373:5
coin 67:12 243:2
coincidentally 316:1
coll 4:7 6:7 366:15 366:16 389:3

407:12
collaborate 42:18 415:15,19
collaborated 173:14 251:2
collaborating 36:5 40:13 153:20
collaboration 7:13 36:19,21 37:4 38:19 41:8,22 82:16 87:17 97:11 154:2 234:4,13 255:18 261:18 334:17 394:18 407:16 410:10 429:15
collaborations 82:8 97:17 153:22
collaborative 9:18 24:10 39:2,21 42:18 48:13 49:13 50:6 400:16 402:8 410:6 431:4 440:8 444:5 448:7
collaboratively 35:17
collaborators 377:21 396:11 440:6
collated 81:1
colleague 377:22
colleagues 14:7 21:21 22:3 156:7 166:13 225:18 246:20 328:11 370:4 399:7
collect 179:3 393:1
collected 31:18 32:1 388:17 418:10 423:19 451:8
collecting 76:18 77:18 389:20,21 389:22 397:4 414:15
collection 80:3 251:4 310:3 319:3 398:5 402:16
collective 398:16
collectively 35:17
collects 381:2
college 314:12
collegial 120:9
color 78:4 208:3
colors 84:11 163:14
colvin 246:7
combination 208:3 215:21 417:21
combinations 412:12
combine 105:8 210:7 266:16 271:9 273:10 384:16 431:7
combined 245:12 409:22 411:22 417:22 427:13
combines 370:9
combining 218:2
come 9:13 22:15 48:15 82:4 99:3 100:13,15 107:19 109:2 112:9 115:11 129:15 138:12 142:11 146:19 154:12 159:17 162:16 165:16 185:6 186:17,21 203:9 221:22 236:14 259:7 291:16 303:10 326:22 348:21 350:6 368:12 393:17 398:7,21 400:1 443:8
comers 191:13 193:7 237:2
comes 28:1 40:20 60:17 132:22 290:15 294:1 391:9 434:16
coming 7:3 10:13 51:5 82:16 99:10 260:11 287:22 345:7 348:2 353:22 407:1 451:19
comment 8:15 9:2 121:3 123:9 131:3 132:3 133:16 184:21 186:7 188:11 189:10 191:5 196:11 198:20 201:1 230:17 287:20,21 288:13 289:6 291:16 292:3 339:14 341:2 342:18 345:12 349:3 359:4 363:7 443:22 446:22 448:6 450:15,18 451:5 452:9
commentaries 92:14
commentary 31:9 408:4
comments 200:20 272:3 359:1 405:9 430:2 450:7,21,22
commercial 119:12,18 161:8 417:5
commercializati... 206:1
commercialize 159:2
commercially 447:14
committee 20:1 219:12 223:10 233:9 442:13
common 30:8 42:20 85:5 125:8 127:5 210:9 215:5 215:5 298:4 373:17,18 375:9 375:10,12,13,21 393:14 419:6,7 429:4
commonly 169:8 307:2 309:4 406:9
communicate 61:21
communication 342:5
communities 442:10
community 19:19 26:14 46:15,20 51:10,19 52:20 53:15 56:22 57:4 59:6 81:19,21 100:14,15 101:13 108:7,7 185:15 196:9 202:17 218:22 291:9 295:5 339:17 345:17 352:1 410:16,17,19,22 413:10 417:15 418:21 440:13
comorbidities 11:5 15:1
comorbidity 387:10
companies 15:11 17:9 73:21 92:17 106:22 192:1,8 218:16 402:14 430:5,11,18,19,22

431:5,10
companion 302:12
company 1:20 113:10 161:9 219:17 234:4 278:14 296:17
comparator 316:12 434:5
compare 130:5 144:22 146:21 216:4 278:22 371:10,12 405:18 448:7
compared 47:4 88:4 139:6 141:20 144:14 145:8,12 220:12 232:10 239:3 252:12 253:6 287:8 302:17 375:9 376:7 382:6 383:1 386:5,6,22
compares 236:20
comparing 144:4 147:1,2 253:2,5 285:21
comparison 70:4 146:8 229:19 303:5 312:14
compartment 207:19 208:16
compatibility 142:6
compatible 368:6
compelling 13:18 14:6 390:10,19
competing 262:17 277:11
competition 411:11
complained 100:10
complaining 34:12
complement 174:10,17,19 175:1,7,12,13
complementary 97:7 414:12
complements 291:11
complete 312:7 421:22 422:3 427:22
completed 80:21 80:22 418:3,16 423:5 429:6
completely 94:6,7 171:4 259:2 261:10,10 287:14 318:12 322:10 323:3 373:10 400:10 417:9 447:21
complex 44:22 45:2 68:8 167:20 189:7 257:16 341:7 343:21 365:19 373:1 403:7,9,18
complexity 158:17
complicated 91:2 168:4 177:8 199:12 315:7 437:18
complication 381:7
complications 368:13 370:17 379:21 380:8,17 381:4 384:4 385:17 386:15 387:18 388:3
component 67:7 129:21 130:12 244:17 260:3 263:18 266:13 268:4 275:15,17 343:6 352:9,11 420:3
components 256:16 275:11 287:1 291:12 352:18
compose 78:21
composite 105:10 223:20 224:2,11
composition 308:20
compounds 37:9
comprehensive 174:11 233:12
compromised 284:18
computational 144:6 146:6 150:8
conceivably 293:16
concentrate 56:19 428:21
concentrations 168:19 169:4
concept 63:12 112:5 116:10 142:12 162:3 189:4 194:5 205:17 206:3,8,18 318:7 340:4,9 440:11
conception 352:3
concepts 29:7
conceptualize 140:19
concern 13:4
concerned 229:15
concerning 244:6
concerns 431:11
concert 74:14
concerted 100:17
concise 61:14
concisely 74:22
conclude 270:3 313:3
concluded 95:7
concludes 453:3
concluding 89:10 369:18
conclusion 57:14 83:4,15,16 95:22 186:15 216:18 271:4 380:5 388:1
conclusions 58:4 95:19
conclusive 169:17 170:13 172:17 179:11
concordance 203:3 224:14
condition 329:20 330:4 331:8 434:17
conditioning 254:19
conditions 248:8
conduct 69:18 393:6
conducted 1:7 106:13 369:12 418:11 423:5
conduit 340:12
conduits 339:1
conference 8:8 342:9 396:14,15
confidence 85:2 355:19 371:16 374:11 426:9
confident 89:9 131:22
confidential 119:11,15,19
confidentiality 431:6
confidentially 431:6

confirm 69:22 78:8 120:6,7,10 173:14 254:3 414:11
confirmatory 70:1
confirmed 70:3 95:9 265:13 370:9
confirms 180:12
conflict 254:8,9
confound 344:22
confounder 312:16
confounders 344:11 349:6
confounding 321:22 382:4
congeners 10:18
congratulate 82:5
congress 409:5 410:15
conjunction 71:12 73:13 115:2 148:12
connect 106:19
consecutive 139:3 151:12 215:15
consensus 17:21 20:10 39:17 51:11 56:22 57:5 81:19 97:19 133:11 142:15 154:2 329:2
consent 17:20
consequence 323:7,16 332:19
conservation 285:5
consider 38:3 72:6 76:20 80:12 136:8 222:9 223:2 294:5 319:6,8 339:11 385:9 404:19 449:11
considerable 36:5 255:17
consideration 170:9 194:9 278:6 377:3
considerations 52:1 53:9 110:21 112:12 151:17 152:3
considered 52:5 70:9 72:4
considering 255:7
consisted 223:20 223:22
consistency 85:13 89:8 91:21 92:4 151:3
consistent 89:11 91:10 94:7 151:5
consistently 198:9 412:10
consists 174:1
consolidate 74:21 195:7
consolidated 416:4,7 417:12
consolidation 416:17
consortia 35:22 36:4 40:4,11,12 40:15,18 41:12 42:12,16 43:11 49:18 50:2 64:20 81:8 82:16 109:15 153:22 154:1 177:13,14 247:6 377:9,19 391:16 391:17,18,20 393:12,16,17 394:2,8,10 395:12 396:7,21 398:20 406:6 407:9 439:1
consortium 3:10 7:7,14 14:11 16:14,16 17:8 20:20 21:4 23:5 33:2 38:18 39:2 43:7,8 47:8,12,15 51:4 55:11 64:10 72:9 73:8 74:4,7 77:8 79:13,14 82:8 86:8,11,13 87:6 97:12,13 101:22 102:5 103:11 124:18 170:4 220:3 233:2 246:4 255:17 261:5 266:6 327:14 388:14 392:18 393:4 395:14 400:5 409:9 410:15 419:1,5 431:8 438:3
consortiums 400:13
constant 128:20
constrained 380:12
construct 48:6
constructed 102:5 104:3 227:15
consulting 138:19
contacted 18:12
contacts 22:4
contain 257:13 312:13
contains 285:7
contamination 250:22
contemporary 368:10
content 300:16
context 43:18,21 43:22 44:3,6,11 44:13 46:12 47:12 47:20 48:8,17 53:11 57:14 60:14 61:13 62:1,4,13 64:4,5,16 66:2,16 67:5 68:15 70:19 70:20 71:10,18 79:16 95:21 96:3 103:10,20 111:14 111:15,20 112:17 112:20 114:4,11 114:20,22 115:5 117:2 118:11 119:1 121:12,13 121:15 124:4 129:14 148:9 161:19 171:6,18 176:17 177:5 188:8 192:7 195:11 198:12 202:9 203:1 205:7 216:15 227:15 228:11 230:10 235:18 239:14 243:9 247:11 253:21 261:20 292:1,10 300:20 301:3,4 312:4 315:10,12,13 325:15 326:8 351:22 354:19 367:11
contexts 70:18
continually 150:12
continue 15:20 86:4 238:5 254:20 299:9 313:7 347:17 377:11,12 377:13,13 417:4 417:17 422:5 446:18
continued 33:16 83:17 86:13 413:4 413:15 417:14,19
continues 23:18 307:10 378:21

continuing 22:2
continuous 136:6 151:3 393:11
continuum 237:5 241:8
contract 33:14 75:21
contributed 82:18 172:8
contributes 370:2
contributing 315:4 341:15
control 197:16 198:3,3,4,5 232:8 249:10 250:6 272:10,11 273:13 278:13,15 288:21 307:18 312:14 315:16 321:1,21 324:2 345:3 359:16 405:4,5 411:6 420:16
controlled 380:4 388:19,20
controlling 183:15 183:18 379:11 382:20
controls 80:19 252:12 316:17 320:9 322:7 323:2
controversial 177:4
controversy 86:9 86:10
convening 39:3
conventional 37:19 46:7 71:12 302:18
convergence 394:19
conversation 61:20 65:2,17 69:10 108:20 110:13 137:5 198:11 340:18 341:8 353:7 362:12 404:17 439:14
conversations 191:1
conversely 307:9
convert 344:7
converted 268:9
convince 57:7 59:6,7 331:3
convincing 94:8
cool 181:8
cooper 342:8
cooperative 408:8 409:8,10 410:9 411:14 412:7 415:9 416:1 443:15
cooperatives 449:5
coordinate 103:16
coordinated 131:7
coordinating 395:11
coordination 39:3 97:15 139:10
coordinator 402:20
coordinators 233:7
cope 447:18
copy 248:22
cord 365:9,11
core 17:18 131:15 143:18
coresh 2:17 5:14 81:16 82:3 123:17 124:14 125:13 127:11,13 128:3
corner 28:17
cornerstone 378:16
corollary 141:11
corps 233:8
correct 304:8 325:5,6,9 357:19 391:19
correction 325:15
correctly 54:10
correlate 63:19 65:12 201:7 207:2 215:17 280:19 330:16 365:3 376:21 433:8
correlated 126:8 146:13 364:18 421:19 424:15 432:22
correlates 67:14 69:9 105:18
correlation 65:11 93:11 94:2 146:14 330:17 331:11,16 331:20,21 361:19 371:22 373:15
correlations 94:4 375:8 376:3
correlative 151:19
cosmolioptis 153:21
cost 39:11,12,13 209:8 343:22 368:12 377:2 380:12,13,13,18 381:10 385:11,19 385:20,21,22 386:3,4,5,10,19 387:1,2 388:3,5
costly 37:20
costs 385:16 386:1 386:9 388:7
cottage 378:22
cou 44:7,7 254:10
counsel 454:8,11 455:6
count 248:21
counted 134:13
countries 130:18
country 192:10 265:22 383:12 440:19 449:18
counts 248:20
county 381:1
couple 13:20 23:12 32:13 33:3 42:6,11 65:4 73:18 76:19 154:17 169:15 173:21 174:9 276:13 301:14 331:9 445:6 450:14
coupled 247:17
course 33:16 51:16 70:5,14 71:6,16 88:12 104:20 129:20 131:12 139:17 158:15 163:21 207:1,6 209:3 210:10 225:21 259:22 261:18 264:10 266:11,11 274:5 275:18 277:9 279:13,14 280:8 287:11 291:8 315:15 317:8 318:19 319:2 323:20 325:18 326:20 355:17 385:13 391:5 405:7
cover 129:16
covering 260:21
cox 13:14
crada 431:4
craft 71:18
crazy 430:6

create 53:8 66:2 107:4,5 215:20 221:10 247:19 250:3
created 12:7,17 19:22 20:20
creates 61:19
creating 64:4,5
creatinine 46:16 71:13 78:6 79:15 83:9 90:6,7 93:19 127:19 136:16 160:5 204:8 213:3 220:13 222:15,16 225:10 263:19 293:18 303:13 310:5 311:13 318:19
creatinines 89:18 303:11 353:12
creation 76:14
credit 20:8 87:17
criteria 63:10 82:11 149:6,19 150:7 162:8 180:12 190:21 221:16 260:13 278:16 300:18 312:8 334:10,12 334:15 380:5 403:17 447:5
criterion 91:15
critical 7:15 10:20 11:8 16:8,15 20:11 35:5 40:3 41:17 42:8,13 43:7,9 51:2 55:9 73:13 74:15 76:4 76:14 203:12 287:2 450:20
critically 340:4
criticized 127:15
cross 98:5 180:19 415:11
crossed 40:5
crosses 21:17
crossmatch 176:11
crosstalk 174:17 184:19 284:13 297:1 348:19 360:18 361:7,13 444:16 445:14 452:5,14
crucially 388:13
csa 383:1,7,13 385:2
csi 387:2
csl 20:22
cti 14:8
ctla 178:12
ctla4 172:11 178:4 178:19
ctoc 177:13
ctot 3:10 32:11 153:22 158:8 178:21 179:8 181:19 191:3 217:14 219:13 221:19 229:4 233:2,9 247:6 249:8 254:17,21 273:2 359:12 391:18 442:22
cumulative 403:14
cup 205:18 362:22
curated 258:21
cure 280:5
cures 61:2 111:2 119:8,21 132:14 194:12 340:11
curious 274:21 288:10 363:21
current 10:18 20:21 23:6 26:15 70:4,7,10 149:2 191:9 199:20 204:8 216:4,7 258:3 280:19 281:17,18 282:6 290:17 292:13 301:2 368:7 369:18 378:17 385:14 390:1 445:11
currently 36:4 41:12 134:4,21 165:13 188:17 204:18 227:19 228:3 231:14 239:16 242:11 243:11 247:9 271:11 272:15,22 288:18 360:5 372:19 386:16 387:7,19 451:9
curve 78:2,5 80:12 90:2 140:12 160:9 253:3
curves 264:15
cushion 358:16
custom 210:6 250:3
customize 210:11
customized 209:6
cut 58:10,10 70:2 167:3 317:12 390:10 439:21 440:1
cutting 74:6
cxcl10 248:4
cxcl9 160:7 163:15 248:3
cycle 260:2
cyclosporin 145:22 371:4
cyclosporine 78:13 320:3
cyp3a5 169:5 170:4 171:21
cystatin 71:13
cystic 194:4
cytokine 306:1
cytokines 306:15
cytometry 304:11 304:14 316:9,21
cytotoxicity 175:13

d

d 6:10 7:1 316:6
d.c. 1:22 247:1
dacvpm 2:11
daily 10:21 14:21 14:22 22:21 52:13 347:14
damage 275:21 318:22 351:3,4
dan 12:18 231:20
danger 186:12
dark 73:16
data 12:17 14:6,19 25:13 27:7,8 29:14,15 30:14 31:12,15,15,16,17 31:17 32:1,4,7,12 32:14,16,19 43:5 43:7,10 47:9,9 58:9 59:11 65:8 65:15 66:17 69:15 69:16,19,20,22 70:1,1,3 71:19,19 75:7 77:6,22 78:10 79:3,5 80:3 80:10,22 81:22 82:13,15,20,21 83:12 84:19 85:14 87:14,15 88:18 89:12 90:17,20,21 93:3,6 96:5,5,10 97:7,15 98:4 103:9,14,14,16,16 103:17 104:2,5,11 104:11 105:22 106:1,14,16,17,17 106:18,19 107:4,5

107:7,22 110:2 111:17,22 114:22 115:14,16 118:18 118:21 119:5 124:19 125:6,9,10 125:19 127:6 128:9,12 129:6 131:21 135:10,21 136:4,4 141:17 151:4,10,21 160:2 160:5 164:11 168:12 170:8,11 173:4 175:4,21 186:17,22 196:22 203:19 204:2 207:5 209:9 210:3 210:7 211:8 212:10,11 217:21 219:21 220:3 223:8,10 227:13 229:4,12,18 233:4 233:21 235:7,10 241:3 242:16 244:20 247:3 249:7 252:13 256:7 257:17 258:22 259:16 261:19 262:22 265:15 267:1 268:1 269:9,10 270:19,22 273:21 275:9 276:7 279:18 281:4 291:5 297:4,20 301:2,16 304:15 306:2 309:10,18 309:22 310:2,8 312:3 314:10 318:5 330:13,19 331:2 332:1,2 333:16 334:16,20 340:17,19 361:18 366:20 367:8 374:22 377:15 379:22 380:21,21 380:22 381:2 384:6 385:21,22 387:7,8,8,19 389:20,21,21,22 390:10,19,21,22 391:1,2,4,5,7,9,10 391:11,14,15 392:1,11,12,15,16 392:17,20 393:1 393:10 397:1,4 398:5 399:9,14 401:18 402:16 418:6 419:6,7 431:5 433:7

database 32:1 167:16 258:11,15 258:19,20 259:4 259:21 262:8 418:6

dataset 129:8

datasets 31:19 32:2,2 87:2 103:22 106:21 107:1 128:12 215:22 235:3 243:9 244:13 267:13 388:17

datatypes 69:12

date 20:18 177:2 233:3 455:13

daughter 390:19

daunting 98:16

david 4:11 6:9

day 7:18 8:7,8,10 8:14,20,22 9:1 15:21,21 37:22 38:2 49:8 51:16 51:17 90:22 262:7 277:20 278:7,10 278:16 285:15,15 290:17 321:6 347:3,3,13,13 358:11 389:12,12 389:14 448:17 451:17 453:5

days 73:16 160:17 163:19,20 167:6

dcaf 154:1 168:20 170:14 173:11 174:1 177:13

dcc 223:9

dch 3:11 5:21

ddts 60:6

de 75:1 139:5,8,20 140:3,11 141:1 145:15,15 146:4 148:15 151:19 152:14 183:14 196:18 224:4,12 238:8 331:13,14 332:8 418:5 448:18,20

dead 10:6 198:17 198:22 348:12

deal 379:22 402:4 408:1 426:8 440:8

dealing 64:20 69:1 185:8 279:3 351:1 351:2

dealt 109:15

death 99:4 296:10 342:17 358:13 382:8,9,22 383:3 383:4,5,6,21 387:22 442:7

debate 171:19 196:6 313:1

decade 54:10 86:16,17 96:16 99:1 125:17,17,21 248:1 252:2 303:13 419:17

decades 87:13 99:1 227:19

deceased 159:3 174:3 373:22 399:11

decide 48:10 49:2 71:14 403:1 405:1 448:19

decided 24:9 25:8 25:10,21 87:21 162:12,15 248:14 438:12 452:10

deciding 448:16

decision 51:21 52:2,7 59:21 90:20 119:10 151:22 448:16 449:11

decisions 1:4 17:5 25:9 131:19 155:4 165:20 325:16

declared 190:11

declination 271:12

declinations 257:21

decline 81:17 82:6 84:21 91:7 94:10 95:10,12 96:1 139:16,19 173:11 211:1 332:4,12,14 332:19 333:13,17 334:1 335:3,8 345:6,8

declined 332:7 374:3

deconstruct 258:17

decrease 91:11 165:14 315:2,18 326:9 354:18

decreased 155:15 183:12

decreases 397:9

decreasing 268:14

decrement 434:15 434:21

dedication 417:10

deep 185:17 215:15
deeply 61:2 168:8
default 232:18
defect 306:11
define 63:20 84:8 119:2 121:20 136:20 142:18 176:22 177:16 230:14 294:12 339:5 362:1 377:13
defined 38:22 45:22 63:9 86:3 134:20 150:22 192:18 220:11 264:1,8 296:5 335:9 339:6 343:5 373:9 379:13 381:4 393:4 417:3
defines 48:16
defining 67:19 119:4 121:6,11 173:6 176:8 197:22
definite 177:5
definitely 23:13 32:7 123:13 394:3 443:3
definition 38:22 45:22 56:6 97:13 122:13 220:7 221:18 222:14,16
definitive 93:18 421:5,17,19 422:5 422:9 435:3
degenerated 248:13
degradation 174:22
degree 141:20 263:21 312:6 318:22 354:9
degrees 68:13
dekesnoy 143:18
delayed 11:10 157:17
delighted 233:21
deliver 75:7
delta 223:22
delve 168:8
demanded 225:2
demands 15:10
demographic 370:10
demonstrate 119:6 160:6 240:9 244:14 253:4 330:5 395:22
demonstrated 227:9 229:18 244:8 252:1 257:20 271:12 327:10
demonstrates 419:15
demonstrating 70:12 244:13
demonstration 257:5 327:2
denise 153:17
denominator 42:21 125:8
denominators 127:5
density 265:3
depend 127:18 336:12
dependent 85:3 175:13 183:17 314:19 321:13
depending 68:13 179:21 312:1 343:3 416:21 417:18
depends 103:9 295:13,15,16 298:18
depleting 369:4 374:1,2
depressed 348:4
depth 12:10 55:19
derivation 265:3
derived 78:10 322:3
describe 168:16 320:16 328:15 343:2 352:12 371:5
described 75:12 131:6 135:9 302:1 322:13 378:12
describes 76:11,14 438:7
describing 260:3 265:17 370:5 371:6 372:14
description 61:14 117:2 352:19
descriptive 64:12
desensitization 400:19
design 44:9 45:7 45:11 153:11,13 182:7,8,21 184:18 187:7 198:6 199:1 199:9 224:19 229:12,14 260:7 260:13 277:17 305:10 316:8 331:3 336:7 362:4 404:19 405:10,11 405:14 409:2 415:2 420:9 422:22 425:14 427:1 428:5
designate 132:6
designated 409:2
designation 132:10,21 134:17
designed 45:5,8 79:1 189:5 223:7 229:16 257:12 354:17 426:21
designing 199:9 409:1
designs 38:6 95:7 101:18,18 105:1 166:2 181:6 190:8 408:17 421:2
desired 121:6,8,11
desk 8:16
desperate 388:16
despite 18:10 155:3 163:1 368:15
detail 79:9 80:8 126:21 257:11,16 260:12 308:5 359:2
detailed 32:10 126:12 184:6 308:6 369:15 387:8 398:5
detailing 256:14
details 29:16 94:12 215:3 258:7 261:17 429:1 435:10
detect 156:3 160:22 162:13 166:3 216:12 226:21 228:22 232:4
detected 160:13
detecting 160:19
detection 204:13 215:11
determination 75:3 135:2 225:1
determine 172:22 173:1 222:18 234:22 255:1 292:1 388:9

412:19 419:21 425:1,17 426:9 428:1
determined 14:18 58:11 147:8 310:5
determines 135:1 144:2
determining 255:3
develop 15:1 26:22 27:16 29:11 29:19 31:21,22 43:12,19 61:13 99:8 102:21,22 139:7,10,12,20 161:12 163:6 164:14 165:15 178:9 195:13 240:11 241:20 242:22 243:4 245:20 255:13,13 306:13 329:20 353:16 363:18 379:17 424:13
developed 27:20 33:10 38:12 43:17 105:15 140:11 142:7,19 143:5 144:5 146:7 163:18 164:17,19 180:16 184:10 207:9 208:19 235:6,13 238:16 239:11 242:12 247:2 252:21 293:20 315:14 388:14 424:21 431:3
developers 37:17 58:6 113:16
developing 18:3 25:6 26:16 30:4 106:19 108:12 121:5 139:5 145:17 152:5 153:1,8 157:18 167:15,18 185:19 198:5 236:13 239:6 242:19 247:8 308:3 364:7 366:20 377:6,8 391:14 425:4 443:19
development 8:21 15:13 17:20 18:4 24:11 26:17 27:1 27:3,5 28:6,20,22 29:1,8,11,19 31:22 32:20 33:10 36:10,12,13 37:9 37:15 38:7,9,11 40:19,19 41:5,6 42:1 43:15 44:1 45:13,18 46:7,10 46:12 48:7 49:3 49:20 50:8 52:2,8 52:16,22 53:16 54:18,21 57:12,16 57:21 58:8 59:8 59:17,20 60:7,8 60:16,22 61:3,15 62:3 64:7,19 65:6 65:9 72:5 73:2 75:15,16 92:18 101:4,6 102:12,22 103:1,2 104:19 111:12 112:17,21 112:22 113:4,15 115:11 117:3 121:11,14,19,22 122:8,11,13,15,22 123:4,6 132:17 133:6,8,13,14,17 133:19,20 134:5 134:18 138:4 149:8 180:11 181:15,18 182:1 183:14 187:11,20 188:9 196:13 198:21 230:17 245:22 247:8 253:22 265:4 277:5 289:11 290:18 291:22 292:2,11,12 295:17 310:7 313:13 315:6,8 329:9 337:8 339:15,18 340:6 340:12 349:10 360:13,16 361:6 361:15 377:18 383:18 387:11 388:10 413:18 430:16 432:8 453:5
developmental 306:11
developments 121:8
device 15:13
devices 150:3
devine 420:9
diabetes 385:8 393:16
diabetic 196:3
diagnose 160:3 161:5,6 162:2 184:17 227:19 228:3 234:22 239:8,10 254:12 313:10
diagnoses 370:16
diagnosis 155:22 167:14,14 239:15 247:19 253:10 254:4 267:11 276:4,8 292:16 334:8 335:10 354:17 381:7 448:15
diagnostic 48:18 58:19 62:6 63:3 159:10 239:18 246:17 248:6 253:11 254:2,7,10 292:10 327:5,6 359:5 363:11 381:5
diagnostics 58:17 232:4 362:19 363:5
diagonal 77:19
diagram 88:16 220:15 412:5
dial 360:2
dialogue 116:6 119:22 132:16 133:8 299:9 450:17
dialysis 14:14 15:3 341:21 342:5,16 342:17 348:13,13 358:14
diarrhea 14:22
dictionary 261:20
die 14:18 341:4 346:9 436:11 440:4
died 345:18,19
dies 298:9
differ 296:20 379:5
differed 385:19
difference 14:19 102:2 144:15 179:17 191:11,18 193:22 213:8,14 252:3 296:7,15 303:9 308:7 311:18,20 320:8 322:3,20 325:7 335:19,21 364:11 434:4 436:22 437:2,7,14,15 441:18 442:9 443:6

differences 52:5 107:17 144:10 175:22 192:4 232:4 296:14 302:19 303:15 326:1 374:16 380:2 381:18,19 382:20 384:11,18 387:3 407:19 432:19 441:15 449:4
different 19:2 32:20 37:7,16,22 40:15,17 43:6 48:16,22 49:9,14 56:21 62:11,16,19 63:17 68:21 70:3 70:19 71:7,9 73:11 84:16 87:10 88:16 96:2,2,10 98:15 103:5 107:11,13 108:5 110:17 113:4,22 114:3 117:7,12,12 124:4 130:9,16 140:13 144:12,20 145:4 146:21,22 148:2 152:19 166:7 171:4 172:9 187:9 191:22 196:15 201:4 215:21 221:5 253:19 255:7 257:21 258:1,1,22 261:10,11 263:12 265:14,22 267:3 267:14 268:10 269:11 271:12 278:11,22 285:22 292:5 297:18,20 304:16 305:9,10 305:10,14,16 309:2,4,11 310:2 312:1 316:2 318:20 319:5,18 320:12 323:4 324:15,15 326:11 339:1,3,10 342:14 348:4,20 351:15 354:13,14 365:4 365:14 367:8 371:19 380:1 400:16 401:11 403:6 409:11 411:10 412:12 415:9,11,12 416:1 416:5,19,21 417:21 426:14 429:4 432:17 435:11 441:1 448:14
differentiable 214:2
differential 187:9 309:4 360:22 386:4,22 388:2
differentially 221:4 227:2 304:4 304:6,22
differentiate 58:16 238:11 242:7 243:1 316:11 322:5
differentiation 306:12 317:8
differently 52:13 346:21 354:2
differs 65:5
difficult 74:21 99:8 100:5 101:10 101:16 158:20 159:1 212:3 217:22 247:14 248:8 257:10 273:9 331:3 389:21 397:4 431:17,20 432:4 432:17 438:3
difficulties 412:20
difficulty 14:22 189:21 196:16
dilute 182:4
dimension 288:5
dimensions 288:11
diminish 218:15
dinner 11:20
dipstick 161:13 267:16
direct 110:13 124:12 332:21 413:8
direction 26:15 291:7 346:5 454:5
directions 19:2 27:16
directly 161:15 410:12
director 7:7 21:11 51:3 55:10 414:6
directors 13:1
directs 13:16
dirk 19:6
disagree 41:15 356:5
disappear 86:22
disappointing 120:15,16
discard 80:13
discipline 117:13
disciplines 117:7
disclaimer 36:11
disclosure 314:8
disclosures 9:21 23:9 73:7 138:19 167:4 202:11 219:15 234:2 247:10 300:15 367:16 408:4
discomfort 353:19
discontinuation 369:12
discontinued 369:11
discordance 217:4
discovered 273:7
discoveries 429:10
discovery 59:3 110:5 136:1 221:11,20 222:6 222:19,22 236:8 236:17 240:6
discriminate 107:15
discrimination 262:16
discuss 16:22 70:11 84:2 96:20 196:20 329:7,19 350:6 370:17 378:1
discussed 12:2 16:19 235:16 239:4 247:4 333:7 364:4 377:8
discussing 46:22 67:20 131:20 196:15 239:19 344:5
discussion 9:5 17:10 18:11 25:5 55:3 60:19 66:5 67:20 95:8 116:2 137:11 178:5,5,7 190:3 271:22,22 299:7 314:4 316:16 338:17 364:9 421:7 450:18
discussions 9:9 12:12 26:10,13 46:10 102:11 113:11 136:10 180:1 342:10 362:3 378:8

disease 12:3 18:18 43:8,10,12 44:10 44:15 64:10 71:5 71:5 84:7 93:19 117:10 125:5 127:3 131:5,11 134:22 135:19,20 196:2,3,5,5 200:1 200:10,18 254:2 315:20 333:2 340:15,15 368:14 384:5 394:9 409:13 421:12 422:6,16,17 426:20 432:21,21 433:2,3,9 435:7 435:12,17 436:2 436:10
diseases 11:6,11 21:5 194:7 200:14 333:8 397:21 415:12 439:8
disfunction 204:15 223:22 331:13
disincentives 438:3
dismal 99:15
disparities 205:7 370:2
disparity 120:1
dispensed 77:20
distant 130:16 260:21 265:20
distill 323:8
distinct 7:8 419:11 420:18 423:14
distinction 124:16
distinctive 413:7
distinguish 88:15 248:4 250:11
distinguished 308:10
distinguishing 250:5,21
distracts 118:5
distressed 293:7 293:21
distribution 266:3
diverge 311:17
diverse 173:6,6 411:1
diversity 397:9
divided 88:6 345:17
division 7:4 13:17 46:11 116:17 132:15 133:9 328:9 329:11 441:16
dixon 20:4
dna 205:7 218:18 234:17
doctor 288:7 341:14
document 15:7 16:2,10 85:17 92:21 117:4,15 134:8
documents 41:7 59:9 64:2
doing 18:9 21:13 25:3 26:21 29:17 31:6 36:13 40:16 44:20 57:2 69:7,7 108:8 110:4 124:4 146:6 156:8,11 159:3 162:14 165:22 166:10 168:1 174:8 185:22 186:3,12 187:14 189:14,16 204:18,22 205:1 209:4 211:14 217:12 222:8 230:1 234:16 235:9 242:14 250:19 253:14,16 255:12 262:7 269:6 273:11 284:11,12,17 286:13 291:8 293:11 313:4 317:7 341:15 353:10,10 393:13 394:11 397:8 399:16,17 400:2 400:10 401:5 402:20,22 404:7 404:10,13 407:1 420:4 431:18 441:6
domain 50:3 144:1
domains 127:22
dominant 140:9
dominantly 376:18 378:19
donor 138:16 139:5,8,12 143:14 143:22 144:4,11 144:15,21 145:11 146:16 151:7 156:17,21 157:3 158:18,18 159:4 168:5,15 174:3 177:9 185:13,19 185:22 206:6,9,11 206:12,14,19 207:7 208:6 209:13,20 210:5 210:11 212:17,18 237:8,8 245:8,12 302:22 309:12 354:10,13 370:19 371:8 374:8 376:19 378:20 379:14 382:20 387:5 388:9 392:3 394:6 397:12
donors 162:5 174:6 318:16 370:11 394:17 399:11 401:6,8
doplot 252:10
dose 1:5 135:1,2,2 169:10,12 171:2 205:3 347:6 354:1 361:3,4,5 387:9
doses 292:6 349:8
dosing 169:15 170:5,7,10,20 171:22 347:8 361:2
dotted 230:12
doubling 83:8 90:5,7 93:19
doubt 59:5 64:12
doubting 51:20
dovetails 291:10
downregulated 250:7 252:5,18,19 253:1
downstream 117:6
downtown 12:22 17:13
dozen 76:19
dp 150:9
dq 145:15,17 146:2,3 147:6,16 147:17,17 148:2,4 150:9 152:14
dr 7:2,5,16,17,17 8:22 9:12,15,16 13:14 16:10 23:3 23:3,4,7 34:22,22 35:2,6,12,12,20 36:2 38:10,15 39:15 40:7,21,21 41:2,3,14 50:4,11 50:17,18,20,20 51:1,6,6 53:6 54:3 54:5 55:7,8,13

72:1,7,21,22 81:5 81:16 82:3 98:1,8 98:13 108:18 109:19 110:15,22 113:2,18 114:19 115:16,19,20 116:6 120:5,11,22 121:18 122:6,7,18 123:8,17 124:14 125:12,13 127:9 127:11,12,13 128:2,3,14 129:20 131:17 132:12 133:15 134:2,3 135:6,14 137:3,14 137:20 138:7,11 144:7,8,14,18,19 145:1,3,6,9,15,17 146:1,3 147:6 148:1,3 149:5 150:9 151:14 152:14 154:7,11 166:15,16,20 177:19 178:1,3,18 179:12,13,14 180:4,22 181:9,11 181:17 183:10,20 184:20,22 186:7,9 186:10 187:4 188:11 189:10,11 189:12 191:5 192:21,21 193:1,2 193:2,3,11,15,15 193:16 194:3,15 194:15,16 195:15 195:18,22 196:11 198:20 200:8 201:10,15,20,22 202:4 219:6,7,11 233:9,15,15,16,20 246:13,13,16,19 255:22,22 256:1,5 271:20 272:4,13 273:12,14,15,16 273:17,18,19,20 274:4,14,17,18 275:3,4,5,6,10 276:13,22 277:1,8 279:10,14 280:12 281:1,8,19,22 282:3,10,13,16 283:1,2,3,4,5,6,7 283:8,10,11,14,15 283:16,18,20,21 283:22 284:1,2,3 284:4,5,6,9,10,11 284:12,14,19,21 285:11,12,13,14 285:19,20 286:1,3 286:8,14,21,22 287:3,4,5,15,16 287:17,20,21 288:15 289:4,6 290:15 291:15,15 291:17 292:7,21 294:21 295:10,12 295:13,15,16 296:4,22 297:2,7 297:8,11,12,17,22 298:1,11,14 299:4 299:6,10,16,22 300:2,8 313:17,17 314:1 328:1,1,6 334:18 336:17 337:2 338:3,13,19 338:20 339:12 340:20 341:1,3,7 342:8,18 345:1 346:11,14 347:16 347:19,20 348:18 348:20 349:3 350:14 351:8,14 351:21 353:8 354:4 355:13 356:2,3,4,5,6,9,10 356:12,18,19,21 356:22 357:1,3,6 357:7,8,9,11,13 357:14 358:7,10 359:3 360:12,17 360:19 361:8,12 361:14,15,16 362:6,10,12,21 363:3,5 364:1,3,5 364:6 365:7,21 366:6,8,12,15,18 366:21 367:4,5,13 370:4,17 377:22 378:4,11,18 380:20 383:10 388:14 389:3,3,7 389:10 395:17 407:12,12,17 412:11 429:22 430:3,10 431:15 431:16 432:5,6,16 434:2,6,7,10 435:22 436:6,8,13 436:14,15,16,18 437:9,10,20,20,22 437:22 438:7,10 440:6,11,15 441:12,13,14 443:13,14,18,21 444:20 445:5,17 445:19 446:22 448:5 449:14,15 450:6,11 452:6,11 452:16,20 453:2

draft 14:9 171:17 254:8

drafted 15:6 16:3

drama 154:13

dramatic 98:19 412:5 429:18 433:17 435:20 437:1

dramatically 99:21 420:19

draw 58:4 186:15 370:18

drawn 56:22 61:8 61:9 62:20 372:6

drew 92:13

dried 101:5

drift 204:7

drive 22:21 47:13 65:17 100:14,17 102:2 182:6 215:11 325:15 441:4

driven 70:16 98:4 108:6 114:4 319:1 353:4

driver 140:22

drivers 153:18

drives 197:15

driving 41:10 140:20 203:7 214:7 388:7

drop 84:21

dropouts 131:13 337:15

drove 213:19 416:16

drug 1:12 8:21 10:14 13:3,10 16:6 18:3,3 24:11 26:2,16,22 27:2,5 28:5,19,22 29:1,7 29:11,18 30:13 31:7,21 32:20 33:10 35:9 36:10 36:12,13 37:9,14 37:16 38:7,9,11 40:19 41:5,6 42:1 43:13,15 44:1 45:13,18 46:7,9 46:12 48:6 49:2 50:8 52:2,7,15,22 53:16 54:18,21 57:12,16,20 58:6 58:7 59:8,17,19 60:6,8,15,22 61:3 61:15 62:2,3 64:7

64:19 65:5,7,8 72:4,14 75:14,16 77:8,8 85:21 92:18 93:7,20 101:4,6 102:12,20 102:21 103:1,2 104:19 111:12 112:17,21,21 113:4,10,14,16 115:11 117:3 121:5,10,14,19,21 122:8,11,13,15,21 123:4,6 126:18 127:19 128:19 129:11 131:5,12 132:17 133:6,7,13 133:13,17,19,20 134:5,18 135:11 149:7,15,16 153:11 155:8 157:6 162:16 163:4,9 170:10 180:10 181:15,18 182:1,10,22 183:14 185:4,5 187:10,11,13,15 187:19 188:9,21 191:7 192:9 193:21 195:10 198:21,21 199:1 199:13,17,21 200:2,6 205:3,11 210:15 216:15,19 217:9 218:5,15,20 218:20 230:17 245:21 247:8 253:22 277:5 278:14,19,20 289:10 290:18 291:22 292:2,11 292:12,20 295:17 295:18 302:18 310:7 313:8,13 315:6,7,9,10 329:9,21 337:8 339:15,18 340:5 340:11 344:8,9 346:3 349:8,10 353:22 355:14,15 355:21,22 360:2 360:11,13,15,22 361:2,3,4,6,15,20 363:18,18,20,21 405:14 409:18 413:18,18 417:20 430:16 432:8 434:3 436:9 453:5

drugs 10:4 25:6 25:13,22 28:18 29:12 45:17 96:2 121:14 136:20 148:20 162:6,14 163:7 165:11,13 186:6 187:22 188:20 189:3 191:9,9 194:4 199:12 254:19 282:6 301:9 312:20 315:10 324:15 346:1 347:8,13 348:21 350:19 404:6 409:12,20,21,21 428:3 436:1 437:9

dsa 27:9 139:21 140:3,5,6 141:1 145:15,15 146:4 147:16 148:16 151:19 152:14,20 162:11 163:6,10 163:10 164:14,17 164:19 176:11 183:14,17 184:1 184:10 190:16 224:4,12 238:8 267:20 274:11 276:17 285:1 313:5 330:13 331:13,14,17

dsas 105:14 145:17 331:11,21 353:16

dsmbs 234:3

dublin 78:18

duct 76:18 77:18

due 99:13 130:7 369:20

duke 11:15,15

duration 107:18 179:16 339:20,22 387:9

dvm 2:11 5:10

dx 424:22 425:17

dying 341:22 342:16

dynamic 44:18 264:21 271:5 279:9

e

e 2:1,1 5:2 7:1,1

earlier 18:2 46:22 50:7 75:12 78:8 99:2 135:22 155:17 183:13 204:12 216:9 230:17 239:4 289:19 333:5,7,12 333:15 335:19 342:9 383:21 421:17 432:7 433:16 452:8

early 10:1 11:16 25:9 53:20 68:20 75:15 110:21 112:1 135:2 165:18 169:18 183:22 201:16 211:10 214:18 218:7 236:11 238:7 247:3 264:16 269:17 272:8 279:5,7 297:4 328:17 336:3 354:17 368:5 410:7 412:3 412:13 418:9 420:17,18,22 421:3,4 422:1 423:7,12,13,20,21 425:2 426:14 433:20 435:2 439:14

easier 20:10 39:16 66:14,20 253:15 437:19

easiest 63:2 190:6

easily 67:8

easy 86:1 190:7 225:2 256:11 333:4 363:15 440:16

echo 185:1 197:19

economic 258:1 378:1 379:11 380:21 385:9,15

economics 449:17 449:17

ed 90:10

eddie 328:7

editing 87:7

education 342:4

edward 4:5 6:6 328:1

effect 83:13 89:5 94:13,17,18,21 95:16 126:19 128:7,7,16 151:5 171:16 185:22 187:9 199:22 214:17 305:6 320:18,21 323:15 333:1,13 335:14 335:15 348:5 360:7,8 363:8 372:16 376:11 377:1 410:5

428:13
effective 18:1 153:15 200:6 330:4 368:15 369:19 378:14 380:13,14 393:13
effector 175:12
effects 14:21 85:15 95:15 96:2 97:1,6 126:13 128:5 131:12 155:18 162:4 176:22 293:14 312:18 323:9 335:1
efficacious 187:13
efficacy 26:1 27:6 29:2,12 38:10 48:21 96:22 149:2 185:7 186:6 216:19 217:9 218:5,19 347:8 368:2 420:12
efficiency 405:3 411:11
efficient 125:20 127:7 182:8,15,21 393:12 411:22 414:8 420:14,20 421:6
efficiently 415:1
effort 7:19 23:8 24:10 38:14 39:21 47:1 50:2 100:17 115:12 131:7,15 132:22 169:20 173:16 340:16 352:3,16 391:14
efforts 48:14 49:13 110:18,19 291:2 377:13 444:13
egfr 139:15 158:10 184:8 223:22 263:17,17 311:14 332:7,12 332:14,16,17,19 332:22 333:13,17 334:1,7 335:1,3,8 335:9 336:9 345:6 345:13,13,15 346:4 349:5 353:13 426:15 427:9
egfrs 344:4
egos 440:4
eight 225:1,8,16 226:6 261:1 286:11 321:7 405:1
eighty 236:5
either 20:8 37:16 79:21 103:6 128:11 171:2 220:17 225:17 232:14 252:15 427:9
elastic 250:8,9 252:20 364:16,17
electrostatic 146:12
elements 62:4 116:12,20 387:7 419:7
elevated 158:14 252:11
elevation 160:4
eligible 292:15
eliminated 236:12 236:14
elispot 156:18 165:2,4 349:18
ellison 341:14
elusive 368:21
ema 74:9,12,13 75:7,13 76:4,12 80:14 81:1,13 92:15
embarked 189:9
embedded 448:12 449:7
embracing 340:10
eme 73:13
emerge 135:22 441:21
emerging 271:15
emeritus 3:2
emory 3:15 255:19 300:3
emphasis 82:15
emphasize 82:13 132:5 226:19 345:5
emphasized 77:6 91:6
empiric 301:11
empirical 371:12 409:18
empirically 227:20,21 231:2 232:12 409:12
employ 158:20 197:18
employed 380:14 454:8,11 455:7
employee 408:4 454:10
employing 27:14
encountering 408:19
encourage 41:9 48:1 49:1 50:10 341:17 451:4
endeavors 33:15 36:2
ended 78:14 163:5
endorsed 432:12
endorsement 61:7 82:1 103:7 104:12 108:2 135:5
endothelial 208:15
endowment 439:3
endpoint 62:7,22 66:9,11,17 67:1 81:17 82:6 85:9 95:10,14 98:17,17 99:5,9,22 100:3,9 103:1 104:3,7 105:2 106:6,11,12 106:14 107:15 108:13 114:11 115:8 122:1 131:10 145:16 182:20 191:12 194:19 198:22 199:4,11 201:8 223:20 224:11 239:18 243:15,18 290:18 294:14 327:8 328:4,20 329:5,16 330:18 330:20,22 331:1,4 331:6,17 332:17 332:18 333:5,10 334:1,2 335:16 336:4,5,9,13 338:15 343:21 344:5,7 346:19 350:4,8 355:9 361:9,22 421:17 421:20 422:6,14 423:3 432:19 433:22 435:4
endpoints 12:21 19:1,8 24:12 26:2 38:6 75:18 98:10 98:12 100:13,14 100:16,18,22 101:16 102:17 103:19 104:20 105:5,6 114:2 153:10 190:21 224:10 227:7 263:12 277:7 294:11 329:3

330:11 336:3 339:9 340:2 350:13 354:6 406:9 421:8,16 422:9 423:2 432:8 432:10,12
ends 153:14 298:19 446:20
enemy 256:21
energy 30:21 395:9,12,21
engage 42:1
enhance 190:8 247:19 287:1
enhanced 207:16 287:6
enjoyed 287:21
enrich 121:22 148:18 155:6 165:10 187:20 188:6 210:16 427:1
enriched 190:5 207:21 208:17 209:17
enriching 165:8 231:3
enrichment 48:20 64:14,15 66:13 115:9 148:22 153:13 155:10 182:18 187:6 191:6,16,19 193:12 196:17 228:19
enroll 189:18 190:6 191:13,16 398:13 449:21
enrolled 79:3 162:21 225:3 234:14 310:19 401:3 412:7 445:2
enrolling 449:12
enrollment 276:16 398:10,11 402:12 402:13,14 403:17
enrollment's 393:20
ensure 335:14 410:18
entails 47:2
entered 414:8
entering 259:3
entire 24:10 59:5 65:14 138:17 139:17 149:17 220:3 414:7
entity 38:14 39:12 109:18
environment 49:21 279:9 347:9 417:6
envision 438:7
epi 97:10
epidemiologic 85:13 106:3 367:10
epidemiologist 54:7
epidemiology 125:18 367:1
episode 344:12 448:22
episodes 203:22 223:17,18
epitope 143:12,15 143:18 164:13,17 164:19 245:10
equal 88:2 274:1
equate 344:10 372:12
equation 170:7 263:18 440:13
equations 274:5 274:13 276:1
equivalency 185:6
equivalent 144:18 413:2
er 423:20
era 414:9 420:8 423:6
ergun 3:4 5:16 137:18
error 94:14
errors 93:8
especially 25:3 69:5 84:14 231:14 359:9 393:21 397:19 403:18 405:15 446:9
esrd 88:5,12 89:20 90:8 91:8
essential 230:2 416:9 420:3 429:17
essentially 105:15 210:13 428:5 449:13
establish 90:13 103:21 288:2 409:6
established 44:17 81:20 90:11 91:4 93:14 102:18,19 150:16 409:7 410:18
establishing 63:11 150:15 151:11 444:5
estimated 83:7,10 89:4 90:4 95:12 95:16 127:9 139:15 270:9 376:5 385:12
estimates 127:14 371:12
et 65:15 91:3 206:16,21 209:22 211:11 215:7 220:20,21 233:8 244:11 283:8 337:16 358:19
ethnically 173:6 411:1
ethnicity 136:5 173:5 262:7 401:10,13
eu 73:19 78:17
europe 129:2 260:10 327:16
european 169:9
evade 364:5
evaluate 17:22 216:19 408:10 422:5
evaluated 45:15
evaluating 148:20
evaluation 35:9 115:3 130:4 131:21 261:2 263:8 264:20 265:4 409:19
evaluations 265:5 265:10
event 91:19 143:10,11 183:8 184:11 210:1,16 210:17 238:12,13 296:9,14,19,21 363:13 403:12
events 11:17 16:14 30:2,5,7 32:9 89:20 130:2,7 197:7 259:12 265:8,15 280:10 296:6,7
eventual 433:21
eventually 104:22 106:13 197:8
everly 8:22 406:21
everybody 73:22 87:1 90:19 97:20 107:2 113:15 137:18 167:12

223:11 230:7 293:1 298:18 304:18 360:5 363:1 366:9,12 390:18 395:11 433:12
everybody's 62:20 348:3
everyone's 18:8
everything's 226:20
evidence 1:4 47:10 47:11,20 48:10 49:12 53:12 55:1 55:12 60:18 61:18 63:2 64:22 65:6 66:5 67:6,7,21 70:14,15 71:1,2,6 71:16 78:7 81:13 84:21 85:2,6,11 85:22 86:2 87:21 92:16,18,22 95:3 114:3,12,16 122:2 129:13 131:20 155:13 158:10,13 159:7 160:19,21 164:3 220:7 229:7 230:21 302:6 309:9 377:20 379:17 383:16
evidentiary 66:19 149:19 150:7 229:6 300:18
evolution 81:12 290:13
evolutionary 290:14
evolve 114:21 365:20 378:22
evolved 300:14
exact 224:10
exactly 52:18 91:12 110:2 187:14 197:4 198:19 222:17 405:11 449:9
examine 379:9
examined 89:6 95:15 262:5 335:4
examining 53:10
example 38:9,19 43:2 45:19 47:14 47:14 49:10 64:9 68:1 72:11,18 95:18 116:19 125:3 133:7 138:5 144:7 158:7 179:8 188:14 191:2,8,12 194:3 197:4 270:3 270:22 278:9 298:4 338:21 340:14 354:8 363:8 369:1 372:7 376:4,20 384:19 384:22 388:6 392:2 421:21 434:12 435:6
examples 36:8 37:1,2 42:14,15 42:20,21 46:15 49:6,9 197:4 254:10 329:2 420:9 423:5 432:12 435:22 436:9 437:6
exceed 78:6
exceeded 78:1
exceeds 100:1
excellent 138:4 141:15 438:1
exchange 261:19 354:13
excited 10:2 204:22 255:7
exciting 18:22 58:6 74:11 186:11 338:12
exclude 278:8
exclusion 149:7 260:13 278:16 334:10
exclusions 63:10
exclusive 52:4
excuse 118:1 425:11
exec 21:10
execute 12:4
executed 340:1
executive 7:6 51:3 55:10
exercise 288:11 314:20 334:3,4,21 336:6
exercises 180:19
exhausted 428:9 435:18
exhilarating 19:1
exist 51:19 53:15 143:22 144:11 145:3 297:13 313:11
existed 81:21
existence 347:1
existing 271:11
exists 27:11 32:5 46:19 69:19 173:7 391:18
exome 206:11 207:5 209:4
expand 27:17 47:1 124:20 129:18 195:13 410:15 413:10
expect 75:6 207:7 243:3 278:17 285:9 295:7
expectation 374:12
expectations 66:18,18,19 67:4 151:2 288:2,3,8,9 444:9
expected 371:19 374:7 385:7
expecting 262:19
expensive 253:17 386:17 389:22 397:5
experience 35:18 36:6 38:18 39:8 40:3 176:21 196:10 296:21 341:10,11 387:20 407:8
experienced 91:18
experiment 141:13 379:9
experimental 306:3 405:7 420:14 428:3,19
experimentally 365:14
experimented 47:6
expert 79:6 117:10 178:18 329:1
expertise 30:13,22 39:8 49:8,13 398:17
experts 46:17,20 48:15 116:15 118:5 351:19
explain 48:5 51:7 105:12 251:8 365:1 395:2
explained 91:18 102:19 320:10 374:12,18 375:4,6 376:1 378:19
explaining 47:2
explains 377:1
explanation 429:13

exploratory 69:22 70:1 351:13 361:6
explore 101:19 377:18
exploring 442:21
explosion 431:20 432:1
exportability 260:1,18
expose 149:13
exposed 78:11 79:22 80:17,18 228:2
exposes 301:13
exposure 46:3 79:19 80:4,4,4 149:11 228:14 370:12 387:9
expressed 206:6 206:14 208:14,14 208:15 221:4 227:2 251:21 252:14 304:4,6,22 307:2 310:10 365:9,10 452:9
expressing 206:9
expression 238:4 246:17 249:3 250:13 254:11 255:9 304:20 306:21 307:16 309:21 316:22 317:21 322:2 323:6,18 325:3 424:18
expressive 309:5
extended 410:21
extends 385:15
extensive 35:18 215:1 306:1
extent 79:18 250:13 301:7
external 240:19 254:21 258:20
extreme 302:5 311:8
extremely 196:14 197:17 205:10,14 217:3 238:13 239:3 340:16 429:16
extremes 425:21
eye 1:21

f

fabulous 129:1 205:6 353:13
face 37:14 64:21 70:5 257:10 330:7 408:1
facilitate 49:14 402:11 450:14
facilitated 17:8
facilitates 174:22
facing 36:16
fact 31:13 34:13 35:14 41:1 126:14 129:6 131:10 139:10 147:16 149:16 150:1 187:14 193:5,7 207:15 214:7 216:16 220:9 239:22 241:18 257:2 263:15 267:10 269:8 282:13 305:15 319:17 345:22 360:3,4 376:15 378:21 379:9 381:21 382:21 423:18 426:4
factoid 202:16
factor 64:15 115:9 174:22,22 245:8 245:12,12 322:9 350:16 354:10 373:15 374:14 375:7 376:20
factors 115:3 146:19 155:3 157:15 169:21 170:1 195:7 198:4 199:7 206:21 236:20,21 239:4 242:22 243:22 262:5 288:19 321:22 323:19 350:15,22 371:9 372:14 374:8,18 375:6 376:2,19 377:2 378:20 379:12,14 382:4 382:21 387:5 438:5
faculty 9:22 406:14 443:18
fail 16:1 37:10 195:1 199:5 292:14
failed 197:1 292:13 445:5
failing 22:13
fails 198:21 199:21
failure 130:6 148:16 173:2,10 180:21 186:18 199:6 264:13,18 268:20 332:15 376:5 382:9,11 383:4,8,22,22 387:22 441:19
failures 37:10,12 257:4 264:14 269:22
fair 95:11 121:15 269:19 284:5 309:8,18 441:9
fairchild 246:21
fairly 101:5 112:1 179:9 253:3 302:10 321:5
faith 120:20
falk 11:21
fall 18:22 80:5 134:20 248:18
falling 241:13
false 70:9 160:10 160:11 216:11 326:11,11,12,15
familiar 11:13 26:18 46:8 83:6 381:12
family 22:19 413:14
famous 12:21 440:9
fan 127:22
fancy 256:10
fantastic 186:11
far 41:16 151:11 178:11 229:14 233:10 293:1 312:3 346:8 379:8 395:6
farkas 1:18 454:2 454:17
farther 340:3
fascinating 397:13
fashion 97:8 202:14 412:2
fast 2:19 5:15 86:15,16 167:3 213:12 242:15 406:17
faster 88:12 139:22 184:9 398:10,10
fastest 170:21
fatal 434:17
favor 449:18
favorably 107:20
favoring 369:8
favorite 79:10
fc 175:10

fcahs 3:5 5:17
fda 2:3,9,12 3:4,17 4:1,7,17 7:9,12,13 7:17 8:2 12:5 13:8 15:17 17:16 21:2 22:1 23:21 24:18 26:4,13 27:20 28:7 31:8 32:5,6 33:14 35:3,10 40:7,9 41:2,7 44:16,17 46:5 47:21 48:14 50:2 50:11,21 54:9,12 56:3 57:13 58:8 60:7 61:6,22 72:22 73:13 74:8 74:12,14 75:7,13 75:19 76:4,11 81:1,10,12 83:3 83:22 90:6,14 92:14 96:8 97:11 97:16 102:8 104:17 108:10 109:11 110:7 112:1,4,12 113:3 113:15 134:5 137:20 150:4 180:5 181:13 189:8 194:10 201:19 240:13 242:13 272:1 299:10,21 300:8 314:2 331:4,7 333:22 336:7 339:2,6 340:10 342:11 350:7 351:10 404:18 432:13 433:1 434:11 435:15 439:8 450:20
fda's 47:2 100:12 135:4
fear 113:19 348:13
feasible 111:13 112:15 118:16 239:17 339:22
features 68:10 198:12 409:2 420:10
february 13:9 19:21
federal 386:16 408:4 442:2,8 448:1,1
feed 61:17 264:16
feedback 21:8 104:10
feel 13:13 112:10 119:15,17 302:3 323:3 356:13 363:11
feels 120:12
fell 77:19 222:12 238:17 250:19
fellow 109:9 180:10
fellows 246:22
felt 144:2 411:21 414:11,22
female 206:4 346:12
ferness 203:2
fibrosis 141:3 194:4 214:4 218:15 242:19,22 243:4,22 244:1,2 245:20 255:13 263:22
field 7:11 10:13 12:15 13:4 14:12 14:17 18:7 19:11 19:16 24:7 27:22 28:4 47:22 101:3 105:9 177:8 287:9 343:1 377:10 378:21 390:13 403:7 430:17 440:14
fields 10:13
fifth 8:12
figure 30:7 60:12 123:1,5 167:22 213:3 229:3 230:19
figured 29:5 304:3
file 391:3
files 441:19
filling 411:20
filtration 157:21
final 98:7 108:12 177:2 205:8 263:2 336:4,12
finality 291:6
finally 9:2 20:18 22:7 34:11 96:21 175:8 380:10,17 383:8 385:9
financial 408:3 451:4
financially 454:12 455:8
find 9:9 34:16 105:2 112:11 113:8 115:1 120:1 120:16 146:19 155:5,19 162:15 194:13,19 237:7 276:20 326:1 333:19 338:4,11 339:21 394:6 421:13 445:7
finding 47:7 129:6 189:22 201:7 305:11 416:20 427:21 428:5
findings 219:13
fine 163:9 176:15 176:16 226:20 353:12,14
fingers 40:4
finished 83:21 231:18
finishing 83:19
first 8:10,14 17:6 25:14 32:8 43:2 46:7,8 47:16 53:8 62:5 67:9 76:10 88:3 94:17 102:1 102:15 109:12 112:3 116:7 118:4 124:15,21,22 128:16 132:3 133:6 138:7 146:12 153:2,4,6 153:6 159:20 178:20 181:14 186:10 188:7 194:4 198:14 201:22 205:5 219:15 221:3 225:14 227:16 233:22 235:12 263:7 265:6,7 267:4 277:15,16 279:20,21 281:6 284:7,16 292:13 292:14 298:5 300:2 302:11 304:2 305:20 312:2 328:21 340:13 366:21 368:8 369:4,9,10 369:12 372:17 375:20 386:1,8,20 386:21 398:3 411:12 423:6 435:15 438:13 442:13,21 445:5 447:16 448:11 450:10 452:1
fit 14:3 32:14 44:17 62:15,19 103:8 112:17 122:15 132:7

133:7,16,22 134:16,17,21 135:3 150:6 230:8 230:12,13,15 264:13 306:8
fits 32:15 39:15 51:15 64:18 121:21 140:17 235:21 306:15
fitted 267:1
fitting 305:15
five 9:3 14:14 34:1 34:9,10 35:21 36:3 105:21 128:17 141:20 153:4 233:2 234:10 237:10 238:1 259:15 264:17 286:11 290:11 294:9 297:16 298:5,16 319:7 327:14 335:11,17,22 343:13,15,18,20 382:15 398:3 407:9 408:14 415:9,13 419:16 420:1,2 447:17 451:10
fixated 361:8
flavio 10:3,8 14:8 21:22 217:14 442:14
flavio's 273:3
flavor 168:17 394:8
fledgling 109:15
flexibility 73:15
flexible 196:21
flipping 243:2
flips 381:21
floor 108:21 121:1 287:18 346:16
florence 22:8
florida 401:7 402:3
flow 304:11,13,14 316:9,9,21
flowing 41:19
fluctuations 85:5
fluidigm 209:6 318:3
fly 350:8 395:6,8
flying 395:4
focus 8:10 15:15 77:14 87:21 111:2 118:20 183:14 205:11 219:13 220:21 269:8 297:14 339:18 348:22 412:16,18 417:4 421:15 428:21
focused 8:21 13:11 51:18 53:2 54:20,22 117:19 117:20 118:6,10 122:21 142:20 184:14 187:1 294:3 346:18 453:5
focuses 220:4
focusing 138:13 209:1 265:19
fold 90:7 91:8,9,16 91:17
folks 8:18 54:15 57:8 61:20 109:1 109:9 137:7 292:3 339:2 392:10
follow 56:3 89:14 99:4,16 104:5 106:8,10 130:2 161:14 178:4 193:16 259:9,12 261:1 267:19 270:17 287:20 296:18 321:18 328:19 338:19 373:10 380:18 390:18 392:21 400:2 421:14 424:11
followed 17:11 19:3 69:22 125:4 224:22 388:7 403:21 425:22
following 14:13 200:8,21 228:4,9 228:12 232:16 234:16 300:4 334:7 335:9 337:13
food 1:12
forbid 15:2
force 253:22 446:5 446:12
forego 232:17
foregoing 454:3
foresee 17:1
foreseeable 354:22
foreshadowing 358:10
forest 89:6 221:8 221:9 227:4
forever 259:5 294:8 298:21 341:4
forgo 73:11
forgot 175:15
form 33:5 236:17 247:4
formal 9:4 57:11 135:3 157:22
formally 86:12
format 9:2 430:8
formation 395:4,8
formed 7:14 234:4 390:4
forming 86:11
forms 37:16 228:17 244:19
formula 438:12
forth 25:4 26:12 196:7
fortunate 86:8 316:19 358:11 409:4
fortunately 48:12 77:20 86:12 103:16
fortune 73:7 129:5
forum 142:15
forward 22:2,22 26:14 33:11 34:15 40:5 45:17 47:13 52:20 55:3,4 76:1 76:20 78:7 102:3 108:6,11 112:13 114:9 120:4 137:12 143:8 154:4 159:6 181:7 193:18 196:21 218:17 254:20 287:2 289:9,15 290:5,21 291:2,4 291:7 298:6 314:7 352:4,18,22 353:7 359:8 390:13 426:8 453:3
forwards 125:20
found 85:22 158:3 164:16 173:21 211:21 224:3,10 224:13 230:10 289:16 305:13 309:3 325:8 375:18 376:1 411:7,9,19 422:8 422:14 423:19 424:1,4 426:4,18 430:20 439:20 440:2

foundation 96:9 131:9 167:10
founder 219:15
four 8:11 14:12 26:22 33:6,8 35:21 36:3 134:9 146:19 209:7 226:6 237:13 267:17 280:9 289:16 392:11 411:13,21 414:20 417:12 419:13 420:1
fowler 3:16 195:17,19,20 341:1 362:9 363:2 452:2
frame 182:15 278:6 377:14
frames 378:8
framework 53:9 60:5 65:17 72:19 104:17 227:12 335:5,6
frameworks 122:16
framing 367:10 368:1
france 2:22 3:22 105:7 107:9 129:1 130:17 256:2,20 259:5 396:22
francisco 3:12,13 202:1
frcp 3:1,11 5:21
frcpc 3:5 5:17
frcpi 3:18 5:22
free 147:16 179:2 249:12 346:22 347:1 348:15 374:3 385:14 390:7,7 421:12 422:7 432:20,21 433:2,3,8,9,18 434:4,8,14 435:20 436:4,14 437:1,7
freestanding 393:11 396:8
frequency 320:19
frequent 255:12
frequently 149:6 175:20
friedewald 220:1 233:1
friedewald's 251:3
friedman 2:14 5:13 68:4 72:7,21 120:5 135:7,14
friendly 416:12
friends 439:21
front 58:2 75:20 122:9 137:10 245:3 395:9,10
frontiers 175:5
fruit 35:15 210:10
frustrating 86:1
fsgs 348:6
fta 80:14
fuentes 4:2 6:5 313:18 314:1 349:3 351:8 364:1 364:3,6 446:22
fulfill 199:4
fulfills 114:7
full 75:9 111:6,14 111:18 136:7 180:17 214:20 295:22 314:11 331:7 333:6 336:11 352:19 402:20 434:1,13 435:1,15
fully 86:3 112:10 288:6
fun 55:15 70:17 70:18 395:2
function 11:1,3 27:9 70:22 71:4 84:9 105:12,13 139:22 140:2 157:11,17 169:7 169:11,21 173:1 173:12 220:11 226:19 228:9 231:4,9 249:4,19 293:11 294:12,13 295:8 302:15 303:10 307:21 309:16 310:4 311:12,15,19 317:12 318:17,19 330:14 331:15 332:4 333:3 345:9 349:5 352:6
function's 22:16
functional 139:15 179:16 207:3 266:9 267:20 271:10 309:10 316:21 334:6 417:1
functionally 309:11
functioning 380:12
functions 175:12 293:2
fund 393:2
funded 168:1,21 173:12 205:20 217:13 219:14 233:3 234:8 255:16 396:5 407:1 408:8 410:8 413:5 447:13,14
funder 431:22 432:1
funding 17:10 19:18 33:15,17 215:15 218:22 233:10 327:19 367:17 410:14 416:3 441:18 443:6 447:8,9,9 448:2
funds 441:19
further 55:7 73:5 105:20 117:6 127:21 150:20,21 152:3,6,7 164:20 185:16 235:10 244:22 291:13 303:6 305:13 311:17 369:16 427:12 454:10
furthering 76:16
futility 420:13
future 25:20 27:16 33:11 34:5,19 55:5 87:21 88:8 88:20 95:21 126:17 185:16,18 186:4 210:10 278:3 355:1,9,20 414:16 418:7

g

g 7:1
ga 3:15
gain 61:6 103:4 205:21 346:5
gained 36:6 42:9
gaining 280:9
gallon 246:7
gambita 325:2 327:14
game 447:15 448:3
gamma 156:22 175:10
gansevoort 87:8
gap 60:22 61:12
gaps 75:14 76:12 203:13

gardner 16:10
garner 81:22
garnering 80:10
gary 2:14 5:13 68:4 72:7,20 81:5 132:11 135:7
gaston 11:19 399:15
gather 269:9
gathering 65:15
gears 45:3 81:15 82:1 328:12
geese 395:6,8,9
geisinger 125:3
gelder 168:9
gen 428:1
gender 136:5
gene 175:11 177:6 213:19 215:20 236:14 238:3,4 239:1,10 244:19 245:14 246:17 248:3,17 250:10 251:1,16 252:5,21 255:4,8 304:1,20 304:22 309:21 316:22 317:21 323:6,18 324:20 325:3 424:17
general 19:15 36:11 104:17 110:19 129:2,17 177:21 178:13 180:5 320:13 322:9
generalizability 125:14
generalization 67:2 257:17
generally 191:13 198:20 382:1
generate 136:4 260:17
generated 209:6 267:17 278:1 285:6 314:10
generating 71:20
generation 49:12 260:8 440:7
generic 443:15
genes 167:21 172:10,12 173:9 213:20 215:5,10 221:4,6,11 227:2 235:14 236:18 240:10 241:5 248:21 249:22 250:6,7,12 251:21 252:4,14,17,21 281:12 306:22 307:1,1,4,7,17 309:3,5 310:21 316:2 318:4 319:14 322:1,5,8 322:15,18 324:19 324:20 325:11,21 424:14,18
genetic 291:12
genetics 170:11
genie 221:8
genius 398:18
geno 168:21 170:8 170:14 328:13
genome 168:6 207:14
genomic 166:17 176:18 233:18 234:20 286:19 359:21
genomics 168:13 168:15,21 170:14 173:12 174:1 219:17 233:11 234:9 280:18 284:1 286:16,17
genotype 169:15 170:5 175:17 188:22
gentleman 328:7
geographical 130:15 265:19
getting 22:5 23:22 25:6 30:4 34:4,14 46:6 50:3 83:15 115:14 116:16 125:21 138:6 139:14 142:17 146:3 156:13 184:1 200:2,22 203:9 210:7,13 225:7,8 246:9 326:6 340:17 345:22 354:13 379:4 386:17 387:1 437:19 441:2
gfr 81:16 82:6 83:7,10 84:1,2,10 84:12,21 88:13 89:4,15,16,22 90:2,4 91:7,9 92:3 93:17 94:17,19 95:12,15,16 127:9 127:21,22 135:20 135:21 136:22 211:1,11 266:10 266:11,13 267:20 279:21 332:4 344:9 348:4,7 376:6
gfr's 88:11
gfrs 136:19
gi 170:12
gifford 21:16 23:17
gift 34:5
gist 131:15
give 18:6 34:3 36:8 42:19 43:3 45:21 51:15 58:22 83:4 87:16 96:4 97:13 105:16 117:3 122:10 129:12 137:15 153:1 158:4 161:13 165:13 166:21 171:12 182:21 194:3,6 202:16 205:3,17 211:16 216:11 217:18 225:19 232:7 235:8 258:7 278:19 279:18 284:22 286:4,8 349:19 364:18 390:6 395:13 403:11 406:10 407:9 408:7 420:8 423:4 425:12,13 427:12 432:11 433:4 434:12 435:6 439:5 452:9
given 63:12 64:19 66:1 68:18 86:11 88:19 110:1 148:8 200:21 227:12 274:1 311:3 324:16 372:8 373:1 380:4 414:5 434:13 435:1
gives 105:11 106:9 167:10 196:20 266:17 366:3
giving 35:7 51:18 72:2 109:17 118:6 134:17 164:21 193:9 226:14 235:7 248:21 273:5,5 282:6 314:2 412:11
glad 96:20
glimpse 35:21 43:4 232:8
globally 87:4 308:12

globe 89:9
glomerular 157:20
glomerulitis 298:3
glomerulus 76:17 77:17
glossary 48:15 49:1 62:9,10
go 7:2 9:11 18:15 21:3 22:20 24:2 25:17 28:13 33:1 36:15,15 40:14 42:16 43:4 48:1 49:17 53:12 55:19 59:10 60:5,12 62:17 66:3,5,12 67:19 71:14 79:9 79:15 80:8 92:6 94:11 103:6,9 105:12 108:15 109:21 114:9,16 115:13,20 117:11 120:3 122:6 123:12 125:7,17 129:7,21 132:15 141:8,9,10 151:16 162:9 176:5 186:21,21 192:7 192:12 194:16 195:2,18 196:19 212:6 215:3 221:3 227:14 229:4,4 235:6 240:11 241:19,22 242:1,3 243:4 260:14 295:12 298:5 302:8 303:3 306:20 311:16 312:9 321:2 324:12 337:17 338:3,21 341:1,20 348:13 350:5 351:6 352:5 353:18 355:10 359:18,19 366:13 367:21 391:22 392:14 394:6 397:8 401:19 403:3 404:15 408:11 418:18 419:22 426:8 429:1 431:7 438:21 444:2 450:13
goal 12:2 107:21 198:8 199:1 210:12 258:16 259:16 261:9 274:12 295:1 298:20 352:15 376:15
goals 9:1 17:10 105:20 414:20
gocar 240:5,15 241:2 244:20 246:4 281:2
god 15:2 254:8
goes 39:21 46:9 52:9 53:19 61:2,8 70:17 120:13 132:22 230:16 244:14 288:1 289:8 301:5 308:5 340:20 352:12 420:13
going 8:10 9:12 11:8 12:4 14:18 16:1 17:3 18:8,11 18:12 22:17,20 25:10,18 26:16,20 26:21 27:1,2,3 29:6 31:13,17,18 31:21 33:6,7 34:15 35:10 36:8 36:12 42:14,19 43:1,3,19,22 45:3 45:9,20 46:22 47:20 48:4,18,18 48:19,20,20,21 51:14,14 52:5,14 52:18,21 53:2,8 53:17 54:18 55:11 55:15,17,19 56:6 56:18 58:4,8,9 59:22 60:5,10,15 60:20 61:17 62:3 62:17 63:14,21 64:8 66:19,21 67:3,5 68:5 69:11 69:13 71:6 72:9 73:5 74:20 75:22 76:1 77:21 79:9 80:8 81:2,5,16 83:8 84:4,17 85:7 88:2 98:2,7 100:4 101:13 102:22 103:5,14,19,21,21 104:3,9,10,22 105:17,21 106:1 106:12 108:10,15 110:12 113:18 114:9,10 118:17 118:20 121:2,20 123:11,15,20 124:1,10 125:19 125:20 127:21 128:15,15,22 129:11 131:8 135:15,21 136:3,6 137:6 138:5,13 139:20 140:5 143:6 151:15 154:9 156:1,6 158:16,19 159:4 159:12 163:12 164:10,14 165:15 166:11 167:22 168:8 173:1 177:22 181:7,13 182:4 184:9,10,11 185:5 187:22 190:14 191:20 192:12 193:7 195:22 196:3,6 197:16,18,20 201:2,6 202:2 203:8,13,16,18 204:4 205:9,13,17 210:3 211:2 212:10 213:3,4 214:20 215:3 218:7 219:13,21 220:3 225:22 226:4,5,21 227:14 230:4 233:18 241:14 242:15,20 245:20 256:2 258:12 260:2 261:17 262:20 283:11 287:2 293:13 294:17 295:10,18,21 296:6,9,20,21 297:20 298:1,2,4 299:1,18 300:3,12 300:17 302:8,9,10 303:19 305:8 306:13,18 314:10 315:8,9 318:6 325:12,17 328:2 328:12,13 340:2 344:12 347:2 350:8 352:17 354:4,11 360:6 362:8 366:9,13 367:18 389:5,10 389:12 391:3 394:16 396:16 398:14 402:15 403:16 405:20 406:15,17 407:14 420:6,15,19 421:11 423:4 430:11 432:3 435:9 438:8,15 439:1 441:22

442:5,17,18 443:11 448:8,20 449:4,6 450:9,13
gold 65:13 67:14 69:4 204:8 229:20 229:21
good 23:14,19 25:4 26:6 33:20 34:17 35:6 47:7 70:17 73:3,7 74:14 87:12 90:15 90:18,22 93:11 94:2 101:8 109:20 116:16 117:3 118:6,9,14 120:18 124:2 127:15,16 127:17 129:5 137:18 162:4 173:4 187:4 195:13 209:9 231:18 242:21 245:19 250:20 256:5,22 257:4,7 257:7 264:8,15 268:18 269:3,19 269:22 272:13 276:20 278:2 280:3 282:21 285:4 289:3,5,21 294:5,19 295:8 299:8,16 302:15 303:10,22 306:7 314:18 316:15 317:1,9,10 328:6 343:15 344:17 345:1 350:20 355:6 366:15 389:22 390:20 391:10 393:18 394:14 395:19 396:14,21 398:3 398:21 421:11 440:7,20 445:3
goods 209:8
goose 395:10
gorilla 407:22
gosh 39:20 362:7
gotten 73:3
gottlieb 40:21 41:2
government 7:20 386:17 430:13,22 448:1
gpdc 274:11
gradation 153:1
grade 142:2 224:1
graded 272:19,20 381:14
grading 267:6,11
graft 11:10 27:8 29:15 99:4,13 100:1 105:21 119:3,6 123:14 130:2 139:6 140:10,12 141:3 141:12,15,18,19 148:16,16 151:19 151:20 155:22 157:17 173:10 184:12 189:20 201:17 202:10,18 202:18 203:19 204:15 211:19 215:18 216:21 227:18 232:15 237:19,22 238:1,8 241:18 242:2,20 243:7,11,13,13 244:1,22 245:16 245:18,20 255:13 257:3 264:18 268:20,22 270:21 275:14 277:2,3,4 277:6,13 278:4 288:12 289:12 290:3,7 296:11 298:8,9,16 330:20 331:12,12,22,22 332:1,8,15 334:16 351:18 354:21 362:2 369:20 376:14 379:20 380:16 381:20 382:9,11,18 383:4 383:8,21,22 387:22 441:19,19
graft's 16:1
grafts 11:4 99:12 292:17 359:5
gram 267:16,16
grams 87:5
grand 120:8
grant 167:22 303:18 408:9,13 410:3 438:22,22 447:13
granted 14:20 91:1 106:8
grants 154:17 401:2 410:22 438:16
granular 142:3 167:16 377:16
granzyme 248:4
graph 65:21 171:9
graphically 61:9 65:20 176:20
graphs 171:9
grateful 73:1
gratified 92:17
gratis 17:8
graveyard 10:8
gray 324:22 325:4
great 1:15 21:14 34:18 51:12 52:14 54:2 55:13 98:1 135:14 138:2 154:11 162:14 167:20 180:10 189:6 198:11,14 248:12 341:10,11 346:5 353:10 391:15 394:3 396:7 397:22 406:6 426:8 439:11 441:8
greater 90:8 91:9 179:20 186:6 220:9 223:18,22 225:14 228:5 372:12
greatest 123:3
grew 413:7 430:16
grid 149:19 150:7
grinder 125:8 340:21
ground 22:6
grounded 370:7
group 12:19 15:17 15:18 17:14 19:4 21:1 23:19 29:20 32:16 39:3 47:8 77:9 87:8 97:14 97:15 108:22 116:4 118:9 126:7 126:18 139:18 142:14,14 153:3,8 154:2 160:22 164:15 166:8 184:4 202:20 210:15 222:12 228:20 238:19 241:12,14,18,19 241:21 251:3 258:10 278:17 294:2 301:15 303:5,7 305:12 309:1,20 311:14 312:12,16 316:12 316:13,17 318:7 318:21 332:6 333:19 353:19 364:11,11,13 369:22 377:22 393:5,9 394:5

396:2 397:20 399:10,13 402:8 405:4,7 407:4 408:8 409:8 410:3 411:15,16,22 412:3,7 416:1,6 417:13 419:9 444:6 448:12
group's 174:20
groups 48:14 148:3 172:14,21 183:21 213:11 238:10 278:22 291:8 312:14 319:5 327:15 344:2 356:14,15 359:6 398:13 405:5,16 409:10 410:9 411:10,14 411:17,21 415:9 416:5,10 417:10 417:13 418:22 419:2,5,10
grow 23:18 86:13 413:7
growing 42:15
growth 75:19
guarantee 86:21 92:20 445:10
guess 24:2 95:18 122:12 184:5 196:6 214:5 225:19 261:22 292:3 392:10 429:14 449:15
guessing 133:13
guestimate 280:17
guests 7:21
guidance 40:1 64:2 73:15 92:21 108:20
guide 108:11 116:4 155:10 228:19 240:2 302:1
guideline 369:2,7 369:13 373:11
guidelines 84:7,19 170:4 368:22
guiding 76:5 354:20
guy 65:21
guys 122:16 275:6 284:10 290:12 347:16 389:16 396:22 400:8
gwa 168:18
gwas 169:3 172:22

h

half 21:12 162:21 163:7 169:22 170:6 325:21,22 428:16
hallmark 442:5
hallway 137:15
halmond's 399:10
halt 436:1
hampshire 1:14
hand 94:16 236:17 237:21 405:3
handle 321:17 397:22 398:3
handled 133:18
hands 17:4
handy 398:8
hanging 35:15 210:10 450:12
happen 11:8 24:9 26:6 41:13 65:2 70:5 110:14 162:2 164:10 167:22 301:13 340:2,13 406:18 441:22
happened 120:20 165:3 231:22 318:10 319:16 400:21 412:5 431:2 438:19
happening 99:2 157:20 196:2 207:19 211:13 214:17 415:14
happens 31:20 56:9 60:21 207:13 228:5 241:19 278:19 297:10 323:22 399:19
happy 7:22 55:14 84:2 90:9 166:11 232:21 350:12 358:21 406:7 439:17 451:22
harboring 228:16 231:6
hard 18:5 30:2 93:4 118:2 122:12 189:18 232:9 266:21 302:20 339:8 354:22 363:17 392:22 398:12,12 402:8 402:21 403:18 404:13 413:12 431:12 451:16
harder 88:21
hardest 62:22
harmonization 80:2 416:12
harmonized 419:8
harness 203:10 208:22
harnessed 125:2
harnessing 15:9 125:5
harvested 33:22
hazard 93:12,14 145:16 146:3 382:5,7
hdl 91:2
he'll 30:20 98:10
head 4:3 105:11 126:20 128:21 146:7,7 254:9 381:21 403:9
headaches 14:22
headed 49:2 123:16
heading 246:21
heads 191:1
health 3:16 12:8 14:1,4 87:2 125:7 195:21 211:16 212:8 347:4 381:1
healthcare 28:1
healthy 26:12 77:14 78:19 79:21 136:12,22 316:17 320:8 321:1 322:6 322:14 323:2
hear 7:15 20:12 21:6 26:20 43:16 44:3 49:16 140:5 140:21 156:1,7 159:12 184:15 235:10 281:12 338:6 359:2 360:6 364:20,20 388:14 449:15 450:21
heard 75:17 82:12 98:15,22 101:16 101:21 103:20 108:4 138:2 155:11 159:11 183:3 247:18 253:10,19,19 271:14 273:20 328:22 344:14 351:14 358:18,22 359:6 362:21 364:16 383:20 386:14 387:13 439:20
hearing 13:8,8,10 358:14 367:10
heart 176:4

heat 84:11 250:4 251:6
heck 66:14
heeger 3:8 5:18 151:14 153:22 154:8,11 181:17
held 67:18 359:14
hello 51:1 366:12
help 14:8 18:2,12 21:18 24:16 30:22 31:10 48:10 54:19 54:21 55:16 112:1 115:14 118:4 156:5 164:16 205:21 230:19 247:19 313:10 329:11 377:14 396:10,13 403:8 450:14
helped 83:1 218:22
helpful 84:6 116:21 124:7 173:5 197:17 255:10 258:14 277:21 278:13 391:3 394:16 397:1 398:6
helping 21:19 74:15 87:7 116:4 177:16 192:11
helps 44:9 47:12 126:22 187:20 420:13 421:6,21
hematologic 170:12
hemodynamic 94:18
hepatocellular 376:4
her2 423:22
hereto 454:11
hernandez 4:2 6:5 313:18 314:1 349:3 351:8 364:1 364:3,6 446:22
hesitant 449:21
hesitate 112:14
heterogeneity 89:6 92:4 128:5 130:14,21 181:21 190:21 198:7,13 198:17 261:8,15 261:21 371:21
heterogenous 291:4
hey 449:11
hi 54:6 450:11
hierarchical 371:8 374:4
high 35:15 53:17 72:2 85:22 86:2 148:15 149:10 152:15 153:3,8 157:10 158:6 164:17 176:8 179:9 183:7 195:12 205:21,21 237:16 238:6 239:3 241:8,14,18 241:19 243:10 245:3,9,13 249:21 280:17 281:16 282:17 288:2,8 291:19 298:15 302:9 306:14 310:12 320:15 369:5 422:3 425:5
higher 71:16 84:12,13,13 88:5 91:14,19 92:3 145:19,22 157:6 158:9 160:6,17 183:8 191:16 207:8,11,22 214:11 231:5 241:17 242:1,2 251:15 323:2 324:9 331:14 332:7,13,14 372:11 382:10 385:1,6 387:1 388:5 412:15 449:22
highest 85:11 86:5 165:10,18 290:7
highlighted 14:13 79:12 323:14 375:16
highlighting 19:20
highlights 185:11
highly 126:8,17 208:14,14,15 210:16 215:6 244:21 281:2 369:19 424:15
highway 123:11
hill 154:14
hints 120:3
histologic 220:7 227:10 231:10
histological 56:14 247:14 273:8 436:2,5,16
histologically 214:2 216:21 217:6 225:16 226:5,6
histologies 435:21 436:21
histology 190:17 212:2 266:8 269:12 275:12 427:9 428:8 435:15 436:10
historical 15:7 334:4
historically 99:11 452:18
history 7:15 24:21 54:10 188:3 397:19,21,22 408:7,11 413:11 417:10 433:7
hit 27:19 137:6 288:3 302:9 344:12 446:14
hits 114:8
hla 13:1 138:9 139:5 140:8,8,16 140:17 141:11,18 142:6 143:8,14,22 144:5,8,14 146:8 146:10 149:21 150:3,3,4,8,15,19 152:4 186:4 195:4 205:7,15 206:9 207:6,7,14,18,19 208:2,6,12 210:7 210:8 237:9 239:1 245:9 255:11 284:7 392:3 394:6
hlamatchmaker 144:6
hmm 48:17
hoffman 16:16
hold 67:3
holden 16:13 17:7
holistic 258:13 259:17 342:3
holistically 351:7
hollinger 2:11 5:10 50:21 54:3,5 54:6 110:22 114:19 115:19 116:6 120:11 121:18 122:6,18
home 161:14 214:4,8 216:20 265:12 407:6
homogeneity 182:6,19 183:6
hone 121:12
honest 17:3 430:22

honor 73:9 336:21
honoraria 138:20
honored 8:1
hope 7:10 32:15 126:10 295:7 301:12 367:11 408:12 439:15 443:1 444:21
hoped 32:21
hopeful 108:12 429:8
hopefully 25:19 31:6 33:9 40:4 60:21 83:5,20 86:17 104:12 129:12 289:11 329:16 333:3 336:10 345:10 412:22
hopes 414:1
hoping 338:21 443:4
hopkins 2:18 97:14
horizon 373:3 438:9
horizontal 250:12
hormonal 424:2 425:4,6 426:5,6 426:10,11,12
hormones 424:5 425:12,13,20
horror 439:21
horse 198:17
hospital 4:9 234:12 366:22
hospitalization 386:2
hospitals 447:3,9
hot 10:4 167:6
hour 209:7 389:8
hours 267:16 449:1
house 103:16
housekeeping 8:4 393:18
howling 28:17
hub 215:5
huge 194:14 260:2 393:20
human 285:21
humans 141:13 195:14 286:11
humoral 378:15
hundred 73:18 254:22
hundreds 304:4 399:13
hungry 340:17
hurt 165:3
hurting 192:12
hy 206:3,5
hybridized 248:18
hypertension 351:3
hypocholestere... 351:2
hypotheses 303:17
hypothesis 70:2 258:9 360:10 390:18
hypothesize 249:1 274:19 335:13
hypothesized 365:16
hypothetical 191:18

i

i.e. 236:12 330:20 331:1,17
ibm 395:3
ibox 27:14 32:8,14 105:15 107:8 129:2 190:12 211:1 258:6 260:7 261:3 265:13 266:2,22 267:4 268:4,11,14,17 269:1,17 270:4,6 270:12 271:1 276:14 279:16,20 280:8 282:20 284:22 286:4 288:22 290:22 293:22 298:2,15 310:1 343:8,14 352:16 355:2 401:19
icahn 3:9,19
icam 172:12
iceberg 207:17
idea 26:9 33:5 53:7,22 104:1 105:8 109:13 125:2 128:12 129:17 161:20 175:11 180:15 193:17 197:21 210:5 239:19 290:16 314:15 338:20 352:16,21 352:22 395:12,19 403:11 431:17
ideal 11:1 99:6
ideally 161:11 165:16
ideas 33:19 34:17 34:17,18 351:20 398:21
identical 141:11 224:12 372:5 392:3 394:6
identification 203:15
identified 102:16 143:17 173:17 189:15,20 193:19 215:4 221:21 235:14 236:18 240:11 245:4,5 248:1 250:10 253:20 292:18 317:13 319:15 323:20 324:3,4,6 325:20 327:4 334:20 356:16 418:5 424:14 426:15
identifies 169:3 192:6 237:19 243:5 245:15
identify 17:22 18:1 102:1 137:22 153:7 158:13 169:6 170:16,22 176:21 204:7 235:2 243:12 245:2,13 247:19 252:14,16 255:4 276:14 282:17 294:13 299:19 312:5 314:16,17 315:1 317:18 423:8 448:13
identifying 115:10 173:8 228:14 243:10 245:19 248:3 251:17 252:7 281:16 292:12 328:3,19
ifta 224:1 267:8 274:20
igg 139:12 175:11
ignoring 350:14 350:16
iii 103:22
il 2:16 172:12,15 217:18 273:5 305:20,21 369:3 370:20 372:20 373:7,16 374:1 381:17,21 382:6 386:6
illustrate 193:4

illustrating 220:15
image 138:18
imagine 159:3
imagined 347:21
imaging 340:14
immediate 20:3 373:3 425:10,18
immediately 17:20 30:17 203:18
imminent 438:8
imminently 75:6
immune 140:18 141:6 142:16,21 142:22 157:2 159:15 166:22 168:14,14 172:6 172:15 176:8,18 177:16 183:4 200:13,19 202:2 206:22 208:15 213:18 228:15 233:18 239:14 247:11 293:12 300:5 307:21 316:19 318:22 319:1 327:12 347:14 359:21
immunity 156:18 157:1 213:22 315:16
immunization 379:16
immunogenicity 146:10 148:7 206:6
immunologic 139:11 281:21 368:16 369:5 373:9 382:2
immunological 235:17 281:10,16 299:20 441:20
immunologically 368:6
immunology 4:3 175:5 250:1
immunoregulato... 305:22 306:15
immunosuppress 172:16 231:17
immunosuppres... 228:15 302:18 322:2 323:9 376:17 378:17 388:12
immunosuppres... 10:12 320:14 323:10
immunosuppres... 349:12
immunosuppres... 11:4 136:16 141:15 149:11,13 151:6 154:21 155:2,16,19 162:10 165:14 172:1 179:22 229:1 239:21 240:1,3 282:15,18 301:7,19 302:14 303:14 310:15 311:1,12 312:2,15 312:17,22 313:6 314:19 315:2,18 315:20 318:20 321:11,13,14,16 322:16 324:13 325:5,6,10,13 326:14,17 327:1,2 345:4 349:7,9,11 349:15 355:12 359:10 367:15 368:3,4,13,16 369:1,14,18 370:1 370:6,22 374:22 375:18 376:8,10 376:11,13 377:5 379:8,10,18,21 381:15 383:7,14 383:19 384:3 385:10 387:4,9,15 387:15,16 388:2 388:21 390:2,13 442:3
immunosuppres... 355:15
immunosuppres... 261:12 301:9 306:1 313:21 354:14 368:18 380:7 392:5 394:21
immunotherapy 369:8 422:13 427:15 432:3 435:8,10
impact 100:2 196:4 203:19 243:13 288:12 343:9 362:18 379:10 380:15,16 382:12 384:16 385:15 404:12 450:1
impactful 380:1
impacts 385:11
impair 14:21
impatient 20:13
implement 268:1 287:12 351:9 448:22
implementation 46:15 170:4
implemented 16:8
implicate 383:18
implications 161:4 378:2,11 385:9
implicit 441:17
import 258:22
importance 221:8
important 25:5 28:2,4,5,5,15 39:18 56:7,16 58:15 59:2,16 63:14 64:5,13 65:13 68:17 69:5 69:10,21 71:17 82:5,17 84:14,15 84:18 88:15 89:11 91:12 99:12 110:8 113:13 118:13 124:16 129:20 130:8,12,13 140:7 155:21 156:4,11 158:1 159:8 168:11 174:16 175:1 184:17 195:8 196:14 204:6 205:11,14 209:3 211:17,17 212:12 216:17 217:3,3 220:16 223:2 226:1,2,4 226:16 230:22 240:20 256:16 259:1 260:3,17 261:7 262:12 263:8,18 264:6,19 264:21 265:8,16 265:21 266:7,10 266:11,12 269:15 271:13 274:2,7,7 274:15,20 275:10 275:13 276:10 277:9,15 278:5,8 278:12 282:5 284:6 286:14,16 288:18 289:4 297:16 299:6 303:15 305:21 307:20 308:17 309:20 314:4,5 316:6,11 317:17

321:3 340:4 343:17 345:5 351:6 383:20 384:2 388:13 397:6,7 414:13,15 414:17 416:16 430:14 447:15 449:6,16
importantly 85:14 91:13 102:6,8 153:5 230:1 254:18 263:3 269:20 275:22 277:10 316:16 317:9 320:5
impossible 263:1 294:13 304:5 390:1 396:5
impressed 338:1
impressive 91:22 92:4
impressively 91:9
improve 11:5 24:8 36:15 102:12 155:5 158:16 166:4 211:10 271:16 287:12 376:14 377:19 383:17
improved 94:15 141:12 147:7 148:5 149:1 227:18 237:11 271:8,14
improvement 147:15 150:18
improves 266:19 397:9
improving 10:22 11:2,3 12:2 127:14
inactivity 347:15
inadequate 149:13 228:22
inadvertently 250:18
inaudible 8:11 28:11 106:11 131:11 167:12 175:14 179:2,15 179:16,17,18,19 179:20,21,22 180:2,3,11 185:19 189:21 191:7 196:15 203:20,20 208:3 217:18,21 234:18 244:15 248:6,7 250:1,10 256:20,20 258:11 258:19 259:6,12 259:17 260:18 261:6,11,15 262:5 262:5,8,10,11,14 262:14 264:2,2,3 266:14,14 267:3,8 267:19 268:8 269:16 270:1,2,7 270:17,18,21 271:6,9 274:8 275:15 277:3,9,10 277:12 279:17 280:1,5,5 285:22 286:3,17 288:19 293:8 296:2 299:21,22 314:9 315:1,9,16,22 316:20,22 317:15 317:16,17 318:13 318:16 319:11,20 320:13,17,18 321:9,12,21 322:16,21 323:4 323:12,21 324:11 324:17,21 325:4,9 325:14 326:13,14 326:15,17 327:8,8 327:12 332:6 334:16 337:1,4,5 337:9,11,14,16,18 337:18,19,21 338:1,2,21 340:2 342:9 346:12 348:12 349:7,21 350:20 354:7 360:20 365:6 390:3,12 417:18 426:16 427:10 435:22 438:10 440:18 447:11
incarnate 76:15
incentivize 107:18 415:4
incidence 358:4 368:7 384:3,12,18 385:1,3,7 403:14
incidents 388:3
incipient 156:4
include 20:22 25:16 165:19 281:2 290:7 371:17,22 377:6 384:2
included 173:3 210:14 221:12 234:10 281:3 292:19 317:6 327:15 381:8 387:8 392:5 439:13 440:10 442:18 447:4,11
includes 39:5 64:12 249:7
including 7:20 78:13 95:8 159:13 169:1 182:2 186:3 220:19 233:9 255:18 272:10,11 286:5 368:13 371:2 373:6 379:13 380:21 383:1 384:4 387:10 440:11
inclusion 63:9 149:6 190:21 217:1 260:13,22 278:15 334:10 380:5
incoming 11:22 20:2
incompatible 255:11,11 284:8
inconvenient 357:5
incorporate 28:19 52:6 166:1
incorporated 219:17
incorporating 245:10 371:14
incorrect 357:20
increase 66:21 91:11 187:21 199:15 230:5 231:13,15 310:5 326:13 354:21 383:6 436:2
increased 82:15 92:1,2 146:3 149:11 172:1 185:7,7 213:22 214:3 247:17 255:4 321:8 374:2 383:2 386:5,10
increases 95:11
increasing 10:22 197:6 268:16 351:1 373:5
increasingly 381:3 417:2
incredible 446:4
incredibly 445:21
incremental 290:20 291:3
ind 353:4
independency 262:14 274:11

independent 151:19 157:13,17 179:6 209:10 224:8 229:19 235:3 240:16 241:10 260:19 263:6 271:7 322:2 322:10 324:13 409:19 410:2
independently 79:7 80:22 145:17 148:17 227:6 415:20
index 237:9
indicate 140:3
indicated 318:22 348:11
indicates 139:9 183:13
indication 164:21 236:6 372:22
indications 11:9
indicative 364:10
indicator 46:1 139:21 433:20
indiscriminate 231:2
individual 12:5 16:13 18:12 21:17 46:9 80:21 109:4 110:19 126:5 133:17 185:19 188:9 196:16 232:5 237:10 238:11 245:2,3 260:5 281:16 282:17 339:7,16 349:9,15 416:1 419:12
individualize 155:5 201:8 229:1
individualized 1:6 165:20
individually 155:4 392:19 398:19
individuals 16:21 21:12 70:21 71:4 71:5 73:18 75:3 78:19 80:17,18,18 168:15 170:14 176:21 179:19 180:1 193:20 237:13,19 238:12 238:16,19 241:22 242:3,4,7 243:3,6 243:10,17 244:1,2 244:18,21 245:6 245:13,19 248:5 249:3,18 250:21 251:17,19 281:2 445:1 450:17
induce 269:15
induced 72:14 77:9
induces 143:9
induction 162:6 165:13 238:18 280:22 319:8 367:2,14 369:3 370:20,22 372:18 372:19,22 373:2,4 373:6,13,19 374:3 374:13,16 375:2 379:18 381:13,15 384:13,16 385:11 386:4,7,18 388:1 388:6
inductions 390:16
industry 7:20 15:18 17:15 19:18 20:17 23:18 25:4 25:5 28:21,22 30:3 42:3 102:9 107:3,19 314:6,9 350:2 378:22 414:18 430:13 438:4
ineffective 405:2
inept 396:2
infamous 12:21
infected 13:15 248:9
infection 160:9 164:3,3 315:19 326:10 368:14 384:14
infections 78:20 160:12,13 384:4 384:18
infectious 13:15
infectives 13:11
inflammation 159:11 202:9 211:9,9,19 214:6 215:11 216:10 217:5,16,19 218:1 218:6 245:15,16 245:17 264:1 272:15,21 273:9 275:14,15 285:1 354:17 357:10 359:17
inflammatory 248:8
influence 199:8 320:4
influenced 421:18
influencing 323:19
inform 228:8 232:5
informal 345:17
information 15:10 74:22 77:12 79:8 119:12,21 145:12 158:5 179:3 180:12 203:11 209:1 217:2 226:14 247:20 267:13 316:5 319:9 336:1 341:13 355:17 362:4 367:11 370:8,12,19 377:16 418:8
informative 126:7 163:21,22
informed 136:15 267:1 340:11 388:12
infrastructure 50:9 416:7,9 438:20 443:2 445:9 447:10
infrequently 380:3
infused 217:16
infusion 441:5
inherent 94:4 280:16 380:6
inhibitor 168:10 168:18 345:16 371:4 376:7
inhibitors 161:22 162:17 346:10 369:9
inish 2:10 5:9 7:5 9:16 35:7 40:2 50:20 51:1 54:5 55:14 72:21 73:2 98:14 109:19 110:22 132:2 173:3 355:4 389:19 397:20
initial 157:7 199:11 240:6 250:19 251:1 316:8,14 318:14 324:8 327:13 385:16 388:5 413:4,12 437:5
initially 135:17 157:22 236:13 247:7 316:4 419:18 430:12

initiate 336:8
initiated 11:15
initiative 3:16 12:8,9,11 14:1,4 14:11 16:8 41:18 42:8 76:14 133:16 134:1 166:22 167:13 168:22 177:15 195:21 348:11 447:2
initiatives 42:6,22 102:3 167:11 418:3 447:22 448:2
initiator 140:17
injured 204:11
injuries 353:20
injury 72:15 77:8 77:9,13 154:10 155:22 156:4 160:8,14 166:4 174:19 202:10,18 203:11 204:7,13 212:22 213:1,4 214:5,16 215:18 216:2,12,13,16 250:15,16,17 262:9 263:22 274:20 344:19 346:18 347:1,10 347:15 348:15,22 351:5 352:8,12 354:1 357:7 358:19 368:16
inker 93:4
innate 213:22
innovation 16:6 28:12 36:9,19,20 38:19 362:20
innovative 415:2
inpatient 381:6
input 103:12 124:12 168:5 439:17
inquisition 120:8
inside 129:21
insights 127:1
inspiring 22:2
instability 435:9
instance 47:8 78:17 79:12
instances 102:14 321:20 448:21
institute 7:15 40:3 43:9 51:2 55:9 73:14 74:15 76:4 407:14 408:6 414:5,10 415:8 441:16 450:21
institution 289:1 418:22
instructive 183:19 184:15
instrumental 9:17 23:22 106:6 107:7 233:3
insult 71:8
insults 135:9,10
insurance 195:6 384:9
int 274:11
intact 139:11 176:12
integral 219:2
integrate 259:18
integrated 32:1 257:3 287:13 377:15
integrating 46:6 96:10
integration 257:17
integrative 266:12 271:5
intellectual 326:21
intend 334:12
intended 62:14 63:6,18
intending 122:20 328:17 329:15
intent 111:4,9 112:3 115:21 116:13 117:8 119:9,16 183:5 302:13
intention 92:11
intentionally 136:14
interact 61:6
interacted 77:4
interacting 116:3
interaction 12:11 116:1 120:9 177:9
interactions 10:11 113:3
interactive 452:21
interacts 141:4
interchange 316:19
interchanged 316:4
interest 22:10 25:6 256:16 371:13 372:6,10 372:15 384:1 394:4 423:3 431:1 431:2 451:5
interested 8:17 43:4 96:15 140:6 156:9,17 159:21 166:9 181:3 206:15 218:17 370:5 397:12,20 400:19 404:9 432:7 451:21 454:12 455:8
interesting 35:12 39:14 126:2 154:15,20 165:6 175:8 176:2 224:17,18 238:15 241:11 245:11 246:2 251:20 279:1 281:8 307:17 311:10 314:4 324:10
interestingly 42:20 96:18 175:15 226:7
interfaced 260:4
interfere 277:12
interferon 156:22
interferons 159:15
interim 334:2 336:3,9 420:11
intermediate 148:15 152:15 153:8 238:6,17 241:12,21 421:15 423:1 426:5
internal 265:18
internally 136:10
international 17:8 19:3 97:17 260:8 369:16
internet 119:10
interpret 58:9
interpretable 380:5
interpretation 57:16 92:15 276:5 371:15
intersection 192:20
interstitial 263:22
interval 371:16
intervals 374:11
intervene 243:7
intervention 46:3 79:18 190:4 268:6 268:10 269:18 270:13 282:6 289:18,19 333:1,2

335:14,15 419:22 420:5 421:18
interventional 11:18 272:6,7 296:8 363:10
interventions 93:8 114:2 258:4 355:4
intolerance 254:18
intolerant 317:14
intra 247:15
intraclass 371:22
intragraft 252:1
intriguing 172:3 174:8
introduce 50:20 50:21 54:3 55:8 121:3
introduced 40:8
introducing 56:21 59:18 220:6
introduction 35:1 55:14 246:16
introductory 202:14
invasive 204:9,17 228:1,6 231:3 247:16 253:11 263:20 357:18
inventions 205:22
invest 296:18
investigational 138:21 417:22
investigations 4:14 418:8
investigator 416:17 447:7
investigators 15:11 19:4 77:4 87:9,11 97:16,18 246:5 334:19 410:10 413:9
investment 431:1 432:2
invitation 138:12 256:6
invite 9:7 109:1 328:10 359:1
invited 300:10
inviting 23:8 234:1 300:9 378:5 407:18
involve 253:11
involved 19:17 30:4 109:10 213:20 246:5,8,10 342:3 353:6
involvement 413:8
involves 39:4
iom 415:7
ip 161:10 431:9
irb 394:15 415:17
irbs 405:22
ireland 173:3
irrelevant 304:12
irrespective 240:3
irrespectively 266:9
isaec 16:14
isolated 140:14 215:9 249:8 251:5
issuance 74:7
issue 31:7 37:13 37:13 40:17 70:6 95:17 126:14 158:12 203:9 248:11 249:14 299:1 315:7 341:7 346:17 390:9 391:19 392:11 393:2,20 396:18 399:3,5 403:5 404:8 412:1 431:10
issued 74:8,9 75:3 80:14 369:17
issues 19:17,18,20 31:10 40:17 257:9 290:2 297:18,19 298:22 364:7 385:14 390:17 399:4 408:1 422:21 441:6
it'll 127:18 203:9 216:12
item 442:8
items 135:3
iterative 116:2
itn 310:18 312:4

j

jamale 246:6 334:18
janet 41:3 50:4,11 188:16
january 11:19 18:13
jci 302:12
jeopardy 451:15
job 21:18 220:5 244:4 407:7 445:3
jobs 445:2
john 2:13 5:11 46:22 48:4 49:16 55:8 72:1,11 73:2 74:17 109:14 110:15 113:21 220:1 233:1 251:3
johns 2:18
join 339:2 367:7
joined 18:17 21:1 54:8 340:12
joint 17:14 142:14 340:9
jokes 389:11 397:18
josef 2:17 5:14 81:16
journal 174:13 203:21
judgment 280:20
juices 41:19
july 416:2
jump 18:8 109:4 326:21 327:7 349:9 358:7
june 50:11 426:2
jung 335:4,6
junior 406:14 443:18

k

k 150:4 175:14
kakani 452:16,17
kappab 215:7
karen 246:21 252:6
karynn 455:2,13
katherine 2:11 5:10
katherine's 121:4
kathy 50:21 54:3 54:6 110:16 115:20
kaufman 20:4
kdigo 84:7 369:2 373:10,10
keep 42:15 43:18 117:19 118:10 184:13 290:4 291:8 356:13,14 407:5 443:4 450:20
keeping 407:1
keeps 136:3 177:12 197:13
keeting 452:12,13
ken 3:14 6:4 20:2 24:22 29:9 31:3 103:18 300:2 314:14,22 315:21 317:16 320:10 358:12 359:4 363:17 389:13 394:1
ken's 193:16

keslar 246:21 252:7
kevin 3:16 195:20 340:22 350:17 362:6 383:20 452:1,2
kevin's 200:8
key 13:2 37:1 87:11 102:16,17 153:21 257:13 368:1
khi 20:16
kid 28:11
kidding 269:8
kidney 3:16 11:12 12:2,8 14:1,4 18:18 22:14,16 25:10,13,14 34:8 64:10,11 68:6 70:21 71:3,3,9,12 72:12 77:9,13 84:7,8 96:9 98:18 124:3 125:5 148:14 149:15 152:11 154:10 157:10 159:11,19 161:22 168:4,19 173:2,12,15 175:21 181:16 195:20 196:2,3,5 202:3 204:20 206:12,14 207:22 208:14 216:2 228:9,12 229:2 249:14,15,16 253:16 256:3 257:3 259:3 260:9 283:12 284:10,18 285:18 286:10 295:2,6,15 297:19 298:18 300:4,6,21 303:10 305:3,4,6 310:16 311:12 312:5 313:19 319:3 330:2 333:8 340:15,15 343:3 344:19 349:5 351:4,5 352:6 367:2 368:6,8,22 372:18 374:21 379:3 388:4,4 392:3 394:7 397:12 398:1 399:19 400:11 401:16 403:21 404:2,4,20
kidneys 124:4 206:5 243:5 245:19 282:21 293:7,8,9,21 294:8 298:21 303:1 345:18 346:9
kill 395:19
killer 213:21
kim 21:16,18 23:17
kind 14:19 17:1 18:6 22:21 26:8 28:13,13 30:17 31:16,17 38:22 41:14 44:2 53:3 54:16 61:8 72:2 109:17 110:19 114:17 116:7 120:3 122:12 123:10,16 124:12 124:12 125:8 126:14 130:21 131:14 138:12 147:22 157:4 159:19 161:2 167:10 181:6 182:18 186:3,4 187:18 190:17 196:14 202:6 203:6,13 204:5 205:21,21 206:2 208:4,11,19,22 209:1 210:6 212:4 215:6,8 216:2,9 217:1,12 218:2,18 224:17 230:20 253:14 256:6 259:18 261:21 264:5 265:8 272:18,18,19 274:10,22 276:1 277:16 280:4 283:4,12 284:14 285:7 287:14 288:1 290:16 291:1 294:22 298:19 301:12 303:2 305:11 306:15,21 307:17 308:16 339:9 344:19 346:7 351:5,15 352:3,9 354:6 361:8 389:12,13 390:21 395:2 396:7,16 397:16 399:18 409:16 415:10 416:6 430:9,16 438:15 439:6,9
kindly 122:17 451:18
kinds 49:17 159:13 165:7 166:10 423:14 431:14
king's 314:12
kiosk 8:5 137:10
kirk 10:1
kit 216:2
kits 161:7
klaus 30:20
knew 11:14 276:17 320:11 424:4
knock 397:15
know 8:18 10:15 13:18 15:21 20:11 20:18 21:15,16 22:7 27:22 28:17 30:17,18,19 33:20 34:4,6 35:14 36:7 37:18 40:1 45:4 48:4 51:12,16 52:9,11 56:13 57:17 58:8 60:4 62:20 63:5,6,10 63:11 64:11,20 65:16,22 66:9,11 68:19,21 69:4 72:3,15 75:12 81:8,10 83:2,3 85:1 86:1,4 90:13 91:16 94:7 96:7 96:11 97:18 98:2 101:5 107:6 108:22 109:8,12 109:13,14,17 110:16 111:7,8 112:14 113:9,19 114:17 115:1,9 117:1,1,10,21 120:2,6,12,14 122:2,9 124:9,10 124:12,13 127:7 127:13,15,20 130:16 131:13 135:10 154:17 156:4,8 157:6,14 158:12,15,20 159:14 161:9 163:15 164:5,11 164:19 165:15 166:8 167:12 169:10 170:5 175:17 177:7 178:12 183:16 184:8 185:11 186:13,14,16,18

186:19,21,22 189:17 190:15,18 191:3 194:8,11,21 194:21 199:12 200:16,19 204:2 204:10,21 218:16 225:21 226:3,13 228:5,17 229:15 231:22 247:13 250:9 251:9 253:13 254:9 256:19 258:22 261:4 262:7 263:11,13 265:7 267:6,8 269:4 270:15,18 272:8 272:20 273:20 274:7,19 275:1,9 275:18 278:3 279:22 280:10,21 282:4 283:6,8,15 284:7 285:19 286:6 288:11,16 288:16 289:14,20 290:3,5,8,22 291:4 293:6,10,13 293:16 294:2,2,7 294:8,13,14,16,17 294:18,21,22 295:2,4,6 297:9 298:21 305:5 310:1,15 312:12 316:5,10 321:14 322:12 326:2,6 329:10,22 330:18 333:22 335:7 336:18 338:20 339:10 341:7 342:3 343:14 344:1,11 345:9,10 345:22 346:2,4,8 346:10,17 348:10 349:1,8,19 350:1 350:2,9 351:9,10 351:22 352:1,2,5 352:8,10,21 353:14,20 354:11 354:15 355:8,11 355:18 358:18 359:11 360:15 361:17,18 363:3 363:18,19,20,21 363:21 365:6,17 368:3,15 372:20 376:9 377:4 378:22 379:2,4 389:11 390:6,8 392:2 393:18,19 393:20 396:1,8,19 397:15,18 398:17 399:16 401:11,13 401:16 402:10 403:1,12,15 405:21 407:5 424:7 425:2 430:11 432:16 434:17 438:11,16 439:21,22 441:18 442:6,10,15,20,22 443:3,15,16 444:18,22 445:16 446:5,10 447:20 450:3,10 451:18 451:22

knowing 83:15 108:21 352:14 353:1 449:9

knowledge 111:14 111:15 180:1 199:14,18 360:1 454:7

known 12:6 79:22 136:19 227:7 345:8 368:17 410:18

knows 230:7 378:14 389:13 391:2 392:6

kriesche 2:19 5:15 98:8,13 124:18 128:14 154:7 166:15 177:19 179:12 180:4 181:11 184:20 186:9 189:11 192:21 193:2,15 194:15 195:15,18 196:11 201:10

krieschea 137:20

krista 4:8 6:8 366:21 379:13

kristine 442:4

kuypers 19:6

l

lab 13:1 150:1 177:12 179:5 219:2 235:9 246:10 248:1

label 62:2 138:20 285:22

labels 121:14

laboratory 149:22 377:17

labs 153:18

lack 235:16 247:15 257:16,17 257:19,20 330:19 387:8,10,13 411:11

lacking 117:2 267:13 288:18

lacks 206:7,10

ladies 328:7

lahey 4:12

laid 35:13 40:1 50:1 109:5 194:12

lamonge 188:16

landscape 72:3 106:16 370:5

lanes 286:20

language 61:22 150:8 267:7

large 11:18 106:17 107:1 127:5 144:3 196:19 199:2,2 208:8 210:4 215:22 243:13 246:10 275:1 327:18 329:4 330:8 374:16 377:9 380:3 381:2 382:3 411:14 417:2,17 425:14 426:21 427:20,22 437:13,14

largely 213:2 380:11,19

larger 87:2 125:7 192:19 196:9 197:9 342:6 398:9 411:8

largest 25:11 64:21 431:22

larry 4:15 443:21 443:22 444:17 445:4,12,15

lasting 9:4

lastly 242:16

late 37:11 53:20 163:10 184:2 204:13 238:8 297:10 299:8,18 365:15 412:14

laughter 283:17 286:7 294:20 338:9 364:2 366:5 389:9 395:16 440:5 443:17 452:15,19

launch 11:17 416:11

launched 101:22

law 61:1,4

laws 369:20

ldo 342:4

lead 40:2 106:7 141:12 360:15 429:9
leader 167:18
leaders 47:22 314:6
leadership 21:20 41:8 154:3 396:3
leading 87:9 102:7 140:18 141:3 330:1 419:9
leads 106:4 141:1 142:4
leaps 290:19
learn 49:15 65:20 69:21 78:7 98:20 199:13 401:14 404:21
learned 36:7 47:5 347:10 448:10
learning 36:14 78:22 120:9 124:5 215:8 235:1 243:8 268:2
learnings 75:18 78:16
leave 121:19
leaves 271:20 408:19
led 19:5 41:18,21 217:14 340:16 447:7
left 10:3 73:22 74:1 88:22 169:2 171:10 172:8 221:1 232:9 236:17 237:20 239:22 250:4,15 251:22 252:9,16 384:13
legal 119:19
legitimate 110:11 191:7
lengthen 339:20
lentine 4:8 6:8 366:21 367:4,5 378:11,18 380:20 383:10 437:20 440:11 441:12
lesion 267:6,11 275:18 298:4
lesions 275:17,20 276:6
leslie 93:4
lesser 91:15 179:21
lesson 162:18
lessons 256:19 406:4
letter 15:6 31:8 74:8,9 75:3 80:6 111:4,9 112:3,4,6 115:21 116:4,13 117:8 119:9,10,16
letters 80:14
leukemia 412:6
leukopenia 170:17 172:4
level 22:6 51:18 53:3,17 60:17 63:1 65:6 71:1,16 72:3 85:6,11 92:15 104:11 131:20 142:18 144:10,20 147:8 149:5 160:6 163:10 230:21 257:11 291:5 320:22 334:20 348:2 349:7 350:20,21 355:15 355:21,22 363:22 366:3,7 368:21 370:7 371:9,9 374:6 375:1 387:10,14 391:14 418:6 422:4 423:8 436:5,17
levels 114:3 122:2 147:13 151:6 169:11,18,20 176:10 318:20 355:14 447:5 448:3
leverage 18:16 193:13
levey 87:6 92:13
lewis 90:10
liaison 21:2
licensing 234:5
lie 185:18
life 11:5 204:1 258:18 262:21 288:12 330:3 341:16 343:6,22 395:20 412:22
light 78:3,5 111:10
liked 143:20 193:12
likelihood 27:7 242:19 374:16
likewise 58:10,12 58:20 66:11
limit 7:22 95:1 451:13
limitation 313:12 387:6
limitations 380:6 441:3
limited 12:14 82:20 84:20,20 85:2 93:6 108:6 150:1 200:16 333:16 387:7 390:15
limits 94:22 368:17
line 77:19 197:10 232:14 238:10 289:7 292:13,14 292:15 369:4,9,10 442:8
linear 335:1 381:9
lines 81:19
link 63:22 129:9 182:19 302:7 370:15
linkage 370:13
linkages 370:7 377:16
linked 344:16,19 385:5
linking 167:14,14
links 40:14,15 63:17 150:15
lisa 188:16
list 28:8 36:3 40:12 87:11 116:19 134:6
listed 35:22 134:8 134:9 135:3 329:3 414:2,21
listen 82:4 407:19
listening 97:19
liter 267:16
literature 31:7 172:8,18 178:11 332:2 333:18
little 22:16 34:6 52:12 55:19 63:1 63:3 68:5 86:1 92:3 95:17 96:11 99:2 104:4 105:11 108:3 120:2,13 128:22 129:19 147:10 151:15 156:2 160:2 173:9 186:2 194:17 205:15 218:6 230:11 244:6 258:12 286:6 292:7 302:21 305:13 339:16 341:7 345:16

347:11 348:3 366:10 382:10 390:14 394:10 395:17 409:1 419:15 420:6,9 433:14 439:9 441:1
live 195:5 341:4 412:22
liver 308:1 312:19 367:3 368:10 369:16 375:15,18 375:19,22 376:4
living 14:21 162:5 174:5 302:22 392:3 394:6 397:12 401:5,8
load 164:13
local 441:4,9
locally 87:18
locked 79:5 150:10 222:1,2,2 248:18
logistic 321:22
logistics 337:12 441:6 449:3
logo 395:1,3,3
loi 112:11 118:17
london 74:13 78:18 314:12
long 11:2 29:14 34:7 51:7 73:1 93:4 94:17,20 100:10,11 101:10 104:5,6 105:19 106:19 126:8 128:10 129:9 142:11 154:19 162:4 203:19 227:7,18 256:10 257:3,8 259:19 262:4 269:14,22 270:12,17 275:14 285:18 294:4,6,6 294:12,12 295:6 295:20,22 296:5 296:10,19 298:8,9 298:16 315:3 330:1,9 337:6,6,8 337:9,20,21 338:18 339:8 341:2 342:21,22 343:10,19 344:10 346:6 351:18 354:18,21 356:22 357:9 368:17 376:14 379:20 381:11 386:14 392:20 397:3 406:16 412:22 413:11 421:14 424:11,20 433:7 434:14 435:19 440:3 444:13 448:9 449:11
longer 16:18 54:11 57:1 318:18 451:21
longstanding 82:17 117:17
looing 178:15
look 11:17 15:21 32:7 33:11 41:9 49:1 53:8,9 55:3,4 56:20,20 60:20 62:9 65:8,10 68:9 71:1,10 72:17 78:2,13 84:1 86:14 88:9 89:20 90:3 92:1 94:20 96:1 103:21 104:2 104:22 105:1 107:19 112:2,19 116:7,12 117:6 120:4 123:9 126:2 126:4 127:22 128:6 129:11 135:18 136:13 137:11 140:9 142:15 144:4,9 145:15 146:9 147:13,16,19 148:1 155:7 159:22 163:13 166:22 169:10 170:18 174:21 179:6 180:3 183:1 184:2 186:2,18,22 187:8 189:12 195:2 196:1,1 202:10 203:12 205:5 206:3 207:6 207:13 210:18 211:18 212:8,13 214:8 215:15,16 216:3,15 217:22 218:5 230:22 234:20 237:1,12 237:12,18 238:21 239:1 241:9,12,12 241:17 242:20 244:17 247:22 249:2,3 252:11 255:8 279:6 281:9 288:6 294:4,11 295:14 308:2 310:10 311:9,13 312:19 335:18 341:17 342:14 347:1,12 357:7 360:21 365:6 370:22 382:12,19 383:4 386:1,9 399:7 400:13 401:10 411:4 421:3,21 422:1 430:6 433:15 453:3
looked 29:16 82:6 89:17 91:6 123:20 126:2 135:11,15 135:17 139:3,14 139:15,16 146:11 164:2 165:1 168:14 172:14,21 178:11,17 213:18 213:20 215:3 221:3 223:17 224:7 236:11 237:4 238:16 251:12 289:14 297:5,9 304:3,20 307:4 310:20 320:12 348:6 375:14 437:1
looking 15:4 19:8 19:9 27:14 29:12 29:13 31:7 32:3,9 32:19 52:16 58:1 65:11 71:20 72:2 72:12 79:7,17 83:12 94:16 110:12,20 115:14 116:18 118:5 124:1 145:11,13 146:15 148:5 150:5 151:8 159:9 160:3 175:18 178:22 180:19 182:5 183:15 184:7 185:20 186:1 189:8 194:20 196:2 204:14 205:6,8,8 205:11 206:8 207:17 212:2 237:2,21 238:3,4 238:7 239:8 243:22 249:3,9 256:13 277:2 290:10 309:6 314:15 318:4 320:11 328:20 335:18 345:6 346:18,20,22 347:3,13 349:1

374:10 381:11 391:12 392:3 405:13 409:13,19 411:10 423:1 436:4,12
looks 26:2 29:11 29:12 175:4 391:9 395:3 420:15
lorenzo 246:7
lose 120:20 203:22 242:20 243:4 276:1 283:11
losing 139:22 277:13 292:16 359:16
loss 27:8 99:4,4,11 99:15 130:3 139:1 140:1,19 141:3 145:12 151:20 169:7,11,21 189:21 201:18 237:19,22 238:1,9 241:18 242:3 243:7,11,13,13 244:1,22 245:18 245:21 256:3,11 257:9 259:20 260:6 268:22 270:21 275:14 277:2,3,4,6 290:3 290:7 296:11 330:2,17,20 331:1 331:12,22 332:1,5 332:8,21 333:18 334:8 335:4,11,17 336:13 346:18 349:1 362:2
lost 99:12 259:9
lot 9:20 10:11 11:14 18:10 26:20 30:1 31:1,15 32:4 33:3 34:17 41:19 41:19,20,21,21 42:5,6 47:1 55:13 55:18 66:14 82:14 87:7 90:18 97:10 97:19 99:5,12,19 100:15 103:9,12 103:14,20 106:12 107:4,6,6,10 108:5 109:15 110:17 118:18 123:11 125:19,21 127:14,21 130:14 140:22 153:3,17 155:18 176:10 182:2 187:15 189:13 190:20 207:16,18 211:20 215:13 219:2 251:21 257:9 259:8 263:17 265:9 269:12 275:8 288:15,16 291:4 302:3 315:17 318:4 323:18 327:11,15 328:22 341:13 343:12,13 344:14 352:18 360:4 361:17,18 378:8 391:2,5,11,13,15 391:17,18 394:3 394:17,17 395:20 397:10 398:17 399:1,11 400:7,16 400:17 402:13,14 404:3 405:22 418:17 421:7 427:3 431:12 433:7 435:2 437:16 439:20 441:2,3 444:6,7 446:12
lots 21:8 89:16,20
loud 56:7 289:18
louis 4:9,10 366:22,22
loupy 2:21 3:21 6:2 105:7 107:8 129:20 256:1,5 274:4,17 275:3,5 275:10 276:22 277:8 279:10,14 283:1,3,5,7,10,14 283:16,20,22 284:2,4,6,10,12 284:14,21 285:12 285:14,20 286:3,8 286:21 287:3,5,16 287:21 288:15 289:4
loupy's 363:7
love 230:19 358:16
lovely 22:10
low 100:2 148:15 149:4,12 152:15 153:8 155:19 157:9 158:6 162:7 162:13 163:10 164:18 169:18,19 181:20,20,22 191:13 210:10 238:6,19 257:11 276:18 279:4 280:17 281:21 282:20 285:3 290:4,9 320:18 321:5 324:11,12 348:5 355:14 368:10 376:5 382:2 392:6 402:12 425:3,3
lower 66:19 83:10 84:12 88:11 90:5 107:16 114:15 125:10,11 139:6 147:4 157:6,11,12 158:10 199:11 228:16 231:5 238:17 319:21,22 320:20 327:2 382:22 385:2 388:7
lowest 147:5
lucky 105:6 215:14 413:3
lunatic 177:13
lunch 137:9 201:13,14 426:14
lunches 8:5
lung 193:20 416:20,21
lymph 423:21
lymphoblastic 412:6
lymphocyte 369:4
lymphoma 175:18

m

m 2:15 3:11 5:21 5:21
ma 4:12
machine 268:1
magnitude 151:5 252:3
main 23:10,15 162:18 450:18
maintain 22:3 307:15 419:11
maintaining 22:1 337:13
maintenance 171:4 367:2,14 369:8 370:22 374:21 375:5,14 379:19 382:12 384:17 386:20 388:1 390:12
major 67:8 83:12 94:21 139:1 261:16 266:1 298:3 299:1 330:6 359:8 419:5
majority 349:12 381:2 383:12

405:6 425:9
making 9:17 51:9 51:21 52:2 59:21 116:9 117:14 118:21 152:1 155:4 193:22 197:11 345:2 360:1,13
male 121:2 122:4 131:1 132:2 180:8 181:8,10 187:17 191:20 197:19 198:16,19 201:1 206:4 279:2,13 280:13 281:7,17 281:20 282:1,4,11 282:14 287:19 289:3,5 296:2 298:10,13 299:3 299:15 336:22 337:3 338:4,6,8 338:10,11,14 339:13 345:11 356:1 357:22 358:5,8 445:20
malignancies 78:20
malignancy 384:4 384:12 387:11
mammogram 267:21
man 331:10 339:12 389:16
manage 204:20 348:14 351:7 385:17
managed 39:3 193:21 273:1,1
management 155:10 167:17 203:7,13 229:2 232:5 315:5 378:15 379:3 419:6
manager 447:20
managers 327:19
managing 210:20
mandate 100:13 393:1 442:2
mandated 111:3 132:13 291:11
manhattan 169:2
manitoba 3:6 138:8 201:21 333:20
mannon 2:4 5:6 5:19,22 7:16 9:12 9:15,16 23:3 35:12 51:7 166:16 166:20 178:1,3,18 179:13 194:15,16 200:8 246:16,19 255:22 273:20 274:14,18 275:4,6 299:11,22 347:16 347:20 351:14 362:6,21 363:3 441:14 443:14,18
mannon's 39:15
manual 39:1 261:19
manufacturer 373:1
manuscript 233:5 302:12
map 61:10,19 84:12 118:8 217:18,21 227:2 250:4 251:6 261:21
mapped 208:13 221:4,5,11
marc 4:7 6:7 366:16
march 20:19 101:22
margaret 4:13 6:11 407:13
margin 353:11
maria 4:2 6:5 302:13 312:15 313:17 362:7 363:17 365:9
maria's 305:8
mariolopathy 151:20
mark 2:7 5:7 6:10 7:17 17:15 19:14 20:3 23:4 52:6 102:18 119:16,17 256:8 295:11 356:7 389:4 438:2 443:22 445:20 446:18
marked 368:11
markedly 378:17 380:1 387:3
marker 128:17 129:18 156:19 176:18 192:5 254:2 303:22 305:1 319:15 338:15 349:5,7 428:6
markers 176:20 184:1 187:7 190:18 292:17 304:11 305:14 364:10,12,17,22 365:3 427:14
market 198:3 199:2,17,18 295:18 339:4,8 362:19
marketing 106:8 106:10 339:6
martha 16:14
marvelous 21:18
maryland 255:19 454:19
mast 213:21
master 45:4,6,10 45:15 188:14,18 188:21
matas 154:1 399:15
match 318:15 423:14,16 428:3 428:14,17
matched 303:1,4 318:15
matching 80:19 150:9
matchmaker 146:5
material 219:19
mathematical 364:14
matt 406:21
matter 116:15 196:19 197:17 220:9 274:3 284:1 290:3 322:16 323:4 419:9
maturational 308:9,20
mauve 78:5
maximum 209:2
maxrebo 305:21
mayo 2:8 32:16 389:4 394:14 397:10 401:7 402:1,2,3 439:4
mb 3:7,18 5:22
mba 2:15 4:11 5:21
mbchb 4:5 6:6
mcp 134:22
md 1:7,16 2:3,4,7 2:14,15,17,19,21 3:1,4,5,8,11,14,18 3:21 4:2,7,8,11,13 5:5,6,7,13,14,15 5:16,17,18,19,21 5:21,22,22 6:2,4,5

6:7,8,9,10,11
mdh 234:13
mean 10:6 18:18 21:12 53:5 56:7,9 58:18 65:19,22 69:18 89:22 91:22 100:1 109:21 113:10,13 119:4 129:1 136:18 169:10 174:14 188:6 190:6 191:6 191:8 193:19 194:7,17,21 201:10 207:2 215:19 216:22 274:18 279:22 289:19 290:2,15 291:6 294:8,15,22 297:5 298:6 343:13 346:15,22 347:1,11,21 348:7 348:9,10,17,21 351:20 355:13 356:7 390:13,18 391:7,8 430:12 431:17 438:11 439:8 441:14 442:3,7,15 443:4
meaning 93:16 136:13 143:20 199:21 259:6 264:21 268:18
meaningful 95:20 105:8 192:4 335:16
means 44:1,2 56:8 188:3,9 204:18 223:6 227:22 268:14,15 291:7 326:12 352:20 372:7
meant 59:19 244:7 312:3 425:18
measure 27:10 58:13,18 68:18 81:20 100:6 101:10 111:13 112:15 157:1 159:20 171:15 249:2 330:13 333:4 349:16 372:3
measured 46:1 56:15 126:17 163:16 265:13 375:5
measurement 88:17,19 105:13 281:18
measurements 159:10
measures 27:17 85:4 142:6 171:1 172:3 264:16 370:14,16,18 371:21
measuring 127:20 163:13,20 254:2
meat 125:8 340:20
mechanism 135:12 150:17 365:17 366:6
mechanisms 365:12,21
mechanistic 106:3 142:18 366:2
median 139:3 261:1 371:18 372:4,7,11 374:14 375:3
medians 372:3
mediated 11:9 130:11,11 140:20 153:9 174:19 175:6 207:9,10 209:15,16 251:22 252:15 253:7 255:8 268:8 270:8 275:16 328:4 329:22 332:10,20 333:9 344:20 398:14
medical 4:6 137:19 154:8 219:8 258:1 275:1 328:8 366:16 380:17 393:5
medicare 370:15 380:22 381:5 384:8,9 385:22 386:21
medication 240:4 293:15,16
medications 11:4 291:20 292:5,6 370:14
medicine 2:16 3:2 3:9,19 22:18 167:8 219:8 232:3 233:17 408:18 414:5,9,11 415:8 420:8 423:6
meds 145:20
meet 7:18 66:6 78:6 87:9 114:14 121:8,12 198:22 312:7 339:8 444:9 444:14
meeting 1:2 9:3,12 12:20,22 16:14,21 16:22 17:7,11 18:21 19:13 20:7 84:14 90:10 126:1 178:5 199:10 246:22 426:2
meetings 7:11 108:5,10 113:8 203:1 358:12
meets 114:14 403:17 421:4
meghan 365:16,22
meier 2:19 5:15 98:8,13 124:17 128:14 137:20 154:7 166:15 177:19 179:12 180:4 181:11 184:20 186:9 189:11 192:21 193:2,15 194:15 195:15,18 196:11 201:10
melanoma 384:19
member 9:22 72:8 177:14
members 9:16 23:17,19 24:18 26:7,13 72:22 74:5,12,13 77:10 233:1 393:9 413:15 442:15
membership 33:16
memo 120:13
memory 12:4 142:22 157:1 183:4,4 276:19
mention 15:14 302:13 396:20
mentioned 24:15 26:7 29:13 38:16 41:11,14,16 50:7 114:20 130:9,13 178:4 189:7 233:1 243:20 276:10 281:10 289:18 292:9 315:21 327:5 333:12,15 334:5 393:22 417:13 432:9
mentioning 404:16 438:2
merge 307:18 399:18 412:2

merit 178:15 194:18 195:3
message 37:4,8 39:15 40:9 41:10 50:12 214:4,8 216:20 265:12
met 16:4 60:18 68:12 90:10 221:16,18 222:14 222:15 288:8 390:19 402:6 441:22
meta 89:4,5,7 309:2
metabolism 168:10,11
metabolite 369:10 371:3
metalation 206:21
metanalyses 95:5
meteor 392:2
method 132:18 145:13 146:6 253:18 254:12
methodologies 134:19
methodology 250:10 374:20
methods 95:7 146:7,9,15,22 323:17 380:19 381:8
mfi 267:13
mic 179:15,16,18 179:18,19,20,21 179:22 180:2,3 272:1 296:3 337:1 337:4,6,9,11,14 337:16,18,18,19 337:22 338:1,2 339:12 346:13 435:22 438:10
michael 1:18 2:13 2:15 5:11,21 46:22 48:4 49:16 55:8 72:1,12 73:2 74:18 109:14 110:15 113:21 174:11 219:7 454:2,17
micro 264:1 274:18
microarray 227:1 240:7 316:3
microarrays 317:21
microcirculation 285:1
microphone 451:12
microphones 120:7
microsatellite 435:8
microscope 205:8
microvascular 274:19
mics 109:2
middle 118:14 159:5 250:14 345:18 451:12
mike 32:11 187:5 192:14 205:18 219:10 251:2 291:16,22 292:8 292:10 296:20
mike's 342:19
mild 44:9
miles 441:5
milestone 7:11
millie 246:6
milligrams 321:6
milliliters 94:19
million 87:3 123:19 124:8,15 125:17 273:21 389:11 397:18 409:6
mils 139:19
mimic 65:12
mind 31:5 41:18 43:18 186:20 290:4 294:1 450:20
mindset 54:17
mine 255:10
minimally 204:9
minimization 130:10 141:4 301:6 359:15
minimize 11:5 170:21 379:20
minimized 375:8 375:11
minimizing 204:16 369:19
minimum 334:15
minnesota 168:22 395:1
minnesota's 174:4
minnie 3:11 5:21 186:16 201:22 219:6 220:5 226:15 227:16 272:5,6 354:16
minor 326:3
minority 298:6 411:1
minus 126:16,16 139:19 425:20 427:15
minute 139:19 398:15 451:13
minutes 9:4 74:22 82:9 137:16 167:2 202:15 271:21 378:10 408:11 417:17
misclassification 149:10,12
misconceptions 19:16
miseq 240:12
misled 421:10
mismatch 138:9 138:14 140:19 141:22 143:9 144:8,14,18,19 145:1,3,6,10 146:8 147:5,14,17 148:1,8,10 150:15 152:4 164:13 195:4 206:4,13 207:1 209:13,14 239:1 245:9 303:3 359:20
mismatched 138:15 141:18 206:19
mismatchedness 146:16
mismatches 142:1 145:2,3,8,10 146:1,2 147:14,17 164:18,19 207:7 207:12 208:4 237:11,14
mismatching 140:16,17 141:5 141:20 143:4 145:7 146:5,11,12 146:13 149:5 205:9 237:10 245:11 354:9,9
missing 207:16 211:4 214:14 268:1,2 291:13 356:2,14 357:2 362:3 391:5
mission 17:10
misstep 52:19
missteps 197:11
mix 124:2 309:22 401:9
mixed 184:3,6 335:1

ml 84:22 126:16 126:19
mls 126:16,16
mmf 162:7 322:21 371:3
mn 2:8
mo 4:10
mod 134:22
modalities 415:11
modality 415:10 417:20
model 19:10 29:16 36:15,20 37:20 38:18 41:22 42:19 43:13,14 44:15 47:12 49:17 89:3 102:13 105:10 126:20 130:22 131:4,6 133:20,22 134:22 145:14 147:2,4,4 221:8,9 221:10 222:2 259:22 260:17 263:2,6 264:4,11 264:14,16,21,22 277:4 286:9 291:14 298:3 306:16 310:2,6 335:1,2 340:11 348:15 359:21 371:15 384:22 400:14 407:15 409:8 410:3 424:16,18 427:20 429:15 445:13
modeled 107:8 297:15
modeling 104:9 106:20 126:21 181:4 334:3,4,21 335:5,6 336:6 371:8
models 27:12 38:17 44:21 78:11 129:21 146:19,21 147:3 180:11,15 180:17 227:4 262:15 264:7 271:8 306:3,3 340:9,12,17 343:8 371:10,22 372:13 374:4,13,15 444:7
moderate 44:10 299:11 450:9
moderating 137:20
moderator 7:6 110:16 201:20 300:1
moderators 8:22 378:5
modernization 41:1,5 50:7 414:21
modification 168:14
modify 115:6,7 420:22
modulating 150:12
module 215:6
molecular 56:13 138:9,14 143:4,9 144:9,20 145:2,13 146:8 148:1,10 150:17 152:4 159:13 211:16 212:8 213:7,10,15 214:6 215:17 217:5 232:3 273:10 352:9,11 353:11,20 354:1 359:19 363:19,22 365:22 366:3,7 387:14 412:17,18 416:22 419:20 423:16 427:4 428:2,9,12,20 433:13 436:20
molecularly 211:22 212:1 216:22 366:1 417:3
molecule 138:15 138:17 143:15 144:9,11 152:20
molecules 144:5
moment 76:10 80:16 104:4 154:14 356:11,12
moments 74:18
momentum 406:20
money 33:18,19 195:5 199:17,17 199:18 293:5 326:5 391:13 401:1,2 438:20,21 438:22 439:5,6 443:3
monitor 48:21,21 228:12 230:18 253:18 293:17,19 359:5 420:12
monitored 253:13
monitoring 48:19 171:14 190:15,16 190:16 202:2,8,8 204:9 210:20 216:15 217:9 220:19 231:15 239:14 240:2 247:12 254:4,13 267:19 271:10 347:7 362:11 377:7 390:3 420:11
monograph 167:8
month 94:17 213:9 214:1,9 217:17 224:2 234:19 239:11 241:2 242:18 244:3 289:17 335:9 375:17
monthly 16:19 18:10 396:15
months 13:6 16:4 17:6 20:5 22:16 84:9 153:7 157:20 158:11 162:9 212:15 220:17,18 224:1 234:18,19 234:19,20 236:4,5 236:8,12 239:13 241:11 242:19 263:10,10 279:7 279:15,15 280:3 281:6 321:7 365:18,19 371:1 375:20 376:5,6 426:1 444:18,19 446:1,4,15
moon 28:17
mooney 4:13 6:11 407:13,17 430:10 431:16 432:16 434:6,10 436:6,13 436:15,18 437:10 437:22 438:7
morbidities 156:6
morbidity 156:2 301:8 358:18 368:2
morgan 87:5
morning 19:4 23:11 35:6 137:7 137:18 161:3 301:17 302:1 333:7 340:18 387:13 404:17 453:4
morphology 352:8
morris 3:1 21:21 133:15 135:6 183:10 198:20

272:4 273:12,15 273:17 292:7 363:5 364:5 365:21 366:19 429:22 432:6 434:2,7 435:22 436:8,14,16 437:9 437:21 443:21 445:19 448:5 449:14
mount 3:9,19 154:8 206:5 233:17 234:4,11 255:19
mouthful 427:2
move 22:2,22 26:14 28:20,21 40:5 50:19 53:15 55:2 66:21 75:4,9 75:15 76:3,3,20 77:16 78:7 97:3 112:8 114:17 135:18 180:5 181:13 204:12 238:10 280:8 287:2 294:22 314:7 352:11,13 352:22 353:7 377:22 390:13 421:5 422:4 451:22 452:3
moved 45:17 135:18 314:8 400:6,6 433:15 439:9
movement 268:12 289:9
movements 268:5
moving 28:1 68:3 75:22 86:15,16 111:4 126:1 177:21 193:18 195:8 205:15 254:20 306:20 310:6 439:10 440:12
mpa 172:2
mph 2:11 5:10
mpv 222:19 236:19,21 237:17 240:18 241:6,7
mpvs 239:2 244:10
mrc 447:8
mrcp 4:5 6:6
mrna 235:2 249:2
mta 395:3 406:13 445:1
mtak 400:4
mtor 371:4 376:7 387:1
multi 32:3 49:11 158:7,17 212:15 234:10 381:9 382:19 384:21 388:16 391:11 394:12 397:6 402:12 412:12 415:10 417:20 444:4
multidimensional 258:11,15
multiple 20:17 32:2 35:19 39:4,7 41:11 45:8,16,16 63:13 81:11 188:18,19,22 201:7 212:20 235:3 240:22 242:11,11 245:22 246:4 359:6 405:5 427:1 428:4 430:21 435:21
multiply 404:5
multivariate 145:14 146:18
murphy 3:18 5:22 172:7 178:18 179:14 193:2,15 193:16 195:22 233:16,20 246:14 281:1,8,19,22 282:3,10,13,16 283:2,4,6,8,11,15 283:18,21 284:1,3 284:5,9,11,19 285:11,13,19 286:1,14,22 287:4 287:15
murphy's 287:20
mutation 427:11
mutations 169:7 426:15,15
mutually 52:3
mycophenolate 168:11 170:12 369:10
mystically 194:20

n

n 2:1 5:2,2 7:1
nader 246:7
naivete 18:8
naki 308:6
name 7:3 51:1 54:6 77:11 137:18 195:20 299:21 328:7 366:15 426:3 451:11,20
named 16:13
names 76:21
nancy 22:4
nanostring 248:14 249:2 250:1 254:11,14
narrative 326:16
narrow 186:13 187:2 188:13 192:5 194:18
narrower 199:10
narrowing 195:8 200:5
narrowly 411:20
national 96:9 167:8 267:5 367:15 370:5,7,20 371:18 379:9 407:14 408:6,14 409:6 411:3,13 413:7 417:7 427:19,20 429:8
nationally 379:8
native 253:16 351:4
natural 213:21 397:18,21,22
nature 180:16 184:6
navigate 72:18
naysayers 169:14
naïve 276:18 279:3 308:9,16
nci 408:8,10 409:7 410:13 414:6 416:2 417:7 438:19 439:6
ncop 410:18
near 8:14 302:16 313:13
nearly 379:6 389:22
neat 97:14
necessarily 97:5 119:14 182:3 256:9 314:18 339:20 399:22 422:13
necessary 81:22 131:8 161:15
necessity 319:3
necker 2:22 3:21
need 24:3 28:3 35:13,13 36:17 37:22 38:2,5 41:22 42:1,3 44:12 47:21 48:7

50:13 52:3,5 53:12 55:1,21 60:8,22 61:13 63:5,19 66:1 67:5 67:8 68:12,17 71:1 83:2 85:10 85:22 90:20,21 93:10,22 97:2 98:3 101:9 103:20 104:18,19 106:10 107:21 111:12,22 112:21,22 116:12 117:3,4 121:19 122:20 127:1,5,21 141:14 169:12 170:22 174:14 176:8,16 177:7 181:6,18 182:3,6 183:2 185:16 187:18 190:13 194:1,9,14,19 201:3,11 214:14 214:15 218:12 227:16 228:7 239:19 253:10,10 253:16,18 254:20 257:2,22 263:14 282:7 286:16,20 296:14 299:7 300:17 301:3,6 314:22 323:5,8,17 325:12,14 326:7 327:3 330:20 339:15,15,18 340:18 343:1 349:10,11,21,22 353:15 357:19 360:2,4,11 361:3 361:3,20 362:8,10 365:20 367:20 377:8 379:20 380:4,7 382:2 388:16 392:15 393:2 403:20 405:15 420:12 424:6 425:4 426:10,12 439:5 440:22 445:17 446:19 450:8

needed 14:5,5,6 16:17 24:12,16 38:17 47:10,11 48:11 69:8 107:17 130:1 255:1 261:18 314:21 317:20,22 326:1,2 385:17 388:8 392:13 414:20 415:3,4 416:8,18 417:1,4 425:6

needle 28:1 352:13

needs 9:14 10:20 13:10 15:8 24:5 24:11 40:18,22 41:1 42:4 44:14 50:14 53:6,12 60:18 61:5 97:7 103:17 110:14 115:2 143:5 170:19 176:7 181:15 200:12 235:14 246:15 315:17 327:9 337:22 342:7 355:20 364:12 377:6 439:13

negative 157:8,12 176:11 222:19 226:9,10 227:22 231:7 232:14,16 272:10 293:12 326:12 349:2 364:13 423:21,22

negotiation 106:22

neither 327:3 450:20 454:7 455:6

nelson 21:10

neoadjuvant 422:2

neonatal 18:17

nephrologist 247:21 283:2

nephrologists 79:6

nephrology 11:20 12:1 326:10

nephropathy 248:10 249:6,20 249:20 253:7 254:13 276:9 344:12

nephrotoxic 135:8 136:20 344:8,8

nephrotoxicity 315:19

nephrotoxin 80:1

nervous 9:20 281:12

net 156:5 250:8,9 252:20 364:16,17

netherlands 87:8

network 15:5 28:12 259:1 300:5 316:20 327:12,13 389:6,18 408:14 415:22 416:4 417:8 418:20 419:2,8 427:19 444:22 445:1

networks 101:17 377:10,19 407:15

neutral 49:21

never 86:2 100:9 123:20 135:12,12 175:18 311:6,7 312:11 347:21 350:8 362:21 395:14 396:14 412:11 420:15

nevertheless 98:18

new 1:14 3:10,20 9:22 10:4,14 11:1 13:3 17:14,19,22 24:8 26:22 28:18 29:12 30:4 36:13 38:5 45:14 47:3,4 52:21,22 69:16,18 70:8 71:15 83:19 100:13,14,17 104:19 105:2 107:16 135:11 155:8 165:11 173:17 174:7 186:5 197:13 207:11 212:11 233:17 239:22 240:4 247:19 252:21 254:15 260:11 265:15 287:13 292:15,19 295:18 318:12 322:15 324:5 351:22 353:22 354:3 360:22 373:2 383:19 385:8 398:8 416:3 417:7,9 418:3 423:11,14 427:19 428:3,18 429:9,10

newell 3:14 6:4 20:2 113:18 115:16 191:5 193:1,3 300:2,8 314:14 320:10 327:5 341:8 342:18 354:4 360:12 361:8,15 365:7 366:6

newer 348:21

news 299:8

newsletter 375:17

nf 215:7
ngs 427:22
niaid 20:16 168:21 217:13 219:14 233:3 234:8 255:16 310:18 441:19
nice 30:10 34:5 61:19 63:18 65:16 81:7 108:8 125:14 152:18 184:4 190:22 208:18 271:15 289:15 352:7 363:6 403:2 407:19
nicely 94:12 122:16 184:5 221:5 244:19
nickerson 3:5 5:17 138:7,11 155:12 164:11 176:9 177:15 180:9,22 181:9 183:20 187:4 192:21 193:11 201:20 205:6 219:6 246:13 271:20 273:19 287:17 291:15 295:10,13 295:16 296:4 297:7,11 359:3 360:17,19 449:15
niddk 167:13 215:15 441:18
night 159:5 197:14 350:19
nih 10:1 48:14 102:8 167:11 212:15 223:9 234:8 367:16 401:2 438:16 441:16 447:2
nine 204:1 322:5 365:19
nkf 97:16
nodat 384:20 387:11
nodding 341:12
node 423:21
noise 218:5 344:21
nomenclature 52:19
nominating 166:21
non 11:1 186:4 206:9 207:14,19 208:12 210:8 213:14,17 214:10 272:20 344:8 384:19 417:20
nonacademic 381:3
nonadherence 141:4
nonadherent 350:17,18,19
nonclinical 47:17 47:18
noninterventional 334:4
noninvasive 155:22 159:10 202:2 204:5,9 217:2 228:7 253:5 253:16 256:14 287:13 357:19 358:16 359:9 362:11,16,19 363:14
noninvasively 160:13 214:19
nonprofit 39:5
nonrejection 251:18
nonresponse 231:10
nonstandard 373:22
nontolerant 308:8 308:11
noon 200:22
nope 452:2
normal 46:2 70:22 71:4 77:14 79:21 135:20 136:12,19 136:22,22 162:12 214:2 412:22
normalize 79:14
north 260:10
northwestern 2:16 219:8 220:2 221:14 225:19 233:11 234:11 255:18
norwegian 399:3
norwegians 397:12 401:11
notably 369:13 373:4,12
notary 454:1,18
note 39:16 84:18 251:20 366:9 375:15 446:1 451:4
noted 85:5 155:17 160:15 369:22
notes 20:9
notice 76:22 78:3
noticed 183:10
notion 19:8 22:5
novartis 77:3,10
novel 10:16 18:3 26:16 38:6,6 45:3 45:6 101:17 148:20 183:9 190:8 217:10 239:22 339:10
novelty 271:4
november 74:6
novo 139:5,8,21 140:3,11 141:1 145:15,15 146:4 148:16 151:19 152:14 183:14 224:4,12 238:8 331:13,14 332:8 448:18,20
nuanced 95:17 340:4
nuances 84:16
nucleotide 166:18
nudge 451:18
nullify 83:14
nulojix 10:17
number 8:18 10:22 25:11 62:19 76:21 77:3,22 78:17 85:3,3 86:7 89:18 92:17 96:8 100:6 108:19 112:7 116:21 136:17 144:10 169:11 173:8 197:6 199:18,20 223:2 231:1,7,13 243:11 248:21 249:13 257:15,15 261:15 270:14 294:5,7,10 296:5 296:7 302:8 308:14,17,22 325:1 327:18 367:9 397:14 404:5 427:22 432:2
numbers 107:16 194:19 208:8,10 305:16 381:20 404:21
nurses 327:19
nutshell 79:20
nw 1:21
ny 3:10,20

o
o 5:2 7:1
o'clock 201:11 453:4
o'connell 19:5 246:6
o'doherty 2:10 5:9 7:6 50:20 51:1,2 55:7 72:1 81:5 98:1 108:18 110:15 120:22 137:3 290:15 338:19 351:21
oak 1:13
obesity 351:1
objective 55:16 59:12 105:2 228:18 334:6 376:16
obligation 363:14
observation 277:13
observational 82:21 85:13 89:13 92:10 94:8 95:4 124:19 128:8,12 229:13,15 401:4 446:3 447:12,12
observationally 87:22
observed 130:7 264:14 374:18
observer 247:13
obstacle 86:5
obtain 71:19 77:15 106:14
obtained 421:16
obtaining 167:13
obvious 88:10
obviously 32:15 99:19 100:8 102:13 104:21 107:21 128:15 129:14 195:4,5 197:5,7 220:1 223:7 231:1 246:11 255:15 263:18 301:22 336:12 345:3 413:18 417:8 421:16 422:20
occasionally 415:15
occur 265:8 278:4
occurring 212:22 214:5,5,7,12 342:10
occurs 118:14
ocp 134:1
october 12:8
odds 372:3,4,7,9 372:11,13 374:14 375:3
offering 445:15
offerings 161:8
offers 369:7
office 13:14,16 15:6 16:5,5 17:12 35:2 133:18
officer 4:6 55:9 328:8 366:16 454:2
officers 137:19
offices 17:13
officially 20:19
oftentimes 248:13 252:2
oh 15:17 30:19 39:20 86:15 254:8 272:7 283:14 286:5 303:4 309:19 362:7,22 367:19 399:5 431:16 452:6,16
ojay 184:4
okay 11:22 20:12 110:22 114:15 125:12 127:12 128:1,2 147:11 180:4 181:11 195:15 201:15 227:11 270:18 273:12,15 275:11 276:17 278:14 285:16 286:9 287:11 289:6 293:14 295:12 299:16 326:7 337:3 357:17 361:1 407:17 430:10 432:5 433:18 434:10 452:3,6,17
old 28:13 194:22 240:4 324:2 393:1
older 145:18 373:17 375:9
omix 167:15
once 59:13 71:16 96:7 106:12 133:3 139:14 164:2 199:12 225:5,7 313:10 320:2 418:4,15
oncologic 434:2
oncology 19:9 101:15 167:17 187:15 196:1 292:14 393:8,8,14 393:16 394:9 403:2 405:7,18 406:1,4 407:15,22 408:19 410:17 411:12,16 412:2 417:15 421:9 429:10,16 431:19 432:9,18 436:9 441:15 448:8,15
oncotype 424:22 425:17
one's 192:12
ones 10:21 107:13 109:5 140:15 165:10 318:15 320:20 324:4 393:8 447:8
ongoing 96:7 267:2 285:9 288:22 427:16 429:6
online 131:17 175:5 200:9
onset 171:3 255:5 385:8
oops 237:18
open 8:1,15 272:1 419:3 430:1 433:19 443:20 449:10 450:8,15
operated 410:2
operates 418:20
operating 232:4 415:20 418:17
operationally 317:13
operative 365:18 365:18 387:18
ophthalmologic 13:17
ophthalmology 7:4
opinion 298:6 390:15 449:6
opinions 337:7 408:5
opportunities 10:5 18:19 383:17
opportunity 17:1 18:16 35:8 82:4 110:7 116:16 154:12 182:16 187:5 196:20 219:12 314:3 329:10 367:7 388:22 450:16

opposed 138:16 186:22 360:7 419:17
opposite 174:5
opsa 4:17 6:12
opt 86:20 400:17
optimal 388:9
optimally 347:6 377:5
optimistic 34:19
optimization 178:22 249:10 379:17
optimize 198:6
option 18:13
options 16:20 189:8
optn 387:8
orange 140:11
order 8:5 61:5 65:1 67:4 93:10 98:21 137:9 169:12 225:11 229:1 337:22 392:12 446:19
ordered 308:14
ordering 137:9
organ 21:5 25:17 137:2 203:11 206:17 215:3 247:5 255:16 343:4 366:17 373:22 378:16 379:4,12
organization 18:15 21:6 22:6 39:4,6 41:3 391:8
organizational 17:7 19:13 20:6
organizations 39:5 198:1
organized 393:5
organizers 138:12 233:22 367:6
organizing 219:11 234:1 300:9 393:9
organs 10:22 11:1 27:18
original 115:17 303:17 304:10
originally 102:7 300:22
oros 365:15
ots 17:2,16,16
outcome 64:10 82:12 83:8 85:15 91:22 93:13,15,16 93:18 126:17 134:10 142:8 146:20 155:6 158:17 166:8 176:1 182:4,20 185:6 187:2 189:2 201:5 207:3 211:10 227:8 229:9 294:4,6,6 295:6,19,22 301:20 329:4 344:10 346:6 351:12,13 353:16 354:12,18 356:7 357:1 362:18 381:11,13,16 404:12 424:20 432:15 433:22,22 435:19 454:12 455:8
outcomes 11:2 15:4 24:8 69:3 97:4 99:21 104:6 105:19 106:19 126:9 128:9,10,18 129:9 141:16 151:18 154:19 155:2 158:5 163:2 165:3 166:4 169:15 197:15 227:18 232:6 234:22 235:1 276:21 288:20 290:10 343:22 349:2 370:3,12 376:14 379:11 380:10,16 382:8 382:13 383:17,21 384:1 387:21 388:13,18 441:20 449:19 450:1
outline 19:1 36:11 82:10 300:17
outlined 16:11 62:8 80:6 290:16 380:19
outlining 243:20 243:21
outpatient 381:6
outperforming 236:22
outperforms 271:11
output 264:4
outputs 78:21
outside 8:5,8 24:17 25:2 137:10 198:5
overall 59:17 128:16 147:1 332:15 412:9 421:12 422:6 433:1,5,9 434:5 434:15 436:3,11 437:2,8
overarching 45:7
overboard 321:2
overcall 223:5
overcome 257:9 258:5 345:10 349:21 352:4
overfeed 262:15
overfitting 244:7 244:15
overimmunosup... 358:3
overlap 240:7,8 252:8
overlooked 304:18
overnight 41:13
overseas 22:3
overtake 71:15
overview 20:7 51:15 138:3 167:1
overwhelmed 447:21
oxymoron 398:11

p

p 2:1,1 4:2 6:5 7:1 267:15 319:16
p.m. 201:12 366:10
pachenko 153:18
package 44:16 59:6 60:19 110:6 111:5,6,19 112:11
pad 269:5
page 5:1,4 6:1 21:4 55:22 56:17 96:13
paid 185:12 262:15 284:15 389:19 400:22 401:2 442:4 445:8
painful 34:7 339:17
pair 210:11
paired 221:12 227:1 229:14 354:13 394:17 447:10
pairs 148:17 210:5
pancreas 249:15 249:17 400:7,9,12
panel 9:8 55:3 169:9 210:8 221:1 238:4,7 245:2

250:14 254:11,14 332:11
panels 215:16 304:11,13
panned 421:13
paper 17:21,21 19:14 31:2,6,9 34:9 41:18,21 42:5,7 47:19,19 47:22 48:1 67:17 173:13 174:11 175:15 176:2 184:4 188:15 244:10 301:15 302:11 305:8,18 305:20 333:18 341:15 356:8 402:4
papers 31:3 41:16 84:2 88:22 175:8 175:9 215:2 301:14 302:8 397:10 405:9
par 147:9
paradigm 83:14 340:5 410:8
parallel 351:11
parameter 258:14 263:4 274:4 317:4 349:20
parameters 27:10 105:8 185:8 186:3 211:14 257:14 259:11,13,17 262:6,13 264:5 268:3 270:5 271:9 271:10 274:7,8 277:17,18,19 278:7 285:17 286:9
parametric 180:16,17
paramount 346:19
paratope 143:12 143:15
parekh 2:9 5:8 7:17 35:2,6 50:18 53:6 134:3
parenthetically 396:19
paris 2:22 3:22 32:15 78:18 184:4 256:2 258:10 260:17
part 7:19 21:4 27:11 32:12,17 58:6 59:4 61:19 62:13 63:19 65:16 73:8,10 102:9 103:15 106:17 110:8 118:14 120:21 123:14 124:17 130:14 134:3 136:3 166:21 168:20 171:2 174:18 184:18 187:10 204:4 207:14 212:15 224:18 226:2,3 228:17 249:22 253:8 275:12 277:14 278:8 288:1,10 319:8 329:9 339:11 342:6,7 344:5 365:13 379:12,16 389:12 389:13 398:11 399:4 401:2 408:16 440:13 450:16 451:1
partial 312:7 325:21
partially 400:3
participants 87:3 89:2 125:4 260:16
participate 7:10 9:9 86:20 314:3 378:5 410:20 413:13,16 416:14 419:1 447:19
participated 9:19 13:7,21 20:16 318:13 358:12 410:12 413:15 417:11,15
participates 87:2 418:22
participating 73:19 261:3 269:11 279:16
participation 12:10,11 337:14 341:16 415:5
particular 110:19 126:8 132:17 133:4,9 135:10 169:3 200:13 262:16 267:22 284:15 408:20 418:13,21 419:9 419:19 420:3 423:15 424:13 426:18 427:4,9,11 428:2,11,12,20
particularly 7:9 22:4 77:2 159:19 168:9 175:14 253:12 255:10 388:18 412:21 413:14 428:18 432:3 435:12
parties 454:9,11 455:7
partition 193:5,8
partly 400:22
partner 439:7
partnering 41:12 49:22
partners 20:18,22 43:11 56:10
partnership 7:16 20:21 26:4 36:1 100:20 113:5,5,14 113:17 367:13
partnerships 11:14 27:21 28:9 35:4,11,19 36:9 36:21 38:20,21 40:11 41:19 42:6 42:10,11,13 50:6 439:10
parts 386:16
party 109:18 125:14
passe 29:5
passion 22:7
patents 234:5
path 2:10,13 7:15 9:17 16:8,15 18:11,13 20:7,21 21:3 23:22 24:18 30:12,21 33:17 35:5 40:3 41:17 42:8,13 43:8,9,19 43:20 44:20,21 51:2 55:9 73:14 74:15 76:4,14 79:16 88:4,4 102:13 107:3 108:11 109:21 131:8 289:15 300:9 450:20
pather 109:9
pathogenic 46:2
pathologic 84:16 421:22 422:3
pathologies 184:2
pathologists 202:21 203:4 242:21 401:22 402:1,2,3

pathology 127:2 167:13 274:1 377:17
pathophysiology 127:4
paths 290:5
pathway 25:9,17 44:19 46:5,9,10 47:7 49:7 55:17 110:14 112:13 135:4,5 140:9 161:2 329:1 332:21 392:14
pathways 46:6,8 49:7 53:7 97:6 103:5 194:10 227:3 328:18 365:4 366:2
patient 1:6 7:21 8:21 11:6 13:5 15:11,21 22:12 48:19 63:11,12 66:13 99:15 100:1 104:11 107:16 123:14 126:5 128:20 129:3 144:12 160:4,16 165:2 167:7,16 172:18 173:16 179:4 182:7 186:15 188:19,22 189:2,14 190:6,10 190:12 198:14 199:22 200:11 204:19 205:4,12 205:13 209:2,5 210:15 212:5 218:4 222:9,11 224:20,22 235:20 247:15 259:7 260:5 263:15 265:1 266:15 267:19 268:9,19 268:21,21 269:1 270:5,6,11,16,20 276:15 278:16 285:15,15,16 286:10 289:13 291:5 293:17 298:8,15,17 315:16 317:6 323:6 325:13 332:15 334:11,20 339:16 343:21 349:8 351:7 358:15 362:21 366:1 368:20 370:7,9 371:8 372:8 376:14,19 377:2,20 379:14 379:19 380:16 382:14 383:3,22 390:4,16 391:14 394:22 399:19 409:14 411:20 414:13 418:5 419:19,22 426:17 428:17 439:4 443:7 447:10 453:5
patient's 144:8 263:13 369:14 425:1
patients 11:2 14:13,16,17 25:7 25:13,14 28:3 30:1,6,15 37:17 42:2 61:15 77:13 88:1,17,19 89:16 99:12 100:6 104:7 123:19 124:8,15 124:20 135:19 136:14,18 138:1,5 139:4,7,17,18,20 140:10,13 145:4 147:12 148:19,21 155:1,7 158:9,14 161:13 162:8,20 163:4,7,8,18 164:1,10 165:4,8 165:11,21 168:20 171:21 175:21 178:7,9,14,16 179:8 182:2,11 184:9 185:3 188:22 189:19,22 190:15 191:13,16 192:17 194:7,8 196:8 200:11,13 203:7,15 204:21 208:2,7 210:19,21 210:21 211:8 212:18,21 213:2,5 213:11,12,13,16 220:16,20 221:16 222:11 223:4 225:15 226:8,10 226:11,18 227:9 228:2,6,9,12,14 228:15,19 230:18 231:4,5,8 232:5 232:11,12 234:15 235:17 236:3,7,8 237:3 240:6,8,9 240:14,14,18 241:11,13,15,16 243:8,11 247:16 248:9 249:8 250:11,18 252:10 253:5,12,19 255:9 256:17 257:15 259:3,9 260:9 261:6,6 268:13,16 270:19 278:21 284:17 285:3,7 290:1 292:5,13 293:2,6 295:7,22 296:18 297:3,5,9 297:13,16 299:2 299:19 301:13,18 302:14,17 303:20 305:9 307:14 308:7,14 309:14 310:11,13,14,19 310:22 311:5,7 312:13 313:4 314:17 315:1 317:11,19 318:8 318:17,21 319:5 319:16,18,20,21 320:5,18,19 321:4 321:11 322:6,19 323:19 324:1,1,3 324:6,7,9,11,14 324:16 325:1,9,10 325:19,20 326:3,9 326:21,22 332:9,9 334:14,20 341:14 345:7 347:6 348:11 349:15 350:16,17 353:14 358:12,14,21,22 360:14 364:13 368:5 369:2,6 372:4 373:6,12,17 373:19 375:9,10 375:12,22 379:6 380:2,9 382:2,8 382:16 383:13,18 384:1,8 386:13 387:17 388:11 392:1,7 399:14 401:4 403:16,19 404:2,11 405:1,6 405:17 408:20 410:1,19 411:3 413:14 415:5 417:18 419:14,18 419:21 422:18 423:9,15 424:6,7 424:12 425:2,9,16 425:20 426:4,10 427:3,4,8,14,22 428:7 429:2 433:12 434:7 435:13 436:11

441:9,17 444:11 444:18,18 445:2 446:15 447:4,17 448:13 449:22
patrick 12:6,13 13:22
pattern 95:15 261:11 371:19
patterns 383:9
pause 24:22 137:4 450:7
paved 44:21 81:8
pay 87:19 200:1,3 267:22 366:4 373:18 375:13 392:11 430:14
paying 154:12 200:2 447:3
payment 380:22
payor 200:1
pcr 244:9 248:2 318:2
pdufa 194:12 340:10
pediatric 411:12 411:16 412:1 416:6 417:13
pee 362:22
peers 396:1
pellet 215:9 249:7 251:5 304:21
pellets 248:3
penalized 250:9
people 7:19 18:9 21:9 23:20 24:3 24:15,16 25:2 26:18,19 27:12 30:12 34:11,16 52:12 54:12 65:20 65:20 86:4 87:13 90:11 97:10,19 99:5 109:7 116:12 120:15 122:19 124:6,9 125:9 127:15,16 137:15 155:14,20 156:13 157:5,11 158:1,3 158:6 160:7,12 162:14 164:17,18 166:9 171:8,9 180:2 194:21,22 195:1 200:20 201:4 207:8,8 208:18,20 209:15 209:18 211:2 213:8 218:22 219:1,20 223:17 242:22 270:15 280:21 281:11 282:8 288:3 290:6 290:7 292:16,18 303:11 327:11 331:12,14 341:9 341:10 344:6 347:5 350:3 351:10 353:6 361:18 363:15 364:20 381:12 386:17 387:1 390:5 391:7 393:15 396:1 397:11,14 398:9 398:20,22 399:5 400:6,16,18 401:13,15,19,21 402:6 407:1,5 410:4 431:13 435:17 440:4,7,10 441:4,9 442:17 445:9,22 448:22 449:7 450:4
people's 397:15
perceive 75:14 449:21
percent 28:3 78:1 83:9,10 84:22 89:3 90:3,4,5 91:7 94:10 95:12,13,22 99:14 100:1 123:22 124:8 141:21,22 142:2 152:16,17,17 170:15 176:14 192:6,10 193:6,8 193:20 203:5 204:11 205:1 211:5,21,22 220:9 220:12 222:20,20 222:21,22 224:14 225:15,20,20 226:11 227:9,21 228:5 230:3,4 268:21 269:2 295:7 301:20 302:2,2 310:11,14 310:15 311:2 318:18 325:1 368:9 371:16 373:5,7,8,8,14 374:10,12 375:4,6 375:19 399:6,8,12 399:12 401:5,8,12 401:13 403:13,13 403:20 412:10,14 425:9 429:3 430:9 430:9 440:18,18 444:2,2 449:20
percentage 91:13 91:17 308:16 310:12 316:10 321:8 324:13 430:7 431:15,16
perception 187:19 188:1
perceptions 76:12
percolated 291:1
perfect 24:5 115:22 262:20,22 267:6 271:14 396:4 433:20
perform 106:15 147:17 242:6 255:1 265:9 266:4 417:2
performance 67:10 68:16 151:1 216:6 222:6 224:15 227:4 229:22 230:1 250:15 253:1 257:21 262:16 264:8 266:8,17 271:8,12 276:1 278:2 282:22 285:5 287:10 347:3
performed 236:3 244:13 263:9 264:12 265:6
performing 60:1,2 239:3 241:8 267:18 403:22 439:22
performs 147:9 241:1 244:21
period 8:15 9:6,6 24:22 88:6 89:22 170:21 203:17 218:7 234:15 259:14,14 269:17 307:13 310:20 385:19 386:1 388:5 430:19
periods 89:18 371:1
peripheral 190:16 221:13 305:2
permits 155:9 265:15
permitted 85:1
persistent 225:17 228:4 406:11
person 16:22 21:15 22:10 116:3 116:9 190:20 402:22 451:22

personal 10:11 254:6 408:5
personality 419:11
personalizing 315:5
perspective 19:19 54:17,18 88:1 109:9,17 195:20 247:7 334:5 342:12,13 344:1
persuading 333:22
peter 3:5,8 5:17 5:18 138:7 153:22 154:8 155:12 164:11 176:9 177:15 180:9 183:10 185:1,10 192:2 201:20 203:2 205:6 208:8 245:10 272:4 334:18 359:12 445:19,20 449:14 450:6
peter's 164:16 186:8 196:22 301:16 333:19 354:8
pfizer 2:14 72:8 77:10
ph 30:20 32:15 77:12 90:10 94:14 107:21 121:7 129:22 142:15 143:18,19 144:8 147:19 151:20 153:17,18,21 154:1 166:22 168:21 169:11 171:1 173:13 174:11,12 176:12 179:10 184:5 188:16 196:18 198:8 203:2 208:6 217:15 223:9 231:20 233:3,8,9 237:6 240:9 242:2 246:6,6,6,7,7,7,21 248:1 252:10 257:17 259:10,12 260:2 261:10 262:17 264:9 267:1,21 269:5,15 269:19 272:9,9 274:11 275:17,21 277:11,11 301:15 304:19 305:21 308:6 318:3,5 319:17 324:17,19 325:2,7,22 332:5 334:18 335:4,11 338:1 341:14 342:8 347:5 365:15,17 376:12 380:22 390:4 399:10 400:5 408:8 445:1 447:5 447:7,8 448:5 452:4,12,16
pharma 77:1,5 189:13 196:8 199:6 444:4
pharmaceutical 73:21 106:22 192:8 198:1 350:2 385:16 414:18 430:4,18
pharmaceuticals 2:20
pharmacogenomic 171:7,20
pharmacogeno... 168:7 170:3
pharmacology 133:18
pharmacy 370:13
pharmd 4:17 6:12
phase 32:3 37:11 37:11,11 45:11 78:22 103:22 118:15,17 129:7 142:5 148:19 181:4 391:12 397:8 402:12 421:2,5 423:13 438:14 444:10
phd 2:9,10,13,21 3:11,14,17,21 4:1 4:2,7,8 5:8,9,11 5:20,21 6:3,4,5,7 6:8
phenomenal 446:16
phenomenologi... 365:22
phenotype 223:4,5 223:16 224:5,6,8 224:13,16 227:6 230:3 276:15 281:10,14,14 300:20 303:21 304:16 307:8,9,11 307:15 308:18
phenotyped 255:1
phenotypes 18:2 247:20 300:20 311:8
phenotyping 308:6
phil 246:5
philip 19:5
phone 16:21 402:13
physicality 404:7
physician 410:13 410:13
physicians 15:19 410:19 413:13,13 415:5
physiological 56:14
pi 87:6 217:14 220:2,2 273:3
pick 157:5 211:6 214:18,19
picked 158:2 428:6
picking 292:7 354:1
picture 79:10 97:11 219:1 232:1 342:6 365:5
pie 118:4
piece 61:20 75:1 118:14 289:14,14 367:10
pieces 64:13 134:14
pilot 47:5
pin 358:16
pink 238:1
pipeline 10:2,6 12:3 14:10 37:10 37:15 92:19 101:6 188:10
pipelines 258:21
pitch 195:9
pivotal 328:16 329:6,14 337:9 388:20
pivots 47:11
place 13:13 34:11 35:20 61:4 64:21 75:19 111:10 115:13 118:9 120:17 123:2 136:20 152:5 173:10 178:6 384:21 406:15 411:12 416:11 427:16 431:11
places 404:13

plan 38:11 104:9 106:20 111:6,18 112:2 118:19,20 121:7,12 187:11 332:16 336:7 355:20
planned 7:13
planning 25:19 44:9 52:10 81:11 219:19 232:9 345:2 363:9
plant 168:3 315:5
plasma 306:13 322:13
platform 108:1 172:19 240:13 241:5 242:13 248:15,19,19,20 249:2 317:22 417:1
platforms 170:16 240:10 242:11 253:20 259:1 261:22
plausibility 85:12 105:5 159:18
plausible 306:6
play 430:14
played 23:22
please 8:17 9:12 43:4 112:13 117:4 180:7 186:9 195:18 299:11 446:18
pleased 256:7
pleasure 7:8 54:2 73:9 202:5 445:21
plenty 204:2
plot 169:2 250:5
plots 89:6 250:15 251:16 252:6 265:4 371:6 374:9
plotted 93:6,13 183:11
plus 36:4 41:13 42:10 77:17 239:1 286:17 417:9 425:13,20 427:15
pneumonia 384:19 385:1
podium 9:13 13:15 73:17
point 43:14 66:15 86:19 88:2,3 90:5 94:12 102:6 103:12 104:12,15 109:6 113:2 125:15 128:19 137:7 150:5 168:1 175:3 177:2 185:2 187:5 193:3,16 194:8 197:20 200:8 214:1 234:3 236:10 237:20 241:2 242:2 245:22 259:2 265:9 276:3,19 277:20 278:12,18 285:8 286:14 287:3,16 289:16 293:5 295:8 296:4 296:5,15,16 311:17 312:11 315:11 318:1 323:7 327:17 329:10 335:19 337:7,16 338:17 345:1 347:2 348:9 353:1 355:19 356:14 359:22 361:16 362:12,13 364:3,22 374:9 383:10 384:9 399:17 438:17 439:2 445:6
pointed 99:5 216:8 365:15
pointer 303:2
pointing 101:4
points 58:10,11 70:2 80:3 96:11 137:1 240:22 265:14 284:6 302:9 304:19 311:5 382:15
policy 12:7 14:2 17:12 21:11 39:1
political 447:5
pollinate 98:6
polycystic 18:18 64:10 340:15
polymorphisms 143:22 166:18 174:10 175:11
polyomavirus 248:10 249:6 250:18
pool 185:22
poor 147:20,21 155:2 227:7 244:4 287:10 315:5
poorest 140:15
poorly 94:1
populated 227:3
population 63:12 91:13,18 101:7 125:3 144:22 149:17 152:18 155:9 172:19 173:7,17 174:3,4 178:13 182:11 186:16 187:3 188:1,13 190:5,7 192:3,6,13,16,19 193:9,10 194:19 195:9 197:9,13,15 200:5,7 203:15 222:13 229:13 230:2 236:21 271:7 279:4 281:1 281:4,5 282:21 284:16 308:21 317:19 334:11 349:13,14 381:19 409:15 411:20 443:7
populations 13:12 128:20 129:3,4,12 179:4 182:7 187:10 189:15 198:14 259:6 285:6 398:10 411:1
portal 415:18
portion 198:12
pose 109:2
position 14:5 314:13,18
positive 157:10,12 158:9 163:17 164:1 165:9 176:11 216:11,12 222:18 223:3 226:8,9,11 232:16 272:11 326:11,12 329:16 333:13 336:8,9 423:20 446:1,12
positives 70:9 160:10,11,11
positivity 163:16 165:2,5
possibilities 70:20 171:16
possibility 266:18
possible 114:12 158:21 270:7 330:10 344:13 398:12
possibly 27:16 33:10
post 11:11 27:7,8 29:13,15 53:20,20 106:8,10 129:22 153:2 156:19

158:5,14 160:5 168:3 189:14,15 190:4,10 191:2 200:11,17 201:16 204:5 210:19,19 217:7 218:7 234:21 238:12,14 239:13 259:14 263:9,10 265:6 268:11 269:16 270:8 277:17,19 278:10 285:17 297:4 299:8,18 339:5 359:13,15 368:8 370:2 371:1 375:1 379:14 380:17 381:4 387:18 388:4,18
posted 119:9
poster 31:16 300:11
posts 295:1
pot 255:6
potency 376:10
potent 376:21
potential 15:12 16:11 19:10,17 20:17 27:15 76:17 76:19 99:17 137:22 138:3 144:13 171:6 191:9,18 201:16 230:22 231:1,12 243:14 245:21 299:18 301:8 306:8 331:17
potentially 60:11 75:9,21 98:21 100:22 107:16,17 127:3 149:11 161:5,21 167:15 180:15,20 195:12 197:2 218:14 235:19 238:20 243:6,18 246:1 247:18 254:1 282:8 305:22 333:10 358:19 381:19
potentials 11:10
pound 407:22
power 91:20 94:14 95:11 266:18 285:1 310:6
powerful 96:18 308:3 340:16 354:10
ppps 35:11 37:5 39:21 40:2 50:5
ppv 222:21 230:5 236:19,21 237:16 240:18 241:7
ppvs 239:2 244:10
pra 149:4 176:14
practical 39:22 337:16 343:11
practice 20:10 39:17 52:1 130:16 181:15 261:11 367:15 369:1 372:18 376:19 378:2,13,20 380:9 383:16
practices 8:13 155:1 394:20
pre 53:18 70:13 138:1 166:22 168:3 200:11,17 234:21 235:13 268:11
preceding 79:11
precisely 126:18 221:18
precision 89:21 167:7 183:2 232:2 408:18 414:9 420:8 423:6
preclinical 75:16 78:10,16 80:10 121:7 135:17
precompetitive 26:11 38:15 43:11 102:10
predetermined 58:12
predict 88:8 93:14 97:4 105:21 114:1 162:1 226:4 234:22 278:2 282:7 295:2,3 296:15 307:10 310:21,22 331:5 333:14 335:22 351:18 354:11 359:14 360:11
predictability 147:7 276:20
predictably 228:20
predicted 213:10 307:6 335:6,10 359:18 432:14
predicting 29:14 128:10 146:10,20 147:15,19 148:7 152:14 244:4 257:3 275:13 313:20
prediction 85:14 95:21 142:7 243:22 256:3 279:11 281:5 294:18 340:1
predictive 17:22 18:1 27:12 47:15 55:10 72:8 73:8 74:3 77:7 79:13 88:20 89:11 104:8 126:17 128:17 130:6 156:19 176:20 264:13 276:1 294:17 307:16 310:2,6 328:3 332:17 388:11
predictor 308:3 344:17
predictors 38:7 186:18,19 271:15
predicts 27:7 242:18 308:21
prednisone 162:7 319:22 320:1,19 320:20 321:6 322:21 324:11 325:3,4 390:12
predominant 144:1
predominantly 13:11 103:22 174:3 252:22 254:6 302:22
preferably 338:16
prefile 234:21
preformed 148:13
pregnancy 161:12
preliminary 129:6 175:4,21 217:21
premature 177:6 337:15
premise 138:22
prepare 142:5
prepared 90:10 112:10 455:3
preponderance 65:8
prerogative 280:8
prescribed 370:14
prescribing 370:6 371:18
presence 13:7 79:17 254:2 264:2
present 8:1 77:11 82:4 84:9 150:14 169:7 206:15

210:3 212:10,10 219:12,21 220:3 223:11 233:21 245:7 389:1
presentation 23:4 98:2,7 180:9 271:15 287:22 300:16 352:7 408:16
presentations 9:4 53:18 108:9 138:2 367:9 438:1
presented 18:13 18:20 20:7 84:3 90:16 96:5,19 114:22 116:11 359:13 361:18
presenter 35:1
presenters 239:7
presenting 13:9 81:16 118:18 234:7 246:20 347:18
president 11:22 16:18,19 20:2,3
prespecified 258:21
prespecify 230:5
pressure 22:17 46:16
pretend 250:9
pretransplant 142:16 157:19 164:8,9,20 165:2 165:4 181:16 185:4 190:6 208:5 209:2 259:14 277:18,21 280:15 359:19
pretty 27:22 61:18 63:9 67:8 73:16 94:3 110:6 111:10 189:18 209:9 243:1 287:11 290:3 293:13 294:19 394:20 398:3 403:7,12,12 418:10 439:14 446:8,16
prevalence 178:13 317:18
prevalences 312:1
prevalent 11:7 222:13 229:13 230:2
prevent 156:2 197:11 243:7,13 344:18
prevented 306:11
prevention 363:10 411:5
prevents 436:9
previous 7:12 36:15 220:13 239:7 339:14 424:20
previously 63:16 157:4 203:20
pricing 199:21 200:4
primarily 29:10 257:12 394:13
primary 32:2 105:2 138:10,22 139:21 140:18 143:1,3,6 148:14 149:3 150:16 152:10 183:4,14 183:17 334:6 384:1,9 418:4 423:3 432:18 433:21,22
prime 172:2 210:1
priming 447:7
principle 164:6 244:17 246:5
principles 48:3 52:21 81:21 418:18
prior 80:4 173:14 205:12 223:11 235:17,19 245:13 255:5 375:10 387:11
priorities 28:21
prioritize 415:3
prioritizing 352:16
private 7:16 11:13 20:20 26:4 27:21 28:8 35:4,11,22 36:9,21 38:20,21 40:11 42:12 100:20 439:10
privilege 202:5
privileged 314:13
pro 27:17 171:1 172:3
probability 130:6 187:21 238:5 241:9 264:13 268:20,22 270:14 271:3 317:5 319:13,21,22 320:4,6 322:18,22 323:2
probably 9:18 31:4 34:3 63:2 64:20 77:4 105:22 117:11 118:17 143:4 176:6 184:11 185:5,14 185:15 192:1 201:2 204:22 252:2 256:21 257:7 261:13 281:18 291:22 293:5 304:8 305:4 310:16 341:13 343:15 389:22 398:20 400:14 406:15 414:3 425:4,6 431:22 435:9 444:21 445:5,6
probe 221:10
probes 248:17
problem 15:19 60:9,9,11 101:4 141:21 189:15,20 190:11 194:22 205:5 244:15 301:10 333:15 345:10 365:13 367:22 391:4,10 402:13,16,17 407:3 447:1 450:2
problematic 239:5
problems 112:22 181:19 182:1 330:6 349:4 351:1 407:19 421:1 444:7
procedure 113:20 253:12,18 265:18
procedures 39:2 268:2 416:11
proceed 212:4
proceeding 454:3
proceedings 454:4 454:6
process 24:11,19 28:19 29:17 31:20 34:10 40:1 41:6 49:11,11 52:7 53:11 56:2,3 57:12 59:20 60:4 61:8 67:20 68:4 72:11,17,18 73:2 74:19 75:6 79:6 81:10,14,18 98:3 100:18 103:7,8 104:15,19 106:8 109:14,17,21 111:2,3,3,8,9,16 114:13,21 115:22

116:3 120:8,9,21 121:22 123:13 124:6,13 132:13 132:14 134:12 140:4 168:5 242:13 260:12 300:13 301:11 328:15 329:9,13 333:2 338:22 353:3 451:4
processes 34:7 46:2,2 50:8 73:12 75:13 81:12 84:16 121:17 141:2 156:14 339:3
produce 103:9 104:11 305:19 306:14,15 369:21 372:13
produced 76:9
produces 101:8
product 39:13 40:19 46:12 108:12 299:22
productive 397:3 414:8
productivity 406:20
products 7:5 366:17
professor 285:22 286:3
professors 286:12
professorship 401:1
profile 32:14,16 121:9 165:17 213:15 245:4 255:13 260:6 368:19 369:14 373:9
profiles 121:6 376:11
profiling 26:3 30:13 102:20 234:21
profit 39:6
profound 312:18
prognosis 82:8 86:8 97:12 275:19 280:9 285:10
prognostic 62:6 64:14 66:12,15 114:1 138:9 148:9 148:10,21 152:10 160:19 191:6,15 191:19 235:21 257:13 259:11,13 262:6,13 264:5 279:6 287:9 363:11
prognostically 228:21
prognosticate 256:10 257:8
prognosticating 276:21
prognostication 257:6 258:9 259:19 262:22
program 46:13 47:3 54:8,8,15 55:9 56:19 64:19 109:10 110:17 112:6 132:17,17 133:6,8 205:20 295:17 315:14 328:22 408:8,9,13 408:15 410:17 411:3 414:1,7 415:22 416:3,4 447:20
programmed 34:11
programs 188:9 205:1 211:6 212:16 230:7 231:14 315:7,8 381:1 392:19,22 393:5 399:21 400:4,5 402:19 416:5 440:19,19
progress 51:9 82:14 86:12 98:19 98:21 107:6 108:3 141:7 196:4 289:9
progresses 448:17
progressing 213:16
progression 44:15 53:22 84:19,22 87:20 88:4,7 95:20 131:11 255:14 432:20 433:2,8,18 434:3 434:8,14,19 435:20 436:1,4,10 436:14 437:1,7,12
progressive 212:22 345:8
progressor 214:10 214:10
progressors 213:13,14,17
project 133:9 270:16,20 278:21 279:18 327:18 342:4 379:16,17 400:1
projected 269:20
projection 270:11
projects 17:18 33:8,11 196:16 358:3
proliferating 327:9
proliferation 213:21
promise 232:2
promising 45:17 175:4
promoting 16:6
promotional 117:21
prompted 337:5
proof 63:12 164:6 318:7 452:20
properly 254:1
properties 303:21 306:4
proponents 25:1
proportion 223:4 324:9,10 371:13 372:1 373:12 374:18
proposal 112:5 206:2
proposals 418:15
propose 114:10 212:7 339:3 410:4
proposing 104:15 111:14 347:22
proprietary 59:15 119:12
prospect 152:8
prospective 69:14 69:15,16 75:5 79:2 80:16 151:12 151:13 196:13 234:10 259:10
prospectively 45:5 189:5 388:17
protect 119:11
protection 431:9
protective 93:15 93:18 209:18 306:8
protein 145:7 215:21 218:18 246:17 263:19 328:14 365:10
proteins 172:13 175:1
proteinuria 27:9 105:14 124:2

211:1 216:5 262:1 266:13 267:20 274:9 330:13
proteomic 215:14
proteomics 215:16
protocol 45:7,10 45:15 154:22 188:14,18,21 204:18,19 211:6 211:14,18 212:13 212:14,20 213:9 214:1,9 217:17,20 220:2,8,17 221:17 222:10 224:20 231:6 236:6 261:19 262:9 265:9 267:18 297:20 301:19 319:8 399:17 404:13
protocols 45:4,6 258:21 378:17 383:15 390:3
proud 21:3
prove 59:22 303:20
provide 49:21 112:6 131:8 155:6 171:2 177:4 199:22 218:3 263:8 388:11 410:21 416:8
provided 15:7,7 76:9 111:20 122:17 219:19 229:5 252:7 414:14
providers 233:8 388:11 449:9
provides 33:15 60:5 387:20
providing 111:17 130:20 379:9
pstc 78:10 80:2 136:10
psychosocial 288:5
ptt 347:5
public 7:16 8:1,15 11:14 12:7 13:7,8 14:1 17:12 20:20 21:11 26:4 27:21 28:8 35:4,11,22 36:9,21 38:20,21 40:10,11 42:12 50:3 59:14 100:20 104:5 108:9 119:22 133:1 244:20 414:12,14 418:6 431:22 439:10 442:6 447:8 450:8,15 451:1 454:1,18
publically 173:20
publication 68:2 76:6,8,11,16 139:2 152:12 157:7 175:5 332:5 333:19
publications 93:1 174:9
publicly 133:5 243:9 244:12 413:5 418:14
published 19:14 42:8,11 47:22 67:17 83:6 84:4 84:19 92:8 94:11 130:1 169:18 170:8 172:12 174:12 176:2,13 179:3 203:3 215:2 219:22 242:16 247:3 302:12 315:22 322:13 341:18 418:5
publishing 357:3
pull 47:9,10 202:20 439:3
pulled 251:13
pulmonary 117:10
punch 405:8
punt 128:22
pure 184:3 266:9 267:20 421:20 423:3
purely 301:11 409:17
purported 131:22
purpose 44:8,13 44:17 62:15 103:8 122:14 132:7 133:16 134:1,16 134:17,21 135:4 150:7 283:19 285:13 411:2 450:15
purposely 221:21
purposes 142:17 161:8
pursue 83:21 87:10 110:2
pursuing 181:3
push 57:5
pushback 442:14
pushed 443:9
pushing 40:22
put 23:8 24:21 32:18 33:18 34:11 47:1 61:4 70:17 70:18,18,19 75:19 104:9 106:18 117:18 119:13 123:2 133:22 139:2 145:14 146:18 155:7,13 155:20 161:19 171:9 175:16 188:8 208:21 211:12 218:11 219:1 221:7 227:12 229:5 230:11 274:3 278:4,20 279:14 290:5 310:1 391:7 391:13,18 394:1 405:19 410:5 415:18 416:3,10 418:6 419:2,13 421:2 428:10 431:9,11 444:21 447:2 448:20
puts 145:21 161:2
putting 30:3 122:9 168:4
pyelonephritis 385:4

q

q&a 137:5
qcsf 205:20 211:21
qp 118:15
quadrant 77:21
qualification 47:3 47:17,21 49:4,8 49:10,20 54:8,16 55:2,17 56:19 57:2,3,10,13 58:17 59:3,13 61:3 64:3 65:5,10 66:6 67:22 68:4 69:12,21 72:10 75:2,9 81:10,11 81:18 82:2 98:4 100:18 103:7 109:10,14 110:4 110:10 111:5,6,16 111:18,19 112:6 112:10 113:3,12 115:12 118:19,19 132:7,13,22 133:3 133:21 134:5,14 295:20 328:21

353:4
qualifications 47:18,19 56:10 151:11
qualified 47:16 53:6 56:11 58:7 59:13,22 60:3 63:7 68:6 98:11 113:6 122:21 132:19 133:2,4 134:7,9,10 182:10 188:5 295:20
qualify 53:4 55:12 58:21 61:21 100:21 123:3 132:4,8 182:22 295:22
qualifying 149:14
qualities 172:16
quality 11:5 58:13 59:10 147:1,3 262:7 343:6,22
quantification 263:5 374:6
quantified 131:10
quantifies 371:22 372:4
quantify 30:3 83:12 266:8 330:21 333:4 335:20
quantifying 147:12
quantitate 217:2
quantitative 43:12 108:1 133:19,20 180:11 248:2 330:19 331:2 332:3 333:16 361:21
quantitatively 126:3
quantity 248:12
quarter 75:8 80:20
question 9:5 24:3 44:14 62:14 88:3 88:21 89:1 91:5 100:8 109:20 111:7 113:18 122:5 123:8,17 124:14,17,21 128:3 131:17 132:3,11 135:7,14 142:1 146:20 164:8 178:1 180:7 180:7,14 181:14 184:20 189:5 200:9,17 207:1 213:6 224:9 256:8 266:22 272:4,13 276:21 277:1,9,14 277:15 279:5 280:14 282:19 283:1 287:17 288:1 291:17 293:22 294:1 295:9 296:13,17 297:3 298:12 299:13 336:20 337:4,6 342:20,22 344:4 351:16 357:22 364:5 368:20 384:7 395:21 406:11 409:14 415:21 420:4 425:8 430:3 432:6,17 437:20 441:11
questions 8:7 9:6 37:21 44:22 45:2 45:8 83:20 96:20 108:16,19,21 109:2,4 166:12 177:22 178:20 180:6 181:12,13 232:20 235:11 271:22 272:2 276:14 278:22 336:19 398:9 414:15,17 417:4 430:1,4
quick 43:4 196:11 345:12
quickly 19:3 162:19 235:6 302:10 306:21 312:10 355:7 383:11 423:4 448:13
quiescence 216:16 217:10 347:14 358:2 359:7,7
quiescent 172:15 212:1 228:15 293:12 359:10,12
quit 313:15 403:1
quite 11:16 23:13 32:10 76:21 91:21 93:9 96:15 102:14 114:12,14 125:14 126:6,10 127:6 147:20 160:10 175:19 202:17 208:18 235:6 247:14 303:12,14 322:12 325:8 368:9 392:22 411:10,14 437:1 437:13,13 446:4
quorum 358:1
quote 232:2

r

r 2:1 7:1
r&d 46:9 49:7 329:8
race 149:5 176:13 209:21 373:18
radiographic 56:14
radiotherapy 409:20 413:20
raise 14:2 272:2
raised 288:17 346:17 358:1
raises 165:6
raising 194:6
ran 416:13
randall 3:1 21:22 366:18
random 89:5 221:8,9 227:3 372:6
randomization 162:22
randomize 162:16 273:3 427:5
randomized 32:3 45:5 93:5 129:22 130:1,12 162:20 189:4 232:8 260:20 261:6 269:15 271:7 272:16 273:4 278:13,15,16 388:19 391:12 425:19 427:1
randomly 251:13 372:10
randy 21:21,22 183:20 362:6 363:4 365:7
range 93:22 134:11 136:19 145:2 203:5 374:15
ranging 361:6
rank 274:6 308:14
ranking 275:20
rapid 13:10 84:22 88:3 253:17
rapidly 30:14 141:7 416:11

rare 194:7 196:5 200:10,14,18 330:3 392:22 403:12 428:22 429:3 433:16
rarely 383:15
rate 88:7 139:16 139:18,22 157:21 179:9 183:8 203:4 240:2 242:2 249:20 264:18 290:3,7 296:9,21 302:2,3 335:8 345:6 371:18 392:6 399:6 422:3 433:17,19 434:5 436:12
rates 100:2 296:19 368:9,12 384:14 384:15 385:2 388:8 442:7
ratio 93:12,14 263:19 267:15 372:7 382:5
rationale 69:4 106:3 150:14 229:10
ratios 145:16 372:3,12,13 374:14 375:3
ray 399:10
rct 151:14
rcts 152:7,8
reach 35:16,16 57:4 70:10 83:1 91:20 169:13
reaching 16:21
reaction 121:4 319:1
reactive 156:18 158:19
read 16:10 27:20 37:3 45:22 56:7 80:16,19 156:22 167:9 170:20 172:17 173:19 174:13 188:20 203:6 248:19,20 303:17 405:9
readily 257:22 448:13
readiness 109:22
reading 39:19,20 351:5 402:5
readouts 328:14 328:14 347:14
ready 109:13 111:8,21 131:18 355:5
real 182:16,21 210:1 258:18 262:21 263:21 313:12 352:17 370:13 379:22 380:9 387:20 390:9 391:19 392:1 407:3 444:7 445:16
reality 205:19 212:21 395:18
realize 67:2 82:20 118:2,3 122:8 353:11 407:21 432:7 433:11
realized 250:20
realizing 423:2
really 10:15,20 11:8,13 12:14,14 13:13 15:14 16:7 18:5,6,14 19:21 20:12 21:13,19 22:1,13 23:10,15 24:12,14 26:6 27:15 28:16 30:22 31:12 32:21 33:4 35:13 39:15 40:18 42:17 44:21 47:1 47:12 48:5,5 49:18 50:2,5 51:18 53:7,13 55:14,16 59:12 60:18 61:4 62:4 62:14 63:17,18,20 65:11,13 67:12,19 67:21 70:11 75:4 76:9 78:21 80:15 81:2,8 82:17 83:13 85:6,10 87:13,16,19 88:22 89:10 93:6,13 94:13 97:10,16,18 98:2,5 99:3,6,12 100:4,13,17 102:6 102:7 103:15 105:6 106:11,14 106:15 107:13 108:5,8,8,11 109:20 113:4,10 118:2,6,12 120:18 122:12 124:10 125:21 126:13,15 140:3,17,20 141:5 142:4,8,11,13,17 143:4,9 145:12 147:14,15 148:20 155:4 159:14 160:9 161:8 164:21 165:6,15 167:10,19 168:16 169:12,19 170:9 171:15 174:13,18 177:8,16 181:6 182:6 184:17 185:1,2,11 186:5 186:11 187:22 190:22 193:8 196:4,19,22 197:11,12,13 202:5 203:14,18 204:5,11,16 205:2 206:16 207:17 209:3 210:9,14 213:12,13 214:16 214:18 216:18 218:21 226:16 230:15 234:14,20 235:1,8,15 238:9 239:11 241:11 246:10,16 247:6 256:7 257:1,10 259:16 265:22 272:18,20 276:10 284:17 287:6,21 288:6,10 291:3 294:4 296:20 297:18 298:20 302:20 303:1,4 304:6 308:10 312:9 316:18 337:17 340:5 342:15 344:10,14 346:15,20 347:6 353:5,10 354:12 354:20 360:11 363:22 367:6 377:4 378:8,21 380:7 386:9 387:13 390:9,15 391:6,6,13,22 392:17,20,22 394:4,16 395:3 396:2,12,21 397:6 397:21,22 399:2 399:20 402:21 404:19 405:15 406:13,17 408:21 409:12,13 410:10 411:2 412:11 413:5,6 414:5,7 414:11,12 415:4 415:20 416:16,18 416:19 417:1 419:2,7 421:11 423:2 426:11 427:19 428:21 430:12,14 431:12

431:20 433:8,12 435:19 437:14,22 438:15,20 440:16 440:17,20 441:2 442:10 443:2 445:7 448:4,19
realm 44:4,5 113:12 122:19 131:13
reapply 269:1
rearrangement 427:10
rearrangements 426:16
reason 23:10 55:20 68:2 105:10 106:11 117:5 143:19 208:21 222:8 280:7 284:15 287:5 290:22 296:22 297:2 298:18 306:6 358:17 390:10 399:2,4
reasonable 85:1 90:19 160:10 295:6
reasonably 62:21 66:16 85:18 106:5 107:14 114:10 331:4 333:14 335:21 361:9
reasons 23:16 194:18 201:4 249:13 312:22 318:9 350:11
recalculate 264:22 269:1
recalibration 136:7
recall 41:13
receipt 373:22
receive 115:21 260:9 369:3 372:5 373:6,19,20 382:16 432:13
received 382:8,16 426:5
receiving 302:17 311:1 372:9 373:12 375:19 383:13
receptive 116:22 117:5
receptor 143:9,10 143:14 175:10 273:6 306:22 307:1 369:3 370:21 372:21 373:7,16 374:1 381:22 382:6 386:6
receptors 381:17
recipient 138:16 144:5,16,21 145:6 145:8,11,18 146:16 156:21 167:21 168:13 172:9 173:2 175:22 177:10 185:13,19 200:10 206:7,10,11,20 207:7 208:6 209:13 210:5,11 235:13 236:1 237:9 245:3,12 291:18 327:6 343:4 370:19 379:4,14 382:21 388:10
recipients 145:5 148:15 149:16 161:22 185:20 206:4 209:7 256:4 300:6,22 301:9 302:22 310:16 312:6 316:11 318:13 319:4 320:22 370:10 375:11,15
reclassification 266:18
reclassify 266:15
recognition 185:21 206:22
recognize 14:20 76:21 100:20 153:16 213:2 217:4,6 218:21 379:12 380:11 381:17 382:1 386:12
recognized 181:19 217:17,20 330:1,3
recognizing 143:14 207:20
recommend 414:7
recommendation 174:21
recommendations 54:22 112:7 116:16 118:7,7 119:11 120:18 369:7
recommended 16:12 142:20 369:2 376:15
reconcile 191:21 227:13
reconvene 201:12
record 451:2,7 454:6
recorded 370:11 454:4
records 319:10 381:1
recover 199:6
recovery 279:22
recreating 402:18
recruit 444:13 446:7,18 447:16
recruited 14:7 78:19 446:2
recruiting 337:12 446:17
recruitment 444:9 444:15 446:14,19 447:1 448:3
recur 374:5 412:20
recurrence 424:13 424:16 425:1,3,4
recurrent 11:11 392:8 425:11
recurs 423:10
red 79:12 140:12 163:15 207:8 209:12 268:16
rederive 150:6
redid 304:13
reduce 198:13,17 209:5 301:8 332:22 386:14
reduced 171:2 198:7 215:8 236:15 306:22 368:4 382:8 454:5
reducing 231:1,7
reduction 83:9,11 93:17 119:3,6 335:17 368:11 380:8 383:5,15
redundant 171:11
reevaluation 136:6
reference 68:20 90:4 119:14 175:16 188:15 371:14 372:15 382:7
referenced 78:8 117:15,16,17 371:10
references 117:4 117:12,18

referred 135:22 323:11
referring 74:18 292:8
refine 105:20 291:13
refined 84:1 150:20 152:11
refinement 152:4
reflect 111:19 307:20 333:1 349:8 380:8
reflected 212:9 382:14
reflects 334:11 374:10 378:21
reflex 216:14
regard 178:21 198:14 291:1
regarding 82:2 138:2 370:18 376:9
regardless 67:3 363:9 428:7
regards 178:19 210:22 211:10 235:15 246:1 347:17
regimen 1:5 179:2 261:12 302:18 354:14 371:6,10 371:11,13,14,17 371:20 372:1,5,9 372:15 374:13,22 376:12,17 378:19 380:13,14,15 382:22 383:7 384:17,17 385:10 386:7 387:4 388:9 394:21
regimens 178:8 179:1 369:19 373:13 375:8,11 375:22 376:10 379:19 381:14,16 382:13 383:1,2,14 383:19 385:1,2 412:13 432:20
regiments 178:15 376:22,22 388:5
region 144:1,2 371:7
register 65:7 258:19
registered 260:15
registration 8:16
registries 104:6 257:11
registry 370:8,11 370:20 384:6 390:22 391:1 446:3
regression 89:7 252:20 321:22 381:10
regular 103:6 305:16 329:6 336:11
regularly 17:2 86:20
regulated 215:6 248:7
regulators 42:2 59:7 65:3,18 69:6 72:5
regulatory 15:10 16:7 19:17 44:19 52:2,7 53:10 54:18 57:7,11,17 58:1 59:21 60:1 66:18 103:4 108:2 109:22 135:5 217:15 290:17,20 303:19,21 306:4 309:13 350:7 352:13 353:3 431:13
reimburse 450:3
reinventing 34:17
reiterative 131:20
reject 207:8 208:20 209:18
rejection 11:10,10 18:2 99:4,11,13 100:2,3 130:10,11 130:11 140:20 148:16 151:20 152:21,21 153:9 157:9,18 158:10 159:12 160:4,7,16 160:17,19 161:1,6 162:11 163:6,18 164:5 172:2,10 173:15,18,22 175:7 179:9 184:16 191:8,11 191:17 202:3,9,19 203:22 207:9,10 209:16,16 211:7 212:19 214:13,18 214:21 215:4 218:13 220:5,8,22 221:6 222:15,16 222:17 223:18,21 223:21 224:20 225:15,21 226:22 227:3,17 228:4,16 228:17,22 231:6,9 234:9 236:10,11 236:12 237:3,4 238:7,8 239:9,10 239:15 240:21 241:16,16,20 242:5,5,6,8,9 248:5 249:5,13,15 249:17 250:5,12 251:7,7,14,17,18 251:22 252:8,15 252:17 253:2,7 254:3,13 255:6 268:9 272:9 280:6 281:6 313:5 328:5 329:22 332:10,20 332:20 333:9 344:20 345:14,19 345:21 346:7,9 349:14 356:16,19 366:7 368:5,7,9 368:11 369:20 376:13,21 378:15 387:16 388:8 392:6 398:14 399:6 404:8,10 448:21
rejections 163:15 165:3 178:10 184:6 207:11 220:10 237:15,16 251:15 254:18 270:8
relate 330:19
related 79:18 83:13,17,21 96:22 113:19 124:3 133:17 179:14 209:20,21 221:6 235:8 303:18 304:7,9 309:5 316:2 354:6 357:9 368:13 388:12 390:17 413:19 422:21 454:8 455:6
relatedness 144:21 145:13
relates 372:17
relation 374:11 438:4
relationship 69:2 143:16 151:18 179:7 229:8 331:2 332:3 333:16 334:7 335:2 361:21

relationships 143:13 430:18
relative 91:16 138:16 147:3 303:5 454:10
relatively 47:3 101:7 162:10 253:15 279:4 297:4 380:12 382:11 383:11 404:21
relaxed 113:9
release 159:15
released 159:16 429:7
relevance 99:22 202:12 365:1,2
relevant 146:15 154:18 155:8 160:1 161:16 167:5 227:2 306:18 364:21 365:11 367:16 450:5 451:5
reliable 112:15 118:16 177:7
reliance 202:18,18
relied 57:15
rely 177:6
relying 203:6 211:14
remained 225:10
remarkable 379:1
remarks 7:22 451:21
remember 58:15 113:9,13 119:7 178:6 286:16 311:4 324:21 393:2 442:16,16
remind 263:4 293:1
reminded 15:15
reminding 164:12 164:12
remove 71:14 275:22
removing 254:19
renal 27:9 70:22 71:4 93:19 105:12 105:13 135:9 220:11 223:21 226:19 228:9 231:4 234:14 293:2,11 302:15 310:4 311:15,18 331:13,15 332:4 345:9
renalytix 234:3
renata 1:7 2:3 5:5 7:3 9:16 13:21 21:2 35:7
renata's 15:6 121:4
rene 143:18,20
rental 330:14
reorganized 417:12
repeat 95:10 225:2,9 228:6
repeated 164:2 254:5
repeatedly 68:19 253:10
repertoire 308:20
repertoires 308:8
report 167:10
reported 1:18 343:21
reporter 248:17
reporting 1:20
representation 17:16 121:16
representative 74:3
representatives 76:15
representing 14:1
represents 152:16
reproduce 105:17
reproducibility 69:20 229:18
request 54:20
requested 13:7
requester 116:8,8 116:22
requesters 61:20
requesting 12:10
require 114:3
required 55:12 58:13 61:18 64:22 65:7 66:5 67:21 71:17 74:19 129:13 222:10 232:17 243:12 381:6
requirement 119:8
requires 49:12 158:18 379:21 404:11
requiring 330:8
requisite 77:15
reran 221:9
reroute 112:13
rescore 130:4
rescue 189:16
research 35:10 117:16,17 125:1 154:17 161:7 169:17 233:7 327:19 377:22 391:8,16,17 392:18 393:4 395:14 396:21 397:6 399:22 402:20 406:5 407:9 409:8 410:15 411:13 414:16 419:5,12 420:4 430:15,21 431:4,8 444:22 448:4,11 449:7
researchers 418:7 418:15
reserve 200:21
reservoir 418:11
residents 286:13
resistance 75:1
resistant 178:10
resolution 148:7
resolve 226:12
resolved 226:10
resolving 86:10
resource 409:8
resources 39:9 49:12 353:5 377:2 385:17 397:18 411:8 421:9
respect 292:22
respected 396:2
respectively 152:17
respects 422:22 433:16
respond 211:3 225:16,20,20,22 226:5,5 268:15 355:3
responding 437:5 442:6
response 16:3 38:7 46:3 66:9,22 71:8 112:3 139:11 140:18 141:6 150:16 151:4,7 157:2 172:6 175:17 176:19 185:21 192:22 206:5 215:5 227:10 231:10 313:21 359:4 360:21 421:22 422:4 433:17,19 435:20

responses 70:8 114:1 158:19 159:16 175:20 183:17 200:19 254:15 309:12
responsible 16:6
responsiveness 183:5 359:21
rest 190:1 207:13 298:22 316:12 322:4 394:22 397:1 429:4 440:10
restarting 114:13
restrict 193:14 259:13
restricted 182:11
restrictive 193:17 194:2
restroom 366:10
result 41:17 42:5 89:8,19 92:7,12 159:5 226:17 300:5
resulted 90:7
results 92:5,9 93:22 96:19 101:9 126:12,12 158:4 158:16 177:3 201:9 234:7 336:9 336:12 349:13 377:17 418:4 426:1 429:7
resume 366:10
rethinks 24:10
retrospect 152:6
retrospective 69:15 151:13 319:2
return 15:3
returned 14:14
revenue 199:2,11 199:16
review 16:7 47:8 57:11,17 59:20 116:9,17 119:19 132:15 133:8 135:5 174:11 367:18 414:6,10
reviewable 120:14 120:19
reviewed 223:8,10 380:16 410:4
reviewer 366:17
reviewers 37:16 116:17
reviewing 117:7 342:4 367:19,22
reviews 304:20 413:22
revised 115:17
reviving 14:9
rewarding 428:15
rfa 416:3 443:1,4
rhabdomyosarc... 411:18
rhia 4:16 448:5,6
ribbon 442:19 443:14
rich 379:22 439:4
richer 342:13 387:12 388:17
richness 125:10
rid 276:5 277:18 364:12
ride 90:14
right 1:5,5 7:5 12:20 23:7 27:18 27:20 28:6,14 33:21 34:16 43:1 43:14 48:8 52:19 56:12,16 57:6,6 58:2,11,19 59:14 59:15 61:9,16 62:2,15 63:10,19 64:6,12 65:18 67:3,15,20 68:17 68:19 69:6,14 70:14,15 74:20 76:2,13,16 80:15 81:2 83:14,18,20 84:11 85:9,11,22 86:6 87:18,21 88:14,16,16 89:7 89:13,22 90:19 91:10,22 92:19 93:20 94:21 96:4 97:3 99:1 101:15 105:2 110:3,5 122:11 123:14 124:22,22 125:2,6 125:10,18 126:9 127:6,10 128:4,15 134:18 149:3 155:14 160:15,20 162:13,17 163:7 163:18 164:14 165:12 169:10 171:9 176:4,20 185:22 187:15 189:21 190:7,22 193:6 197:22 201:15 205:3,3,3 212:4 226:21 232:1 250:5,16 271:20 273:17 276:17 277:7 279:2 281:7 288:2 288:3 290:1,6,11 290:13,19 294:2,9 295:1,16 296:11 297:6,13,14,17 299:12 303:4 306:9 307:9 332:11 341:3,5 342:22 343:12 345:17 346:4 348:3,15 353:3 355:17 357:8,20 360:14 366:8,8 367:21 384:14 389:14,20 390:2,7 391:1 393:19 395:5,6,9,19 396:22 401:19 404:3 405:21 422:1 427:16 438:12 440:8,17 441:3,5 445:4 446:1,18,20 450:13,15
rightfully 128:18
rigorously 31:18
rise 80:5 204:10
rising 368:12
risk 13:3 48:9 61:16 66:4 84:12 84:12,13 87:22 88:5 90:2,8 91:8,9 91:14,16 92:1,2 95:21 130:6 138:1 142:2,16,21,21,22 143:7 145:19,20 145:21 146:1 147:13 148:15,18 148:19 149:3,4,9 149:10,12 151:3 152:15,15 153:1,3 153:8 154:10 155:3,9,9,19 156:19 157:6,9,10 157:14 158:6,15 162:7,13 164:9,21 165:10,18 166:19 167:1 168:15 171:1 172:1 176:9 176:18 177:16 181:20,20,21,22 183:3,7 184:1 191:13,16 192:4 193:5,12 195:12 201:17 203:15 205:21 208:7 209:3 216:9 218:13 228:2,16

231:5,15,19 235:17,18,22 237:9,13,16,18,19 237:21 238:1,3,6 238:12,17,19 241:14,17,18,19 242:8 243:10,16 243:19 244:18,19 244:22,22 245:2,3 245:9,12,12,13,14 245:17,18,20 247:17 256:3,10 257:8,13 259:19 260:1,4,7 261:1 261:13 262:17 263:7 264:12,20 265:4,5 266:16 270:6 274:10 276:18 277:11,21 279:4,17 280:7,15 280:17,17 281:16 281:21 282:20 285:3 290:9 291:19 292:16 299:20 315:18 326:9,10 330:16 330:20,22 331:14 331:22 332:1,4,7 332:14 333:17 334:8 335:3,11,22 342:5,10 360:8,9 361:4 362:2 368:5 369:5,14 373:9 376:12,21 377:6 382:2,22 383:2 386:14 423:8 424:14,15 425:1,3 425:10,10,17,18 426:5,9 449:22
risking 196:18
risks 149:17 168:3 173:15 230:22 231:12 301:13 387:16
rita 12:18 14:7 21:21
rituximab 175:18 175:19
rna 234:17 248:11 248:16,18 249:7,7 254:11,14
rnaseq 206:12 236:3 239:12 240:7
road 61:10 114:16 296:16
roadblocks 113:1
roadmap 48:6,7 76:9
rob 11:17 246:21 246:21 247:10 255:15
robert 4:18 452:6 452:7
robust 66:4,15 129:17 257:2 323:17 377:6
robustness 261:12
roc 77:18
rochester 2:8 395:1,5,7 401:6 402:2
roe 223:9 233:3
role 23:22 35:4 36:9 42:12 49:18 176:18 288:11 291:20 311:21 414:13 430:14
roll 355:7
ron 11:21 87:7
ron's 12:1
room 1:15 8:6,8,9 20:9 21:10,15 22:15 26:18,19 51:12,12 54:12 74:11 75:4,11 76:7 77:3 137:8 150:18 166:9 168:14 189:13 202:7 255:18 314:6 407:22 439:18 446:14 451:12 452:2
ros 7:16 9:12 24:21 33:20 273:19 299:10,22
rose 452:4,4
roslyn 2:4 5:6,19 5:22 166:16 246:16
rosy 407:10
roughly 304:2
route 329:8,8
routes 132:6,9
routine 42:1 358:15
rt 318:2
rule 148:12 444:1
rules 8:4 49:22
ruling 228:13
run 75:11 87:15 200:3 210:8 217:13 259:22 270:12 403:7 415:1 431:8 436:19,21
running 33:1 177:12 402:11
runs 13:14
rushing 235:4

s

s 2:1 5:2 7:1
safe 73:10 74:7 78:9 79:13 80:1 301:7 313:8
safely 40:5
safer 73:10
safety 11:15 13:3 13:5 15:11 24:12 26:3 27:3 30:13 31:7 38:9 47:15 48:21 55:10 68:1 68:6 70:21 71:3 71:12 72:9,12 73:8 74:3 77:7 79:13,16 96:22 97:7 102:20 103:2 127:6,8 156:5 171:8,13,21 183:5 185:7,8 186:6 218:20 359:14
saint 4:9 366:22
salary 445:8,9
sales 195:9
samonego 246:6
sample 208:5 209:8 215:12,18 221:13 222:3 251:4 310:4 316:19 336:2
samples 77:15 78:15,21 79:4 151:10 221:12 225:12 227:1 229:14,17 246:9 249:16 250:22 251:12,13,13 254:21,22 255:2,6 293:4 303:19 322:17
sampling 234:17 247:13
san 3:12,13 202:1
sanofi 29:22
sans 308:6
saps 395:20
sarwal 3:11 5:21 184:20,22 188:11 194:3 202:1,4 272:13 273:14,16 273:18 346:11,14 347:19 348:18,20 350:14 353:8 355:13 356:3,5,9 356:12,19,22 357:3,7,9,13

sauer 2:13 5:11 55:8,13 109:19 113:2
saved 269:21 270:1
savings 388:5,7
saw 20:4 90:3 91:7 91:11 139:4 140:7 160:20 224:14 254:17 267:4 312:2 411:12
saying 51:17,19 72:15,17 88:10 114:20 117:21 121:10 192:2,14 193:11 195:22 231:18 301:5 308:17 309:6 339:19 343:19 352:3 361:1 443:11
says 31:3 78:4 120:14 304:8 305:1 311:22 356:8 364:11
scale 210:4 417:2
scanned 401:17
scanner 401:17
scarring 275:12 275:13,21
scary 442:7
scenario 201:9 260:21 268:10 339:10
scenarios 130:9 180:20 198:2
scheduled 227:20 227:21 231:2 232:13
school 3:2,9,19 28:13 154:8 219:8 233:17
schroeder 14:8 21:22
science 16:5 35:3 57:6 83:19 167:9 290:20 352:13 414:14 415:2 418:13 430:15
scientific 46:19 57:22,22 81:19 87:17 113:5,11 133:11 150:13 219:16 431:2
scientifically 46:14
scientist 90:15
scientists 15:20 57:7 70:16 95:8
scope 12:14 367:22
score 105:10 147:4 148:10 149:9 152:4 205:21 215:20,21 237:13,18 238:3 241:9 244:19 245:14 256:3 265:1,15,17 266:3 266:4,9,12 267:8 267:20 268:14,17 269:2,17 270:12 274:3 275:12 278:1 285:2 298:15 425:3,6,11 425:17,19 426:9
scores 147:1,2,5 214:3,9 251:16 274:13
scoring 105:16 130:15 257:18,19 260:20 266:19 271:11 276:4,6,7 276:8 277:21 280:18 287:9 290:22
scott 40:21
screaming 28:17 75:11 451:16
screen 177:22 326:2 426:22 427:3,22 428:6,17 429:3
screened 417:18 419:18
screening 45:14 232:14 409:12,18 428:21 429:9
screens 109:6
se 354:21
seal 393:18
seamlessly 421:5
search 134:5
seat 366:13
seattle 15:15
second 8:20 9:1 17:11 19:12 46:14 62:13,21 71:10 118:15,18 137:16 137:21 142:5 188:8 204:4 222:12 226:2,3 236:9 239:6 244:8 244:9 270:10 277:1,14,14 285:8 292:15 329:1 350:22 386:21 395:2 447:18 448:14
secondary 231:17 351:12 377:15
secret 119:12,15 119:17,18
section 1:15 61:2 235:22 299:11
sediment 304:21
see 15:21 21:4 22:9 26:8 29:4 37:7 40:15 41:10 42:17,21 50:10 53:19,21 62:18 64:9 74:17 75:2 75:20 76:11,15,18 77:20,21,22 78:2 79:12,17 80:1,3,5 80:11 81:7 88:17 89:8,15 93:7,11 96:19 98:5 104:4 104:7 108:18 110:17 118:16 120:19 124:2 134:6 135:13 138:17 145:18 146:14 148:4 161:11,14,18 162:1 169:2,22 172:11 175:20 176:19 179:7,12 179:17,20 180:10 182:12 187:12 191:4 192:1 207:6 207:11,15,15,20 208:4,9,10,11,17 209:11,14,19 210:1,21 212:16 212:20,21 213:15 213:17,19 214:3 214:10,11 215:8 215:22 216:3,5 219:20 222:11,19 232:9 236:16 237:5 238:9 241:8 251:5,13 252:3,22 258:4 260:11 263:7,19 264:9,11 265:5,20,21 266:2 266:14 267:7,21 268:13,21 269:18 270:22 278:14 280:21 285:15 287:12 289:13,15 289:20 296:14 297:10 301:12 302:20 308:18 309:21 311:2,19

318:10 319:20 320:7 322:17,20 324:8 331:20 332:12 333:12 335:18 336:8 348:5 350:4 351:11,11 353:15 361:10,15 362:7 365:5 381:14,20 382:6,7,13,14,18 382:21 383:5 384:11,15,17,22 385:4,16 386:3,5 386:7,19,22 401:7 401:7 406:16 412:4 414:21 417:16 420:14,22 425:22 428:11 434:20 437:7 438:18 442:5
seeing 32:20 147:18 153:3 183:21 217:5 281:14 420:17 422:3 434:19 435:20 453:4
seek 106:14 108:10
seeking 103:10 429:9
seeks 199:3
seen 10:7 37:6,15 45:4 65:18,19 82:14 102:4 104:14 107:10 136:21 138:4 151:5 178:3 227:14 236:2 319:14 322:3 331:9,10,15 420:1 435:2,4 436:22
segregation 152:18
select 205:13 210:14 218:19 321:11 324:15 325:11 327:1 334:11 364:10 427:3,8
selected 79:15 192:3 212:18 301:18 325:2 326:13 334:17 364:22 372:10
selecting 185:3
selection 48:20 209:2 218:4 235:20 325:13 334:11 347:12 379:18 380:15 385:10
selects 364:17
self 373:18
semi 180:16
send 30:20 116:14 202:22,22 276:7
sending 50:12
senetal 174:11
senior 90:14,15
sense 91:15 97:1 102:11 112:16 125:18 141:5 147:3 150:11 171:12 196:6 235:9 294:16 339:14 373:15 375:8 376:3 415:10 430:13 444:4
sensitive 70:7 216:10
sensitivities 239:2 244:11
sensitivity 147:21 151:2 221:22 278:9 284:21 316:15 317:1
sensitization 373:18,21
sensitized 281:3 375:12
sent 32:12
sentence 64:9
separate 74:9 129:10 148:2 216:1 339:16 407:6 411:13 416:6 419:5
separated 409:17
separately 94:11
separating 208:18
separation 208:9 208:11 210:1
sepsis 384:19 385:4
september 1:8
sequencing 185:17 186:3 206:11 207:5 209:4 240:12 241:4 428:1
serial 220:18 229:16 255:2 334:16
serially 163:16,20 228:11
series 8:11 12:17 95:5 165:18 169:6 175:9 423:17
serious 30:1 32:9 330:3
serum 46:15 71:13 78:6 83:8 89:18 90:6,7 93:19 139:13 160:4 204:8 213:3 225:9 398:7 401:18
served 12:19
service 409:7
services 233:7 415:16
session 8:12,17 9:3 16:11 35:2 50:19,22 51:14,17 53:2,21 108:15 137:5,6,16,21,21 166:16 168:9 184:16 200:21 201:11,13,16 256:12 292:9 299:8,13,17,17 300:1 336:18 360:6 366:14,18 366:19 378:6,6 430:1 450:8,10,14 450:22 452:18 453:3
sessions 8:12,20 52:10 200:18 219:19 299:7
set 25:9 51:18 70:1,2,3 92:22 102:16 117:11 118:6 120:18 192:15 209:11 213:19 215:20,21 216:2 221:11,20 230:4 235:2 236:8 236:9,14,15,17 237:1 238:22,22 239:1,11 240:6,14 240:15,17 241:6 241:10 243:8,8 244:5,20 249:7 250:1,3,10 252:21 255:4 265:3 267:1 285:4 288:7 297:4 314:14 315:22 316:1,17,18,18 317:9,10 322:15 322:18 372:8 379:22 384:7 387:8 393:7 428:12 430:20 431:13

sets 221:10 255:8 322:5
setting 52:16 53:3 129:10 181:16 217:8 247:11 258:3 346:6 432:21,22 433:3,4 435:7,12
settings 258:1
seven 134:7 174:1 258:4 264:17 268:20 270:21 271:2 286:11 379:5
seventy 211:22
severity 434:17
shake 403:9
shamelessly 219:18
shannon 4:17 450:9,10
shanon 6:12
shape 108:9 112:2
shapes 37:16
share 36:22 37:2 39:7,8,8,9,11,11 43:3 47:9 74:10 87:14 103:13 138:13 174:9 256:7 367:8,12 372:17 397:1
shared 252:4 342:11
shareholder 219:16
sharing 37:3 38:14,15 43:1,5,6 43:6,9 49:14,15 77:6,11 107:4 340:8 393:10 431:5 451:21
sharings 49:17
sharp 201:12
she'll 35:3
shed 305:3
sheet 8:16
shelf 230:6
shepherds 73:4 74:15
shift 45:3 82:1 420:6
shifted 412:16
shifting 375:21
shifts 375:18
shoes 13:1
short 54:14 96:3 178:1 262:4 269:14 290:10 346:5 354:13 449:19 452:18
shorter 107:17
shortest 170:21
shortly 21:7 84:4 92:8 178:1
shot 198:8
show 22:12 29:18 61:9 82:22 89:12 89:19 90:21 92:12 95:18 107:17 151:4,21 156:10 160:2 163:3 191:11,17 192:4 196:8 217:11 224:18 231:10 235:5 240:17 249:5 252:6 261:4 261:17 262:20 270:11,12 276:11 300:12 302:15 304:10,14 314:10 318:6 328:13 330:8 331:2 354:22 361:20 363:12 404:12 432:19 433:17
showed 35:21 36:1 36:3 56:5,18 63:16 92:1 140:1 140:2 157:7 184:8 227:4,5,8 229:9 229:11,22 250:20 304:1,14 306:10 332:6 365:9 383:11
showing 93:16 152:22 153:20 164:12 175:22 208:8 241:3,6 244:3 250:15 361:18 363:8 406:20
shown 9:7 10:3 19:1 105:18 125:9 169:9 171:13,14 173:19 176:3 177:22 183:22 185:10 219:3 237:20 239:9 242:1 250:4,7,12 250:13 251:11,22 252:16,19 253:2 305:20 309:9 322:19 330:15 365:17 374:9 378:18 419:15 420:15
shows 10:8 98:2 132:6 141:18 176:9 188:3 212:2 221:1 222:5 223:13 250:14 264:15 307:13 308:13 311:13 312:17 323:15 331:11,16,19 332:3 354:8 361:19 396:16 434:3
shukal 3:17 5:20 201:19
shy 287:8
sic 442:4
side 14:21 23:17 40:7 67:12 76:13 77:5,5 107:3,3 162:4 236:17 237:21 293:14 315:11 376:10 416:17
sides 107:2
sights 184:14
sign 8:15,18 23:19 451:8
signal 183:18 420:18 421:3,4 423:13 427:20 428:5 429:9
signals 429:10
signature 214:12 251:2,16 300:21 306:18,19,20 311:3,22 312:4,13 312:21 313:6 317:18,20 318:5 321:10,12,15 324:2,9 326:22 454:16 455:12
signatures 213:18 364:8
signed 451:10
significance 224:11 364:19
significant 28:16 58:10 92:2 101:9 105:13 128:21 168:5 173:22 174:18 223:19 252:8 253:3 254:17 303:9 331:16,20,21 378:13 384:17 414:4 429:18 431:10 434:21

significantly 139:6 216:6 252:11 311:15 330:16 335:10 371:19 383:2
signing 350:3
silent 227:17
silver 1:16 12:22 74:12
similar 41:4 59:9 103:17 148:3 158:4 239:7 252:11 271:6 301:16 302:13 305:11 317:13 374:20 379:4,6 380:11 382:11 383:8 385:3
similarities 98:5 121:16
similarity 173:5
similarly 249:14 255:12 384:13 386:19
simple 61:19 83:2 266:13 276:3 341:3 342:15 344:7
simply 111:11 302:5 308:11 341:5
simulates 43:13
simulating 180:20
simulation 44:8 44:11 135:1 181:3
simulations 82:22 92:12 94:9 95:4,6
simultaneously 291:21
sinai 3:9,19 154:8 233:17 234:4,11 255:19
single 32:13 38:13 39:12 166:17 188:7 223:12 232:14 263:4 266:5 270:20 274:4 315:9 349:19,19 392:14 396:6,6 398:6 402:18 405:4 411:22 440:22
sir 299:12 367:20
sirolimus 384:22 385:5,6
sister 22:11 386:16
sister's 22:20
sit 26:9
site 220:2 268:7 305:5
sites 78:17 233:7 234:11,19 394:14 400:18
sitting 20:2 109:3 197:12 343:18 398:21 404:18
situation 326:14
situations 189:7 276:11
six 10:5 75:1 79:6 162:9 213:9 214:1 214:9 217:17 236:4,5,7,12 237:10 241:1 263:10 279:15 281:6 309:2 321:7 375:20 376:5,6 382:15 444:18 446:1
size 91:20 172:19 380:6
sizes 336:2
skewed 242:4
skills 454:7
skin 384:19
skip 253:7
sledgehammers 176:15
sliced 117:22
slide 10:7 26:8 35:20 37:7,8 39:15,20 45:10 56:18,20 63:16 73:22 76:13 82:11 102:4 104:14 125:8 132:6 141:9 141:10 174:14,15 193:4 202:14,21 203:5 217:11 218:12 221:1 265:12 328:18 331:10,10,19 336:14
slides 9:7 30:20 55:18,21 62:18 132:4 171:12 173:20 183:11 188:15 328:13 331:9 367:19
slightly 305:9,10 318:14 328:13 346:21 381:16,22 382:7 426:13
sliver 194:5
slope 84:22 88:20 126:15 183:12 266:11 332:22 333:13,17 335:3,9 335:21 348:7 353:13
slopes 84:1 96:10 96:13,18 126:2,3 126:4,5,7,12 335:18,20
slow 18:5
slowly 193:22 213:13 345:8 402:15
small 18:15 27:22 85:5 101:7 151:14 164:5 179:4 192:9 192:17 196:19 199:17 257:15 272:7 364:13 381:18 386:7 397:19 404:21 405:16 409:11 437:13
smaller 91:20 92:3 153:14,15 182:15 187:1 208:10 374:18 411:17 417:2 443:7
smart 389:16 390:5
smarter 398:17
smattering 76:19
smoldering 141:2
snacks 8:6
snip 169:3
snp 175:22 183:4 209:5,6,10,13
snps 170:16 171:7 172:6,15,22 173:8 173:15,17 174:21 175:9 176:5,19 178:4,12,19 179:14 209:12 210:6
snyder 205:18
societies 19:22 22:3 23:12,14 102:6 103:13 439:3 442:2 443:9 443:11 448:1
society 11:20 19:5 21:17 369:17 375:16
software 144:6 150:4,10,11,12 152:6 230:6
softwares 221:5
sole 312:19

solid 110:6 137:1 215:3 230:11 366:17 378:16 379:12
solomon 231:20
solution 101:12
solutions 36:20
solvable 450:2
solve 60:9,10,11 66:2
solved 60:22
somebody 20:8 74:1 293:3 346:6
someone's 435:14
someplace 196:7
somerville 29:21
somewhat 83:6 114:14 177:3 309:22 368:18
song 15:5 348:10
soon 30:11 278:3 362:8 441:22
sophia 324:17
sophisticated 94:3 142:6 176:10
sorry 68:9 111:5 116:1 122:5 202:8 223:15 244:8 341:14 346:14 357:15 362:7 452:8
sort 10:18 24:16 27:19 83:1,18 84:11 85:11 86:4 87:16 91:6 92:16 96:2 116:2 124:3 124:11 127:14 156:13 157:1 159:22 161:14 164:20 165:13,16 166:5 167:15,17 168:2 170:18 171:12,15 173:9 176:9 181:4 190:2 190:13 230:12 252:8 275:4 280:16,19,19,22 289:10,12 304:5 311:1 346:2 358:10 409:18 410:3 445:18
sorts 94:3 390:16
sound 340:3
source 343:3
sources 95:4 233:10 370:8 377:13
south 130:17 275:7
southeast 173:8
space 26:11 38:15 43:12 98:18,18 100:7 102:8,10 104:1 107:19 123:4 135:17,18 326:13 352:2,14 393:6
sparing 371:3,4 375:22 382:17,22 383:6 385:3 387:1
speak 328:10 408:22
speaker 5:4 6:1 120:22 121:2 122:4 131:1 132:2 138:7 154:7 166:15 180:8 181:8,10 187:17 191:20 197:19 198:16,19 201:1 201:22 219:7 233:16 246:15 256:1,12 279:2,13 280:13 281:7,17 281:20 282:1,4,11 282:14 287:19 289:3,5 296:2 298:10,13 299:3 299:15 300:2 313:17 328:1 336:22 337:3 338:4,6,8,10,11 338:14 339:13 342:20 345:11 346:12,16 356:1 357:22 358:5,8 366:21 389:4,8 407:13 445:20 450:10 451:14 452:1
speakers 49:9 52:10 79:11 98:16 120:6 132:3 177:20 292:9 430:1 451:10 453:6
speaking 73:17 267:7 339:1 367:1 389:5
speaks 96:21
spearheaded 432:9
special 13:11
specialties 258:17
specialty 415:13
specific 11:9 27:13 42:19 46:11,11,12 54:19 57:15 61:14 72:11 77:22 79:11 96:4 97:2 101:12 109:5 115:5 133:7 136:8 139:5,8,12 151:7,9 154:22 170:19 171:1 180:7 181:12 186:15 198:2,10 200:12 212:17,19 216:10 248:17 251:11 289:19 304:8 309:12 315:6 322:12 339:5 344:15,20 381:7 384:18 393:6 394:4,9 399:22 409:14 410:22 411:17
specifically 12:9 60:14 95:16 102:3 102:21 105:4,20 133:19 140:7 146:3 155:7 185:21 254:3 284:20 367:12 369:9 370:12 372:21 374:17
specificities 239:2 244:11
specificity 144:3 151:7 221:22 316:15 317:1
specifics 118:5 138:6
specified 70:13
specimen 212:8 398:5 422:2
specimens 274:22 398:7 424:11,19
speculate 351:16
speed 59:20 415:1
spend 48:3 258:12 378:10
spending 209:4
spent 16:20 269:6
sphere 439:7
spinal 365:9,11
spleen 206:15
spline 89:4
spoken 441:18
sponsor 339:6 353:4
sponsors 131:9 432:13
sporadically 350:18
spread 382:13,18

spring 1:16 12:22 74:12
spy 45:11,14
square 321:19
srtr 141:17 370:20
st 4:10 366:22
stability 318:4 347:9 351:18
stable 139:17 161:22 213:2 216:21,21,22 220:11 221:16 222:9,10,15,16 225:10 226:19 228:9 231:4,9 249:4,18 250:21 252:10 253:6 293:2,6,11 306:19 307:5 311:4 317:11,19 318:17 319:4 324:1 353:12
stacked 371:6
staff 8:8,9 13:21 21:14 410:13
stage 45:18 93:19 111:3,10,10 112:3 112:4,8 118:19 120:17 314:14 423:7,12,20,21 425:2 426:14 436:10
stages 109:16 111:18 133:1 355:18 436:2
staging 84:10
stakeholder 39:4
stakeholders 7:20 39:7 42:2 95:9 102:9 107:19
stand 58:2 109:8 299:12
standard 27:4 37:18 65:13 67:14 69:4 70:4,8,10 93:8 101:8 149:2 162:9,10 166:5 183:8 204:8 216:4 216:8 225:13 229:20,21 232:10 232:19 240:1 250:2 272:15,17 273:1 292:20 296:8 393:10 398:6 400:1 420:16
standardization 156:10
standardize 106:17 156:12
standardized 15:4 45:5 158:22
standards 12:17 68:20 435:18
standing 51:12 402:19 406:5 416:9
standpoint 162:22 165:12 343:11
stanford 3:2,3 205:18 211:20
stanley 452:3,4
star 142:13,14 154:2 166:22 174:8 177:14 391:3
stark 441:15
start 8:4 9:11 25:10 32:19 48:6 66:14 84:7 101:14 101:20 103:1 105:11 109:14 111:8,11,21,22 112:14 121:11 128:21 137:16 138:5 163:10 181:5,17 194:6 202:13,15 208:9 208:18 216:1 256:8 277:8 290:16 294:11 306:5 311:16 328:17 329:15 336:21 348:7 350:3 353:10 381:11 392:9 395:14 402:21 417:7 453:4
started 7:2 19:21 34:13 88:1 99:20 108:4 112:20 121:6 163:5 193:18,22 196:8 205:18 221:15 226:13 258:6 270:15 307:11 314:16 352:2 359:17 366:13 394:12,13 408:9 410:17 415:17 438:12
starting 30:11 88:2 111:4,9 112:11 138:22 148:6 262:6 264:5 280:3 297:9 338:17 396:8 430:14
startling 14:19 202:17
starts 60:8 280:2
stat 264:8 269:19
stat1 215:7
state 19:16 61:12 63:14 280:4 313:10 347:4 387:15 451:6 454:19
stated 57:14
statement 14:5 17:10 48:7 53:11 56:8 62:2 66:1,1 112:18 121:13 142:4,10 157:17 171:18 177:5 188:12 192:7 227:15,16 254:10 256:11 261:20 301:6 326:7 344:7 358:13 369:17
statements 84:20 95:17 117:14 121:15 191:21
states 28:2 73:20 79:2 173:8 410:11 411:4 446:2,11
statistical 65:14 70:13 147:8 151:17 187:11 224:10 230:5 323:17 381:8
statistically 223:19 331:21
statistician 90:14 117:9 317:3 319:12 321:19 324:18 334:22 364:9
statisticians 327:16
status 15:8 58:22 59:1 110:3 132:21 133:3 166:7 254:2 263:13,15 265:1 307:21 308:9,21 334:16 370:9 373:21
stay 162:16 169:19 259:4 325:22 347:9 381:6 395:7
stays 381:7
steady 280:4 318:8 348:2
steeper 183:12

steering 17:14 19:22 223:10 233:9
stegall 2:7 5:7 6:10 7:17 17:15 19:14 20:3 23:5,7 34:22 35:13,20 38:10,16 40:7 41:14 51:6 123:8 125:12 127:9,12 128:2 189:10,11 189:12 289:6 295:12 297:17 298:1,11,14 299:4 341:3 362:12 388:15 389:4,7,10 395:17 407:12 412:11 430:3 431:15 432:5 438:1,10 440:6,15 441:13 443:13 444:20 445:5,17
step 48:5 49:11 75:9 76:5 99:10 102:15,21 111:3 118:3,15,15 128:18 132:14 135:15 143:8 153:1 156:13 158:17 185:16 187:18 198:15 248:16 256:18 261:19,19 266:7 291:2,3,7 350:1 352:4 359:8 362:2
stepping 49:4
steps 49:12 74:19 75:15,17 76:3 100:21 106:15 258:5 290:20
steroid 249:12 371:3 375:21 382:21 383:6,15 385:3 387:1
steroids 272:12 320:5,6 321:5,7 369:11 371:3 382:17
steve 20:5 340:16
steven 2:14 5:13 16:16
stick 277:17,19 280:7 286:19
stimulate 305:21
stimulator 174:20
stoke 108:20
stole 229:3
stop 71:21 81:2 153:16 162:19 163:1 166:11 246:22 310:15 312:21 400:9
stopped 136:15 249:12 301:21 437:4,5
stopping 63:10 449:10
stories 36:22 91:2 439:21
story 12:17 262:4 269:14
straight 159:6 319:19 352:18
straightaway 109:8
strategic 41:6
strategically 197:7
strategies 50:8 148:22 198:2
strategy 16:11 78:8 170:20 182:18 191:7,15 193:12 197:22 198:11 248:6 254:7 258:6 323:13 339:6 353:2,3
stratification 149:7 156:20 164:9 183:3 187:6 187:8 193:13 196:12 197:2 228:19 233:19 235:19,22 243:16 243:19 257:13 260:4 261:13 360:9,19,20 377:7
stratified 360:8 394:21
stratify 152:14 157:5 185:3 218:19 235:17 244:18
stratifying 153:5 205:12 231:3,5,8 244:21
stream 77:9
streamline 59:19
streamlined 416:7 424:17
street 1:21 154:13
strength 70:14,15 85:13 193:13 261:16
strengths 266:1
stress 287:7 315:5
strict 163:1 301:18
striking 188:4
stringent 114:18
strive 377:12
strong 37:19 40:8 89:8 97:3 106:2 200:13,19 319:15 320:4,17 358:13 375:2
strongly 22:5 274:9 376:22 432:22
struck 273:22
structural 143:12 150:19
structure 20:11 39:17 84:8 103:11 131:4 258:16 363:19
structured 98:3 255:8 259:21
struggle 253:15 294:7 354:5 365:8
struggling 22:13 230:10
stuck 267:5 296:9 296:12
student 269:5,5
studied 157:3 178:14
studies 19:7 75:5 80:17 82:21 89:13 93:12,22 94:1,5,8 95:4 119:5 125:1 155:7 156:5 157:6 169:16 172:7 189:14,18 190:22 192:15 194:17 215:2 218:3 234:6 239:21 249:9,9 255:1 273:3,4 300:5,18 309:2 317:7 318:14 327:17 330:5,7 344:14 346:1 348:6 349:10,14 367:17 382:3 393:17 397:9,19 398:12,16 400:17 403:3 405:14 438:15 447:7,11 447:12,13 449:10
study 32:12 92:1,3 130:9 151:12,13 158:8 159:22 161:19 162:19 163:1 164:5 166:5

168:18 170:13 176:12 205:17 212:13,15 219:14 220:4,15 221:2,19 222:4 223:7 224:18 229:12,13 229:15 233:2 234:8,10 243:12 246:10 249:15 258:8 260:7,9,13 260:14 262:13 270:17 277:16 285:9,21 288:22 301:21 305:10 309:7 310:9 315:21 316:14 317:17 319:14 321:21 325:2 327:13 329:5 332:16 334:5 336:7 345:7 348:2 348:16,18 359:12 360:14 372:17 375:14 387:6 392:2 397:14 398:10,11 403:5 404:21 424:19 444:5 446:3,3 447:16,18,19
studying 156:17 165:11 178:15 344:15 396:9
stuff 87:19 186:1 207:16,18 211:4 257:8 278:4 280:22 445:18
stumbled 36:7
style 451:15
sub 138:14
subacute 202:3 272:9
subar 227:9,17 228:14 231:17
subcategories 68:12
subclinical 140:21 141:1 156:3 161:1 166:4 184:11,16 202:7,9 203:10 211:7,19 214:16 217:16,19 218:1 220:4,10,22 222:17 223:18 224:20 225:15,21 226:21 228:4,16 228:22 231:6,9 239:9,15 245:16 245:17 255:5 272:14,20 273:9 356:16,17 399:6 404:8,10
subclinically 161:6
subcohort 187:13 222:7 361:4
subgroup 178:9
subgroups 397:19
subject 116:14 138:3,6 225:6 247:12 285:8 288:22
subjects 79:3,21 79:22 136:22 225:6 292:18 404:22
submission 54:20 108:2 115:17,18 116:8,9,18,20 118:8 120:14 122:22 152:12 353:5
submissions 54:16 110:21 117:20 119:3 133:17 134:11
submit 104:11 418:15
submitted 44:15 44:16 81:1 84:5 116:4 242:17 438:16
suboptimal 154:20
subpopulation 149:15
subscores 273:22 274:14
subsequent 88:5 91:8 111:18 123:12 182:12 184:1 200:18 245:17,18 334:9
subsequently 80:13,20 90:8 129:15
subset 192:17 305:17 320:12,14 320:16 327:5 419:21
subsets 136:5 152:19 405:16 417:3
subsetting 127:2
substantial 91:8 369:21 375:3 411:9
substantially 368:4
substantiation 111:19
substitute 267:10
substitutes 346:2
subsumed 132:9
subtly 309:4
subtype 422:18
subtypes 45:16 127:3 188:19 408:21
succeed 87:18 198:9 199:10 420:21
succeeded 86:10 197:2
success 12:16 36:22 37:4 94:14 116:16 187:21 196:8 302:2,3 406:6,8
successful 23:16 47:14 56:4 65:1 116:20 188:2 343:2,9 378:16 406:12 429:16
successfully 102:14
sudden 344:9
suddenly 98:20
sue 248:1 304:19
suffice 79:10 80:9 418:19
sufficient 130:2
suggest 235:20 239:17 240:22 243:17 245:1,9 302:7 324:5
suggested 319:17 359:13
suggesting 119:13 238:17 307:19 369:11
suggestion 288:14
suggestions 112:7
suggests 88:13 160:18 164:20 217:22 245:5 369:13 379:7 383:16
suitable 327:1
suite 1:21
summarized 258:16 384:16
summarizes 328:18
summary 26:15 76:2 86:7 92:13

95:3 172:7 226:18
summer 402:7
supplemented 106:2
supplements 96:14
support 36:1 46:19 65:8 67:21 73:1 74:8 80:7,14 107:22 114:22 115:15,17 233:10 301:2 329:12 413:4,4 441:16 447:10
supported 14:6 21:13 22:5 46:14 94:10 367:17 417:5,14
supporting 41:8 50:5 73:15 300:19 309:18 333:21 374:15 406:22
supportive 17:3 40:9 50:4
supports 133:21
supposed 389:19
suppress 309:11 309:15 354:2
sure 13:20 55:21 57:18 68:18 109:1 110:5 114:4 116:1 116:15 117:15,17 118:21 119:2,20 122:21 206:13 230:13,15,19,19 277:22 293:13,17 294:17 299:15 304:12 314:17 360:14 391:9 418:19 419:4,8 441:3 442:5 443:13
surely 193:22
surface 144:10 211:13 305:14
surgeon 124:11
surgery 409:21 413:21
surgical 422:2
surmise 241:21
surprise 223:14 223:14 263:3,21 286:12 316:4
surprised 342:11
surprising 226:16 305:11 335:7
surprisingly 375:17
surrogacy 88:22 93:10 95:21 96:21
surrogate 19:8 62:22 66:8,17,22 82:11 83:8,11 85:8,10,16,18,18 85:19,21,22 90:12 90:13,16 91:4 93:13 95:14 97:2 97:5 98:17 101:15 106:5,10,12,14 107:14 108:13 114:2,10 128:7 182:19 201:8 243:18 294:11,14 295:21 328:4,20 329:3,16 330:11 330:18,19,21 331:4,6,17 332:17 332:18 333:5,10 334:1,2 336:3,9 338:15,15 339:4 354:3 355:8 357:15 361:9 406:9 421:8,11,20 422:8,14,15 432:8 432:10,12 433:21
surrogates 82:19 91:1 423:3
surveillance 162:11 220:8,17 221:12,17 225:8,9 226:22 227:20,22 228:8,21 231:2,13 232:11,13,17,18 253:14 254:15
survey 345:16
survival 14:15 29:15 99:14,15 100:1 105:21 123:15 139:4,6 140:10,12 141:12 141:19 147:16 180:17 183:11,12 203:19 270:9,14 271:2 289:13,13 298:8,9,16 331:12 331:18 332:15 333:3 337:20 343:5 346:22 347:11 354:21 368:17 379:19,20 381:8,14,21 382:14,15,18 412:6,9,13 413:2 421:12,12 422:6,7 432:18,20,21 433:1,2,3,5,9,9,9 433:18 434:4,5,5 434:9,14,15,22 435:21 436:3 437:1,2,8,8
susan 21:10
susceptibility 176:17
sustained 177:12
sustaining 391:20
swapna 452:16,17
swinging 345:20
switch 171:3 293:15 299:7
switching 172:5 291:20 292:4
swung 346:8
sydney 234:12
sykes 365:16
symmetric 91:12
synergy 30:16
synthesize 201:6
system 34:8 105:16 130:15 167:20 257:3,18 257:19 258:3,11 258:15 259:4,19 260:20 261:10,13 262:18,21,22 263:9,14 266:19 266:21 267:3 268:4 271:5,5,11 271:16 276:2,12 277:4,21 278:7 280:18 287:6,9,12 287:14 288:19 291:1 413:6,7 414:12 419:6 445:11
systemic 350:22
systems 87:3 125:7 200:14 257:18 265:20 380:7 416:1

t

t 5:2,2 73:10 74:7 78:9 79:13 80:1 130:10 139:9 140:20 143:10 153:9 156:18 159:17 175:6 183:4,15,17,18 184:13 207:10 209:16 213:20 217:15 251:21 252:15 253:6 268:8 274:2 275:16 303:19,20 309:15 346:3

t1 308:10,16
t2 308:10,16
table 39:7 42:3 109:3 112:9 115:12 173:19 222:5 269:6,7 439:13
tac 170:1,5,7 348:2 385:2
tackle 178:2
tackled 96:16,16
tacrolimus 78:13 145:22 162:3,7 168:19 169:4 171:22 178:14 249:11,11 320:3 324:10 325:9,11 369:9 371:2 385:7
tactical 103:15
tailor 369:15 377:5
tailoring 369:13 376:11
tailorx 426:3
take 14:20 18:11 18:16 20:13 30:13 33:7,20 34:7,15 42:14 50:22 51:8 57:4 62:9 73:5 75:20 87:15 91:1 100:21 104:2 110:9 129:8 131:18 141:14 145:5 149:18 156:20 161:18 185:16 191:8 202:21 208:1,5 210:6 212:3,7 213:11 214:4,8 215:20 216:20 218:10 227:11 256:17,19 262:1 265:12 267:14 290:19 295:19,21 297:16 299:13 309:12,21 324:19 329:10 330:9 344:12,13 350:19 352:13 353:8 354:7 363:1 366:12 395:2 398:15 407:5 418:5 427:19 433:1,3 438:5,8 440:3 449:20
taken 33:5,17 51:7 92:17 136:11 200:13 240:21 284:19 303:14 324:14 326:3,18 348:9 424:9 454:3 454:9
takes 20:10 27:6 38:14,14,15 39:6 39:13,17 49:11 51:10 57:4 97:10 97:19 169:19 269:12 358:13 395:10 397:3 398:22 444:12
talented 445:21
talk 8:12,22 15:17 25:1 28:9 31:13 31:14,14 35:3,8 35:10 36:12 42:10 49:5,16 55:15 63:1,3 66:3 68:5 72:3 82:10 85:6 96:4 104:3 110:18 122:10 138:8,20 144:7 151:15 154:9,16 166:17 166:21 167:2 172:6 186:2 200:18 202:2,5,12 202:14 203:8,14 203:16 204:4,4 205:6,9 219:20 233:17 256:2 294:3 299:18 300:3 302:4,6 312:15 313:19 328:2 344:3 361:11 363:7 391:16 395:14 398:15 404:16 408:12,17 420:7 422:20 439:17
talk's 53:8
talkative 108:22
talked 15:16 19:6 19:15 38:8,10 45:21 53:6 90:15 96:8 104:18,21 107:22 210:18 280:14 314:14 326:8 360:20 385:18
talking 16:15 29:2 45:2 49:5 55:11 69:6 72:10 98:10 119:3 142:8,9 143:1 148:13 156:14 161:3,16 192:20 246:16 263:17 267:9 288:17 290:18 306:5 342:8 343:20 348:21 350:3,6,15 352:7 378:10 393:15 398:21 399:15 405:16 443:5 446:6
talks 10:6 109:5 183:3 190:15 203:21 354:16 391:1
tambur 154:3 177:15
tamoxifen 423:22 424:2
tap 169:11
tapering 240:1
target 97:1,6 121:6,8 135:12 150:20 151:8 155:18 169:13 188:1 249:22 363:20 428:19
targeted 187:15 240:11 241:4 422:11 426:18 427:11 428:11
targets 423:15 426:19 429:10 436:21 444:15 446:15,19
task 17:14 86:11 98:16 257:10 271:13 353:21
taxpayers 413:5
tb 18:18
tcmr 150:21 153:6 183:11,13,22 184:14 208:19 276:9
team 256:13 448:12
teams 246:8 449:8
teasing 286:15
technical 189:21 196:15 240:9
technicians 327:18
techniques 338:12
technological 38:1
technologies 18:1 167:15 208:22
technology 15:10 248:15 351:15
tell 9:13 17:4 76:2 82:9 120:12 126:18 160:14 163:12 164:9,13 165:17 235:11

242:21 251:9 274:6 283:4 286:4 302:21 309:19 311:10 313:8,14 359:6,17 397:2 444:17
telling 37:9,18 157:19
tells 112:4 167:21 208:1 283:11 313:11
template 261:20 444:6
templated 64:2
temptation 187:1
tend 169:19 406:12
tends 449:18
tenure 54:14
term 11:2 26:17 29:14 94:17,20 96:3 101:10 104:5 104:6 105:19 106:19 126:8 128:10 129:9 143:20 146:17 154:19 162:4 203:19 227:7,18 256:10 257:3,8 259:19 266:15 269:22 270:12,17 275:14 290:10 294:4,6,6,12,13 295:6,20,22 296:5 296:10,19 298:8,9 298:16 315:3 330:1 337:6,8,9 337:20,21 338:18 341:2 342:22 343:11 344:10 346:5,6 349:20 351:18 354:18,21 356:22 357:9 368:17 376:14 379:20 381:11 386:14 392:20 406:16 421:14 424:11,20 435:19 449:19
termed 26:10 143:19 148:11
terminal 306:11
terminology 31:11
terms 15:11 38:4 63:9 75:13,14 78:9 79:17 80:2 82:10 83:17 85:4 85:8 87:20 89:9 91:21 119:2,20 126:1 128:4 140:16 144:20 146:15 147:15 149:19 150:13,17 151:1,6,10,17 152:9,13 157:20 167:11 171:4,6 172:3 180:10 197:6 223:6 230:21 253:9 280:21 300:15 301:2 337:20 343:10 412:5 423:9 430:10 435:2
territory 398:3
tertiary 446:10
test 129:10 156:21 157:10,12,13 161:12 164:20 166:2 189:1,2 216:2 219:18 222:18 223:3 226:9,9,10,11,14 228:1 232:15,15 232:16 260:1,18 261:12 268:5 293:5,12,20 307:10 316:17 326:12,16 362:11 409:9
tested 129:16 222:3 282:20 284:20 293:4,8 412:11
testes 206:16
testing 32:8 47:15 55:10 72:9 73:8 74:4 75:18 77:7 79:13 107:7 148:12 171:20,20 273:11 346:1 417:2 425:16
tests 115:4 164:2 165:7,9,18 232:16 326:11 358:16 359:18,19 362:16
teun 168:8 169:16
tgf 172:16
thank 7:3 8:2 9:16 12:18 21:9 23:1,3 23:11 34:20,22 35:7 44:20 50:15 50:17,17 51:5 52:9 54:5 55:6 71:21 73:4 81:3 82:3,3 97:21 98:1 98:13 107:1 108:16 110:22 120:11 132:1 134:2 135:6 138:11,12 154:5 166:13,20 177:17 177:19 179:12 180:4,13 202:4 219:4,6,11 233:6 233:13,15,20,22 246:3,3,11,13 255:15,20,22 256:6 271:17 283:1,3,5,16,16 289:5 300:1,7,8 313:15,22 314:1 327:11,21 328:6,9 329:11 336:15,22 340:7,8 367:5,6 367:21 377:21 378:4 389:1,3 406:21 407:10,12 407:17 429:12,20 429:22 432:5 437:22 441:12,13 446:17,21 450:6 450:11 452:11,21 453:2,5,6
thanks 23:7 35:20 55:13 72:1,21 81:5 109:19 110:15 128:1,2 137:11 154:11,12 201:13 287:22 334:17 339:13
thematic 110:20
theme 53:13,21 368:1 392:8
themes 13:2 374:5
theoretical 73:6
theoretically 180:18
theory 20:10 39:16 326:9
therapeutic 7:14 12:3 14:3,10,11 15:12 17:19 23:5 46:11 98:18 100:7 102:12 170:19,20 172:4 199:22 253:9 258:3 268:5 269:18 270:13 329:21 337:19 355:4 363:8 413:19,20 446:8
therapeutics 7:7 10:9 33:2 51:3 98:12 101:22 102:5

therapies 10:19
11:1 13:3 45:16
107:16 187:16
188:18 194:11
254:16 426:18
428:19 434:18
437:4
therapy 10:12
24:8 99:7 158:16
162:6 165:13
166:3 171:5
189:17 192:5
197:13 238:18
268:15 292:13,14
292:15 325:19,22
339:7 354:21
367:2 369:3 371:2
372:19 373:6
375:10,15,20
384:13 385:6
386:20,22 387:2
394:5 405:1
412:21 413:1
420:15 422:2,5
423:12 424:1
425:6 426:6,7,11
426:12 427:6,11
427:12 428:10
429:19 437:5
441:4 448:22
thing 21:5 22:20
23:14 24:17 26:12
30:10 41:4 50:1
56:14 58:15 63:5
64:9 66:7 82:18
83:11 90:22 97:14
113:13 116:7
117:22 123:22
146:12 184:17
204:3 216:17
220:16 225:14
231:18 256:13
281:9 282:5
288:15 290:14
291:11 298:19
306:17 307:19
311:10 312:19
331:20 340:7
341:19 342:15
350:22 360:16
363:16 386:13
390:20 391:21
394:14 397:15,16
397:17 399:15,19
402:5,10 416:16
420:17 422:8
425:5 427:18
437:15 438:13
439:12 440:7
441:2 448:14
things 15:9 19:21
22:21 25:15,16
27:9 31:16 33:20
34:15 38:13 40:20
48:10 49:13 51:8
52:3 65:4 77:19
85:1 89:20 90:19
93:2 101:19
102:11 104:20
118:1,2 123:11
125:21 131:14
145:12 156:16
161:19 165:7,15
166:10 168:2
172:11,15 173:21
185:8 189:6
191:22 198:4
202:6 205:9
239:16 264:7
266:17 288:16
289:21 291:8
293:13 300:15
308:1 310:3 323:7
339:19 343:7,8
344:22 351:3
354:16 355:14
363:6 365:8 394:3
398:22 400:17,19
401:3 430:9
438:16,17 441:21
447:21 448:10
450:14
think 9:22 10:14
10:21 12:7 18:7
20:4,19 23:13,14
23:15,19 24:6,13
24:22 25:3,4 26:5
26:11 27:19 28:7
28:15,15 29:2
30:9,11,18,19,21
31:3,12 32:6 33:5
33:7 34:13 37:3
39:19 40:2,4 41:2
41:14 48:17,17
51:6 52:12 53:15
56:1,11,20 58:16
59:2 61:10 62:1
62:20 63:5 65:4,6
65:15,22 66:7
67:9 69:7,11,17
81:7,13 82:14,15
82:18,22 83:5,14
84:6 86:15 90:20
90:22 92:20 93:1
94:6 96:1,22
97:13 98:2 107:12
108:14 109:12
110:8 113:16
116:20 120:16
123:9,16 124:5,16
126:22 128:3,6,11
130:20 131:19
134:9,12 135:14
137:3,14 142:8
143:6 145:9
147:18 149:20
150:11,13 151:9
153:12 154:21
155:16,17 156:10
158:1,20 159:1,6
161:2 165:6,22,22
167:6,17 168:8
170:19 171:7
173:16 174:17
176:9,15 177:5
180:10,22 181:2,4
181:5,18,19,22
182:9,16,16 183:2
183:3,21 184:7,10
184:15 185:1,1,4
185:10,15 186:4
186:10,12 187:4,5
188:2,13,16 189:8
190:2,12,13,19
192:2,7,14,19,21
193:3,19 194:1,9
195:3,7,8,9,15
196:1,13,22 197:7
197:19,21 199:7
200:22 201:3,11
202:17 205:13
208:21 210:12
216:8,13,14,20
217:2,7 218:9,9
223:14 226:13,15
226:20 227:16
229:14 230:9
241:12 242:10,15
245:21 250:7
253:8,21 254:5
262:21 264:6
278:9 279:1,3
280:14 282:1
283:12 285:5,18
286:14,16 287:5,7
288:5,18 289:1,8
289:19 291:15,22
292:8 293:10
294:11 295:10,13
297:3,17 298:5,7
298:14,14,17,20
299:2,5 300:13
301:5 303:1
312:18,22 313:2
313:12,15 314:3,5
314:7 315:3 321:3

323:5,5,13,20 325:7,8,12,14,15 326:17,20 327:4 330:10,12 331:10 336:14 337:7 338:19,20 341:7 341:12,20 342:1,2 342:6,13,20,21 343:1,4,10,10,11 343:14,17,18 344:21 345:9,19 345:21 346:1,16 346:18 347:20 348:6,7,14,16,16 349:4,11 350:5 352:8,21 353:8,9 353:12,18 354:5 355:2,9,15,20 358:4,17,21 359:8 359:22 361:10 362:11,15 363:6 363:20 364:21 365:5,7,10,12,12 378:6 380:10 383:21 387:13,21 389:19 390:9,17 390:20,22 391:15 391:19,21 392:16 392:17 393:7,22 394:8,10 395:13 396:11,21 397:7 397:13,20 398:19 399:14 400:13 402:6,15 404:16 404:18 405:12,12 405:14,21 406:1,2 406:4,13,17,19 416:15 419:16 422:21 429:15,17 431:17,21 432:1 432:17 433:15 438:11,13,17 439:2,5,12,15 440:2,13,17,20,22 441:14 442:2,6,8 442:10,11,12,20 442:21 443:5,10 444:20 445:19 447:1,15,22 448:10,11 449:1 450:2,3,4 452:20 453:2

thinking 11:7 13:6 15:1 18:14 38:4 41:20,21 58:9 82:19 87:7 94:22 96:12 109:16 110:3,4,9 121:10 124:19 168:6 175:6 180:14 181:5 182:17 190:13 199:8 202:6 254:6 295:5 315:13 342:15 346:20 355:16 396:8 405:13 407:20 423:13 446:9

third 20:6,6 46:21 109:18 133:10,10 166:15 241:5 328:1 329:7 386:21

thirds 174:5 304:7

thought 11:22 18:19 39:14,20 42:9 126:11 136:11 143:21 171:11 174:9 175:18 181:20 183:19 194:17 224:17 229:6,6 230:12,13 276:18 288:7 289:7 300:10,13,22 304:2 317:3 321:12 347:22 378:10 395:15 396:1 399:20 400:8 421:11 422:9 424:15

thoughtfully 83:21

thoughts 112:12

thousands 207:21 293:4

threatening 330:3 443:10

three 9:3 16:11 33:6,8 37:1 42:14 42:19,22 46:5 49:7 83:19 84:9 89:17,19 98:15 111:3 114:8 120:20 126:4 132:14 133:1 146:15 148:2 152:22 162:6 169:20 179:10 183:3,6 193:5 213:8 221:5 234:15 235:5 239:11,13 240:19 242:18 244:3 260:20 263:10,11 264:17 268:6,10 268:10,17 271:7 272:16 275:11 279:15 280:3,9 286:10 291:18 306:22 307:4,7,14 310:20 311:5 318:18 326:5 328:18 334:16 343:19 356:14 365:18 367:17 382:5 394:14 396:17 409:22 414:2 423:4 426:1 428:16 430:4 442:4

threshold 83:1,2 83:10 151:22 214:17 221:21 222:2,18 326:19

thresholds 83:2 295:4

throw 13:1 286:18 351:18

throwing 283:19

thursday 1:8

thymoglobulin 370:21 372:22 373:7,16 382:9 385:12 386:5,10 388:6

tied 284:7

ties 49:18

tight 146:14

tim 14:8 21:22

time 7:10 8:16 12:20 16:20 18:17 20:10,14,15 21:14 21:19 27:20 28:10 33:1,21 34:7,15 37:7 39:17 48:4 51:8,8,10 62:9 69:1 81:3 93:4 100:3,10,11 109:6 137:7 148:11 163:7,17 165:14 165:20 172:2 182:15 186:13 188:7 200:16 201:10,15 204:1 209:7 213:5 214:1 214:3,12 215:9 216:1 217:16,19 220:19 236:10 237:20 240:22 241:1,2 242:2 243:6 253:17 257:20 258:12 260:22 261:1 263:7,14,16 265:2

265:4,9,14 268:19 269:13,18,21,22 270:5,7,8 271:14 276:15,16,19 278:6 279:6,15,19 289:16 294:2 295:8 296:14,16 297:14 299:14 300:14 306:19 307:5,6,13,17,22 308:3 310:19 311:4,5,15 314:11 323:7 330:9 335:1 335:19 340:3 345:6,16 349:1 353:17 360:2,10 363:7,17 365:15 365:20 374:2,3 375:19 376:17 382:19 384:12,14 384:15 385:19 386:18 389:15 392:14 395:20 396:15 397:3 400:8 402:11,18 402:20 409:7 410:3,7 413:22 414:6 415:7,17 416:8 417:4 418:9 419:10 422:20 423:19 427:13 428:15 431:9 434:20 441:5,22 445:8 448:17,19 451:13,19 452:22

timeline 264:19 277:16 279:11

timelines 49:21 75:21 86:15 98:22

times 18:6 26:9 37:6 56:9 120:20 125:9 188:13 273:21 288:3 290:10 326:5 391:4 404:5 421:10 445:6

tip 207:17

tissue 445:17

tissues 401:18

title 138:8 166:17 313:18

titled 137:22

tma 276:9

today 8:2 16:12 24:1,18 25:10 34:14 42:11 43:17 49:6,9 51:6,11 52:17 53:14 54:3 55:11,15 140:5,22 143:2 149:4 151:21 152:9 155:18 156:15 168:16 201:22 202:5,12 203:14 208:22 210:21 212:10 214:14 219:3,13,20,21 220:4 233:21 234:7 235:5 261:4 262:20 273:21 294:5 328:15 340:1 355:3 362:3 367:7 377:8 378:8 405:20 407:18 413:13 422:20 431:19 439:13 443:9

today's 257:1 453:3

tofacitinib 272:9

told 208:7 307:2 359:15 389:7 397:17

tolerance 11:11 136:17 300:4,5,18 300:21 302:4,7 303:18 308:2,3,21 312:5,19 313:19 313:20 316:20 319:13 321:20 322:4,6 323:1 324:4 327:12,13 363:22 365:6,11 365:13

tolerant 300:6,20 307:6,14,15 308:7 308:11 309:12,14 310:22 311:11 312:5,13 313:10 317:5 319:21 320:4,7,8,22 321:16 322:18 323:11 325:20 327:6 366:1

tolerate 155:1,15

tom 341:14

tomorrow 43:17 44:5 86:22 359:2 453:4

tomorrow's 358:11

tong 15:4

tons 286:8

tool 27:3,4,5,6,14 29:11,12 30:6 32:8 43:15,17 44:1,9,11,18 45:13,13 48:7 54:18 103:1,3 121:11 135:1 153:12,13 187:8 187:20 193:14 247:8 253:22 289:11,17,17 292:1,11,12 307:9 310:7,13 313:13 355:3 360:13

toolkit 198:6

tools 18:4 26:17 27:1 28:22 29:2,8 29:19 31:22 32:20 33:10 38:7,9,11 49:3 53:1 60:7 61:3 94:3 102:22 113:15 121:14 122:3 133:19 134:5,10,18,19,21 149:7 176:15,16 180:11 185:17 197:22 198:1 253:11 256:10 257:22 302:1 339:21 359:5,14 377:7 432:9

top 171:14 172:11 238:3,4 291:1 395:18

topic 167:6 172:5 246:20 256:2 257:1

topics 87:10 96:17 450:18,18

total 36:4 64:11 195:3 236:3 316:11 318:13

totally 26:18 40:17 286:2 306:2 312:8 407:6 447:15

touch 13:19 74:20

tough 45:19 156:1 348:14

town 379:2

toxic 161:21 413:1

toxicities 369:21

toxicity 79:18 168:18 170:12,13 171:3 276:9 368:19 376:13 437:16

toxins 78:12

track 173:10

tract 160:12

trade 119:12,15 119:17,18 384:2

traditional 145:7 145:11 271:10 434:3
traditionally 181:22
trail 270:16
trained 247:22
training 11:16 238:22 240:14,17 241:5 244:5 253:1 316:18,18 317:9 440:8
traits 370:10
trajectory 199:20
transcribed 451:1
transcriber 455:1
transcript 455:3
transcription 206:20 248:2 251:6 322:8
transcriptogeno... 256:14
transcriptome 165:19
transcriptomic 247:18
transcripts 248:3 248:7 304:3
transfer 315:6
transform 13:4 340:5 408:13
transformation 317:22
transformed 261:16
transforming 12:15 18:7 19:7
transition 21:20 51:22 192:16 337:5
transitional 305:19 306:7 308:10 309:14 320:15,21 321:1,9
translate 52:15 152:21 271:1,2
translated 270:13
translates 147:6
translation 4:3 137:1
translational 16:5 35:3 418:13
transparency 119:9 134:4
transparent 451:3
transplant 7:4,7 7:14 8:13 10:2,8 11:3,12 13:16 14:3,10 15:8 17:16,22 19:19 23:5 25:2,7,13,14 27:1,7,8,22 28:4 29:14,15 30:1,6 30:15 33:2 35:14 51:3 53:22 72:16 96:1 100:14 101:13,21 102:5 108:22 123:10 124:9,19 136:8,11 136:17 148:11,14 149:15 153:2,7 154:19 156:19 158:5,14,14 159:4 159:11 160:5 161:1,22 164:15 168:3,20 169:1 173:2,15 174:2,13 175:21 176:14 177:8 189:14,16 190:4,7,11 191:2 200:10,11,17 201:17 202:19,21 203:16,17,17,18 204:5,20 205:1,12 207:10,10 208:9 209:16 210:2,17 210:19,19 214:15 217:7 218:8,13,14 218:15,20 219:17 228:12 229:2 233:6,11,12 234:15 235:13 236:2 238:12,14 239:14 246:8 247:5 249:14,16 255:16 256:4 257:11,18 258:18 259:3,5,7,14 260:10,18 263:7 263:10,11 264:2 264:12,17 265:6 270:6,9 276:16 277:17,19 278:1 278:10 279:21 280:4 285:17 288:5,20 297:4,19 299:8,19,22 300:6 300:22 301:9 303:6,8,13 307:22 308:2,4 310:4,16 311:16 312:6,20 313:4 315:17 319:3 326:15 328:9 329:11 332:8 334:15 341:9,11,16 343:2 352:1 359:13,15 360:2,10 366:20 368:8,10,22 370:2 370:3,8,19 371:1 371:7 372:18 373:21 374:3,21 375:1,11,15,16,19 379:3 380:17,18 381:1,4 384:6,9 385:8,10 386:4,20 387:5 388:4,4,18 392:19 394:13 399:19 402:20 406:3 439:12 441:10 444:10 448:9,19 449:17 449:18
transplant's 24:4 192:8 403:7 440:15,16
transplantation 1:4 9:14 12:12 14:14 15:2,5 17:1 18:4 19:5,7 24:15 24:17 25:11 26:14 30:4 53:19,20 84:15 98:19 99:20 101:1,3,6 102:15 102:20 103:2 105:3,17 107:12 137:2 138:1 141:12 152:11 202:3 234:21 235:1,18,19 245:14 265:14 287:7 300:4 313:20 315:8 319:7 330:2,7 340:6 366:17 367:3 368:6 369:17 378:16 379:13 385:20 386:11,18 393:21 397:7 398:1 400:7 400:9 404:20 405:15,18 406:2,9 407:20 446:6,13 448:18 449:5,13
transplantations 13:9
transplanted 203:11 206:16 351:4 401:16
transplants 25:12 25:17 136:9 141:14,21 152:16 192:10 195:14 215:4 228:10 291:18 390:4 391:18 392:4

394:7 397:13 400:12,12 401:9 403:21,22 404:2,4 440:18 444:2
transportability 257:19 264:20
transported 130:22
travel 441:9
treat 92:11 144:17 166:6 189:2 211:7 211:9,9 214:19 216:19 218:16 225:13 272:10,11 281:20 427:10,14
treated 144:18 162:6 171:21 178:16 224:21 225:15 227:9 231:8 272:16 282:9 292:19 411:3 425:21 426:10,11
treating 272:8 363:12 424:5
treatment 1:4,6 85:15 95:15 115:10 128:5 130:10,10 171:15 178:9 212:4 228:4 231:11 262:9 268:7,8,11,19,22 270:7,10 282:7 313:21 319:5 330:4 335:13,15 343:16 344:17 373:20 377:20 409:14 410:1 411:5 415:11 422:1 425:5 429:5 429:6,11 448:16
treatments 11:11 45:14 128:19 129:4,11 217:10 280:22 319:18 408:10
trees 34:1
tremendous 16:20 21:13 442:14
tremors 14:22
trend 169:19
trex 240:12 241:3 241:6 242:12 272:8 273:5
trial 38:5,6 43:13 45:7 62:7 63:11 64:19 69:18 93:21 95:6 101:17,18,18 105:1 107:17 122:1 128:7 131:6 131:12 153:13 156:11 166:2 177:1 180:20 181:6 182:3,7,8 182:14,20,21 184:18 186:6 187:1,21 188:6 189:3,5 190:8 196:18 197:1,3 198:21 199:1,3,9 199:15 232:8 260:20 269:6,9,15 270:1,2,21 272:8 272:14 277:5 278:14,15 292:19 325:18 326:3 328:16,20 329:6 329:14,15 331:3 332:17 334:3,12 337:8,9,12 345:2 347:17 361:2,2,5 361:20 362:5 377:9 392:5,8,12 392:13 393:20 396:6,6 402:18 403:17 404:3,7,10 404:19 405:10,11 405:14 408:17 414:12 415:2,15 418:4,11,13,15 419:1,9 420:13,17 420:22 421:5 423:11,13 424:20 425:15 426:2,3,21 427:7,8,16,21 428:10,14 429:5,9 430:5 444:5,10,13 448:20 449:12
trials 11:18 32:4,6 43:10 44:10 45:1 45:3,6 64:15 66:10 79:2 81:17 82:7,19,20 87:22 91:19 92:10,11 93:3,5,5 94:6 95:4 95:6 98:12 99:8 104:1,2 106:6,12 126:3,9 128:4,6,9 129:9,16,22 130:1 130:7,13 148:19 149:2 153:11,15 155:14,20 156:8 161:4,16 165:9 167:7 176:13 178:22 182:2,12 184:14 185:4,5 186:13 188:12 190:20 191:7,14 194:22 198:6 199:9 205:11 210:15 216:15 217:9,13,14 218:17 235:20 243:17 247:5 249:12 254:16,18 255:16 258:2 261:7 263:12 265:11 267:2,2 268:6,17 269:20 271:7 290:8 317:6 327:9 337:13 339:21,22 350:4 363:10,10 377:9 377:19 380:4 388:20,20 391:12 393:6,13,21 394:16 397:8 401:4,15 402:12 403:8 404:20 405:20 406:1,10 407:15,21 409:2 409:17 410:4,8,12 410:20 412:8 413:6,11,15,16,19 415:1,3,6,18 416:11,13 417:8 417:16,17,20,21 419:14,16,18 420:2,7,11,21 421:3 423:1,5,18 424:10 430:7 431:8,19 432:1,2 433:7 436:19,22 440:21 441:7 442:13 444:22 447:4,13 448:7,9 449:22
tricky 87:14
tried 14:2 28:18 102:14 158:3 161:19 218:11 227:11 230:9,11 230:14 277:3 301:19 302:19 306:17 307:5 309:2,17,21 310:9 313:2 329:20 349:17 397:16 408:13 416:10 442:12
triggered 204:15
triple 302:18 371:2 375:9,20 376:7 386:22
triplet 148:18

trivial 311:20
trouble 293:3
trough 169:4 170:1,20 350:20
troy 29:21
true 20:12 67:3 182:12 216:12 232:14 251:18 271:5 284:14 302:4 363:13 432:14 444:1 454:6
truly 28:2 113:14 120:10 190:4,5 405:12 408:14 416:4
trumps 392:16
trust 406:19
truth 70:11 341:22 342:1 345:21
truthfully 342:16
try 22:17 53:14 86:4 103:19 105:9 105:17,21 110:1 116:10 122:7 123:5 147:11 156:11 161:21 162:15 165:11,20 185:2 191:21 197:12,20 205:16 205:22 207:4 208:2 211:7 215:1 215:16 227:13 248:14 257:1 276:14 295:11,11 300:17 311:11 342:2 345:3 351:8 377:12 396:15 399:20 400:1 406:8 408:11 410:15 411:2 412:22 423:14 443:11
trying 11:6 59:16 59:17 61:20 93:14 95:18 98:20 99:1 100:20 102:2 113:14 142:15 150:5 180:2 181:1 191:1,22 193:4 204:17,19 217:18 230:19 235:4 255:12 290:5 295:14,18 310:1 314:6 339:20 344:3 347:6,12 361:8 365:10 368:1 398:8 404:6 406:7,22 412:18 420:20 426:13 427:21 438:14,21 438:22 439:18 440:9
ttc 2:20 17:14 23:17 24:3 25:15 26:21 31:12 33:14 38:11 40:2 49:16 98:9 104:16 124:18 128:4 289:8 291:2 328:10 344:6 352:2 391:13
tubular 78:12 263:22
tumor 45:16 411:17 416:22 417:19 419:20 426:17
tumors 326:10 423:15 427:3,4 428:1 435:13 437:5
turn 23:21 32:21 126:19 131:4,5 180:16 289:22 398:22
turnaround 209:7 253:17
turned 157:13 397:10
turning 54:17
turns 88:20 90:12 90:18 95:11 127:18 189:17 225:22 392:4 398:17
turtiles 237:6 238:6
twenty 406:3
twice 372:9
twin 22:11 141:14
two 8:20 17:18 19:22 21:12,12 25:22 26:22 29:4 29:7 31:21 32:20 33:9 38:11 45:12 46:7 47:4 48:13 52:3 61:4 62:4 64:5,13 67:8 68:10 70:18,19 75:5 77:2 79:2 80:16 84:3,4 88:1 88:19 89:17,18,21 94:18 99:1 103:13 120:19 121:16 126:4,11,19 130:4 132:6,9 134:14,21 135:3 142:21 145:5 147:17 164:1 171:11,16 174:5 179:11 182:20 183:10 185:5 191:21 196:9 199:7,20 200:20 203:21 213:11 222:8 225:1 232:15 234:16 236:5 237:22 238:10 239:7 240:7,10 242:17 243:9 244:12 249:15 250:18 252:9 257:15 259:15 266:21 269:6,7 273:3 278:22 279:8 280:3,9 283:20 284:4,6 304:7 307:16 310:21 311:9 314:9 321:5 322:10 324:6 326:4 327:16 334:18 337:10,12 337:17,21 338:16 338:17 342:9 343:19 350:14 356:3 358:11 372:6,7,19 381:6 391:1 396:17 402:1,2,3 411:14 411:16 425:21 428:16 430:3,4 431:7 441:21 443:1 451:13
type 11:3 94:13 158:22 193:20 230:14 306:7,9 307:19 343:4 359:20 378:2 392:15,16 416:16 416:21 428:7 429:8
types 27:18 43:6 46:4 48:13,16,22 49:15 113:22 142:21 151:10 181:3 185:5 290:1 304:16 308:12 310:2,7 384:15 390:16 392:1 394:22 401:9,12 413:10,19 416:19 417:21 426:15

430:21
typewriting 454:5
typical 444:10
typically 17:20
typing 150:3,3,4 245:9

u

u.s. 34:9 73:9 130:17 173:7 205:1 212:16 367:15 370:7 409:5
ubiquitous 395:5
ucb 4:4 313:18
ucsf 217:12
uk 327:15 447:1,9
ulf 2:19 5:15 29:10 98:8 124:17 137:20
ulf's 197:20
ultimate 99:7 352:14
ultimately 52:22 80:6 103:9,10 104:10 106:4 107:13,18 108:1 141:3 142:17 237:15 277:5 291:9 295:19 339:8 352:6 360:22 363:12
umbrella 417:17 423:11 427:7
umpteen 189:3
unable 11:19 173:14
unacceptable 16:1
unadjusted 371:5 381:9,20,22
unaware 306:2
unc 12:1
uncertainty 37:14
uncharted 398:2
uncomfortable 353:9
uncover 214:16 353:19
undergo 312:6
undergoing 21:19 215:4 247:9 318:8 368:5
underlying 135:19 135:20 242:8 245:15 381:19
understand 18:9 54:10 55:16 56:8 57:19 61:15 62:10 64:18 69:9 109:16 110:1 113:21 116:10 132:8 163:11 168:2 203:10 239:20 257:2 279:8 284:11 286:22 325:19 342:21 344:18 360:4,12 365:2 412:16,18 420:21
understanding 12:5 19:16 23:20 52:14 53:4 81:22 93:1 108:6 127:2 127:3 130:21 150:13,17,20 199:14 203:14 342:7 387:14 416:18 449:4
understood 95:20 154:20 185:9 288:6 436:20
undertake 131:16
undertaken 100:17
undertaking 82:5
undertakings 23:6 82:17
underway 140:4 152:7,8
underwent 220:16 425:16
undesired 176:22
undiagnosed 242:3
undo 324:19
unfamiliar 26:19
unfortunate 392:13
unfortunately 191:4 288:21 330:17
unfunded 393:1
unidentified 121:2 122:4 131:1 132:2 180:8 181:8,10 187:17 191:20 197:19 198:16,19 201:1 279:2,13 280:13 281:7,17 281:20 282:1,4,11 282:14 287:19 289:3,5 296:2 298:10,13 299:3 299:15 336:22 337:3 338:4,6,8 338:10,11,14 339:13 345:11 346:12 356:1 357:22 358:5,8 445:20
uniform 379:8
unifying 412:2
unintentionally 136:15
unique 149:21 252:15,17 303:12 305:17 351:11 413:6 419:14
uniquely 252:14
united 28:1 73:20 79:2 173:8 410:11 411:4 446:2,11
universally 149:21
universe 76:16
university 2:5,18 3:2,6,12,15 4:9 138:8 166:16 168:22 201:20 202:1 221:15 233:12 255:19 300:3 366:22
unknown 222:3
unmasking 231:17
unmet 9:14 10:20 13:9 15:8 24:5,11 35:13 40:18,22 42:4 44:14 50:13 53:11 98:3 101:9 104:18 170:18,22 176:8 181:14,18 183:2 194:14 253:9
unnecessary 228:1,2 231:7
unnoticed 241:22
unos 141:17 371:7
unreasonable 348:6
unrelated 209:21
unselected 259:2 271:6 284:16 285:6
unsuccessful 326:6
untouched 129:8
unusual 21:16 302:21
updatable 263:15
update 264:22 269:10 407:10
updated 100:9 261:4 270:14
updates 269:12

updating 20:22
upper 77:21
upregulated 250:6 252:4,17,19,22
upregulation 255:4
ups 451:8
urinary 79:14,15 160:12 165:19 218:3 248:2 304:21
urine 78:14 159:20 163:16 212:7,9 215:9,12 215:16,18 216:4 217:1 247:22 248:11,12 249:3,7 251:5 254:11,14 255:9 273:11 358:20
usable 257:6
usage 65:7
use 20:18 43:18,21 44:1,3,6,11,13 46:19 47:12,20 48:8,17,19 52:1 53:11 55:17 56:1 57:14 58:7 60:14 61:13,14,22 62:2 62:4,13,15 63:8 63:15,22 64:4,6,7 64:17 66:3,12,16 66:20 67:5 68:14 68:15 69:19 70:1 70:19,20 71:11,18 79:16 82:13 85:10 88:18 90:4 94:10 94:22 95:1 96:4 103:10,20 111:14 111:15,20 112:17 112:19,20 114:4 114:11,20 115:1,5 115:7,9,15,16 117:2 118:12 119:1 121:12,13 121:15,20 122:22 129:6 132:4,8,16 132:18 133:1,5,6 133:7,14 135:19 138:21 142:19 148:9 149:4 156:14 157:4 161:5 162:1 165:8 170:6 171:6,18 175:19 176:11,17 177:5 178:22 187:7,19 188:7 191:18 192:7,9 195:10 196:17,17 198:12 199:13 217:8,8 218:18 227:15 228:8,11 228:18 229:10 231:14 235:18 239:14 243:10 247:12 248:14 249:1 253:21 254:4 256:9 257:5 257:22 261:20 262:17 267:16 270:4,4 274:8,12 275:2,2 276:3,8 277:11,16 292:2,4 292:10,17 293:16 300:21 301:3,4,22 312:4 314:21 315:12,12 320:2 321:10 323:15,22 324:2,12 325:13 325:15 326:8,15 327:7 329:5,17 330:11 332:16,18 333:6 334:10,12 340:13 343:7 354:19 355:7,11 355:21 360:1,3,13 361:1,5,19 365:3 366:9 367:11 369:8 370:13 371:6,6,8,13,17 371:18,20 372:1 373:4,8,15 374:2 374:7,21 376:7 380:20 381:13,15 383:15 386:12 390:8,11 394:20 395:9 404:6 406:9 416:10 418:7 420:10 422:13 427:20 435:16 443:3 446:13
useful 43:22 83:11 83:11 85:7,17 88:13 95:2,10 100:16 127:4 128:13 160:18 192:15 197:5,6 256:15 257:12 265:10 307:8,12 310:13,17 329:12 333:10 354:19 377:14
usefulness 151:22 196:12
user 416:12
users 64:17
uses 63:13,18 98:12 129:15 150:8 230:7 275:8 322:9 395:11 419:6
usphs 2:11
usually 195:1 199:5,6 293:18 389:14
utility 161:15 343:22 359:14
utilization 183:1 369:22
utilize 69:13 248:9 384:8
utilizing 252:13
utrecht 174:12

v

valid 353:1
validate 130:15 235:3 241:4 260:19 276:12 277:10 279:18 334:6
validated 27:17 85:19,20 215:10 240:19 242:10,12 244:12 254:1 257:2 258:3 293:2 293:9,20 301:11 329:4 333:5 391:7
validating 32:7 129:2,21 271:6
validation 59:4 67:9,13 68:11,11 68:16 118:13,20 123:12 129:7 136:2 149:20 152:6,8 156:9 157:22 159:22 161:2 176:7 177:1 177:7 180:19 209:11 210:4 221:14 222:4,7,21 222:22 230:4 236:9,9,15 237:1 238:22 240:15 241:10 243:8,21 247:9 251:3 254:21 260:2,8,19 262:17 265:16,18 265:19 266:5 285:4 317:10,16 317:20 327:20 355:18 424:19
validity 238:21 240:9
valuable 347:21

value 199:21 200:4 362:15 370:9
values 160:15,17 220:13 319:17 347:5
van 168:8
vanguard 81:9
variabilities 239:8
variability 96:3 197:14 247:16
variable 126:6 151:3 197:3 237:8 239:8
variables 237:8 263:6 275:22
variance 208:6,12 372:1
variant 206:13,14 206:18 207:1,7,11 209:13,14
variants 10:18 169:20 207:14,21 208:2,3,13 209:17 210:8,9,14
variate 381:9 382:19 384:21
variation 169:22 173:22 318:19 367:1,14 371:5 372:12 374:6,7,13 374:19,21 375:1,5 376:2 377:1,14 378:12 380:20 381:12 385:3 386:3,19
variations 386:7
varied 374:7
varies 343:2 370:1
variety 135:9 136:9 170:16 172:11 379:11 380:1 435:11
various 59:18 68:13 78:11 84:16 95:9 116:17 381:13 384:14 420:18
vary 266:3 368:18 373:9,13 376:10 376:18 378:17 379:4 387:3
varying 122:2
vascillis 153:20
vascular 172:12
vasculopathy 176:5
vast 405:6
velidedeoglu 3:4 5:16 137:14,19
veloxis 2:20 98:8
verification 99:7
versatility 123:3
version 150:10,10 181:1
versus 98:11 140:8 145:22 147:20 148:6 149:2 157:12 160:8 183:9 185:7 194:16 209:22 237:3,15 238:12 239:18 244:2 246:17 248:5 249:4 250:6 251:18 253:2 273:5,5 294:6 303:8 311:6 323:14 366:1 368:20 372:15,21 373:16 374:1 376:13
vertical 250:14
veterinarian 54:7
viability 296:17
view 277:20 337:8 337:16 364:22
viewed 323:9 430:22
viewpoints 110:20
village 446:7
vincenti 14:8 217:14
violating 119:20
viral 11:6 248:10 384:20 385:5
virus 160:13 276:9 358:4
viseon 380:22 381:2 385:21
vision 12:4,14 438:6
visit 311:3 402:7
vitaeris 4:6 328:2 328:8 392:10
vitro 58:16,19 309:15
voice 41:3,7
voices 50:12 101:3
volcano 250:5
volume 64:11
volunteers 77:14 78:19 79:21 136:13,22

w

wait 42:9 256:18 293:18 353:15
waiting 125:20 433:5,21 435:3
wake 366:10
walked 338:21
wang 4:1 6:3 299:10,16,21 313:17 328:1
want 12:16,18 21:9 22:18,19 23:10 35:7,15 37:2 43:2 44:13 45:19 48:3 52:6 53:21 54:14 60:9 60:13 63:7,8 66:1 66:2 67:16 69:18 69:19 74:10 82:3 85:10 87:15 93:11 101:14 110:2,5,9 111:1,22 115:13 116:1,15 117:11 118:16 120:3,7 121:18 131:4,15 132:5,12,16 137:15 138:11 141:9 147:11,22 149:18 161:18 163:14 165:10,11 166:1 177:6 186:21 191:5 194:3 200:20 202:6 204:7,11,16 205:2,2 209:3 210:16 219:11,22 225:6 232:22 233:6 234:2,3 235:8 246:3 251:9 255:15 260:12 262:15 263:3 272:2 274:6 277:6 279:19 284:22 290:6 291:21 292:22 293:19 294:4,22 295:1 303:7 313:10 318:5 339:2 340:5 345:11 351:10,11 352:5 358:15 361:12,14,16 362:9,22 363:16 372:17 392:8 395:20 396:3,13 402:11 403:2 404:15 408:3 412:22 441:4 448:22
wanted 17:19 18:6 28:22 82:10,13 97:9 106:9 122:7

161:21 163:11 171:17 184:22 202:13,16 231:20 232:1,2,7 258:8 258:18 276:5 278:13,20 287:6 293:14,15 314:20 318:10 321:10 337:4 342:18 346:14 365:2 395:13 415:18 437:22 438:5 445:7,22 446:17 446:22 447:19
wanting 218:10
wants 25:15,16 178:2 192:22 195:16 291:3 348:10
warehouse 106:18
warranted 149:12 149:14
washington 1:22
watching 12:22
way 18:14 28:22 31:21 32:18 45:9 57:18 60:2 62:1 75:16 76:1,5,17 76:18 81:9 84:1 90:9 97:3 102:7 103:8 110:13 111:13 112:15 113:17 115:5,10 123:9,10 128:11 128:13 133:10,11 142:11 145:11 147:1,12 155:6 157:1 161:11 165:21 170:10 190:13 192:1 193:18 196:21 197:16,17 199:8 200:5 216:14 218:4 223:5,8 226:21 227:19 228:3 230:18 240:2 256:16 259:21 264:7 282:8 289:20 308:13 309:6 313:9 325:17 338:5,10,12,14 342:3 347:22 351:6 358:9 361:1 393:7 395:15 400:2,13 404:20 405:13,22 408:21 409:1 416:12 422:22 436:3,12 441:3 443:19 449:8
ways 29:12 56:21 59:9 69:1 88:9 155:5 192:11,11 194:13 245:22 378:6 393:3 441:10
we've 10:7 28:18 29:5 36:6,7,7,13 36:14 45:4,21 47:4 49:5 68:6 73:22 80:9 81:10 82:18 83:17 86:17 86:19 87:3 91:2 92:16 125:2 131:10 135:15 136:10,11,21 144:17 150:9 151:5,11 152:1,5 153:9,20,21 156:8 156:16 159:9,10 159:21 169:6,18 210:18 211:20,21 215:1,13,14,19 235:16 239:19 241:1 242:1 245:4 247:21 253:19 263:17 279:4 293:4 294:3 315:13 344:14 346:17 347:10 349:17,18 351:14 353:22 357:3 362:3 364:16 367:9 378:9 386:14 387:13 401:3 404:9 413:22 420:1,8 421:10 423:5 426:14,21 427:7 427:13,18 429:13 429:19 431:3,9,11 433:15 435:2,4 436:19,19,21,22 439:14 448:10 449:1
weaker 90:18
weakness 261:16
wean 301:12,19 311:11
weaning 302:5 312:7,11
web 291:17
website 36:1 40:10 43:5 57:13 134:16
websites 42:16
wedding 22:9
weeb 153:17
week 22:8 163:19 225:9,16 369:12 452:9
weeks 13:20 75:2 225:1,1 226:7 279:21 442:1
weight 111:10 273:22 274:1,5
weighted 274:5,13
welcome 7:8 299:17 451:6,11
welcoming 137:12
went 14:16 44:18 164:7 224:7 225:18 238:15 251:12 302:2 303:17 304:13 305:12 317:7 321:19,20 328:15 401:5,10 422:11
west 22:8
westferry 74:13
westmead 234:12
whack 193:9
wheel 402:18
whilst 314:11 329:12
whirlwind 429:12
white 1:13 17:21 31:2,3,6 41:16,18 41:21 42:5,7 209:14
wide 93:9 135:9 186:21 187:22 370:2
widely 46:18 287:10 370:1 373:13
wider 188:2
wife 34:2 78:4
willing 296:18 439:5
willman 455:2,13
wilms 411:17
win 113:16 199:3 199:3
winding 285:13
wing 170:6
winning 324:5 325:21
winnipeg 3:6
wins 113:15,16
winter 395:7
wisconsin 234:12
wise 135:15 153:1
withdraw 161:21 239:20 315:1

withdrawal 154:10 156:5 163:4,5,9,21 240:3 254:16 318:9 323:1
withdrawn 163:8
withdrew 164:10
withholding 119:21
women 423:20
wonder 274:22 288:12
wonderful 220:5
wondering 288:4 432:11 450:4
woodcock 36:2 40:21 41:4 50:4 50:11 188:16
woodward 4:17 4:18 6:12 450:9 450:11 452:6,7,7 452:8,11,16,20
word 132:4,8 313:9
words 18:3 55:22 57:17 65:11,20 68:15 171:10,10 261:9 264:11 266:16 269:16 276:16 372:11 434:7 436:3
work 15:3 30:17 30:20 35:16 37:20 49:15 50:13 52:15 53:17 56:10 65:17 77:9 83:17,18 86:7 87:13 92:21 93:2,21 94:1,1 96:7,12 107:4 113:6 118:2 122:19 123:1,5 126:21 127:13 129:1,3,22 138:13 153:17,19,19 164:6 166:12 168:20 174:8 186:11 194:13 200:2 211:20 215:14 219:2,12 231:21 245:10 279:20 282:5 288:19 296:13 300:13 309:1 328:16 329:19 341:21 364:15 367:13 388:8 389:1 398:9,18,19 399:1,21 401:21 401:22 406:5,7,15 413:12 415:19 419:7 422:15,17 428:12 430:5 431:12,13 434:9 439:1 445:10,21 448:10
worked 23:11,13 27:12 30:12 47:5 51:7 54:9,13,15 72:12,17 73:12 90:17,17 91:4 93:4,20 107:2 289:17 398:20 410:9 422:16,17 445:9 448:9 449:3
worker 107:21
workgroup 2:20 26:1 29:9 98:9,10 102:18,19 103:19 104:16 171:2
workgroups 23:6 26:1 29:4,7 103:13,17
working 10:1 24:13 29:21 41:9 42:17 43:11 52:20 53:13 54:11 55:4 72:11 74:14 77:9 77:12 81:9 103:15 105:7 110:16 112:1 116:22 120:4 122:18 142:13,14 154:2 245:6 251:10 266:21 269:5 291:9 324:18 329:13 350:2 352:1 379:3 402:8 430:10
works 16:13 32:18 36:8 37:19 50:2 57:18,18 59:7 99:7 123:10 191:10 192:17,19 361:10 363:21,22
workshop 7:12 8:2 19:1 67:18 83:4,22 92:9 95:7 97:12,17 137:17 137:22 178:6 299:17 376:16 450:16,19 451:8 452:21
workshops 9:18
workup 333:21
world 28:3 31:4 150:1 158:2 183:22 256:9 308:2 356:15 370:13 379:22 380:9,12 387:20 392:1 405:20 445:16 446:10
worldwide 28:11 351:2 394:2
worried 406:17
worse 22:17 125:21 145:9 225:17 345:13,14 353:16 354:12
worsen 15:2
worth 435:9 442:20 443:11
worthless 310:12
wow 452:16
wrap 137:4 312:9 362:8
write 19:13 86:4 356:8
writes 200:10
writing 14:12
wrong 48:9 61:17 123:18 304:10 312:8,14 357:15 357:16
wrote 10:3 20:9 31:2 34:9 92:7,9 116:19 256:20 302:11 397:10

x

x 93:13

y

y 209:19
yan 4:1 6:3 299:10 299:21
yang 25:22
yard 33:22
yardstick 347:7
yeah 31:2 83:18 98:13 109:19 121:2 128:14 129:20 180:8,22 193:1 195:17 198:19 272:4,13 273:20 274:17,18 275:3,3,5,5,5 276:22 277:8 281:22 283:7,7,10 283:22 284:2,2 286:21 287:4,19 288:15 290:15 292:21 295:16 297:7,11 299:5 338:8,13 339:13 341:1 345:1 346:14 348:18

360:17 362:9
363:5 365:21
436:6,8,13,15,18
443:22 445:18
449:14
year 14:15 29:15
33:4 54:8 67:17
85:1 89:17,21
99:14 101:8 104:2
104:4 105:16,21
108:9 121:7
123:14 126:4,11
126:12,15 128:9
128:17,17 130:3,4
139:3,19 153:6
157:11 184:5
188:15 189:22
258:20 259:15
263:9 265:6,7
270:19,22 278:6
278:21 279:6,15
280:8 283:9
285:17 289:12,17
294:3 295:3
297:18,19 298:16
302:15 310:20
328:17 329:15
334:15,16 336:8
343:12,13 344:3
368:8 385:21
386:8,21,21
392:21 400:12,13
401:19 403:13
412:9 420:1
438:21,21 442:13
year's 178:6
years 10:5,15
11:16 21:12 23:9
23:12 26:22 27:13
33:4,6,8 34:1,9,10
36:6,14 42:7,7,9
42:11 44:16 46:17
47:5,6 57:4,5 61:4
85:3 86:7,14
89:19,21 90:12,20
95:13 96:8 105:7
123:22 124:9
125:4 139:6
141:20 142:10,11
153:2,4 156:17
186:14 204:1
234:15,16 237:22
238:1 258:7
259:15,15 261:1
262:3 263:11
264:17 266:21
268:20 269:6,7
270:1,2,9 271:2
279:8 280:9
285:20 286:11,11
290:11 294:9,10
294:10,18,18
295:2,3 296:17
297:6,9,10,16,21
298:5,16 299:1
303:8 307:14
314:9 318:18
319:7 323:10
327:14 332:13
334:9 335:12,17
335:22 337:10,17
337:21 338:16,17
343:13,15,18,19
343:20,20 353:15
357:4 369:1 379:1
382:5 397:11
398:2,4 400:22
401:5 403:14
404:9 405:8,19
407:9 408:9,11,14
417:9 419:13,17
420:2 423:17
428:16 429:13
431:3,17 438:8
440:3 442:4 443:1
447:17
yesterday 134:8
134:13
yin 25:22
york 3:10,20
233:17
young 22:18
younger 145:19
you're 83:18

z

zero 141:18,22
147:14,19 262:7
277:20 278:7,10
278:17 297:14
zones 138:15