

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22

FOOD AND DRUG ADMINISTRATION (FDA)  
FDA Rare Disease Day 2020:  
Supporting the Future of Rare Disease  
February 24, 2020

-----

REPORTED BY: Eliza Spikes, Notary Public  
JOB No.: 3854897

Job No. CS3854897

1 DR. JANET MAYNARD: Good morning and  
2 welcome to this public meeting, FDA Rare Disease Day  
3 2020, Supporting the Future of Rare Disease Product  
4 Development. My name is Janet Maynard. I am the  
5 director of the Office of Orphan Products Development  
6 at FDA, and I am excited to have this opportunity to  
7 engage directly with you to help support the future of  
8 rare disease product development.

9 We would like to welcome the various  
10 rare disease stakeholders who are here today,  
11 including patients, family members, patient advocacy  
12 organizations, healthcare professionals, and  
13 individuals from academia, industry, and government,  
14 including many from FDA. Many individuals are here in  
15 the Great Room at FDA for this very important meeting.  
16 We know it can be challenging to travel to FDA, and we  
17 thank you for being here today.

18 In addition, thank you to those joining  
19 by webcast. We understand that not everyone can be  
20 here in person, and we appreciate you taking the time  
21 to participate and contribute online.

22 Developing a treatment for a rare

1 disease can present unique challenges. The goal of  
2 this meeting is to obtain stakeholders' perspectives  
3 on challenges and solutions in rare disease product  
4 development and identify commonalities that can  
5 support product development across a variety of rare  
6 diseases. To accomplish this goal, we have a full  
7 agenda today. We will review this agenda after we  
8 review a few logistic and housekeeping points.

9           First, please silence any cell phones  
10 or mobile devices, as they may interfere with the  
11 audio in the room today. If you haven't already, we  
12 ask that all attendees sign in at the registration  
13 tables outside of the meeting room. Restrooms are  
14 located in the lobby, past the coffee area, to the  
15 right and down the hallway. At any point if you need  
16 to get up for any reason, please feel free to do so.  
17 There are smaller rooms available around the Great  
18 Room if you need space either during the meeting or at  
19 lunch.

20           If you have any questions, please ask  
21 the volunteers at the registration desk. If you would  
22 like to pre-order your lunch, please go to the food

1 kiosk outside of the conference room. The pre-ordered  
2 lunches need to be purchased by 3:30. Thus, if you  
3 have not pre-ordered your lunch but would like to, we  
4 recommend you pre-order now.

5 If you decide not to pre-order, you may  
6 purchase snacks, sandwiches, and food items a la  
7 carte. The kiosk outside the conference room will be  
8 open from 8:00 until 5:00 to obtain food and drinks.

9 For media inquiries, our press officer,  
10 Monique Richards, is here today. If members of the  
11 media are here today, please sign in. And if you have  
12 any questions or are interested in speaking with FDA  
13 about this meeting, please connect with Monique  
14 Richards.

15 This meeting is intended to give FDA  
16 the opportunity to listen and interact with rare  
17 disease stakeholders, so the FDA participants and  
18 other FDA employees will not be available to make  
19 statements to the media.

20 Please note that if you are asked to  
21 participate in an on-camera or off-camera interview,  
22 you may accept or decline that invitation at your own

1 discretion.

2 For the wi-fi in the great room, the  
3 network and passcode are displayed on the screen. A  
4 public docket is open until March 29th to submit  
5 comments. We highly encourage you to do so.

6 This meeting is being transcribed and a  
7 live webcast is being recorded. There will also be  
8 filming in the Great Room today. If you have any  
9 questions, please contact Monique, and she is happy to  
10 address these questions. For urgent issues, please  
11 speak to the registration desk staff or any FDA staff  
12 you see in the room wearing name tags.

13 In case of an emergency, please exit  
14 the Great Room and follow the exit signs to leave the  
15 building.

16 Also, please let us know how the  
17 meeting went today. For individuals in the room,  
18 evaluation forms will be placed on your seats at  
19 lunch. If you do not receive one, please stop by the  
20 registration table. For individuals on the web,  
21 evaluation forms will be emailed to you.

22 We will now review today's agenda. The

1 goal of this meeting is to obtain stakeholders'  
2 perspectives on challenges and solutions in rare  
3 disease product development and to identify  
4 commonalities that can support product development  
5 across a variety of rare diseases. To accomplish this  
6 goal, we will have a variety of remarks and panel  
7 discussions from various rare disease stakeholders.

8 The morning session will focus on  
9 registry and natural history data collection to  
10 support rare disease product development. The  
11 afternoon session will focus on new opportunities and  
12 challenges in rare disease product development.

13 In terms of the morning agenda, after  
14 the conclusion of my welcome, Dr. Abernethy will  
15 provide opening remarks. We will then have a panel  
16 discussion with FDA senior staff, followed by a 15-  
17 minute break, and then a panel regarding natural  
18 history and registry data in rare diseases. We will  
19 then break for lunch at  :30.

20 In terms of the afternoon agenda, the  
21 FDA Commissioner, Dr. Hahn, will provide opening  
22 remarks for the afternoon, and then we will have a

1 panel with the FDA Medical Product Center directors.  
2 We will then have a ten-minute break, followed by a  
3 panel on perspectives on individualized therapies, and  
4 then a panel on the ecosystem of rare disease product  
5 development.

6           During the panel throughout the day,  
7 there will be the opportunity for those in the room  
8 and on the web to ask questions and provide  
9 perspectives. For those in the room, please raise  
10 your hand if you would like to speak. We will bring a  
11 handheld microphone to you. Alternatively, you may go  
12 to one of the microphones that are located throughout  
13 the room. You may remain anonymous or state your  
14 name, and we encourage you to state the disease area  
15 you are representing if that is applicable.

16           For transparency purposes, when you are  
17 sharing a comment, we ask that you please disclose if  
18 you are affiliated with an organization, if your  
19 travel has been funded, or if you have any significant  
20 financial interest in rare disease medical product  
21 development.

22           For those on the webcast, please type

1 your comments in the chat feature. We will be  
2 periodically checking in to see what our remote  
3 attendees are sharing in the chat box.

4 After the last panel in the afternoon,  
5 we will have an open public comment period. The open  
6 public comment period will provide anyone in the  
7 audience the opportunity to make a comment. To  
8 participate in that, you would have needed to sign up  
9 prior to the meeting or sign up today at the  
10 registration table. Participation is first-come-  
11 first-served and can accommodate up to nine  
12 commenters.

13 We will close the sign-up for the open  
14 public comment period at the end of our afternoon  
15 break around 2:00 PM or when the sign-up is full.  
16 Speakers will each have three minutes to speak. If  
17 there is additional time at the end of the open public  
18 comment period, individuals in the room can share  
19 remarks on a first-come-first-served basis during the  
20 remaining time. After the open public comment period,  
21 I will provide closing remarks.

22 Now we will briefly cover a few rules

1 of engagement for our discussion today.

2 We encourage all individuals to  
3 contribute to the dialogue, either today in the  
4 meeting or through the public docket. We appreciate  
5 the opportunity to hear your perspectives. The views  
6 expressed today are personal opinions. Please be  
7 respectful of others and allow participants to finish  
8 sharing their experiences without interrupting.

9 Participants in the room should use microphones so the  
10 webcast attendees can hear their remarks. And please  
11 complete an evaluation form to let us know how the  
12 meeting went today.

13 After the meeting ends today, there  
14 will be additional opportunities to interact with FDA.  
15 The Patient Affairs Staff and the Office of Orphan  
16 Products Development are here and want to stay in  
17 contact with you, whether it's helping you stay  
18 connected with other activities at FDA or addressing  
19 any future questions you might have.

20 This slide contains our contact  
21 information. Also, if you choose to tweet about  
22 today's meeting, please use #FDARare2020.

1           In closing, I want to thank everyone  
2 for participating today, and I look forward to a very  
3 productive meeting. Thank you.

4           So our introductory remarks will be  
5 given by Dr. Amy Abernethy, who should be arriving  
6 shortly, or is here. Great. Thank you, Dr.  
7 Abernethy. So Dr. Amy Abernethy, MD, PhD, is an  
8 oncologist and internationally-recognized clinical  
9 data expert and clinical researcher. As the Principal  
10 Deputy Commissioner of Food and Drugs, Dr. Abernethy  
11 helps oversee FDA's day-to-day functioning and directs  
12 special and high-priority cross-cutting initiatives  
13 that impact the regulation of drugs, medical devices,  
14 foods, and tobacco.

15           As the Chief Information Officer, she  
16 oversees FDA's data and technical vision and its  
17 execution. She has held multiple executive roles at  
18 Flatiron Health and was a professor of medicine at  
19 Duke University School of Medicine, where she ran the  
20 Center for Learning Healthcare and the Duke Cancer  
21 Care Research Program.

22           Dr. Abernethy received her MD at Duke

1 University, where she did her internal medicine  
2 residency, served as chief resident, and completed her  
3 hematology-oncology fellowship.

4 She received her PhD from Flinders  
5 University, her BA from University of Pennsylvania,  
6 and is boarded in palliative medicine. Welcome to Dr.  
7 Abernethy. Thank you.

8 DR. AMY ABERNETHY: Thank you very  
9 much. I think somebody's calling us with beeps.

10 Thank you all for being here with us  
11 today. Your voice is so important to how we take this  
12 journey forward.

13 So as I reflect on where we are today,  
14 I reflect on the fact that the combination of  
15 government incentives -- maybe we should check.  
16 Anything you need from me? I sort of feel like E.T.  
17 The combination of government incentives, scientific  
18 advances, and the promise of commercial opportunity  
19 has fueled extraordinary investment in orphan drugs.

20 Since the passage of the Orphan Drug  
21 Act in 1983, the number of orphan indications approved  
22 in the U.S. has risen dramatically.

1           In addition, the proportion of novel  
2 drugs that are for orphan indications has tended to  
3 increase over time as well. In 2018, we saw a record  
4 number of drugs and biologics approved for rare  
5 diseases. In 2019, we continued to make strides in  
6 the treatment of these rare diseases. And  
7 specifically in 2019, the Agency approved 22 novel  
8 drugs and biologics with orphan disease designation  
9 and a total of 76 orphan indications.

10           These product approvals addressed many  
11 unmet medical needs. Some of the approvals included  
12 new and expanded uses of already FDA-approved drugs.

13           For example, FDA originally approved a  
14 drug in 2014 for the treatment of patients with  
15 idiopathic pulmonary fibrosis. This is a serious and  
16 sometimes fatal lung disease that results in lung  
17 scarring and that gets worse and makes it hard for  
18 people to breathe.

19           In 2019, it was approved by FDA to slow  
20 the rate of decline in pulmonary function in adults  
21 with another disease called interstitial lung disease  
22 that's associated with systemic sclerosis or

1 scleroderma. These are rare lung conditions.

2 This was the first FDA-approved  
3 treatment for the rare lung conditions and represents  
4 the shift of a drug approved in one setting to now an  
5 orphan indication.

6 Not only have we seen tremendous growth  
7 in the development of products for rare diseases, but  
8 the very landscape of rare disease product development  
9 is changing. There is an increase in the development  
10 of targeted therapies, more interest in the  
11 development of biologics, including gene therapies,  
12 and tremendous growth in the oncology space.

13 Moreover, orphan drug research and  
14 development has led to medical breakthroughs and  
15 further scientific understanding across a wide range  
16 of conditions beyond rare diseases. But despite the  
17 success, we remain cognizant that developing rare  
18 disease treatments remains enormously challenging.  
19 Working with stakeholders, especially patients and  
20 patient groups, it's critically important in  
21 addressing the challenges.

22 Given that rare diseases are rare by

1 definition, it's important to learn as much as we can  
2 from each patient with rare conditions.

3           Patients living with rare diseases and  
4 their families can provide invaluable insights that  
5 directly impact medical product development and  
6 improve day-to-day care in the clinic for people today  
7 and in the future. Our unique experiences as patients  
8 provide critical input into which then helps inform  
9 the design of clinical endpoints which help us  
10 understand what will be most meaningful in your day-  
11 to-day lives as medical products are developed.

12           People who are willing to participate  
13 in natural history studies help provide data points  
14 that can be tracked over time and allow us to better  
15 understand disease progression in the real world.  
16 Participation in clinical trials facilitates getting  
17 safe and effective therapeutic options to the market.

18           Understanding the natural history of  
19 rare disorders is critical to developing appropriate  
20 clinical trial endpoints for rare diseases, because  
21 otherwise these diseases are poorly understood. It  
22 also helps us understand how the disease course can be

1 variable across patients.

2 Detailed natural history case studies  
3 are also used to create historical controls that can  
4 be used to evaluate the efficacy and safety of new  
5 treatments and similar trials, this way decreasing the  
6 need to randomize patients when it is unethical or  
7 impossible to do so.

8 In this morning session, we will hear  
9 from rare disease stakeholders on opportunities and  
10 challenges in the use of registry and natural history  
11 data to support rare disease medical product  
12 development.

13 As we think about data to support rare  
14 disease product development, it's also important to  
15 consider real world data and real world evidence.  
16 Real world data and real world evidence are playing  
17 increasingly important roles in all facets of the  
18 healthcare ecosystem. What is it? These are data  
19 collected during the routine process of providing  
20 healthcare, like through the electronic health record  
21 or through a glucose meter. And clinical evidence  
22 generated from the analysis of these data help to

1 provide meaningful insights as to how patients fare  
2 t eh real world when exposed to medical products  
3 outside the rigid and uniform settings that we usually  
4 see in clinical trials.

5 The healthcare community is using these  
6 types of real world data to support coverage decisions  
7 and to develop guidelines and decision support tools  
8 for use in clinical practice.

9 Medical product developers are also  
10 using real world data and real world evidence to  
11 support clinical trial designs and observational  
12 studies to generate evidence to support approval of  
13 novel treatment approaches.

14 FDA uses real world data and real world  
15 evidence to monitor post-market study information,  
16 informing safety and our regulatory decisions.

17 In response to the 21st Century Cures  
18 Act, FDA developed a real world evidence program to  
19 evaluate the potential uses of real world data in  
20 generating evidence of product effectiveness to help  
21 support approval of new products for new indications,  
22 including in the rare disease space, or to help

1 support and satisfy post-approval study requirements.

2 Stakeholders can engage with us,  
3 particularly patient engagement. And this has been  
4 and will continue to be an important part of our real  
5 world evidence program.

6 With these exciting opportunities for  
7 the use of data, it's important that FDA modernize our  
8 technology platforms so that we can support the  
9 advances coming to make a difference in your lives and  
10 our lives.

11 In September, the FDA rolled out our  
12 Technology Modernization Action Plan. This is an  
13 ambitious strategy that includes modernizing our  
14 technical infrastructure in ways that allow us to  
15 receive, analyze, and use data in ways to support our  
16 regulatory mission.

17 One way we are working to meet this  
18 goal is by designing technical interfaces and tools to  
19 enable to streamline submission and review of data.  
20 Creating standard, digital safety reports is an  
21 important step towards more sophisticated data and  
22 technology solutions at the FDA and to support

1 efficient development of safe and effective medical  
2 products.

3 In support of rare disease product  
4 development, the FDA will strengthen the information  
5 technology processes and our orphan drug technology  
6 modernization efforts. This effort will streamline  
7 the orphan drug designation request process by moving  
8 from paper-based processes to a new cloud-based online  
9 submission portal. The new online portal will allow  
10 sponsors to submit orphan drug applications  
11 electronically. This effort is another example of  
12 FDA's commitment to broader efforts in overall  
13 technology modernization and orphan diseases.

14 Importantly, the foundation of these  
15 technical enhancements are supporting the development  
16 of safe and effective products for rare diseases for  
17 patients and families.

18 I am grateful to be part of an agency  
19 so committed to integrating the patient perspective in  
20 everything that we do. Patients and the care of the  
21 American people is the heart of a regulatory mission,  
22 and this is our core focus.

1           It's essential that we work with you,  
2 all of us, those who are directly impacted by  
3 diseases. And this informs our efforts as we move  
4 forward. We are here to listen and work together with  
5 you.

6           Thank you for the opportunity, and we  
7 want to make sure you know we're listening. Thank  
8 you.

9           DR. JANET MAYNARD: Thank you so much  
10 to Dr. Abernethy. And now I am pleased to invite our  
11 first panel up on the stage. So as they come,  
12 everyone can take a little bit of a stretch. I know  
13 it's a long day, and we're so excited to have you  
14 here.

15           So our first panel will be a discussion  
16 with FDA Senior Staff. Thank you.

17           DR. ERIKA TORJUSEN: So first, I just  
18 wanted to say thank you for being here today. Any  
19 time that we can get together and discuss rare  
20 diseases is certainly a special day. So I wanted to  
21 thank you all again.

22           I just wanted to introduce myself. My

1 name is Erika Torjusen, and I am the Director for the  
2 Rare Pediatric Disease Designation Program, as well as  
3 the Humanitarian Use Device Designation Program, as  
4 well as the Pediatric Device Consortia Grants Program.

5 So my purpose when I come to work every  
6 day is actually to promote and support the development  
7 of products to treat rare disease and special  
8 populations, small populations, such as pediatric  
9 patients. So this is a cause that's very near and  
10 dear to my heart.

11 So we have the great fortune of being  
12 the first panel for today. And so we are going to be  
13 laying the groundwork for the discussion regarding  
14 natural history and registry data, with a focus on the  
15 regulatory perspective. Our goal is to allow about 20  
16 to 30 minutes for audience participation, both in the  
17 room as well as online. So that's going to occur in  
18 the second part of our panel today.

19 So first I'm going to introduce our  
20 panel by name, and then I'm going to give each of our  
21 panel participants an opportunity to provide a five-  
22 minute background on where they are in the agency,

1 what role they fulfill in the agency, and also provide  
2 you with a couple of key points regarding their  
3 perspectives on natural history and registry data.

4 So first I'm going to introduce Dr.  
5 Stein, who is immediately to my right. Next is Dr.  
6 Caños, and then next we have Dr. Bryan. So I'll have  
7 you start, Dr. Stein, first, providing your five-  
8 minute introduction.

9 DR. PETER STEIN: Great. Thank you  
10 very much. I want to thank everyone for being here  
11 today. This is such an important day and opportunity  
12 to hear from patient groups from other stakeholders  
13 about their perspectives on the work that we all do  
14 together to develop drugs for rare diseases.

15 I am the Director of the Office of New  
16 Drugs, which is the office that regulates drugs that  
17 are coming in from approval. It also regulates drugs  
18 that have been approved and participates with other  
19 offices in assuring their continued safety and the  
20 appropriate continued benefit-risk of those drugs.

21 And I say new drugs, but as Dr.  
22 Abernethy mentioned in her opening remarks, many of

1 the drugs that we are seeing are for rare diseases,  
2 orphan designated diseases. Indeed, as she mentioned,  
3 last year it was about 40 or 50 percent and the year  
4 before that, about 60 percent of the new drugs that we  
5 approved were for rare diseases.

6 So, much of the work that we do across  
7 my organizations is involved in supporting companies  
8 during their development phase, during the IND  
9 development phase for rare diseases, and then  
10 reviewing applications for rare diseases. And that's  
11 a large part of what we do in many different parts of  
12 our organization. We have an Inborn Errors Team that  
13 works on particular rare diseases that involve enzyme  
14 deficiencies and related conditions. But across all  
15 of the different divisions -- neuroscience and  
16 endocrine and many other divisions -- we see  
17 applications both for the development and then for  
18 approval of drugs for rare diseases. So we are  
19 extensively involved in helping to find ways to treat  
20 these important diseases.

21 I'll just say a few words about natural  
22 history studies, because I think we're going to spend

1 a fair amount more time both on this panel and in the  
2 next panel talking about these really important means  
3 of gathering information about these disorders.

4           Natural history studies really refer to  
5 studies that are collecting information or obtaining  
6 information about the clinical course, presentation,  
7 and progression of diseases. It can be both  
8 retrospective -- so chart reviews, using medical  
9 records, using other sources of information, it can be  
10 cross-sectional within the cross-data that's existing  
11 -- or, very importantly, it can be prospective  
12 collection of data. Really collection of pre-  
13 specified data, data that is specific to the  
14 objectives of that study that informs. And we often  
15 will refer to that as a registry. It's really a  
16 platform for collecting prospective information.

17           And what I'll say is at a high level  
18 these are incredibly important projects, incredibly  
19 important activities, because it informs much of what  
20 we do and how we think about rare diseases, defines  
21 the course of the rare disease, its presentation, its  
22 diversity and heterogeneity, its complications, the

1 burdens of its treatment. All of that can inform  
2 everything from how we design clinical studies, it can  
3 serve as control groups, external control groups for  
4 clinical trials, they can help us to develop  
5 instruments like clinical outcome assessment tools and  
6 biomarkers, and so many other purposes. So these are  
7 critical sources of information that help us develop  
8 drugs and help us approve drugs for rare diseases.  
9 And I guess we'll dig into some of the specifics of  
10 that broad overview.

11 DR. ERIKA TORJUSEN: Thank you. Dr.  
12 Caños?

13 DR. DANIEL CAÑOS: Thank you. I am the  
14 Acting Director of the Office of Clinical Evidence and  
15 Analysis, and I work in the Office of Product  
16 Evaluation and Quality within the Center for Devices  
17 and Radiological Health. And so really our office is  
18 geared to address some of the challenges and the needs  
19 to incorporate evidence from a clinical experience  
20 into regulatory decision-making.

21 Really, you know, we just finished our  
22 reorganization last year to this opaque structure.

1 And my office supports the Office of Health  
2 Technologies. Individual device technologies are  
3 within these offices, cardiovascular, ortho, et  
4 cetera. And our office supports the development of  
5 evidence from clinical experience from the conduct of  
6 studies for even such as protections. Good clinical  
7 practice, laboratory practice.

8 Also on the epidemiology side to  
9 address the -- assess the relevance and reliability as  
10 well as to the quality and completeness of data  
11 sources, devise aspects for the analytic portion, and  
12 then also the outreach and collaboration with  
13 hospitals and providers. So really trying to provide  
14 kind of a soup to nuts support and assessment of  
15 clinical evidence and really kind of breaking down  
16 some of the artificial barriers between the standard  
17 clinical trials and really viewing it from a holistic  
18 approach as far as the evidence generation. And  
19 through supporting that, we are developing and  
20 assessing real world evidence sources, registries, as  
21 was mentioned, and really partnering with, you know,  
22 Office of the National Coordinator and with ARC, other

1 stakeholders, industry, professional societies,  
2 patients, and academia to assess the quality of data  
3 sources, developing registry infrastructure, and  
4 developing a maturity model to assess the ability of  
5 certain registries to address questions for the  
6 various stakeholder community.

7           And in doing so, establishing this  
8 infrastructure, we can assess clinical reported  
9 outcomes, observed reported outcomes, patient reported  
10 outcomes, develop the infrastructure to capture these  
11 items. And we are working towards a large  
12 infrastructure.

13           So registries -- I think we'll get a  
14 chance to talk about this -- there are some plusses  
15 and minuses to registries, some limitations in what  
16 can be captured. But we are approaching evidence  
17 generation from, as I mentioned, a larger holistic  
18 approach and really thinking about a collaborative  
19 stakeholder community for evidence generation. So not  
20 just the registry infrastructure, but also looking at  
21 electronic health records, medical billing claims  
22 information, and tying all this information together

1 for a national evaluation system for health  
2 technologies.

3 So we've actively supported the  
4 creation and use of real world evidence and have  
5 undertaken many activities to support this. One is  
6 through promoting implementation of unique device  
7 identifiers, also increasing the use of regulatory  
8 decision-making that utilizes and leverages clinical  
9 evidence. It's supported over 50 regulatory decisions  
10 within CRDH. And then, as I mentioned, we're  
11 partnering to build a National Evaluation System for  
12 Health Technologies that can capture this information  
13 and address with real world evidence the regulatory  
14 questions at hand.

15 So with this system, the National  
16 Evaluation System for Health Technologies Coordinating  
17 Center has stood up. And it's more than 12 network  
18 collaborators, which represent 195 hospitals, 3,942  
19 outpatient clinics, and over 494 million patient  
20 records. And this is just the start of the system.  
21 In the coming months they're going to establish and  
22 release a quality framework document as well as a

1 methodology document which partners well with the  
2 guidance document that was released with CDRH and CBER  
3 with respect to real world evidence uses for  
4 regulatory decision-making that kind of map out the  
5 needs for relevance, reliability, quality, and  
6 completeness that we assess when looking to leverage  
7 this data for regulatory decisions.

8 DR. ERIKA TORJUSEN: Thank you.  
9 Excellent. And now Dr. Bryan.

10 DR. WILSON BRYAN: I'm Wilson Bryan. I  
11 am a neurologist with a background in neuromuscular  
12 disorders. I now serve as Director of the Office of  
13 Tissues and Advanced Therapies in the Center for  
14 Biologics.

15 Advanced therapy is a somewhat  
16 pretentious term that we borrowed from the Europeans.  
17 It generally refers to cell therapies and gene  
18 therapies. And the Office of Tissues and Advanced  
19 Therapies, which I refer to as OTAT, one of the best  
20 things I like about working in OTAT is that over 90  
21 percent of our applications are for serious and life-  
22 threatening diseases. Approximately 50 percent are

1 for rare diseases. And several of the gene therapies,  
2 there aren't -- we don't have many products approved  
3 yet. But the science over the last couple of decades  
4 has really moved forward quickly. And so we have very  
5 exciting products in development that will be coming  
6 out over the years ahead.

7 One product that I will mention, a gene  
8 therapy that we approved last year, is Zelgensma, a  
9 treatment for spinal muscular atrophy.

10 Now, spinal muscular atrophy, if you're  
11 not familiar with it, it's a bad disease. It's a  
12 neuromuscular disorder. The form of SMA, spinal  
13 muscular atrophy, that was studied was an infantile  
14 form. So these infants start becoming weak by the age  
15 of six months, and most are dead by the age of two  
16 from respiratory failure.

17 There are now two products approved for  
18 SMA. This is a huge change for patients and for their  
19 families. For decades there was nothing. And key to  
20 development of this gene therapy for SMA was the  
21 natural history data, the natural history study. It  
22 wasn't a big natural history study. The natural

1 history control that we used only had 23 patients.  
2 Twenty-three. That's almost nothing. But it can be  
3 enough if the course is reliable.

4           Where we get into trouble is when  
5 natural history data don't give -- don't seem  
6 reliable, don't give reliable endpoints. Highly  
7 variable pools. But when the course is predicable and  
8 we can get reliable endpoints, then natural history  
9 data can be used in some cases as the control for  
10 Phase III studies as was done with infantile SMA. I  
11 expect that you'll hear more about that in the next  
12 session from Dr. Kaufmann, who has been more closely  
13 related with this development than I have.

14           With the sequencing of the human  
15 genome, there are now thousands of genetically-defined  
16 diseases. Many of them very rare, many of them very  
17 bad diseases. And we know that we will get at some  
18 point the technology to address these with gene  
19 therapy. We haven't yet figured out how we're going  
20 to get that therapy for every patient who has those  
21 rare disease. And we at CBER are very committed to  
22 working with other stakeholders like the NIH to figure

1 out how every patient with a rare genetic disease is  
2 going to get a treatment that works. And that's years  
3 ahead, but that's where we're going.

4 DR. ERIKA TORJUSEN: Thank you all for  
5 those introductory comments and remarks. So,  
6 actually, I see we've used already a good amount of  
7 our time. So I think what I'm going to do is I'm just  
8 going to have one question for you all, and we'll see  
9 where we're at. And then we might actually be able to  
10 open it up to the audience for audience participation  
11 where they can ask some questions of our panel  
12 members. So first we're going to ask one question to  
13 you all.

14 So given your knowledge and experience  
15 with natural history and registry data, do you have  
16 any examples of lessons learned that you would like to  
17 share with the audience today? We'll start with you  
18 again, Dr. Stein.

19 DR. PETER STEIN: Well, just to pick up  
20 on some of the things that I think you've already  
21 heard. Natural history studies can be used in a whole  
22 range of ways. And I think we're going to speak a

1 little bit more about their use as external controls  
2 so that we can take information from a single-arm  
3 trial and have a comparison group that allows us to  
4 draw conclusions and potentially to use that as the  
5 basis to approve a drug or to approve a biologic, a  
6 gene therapy.

7 But to be able to do that requires that  
8 the natural history information be very rigorous, that  
9 it be collected in a way that provides detailed  
10 information that's comparable to the information that  
11 we're getting in the clinical trial. And that's  
12 really the challenge. Because very often the natural  
13 history information we get is not necessarily on  
14 comparable patients, doesn't necessarily have a  
15 comprehensive data collection or similar data  
16 collection, data quality issues may occur.

17 So I just want to step back and think a  
18 little bit about how we can utilize this information.  
19 Now, again, very often we do have to look towards  
20 randomized clinical trials, because they provide a  
21 very rigorous way of being able to compare the  
22 treatment to a control group. And sometimes those

1 really are the only ways that we can go when there is,  
2 for example, a small effect size or a heterogeneous  
3 population where we don't have the natural history  
4 well-defined.

5 But where there is a larger expected  
6 effect size and where we have data that provides us  
7 clear information with a predictable clinical course  
8 and detailed information down to the patient level, it  
9 does support our ability to use natural history  
10 comparison groups, whether from a registry or from  
11 retrospective chart reviews.

12 But I think it's important just to  
13 think about, again, what's needed to make that work.  
14 It does mean that we've defined the patient population  
15 in that comparison group very clearly. Are we sure  
16 that those patients are actually similar to the  
17 patients in the stage and the stage of progression and  
18 the type of disease that they have? Diagnostic  
19 criteria, for example, change over time. If we look  
20 at diagnostic criteria from 10 or 15 years ago, we may  
21 be looking at different patients than the current  
22 study that we're trying to compare those patients to.

1 Or the outcome assessments; were they assessed in a  
2 similar way? Very often we found that the types of  
3 methods and outcome measures and the way the disease  
4 was assessed over time changes from when it was looked  
5 at 10 or 20 years ago to how it's being collected in  
6 the context of the clinical trial.

7 Are the treatments that the patients  
8 are getting concurrently similar or quite different?  
9 And what is the data quality? Was it really collected  
10 for this purpose, or is it collected for clinical care  
11 where some of the information that we need is there,  
12 and some of the information we need might not be  
13 there.

14 So that all provides substantial  
15 challenges when we get a comparison group submitted  
16 compared to a single arm trial, can we really compare  
17 it. And I really would push to say that what's really  
18 critical as we go forward and are working  
19 collaboratively together with patient groups and with  
20 other stakeholder groups as we think about the  
21 development of registries' prospective collection of  
22 information, the design of those, the infrastructure

1 of those, the data quality issues become absolutely  
2 essential as we move forward. As there is marked  
3 advances in our ability to identify new drugs and new  
4 biologic therapies, our opportunities to treat rare  
5 diseases are going to continue to expand. But if  
6 we're going to be able to use natural history or  
7 registries for that, we have to make sure that the  
8 quality of that data improves over time dramatically  
9 so that that data really provides us with a comparison  
10 group that's robust and from which we can draw  
11 conclusions.

12                   And we've had some examples of natural  
13 history studies where they're quite limited  
14 information. And what our groups here do is do  
15 everything they can to ask more and more from the  
16 sponsor to go back to the medical records to pull all  
17 kinds of information that help us to do the best  
18 comparison we can. And sometimes it requires us to  
19 just continue to collect data over time so that we can  
20 see whether the course of the disease really differs  
21 from the course that we're seeing with the treatment  
22 group.

1           So what I would say is there is lots of  
2 examples over the past about 15 years. We've approved  
3 something like 20 drugs using external control data.  
4 So quite a few drugs approved that way, outside of  
5 oncology. Oncology is even more than that. But in  
6 each one of them, I would say that we've seen  
7 substantial challenges in trying to get matched  
8 groups. It requires a lot of work to be able to draw  
9 a robust conclusions. So we certainly want to make  
10 sure that the drugs we're approving are effective and  
11 are safe.

12           And so I think one of the things we  
13 have to underline is the importance of the quality of  
14 the data and of the completeness of the information so  
15 we can actually increasingly use these kinds of  
16 studies to make decisions as early as we possibly can.

17           DR. ERIKA TORJUSEN: Thank you. And  
18 Dr. Caños, do you have anything you'd like to add from  
19 the CDRH perspective?

20           DR. DANIEL CAÑOS: Yeah. I think you  
21 really hit the nail on the head as far as the quality  
22 and the representativeness of the evidence that's out

1 there, as well as the definitions, you know,  
2 consistent definitions and how those outcomes are  
3 ascertained really are challenges that we are seeing  
4 with evidence from clinical experience.

5           And I'd like to speak to some of the  
6 work items that we have at CDRH and are working to  
7 actively address those concerns. We have funding  
8 through a Patient-Centered Outcomes Research Trust  
9 Fund through that through a grant we are working with  
10 stakeholder community. Patient representatives are in  
11 these meetings or on the calls as well as industry  
12 stakeholders, professional societies, and academia.  
13 And working within selected registries, 12 coordinated  
14 registry networks that we are targeting and  
15 developing.

16           We are trying to arrive at a core data  
17 set, definitions and variables to be routinely  
18 collected within each of these registry sets and  
19 critically assessing the capabilities of these  
20 registries to address regulatory questions. And  
21 within that same effort, we are also working on  
22 increasing the quality from these registries so that

1 there can be a fair appraisal of these evidence  
2 systems.

3 And in my introductory comments, I  
4 mentioned this National Evaluation System for Health  
5 Technologies Coordinating Center, housed within the  
6 Medical Device Innovation Consortium, the MDIC. This  
7 NEST will kind of point to certain nodes within the  
8 healthcare system. Network collaborators that I  
9 mentioned before, registries. And, you know, the work  
10 of this trust fund effort is to provide that evidence  
11 and our -- kind of the assessment from the stakeholder  
12 community of the quality of the evidence from those  
13 individual registries. So that takes out some of the  
14 guesswork up front as folks, you know, look to the  
15 registries that they know where the stakeholder  
16 community is as far as the quality and completeness  
17 and representativeness and the definitions that are  
18 utilized so that folks know where to go to, where the  
19 system can point to where those nodes could be and  
20 areas that we can, frankly, improve.

21 In addition to that, you know, we have  
22 on the structure side, and we are working to build the

1 infrastructure and collaborating with the stakeholder  
2 community.

3           On the methods side, from the epi and  
4 the biostatistical side, we are working to leverage  
5 external evidence as best we can. As you mentioned,  
6 it can be utilized at times when appropriate for  
7 control arms within studies. We are working from the  
8 evidence standpoint and biostatistical standpoint to  
9 develop methodologies where we can borrow certain  
10 parts of data if it were to be found to be  
11 representative. And so it could lend some support or  
12 lesser support if the populations aren't  
13 representative of the population, the indication for  
14 which the sponsor is seeking.

15           In addition to supplementing the  
16 control arm, it could supplement some portions of the  
17 treatment arm. And these are methodologies that we  
18 are publishing off of and also jointly developing  
19 through research work as well as collaborations  
20 through the MDIC.

21           So, you know, we're trying to approach  
22 it from a few different aspects; the methodological,

1 the analytics side, the partnership side for  
2 developing the infrastructure, as well as the  
3 methodologies to really maximize the use of evidence  
4 from the clinical experience for regulatory decision-  
5 making.

6 DR. ERIKA TORJUSEN: Excellent. Thank  
7 you. And Dr. Bryan, do you have anything you'd like  
8 to add from the CBER perspective? I know you touched  
9 on some of this in your introductory comments.

10 DR. WILSON BRYAN: Just a couple of  
11 things. First, when advocacy groups or drug companies  
12 or the NIH, whoever starts a natural history study, I  
13 think they usually have in the back of their minds  
14 that these data will hopefully be used as a control in  
15 clinical trials. But natural history data do so much  
16 more than that. They are very important for designing  
17 the development program, for deciding what endpoints  
18 to use, what populations to study, and how long is the  
19 trial going to need to be to see a change in that  
20 endpoint in that population.

21 Too often we have scientists,  
22 investigators come to us with a new, exciting product

1 that they've been working on in the lab. And these  
2 are often gene therapies. And they're ready to give  
3 it to humans. And they ask us at the FDA to tell them  
4 what the clinical trial should look like. And it's a  
5 rare disease, there haven't been clinical trials done  
6 in this genetically-defined disease before. We don't  
7 know the answers. Those of you who have met with us  
8 many times know we often don't know the answers.

9           And so it's very important that the  
10 scientists who are working on these rare genetic  
11 diseases, as soon as they start working in the animal  
12 models, that's the time that they need to be starting  
13 to talk to the clinicians about the human disease so  
14 that those natural history studies are being started  
15 well before it's time to actually do the clinical  
16 trials.

17           So people just need to talk to each  
18 other in this business. And too often the scientists  
19 have been too isolated. And we need to get the  
20 natural history study started much earlier.

21           DR. PETER STEIN: If I could just  
22 underline that, because I think that's such an

1 important point. Very often when scientists dive into  
2 trying to identify the genetic background and  
3 understand the biology of the disease and begin to  
4 work on targeting it, there is very little known.

5 There is often case reports and case series that are  
6 highly selective and don't necessarily collect all of  
7 the background information on the heterogeneity of the  
8 disease or its course, or really what are the more  
9 common complications or its rate of progression.

10           So, very often they jump in looking at  
11 five or ten case reports or case series, thinking that  
12 defines the natural history and that should be  
13 sufficient. But when it comes to us and we really  
14 want to understand, well, how long, how large, what  
15 endpoints, what patients should be included, what's  
16 the range of the disease, that is not known without  
17 having done a properly-performed natural history  
18 study, whether it's looking retrospectively, or even  
19 better, prospectively collecting that information.  
20 That's a gap, and I think that's the disconnect.  
21 Scientists may not realize when they're in the lab  
22 that that information doesn't really exist in a robust

1 way that can be used to inform clinical program  
2 development. So I just want to underline the  
3 importance of that early collaboration between patient  
4 groups, other stakeholder groups, academics, the  
5 scientists, FDA where we can help out with this, to  
6 try to really work together to get these studies  
7 moving so that there is -- so that when they are ready  
8 to bring something to the clinic, we understand the  
9 disease well enough to actually design an informative  
10 program. I think it's really important to underline  
11 that.

12 DR. ERIKA TORJUSEN: Excellent. Thank  
13 you. And so I just want to finish with one very, very  
14 brief question just to finish this topic, because I  
15 think this is an important one.

16 DR. PETER STEIN: You mean you want us  
17 to be brief.

18 DR. ERIKA TORJUSEN: Maybe. I do want  
19 to have time for the audience participation. So I  
20 just wanted to know, do you have any recommendations  
21 on when sponsors or advocacy groups should reach out  
22 to the agency regarding whether they're going to be

1 using a natural history study, designing a natural  
2 history study or registry? Do you have any advice or  
3 recommendations in that regard?

4 DR. PETER STEIN: Well, I think the  
5 answer is early. And we are very much open to have  
6 these kinds of discussions with stakeholder groups to  
7 provide direction, to engage with them. And we are  
8 working on a rare disease accelerator, which is  
9 intended to be a new infrastructure for registries so  
10 that we can support and work with patient groups to  
11 develop these. This is a collaboration with NORD and  
12 with the C-Path Institute to try to provide this for  
13 patient groups as a resource.

14 But I would say early. You know, come  
15 to the division early. If there's a program going on,  
16 if there's development in this area, talk to us about  
17 what we think might be needed. We are here to try to  
18 be collaborative and to be part of the solution.

19 DR. ERIKA TORJUSEN: Excellent. Thank  
20 you. And do you both agree with that recommendation?

21 DR. WILSON BRYAN: Yeah. It's a  
22 challenge, because we know that there are thousands of

1 rare diseases. And we would like to see natural  
2 history studies in all these thousands of rare  
3 diseases. Now, does the Agency have the capacity to  
4 work on the trial designs for thousands of natural  
5 history studies? I'm not sure that we do. But we  
6 want to do what we can.

7 But I think more of us need to develop  
8 expertise in how to do these natural history studies  
9 so that they meet regulatory requirements, you know,  
10 formative for a drug development.

11 DR. ERIKA TORJUSEN: Excellent. Thank  
12 you. So I think I would like to open it up to  
13 audience questions at this time. So if anyone does  
14 have a question, please step forward to one of the  
15 microphones in the room. And also, we expect that we  
16 will receive some questions online as well. So we're  
17 going to bounce our about 20 minutes left for the  
18 audience questions then.

19 So I'll start with the gentleman all  
20 the way down in the corner there in the white shirt.

21 DR. DEAN SURH: Great. Good morning.  
22 Thank you for hosting us here today. I am Dean Surh

1 with the  Foundation. Just a couple of comments  
2 more than a question. You know, engaging -- and I  
3 don't know our audience, but I presume it's pretty  
4 diverse in terms of experience and so on. So just two  
5 comments more directed perhaps at them.

6 Engaging early with the FDA is really  
7 important. They're always willing to converse. And  
8 the same thing with any pharma or academic research  
9 partners.

10 But I've got to tell you, I don't think  
11 my crystal ball is any better than the FDA's, or in  
12 some cases the scientist's when we're putting programs  
13 together. And oftentimes particularly advocacy groups  
14 are years if not decades in front of the science or  
15 the regulatory reviews of therapies that are yet to  
16 even be thought of, much less emerge.

17 And so I just want to emphasize that a  
18 very structured natural history study/registry is  
19 typically targeted to validate a particular point.  
20 And if you don't know what that point is, which might  
21 be a clinical trial endpoint, if you don't know what  
22 that is, that doesn't mean you shouldn't start with

1 your natural history and your registry. And for  
2 patient organizations, gathering data, we know the  
3 disease from a certain perspective, typically not so  
4 much a scientific perspective. But to gather that  
5 data early, gather it broad. Maybe it starts with  
6 demographics and some of those basics so that you can  
7 go back to those families when you get closer to a  
8 clinical trial and dig in deeper.

9 I just really want to encourage you to  
10 think about that process needs to start very, very  
11 early. And it's extremely valuable. Some will say  
12 it's not scientific. You know what? Knowing where  
13 the patients are, that's where the science starts.  
14 And so we need to start our work early.

15 DR. ERIKA TORJUSEN: Thank you for that  
16 comment.

17 DR. ANNETTE BAKKER: Annette Bakker,  
18 President of the Children's Tumor Foundation. First  
19 of all, I think this is fascinating as a panel. Thank  
20 you so much.

21 I have a question with regards to would  
22 it make sense to start thinking -- because I heard a

1 lot about longitudinal natural history data, and the  
2 quality, and therefore the use of that data. Is there  
3 an opportunity here maybe to collaborate across the  
4 sector to develop some kind of framework, let's say  
5 some umbrella framework for this is what quality looks  
6 like, especially for these very rare diseases where  
7 people collect data and then it ends up not to be the  
8 right data? Is there any guidance that you guys are  
9 developing to say, okay, this is a framework,  
10 infrastructure as the minimum data set to start  
11 collecting data that people at least collect in the  
12 beginning the right data?

13 DR. ERIKA TORJUSEN: That's a great  
14 question. Who would like to tackle that first?

15 DR. PETER STEIN: Just as a -- I mean,  
16 I couldn't agree more that being really thoughtful  
17 about what you're going to collect is critical. And I  
18 would say, you know, a couple of things as resources.

19 We have a guidance that was recently  
20 released on natural history studies that does talk  
21 about a number of the elements that might be  
22 collected. A lot of what's collected really has to be

1 based upon what the purpose and the objectives and the  
2 particular leads in that disease are for further  
3 information.

4           But I also think it's very important to  
5 partner with experts, epidemiologists or others who  
6 have a better understanding of sort of the structure  
7 and the architecture of the data and can work with the  
8 patient groups and can work with academic groups or  
9 other stakeholder groups to really define what's the  
10 gaps, what do we need to know, what are we trying to  
11 do with this study so that it's designed properly.  
12 Because data quality, completeness, and consistency is  
13 absolutely critical.

14           It's wonderful to put a lot of  
15 different kind of data into a database, but if it's  
16 not rigorously defined and appropriately collected  
17 with appropriate attention to detail and quality and  
18 lack of missingness, then the utility of it will just  
19 -- it will be still useful, but its utility will  
20 certainly be much less.

21           So prospective definition, working with  
22 experts. There is a lot of literature out there about

1 registries, what can be collected, and different  
2 frameworks that can be used as resources. And we are  
3 a resource as well.

4 DR. WILSON BRYAN: And we have a  
5 guidance out that talks about --

6 DR. ANNETTE BAKKER: I saw that. But I  
7 think the question of connecting them, maybe allow  
8 especially those ultra-rare diseases to maybe come  
9 together as a bigger group. Right? If we start  
10 collecting it across diseases maybe in a similar way.  
11 I don't know, I'm just...

12 DR. WILSON BRYAN: And you're talking I  
13 think about the specific data elements as well.

14 DR. ANNETTE BAKKER: Or like those that  
15 will be used, as you said, for clinical trial design  
16 and for really to understand the course of a disease.  
17 I think there is some rigorousness maybe in...

18 DR. WILSON BRYAN: Well, certainly I  
19 think we all believe in gathering rigorous data to try  
20 to move this ahead. Doing these natural history  
21 studies is not easy.

22 DR. ANNETTE BAKKER: Exactly.

1 DR. WILSON BRYAN: It's a lot of work.  
2 And many natural history studies that have been done  
3 in the past -- I'm going to say probably most -- were  
4 done by academic clinician investigators trying to  
5 understand a particular disease. I remember back in  
6 the early 2000s going to a conference on spinal  
7 muscular atrophy. And they had just completed a large  
8 natural history studying SMS. And I asked, well,  
9 okay, these different endpoints that you looked at,  
10 how much of a change in these endpoints makes a  
11 difference to patients? How much is clinically  
12 meaningful? And the answer I got was, well, we  
13 couldn't figure out how to assess that, so we didn't  
14 look. And I'm thinking you just did a four or five  
15 year natural history study, and you didn't look to see  
16 how much of a change matters to patients?

17 It's important, as Dr. Stein mentioned,  
18 to talk to other people who do this and look at other  
19 trials and figure out how to get the information  
20 that's going to be useful for drug development.  
21 Because I can tell you here at the FDA, we want to  
22 know how much of a change matters to patients. And we

1 have to get the -- that's the kind of information  
2 that's key to a regulator that to an academician just  
3 might not occur to them when they designed the trial.

4 DR. DANIEL CAÑOS: So I just wanted to  
5 add that I completely agree with your comment. And  
6 the NEST Coordinating Center, as I mentioned, being a  
7 multi-stakeholder community, is a collaborative  
8 community, meaning that that community comes together  
9 and serves the purposes of the entire community.

10 So in Dr. Abernethy's opening comments,  
11 remarks, she mentioned not only the FDA's regulatory  
12 body, but also the payor perspective. And you've  
13 heard mention of the patient perspective; what is of  
14 value to the patient? And clinically, you know, what  
15 is a clinically meaningful difference. And within  
16 this multi-stakeholder community and this  
17 collaborative community, those discussions are  
18 ongoing. And that's part of that methods framework  
19 document I mentioned that's going to come out from  
20 NEST Coordinating Center, as well as the quality  
21 framework to really speak to as to this collaborative  
22 community what is meaningful for methodologies within

1 the framework for medical devices.

2 DR. WILSON BRYAN: I'd like to add  
3 something to the comment from the gentleman who spoke  
4 first about having broad data collection in these  
5 natural history studies.

6 It's also important that, particularly  
7 for these rare diseases, that you enroll every patient  
8 that has the disease and try not to be selective in  
9 just enrolling a small group. Now, we realize that  
10 means more effort, more resources. But not going in  
11 with preconceived notions about which patient are  
12 going to be informative and which patients are going  
13 to respond to the intervention. I think enrolling all  
14 the patients with a rare disease when you're starting  
15 a natural history study is important if feasible.

16 DR. ERIKA TORJUSEN: Thank you.

17 DR. PETER STEIN: And just as a quick  
18 sort of follow-up as well. I did like the comment  
19 that he made about getting started. Because, you  
20 know, while we're talking about the rigor and the  
21 importance of complete data and data quality,  
22 sometimes just getting started, identifying the

1 patients, pulling them together, creating a network,  
2 that has real value. And it may be over time there is  
3 a need to evolve it towards other objectives such as  
4 providing a really robust data set as a comparison for  
5 an external control arm for clinical trial. But early  
6 on just creating that network of engaged stakeholders,  
7 of engaged patients and parents and families and  
8 physicians and identifying the patients can be hugely  
9 important. And it may be over time that more rigor  
10 and more consistency of what's collected comes into  
11 it.

12 We certainly don't want to discourage  
13 you getting started, because getting started is  
14 critical. Downstream we can think about additional  
15 ways that natural history study or registry can  
16 evolve.

17 DR. ERIKA TORJUSEN: So I would also  
18 now like to just make sure that we acknowledge we have  
19 a very large online presence today for this meeting.  
20 I believe we have well over a thousand individuals  
21 registered today. So I would like to use this time  
22 just to check in  e and wee if we have any questions

1 from the online community.

2 DR. ERIKA TORJUSEN: The first comment.  
3 Yes.

4 DR. JANET MAYNARD: Hi. Can you hear  
5 me?

6 DR. ERIKA TORJUSEN: Yeah.

7 DR. JANET MAYNARD: We do have a lot of  
8 questions. So to start, what is your perspective  
9 about using the placebo group from approved drug  
10 clinical studies as the comparator group for a new  
11 medicine for rare disease.

12 DR. ERIKA TORJUSEN: Excellent. So we  
13 have about ten minutes left.

14 DR. PETER STEIN: Just to say I think  
15 that in those examples where that's been done, I think  
16 that can be a very rigorously-collected set of  
17 information if it's collected -- again, it's the same  
18 set of considerations; what was collected, over what  
19 time it was collected, what were the patients who were  
20 in that placebo group. All of those will be relevant  
21 to whether it can serve as a comparison group. But if  
22 it was rigorously collected data, that can certainly

1 and has been used as a comparator group for subsequent  
2 trials.

3 DR. ERIKA TORJUSEN: And do you have  
4 anything else to add?

5 DR. DANIEL CAÑOS: Not on the drug  
6 placebo side, no.

7 DR. WILSON BRYAN: I would agree. I  
8 think we are very fortunate when we're in that  
9 situation and have such data. And in most cases in  
10 rare diseases, we don't have such data.

11 DR. ERIKA TORJUSEN: Excellent. And  
12 maybe we'll come over -- I'm sorry, we'll come over  
13 here.

14 DR. JANA OBERMAN: Hi. I'm Jana  
15 Oberman from Ovid Therapeutics. Just quickly going  
16 back to the dialogue around timing. I think we all  
17 agree in theory that engaging early and often with  
18 regulators is critical, and well before you're in the  
19 clinic so that we can design these natural history  
20 studies optimally. But in practice, I think we all  
21 know that we are only granted typically one pre-IND  
22 meeting. And so our hands are often tied in trying to

1 figure out how to engage well in advance, but not  
2 using that opportunity too far in advance when things  
3 can often change a few years before you do enter the  
4 clinic. So do you have any specific recommendations  
5 on how we can go about interacting with you more  
6 effectively?

7 DR. WILSON BRYAN: I'll be honest. I  
8 have limited experience in this. I did get a call  
9 about two or three years ago from a scientist who was  
10 working on several different genetic disorders, very  
11 rare disorders, and said that he was going to develop  
12 a gene therapy for these variety of disorders and  
13 wanted to do five different natural history studies.  
14 And I said I can't review five natural history  
15 studies. Send me two. Send me two protocols for  
16 natural history studies. And I enlisted some  
17 statisticians to help me look at them, but they were  
18 never submitted. They never came in.

19 And I think that reflects the  
20 challenge, that it's not easy to get these things  
21 done. And the scientists who are working in the lab,  
22 they've got a lot of other things on their minds. And

1 they often just don't get around to working with  
2 someone to get the natural history studies done. But  
3 I expected most of us here at the FDA would love to  
4 see a protocol for natural history study. And they'll  
5 probably do what I did, which is dig around to try to  
6 find somebody to take a look at it. Now, hopefully  
7 we'll get better than that.

8 DR. PETER STEIN: And just as a quick  
9 comment. First of all, while we typically have one  
10 pre-IAB meeting, try to be flexible about it. So that  
11 there's not -- that's not a statutory regulatory  
12 limitation, just practical. We also have the CPIM  
13 meetings, which are forum for stakeholder groups to  
14 come in a sort of non-binding way, but can have a very  
15 informative, particularly earlier, discussion with us.

16 We also often attend patient  
17 stakeholder meetings for patient-focused drug  
18 development meetings and talk about registries and,  
19 you know, have an interactive discussion. We're on  
20 panels and in a lot of different patient stakeholder  
21 meetings under the rare disease group and the inborn  
22 error group. And many other of our division staff go

1 to these meetings and interact with stakeholders.  
2 Academic meetings. There's lots of forums in which we  
3 are there or where you can come and speak with us.

4 But again, I think if there's a program  
5 ongoing and we can be helpful in directing that,  
6 that's what we're going to try to do.

7 DR. ERIKA TORJUSEN: And Dr. Caños, do  
8 you have anything to add from the device perspective?

9 DR. DANIEL CAÑOS: So I think Dr.  
10 Stein's comment with respect to our external  
11 engagement is really where we find a lot of value,  
12 right? So some of the questions that come in with  
13 those pre-submissions are questions that the community  
14 may have at large. And so those meetings in the pre-  
15 competitive space where we can discuss and provide our  
16 thoughts or feedback is many times far more effective  
17 and can address the wider stakeholder community  
18 questions. And so when those pre-submissions come in,  
19 they're more targeted questions that we can, you know,  
20 kind of dig into and help out with. So I think the  
21 external stakeholder and our engagement has been very  
22 crucial.

1 DR. PETER STEIN: Just as another  
2 opportunity, is we have a biomarker qualification  
3 program both for CO8 patient-reported outcomes as well  
4 as biomarkers, which is many patient groups that are  
5 looking to find endpoints and measures that they can  
6 develop so that will facilitate drug development  
7 interact with us in that way as well. That's another  
8 opportunity.

9 DR. ERIKA TORJUSEN: So we have a  
10 little more than five minutes. So I just wanted to  
11 just check one more time about if there's another  
12 question online.

13 DR. AMY ABERNETHY: Okay. Can you hear  
14 me okay?

15 DR. ERIKA TORJUSEN: Yes.

16 DR. AMY ABERNETHY: So from a patient  
17 perspective, how does an individual caregiver or rare  
18 disease patient make sure their data is being  
19 collected properly, their clinicians are aware of the  
20 value of collecting specific information with respect  
21 to their disease progression, and their data is being  
22 shared to every relevant disease and/or investigator

1 that can make use of their information?

2 DR. ERIKA TORJUSEN: Would you like to  
3 start, Dr. Bryan?

4 DR. WILSON BRYAN: I actually think  
5 that patients and patient advocacy groups do have a  
6 lot of influence in this arena. And they need to use  
7 that influence more aggressively I think in ensuring  
8 that their data is available not just to the one  
9 scientist or one pharmaceutical company that they're  
10 working with, but generally available to everyone  
11 working in the field.

12 And I think that advocacy groups and  
13 patients do have the ability to have those  
14 negotiations and ensure that open access to their  
15 data, but it needs to be done up front when the  
16 natural history studies are just beginning. And so I  
17 think it can be done, and it's very important.

18 DR. PETER STEIN: So patient voices is  
19 crucial. And I mentioned the reorganization that we  
20 just finalized last year, part of which was the  
21 establishment of a patient science engagement aspect.  
22 And we've had public workshops last year and are

1 working to put together a few others as well this  
2 year, which are fantastic venues for engaging in that  
3 exact conversation. Right?

4 Dr. Abernethy had mentioned, you know,  
5 that information and clinical evidence that's  
6 generated from the medical devices that patients  
7 actually carry on them. And, you know, we talked  
8 about patient-reported outcomes and patient voice.  
9 And so I think it's very important for patients to  
10 talk about what is meaningful for them, how can they  
11 be engaged in the research, and also get information  
12 out of that research and make sure that there is that  
13 kind of the bang for the buck that the question was  
14 kind of alluding to.

15 So, you know, we'll look forward to  
16 hearing more from patients engaged in that  
17 conversation and in the workshops that we will be  
18 establishing within the early spring and kind of late  
19 spring and early summer.

20 DR. ERIKA TORJUSEN: Dr. Stein, do you  
21 have anything else you'd like to add?

22 DR. PETER STEIN: Just to underline

1 that when you're -- if you're interested in  
2 participating in a registry, which is a wonderful way  
3 of accumulating information that's defined and for a  
4 particular purpose, it's important to understand how  
5 that information is to be shared. Is it open access,  
6 or is it more restricted? And I think it's very  
7 important to assure up front that that information is  
8 appropriately curated, that there's appropriate  
9 respect for privacy, and that there are appropriate  
10 controls, but also that there is access for  
11 researchers for use of the data so that it can really  
12 be used to provide the various purposes that this  
13 important data can be used for. So there's access.  
14 It's not just for one company or one academic  
15 organization, but that it can be broadly accessed.  
16 And you can assure that by asking questions when your  
17 data is being entered, what are the access rules for  
18 this, what kind of researchers can utilize this  
19 information?

20 DR. ERIKA TORJUSEN: That's a great  
21 point. Thank you. And I think we have two minutes  
22 left, so I just wanted to get one more question in.

1                     MAN:    And very quickly.    Goody  
2    morning, everyone.    As a patient suffering from  
3    myositis, interstitial lung disease, and pulmonary  
4    arterial hypertension, one of the things when you're  
5    talking about looking at the patient in your studies,  
6    natural or otherwise, the gentleman said at the first  
7    statement about -- I can't remember exactly, but it  
8    had to do with looking at the patient in its entirety.

9                    One of the reasons why my treatment has  
10   taken so long is because I was exposed to secondhand  
11   smoke.    And I would like to ask if at any point in any  
12   of your research -- I know I'm looking at the National  
13   Institute of Health -- environmental factors are taken  
14   into consideration.    But I haven't seen anything  
15   that's dealing with the patient and indoor air  
16   quality.    So that's either a question or a comment  
17   about how you're approaching that from your  
18   perspective.    So I'd like to know if any of your  
19   research that you're doing addresses that factor.

20                    DR. PETER STEIN:    You know, I can't --  
21   I don't have the answer to that question.    I'll try to  
22   find out, but I don't have the answer.    But I do want

1 to just point out -- I mean, what you've raised is  
2 exactly I think the importance of talking to patients.  
3 Because your asking that question might prompt someone  
4 designing a registry to say let's collect that  
5 information, let's make sure that that's something  
6 that we're going to pre-specify and assure that we are  
7 collecting information on second hand smoke, or other  
8 risk factors, or other environmental factors.

9 So your experience of the disease, what  
10 you see is impacting you is incredibly important in  
11 helping us inform how that information should be  
12 collected so we can answer the question that you are  
13 raising.

14 **WOMAN:** Yes. Thank you.

15 DR. ERIKA TORJUSEN: And I don't know  
16 if any of you have a quick point to add to that.

17 So I think at this point I just want to  
18 say thank you to our panel members for the insightful  
19 discussion, as well as our audience for their  
20 participation, as well as online. It's greatly  
21 appreciated. And also our panel members have kindly  
22 offered to stick around in the conference room for you

1 to be able to ask questions during the break, which  
2 immediately follows this panel. So if any of you  
3 didn't get to ask the panel a question, they will be  
4 available for the next few minutes during the break.  
5 Thank you all very much. Thank you.

6 (Break)

7 DR. TERESA MULLIN: Please take a seat,  
8 and we're going to get going with the second panel  
9 now. And, again, I wish you a very nice morning, and  
10 thank you and welcome to everyone in the room and on  
11 the webcast.

12 This is panel two on Natural History  
13 and Registry Data in Rare Diseases. So I think we're  
14 going to get into a little bit more perhaps technical  
15 depth. The first panel did a very nice job laying out  
16 the issues for us. And we're going to discuss them  
17 even more, because there's a lot to discuss.

18 I'm Theresa Mullin. I'm the Associate  
19 Director for Strategic Initiatives in the Center for  
20 Drugs and at FDA.

21 So I'm going to -- with me we have a  
22 fantastic panel today, so we're going to get a lot of

1 depth, rich depth and insight from these folks.

2 So first we have Katie Donohue. She is  
3 the Clinical Team Leader in the Division of  
4 Gastroenterology and Inborn Error Products in the  
5 Office of New Drugs and FDA Center for Drugs.

6 Jen Farmer, the Chief Executive Officer  
7 of Friedreich's Ataxia Research Alliance. Petra  
8 Kaufmann, Vice President of R&D and Translational  
9 Medicine at AveXis, It's a Novartis company. Anne  
10 Pariser, the Director of the Office of Rare Disease  
11 Research in the National Center for Advancing  
12 Translational Science at NIH. And Klaus Romero,  
13 Executive Director of Clinical Pharmacology and  
14 Quantitative Medicine at the Critical Path Institute.

15 Welcome to you all. I'd like to ask  
16 you now to please give a little bit more of a  
17 description of your background, each of you. And  
18 starting with Katie, what are some of your key  
19 takeaway messages to just sort of set the stage here  
20 regarding the value and sustainability and other  
21 aspects of registry data and natural history studies  
22 that you'd like to talk about in this panel?

1 DR. KATHLEEN DONOHUE: Sure. Good  
2 morning and welcome. I'm excited to be with you  
3 today. I work on developing treatments for patients  
4 with rare diseases, inborn errors of metabolism. And  
5 so this is sort of the front lines. And I'm really  
6 appreciative for the questions we've had from patients  
7 so far. I think they kind of ask the \$64,000  
8 questions. You know, what data do we need to collect,  
9 when should we start. And you're hearing the right  
10 answers. Start now.

11 And I think the key pieces of  
12 information that we need are -- do you want comments  
13 or just intros?

14 DR. THERESA MULLIN: I think you can  
15 start with your overarching messages or things that  
16 you want to come back and talk more about.

17 DR. KATHLEEN DONOHUE: Okay. So I  
18 think the first step is we believe so strongly in the  
19 importance of natural history data that the FDA has  
20 launched a Cures Accelerator Initiative that Theresa  
21 Mullin is actually leading and Klaus Romero is also  
22 working on. And it's a common platform. Right? So

1 we don't think that patients and their caregivers  
2 should have to be data scientists in order to help  
3 move the field forward. And so that platform is there  
4 to serve as a common infrastructure. And so we don't  
5 need to be an expert in how to manage the database,  
6 we've got some help. So I really just want to put  
7 that plug out there. And then in terms of what data  
8 we need to collect, we can circle back to that later.

9 DR. THERESA MULLIN: Okay, very good.  
10 Thank you.

11 JEN FARMER: Hi, I'm Jen Farmer I'm  
12 the CEO of the Friedreich's Ataxia Research Alliance.  
13 And my experience with FARA has largely been in the  
14 development of both our patient registry and our  
15 natural history study.

16 And so in 2005, I was initially hired  
17 to start a patient registry. And that was a patient-  
18 entered registry. So anybody was entering their own  
19 information from their home onto a web portal. And  
20 that registry was so valuable for us in really  
21 identifying where patients are, establishing better  
22 prevalence of the disease. And we were able to use

1 that registry for the next 15 years to help enroll  
2 research studies and clinical trials.

3 At the same time, several of our  
4 clinician researchers also started studies and  
5 clinical outcome measures. And FARA worked closely  
6 with those clinicians to parlay that into a natural  
7 history study. And so we've had a prospective natural  
8 history study with clinician-entered data going for  
9 almost 18 years now. Yeah.

10 And so, you know, as much as I can  
11 share with everyone what our experience has been with  
12 both a patient registry -- from my perspective that's  
13 patient-entered information -- as well as natural  
14 history prospective studies and sort of the role of  
15 the advocacy group in facilitating that, I'd like to  
16 be able to share those experiences with everyone  
17 today. And thank you for having me.

18 DR. THERESA MULLIN: Thank you.

19 DR. PETRA KAUFMANN: Good morning. My  
20 name is Petra Kaufmann. I am a neurologist. And for  
21 most of my career, I've been taking care of patients  
22 with rare neuromuscular diseases. So having taken

1 care of patients with rare neuromuscular diseases for  
2 most of my career, I decided a couple of years ago to  
3 leave the NIH where I actually was directing the  
4 Office of Rare Disease Research, which now Anne is  
5 heading so capably. But I decided to move to industry  
6 and work on gene therapy because I saw these  
7 transformative effects and thought finally as a  
8 neurologist I can do more than make a diagnosis and  
9 help my patients. So I'm excited to be here.

10 And I'd like to in particular share an  
11 experience that I had from going back to my time at  
12 Columbia University where I had the opportunity to  
13 work with colleagues from the Boston and Philadelphia  
14 Children's Hospital on a natural study.

15 At the time, there was really no  
16 effective treatment for patients. So we would see the  
17 patients with spinal muscular atrophy, and when we  
18 first saw them, they would be at their strongest and  
19 then just, you know, get worse. And asking the  
20 families at the time to participate in a natural  
21 history study was asking a lot. Because, you know, we  
22 were saying this is to develop better treatments, but

1 it wasn't so clear really when it would happen.  
2 Right? And they were the heroes, because they did  
3 this and came repeatedly with sick children to the  
4 centers. But it was then so gratifying to see how the  
5 data set, and then another one that we launched when I  
6 was at the NIH with NeuroNex, another second  
7 independent data set that actually helped to get the  
8 gene therapy to patients.

9           And looking back, I would like to share  
10 with you what are some of the things that I think were  
11 important and made this happen that also in now in my  
12 new capacity where I try to work with other  
13 communities on natural history data sets and studies,  
14 what are some of the things that could have been even  
15 better, to make this even more fit for purpose.

16           And I think, you know, the challenges  
17 are often funding. So in some of the diseases I have  
18 been working on, you know, natural history studies  
19 don't get easily funded by the NIH. Sorry to look at  
20 you, but -- and I get the challenge. When I was at  
21 the NIH, there was like thousands of rare diseases.  
22 And how do you pick one without getting, you know,

1 into this difficulty of justifying that choice over  
2 another. So I think that emphasizes the point of,  
3 (A), we have to look at this as a platform and make it  
4 efficient so that we can get to all the many, many  
5 diseases and the many, many patients and leave no one  
6 behind. And the second point there is that, you know,  
7 were lucky we got funded by the SMA Foundation. That  
8 made it possible.

9 And then the second point is to really  
10 make sure that the data are fit for purpose. So, for  
11 example, a study where patients come every two years  
12 and miss half of the visits.

13 Well, for practical purposes for drug  
14 development and for trial planning, that's not really  
15 going to give you what you need. So better to invest  
16 and focus on more frequent visit, on avoiding missing  
17 data and making it easy for patients to come  
18 (inaudible), you know, once (inaudible) where we  
19 actually, you know, got funding for patients to -- we  
20 helped them travel or we went to them even. So you  
21 have to think outside of the box to get high-quality,  
22 complete data. Frequent visits, especially in the

1 beginning, and as fit for purpose as possible. That  
2 can be done by talking early to people who have  
3 experience in drug development or, when available,  
4 even having regulatory -- like having interactions  
5 with regulators. I think that's some of the things  
6 that make the data sets useful, but also that, you  
7 know, could have been even improved upon. And I look  
8 forward to hearing more from the other panelists and  
9 share more detail. Thank you.

10 DR. ANNE PARISER: Good morning. I'm  
11 Anne Pariser. I'm with the Office of Rare Diseases  
12 Research at NCATS, NIH. So thank you for inviting me.

13 I've been with NIH for the past three  
14 years. But prior to that, I spent more than 15 years  
15 here at the FDA. First, actually, with the Inborn  
16 Errors Metabolism Team, and then started the Rare  
17 Diseases Program, started in 2010.

18 So I've been on the receiving end of  
19 natural history studies, been promoting natural  
20 studies, and now we are trying very hard to help  
21 people develop natural history studies.

22 So we do this through some of our

1 research networks that we have at NIH, but also I  
2 heard questions to this effect; where can patients go  
3 for some information on how to do this. So I'm just  
4 going to throw a shameless plug here for a program  
5 that we have. It's called RaDaR, which stands for  
6 Rare Diseases Registry. I've left some flyers at the  
7 desk here. But if you don't get a flyer, just Google  
8 NIH Rare Disease Registries, and you will find it. So  
9 I just have to throw that out.

10 DR. KLAUS ROMERO: Thank you. Klaus  
11 Romero, the lead for the Clin. Pharm and Quantitative  
12 Medicine program at the Critical Path Institute.

13 We are the ones leading, together with  
14 NORD, the Rare Disease Cures Accelerator. That was  
15 the effort mentioned by Dr. Stein in the previous  
16 panel. And essentially what that platform is intended  
17 to do is provide a home for the standardization and  
18 the integration of patient-level data across rare  
19 diseases. And this stems from the experience that  
20 we've gathered at the Critical Path Institute with the  
21 support of the FDA and being able to integrate data  
22 from registries, observational studies, and clinical

1 trials from industry.

2           And I want to make sure that this sinks  
3 in. Because there's always this perception that  
4 industry protects their data. I understand that, and  
5 I don't dispute that fact. But being able to  
6 integrate patient-level data from industry trials, not  
7 only the control arms but also the active arms, from  
8 the contributions that we've gotten from our industry  
9 members across our different consortia. We've been  
10 doing that for the past 15 years.

11           And we have a few examples in rare  
12 diseases where, for example, we have the largest  
13 integrated patient-level database from clinical trials  
14 in Duchenne muscular dystrophy. And in fact next  
15 Thursday we're going to have a meeting with the agency  
16 who are writing one of our submissions for the  
17 quantitative drug development tool intended to  
18 optimize clinical trials for that condition.

19           We want to be able to replicate that  
20 across rare diseases, and we want to provide a  
21 platform for those data to be integrated. So the data  
22 from the NIH, the data from industry, the data from

1 registries that the patients entered, but also the  
2 registries that are formally set up at the centers  
3 that actually see those patients in clinical care.  
4 That's the vision.

5           And so we are in the process of  
6 integrating, like I said, the data we already have  
7 from our consortia that deal with rare diseases,  
8 Duchenne muscular dystrophy, polycystic kidney disease  
9 where we have three of the largest registries already  
10 integrated, Huntington's disease, and then  
11 Friedreich's Ataxia, where we have a large integrated  
12 database of different data sources. So that's the  
13 vision. That's the intention.

14           And of course a lot of things were said  
15 in the previous panel and in the comments right now  
16 that really set up the value proposition for what we  
17 intend to do. Because it's not just -- you're  
18 absolutely right, having frequency of observation at a  
19 frequency that actually makes sense for clinical  
20 trials is important. But also having the long-term  
21 follow-up to understand the linkage between those  
22 frequently-measured things that matter in a clinical

1 trial versus what happens later in the lives of those  
2 patients. And not a single source can provide all  
3 those pieces of information. And that's why you need  
4 to be able to integrate all those components together.  
5 So that's me, that's the group I represent. And I'll  
6 stop at that.

7 DR. THERESA MULLIN: All right. So my  
8 next question is sometimes people talking about  
9 registries use that term almost interchangeably with  
10 natural history studies. So I'd like to ask this  
11 panel, since you've obviously deeply experienced, you  
12 know, how do you think and define those? Are they  
13 almost synonymous, or are they really rather distinct?  
14 And so how might you define them if they are a bit  
15 distinct, and what roles do you think each of those  
16 could or should play in supporting drug development?

17 DR. KATHLEEN DONOHUE: I tend to think  
18 of natural history as sort of a spectrum. And so  
19 sometimes it's our clinical understanding of a disease  
20 based on seeing patients and patients' direct  
21 experience of the disease. It can be sort of  
22 qualitative. Whereas a registry implies to me a

1 certain level of scientific rigor. You know, you're  
2 planning to collect certain kinds of information at  
3 certain timepoints. And so the level of scientific  
4 rigor with which the data is collected has a lot to do  
5 with how far it can take us.

6 JEN FARMER: And I think some of the  
7 comments from the first panel are also important to  
8 discuss, which is natural history studies specifically  
9 can be retrospective or prospective. And so I think  
10 it's important to think about what type of natural  
11 history study it is, what the scope of the study is  
12 going to be.

13 When we started our natural history  
14 study, it was focused primarily on the neurological  
15 aspects of the disease over time realize you know, the  
16 cardiac aspects of this disease and the endocrine  
17 aspects of this disease are also important. And so we  
18 were able -- that natural history prospective study,  
19 we were able to add additional outcome measures and  
20 expand the focus of the natural history to be beyond  
21 one system into multiple systems.

22 And so sort of going to your point

1 about fit for purpose, one nice thing about some of  
2 these studies is you can start with one purpose in  
3 mind, and then grow and expand from there. Which is I  
4 think why sometimes the terminology gets confused.  
5 Right?

6 DR. PETRA KAUFMANN: I agree. I think  
7 that some of the nomenclature is really historical.  
8 We have to think about step back and say what do we  
9 really want. You know, we all want to make sure that  
10 these innovations that are now upon us, and we are  
11 opening almost like a new era of medicine with really  
12 targeted treatments, that these innovations can  
13 benefit as many patients as possible as quickly as  
14 possible.

15 So if it takes us like ten years for  
16 each rare disease to do a natural history study and  
17 enormous resources, then we will not get to everybody.  
18 So I think registries, whatever you call it, or  
19 natural history studies, the words come from the  
20 different groups that maybe started them. Sometimes  
21 registries are started patient groups, and they are a  
22 very grassroots, maybe low-resource endeavor. Natural

1 history studies sometimes are started by academic  
2 investigators who play another role in the ecosystem  
3 or they are started by industry. What matters is that  
4 the data are shared and that they are all collected  
5 with the same purpose in mind and that they think  
6 about that purpose. So I don't really know that that  
7 distinction in the long run will hold. I think the  
8 goals are important, and they are shared. And like  
9 you said, there is different levels perhaps at the  
10 beginning versus when you get closer to developing the  
11 treatment. But it should all be as integrated as  
12 possible, and patients should demand that the data are  
13 being used for direct development or treatment  
14 development.

15 DR. ANNE PARISER: So how we have been  
16 defining these is -- registry is a very broad term.  
17 It's really any organized collection of data, usually  
18 observational data. So there can be many different  
19 types of registries.

20 A natural history study, the intention  
21 of the natural history study is to really define the  
22 disease, define the entire scope and spectrum of the

1 disease.

2           So I think someone was mention this in  
3 the last session, but a registry could be for example  
4 a communication registry. This could be the first  
5 effort to try to organize the community, and you could  
6 be collecting some very simple data, people's emails  
7 and maybe how old they are and do they want to be  
8 contacted or not if there's research. And you can go  
9 to the total opposite end of the spectrum and be  
10 collecting very detailed clinical data that could have  
11 MRIs and biopsies and genetics. And then there's  
12 everything in between. And as mentioned, this can  
13 evolve over time. You may start one place and then  
14 start to go in a different direction or broaden out  
15 from where you were.

16           And I just want to emphasize these are  
17 all useful, and it can really depend on where you are  
18 in your research program. And the first step in a  
19 research program is often a very simple communication  
20 registry that someone can operate off their home  
21 computer off a spreadsheet for really no cost at all.  
22 And many times we've seen that serve to really unite

1 the community and really get a program together.

2 So all efforts are good. It's about  
3 being very organized in the way that you do it,  
4 defining your terminology, be transparent, and share.

5 DR. KLAUS ROMERO: Yeah. I think Anne  
6 hit the nail on the head. In the world that I  
7 operate, I don't like to have terminology get in the  
8 way of progress. So because the intention of the work  
9 that we do is so we integrate all data sources that  
10 are relevant, it really doesn't matter really to me if  
11 you call it, oh, this is a patient-entered registry  
12 versus a formalized registry in a center of excellence  
13 versus an observational study and clinical trials from  
14 industry. Sure, I understand the distinction between  
15 those if you want to categorize them for funding and  
16 for publications, all those things. And of course the  
17 clinical trials from industry that are intended for  
18 driving regulatory discussions.

19 But in the world that we operate, we  
20 want to integrate all those pieces of information.  
21 Because it's all those pieces of information that give  
22 you the different angles from which to approach

1 starting to generating the answers as to, okay, what  
2 are the sources of variability, what are the measures  
3 that actually matter to the patients and objectively  
4 to drive drug development decisions and capture drug  
5 effects, determine baseline severity so that we can  
6 set up the inter criteria for a clinical trial, which  
7 again, relates to the source of variability of disease  
8 progression and drug effects. The placebo effect,  
9 especially in certain neurological conditions, that is  
10 absolutely critical. You need to understand the onset  
11 and magnitude, duration, variability. And that's  
12 going to become critical when you want to optimize  
13 clinical trial design.

14 So I just want to echo some something  
15 that was mentioned in the previous panel. Sure, using  
16 and optimizing control arms using quantitation and  
17 looking at disease progression is awesome, but that's  
18 not just the only thing that comes out of integrating  
19 and quantifying the diseases themselves, the many  
20 diseases themselves, because that's what gives you  
21 understanding of all the aspects that really matter  
22 when you want to design a clinical trial. Because

1 what's the name of the game here? If we want to  
2 accelerate drug development for rare disease, we need  
3 to provide industry with the tools so that they can  
4 design optimal trials. Because if the value  
5 proposition for industry is going to be I have too  
6 much uncertainty, that gets up the chain of command in  
7 their dealing with other therapeutic areas where they  
8 may say, well, mine certainly is not that great.

9 So the name of the game is really  
10 understanding and quantifying uncertainty so that you  
11 can deal with that uncertainty and you can provide a  
12 value proposition with optimized clinical trial.

13 DR. THERESA MULLIN: Thank you, Klaus.  
14 So I've been hearing some people talk about having  
15 your registry data be fit for purpose. Okay? So I'd  
16 like you now to talk about best practices that you've  
17 seen and what you've encountered in registries that  
18 you've had to deal with or look at, or maybe have  
19 developed.

20 And then also for those of you who've  
21 looked across areas, just what are weaknesses that  
22 you've seen that have made a registry less than what

1 you'd ideally like to see for fit for purpose?

2 DR. KATHLEEN DONOHUE: So I think I  
3 want to start with the question that one of our  
4 patients asked, which is how can I make sure that my  
5 data is going to be used by the people who need it.  
6 And the answer to that is something called a data use  
7 agreement. Klaus Romero's group is really good at  
8 this. They have a lot of experience with negotiating  
9 these. And getting this right from the beginning can  
10 save you a ton of time on the back end. So wherever  
11 you are in developing a registry, taking some time out  
12 to think about what am I going to ask patients to sign  
13 in terms of how we're going to store their data, who  
14 we're going to share it with, and how that's going to  
15 work. So getting that right really helps. It's sort  
16 of like the cornerstone of your registry. So that's  
17 the first step.

18 And then the second step in terms of  
19 what data to collect. I can touch on some broad  
20 categories, but this is where having an epidemiologist  
21 who is an expert in how to do these kinds of  
22 observational studies can really help to future-proof

1 your registry. So, you know, you may be starting out  
2 with just patient contact info, but if your vision is  
3 to grow it eventually into something that could help  
4 inform the design of clinical trials or even serve as  
5 an external control, well, you're going to need to  
6 anticipate some of those needs.

7           And so it's things like how are  
8 patients coming to attention. Right? That's changing  
9 over time. So it used to be you had to present with,  
10 you know, the canonical symptoms of a disease in order  
11 to get a diagnosis. The diagnosis may have been  
12 clinical for a lot of patients. But now we have  
13 patients who get diagnosed because of genetic testing  
14 once an older sibling is diagnosed. And so the  
15 natural history of those two patients is going to be  
16 so different. We have to be able to understand that.

17           So how are patients coming to medical  
18 attention? What were the results of those genetic  
19 tests? Do we have other biomarker tests that are  
20 getting done, and can we capture the results of that?  
21 Units. It's so boring. But if units are different,  
22 this creates such a headache. Like, thinking about

1 that really matters. And epidemiologists can help us  
2 do that.

3 And then I think the next area where  
4 there's a lot of opportunity for academic clinicians  
5 who care about patients to sort of move this forward  
6 is writing guidelines.

7 So if there's a guideline that says we  
8 need functional testing every year, whether it's lung  
9 function or a six-minute walk test, whatever that  
10 functional testing is. But we need some sort of  
11 disease monitoring at regular intervals that's  
12 standardized and can be done all around the world in  
13 the same way. And we're going to use the results of  
14 that testing in order to drive some of the supportive  
15 care, whether that's swallowing tests to inform when  
16 we're going to put in feeding tubes, or walking tests  
17 that might be able to inform when we're going to need  
18 to add in assistive devices like walkers or  
19 wheelchairs or things like that. So all patients are  
20 getting care of some kind. And standardizing the  
21 predictors for when patients are going to need that  
22 and how they're going to get that is really helpful

1 because that standardization is powerful  
2 scientifically. And then it creates a shared  
3 infrastructure around the country and across the world  
4 for how often those things are getting monitored.

5 So it's one of the reasons why the  
6 oncologist basis had so much luck with -- and it's not  
7 luck, it's really hard work -- with natural history  
8 controls, is that they've got guidelines saying you've  
9 got to image these patients at pre-specified intervals  
10 to look for progression, and that's happening in the  
11 same way all across the country and globally. And  
12 that's really powerful information.

13 And then lastly, tying that functional  
14 testing, whether it's imaging or walk tests or lung  
15 function, tying that to the clinical outcomes that  
16 really matter to patients. Right? You know, I've  
17 never had a patient come and talk to me and complain,  
18 doc, my FEV1 is low, but they tell me I can't walk up  
19 the stairs. Right? So tying it to how a patient  
20 feels is another really powerful thing that registries  
21 can do. And then we don't have to run the clinical  
22 trial all the way to a clinical endpoint, which is

1 hard in rare diseases, we can use that functional  
2 data. Because we already know from the registry that  
3 it predicts the clinical outcomes that really matter  
4 for patients.

5 JEN FARMER: Well, just to underscore  
6 your point of getting proper consent and data sharing  
7 up front, when we started our clinical outcome measure  
8 study in 2004, our consent was not broad enough for  
9 the data sharing that we eventually needed. And by  
10 the time we realized that, we were more than 500  
11 patients in and needed to go back and re-consent  
12 everyone. Fortunately, people were coming back  
13 annually for visits, and so we were able to eventually  
14 accomplish that. But yeah, lived that one.

15 So, you know, we set out on our  
16 clinical outcome measures study so that we could help  
17 support clinical trials down the road. And we were  
18 fortunate to get some good advice as well, which was  
19 that the data needed to be collected in a rigorous  
20 way, that we needed standard operating procedures,  
21 case report forms. We needed a robust database that  
22 would handle queries to make sure that the data was

1 being captured correctly and in a very standardized  
2 way. So I'm fortunate for that, because we made that  
3 transition to an electronic data capture system with  
4 data oversight only two or three years into that  
5 clinical outcome measures study. So that was -- you  
6 know, I did not appreciate all of those things when we  
7 got started, but I'm very grateful for them because we  
8 were able to then use those standard operating  
9 procedures and case report forms in future clinical  
10 trials.

11 And we only have around eight centers  
12 in the United States that are collecting this data,  
13 but those sites are now kind of clinical trial-ready  
14 sites for FA clinical trials. And that was also one  
15 of our goals and objectives.

16 But one of the challenges with only  
17 eight sites is the burden is on the patient to  
18 participate and be in the study and contribute data.  
19 And so we couldn't collect data as often as you might  
20 like in a clinical trial. We couldn't ask people to  
21 come back, you know, once a month or every few weeks.  
22 And so we settled with annual visits and being very

1 systematic and collecting the same data every single  
2 year. And that really has helped over time figure out  
3 which of those measures are going to be the most  
4 sensitive to change in a particular subgroup of our  
5 population. And we're now at a point where all of  
6 that has come together to help us with clinical trial  
7 design.

8           But what we don't have is really what  
9 that placebo response looks like. And we learned that  
10 the hard way as well in doing some of our initial  
11 clinical trials. Those first few trials we did, we  
12 observed the placebo response. Could have not  
13 anticipated it from our natural history data or our  
14 clinical outcome measure data. And, you know,  
15 realized that, okay, this is the next gap we really  
16 need to address if we're going to use this to help us  
17 design better clinical trials.

18           And we've been able to take our outcome  
19 measure study and natural history study and combine  
20 that with the placebo data from four clinical trials  
21 that have been completed. And that's the basis for  
22 this FA-integrated collaborative database that's now

1 at C-Path to help us understand that placebo response  
2 and hope they design better trials in the future with  
3 that data in hand.

4           And so I guess the point I'm making is  
5 you have to be flexible over time. you have to  
6 realize that, you know, you're going to make some  
7 progress in certain areas, and then you're going to  
8 learn there are some gaps that you still need to  
9 address. And being able to kind of maneuver is  
10 important.

11           And I was humbled early on. Sharon  
12 Hesterlee, a colleague, told me about ten years ago --  
13 I was so excited. You know, we had our clinical  
14 outcome measures study that was now becoming a natural  
15 history study. We were using good data collection  
16 process. We had all this in hand. And I'm like, this  
17 is great. We're done. And she was like, no, no.  
18 Sorry. You're not going to be done with this. You're  
19 never done with this. And I was really deflated. But  
20 I understand a lot of what she was saying, and I'm  
21 really glad she told me that then so that we started  
22 thinking about this, about how we're going to continue

1 to meet the needs.

2 And, you know, now I'm thinking about  
3 when there are approved therapies, how this registry  
4 helps us understand the evolution of the natural  
5 history in light of therapies in the disease.

6 So it really is a process. And I think  
7 understanding that and knowing you're not going to  
8 tackle everything at once is really important. But  
9 trying to set something up that is flexible and  
10 adaptive over time is critical.

11 DR. PETRA KAUFMANN: Lots of great  
12 points made already. So I would just add maybe one  
13 thing. So we are fortunate because of all the work of  
14 FARA and being able to access the data through the  
15 Critical Path Institute to build on that strength,  
16 which makes a big difference when you try to bring  
17 gene therapy to a real disease. So now there is, you  
18 know, thousands of rare diseases, millions of patients  
19 waiting for these kinds of treatments. So how can we  
20 make sure that -- I think that would be an important  
21 aspect, that not every endeavor is reinventing the  
22 wheel, but that we can have almost like a platform

1 approach, that we can use lessons learned from  
2 diseases where there is already more drug development.  
3 And also think about perhaps outcome measures. Maybe  
4 some functional measures don't need to be redesigned  
5 for each subtitle of a disease or some patient-  
6 reported outcomes or quality of life measures could be  
7 used or borrowed sort of from other indications.  
8 Because I think if you're having sharing and having  
9 some platform approach to this will help us all get  
10 there faster.

11           And I think I did a great job teeing  
12 this up for you, Anne.

13           DR. ANNE PARISER: I mean, there's been  
14 a lot of great points made, so I'll just maybe hit on  
15 two.

16           At the end of the day, we really need  
17 to end up with something that's interpretable. So any  
18 reasonable, regular investigator or patient group  
19 could take this data and really know what it is that  
20 you're talking about. And so you need to spend a lot  
21 of time on the really tedious, boring parts of really  
22 defining that data and make sure the metadata is very

1 understandable and is transparent. There's nothing  
2 worse than seeing a year's-long collection and at the  
3 end of the day not being really able to figure out  
4 what they meant.

5 I'll give you one example we had for a  
6 GI disease many years ago. We were using the medical  
7 term dysphasia. And to some people that meant pain  
8 with swallowing, to some people that meant I couldn't  
9 swallow, some people meant choking, some people meant  
10 food impact. And so we had all this dysphasia, and  
11 nobody really know what that meant. And that's really  
12 terrible to be looking at at the end of the day and  
13 not being able to really understand what was intended.

14 And then the second one, it's really  
15 important to get all the critical stakeholders there  
16 from the beginning, and especially the patient groups,  
17 but the investigators as well. It's important to  
18 investigators. Is it necessary or is it important to  
19 patient? But you want the spectrum represented there.

20 And for the patients especially we  
21 think -- I heard this from Jen. Again, these go on  
22 for years. And to really burden the patients with

1 some of these just really can burn out your community.  
2 So just make sure that when the protocol is together,  
3 you spend a lot of time deciding what exactly you want  
4 to collect. You can't collect everything. So some  
5 tough decisions have to be made. But we want people  
6 to be able to stick with this over time so that we can  
7 really understand the disease.

8 DR. KLAUS ROMERO: Yeah. I agree with  
9 everything that has been said. The one thing that I  
10 would add to sum up what is truly needed if you want  
11 to succeed in setting up a registry or an  
12 observational study is to essentially think about the  
13 following things. The consent, and set up the consent  
14 in a way that doesn't inhibit and stifle innovation  
15 and that ensures that the data will have its maximum  
16 impact beyond the primary analysis that is intended.  
17 And that's something that is critically important to  
18 patients. They don't want to see their data die with  
19 the primary analysis. That's a message that we have  
20 heard loud and clear, not just in rare diseases.

21 Think about how to set up the structure  
22 of how you are going to collect and what you're going

1 to collect. And that's a question about standards of  
2 data. And this doesn't mean that all of the sudden  
3 we're going to start telling people what to do.

4 That's not the case. But what we're saying is that  
5 whatever you do, this is the kind of information that  
6 you need to collect so that it becomes ensured that  
7 whatever you collected becomes reproducible.

8           And there's a big lesson from industry  
9 to learn here, because as my colleagues from industry  
10 well know, as of December of 2017, CDER mandates that  
11 every single data point from all the studies that  
12 industry submits to the Agency have to come in this  
13 forum called CDISC, the Clinical Trial Data  
14 Interchange Standards Consortium standards. That set  
15 of standards were designed for that kind of purpose.

16           But if you think about those standards,  
17 that's like a coin with two sides. One side is the  
18 control terminology. And that's where the NIH is  
19 absolutely critical for that so that you call sex the  
20 same way. And that's like the simplistic sample of a  
21 very intuitive, binary variable. Well, my FDA  
22 colleagues know that when we started doing this in

1 Alzheimer's disease, we started with nine clinical  
2 trials from industry. Nine different ways, I kid you  
3 not, of collecting sex. As I told people, that's the  
4 best example of misuse of creative time, but that's  
5 the reality of things. And that gets even more  
6 complicated when we start dealing with biomarkers and  
7 with outcome measure scales and patient-reported  
8 outcome instruments and all that stuff. So that's  
9 critical, the control terminology side of that coin.

10 But then there's another side of that  
11 coin, and that's the data structure. And that's where  
12 people get really confused and they don't care, and  
13 it's boring, and nobody pays attention. That's  
14 equally important, because that's what sets up the  
15 data platform and organized in such a way that it  
16 becomes interpretable.

17 So even though CDISC is not a mandate  
18 of observational studies or for registries, just the  
19 control terminology piece, if people were to adopt  
20 that just from the bat, that would solve a lot of the  
21 headaches that we have to go through whenever we get  
22 our hands on data and we have to standardize every

1 single piece of data. So that's another important  
2 point.

3 And we're here to help. If you want to  
4 talk to us on how to annotate your case report forms  
5 and think about how to set up a structure of a  
6 database, we would be more than happy to have that  
7 conversation.

8 DR. THERESA MULLIN: Thank you. And  
9 could I just ask Anne, is this something that the  
10 information on radar, does it also speak to the data  
11 standards? So if people wanted to understand what  
12 they might want to do today, could they get some  
13 information about that at the website that you've  
14 mentioned?

15 DR. ANNE PARISER: Yes. We do have  
16 that on the RaDaR website. So RaDaR is actually --  
17 it's set up -- and book isn't the right term, but it's  
18 set up deliberately in a very walk-you-through-this  
19 manner. How to get started, we have downloadable  
20 checklists, we have spreadsheets, we have referrals to  
21 things like fair data practices and some more of these  
22 data management terms.

1           So I would really urge you to go take a  
2 look. We built this with the patient community in  
3 mind. We wanted people to come to this new, not being  
4 database managers or architects, and be able to set  
5 this up on their own. And you can also come ask us  
6 for help. We would be glad to.

7           DR. THERESA MULLIN: Thank you. One  
8 more kind of question I would like to just ask our  
9 panel, and then I want to turn it to the audience and  
10 the people on the webcast.

11           In earlier discussions we talked about  
12 sustainability as an issue. So if you have any more  
13 to say about either sustainability and/or the  
14 international aspect, because rare diseases are ones  
15 where in particular you want to try to take a global  
16 approach, if you can, to try to capture more of the  
17 community with that disease. So if you have anything  
18 you want to add about those or another point to make  
19 before we turn to questions, that would be great.

20           DR. KATHLEEN DONOHUE: I want to hear  
21 your questions.

22           JEN FARMER: So sustainability is a

1 very big issue, and it's something that our  
2 organization made a commitment to early on in making  
3 sure that, you know, at least a certain portion of our  
4 resources were being put towards the sustainability of  
5 these resources as they were being built. But it does  
6 limit what we can do as well, because our resources  
7 are not unlimited, and usually in the rare disease  
8 space, our advocacy organizations have very limited  
9 resources. And so that does dictate what you're  
10 really able to do. And especially on an international  
11 level the resources that are required to have a  
12 registry that is compatible with every language that  
13 you're going to need is very difficult. That's a  
14 really high bar. And also having clinician-entered  
15 data as well that's going to be collected  
16 internationally is challenging just in terms of all of  
17 the different rules around privacy and data handling  
18 across different countries becomes really challenging.

19 And so, you know, again, similar to the  
20 advice that came out earlier, based on what you can  
21 invest in, you know, scope it for where you are. But  
22 I think it's important to remember that this is a

1 long-term investment for organizations, especially if  
2 it's an advocacy organization that's taking on the  
3 development of these tools and resources. It's not a  
4 one-year project, it's not a two-year project; it's a  
5 long-term project. And plan for it that way. And  
6 that's I think a very important point.

7 DR. THERESA MULLIN: Okay. Thank you,  
8 Jen.

9 DR. PETRA KAUFMANN: So these kinds of  
10 data sets are really for the benefit of patients. And  
11 the patients are in there for the long term, and  
12 therefore I think they are probably the best and most  
13 sustainable sort of guardians of these, with the  
14 support of other partners who need them. And having  
15 the patient groups guardians in my experience is also  
16 easier in terms of international collaboration,  
17 because there are different privacy laws and  
18 regulations in different regions of course, as we all  
19 know. And different institutions who may become  
20 guardians of data for reasons that -- you know, if it  
21 was started by an investigator there -- have greater  
22 difficulty kind of getting through these regulations

1 and rules. And therefore I think when patient groups  
2 are involved, that's an advantage. And also the data  
3 don't necessarily have to move across jurisdictions,  
4 but there can be, you know, sharing of data sets  
5 potentially that could make that easier.

6 DR. ANNE PARISER: Very, very quickly.  
7 Try not to go it alone. There are many groups out  
8 there now and the rare disease umbrella groups who  
9 have set up platforms, a platform being a durable  
10 infrastructure that can support multiple studies. So  
11 there are several out there, and I would just urge you  
12 to look around and reach out.

13 DR. KLAUS ROMERO: And just to  
14 understand the cultural aspects. Because we know that  
15 there are clusters of rare diseases in different  
16 geographical locations. And understanding the  
17 cultural aspects when you want to get in and run an  
18 observational study and start a registry, that is  
19 critical.

20 DR. THERESA MULLIN: Thank you very  
21 much. I see we have a number of people. And I wasn't  
22 looking, so I don't know who was up first. So I will

1 start with -- just if you don't mind, and go one by  
2 one. Yes?

3 MARIA PICONE: Hi. Thank you. Maria  
4 Picone. I'm the CEO of TREND Community, and I also  
5 have a daughter who has Prader-Willi syndrome.

6 And I just wanted to expand upon Dr.  
7 Pariser's point about the importance of educating the  
8 community as our understanding of our diseases evolve.  
9 My daughter last year was also diagnosed with  
10 narcolepsy. And I know that questions have been added  
11 to the registry about narcolepsy and also cataplexy.  
12 But I wonder, you know, do the people who are  
13 completing the surveys understand what is cataplexy?

14 And I know, Jen, when we worked  
15 together and pain emerged as a very sort of maybe not  
16 underrecognized symptom, but something that people  
17 weren't associating with, you know, as related to the  
18 FA. You know, how do we educate our community members  
19 so that not only are we collecting the right data, but  
20 that people know how to answer those questions early  
21 on.

22 DR. THERESA MULLIN: Who would like to

1 take that question? This goes a little bit to I guess  
2 the sort of point that Anne Pariser was making about  
3 the terminology that might make sense to a clinician  
4 after years of training.

5 JEN FARMER: Yeah. So, I mean, one is  
6 to have a data manual, publish it, and put it up on  
7 the web and just be extremely transparent. But we've  
8 also seen people put video clips and things on their  
9 website. I think most of information sharing now is  
10 via the internet. And there are many tools that are  
11 very accessible to patients.

12 DR. KLAUS ROMERO: And understand from  
13 the industry perspective what appetite there is and  
14 what interest there is in tackling that specific  
15 aspect of the disease. Because that's going to help  
16 you understand what information you want to prioritize  
17 collecting over others. So the bottom line message is  
18 not approaching that as a truly intellectual exercise,  
19 but have a clear end in mind with practical  
20 applications. And that's where connecting with  
21 industry -- and patient groups have that unique  
22 ability to have that bridge with industry.

1 DR. THERESA MULLIN: Thank you. Yes?

2 MEGAN O'BOYLE: Thank you. My name is  
3 Megan O'Boyle. I ma the PI for the Phelan-McDermid  
4 International Registry. But first and foremost, I'm  
5 Shannon's mother. And Shannon has Phelan-McDermid  
6 syndrome.

7 I did what most groups do when you  
8 start a registry; I started from scratch, I asked  
9 questions. We asked stakeholders for help,  
10 researchers. Even Dr. Pariser was at FDA when we  
11 started our registry. And we tried to do everything  
12 right, and we did a lot of things wrong. I have whole  
13 presentations on what we did wrong. And I'm watching  
14 other brand-new genetically-found diseases do the same  
15 thing over and over again.

16 So I just want to put in a plug for  
17 RaDaR and also NCATS has the toolkit for drug  
18 development, which takes you from the registries to  
19 post-market. Had we had RaDaR, I would not have a  
20 presentation on all the mistakes we made. The  
21 overburdening, the too many questions. We had the  
22 knowledge to have IRB and things like that that other

1 groups did not.

2 I just want to make a plea. You all  
3 don't have to answer this. But for anybody who has  
4 not started a registry, there are platforms that  
5 exist. And some charge you money. And you all use  
6 the word investment. I understand that. It's taken a  
7 huge investment, half a million dollars for our  
8 organization over the years, for very little return in  
9 many ways. And I really believe that rare diseases in  
10 particular should not have to spend all their research  
11 money on collecting data that is going to be used by  
12 other stakeholders.

13 And the other thing is there are also  
14 free options. And that means you're giving up your  
15 ownership or stewardship of the data.

16 I have a huge problem with rare  
17 diseases collecting data from the families they trust  
18 and having a platform sell it to biotech and make  
19 millions and millions of dollars off of selling my  
20 data. I don't mind if somebody makes millions of  
21 dollars, but one, be transparent with me, and two,  
22 share the rewards.

1           So I think everybody needs to step back  
2 and think about this sense of patient ownership.  
3 Again, the rare disease community more than anywhere,  
4 this is a sacrifice. Our families, to answer a  
5 survey, they're giving up a meal or a shower. You  
6 know, special time while their kid is in school. And  
7 I really think that there should be some respect to  
8 the patient community for that. Thank you.

9           DR. THERESA MULLIN: Thank you.

10           ERIC HARTMAN: Hi, I'm Eric Hartman.  
11 I'm the director of advocacy for the Choroideremia  
12 Research Foundation. And we are fortunate enough to  
13 have two gene therapy trials underway, and a third  
14 about to begin. One of the challenges that we have  
15 found in our disease is one in 50,000, supposedly  
16 6,000 in the United States, is we believe 70 percent  
17 of our patient population hasn't been genotyped to  
18 actually know they have that disease. So our  
19 challenge right now is our known patient population,  
20 we may only have 30 percent. But on a global basis,  
21 we are trying to find our patient population. We  
22 started our own patient registry, but it's just a

1 contact registry. And we are receiving huge pushback  
2 from -- you spoke earlier about the international  
3 invocations, the cultural problems, because we are  
4 based in the United States, of this huge prejudice  
5 that seems to be out there about our data being stored  
6 here and whether or not it's GDPR-compliant, which it  
7 is. But are there -- we're struggling. And we've got  
8 patients all over the world that we're trying to find  
9 because we have these potential treatments. One is  
10 already in Phase III and all the patients have been  
11 treated. So we're trying to locate those patients and  
12 we're trying to find some means of fighting against  
13 the perception of non-GDPR as opposed to needing to  
14 set up registries globally in a more regional basis.  
15 And I don't know if you guys have any suggestions on  
16 how to fight that.

17 DR. THERESA MULLIN: Anne?

18 DR. ANNE PARISER: Well, one suggestion  
19 is to try to find a local champion within country.  
20 You don't have to keep the data all in one place just  
21 so long as you're interoperable and you're able to  
22 share. That's one thing that you can try.

1 DR. KLAUS ROMERO: And be very clear  
2 about the fact that if you are indeed GDPR complaint,  
3 get that message out there. Don't be shy about  
4 tooting that more.

5 JEN FARMER: Yeah. We encountered very  
6 similar challenges when reaching out to the  
7 International community and trying to help them  
8 understand why being in the registry was important.  
9 There were just very different understandings around  
10 what the patient's role is in research even. And we  
11 have been spending more and more time building  
12 relationships locally with individual patients,  
13 patient families who can be spokespeople, who can  
14 speak the same language and really share the  
15 experience and what the goal and the objectives are of  
16 these registries, and that it's not just a U.S. thing  
17 or a FARA thing; that this really is an international  
18 effort.

19 We rebranded our registry. We changed  
20 the name so that it's not FARA at all. And we brought  
21 our international partners onto the governance and  
22 oversight of the registry as well. And so it's been a

1 lot of bridge building with the international  
2 community so that they feel confident in the registry  
3 and they also understand their level of ownership and  
4 involvement in that resource for the international  
5 community. But it's a challenge.

6 DR. THERESA MULLIN: I think we might  
7 have time for one more question. And I'm going to ask  
8 maybe if we take a webcast question. Because those in  
9 the room can follow up with the panel I think would be  
10 a way to go. Are there any questions on the webcast?

11 DR. AMY ABERNETHY: Yeah, sure. How  
12 does the Accelerator help the sustainability,  
13 international aspect, and data standards?

14 DR. KLAUS ROMERO: Works for me. Yes.  
15 Great question. So in terms of the data  
16 standardization, what we do every single time whenever  
17 we set up a data platform of any kind, and this one in  
18 particular, is we do an extensive remapping and  
19 standardization and curation of the data. That's for  
20 existing data that are contributed into the platform.

21 Now, the more important thing is that  
22 we want to establish this learn and confirm

1 (inaudible). So as we start integrating the data, we  
2 will find gaps with the standardization and quality of  
3 the data, the reliability of the information. We  
4 always communicate that back to the contributor in a  
5 positive way. We're not pointing fingers. It's just  
6 the reality of the beast. But that's a very powerful  
7 tool that the contributor can then use to then  
8 prioritize their funding to make sure that they  
9 collect information that is relevant in a probably  
10 different way, et cetera. So that's about  
11 standardization.

12 And the other part of the question was  
13 about sustainability. Well, we don't monetize the  
14 data. We don't -- we're not charging for data  
15 accessibility, we're not going to make millions out of  
16 sending the data. That's not the intention. The  
17 impact of what we do is that in generating the  
18 solutions for drug development, quantitative models  
19 that will help you optimize clinical trials aside, all  
20 those tools will also be publicly available once they  
21 get endorsed by the regulatory agencies.

22 So the sustainability is essentially

1 tied to the fact that the acceleration of drug  
2 development is going to be realized and the patients  
3 will have access. And through having the access, then  
4 they can have discussions about further funding,  
5 research in that particular area.

6 And there's another part that I forgot,  
7 but I think we're out of time.

8 DR. THERESA MULLIN: All right. I want  
9 to thank our panel very much, and thank you all. And  
10 so with this we'll close for lunch I guess.

11 (Break)

12 DR. NINA HUNTER: I am Nina Hunter. I  
13 am Director in the Office of Clinical Policy and  
14 Programs. And I am delighted to introduce Dr. Stephen  
15 M. Hahn, who was sworn in as the 24th Commissioner of  
16 Food and Drugs on December 17th, 2019.

17 Dr. Hahn is a dedicated clinician,  
18 having trained in both medical oncology and radiation  
19 oncology. In his previous leadership roles, he has  
20 always carefully balanced executive management with  
21 clinical time to continue to serve oncology patients,  
22 his true passion.

1                   Prior to joining the FDA, Dr. Hahn  
2 served as Chief Medical Executive at the University of  
3 Texas and the Anderson Cancer Center, a facility that  
4 cares for more than 140,000 patients a year.

5                   Before joining MD Anderson, he served  
6 as chair of the Radiation Oncology Department at the  
7 University of Pennsylvania School of Medicine from  
8 2005 to 2014.

9                   Dr. Hahn earned the rank of Commander  
10 in the U.S. Public Health Service Commissioned Corps  
11 while at the National Institute of Health's National  
12 Cancer Institute, where he also completed a fellowship  
13 in medical oncology and a residency in radiation  
14 oncology. He also completed a residency in internal  
15 medicine at University of California San Francisco.  
16 Please join me in welcoming Dr. Hahn.

17                   DR. STEPHEN HAHN: Thank you, Nina,  
18 very much for that introduction. And it's really  
19 terrific to be here today. This is very meaningful.  
20 Of all the things that Nina said, one thing she didn't  
21 is that my wife and I are parents of four children.  
22 And nothing is more important in life. We just had

1 our first grandchild. And I know that what we're  
2 going to talk about today is very much close to  
3 families and of great importance to the American  
4 people. So me it touches home in many ways, but  
5 perhaps most importantly, personally.

6 So thank you very much for joining us  
7 today. I hear we have a great turnout, both in this  
8 room and online. So thank you very much. And of  
9 course this coincides with the commemoration of Rare  
10 Diseases Day. It is really terrific to see such a  
11 broad group of stakeholders and innovators, drugs and  
12 product developers, clinicians, researchers, and most  
13 importantly, patients and their families.

14 Together, by engaging in conversations  
15 like these, by sharing information, and frankly, by  
16 listening to each other -- and that's FDA's number-one  
17 job here, is to listen to you, the stakeholders in  
18 this room -- we can more effectively collaborate in  
19 support of our shared goal, which is the development  
20 of new and better treatments for rare diseases.

21 I spent a good portion of my career, as  
22 Nina mentioned, researching and treating cancer, and

1 in particular treating patients with sarcoma. This  
2 challenge of rare disease is something that's been  
3 central to my work as a clinician and very important  
4 and has personal meaning to me. And that's because  
5 many cancers, and nearly all of the pediatric cancers,  
6 are themselves rare diseases. And this has given me  
7 an opportunity to witness and in some cases be part of  
8 the extraordinary developments that we're seeing in  
9 the medical product sphere to treat patients with rare  
10 diseases.

11 But just as important is the impact  
12 that our work together with patients has helped us to  
13 formulate and reinforce some of the most important  
14 priorities for the FDA in the upcoming year. We have  
15 defined three priorities, and I think these priorities  
16 are very, very important for this particular group,  
17 and I'll try to explain why.

18 The first is to promote choice and  
19 competition through innovation. Everything we can do  
20 to increase the innovation, particularly for patients  
21 and families with rare diseases, would be very, very  
22 welcome and important to us.

1           The second is empowering the American  
2 consumer. That includes patients as well as consumers  
3 of over-the-counter and other medical products. And  
4 finally, using data, empowering data, unleashing data  
5 so that we can better get to the answers that we need  
6 to get to. And I think that's one area that's  
7 particularly important in the rare diseases. Because,  
8 as you know, these diseases are rare. We don't have  
9 the liberty of performing large-scale clinical trials  
10 to get to the right answer. And so how we use data in  
11 very fruitful ways will be important to advancing the  
12 field. And I am encouraged by the impressive advances  
13 we've seen and the innovation around the country and  
14 the world for rare diseases.

15           Consider that also since the passage of  
16 the Orphan Drug Act in 1983, FDA has approved more  
17 than 800 drugs and biologics for rare disease  
18 indications. Last year alone the Agency approved 22  
19 novel drugs and biologics with orphan drug  
20 designation.

21           I'm going to list off some statistics  
22 which may or may not be interesting to you. But the

1 point of this isn't to brag about the Agency, but just  
2 to highlight that these innovations are coming fast  
3 and furious and that we need to do more and we need to  
4 be cognizant and that there are a lot of unmet medical  
5 needs out there. And hopefully what's happened in the  
6 past couple of years can accelerate even more.

7 To break down the numbers even further,  
8 CDER, the Center for Drug Evaluation and Research, 21  
9 of 48 novel drug approvals last year, or 44 percent,  
10 were for orphan products. And in the Centers for  
11 Biological Evaluation and Research, CBER, 20 percent,  
12 or one in five of the biologic approvals were orphan  
13 product.

14 Now, this is an area that I want you to  
15 pay very close attention to in the next couple of  
16 years, because we will see dramatic increases in the  
17 number of biologics that will come across the playing  
18 field for all of us. And these are where I think  
19 we'll see some major advances in rare diseases.

20 And some specific examples. We  
21 approved the first triple combination therapy to treat  
22 patients with cystic fibrosis, the first treatment for

1 neuromyelitis optica spectrum disorder, a new  
2 treatment for tenosynovial giant cell tumor, a tumor  
3 that I had seen in practice myself, and a gene therapy  
4 to treat pediatric patients with spinal muscular  
5 atrophy. And of course we've all seen how that has  
6 affected children with this. And it's just a  
7 remarkable event, something that I hope we'll see more  
8 of in the near future.

9           Last year we approved also 76 rare  
10 disease indications, which means the drug label that  
11 we have is expanded for many new uses to treat  
12 patients with rare diseases.

13           We've also seen advances in medical  
14 devices, not to forget that important part of the  
15 medical product sphere. And since 1990, FDA has  
16 approved 77 medical devices, including the last three  
17 for orphan indications. Last year three for orphan  
18 indications over the Humanitarian Device Exemption  
19 Program.

20           So what do these numbers really mean?  
21 That we live in a time of unsurpassed innovation, of  
22 rapidly advancing science, that is really I think

1       unprecedented around the world. And it isn't just  
2       wishful thinking to say that we will find treatments  
3       and potentially cures for many rare diseases that have  
4       significant unmet needs, it's because we are spending  
5       a lot more time and energy across the country and the  
6       world with researchers and innovators in developing  
7       these products. But it also means, as I said, that we  
8       have much work to do, and we cannot step back from  
9       these efforts.

10                 At FDA we are working hard to support  
11       the innovation that we are seeing across the world and  
12       to speed the development and regulatory process. We  
13       also welcome your input into how we are doing and how  
14       we can further support this innovation. And I've  
15       spoken to a few stakeholder groups, and I know that  
16       there are concerns about this, the ways that we  
17       approach things, maybe some of the processes we have.  
18       And we do want to hear from you, and we do want to  
19       adapt to this changing world that we see.

20                 The Agency has already done quite a bit  
21       to lower regulatory burdens for innovators. And I  
22       think this is important because we need to increase

1 competition and choice for patients and providers, and  
2 we need to provide the necessary support and  
3 information about our regulatory requirements; that is  
4 clarity about the regulatory schema. We need to  
5 continue further along this path.

6           It is also important to emphasize that  
7 we are always going to balance speed and efficiency  
8 and the real need across this country to get therapies  
9 as quickly as possible to people with our gold  
10 standard of protecting safety and efficacy. I do not  
11 think that one precludes the other; I think that we  
12 can do both. I think the arguments that as we move  
13 forward with efficiency and speed that we give up on  
14 our gold standard are untrue. And I look forward to  
15 working on ways that we can process improve so that we  
16 can get to the absolute best place in approval of  
17 these products. We will always continue to look for  
18 ways to improve. And again, your input will be really  
19 important for that.

20           The other big part of this that I  
21 wanted to mention is the essential role of you,  
22 advocates, as well as families and patients with rare

1 disorders. Another one of our priorities, as I said,  
2 is particularly relevant here, and that is empowering  
3 the American people. That's giving information to  
4 people about the products that we regulate, but also  
5 hearing back from people about what they need in terms  
6 of medical products, both for themselves and for their  
7 family.

8 To effectively support the development  
9 of treatments and to inform our understanding of any  
10 given rare disease, patients must be involved in the  
11 process. And I look forward to working with you to  
12 see that happen more and more. Because what matters  
13 to patients and families should matter to us as  
14 regulators of these medical products.

15 The FDA has increasingly incorporated a  
16 patient-focused approach to its work, adding a number  
17 of effective ways to include the patient's voice in  
18 evaluating and developing treatments for disease, such  
19 as the patient-focused development initiative, our  
20 Rare Disease Patient Listening Sessions, and through  
21 public meetings like this one.

22 But what I can promise you is that in

1 addition to listening, we will do the absolute best  
2 job we can and we will uphold our faithfulness to the  
3 gold standard of assessing the efficacy and safety of  
4 the products that we look at.

5 I only want to end by talking about the  
6 power of data. This is the third priority that we've  
7 established for the Agency for the upcoming year. And  
8 one particular benefit that can come from the  
9 involvement of patients' concerns and patients' voice  
10 is an extraordinary powerful resource for finding  
11 answers; and that is using rigorous data.

12 Ensuring the availability and high  
13 quality of data enables us to maximize the  
14 extraordinary potential of science, better support the  
15 development of new medical treatments and cures, and  
16 increase the knowledge of patients and consumers that  
17 have to make informed decisions about FDA-regulated  
18 products.

19 We must, for example, make much more  
20 effective use and integration of patient-level data  
21 such as patient-reported outcomes, electronic health  
22 records, the data from clinical trials, medical

1 studies, and patient registries. And we have to have  
2 a better and more robust way of integrating all of  
3 these data sources into our regulatory decision making  
4 process.

5           Terrific work is being done at this  
6 Agency to modernize our approach to data. Much more  
7 needs to be done. And we welcome your input into  
8 helping us do that.

9           So we will continue to do everything we  
10 can to attain more and better data for the work that  
11 we're doing, to be more proactive in gathering these  
12 data, and to be more creative and thorough in our  
13 analysis of it.

14           I want to emphasize one other point.  
15 And that is that we will use the data that exists to  
16 make the absolute best decisions for the American  
17 people. I promise you that as FDA Commissioner, that  
18 we will always adhere to the science that we have.  
19 Sometimes that means we will make a decision that we  
20 later need to revisit because additional data are  
21 available. This is the sign of a learning  
22 organization. This is the sign of a health

1 organization. This is what we want FDA to do. And so  
2 I want all Americans to understand that we will be a  
3 learning organization, that we will look back at the  
4 decisions that we make, and we will use all the time  
5 and the most up-to-date data that we have, and  
6 science, to address those decisions and make the  
7 changes that are necessary, again, in the best  
8 interest of the American people.

9 So I end my remarks this afternoon by  
10 citing the extraordinary advances in research. I come  
11 from a research background, and it's so terrific to  
12 see that. I want FDA to continue to be the enabler of  
13 that research and innovation. It is an exciting time  
14 for rare disease product development. And with your  
15 help, I know what we can do even more.

16 The challenges we face -- scientific,  
17 economic, and medical -- are significant. We are all  
18 resource-constrained. But there are ways around these  
19 resource constraints if we work together and we use  
20 data appropriately. Some of this relates to the  
21 essence of rare diseases; the small size of the  
22 populations which can pose a significant challenge to

1 clinical research. This is the tragic irony. Because  
2 as you've heard time and again, the underlying  
3 challenge of rare diseases is that while they are rare  
4 individually, collectively they are not. There were  
5 7,000 of them listed by us as rare diseases. Our  
6 priority at FDA is to help find and support the  
7 development of new treatments and cures -- yes, cures  
8 -- for rare diseases, and to do everything we can to  
9 advance this agenda through approvals, new and  
10 creative trials, funding of new research programs, and  
11 in other ways. And with your help, I believe we'll  
12 get there.

13 Most importantly, we look forward to  
14 listening to you. We will incorporate your input into  
15 our decision-making. We want to work with you and all  
16 of you who are here today to support rare disease  
17 product development. Together, we can and will find  
18 the answer and overcome these challenges.

19 I want to thank you for your  
20 participation today. It is so meaningful for the  
21 agency. And anything we can do to help you and your  
22 groups, your patients and your families, we are here

1 to do that. Thank you very much.

2 DR. NINA HUNTER: Thank you. That was  
3 a wonderful way to kick off the afternoon. And now we  
4 will transition to a panel with our FDA Medical  
5 Products Center Directors. If they could come up to  
6 the stage, that would be great. I know we're running  
7 a few minutes ahead of schedule, so they might not all  
8 be here yet. So while they are gathering, I just  
9 wanted to take a moment to thank all of you who are  
10 here today and also thank everyone who was involved in  
11 planning today's meeting. Thank you.

12 DR. JANET MAYNARD: So I am Janet  
13 Maynard. I may not have a microphone that's on. No,  
14 it sounds like it's on. Great.

15 So I am the Director of the Office of  
16 Orphan Products Development. And I am so excited to  
17 be up here to have a discussion with the Medical  
18 Product Center directors.

19 So the Office of Orphan Products  
20 development is located actually outside of the Medical  
21 Products Center. And I will say one of my favorite  
22 part of my jobs is working with the center directors.

1 And as I mentioned, the planning for this was -- a lot  
2 of folks were involved, and we had cross-agency  
3 representation from each of the medical product  
4 centers. And I think that's just one example of the  
5 type of dedication we have at FDA to supporting rare  
6 disease product development.

7 And with that, I will let each of them  
8 introduce themselves. I have Dr. Marks right next to  
9 me, and then Dr. Woodcock and Dr. Shuren.

10 DR. PETER MARKS: So I am Peter Marks.  
11 I direct the Center for Biologics Evaluation and  
12 Research. We handle the biologics that include blood  
13 products, vaccines, and cell and gene therapies. And  
14 that probably gets us into the rare disease space  
15 most, as well as certain products for hemophilia and  
16 other bleeding disorders that are derived from blood  
17 products. So that's all I have to say.

18 DR. JANET WOODCOCK: I'm Janet  
19 Woodcock. I'm Director of the Center for Drugs. And  
20 we handle small molecule drugs and therapeutic  
21 proteins of different sorts.

22 DR. JEFFREY SHUREN: Hello, I am Jeff

1 Shuren, Director of the Center for Devices and  
2 Radiological Health. And we oversee gizmos.

3 DR. JANET MAYNARD: I like that,  
4 gizmos.

5 So the theme of today's meeting is  
6 supporting the future of rare disease product  
7 development. What are some of the opportunities and  
8 challenges you are each seeing in your centers in  
9 terms of those considerations?

10 DR. JANET WOODCOCK: Well, I think the  
11 greatest challenge, as we all know in this room, for  
12 rare diseases is we just don't know enough about them.  
13 And there aren't very many patients to study when we  
14 do get some intervention we want to test. And so of  
15 course we're doing various things to try and address  
16 that.

17 But just this morning I had something  
18 come across my desk. And they were saying this is a  
19 very rare and very serious disease of children, it  
20 causes neurodegeneration. But some people don't seem  
21 to get neurodegeneration, and some do. And some  
22 progress fast, and some progress slow. And, you know,

1 how in the heck are we going to tell if something is  
2 working? So that's one of the challenges.

3 And I think the opportunities is with  
4 the genomic revolution and many other advances, we're  
5 getting much more precise in our understanding of  
6 what's going on with a lot of these diseases. And we  
7 can actually devise interventions, you know, against  
8 them. But the testing still remains a challenge, and  
9 that's what we're going to talk about I think a bit is  
10 developing registries and natural history studies and  
11 so forth so that we can just have some better  
12 understanding of disease and its variability is really  
13 going to help in developing treatments.

14 DR. PETER MARKS: I agree with  
15 everything that Janet said. Just the other piece is  
16 that we're able to develop therapies conceptually or  
17 in the laboratory space. But part of this is can we  
18 manufacture them in a way that is efficient that can  
19 meet the needs of the rare disease space. Because  
20 these products, these cell and gene therapy products,  
21 one wants them to be manufactured with the same high  
22 level of quality, whether it's for treatment of one

1 patient or a million patients. Right? And making  
2 sure that you have a level of quality.

3 Now, obviously there might be some  
4 differences there. I don't mean to exaggerate. But  
5 we do want to make sure that these are high-quality  
6 products. And figuring out a way to make sure that we  
7 accomplish that is one of the challenges.

8 DR. JANET WOODCOCK: And that they  
9 remain affordable or become affordable, which is  
10 another challenge.

11 DR. PETER MARKS: That's right.

12 DR. JEFFREY SHUREN: So I echo a lot of  
13 the points that were made. And the challenge on  
14 validation for small patient populations is even more  
15 acute in the device setting because of return on the  
16 investment. You have a number of the former products  
17 can get high payments for their use, but that doesn't  
18 exist on the device side.

19 And the second is when Congress was  
20 approaching this in the pharma space, they could  
21 provide an economic incentive for market exclusivity.  
22 That doesn't exist for the devices, because your

1 competition can reengineer around your IP, and so that  
2 market exclusivity is essentially meaningless. So  
3 Congress instead came up with a regulatory incentive  
4 in which they changed the standard to come to market  
5 if you're for a very small patient population. That's  
6 Humanitarian Device Exemption. And that used to be  
7 what we think of as an instance of about 4,000  
8 patients a year. Now it's 8,000. A lot of bells and  
9 whistles. Many cases you can't collect a profit,  
10 reporting requirements, and you had to have an IRB  
11 approve the use in a patient. Now you can use a local  
12 committee.

13 So between that and the fact that low  
14 otherwise payment, we've not seen a lot of development  
15 under that HDE pathway. We've got ideas on how to fix  
16 it, but if something does not change and we're not  
17 willing to think out of the box and do some new  
18 things, then we will continue to not provide proper  
19 service and care to the patients in this country.

20 DR. JANET MAYNARD: That was very  
21 helpful. Are there certain things within your center  
22 that you're doing to support these opportunities and

1 challenges that you're seeing?

2 DR. JANET WOODCOCK: Well, I think you  
3 may have just heard about the rare disease  
4 accelerator. There was some discussion. So that's  
5 one of the things we're doing. You know, there's a  
6 whole range of ways in which patient advocacy groups  
7 and other groups can work with the Agency and with  
8 industry to develop better tools to get these drugs on  
9 the market faster and get them studied correctly. And  
10 that's everything from, as I said, having a good  
11 patient registry, or even a patient -- I mean, a  
12 registry -- what (inaudible) has done. Okay? I am  
13 rare and you can identify the patients and you have  
14 information what's happening to them and so forth.  
15 Accelerator would take that to a different level and  
16 have really quantifiable data elements so we could  
17 perhaps construct what they call, you know, external  
18 controls. Because you certainly hear from people with  
19 rare diseases, they don't like to be on placebos for a  
20 really long time, all the way through to supporting  
21 trial networks. And there's this whole area of  
22 biomarkers, patient-reported outcomes, clinical

1 outcome assessments. What are all these?

2 Well, these are ways that you can  
3 measure change and tell whether change occurred. And  
4 for rare diseases, often none of that has been  
5 developed. So working on any of those or on the  
6 biomarkers are critically important because a drugs  
7 that has a biomarker they can use as a what we call  
8 pharmacodynamic marker can be developed much, much  
9 faster and is much more successful usually than drugs  
10 where they're just flying blind and relying on maybe  
11 the symptoms get better in a couple years or  
12 something.

13 If you use something you can measure in  
14 the blood or in the lungs or whatever and you know  
15 you're making a change much earlier, then that really  
16 helps spur development and you can figure out the dose  
17 and so forth.

18 So we have initiatives along that whole  
19 spectrum, all the way from, you know, we put in some  
20 money for IAMRARE, you know, back when that was  
21 started, all the way through to biomarkers and so  
22 forth and so on. But of course we can't do this

1 alone; we have to do it with community. And I really  
2 feel that drug development science part, the part that  
3 goes on after drug discovery, that science really  
4 needs a lot of work and it needs a lot of attention  
5 and probably funding by various sources to develop all  
6 these tools so we can develop rare disease treatments  
7 better.

8                   And I see Chris Austin is here. I  
9 think he probably agrees with me. Yeah. You know,  
10 over at NIH or NCATS, there's a portion, a very small  
11 portion, that's trying to work on this. But in  
12 general, much of the basic science enterprise doesn't  
13 do this. They aren't interested or it isn't their  
14 area of expertise. And it's critically important that  
15 we have the basic science to bring forth new insights  
16 that we can then use to develop treatments. But we  
17 also have to have the tools to develop the treatments,  
18 and they're kind of scarce right now.

19                   DR. JEFFREY SHUREN: And all those are  
20 along the lines of how do we sort of de-risk the whole  
21 process and make more efficient that generation of  
22 evidence to assess these medical products. And we

1 have very complementary efforts around these  
2 developments of -- we'll call them medical device  
3 development tools, these either non-clinical or these  
4 biomarkers or patient-reported outcomes and have in  
5 place a whole very streamlined system for qualifying  
6 those markers, and we engage with the developers,  
7 academic centers on developing. And we had a few come  
8 out just this past year. Patient-reported outcomes,  
9 terribly important. We are now seeing over 60 percent  
10 of the clinical trials for high-risk devices now  
11 include patient-reported outcomes. And we're trying  
12 to push that more and more.

13           One of the other exciting things is in  
14 the area of pediatrics. Because that's one area in  
15 which we're seeing very little innovation occur in the  
16 device space, unfortunately. Over the past decade,  
17 only about ten percent of the high risk of these HDE  
18 devices have been for an indication just for  
19 pediatrics and for less than 18 years. Only about  
20 four percent for infants and toddlers.

21           So we've been working with some of the  
22 major pediatric hospitals in the U.S. on setting up

1 what we call Ship, a System of Hospitals for  
2 Innovation in Pediatrics. Because the challenge here  
3 is you have sort of wide -- you have these very tiny  
4 pediatric populations spread out across the country.  
5 We need to link them together so we can get the  
6 patients, we get the top expertise, and we get the  
7 kind of good monitoring on them to get that evidence  
8 on the clinical side, on the non-clinical side. It is  
9 critical. And if we can combine that with very  
10 important regulatory reform -- and hopefully we can  
11 talk about this, some call it progressive approval --  
12 we can have a very refined engine to drive the  
13 development of new technologies for patients with rare  
14 diseases, and in particular for our children.

15 DR. PETER MARKS: And I think from our  
16 perspective in terms of gene therapies, it's  
17 increasingly clear that there are going to be any  
18 number of individualized gene therapies that are going  
19 to come along. And we have to put together  
20 essentially a pathway that those can follow in this  
21 area. And even -- there's rare diseases and there are  
22 diseases that are -- diseases that are very rare,

1 diseases that are not so rare. Even in the not so  
2 rare diseases, they become rare once you break them up  
3 into all the different genetic mutations. And so  
4 having pathways to deal with how one can think about  
5 the individual genetic mutations that might be  
6 addressed even within one of the more common rare  
7 diseases is really necessary.

8           So we're really thinking about how we  
9 can address that by leveraging what information we  
10 have. So the idea is that as we put together things  
11 moving forward, we're not thinking we need a lot of  
12 new regulatory authorities; we just need to leverage  
13 the ones we have to think about how people can  
14 leverage applications.

15           In other words, if a product has been  
16 made using one manufacturing technique and only a  
17 small modification has been made to that product so  
18 that it can address a different disease or a different  
19 subset of a given disease, can we allow the  
20 manufacturer to leverage the application of the  
21 original product as they have this modified product.

22           And so those types of things are things

1 we're having a vigorous dialogue about. Hopefully  
2 that will be articulated at some point in guidance.  
3 We also realize that we need to do all the things that  
4 go into product development on a very small scale, yet  
5 in a very efficient scale.

6           And so next Tuesday we'll be having  
7 right here in this room a workshop on individualized  
8 therapies, because we realize that at this point we  
9 have to start to think about how we can very  
10 efficiently do the non-clinical development, the  
11 clinical development, and the manufacturing of these  
12 products as well as how we can maintain the  
13 availability of them once they actually have been  
14 produced. Because one of my concerns is that we don't  
15 want to repeat mistakes that have been made in the  
16 past.

17           There was a gene therapy that was  
18 approved in Europe for a relatively rare disorder, and  
19 it was actually marketed for a time, but it's now off  
20 the market because it wasn't commercially viable. So  
21 this goes back to what Janet mentioned, which is that  
22 unless we can find ways towards commercial viability

1 or towards some sustainable method that these products  
2 can be provided, we're not going to be doing the job  
3 that we need to for patients in need.

4 DR. JANET MAYNARD: Thank you very  
5 much. And one thing you mentioned, Dr. Marks, was  
6 about leveraging and how can we do the best that we  
7 can possibly do for patients and families for rare  
8 diseases. And I know many patients and patient  
9 advocates frequently ask how can I get involved, what  
10 can I do to really help with product development. Do  
11 you have recommendations for patients and patient  
12 advocates who are interested in getting involved in  
13 rare disease product development?

14 DR. PETER MARKS: Well, I'm going to  
15 let Janet continue on. But I think one of the things  
16 that I would say is that one of the key things we need  
17 to understand for any of these products is the natural  
18 history of the disease to begin with. And to the  
19 extent that you might be waiting for somebody to  
20 develop that gene therapy, in the meantime while  
21 they're developing that gene therapy, getting baseline  
22 information on the course of disease, how fast people

1 decline, is really -- or how something changes over  
2 time, that's really important. Because then when you  
3 actually have the intervention, one can see if one is  
4 making a difference. And that's really important, to  
5 be able to have some clinical measure in addition to  
6 the ability to measure the product that's being  
7 replaced by a gene therapy.

8 DR. JANET WOODCOCK: Yeah, I agree.  
9 And practical ways to do that. Of course people with  
10 rare diseases should try to link together on social  
11 media or whatever and form a force, you know, so  
12 you're not just one individual struggling against the  
13 disease. And I know many, many groups have done that.  
14 Once you become a tight enough force or group, then  
15 it's possible to think about collecting these kind of  
16 data. And the NORD IAMRARE and the to-be accelerator  
17 would be two mechanics, but by no means not the only  
18 ones in which to do that.

19 Further down the pathway, like I said,  
20 working with or sponsoring preference studies, like  
21 has done by CDRH in certain areas, or developing PROs  
22 or working with the professional societies and medical

1 experts on biomarkers, raising money for that. All  
2 those things are really important, every single one of  
3 them. And they come at different stages. But  
4 unfortunately once somebody has a candidate product in  
5 hand, they wanted to have all that information a while  
6 ago. It's kind of too late. And that's one of the  
7 reasons it takes so long often, even after a discovery  
8 is made in the lab. People can't figure out why --  
9 you know, I only heard of one patient that's ever had  
10 that disease. Like, how do I go from here? How am I  
11 going to test it, how am I going to evaluate it?

12 And so all these things need to be done  
13 in advance, and you can know if you're working on them  
14 that you're actually improving the probability that  
15 some treatment will occur in the future.

16 And in fact as Jeff said, you will be  
17 interesting developers in that disease, because they  
18 want to have a pathway that isn't so unbelievably  
19 risky to follow down.

20 DR. JEFFREY SHUREN: And to build off  
21 of that, if you think about it, pretty much everybody  
22 is or has been or will be a patient. So we kind of

1 think sometimes as patients as maybe passive  
2 recipients, or give us your thoughts. We have an army  
3 of patient scientist. And that's also what we need to  
4 come to bear to sort of help us, both in product  
5 development and evaluation. Today there are patient  
6 communities, they are do-it-yourself technology being  
7 put together. And now we're thinking about how can we  
8 in fact enable patients for developing technology that  
9 can help them in their own lives.

10 DR. JANET WOODCOCK: I have one more  
11 thing. I know an individual, and he's written a book.  
12 I think it was called My Chase for a Cure or  
13 something. I forget what it's called. But anyway, he  
14 was in college when he first developed a life-  
15 threatening illness. He almost died. And then he had  
16 relapses when he was in med school. Almost died. He  
17 found out -- here's what he found out. It was a rare  
18 disease. Nobody knew how to treat it. All people had  
19 different treatments. Okay? Every expert you went to  
20 had different hypotheses about what caused it and all  
21 this stuff. He had a variant that didn't respond to  
22 what people usually started with. People had no idea

1 what to do next. So they decided to treat him with  
2 chemotherapy. Okay? Which they did for a while. But  
3 then he continued to have relapses.

4           And now he had a leg-up because he was  
5 a med student. But still he wasn't like some advanced  
6 expert. And he went ahead and -- but he found the  
7 experts. They hadn't gotten together. And this --  
8 Chris is, you know, something should be done about  
9 this, right? They hadn't gotten together and figured  
10 out the pathways, they hadn't shared information and  
11 data on the patients. There were little islands  
12 around the world where people had information about  
13 this disease. And they didn't have a consortium, they  
14 hadn't shared materials together.

15           And so he did some of those things, and  
16 he was able to find a treatment, an existing treatment  
17 that he tried and has kept him in remission. He sent  
18 me a picture of his baby and also a copy of his book.

19           So, you know, I agree about patient  
20 scientists. I really think patients have much more  
21 than they think as far as knowledge of their own  
22 disease and ability to contribute if we can only help

1 provide those pathways.

2 DR. JANET MAYNARD: And speaking about  
3 sort of forward-looking, we've seen additional  
4 interest in sort of the development for ultra-rare or  
5 small populations. And we have a panel this afternoon  
6 that's going to talk about perspectives on  
7 individualized therapies. But I was interested from  
8 your perspectives kind of what are you seeing in this  
9 space and how are you helping to address the  
10 regulatory considerations?

11 DR. PETER MARKS: So there's a  
12 tremendous amount of interest in this space, whether  
13 it's for antisense oligonucleotides, cell therapies  
14 that are specifically designed for one person's cancer  
15 or gene therapies that are developed for very small  
16 populations of patients, because they might be for one  
17 individual's mutation that might turn out to be either  
18 unique or only in a few patients. So we clearly have  
19 to find a way to get from where we are to being able  
20 to have treatments that get to patients.

21 So there are two pieces to that. There  
22 is the piece of how you go about getting the

1 regulatory perspective done, and the piece of how you  
2 go about getting the manufacturing done. We are  
3 collaborating with NCATS -- so you're going to hear  
4 from Dr. Austin later -- towards trying to find a way  
5 forward in some type of a public-private partnership  
6 that might happen in the future that can help with  
7 some of the -- serve as a model for how one could  
8 potentially get the manufacturing done.

9           And then from the regulatory  
10 perspective, I do think it's going to be a matter of  
11 thinking of how we can leverage as much as possible  
12 for these things. And it may not be that there's one  
13 size that fits all. It may be that some things will  
14 be -- that will treat a number of people will be  
15 things that could ultimately be a licensed product.  
16 There may be things that will never be a licensed  
17 product and will just be made available perpetually  
18 under an investigational new drug application, at  
19 least for right now. Because ultimately it's possible  
20 that 10, 15 years down the line many of the things  
21 that we're having difficulty doing in terms of making  
22 gene therapy vectors, those things will go away as we

1 have more advanced technologies. It's just the  
2 manufacturing is just not caught up to the rest of the  
3 science. In other words, this is one of these cases  
4 where science making the gene therapies and our  
5 science of being able to understand the genome has  
6 advanced far beyond where the technology to  
7 manufacture products in this space has.

8 DR. JANET WOODCOCK: On the smaller  
9 molecule side, we have had a number of applications  
10 for individualized treatment. In other words,  
11 molecules that were designed with a single patient in  
12 mind. Some of these have been made public. But we've  
13 had more than that, and we understand that we're going  
14 to see many more. So we're developing some policies  
15 on this. Because when you get down to a genetic  
16 level, actually, except maybe for some twins, most  
17 people are unique, completely unique. And therefore  
18 it's not surprising that when you talk about a rare  
19 disease and you start looking at the genetics that are  
20 causing that rare disease, there's going to be very  
21 unique genome across each person. And so how you  
22 address that if you're going to have a genetic

1 therapy, then that genetic therapy may be unique to  
2 each person or perhaps a small subset of people. And  
3 this is true even for relatively more common genetic-  
4 based disease.

5           So I regard this as a very interesting  
6 development. Like Peter said, we're wrestling with  
7 all the regulatory issues that we have to deal with  
8 and the issues of how these could be commercialized  
9 and so forth. But for people with ultra-rare diseases  
10 that have a genetic cause, I think this is something  
11 to, you know, have some hope, okay, that actually it's  
12 possible to develop an intervention that might help  
13 them. So we are on top of this I think is the best  
14 way to say.

15           DR. JEFFREY SHUREN: Yeah. And I would  
16 say that we understand I think the overall  
17 implications here. One of the issues in this very  
18 rare space is that we need to be thinking really  
19 globally. Because we don't want to reinvent the wheel  
20 over and over again in different countries. Right?  
21 If you have something that affects only five people in  
22 the United States, we don't want to have to have this

1 reinvented in Asia, in Africa, in Europe over and over  
2 again.

3           So I think we as a regulatory authority  
4 need to work with our global colleagues to find ways  
5 to really facilitate the development of these and  
6 break down barriers. Because sometimes we do have  
7 different regulatory structures and different  
8 regulatory frameworks that might inhibit the ability  
9 of these products to make their way from one  
10 regulatory jurisdiction to the other. And nobody  
11 wants to undermine another regulatory authority. I  
12 think if we don't come together and find ways to work  
13 together to find essentially common ground here, we'll  
14 do patients a disservice.

15           DR. PETER MARKS: So we get involved in  
16 these very small populations in a variety of ways. ON  
17 the one hand, it's the diagnostics, you know, to  
18 figure out sometimes who are these individuals. And  
19 we've been trying to foster in the genetic space  
20 databases and kind of that pooling of information on  
21 genetic variance. Because a lot of these, they are  
22 one-offs or few-offs, and you have to be able to

1 collect that information.

2 And I'll put a plug in, by the way.

3 While not a tiny, tiny population, but it is rare  
4 disease. Friday we did approve the very first test  
5 for Fragile X syndrome and carriers.

6 The second place is on people's  
7 anatomy. Your anatomy is very unique. And we have  
8 already cleared devices we're 3D printing being made  
9 specific to your anatomy.

10 And then third is this issue I  
11 mentioned about that regulatory incentive,  
12 Humanitarian Device Exemption. It's really tiny  
13 populations. And Congress changed the standard.  
14 Instead of reasonable assurance of safety and  
15 effectiveness, it's really a reasonable assurance of  
16 safety and probable benefit.

17 And the challenge here is in spite of  
18 that, the incentives aren't strong for development.  
19 And once you get past 8,000, suppose it's 8,500  
20 patients, guess what? You've got butkis. That's it.  
21 And then nothing that pushes you to get the rest of  
22 the data. So our idea on progressive approval is the

1 following. Let's not make the limit 8,000. You can  
2 keep HDE. But let's keep the standard of HDE in a  
3 small population. It could be 9,000, 10,000, 20,000.  
4 But then you have to get the rest of the data within a  
5 certain amount of time. So within three years you  
6 show reasonable assurance of safety and effectiveness.  
7 And if not, your approval sunsets. So you've got a  
8 hammer. And we tie it with two other things.

9           One, in order to do it, you have to  
10 have an existing data source where you can get that  
11 information. Right? So you're not doing a one-off  
12 clinical trial. There's a registry maybe available  
13 and that data is being collected anyway, so you know  
14 you're going to get the data.

15           And the second is in some cases, we  
16 might restrict distribution to those centers that  
17 actually have good oversight, good monitoring. And  
18 that bring us back to (inaudible)

19           So if on the pediatrics side we have  
20 progressive approval and (inaudible), we could have a  
21 very powerful engine for driving development  
22 technologies. But not only that, driving the evidence

1 to then better understand the use of technologies when  
2 out on the marketplace.

3 DR. JANET WOODCOCK: I just want to  
4 say, Jeff, my brother has two of those custom things  
5 in his body, and he's really happy.

6 DR. PETER MARKS: I would say that one  
7 of the wonderful things about genomic medicine is that  
8 we are lucky that in some cases if we do things right,  
9 if we have the right baseline data, if we have the  
10 right construct, we're lucky in that it doesn't take  
11 that many patients to actually see that something is  
12 working. Right? If somebody is not making any of  
13 something and they're dying because of that absence by  
14 a few years of age, and you make that something and  
15 they're not showing a decline and they're alive after  
16 a given timepoint, it doesn't take that many patients  
17 before you feel confident here. And so that is a  
18 great advantage here.

19 It's one of the reasons why we don't  
20 really have to -- it's perhaps a little bit different  
21 in biologics than it is in devices, because we can use  
22 our current framework to find efficacy, findings of

1 efficacy without having to stretch things too far out  
2 of our existing regulations, and I think it's very  
3 exciting.

4           And this goes to why doing the right  
5 pre-work, not settling for the wrong construct in  
6 terms of design of the therapy, being thoughtful, is  
7 so important in this area. Because these things, when  
8 they work, they can work really amazing.

9           I think the example that Commissioner  
10 Hahn noted about the therapy for spinal muscular  
11 atrophy, this is truly amazing. I mean, you're taking  
12 a disease that formerly was really uniformly fatal for  
13 Type I spinal muscular atrophy by two or three years  
14 of age, and now you have not just the children alive,  
15 but they're alive and they are for all intents and  
16 purposes normal. And that's truly remarkable. And  
17 that's just something that is incredibly gratifying  
18 for all of us who work here. I'm sure it's incredibly  
19 gratifying for their parents and their families. And  
20 I think it's wonderful to all share in this success.  
21 And we want to try to bring that to a greater number  
22 of diseases.

1 DR. JANET MAYNARD: So speaking of  
2 sharing, we would love the opportunity to hear your  
3 questions or perspectives from the audience. So if  
4 folks want to come up to the microphone, or please  
5 feel free to raise your hand and someone can bring a  
6 microphone to you.

7 WOMAN: Hi. I am a patient scientist,  
8 like someone said in the panel. I have Parry-Romberg  
9 syndrome, and I am a health outcomes researcher. So I  
10 analyze data on patients' reported outcomes, EHRs,  
11 claims, et cetera.

12 And they're mostly in a Facebook group.  
13 I connected on a Facebook group. After spending 20  
14 years without having met anyone with the same disease,  
15 I connected with a Facebook group that has about 1,200  
16 members that are spread across the globe, among which  
17 there are some identical twins, which is always  
18 interesting, like we mentioned, when we want to  
19 investigate genetic ideology.

20 So my question is for me as a health  
21 outcomes researcher, I see there the potential of a  
22 really amazing pool of data. But how can we leverage

1 this potential when people are spread across the  
2 globe? As you mentioned, we can't just ask them  
3 questions and make a study out of it. So how could we  
4 use these patients, how can we recruit these patients  
5 and really develop a study that has validity?

6 And the other question is not only  
7 recruiting for this, but how can we establish  
8 international collaborations between researchers that  
9 are doing research?

10 So I also participated in a research  
11 study that is trying to investigate the ideology of  
12 the disease. In months of work the investigator  
13 collected three samples. And all of these people in  
14 the Facebook group would be willing to participate.  
15 It's just that they cannot physically come here. So  
16 that's my question. Thank you.

17 DR. PETER MARKS: This is an  
18 interesting place where I think what you're saying is  
19 there are examples of collaborations which have been  
20 effective. And I guess this is where in the rare  
21 diseases space I think there might be an opportunity  
22 for sharing, because there are some where I think

1 people have very effectively brought together  
2 international collaborations with being able to do  
3 similar things of trying to get an investigator in  
4 each country of several of -- from several counties to  
5 be the lead investigator so that they can collect  
6 samples and share them under a protocol.

7           And so I would encourage you after this  
8 to network around a little bit. Because I'm pretty  
9 sure that I see people in the room who have helped  
10 facilitate some of that. It sounds like you're a  
11 little bit more on the early end of things. But  
12 still, getting those samples. And there's nothing  
13 that prevents, you know, multinational protocols from  
14 taking place, especially for sample collection where  
15 it doesn't even require global regulatory approvals.  
16 But even on the space where there have been  
17 interventional trials, clearly multinational trials in  
18 this space are quite possible.

19           DR. JANET WOODCOCK: Yeah. I think  
20 once the disease accelerator gets really set up, its  
21 intent is to be a good repository for the information  
22 once it's gathered. And it certainly is intended to

1 be international, not just in one country.

2 I think one thing is to find an  
3 investigator somewhere in the world who is really  
4 interested and motivated and thinking outside the box  
5 on how you do these things and how you might set up a  
6 consortium and a collaboration. So I think there are  
7 such folk around. It would have to be somebody who is  
8 working in the disease space who is willing to think  
9 beyond the individual investigator paradigm, and how  
10 do you set up a disease network so that you can really  
11 collect information, the specimens, and nothing is  
12 lost.

13 But that's great, you've gotten so far.  
14 It's a good step, because a lot of rare diseases  
15 aren't even there yet.

16 DR. JEFFREY SHUREN: And don't forget  
17 there may be opportunities on technology, too.  
18 Because if there are things you need to measure,  
19 sometimes those could be sensors or other information  
20 that doesn't require a blood sample, maybe some other  
21 kind of specimen. And that allows for gathering data  
22 from basically anywhere on the planet.

1 DR. JANET MAYNARD: Great point.

2 KHRYSTAL DAVIS: Hi, my name is  
3 Khrystal Davis. I am the founder of Texas Rare  
4 Alliance. And I am attending from a travel grant from  
5 Every Life Foundation. I am also an SMA mother to a  
6 Type 0.5 SMA patient.

7 Our son, Hunter, is now eight years  
8 old. He landed in the NICU at birth with respiratory  
9 failure. At eight weeks of age, we finally received a  
10 diagnosis. And eight weeks later, Hunter received his  
11 first (inaudible) ASO treatment in Cancun, Mexico. We  
12 continued those treatments for five years until he was  
13 able to cross over to the Spinraza EAP. And based on  
14 the trials, Hunter would not have qualified for  
15 treatment.

16 So I want to advocate for access for  
17 all patients across the spectrum of the disease for  
18 access in the clinical trials. And we're seeing it  
19 made increasingly clear that although the FDA is  
20 willing to grant a broad label on the basis of the  
21 data from the clinical trial, we're seeing the payors  
22 decline coverage because there are no data points on

1 those patients. And we know firsthand Hunter would  
2 not have qualified. But he is here today because he  
3 did receive those treatments. And what can we do  
4 collectively to change that, to make sure that we do  
5 bring all these patient into the trials?

6 DR. PETER MARKS: So I can start. And  
7 thank you for that. I think it is challenging. I  
8 think there are a variety of things we've encourage  
9 people to do, which is, (A), try not to have very  
10 restrictive registry criteria to the extent that one  
11 can. Unfortunately, sometimes the fastest way to get  
12 something approved is to take a more homogenous  
13 population.

14 That being said, we don't have any  
15 problems -- I mean, the problem is often not at the  
16 FDA level with expanded access and access outside of  
17 trials, it's that -- and this goes back to something I  
18 keep harping on manufacturing -- it's that they cost  
19 so much and are so complex to make that, for instance,  
20 in the gene therapy space, oftentimes manufacturers,  
21 particularly small ones, can't afford to make  
22 additional doses of their therapies.

1 I'm not defending that. Okay? The  
2 problem is that you may say how can this be? These  
3 are gene therapies. How can you make --  
4 unfortunately, these gene therapies, the way we  
5 currently get gene therapy into people is we use viral  
6 vectors. Those viruses have to be made. The way they  
7 are made is they are made in cells. Because they are  
8 toxic to the cells that they are made in, one actually  
9 has to grow up a lot of these things. And the  
10 production of these things turns out to be relatively  
11 complicated, relatively costly.

12 So one of the things we're very  
13 interested in working on at Center for Biologics is  
14 how we can work with others to try to bring down the  
15 cost of production of these. That's not a total fix,  
16 but hopefully if it wasn't so expensive to make these  
17 products, people would be more willing to give them  
18 out on expanded access and companies would be more  
19 willing to have broader inclusion criteria for  
20 protocols besides their main protocol.

21 Again, I don't have a complete solution  
22 here, but I agree with you. We can't leave people

1 behind in this situation.

2 DR. JANET WOODCOCK: Yeah. And we've  
3 talked before. FDA I think is becoming more aware of  
4 this situation. It used to be we would hear people  
5 who were studied in a trial, and then we'd say who it  
6 was reasonable to also be included in the indication.  
7 And we would often have some special study saying  
8 renal failure or whatever so we can include those  
9 people and the right dosing.

10 But now that isn't the case. And we  
11 are having some work to raise awareness amongst the  
12 staff. Seminars are being held and everything about  
13 how the label effects coverage and access to treatment  
14 and reimbursement for treatment.

15 As Peter said, on the trial side, if  
16 there is enough material, then it's very reasonable to  
17 include other people, not maybe in the main trial if  
18 you're worried, or you can have an arm in that trial  
19 that isn't the randomized comparison arm, but it's  
20 actually to provide safety and additional types of  
21 people beyond the people, you know, that you have  
22 otherwise enrolled.

1                   KHRYSTAL DAVIS: Yeah. And just to  
2 follow up. We are starting to see that being done.  
3 But also we need to advocate if possible that they are  
4 done contemporaneously so that that data can be  
5 included in the label packet as well. Thank you.

6                   SANDY SIAMI: Sandy Siami, HealthCore.  
7 I have been doing research in rare diseases and orphan  
8 devices for about 25 years now, specifically in  
9 pediatrics to --

10                  DR. JANET MAYNARD: We can't hear you  
11 very well.

12                  SANDY SIAMI: Sorry. So my question  
13 is, because this population in rare diseases, they are  
14 rare, right? They're hard to find. What role do you  
15 think artificial intelligence or machine learning can  
16 play in clinical trials to help get these drugs and  
17 devices to the market?

18                  DR. PETER MARKS: Some of this has to  
19 do with whether there could be more collaborative ways  
20 of finding patients. I think maybe that's part of  
21 this, is patient identification. One of this has been  
22 -- you know, the holy grail would be we have one

1 essentially wonderfully interchangeable electronic  
2 medical record in the United States instead of a  
3 balkanized version of hundreds of different medical  
4 records. And if you had, you could imagine that as  
5 part of entering your medical record, you could say,  
6 oh, I would want to be considered for clinical trials  
7 or not. And if that was checked that you wanted to  
8 be, you could imagine an artificial intelligence  
9 program that could probably search up so you could be  
10 on a list of things that -- a list of queries, you  
11 know, if the database was queried, an investigator  
12 could find everyone with Fragile X syndrome or  
13 everyone with SMA.

14 But currently the way we are working  
15 with our electronic medical records system, it does  
16 not work that way. And that is the nature of how  
17 things are. It's easier in some -- this is where some  
18 of the European countries have a one-up on us where  
19 they have a single medical records system in certain  
20 Nordic countries where you can use AI right now. And  
21 the issue here is maybe this is someplace we'll get  
22 to.

1 I think it does have to be done very  
2 carefully, because I think we want -- it's patient  
3 autonomy. You should be able to participate if you'd  
4 like and opt-out if you don't want to. But we're a  
5 little ways from getting there.

6 DR. JEFFREY SHUREN: And I think also  
7 there is the use of those technologies for going  
8 through information to developing better tools for  
9 identifying patients who have particular rare diseases  
10 as well.

11 DR. JANET MAYNARD: Good point. And  
12 I'll look over to see if there's questions from the  
13 web.

14 DR. NINA HUNTER: Yeah, sure. So this  
15 was brought up a little bit earlier. But we have seen  
16 some orphan drugs approved by FDA, but not EMA. Is  
17 there any collaboration and progress between the FDA  
18 and the EMA to harmonize the scientific and regulatory  
19 requirements for orphan drug development and  
20 registration?

21 DR. PETER MARKS: So I can start on the  
22 gene therapy end. There actually is a lot of dialogue

1 between EMA and FDA on trying to work together in this  
2 space. It's not perfect yet, but we have a dialogue  
3 that's ongoing and that will continue.

4 And more so even than just with EMA, I  
5 was at a meeting last week at the World Health  
6 Organization because there is a goal kind of more  
7 globally to try to harmonize what's going on,  
8 particularly in this rare disease space. Because  
9 everyone realizes that, again, we can't all have  
10 different expectations of what a submission will look  
11 like for a product that's only going to treat 50  
12 people globally, or else it's just not going to work.

13 So are we there yet so that it's  
14 perfection? Maybe not yet. But I do think that the  
15 dialogue has been opened and it will hopefully  
16 progress in the not-too-distant future.

17 Just to be honest about what happens in  
18 life, the EMA had a move that they had to take because  
19 EMA previously was located in London. And something  
20 happened politically, geopolitically. They had to  
21 move to Amsterdam. That slowed things down a little  
22 bit. And right now we have an outbreak that's also

1 probably slowing things down a bit. But the dialogue  
2 is going on.

3 DR. JANET WOODCOCK: As far as small  
4 molecules, we do have a lot of harmonized standards.  
5 But it's clear that between the EU and FDA in U.S. and  
6 many other countries, we may not have the same  
7 approval decisions. And that is a matter of sort of  
8 national sovereignty. Usually we're working off the  
9 exact same data set.

10 And if things are approved in Europe,  
11 often the European folks will have more difficulty  
12 obtaining reimbursement even than in the United  
13 States. And we've already discussed some of the  
14 difficulties here. So a lot of this gets into how the  
15 healthcare systems are set up and what their standards  
16 are and so forth.

17 But we do work very closely with them.  
18 We are aware of all these things. We talk neurologist  
19 to neurologist and infectious disease doc to  
20 infectious disease doc and everything. But the  
21 approval decisions overall are taken up at a somewhat  
22 higher level.

1 DR. JANET MAYNARD: Great. Another  
2 question in the room?

3 DR. BARBARA GILLESPIE: I am Barbara  
4 Gillespie. I'm an adult nephrologist. I work at  
5 Covance as CRO that works with sponsors to run trials.  
6 And I'm here on behalf of the Kidney Health  
7 Initiative, which is a private-public partnership with  
8 the FDA.

9 So, Dr. Woodcock, you spoke at one of  
10 our meetings in the last few years about platform  
11 trials as one approach to innovative designs.

12 And I guess my question is I know the  
13 experience in oncology with I-SPY has been great. But  
14 our oncologists are years ahead of us with  
15 infrastructure and other kind of partnerships. So I  
16 wanted to hear from any of you on this stage or anyone  
17 in the room. What has the experience been with  
18 platform trials in other therapeutic areas? Like I  
19 said, I'm an adult nephrologist, but our kids who  
20 start off with things like nephrotic syndrome, IgA  
21 nephropathy and FSGS grow up to be adults, and we  
22 still don't have any approved drugs. And we've got

1 many sponsors looking at these trials. The efficiency  
2 of having a standard of care and a placebo arm that's  
3 shared is really wonderful, but there's a lot that  
4 goes into these survivals.

5 DR. JANET WOODCOCK: It's very  
6 frustrating to me, you know, to be very honest, there  
7 isn't funding, there isn't any kind of funding to set  
8 up networks for say pediatric nephrology problems or  
9 pediatric pulmonary diseases. So as you all know, the  
10 Cystic Fibrosis Foundation basically did this by  
11 establishing centers of excellence and by genotyping  
12 and following all their patients in a registry that  
13 Everybody came to those centers of excellence, which  
14 is most of the people.

15 Now, most rare diseases don't have the  
16 kind of funding to be able to set those things up, but  
17 they also have severely affected patients who would  
18 benefit from such a platform.

19 So I don't know. I think that we all  
20 probably need to think about the need for some stable  
21 funding to set up such networks, clinical trial  
22 platforms that could support clinical trials in a

1 variety of areas probably organized around experts,  
2 like pediatric nephrologists, pediatric neurologists.  
3 If there were some kind of funding made available that  
4 was stable, then I think that would go a long way.  
5 And then disease organizations could take the next  
6 steps to bring their patients together and try to work  
7 through something to set up a standing trial. But  
8 right now it's really, really hard.

9 I know a number of disease groups, and  
10 there are probably some people in this room that are  
11 trying to do this. So a number of disease groups are  
12 trying to set up master protocols for their disease.

13 DR. BARBARA GILLESPIE: Well, and I  
14 guess just to follow up, in addition to the finding,  
15 it's how do you incentivize sponsors to really  
16 collaborate, come together, the data sharing. I mean,  
17 we say that in many meetings, but the reality is --  
18 and I'm sure there are sponsors in the room -- there's  
19 a lot of pushback. And it's just what kind of  
20 incentives are there, regulatory and otherwise, to try  
21 to help that conversation, too.

22 DR. JANET WOODCOCK: Well, I mean, sort

1 of chicken and the egg problem. If you had the  
2 centers of excellence and you had all the patients,  
3 then people would have to come to you. Right? And in  
4 my mind that would be better than setting up specific  
5 trials for specific drugs or gene therapies or  
6 whatever in development, to have them all evaluated in  
7 the same platform so we could see how they perform  
8 against each other. But there you have to have that m  
9 aster protocol in place and the centers of excellence  
10 in place. Then you've got some leverage.

11 DR. BARBARA GILLESPIE: Okay. Thank  
12 you.

13 DR. JANET MAYNARD: Great. Thank you.

14 CARRIE BARNHART: Hi. My name is  
15 Carrie Barnhart, and I have seven rare diseases. And  
16 I'm here today with a travel grant through Every Life  
17 Foundation. Not only do I have seven rare diseases,  
18 but I have 12 very painful conditions. And many of my  
19 diseases don't have any treatment. Or the one  
20 treatment there is causes anaphylaxis for me. So the  
21 overarching theme of why I'm here is I work with a lot  
22 of different disease groups. My son has four of my

1 diseases. And along with all of these diseases, like  
2 complex regional pain syndrome, Ehlers Danlos, lupus,  
3 all of these conditions cause a lot of massive pain.

4 And while it's never going to go away  
5 and there's no treatment for some of these diseases,  
6 what is the FDA going to do about treating pain until  
7 there is a treatment for the disease? With some of  
8 the pain treatments being taken off the market, a lot  
9 of pain patients are in agony. They're dying early.  
10 So I was just wondering what the FDA is going to do  
11 between here and finding the cure for the disease.

12 DR. JANET WOODCOCK: Well, I think we  
13 haven't taken that many pain treatments off the  
14 market. The problem is that people are becoming much  
15 more careful or cautious you might say about  
16 prescribing opioids in particular because of the  
17 opioid epidemic.

18 We are very aware that there are many  
19 people with chronic pain who need treatment. And FDA  
20 is continuing to try and balance that need against all  
21 the concerned people have about the loss of life and  
22 so forth that's coming on with opioid use disorder,

1 and overdose is consequent to that.

2 And we don't have a lot of good  
3 alternatives. We have acetaminophen, we have the non-  
4 steroidal anti-inflammatory agents, we have opioids.  
5 You know, our choices are kind of slim. And we have a  
6 few other special treatments for very special kind of  
7 pain.

8 We are working with the pharmaceutical  
9 industry to try and find new pain treatments that  
10 don't have the liabilities of many of the current  
11 analgesics that we have. But that's turning out to be  
12 pretty hard.

13 So I think the patients who are  
14 experiencing difficulty accessing pain medicine or  
15 having their pain adequately treated are probably  
16 experiencing some of the swinging of the pendulum from  
17 the opioid epidemic. And we have put out information  
18 to doctors and so forth warning people you shouldn't  
19 taper patients rapidly and you should individualize  
20 treatment. And other people have done that as well.  
21 But there's still -- because of the consequences of  
22 the epidemic, there is a tremendous concern about

1     prescribing opioids in particular.  And of course some  
2     of the other medicines have their own liabilities.  
3     Many people, for example, can't take NSAIDS.  It's  
4     very challenging.

5                     CARRIE BARNHART:  Just a follow-up.  
6     You had asked about patient advocate groups kind of  
7     doing the research.  Well, there are a lot of pain  
8     advocate groups that have done the research on opioids  
9     for example and have found, you know, that it's  
10    actually a lot less damage from opioid use.  Like  
11    people that are dependent on it to have quality of  
12    life, to be able to get out of bed, to be able to go  
13    to work, to be able to watch their kids.  And it's  
14    staggering what the research shows versus what's  
15    actually told out there.  So there's this  
16    fearmongering going on.  And so a lot of patients like  
17    me have huge, huge barriers to be able to get  
18    management.

19                    DR. JANET WOODCOCK:  Yeah.  We  
20    recognize that.  There was even a little piece in the  
21    New England Journal of Medicine about this.  I think  
22    they called it social toxicity or something like that,

1 where somebody was removed from his opioids, and he  
2 eventually lost his job because he couldn't get to  
3 work anymore, and then he got arrested because he was  
4 trying to get some pain medicine on the street. And  
5 these examples show that we really have to keep the  
6 patient in mind. It should be about the patient and  
7 what they need.

8                   And of course these opioids are  
9 addictive. We know that. And we know some people can  
10 abuse them. But we know other people have their pain  
11 controlled very well by them and don't develop these  
12 problems. So it's really a matter of  
13 individualization again.

14                   DR. JANET MAYNARD: Thank you. And  
15 I'll look to the web again to see if we have a web  
16 question. No web questions? Great. In the room?

17                   SHEILA MIKHAIL: Hi. My name is Sheila  
18 Mikhail. I am the CEO and co-founder of AskBio.  
19 AskBio is a AAV gene therapy company that was founded  
20 back in 2001, way before it was popular to be in gene  
21 therapy. We were founded by researchers and parents  
22 who have children with devastating diseases. WE also

1 happen to be working on pain, just as a side note.

2 My comment relates to the SMA mother.

3 Our technology is used in the AveXis therapeutic.

4 It's the self-complementary vector. It breaks my

5 heart to hear her comment.

6 We have worked very hard on

7 manufacturing. We've spoken with Dr. Marks in the

8 past. Our manufacturing system is we believe the

9 highest-yielding gene therapy manufacturing

10 technology. We put a certain portion of our capacity

11 aside for non-profit purposes. We formed a foundation

12 called Columbus Children's Foundation where we

13 dedicate a portion of our technology, manufacturing

14 capacity, and technology for the development of ultra-

15 rare indications. To date we've treated 20 patients

16 with ADC deficiency with no charge. Let me say that

17 again, no cost to the patients.

18 So a lot of in biotech are not here

19 just to make a lot of money; we remember our origins,

20 and those are our patients and parents who have

21 suffered. And we don't want to continue suffering.

22 So my question is, how do I help that

1 mother? How do I make our manufacturing and how  
2 digital enable our foundation to help that mother so  
3 that she can actually have access to therapeutics that  
4 are on the market and have been proven that they're  
5 effective.

6 I think there's no greater travesty  
7 than having a drug available that we know works and  
8 not having it available to a patient who is suffering.

9 DR. PETER MARKS: Well, I think there  
10 are a couple different things that can be done. I  
11 think first of all one of the questions that goes for  
12 some of the gene therapies is one of the simple things  
13 to do is to also ask the companies, which sometimes  
14 people don't do. But I think at this point for some  
15 of the companies, the easiest thing for a gene therapy  
16 that's already licensed is to try to go back to that  
17 company and see if that can be made available as part  
18 of an expanded access program. Because there the  
19 product is being made. One doesn't have to go after a  
20 new licensing process, one doesn't have to look at a  
21 different manufacturing process.

22 On the other hand, I think turning to

1 exactly what you're saying is one of the reasons why  
2 we, in collaboration with NCATS, National Center for  
3 Advancing Translational Sciences, are interested in  
4 seeing if we could put together some type of a public-  
5 private partnership to be able to use that capacity  
6 that -- we've had more than one. I think what you  
7 articulate is very nicely said by any number of gene  
8 therapy companies that want to use their excess  
9 capacity to help benefit people with ultra-rare and  
10 very rare diseases. And the question is how do you  
11 make that work.

12 And so putting together the  
13 infrastructure to make that work is part of what needs  
14 to happen. And so we're working towards that. And I  
15 hope we're not too far off. Thanks.

16 DR. JANET MAYNARD: Thank you. Any  
17 other questions from the audience in the room?

18 WOMAN: (inaudible) Foundation.  
19 Excellent panel. Thank you so much.

20 One quick thing I wanted to throw out  
21 there when this discussion was happening about our  
22 platform trials. So we are in fact now collaborating

1 with the Innovative Medicines Initiative, which is a  
2 European initiative. It's really a public-private  
3 partnership between industry and European Commission.  
4 And they have money, I just want to say.

5           So we are now developing a platform  
6 trial for four different diseases, of which NF is one  
7 of them. And we are also developing a platform trial  
8 in the U.S., which is more with a couple of centers.  
9 But I think the real maybe opportunity if we want to  
10 do something creative is maybe to start in Europe.  
11 Because of the public hospital system, we have  
12 released that political barrier. But it's so  
13 optimistic.

14           DR. JANET WOODCOCK: Agreed. And  
15 European Parliament is putting up the money for --

16           WOMAN: Exactly.

17           DR. JANET WOODCOCK: -- IMI  
18 initiatives. And that is very translational. It's  
19 not just basic science. And the industry is providing  
20 in the public-private partnership in kind activity.

21           WOMAN: Exactly.

22           DR. JANET WOODCOCK: So they have some

1 ownership as well that keeps it grounded in the  
2 practicalities of drug development. So we work with  
3 IMI very closely. And congratulations for getting  
4 some trials up and running.

5 WOMAN: Thank you. And the interesting  
6 thing is that in fact the next IMI is probably going  
7 to be called IHI. So Innovative Health Initiative,  
8 where standard devices and everything else will be  
9 included.

10 DR. JANET MAYNARD: Thank you. Are  
11 there other questions in the room? Other questions in  
12 the room? Okay. Well then why don't we break  
13 slightly early so that we'll have a 15-minute break  
14 instead of the initially planned ten-minute break. So  
15 we'll have a little bit of extra time. And we'll plan  
16 to reconvene at 2:00. Thank you.

17 (Break)

18 DR. JANET MAYNARD: -- individualized  
19 therapy, so if our panelists don't mind coming on the  
20 stage, that would be great, please.

21 MAARIKA KIMBRELL: All right,  
22 everybody, so I guess we're getting started. We're on

1 Panel Number -- is it -- 4 this afternoon and we're  
2 going to be speaking about perspectives on  
3 individualized therapies. The goal of this session is  
4 to provide various perspectives on individualized  
5 therapies with an emphasis on regulatory  
6 considerations.

7 As with some of the other panels  
8 earlier today, I'll begin with some very brief  
9 introductions and then turn the floor over to our  
10 esteemed panelists to give a more -- a deeper  
11 introduction and some perspectives from them, and then  
12 we'll move on to questions. I have questions, but I  
13 also hope to hear questions both from you all here at  
14 White Oak as well as folks online.

15 So briefly, I'll introduce myself. My  
16 name is Maarika Kimbrell. I'm the deputy director of  
17 the Office of New Drug Policy which was a recently  
18 established office in the Office of New Drugs. It  
19 came about as a result of a recent reorganization and  
20 I'm serving as a panelist for the folks here. We've  
21 got a great group of people and I think we're going to  
22 have a very good discussion.

1                   So we have Ella Basala, Petroula  
2                   Smpokou, Julia Vitarello, Ciela Witten, and Timothy  
3                   Yu. We're going to introduce folks not quite in the  
4                   order that we're sitting, because we discussed this  
5                   earlier and it wasn't alphabetical, but we're sitting  
6                   alphabetically, so first, Julia.

7                   JULIA VITARELLO: Hi. My name is Julia  
8                   Vitarello and three years ago my daughter, Mila was  
9                   given a death sentence. She was diagnosed with Batten  
10                  disease which is a rare neurogenetic disease that's  
11                  fatal. No treatments, no cures. This was the same  
12                  little girl who was a typically little Colorado girl  
13                  who was hiking and skiing. She was swimming and  
14                  biking and rock climbing by the time she was two. She  
15                  was advanced, normal, and singing all the words to her  
16                  favorite songs, to "Puff, the Magic Dragon."

17                  She was learning her ABCs. And at six  
18                  years old, she lost her vision and she was diagnosed  
19                  with Batten disease and I was told that she was going  
20                  to lose very quickly her last words. She would say  
21                  mommy for the last time. She would take her last  
22                  steps. That we should buy a wheelchair, that her

1 brain would atrophy and eventually be an empty skull  
2 and that she would die in the next five years. As you  
3 can imagine, life as we knew it was over that day.

4 I was told that there are no tools in  
5 the toolbox. It was empty. There was nothing we  
6 could do. There was very little understood about this  
7 disease. So I started speaking with other rare  
8 disease parents who'd been fighting for their children  
9 across many diseases. I spoke with scientists and  
10 doctors around the world.

11 I read everything I could get my hands  
12 on around Batten disease, around lysosomal storage  
13 disease, and I learned pretty quickly what I needed to  
14 start a foundation, raise a lot of money. And I  
15 started doing that and telling Mila's story to anyone  
16 and everyone who would listen. At some point, I  
17 realized Mila was missing a mutation. She needed two.  
18 It was autosomal recessive and one of them was not  
19 able to be found.

20 So in my desperate plea to find a lab  
21 that would help me find the missing mutation so I  
22 could test my two-year-old son, who seemed completely

1 normal at the time, and to be 100 percent sure that my  
2 daughter, in fact, did have Batten CLN7, a rare form  
3 of a rare disease, I reached out on social media and  
4 crossed paths with Dr. Timothy Yu, and I will let him  
5 tell the story of -- he speaks about what happened  
6 after that, but in one year's time from when she was  
7 diagnosed, I was told that my child had never lived  
8 with that disease.

9           One year later, we were moving from  
10 Colorado to Boston and Mila was receiving a new drug  
11 tailored just to her called Milasen and she became the  
12 first person in the world to receive a drug tailored  
13 to one patient. And suddenly the no hope turned into  
14 a real second shot at life. Mila was seven years old  
15 when she was diagnosed -- I'm sorry, when she was  
16 treated and obviously, had lost quite a lot, so she,  
17 you know, is in a place where she's must better than  
18 where she should be right now and I'm incredibly  
19 grateful not only to Dr. Yu and his team, but to the  
20 FDA.

21           I was told the FDA was going to slow  
22 progress, and instead, they absolutely played an

1 instrumental role in making this making this treatment  
2 happen and collaborated with Dr. Yu and his team.

3 So thank you very much from myself, my  
4 daughter, my family for giving her this second chance  
5 at life and I just want to kind of end my thought here  
6 with, I stay up every night thinking about the  
7 millions of children that -- you know, I don't know  
8 how it's possible, but there are millions of children  
9 that have been diagnosed with rare diseases, enduring  
10 every day, and I think about the possibility that a  
11 treatment like Mila's might be able to actually help  
12 some of those children.

13 The sum ends up being quite a big  
14 number when it adds up, and I see this as a real  
15 exciting time of opportunity and obligation to really  
16 explore a path of allowing treatments like Mila's to  
17 be able to be accessible across many, many rare  
18 diseases and hope that there will one day be a tool in  
19 the toolbox for many of those families that otherwise  
20 would have no hope.

21 MAARIKA KIMBRELL: Thank you, Julia.  
22 I've heard you speak before, and I just wanted to say

1 that every time, it's almost more and more powerful,  
2 so thank you for joining us. So we've obviously heard  
3 from a parent and caregiver and an exceptional  
4 advocate, and so now, let's turn to the sponsor  
5 investigative perspective.

6 DR. TIMOTHY YU: Thank you, Maarika.  
7 And first of all, I want to thank all of you for the  
8 chance to come and participate in this Rare Disease  
9 Day here at the FDA. I'm sitting on this stage as an  
10 example of a physician scientist who's been able to  
11 take advantage of new tools that are available to us  
12 in 2020 -- or actually, beginning in 2017, but in this  
13 new age. They're really wonderful tools for drug  
14 development that are available to us, built off of  
15 many people's decades of hard work.

16 We are also in the privileged position  
17 of having wonderful diagnostic tools, being able to  
18 sequence genomes for patients and find the answers  
19 that were often so elusive in many people's diagnostic  
20 odysseys going up to this point. And thirdly, in  
21 addition to being -- having the privilege of having  
22 great therapeutic tools and diagnostic tools, really

1     benefitting from a time of renewed flexibility and  
2     innovation on the part of the FDA to think about  
3     creative ways to apply these tools.

4                     I want to fill in some of the details  
5     as to how we came to develop what folks are saying is  
6     one of the first examples of a truly individualized  
7     genomic medicine for Julia's daughter, for Mila. We  
8     were fortunate to meet her off of social media in  
9     January 2017 and we were fortunate to be able to offer  
10    whole genome sequencing for her that not only  
11    established a diagnosis, not only named the rare  
12    disease that she had, but also pinpointed the exact  
13    mutation that Mila had.

14                    It's an interesting time. It used to  
15    be that once we categorized the disease, that that was  
16    essentially where you stopped. You would be able to  
17    provide a diagnosis, a prognosis, and you would begin  
18    working on, say, a gene therapy or a small molecule  
19    approach. And I think it's an interesting time. The  
20    way -- the reason I say that is that now, being able  
21    to pinpoint the mutation, as in Mila's case, sometimes  
22    allows you opportunities that we didn't know existed

1 previously.

2                   You've heard in earlier sessions how  
3 there are 7,000 different rare diseases and it's  
4 wonderful that we're able to name them and diagnose  
5 them, but tackling them one at a time is a daunting  
6 task.

7                   Well, we were able to find in the  
8 instance of your daughter that she had an unusual type  
9 of mutation that's a type of splicing mutation that  
10 afforded a mechanism to potential treatment that  
11 didn't require us to know that much about the disease  
12 process, to know that much about the mechanism of this  
13 defective gene, and it allowed us to develop a drug  
14 for her modeled after a drug that you've already heard  
15 about called SPINRAZA for spinal muscular atrophy and  
16 customize it quickly for her, based on studies of her  
17 own tissue samples.

18                   And with a lot of support from many  
19 people in academia and industry and from the  
20 regulatory space with the FDA, the Division of  
21 Gastroenterology and Inborn Errors, we have been  
22 treating her with this for the last few years, and to

1 what we believe is meaningful impact on her course of  
2 disease and improvement in her quality of life. So  
3 I'm up here to share a little bit of the story with  
4 you from the standpoint of a physician investigator  
5 who sees this as a wonderful opportunity to think of  
6 creative -- to develop creative different ways of  
7 tackling rare disease.

8           We've talked about finding the gene,  
9 about developing therapies, about understanding the  
10 natural history. Well, one other potential tool here  
11 is to develop treatments that might work across  
12 multiple different diseases that can be applied,  
13 depending on the type of mutation that you might have,  
14 in Mila's case, a particular type of splice mutation.

15           But our tools are increasingly being  
16 matched not just to the disease, but to the type of  
17 mutation. Single-letter changes in the genome can be  
18 fixed, in principle, with CRISPR gene editing.  
19 Nonsense mutations have other approaches splicing  
20 mutations like Mila had can be addressed with yet  
21 other approaches.

22           So I'd like to just -- I'm using my

1 time on the stage here to encourage the room, folks in  
2 the room, advocates, industry representatives, and the  
3 FDA, to continue along this vein of flexibility and  
4 thinking about creative ways to apply these new  
5 opportunities.

6 MAARIKA KIMBRELL: Thank you, Dr. Yu.  
7 So now from an investigator to an actual patient.  
8 Ella, would you take the next turn?

9 ELLA BALASA: Sure. I received an  
10 individualized therapy called phage therapy in January  
11 last year. If you're not familiar, phage therapy is  
12 the use of a very specific virus to attack a specific  
13 bacterial host. I have cystic fibrosis and this  
14 disease is characterized by bacterial infections in  
15 the lungs, predominantly. And over time, these  
16 bacterial infections lead to lung damage, lung  
17 scarring, and then eventually, respiratory failure.

18 So over the past two to three years,  
19 I've been dealing with progressively more severe and  
20 more severe lung infections. I've been -- I had been  
21 using intravenous antibiotics to treat these  
22 infections and using longer courses of treatment and

1 for, obviously, more stronger therapies as well, and  
2 even though that this wasn't sustainable for the long  
3 term with antibiotic resistance.

4           And so I heard of phage therapy in  
5 November of 2018 and I saw a documentary of a patient  
6 with CF who was treated by Yale -- Yale University  
7 Researchers -- and I contacted these researchers and I  
8 was very interested in having this therapy. And I  
9 communicated directly with them and they were very  
10 receptive and willing to answer my questions about how  
11 this therapy might interact with my body and with the  
12 bacteria in my lungs, and I have a biology background  
13 and so I think that that was helpful and made me more  
14 confident in understanding this therapy and making the  
15 decision to receive the treatment.

16           I didn't have the support of my doctor  
17 at VCU, my pulmonologist, my CF doctor, because he  
18 wasn't familiar with phage. He, you know, wasn't --  
19 didn't support that there's -- there's no evidence to  
20 it, right, it was an experimental therapy. It's not  
21 FDA approved. But I decided to go through with the  
22 therapy. So by January of 2019, I was very ill. I

1 had been dealing with a very resistant infection on  
2 multiple weeks, like, over five weeks of IV  
3 antibiotics and not seeing any relief from my  
4 symptoms.

5 I was on supplemental oxygen 24/7. I  
6 was having fevers. I was doing breathing treatments  
7 every two hours to try to clear out the lungs from  
8 just filing up with mucus. And so at that point, you  
9 know, I knew that the benefit would outweigh the risk  
10 of trying a treatment that really only a handful of  
11 patients had tried before me in modern history in the  
12 U.S.

13 And so, you know, it was kind of where  
14 I was in a dire situation and that was certainly a  
15 factor in my decision to pursue it, because I knew I  
16 needed an alternative. And so I traveled up to Yale  
17 University to receive treatment and Yale had offered  
18 for my doctor to deliver the medicine, to give the  
19 medicine to me at VCU, my home hospital, but because  
20 he was unwilling and unable, really, to navigate the  
21 INDE, IND process and finding the appropriate  
22 paperwork protocol process and as far as also the IRB

1 with the hospital at VCU, he was not able to do this  
2 for me.

3           So I traveled up to Yale and it was --  
4 it was difficult, because I wasn't sure if I was even  
5 going to be able to physically make the trip; I was  
6 that ill. But, long story short, I received the  
7 therapy and within about a week's time, I started  
8 clearing the -- that particularly terrible infection  
9 that I had and because of my positive outcomes, I've  
10 really been an advocate for getting this therapy to a  
11 larger number of patients that are in need or that are  
12 facing, you know, antibiotic-resistant infections and  
13 are dire need.

14           MAARIKA KIMBRELL: Thank you. So I  
15 think listening to you, I was reminded of a couple of  
16 things from this morning. One is clearly being a  
17 patient scientist yourself, and the other was Dr.  
18 Marks' earlier mention of this being a good example of  
19 what is often thought of as a more common condition as  
20 -- once broken up become something rare, and in this  
21 case, truly individualized. So thank you.

22           So now, let's turn to hear some

1 perspectives of some esteemed American regulators. So  
2 why don't we start with Dr. Witten?

3 DR. CELIA WITTEN: Yes, thank you. I'm  
4 Celia Witten. I'm the deputy director of the Center  
5 for Biologics and FDA and as Dr. Marks said at the  
6 previous session, that's the center at FDA that  
7 regulates blood products, vaccines, and cellular gene  
8 therapy. So in particular, the area of individualized  
9 therapies, some of the products that we have under our  
10 oversight would include phage therapy, gene editing,  
11 gene therapy, and some vaccines for treatment of  
12 cancer.

13 And all of these therapies or potential  
14 therapies have an increasingly important potential  
15 role that they can play in the lives of patients. So  
16 we really need to try to pay attention to how we can  
17 facilitate their development and availability. And  
18 some of them, of the kind of therapies that I just  
19 mentioned, some of them may be made for a specific  
20 patient and some may be customized for a patient, but  
21 either way, they're really made for an individual  
22 patient or a small group of patients.

1                   And a lot of these, the typical  
2 development path followed for -- it's not the  
3 traditional drug development pathway, which is  
4 development by a pharmaceutical company. But a lot of  
5 these products begin in an academic lab and a lot of  
6 the activity is in an academic lab and as I think  
7 we've just heard from the two patients or family  
8 members who've just spoken, and I don't know if the  
9 current system would like to, you know, work to try to  
10 facilitate availability for treatments for all  
11 patients who need it.

12                   The regulatory framework that we have  
13 right now, I think, has the flexibility to accommodate  
14 these kinds of treatments as we just heard two  
15 examples of, and we have other examples in our center  
16 of things, even, that have gone through to licensure  
17 that maybe aren't quite individualized therapies but  
18 have had some similar kinds of aspects: CAR-T cells  
19 for certain kinds of cancers or cord blood would be  
20 examples where we've exercised considerable  
21 flexibility.

22                   So what is needed to facilitate

1 development of these products and availability to  
2 patients? I think that's one of the things we're all  
3 interested in doing or hearing about. One thing, just  
4 make a couple observations. One is, there's a lot of  
5 different models of collaboration right now and some  
6 amazing individuals and organizations who are leading  
7 these collaborations to develop individualized  
8 therapeutics and also a number of models for data  
9 sharing.

10 I think we need to learn from these  
11 examples to find a way to develop these products as  
12 efficiently as possible, but I think it's possible  
13 that some new models of collaboration are -- may be  
14 needed, too, that include different stakeholders from  
15 who has traditionally been included. I mean, I'm  
16 struck not just at this meeting, other meetings I've  
17 been to, by the really heroic roles that have been  
18 played by family members and patients advocating for  
19 their families and their -- and themselves, but I  
20 don't -- I think we'd like to think, eventually, that  
21 there could be a system where you don't have to go to  
22 these heroic efforts to have a treatment available.

1 I mean, people shouldn't have a job of  
2 finding treatment for their family members or  
3 themselves. So that's -- should be a goal we all, you  
4 know, think about; although, there's certainly room  
5 for many kinds of models. So one thing Dr. Marks  
6 mentioned in the previous session and I'm just going  
7 to reiterate, that we're having a workshop. CBER is  
8 having a workshop on March 3rd to discuss some of  
9 these issues in further detail, both the technical  
10 issues related -- and these all echo themes that  
11 you've heard so far about manufacturing.

12 You know, we hear estimates of  
13 manufacturing capacity for AV vectors for all the  
14 projects that people would want to do at this time  
15 that we've heard from investigators, that they have to  
16 wait in line for availability of the vectors. And  
17 I've heard anywhere from we need tenfold more  
18 manufacturing capacity to a thousand-fold more  
19 manufacturing capacity just for AV vectors which is a  
20 promising area for gene therapy development.

21 So the manufacturing issues,  
22 preclinical testing, clinical testing, and

1 collaborations will all be discussed in this workshop,  
2 and I don't want to go on for too long, because I know  
3 we have another speaker and we want to take questions,  
4 but I just do want to mention one thing that is  
5 important also to keep in mind, which is that we have  
6 really -- when we think about these applications, we  
7 really think about that we should have two goals here.

8           One is, if there's an individual  
9 patient or a small number of patients who are in need,  
10 it's what is that patient or that small group of  
11 patients' need right now and how can we facilitate  
12 development of that product for that patient or that  
13 group. But a related question, and I think also  
14 important, is how can we leverage what we learn from  
15 that one patient or one program that will help us for  
16 the next patient and the next program?

17           Because many of our products and our  
18 product applications share something in common. If  
19 you develop a gene therapy with a AV vector for a  
20 disease or for related disease with the same mode of  
21 delivery, hopefully you will be able to learn  
22 something from one application that you can apply to

1 another. And there's a lot of challenges in doing  
2 this. I mean, phage therapy is a good example. How  
3 do you learn -- each patient may have a different  
4 resistant infection.

5           There may be a treatment developed on  
6 an individual basis for them. But still, I think we  
7 want to figure out as we go through this and as we  
8 keep in mind the needs of each patient and their  
9 family members, how are we going to also keep in mind  
10 the next patient and the next patient after that.

11           MAARIKA KIMBRELL: Thank you, Celia.  
12 Now we'll turn from CBER to -- back to CDER.

13           DR. PATROULA SMPOKOU: Hi. My name is  
14 Patroula Smpokou. I'm a clinical team leader in  
15 Division of GI and Inborn Errors Products in the  
16 Office of New Drugs in CDER. Thank you very much for  
17 the invitation to speak here. So by way of  
18 background, I'm a pediatric clinical genetics --  
19 geneticist and I practice clinical genetics for  
20 several years and also I was involved in research  
21 before joining the agency and so I think from my  
22 perspective, the case of individualized or targeted

1 therapies is very, you know, dear and near to my heart  
2 and, of course, very, very fascinating.

3 So I was fortunate enough to be  
4 involved along with, you know, collaborate with team  
5 on the application for Milasen. This was a tremendous  
6 opportunity for both myself and the team to learn from  
7 both team members, group, from the family, from -- you  
8 know, we all were very invested in trying to figure  
9 out how can we best fill the gaps and truly pave a new  
10 and novel way of looking at this case.

11 So obviously, this individualized  
12 (inaudible) therapies is a very, very novel approach  
13 and I think, you know, what you're hearing today is  
14 really very good example of collaboration but also  
15 creative thinking and really being as flexible as one  
16 can be, keeping in mind the end goal and also the end  
17 result, right. So I guess first of all, I know the  
18 panel previously talked about natural history studies  
19 and (inaudible) the disease.

20 So in Batten disease, there are some  
21 natural history studies and there's, of course,  
22 observation in day-to-day clinical practice from

1 physicians in that case, you know, and of course Julia  
2 knows this better than anybody.

3           There was kind of a clear path of where  
4 this would lead and so the question, at least from our  
5 perspective and the team's perspective is what do we  
6 need at a minimum to make sure that we satisfy the  
7 regulatory requirements the way that FDA interprets  
8 the regulatory requirements, and of course place those  
9 in the context of this individualized therapy and the  
10 individual patient.

11           And so in that spirit, I think, from  
12 our clinical team, our toxicology team, our clinical  
13 pharmacology team, so everybody kind of came together  
14 and actually had very frequent interactions with Tim  
15 and his team and it was one of those times that I feel  
16 like I was just so excited to be involved with this,  
17 that as soon as update came from Tim about, you know,  
18 what's going on, how Mila is doing, and what dose  
19 should we do next, I would drop everything and just  
20 read it and, you know, try to figure out and email  
21 people and say, okay, here's what we have now, what  
22 should we do next.

1                   And so it was great -- of course, very  
2                   satisfying because for myself, I've seen those  
3                   children, I've diagnosed those children and so I very  
4                   well know how the patients and the families think. So  
5                   I mean, from a regulatory perspective, you know, it  
6                   can be very difficult. This is novel. We're not used  
7                   to it. FDA is not used to it. (inaudible) it's a  
8                   normal paradigm and the question becomes, do you fit  
9                   this into your traditional paradigm or do you created  
10                  a brand new paradigm, right, for those individualized  
11                  therapies.

12                  And the question is, we probably do a  
13                  little bit of both, which is what our team also did.  
14                  You know, you really have to understand the  
15                  regulations deeply to really know why was it a  
16                  regulatory climate. It's not only, okay, well, you  
17                  make two studies or in two different species for  
18                  toxicology, but why is that and what could we do, you  
19                  know, to get the minimum amount of, let's say,  
20                  toxicology data, right, to have some assurance of  
21                  safety so that the patient can get treatment.

22                  So I feel like our team really did a

1 fantastic job really coming together and thinking  
2 through this and not just saying, well, that's a  
3 requirement and that's the end of it. Because that  
4 just wouldn't work, and we knew that. So a lot of  
5 lessons learned, I would say, from this case and we  
6 continue to learn as we, and of course, Tim and Julia  
7 follow Mila and how she's doing.

8           It's been very inspiring for all of us  
9 and I'm sure everybody in the room would agree and I  
10 know that from a part of CDER and OND, there's active  
11 work being done to bring people together to think  
12 through the challenges and also think creatively and  
13 realistically about how we can help in this process to  
14 move those therapies forward.

15           MAARIKA KIMBRELL: Thank you. So  
16 listening to the five of you, I've got two questions  
17 that have come to mind. The first relates to, I think  
18 maybe each of you referenced the need for flexibility  
19 and responsiveness from a regulatory perspective in  
20 these areas, and what that brought to mind for me was  
21 considerations of benefit and risk when you have  
22 previously uncharted waters in a treatment.

1                   And so could each of you sort of  
2 reflect on how you experiences with individualized  
3 therapies have brought -- how you've considered  
4 benefit and risk and how it might be different from  
5 other areas or may be similar, and from your various  
6 perspectives as patients, as parents, as regulators,  
7 and as physicians?

8                   ELLA BALASA: Well, when I received the  
9 therapy, as I mentioned, I was in a dire need where I  
10 -- my life was at risk, and so I think that's an  
11 important consideration when deciding what is the  
12 appropriate time to do an individualized therapy or if  
13 at all, and weighing that benefit and risk analysis.  
14 For phage therapy, personally, it's something -- this  
15 is not -- it is a new therapy, but it's been around  
16 for a while and it had been tested in patients before,  
17 so I wasn't the first.

18                   So I think that made me more  
19 comfortable with trying something that has been  
20 researched, has been shown to be effective; whereas,  
21 you know, with a case like Mila's, that would've been  
22 uncharted completely and so I think that that is a big

1 factor in determining whether, you know, or  
2 understanding the risks and the benefits.

3 DR. PATROULA SMPOKOU: So I guess I can  
4 go next. So that's a really important point and I  
5 guess it goes back to assessing the benefits versus  
6 the risks because the risks, of course, you cannot  
7 really assess by itself at any point in time, so from  
8 a regulatory perspective, I think every decision or  
9 almost every decision that we make and at least the  
10 way that I think about it is truly a benefit/risk  
11 assessment.

12 So the case -- in the case of  
13 individualized targeted therapies and in this  
14 particular case with Milasen, we're dealing with a  
15 neurodegenerative disease, very severe with quite  
16 clear trajectory, of course with variable progression,  
17 but we have a good idea of kind of what to expect in  
18 general, so I would say that in order to determine how  
19 much safety data, for example, you need to assess  
20 whether and IND is what we call safe to pursued, and  
21 also what dose to use, how to escalate the dose, but  
22 so a benefit/risk decision.

1                   And also, you know, what data are  
2                   emerging, how's the patient really responding to  
3                   treatment, what toxicology information do we have from  
4                   animals to maybe guide our safety monitoring to put in  
5                   that benefit/risk determination and then, of course,  
6                   how does the patient themselves report or if they're  
7                   not able to self-report, what does the family think  
8                   about how they're doing, either objectively,  
9                   subjectively. And in that way, you can put kind of  
10                  the picture together.

11                  I do believe, though, that at the end  
12                  of the day it's a truly benefit/risk decision from the  
13                  patients' and the families' standpoint. I don't know  
14                  that anybody else can make that decision, truly.  
15                  That's something that at least, you know, and for  
16                  Milasen, and I communicate that very clearly, you  
17                  know, these are the requirements. This is what, at  
18                  minimum, we want to see. We'll be in close  
19                  collaboration, and we were, and we had a very open  
20                  communication.

21                  But in terms of tool making decisions  
22                  about increasing the dose or, you know, or decreasing

1 the dose or making changes to the frequency or  
2 decisions about continuing or not continuing the  
3 treatment, I think in terms of providing all the  
4 information you have, it's really the family's  
5 ultimate decision to really weigh, what does the risk  
6 mean to them. Because, of course, patients with rare  
7 diseases, we know that very well, the definition of  
8 risk is very different that someone who may have more  
9 mild or more common disease with a very different  
10 trajectory.

11           And so we recognize that, that the risk  
12 threshold is very different and so I don't know that  
13 you can ever really truly appreciate that unless  
14 you're a patient with a rare disease, and so from a  
15 regulatory perspective, we can have an idea of what  
16 maybe the benefit is. We can have an idea of what  
17 maybe some of the side effects have been, but putting  
18 this together to actually make a decision in the case  
19 of a individualized therapy is really difficult and  
20 the patients and the families are truly the ones who  
21 can make that decision, so -- but just to point out  
22 that I think the risk, a lot of times, as you said,

1 can be defined very differently by different people.

2 JULIA VITARELLO: Thank you, Patroula.

3 I feel like you said a lot of what's been on my mind.

4 Leading up to Milasen -- to Mila receiving Milasen, I

5 have to be honest that the risk/benefit analysis was

6 pretty straightforward and black and white to me.

7 When I faced it, was the risk of treating Mila versus

8 the risk of not treating Mila. It was very specific

9 to one person, to my daughter, and what was going to

10 happen to her if she wasn't treated was very black and

11 white. She was going to lose all of her abilities in

12 a few years and she was going to die.

13 And the risk of treating her was an

14 unknown, and Dr. Yu and I had a very good

15 communication, on a daily basis, practically, and I

16 was -- feel like I was educated as much as possible in

17 what the possible risks were and we really didn't

18 know. There was no other patient in the world

19 receiving Milasen and there was actually almost no

20 other patient in the world receiving a drug like hers.

21 And I have to be honest. I never spent

22 more than one second questioning whether or not Mila

1 should start Milasen or not. There was no other  
2 option. There was no other treatment and Mila was  
3 losing her abilities rapidly, by the week, by the  
4 month. She was losing her -- down to two words and  
5 then the one word and down to no words in just a  
6 month. Taking five steps, one step, couldn't step at  
7 all by herself. And so for me, this was a great  
8 opportunity.

9 I was afraid that -- Mila was not  
10 having any pain, and so I was afraid that maybe, you  
11 know, Mila would start having excruciating pain and  
12 that was scary to think about; however, it absolutely  
13 did not influence my decision whatsoever, because the  
14 other option was, is that she was going to lose all  
15 her abilities and die. And so it was a pretty easy  
16 kind of risk/benefit analysis on my part.

17 I would just say that communication was  
18 really important in terms of being able to do my very  
19 best as a non-scientist, non-physician of  
20 understanding what Milasen entailed and believing that  
21 there was some reason to have hope that Mila could  
22 have a stable disease or potentially much less

1 quickly, I guess, declining as she was going at that  
2 moment in time. And so it did offer real hope. This  
3 was not voodoo, kind of wild stuff that, you know, it  
4 was an unknown. It was a legitimate hope that Mila  
5 was given, so I weighed this, too, and it was pretty  
6 black and white for me.

7 DR. CELIA WITTEN: I would like to  
8 reframe the question slightly the way that we think  
9 about it. But let me say it's obviously always case  
10 by case. I think the facts are different, but it's  
11 really a risk/benefit decision in the face of a  
12 certain amount of uncertainty or an amount of  
13 uncertainty.

14 And that amount of uncertainty may  
15 vary, depending on the application, and so to say who  
16 makes the decision or how you make the decision, I  
17 think it depends on a lot of things, but the  
18 uncertainty has to be taken into account. And there  
19 are other considerations, too. For example, if you  
20 look at the spectrum of the products that we've --  
21 that I mentioned are addressed in our center from  
22 phage therapy to gene editing, gene editing can't be

1 withdrawn.

2                   It's not something where you can do a  
3 dosing study and then stop it or anything like that,  
4 so for these different situations, you -- and you may  
5 have a different understanding in different cases  
6 about how likely it is to be of benefit. Like, if you  
7 have a lot of uncertainty about risk but a fair amount  
8 of certainty about benefit, you might be willing in  
9 some circumstances to act on that.

10                   So I think it would be hard to answer  
11 generally, except to say that I think the uncertainty  
12 about the information you have supporting the  
13 application is also important.

14                   DR. TIMOTHY YU: So a little bit of  
15 background on how we thought about benefits and risks  
16 as we were considering whether to offer this therapy,  
17 whether we had done sufficient work, we were just --  
18 had we done sufficient work to justify our offering  
19 this hope to Mila and her family. So just to level  
20 set so folks know what was done for this drug, we  
21 decided that we wanted to go after a splicing defect,  
22 a defect in the way that Mila's gene was being

1 assembled.

2                   And there are very simple but effective  
3 tools for looking and studying splicing if we wanted  
4 to, using patient-derived cells. So to be very  
5 concrete about it, we took a very small skin biopsy  
6 from Mila and then grew those in the laboratory and  
7 then studied her gene with and without the drug and  
8 were able to show that upon application of our drug,  
9 the splicing defect, the gene assembly defect would  
10 reverse itself upon application of this new  
11 investigational drug.

12                   So that gave us some strong basis for  
13 thinking there could be a mechanistic improvement  
14 here. We took it a step further and we also shared  
15 with the FDA data showing that would her cells  
16 actually become healthier when you've given this drug,  
17 and we showed that this disease was known to change  
18 the way that cells recycle proteins and, in fact, in  
19 the absence of this gene working properly, cells would  
20 fill up with products that were meant to be recycled  
21 but never actually made it to be recycled.

22                   And so they would build up and

1 accumulate trash, so to speak, and what we found was  
2 that treatment of her cells with those -- with that  
3 drug was sufficient to allow recycling to happen again  
4 and so they actually got healthier in front of our  
5 eyes. We could see this and you could -- we could  
6 build up a scientific rationale. This was not a shot  
7 in the dark. This was something that looked  
8 scientifically plausible.

9 All that being said, there were still  
10 many, many unknowns and that standard that I just  
11 described, while it was good in this particular  
12 instance, that's not always sufficient for a rare drug  
13 application to go through. But in this case, as we  
14 discussed, we were up against a disease where the  
15 natural history is very clear. The risks were very,  
16 very clear and we could talk about them with Julia and  
17 Mila's father and work through what exactly all of  
18 this meant to you all.

19 And it's a very individual discussion.  
20 I think that's the interesting part of this. Now, if  
21 we take an agency which holds great institutional  
22 knowledge about proper drug design and safety at the

1 level of populations, and now we throw in the  
2 application of that knowledge towards drugs that might  
3 just go to a single patient, the good news -- the  
4 decisions are so personal and so individualized, and  
5 they have to do with the physician-patient  
6 relationship and how one talks through our assessments  
7 of these risks and benefits.

8 But the good news is that the agency is  
9 populated with plenty of folks who have counseled  
10 patients on these exact issues in their own practices,  
11 and so I think the novel piece here is figuring out  
12 how the regulations that apply to protecting public  
13 health apply in the situation now where you're  
14 juxtaposing that onto individual decisions by  
15 individual families.

16 So I think that that's the part, you  
17 know, we're really grateful that you reached out on a  
18 limb to extend that paradigm to this case and looking  
19 for ways that we might continue doing that.

20 MAARIKA KIMBRELL: Great, thank you.  
21 I've got one more question and then I think we'll open  
22 it up to the audience, but we're, as we predicted,

1 eating up a lot of time, so maybe we could try to keep  
2 this one quick, but I do want to hit it.

3 So one of -- Celia, I think it was you,  
4 talked about these situations often being successful  
5 when there's somebody heroic in the mix gluing  
6 everything together or I tend to think of it as sort  
7 of the stars aligning in a particular situation, and I  
8 think our aim is that this shouldn't only be  
9 successful when the stars align perfectly or when we  
10 have heroic family members or investigators or whoever  
11 working to make something happen.

12 So what can we do, especially as  
13 regulators and -- to sort of ease that process, to  
14 ensure that these treatments are available to the less  
15 than amazingly heroic among us and then also what --  
16 in that vein, what were your reflections on working  
17 with FDA and from the FDA or sort of with the  
18 investigators of what works well, what was successful,  
19 what comes to mind as important to keep in mind for an  
20 efficient process?

21 ELLA BALASA: So I didn't have any  
22 direct communications with the FDA in my treatment. I

1 really -- I really communicated with the investigator  
2 and -- but I think, you know, as far as my case, my  
3 doctor couldn't take on that role of being the  
4 investigator. And I think that this is quite common.  
5 You know, it can be, I think, a daunting and arduous  
6 process to find the appropriate IND, making sure your  
7 protocol is streamlined, and all the communications  
8 that come along with that with the FDA.

9 I think a lot of new providers or  
10 investigators aren't aware or aren't able to do this,  
11 and I think, really, part of the FDA to help and  
12 create guidelines and really walk -- help them walk  
13 through this process so that more patients are able to  
14 access these treatments, I think a lot -- you know,  
15 there's certainly roadblocks all along this, from --  
16 honestly, I'm a patient that advocated for myself, but  
17 if I didn't have a provider that was willing to take  
18 on my case or if the communications with the FDA  
19 weren't streamlined, it wouldn't have happened. So  
20 that's really, like, the stars had to align, as you  
21 were saying.

22 And also, I think, to remember that

1 it's a resource intensive experience or process for  
2 the investigator, too, because they have to  
3 communicate with the patient. I had to feel  
4 comfortable that he had my best interests in mind and  
5 my health in mind and -- when has to communicate with  
6 the FDA, and then along with the creation or the  
7 collaboration for the creation of the investigational  
8 therapies. So it's quite a bit on an investigator to  
9 navigate all that.

10 JULIA VITARELLO: I was incredibly  
11 impressed with how Patroula and her team shifted from  
12 a paradigm that they were used to where there was one  
13 drug for thousands of people to entirely new paradigm  
14 that they had never faced before where the ripple  
15 effect was one. So it was Mila. No one else was  
16 taking Milasen and they were able to change, they were  
17 able -- faced the risk/benefit analysis and look at  
18 what the risk of treating Mila was versus the risk of  
19 not treating Mila and really treat her as one  
20 individual patient which reminded me a little bit of  
21 something like a brain tumor and removing a brain  
22 tumor and, you know, a doctor has a conversation with

1 me that says, you know, Mila has a brain tumor and we  
2 can take it out or we can leave it in, and, you know,  
3 having that kind of back and forth discussion of the  
4 risks of taking it out versus the risk of not taking  
5 it out for that specific patient.

6           And I really applaud Patroula and her  
7 team for shifting to a really different mentality that  
8 they were not used to and really thinking about Mila.  
9 And as we moved forward, now, this has opened up a  
10 potentially new field of medicine, of really truly  
11 personal medicines, and what I see is I see Mila and  
12 she was treated. And when I see potentially, you  
13 know, millions of children just with fatal diseases  
14 alone that could potentially -- we don't know yet --  
15 could potentially benefit from a treatment like Mila's  
16 and how do we get from Mila to really, truly making a  
17 difference, not just treating another two or three  
18 Milas, but really offering a tool in the toolbox  
19 across many, many diseases, and that's going to  
20 require working off of this new entirety and thinking  
21 how do we face risk/benefit analysis when there's one  
22 child or two or three and it's not being given to

1 thousands of people.

2           And so I just hope that -- my hope is  
3 that we see more of this really out-of-the-box  
4 thinking and really realize that most people like me  
5 don't have any options and that this offers something  
6 exciting, but it needs very careful and very  
7 aggressive pushing forward and opening up a new  
8 potential field of medicine. So thank you for  
9 everything you've done. I hope it continues.

10           DR. TIMOTHY YU: Okay. I thought I  
11 would like to say that cases like Ella's, cases like  
12 Mila's, these individualized cases, they require  
13 thinking, in a way, very small. They require thinking  
14 about individual patients' needs, about their  
15 particular assessments of risks and benefits, and they  
16 require thinking about treating that one patient in  
17 the doctor-patient type of way.

18           But in a way, even though these  
19 individualized cases set a template and allow us to  
20 try something new, it's worth the walk only if we also  
21 figure out how to think big. And the question is,  
22 it's not that we want to convert drug therapists' and

1 drug developers' efforts towards now instead of  
2 treating whole classes of disease at once, now just  
3 treating single patients at once. That's not the  
4 point of that. That doesn't make sense, right.

5           The point is that how can we leverage  
6 these wonderfully advancing tools to develop  
7 individualized treatments and then figure out how to  
8 scale it? And the true measure of success, I think,  
9 in this space, if we do this right, is that these  
10 first examples will pave the way for further examples  
11 such that each example that follows it gets easier and  
12 easier, not more difficult and more difficult. I  
13 think that that should be the goal of what we try to  
14 do from this point doing forward, thinking about how -  
15 - the lessons that we draw. Well, if you focus one,  
16 you -- one patient, you can get amazing things done,  
17 and can we use that to develop policies that allow  
18 that to scale and so that each patient informs and  
19 makes the next patient's journey that much easier. I  
20 think that that's a really critical piece that I see  
21 coming from this.

22           DR. PATROULA SMPOKOU: Yeah, I wanted

1 to add, the one important piece that I thought was  
2 critical in this is the diagnosis, right, so Julia  
3 talked about how there was just mutation found and you  
4 kept looking and you kept looking and if you didn't do  
5 that, you wouldn't be here, right?

6 So and the diagnosis is many of the  
7 rare diseases and in the inborn errors metabolism  
8 which is the area that I work in is sometime actually  
9 quite challenging, even in this era of this, you know,  
10 genetic revolution and all the tools that we have and  
11 all the technologies, because even if you find on  
12 mutation or two, we still have to put it in context of  
13 the patient themselves.

14 What we see sometimes is that there's  
15 no specific guidelines of how the diagnosing of those  
16 patients or how to treat them, now to follow them over  
17 time, and that really becomes an obstacle when you try  
18 to really look at a specific patient's mutation, for  
19 example, and kind of inferring how the patient may,  
20 you know, progress with a disease over time.

21 So I think what we were discussing  
22 today about Mila's case and other cases, is actually a

1 great example of all the fundamental concepts that I  
2 think were discussed throughout the day today which  
3 basically is the diagnosis is really the most  
4 important step in the awareness of rare diseases, and  
5 really, the outreach to patients who may not otherwise  
6 have access to some of those technologies through some  
7 infrastructure and networks, but also a very  
8 delineated trajectory of disease.

9           So if we didn't know anything about  
10 Batten disease, right, then that would be a very  
11 different story and so the natural history of disease,  
12 we all talk about this, but it just becomes so  
13 critical because if you don't know the trajectory of  
14 the disease and you don't know what to follow, when to  
15 follow it, what to focus on, and so, you know and the  
16 other piece of that is really the collaboration, the  
17 communication that I know we touched upon and so at  
18 least from my perspective in my division, we're  
19 involved very much in outreach and engagement and so  
20 when I myself try to attempt meetings and really learn  
21 from the outside and so I think at least for me that  
22 becomes important because you realize, what is it that

1 the community wants.

2 But 00:53:25 also the gaps that there  
3 are there and how can we, you know, as FDA, maybe help  
4 in that way to fill those gaps or bridge those, you  
5 know, those gaps in some way. For example, I go to  
6 meetings and then I hear some investigators talking  
7 about, well, FDA doesn't know, you know, what we do  
8 and what we want and I'm kind of a fly on the wall and  
9 try to listen and say, okay, what is it that we're  
10 just really not getting across.

11 And some of those actually end up in  
12 guidances, and we wrote two guidances recently on  
13 inborn errors and this is where a lot of, kind of, the  
14 engagement comes in to try to tackle some of those and  
15 this actually trickled down to how to bring people  
16 together, really, to work together in this very mobile  
17 space and the trajectory of the space is going to be  
18 changing a lot and, of course, the basic principles  
19 will apply always, and I think we all need to be aware  
20 of what those are, but also how to apply them in a  
21 flexible way, in a creative way, and really a way that  
22 makes sense to kind of all parties involved.

1 DR. CELIA WITTEN: So one thing I'll  
2 just mention, that I know this comes up a lot in  
3 different contexts, but it's critically important  
4 here, and that's about sharing information so we can  
5 learn from what we've done.

6 And it seems like it's always a hard  
7 target to hit, but in this case, it's really important  
8 because we can talk about learning from our experience  
9 or people learning from their experience, working with  
10 FDA or us learning how to work with people to develop  
11 these, but if we really want to -- and I agree with  
12 what you said, if we want to scale this, then I think  
13 we have to think simultaneously about how we're going  
14 to learn from each of these experiences, not just  
15 about the process, but about what we saw -- what we  
16 saw from whatever preclinical testing that was done or  
17 bench testing and how that -- what we learn from the  
18 patients.

19 MAARIKA KIMBRELL: I think that takes  
20 us back to Dr. Yu's comment of focusing on both  
21 thinking small and thinking very big at the same time.  
22 So on that note, if there's any questions from the

1 audience, we'd be happy to take them.

2           AMY DAHM: Hello. My name is Amy Dahm.  
3 I'm with the Cushing's Support and Research  
4 Foundation. I myself am a Cushing's patient and I  
5 also have postoperative adrenal insufficiency. And  
6 Dr. Stratakis at the NIH has been research that's  
7 showing that there are some genetic mutations that can  
8 at least contribute to Cushing's. So given that and  
9 given CRISPR, my colleagues and I have been wondering  
10 what would that look like?

11           Like, what would it look like if you  
12 took CRISPR and Cushing's and -- would it be a  
13 complete prevention of it? Would it be a complete  
14 reversal of it? Like, would you have it one day and  
15 then the next, you wouldn't? Like, what does it look  
16 like?

17           DR. CELIA WITTEN: I think that it's --  
18 I'm optimistic that in the long run we'll be able to  
19 figure out how to answer questions like that, but I  
20 think people are just starting to use -- you know,  
21 well, they have been under study for a couple years,  
22 but we're just starting to learn about how to make

1 gene editing tools useful. But the basic idea is to  
2 make a correction of the genetic defect in the cell in  
3 each cell.

4 The challenge -- well, there are many  
5 challenges, but one of many challenges is how to get  
6 it to the cell, how to -- if you can figure out how to  
7 correct the defect, how do you actually deliver it?  
8 So if you could perfectly deliver it and make these  
9 changes, then you would be good to go, but that --  
10 there's a big different -- distance between where we  
11 are not and getting there, so I'm certainly optimistic  
12 that we'll get there, but that's the current state of  
13 things.

14 AMY DAHM: Thank you.

15 MAARIKA KIMBRELL: Do we have time for  
16 one more question? One more question.

17 CHRIS DEMARCO: Hi. My name is Chris  
18 DeMarco. I was diagnosed with a rare -- ultra, ultra  
19 rare disease. It's a one-in-a-million, back last year  
20 and very quickly found out there was no research, no  
21 patient registry, no foundation supporting the  
22 disease. We started a patient registry very much like

1 -- my world changed at that moment, you know, to try  
2 to create something that would actually, you know,  
3 look for a cure for this disease.

4           One thing I found, though, is it's  
5 interesting. As soon as we got the momentum going,  
6 that people are very interested in getting engaged  
7 and, you know, we've talked about a proof of concept  
8 for liver gene therapy, but a lot of it comes down to  
9 funding, you know, and so I'd be interested to know  
10 the -- from a individualized therapy, this is an ultra  
11 rare. It's like one in a million, so it's -- we found  
12 maybe about 20-some-odd patients around the world so  
13 far.

14           But being able to get someone  
15 interested in funding something like, if we got  
16 positive results from the liver gene therapy, you  
17 know, you're talking about individualized therapies,  
18 it's got to be significant amount of money.

19           DR. CELIA WITTEN: Yeah, I think that  
20 is a challenging area, which is why I think we're --  
21 we have to discuss that collectively because I don't -  
22 - a lot of these, it's hard to see what the commercial

1 model, you know, what the model is for making these  
2 commercially viable efforts. So I don't think it's  
3 going to follow any kind of traditional pharmaceutical  
4 company supports it, kind of model. But I know you  
5 have probably -- Dr. Yu would have something to say.

6 DR. TIMOTHY YU: Thank you for  ise  
7 that question. It's one of the biggest challenges in  
8 this space. I think that what we have are issues of  
9 drug design, drug testing, manufacturing, toxicology,  
10 and then administration. And we have standards that  
11 have evolved for how to do those things safely and  
12 effectively. By and large, many of those standards --  
13 all of those standards have evolved with the best  
14 interests of patients in mind to protect their safety  
15 and to ensure the utility of the drugs that actually  
16 make it through the pipeline.

17 But I would -- I might argue personally  
18 that many of those standards have evolved in the area  
19 of big drugs like statins that might be given to tens  
20 of thousands of patients at a time. Now, I know  
21 that's an over simplification that that there are many  
22 forward-thinking ways about how to apply these

1 standards to smaller and smaller populations where  
2 that kind of investment can't be easily raised, but  
3 not take that drug development process and now apply  
4 it to a single patient for a family that's in dire  
5 need, and you've gone and blown up the problem even  
6 bigger.

7           These are really expensive projects and  
8 as -- I'd say, there's no norm. I'd say our first  
9 case, our one -- our first case of a brand new drug  
10 developed for a patient doesn't establish a norm. It  
11 just highlights an issue that needs to be solved,  
12 which is that it takes too much money to navigate all  
13 of those steps that I described and we just have to be  
14 creative about finding solutions.

15           I'll put in one brief plug. I'll say  
16 that for the particular route that we chose, we chose  
17 to use an antisense oligonucleotide drug approach, and  
18 that's an approach that has been around for about 30  
19 years. The basic manufacturing process has -- it  
20 relies on chemistry that was developed 30 years ago --  
21 actually, a lot more than 30 years ago, and as far as  
22 manufacturing processes go, I think arguably it's

1 among the simpler, much simpler than, say, gene  
2 therapies.

3           So you can mitigate the costs of  
4 manufacturing in a case like that, but on animal  
5 testing and toxicology, that's still extremely  
6 expensive, so finding ways to really make this work  
7 will require thinking about ways where we can leverage  
8 results from one experiment to another experiment of a  
9 close -- involving a closely related drug and another  
10 experiment involving another closely related drug.

11           If we're learning from each of those  
12 and the learnings bolster one another, we should be  
13 able to shrink that gap. I don't know if it will be  
14 sufficient, but we have to try.

15           MAARIKA KIMBRELL: Great, thank you.  
16 And I think we're about to be dragged off the stage.  
17 So let's -- I think Dr. Maynard's going to introduce  
18 the next panel, but thank you everyone and thanks to  
19 the panelists.

20           DR. JANET MAYNARD: Thank you so much,  
21 and if I could invite our last panelists, Panel 5, the  
22 Ecosystem of Rare Disease Product Development, on the

1 stage. If you don't mind sitting in the order on the  
2 screen, it will just make it easier as I put your name  
3 under. So Susan, you can sit here. Yep, then Martha.

4 DR. SUSAN MCCUNE: That's --

5 DR. JANET MAYNARD: Oh, no, I'm sorry.  
6 Chris.

7 DR. SUSAN MCCUNE: All right. Good  
8 afternoon, everyone. Wow. So we're bringing it home,  
9 guys.

10 DR. CHRISTOPHER AUSTIN: They're all  
11 still here.

12 DR. SUSAN MCCUNE: I know, and  
13 everybody wants to hear everything you have to say.  
14 So I'm really excited to be moderating this panel and  
15 I'm really excited because I'm not going to have to do  
16 much talking because I have real experts up here on  
17 stage.

18 So I'm Susan McCune. I'm the director  
19 of the Office of Pediatric Therapeutics in the Office  
20 of the Commissioner at the FDA and a little background  
21 on me is that I'm a pediatrician and my subspecialty  
22 is newborn intensive care, so we're going to the

1 extreme, young extreme for me and it's always an  
2 opportunity for me to think about how to move some of  
3 these therapies forward in the neonatology space.

4           And as I was talking to Janet, it's  
5 nice that I was going to help to focus some of the  
6 discussion today on pediatrics, but I don't need to  
7 because we've actually had a lot of really good  
8 discussion about pediatrics throughout the day in all  
9 of the panels.

10           So I know that we will continue to do  
11 that here as well, but I don't think we have to  
12 highlight it as much as I thought we were going to.  
13 So with that, we're going to talk about the ecosystem  
14 of rare disease product development, especially  
15 related to a lot of collaborations and we kind of  
16 talked about that sort of through the course of today.  
17 I'm going to let all of my august panel members kind  
18 of introduce themselves and as you're introducing  
19 yourself, tell us kind of a little bit about high  
20 level, what you think in terms of where we are in  
21 terms of the ecosystem and collaborations for rare  
22 disease product development and then I'll ask maybe

1 some specific questions as we go along and then we'll  
2 open it up for panel discussion after about half an  
3 hour. So, Chris, why don't we start with you?

4 DR. CHRISTOPHER AUSTIN: Yeah, sure.  
5 So thanks. I'm the person that the panel -- one of  
6 the panelists kept talking about, so I -- my ears were  
7 burning. I'm the director of a part of NIH you may  
8 never have heard of. It's called the National Center  
9 for Advancing Translational Sciences. It's one of the  
10 institutes at the NIH. If you were here for the panel  
11 this morning on natural history studies, you would  
12 have heard Ann Pariser. She runs our Office of Rare  
13 Diseases Research, which is part of NCATS.

14 I guess my perspective about the  
15 ecosystem is -- I guess I might summarize in two ways.  
16 First, the fact that we're having this meeting at all,  
17 I think we all need to celebrate and you need to  
18 congratulate yourselves for getting us here. Twenty  
19 years ago, when I was laboring away, as a lot of were  
20 then in this field, it felt very, very lonely and it  
21 doesn't anymore, and that's because of the efforts of  
22 a lot of people at the FDA, a lot of researchers, but

1 also a lot of patients like you.

2           And the only reason we've gotten here  
3 is because of the collaboration with all of you. At  
4 NCATS, we like to say that everything we do is a  
5 collaboration and, in fact, that is true, and that's  
6 because the field of translation, which we do, is, as  
7 we like to say, is a team sport. I don't care how  
8 smart you are, how motivated you are, you cannot  
9 successfully transform a fundamental discovery into an  
10 intervention that is shown to improve human health --  
11 that's what translation means in medical parlance --  
12 by yourself.

13           And I think one of the changes that  
14 we've seen which have enabled some of the remarkable  
15 things that we've seen in the last few years is this  
16 slow change toward teamwork. Scientists are not  
17 trained to be -- at least, traditionally they have not  
18 trained to be team members. My own well-meaning  
19 mentor when I was growing up told me never to  
20 collaborate with anybody, because all you're going to  
21 do is get scooped and, you know, you'll get hurt and  
22 all these things.

1                   And she was very well meaning and  
2 looking out after my best -- what she thought was best  
3 for me, and I think in basic research, that can  
4 happen. But in translational research, you just can't  
5 get anywhere without doing this, so I think I'm really  
6 pleased about where we've gotten. You should know,  
7 however, that your academic colleagues are swimming  
8 upstream in this kind of behavior.

9                   It is still not rewarded as it should  
10 be in the academic world. We're trying very hard at  
11 our place to change that and we need all the help we  
12 can get. And when I look at the limitations that we  
13 have to getting to the dream that we all have, so how  
14 do we take these extraordinary examples like Milasen  
15 that you just heard or the SMA example or others you  
16 probably know, and making that promise a reality for  
17 the many, many, many people for whom it is technically  
18 possible now -- which itself is a miracle -- what is  
19 that going to take?

20                   It is going to take all of us to up our  
21 game another order of magnitude to working together  
22 and to realize that we have much more in common than

1 what separates us. We may have different disease  
2 names, but they're all rare diseases. They're all  
3 connected in one way or another. And what we see over  
4 and over and over again is the more -- we have a very  
5 diverse team of people who thought they had nothing to  
6 do with each other that gets together to work on a  
7 common problem.

8 That's when magic happens, and I think  
9 the more we do that and the more we pull together as a  
10 community, whether it's with data or looking for  
11 commonalities among diseases or platform technologies  
12 like we've been talking about or regulatory approaches  
13 like is all -- been talking about, the more we do  
14 that, the faster we'll make headway.

15 DR. SUSAN MCCUNE: Thank you. Martha?

16 DR. MARTHA DONOGHUE: Hi, good  
17 afternoon. Is this working?

18 DR. SUSAN MCCUNE: Mm hmm.

19 DR. MARTHA DONOGHUE: Excellent. My  
20 name is Martha Donohue. I am a pediatric oncologist  
21 and clinical team lead for the team that oversees the  
22 regulation of new cancer drugs to be developed for

1 gastrointestinal cancers and I also do quite a bit of  
2 work through the Oncology Center of Excellence on  
3 pediatric oncology initiatives and it's a pleasure to  
4 be here, so thank you so much for having me.

5 I guess to summarize sort of where I  
6 think the ecosystem is for development of rare -- of  
7 drugs to treat rare cancers, I think the ecosystems is  
8 alive and well. It's evolving and changing and is  
9 extraordinarily complex and it's exciting to be a part  
10 of it, even in a very small way.

11 And the field of oncology, I think,  
12 mirrors a lot of sort of what we're seeing for a lot  
13 of other diseases in that, with the advent of  
14 personalized medicine, we're seeing some amazing  
15 advances and potential for development and approval,  
16 actually, of drugs to treat a variety of diseases that  
17 heretofore we were having very limited success for.  
18 One example is the approval larotrectinib and  
19 entrectinib for NTRK fusion solid tumors and for one  
20 of the very first time, we were able to approve a drug  
21 not based upon sort of the histology of the tumor or  
22 where the tumor was in your body, but rather the

1 molecular underpinnings of that tumor and what was  
2 driving that tumor.

3           And while these are amazing success  
4 stories, they also highlight the challenges of  
5 development of drugs to treat rare cancers, so while  
6 we were able to give a relatively broad indication for  
7 these two drugs based upon a biomarker and tumor, at  
8 the same time these biomarkers were extraordinarily  
9 rare for almost every cancer, so less than 0.1 percent  
10 to 0.2 percent of all types of adult cancers would  
11 have this biomarker and on the other hand, you'd have  
12 some very, very rare pediatric tumors such as  
13 infantile fibrosarcoma that would have this biomarker,  
14 but those cases would only be a handful.

15           And so looking at the drug development  
16 paradigm for -- those particular drugs highlighted a  
17 lot of the challenges for rare disease drug  
18 development. How do you find the patients,  
19 particularly when you're thinking about clinical  
20 trials for a drug? How do you enroll patients where  
21 there only may be a handful of sites, and yet the  
22 patient may be thousands of miles away? And how do we

1 assess effectiveness of a drug when we don't do a  
2 randomized clinical trial and certainly where placebo  
3 control would not be ethical?

4           And so when we're looking at specific  
5 cases like that, it kind of helps us to kind of  
6 innovate and drive collaboration and communication  
7 with one another and be flexible and creative and all  
8 those other attributes that I'm hearing a lot of other  
9 people speak about on this panel. And it's, you know,  
10 examples like this and our increased understanding of  
11 the molecular biology of cancers that's transforming  
12 the way we look at cancer drug development, where we  
13 typically would have the luxury of large trials and  
14 big development programs for lung cancer and colon  
15 cancer, for example.

16           Now, we're seeing smaller and smaller  
17 pieces of pie within those large cancers and we're  
18 having to figure out, how do we develop drugs  
19 efficiently and get these drugs to patients faster?  
20 You know, at the same time, we're looking at not just  
21 developing drugs. We're looking at developing the  
22 technologies to identify patients who could benefit

1 from these drugs, and so that adds a degree of -- an  
2 additional degree of complexity to drug development.

3 So in order to address these challenges  
4 and many opportunities that we have to get drugs to  
5 patients more quickly, collaboration, communication,  
6 working together becomes even more imperative than it  
7 once was. It's always been important, but as we're  
8 seeing more and more things become rare diseases, it's  
9 forcing us in many good ways to work together. And so  
10 what I've seen, at least, in the area that I work in  
11 at the agency over the past five to 10 years, is  
12 increased energy being spent toward this collaborative  
13 process.

14 We have the Oncology Center of  
15 Excellence forum in the Office of the Commissioner,  
16 and the reason for the Oncology Center of Excellence  
17 is for us to collaborate with one another more closely  
18 across centers so that we have a better understanding  
19 of what's going on with cancer drug development in the  
20 Center for Biologics, the Center for Devices and  
21 Radiologic Health, and the Center for Drug Evaluation  
22 and Research so we can work together to streamline

1 things to the extent possible and to share  
2 information.

3 We're also seeing increased emphasis on  
4 working outside of our own organization, working --  
5 reaching across the pond to work with European  
6 regulators, for instance, and we're seeing true  
7 tangible success from some of these efforts.

8 We're just piloting a program now  
9 whereby we're reviewing drug applications in a  
10 coordinated way with other regulatory authorities and  
11 I think that we're early stages for that, but that  
12 provides us with an opportunity to talk to one another  
13 more, maybe streamline evaluation of a specific  
14 application to benefit patients, but also learn from  
15 one another in the long term so that we can learn to  
16 work together even early in the drug development  
17 process.

18 So I guess I'll end there, but I do  
19 think it's an exciting time to be in this environment,  
20 rare disease development. I think there's a lot of  
21 energy being applied to it and a lot to learn and a  
22 lot to do.

1 DR. SUSAN MCCUNE: Sheila?

2 SHEILA MIKHAIL: Hi. My name is Sheila  
3 Mikhail. I'm the CEO and co-founder of AskBio.  
4 AskBio is an AV gene therapy company. It started off  
5 as a collaboration, so collaborations are at our  
6 roots. It was started by parents who had children  
7 with devastating disease. Traditional medicine didn't  
8 provide them with any answers, so they reached out to  
9 researchers.

10 These were very educated research  
11 patients -- research scientist's patients. They read  
12 every single paper. They looked at all different  
13 types of alternative medicines and they were extreme  
14 advocates for their children, really admirable people.  
15 They reached out to Jude Samulski who was the first to  
16 clone AAV for therapeutic purposes. He's the  
17 scientific founder of our company. And if it wasn't  
18 for those parent collaborators, we wouldn't be here  
19 today.

20 For a long time, gene therapy was not  
21 seen in the best of light. People thought it was too  
22 risky and it was too much science fiction. I would go

1 to different investor conferences with all the Wall  
2 Street crowd and they would just walk away from me.  
3 It was almost like I had the Coronavirus written on my  
4 forehead.

5 Today, it's a different era, but again,  
6 I think the number one thing that I want to say is you  
7 really have to collaborate with patients because  
8 that's what makes your effort sustainable. They can't  
9 walk away, in many instances, from their endeavors and  
10 their money is short of a short-term goal. But having  
11 -- making treatments that have benefit for patients is  
12 a much more long-term, sustainable objective. Over  
13 the years, we have developed treatments for Duchenne's  
14 and in a second I'm going to talk about that and how  
15 we use collaborations to advance that drug.

16 We also developed treatments for giant  
17 axonal neuropathy, and in that case, we had parents  
18 who had Relay for Life races and bake sales, but on  
19 the basis of those grass roots fundraising efforts, we  
20 actually have treated several patients and with the  
21 collaboration of NIH and the support of NIH.

22 We have also advanced treatments for

1 hemophilia which are now being advanced by Takeda.  
2 We're in the clinic right now for a Pompe and heart  
3 failure -- late stage heart failure. We'll be in the  
4 clinic hopefully by the end of the year for MMA and  
5 limb-girdle 2i. We're also working on Huntington's  
6 which we hope to be in the clinic next year. Gene  
7 therapy is exciting.

8                   It has a lot of potential and it's  
9 giving a lot of hope to patients, and I'm very  
10 fortunate to be part of this change in making history.  
11 The example that I want to give is in the treatment of  
12 -- the development of the treatment for Duchenne's  
13 muscular dystrophy. As I mentioned, we started our  
14 efforts at a time when gene therapy was perceived as  
15 science fiction. We could not get funding for the  
16 product.

17                   We had parents who literally put in  
18 their own money, did bake sales, did a lot of things  
19 to advance a therapeutic. GSK, this is another  
20 example of a collaboration, gave us access to a capsid  
21 that they just had sitting on the shelf and that  
22 allowed us to use what we thought was going to be the

1 best capsid available.

2 We collaborated with academics who had  
3 the dog models, the Golden Retriever dog models and  
4 didn't have a lot of money, so people are just -- are  
5 kicking into this effort. We went into the clinic  
6 with the support of the Muscular Dystrophy  
7 Association. If it wasn't for their support, we  
8 wouldn't have gone into the first -- into the clinic  
9 the first time. At that time, it was in the last  
10 2000s.

11 People were very skeptical of gene  
12 therapy, so we could only inject in the muscle and in  
13 very small area, only put a small amount of virus into  
14 little boys the size of an eraser. Not -- knew it  
15 wasn't going to have therapeutic effect, but we had to  
16 demonstrate that it was safe, baseline safety. We  
17 were successful there.

18 Again, we went back up to Wall Street.  
19 We had dogs out nine years showing that we could  
20 correct the dog model. Could not get funding.  
21 Everybody said, it would not work. (inaudible)  
22 stepped up, helped us -- another collaboration -- with

1 the funding to do all the I&D enabling studies. We  
2 ran out of money, but we had the opportunity to  
3 collaborate again with Pfizer. Pfizer has taken the  
4 drug into the clinic.

5           They now own all rights to it, but  
6 we're very happy because we have met many of the boys  
7 in that clinical trial and they should be in  
8 wheelchairs today but instead, they're playing Little  
9 League baseball and they're enjoying swimming lessons,  
10 and that's why most of us in this space do what we do.  
11 We get up in the mornings because we want to make a  
12 difference in patients' lives and we have had had the  
13 satisfaction of ASPIRE, of having that impact on  
14 patients.

15           The other thing I want to mention is  
16 our foundation, because it's equally important to me  
17 as the for-profit part of our business. Columbus  
18 Children's Foundation was founded -- again, we were  
19 very patient motivated to address the needs of ultra  
20 rare indications that can be treated by gene therapy.  
21 We do this through a nonprofit structure. These are  
22 indications with 100 or so or fewer patients.

1           We don't have a hard stop, but we know  
2           that those are not commercially viable indications,  
3           and so we donate our technology, our manufacturing  
4           capacity, our (inaudible), our regulatory, our legal  
5           support to the advancement of these drugs. Today,  
6           we're working on AADC, amino acid decarboxylase  
7           deficiency. That's a mouthful. And we have treated  
8           20 patients free of charge. I think we're one of the  
9           few groups that has done that.

10           We're also -- have in our pipeline for  
11           the foundation (inaudible). So those are the diseases  
12           we're working on. Thank you.

13           DR. SUSAN MCCUNE: Vasum?

14           DR. VASUM PEIRIS: Thank you. Mic's  
15           on. Perfect. First of all, thank you very much for  
16           everybody for continuing to stay here. This is a very  
17           important cause and it's wonderful that as we've  
18           talked about before, that the meeting is happening. I  
19           just want to thank Janet and the entire OOPD team that  
20           has put this together and all of the people that have  
21           worked to get this to happen, so it's wonderful to see  
22           so much registration and so much interest across the

1 country and across the globe in these issues where  
2 rare diseases.

3 Very simply put, in terms of  
4 introductions, I'm going to build on what Jeff, Dr.  
5 Shuren, the center director mentioned. For the  
6 purposes of this panel, I am the gizmo guy, so I'm the  
7 chief medical officer for pediatrics and special  
8 populations at the Center for Device and Radiological  
9 Health. My clinical background is in pediatrics,  
10 (inaudible) pediatrics, pediatric cardiology, and  
11 adult congenital cardiology.

12 So I really had an opportunity in  
13 private practice to see everything from the fetus,  
14 prenatal, perinatal medicine all the way through the  
15 hundred-year-old and you can imagine in a field like  
16 congenital heart disease, it's extremely device rich,  
17 but certainly very much also dependent on medications  
18 and I'm sure to (inaudible) share great deal of  
19 insights with Susie with respect to any neonatology as  
20 well.

21 There's a lot of topics to address, but  
22 I'll try to focus on that you brought us towards, as,

1 you know, what is the ecosystem, what is the state of  
2 the ecosystem and where are we going, really. I think  
3 it is wonderful that we are coming together and that  
4 there again, there's so much interest. There is a  
5 great deal of work that's being done, I think, in the  
6 biologics and drug space.

7           There continues to be great potential  
8 in the device space and I think as we move forward, we  
9 recognize how much devices and advancing technologies  
10 will make a difference in patient lives and the  
11 difference that they make every single day in patient  
12 encounters. If you really think about it, when you go  
13 to a doctor and you have a doctor visit, there's a  
14 higher likelihood that you actually might engage with  
15 a medical device -- you know, a thermometer, a  
16 dipstick, a blood pressure cuff -- than you might with  
17 a drug.

18           That that's something to be cognizant  
19 of as we think about how technologies are affecting  
20 lives and especially with respect to small populations  
21 and rare diseases. We -- a couple of the earlier  
22 panels alluded to this a little bit, but I think

1 there's necessity to really work -- maybe focus on  
2 this a little bit more, but with respect to how we can  
3 begin to advance technologies to truly serve the  
4 purposes of small populations, pediatrics, and rare  
5 diseases, we have to begin the potential of the  
6 ecosystem together.

7           And the issue around collaboration that  
8 Chris mentioned, I think is an important one. I'll  
9 just highlight one point around that very historical  
10 notion that people were told back in the day, perhaps,  
11 don't collaborate because your academic careers really  
12 are based off of you being the leader, you being the  
13 thought leader, you taking forward research.

14           It's wonderful to see that medical  
15 schools across the country in their mission statements  
16 now are putting in that they -- one of their purposes  
17 is to develop collaborative professions. And that  
18 collaboration over time can make a significant  
19 difference.

20           And from where we are right now, when  
21 you think about how do we optimize the potential of  
22 the ecosystem, we've got to bring together issues not

1 just in the regulatory space, not just in the clinical  
2 space, but in the economic space as well because we  
3 recognize that there are a great deal of efforts that  
4 could be considered perhaps one-offs, a great deal of  
5 philanthropic investment in certain area, either  
6 certain aspects of Milasen or a specific disease or a  
7 specific drug or a specific medical product.

8           What we want to get towards is a  
9 platform that allows anybody with great ideas, great  
10 potential, to be able to invest in the development of  
11 medical products for rare diseases, especially in the  
12 pediatric population. One of the things that Dr.  
13 Shuren mentioned earlier is the SHIP Program. That's  
14 the System of Hospitals for Innovation in Pediatrics.  
15 It is a program and a framework that we've put  
16 together to really consider what is the next step in  
17 an ecosystem that truly works for the benefits of  
18 small populations and pediatrics.

19           How do we begin to bring together  
20 individuals and organizations across the ecosystem and  
21 across the spectrum to truly begin to think  
22 differently around investment in pediatrics so that we

1 can actually get to a point where when technologies  
2 are being developed, pediatrics, rare diseases, small  
3 populations are considered as part of the deal. It's  
4 going to be an afterthought. It's not going to be  
5 done years later.

6 It's not going to be considered as a  
7 potential and perhaps never get there because there's  
8 additional costs and legal issues afterwards, but it's  
9 going to be done from the beginning. So I'll stop  
10 there. Lot more to talk about, but hopefully that  
11 gives you a little bit of introduction of where we're  
12 headed.

13 DR. SUSAN MCCUNE: Rhiannon.

14 RHIANNON PERRY: My name is Rhiannon  
15 Perry. I was born with sickle cell and lupus. For  
16 about 13 years, I was in and out of the hospital  
17 working on fixing the issues that both the combination  
18 of sickle cell and lupus have caused. Around four  
19 years ago, I took part in an experimental  
20 haploidentical bone marrow transplant to cure both  
21 diseases and now that I'm cured, I'm working with  
22 organizations like Hope for Henry and the ICAN

1 Initiative to help bring awareness to those rare  
2 diseases and the causes.

3 ICAN and being part of the Hope for  
4 Henry patient and team board collaboration is a really  
5 important step to bring more awareness to these  
6 diseases and to start a communication and  
7 collaboration with patients and the environment and  
8 the community around and to better educate more people  
9 about the things that are going on with those  
10 diseases.

11 DR. SUSAN MCCUNE: So thank you all  
12 very much. I think as you all have seen, we have  
13 pretty much representatives of most of the  
14 stakeholders either in your past life or your current  
15 life up on the stage in terms of patient advocates,  
16 academia, industry, and government entities. And  
17 round five years ago, we started the International  
18 Neonatal Consortium and really thrilled at that time.  
19 It was one of the first consortia efforts that were  
20 undertaken and I'm thrilled today that every panel had  
21 talked -- has been talking about public-private  
22 partnerships and consortia efforts and I'm going to go

1 back to Rhiannon to start the conversation.

2 Rhiannon mentioned ICAN, which is the  
3 International Children's Advocacy Network, and has  
4 been very, very important in understanding what end  
5 points and what clinical trials are meaningful for  
6 pediatric patients. And so my question to the folks  
7 on the panel is, all of us have been involved in  
8 consortia efforts. Clearly, we not have -- we're now  
9 getting an experience that's in -- upwards of years,  
10 and now we probably have a good deal of insight into  
11 what has worked really well and where there's some  
12 challenges associated with consortia efforts.

13 So I'm going to open it up and start  
14 maybe with Rhiannon at the end, just talking about  
15 what are the -- what are some of the examples of  
16 successful efforts from the consortia perspective,  
17 what are done well, and then where are -- where do we  
18 have some challenges.

19 RHIANNON PERRY: So like I said before,  
20 I work with Hope for Henry and so we have a patient  
21 advisory council and then we also have a teen board  
22 where teens in the community can come take part of

1 programs and fundraisers for Hope for Henry to better  
2 provide incentive programs for patients and so we did  
3 -- collided those two programs or groups to take part  
4 in the ICAN chapter and so with the ICAN chapter, we  
5 do a lot of community work.

6           There are two important parts. There's  
7 education incentive and then there's also the feedback  
8 incentive and so the education incentive part is where  
9 we go into Children's National Medical Center and we  
10 talk with researchers and doctors and those who are in  
11 the field who can explain what they do, why they do  
12 it, and how they do it and better educate us on the  
13 importance of their role in the community.

14           And then we also, what the feedback  
15 initiative is, a lot of the patients are able to look  
16 at these programs that are implemented to help them  
17 and to kind of discuss what's good and what's bad  
18 about it. So the ICAN program is great because we are  
19 able to collaborate with the community and we're able  
20 to spread awareness about these diseases and illnesses  
21 that really need to be brought up. And one thing that  
22 we can definitely work more on is our outreach in

1 reaching other communities, other areas in the world  
2 to bring more awareness to that.

3 DR. SUSAN MCCUNE: Thank you. So we're  
4 going to go right back -- right back the way we came.

5 DR. VASUM PEIRIS: Oh, I thought we  
6 were going to go hand written here. Your focus is  
7 really around what is -- what's working well in  
8 consortia, perhaps what's not, how do we improve, that  
9 type of...

10 DR. SUSAN MCCUNE: Yes.

11 DR. VASUM PEIRIS: Yeah.

12 DR. SUSAN MCCUNE: You know, what's the  
13 experience, because now we've been -- each of the  
14 panels before us has really talked about public-  
15 private partnerships and consortia efforts and  
16 everyone has some experience with that. And what have  
17 we learned that works or that people know kind of from  
18 your experience what's worked, and then what are some  
19 challenges that maybe other folks can help in --  
20 address some of those challenges?

21 DR. VASUM PEIRIS: Yeah. So thanks.  
22 It's a great question and I think something that

1 absolutely makes a difference for the types of  
2 initiatives that are necessary to really move forward  
3 in the field of rare diseases. I know that there have  
4 been a number of different consortia efforts that have  
5 some together in an attempt, in their own spheres to  
6 break down silos.

7           And what you recognize sometimes is  
8 that perhaps there are still silos within those  
9 consortia and so how do we begin to get to a point  
10 again where we truly are beginning to take a look at  
11 this from a very global standpoint where the entire  
12 ecosystem is being optimized, truly, for the benefits  
13 of patients and that is a little bit of the work, I  
14 think, that we're trying to do right now with the  
15 consortia that we're developing for around SHIP.

16           We wanted to ensure that stakeholders  
17 across the ecosystem are involved, patients included,  
18 but that also includes, again, not just that  
19 regulatory world like I mentioned before. It also  
20 brings into play the individuals that invest in the  
21 development of these medical products, like  
22 (inaudible) Funds, Angel Funds, all of that, because

1 without creating a system that brings together all of  
2 those different players, it's really difficult to make  
3 a -- to develop a platform and a system that truly  
4 makes a difference for patients.

5           So making sure that when we do develop  
6 consortia that all the right individuals are -- and  
7 organizations and perspectives are represented. It  
8 is, I think, very simply put, naively put, important.  
9 But making that take effect, that sometimes is a  
10 challenge and how do we truly continue momentum and  
11 bring all of those individuals together in a  
12 collaborative community type atmosphere to be able to  
13 move this field forward.

14           DR. SUSAN MCCUNE: Sheila?

15           SHEILA MIKHAIL: I find that people are  
16 usually more cooperative in collaborations when they  
17 have something to gain and little to lose. And what I  
18 mean by that is often, they work much better when  
19 there's not competing interests, but when there's  
20 synergistic interests or new opportunities. So I  
21 think of, for example, a lot of the collaborations  
22 that -- and consortiums I'm involved in, where there's

1 a complement of gene editing technology with AV  
2 delivery technology, that works extremely well vis-à-  
3 vis to AV companies working maybe on the same  
4 diseases, that works less well.

5           Where there's a new use of a  
6 technology, for example we discovered that a Doggybone  
7 technology -- Doggybone DNA technology that's used for  
8 vaccines can be used to produce plasmoid without big  
9 bioreactors and E. coli, so it's safer for patients,  
10 it's quicker. I will reduce manufacturing costs.  
11 That was a good collaboration because there was  
12 something for everybody to get out of it, right,  
13 nothing was being taken away. There was only upside.

14           Where there's safety issues that affect  
15 technology, it's to everybody's interest to make sure  
16 that patients have the highest level of safety and  
17 that we address these as an industry. So for example,  
18 in our space, it's well known that there is often  
19 transaminitis associated with the delivery of AV  
20 therapeutics, so many of us come together to try to  
21 address those issues, share data, try to make sure  
22 that we optimize the safety of our therapeutics for

1 patients.

2                   Where there's industry standards that  
3 affect everybody, once again, titering is a big issue,  
4 titering of our material -- AV material in the  
5 manufacturing process. That's another area where  
6 people come together because there's a common  
7 interest. So I think there's many places where people  
8 can play nicely together, but I think we all have to  
9 be knowledgeable that sometimes there are tensions  
10 because we're also forced to compete.

11                   DR. SUSAN MCCUNE: Martha?

12                   DR. MARTHA DONOGHUE: Hi. I guess I'll  
13 speak a little bit to an example in pediatric oncology  
14 and I think of rare disease drug development, drug  
15 development to treat rare cancers, really need to be a  
16 global enterprise and because of the issues relating  
17 to the rarity of pediatric cancers or pediatric  
18 diseases in general, there are sometimes complimentary  
19 or competing regulations in various countries that  
20 will either mandate clinical trials in pediatric  
21 patients or offer incentives.

22                   And for the most part, I think these

1 regulations are wonderful and important, but they also  
2 have the potential to cause differences and they way  
3 we're applying these regulations that can scuttle or  
4 certainly make drug development for children more  
5 difficult and we were running into that a little bit  
6 in the past with respect to oncology with varying  
7 regulations in in Europe requiring one thing and then  
8 the timing of our incentive process sort of being a  
9 mismatch.

10           And so companies who are looking to  
11 develop drugs globally, it puts them in a bind,  
12 frankly, I think some of the time, because they're  
13 getting different advice and really what we want is  
14 one clinical trial that's going to answer a scientific  
15 question rather than something more distinctive than  
16 that, so a new regulation that's going to come in  
17 effect in August whereby the U.S. we're going to be  
18 able to require certain pediatric investigations for  
19 cancer therapeutics being developed in adult patients  
20 that have a mechanism of action that's applicable to  
21 oncology and in children -- to cancers in children.

22           And it's very exciting and I think it's

1 really going to help move drug development forward for  
2 children, but we're in a circumstance -- will be in a  
3 circumstance soon where we're thinking about, okay,  
4 well we have lots of drugs, maybe four, five, six  
5 drugs with a particular mechanism of action but yet we  
6 have a very small pool of patients and so how do we  
7 figure out how best to study these drugs in children  
8 so that we're not duplicating our efforts and  
9 certainly not competing with one another?

10           And if so -- they developed in Europe  
11 back -- starting in about 2013 an organization called  
12 Accelerate and what's unique about this organization  
13 is that it brings together patient advocacy groups,  
14 international regulators, companies developing drugs  
15 for cancer, and scientists all together in a pretty  
16 competitive space on a regular basis to take on  
17 certain issue and try -- and really encourage free  
18 flow of information to help everyone make the best  
19 decisions possible to develop drugs more efficiently  
20 for kids.

21           And while it started in Europe,  
22 recently, over the past year-and-a-half to two years,

1 they've been increasing involving in the -- with the  
2 U.S. as well with the help of an advocacy group called  
3 (inaudible). We had our first meeting in the United  
4 States this fall and this particular one was on  
5 development of a particular class of drugs called  
6 epigenetic modifying agents for patients with cancer,  
7 for pediatric patients with cancer.

8           And because of the ability to have this  
9 informal communication with one another, I think we  
10 all walked away with a better understanding of what  
11 was important to patients, which drugs within that  
12 class might have the most promise for treating  
13 pediatric cancers, and while we didn't come away with  
14 any definitive decisions, I think we all came away  
15 with increased understanding of one another and better  
16 -- to make the best decisions that we could for  
17 patients.

18           So I think that's one excellent example  
19 of sort of a new way to collaborate in a pretty  
20 competitive way. We're all sort of having the same  
21 goals, but I think also respecting the competition  
22 piece of it as well. And I think we still have a lot

1 of challenges. I think we need to bring in other  
2 regulators into this conversation, not just Europe and  
3 U.S.

4 I think at this particular meeting, we  
5 had representative from Australia as well, but I think  
6 the more people we can bring to the table to have  
7 these discussions, the better and, of course,  
8 sometimes the ability of our infrastructure to handle  
9 complexities can be really tested when we're thinking  
10 about how quickly science evolves and changes, so we  
11 may come up with a plan that we think is perfectly  
12 reasonable and wonderful to move something forward and  
13 then something new can come up and in science that may  
14 make us need to relook at things and shift  
15 trajectories. So I'll stop there.

16 DR. SUSAN MCCUNE: Chris?

17 DR. CHRISTOPHER AUSTIN: I'm going to  
18 take Martha's example and up her 10. So, sort of  
19 think of -- it's hard for me to pick one of these.  
20 Everything we do is a collaboration, but I decided,  
21 like a lot of scientists, you learn the most from the  
22 extreme phenotype which is... So I decided in a fit

1 of collaboration to become the chair for three years  
2 of something called the International Rare Disease  
3 Research Consortium. It is a consortium of about 65  
4 organizations from 22 countries on five continents.  
5 It includes all the major funders: NIH, you know,  
6 European Commission, Japan, Canada, Australia, China,  
7 you name it, as well as about 15 companies 15 patient  
8 groups, and a whole bunch of scientists.

9           And they literally speak 40 different  
10 languages. They come from the entire spectrum of  
11 research from genetics to public health and  
12 regulation, everything in between, and they were  
13 brought together -- we were all brought together by a  
14 common enemy and one of my points has got to be, you  
15 got to keep the focus on the common enemy because if  
16 you don't, everybody starts focusing on the other guy  
17 who's there enemy.

18           And so the common enemy here is the  
19 enormity of the rare disease problem. Those of you  
20 who've heard me talk will know that I am fond of  
21 saying where -- unfortunate truth, that at the current  
22 rate of progress, which is really quite remarkable,

1 but at the current state of progress it will be 2,000  
2 years before there is a treatment for all rare  
3 diseases.

4           So we have to do things differently.  
5 That is just not an acceptable answer. And it doesn't  
6 have to be, but all of these folks were brought  
7 together by this common desire to say, well, if we  
8 coordinate what we do internationally and so the NIH  
9 knows what the European Commission is doing, would  
10 know what AMED is doing in Japan. We know we're  
11 working on the same thing. We can divide and conquer.  
12 The genome project was done that way, if you remember  
13 this.

14           And so what are the lessons from this  
15 absolutely scarring experience, I must say, of three  
16 years? It was actually an enormous pleasure, but what  
17 I learned was that first of all, it is critical that  
18 leadership -- leadership's really important in this  
19 case -- keep articulating what the goal is, what --  
20 why are we all here. And it -- that sounds sort of  
21 obvious, but it's easy to lose track in the nitty-  
22 gritty of individual projects, why we're doing this.

1           I just imagine Bill Belichick used to  
2 do before he started losing football games. To  
3 anticipate that there will be different languages and  
4 people will misinterpret each other, they will  
5 misinterpret each other, so you have to have the  
6 translators amidst the sort of senior people who look  
7 out for this at meetings and when something like that  
8 happens, say, what they probably meant is -- they're  
9 like -- it's like a marriage counselor, which I think  
10 we've all experienced where -- so that's really  
11 important.

12           Third, you got to be really up front  
13 about the money, because in the end, it always comes  
14 down to money. Things always come down to money, no  
15 matter how much people say, oh, well, kumbaya, we're  
16 all in this together; everybody's got their budgets.  
17 Everybody's got issues they got to deal with, so be up  
18 front about that. And fourthly, be up front about the  
19 credit issue, so we all love to work together and all  
20 that stuff, but we all have a boss, too, and that  
21 boss, frankly, doesn't care what Joe Schmo in Japan  
22 got valued -- the value out of what you did.

1           You know, he or she wants to know  
2 where's the beef, from you, and so you have to design  
3 what you do to have more than enough credit to go  
4 around, or else the thing is toing to fall apart and  
5 people are going to leave because they're going to  
6 have to choose between their own job and that they  
7 really want to do. And that's a false choice they  
8 shouldn't have to make, and it's manageable, but you  
9 have to do it -- you have to do it prospectively.

10           And so I guess my lesson from this was  
11 that with good proactive leadership and people who are  
12 sort of like-minded, which these kinds of consortia  
13 tend to attract, and proactive management of the  
14 problems that you know are going to appear, these can  
15 be extremely effective and so I'd urge you to realize  
16 that they can be done, but you can't just let it --  
17 think that it's going to work on its own, because it  
18 really won't.

19           DR. SUSAN MCCUNE: So on that note,  
20 with about 15 minutes left in the session, I'm going  
21 to open it up for questions here in the room, and  
22 while people are coming to the microphones, I didn't

1 know if there's anyone online that had a particular  
2 question for us. No. Okay. It's late in the  
3 afternoon. Dr. Epps is moving to the microphone.

4 DR. EPPS: At the microphone. I wanted  
5 -- I had a question. I want to circle back to  
6 something that Rhiannon had mentioned as a challenge,  
7 which is bringing in all communities. We know that  
8 rare diseases affect folks in every community. I  
9 wanted to ask the panel, starting with Rhiannon, any  
10 thoughts she had on how to bring other -- folks in  
11 other communities in to this process and to ask other  
12 panelists what sort of activities or actions they have  
13 been doing up to this point to try to make that  
14 happen.

15 RHIANNON PERRY: So to start, with the  
16 Hope for Henry, Children's National Medical Center  
17 chapter of ICAN, we've reached out to many different  
18 hospitals to implement those programs there and to try  
19 to gather people and a group of people who are willing  
20 to go out and speak about these issues and hold  
21 conferences for others to come in and speak about it  
22 and communicate, share their thoughts and things like

1 that. So that's one of the efforts that we're really  
2 trying to take now.

3 DR. EPPS: Are you guys using a lot in  
4 terms of social media to reach out to other folks?

5 RHIANNON PERRY: Definitely.

6 DR. CHRISTOPHER AUSTIN: I guess the  
7 only thing I would say is if you think about a sports  
8 team, so I was in Boston for 20 years and the Red Sox  
9 would be pathetic to being really good. When they  
10 were pathetic, I was like one of, like, four people at  
11 the ballpark. And when they started winning, all of a  
12 sudden everybody was a Red Sox fan. So having some --  
13 people love to be part of the winning team. And so I  
14 think all of us have experienced this, that we all  
15 have long-term goals but you've got to start winning  
16 individual baseball games, and that will bring in more  
17 people so there's this adage that we all have.

18 You know, got to have some short-term  
19 confidence building measures. That's really  
20 important. And it's -- and all of us say, well, gosh,  
21 you know, that's just -- it's such a small step and it  
22 doesn't really matter because it's not -- it's

1 infinitesimal the way we want to go. It really  
2 matters because it will bring other people in who will  
3 make your team bigger and stronger.

4           SHEILA MIKHAIL: Just to build on that,  
5 sometimes, too, it's -- the team maybe isn't your  
6 company or your organization, but it's a field. I  
7 feel like for AV gene therapy, we had to do that. In  
8 the early days, we gave out a lot of our technology.  
9 AveXis uses our technology and that's a major --  
10 almost every single company out there uses some form  
11 of our technology.

12           We're making our manufacturing process  
13 available and we're doing that because the industry is  
14 still very vulnerable and we need to have some more  
15 wins. So when the SMA drug was approved, that was  
16 really good and now, hopefully, the DMD drug will be  
17 approved and the hemophilia drugs look. But there's,  
18 you know, like you mentioned, 7,000 diseases, rare  
19 diseases, and we're still hopeful that we can go into  
20 the main pathway diseases.

21           With Medtronic's help, we're not in  
22 heart failure and that's a pretty big step. At least

1 with monogenetic diseases, you know what the drug is.  
2 The drug is basically replacing the defective genes,  
3 the good gene that's going to do the work that the  
4 defective one can't. We get to pathway diseases, and  
5 there's a lot of different targets and you hope you  
6 get the right one. So, anyway, for us, I agree with  
7 that, but I think our team is much bigger. For us,  
8 it's an evolving field.

9 DR. VASUM PEIRIS: And I'd just build  
10 on that team concept, since you laid it out so well.  
11 For the Red Sox, it was probably the four people that  
12 knew plus my entire pediatric EPT. They were always  
13 there. That's all we talked about during rounds. But  
14 on the team concept, there's a big team that can do a  
15 great deal of great work. You know what that team is?  
16 HHS, the government. Right.

17 That team is doing a lot of work. What  
18 if -- again, to Susie's question -- what if there is  
19 better collaboration, NIH, CMS, FDA, and others that  
20 came together to try to begin to truly address this  
21 across the spectrum? How do we begin to develop more  
22 of a collaborative environment within those teams?

1 Those teams can make a huge difference and create  
2 platforms and systems that can help everybody to have  
3 better success.

4 All the individual projects, all the  
5 individual areas that people are working on right now,  
6 that team can come together and help all of those  
7 other individuals.

8 DR. SUSAN MCCUNE: We have three more  
9 questions lined up.

10 ANNA CHRISMAN: Hello everyone. Good  
11 afternoon. My name is Anna Chrisman and I am from  
12 Genentech. My question was really about  
13 standardization, so this was mentioned a lot  
14 throughout the different panels and there's also, in  
15 context of consortium, I'd imagine that's important as  
16 well. So the panel earlier had discussed the rare  
17 disease accelerator and (inaudible) best practices  
18 from NIH and the need for standardization from that  
19 perspective. Is anything similar envisions for  
20 investigator sponsors' studies, and if so, do the  
21 panelists have any feedback on lessons learned they  
22 could share regarding standardization of data there

1 and how sponsors and investigators could get that type  
2 of feedback?

3 DR. CHRISTOPHER AUSTIN: Go for it.

4 DR. VASUM PEIRIS: I'll start you off.  
5 I don't have another good story about teams, but  
6 standardizing data, right. One of the areas that CDRH  
7 has been working on for quite some time is an actual  
8 evaluation system for health technology. How do we  
9 begin to get to a point where hubs across the country  
10 and potentially across the world have access to  
11 certain levels of data and can actually share that  
12 data in a secure way?

13 Very simply put, the way that I naively  
14 look at it is, there is data that we acquire every  
15 single day in EHRs and that is put into patient  
16 management. That data can be refined. Certain data  
17 elements can be developed, and it can get to a point  
18 where that data is so refined where -- and abstracted,  
19 that you have a specific data element that can make a  
20 difference for both regulatory and public health  
21 decisions across the entire country or potentially  
22 across the world.

1           But ultimately, from a regulatory  
2 standpoint, if you want to look at it that way, you  
3 can get to a point where that information can be  
4 aggregated and potentially help facilitate and  
5 accelerate development of medical products.

6           DR. MARTHA DONOGHUE: Yeah, in our  
7 space, we've talked about having a drug master file  
8 for capsids. Right now, we have that for  
9 manufacturing, so anybody who uses our system, right,  
10 they can refer back to our master file that's filed  
11 with the FDA. But we could envision a world where a  
12 lot of the capsids that are now coming off patent like  
13 AV8 and 9, which are used in a lot of products, if  
14 there was a master file filed at the FDA that  
15 investigators could refer to, it might accelerate drug  
16 development.

17           The capsids have a certain tropism,  
18 right. They're always going to have a certain  
19 tropism. The thing that's changing is the drug that  
20 you're putting and essentially it's the gene that you  
21 want to express. And so it could simplify and  
22 accelerate getting I&Ds filed.

1 DR. SUSAN MCCUNE: So moderator's  
2 prerogative. I'm going to say that we have three last  
3 questions and everybody has to keep their answer  
4 short. So we're going to go one, two, three and then  
5 we'll be done.

6  MAN 1: Okay, I'm Anna (inaudible)  
7 the president of the Children's (inaudible)  
8 Foundation. I have two things that I would like. I  
9 want -- I'm going to start with hope and then I have a  
10 request. So hope is that we've had some very large  
11 collaborative initiatives and -- within the NF  
12 community and they have really delivered, and NCATS to  
13 say that Chris puts his axe where his words are, NCATS  
14 was a big part of that collaborative effort and the  
15 drug that was identified through that (inaudible) is  
16 now ready to go into clinical trial, so that's the  
17 hope.

18 The request is that collaboration is  
19 really hard and I will say it's a combination of stick  
20 and carrot and I don't know whether I should start  
21 hitting with the carrot as well, but I'm not sure.  
22 But the thing that I -- we have discovered over the

1 last five years that we've really had this big  
2 collaborative consortia is that there's two elements,  
3 I think, to successful collaborations.

4 One, is an incentive. Try to  
5 understand why people don't want to collaborate and  
6 try to pull them over to the side where you want them  
7 to be. But the second thing, and this is a request, I  
8 think there is also something where we really need  
9 help from federal agencies and that's around policies.  
10 It is unacceptable, Mr. and Mrs. Hospital Service that  
11 you are competing between hospitals and yet there not  
12 one shared place where everybody shares their clinical  
13 information, especially in the rare disease community.

14 It is not acceptable, Mrs. and Mr.  
15 Researcher that you develop animal models with  
16 taxpayer dollars and that these animals are not  
17 available for drug testing. Here, we need help.  
18 Here, we need policies. Chris, I see you smile  
19 because I know... I'm looking, but I see --

20 DR. CHRISTOPHER AUSTIN: You're  
21 speaking my language. Yeah.

22 WOMAN 1: But I see -- I think we need

1 to start thinking. Really, there we need you guys  
2 because we as patient associations, patient  
3 organizations, and with our patients, especially in  
4 the rare disease community, it's really, hard because  
5 the patients are going to be activists but then  
6 they're going to be activists against their treating  
7 clinicians, which is really not a good thing to do.  
8 So we need policies. So this is my request. So my  
9 hope is it works and Chris helped. My request is,  
10 please help us with policies. And I would like to get  
11 a reaction.

12 DR. CHRISTOPHER AUSTIN: A great point,  
13 and I'm just going to maybe just build on that and  
14 hopefully augment this. Since (inaudible) pediatrics.  
15 That's what we're trying to do, right? We are trying  
16 to overcome a number of different issues in the system  
17 that isn't necessarily optimally supporting device  
18 innovation for pediatrics and small populations. But  
19 one of those issues, right, is that notion of small,  
20 geographically disbursed heterogenous populations that  
21 we just can't get all the information for. Well,  
22 where do all those populations get care? Those

1 populations get care at the pediatric academic medical  
2 centers across the country, right, and across the  
3 globe. So if we can bring those systems together --

4 WOMAN 1: Yep.

5 DR. CHRISTOPHER AUSTIN: -- and ensure  
6 that there is a method by which to aggregate that the  
7 information and the data that's being developed plus a  
8 system that accounts and accommodates for a number of  
9 other legal issues, regulatory issues, economic  
10 issues, then perhaps we will have a system that truly  
11 supports innovation for small populations and if you  
12 can support innovation for small populations, you will  
13 accelerate innovation for all populations.

14 WOMAN 1: Yeah, exactly. Exactly.  
15 Yeah.

16 DR. SUSAN MCCUNE: All right, off to  
17 the left over here.

18  N 1: Okay. Eric (inaudible)  
19 research foundation. This question is probably for  
20 Dr. Austin.

21 Having worked with your international  
22 consortium for as long as you have, one of the things

1 that we have encountered as we get closer -- we're in  
2 Phage 3 on one of our trials, is it turns out we are  
3 beginning to realize that we need to build a network  
4 of patient advocates that can speak within the  
5 countries, whether it's the European Union or even  
6 Australia, places like that, that we need a network of  
7 advocates that are going to be ready on our own behalf  
8 to go before their own regulators, even after it's  
9 gotten approved here in order to be able to argue the  
10 importance of this treatment within those individual  
11 countries. Is that the case?

12 DR. CHRISTOPHER AUSTIN: Yeah. Oh,  
13 yeah, definitely. And I would say -- so what we did  
14 within IRDRC, is because it was an umbrella  
15 organization, in order to be a patient advocacy group  
16 within IRDRC, you had to be representing an entire  
17 country. So for instance, NORD was a member and URS  
18 and Europe and those kinds of things. And -- but they  
19 of course, then have a relationship with each -- they  
20 all have member organizations and in more ways it was  
21 -- what was wonderful about that experience was that  
22 (inaudible) is, I think, ahead of almost everybody and

1   NORD'S pretty good, but then we had a patient  
2   organization from Botswana that was significantly  
3   smaller and had significantly less experience and so  
4   what this allowed was this sort of big brother/big  
5   sister relationship.

6                   But you're absolutely right. That's  
7   what these countries needed. But what we discovered  
8   was that U.S. and Europe, we lose track of how far the  
9   culture has come to take the patient seriously. In  
10  Japan, for instance, which is a very hierarchical  
11  culture and is still quite male dominated, male  
12  oriented, most of the patients are moms, like they are  
13  here, not all, but a lot of them are and so that is a  
14  very hard thing for the culture to deal with.

15                   How do you overcome those two big  
16  cultural barriers? And so we do a lot of work and  
17  continue to with the other countries and say, well,  
18  that was once the case in the United States, too, and  
19  so how have we overcome that? But yes, this is  
20  absolutely essential. The other thing that the --  
21  each of the countries has to do which the United  
22  States hasn't done yet, of course, but we managed to

1 get around it anyway because we have the Orphan Drug  
2 Act and other things, is to have a national rare  
3 disease policy and those national rare disease  
4 policies are almost always run from the patient  
5 groups. They make it possible.

6 MAN 1: Thank you.

7 DR. SUSAN MCCUNE: Last question.

8 WOMAN 2: It's not so much a question  
9 as a statement. I'm the proud mom of that young lady  
10 right there and, you know, we have been through quite  
11 a journey listening to some of the other people in  
12 here, so I definitely sympathize with everyone here.  
13 But I feel like I'm in a room of geniuses with big  
14 hearts who are overlooking on major thing and that's  
15 your basic, most profitable equity, your biggest  
16 equity is your patients.

17 And I feel like I've been sitting here  
18 and I've been listening to humongous words, huge  
19 terminology that is way above me, and I'm the biggest  
20 commodity. What we're doing with ICAN and Children's  
21 Hospital and some of these other -- on Be The Match  
22 and doing all these other kind of things to kind of,

1 like, bring wellness and give back to all of you, who  
2 have given so much to us, is that it's so 30,000 feet  
3 up there that John Q. Public can't join you to be a  
4 part of your consortium.

5           And the reason why and the only way  
6 that you will get a consortium is if John Q. Public  
7 jumps on board to what you are doing and sees your  
8 vision the same way that you see the vision. So I'm  
9 excited to be here. I'm so happy that we get the  
10 opportunity to come and share our experiences with  
11 you. But from a patient, from a parent, and from John  
12 Q. Public just sitting out there, I have no idea what  
13 you're talking about.

14           And if I don't have an idea of what  
15 you're talking about, I can't advocate on Capitol Hill  
16 the way I am with Be The Match to bring some of the  
17 initiatives that you want to happen. If you want us  
18 to work with Japan and China and all that, it's going  
19 to take 10,000 Americans to jump on board to say, hey,  
20 John Q. Government, this is what we, the American  
21 public, want. We want you to bring down the walls and  
22 the barriers that prevent us from working together,



country to country, community to community to

2 community to community.

3                   And you're losing -- your biggest  
4 advocacy here is your patients. It is the people with  
5 the rare diseases and all of your little subgroups  
6 coming together and saying, we are the rare disease  
7 community. It's not just us. It's our families who  
8 are affected by it and that's where you grow your  
9 consortium. So I applaud each and every one of you  
10 for that, but we got to bring it from here back down  
11 to the grass roots if you want to see improvement.

12                   DR. SUSAN MCCUNE: So I think that's  
13 the best last word for our panel, and with that I'd  
14 like to really thank the panel for all your comments.

15                   DR. JANET MAYNARD: Thank you so much  
16 to our panelists. We really appreciated that session.  
17 So now, we will transition to the open public comment  
18 period and Catherine Park will introduce that period.  
19 Thank you.

20                   CATHERINE PARK: Well, hello everyone.  
21 Thank you so much for being here and for such a great  
22 meeting. We are now doing to start the open public

1 comment portion of the meeting. Today, we have nine  
2 speakers registered and each of them will have three  
3 minutes to speak. If a speaker finishes early, we  
4 intend to move on to the next speaker. We will call  
5 each speaker by their name.

6 If there is additional time after, we  
7 will open the mic up to the room. When it is your  
8 turn, please approach the podium to your left to  
9 provide your comments. For transparency purposes, we  
10 ask you please disclose if you're affiliated with an  
11 organization, if your travel has been funded, or if  
12 you have significant financial interest in rare  
13 disease medical product development.

14 As you are speaking, you'll notice you  
15 have a timing light to guide you. The green light  
16 will indicate when you can begin speaking. It will  
17 turn yellow when you have 30 second left in your time.  
18 The timer will turn red when your time has come to an  
19 end. If you have not concluded your remarks by the  
20 end of your allotted time, I will ask you to do so  
21 kindly.

22 As a reminder, you also have the option

1 to submit comments to the docket which will remain  
2 open until Sunday, March 29th. Again, you can find  
3 additional information about this in the Federal  
4 Register Notice. If you are signed up for an open  
5 public comment slot, you are welcome to make your way  
6 to the first two rows in front of the podium at this  
7 time. Over there. If you would prefer to use a hand-  
8 held microphone and remain in your seat, please raise  
9 your hand when I call your name and will bring the mic  
10 to you.

11 I am now calling the first speaker in  
12 the open public comment period, Mary McGowan.

13 MARY MCGOWAN: Good afternoon. I'm  
14 Mary McGowan, executive director of Myositis  
15 Association. I have no travel stipend to be here and  
16 no financial interests. I would like to thank the FDA  
17 for this public hearing and for allowing me to speak.  
18 Again, my name is Mary McGowan. I'm the executive  
19 director of the Myositis Association. We are an  
20 international umbrella organization for numerous rare  
21 artery, muscle degenerative diseases including  
22 dermatomyositis, polymyositis, necrotizing myopathy,

1 and inclusion body myositis among others.

2 In my brief comments, I will address  
3 challenges across many chronic rare diseases. These  
4 include diagnosis, clinical trial participation,  
5 unique needs of women, and underserved populations,  
6 and the important of support systems.

7 Delay to diagnosis is a great concern.  
8 Those living with artery diseases see on average eight  
9 doctors and take five to seven years to receive the  
10 proper diagnosis. This has significant impact on  
11 patients' health and risks of mortality, mental  
12 health, and eligibility for future clinical trials.  
13 With such a significant delay in diagnosis, patients  
14 miss the window of opportunity for early treatment and  
15 symptom management which my result in progression of  
16 disease that is often irreversible and requires more  
17 complex treatments, some with harsh side effects, to  
18 address the damages done.

19 Additionally, repeated misdiagnosis  
20 creates a mistrust of the medical community. Finally,  
21 delay to diagnosis means that the time patients  
22 receive their diagnosis complications they have

1 incurred may make them ineligible for clinical trials.

2           Clinical trials are the beacon of hope  
3 for patients and their loved ones. We need to do  
4 better to ensure that clinical trials are for all  
5 individuals. Women make up 80 percent of all  
6 autoimmune diseases; yet it has been shown that women  
7 participate in clinical trials at a lower rate than  
8 met, something the FDA has already been working on to  
9 address through policy changes and the Women in  
10 Clinical Trials campaign.

11           In considering trial design and patient  
12 engagement, it behooves us to hear the unique  
13 challenges that women with rare diseases face,  
14 including future fertility, balancing family, job, and  
15 the increased likelihood of being caregivers for  
16 others with health problem. These issues are  
17 compounded by the complexities of their own rare  
18 disease. For women with myositis seeking to have  
19 children, concerns about participation in clinical  
20 trials are multiplied by the knowledge that increased  
21 flares can make it more challenging for them to care  
22 for their children and the stress of a regimen of an

1 autoimmune disease trial increases the risk for  
2 autoimmune disease flares.

3           Additionally, women with a rare disease  
4 are at a more significant risk of financial and mental  
5 health challenges. Creating support systems for women  
6 living with rare diseases like myositis is virtually  
7 important to improve opportunities for clinical trial  
8 participation for women, in order to ensure that all  
9 treatment options meet the differing biological needs  
10 of both genders.

11           Similarly, we must consider the unique  
12 challenges for those in underserved and diverse  
13 populations living with a rare disease like myositis.  
14 Women of color have the highest prevalence of  
15 dermatomyositis and polymyositis. They also tend to  
16 be diagnosed younger with more severe disease and have  
17 a higher mortality rate. It is crucial to have  
18 significant representation for this population in  
19 clinical trials, but there are a number of barriers.

20           Again, these patients tend to be sicker  
21 at the time of diagnosis which means that they often  
22 do not meet eligibility criteria for many clinical

1 trials. Additionally, most individuals from  
2 underserved populations are distrusting of  
3 experimental treatments and clinical trials due to  
4 historic breaches of trust. The population --

5 CATHERINE PARK: Thank you so much for  
6 sharing. Thank you.

7 MARY MCGOWAN: Thank you very much for  
8 your attention, in particular to the FDA for your  
9 extraordinary work. Appreciate it.

10 CATHERINE PARK: Thank you. Next we  
11 have Matt Buck.

12 MATT BUCK: Thank you. I'm Matt Buck.  
13 I'm vice president of regulatory affairs at Ionis  
14 Pharmaceuticals. I'm here today representing the n-  
15 Lorem Foundation which is a nonprofit, so I have both  
16 industry in here, representing nonprofit. I guess  
17 we're industry then. Yes, I have a financial disease  
18 in rare disease drug development.

19 So the mission of the n-Lorem  
20 Foundation is to charitably provide investigational,  
21 antisense oligonucleotides to treat patients with  
22 ultra rare disease which affect about one to 10

1 patients. The foundation was established at the end  
2 of 2019 and our mission, of course -- sorry, our goal  
3 and who we work with is Ionis Pharmaceuticals and the  
4 Undiagnosed Disease Network, the UDN, to provide these  
5 individual therapeutics.

6 We were just established at the end of  
7 2019 and we've already identified our first case, our  
8 first patient for an individualized therapeutic. In  
9 the coming months, we will have more cases, so here  
10 today, I am here to emphasize some of the  
11 recommendations that we've already shared with the  
12 FDA. We've already had the opportunity to speak with  
13 key personnel at CDER and we appreciate that  
14 opportunity.

15 And we recognize that there are two FDA  
16 draft guidances on individual therapeutics, and we  
17 appreciate that work. But knowing that there will be  
18 cases for us to bring forward to FDA in the coming  
19 months, I just want to emphasize our recommendations.  
20 One of those is that, ideally, CDER would have a sole  
21 division within the FDA that would manage individual  
22 therapeutic INDs. And that is so that a single

1 philosophy or standard can be uniformly applied to all  
2 of the evidentiary requirements.

3           Second, with respect to evidentiary  
4 requirements, when it comes to ASOs that are well  
5 characterized, that we would be able to utilize what  
6 we know about that platform to establish more minimal  
7 data standards which we believe would be -- examples  
8 are a single-species tox study such as single-species  
9 rodent tox package and of course an abbreviated  
10 stability program.

11           And finally, just the identification of  
12 one or two FDA project managers that might be assigned  
13 to individual therapeutic INDs would be extremely  
14 helpful as we come to the FDA in the next couple of  
15 months with several of these cases. So with that, I  
16 provide my recommendations and we will, of course,  
17 follow up with the written recommendations to be  
18 provided to the docket at the end of the month, and  
19 thank you for your time.

20           CATHERINE PARK: Thank you, Matt.

21           Next we have Michelle Adams.

22           MICHELLE ADAMS: Hi, I'm Michelle

1 Adams. I'm with the National Organization of Rare  
2 Disorders and I don't have any disclosures. Thank  
3 you. On behalf of the 25 to 30 million Americans with  
4 one of the over 7,000 rare disease, would like to  
5 thank the FDA for holding this meeting today to  
6 commemorate and celebrate rare disease week.

7           NORD is a unique federation of health  
8 organizations dedicated to helping people with rare  
9 diseases through educations, advocacy, research, and  
10 patient services programs. NORD is proud to serve as  
11 the host and sponsor of Rare Disease Day and the  
12 United States as we have been doing each year since  
13 2009 with our partner organization (inaudible) invited  
14 us to join the campaign they had started in Europe the  
15 previous year.

16           Rare Disease Day is observed in  
17 community settings, governmental legislative offices,  
18 school classrooms, college campuses, and hospitals,  
19 all to make the voices of rare disease patients heard.  
20 It is truly inspiring to know that people around the  
21 country are coming together at events like this one  
22 with the shared goal to promote awareness and improves

1 the lives of all people living with rare diseases.

2 As I mentioned, it is estimated that  
3 are over 7,000 rare diseases and over 90 percent of  
4 rare diseases still don't have an FDA-approved  
5 treatment indicated to treat their disease. As we  
6 heard from Dr. Hahn today, FDA shares NORD's goal of  
7 ensuring that more effective and safe treatments for  
8 rare diseases become available. All the panels today  
9 have been incredibly informative and what is  
10 especially clear is that FDA focus in part on natural  
11 history registries.

12 As we heard this morning, natural  
13 history registries offer a unique, exciting  
14 opportunity to collect and share information about the  
15 progression and health impact of a rare disease. NORD  
16 is thrilled to be partnered with C-Path, a rare  
17 disease cures accelerator as both Dr. Woodcock and Dr.  
18 (inaudible) mentioned earlier today also.

19 Thank you, FDA, for providing this  
20 opportunity. NORD is a leader in this space. In  
21 2014, NORD launched the IAMRARE Registry Program. It  
22 also launched (inaudible) today. The platform is

1 designed with extensive input from FDA, NIH, patient  
2 advocacy organizations, and other health experts. The  
3 IAMRARE hosts over 40 rare diseases, natural history  
4 study partnerships, and 20 of which were developed in  
5 part through a cooperative agreement with FDA. The  
6 IAMRARE Registry Program works in collaboration with  
7 patient and advocacy organization and industry  
8 partners to capture natural history data.  
9 Importantly, the emphasis is on input from the patient  
10 and caregivers' perspective.

11 And to the point where this morning,  
12 (inaudible) to our registry, but patients bear no cost  
13 for participating. With better information about a  
14 rare disease natural history registers will also allow  
15 for more effective treatment targets, more specific  
16 end points, and more efficient clinical trials. We're  
17 hopeful as it is that rare disease patients will get  
18 better, more effective treatment sooner. Thank you.

19 CATHERINE PARK: Thank you. Next we  
20 have Tisha Wang.

21 TISHA WANG: Hi. My name is Tisha  
22 Wang. I'm a pulmonary physician and clinician at

1 UCLA. I thank you for the opportunity to speak today.  
2 As the clinical director and vice president of the  
3 Pulmonary Alveolar Proteinosis or PAP Foundation. My  
4 travel was funded, but I have no financial interest  
5 here.

6           PAP is a rare disease without any  
7 approved therapy in which patients drown in their own  
8 surfactant proteins and develop shortness of breath  
9 and respiratory failure. In 2005, I was a trainee and  
10 I met a woman in her 20s with severe PAP. She was  
11 obese, in a wheelchair, on oxygen, and she came  
12 monthly for (inaudible) out the protein. She was so  
13 sick that I became convinced that she was going to die  
14 of this disease.

15           Based on what we knew about the cause  
16 of PAP which is that her cells and her lung were  
17 broken because they didn't have access to her protein,  
18 it made sense to me to try this protein and it is  
19 called GM-CSF. We tried it off label. In hindsight,  
20 we were both so young, but we trusted each other. We  
21 took a chance together and I gave her the protein and  
22 over the next six months, we actually cured. She was

1 dramatically cured.

2           Fifteen years later, she is still  
3 cured. She's now a therapist with a master's degree.  
4 She's an athlete and witnessing her recovery has been  
5 one of the most meaningful moments in my career. Over  
6 the next decade, I accumulated a large number of PAP  
7 patients and began collaborating with Dr. Bruce  
8 Trapnell at the Rare Lung Disease Consortium to do  
9 research.

10           I continued using off-label GM-CSF for  
11 many of my PAP patients with success, and learned that  
12 Dr. Trapnell and others were doing the same. In 2016,  
13 with one of my PAP patients in Los Angeles, we  
14 reinvigorated the PAP Foundation, a patient advocacy  
15 organization with the mission of getting an FDA-  
16 approved therapy and ultimately a cure for this  
17 devastating disease.

18           We've been able to connect with  
19 hundreds of patients in the meantime and hear about  
20 their experiences of being told they have no options  
21 for therapy. Some have since died or required lung  
22 transplant. Through the foundation, however, we've

1 been able to hear a number of success stories of  
2 individual patients using GM-CSF with improved quality  
3 of life and exercise tolerance and decreased need for  
4 whole-lung lavage and oxygen.

5 In fact, a number of patients improved  
6 on GM-CSF and stopped, only to have their disease  
7 recur off therapy. Fortunately, the research has  
8 progressed in the last decade. We have a Phase 1  
9 trial in the U.S., two recently completed randomized  
10 control trials, all using inhaled GM-CSF and available  
11 results from the patient and (inaudible) trials  
12 indicate that this medicine improves several outcomes  
13 in PAP, pulmonary function tests, oxygen in the blood,  
14 the amount of abnormal surfactant present, and the  
15 quality of life of these patients.

16 We at the foundation find these results  
17 encouraging and consistent with the experience of our  
18 patient community. So we at the PAP Foundation remain  
19 steadfast around a mission to become one of the few  
20 rare diseases to have an FDA approved therapy for our  
21 patients. We're committed to working very closely  
22 with the FDA to achieve this and applaud the FDA for

1 granting breakthrough therapy designation for  
2 Molgradex, which is a formulation of inhaled GM-CSF.  
3 What is striking about this meeting and being her all  
4 day today is that everybody in this room is on a  
5 mission.

6 The missing is slightly different for  
7 all of us and it's inspired by different things, but  
8 we're all on a mission. And so I think my last  
9 statement to the FDA probably mirrors the sentiment in  
10 this room which is that our patient and our physician  
11 community is more than willing to commit our time, our  
12 knowledge, our personal experiences, our resources,  
13 really whatever is necessary to move us forward in  
14 conjunction with the FDA.

15 Thank you again for the opportunity to  
16 speak on behalf of the PAP Foundation, the PAP patient  
17 community today.

18 CATHERINE PARK: Thank you. Next, we  
19 have Jen McNary.

20 JEN MCNARY: Hi, thank you. I'm Jen  
21 McNary, a rare disease advocate, mom of three sons  
22 with rare disease. I'm the founder of One Rare, a

1 board member of various organizations, and a  
2 consultant in the rare space, but for these purposes,  
3 I don't believe I have any relevant financial  
4 disclosures. I self-paid for my travel.

5           The end of one discussion today was  
6 incredibly important to me and it's been discussed at  
7 other venues this year, such as JPMorgan, in thinking  
8 about this concept a little broader throughout the  
9 day, as we realize the benefits of precision genetic  
10 medicine and end of a few will become increasingly  
11 more common. It is imperative that the agency adapt  
12 and implement a more consistent approach, however, to  
13 ensure the same standards are being applied across  
14 divisions and across disease states, assuming that  
15 it's a monogenic disease and that the therapy is  
16 replacing missing genes.

17           I recently wrote a blog where I spoke  
18 about my conversations with Dr. Peter Marks regarding  
19 this topic and while I am increasingly confident that  
20 the top officials such as Dr. Marks, Janet Woodcock,  
21 et cetera, appreciate and understand the importance of  
22 flexibility when reviewing these types of data, I want

1 to continue to ensure that this trickles down  
2 throughout the entire agency to allow a visible path  
3 forward for good science.

4 Switching gears, in the spirit of being  
5 wholly supportive of faster FDA approvals, I would be  
6 remiss in not also mentioning a troubling situation in  
7 the access and reimbursement landscape that's going to  
8 affect us all. I'm aware that in order for innovation  
9 to best serve patients in this room, two things need  
10 to happen, clear pathways for development and  
11 ultimately access and reimbursement.

12 Several organizations have recently  
13 published concerns about ICR, its utilization of the  
14 quality to determine the value of a new therapy for  
15 rare disease, but in my opinion the most effective was  
16 that published by the National Council of  
17 Disabilities. They found sufficient evidence of the  
18 discriminatory nature of qualities to warrant concern,  
19 including concerns raised by bioethicists, patient  
20 rights groups, and disability rights advocates about  
21 limiting access to life-saving medications.

22 In a recent article, the Pink Sheet,

1 ICR calls itself an expert to help the FDA understand  
2 the importance of patient relevant outcomes and  
3 consistent end points. ICR says that its work could  
4 advance greater use of patient relevant outcomes in  
5 drug development. As the commissioner mentioned, the  
6 FDA is doing an amazing job of incorporating the  
7 patient voice into drug development and uses rigorous  
8 methods to evaluate and approve new innovative  
9 therapies.

10 Yet ICR attempts to play at the same  
11 evaluation of already approved drugs. I would urge  
12 that the agency consider decline this offer to partner  
13 with this self-appointed and blatantly discriminatory  
14 organization in favor of working with foundations,  
15 some of which are in this room: EveryLife Foundation,  
16 ARM, IGT, (inaudible). They all have a proven track  
17 record of supporting patient needs and so I would  
18 encourage the agency to instead look to them. Thank  
19 you.

20 CATHERINE PARK: Thank you. Next, we  
21 have Khrystal Davis.

22 KHRYSTAL DAVIS: I'm Khrystal K. Davis.

1 I'm an SMA mom, founder of Texas Rare Alliance, and I  
2 received a grant from the EveryLife Foundation that  
3 covered my travel today. We cannot treat what we do  
4 not diagnose. Commissioner Hahn recognized the  
5 innovations are coming fast and furious and that we  
6 need to do more, faster, to meet unmet needs.

7 I believe this is especially true in  
8 access to the diagnosis. We are undeniably failing in  
9 the timely diagnosis of rare disease patients. It  
10 takes an average of five to seven years to accurately  
11 diagnose rare disease patients. Sadly, many children  
12 with rare diseases will not survive to their fifth  
13 birthday. Many of these children will not survive to  
14 receive a diagnosis. We can and must do better in  
15 diagnosing rare disease patients.

16 When we fail at diagnosing rare disease  
17 patients, that failure impacts everything in the  
18 process that follows. Undiagnosed patients cannot  
19 participate in patient registries and natural history  
20 studies which then fails to include the true spectrum  
21 of rare disease patients, especially diverse and  
22 underserved patients.

1                   Undiagnosed patients cannot drive  
2 research. Undiagnosed patients cannot inform the  
3 design of clinical trials and they cannot participate  
4 in clinical trials. Undiagnosed patients cannot  
5 follow the appropriate standards of care for a better  
6 chance of survival to see an approved treatment.  
7 Undiagnosed patients cannot access approved treatments  
8 and this is unacceptable.

9                   Dr. Marks discussed the advantage of  
10 leveraging existing resources in responding to the  
11 anticipated number of individualized gene therapies.  
12 We must also leverage existing resources to  
13 drastically reduce the diagnostic odyssey for rare  
14 disease patients. Whole genome sequencing offers the  
15 opportunity to identify thousands of known rare  
16 diseases and plays an invaluable role in discovering  
17 new rare diseases.

18                   Project Baby Bear Data from the work of  
19 Dr. Stephen Kingsmore in Rady Children's Genomic  
20 Institute for Genomic Medicine shows that rapid whole  
21 genome sequencing improved health outcomes while  
22 decreasing healthcare spending for California NICU and

1 PICU critically ill patients with unknown etiologies.  
2 This impressive and actional model needs to be adopted  
3 in all states. Whole genome sequencing not only  
4 improves access to the diagnosis, it also improves  
5 access to treatments by helping develop potential  
6 treatments, identify patients for clinical trials, and  
7 determine proper treatments for rare disease patients  
8 utilizing personalized medicine.

9           Whole genome sequencing offers an  
10 opportunity to move from failing at diagnosing rare  
11 disease patients to excelling at diagnosing rare  
12 disease patients. We must work to change the culture  
13 to leverage genomic data. We need funding to improve  
14 access to whole genome sequencing and improved health  
15 literacy for genomic medicine for providers, patients,  
16 and caregivers. Access begins with the diagnosis.

17           CATHERINE PARK: Khrystal --

18           KHRYSTAL DAVIS: We cannot treat what  
19 we did not diagnose.

20           CATHERINE PARK: Thank you.

21           KHRYSTAL DAVIS: Thank you.

22           CATHERINE PARK: Next we have Kelly

1 Thornton.

2                   KELLY THORNTON: Hello. My name is  
3 Kelly Thornton and I am with an organization, Pain  
4 Advocate Warriors and they're financially funding me  
5 and the American Pain and Disability Foundation.  
6 Hello. So the FDA needs to follow existing FDA  
7 protocols and stop being driven by the prevailing  
8 winds from political forces. I am on behalf of  
9 chronic pain patients.

10                   So, okay. The CDC is trying to drive  
11 policy based on their poorly written and poorly  
12 understood 2016 opiate prescribing guidelines,  
13 providing themselves incompetent and not ground in the  
14 best interest in U.S. public, especially not in the  
15 best interest of chronic pain patients who depend on  
16 analgesics for quality of life.

17                   The FDA -- excuse me. The FDA alone is  
18 in authority, yet we now have the CDC, 50 state  
19 governments, U.S. Congress, U.S. Senate, President of  
20 the United States, and even certain members of the  
21 media all trying to force additional overlapping,  
22 burdensome, contradictory political motivated,

1 unscientific regulations on opiates.

2           The U.S. government needs to get out of  
3 the doctor's office and leave it 100 percent up to the  
4 FDA to regulate and approve what medicines are on the  
5 market. The FDA's full prescribing information  
6 already contains limits and conditions and guidelines  
7 tailored to all drugs, and that is all that is needed.  
8 All other parties need to, frankly, get out because  
9 not only are the misinformed of the facts, their  
10 politicalize guidelines have cause as much death and  
11 misery for chronic pain patients while not helping  
12 addicts whatsoever.

13           Sheriffs, which in the report, they are  
14 not seeing prescription drugs found on deceased  
15 overdose victims, but instead see illicit fentanyl,  
16 heroin, and other illegal drugs such as  
17 methamphetamines, for at least the last eight years  
18 now. Can't CDC and others outside the FDA see their  
19 own data doesn't add up? A recent study said 1.3  
20 percent of overdose fatalities were caused by patients  
21 taking their own prescribed opioids, so 98.7 percent  
22 are due to illicit or illegal activities. Pounding

1 that 1.3 percent down to zero percent is more likely  
2 to kill hundreds or thousands of times more as  
3 disabled and elderly patients are suddenly on the  
4 street buying heroin for pain relief and getting God  
5 knows what in their cartel-provided medicine.

6 How about we do something right for a  
7 change instead of driving good people to end their  
8 lives via suicide or become criminals? If that is  
9 what our society has decided to become, perhaps our  
10 nation needs to dissolve and let each state become  
11 independent, because our federal system is not helping  
12 people who need help the most. It is, in fact,  
13 crucifying, torturing, and driving people who've  
14 worked their entire lives to support this nation into  
15 --

16 CATHERINE PARK: Kelly --

17 KELLY THORNTON: -- a state of insanity  
18 because --

19 CATHERINE PARK: Thank you so much.

20 KELLY THORNTON: -- regulation.

21 CATHERINE PARK: Thank you.

22 KELLY THORNTON: Please stop their

1     perpetrating going into circles. Please. Thank you.  
2     I didn't get to finish it.

3                     CATHERINE PARK: Next, we have Amanda  
4     Proctor. Okay. Then next, we have Bonita Talotti.

5                     BONITA TALOTTI: Good job.

6                     CATHERINE PARK: Thank you.

7                     BONITA TALOTTI: Hello. Good  
8     afternoon. Thank you so much for having all of us  
9     here. My name is Bonita Talotti. I'm a patient  
10    living with Ehlers-Danlos syndrome. I'm here today on  
11    my own representing our organization as one of the  
12    volunteers local EDS -- Metro EDS and HSD support  
13    group. No one's funded my travel. I'm just coming  
14    from Virginia.

15                    I'm here today to talk about access,  
16    one of the few things that was not talked about  
17    throughout the day. I heard a lot today about patient  
18    focused, patient centered, individualized treatment,  
19    but very little to no discussion on access. I found  
20    out about Ehlers-Danlos syndrome four years ago, after  
21    I'd been taking ciprofloxacin for three years and  
22    finally connected the dots and recognized cipro did

1 something to me. It turns out, cipro is actually a  
2 fluroquinolone antibiotic that is contraindicated for  
3 patients with Ehlers-Danlos syndrome and unfortunately  
4 for me, FDA did not connect the dots and come up with  
5 the black box warning until 2018 about two years after  
6 I was diagnosed.

7 I'm here today to point out that we, as  
8 patients, deserve and need to have the full facts of  
9 the drugs that are being prescribed to us. I didn't  
10 know at the time that I was given cipro that it can  
11 lead to tendinitis or tendinosis. My shoulder, which  
12 has been hurting throughout the day, is a result of  
13 EDS as well as ciprofloxacin. I didn't know that  
14 ciprofloxacin could destroy my gut. Indeed, I was  
15 never informed that I should even take a probiotic.

16 I didn't know that amitriptyline would  
17 result in orthostatic intolerance. I didn't know that  
18 naproxen which is what's been prescribed for me for my  
19 shoulder could result in GI risks of bleeding. None  
20 of this was ever informed to me or disclosed to me,  
21 rather. I had to find that out from various other  
22 sources.

1           As patients, we need to know exactly  
2 what it is that we're taking. We need to know the  
3 benefits as well as the risks. We also have another  
4 access issue that's really never talked about in any  
5 public meeting I've ever gone to, at FDA or at any  
6 other event, and that's financial. We as patients  
7 don't have access financially to all the latest  
8 technologies or treatments, the new drugs, the new  
9 devices, CRISPR, gene editing, gene therapies.

10           What good does all the innovations do  
11 if we as patients can't even afford them? I would  
12 urge industry, FDA, and other stakeholders to  
13 recognize that we have a serious financial access  
14 issue. If our payors aren't covering these things, we  
15 can't access them, plain and simple. I won't get into  
16 the opioid debate, but I will say this. We as  
17 patients don't have access to alternatives to opioids  
18 as well. What good does anything do if we don't have  
19 access to anything?

20           We as patients need access, first and  
21 foremost. Thank you.

22           CATHERINE PARK: Thank you so much.

1 This concludes the open public comment period. We  
2 really appreciate everyone participating today. I  
3 will now transition to Janet Maynard to provide  
4 closing remarks. Thank you.

5 DR. JANET MAYNARD: So we're going to  
6 transition to closing remarks, because unfortunately  
7 we're out of time for the open public comment period.  
8 So on behalf of FDA, I'd like to thank all of the  
9 panel participants, speakers, and everyone in the  
10 audience here in the Great Room and also on the  
11 webcast for participating in today's meeting. We  
12 greatly appreciate your attention and your interest in  
13 these topics.

14 This has been a very important meeting  
15 to all the participants including FDA, patients,  
16 researchers, and the industry representatives. We  
17 greatly appreciate perspectives and personal  
18 experiences that were shared with us today. Today, we  
19 heard that patients are at the heart of all that we  
20 do. There are exciting opportunities in rare disease  
21 product development, and great unmet needs of patients  
22 and families living with rare diseases. In the

1 morning, we heard about natural history and registry  
2 studies. Key points included the importance of  
3 patients and patient advocates in these studies and  
4 the need to think globally and evolve over time.

5 In the afternoon, we heard about the  
6 importance of collaboration, leveraging data, and  
7 learning from each other. This was a very informative  
8 meeting for us here at FDA. Rare diseases have  
9 enormous impacts on patients and families and the need  
10 to develop new therapies for rare diseases is immense.  
11 We look forward to incorporating what we have learned  
12 today into the agency's thinking on rare disease  
13 product development. Your perspectives and voices  
14 were heard today.

15 Working together, we can support  
16 optimal development of safe and effective products for  
17 patients with rare diseases. I want to let you know  
18 that just because the meeting is over, it doesn't mean  
19 that this is the last or only opportunity to interact  
20 with FDA. Today you heard from FDA's staff and the  
21 agency who want to hear from you and learn about your  
22 experiences. If you don't know where to start, the

1 patient affairs staff can help. You can send them an  
2 email at PatientAffairs@FDA.gov. They can help you  
3 stay connected with other activities at FDA or address  
4 future questions.

5 You can also connect with the Office of  
6 Orphan Products Development at Orphan@FDA.gov. As  
7 mentioned earlier today, we strongly encourage you to  
8 submit comments to the docket which will be open until  
9 March 29th, 2020. Details on how to submit comments  
10 to the docket can be found on the Federal Register  
11 Notice for the meeting. On your chair, we have placed  
12 a short survey that we hope you will complete so that  
13 we can continue to improve our public meetings.

14 When you are done with the survey, you  
15 can give it to the registration desk or to the FDA  
16 staff working at this meeting, and those are the folks  
17 who are wearing the nametags. For those on the web,  
18 we will be sending you the same survey via the email  
19 address that you registered with. And on that note, I  
20 am closing this public meeting. Thank you. Safe  
21 travels and have a wonderful evening.

22

## 1 CERTIFICATE OF NOTARY PUBLIC

2 I, 3854897, the officer before whom the  
3 foregoing proceedings were taken, do hereby certify  
4 that any witness(es) in the foregoing proceedings,  
5 prior to testifying, were duly sworn; that the  
6 proceedings were recorded by me and thereafter reduced  
7 to typewriting by a qualified transcriptionist; that  
8 said digital audio recording of said proceedings are a  
9 true and accurate record to the best of my knowledge,  
10 skills, and ability; that I am neither counsel for,  
11 related to, nor employed by any of the parties to the  
12 action in which this was taken; and, further, that I  
13 am not a relative or employee of any counsel or  
14 attorney employed by the parties hereto, nor  
15 financially or otherwise interested in the outcome of  
16 this action.

17  
18  
19 

20 3854897

21 Notary Public in and for the  
22 State of Maryland

## CERTIFICATE OF TRANSCRIBER

1  
2 I, Sonya Ledanski Hyde, do hereby certify  
3 that this transcript was prepared from the digital  
4 audio recording of the foregoing proceeding, that said  
5 transcript is a true and accurate record of the  
6 proceedings to the best of my knowledge, skills, and  
7 ability; that I am neither counsel for, related to,  
8 nor employed by any of the parties to the action in  
9 which this was taken; and, further, that I am not a  
10 relative or employee of any counsel or attorney  
11 employed by the parties hereto, nor financially or  
12 otherwise interested in the outcome of this action.

13  
14 

15 Sonya Ledanski Hyde  
16  
17  
18  
19  
20  
21  
22

<b>0</b>	<b>20,000</b> 152:3	<b>3854897</b> 1:8 315:2	<b>9,000</b> 152:3
<b>0.1</b> 238:9	<b>2000s</b> 51:6 245:10	315:20	<b>90</b> 28:20 294:3
<b>0.2</b> 238:10	<b>2001</b> 175:20	<b>3d</b> 151:8	<b>98.7</b> 307:21
<b>0.5</b> 159:6	<b>2004</b> 90:8	<b>3rd</b> 197:8	<b>9:30</b> 4:2
<b>00:53:25</b> 223:2	<b>2005</b> 69:16 115:8	<b>4</b>	<b>a</b>
<b>1</b>	296:9	<b>4</b> 181:1	<b>aadc</b> 247:6
<b>1</b> 276:6 277:22	<b>2009</b> 293:13	<b>4,000</b> 133:7	<b>aav</b> 175:19 242:16
279:4,14,18 282:6	<b>2010</b> 74:17	<b>40</b> 22:3 265:9	<b>abbreviated</b> 292:9
298:8	<b>2013</b> 262:11	295:3	<b>abcs</b> 182:17
<b>1,200</b> 155:15	<b>2014</b> 12:14 115:8	<b>44</b> 119:9	<b>abernethy</b> 6:14
<b>1.3</b> 307:19 308:1	294:21	<b>48</b> 119:9	10:5,7,7,10,22
<b>10</b> 33:20 34:5	<b>2016</b> 297:12	<b>494</b> 27:19	11:7,8 19:10
147:20 240:11	306:12	<b>5</b>	21:22 60:13,16
264:18 290:22	<b>2017</b> 98:10 186:12	<b>5</b> 230:21	62:4 112:11
<b>10,000</b> 152:3	187:9	<b>50</b> 22:3 27:9 28:22	<b>abernethy's</b> 52:10
283:19	<b>2018</b> 12:3 191:5	166:11 306:18	<b>abilities</b> 208:11
<b>100</b> 184:1 246:22	310:5	<b>50,000</b> 109:15	209:3,15
307:3	<b>2019</b> 12:5,7,19	<b>500</b> 90:10	<b>ability</b> 26:4 33:9
<b>11:30</b> 6:19	114:16 191:22	<b>5:00</b> 4:8	35:3 61:13 106:22
<b>12</b> 27:17 37:13	291:2,7	<b>6</b>	142:6 145:22
171:18	<b>2020</b> 1:2,4 2:3	<b>6,000</b> 109:16	150:8 263:8 264:8
<b>12151</b> 316:14	186:12 314:9	<b>60</b> 22:4 137:9	315:10 316:7
<b>13</b> 252:16	<b>20s</b> 296:10	<b>64,000</b> 68:7	<b>able</b> 31:9 32:7,21
<b>140,000</b> 115:4	<b>21</b> 119:8	<b>65</b> 265:3	35:6 36:8 66:1
<b>15</b> 6:16 33:20 36:2	<b>21st</b> 16:17	<b>7</b>	69:22 70:16 75:21
70:1 74:14 76:10	<b>22</b> 12:7 118:18	<b>7,000</b> 127:5 188:3	76:5,19 78:4
147:20 180:13	265:4	271:18 293:4	79:18,19 87:16
265:7,7 268:20	<b>23</b> 30:1	294:3	88:17 90:13 91:8
<b>17869</b> 315:20	<b>24</b> 1:4	<b>70</b> 109:16	92:18 93:9 94:14
<b>17th</b> 114:16	<b>24/7</b> 192:5	<b>76</b> 12:9 120:9	96:3,13 97:6
<b>18</b> 70:9 137:19	<b>24th</b> 114:15	<b>77</b> 120:16	101:4 102:10
<b>195</b> 27:18	<b>25</b> 163:8 293:3	<b>8</b>	110:21 131:16
<b>1983</b> 11:21 118:16	<b>29th</b> 5:4 286:2	<b>8,000</b> 133:8	142:5 145:16
<b>1990</b> 120:15	314:9	151:19 152:1	146:19 148:5
<b>2</b>	<b>2:00</b> 8:15 180:16	<b>8,500</b> 151:19	150:22 157:2
<b>2</b> 282:8	<b>2i</b> 244:5	<b>80</b> 288:5	159:13 165:3
<b>2,000</b> 266:1	<b>3</b>	<b>800</b> 118:17	169:16 174:12,12
<b>20</b> 20:15 34:5 36:3	<b>3</b> 280:2	<b>8:00</b> 4:8	174:13,17 178:5
45:17 119:11	<b>3,942</b> 27:18	<b>9</b>	183:19 185:11,17
155:13 176:15	<b>30</b> 20:16 109:20	<b>9</b> 275:13	186:10,17 187:9
227:12 247:8	229:18,20,21		187:16,20 188:4,7
270:8 295:4	285:17 293:3		193:1,5 198:21
	<b>30,000</b> 283:2		206:7 209:18
			212:8 216:10,13

217:16,17 225:18 227:14 230:13 237:20 238:6 251:10 255:15,19 255:19 258:12 261:18 280:9 292:5 297:18 298:1 <b>abnormal</b> 298:14 <b>absence</b> 153:13 212:19 <b>absolute</b> 122:16 124:1 125:16 <b>absolutely</b> 35:1 49:13 77:18 84:10 98:19 184:22 209:12 257:1 266:15 281:6,20 <b>abstracted</b> 274:18 <b>abuse</b> 175:10 <b>academia</b> 2:13 26:2 37:12 188:19 253:16 <b>academic</b> 46:8 49:8 51:4 59:2 63:14 81:1 88:4 137:7 195:5,6 235:7,10 250:11 279:1 <b>academician</b> 52:2 <b>academics</b> 43:4 245:2 <b>accelerate</b> 85:2 119:6 262:12 275:5,15,22 279:13 <b>acceleration</b> 114:1 <b>accelerator</b> 44:8 68:20 75:14 112:12 134:4,15 142:16 157:20 273:17 294:17 <b>accept</b> 4:22	<b>acceptable</b> 266:5 277:14 <b>access</b> 61:14 63:5 63:10,13,17 94:14 114:3,3 159:16,18 160:16,16 161:18 162:13 177:3,18 216:14 222:6 244:20 274:10 296:17 301:7,11 301:21 303:8 304:7 305:4,5,14 305:16 309:15,19 311:4,7,13,15,17 311:19,20 <b>accessed</b> 63:15 <b>accessibility</b> 113:15 <b>accessible</b> 106:11 185:17 <b>accessing</b> 173:14 <b>accommodate</b> 8:11 195:13 <b>accommodates</b> 279:8 <b>accomplish</b> 3:6 6:5 90:14 132:7 <b>account</b> 210:18 <b>accounts</b> 279:8 <b>accumulate</b> 213:1 <b>accumulated</b> 297:6 <b>accumulating</b> 63:3 <b>accurate</b> 315:9 316:5 <b>accurately</b> 303:10 <b>acetaminophen</b> 173:3 <b>achieve</b> 298:22 <b>acid</b> 247:6 <b>acknowledge</b> 54:18	<b>acquire</b> 274:14 <b>act</b> 11:21 16:18 118:16 211:9 282:2 <b>acting</b> 24:14 <b>action</b> 17:12 261:20 262:5 315:12,16 316:8 316:12 <b>actional</b> 305:2 <b>actions</b> 269:12 <b>active</b> 76:7 203:10 <b>actively</b> 27:3 37:7 <b>activists</b> 278:5,6 <b>activities</b> 9:18 23:19 27:5 269:12 307:22 314:3 <b>activity</b> 179:20 195:6 <b>actual</b> 190:7 274:7 <b>acute</b> 132:15 <b>adage</b> 270:17 <b>adams</b> 292:21,22 293:1 <b>adapt</b> 121:19 300:11 <b>adaptive</b> 94:10 <b>adc</b> 176:16 <b>add</b> 36:18 40:8 52:5 53:2 56:4 59:8 62:21 65:16 79:19 88:18 94:12 97:10 101:18 221:1 307:19 <b>added</b> 105:10 <b>addictive</b> 175:9 <b>addicts</b> 307:12 <b>adding</b> 123:16 <b>addition</b> 2:18 12:1 38:21 39:15 124:1 142:5 170:14 186:21 <b>additional</b> 8:17 9:14 54:14 79:19	125:20 146:3 160:22 162:20 240:2 252:8 285:6 286:3 306:21 <b>additionally</b> 287:19 289:3 290:1 <b>address</b> 5:10 24:18 25:9 26:5 27:13 30:18 37:7 37:20 59:17 92:16 93:9 126:6 130:15 139:9,18 146:9 148:22 240:3 246:19 248:21 256:20 259:17,21 272:20 287:2,18 288:9 314:3,19 <b>addressed</b> 12:10 139:6 189:20 210:21 <b>addresses</b> 64:19 <b>addressing</b> 9:18 13:21 <b>adds</b> 185:14 240:1 <b>adequately</b> 173:15 <b>adhere</b> 125:18 <b>administration</b> 1:1 228:10 <b>admirable</b> 242:14 <b>adopt</b> 99:19 <b>adopted</b> 305:2 <b>adrenal</b> 225:5 <b>adult</b> 168:4,19 238:10 248:11 261:19 <b>adults</b> 12:20 168:21 <b>advance</b> 57:1,2 127:9 143:13 243:15 244:19 250:3 302:4 <b>advanced</b> 28:13 28:15,18 145:5
--	---	--	--

<p>148:1,6 182:15 243:22 244:1 <b>advancement</b> 247:5 <b>advances</b> 11:18 17:9 35:3 118:12 119:19 120:13 126:10 131:4 237:15 <b>advancing</b> 67:11 118:11 120:22 178:3 220:6 233:9 249:9 <b>advantage</b> 104:2 153:18 186:11 304:9 <b>advent</b> 237:13 <b>advice</b> 44:2 90:18 102:20 261:13 <b>advisory</b> 254:21 <b>advocacy</b> 2:11 40:11 43:21 46:13 61:5,12 70:15 102:8 103:2 109:11 134:6 254:3 262:13 263:2 280:15 284:4 293:9 295:2 295:7 297:14 <b>advocate</b> 159:16 163:3 174:6,8 186:4 193:10 283:15 299:21 306:4 <b>advocated</b> 216:16 <b>advocates</b> 122:22 141:9,12 190:2 242:14 253:15 280:4,7 301:20 313:3 <b>advocating</b> 196:18 <b>affairs</b> 9:15 290:13 314:1</p>	<p><b>affect</b> 259:14 260:3 269:8 290:22 301:8 <b>affiliated</b> 7:18 285:10 <b>afford</b> 160:21 311:11 <b>affordable</b> 132:9,9 <b>afforded</b> 188:10 <b>afraid</b> 209:9,10 <b>africa</b> 150:1 <b>afternoon</b> 6:11,20 6:22 8:4,14 126:9 128:3 146:5 181:1 231:8 236:17 269:3 273:11 286:13 309:8 313:5 <b>afterthought</b> 252:4 <b>age</b> 29:14,15 153:14 154:14 159:9 186:13 <b>agencies</b> 113:21 277:9 <b>agency</b> 12:7 18:18 20:22 21:1 43:22 45:3 76:15 98:12 118:18 119:1 121:20 124:7 125:6 127:21 129:2 134:7 199:21 213:21 214:8 240:11 300:11 301:2 302:12,18 313:21 <b>agency's</b> 313:12 <b>agenda</b> 3:7,7 5:22 6:13,20 127:9 <b>agents</b> 173:4 263:6 <b>aggregate</b> 279:6 <b>aggregated</b> 275:4</p>	<p><b>aggressive</b> 219:7 <b>aggressively</b> 61:7 <b>ago</b> 33:20 34:5 57:9 71:2 93:12 96:6 143:6 182:8 229:20,21 233:19 252:19 253:17 309:20 <b>agony</b> 172:9 <b>agree</b> 44:20 48:16 52:5 56:7,17 80:6 97:8 131:14 142:8 145:19 161:22 203:9 224:11 272:6 <b>agreed</b> 179:14 <b>agreement</b> 86:7 295:5 <b>agrees</b> 136:9 <b>ahead</b> 29:6 31:3 50:20 128:7 145:6 168:14 280:22 <b>ai</b> 164:20 <b>aim</b> 215:8 <b>air</b> 64:15 <b>align</b> 215:9 216:20 <b>aligning</b> 215:7 <b>alive</b> 153:15 154:14,15 237:8 <b>alliance</b> 67:7 69:12 159:4 303:1 <b>allotted</b> 285:20 <b>allow</b> 9:7 14:14 17:14 18:9 20:15 50:7 139:19 213:3 219:19 220:17 295:14 301:2 <b>allowed</b> 188:13 244:22 281:4 <b>allowing</b> 185:16 286:17 <b>allows</b> 32:3 158:21 187:22 251:9</p>	<p><b>alluded</b> 249:22 <b>alluding</b> 62:14 <b>alphabetical</b> 182:5 <b>alphabetically</b> 182:6 <b>alternative</b> 192:16 242:13 <b>alternatively</b> 7:11 <b>alternatives</b> 173:3 311:17 <b>alveolar</b> 296:3 <b>alzheimer's</b> 99:1 <b>amanda</b> 309:3 <b>amazing</b> 154:8,11 155:22 196:6 220:16 237:14 238:3 302:6 <b>amazingly</b> 215:15 <b>ambitious</b> 17:13 <b>amed</b> 266:10 <b>american</b> 18:21 116:3 118:1 123:3 125:16 126:8 194:1 283:20 306:5 <b>americans</b> 126:2 283:19 293:3 <b>amidst</b> 267:6 <b>amino</b> 247:6 <b>amitriptyline</b> 310:16 <b>amount</b> 23:1 31:6 146:12 152:5 202:19 210:12,12 210:14 211:7 227:18 245:13 298:14 <b>amsterdam</b> 166:21 <b>amy</b> 10:5,7 11:8 60:13,16 112:11 225:2,2 226:14</p>
--	--	---	--

<b>analgesics</b> 173:11 306:16 <b>analysis</b> 15:22 24:15 97:16,19 125:13 204:13 208:5 209:16 217:17 218:21 <b>analytic</b> 25:11 <b>analytics</b> 40:1 <b>analyze</b> 17:15 155:10 <b>anaphylaxis</b> 171:20 <b>anatomy</b> 151:7,7 151:9 <b>anderson</b> 115:3,5 <b>angel</b> 257:22 <b>angeles</b> 297:13 <b>angles</b> 83:22 <b>animal</b> 41:11 230:4 277:15 <b>animals</b> 206:4 277:16 <b>ann</b> 233:12 <b>anna</b> 273:10,11 276:6 <b>anne</b> 67:9 71:4 74:10,11 81:15 83:5 95:12,13 100:9,15 104:6 106:2 110:17,18 <b>annette</b> 47:17,17 50:6,14,22 <b>annotate</b> 100:4 <b>annual</b> 91:22 <b>annually</b> 90:13 <b>anonymous</b> 7:13 <b>answer</b> 44:5 51:12 64:21,22 65:12 86:6 105:20 108:3 109:4 118:10 127:18 191:10 211:10 225:19 261:14 266:5	276:3 <b>answers</b> 41:7,8 68:10 84:1 118:5 124:11 186:18 242:8 <b>anti</b> 173:4 <b>antibiotic</b> 191:3 193:12 310:2 <b>antibiotics</b> 190:21 192:3 <b>anticipate</b> 87:6 267:3 <b>anticipated</b> 92:13 304:11 <b>antisense</b> 146:13 229:17 290:21 <b>anybody</b> 69:18 108:3 201:2 206:14 234:20 251:9 275:9 <b>anymore</b> 175:3 233:21 <b>anyway</b> 144:13 152:13 272:6 282:1 <b>apart</b> 268:4 <b>appear</b> 268:14 <b>appetite</b> 106:13 <b>applaud</b> 218:6 284:9 298:22 <b>applicable</b> 7:15 261:20 <b>application</b> 139:20 147:18 198:22 200:5 210:15 211:13 212:8,10 213:13 214:2 241:14 <b>applications</b> 18:10 22:10,17 28:21 106:20 139:14 148:9 198:6,18 241:9	<b>applied</b> 189:12 241:21 292:1 300:13 <b>apply</b> 187:3 190:4 198:22 214:12,13 223:19,20 228:22 229:3 <b>applying</b> 261:3 <b>appointed</b> 302:13 <b>appraisal</b> 38:1 <b>appreciate</b> 2:20 9:4 91:6 207:13 290:9 291:13,17 300:21 312:2,12 312:17 <b>appreciated</b> 65:21 284:16 <b>appreciative</b> 68:6 <b>approach</b> 25:18 26:18 39:21 83:22 95:1,9 101:16 121:17 123:16 125:6 168:11 187:19 200:12 229:17,18 285:8 300:12 <b>approaches</b> 16:13 189:19,21 236:12 <b>approaching</b> 26:16 64:17 106:18 132:20 <b>appropriate</b> 14:19 21:20 39:6 49:17 63:8,9 192:21 204:12 216:6 304:5 <b>appropriately</b> 49:16 63:8 126:20 <b>approval</b> 16:12,21 17:1 21:17 22:18 122:16 138:11 151:22 152:7,20 167:7,21 237:15 237:18	<b>approvals</b> 12:10 12:11 119:9,12 127:9 157:15 301:5 <b>approve</b> 24:8 32:5 32:5 133:11 151:4 237:20 302:8 307:4 <b>approved</b> 11:21 12:4,7,12,13,19 13:2,4 21:18 22:5 29:2,8,17 36:2,4 55:9 94:3 118:16 118:18 119:21 120:9,16 140:18 160:12 165:16 167:10 168:22 191:21 271:15,17 280:9 294:4 296:7 297:16 298:20 302:11 304:6,7 <b>approving</b> 36:10 <b>approximately</b> 28:22 <b>arc</b> 25:22 <b>architects</b> 101:4 <b>architecture</b> 49:7 <b>arduous</b> 216:5 <b>area</b> 3:14 7:14 44:16 88:3 114:5 118:6 119:14 134:21 136:14 137:14,14 138:21 154:7 194:8 197:20 221:8 227:20 228:18 240:10 245:13 251:5 260:5 <b>areas</b> 38:20 85:7 85:21 93:7 142:21 168:18 170:1 203:20 204:5 256:1 273:5 274:6
---	---	---	---

<p><b>arena</b> 61:6</p> <p><b>aren't</b> 195:17 216:10,10 311:14</p> <p><b>arguably</b> 229:22</p> <p><b>argue</b> 228:17 280:9</p> <p><b>arguments</b> 122:12</p> <p><b>arm</b> 32:2 34:16 39:16,17 54:5 162:18,19 169:2 302:16</p> <p><b>arms</b> 39:7 76:7,7 84:16</p> <p><b>army</b> 144:2</p> <p><b>arrested</b> 175:3</p> <p><b>arrive</b> 37:16</p> <p><b>arriving</b> 10:5</p> <p><b>arterial</b> 64:4</p> <p><b>artery</b> 286:21 287:8</p> <p><b>article</b> 301:22</p> <p><b>articulate</b> 178:7</p> <p><b>articulated</b> 140:2</p> <p><b>articulating</b> 266:19</p> <p><b>artificial</b> 25:16 163:15 164:8</p> <p><b>ascertained</b> 37:3</p> <p><b>asia</b> 150:1</p> <p><b>aside</b> 113:19 176:11</p> <p><b>askbio</b> 175:18,19 242:3,4</p> <p><b>asked</b> 4:20 51:8 86:4 107:8,9 174:6</p> <p><b>asking</b> 63:16 65:3 71:19,21</p> <p><b>aso</b> 159:11</p> <p><b>asos</b> 292:4</p> <p><b>aspect</b> 61:21 94:21 101:14 106:15 112:13</p>	<p><b>aspects</b> 25:11 39:22 67:21 79:15 79:16,17 84:21 104:14,17 195:18 251:6</p> <p><b>aspire</b> 246:13</p> <p><b>assembled</b> 212:1</p> <p><b>assembly</b> 212:9</p> <p><b>assess</b> 25:9 26:2,4 26:8 28:6 51:13 136:22 205:7,19 239:1</p> <p><b>assessed</b> 34:1,4</p> <p><b>assessing</b> 25:20 37:19 124:3 205:5</p> <p><b>assessment</b> 24:5 25:14 38:11 205:11</p> <p><b>assessments</b> 34:1 135:1 214:6 219:15</p> <p><b>assigned</b> 292:12</p> <p><b>assistive</b> 88:18</p> <p><b>associate</b> 66:18</p> <p><b>associated</b> 12:22 254:12 259:19</p> <p><b>associating</b> 105:17</p> <p><b>association</b> 245:7 286:15,19</p> <p><b>associations</b> 278:2</p> <p><b>assuming</b> 300:14</p> <p><b>assurance</b> 151:14 151:15 152:6 202:20</p> <p><b>assure</b> 63:7,16 65:6</p> <p><b>assuring</b> 21:19</p> <p><b>aster</b> 171:9</p> <p><b>ataxia</b> 67:7 69:12 77:11</p> <p><b>athlete</b> 297:4</p> <p><b>atmosphere</b> 258:12</p>	<p><b>atrophy</b> 29:9,10 29:13 51:7 71:17 120:5 154:11,13 183:1 188:15</p> <p><b>attack</b> 190:12</p> <p><b>attain</b> 125:10</p> <p><b>attempt</b> 222:20 257:5</p> <p><b>attempts</b> 302:10</p> <p><b>attend</b> 58:16</p> <p><b>attendees</b> 3:12 8:3 9:10</p> <p><b>attending</b> 159:4</p> <p><b>attention</b> 49:17 87:8,18 99:13 119:15 136:4 194:16 290:8 312:12</p> <p><b>attorney</b> 315:14 316:10</p> <p><b>attract</b> 268:13</p> <p><b>attributes</b> 239:8</p> <p><b>audience</b> 8:7 20:16 31:10,10,17 43:19 45:13,18 46:3 65:19 101:9 155:3 178:17 214:22 225:1 312:10</p> <p><b>audio</b> 3:11 315:8 316:4</p> <p><b>augment</b> 278:14</p> <p><b>august</b> 232:17 261:17</p> <p><b>austin</b> 136:8 147:4 231:10 233:4 264:17 270:6 274:3 277:20 278:12 279:5,20 280:12</p> <p><b>australia</b> 264:5 265:6 280:6</p> <p><b>authorities</b> 139:12 241:10</p>	<p><b>authority</b> 150:3 150:11 306:18</p> <p><b>autoimmune</b> 288:6 289:1,2</p> <p><b>autonomy</b> 165:3</p> <p><b>autosomal</b> 183:18</p> <p><b>av</b> 197:13,19 198:19 242:4 259:1,3,19 260:4 271:7</p> <p><b>av8</b> 275:13</p> <p><b>availability</b> 124:12 140:13 194:17 195:10 196:1 197:16</p> <p><b>available</b> 3:17 4:18 61:8,10 66:4 74:3 113:20 125:21 147:17 152:12 170:3 177:7,8,17 186:11 186:14 196:22 215:14 245:1 271:13 277:17 294:8 298:10</p> <p><b>average</b> 287:8 303:10</p> <p><b>avaxis</b> 67:9 176:3 271:9</p> <p><b>avoiding</b> 73:16</p> <p><b>aware</b> 60:19 162:3 167:18 172:18 216:10 223:19 301:8</p> <p><b>awareness</b> 162:11 222:4 253:1,5 255:20 256:2 293:22</p> <p><b>awesome</b> 84:17</p> <p><b>axe</b> 276:13</p> <p><b>axonal</b> 243:17</p>
--	---	---	--

<b>b</b>			
<b>ba</b> 11:5	<b>ball</b> 46:11	<b>beacon</b> 288:2	<b>benefits</b> 205:2,5
<b>baby</b> 145:18	<b>ballpark</b> 270:11	<b>bear</b> 144:4 295:12	211:15 214:7
304:18	<b>bang</b> 62:13	304:18	219:15 251:17
<b>back</b> 32:17 35:16	<b>bar</b> 102:14	<b>beast</b> 113:6	257:12 300:9
40:13 47:7 51:5	<b>barbara</b> 168:3,3	<b>becoming</b> 29:14	311:3
56:16 68:16 69:8	170:13 171:11	93:14 162:3	<b>benefitting</b> 187:1
71:11 72:9 80:8	<b>barnhart</b> 171:14	172:14	<b>best</b> 28:19 35:17
86:10 90:11,12	171:15 174:5	<b>bed</b> 174:12	39:5 85:16 99:4
91:21 109:1 113:4	<b>barrier</b> 179:12	<b>beef</b> 268:2	103:12 122:16
121:8 123:5 126:3	<b>barriers</b> 25:16	<b>beeps</b> 11:9	124:1 125:16
135:20 140:21	150:6 174:17	<b>began</b> 297:7	126:7 141:6
152:18 160:17	281:16 283:22	<b>beginning</b> 48:12	149:13 200:9
175:20 177:16	289:19	61:16 74:1 81:10	209:19 217:4
199:12 205:5	<b>basala</b> 182:1	86:9 96:16 186:12	228:13 235:2,2
218:3 224:20	<b>baseball</b> 246:9	252:9 257:10	242:21 245:1
226:19 245:18	270:16	280:3	262:7,18 263:16
250:10 254:1	<b>based</b> 18:8,8 49:1	<b>begins</b> 305:16	273:17 284:13
256:4,4 262:11	78:20 102:20	<b>behalf</b> 168:6 280:7	301:9 306:14,15
269:5 275:10	110:4 149:4	293:3 299:16	315:9 316:6
283:1 284:10	159:13 188:16	306:8 312:8	<b>better</b> 14:14 42:19
<b>background</b> 20:22	237:21 238:7	<b>behavior</b> 235:8	46:11 49:6 58:7
28:11 42:2,7	250:12 296:15	<b>behooves</b> 288:12	69:21 71:22 72:15
67:17 126:11	306:11	<b>belichick</b> 267:1	73:15 92:17 93:2
191:12 199:18	<b>baseline</b> 84:5	<b>believe</b> 50:19	116:20 118:5
211:15 231:20	141:21 153:9	54:20 68:18 108:9	124:14 125:2,10
248:9	245:16	109:16 127:11	131:11 134:8
<b>bacteria</b> 191:12	<b>basic</b> 136:12,15	176:8 189:1	135:11 136:7
<b>bacterial</b> 190:13	179:19 223:18	206:11 292:7	153:1 165:8 171:4
190:14,16	226:1 229:19	300:3 303:7	184:17 201:2
<b>bad</b> 29:11 30:17	235:3 282:15	<b>believing</b> 209:20	240:18 253:8
255:17	<b>basically</b> 158:22	<b>bells</b> 133:8	255:1,12 258:18
<b>bake</b> 243:18	169:10 222:3	<b>bench</b> 224:17	263:10,15 264:7
244:18	272:2	<b>benefit</b> 21:20	272:19 273:3
<b>bakker</b> 47:17,17	<b>basics</b> 47:6	80:13 103:10	288:4 295:13,18
50:6,14,22	<b>basis</b> 8:19 32:5	124:8 151:16	303:14 304:5
<b>balance</b> 122:7	89:6 92:21 109:20	169:18 178:9	<b>beyond</b> 13:16
172:20	110:14 159:20	192:9 203:21	79:20 97:16 148:6
<b>balanced</b> 114:20	199:6 208:15	204:4,13 205:10	158:9 162:21
<b>balancing</b> 288:14	212:12 243:19	205:22 206:5,12	<b>big</b> 29:22 94:16
<b>balasa</b> 190:9	262:16	207:16 208:5	98:8 102:1 122:20
204:8 215:21	<b>bat</b> 99:20	209:16 210:11	185:13 204:22
<b>balkanized</b> 164:3	<b>batten</b> 182:9,19	211:6,8 217:17	219:21 224:21
	183:12 184:2	218:15,21 239:22	226:10 228:19
	200:20 222:10	241:14 243:11	239:14 259:8

260:3 271:22 272:14 276:14 277:1 281:4,4,15 282:13 <b>bigger</b> 50:9 229:6 271:3 272:7 <b>biggest</b> 228:7 282:15,19 284:3 <b>biking</b> 182:14 <b>bill</b> 267:1 <b>billing</b> 26:21 <b>binary</b> 98:21 <b>bind</b> 261:11 <b>binding</b> 58:14 <b>bioethicists</b> 301:19 <b>biologic</b> 32:5 35:4 119:12 <b>biological</b> 119:11 289:9 <b>biologics</b> 12:4,8 13:11 28:14 118:17,19 119:17 129:11,12 153:21 161:13 194:5 240:20 249:6 <b>biology</b> 42:3 191:12 239:11 <b>biomarker</b> 60:2 87:19 135:7 238:7 238:11,13 <b>biomarkers</b> 24:6 60:4 99:6 134:22 135:6,21 137:4 143:1 238:8 <b>biopsies</b> 82:11 <b>biopsy</b> 212:5 <b>bioreactors</b> 259:9 <b>biostatistical</b> 39:4 39:8 <b>biotech</b> 108:18 176:18 <b>birth</b> 159:8	<b>birthday</b> 303:13 <b>bit</b> 19:12 32:1,18 66:14 67:16 78:14 106:1 121:20 131:9 153:20 157:8,11 165:15 166:22 167:1 180:15 189:3 202:13 211:14 217:8,20 232:19 237:1 249:22 250:2 252:11 257:13 260:13 261:5 <b>black</b> 208:6,10 210:6 310:5 <b>blatantly</b> 302:13 <b>bleeding</b> 129:16 310:19 <b>blind</b> 135:10 <b>blog</b> 300:17 <b>blood</b> 129:12,16 135:14 158:20 194:7 195:19 249:16 298:13 <b>blown</b> 229:5 <b>board</b> 253:4 254:21 283:7,19 300:1 <b>boarded</b> 11:6 <b>body</b> 52:12 153:5 191:11 237:22 287:1 <b>bolster</b> 230:12 <b>bone</b> 252:20 <b>bonita</b> 309:4,5,7,9 <b>book</b> 100:17 144:11 145:18 <b>boring</b> 87:21 95:21 99:13 <b>born</b> 252:15 <b>borrow</b> 39:9 <b>borrowed</b> 28:16 95:7	<b>boss</b> 267:20,21 <b>boston</b> 71:13 184:10 270:8 <b>botswana</b> 281:2 <b>bottom</b> 106:17 <b>bounce</b> 45:17 <b>box</b> 8:3 73:21 133:17 158:4 219:3 310:5 <b>boys</b> 245:14 246:6 <b>brag</b> 119:1 <b>brain</b> 183:1 217:21,21 218:1 <b>brand</b> 107:14 202:10 229:9 <b>breaches</b> 290:4 <b>break</b> 6:17,19 7:2 8:15 66:1,4,6 114:11 119:7 139:2 150:6 180:12,13,14,17 257:6 <b>breaking</b> 25:15 <b>breaks</b> 176:4 <b>breakthrough</b> 299:1 <b>breakthroughs</b> 13:14 <b>breath</b> 296:8 <b>breathe</b> 12:18 <b>breathing</b> 192:6 <b>bride</b> 106:22 <b>bridge</b> 112:1 223:4 <b>brief</b> 43:14,17 181:8 229:15 287:2 <b>briefly</b> 8:22 181:15 <b>bring</b> 7:10 43:8 94:16 136:15 152:18 154:21 155:5 160:5 161:14 170:6	203:11 223:15 250:22 251:19 253:1,5 256:2 258:11 264:1,6 269:10 270:16 271:2 279:3 283:1 283:16,21 284:10 286:9 291:18 <b>bringing</b> 231:8 269:7 <b>brings</b> 257:20 258:1 262:13 <b>broad</b> 24:10 47:5 53:4 81:16 86:19 90:8 116:11 159:20 238:6 <b>broaden</b> 82:14 <b>broader</b> 18:12 161:19 300:8 <b>broadly</b> 63:15 <b>broken</b> 193:20 296:17 <b>brother</b> 153:4 281:4 <b>brought</b> 111:20 157:1 165:15 203:20 204:3 248:22 255:21 265:13,13 266:6 <b>bruce</b> 297:7 <b>bryan</b> 21:6 28:9 28:10,10 40:7,10 44:21 50:4,12,18 51:1 53:2 56:7 57:7 61:3,4 <b>buck</b> 62:13 290:11 290:12,12 <b>budgets</b> 267:16 <b>build</b> 27:11 38:22 94:15 143:20 212:22 213:6 248:4 271:4 272:9 278:13 280:3
---	--	---	---

<b>building</b> 5:15 111:11 112:1 270:19 <b>built</b> 101:2 102:5 186:14 <b>bunch</b> 265:8 <b>burden</b> 91:17 96:22 <b>burdens</b> 24:1 121:21 <b>burdensome</b> 306:22 <b>burn</b> 97:1 <b>burning</b> 233:7 <b>business</b> 41:18 246:17 <b>butkis</b> 151:20 <b>buy</b> 182:22 <b>buying</b> 308:4	<b>campuses</b> 293:18 <b>canada</b> 265:6 <b>cancer</b> 10:20 115:3,12 116:22 146:14 194:12 236:22 238:9 239:12,14,15 240:19 261:19 262:15 263:6,7 <b>cancers</b> 117:5,5 195:19 237:1,7 238:5,10 239:11 239:17 260:15,17 261:21 263:13 <b>cancun</b> 159:11 <b>candidate</b> 143:4 <b>canonical</b> 87:10 <b>can't</b> 210:22 229:2 235:4 243:8 268:16 272:4 278:21 283:3,15 307:18 311:11,15 <b>capabilities</b> 37:19 <b>capably</b> 71:5 <b>capacity</b> 45:3 72:12 176:10,14 178:5,9 197:13,18 197:19 247:4 <b>capitol</b> 283:15 <b>capsid</b> 244:20 245:1 <b>capsids</b> 275:8,12 275:17 <b>capture</b> 26:10 27:12 84:4 87:20 91:3 101:16 295:8 <b>captured</b> 26:16 91:1 <b>car</b> 195:18 <b>cardiac</b> 79:16 <b>cardiology</b> 248:10 248:11 <b>cardiovascular</b> 25:3	<b>care</b> 10:21 14:6 18:20 34:10 70:21 71:1 77:3 88:5,15 88:20 99:12 133:19 169:2 231:22 234:7 267:21 278:22 279:1 288:21 304:5 <b>career</b> 70:21 71:2 116:21 297:5 <b>careers</b> 250:11 <b>careful</b> 172:15 219:6 <b>carefully</b> 114:20 165:2 <b>caregiver</b> 60:17 186:3 <b>caregivers</b> 69:1 288:15 305:16 <b>caregivers'</b> 295:10 <b>cares</b> 115:4 <b>carrie</b> 171:14,15 174:5 <b>carriers</b> 151:5 <b>carrot</b> 276:20,21 <b>carry</b> 62:7 <b>carte</b> 4:7 <b>cartel</b> 308:5 <b>case</b> 5:13 15:2 42:5,5,11,11 90:21 91:9 98:4 100:4 162:10 187:21 189:14 193:21 199:22 200:10 201:1 203:5 204:21 205:12,12,14 207:18 210:9,10 213:13 214:18 216:2,18 221:22 224:7 229:9,9 230:4 243:17	266:19 280:11 281:18 291:7 <b>cases</b> 30:9 46:12 56:9 117:7 133:9 148:3 152:15 153:8 211:5 219:11,11,12,19 221:22 238:14 239:5 291:9,18 292:15 <b>cataplexy</b> 105:11 105:13 <b>categories</b> 86:20 <b>categorize</b> 83:15 <b>categorized</b> 187:15 <b>catherine</b> 284:18 284:20 290:5,10 292:20 295:19 299:18 302:20 305:17,20,22 308:16,19,21 309:3,6 311:22 <b>caught</b> 148:2 <b>cause</b> 20:9 149:10 172:3 247:17 261:2 296:15 307:10 <b>caused</b> 144:20 252:18 307:20 <b>causes</b> 130:20 171:20 253:2 <b>causing</b> 148:20 <b>cautious</b> 172:15 <b>caños</b> 21:6 24:12 24:13 36:18,20 52:4 56:5 59:7,9 <b>cber</b> 28:2 30:21 40:8 119:11 197:7 199:12 <b>cdc</b> 306:10,18 307:18 <b>cder</b> 98:10 119:8 199:12,16 203:10
<b>c</b>			
<b>c</b> 44:12 93:1 294:16 <b>california</b> 115:15 304:22 <b>call</b> 57:8 80:18 83:11 98:19 134:17 135:7 137:2 138:1,11 205:20 285:4 286:9 <b>called</b> 12:21 75:5 86:6 98:13 144:12 144:13 174:22 176:12 180:7 184:11 188:15 190:10 233:8 262:11 263:2,5 265:2 296:19 <b>calling</b> 11:9 286:11 <b>calls</b> 37:11 302:1 <b>camera</b> 4:21,21 <b>campaign</b> 288:10 293:14			

<p>291:13,20  <b>cdisc</b> 98:13 99:17  <b>cdrh</b> 28:2 36:19  37:6 142:21 274:6  <b>celebrate</b> 233:17  293:6  <b>celia</b> 194:3,4  199:11 210:7  215:3 224:1  225:17 227:19  <b>cell</b> 3:9 28:17  120:2 129:13  131:20 146:13  226:2,3,6 252:15  252:18  <b>cells</b> 161:7,8  195:18 212:4,15  212:18,19 213:2  296:16  <b>cellular</b> 194:7  <b>center</b> 7:1 10:20  24:16 27:17 28:13  38:5 52:6,20  66:19 67:5,11  83:12 115:3 119:8  128:5,18,21,22  129:11,19 130:1  133:21 161:13  178:2 194:4,6  195:15 210:21  233:8 237:2  240:14,16,20,20  240:21 248:5,8  255:9 269:16  <b>centered</b> 37:8  309:18  <b>centers</b> 72:4 77:2  91:11 119:10  129:4 130:8 137:7  152:16 169:11,13  171:2,9 179:8  240:18 279:2  <b>central</b> 117:3</p>	<p><b>century</b> 16:17  <b>ceo</b> 69:12 105:4  175:18 242:3  <b>certain</b> 26:5 38:7  39:9 47:3 79:1,2,3  84:9 93:7 102:3  129:15 133:21  142:21 152:5  164:19 176:10  195:19 210:12  251:5,6 261:18  262:17 274:11,16  275:17,18 306:20  <b>certainly</b> 19:20  36:9 49:20 50:18  54:12 55:22 85:8  134:18 157:22  192:14 197:4  216:15 226:11  239:2 248:17  261:4 262:9  <b>certainty</b> 211:8  <b>certificate</b> 315:1  316:1  <b>certify</b> 315:3  316:2  <b>cetera</b> 25:4 113:10  155:11 300:21  <b>cf</b> 191:6,17  <b>chain</b> 85:6  <b>chair</b> 115:6 265:1  314:11  <b>challenge</b> 32:12  44:22 57:20 72:20  109:19 112:5  117:2 126:22  127:3 130:11  131:8 132:10,13  138:2 151:17  226:4 258:10  269:6  <b>challenges</b> 3:1,3  6:2,12 13:21  15:10 24:18 34:15</p>	<p>36:7 37:3 72:16  91:16 109:14  111:6 126:16  127:18 130:8  131:2 132:7 134:1  199:1 203:12  226:5,5 228:7  238:4,17 240:3  254:12,18 256:19  256:20 264:1  287:3 288:13  289:5,12  <b>challenging</b> 2:16  13:18 102:16,18  160:7 174:4 221:9  227:20 288:21  <b>champion</b> 110:19  <b>chance</b> 26:14  185:4 186:8  296:21 304:6  <b>change</b> 29:18  33:19 40:19 51:10  51:16,22 57:3  92:4 133:16 135:3  135:3,15 160:4  212:17 217:16  234:16 235:11  244:10 305:12  308:7  <b>changed</b> 111:19  133:4 151:13  227:1  <b>changes</b> 34:4  126:7 142:1  189:17 207:1  226:9 234:13  264:10 288:9  <b>changing</b> 13:9  87:8 121:19  223:18 237:8  275:19  <b>chapter</b> 255:4,4  269:17</p>	<p><b>characterized</b>  190:14 292:5  <b>charge</b> 108:5  176:16 247:8  <b>charging</b> 113:14  <b>charitably</b> 290:20  <b>chart</b> 23:8 33:11  <b>chase</b> 144:12  <b>chat</b> 8:1,3  <b>check</b> 11:15 54:22  60:11  <b>checked</b> 164:7  <b>checking</b> 8:2  <b>checklists</b> 100:20  <b>chemistry</b> 229:20  <b>chemotherapy</b>  145:2  <b>chicken</b> 171:1  <b>chief</b> 10:15 11:2  67:6 115:2 248:7  <b>child</b> 184:7 218:22  <b>children</b> 72:3  115:21 120:6  130:19 138:14  154:14 175:22  183:8 185:7,8,12  202:3,3 218:13  242:6,14 261:4,21  261:21 262:2,7  288:19,22 303:11  303:13  <b>children's</b> 47:18  71:14 176:12  <b>children's</b> 246:18  254:3 255:9  269:16 276:7  282:20 304:19  <b>china</b> 265:6  283:18  <b>choice</b> 73:1 117:18  122:1 268:7  <b>choices</b> 173:5  <b>choking</b> 96:9</p>
--	--	---	---

<p><b>choose</b> 9:21 268:6  <b>choroideremia</b>  109:11  <b>chose</b> 229:16,16  <b>chris</b> 136:8 145:8  226:17,17 231:6  233:3 250:8  264:16 276:13  277:18 278:9  <b>chrisman</b> 273:10  273:11  <b>christopher</b>  231:10 233:4  264:17 270:6  274:3 277:20  278:12 279:5  280:12  <b>chronic</b> 172:19  287:3 306:9,15  307:11  <b>ciela</b> 182:2  <b>cipro</b> 309:22  310:1,10  <b>ciprofloxacin</b>  309:21 310:13,14  <b>circle</b> 69:8 269:5  <b>circles</b> 309:1  <b>circumstance</b>  262:2,3  <b>circumstances</b>  211:9  <b>citing</b> 126:10  <b>claims</b> 26:21  155:11  <b>clarity</b> 122:4  <b>class</b> 263:5,12  <b>classes</b> 220:2  <b>classrooms</b> 293:18  <b>clear</b> 33:7 72:1  97:20 106:19  111:1 138:17  159:19 167:5  192:7 201:3  205:16 213:15,16</p>	<p>294:10 301:10  <b>cleared</b> 151:8  <b>clearing</b> 193:8  <b>clearly</b> 33:15  146:18 157:17  193:16 206:16  254:8  <b>climate</b> 202:16  <b>climbing</b> 182:14  <b>clin</b> 75:11  <b>clinic</b> 14:6 43:8  56:19 57:4 244:2  244:4,6 245:5,8  246:4  <b>clinical</b> 10:8,9  14:9,16,20 15:21  16:4,8,11 23:6  24:2,4,5,14,19  25:5,6,15,17 26:8  27:8 32:11,20  33:7 34:6,10 37:4  40:4,15 41:4,5,15  43:1 46:21 47:8  50:15 54:5 55:10  62:5 67:3,13 70:2  70:5 75:22 76:13  76:18 77:3,19,22  78:19 82:10 83:13  83:17 84:6,13,22  85:12 87:4,12  89:15,21,22 90:3  90:7,16,17 91:5,9  91:13,14,20 92:6  92:11,14,17,20  93:13 98:13 99:1  113:19 114:13,21  118:9 124:22  127:1 134:22  137:3,10 138:8,8  140:10,11 142:5  152:12 159:18,21  163:16 164:6  169:21,22 197:22  199:14,18,19</p>	<p>200:22 201:12,12  236:21 238:19  239:2 246:7 248:9  251:1 254:5  260:20 261:14  276:16 277:12  287:4,12 288:1,2  288:4,7,10,19  289:7,19,22 290:3  295:16 296:2  304:3,4 305:6  <b>clinically</b> 51:11  52:14,15  <b>clinician</b> 51:4 70:4  70:8 102:14 106:3  114:17 117:3  295:22  <b>clinicians</b> 41:13  60:19 70:6 88:4  116:12 278:7  <b>clinics</b> 27:19  <b>clips</b> 106:8  <b>cln7</b> 184:2  <b>clone</b> 242:16  <b>close</b> 8:13 114:10  116:2 119:15  206:18 230:9  <b>closely</b> 30:12 70:5  167:17 180:3  230:9,10 240:17  298:21  <b>closer</b> 47:7 81:10  280:1  <b>closing</b> 8:21 10:1  312:4,6 314:20  <b>cloud</b> 18:8  <b>clusters</b> 104:15  <b>cms</b> 272:19  <b>co8</b> 60:3  <b>coffee</b> 3:14  <b>cognizant</b> 13:17  119:4 249:18  <b>coin</b> 98:17 99:9,11</p>	<p><b>coincides</b> 116:9  <b>coli</b> 259:9  <b>collaborate</b> 48:3  116:18 170:16  200:4 234:20  240:17 243:7  246:3 250:11  255:19 263:19  277:5  <b>collaborated</b>  185:2 245:2  <b>collaborating</b> 39:1  147:3 178:22  297:7  <b>collaboration</b>  25:12 43:3 44:11  103:16 158:6  165:17 178:2  196:5,13 200:14  206:19 217:7  222:16 234:3,5  239:6 240:5 242:5  243:21 244:20  245:22 250:7,18  253:4,7 259:11  264:20 265:1  272:19 276:18  295:6 313:6  <b>collaborations</b>  39:19 156:8,19  157:2 196:7 198:1  232:15,21 242:5  243:15 258:16,21  277:3  <b>collaborative</b>  26:18 44:18 52:7  52:17,21 92:22  163:19 240:12  250:17 258:12  272:22 276:11,14  277:2  <b>collaboratively</b>  34:19</p>
--	---	--	--

<b>collaborators</b> 27:18 38:8 242:18 <b>colleague</b> 93:12 <b>colleagues</b> 71:13 98:9,22 150:4 225:9 235:7 <b>collect</b> 35:19 42:6 48:7,11,17 65:4 68:8 69:8 79:2 86:19 91:19 97:4 97:4,22 98:1,6 113:9 133:9 151:1 157:5 158:11 294:14 <b>collected</b> 15:19 32:9 34:5,9,10 37:18 48:22,22 49:16 50:1 54:10 55:16,17,18,19,22 60:19 65:12 79:4 81:4 90:19 98:7 102:15 152:13 156:13 <b>collecting</b> 23:5,16 42:19 48:11 50:10 60:20 65:7 82:6 82:10 91:12 92:1 99:3 105:19 106:17 108:11,17 142:15 <b>collection</b> 6:9 23:12,12 32:15,16 34:21 53:4 81:17 93:15 96:2 157:14 <b>collectively</b> 127:4 160:4 227:21 <b>college</b> 144:14 293:18 <b>collided</b> 255:3 <b>colon</b> 239:14 <b>color</b> 289:14 <b>colorado</b> 182:12 184:10	<b>columbia</b> 71:12 <b>columbus</b> 176:12 246:17 <b>combination</b> 11:14,17 119:21 252:17 276:19 <b>combine</b> 92:19 138:9 <b>come</b> 8:10,19 19:11 20:5 40:22 44:14 50:8 52:19 56:12,12 58:14 59:3,12,18 68:16 73:11,17 80:19 89:17 91:21 92:6 98:12 101:3,5 119:17 124:8 126:10 128:5 130:18 133:4 137:7 138:19 143:3 144:4 150:12 155:4 156:15 170:16 171:3 186:8 203:17 216:8 254:22 259:20 260:6 261:16 263:13 264:11,13 265:10 267:14 269:21 273:6 281:9 283:10 285:18 292:14 310:4 <b>comes</b> 42:13 52:8 54:10 84:18 215:19 223:14 224:2 227:8 267:13 292:4 <b>comfortable</b> 204:19 217:4 <b>coming</b> 17:9 21:17 27:21 29:5 87:8 87:17 90:12 119:2 172:22 180:19	203:1 220:21 249:3 268:22 275:12 284:6 291:9,18 293:21 303:5 309:13 <b>command</b> 85:6 <b>commander</b> 115:9 <b>commemorate</b> 293:6 <b>commemoration</b> 116:9 <b>comment</b> 7:17 8:5 8:6,7,14,18,20 47:16 52:5 53:3 53:18 55:2 58:9 59:10 64:16 176:2 176:5 224:20 284:17 285:1 286:5,12 312:1,7 <b>commenters</b> 8:12 <b>comments</b> 5:5 8:1 31:5 38:3 40:9 46:1,5 52:10 68:12 77:15 79:7 284:14 285:9 286:1 287:2 314:8 314:9 <b>commercial</b> 11:18 140:22 227:22 <b>commercialized</b> 149:8 <b>commercially</b> 140:20 228:2 247:2 <b>commission</b> 179:3 265:6 266:9 <b>commissioned</b> 115:10 <b>commissioner</b> 6:21 10:10 114:15 125:17 154:9 231:20 240:15 302:5 303:4	<b>commit</b> 299:11 <b>commitment</b> 18:12 102:2 <b>committed</b> 18:19 30:21 298:21 <b>committee</b> 133:12 <b>commodity</b> 282:20 <b>common</b> 42:9 68:22 69:4 139:6 149:3 150:13 193:19 198:18 207:9 216:4 235:22 236:7 260:6 265:14,15 265:18 266:7 300:11 <b>commonalities</b> 3:4 6:4 236:11 <b>communicate</b> 113:4 206:16 217:3,5 269:22 <b>communicated</b> 191:9 216:1 <b>communication</b> 82:4,19 206:20 208:15 209:17 222:17 239:6 240:5 253:6 263:9 <b>communications</b> 215:22 216:7,18 <b>communities</b> 72:13 144:6 256:1 269:7,11 <b>community</b> 16:5 26:6,19 37:10 38:12,16 39:2 52:7,8,8,9,16,17 52:22 55:1 59:13 59:17 82:5 83:1 97:1 101:2,17 105:4,8,18 109:3 109:8 111:7 112:2 112:5 136:1 223:1
--	--	--	--

236:10 253:8 254:22 255:5,13 255:19 258:12 269:8 276:12 277:13 278:4 284:1,1,2,2,7 287:20 293:17 298:18 299:11,17 <b>companies</b> 22:7 40:11 161:18 177:13,15 178:8 259:3 261:10 262:14 265:7 <b>company</b> 61:9 63:14 67:9 175:19 177:17 195:4 228:4 242:4,17 271:6,10 <b>comparable</b> 32:10 32:14 <b>comparator</b> 55:10 56:1 <b>compare</b> 32:21 33:22 34:16 <b>compared</b> 34:16 <b>comparison</b> 32:3 33:10,15 34:15 35:9,18 54:4 55:21 162:19 <b>compatible</b> 102:12 <b>compete</b> 260:10 <b>competing</b> 258:19 260:19 262:9 277:11 <b>competition</b> 117:19 122:1 133:1 263:21 <b>competitive</b> 59:15 262:16 263:20 <b>complain</b> 89:17 <b>complaint</b> 111:2 <b>complement</b> 259:1 <b>complementary</b> 137:1 176:4	<b>complete</b> 9:11 53:21 73:22 161:21 225:13,13 314:12 <b>completed</b> 11:2 51:7 92:21 115:12 115:14 298:9 <b>completely</b> 52:5 148:17 183:22 204:22 <b>completeness</b> 25:10 28:6 36:14 38:16 49:12 <b>completing</b> 105:13 <b>complex</b> 160:19 172:2 237:9 287:17 <b>complexities</b> 264:9 288:17 <b>complexity</b> 240:2 <b>compliant</b> 110:6 <b>complicated</b> 99:6 161:11 <b>complications</b> 23:22 42:9 287:22 <b>complimentary</b> 260:18 <b>components</b> 78:4 <b>compounded</b> 288:17 <b>comprehensive</b> 32:15 <b>computer</b> 82:21 <b>concept</b> 227:7 272:10,14 300:8 <b>concepts</b> 222:1 <b>conceptually</b> 131:16 <b>concern</b> 173:22 287:7 301:18 <b>concerned</b> 172:21 <b>concerns</b> 37:7 121:16 124:9 140:14 288:19	301:13,19 <b>concluded</b> 285:19 <b>concludes</b> 312:1 <b>conclusion</b> 6:14 <b>conclusions</b> 32:4 35:11 36:9 <b>concrete</b> 212:5 <b>concurrently</b> 34:8 <b>condition</b> 76:18 193:19 <b>conditions</b> 13:1,3 13:16 14:2 22:14 84:9 171:18 172:3 307:6 <b>conduct</b> 25:5 <b>conference</b> 4:1,7 51:6 65:22 <b>conferences</b> 243:1 269:21 <b>confidence</b> 270:19 <b>confident</b> 112:2 153:17 191:14 300:19 <b>confirm</b> 112:22 <b>confused</b> 80:4 99:12 <b>congenital</b> 248:11 248:16 <b>congratulate</b> 233:18 <b>congratulations</b> 180:3 <b>congress</b> 132:19 133:3 151:13 306:19 <b>conjunction</b> 299:14 <b>connect</b> 4:13 297:18 310:4 314:5 <b>connected</b> 9:18 155:13,15 236:3 309:22 314:3	<b>connecting</b> 50:7 106:20 <b>conquer</b> 266:11 <b>consent</b> 90:6,8,11 97:13,13 <b>consequences</b> 173:21 <b>consequent</b> 173:1 <b>consider</b> 15:15 118:15 251:16 289:11 302:12 <b>considerable</b> 195:20 <b>consideration</b> 64:14 204:11 <b>considerations</b> 55:18 130:9 146:10 181:6 203:21 210:19 <b>considered</b> 164:6 204:3 251:4 252:3 252:6 <b>considering</b> 211:16 288:11 <b>consistency</b> 49:12 54:10 <b>consistent</b> 37:2 298:17 300:12 302:3 <b>consortia</b> 20:4 76:9 77:7 253:19 253:22 254:8,12 254:16 256:8,15 257:4,9,15 258:6 268:12 277:2 <b>consortium</b> 38:6 98:14 145:13 158:6 253:18 265:3,3 273:15 279:22 283:4,6 284:9 297:8 <b>consortiums</b> 258:22
---	---	---	---

<p><b>constrained</b> 126:18</p> <p><b>constraints</b> 126:19</p> <p><b>construct</b> 134:17 153:10 154:5</p> <p><b>consultant</b> 300:2</p> <p><b>consumer</b> 118:2</p> <p><b>consumers</b> 118:2 124:16</p> <p><b>contact</b> 5:9 9:17 9:20 87:2 110:1</p> <p><b>contacted</b> 82:8 191:7</p> <p><b>contains</b> 9:20 307:6</p> <p><b>contemporaneo...</b> 163:4</p> <p><b>context</b> 34:6 201:9 221:12 273:15</p> <p><b>contexts</b> 224:3</p> <p><b>continents</b> 265:4</p> <p><b>continue</b> 17:4 35:5 35:19 93:22 114:21 122:5,17 125:9 126:12 133:18 141:15 166:3 176:21 190:3 203:6 214:19 232:10 258:10 281:17 301:1 314:13</p> <p><b>continued</b> 12:5 21:19,20 145:3 159:12 297:10</p> <p><b>continues</b> 219:9 249:7</p> <p><b>continuing</b> 172:20 207:2,2 247:16</p> <p><b>contradictory</b> 306:22</p> <p><b>contraindicated</b> 310:2</p>	<p><b>contribute</b> 2:21 9:3 91:18 145:22 225:8</p> <p><b>contributed</b> 112:20</p> <p><b>contributions</b> 76:8</p> <p><b>contributor</b> 113:4 113:7</p> <p><b>control</b> 24:3,3 30:1,9 32:22 36:3 39:7,16 40:14 54:5 76:7 84:16 87:5 98:18 99:9 99:19 239:3 298:10</p> <p><b>controlled</b> 175:11</p> <p><b>controls</b> 15:3 32:1 63:10 89:8 134:18</p> <p><b>conversation</b> 62:3 62:17 100:7 170:21 217:22 254:1 264:2</p> <p><b>conversations</b> 116:14 300:18</p> <p><b>converse</b> 46:7</p> <p><b>convert</b> 219:22</p> <p><b>convinced</b> 296:13</p> <p><b>cooperative</b> 258:16 295:5</p> <p><b>coordinate</b> 266:8</p> <p><b>coordinated</b> 37:13 241:10</p> <p><b>coordinating</b> 27:16 38:5 52:6 52:20</p> <p><b>coordinator</b> 25:22</p> <p><b>copy</b> 145:18</p> <p><b>cord</b> 195:19</p> <p><b>core</b> 18:22 37:16</p> <p><b>corner</b> 45:20</p> <p><b>cornerstone</b> 86:16</p> <p><b>coronavirus</b> 243:3</p>	<p><b>corps</b> 115:10</p> <p><b>correct</b> 226:7 245:20</p> <p><b>correction</b> 226:2</p> <p><b>correctly</b> 91:1 134:9</p> <p><b>cost</b> 82:21 160:18 161:15 176:17 295:12</p> <p><b>costly</b> 161:11</p> <p><b>costs</b> 230:3 252:8 259:10</p> <p><b>couldn't</b> 209:6 216:3</p> <p><b>council</b> 254:21 301:16</p> <p><b>counsel</b> 315:10,13 316:7,10</p> <p><b>counseled</b> 214:9</p> <p><b>counselor</b> 267:9</p> <p><b>counter</b> 118:3</p> <p><b>counties</b> 157:4</p> <p><b>countries</b> 102:18 149:20 164:18,20 167:6 260:19 265:4 280:5,11 281:7,17,21</p> <p><b>country</b> 89:3,11 110:19 118:13 121:5 122:8 133:19 138:4 157:4 158:1 248:1 250:15 274:9,21 279:2 280:17 284:1,1 293:21</p> <p><b>couple</b> 21:2 29:3 40:10 46:1 48:18 71:2 119:6,15 135:11 177:10 179:8 193:15 196:4 225:21 249:21 292:14</p> <p><b>course</b> 14:22 23:6 23:21 30:3,7 33:7</p>	<p>35:20,21 42:8 50:16 77:14 83:16 103:18 116:9 120:5 130:15 135:22 141:22 142:9 174:1 175:8 189:1 200:2,21 201:1,8 202:1 203:6 205:6,16 206:5 207:6 223:18 232:16 264:7 280:19 281:22 291:2 292:9,16</p> <p><b>courses</b> 190:22</p> <p><b>covance</b> 168:5</p> <p><b>cover</b> 8:22</p> <p><b>coverage</b> 16:6 159:22 162:13</p> <p><b>covered</b> 303:3</p> <p><b>covering</b> 311:14</p> <p><b>cpim</b> 58:12</p> <p><b>crdh</b> 27:10</p> <p><b>create</b> 15:3 216:12 227:2 273:1</p> <p><b>created</b> 202:9</p> <p><b>creates</b> 87:22 89:2 287:20</p> <p><b>creating</b> 17:20 54:1,6 258:1 289:5</p> <p><b>creation</b> 27:4 217:6,7</p> <p><b>creative</b> 99:4 125:12 127:10 179:10 187:3 189:6,6 190:4 200:15 223:21 229:14 239:7</p> <p><b>creatively</b> 203:12</p> <p><b>credit</b> 267:19 268:3</p> <p><b>criminals</b> 308:8</p>
--	---	---	--

<p><b>crisper</b> 189:18  <b>crispr</b> 225:9,12  311:9  <b>criteria</b> 33:19,20  84:6 160:10  161:19 289:22  <b>critical</b> 14:8,19  24:7 34:18 48:17  49:13 54:14 56:18  67:14 75:12,20  84:10,12 94:10,15  96:15 98:19 99:9  104:19 138:9  220:20 221:2  222:13 266:17  <b>critically</b> 13:20  37:19 97:17 135:6  136:14 224:3  305:1  <b>cro</b> 168:5  <b>cross</b> 10:12 23:10  23:10 129:2  159:13  <b>crossed</b> 184:4  <b>crowd</b> 243:2  <b>crucial</b> 59:22  61:19 289:17  <b>crucifying</b> 308:13  <b>crystal</b> 46:11  <b>cs3854897</b> 1:17  <b>csf</b> 296:19 297:10  298:2,6,10 299:2  <b>cuff</b> 249:16  <b>cultural</b> 104:14,17  110:3 281:16  <b>culture</b> 281:9,11  281:14 305:12  <b>curated</b> 63:8  <b>curation</b> 112:19  <b>cure</b> 144:12  172:11 227:3  252:20 297:16  <b>cured</b> 252:21  296:22 297:1,3</p>	<p><b>cures</b> 16:17 68:20  75:14 121:3  124:15 127:7,7  182:11 294:17  <b>current</b> 33:21  153:22 173:10  195:9 226:12  253:14 265:21  266:1  <b>currently</b> 161:5  164:14  <b>cushing's</b> 225:3,4  225:8,12  <b>custom</b> 153:4  <b>customize</b> 188:16  <b>customized</b>  194:20  <b>cutting</b> 10:12  <b>cystic</b> 119:22  169:10 190:13</p> <hr/> <p style="text-align: center;"><b>d</b></p> <hr/> <p><b>dahm</b> 225:2,2  226:14  <b>daily</b> 208:15  <b>damage</b> 174:10  190:16  <b>damages</b> 287:18  <b>daniel</b> 24:13 36:20  52:4 56:5 59:9  <b>danlos</b> 172:2  309:10,20 310:3  <b>dark</b> 213:7  <b>data</b> 6:9,18 10:9  10:16 14:13 15:11  15:13,15,16,18,22  16:6,10,14,19  17:7,15,19,21  20:14 21:3 23:10  23:12,13,13 25:10  26:2 28:7 29:21  30:5,9 31:15  32:15,15,16 33:6  34:9 35:1,8,9,19  36:3,14 37:16</p>	<p>39:10 40:14,15  47:2,5 48:1,2,7,8  48:10,11,12 49:7  49:12,15 50:13,19  53:4,21,21 54:4  55:22 56:9,10  60:18,21 61:8,15  63:11,13,17 66:13  67:21 68:8,19  69:2,7 70:8 72:5,7  72:13 73:10,17,22  74:6 75:18,21  76:4,6,21,21,22  76:22 77:6,12  79:4 81:4,12,17  81:18 82:6,10  83:9 85:15 86:5,6  86:13,19 90:2,6,9  90:19,22 91:3,4  91:12,18,19 92:1  92:13,14,20 93:3  93:15 94:14 95:19  95:22 97:15,18  98:2,11,13 99:11  99:15,22 100:1,10  100:21,22 102:15  102:17 103:10,20  104:2,4 105:19  106:6 108:11,15  108:17,20 110:5  110:20 112:13,15  112:17,19,20  113:1,3,14,14,16  118:4,4,4,10  124:6,11,13,20,22  125:3,6,10,12,15  125:20 126:5,20  134:16 142:16  145:11 151:22  152:4,10,13,14  153:9 155:10,22  158:21 159:21,22  163:4 167:9  170:16 196:8</p>	<p>202:20 205:19  206:1 212:15  236:10 259:21  273:22 274:6,11  274:12,14,16,16  274:18,19 279:7  292:7 295:8  300:22 304:18  305:13 307:19  313:6  <b>database</b> 49:15  69:5 76:13 77:12  90:21 92:22 100:6  101:4 164:11  <b>databases</b> 150:20  <b>date</b> 126:5 176:15  <b>daughter</b> 105:5,9  182:8 184:2 185:4  187:7 188:8 208:9  <b>daunting</b> 188:5  216:5  <b>davis</b> 159:2,3  163:1 302:21,22  302:22 305:18,21  <b>day</b> 1:2 2:2 7:6  10:11,11 14:6,6  14:10,11 19:13,20  20:6 21:11 95:16  96:3,12 116:10  183:3 185:10,18  186:9 200:22,22  206:12 222:2  225:14 232:8  249:11 250:10  274:15 293:11,16  299:4 300:9  309:17 310:12  <b>days</b> 271:8  <b>de</b> 136:20  <b>dead</b> 29:15  <b>deal</b> 77:7 85:11,18  139:4 149:7  248:18 249:5  251:3,4 252:3</p>
--	---	--	---

<p>254:10 267:17 272:15 281:14 <b>dealing</b> 64:15 85:7 99:6 190:19 192:1 205:14 <b>dean</b> 45:21,22 <b>dear</b> 20:10 200:1 <b>death</b> 182:9 307:10 <b>debate</b> 311:16 <b>decade</b> 137:16 297:6 298:8 <b>decades</b> 29:3,19 46:14 186:15 <b>decarboxylase</b> 247:6 <b>deceased</b> 307:14 <b>december</b> 98:10 114:16 <b>decide</b> 4:5 <b>decided</b> 71:2,5 145:1 191:21 211:21 264:20,22 308:9 <b>deciding</b> 40:17 97:3 204:11 <b>decision</b> 16:7 24:20 27:8 28:4 40:4 125:3,19 127:15 191:15 192:15 205:8,9,22 206:12,14 207:5 207:18,21 209:13 210:11,16,16 <b>decisions</b> 16:6,16 27:9 28:7 36:16 84:4 97:5 124:17 125:16 126:4,6 167:7,21 206:21 207:2 214:4,14 262:19 263:14,16 274:21 <b>decline</b> 4:22 12:20 142:1 153:15</p>	<p>159:22 302:12 <b>declining</b> 210:1 <b>decreased</b> 298:3 <b>decreasing</b> 15:5 206:22 304:22 <b>dedicate</b> 176:13 <b>dedicated</b> 114:17 293:8 <b>dedication</b> 129:5 <b>deeper</b> 47:8 181:10 <b>deeply</b> 78:11 202:15 <b>defect</b> 211:21,22 212:9,9 226:2,7 <b>defective</b> 188:13 272:2,4 <b>defending</b> 161:1 <b>deficiencies</b> 22:14 <b>deficiency</b> 176:16 247:7 <b>define</b> 49:9 78:12 78:14 81:21,22 <b>defined</b> 30:15 33:4 33:14 41:6 49:16 63:3 117:15 208:1 <b>defines</b> 23:20 42:12 <b>defining</b> 81:16 83:4 95:22 <b>definitely</b> 255:22 270:5 280:13 282:12 <b>definition</b> 14:1 49:21 207:7 <b>definitions</b> 37:1,2 37:17 38:17 <b>definitive</b> 263:14 <b>deflated</b> 93:19 <b>degenerative</b> 286:21 <b>degree</b> 240:1,2 297:3</p>	<p><b>delay</b> 287:7,13,21 <b>deliberately</b> 100:18 <b>delighted</b> 114:14 <b>delineated</b> 222:8 <b>deliver</b> 192:18 226:7,8 <b>delivered</b> 276:12 <b>delivery</b> 198:21 259:2,19 <b>demand</b> 81:12 <b>demarco</b> 226:17 226:18 <b>demographics</b> 47:6 <b>demonstrate</b> 245:16 <b>department</b> 115:6 <b>depend</b> 82:17 306:15 <b>dependent</b> 174:11 248:17 <b>depending</b> 189:13 210:15 <b>depends</b> 210:17 <b>depth</b> 66:15 67:1 67:1 <b>deputy</b> 10:10 181:16 194:4 <b>derived</b> 129:16 212:4 <b>dermatomyositis</b> 286:22 289:15 <b>described</b> 213:11 229:13 <b>description</b> 67:17 <b>deserve</b> 310:8 <b>design</b> 14:9 24:2 34:22 43:9 50:15 56:19 84:13,22 85:4 87:4 92:7,17 93:2 154:6 213:22 228:9 268:2 288:11 304:3</p>	<p><b>designated</b> 22:2 <b>designation</b> 12:8 18:7 20:2,3 118:20 299:1 <b>designed</b> 49:11 52:3 98:15 146:14 148:11 295:1 <b>designing</b> 17:18 40:16 44:1 65:4 <b>designs</b> 16:11 45:4 168:11 <b>desire</b> 266:7 <b>desk</b> 3:21 5:11 75:7 130:18 314:15 <b>desperate</b> 183:20 <b>despite</b> 13:16 <b>destroy</b> 310:14 <b>detail</b> 49:17 74:9 197:9 <b>detailed</b> 15:2 32:9 33:8 82:10 <b>details</b> 187:4 314:9 <b>determination</b> 206:5 <b>determine</b> 84:5 205:18 301:14 305:7 <b>determining</b> 205:1 <b>devastating</b> 175:22 242:7 297:17 <b>develop</b> 16:7 21:14 24:4,7 26:10 39:9 44:11 45:7 48:4 57:11 60:6 71:22 74:21 131:16 134:8 136:5,6,16,17 141:20 149:12 156:5 175:11 187:5 188:13 189:6,11 196:7,11</p>
---	--	--	---

198:19 220:6,17 224:10 239:18 250:17 258:3,5 261:11 262:19 272:21 277:15 296:8 305:5 313:10 <b>developed</b> 14:11 16:18 85:19 135:5 135:8 144:14 146:15 199:5 229:10,20 236:22 243:13,16 252:2 261:19 262:10 274:17 279:7 295:4 <b>developers</b> 16:9 116:12 137:6 143:17 <b>developers'</b> 220:1 <b>developing</b> 2:22 13:17 14:19 25:19 26:3,4 37:15 39:18 40:2 48:9 68:3 81:10 86:11 121:6 123:18 131:10,13 137:7 141:21 142:21 144:8 148:14 165:8 179:5,7 189:9 239:21,21 257:15 262:14 <b>development</b> 2:4,5 2:8 3:4,5 6:3,4,10 6:12 7:5,21 9:16 13:7,8,9,11,14 14:5 15:12,14 18:1,4,15 20:6 22:8,9,17 25:4 29:5,20 30:13 34:21 40:17 43:2 44:16 45:10 51:20 58:18 60:6 69:14 73:14 74:3 76:17	78:16 81:13,14 84:4 85:2 95:2 103:3 107:18 113:18 114:2 116:19 121:12 123:8,19 124:15 126:14 127:7,17 128:16,20 129:6 130:7 133:14 135:16 136:2 137:3 138:13 140:4,10,11 141:10,13 144:5 146:4 149:6 150:5 151:18 152:21 165:19 171:6 176:14 180:2 186:14 194:17 195:2,3,4 196:1 197:20 198:12 229:3 230:22 232:14,22 237:6 237:15 238:5,15 238:18 239:12,14 240:2,19 241:16 241:20 244:12 251:10 257:21 260:14,15 261:4 262:1 263:5 275:5 275:16 285:13 290:18 301:10 302:5,7 312:21 313:13,16 314:6 <b>developments</b> 117:8 137:2 <b>device</b> 20:3,4 25:2 27:6 38:6 59:8 120:18 132:15,18 133:6 137:2,16 151:12 248:8,16 249:8,15 278:17 <b>devices</b> 3:10 10:13 24:16 53:1 62:6 88:18 120:14,16	130:1 132:22 137:10,18 151:8 153:21 163:8,17 180:8 240:20 249:9 311:9 <b>devise</b> 25:11 131:7 <b>diagnose</b> 188:4 303:4,11 305:19 <b>diagnosed</b> 87:13 87:14 105:9 182:9 182:18 184:7,15 185:9 202:3 226:18 289:16 310:6 <b>diagnosing</b> 221:15 303:15,16 305:10 305:11 <b>diagnosis</b> 71:8 87:11,11 159:10 187:11,17 221:2,6 222:3 287:4,7,10 287:13,21,22 289:21 303:8,9,14 305:4,16 <b>diagnostic</b> 33:18 33:20 186:17,19 186:22 304:13 <b>diagnostics</b> 150:17 <b>dialogue</b> 9:3 56:16 140:1 165:22 166:2,15 167:1 <b>dictate</b> 102:9 <b>didn't</b> 187:22 188:11 191:16,19 208:17 215:21 216:17 221:4 222:9 242:7 245:4 263:13 268:22 296:17 309:2 310:9,13,16,17 <b>die</b> 97:18 183:2 208:12 209:15 296:13	<b>died</b> 144:15,16 297:21 <b>difference</b> 17:9 51:11 52:15 94:16 142:4 218:17 246:12 249:10,11 250:19 257:1 258:4 273:1 274:20 <b>differences</b> 132:4 261:2 <b>different</b> 22:11,15 33:21 34:8 39:22 49:15 50:1 51:9 57:10,13 58:20 76:9 77:12 80:20 81:9,18 82:14 83:22 87:16,21 99:2 102:17,18 103:17,18,19 104:15 111:9 113:10 129:21 134:15 139:3,18 139:18 143:3 144:19,20 149:20 150:7,7 153:20 164:3 166:10 171:22 177:10,21 179:6 188:3 189:6 189:12 196:5,14 199:3 202:17 204:4 207:8,9,12 208:1 210:10 211:4,5,5 218:7 222:11 224:3 226:10 236:1 242:12 243:1,5 257:4 258:2 261:13 265:9 267:3 269:17 272:5 273:14 278:16 299:6,7 <b>differently</b> 208:1 251:22 266:4
---	---	---	---

<p><b>differing</b> 289:9</p> <p><b>differs</b> 35:20</p> <p><b>difficult</b> 102:13 193:4 202:6 207:19 220:12,12 258:2 261:5</p> <p><b>difficulties</b> 167:14</p> <p><b>difficulty</b> 73:1 103:22 147:21 167:11 173:14</p> <p><b>dig</b> 24:9 47:8 58:5 59:20</p> <p><b>digital</b> 17:20 177:2 315:8 316:3</p> <p><b>dipstick</b> 249:16</p> <p><b>dire</b> 192:14 193:13 204:9 229:4</p> <p><b>direct</b> 78:20 81:13 129:11 215:22</p> <p><b>directed</b> 46:5</p> <p><b>directing</b> 59:5 71:3</p> <p><b>direction</b> 44:7 82:14</p> <p><b>directly</b> 2:7 14:5 19:2 191:9</p> <p><b>director</b> 2:5 20:1 21:15 24:14 28:12 66:19 67:10,13 109:11 114:13 128:15 129:19 130:1 181:16 194:4 231:18 233:7 248:5 286:14,19 296:2</p> <p><b>directors</b> 7:1 128:5,18,22</p> <p><b>directs</b> 10:11</p> <p><b>disabilities</b> 301:17</p> <p><b>disability</b> 301:20 306:5</p> <p><b>disabled</b> 308:3</p>	<p><b>disbursed</b> 278:20</p> <p><b>disclose</b> 7:17 285:10</p> <p><b>disclosed</b> 310:20</p> <p><b>disclosures</b> 293:2 300:4</p> <p><b>disconnect</b> 42:20</p> <p><b>discourage</b> 54:12</p> <p><b>discovered</b> 259:6 276:22 281:7</p> <p><b>discovering</b> 304:16</p> <p><b>discovery</b> 136:3 143:7 234:9</p> <p><b>discretion</b> 5:1</p> <p><b>discriminatory</b> 301:18 302:13</p> <p><b>discuss</b> 19:19 59:15 66:16,17 79:8 197:8 227:21 255:17</p> <p><b>discussed</b> 167:13 182:4 198:1 213:14 222:2 273:16 300:6 304:9</p> <p><b>discussing</b> 221:21</p> <p><b>discussion</b> 6:16 9:1 19:15 20:13 58:15,19 65:19 128:17 134:4 178:21 181:22 213:19 218:3 232:6,8 233:2 300:5 309:19</p> <p><b>discussions</b> 6:7 44:6 52:17 83:18 101:11 114:4 264:7</p> <p><b>disease</b> 1:2,3 2:2,3 2:8,10 3:1,3 4:17 6:3,7,10,12 7:4,14 7:20 12:8,16,21 12:21 13:8,18</p>	<p>14:15,22 15:9,11 15:14 16:22 18:3 20:2,7 23:21 29:11 30:21 31:1 33:18 34:3 35:20 41:5,6,13 42:3,8 42:16 43:9 44:8 47:3 49:2 50:16 51:5 53:8,14 55:11 58:21 60:18 60:21,22 64:3 65:9 67:10 69:22 71:4 75:8,14 77:8 77:10 78:19,21 79:15,16,17 80:16 81:22 82:1 84:7 84:17 85:2 87:10 88:11 94:5,17 95:5 96:6 97:7 99:1 101:17 102:7 104:8 106:15 109:3,15,18 117:2 118:17 120:10 123:10,18,20 126:14 127:16 129:6,14 130:6,19 131:12,19 134:3 136:6 139:18,19 141:13,18,22 142:13 143:10,17 144:18 145:13,22 148:19,20 149:4 151:4 154:12 155:14 156:12 157:20 158:8,10 159:17 166:8 167:19,20 170:5,9 170:11,12 171:22 172:7,11 182:10 182:10,19 183:7,8 183:12,13 184:3,8 186:8 187:12,15 188:11 189:2,7,16 190:14 198:20,20</p>	<p>200:19,20 205:15 207:9,14 209:22 212:17 213:14 220:2 221:20 222:8,10,11,14 226:19,22 227:3 230:22 232:14,22 236:1 238:17 241:20 242:7 248:16 251:6 260:14 265:2,19 273:17 277:13 278:4 282:3,3 284:6 285:13 287:16 288:18 289:1,2,3,13,16 290:17,18,22 291:4 293:4,6,11 293:16,19 294:5 294:15,17 295:14 295:17 296:6,14 297:8,17 298:6 299:21,22 300:14 300:15 301:15 303:9,11,15,16,21 304:14 305:7,11 305:12 312:20 313:12</p> <p><b>diseases</b> 3:6 6:5,18 12:5,6 13:7,16,22 14:3,20,21 18:13 18:16 19:3,20 21:14 22:1,2,5,9 22:10,13,18,20 23:7,20 24:8 28:22 29:1 30:16 30:17 35:5 41:11 45:1,3 48:6 50:8 50:10 53:7 56:10 66:13 68:4 70:22 71:1 72:17,21 73:5 74:11,17 75:6,19 76:12,20 77:7 84:19,20</p>
--	---	--	--

90:1 94:18 95:2 97:20 101:14 104:15 105:8 107:14 108:9,17 116:10,20 117:6 117:10,21 118:7,8 118:14 119:19 120:12 121:3 126:21 127:3,5,8 130:12 131:6 134:19 135:4 138:14,21,22,22 139:1,2,7 141:8 142:10 149:9 154:22 156:21 158:14 163:7,13 165:9 169:9,15 171:15,17,19 172:1,1,5 175:22 178:10 179:6 183:9 185:9,18 188:3 189:12 207:7 218:13,19 221:7 222:4 233:13 236:2,11 237:13,16 240:8 247:11 248:2 249:21 250:5 251:11 252:2,21 253:2,6,10 255:20 257:3 259:4 260:18 266:3 269:8 271:18,19 271:20 272:1,4 284:5 286:21 287:3,8 288:6,13 289:6 293:9 294:1 294:3,4,8 295:3 298:20 303:12 304:16,17 312:22 313:8,10,17 <b>disorder</b> 29:12 120:1 140:18 172:22	<b>disorders</b> 14:19 23:3 28:12 57:10 57:11,12 123:1 129:16 293:2 <b>displayed</b> 5:3 <b>dispute</b> 76:5 <b>disservice</b> 150:14 <b>dissolve</b> 308:10 <b>distance</b> 226:10 <b>distant</b> 166:16 <b>distinct</b> 78:13,15 <b>distinction</b> 81:7 83:14 <b>distinctive</b> 261:15 <b>distribution</b> 152:16 <b>distrusting</b> 290:2 <b>dive</b> 42:1 <b>diverse</b> 46:4 236:5 289:12 303:21 <b>diversity</b> 23:22 <b>divide</b> 266:11 <b>division</b> 44:15 58:22 67:3 188:20 199:15 222:18 291:21 <b>divisions</b> 22:15,16 300:14 <b>dmd</b> 271:16 <b>dna</b> 259:7 <b>doc</b> 89:18 167:19 167:20 <b>docket</b> 5:4 9:4 286:1 292:18 314:8,10 <b>doctor</b> 191:16,17 192:18 216:3 217:22 219:17 249:13,13 <b>doctors</b> 173:18 183:10 255:10 287:9 <b>doctor's</b> 307:3	<b>document</b> 27:22 28:1,2 52:19 <b>documentary</b> 191:5 <b>doesn't</b> 220:4 223:7 229:10 233:21 266:5 267:21 270:22 307:19 313:18 <b>dog</b> 245:3,3,20 <b>doggybone</b> 259:6 259:7 <b>dogs</b> 245:19 310:4 <b>doing</b> 26:7 50:20 64:19 76:10 92:10 98:22 121:13 125:11 130:15 133:22 134:5 141:2 147:21 152:11 154:4 156:9 163:7 174:7 183:15 192:6 196:3 199:1 201:18 203:7 206:8 214:19 220:14 235:5 266:9,10,22 269:13 271:13 272:17 282:20,22 283:7 284:22 293:12 297:12 302:6 <b>dollars</b> 108:7,19 108:21 277:16 <b>dominated</b> 281:11 <b>donate</b> 247:3 <b>donoghue</b> 236:16 236:19 260:12 275:6 <b>donohue</b> 67:2 68:1 68:17 78:17 86:2 101:20 236:20 <b>don't</b> 180:19 185:7 194:2 195:8	196:20,21 198:2 206:13 207:12 218:14 219:5 222:13,14 227:21 228:2 230:13 231:1 232:6,11 233:3 234:7 239:1 247:1 250:11 265:16 274:5 276:20 277:5 283:14 293:2 294:4 300:3 311:7 311:17,18 313:22 <b>dose</b> 135:16 201:18 205:21,21 206:22 207:1 <b>doses</b> 160:22 <b>dosing</b> 162:9 211:3 <b>dots</b> 309:22 <b>downloadable</b> 100:19 <b>downstream</b> 54:14 <b>dr</b> 2:1 6:14,21 10:5,6,7,10,22 11:6,8 19:9,10,17 21:4,5,6,7,9,21 24:11,11,13 28:8 28:9,10 30:12 31:4,18,19 36:17 36:18,20 40:6,7 40:10 41:21 43:12 43:16,18 44:4,19 44:21 45:11,21 47:15,17 48:13,15 50:4,6,12,14,18 50:22 51:1,17 52:4,10 53:2,16 53:17 54:17 55:2 55:4,6,7,12,14 56:3,5,7,11,14 57:7 58:8 59:7,7,9 59:9 60:1,9,13,15
--	--	--	---

60:16 61:2,3,4,18 62:4,20,20,22 63:20 64:20 65:15 66:7 68:1,14,17 69:9 70:18,19 74:10 75:10,15 78:7,17 80:6 81:15 83:5 85:13 86:2 94:11 95:13 97:8 100:8,15 101:7,20 103:7,9 104:6,13,20 105:6 105:22 106:12 107:1,10 109:9 110:17,18 111:1 112:6,11,14 114:8 114:12,14,17 115:1,9,16,17 128:2,12 129:8,9 129:9,10,18,22 130:3,10 131:14 132:8,11,12 133:20 134:2 136:19 138:15 141:4,5,14 142:8 143:20 144:10 146:2,11 147:4 148:8 149:15 150:15 153:3,6 155:1 156:17 157:19 158:16 159:1 160:6 162:2 163:10,18 165:6 165:11,14,21 167:3 168:1,3,9 169:5 170:13,22 171:11,13 172:12 174:19 175:14 176:7 177:9 178:16 179:14,17 179:22 180:10,18 184:4,19 185:2 186:6 190:6 193:17 194:2,3,5	197:5 199:13 205:3 208:14 210:7 211:14 219:10 220:22 224:1,20 225:6,17 227:19 228:5,6 230:17,20 231:4,5 231:7,10,12 233:4 236:15,16,18,19 242:1 247:13,14 248:4 251:12 252:13 253:11 256:3,5,10,11,12 256:21 258:14 260:11,12 264:16 264:17 268:19 269:3,4 270:3,6 272:9 273:8 274:3 274:4 275:6 276:1 277:20 278:12 279:5,16,20 280:12 282:7 284:12,15 294:6 294:17,17 297:7 297:12 300:18,20 304:9,19 312:5 <b>draft</b> 291:16 <b>dragged</b> 230:16 <b>dragon</b> 182:16 <b>dramatic</b> 119:16 <b>dramatically</b> 11:22 35:8 297:1 <b>drastically</b> 304:13 <b>draw</b> 32:4 35:10 36:8 220:15 <b>dream</b> 235:13 <b>drinks</b> 4:8 <b>drive</b> 84:4 88:14 138:12 239:6 304:1 306:10 <b>driven</b> 306:7 <b>driving</b> 83:18 152:21,22 238:2 308:7,13	<b>drop</b> 201:19 <b>drown</b> 296:7 <b>drub</b> 237:20 <b>drug</b> 1:1 11:20 12:14 13:4,13 18:5,7,10 32:5 40:11 45:10 51:20 55:9 56:5 58:17 60:6 73:13 74:3 76:17 78:16 84:4 84:4,8 85:2 95:2 107:17 113:18 114:1 118:16,19 119:8,9 120:10 136:2,3 147:18 165:19 177:7 180:2 181:17 184:10,12 186:13 188:13,14 195:3 208:20 211:20 212:7,8,11,16 213:3,12,22 217:13 219:22 220:1 228:9,9 229:3,9,17 230:9 230:10 238:15,17 238:20 239:1,12 240:2,19,21 241:9 241:16 243:15 246:4 249:6,17 251:7 260:14,14 261:4 262:1 271:15,16 272:1,2 275:7,15,19 276:15 277:17 282:1 290:18 302:5,7 <b>drugs</b> 10:10,13 11:19 12:2,4,8,12 21:14,16,16,17,20 21:21 22:1,4,18 24:8,8 35:3 36:3,4 36:10 66:20 67:5 67:5 114:16	116:11 118:17,19 129:19,20 134:8 135:6,9 163:16 165:16 168:22 171:5 181:18 199:16 214:2 228:15,19 236:22 237:7,16 238:5,7 238:16 239:18,19 239:21 240:1,4 247:5 261:11 262:4,5,7,14,19 263:5,11 271:17 302:11 307:7,14 307:16 310:9 311:8 <b>duchenne</b> 76:14 77:8 <b>duchenne's</b> 243:13 244:12 <b>due</b> 290:3 307:22 <b>duke</b> 10:19,20,22 <b>duly</b> 315:5 <b>duplicating</b> 262:8 <b>durable</b> 104:9 <b>duration</b> 84:11 <b>dying</b> 153:13 172:9 <b>dysphasia</b> 96:7,10 <b>dystrophy</b> 76:14 77:8 244:13 245:6
<b>e</b>			
e 259:9 e.t. 11:16 eap 159:13 earlier 41:20 58:15 101:11 102:20 110:2 135:15 165:15 181:8 182:5 188:2 193:18 249:21 251:13 273:16 294:18 314:7			

<p><b>early</b> 36:16 43:3 44:5,14,15 46:6 47:5,11,14 51:6 54:5 56:17 62:18 62:19 74:2 93:11 102:2 105:20 157:11 172:9 180:13 241:11,16 271:8 285:3 287:14</p> <p><b>earned</b> 115:9</p> <p><b>ears</b> 233:6</p> <p><b>ease</b> 215:13</p> <p><b>easier</b> 103:16 104:5 164:17 220:11,12,19 231:2</p> <p><b>easiest</b> 177:15</p> <p><b>easily</b> 72:19 229:2</p> <p><b>easy</b> 50:21 57:20 73:17 209:15 266:21</p> <p><b>eating</b> 215:1</p> <p><b>echo</b> 84:14 132:12 197:10</p> <p><b>economic</b> 126:17 132:21 251:2 279:9</p> <p><b>ecosystem</b> 7:4 15:18 81:2 230:22 232:13,21 233:15 237:6 249:1,2 250:6,22 251:17 251:20 257:12,17</p> <p><b>ecosystems</b> 237:7</p> <p><b>editing</b> 189:18 194:10 210:22,22 226:1 259:1 311:9</p> <p><b>eds</b> 309:12,12 310:13</p> <p><b>educate</b> 105:18 253:8 255:12</p> <p><b>educated</b> 208:16 242:10</p>	<p><b>educating</b> 105:7</p> <p><b>education</b> 255:7,8</p> <p><b>educations</b> 293:9</p> <p><b>effect</b> 33:2,6 75:2 84:8 217:15 245:15 258:9 261:17</p> <p><b>effective</b> 14:17 18:1,16 36:10 59:16 71:16 123:17 124:20 156:20 177:5 204:20 212:2 268:15 294:7 295:15,18 301:15 313:16</p> <p><b>effectively</b> 57:6 116:18 123:8 157:1 228:12</p> <p><b>effectiveness</b> 16:20 151:15 152:6 239:1</p> <p><b>effects</b> 71:7 84:5,8 162:13 207:17 287:17</p> <p><b>efficacy</b> 15:4 122:10 124:3 153:22 154:1</p> <p><b>efficiency</b> 122:7 122:13 169:1</p> <p><b>efficient</b> 18:1 73:4 131:18 136:21 140:5 215:20 295:16</p> <p><b>efficiently</b> 140:10 196:12 239:19 262:19</p> <p><b>effort</b> 18:6,11 37:21 38:10 53:10 75:15 82:5 111:18 243:8 245:5 276:14</p> <p><b>efforts</b> 18:6,12 19:3 83:2 121:9</p>	<p>137:1 196:22 220:1 228:2 233:21 241:7 243:19 244:14 251:3 253:19,22 254:8,12,16 256:15 257:4 262:8 270:1</p> <p><b>egg</b> 171:1</p> <p><b>eh</b> 16:2</p> <p><b>ehlers</b> 172:2 309:10,20 310:3</p> <p><b>ehrs</b> 155:10 274:15</p> <p><b>eight</b> 91:11,17 159:7,9,10 287:8 307:17</p> <p><b>either</b> 3:18 9:3 64:16 101:13 137:3 146:17 194:21 206:8 251:5 253:14 260:20</p> <p><b>elderly</b> 308:3</p> <p><b>electronic</b> 15:20 26:21 91:3 124:21 164:1,15</p> <p><b>electronically</b> 18:11</p> <p><b>element</b> 274:19</p> <p><b>elements</b> 48:21 50:13 134:16 274:17 277:2</p> <p><b>eligibility</b> 287:12 289:22</p> <p><b>eliza</b> 1:7</p> <p><b>ella</b> 182:1 190:8,9 204:8 215:21</p> <p><b>ella's</b> 219:11</p> <p><b>elusive</b> 186:19</p> <p><b>ema</b> 165:16,18 166:1,4,18,19</p> <p><b>email</b> 201:20 314:2,18</p>	<p><b>emailed</b> 5:21</p> <p><b>emails</b> 82:6</p> <p><b>emerge</b> 46:16</p> <p><b>emerged</b> 105:15</p> <p><b>emergency</b> 5:13</p> <p><b>emerging</b> 206:2</p> <p><b>emphasis</b> 181:5 241:3 295:9</p> <p><b>emphasize</b> 46:17 82:16 122:6 125:14 291:10,19</p> <p><b>emphasizes</b> 73:2</p> <p><b>employed</b> 315:11 315:14 316:8,11</p> <p><b>employee</b> 315:13 316:10</p> <p><b>employees</b> 4:18</p> <p><b>empowering</b> 118:1,4 123:2</p> <p><b>empty</b> 183:1,5</p> <p><b>enable</b> 17:19 144:8 177:2</p> <p><b>enabled</b> 234:14</p> <p><b>enabler</b> 126:12</p> <p><b>enables</b> 124:13</p> <p><b>enabling</b> 246:1</p> <p><b>encountered</b> 85:17 111:5 280:1</p> <p><b>encounters</b> 249:12</p> <p><b>encourage</b> 5:5 7:14 9:2 47:9 157:7 160:8 190:1 262:17 302:18 314:7</p> <p><b>encouraged</b> 118:12</p> <p><b>encouraging</b> 298:17</p> <p><b>endeavor</b> 80:22 94:21</p> <p><b>endeavors</b> 243:9</p> <p><b>endocrine</b> 22:16 79:16</p>
---	---	---	--

<p><b>endorsed</b> 113:21</p> <p><b>endpoint</b> 40:20 46:21 89:22</p> <p><b>endpoints</b> 14:9,20 30:6,8 40:17 42:15 51:9,10 60:5</p> <p><b>ends</b> 9:13 48:7 185:13</p> <p><b>enduring</b> 185:9</p> <p><b>enemy</b> 265:14,15 265:17,18</p> <p><b>energy</b> 121:5 240:12 241:21</p> <p><b>engage</b> 2:7 17:2 44:7 57:1 137:6 249:14</p> <p><b>engaged</b> 54:6,7 62:11,16 227:6</p> <p><b>engagement</b> 9:1 17:3 59:11,21 61:21 222:19 223:14 288:12</p> <p><b>engaging</b> 46:2,6 56:17 62:2 116:14</p> <p><b>engine</b> 138:12 152:21</p> <p><b>england</b> 174:21</p> <p><b>enhancements</b> 18:15</p> <p><b>enjoying</b> 246:9</p> <p><b>enlisted</b> 57:16</p> <p><b>enormity</b> 265:19</p> <p><b>enormous</b> 80:17 266:16 313:9</p> <p><b>enormously</b> 13:18</p> <p><b>enroll</b> 53:7 70:1 238:20</p> <p><b>enrolled</b> 162:22</p> <p><b>enrolling</b> 53:9,13</p> <p><b>ensure</b> 61:14 215:14 228:15 257:16 279:5 288:4 289:8</p>	<p>300:13 301:1</p> <p><b>ensured</b> 98:6</p> <p><b>ensures</b> 97:15</p> <p><b>ensuring</b> 61:7 124:12 294:7</p> <p><b>entailed</b> 209:20</p> <p><b>enter</b> 57:3</p> <p><b>entered</b> 63:17 69:18 70:8,13 77:1 83:11 102:14</p> <p><b>entering</b> 69:18 164:5</p> <p><b>enterprise</b> 136:12 260:16</p> <p><b>entire</b> 52:9 81:22 247:19 257:11 265:10 272:12 274:21 280:16 301:2 308:14</p> <p><b>entirely</b> 217:13</p> <p><b>entirety</b> 64:8 218:20</p> <p><b>entities</b> 253:16</p> <p><b>entrectinib</b> 237:19</p> <p><b>environment</b> 241:19 253:7 272:22</p> <p><b>environmental</b> 64:13 65:8</p> <p><b>envision</b> 275:11</p> <p><b>envisions</b> 273:19</p> <p><b>enzyme</b> 22:13</p> <p><b>epi</b> 39:3</p> <p><b>epidemic</b> 172:17 173:17,22</p> <p><b>epidemiologist</b> 86:20</p> <p><b>epidemiologists</b> 49:5 88:1</p> <p><b>epidemiology</b> 25:8</p> <p><b>epigenetic</b> 263:6</p> <p><b>epps</b> 269:3,4 270:3</p>	<p><b>ept</b> 272:12</p> <p><b>equally</b> 99:14 246:16</p> <p><b>equity</b> 282:15,16</p> <p><b>era</b> 80:11 221:9 243:5</p> <p><b>eraser</b> 245:14</p> <p><b>eric</b> 109:10,10 279:18</p> <p><b>erika</b> 19:17 20:1 24:11 28:8 31:4 36:17 40:6 43:12 43:18 44:19 45:11 47:15 48:13 53:16 54:17 55:2,6,12 56:3,11 59:7 60:9 60:15 61:2 62:20 63:20 65:15</p> <p><b>error</b> 58:22 67:4</p> <p><b>errors</b> 22:12 68:4 74:16 188:21 199:15 221:7 223:13</p> <p><b>es</b> 315:4</p> <p><b>escalate</b> 205:21</p> <p><b>especially</b> 13:19 48:6 50:8 73:22 84:9 96:16,20 102:10 103:1 157:14 215:12 232:14 249:20 251:11 277:13 278:3 294:10 303:7,21 306:14</p> <p><b>essence</b> 126:21</p> <p><b>essential</b> 19:1 35:2 122:21 281:20</p> <p><b>essentially</b> 75:16 97:12 113:22 133:2 138:20 150:13 164:1 187:16 275:20</p> <p><b>establish</b> 27:21 112:22 156:7</p>	<p>229:10 292:6</p> <p><b>established</b> 124:7 181:18 187:11 291:1,6</p> <p><b>establishing</b> 26:7 62:18 69:21 169:11</p> <p><b>establishment</b> 61:21</p> <p><b>esteemed</b> 181:10 194:1</p> <p><b>estimated</b> 294:2</p> <p><b>estimates</b> 197:12</p> <p><b>et</b> 25:3 113:10 155:11 300:21</p> <p><b>ethical</b> 239:3</p> <p><b>etiologies</b> 305:1</p> <p><b>eu</b> 167:5</p> <p><b>europe</b> 140:18 150:1 167:10 179:10 261:7 262:10,21 264:2 280:18 281:8 293:14</p> <p><b>european</b> 164:18 167:11 179:2,3,15 241:5 265:6 266:9 280:5</p> <p><b>europeans</b> 28:16</p> <p><b>evaluate</b> 15:4 16:19 143:11 302:8</p> <p><b>evaluated</b> 171:6</p> <p><b>evaluating</b> 123:18</p> <p><b>evaluation</b> 5:18,21 9:11 24:16 27:1 27:11,16 38:4 119:8,11 129:11 144:5 240:21 241:13 274:8 302:11</p> <p><b>evening</b> 314:21</p> <p><b>event</b> 120:7 311:6</p>
---	--	--	--

<b>events</b> 293:21	179:16,21 213:17	137:13 154:3	65:9 69:13 70:11
<b>eventually</b> 87:3	279:14,14 311:1	185:15 219:6	71:11 74:3 75:19
90:9,13 175:2	<b>exaggerate</b> 132:4	237:9 241:19	78:21 86:8 103:15
183:1 190:17	<b>example</b> 12:13	244:7 261:22	111:15 168:13,17
196:20	18:11 33:2,19	294:13 312:20	217:1 224:8,9
<b>everybody</b> 80:17	73:11 76:12 82:3	<b>exclusivity</b> 132:21	254:9 256:13,16
109:1 143:21	96:5 99:4 124:19	133:2	256:18 266:15
169:13 180:22	129:4 154:9 174:3	<b>excruciating</b>	280:21 281:3
201:13 203:9	174:9 186:10	209:11	298:17
231:13 245:21	193:18 199:2	<b>excuse</b> 306:17	<b>experienced</b> 78:11
247:16 259:12	200:14 205:19	<b>execution</b> 10:17	267:10 270:14
260:3 265:16	210:19 220:11	<b>executive</b> 10:17	<b>experiences</b> 9:8
270:12 273:2	221:19 222:1	67:6,13 114:20	14:7 70:16 204:2
276:3 277:12	223:5 235:15	115:2 286:14,18	224:14 283:10
280:22 299:4	237:18 239:15	<b>exemption</b> 120:18	297:20 299:12
<b>everybody's</b>	244:11,20 258:21	133:6 151:12	312:18 313:22
259:15 267:16,17	259:6,17 260:13	<b>exercise</b> 106:18	<b>experiencing</b>
<b>everylife</b> 302:15	263:18 264:18	298:3	173:14,16
303:2	<b>examples</b> 31:16	<b>exercised</b> 195:20	<b>experiment</b> 230:8
<b>evidence</b> 15:15,16	35:12 36:2 55:15	<b>exist</b> 42:22 108:5	230:8,10
15:21 16:10,12,15	76:11 119:20	132:18,22	<b>experimental</b>
16:18,20 17:5	156:19 175:5	<b>existed</b> 187:22	191:20 252:19
24:14,19 25:5,15	187:6 195:15,15	<b>existing</b> 23:10	290:3
25:18,20 26:16,19	195:20 196:11	112:20 145:16	<b>expert</b> 10:9 69:5
27:4,9,13 28:3	220:10,10 235:14	152:10 154:2	86:21 144:19
36:22 37:4 38:1	239:10 254:15	304:10,12 306:6	145:6 302:1
38:10,12 39:5,8	292:7	<b>exists</b> 125:15	<b>expertise</b> 45:8
40:3 62:5 136:22	<b>excellence</b> 83:12	<b>exit</b> 5:13,14	136:14 138:6
138:7 152:22	169:11,13 171:2,9	<b>expand</b> 35:5 79:20	<b>experts</b> 49:5,22
191:19 301:17	237:2 240:15,16	80:3 105:6	143:1 145:7 170:1
<b>evidentiary</b> 292:2	<b>excellent</b> 28:9	<b>expanded</b> 12:12	231:16 295:2
292:3	40:6 43:12 44:19	120:11 160:16	<b>explain</b> 117:17
<b>evolution</b> 94:4	45:11 55:12 56:11	161:18 177:18	255:11
<b>evolve</b> 54:3,16	178:19 236:19	<b>expect</b> 30:11	<b>explore</b> 185:16
82:13 105:8 313:4	263:18	45:15 205:17	<b>exposed</b> 16:2
<b>evolved</b> 228:11,13	<b>excelling</b> 305:11	<b>expectations</b>	64:10
228:18	<b>exceptional</b> 186:3	166:10	<b>express</b> 275:21
<b>evolves</b> 264:10	<b>excess</b> 178:8	<b>expected</b> 33:5	<b>expressed</b> 9:6
<b>evolving</b> 237:8	<b>excited</b> 2:6 19:13	58:3	<b>extend</b> 214:18
272:8	68:2 71:9 93:13	<b>expensive</b> 161:16	<b>extensive</b> 112:18
<b>exact</b> 62:3 167:9	128:16 201:16	229:7 230:6	295:1
187:12 214:10	231:14,15 283:9	<b>experience</b> 24:19	<b>extensively</b> 22:19
<b>exactly</b> 50:22 64:7	<b>exciting</b> 17:6 29:5	25:5 31:14 37:4	<b>extent</b> 141:19
65:2 97:3 178:1	40:22 126:13	40:4 46:4 57:8	160:10 241:1

<p><b>external</b> 24:3 32:1 36:3 39:5 54:5 59:10,21 87:5 134:17 <b>extra</b> 180:15 <b>extraordinarily</b> 237:9 238:8 <b>extraordinary</b> 11:19 117:8 124:10,14 126:10 235:14 290:9 <b>extreme</b> 232:1,1 242:13 264:22 <b>extremely</b> 47:11 106:7 230:5 248:16 259:2 268:15 292:13 <b>eyes</b> 213:5</p>	<p>308:12 <b>factor</b> 64:19 192:15 205:1 <b>factors</b> 64:13 65:8 65:8 <b>facts</b> 210:10 307:9 310:8 <b>fail</b> 303:16 <b>failing</b> 303:8 305:10 <b>fails</b> 303:20 <b>failure</b> 29:16 159:9 162:8 190:17 244:3,3 271:22 296:9 303:17 <b>fair</b> 23:1 38:1 100:21 211:7 <b>faithfulness</b> 124:2 <b>fall</b> 263:4 268:4 <b>false</b> 268:7 <b>familiar</b> 29:11 190:11 191:18 <b>families</b> 14:4 18:17 29:19 47:7 54:7 71:20 108:17 109:4 111:13 116:3,13 117:21 122:22 123:13 127:22 141:7 154:19 185:19 196:19 202:4 207:20 214:15 284:7 312:22 313:9 <b>families'</b> 206:13 <b>family</b> 2:11 123:7 185:4 195:7 196:18 197:2 199:9 200:7 206:7 211:19 215:10 229:4 288:14 <b>family's</b> 207:4</p>	<p><b>fan</b> 270:12 <b>fantastic</b> 62:2 66:22 203:1 <b>far</b> 25:18 36:21 38:16 57:2 59:16 68:7 79:5 145:21 148:6 154:1 158:13 167:3 178:15 192:22 197:11 216:2 227:13 229:21 281:8 <b>fara</b> 69:13 70:5 94:14 111:17,20 <b>fare</b> 16:1 <b>farmer</b> 67:6 69:11 69:11 79:6 90:5 101:22 106:5 111:5 <b>fascinating</b> 47:19 200:2 <b>fast</b> 119:2 130:22 141:22 303:5 <b>faster</b> 95:10 134:9 135:9 236:14 239:19 301:5 303:6 <b>fastest</b> 160:11 <b>fatal</b> 12:16 154:12 182:11 218:13 <b>fatalities</b> 307:20 <b>father</b> 213:17 <b>favor</b> 302:14 <b>favorite</b> 128:21 182:16 <b>fda</b> 1:1,2 2:2,6,14 2:15,16 4:12,15 4:17,18 5:11 6:16 6:21 7:1 9:14,18 12:12,13,19 13:2 16:14,18 17:7,11 17:22 18:4 19:16 41:3 43:5 46:6 51:21 58:3 66:20</p>	<p>67:5 68:19 74:15 75:21 98:21 107:10 115:1 117:14 118:16 120:15 121:10 123:15 124:17 125:17 126:1,12 127:6 128:4 129:5 159:19 160:16 162:3 165:16,17 166:1 167:5 168:8 172:6,10,19 184:20,21 186:9 187:2 188:20 190:3 191:21 194:5,6 201:7 202:7 212:15 215:17,17,22 216:8,11,18 217:6 223:3,7 224:10 231:20 233:22 272:19 275:11,14 286:16 288:8 290:8 291:12,15 291:18,21 292:12 292:14 293:5 294:4,6,10,19 295:1,5 297:15 298:20,22,22 299:9,14 301:5 302:1,6 306:6,6 306:17,17 307:4 307:18 310:4 311:5,12 312:8,15 313:8,20 314:3,15 <b>fda's</b> 10:11,16 18:12 46:11 52:11 116:16 <b>fda.gov.</b> 314:2,6 <b>fdarare2020</b> 9:22 <b>fda's</b> 307:5 313:20 <b>fearmongering</b> 174:16</p>
<p><b>f</b></p>			
<p><b>fa</b> 91:14 92:22 105:18 <b>face</b> 126:16 210:11 218:21 288:13 <b>facebook</b> 155:12 155:13,15 156:14 <b>faced</b> 208:7 217:14,17 <b>facets</b> 15:17 <b>facilitate</b> 60:6 150:5 157:10 194:17 195:10,22 198:11 275:4 <b>facilitates</b> 14:16 <b>facilitating</b> 70:15 <b>facility</b> 115:3 <b>facing</b> 193:12 <b>fact</b> 11:14 76:5,14 111:2 114:1 133:13 143:16 144:8 178:22 180:6 184:2 212:18 233:16 234:5 298:5</p>			

<b>feasible</b> 53:15 <b>feature</b> 8:1 <b>february</b> 1:4 <b>federal</b> 277:9 286:3 308:11 314:10 <b>federation</b> 293:7 <b>feedback</b> 59:16 255:7,14 273:21 274:2 <b>feeding</b> 88:16 <b>feel</b> 3:16 11:16 112:2 136:2 153:17 155:5 201:15 202:22 208:3,16 217:3 271:7 282:13,17 <b>feels</b> 89:20 <b>feet</b> 283:2 <b>fellowship</b> 11:3 115:12 <b>felt</b> 233:20 <b>fentanyl</b> 307:15 <b>fertility</b> 288:14 <b>fetus</b> 248:13 <b>fev1</b> 89:18 <b>fevers</b> 192:6 <b>fewer</b> 246:22 <b>fi</b> 5:2 <b>fibrosarcoma</b> 238:13 <b>fibrosis</b> 12:15 119:22 169:10 190:13 <b>fiction</b> 242:22 244:15 <b>field</b> 61:11 69:3 118:12 119:18 218:10 219:8 233:20 234:6 237:11 248:15 255:11 257:3 258:13 271:6 272:8	<b>fifteen</b> 297:2 <b>fifth</b> 303:12 <b>fight</b> 110:16 <b>fighting</b> 110:12 183:8 <b>figure</b> 30:22 51:13 51:19 57:1 92:2 96:3 135:16 143:8 150:18 199:7 200:8 201:20 219:21 220:7 225:19 226:6 239:18 262:7 <b>figured</b> 30:19 145:9 <b>figuring</b> 132:6 214:11 <b>file</b> 275:7,10,14 <b>filed</b> 275:10,14,22 <b>filing</b> 192:8 <b>fill</b> 187:4 200:9 212:20 223:4 <b>filming</b> 5:8 <b>finalized</b> 61:20 <b>finally</b> 71:7 118:4 159:9 287:20 292:11 309:22 <b>financial</b> 7:20 285:12 286:16 289:4 290:17 296:4 300:3 311:6 311:13 <b>financially</b> 306:4 311:7 315:15 316:11 <b>find</b> 22:19 58:6 59:11 60:5 64:22 75:8 109:21 110:8 110:12,19 113:2 121:2 127:6,17 140:22 145:16 146:19 147:4 150:4,12,13 153:22 158:2	163:14 164:12 173:9 183:20,21 186:18 188:7 196:11 216:6 221:11 238:18 258:15 286:2 298:16 310:21 <b>finding</b> 124:10 163:20 170:14 172:11 189:8 192:21 197:2 229:14 230:6 <b>findings</b> 153:22 <b>fingers</b> 113:5 <b>finish</b> 9:7 43:13,14 309:2 <b>finished</b> 24:21 <b>finishes</b> 285:3 <b>first</b> 3:9 8:10,11 8:19,19 13:2 19:11,15,17 20:12 20:19 21:4,7 31:12 40:11 47:18 48:14 53:4 55:2 58:9 64:6 66:15 67:2 68:18 71:18 74:15 79:7 82:4 82:18 86:17 92:11 104:22 107:4 116:1 117:18 119:21,22 144:14 151:4 159:11 177:11 182:6 184:12 186:7 187:6 200:17 203:17 204:17 220:10 229:8,9 233:16 237:20 242:15 245:8,9 247:15 253:19 263:3 266:17 286:6,11 291:7,8 311:20	<b>firsthand</b> 160:1 <b>fit</b> 72:15 73:10 74:1 80:1 85:15 86:1 202:8 264:22 <b>fits</b> 147:13 <b>five</b> 20:21 21:7 42:11 51:14 57:13 57:14 60:10 119:12 149:21 159:12 183:2 192:2 203:16 209:6 240:11 253:17 262:4 265:4 277:1 287:9 303:10 <b>fix</b> 133:15 161:15 <b>fixed</b> 189:18 <b>fixing</b> 252:17 <b>flares</b> 288:21 289:2 <b>flatiron</b> 10:18 <b>flexibility</b> 187:1 190:3 195:13,21 203:18 300:22 <b>flexible</b> 58:10 93:5 94:9 200:15 223:21 239:7 <b>flinders</b> 11:4 <b>floor</b> 181:9 <b>flow</b> 262:18 <b>fluroquinolone</b> 310:2 <b>fly</b> 223:8 <b>flyer</b> 75:7 <b>flyers</b> 75:6 <b>flying</b> 135:10 <b>focus</b> 6:8,11 18:22 20:14 73:16 79:20 220:15 222:15 232:5 248:22 250:1 256:6 265:15 294:10 <b>focused</b> 58:17 79:14 123:16,19
--	---	--	---

309:18 <b>focusing</b> 224:20 265:16 <b>fold</b> 197:18 <b>folk</b> 158:7 <b>folks</b> 38:14,18 67:1 129:2 155:4 167:11 181:14,20 182:3 187:5 190:1 211:20 214:9 254:6 256:19 266:6 269:8,10 270:4 314:16 <b>follow</b> 5:14 53:18 77:21 112:9 138:20 143:19 163:2 170:14 174:5 203:7 221:16 222:14,15 228:3 292:17 304:5 306:6 <b>followed</b> 6:16 7:2 195:2 <b>following</b> 97:13 152:1 169:12 <b>follows</b> 66:2 220:11 303:18 <b>fond</b> 265:20 <b>food</b> 1:1 3:22 4:6,8 10:10 96:10 114:16 <b>foods</b> 10:14 <b>football</b> 267:2 <b>force</b> 142:11,14 306:21 <b>forced</b> 260:10 <b>forces</b> 306:8 <b>forcing</b> 240:9 <b>foregoing</b> 315:3,4 316:4 <b>forehead</b> 243:4 <b>foremost</b> 107:4 311:21	<b>forget</b> 120:14 144:13 158:16 <b>forgot</b> 114:6 <b>form</b> 9:11 29:12 29:14 142:11 184:2 271:10 <b>formalized</b> 83:12 <b>formally</b> 77:2 <b>formative</b> 45:10 <b>formed</b> 176:11 <b>former</b> 132:16 <b>formerly</b> 154:12 <b>forms</b> 5:18,21 90:21 91:9 100:4 <b>formulate</b> 117:13 <b>formulation</b> 299:2 <b>forth</b> 131:11 134:14 135:17,22 136:15 149:9 167:16 172:22 173:18 218:3 <b>fortunate</b> 56:8 90:18 91:2 94:13 109:12 187:8,9 200:3 244:10 <b>fortunately</b> 90:12 298:7 <b>fortune</b> 20:11 <b>forum</b> 58:13 98:13 240:15 <b>forums</b> 59:2 <b>forward</b> 10:2 11:12 19:4 29:4 34:18 35:2 45:14 62:15 69:3 74:8 88:5 122:13,14 123:11 127:13 139:11 146:3 147:5 203:14 218:9 219:7 220:14 228:22 232:3 249:8 250:13 257:2 258:13 262:1	264:12 291:18 299:13 301:3 313:11 <b>foster</b> 150:19 <b>found</b> 34:2 39:10 107:14 109:15 144:17,17 145:6 174:9 183:19 213:1 221:3 226:20 227:4,11 301:17 307:14 309:19 314:10 <b>foundation</b> 18:14 46:1 47:18 73:7 109:12 159:5 169:10 171:17 176:11,12 177:2 178:18 183:14 225:4 226:21 246:16,18 247:11 276:8 279:19 290:15,20 291:1 296:3 297:14,22 298:16,18 299:16 302:15 303:2 306:5 <b>foundations</b> 302:14 <b>founded</b> 175:19 175:21 246:18 <b>founder</b> 159:3 175:18 242:3,17 299:22 303:1 <b>four</b> 51:14 92:20 115:21 137:20 171:22 179:6 252:18 262:4 270:10 272:11 309:20 <b>fourthly</b> 267:18 <b>fragile</b> 151:5 164:12 <b>framework</b> 27:22 48:4,5,9 52:18,21	53:1 153:22 195:12 251:15 <b>frameworks</b> 50:2 150:8 <b>francisco</b> 115:15 <b>frankly</b> 38:20 116:15 261:12 267:21 307:8 <b>free</b> 3:16 108:14 155:5 247:8 262:17 <b>frequency</b> 77:18 77:19 207:1 <b>frequent</b> 73:16,22 201:14 <b>frequently</b> 77:22 141:9 <b>friday</b> 151:4 <b>friedreich's</b> 67:7 69:12 77:11 <b>front</b> 38:14 46:14 61:15 63:7 68:5 90:7 213:4 267:12 267:18,18 286:6 <b>fruitful</b> 118:11 <b>frustrating</b> 169:6 <b>fsgs</b> 168:21 <b>fueled</b> 11:19 <b>fulfill</b> 21:1 <b>full</b> 3:6 8:15 307:5 310:8 <b>function</b> 12:20 88:9 89:15 298:13 <b>functional</b> 88:8,10 89:13 90:1 95:4 <b>functioning</b> 10:11 <b>fund</b> 37:9 38:10 <b>fundamental</b> 222:1 234:9 <b>funded</b> 7:19 72:19 73:7 285:11 296:4 309:13 <b>funders</b> 265:5
--	---	---	--

<b>funding</b> 37:7 72:17 73:19 83:15 113:8 114:4 127:10 136:5 169:7,7,16,21 170:3 227:9,15 244:15 245:20 246:1 305:13 306:4 <b>fundraisers</b> 255:1 <b>fundraising</b> 243:19 <b>funds</b> 257:22,22 <b>furios</b> 119:3 303:5 <b>further</b> 13:15 49:2 114:4 119:7 121:14 122:5 142:19 197:9 212:14 220:10 315:12 316:9 <b>fusion</b> 237:19 <b>future</b> 1:3 2:3,7 9:19 14:7 86:22 91:9 93:2 120:8 130:6 143:15 147:6 166:16 287:12 288:14 314:4	<b>gather</b> 47:4,5 269:19 <b>gathered</b> 75:20 157:22 <b>gathering</b> 23:3 47:2 50:19 125:11 128:8 158:21 <b>gdpr</b> 110:6,13 111:2 <b>geared</b> 24:18 <b>gears</b> 301:4 <b>genders</b> 289:10 <b>gene</b> 13:11 28:17 29:1,7,20 30:18 32:6 41:2 57:12 71:6 72:8 94:17 109:13 120:3 129:13 131:20 138:16,18 140:17 141:20,21 142:7 146:15 147:22 148:4 160:20 161:3,4,5 165:22 171:5 175:19,20 176:9 177:12,15 178:7 187:18 188:13 189:8,18 194:7,10,11 197:20 198:19 210:22,22 211:22 212:7,9,19 226:1 227:8,16 230:1 242:4,20 244:6,14 245:11 246:20 259:1 271:7 272:3 275:20 304:11 311:9,9 <b>genentech</b> 273:12 <b>general</b> 136:12 205:18 260:18 <b>generally</b> 28:17 61:10 211:11 <b>generate</b> 16:12	<b>generated</b> 15:22 62:6 <b>generating</b> 16:20 84:1 113:17 <b>generation</b> 25:18 26:17,19 136:21 <b>genes</b> 272:2 300:16 <b>genetic</b> 31:1 41:10 42:2 57:10 87:13 87:18 139:3,5 148:15,22 149:1,3 149:10 150:19,21 155:19 221:10 225:7 226:2 300:9 <b>genetically</b> 30:15 41:6 107:14 <b>geneticist</b> 199:19 <b>genetics</b> 82:11 148:19 199:18,19 265:11 <b>geniuses</b> 282:13 <b>genome</b> 30:15 148:5,21 187:10 189:17 266:12 304:14,21 305:3,9 305:14 <b>genomes</b> 186:18 <b>genomic</b> 131:4 153:7 187:7 304:19,20 305:13 305:15 <b>genotyped</b> 109:17 <b>genotyping</b> 169:11 <b>gentleman</b> 45:19 53:3 64:6 <b>geographical</b> 104:16 <b>geographically</b> 278:20 <b>geopolitically</b> 166:20	<b>getting</b> 14:16 32:11 34:8 53:19 53:22 54:13,13 72:22 86:9,15 87:20 88:20 89:4 90:6 103:22 131:5 141:12,21 146:22 147:2 157:12 165:5 180:3,22 193:10 223:10 226:11 227:6 233:18 235:13 254:9 261:13 275:22 297:15 308:4 <b>gi</b> 96:6 199:15 310:19 <b>giant</b> 120:2 243:16 <b>gillespie</b> 168:3,4 170:13 171:11 <b>girdle</b> 244:5 <b>girl</b> 182:12,12 <b>give</b> 4:15 20:20 30:5,6 41:2 67:16 73:15 83:21 96:5 122:13 144:2 161:17 181:10 192:18 238:6 244:11 283:1 314:15 <b>given</b> 10:5 13:22 31:14 117:6 123:10 139:19 153:16 182:9 210:5 212:16 218:22 225:8,9 228:19 283:2 310:10 <b>gives</b> 84:20 252:11 <b>giving</b> 108:14 109:5 123:3 185:4 244:9 <b>gizmo</b> 248:6
<b>g</b>			
<b>gain</b> 258:17 <b>game</b> 85:1,9 235:21 <b>games</b> 267:2 270:16 <b>gap</b> 42:20 92:15 230:13 <b>gaps</b> 49:10 93:8 113:2 200:9 223:2 223:4,5 <b>gastroenterology</b> 67:4 188:21 <b>gastrointestinal</b> 237:1			

<b>gizmos</b> 130:2,4	291:2 293:22	184:21 186:20	274:5 278:7 281:1
<b>glad</b> 93:21 101:6	294:6	193:5 197:6 199:9	286:13 301:3
<b>global</b> 101:15	<b>goals</b> 81:8 91:15	201:18 208:9,11	308:7 309:5,7
109:20 150:4	198:7 263:21	208:12 209:14	311:10,18
157:15 257:11	270:15	210:1 218:19	<b>goey</b> 64:1
260:16	<b>god</b> 308:4	223:17 224:13	<b>google</b> 75:7
<b>globally</b> 89:11	<b>goes</b> 106:1 136:3	227:5 228:3	<b>gosh</b> 270:20
110:14 149:19	140:21 154:4	230:17 231:15,22	<b>gotten</b> 76:8 145:7
166:7,12 261:11	160:17 169:4	232:5,12,13,17	145:9 158:13
313:4	177:11 205:5	234:20 235:19,20	234:2 235:6 280:9
<b>globe</b> 155:16	<b>going</b> 20:12,17,19	240:19 243:14	<b>governance</b>
156:2 248:1 279:3	20:20 21:4 22:22	244:22 245:15	111:21
<b>glucose</b> 15:21	27:21 30:19 31:2	248:4 249:2 252:4	<b>government</b> 2:13
<b>gluing</b> 215:5	31:3,7,8,12,22	252:4,6,9 253:9	11:15,17 253:16
<b>gm</b> 296:19 297:10	35:5,6 40:19	253:22 254:13	272:16 283:20
298:2,6,10 299:2	43:22 44:15 45:17	256:4,6 261:14,16	307:2
<b>go</b> 3:22 7:11 33:1	48:17 51:3,6,20	261:17 262:1	<b>governmental</b>
34:18 35:16 38:18	52:19 53:10,12,12	264:17 268:5,5,14	293:17
47:7 57:5 58:22	56:15 57:11 59:6	268:17,20 272:3	<b>governments</b>
75:2 82:8,14	65:6 66:8,8,14,16	275:18 276:2,4,9	306:19
90:11 96:21 99:21	66:21,22 70:8	278:5,6,13 280:7	<b>grail</b> 163:22
101:1 104:7 105:1	71:11 73:15 75:4	283:18 296:13	<b>grandchild</b> 116:1
112:10 140:4	76:15 79:12,22	301:7 309:1 312:5	<b>grant</b> 37:9 159:4
143:10 146:22	84:12 85:5 86:5	<b>gold</b> 122:9,14	159:20 171:16
147:2,22 170:4	86:12,13,14,14	124:3	303:2
172:4 174:12	87:5,15 88:13,16	<b>golden</b> 245:3	<b>granted</b> 56:21
177:16,19 191:21	88:17,21,22 92:3	<b>good</b> 2:1 25:6 31:6	<b>granting</b> 299:1
196:21 198:2	92:16 93:6,7,18	45:21 68:1 69:9	<b>grants</b> 20:4
199:7 205:4	93:22 94:7 97:22	70:19 74:10 83:2	<b>grass</b> 243:19
211:21 213:13	97:22 98:3 102:13	86:7 90:18 93:15	284:11
214:3 223:5 226:9	102:15 106:15	116:21 134:10	<b>grassroots</b> 80:22
229:22 233:1	108:11 112:7	138:7 152:17,17	<b>grateful</b> 18:18
242:22 249:12	113:15 114:2	157:21 158:14	91:7 184:19
253:22 255:9	116:2 118:21	165:11 173:2	214:17
256:4,6 268:3	122:7 131:1,6,9	181:22 193:18	<b>gratifying</b> 72:4
269:20 271:1,19	131:13 138:17,18	199:2 200:14	154:17,19
274:3 276:4,16	141:2,14 143:11	205:17 208:14	<b>great</b> 2:15 3:17
280:8	143:11 146:6	213:11 214:3,8	5:2,8,14 10:6
<b>goal</b> 3:1,6 6:1,6	147:3,10 148:13	226:9 231:7 232:7	20:11 21:9 45:21
17:18 20:15	148:20,22 152:14	236:16 240:9	48:13 63:20 85:8
111:15 116:19	165:7 166:7,11,12	254:10 255:17	93:17 94:11 95:11
166:6 181:3 197:3	167:2 172:4,6,10	259:11 268:11	95:14 101:19
200:16 220:13	174:16 180:6	270:9 271:16	112:15 116:3,7
243:10 266:19	181:2,21 182:3,19	272:3 273:10	128:6,14 153:18

158:13 159:1 168:1,13 171:13 175:16 180:20 181:21 186:22 202:1 209:7 213:21 214:20 222:1 230:15 248:18 249:5,7 251:3,4,9,9 255:18 256:22 272:15,15 278:12 284:21 287:7 312:10,21 <b>greater</b> 103:21 154:21 177:6 302:4 <b>greatest</b> 130:11 <b>greatly</b> 65:20 312:12,17 <b>green</b> 285:15 <b>grew</b> 212:6 <b>gritty</b> 266:22 <b>ground</b> 150:13 306:13 <b>grounded</b> 180:1 <b>groundwork</b> 20:13 <b>group</b> 32:3,22 33:15 34:15 35:10 35:22 50:9 53:9 55:9,10,20,21 56:1 58:21,22 70:15 78:5 86:7 95:18 116:11 117:16 142:14 155:12,13,15 156:14 181:21 194:22 198:10,13 200:7 263:2 269:19 280:15 309:13 <b>groups</b> 13:20 21:12 24:3,3 33:10 34:19,20	35:14 36:8 40:11 43:4,4,21 44:6,10 44:13 46:13 49:8 49:8,9 58:13 60:4 61:5,12 80:20,21 96:16 103:15 104:1,7,8 106:21 107:7 108:1 121:15 127:22 134:6,7 142:13 170:9,11 171:22 174:6,8 247:9 255:3 262:13 265:8 282:5 301:20 <b>grow</b> 80:3 87:3 161:9 168:21 284:8 <b>growing</b> 234:19 <b>growth</b> 13:6,12 <b>gsk</b> 244:19 <b>guardians</b> 103:13 103:15,20 <b>guess</b> 24:9 93:4 106:1 114:10 151:20 156:20 168:12 170:14 180:22 200:17 205:3,5 210:1 233:14,15 237:5 241:18 260:12 268:10 270:6 290:16 <b>guesswork</b> 38:14 <b>guidance</b> 28:2 48:8,19 50:5 140:2 <b>guidances</b> 223:12 223:12 291:16 <b>guide</b> 206:4 285:15 <b>guideline</b> 88:7 <b>guidelines</b> 16:7 88:6 89:8 216:12	221:15 306:12 307:6,10 <b>gut</b> 310:14 <b>guy</b> 248:6 265:16 <b>guys</b> 48:8 110:15 231:9 270:3 278:1 <b>h</b> <b>hahn</b> 6:21 114:15 114:17 115:1,9,16 115:17 154:10 294:6 303:4 <b>half</b> 73:12 108:7 233:2 262:22 <b>hallway</b> 3:15 <b>hammer</b> 152:8 <b>hand</b> 7:10 27:14 65:7 93:3,16 143:5 150:17 155:5 177:22 238:11 256:6 286:7,9 <b>handful</b> 192:10 238:14,21 <b>handheld</b> 7:11 <b>handle</b> 90:22 129:12,20 264:8 <b>handling</b> 102:17 <b>hands</b> 56:22 99:22 183:11 <b>haploidentical</b> 252:20 <b>happen</b> 72:1,11 123:12 147:6 176:1 178:14 185:2 208:10 213:3 215:11 235:4 247:21 269:14 283:17 301:10 <b>happened</b> 119:5 166:20 184:5 216:19 <b>happening</b> 89:10 134:14 178:21	247:18 <b>happens</b> 78:1 166:17 236:8 267:8 <b>happy</b> 5:9 100:6 153:5 225:1 246:6 283:9 <b>hard</b> 12:17 74:20 89:7 90:1 92:10 121:10 163:14 170:8 173:12 176:6 186:15 211:10 224:6 227:22 235:10 247:1 264:19 276:19 278:4 281:14 <b>harmonize</b> 165:18 166:7 <b>harmonized</b> 167:4 <b>harping</b> 160:18 <b>harsh</b> 287:17 <b>hartman</b> 109:10 109:10 <b>hasn't</b> 281:22 <b>hde</b> 133:15 137:17 152:2,2 <b>head</b> 36:21 83:6 <b>headache</b> 87:22 <b>headaches</b> 99:21 <b>headed</b> 252:12 <b>heading</b> 71:5 <b>headway</b> 236:14 <b>health</b> 10:18 15:20 24:17 25:1 26:21 27:1,12,16 38:4 64:13 115:10 124:21 125:22 130:2 155:9,20 166:5 168:6 180:7 214:13 217:5 234:10 240:21 248:9 265:11 274:8,20 287:11
--	--	--	--

287:12 288:16 289:5 293:7 294:15 295:2 304:21 305:14 <b>health's</b> 115:11 <b>healthcare</b> 2:12 10:20 15:18,20 16:5 38:8 167:15 304:22 <b>healthcore</b> 163:6 <b>healthier</b> 212:16 213:4 <b>hear</b> 9:5,10 15:8 21:12 30:11 55:4 60:13 101:20 116:7 121:18 134:18 147:3 155:2 162:4 163:10 168:16 176:5 181:13 193:22 197:12 223:6 231:13 288:12 297:19 298:1 313:21 <b>heard</b> 31:21 47:22 52:13 75:2 96:21 97:20 127:2 134:3 143:9 185:22 186:2 188:2,14 191:4 195:7,14 197:11,15,17 233:8,12 235:15 265:20 293:19 294:6,12 309:17 312:19 313:1,5,14 313:20 <b>hearing</b> 62:16 68:9 74:8 85:14 123:5 196:3 200:13 239:8 286:17 <b>heart</b> 18:21 20:10 176:5 200:1 244:2 244:3 248:16	271:22 312:19 <b>hearts</b> 282:14 <b>heck</b> 131:1 <b>held</b> 10:17 162:12 286:8 <b>hello</b> 129:22 225:2 273:10 284:20 306:2,6 309:7 <b>help</b> 2:7 14:9,13 15:22 16:20,22 24:4,7,8 35:17 43:5 57:17 59:20 69:2,6 70:1 71:9 74:20 86:22 87:3 88:1 90:16 92:6 92:16 93:1 95:9 100:3 101:6 106:15 107:9 111:7 112:12 113:19 126:15 127:6,11,21 131:13 141:10 144:4,9 145:22 147:6 149:12 163:16 170:21 176:22 177:2 178:9 183:21 185:11 198:15 203:13 216:11,12 223:3 232:5 235:11 253:1 255:16 256:19 262:1,18 263:2 271:21 273:2,6 275:4 277:9,17 278:10 302:1 308:12 314:1,2 <b>helped</b> 72:7 73:20 92:2 117:12 157:9 245:22 278:9 <b>helpful</b> 59:5 88:22 133:21 191:13 292:14	<b>helping</b> 9:17 22:19 65:11 125:8 146:9 293:8 305:5 307:11 308:11 <b>helps</b> 10:11 14:8 14:22 86:15 94:4 135:16 239:5 <b>hematology</b> 11:3 <b>hemophilia</b> 129:15 244:1 271:17 <b>henry</b> 252:22 253:4 254:20 255:1 269:16 <b>hereto</b> 315:14 316:11 <b>heretofore</b> 237:17 <b>here's</b> 201:21 <b>heroes</b> 72:2 <b>heroic</b> 196:17,22 215:5,10,15 <b>heroin</b> 307:16 308:4 <b>hesterlee</b> 93:12 <b>heterogeneity</b> 23:22 42:7 <b>heterogeneous</b> 33:2 <b>heterogenous</b> 278:20 <b>hey</b> 283:19 <b>he's</b> 242:16 <b>hhs</b> 272:16 <b>hi</b> 55:4 56:14 69:11 105:3 109:10 155:7 159:2 171:14 175:17 182:7 199:13 226:17 236:16 242:2 260:12 292:22 295:21 299:20 <b>hierarchical</b> 281:10	<b>high</b> 10:12 23:17 73:21 102:14 124:12 131:21 132:5,17 137:10 137:17 232:19 <b>higher</b> 167:22 249:14 289:17 <b>highest</b> 176:9 259:16 289:14 <b>highlight</b> 119:2 232:12 238:4 250:9 <b>highlighted</b> 238:16 <b>highlights</b> 229:11 <b>highly</b> 5:5 30:6 42:6 <b>hiking</b> 182:13 <b>hill</b> 283:15 <b>hindsight</b> 296:19 <b>hired</b> 69:16 <b>histology</b> 237:21 <b>historic</b> 290:4 <b>historical</b> 15:3 80:7 250:9 <b>history</b> 6:9,18 14:13,18 15:2,10 20:14 21:3 22:22 23:4 29:21,21,22 30:1,5,8 31:15,21 32:8,13 33:3,9 35:6,13 40:12,15 41:14,20 42:12,17 44:1,2 45:2,5,8 46:18 47:1 48:1 48:20 50:20 51:2 51:8,15 53:5,15 54:15 56:19 57:13 57:14,16 58:2,4 61:16 66:12 67:21 68:19 69:15 70:7 70:8,14 71:21 72:13,18 74:19,21 78:10,18 79:8,11
---	--	--	---

79:13,18,20 80:16 80:19 81:1,20,21 87:15 89:7 92:13 92:19 93:15 94:5 131:10 141:18 189:10 192:11 200:18,21 213:15 222:11 233:11 244:10 294:11,13 295:3,8,14 303:19 313:1 <b>hit</b> 36:21 83:6 95:14 215:2 224:7 <b>hitting</b> 276:21 <b>hmm</b> 236:18 <b>hold</b> 81:7 269:20 <b>holding</b> 293:5 <b>holds</b> 213:21 <b>holistic</b> 25:17 26:17 <b>holy</b> 163:22 <b>home</b> 69:19 75:17 82:20 116:4 192:19 231:8 <b>homogenous</b> 160:12 <b>honest</b> 57:7 166:17 169:6 208:5,21 <b>honestly</b> 216:16 <b>hope</b> 93:2 120:7 149:11 178:15 181:13 184:13 185:18,20 209:21 210:2,4 211:19 219:2,2,9 244:6,9 252:22 253:3 254:20 255:1 269:16 272:5 276:9,10,17 278:9 288:2 314:12 <b>hopeful</b> 271:19 295:17	<b>hopefully</b> 40:14 58:6 119:5 138:10 140:1 161:16 166:15 198:21 244:4 252:10 271:16 278:14 <b>hospital</b> 71:14 179:11 192:19 193:1 252:16 277:10 282:21 <b>hospitals</b> 25:13 27:18 137:22 138:1 251:14 269:18 277:11 293:18 <b>host</b> 190:13 293:11 <b>hosting</b> 45:22 <b>hosts</b> 295:3 <b>hour</b> 233:3 <b>hours</b> 192:7 <b>housed</b> 38:5 <b>housekeeping</b> 3:8 <b>how's</b> 206:2 <b>hsd</b> 309:12 <b>hubs</b> 274:9 <b>huge</b> 29:18 108:7 108:16 110:1,4 174:17,17 273:1 282:18 <b>hugely</b> 54:8 <b>human</b> 30:14 41:13 234:10 <b>humanitarian</b> 20:3 120:18 133:6 151:12 <b>humans</b> 41:3 <b>humbled</b> 93:11 <b>humongous</b> 282:18 <b>hundred</b> 248:15 <b>hundreds</b> 164:3 297:19 308:2	<b>hunter</b> 114:12,12 128:2 159:7,10,14 160:1 165:14 <b>huntington's</b> 77:10 <b>huntington's</b> 244:5 <b>hurt</b> 234:21 <b>hurting</b> 310:12 <b>hyde</b> 316:2,15 <b>hypertension</b> 64:4 <b>hypotheses</b> 144:20 <b>i</b> <b>i&amp;d</b> 246:1 <b>i&amp;ds</b> 275:22 <b>iab</b> 58:10 <b>iamrare</b> 135:20 142:16 294:21 295:3,6 <b>ican</b> 252:22 253:3 254:2 255:4,4,18 269:17 282:20 <b>icr</b> 301:13 302:1,3 302:10 <b>idea</b> 139:10 144:22 151:22 205:17 207:15,16 226:1 283:12,14 <b>ideally</b> 86:1 291:20 <b>ideas</b> 133:15 251:9 <b>identical</b> 155:17 <b>identification</b> 163:21 292:11 <b>identified</b> 276:15 291:7 <b>identifiers</b> 27:7 <b>identify</b> 3:4 6:3 35:3 42:2 134:13 239:22 304:15 305:6 <b>identifying</b> 53:22 54:8 69:21 165:9	<b>ideology</b> 155:19 156:11 <b>idiopathic</b> 12:15 <b>iga</b> 168:20 <b>igt</b> 302:16 <b>ihi</b> 180:7 <b>iii</b> 30:10 110:10 <b>illegal</b> 307:16,22 <b>illicit</b> 307:15,22 <b>illness</b> 144:15 <b>illnesses</b> 255:20 <b>image</b> 89:9 <b>imagine</b> 164:4,8 183:3 248:15 267:1 273:15 <b>imaging</b> 89:14 <b>imi</b> 179:17 180:3,6 <b>immediately</b> 21:5 66:2 <b>immense</b> 313:10 <b>impact</b> 10:13 14:5 96:10 97:16 113:17 117:11 189:1 246:13 287:10 294:15 <b>impacted</b> 19:2 <b>impacting</b> 65:10 <b>impacts</b> 303:17 313:9 <b>imperative</b> 240:6 300:11 <b>implement</b> 269:18 300:12 <b>implementation</b> 27:6 <b>implemented</b> 255:16 <b>implications</b> 149:17 <b>implies</b> 78:22 <b>importance</b> 36:13 43:3 53:21 65:2 68:19 105:7 116:3 255:13 280:10
--	---	--	---

300:21 302:2 313:2,6 <b>important</b> 2:15 11:11 13:20 14:1 15:14,17 17:4,7 17:21 21:11 22:20 23:2,18,19 33:12 40:16 41:9 42:1 43:10,15 46:7 49:4 51:17 53:6 53:15 54:9 61:17 62:9 63:4,7,13 65:10 72:11 77:20 79:7,10,17 81:8 93:10 94:8,20 96:15,17,18 97:17 99:14 100:1 102:22 103:6 111:8 112:21 115:22 117:3,11 117:13,16,22 118:7,11 120:14 121:22 122:6,19 135:6 136:14 137:9 138:10 142:2,4 143:2 154:7 194:14 198:5,14 204:11 205:4 209:18 211:13 215:19 221:1 222:4,22 224:3,7 240:7 246:16 247:17 250:8 253:5 254:4 255:6 258:8 261:1 263:11 266:18 267:11 270:20 273:15 287:6 289:7 300:6 312:14 <b>importantly</b> 18:14 23:11 116:5,13 127:13 295:9	<b>impossible</b> 15:7 <b>impressed</b> 217:11 <b>impressive</b> 118:12 305:2 <b>improve</b> 14:6 38:20 122:15,18 234:10 256:8 289:7 305:13 314:13 <b>improved</b> 74:7 298:2,5 304:21 305:14 <b>improvement</b> 189:2 212:13 284:11 <b>improves</b> 35:8 293:22 298:12 305:4,4 <b>improving</b> 143:14 <b>inaudible</b> 73:18 73:18 113:1 134:12 152:18,20 159:11 178:18 200:12,19 202:7 245:21 247:4,11 248:10,18 257:22 263:3 273:17 276:6,7,15 278:14 279:18 280:22 293:13 294:18,22 295:12 296:12 298:11 302:16 <b>inborn</b> 22:12 58:21 67:4 68:4 74:15 188:21 199:15 221:7 223:13 <b>incentive</b> 132:21 133:3 151:11 255:2,7,8,8 261:8 277:4 <b>incentives</b> 11:15 11:17 151:18 170:20 260:21	<b>incentivize</b> 170:15 <b>include</b> 123:17 129:12 137:11 162:8,17 194:10 196:14 287:4 303:20 <b>included</b> 12:11 42:15 162:6 163:5 180:9 196:15 257:17 313:2 <b>includes</b> 17:13 118:2 257:18 265:5 <b>including</b> 2:11,14 13:11 16:22 120:16 286:21 288:14 301:19 312:15 <b>inclusion</b> 161:19 287:1 <b>incompetent</b> 306:13 <b>incorporate</b> 24:19 127:14 <b>incorporated</b> 123:15 <b>incorporating</b> 302:6 313:11 <b>increase</b> 12:3 13:9 117:20 121:22 124:16 <b>increased</b> 239:10 240:12 241:3 263:15 288:15,20 <b>increases</b> 119:16 289:1 <b>increasing</b> 27:7 37:22 189:15 206:22 263:1 <b>increasingly</b> 15:17 36:15 123:15 138:17 159:19 194:14 300:10,19	<b>incredibly</b> 23:18 23:18 65:10 154:17,18 184:18 217:10 294:9 300:6 <b>incurred</b> 288:1 <b>ind</b> 22:8 56:21 192:21 205:20 216:6 <b>inde</b> 192:21 <b>independent</b> 72:7 308:11 <b>indicate</b> 285:16 298:12 <b>indicated</b> 294:5 <b>indication</b> 13:5 39:13 137:18 162:6 238:6 <b>indications</b> 11:21 12:2,9 16:21 95:7 118:18 120:10,17 120:18 176:15 246:20,22 247:2 <b>individual</b> 25:2 38:13 60:17 111:12 139:5 142:12 144:11 158:9 194:21 198:8 199:6 201:10 213:19 214:14,15 217:20 219:14 266:22 270:16 273:4,5 280:10 291:5,16 291:21 292:13 298:2 <b>individual's</b> 146:17 <b>individualization</b> 175:13 <b>individualize</b> 173:19 <b>individualized</b> 7:3 138:18 140:7
---	--	---	--

146:7 148:10	193:12	262:18 275:3	187:2 251:14
180:18 181:3,4	<b>infectious</b> 167:19	277:13 278:21	278:18 279:11,12
187:6 190:10	167:20	279:7 286:3	279:13 301:8
193:21 194:8	<b>inferring</b> 221:19	294:14 295:13	<b>innovations</b> 80:10
195:17 196:7	<b>infinitesimal</b>	307:5	80:12 119:2 303:5
199:22 200:11	271:1	<b>informative</b> 43:9	311:10
201:9 202:10	<b>inflammatory</b>	53:12 58:15 294:9	<b>innovative</b> 168:11
204:2,12 205:13	173:4	313:7	179:1 180:7 302:8
207:19 214:4	<b>influence</b> 61:6,7	<b>informed</b> 124:17	<b>innovators</b> 116:11
219:12,19 220:7	209:13	310:15,20	121:6,21
227:10,17 291:8	<b>info</b> 87:2	<b>informing</b> 16:16	<b>input</b> 14:8 121:13
304:11 309:18	<b>inform</b> 14:8 24:1	<b>informs</b> 19:3	122:18 125:7
<b>individually</b> 127:4	43:1 65:11 87:4	23:14,19 220:18	127:14 295:1,9
<b>individuals</b> 2:13	88:15,17 123:9	<b>infrastructure</b>	<b>inquiries</b> 4:9
2:14 5:17,20 8:18	304:2	17:14 26:3,8,10	<b>insanity</b> 308:17
9:2 54:20 150:18	<b>informal</b> 263:9	26:12,20 34:22	<b>insight</b> 67:1
196:6 251:20	<b>information</b> 9:21	39:1 40:2 44:9	254:10
257:20 258:6,11	10:15 16:15 18:4	48:10 69:4 89:3	<b>insightful</b> 65:18
273:7 288:5 290:1	23:3,5,6,9,16 24:7	104:10 168:15	<b>insights</b> 14:4 16:1
<b>indoor</b> 64:15	26:22,22 27:12	178:13 222:7	136:15 248:19
<b>inds</b> 291:22	32:2,8,10,10,13	264:8	<b>inspired</b> 299:7
292:13	32:18 33:7,8	<b>inhaled</b> 298:10	<b>inspiring</b> 203:8
<b>industry</b> 2:13 26:1	34:11,12,22 35:14	299:2	293:20
37:11 71:5 76:1,4	35:17 36:14 42:7	<b>inhibit</b> 97:14	<b>instance</b> 133:7
76:6,8,22 81:3	42:19,22 49:3	150:8	160:19 188:8
83:14,17 85:3,5	51:19 52:1 55:17	<b>initial</b> 92:10	213:12 241:6
98:8,9,12 99:2	60:20 61:1 62:5	<b>initially</b> 69:16	280:17 281:10
106:13,21,22	62:11 63:3,5,7,19	180:14	<b>instances</b> 243:9
134:8 173:9 179:3	65:5,7,11 68:12	<b>initiative</b> 68:20	<b>institute</b> 44:12
179:19 188:19	69:19 70:13 75:3	123:19 168:7	64:13 67:14 75:12
190:2 253:16	78:3 79:2 83:20	179:1,2 180:7	75:20 94:15
259:17 260:2	83:21 89:12 98:5	253:1 255:15	115:11,12 304:20
271:13 290:16,17	100:10,13 106:9	<b>initiatives</b> 10:12	<b>institutes</b> 233:10
295:7 311:12	106:16 113:3,9	66:19 135:18	<b>institutional</b>
312:16	116:15 122:3	179:18 237:3	213:21
<b>ineligible</b> 288:1	123:3 134:14	257:2 276:11	<b>institutions</b>
<b>infantile</b> 29:13	139:9 141:22	283:17	103:19
30:10 238:13	143:5 145:10,12	<b>inject</b> 245:12	<b>instrumental</b>
<b>infants</b> 29:14	150:20 151:1	<b>innovate</b> 239:6	185:1
137:20	152:11 157:21	<b>innovation</b> 38:6	<b>instruments</b> 24:5
<b>infection</b> 192:1	158:11,19 165:8	97:14 117:19,20	99:8
193:8 199:4	173:17 206:3	118:13 120:21	<b>insufficiency</b>
<b>infections</b> 190:14	207:4 211:12	121:11,14 126:13	225:5
190:16,20,22	224:4 241:2	137:15 138:2	

<b>int</b> 16:2	259:15 260:7	<b>intervention</b>	<b>investigator</b> 60:22
<b>integrate</b> 75:21	285:12 296:4	53:13 130:14	95:18 103:21
76:6 78:4 83:9,20	306:14,15 312:12	142:3 149:12	156:12 157:3,5
<b>integrated</b> 76:13	<b>interested</b> 4:12	234:10	158:3,9 164:11
76:21 77:10,11	63:1 136:13	<b>interventional</b>	189:4 190:7 216:1
81:11 92:22	141:12 146:7	157:17	216:4 217:2,8
<b>integrating</b> 18:19	158:4 161:13	<b>interventions</b>	273:20
77:6 84:18 113:1	178:3 191:8 196:3	131:7	<b>investigators</b>
125:2	227:6,9,15 315:15	<b>interview</b> 4:21	40:22 51:4 81:2
<b>integration</b> 75:18	316:12	<b>intolerance</b>	96:17,18 197:15
124:20	<b>interesting</b> 118:22	310:17	215:10,18 216:10
<b>intellectual</b>	143:17 149:5	<b>intravenous</b>	223:6 274:1
106:18	155:18 156:18	190:21	275:15
<b>intelligence</b>	180:5 187:14,19	<b>introduce</b> 19:22	<b>investment</b> 11:19
163:15 164:8	213:20 227:5	20:19 21:4 114:14	103:1 108:6,7
<b>intend</b> 77:17	<b>interests</b> 217:4	129:8 181:15	132:16 229:2
285:4	228:14 258:19,20	182:3 230:17	251:5,22
<b>intended</b> 4:15	286:16	232:18 284:18	<b>investor</b> 243:1
44:9 75:16 76:17	<b>interfaces</b> 17:18	<b>introducing</b>	<b>invitation</b> 4:22
83:17 96:13 97:16	<b>interfere</b> 3:10	232:18	199:17
157:22	<b>internal</b> 11:1	<b>introduction</b> 21:8	<b>invite</b> 19:10
<b>intensive</b> 217:1	115:14	115:18 181:11	230:21
231:22	<b>international</b>	252:11	<b>invited</b> 293:13
<b>intent</b> 157:21	101:14 102:10	<b>introductions</b>	<b>inviting</b> 74:12
<b>intention</b> 77:13	103:16 107:4	181:9 248:4	<b>invocations</b> 110:3
81:20 83:8 113:16	110:2 111:7,17,21	<b>introductory</b> 10:4	<b>involve</b> 22:13
<b>intents</b> 154:15	112:1,4,13 156:8	31:5 38:3 40:9	<b>involved</b> 22:7,19
<b>inter</b> 84:6	157:2 158:1	<b>intros</b> 68:13	104:2 123:10
<b>interact</b> 4:16 9:14	253:17 254:3	<b>intuitive</b> 98:21	128:10 129:2
59:1 60:7 191:11	262:14 265:2	<b>invaluable</b> 14:4	141:9,12 150:15
313:19	279:21 286:20	304:16	199:20 200:4
<b>interacting</b> 57:5	<b>internationally</b>	<b>invest</b> 73:15	201:16 222:19
<b>interactions</b> 74:4	10:8 102:16 266:8	102:21 251:10	223:22 254:7
201:14	<b>internet</b> 106:10	257:20	257:17 258:22
<b>interactive</b> 58:19	<b>interoperable</b>	<b>invested</b> 200:8	<b>involvement</b> 112:4
<b>interchange</b> 98:14	110:21	<b>investigate</b> 155:19	124:9
<b>interchangeable</b>	<b>interpretable</b>	156:11	<b>involving</b> 230:9,10
164:1	95:17 99:16	<b>investigational</b>	263:1
<b>interchangeably</b>	<b>interprets</b> 201:7	147:18 212:11	<b>ionis</b> 290:13 291:3
78:9	<b>interrupting</b> 9:8	217:7 290:20	<b>ip</b> 133:1
<b>interest</b> 7:20	<b>interstitial</b> 12:21	<b>investigations</b>	<b>irb</b> 107:22 133:10
13:10 106:14	64:3	261:18	192:22
126:8 146:4,12	<b>intervals</b> 88:11	<b>investigative</b>	<b>irdrc</b> 280:14,16
247:22 249:4	89:9	186:5	

<b>irony</b> 127:1	252:8 256:22	290:12,13,14	143:20 149:15
<b>irreversible</b>	258:2 259:9,10,15	292:22 293:1	158:16 165:6
287:16	259:18 261:22,22	295:22 299:20,22	<b>jen</b> 67:6 69:11,11
<b>islands</b> 145:11	264:19 266:21	301:8 302:22	79:6 90:5 96:21
<b>isn't</b> 271:5 278:17	267:9 268:8,17	303:1 309:9,10,13	101:22 103:8
<b>isolated</b> 41:19	269:2 270:20,21	309:15 310:7	105:14 106:5
<b>issue</b> 101:12 102:1	270:22,22 271:5,6	<b>i've</b> 185:22 190:19	111:5 299:19,20
151:10 164:21	272:8 275:20	190:20 193:9	299:20
229:11 250:7	276:19 278:4	196:16 197:17	<b>job</b> 1:8,17 66:15
260:3 262:17	280:5,8 282:8	202:2,3 203:16	95:11 116:17
267:19 311:4,14	283:2,18 284:7,7	214:21 240:10	124:2 141:2 175:2
<b>issues</b> 5:10 32:16	299:7 300:6,15	282:17,18 311:5	197:1 203:1 268:6
35:1 66:16 149:7	<b>iv</b> 192:2	<b>j</b>	288:14 302:6
149:8,17 197:9,10	<b>i'd</b> 189:22 227:9	<b>jana</b> 56:14,14	309:5
197:21 214:10	229:8,8 268:15	<b>janet</b> 2:1,4 19:9	<b>jobs</b> 128:22
228:8 248:1	272:9 273:15	55:4,7 128:12,12	<b>joe</b> 267:21
250:22 252:8,17	284:13 309:21	129:18,18 130:3	<b>john</b> 283:3,6,11,20
259:14,21 260:16	312:8	130:10 131:15	<b>join</b> 115:16 283:3
267:17 269:20	<b>i'll</b> 181:8,15 224:1	132:8 133:20	293:14
278:16,19 279:9,9	229:15,15 232:22	134:2 140:21	<b>joining</b> 2:18 115:1
279:10 288:16	241:18 248:22	141:4,15 142:8	115:5 116:6 186:2
<b>items</b> 4:6 26:11	250:8 252:9	144:10 146:2	199:21
37:6	260:12 264:15	148:8 153:3 155:1	<b>jointly</b> 39:18
<b>it's</b> 185:8 186:1	274:4	157:19 159:1	<b>journal</b> 174:21
187:14,19 188:3	<b>i'm</b> 181:16,20	162:2 163:10	<b>journey</b> 11:12
191:20 195:2	184:15,18 186:9	165:11 167:3	220:19 282:11
196:12 198:10	189:3,22 194:3,4	168:1 169:5	<b>jpmorgan</b> 300:7
202:7,16 203:8	196:15 197:6	170:22 171:13	<b>jude</b> 242:15
204:14,15 206:12	199:14,18 203:9	172:12 174:19	<b>julia</b> 182:2,6,7,7
207:4 210:9,10	216:16 223:8	175:14 178:16	185:21 201:1
211:2 213:19	225:3,18 226:11	179:14,17,22	203:6 208:2
217:1,8 218:22	231:5,14,15,15,18	180:10,18 230:20	213:16 217:10
219:20,22 224:3,6	231:18,21 232:17	231:5 232:4	221:2
224:7 225:17	233:5,7 235:5	247:19 284:15	<b>julia's</b> 187:7
226:19 227:4,11	239:8 242:3	300:20 312:3,5	<b>jump</b> 42:10
227:11,18,22	243:14 244:9	<b>january</b> 187:9	283:19
228:2,7 229:22	248:4,6,18 252:21	190:10 191:22	<b>jumps</b> 283:7
232:1,4 233:8,9	252:21 253:20,22	<b>japan</b> 265:6	<b>jurisdiction</b>
236:10 237:3,8,9	254:13 258:22	266:10 267:21	150:10
239:9 240:7,8	264:17 268:20	281:10 283:18	<b>jurisdictions</b>
241:19 243:5	276:2,6,9,21	<b>jeff</b> 129:22 143:16	104:3
244:8 246:16	277:19 278:13	153:4 248:4	<b>justify</b> 211:18
247:17,21 248:16	282:9,13,19 283:8	<b>jeffrey</b> 129:22	<b>justifying</b> 73:1
250:14 252:3,4,6	283:9 286:13,18	132:12 136:19	

<b>juxtaposing</b> 214:14	<b>kind</b> 25:14,15 28:4 38:7,11 48:4 49:15 52:1 59:20 62:13,14,18 63:18 68:7 88:20 91:13 93:9 98:5,15 101:8 103:22 112:17 136:18 138:7 142:15 143:6,22 146:8 150:20 158:21 166:6 168:15 169:7,16 170:3,19 173:5,6 174:6 179:20 185:5 192:13 194:18 201:3,13 205:17 206:9 209:16 210:3 218:3 221:19 223:8,13 223:22 228:3,4 229:2 232:15,17 232:19 235:8 239:5,5 255:17 256:17 282:22,22	<b>know</b> 2:16 5:16 9:11 19:7,12 24:21 25:21 30:17 37:1 38:9,14,15 38:18,21 39:21 40:8 41:7,8,8 43:20 44:14,22 45:9 46:2,3,20,21 47:2,12 48:18 49:10 50:11 51:22 52:14 53:20 56:21 58:19 59:19 62:4 62:7,15 64:12,18 64:20 65:15 68:8 70:10 71:19,21 72:16,18,22 73:6 73:18,19 74:7 78:12 79:1,15 80:9 81:6 87:1,10 89:16 90:2,15 91:6,21 92:14 93:6,13 94:2,18 95:19 96:11 98:10 98:22 102:3,19,21 103:19,20 104:4 104:14,22 105:10 105:12,14,17,18 105:20 109:6,18 110:15 116:1 118:8 121:15 126:15 128:6 130:11,12,22 131:7 134:5,17 135:14,19,20 136:9 141:8 142:11,13 143:9 143:13 144:11 145:8,19 149:11 150:17 152:13 157:13 160:1 162:21 163:22 164:11 168:12 169:6,9,19 170:9 173:5 174:9 175:9	175:9,10 177:7 184:17 185:7,7 187:22 188:11,12 191:18 192:9,13 193:12 195:8,9 197:4,12 198:2 200:1,4,8,13,17 201:1,17,20 202:4 202:5,14,15,19 203:10 204:21 205:1 206:1,13,15 206:17,22 207:7 207:12 208:18 209:11 210:3 211:20 214:17 216:2,5,14 217:22 218:1,2,13,14 221:9,20 222:9,13 222:14,15,17 223:3,5,7,7 224:2 225:20 227:1,2,7 227:9,9,17 228:1 228:4,20 230:13 231:12 232:10 234:21 235:6,16 239:9,20 247:1 249:1,15 256:12 256:17 257:3 265:5,20 266:10 266:10 268:1,1,14 269:1,7 270:18,21 271:18 272:1,15 276:20 277:19 282:10 292:6 293:20 310:10,13 310:16,17 311:1,2 313:17,22 <b>knowing</b> 47:12 94:7 291:17 <b>knowledge</b> 31:14 107:22 124:16 145:21 213:22 214:2 288:20 299:12 315:9
<b>k</b>			
<b>k</b> 302:22			
<b>kathleen</b> 68:1,17 78:17 86:2 101:20			
<b>katie</b> 67:2,18			
<b>kaufmann</b> 30:12 67:8 70:19,20 80:6 94:11 103:9			
<b>keep</b> 110:20 152:2 152:2 160:18 175:5 198:5 199:8 199:9 215:1,19 265:15 266:19 276:3			
<b>keeping</b> 200:16			
<b>keeps</b> 180:1			
<b>kelly</b> 305:22 306:2 306:3 308:16,17 308:20,22			
<b>kept</b> 145:17 221:4 221:4 233:6			
<b>key</b> 21:2 29:19 52:2 67:18 68:11 141:16 291:13 313:2			
<b>khrystal</b> 159:2,3 163:1 302:21,22 302:22 305:17,18 305:21			
<b>kick</b> 128:3			
<b>kicking</b> 245:5			
<b>kid</b> 99:2 109:6			
<b>kidney</b> 77:8 168:6			
<b>kids</b> 168:19 174:13 262:20			
<b>kill</b> 308:2			
<b>kimbrell</b> 180:21 181:16 185:21 190:6 193:14 199:11 203:15 214:20 224:19 226:15 230:15			
<b>kindly</b> 65:21 285:21			
<b>kinds</b> 35:17 36:15 44:6 79:2 86:21 94:19 103:9 195:14,18,19 197:5 268:12 280:18			
<b>kingsmore</b> 304:19			
<b>kiosk</b> 4:1,7			
<b>klaus</b> 67:12 68:21 75:10,10 83:5 85:13 86:7 97:8 104:13 106:12 111:1 112:14			
<b>knew</b> 144:18 183:3 192:9,15 203:4 245:14 272:12 296:15			

316:6 <b>knowledgeable</b> 260:9 <b>known</b> 42:4,16 109:19 212:17 259:18 304:15 <b>knows</b> 201:2 266:9 308:5 <b>kumbaya</b> 267:15	<b>late</b> 62:18 143:6 244:3 269:2 <b>latest</b> 311:7 <b>launched</b> 68:20 72:5 294:21,22 <b>lavage</b> 298:4 <b>laws</b> 103:17 <b>laying</b> 20:13 66:15 <b>lead</b> 75:11 157:5 190:16 201:4 236:21 310:11 <b>leader</b> 67:3 199:14 250:12,13 294:20 <b>leadership</b> 114:19 266:18 268:11 <b>leadership's</b> 266:18 <b>leading</b> 68:21 75:13 196:6 208:4 <b>leads</b> 49:2 <b>league</b> 246:9 <b>learn</b> 14:1 93:8 98:9 112:22 196:10 198:14,21 199:3 200:6 203:6 222:20 224:5,14 224:17 225:22 241:14,15,21 264:21 313:21 <b>learned</b> 31:16 92:9 95:1 183:13 203:5 256:17 266:17 273:21 297:11 313:11 <b>learning</b> 10:20 125:21 126:3 163:15 182:17 224:8,9,10 230:11 313:7 <b>learnings</b> 230:12 <b>leave</b> 5:14 71:3 73:5 161:22 218:2 268:5 307:3	<b>led</b> 13:14 <b>ledanski</b> 316:2,15 <b>left</b> 45:17 55:13 63:22 75:6 268:20 279:17 285:8,17 <b>leg</b> 145:4 <b>legal</b> 247:4 252:8 279:9 <b>legislative</b> 293:17 <b>legitimate</b> 210:4 <b>lend</b> 39:11 <b>lesser</b> 39:12 <b>lesson</b> 98:8 268:10 <b>lessons</b> 31:16 95:1 203:5 220:15 246:9 266:14 273:21 <b>letter</b> 189:17 <b>let's</b> 186:4 193:22 202:19 230:17 <b>level</b> 23:17 33:8 75:18 76:6,13 79:1,3 102:11 112:3 124:20 131:22 132:2 134:15 148:16 160:16 167:22 211:19 214:1 232:20 259:16 <b>levels</b> 81:9 274:11 <b>leverage</b> 28:6 39:4 139:12,14,20 147:11 155:22 171:10 198:14 220:5 230:7 304:12 305:13 <b>leverages</b> 27:8 <b>leveraging</b> 139:9 141:6 304:10 313:6 <b>liabilities</b> 173:10 174:2 <b>liberty</b> 118:9	<b>licensed</b> 147:15,16 177:16 <b>licensing</b> 177:20 <b>licensure</b> 195:16 <b>life</b> 28:21 95:6 115:22 144:14 159:5 166:18 171:16 172:21 174:12 183:3 184:14 185:5 189:2 204:10 243:18 253:14,15 298:3,15 301:21 306:16 <b>light</b> 94:5 242:21 285:15,15 <b>likelihood</b> 249:14 288:15 <b>limb</b> 214:18 244:5 <b>limit</b> 102:6 152:1 <b>limitation</b> 58:12 <b>limitations</b> 26:15 235:12 <b>limited</b> 35:13 57:8 102:8 237:17 <b>limiting</b> 301:21 <b>limits</b> 307:6 <b>line</b> 106:17 147:20 197:16 <b>lined</b> 273:9 <b>lines</b> 68:5 136:20 <b>link</b> 138:5 142:10 <b>linkage</b> 77:21 <b>list</b> 118:21 164:10 164:10 <b>listed</b> 127:5 <b>listen</b> 4:16 19:4 116:17 183:16 223:9 <b>listening</b> 19:7 116:16 123:20 124:1 127:14 193:15 203:16 282:11,18
<b>l</b>			
<b>la</b> 4:6 <b>lab</b> 41:1 42:21 57:21 143:8 183:20 195:5,6 <b>label</b> 120:10 159:20 162:13 163:5 296:19 297:10 <b>laboratory</b> 25:7 131:17 212:6 <b>laboring</b> 233:19 <b>lack</b> 49:18 <b>lady</b> 282:9 <b>laid</b> 272:10 <b>landed</b> 159:8 <b>landscape</b> 13:8 301:7 <b>language</b> 102:12 111:14 277:21 <b>languages</b> 265:10 267:3 <b>large</b> 22:11 26:11 42:14 51:7 54:19 59:14 77:11 118:9 228:12 239:13,17 276:10 297:6 <b>largely</b> 69:13 <b>larger</b> 26:17 33:5 193:11 <b>largest</b> 76:12 77:9 <b>larotrectinib</b> 237:18 <b>lastly</b> 89:13			

<b>literacy</b> 305:15	<b>long</b> 19:13 40:18	239:21 261:10	241:22 244:8,9,18
<b>literally</b> 244:17	42:14 64:10 77:20	277:19	245:4 248:21
265:9	81:7 96:2 103:1,5	<b>looks</b> 48:5 92:9	252:10 255:5,15
<b>literature</b> 49:22	103:11 110:21	<b>lorem</b> 290:15,19	258:21 263:22
<b>little</b> 19:12 32:1	134:20 143:7	<b>los</b> 297:13	264:21 270:3
32:18 42:4 60:10	170:4 191:2 193:6	<b>lose</b> 182:20 208:11	271:8 272:5,17
66:14 67:16 106:1	198:2 225:18	209:14 258:17	273:13 275:12,13
108:8 137:15	241:15 242:20	266:21 281:8	281:13,16 309:17
145:11 153:20	243:12 270:15	<b>losing</b> 209:3,4	<b>lots</b> 36:1 59:2
157:8,11 165:5,15	279:22	267:2 284:3	94:11 262:4
166:21 174:20	<b>longer</b> 190:22	<b>loss</b> 172:21	<b>loud</b> 97:20
180:15 182:12,12	<b>longitudinal</b> 48:1	<b>lost</b> 158:12 175:2	<b>love</b> 58:3 155:2
183:6 189:3	<b>look</b> 10:2 32:19	182:18 184:16	267:19 270:13
202:13 211:14	33:19 38:14 41:4	<b>lot</b> 36:8 48:1,22	<b>loved</b> 288:3
217:20 231:20	51:14,15,18 57:17	49:14,22 51:1	<b>low</b> 80:22 89:18
232:19 245:14	58:6 62:15 72:19	55:7 57:22 58:20	133:13
246:8 249:22	73:3 74:7 85:18	59:11 61:6 66:17	<b>lower</b> 121:21
250:2 252:11	89:10 101:2	66:22 71:21 77:14	288:7
257:13 258:17	104:12 122:14,17	79:4 86:8 87:12	<b>luck</b> 89:6,7
260:13 261:5	123:11 124:4	88:4 93:20 95:14	<b>lucky</b> 73:7 153:8
284:5 300:8	126:3 127:13	95:20 97:3 99:20	153:10
309:19	165:12 166:10	107:12 112:1	<b>lunch</b> 3:19,22 4:3
<b>live</b> 5:7 120:21	175:15 177:20	119:4 121:5 129:1	5:19 6:19 114:10
<b>lived</b> 90:14 184:7	210:20 217:17	131:6 132:12	<b>lunches</b> 4:2
<b>liver</b> 227:8,16	221:18 225:10,11	133:8,14 136:4,4	<b>lung</b> 12:16,16,21
<b>lives</b> 14:11 17:9,10	225:15 227:3	139:11 150:21	13:1,3 64:3 88:8
78:1 144:9 194:15	235:12 239:12	158:14 161:9	89:14 190:16,16
246:12 249:10,20	255:15 257:10	165:22 167:4,14	190:20 239:14
294:1 308:8,14	267:6 271:17	169:3 170:19	296:16 297:8,21
<b>living</b> 14:3 287:8	274:14 275:2	171:21 172:3,8	298:4
289:6,13 294:1	302:18 313:11	173:2 174:7,10,16	<b>lungs</b> 135:14
309:10 312:22	<b>looked</b> 34:4 51:9	176:18,19 183:14	190:15 191:12
<b>lobby</b> 3:14	85:21 213:7	184:16 188:18	192:7
<b>local</b> 110:19	242:12	195:1,4,5 196:4	<b>lupus</b> 172:2
133:11 309:12	<b>looking</b> 26:20 28:6	199:1 203:4	252:15,18
<b>locally</b> 111:12	33:21 42:10,18	207:22 208:3	<b>luxury</b> 239:13
<b>locate</b> 110:11	60:5 64:5,8,12	210:17 211:7	<b>lysosomal</b> 183:12
<b>located</b> 3:14 7:12	72:9 84:17 96:12	215:1 216:9,14	<b>m</b>
128:20 166:19	104:22 146:3	223:13,18 224:2	<b>m</b> 114:15 171:8
<b>locations</b> 104:16	148:19 169:1	227:8,22 229:21	<b>ma</b> 107:3
<b>logistic</b> 3:8	200:10 212:3	232:7,15 233:19	<b>maarika</b> 180:21
<b>london</b> 166:19	214:18 221:4,4	233:22,22 234:1	181:16 185:21
<b>lonely</b> 233:20	235:2 236:10	237:12,12 238:17	186:6 190:6
	238:15 239:4,20	239:8 241:20,21	193:14 199:11

203:15 214:20 224:19 226:15 230:15 <b>machine</b> 163:15 <b>magic</b> 182:16 236:8 <b>magnitude</b> 84:11 235:21 <b>main</b> 161:20 162:17 271:20 <b>maintain</b> 140:12 <b>major</b> 119:19 137:22 265:5 271:9 282:14 <b>making</b> 24:20 27:8 28:4 40:5 73:17 93:4 102:2 106:2 125:3 127:15 132:1 135:15 142:4 147:21 148:4 153:12 185:1,1 191:14 206:21 207:1 216:6 218:16 228:1 235:16 243:11 244:10 258:5,9 271:12 <b>male</b> 281:11,11 <b>man</b> 279:18 282:6 <b>manage</b> 69:5 291:21 <b>manageable</b> 268:8 <b>managed</b> 281:22 <b>management</b> 100:22 114:20 174:18 268:13 274:16 287:15 <b>managers</b> 101:4 292:12 <b>mandate</b> 99:17 260:20 <b>mandates</b> 98:10	<b>maneuver</b> 93:9 <b>manner</b> 100:19 <b>manual</b> 106:6 <b>manufacture</b> 131:18 148:7 <b>manufactured</b> 131:21 <b>manufacturer</b> 139:20 <b>manufacturers</b> 160:20 <b>manufacturing</b> 139:16 140:11 147:2,8 148:2 160:18 176:7,8,9 176:13 177:1,21 197:11,13,18,19 197:21 228:9 229:19,22 230:4 247:3 259:10 260:5 271:12 275:9 <b>map</b> 28:4 <b>march</b> 5:4 197:8 286:2 314:9 <b>maria</b> 105:3,3 <b>marked</b> 35:2 <b>marker</b> 135:8 <b>markers</b> 137:6 <b>market</b> 14:17 16:15 107:19 132:21 133:2,4 134:9 140:20 163:17 172:8,14 177:4 307:5 <b>marketed</b> 140:19 <b>marketplace</b> 153:2 <b>marks</b> 129:8,10,10 131:14 132:11 138:15 141:5,14 146:11 150:15 153:6 156:17 160:6 163:18	165:21 176:7 177:9 194:5 197:5 300:18,20 304:9 <b>marks'</b> 193:18 <b>marriage</b> 267:9 <b>marrow</b> 252:20 <b>martha</b> 231:3 236:15,16,19,20 260:11,12 275:6 <b>martha's</b> 264:18 <b>mary</b> 286:12,13 286:14,18 290:7 <b>maryland</b> 315:21 <b>massive</b> 172:3 <b>master</b> 170:12 275:7,10,14 <b>master's</b> 297:3 <b>match</b> 282:21 283:16 <b>matched</b> 36:7 189:16 <b>material</b> 162:16 260:4,4 <b>materials</b> 145:14 <b>matt</b> 290:11,12,12 292:20 <b>matter</b> 77:22 83:10 84:3,21 89:16 90:3 123:13 147:10 167:7 175:12 267:15 270:22 <b>matters</b> 51:16,22 81:3 88:1 123:12 271:2 <b>maturity</b> 26:4 <b>maximize</b> 40:3 124:13 <b>maximum</b> 97:15 <b>maynard</b> 2:1,4 19:9 55:4,7 128:12,13 130:3 133:20 141:4 146:2 155:1 159:1	163:10 165:11 168:1 171:13 175:14 178:16 180:10,18 230:20 231:5 284:15 312:3,5 <b>maynard's</b> 230:17 <b>mccune</b> 231:4,7 231:12,18 236:15 236:18 242:1 247:13 252:13 253:11 256:3,10 256:12 258:14 260:11 264:16 268:19 273:8 276:1 279:16 282:7 284:12 <b>mcdermid</b> 107:3,5 <b>mcgowan</b> 286:12 286:13,14,18 290:7 <b>mcnary</b> 299:19,20 299:21 <b>md</b> 10:7,22 115:5 <b>mdic</b> 38:6 39:20 <b>meal</b> 109:5 <b>mean</b> 33:14 43:16 46:22 48:15 65:1 95:13 98:2 106:5 120:20 132:4 134:11 154:11 160:15 170:16,22 196:15 197:1 199:2 202:5 207:6 258:18 313:18 <b>meaning</b> 52:8 117:4 234:18 235:1 <b>meaningful</b> 14:10 16:1 51:12 52:15 52:22 62:10 115:19 127:20 189:1 254:5 297:5
--	---	---	---

<b>meaningless</b> 133:2	136:22 137:2	314:16,20	<b>mentioning</b> 301:6
<b>means</b> 23:2 53:10	142:22 164:2,3,5	<b>meetings</b> 37:11	<b>mentor</b> 234:19
108:14 110:12	164:15,19 234:11	58:13,17,18,21	<b>message</b> 97:19
120:10 121:7	248:7 249:15	59:1,2,14 123:21	106:17 111:3
125:19 142:17	250:14 251:7,11	168:10 170:17	<b>messages</b> 67:19
234:11 287:21	255:9 257:21	196:16 222:20	68:15
289:21	269:16 275:5	223:6 267:7	<b>met</b> 41:7 155:14
<b>meant</b> 96:4,7,8,9,9	279:1 285:13	314:13	246:6 288:8
96:11 212:20	287:20	<b>megan</b> 107:2,3	296:10
213:18 267:8	<b>medications</b>	<b>member</b> 280:17	<b>metabolism</b> 68:4
<b>measure</b> 90:7	248:17 301:21	280:20 300:1	74:16 221:7
92:14,19 99:7	<b>medicine</b> 10:18,19	<b>members</b> 2:11	<b>metadata</b> 95:22
135:3,13 142:5,6	11:1,6 55:11 67:9	4:10 31:12 65:18	<b>meter</b> 15:21
158:18 220:8	67:14 75:12 80:11	65:21 76:9 105:18	<b>methamphetami...</b>
<b>measured</b> 77:22	115:7,15 153:7	155:16 195:8	307:17
<b>measures</b> 34:3	173:14 174:21	196:18 197:2	<b>method</b> 141:1
60:5 70:5 79:19	175:4 187:7	199:9 200:7	279:6
84:2 90:16 91:5	192:18,19 218:10	215:10 232:17	<b>methodological</b>
92:3 93:14 95:3,4	219:8 237:14	234:18 306:20	39:22
95:6 270:19	242:7 248:14	<b>mental</b> 287:11	<b>methodologies</b>
<b>mechanics</b> 142:17	298:12 300:10	289:4	39:9,17 40:3
<b>mechanism</b>	304:20 305:8,15	<b>mentality</b> 218:7	52:22
188:10,12 261:20	308:5	<b>mention</b> 29:7	<b>methodology</b> 28:1
262:5	<b>medicines</b> 174:2	52:13 82:2 122:21	<b>methods</b> 34:3 39:3
<b>mechanistic</b>	179:1 218:11	193:18 198:4	52:18 302:8
212:13	242:13 307:4	224:2 246:15	<b>metro</b> 309:12
<b>med</b> 144:16 145:5	<b>medtronic's</b>	<b>mentioned</b> 21:22	<b>mexico</b> 159:11
<b>media</b> 4:9,11,19	271:21	22:2 25:21 26:17	<b>mic</b> 285:7 286:9
142:11 184:3	<b>meet</b> 17:17 45:9	27:10 38:4,9 39:5	<b>michelle</b> 292:21
187:8 270:4	94:1 131:19 187:8	51:17 52:6,11,19	292:22,22
306:21	289:9,22 303:6	61:19 62:4 75:15	<b>microphone</b> 7:11
<b>medical</b> 7:1,20	<b>meeting</b> 2:2,15 3:2	82:12 84:15	128:13 155:4,6
10:13 12:11 13:14	3:13,18 4:13,15	100:14 116:22	269:3,4 286:8
14:5,11 15:11	5:6,17 6:1 8:9 9:4	129:1 140:21	<b>microphones</b> 7:12
16:2,9 18:1 23:8	9:12,13,22 10:3	141:5 151:11	9:9 45:15 268:22
26:21 35:16 38:6	54:19 56:22 58:10	155:18 156:2	<b>mic's</b> 247:14
53:1 62:6 87:17	76:15 128:11	194:19 197:6	<b>mikhail</b> 175:17,18
96:6 114:18 115:2	130:5 166:5	204:9 210:21	242:2,3 258:15
115:13 117:9	196:16 233:16	244:13 248:5	271:4
118:3 119:4	247:18 263:3	250:8 251:13	<b>mila</b> 182:8 183:17
120:13,15,16	264:4 284:22	254:2 257:19	184:10,14 187:7
123:6,14 124:15	285:1 293:5 299:3	269:6 271:18	187:13 189:20
124:22 126:17	311:5 312:11,14	273:13 294:2,18	201:18 203:7
128:4,17,20 129:3	313:8,18 314:11	302:5 314:7	208:4,7,8,22

209:2,9,11,21 210:4 211:19 212:6 217:15,18 217:19 218:1,8,11 218:16 <b>milas</b> 218:18 <b>milasen</b> 184:11 200:5 205:14 206:16 208:4,4,19 209:1,20 217:16 235:14 251:6 <b>mila's</b> 183:15 185:11,16 187:21 189:14 204:21 211:22 213:17 218:15 219:12 221:22 <b>mild</b> 207:9 <b>miles</b> 238:22 <b>million</b> 27:19 108:7 132:1 226:19 227:11 293:3 <b>millions</b> 94:18 108:19,19,20 113:15 185:7,8 218:13 <b>mind</b> 80:3 81:5 101:3 105:1 106:19 108:20 148:12 171:4 175:6 180:19 198:5 199:8,9 200:16 203:17,20 208:3 215:19,19 217:4,5 228:14 231:1 <b>minded</b> 268:12 <b>minds</b> 40:13 57:22 <b>mine</b> 85:8 <b>minimal</b> 292:6 <b>minimum</b> 48:10 201:6 202:19 206:18	<b>minuses</b> 26:15 <b>minute</b> 6:17 7:2 20:22 21:8 88:9 180:13,14 <b>minutes</b> 8:16 20:16 45:17 55:13 60:10 63:21 66:4 128:7 268:20 285:3 <b>miracle</b> 235:18 <b>mirrors</b> 237:12 299:9 <b>misdiagnosis</b> 287:19 <b>misery</b> 307:11 <b>misinformed</b> 307:9 <b>misinterpret</b> 267:4,5 <b>mismatch</b> 261:9 <b>missing</b> 73:16 183:17,21 299:6 300:16 <b>missingness</b> 49:18 <b>mission</b> 17:16 18:21 250:15 290:19 291:2 297:15 298:19 299:5,8 <b>mistakes</b> 107:20 140:15 <b>mistrust</b> 287:20 <b>misuse</b> 99:4 <b>mitigate</b> 230:3 <b>mix</b> 215:5 <b>mld</b> 46:1 <b>mm</b> 236:18 <b>mma</b> 244:4 <b>mobile</b> 3:10 223:16 <b>mode</b> 198:20 <b>model</b> 26:4 147:7 228:1,1,4 245:20 305:2	<b>modeled</b> 188:14 <b>models</b> 41:12 113:18 196:5,8,13 197:5 245:3,3 277:15 <b>moderating</b> 231:14 <b>moderator's</b> 276:1 <b>modern</b> 192:11 <b>modernization</b> 17:12 18:6,13 <b>modernize</b> 17:7 125:6 <b>modernizing</b> 17:13 <b>modification</b> 139:17 <b>modified</b> 139:21 <b>modifying</b> 263:6 <b>molecular</b> 238:1 239:11 <b>molecule</b> 129:20 148:9 187:18 <b>molecules</b> 148:11 167:4 <b>molgradex</b> 299:2 <b>mom</b> 282:9 299:21 303:1 <b>moment</b> 128:9 210:2 227:1 <b>moments</b> 297:5 <b>momentum</b> 227:5 258:10 <b>mommy</b> 182:21 <b>moms</b> 281:12 <b>monetize</b> 113:13 <b>money</b> 108:5,11 135:20 143:1 176:19 179:4,15 183:14 227:18 229:12 243:10 244:18 245:4 246:2 267:13,14	267:14 <b>monique</b> 4:10,13 5:9 <b>monitor</b> 16:15 <b>monitored</b> 89:4 <b>monitoring</b> 88:11 138:7 152:17 206:4 <b>monogenetic</b> 272:1 <b>monogenic</b> 300:15 <b>month</b> 91:21 209:4,6 292:18 <b>monthly</b> 296:12 <b>months</b> 27:21 29:15 156:12 291:9,19 292:15 296:22 <b>morning</b> 2:1 6:8 6:13 15:8 45:21 64:2 66:9 68:2 70:19 74:10 130:17 193:16 233:11 294:12 295:11 313:1 <b>mornings</b> 246:11 <b>mortality</b> 287:11 289:17 <b>mother</b> 107:5 159:5 176:2 177:1 177:2 <b>motivated</b> 158:4 234:8 246:19 306:22 <b>mouthful</b> 247:7 <b>move</b> 19:3 35:2 50:20 69:3 71:5 88:5 104:3 122:12 166:18,21 181:12 203:14 232:2 249:8 257:2 258:13 262:1 264:12 285:4 299:13 305:10
--	--	--	---

<b>moved</b> 29:4 218:9	<b>name</b> 2:4 5:12	69:15 70:6,7,13	88:21 92:16 93:8
<b>moving</b> 18:7 43:7	7:14 20:1,20	71:14,20 72:13,18	95:4,16,20 98:6
139:11 184:9	70:20 85:1,9	74:19,19,21 78:10	102:13 103:14
269:3	107:2 111:20	78:18 79:8,10,13	118:5 119:3,3
<b>mr</b> 82:11	159:2 171:14	79:18,20 80:16,19	121:22 122:2,4,8
<b>mucus</b> 192:8	175:17 181:16	80:22 81:20,21	123:5 125:20
<b>mullin</b> 66:7,18	182:7 188:4	87:15 89:7 92:13	138:5 139:11,12
68:14,21 69:9	199:13 225:2	92:19 93:14 94:4	140:3 141:3,3,16
70:18 78:7 85:13	226:17 231:2	131:10 141:17	143:12 144:3
100:8 101:7 103:7	236:20 242:2	189:10 200:18,21	149:18 150:4
104:20 105:22	252:14 265:7	213:15 222:11	158:18 163:3
107:1 109:9	273:11 285:5	233:11 294:10,12	169:20,20 172:19
110:17 112:6	286:9,18 295:21	295:3,8,14 303:19	172:20 175:7
114:8	306:2 309:9	313:1	193:11,13 194:16
<b>multi</b> 52:7,16	<b>named</b> 187:11	<b>nature</b> 164:16	195:11 196:10
<b>multinational</b>	<b>names</b> 236:2	301:18	197:17 198:9,11
157:13,17	<b>nametags</b> 314:17	<b>navigate</b> 192:20	201:6 203:18
<b>multiple</b> 10:17	<b>naproxen</b> 310:18	217:9 229:12	204:9 205:19
79:21 104:10	<b>narcolepsy</b> 105:10	<b>ncats</b> 74:12	223:19 229:5
189:12 192:2	105:11	107:17 136:10	232:6 233:17,17
<b>multiplied</b> 288:20	<b>nation</b> 308:10,14	147:3 178:2	235:11 255:21
<b>muscle</b> 245:12	<b>national</b> 25:22	233:13 234:4	260:15 264:1,14
286:21	27:1,11,15 38:4	276:12,13	271:14 273:18
<b>muscular</b> 29:9,10	64:12 67:11	<b>near</b> 20:9 120:8	277:8,17,18,22
29:13 51:7 71:17	115:11,11 167:8	200:1	278:1,8 280:3,6
76:14 77:8 120:4	178:2 233:8 255:9	<b>nearly</b> 117:5	288:3 298:3 301:9
154:10,13 188:15	269:16 282:2,3	<b>necessarily</b> 32:13	303:6 305:13
244:13 245:6	293:1 301:16	32:14 42:6 104:3	307:8 308:12
<b>mutation</b> 146:17	<b>natural</b> 6:9,17	278:17	310:8 311:1,2,20
183:17,21 187:13	14:13,18 15:2,10	<b>necessary</b> 96:18	313:4,9
187:21 188:9,9	20:14 21:3 22:21	122:2 126:7 139:7	<b>needed</b> 8:8 33:13
189:13,14,17	23:4 29:21,21,22	257:2 299:13	44:17 90:9,11,19
221:3,12,18	29:22 30:5,8	<b>necessity</b> 250:1	90:20,21 97:10
<b>mutations</b> 139:3,5	31:15,21 32:8,12	<b>necrotizing</b>	183:13,17 192:16
189:19,20 225:7	33:3,9 35:6,12	286:22	195:22 196:14
<b>myopathy</b> 286:22	40:12,15 41:14,20	<b>need</b> 3:15,18 4:2	281:7 307:7
<b>myositis</b> 64:3	42:12,17 44:1,1	11:16 15:6 34:11	<b>needing</b> 110:13
286:14,19 287:1	45:1,4,8 46:18	34:12 40:19 41:12	<b>needs</b> 12:11 24:18
288:18 289:6,13	47:1 48:1,20	41:17,19 45:7	28:5 47:10 61:15
<b>n</b>	50:20 51:2,8,15	47:14 49:10 54:3	87:6 94:1 109:1
<b>n</b> 290:14,19	53:5,15 54:15	61:6 68:8,12 69:5	119:5 121:4 125:7
<b>nail</b> 36:21 83:6	56:19 57:13,14,16	69:8 73:15 78:3	131:19 136:4,4
<b>naively</b> 258:8	58:2,4 61:16 64:6	84:10 85:2 86:5	178:13 199:8
274:13	66:12 67:21 68:19	87:5 88:8,10,17	219:6,14 229:11

246:19 287:5 289:9 302:17 303:6 305:2 306:6 307:2 308:10 312:21 <b>negotiating</b> 86:8 <b>negotiations</b> 61:14 <b>neither</b> 315:10 316:7 <b>neonatal</b> 253:18 <b>neonatology</b> 232:3 248:19 <b>nephrologist</b> 168:4,19 <b>nephrologists</b> 170:2 <b>nephrology</b> 169:8 <b>nephropathy</b> 168:21 <b>nephrotic</b> 168:20 <b>nest</b> 38:7 52:6,20 295:19 <b>network</b> 5:3 27:17 38:8 54:1,6 157:8 158:10 254:3 280:3,6 291:4 <b>networks</b> 37:14 75:1 134:21 169:8 169:21 222:7 <b>neurodegenerati...</b> 130:20,21 <b>neurodegenerati...</b> 205:15 <b>neurogenitive</b> 182:10 <b>neurological</b> 79:14 84:9 <b>neurologist</b> 28:11 70:20 71:8 167:18 167:19 <b>neurologists</b> 170:2 <b>neuromuscular</b> 28:11 29:12 70:22 71:1	<b>neuromyelitis</b> 120:1 <b>neuronex</b> 72:6 <b>neuropathy</b> 243:17 <b>neuroscience</b> 22:15 <b>never</b> 57:18,18 89:17 93:19 147:16 172:4 184:7 208:21 212:21 217:14 233:8 234:19 252:7 310:15 311:4 <b>new</b> 6:11 12:12 15:4 16:21,21 18:8,9 21:15,21 22:4 35:3,3 40:22 44:9 55:10 67:5 72:12 80:11 101:3 107:14 116:20 120:1,11 124:15 127:7,9,10 133:17 136:15 138:13 139:12 147:18 173:9 174:21 177:20 181:17,18 184:10 186:11,13 190:4 196:13 199:16 200:9 202:10 204:15 212:10 216:9 217:13 218:10,20 219:7,20 229:9 236:22 258:20 259:5 261:16 263:19 264:13 301:14 302:8 304:17 311:8,8 313:10 <b>newborn</b> 231:22 <b>news</b> 214:3,8	<b>nf</b> 179:6 276:11 <b>nice</b> 66:9,15 80:1 232:5 <b>nicely</b> 178:7 260:8 <b>nicu</b> 159:8 304:22 <b>night</b> 185:6 <b>nih</b> 30:22 40:12 67:12 71:3 72:6 72:19,21 74:12,13 75:1,8 76:22 98:18 136:10 225:6 233:7,10 243:21,21 265:5 266:8 272:19 273:18 295:1 <b>nina</b> 114:12,12 115:17,20 116:22 128:2 165:14 <b>nine</b> 8:11 99:1,2 245:19 285:1 <b>nitty</b> 266:21 <b>nodes</b> 38:7,19 <b>nomenclature</b> 80:7 <b>non</b> 58:14 110:13 137:3 138:8 140:10 173:3 176:11 209:19,19 <b>nonprofit</b> 246:21 290:15,16 <b>nonsense</b> 189:19 <b>nord</b> 44:11 75:14 142:16 280:17 293:7,10 294:15 294:20,21 <b>nordic</b> 164:20 <b>nord's</b> 281:1 294:6 <b>norm</b> 229:8,10 <b>normal</b> 154:16 182:15 184:1 202:8 <b>notary</b> 1:7 315:1 315:21	<b>note</b> 4:20 176:1 224:22 268:19 314:19 <b>noted</b> 154:10 <b>notice</b> 285:14 286:4 314:11 <b>notion</b> 250:10 278:19 <b>notions</b> 53:11 <b>novartis</b> 67:9 <b>novel</b> 12:1,7 16:13 118:19 119:9 200:10,12 202:6 214:11 <b>november</b> 191:5 <b>nsaids</b> 174:3 <b>ntrk</b> 237:19 <b>number</b> 11:21 12:4 48:21 104:21 116:16 119:17 123:16 132:16 138:18 147:14 148:9 154:21 170:9,11 178:7 181:1 185:14 193:11 196:8 198:9 243:6 257:4 278:16 279:8 289:19 297:6 298:1,5 304:11 <b>numbers</b> 119:7 120:20 <b>numerous</b> 286:20 <b>nuts</b> 25:14
<b>o</b>			
<b>o'boyle</b> 107:2,3 <b>oak</b> 181:14 <b>oberman</b> 56:14,15 <b>obese</b> 296:11 <b>objective</b> 243:12 <b>objectively</b> 84:3 206:8 <b>objectives</b> 23:14 49:1 54:3 91:15			

<p>111:15  <b>obligation</b> 185:15  <b>observation</b> 77:18  200:22  <b>observational</b>  16:11 75:22 81:18  83:13 86:22 97:12  99:18 104:18  <b>observations</b>  196:4  <b>observed</b> 26:9  92:12 293:16  <b>obstacle</b> 221:17  <b>obtain</b> 3:2 4:8 6:1  <b>obtaining</b> 23:5  167:12  <b>obvious</b> 266:21  <b>obviously</b> 78:11  132:3 184:16  186:2 191:1  200:11 210:9  <b>occur</b> 20:17 32:16  52:3 137:15  143:15  <b>occurred</b> 135:3  <b>odd</b> 227:12  <b>odyssey</b> 304:13  <b>odysseys</b> 186:20  <b>offer</b> 187:9 210:2  211:16 260:21  294:13 302:12  <b>offered</b> 65:22  192:17  <b>offering</b> 211:18  218:18  <b>offers</b> 219:5  304:14 305:9  <b>office</b> 2:5 9:15  21:15,16 24:14,15  24:17 25:1,1,4,22  28:12,18 67:5,10  71:4 74:11 114:13  128:15,19 181:17  181:18,18 199:16</p>	<p>231:19,19 233:12  240:15 307:3  314:5  <b>officer</b> 4:9 10:15  67:6 248:7 315:2  <b>offices</b> 21:19 25:3  293:17  <b>officials</b> 300:20  <b>offs</b> 150:22,22  251:4  <b>oftentimes</b> 46:13  160:20  <b>oh</b> 83:11 164:6  231:5 256:5  267:15 280:12  <b>okay</b> 48:9 51:9  60:13,14 68:17  69:9 84:1 85:15  92:15 103:7  134:12 144:19  145:2 149:11  161:1 171:11  180:12 201:21  202:16 219:10  223:9 262:3 269:2  276:6 279:18  306:10 309:4  <b>old</b> 82:7 159:8  182:18 183:22  184:14 248:15  <b>older</b> 87:14  <b>oligonucleotide</b>  229:17  <b>oligonucleotides</b>  146:13 290:21  <b>once</b> 73:18 87:14  91:21 94:8 113:20  139:2 140:13  142:14 143:4  151:19 157:20,22  187:15 193:20  220:2,3 240:7  260:3 281:18</p>	<p><b>oncologist</b> 10:8  89:6 236:20  <b>oncologists</b> 168:14  <b>oncology</b> 11:3  13:12 36:5,5  114:18,19,21  115:6,13,14  168:13 237:2,3,11  240:14,16 260:13  261:6,21  <b>ond</b> 203:10  <b>ones</b> 75:13 101:14  139:13 142:18  160:21 207:20  288:3  <b>one's</b> 309:13  <b>ongoing</b> 52:18  59:5 166:3  <b>online</b> 2:21 18:8,9  20:17 45:16 54:19  55:1 60:12 65:20  116:8 181:14  269:1  <b>onset</b> 84:10  <b>oopd</b> 247:19  <b>opaque</b> 24:22  <b>open</b> 4:8 5:4 8:5,5  8:13,17,20 31:10  44:5 45:12 61:14  63:5 206:19  214:21 233:2  254:13 268:21  284:17,22 285:7  286:2,4,12 312:1  312:7 314:8  <b>opened</b> 166:15  218:9  <b>opening</b> 6:15,21  21:22 52:10 80:11  219:7  <b>operate</b> 82:20  83:7,19  <b>operating</b> 90:20  91:8</p>	<p><b>opiate</b> 306:12  <b>opiates</b> 307:1  <b>opinion</b> 301:15  <b>opinions</b> 9:6  <b>opioid</b> 172:17,22  173:17 174:10  311:16  <b>opioids</b> 172:16  173:4 174:1,8  175:1,8 307:21  311:17  <b>opportunities</b>  6:11 9:14 15:9  17:6 35:4 130:7  131:3 133:22  158:17 187:22  190:5 240:4  258:20 289:7  312:20  <b>opportunity</b> 2:6  4:16 7:7 8:7 9:5  11:18 19:6 20:21  21:11 48:3 57:2  60:2,8 71:12 88:4  117:7 155:2  156:21 179:9  185:15 189:5  200:6 209:8 232:2  241:12 246:2  248:12 283:10  287:14 291:12,14  294:14,20 296:1  299:15 304:15  305:10 313:19  <b>opposed</b> 110:13  <b>opposite</b> 82:9  <b>opt</b> 165:4  <b>optica</b> 120:1  <b>optimal</b> 85:4  313:16  <b>optimally</b> 56:20  278:17  <b>optimistic</b> 179:13  225:18 226:11</p>
---	--	---	--

<b>optimize</b> 76:18 84:12 113:19 250:21 259:22	<b>original</b> 139:21 <b>originally</b> 12:13 <b>origins</b> 176:19	<b>overburdening</b> 107:21	75:16 77:15 78:11 79:7 84:15 101:9 112:9 114:9 128:4 146:5 155:8
<b>optimized</b> 85:12 257:12	<b>orphan</b> 2:5 9:15 11:19,20,21 12:2 12:8,9 13:5,13 18:5,7,10,13 22:2 118:16,19 119:10 119:12 120:17,17 128:16,19 163:7 165:16,19 282:1 314:6,6	<b>overcome</b> 127:18 278:16 281:15,19	178:19 181:1 200:18 230:18,21 231:14 232:17 233:2,5,10 239:9 248:6 253:20 254:7 269:9 273:16 284:13,14 312:9
<b>optimizing</b> 84:16		<b>overdose</b> 173:1 307:15,20	
<b>option</b> 209:2,14 285:22		<b>overlapping</b> 306:21	
<b>options</b> 14:17 108:14 219:5 289:9 297:20		<b>overlooking</b> 282:14	
<b>order</b> 3:22 4:4,5 69:2 87:10 88:14 152:9 182:4 205:18 231:1 235:21 240:3 280:9,15 289:8 301:8	<b>ortho</b> 25:3 <b>orthostatic</b> 310:17	<b>oversee</b> 10:11 130:2	<b>panelist</b> 181:20 <b>panelists</b> 74:8 180:19 181:10 230:19,21 233:6 269:12 273:21 284:16
<b>ordered</b> 4:1,3	<b>otat</b> 28:19,20	<b>oversees</b> 10:16 236:21	<b>panels</b> 58:20 181:7 232:9 249:22 256:14 273:14 294:8
<b>organization</b> 7:18 22:12 63:15 102:2 103:2 108:8 125:22 126:1,3 166:6 241:4 262:11,12 271:6 280:15 281:2 285:11 286:20 293:1,13 295:7 297:15 302:14 306:3 309:11	<b>outbreak</b> 166:22 <b>outcome</b> 24:5 34:1 34:3 70:5 79:19 90:7,16 91:5 92:14,18 93:14 95:3 99:7,8 135:1 315:15 316:12	<b>overview</b> 24:10	<b>pap</b> 296:3,6,10,16 297:6,11,13,14 298:13,18 299:16 299:16
<b>organizations</b> 2:12 22:7 47:2 102:8 103:1 170:5 196:6 251:20 252:22 258:7 265:4 278:3 280:20 293:8 295:2 300:1 301:12	<b>outcomes</b> 26:9,9 26:10 37:2,8 60:3 62:8 89:15 90:3 95:6 124:21 134:22 137:4,8,11 155:9,10,21 193:9 298:12 302:2,4 304:21	<b>ovid</b> 56:15	<b>paper</b> 18:8 242:12 <b>paperwork</b> 192:22
<b>organize</b> 82:5	<b>outpatient</b> 27:19	<b>ownership</b> 108:15 109:2 112:3 180:1	<b>paradigm</b> 158:9 202:8,9,10 214:18 217:12,13 238:16
<b>organized</b> 81:17 83:3 99:15 170:1	<b>outreach</b> 25:12 222:5,19 255:22	<b>oxygen</b> 192:5 296:11 298:4,13	<b>parent</b> 186:3 242:18 283:11
<b>oriented</b> 281:12	<b>outside</b> 3:13 4:1,7 16:3 36:4 73:21 128:20 158:4 160:16 222:21 241:4 307:18	<b>p</b>	<b>parents</b> 54:7 115:21 154:19 175:21 176:20 183:8 204:6 242:6 243:17 244:17
	<b>outweigh</b> 192:9	<b>package</b> 292:9	<b>pariser</b> 67:10 74:10,11 81:15 95:13 100:15 104:6 106:2 107:10 110:18
	<b>overall</b> 18:12 149:16 167:21	<b>packet</b> 163:5	
	<b>overarching</b> 68:15 171:21	<b>paid</b> 300:4	
		<b>pain</b> 96:7 105:15 172:2,3,6,8,9,13 172:19 173:7,9,14 173:15 174:7 175:4,10 176:1 209:10,11 306:3,5 306:9,15 307:11 308:4	
		<b>painful</b> 171:18	
		<b>palliative</b> 11:6	
		<b>panel</b> 6:6,15,17 7:1,3,4,6 8:4 19:11,15 20:12,18 20:20,21 23:1,2 31:11 47:19 65:18 65:21 66:2,3,8,12 66:15,22 67:22	

233:12 <b>pariser's</b> 105:7 <b>park</b> 284:18,20 290:5,10 292:20 295:19 299:18 302:20 305:17,20 305:22 308:16,19 308:21 309:3,6 311:22 <b>parlance</b> 234:11 <b>parlay</b> 70:6 <b>parliament</b> 179:15 <b>parry</b> 155:8 <b>part</b> 17:4 18:18 20:18 22:11 44:18 52:18 61:20 113:12 114:6 117:7 120:14 122:20 128:22 131:17 136:2,2 163:20 164:5 177:17 178:13 187:2 203:10 209:16 213:20 214:16 216:11 233:7,13 237:9 244:10 246:17 252:3,19 253:3 254:22 255:3,8 260:22 270:13 276:14 283:4 294:10 295:5 <b>participants</b> 4:17 9:7,9 20:21 312:9 312:15 <b>participate</b> 2:21 4:21 8:8 14:12 71:20 91:18 156:14 165:3 186:8 288:7 303:19 304:3 <b>participated</b> 156:10	<b>participates</b> 21:18 <b>participating</b> 10:2 63:2 295:13 312:2 312:11 <b>participation</b> 8:10 14:16 20:16 31:10 43:19 65:20 127:20 287:4 288:19 289:8 <b>particular</b> 22:13 46:19 49:2 51:5 63:4 71:10 92:4 101:15 108:10 112:18 114:5 117:1,16 124:8 138:14 165:9 172:16 174:1 189:14 194:8 205:14 213:11 215:7 219:15 229:16 238:16 262:5 263:4,5 264:4 269:1 290:8 <b>particularly</b> 17:3 46:13 53:6 58:15 117:20 118:7 123:2 160:21 166:8 193:8 238:19 <b>parties</b> 223:22 307:8 315:11,14 316:8,11 <b>partner</b> 49:5 293:13 302:12 <b>partnered</b> 294:16 <b>partnering</b> 25:21 27:11 <b>partners</b> 28:1 46:9 103:14 111:21 295:8 <b>partnership</b> 40:1 147:5 168:7 178:5 179:3,20	<b>partnerships</b> 168:15 253:22 256:15 295:4 <b>parts</b> 22:11 39:10 95:21 255:6 <b>passage</b> 11:20 118:15 <b>passcode</b> 5:3 <b>passion</b> 114:22 <b>passive</b> 144:1 <b>patent</b> 275:12 <b>path</b> 44:12 67:14 75:12,20 93:1 94:15 122:5 185:16 195:2 201:3 294:16 301:2 <b>pathetic</b> 270:9,10 <b>paths</b> 184:4 <b>pathway</b> 133:15 138:20 142:19 143:18 195:3 271:20 272:4 <b>pathways</b> 139:4 145:10 146:1 301:10 <b>patient</b> 2:11 9:15 13:20 14:2 17:3 18:19 21:12 26:9 27:19 30:20 31:1 33:8,14 34:19 37:8,10 43:3 44:10,13 47:2 49:8 52:13,14 53:7,11 58:16,17 58:20 60:3,4,16 60:18 61:5,18,21 62:8,8 64:2,5,8,15 69:14,17,17 70:12 70:13 75:18 76:6 76:13 80:21 83:11 87:2 89:17,19 91:17 95:5,18 96:16,19 99:7	101:2 103:15 104:1 106:21 109:2,8,17,19,21 109:22 111:13 123:16,19,20 124:20,21 125:1 132:1,14 133:5,11 134:6,11,11,22 137:4,8,11 141:8 141:11 143:9,22 144:3,5 145:19 148:11 155:7 159:6 160:5 163:21 165:2 174:6 175:6,6 177:8 184:13 190:7 191:5 193:17 194:20,20 194:22 198:9,10 198:12,15,16 199:3,8,10,10 201:10 202:21 206:2,6 207:14 208:18,20 212:4 214:3,5 216:16 217:3,20 218:5 219:16,17 220:16 220:18 221:13,19 225:4 226:21,22 229:4,10 238:22 246:19 249:10,11 253:4,15 254:20 262:13 265:7 274:15 278:2,2 280:4,15 281:1,9 282:4 283:11 288:11 291:8 293:10 295:1,7,9 297:14 298:11,18 299:10,16 301:19 302:2,4,7,17 303:19 309:9,17 309:18 313:3 314:1
--	---	--	--

<b>patient's</b> 111:10 123:17	163:20 165:9 169:12,17 170:6 171:2 172:9 173:13,19 174:16 176:15,17,20 186:18 192:11 193:11 194:15,22 195:7,11 196:2,18 198:9 202:4 204:6 204:16 207:6,20 214:10 216:13 220:3 221:16 222:5 224:18 227:12 228:14,20 234:1 238:18,20 239:19,22 240:5 241:14 242:11,11 243:7,11,20 244:9 246:14,22 247:8 253:7 254:6 255:2 255:15 257:13,17 258:4 259:9,16 260:1,21 261:19 262:6 263:6,7,11 263:17 278:3,5 281:12 282:16 284:4 287:13,21 288:3 289:20 290:21 291:1 293:19 295:12,17 296:7 297:7,11,13 297:19 298:2,5,15 298:21 301:9 303:9,11,15,17,18 303:21,22 304:1,2 304:4,7,14 305:1 305:6,7,11,12,15 306:9,15 307:11 307:20 308:3 310:3,8 311:1,6 311:11,17,20 312:15,19,21 313:3,9,17	<b>patients'</b> 198:11 206:13 219:14 246:12 287:11 <b>patient's</b> 220:19 221:18 <b>patroula</b> 199:13 199:14 205:3 208:2 217:11 218:6 220:22 <b>pave</b> 200:9 220:10 <b>pay</b> 119:15 194:16 <b>payment</b> 133:14 <b>payments</b> 132:17 <b>payor</b> 52:12 <b>payors</b> 159:21 311:14 <b>pays</b> 99:13 <b>pediatric</b> 20:2,4,8 117:5 120:4 137:22 138:4 169:8,9 170:2,2 199:18 231:19 236:20 237:3 238:12 248:10 251:12 254:6 260:13,17,17,20 261:18 263:7,13 272:12 279:1 <b>pediatrician</b> 231:21 <b>pediatrics</b> 137:14 137:19 138:2 152:19 163:9 232:6,8 248:7,9 248:10 250:4 251:14,18,22 252:2 278:14,18 <b>peiris</b> 247:14 256:5,11,21 272:9 274:4 <b>pendulum</b> 173:16 <b>pennsylvania</b> 11:5 115:7	<b>people</b> 12:18 14:6 14:12 18:21 41:17 48:7,11 51:18 74:2,21 78:8 85:14 86:5 90:12 91:20 96:7,8,9,9 97:5 98:3 99:3,12 99:19 100:11 101:3,10 104:21 105:12,16,20 106:8 116:4 122:9 123:3,4,5 125:17 126:8 130:20 134:18 139:13 141:22 142:9 143:8 144:18,22 144:22 145:12 147:14 148:17 149:2,9,21 156:1 156:13 157:1,9 160:9 161:5,17,22 162:4,9,17,21,21 166:12 169:14 170:10 171:3 172:14,19,21 173:18,20 174:3 174:11 175:9,10 177:14 178:9 181:21 188:19 197:1,14 201:21 203:11 208:1 217:13 219:1,4 223:15 224:9,10 225:20 227:6 233:22 235:17 236:5 239:9 242:14,21 245:4 245:11 247:20 250:10 253:8 256:17 258:15 260:6,7 264:6 267:4,6,15 268:5 268:11,22 269:19 269:19 270:10,13
-----------------------------------	---	---	--

<p>270:17 271:2 272:11 273:5 277:5 282:11 284:4 293:8,20 294:1 308:7,12,13 <b>people's</b> 82:6 151:6 <b>people's</b> 186:15 186:19 <b>perceived</b> 244:14 <b>percent</b> 22:3,4 28:21,22 109:16 109:20 119:9,11 137:9,17,20 184:1 238:9,10 288:5 294:3 307:3,20,21 308:1,1 <b>perception</b> 76:3 110:13 <b>perfect</b> 166:2 247:15 <b>perfection</b> 166:14 <b>perfectly</b> 215:9 226:8 264:11 <b>perform</b> 171:7 <b>performed</b> 42:17 <b>performing</b> 118:9 <b>perinatal</b> 248:14 <b>period</b> 8:5,6,14,18 8:20 284:18,18 286:12 312:1,7 <b>periodically</b> 8:2 <b>perpetrating</b> 309:1 <b>perpetually</b> 147:17 <b>perry</b> 252:14,15 254:19 269:15 270:5 <b>person</b> 2:20 148:21 149:2 184:12 208:9 233:5</p>	<p><b>person's</b> 146:14 <b>personal</b> 9:6 117:4 214:4 218:11 299:12 312:17 <b>personalized</b> 237:14 305:8 <b>personally</b> 116:5 204:14 228:17 <b>personnel</b> 291:13 <b>perspective</b> 18:19 20:15 36:19 40:8 47:3,4 52:12,13 55:8 59:8 60:17 64:18 70:12 106:13 138:16 147:1,10 186:5 199:22 201:5,5 202:5 203:19 205:8 207:15 222:18 233:14 254:16 273:19 295:10 <b>perspectives</b> 3:2 6:2 7:3,9 9:5 21:3 21:13 146:6,8 155:3 181:2,4,11 194:1 204:6 258:7 312:17 313:13 <b>peter</b> 21:9 31:19 41:21 43:16 44:4 48:15 53:17 55:14 58:8 60:1 61:18 62:22 64:20 129:10,10 131:14 132:11 138:15 141:14 146:11 149:6 150:15 153:6 156:17 160:6 162:15 163:18 165:21 177:9 300:18 <b>petra</b> 67:7 70:19 70:20 80:6 94:11 103:9</p>	<p><b>petroula</b> 182:1 <b>pfizer</b> 246:3,3 <b>phage</b> 190:10,11 191:4,18 194:10 199:2 204:14 210:22 280:2 <b>pharm</b> 75:11 <b>pharma</b> 46:8 132:20 <b>pharmaceutical</b> 61:9 173:8 195:4 228:3 <b>pharmaceuticals</b> 290:14 291:3 <b>pharmacodynamic</b> 135:8 <b>pharmacology</b> 67:13 201:13 <b>phase</b> 22:8,9 30:10 110:10 298:8 <b>phd</b> 10:7 11:4 <b>phelan</b> 107:3,5 <b>phenotype</b> 264:22 <b>philadelphia</b> 71:13 <b>philanthropic</b> 251:5 <b>philosophy</b> 292:1 <b>phones</b> 3:9 <b>physically</b> 156:15 193:5 <b>physician</b> 186:10 189:4 209:19 214:5 295:22 299:10 <b>physicians</b> 54:8 201:1 204:7 <b>pi</b> 107:3 <b>pick</b> 31:19 72:22 264:19 <b>picone</b> 105:3,4 <b>picture</b> 145:18 206:10</p>	<p><b>picu</b> 305:1 <b>pie</b> 239:17 <b>piece</b> 99:19 100:1 131:15 146:22 147:1 174:20 214:11 220:20 221:1 222:16 263:22 <b>pieces</b> 68:11 78:3 83:20,21 146:21 239:17 <b>piloting</b> 241:8 <b>pink</b> 301:22 <b>pinpoint</b> 187:21 <b>pinpointed</b> 187:12 <b>pipeline</b> 228:16 247:10 <b>place</b> 82:13 110:20 122:16 137:5 151:6 156:18 157:14 171:9,10 184:17 201:8 235:11 277:12 <b>placebo</b> 55:9,20 56:6 84:8 92:9,12 92:20 93:1 169:2 239:2 <b>placebos</b> 134:19 <b>placed</b> 5:18 314:11 <b>places</b> 260:7 280:6 <b>plain</b> 311:15 <b>plan</b> 17:12 103:5 180:15 264:11 <b>planet</b> 158:22 <b>planned</b> 180:14 <b>planning</b> 73:14 79:2 128:11 129:1 <b>plasmoid</b> 259:8 <b>platform</b> 23:16 68:22 69:3 73:3 75:16 76:21 94:22 95:9 99:15 104:9</p>
---	---	---	---

108:18 112:17,20 168:10,18 169:18 171:7 178:22 179:5,7 236:11 251:9 258:3 292:6 294:22 <b>platforms</b> 17:8 104:9 108:4 169:22 273:2 <b>plausible</b> 213:8 <b>play</b> 78:16 81:2 163:16 194:15 257:20 260:8 302:10 <b>played</b> 184:22 196:18 <b>players</b> 258:2 <b>playing</b> 15:16 119:17 246:8 <b>plays</b> 304:16 <b>plea</b> 108:2 183:20 <b>please</b> 3:9,16,20 3:22 4:11,13,20 5:9,10,13,16,19 7:9,17,22 9:6,10 9:22 45:14 66:7 67:16 115:16 155:4 180:20 278:10 285:8,10 286:8 308:22 309:1 <b>pleased</b> 19:10 235:6 <b>pleasure</b> 237:3 266:16 <b>plenty</b> 214:9 <b>plug</b> 69:7 75:4 107:16 151:2 229:15 <b>plus</b> 272:12 279:7 <b>plusses</b> 26:14 <b>pm</b> 8:15 <b>podium</b> 285:8 286:6	<b>point</b> 3:15 30:18 38:7,19 42:1 46:19,20 63:21 64:11 65:1,16,17 73:2,6,9 79:22 90:6 92:5 93:4 98:11 100:2 101:18 103:6 105:7 106:2 119:1 125:14 140:2,8 159:1 165:11 177:14 183:16 186:20 192:8 205:4,7 207:21 220:4,5,14 250:9 252:1 257:9 269:13 274:9,17 275:3 278:12 295:11 310:7 <b>pointing</b> 113:5 <b>points</b> 3:8 14:13 21:2 94:12 95:14 132:13 159:22 254:5 265:14 295:16 302:3 313:2 <b>policies</b> 148:14 220:17 277:9,18 278:8,10 282:4 <b>policy</b> 114:13 181:17 282:3 288:9 306:11 <b>political</b> 179:12 306:8,22 <b>politicalize</b> 307:10 <b>politically</b> 166:20 <b>polycystic</b> 77:8 <b>polymyositis</b> 286:22 289:15 <b>pompe</b> 244:2 <b>pond</b> 241:5 <b>pool</b> 155:22 262:6 <b>pooling</b> 150:20	<b>pools</b> 30:7 <b>poorly</b> 14:21 306:11,11 <b>popular</b> 175:20 <b>populated</b> 214:9 <b>population</b> 33:3 33:14 39:13 40:20 92:5 109:17,19,21 133:5 151:3 152:3 160:13 163:13 251:12 289:18 290:4 <b>populations</b> 20:8 20:8 39:12 40:18 126:22 132:14 138:4 146:5,16 150:16 151:13 214:1 229:1 248:8 249:20 250:4 251:18 252:3 278:18,20,22 279:1,11,12,13 287:5 289:13 290:2 <b>portal</b> 18:9,9 69:19 <b>portion</b> 25:11 102:3 116:21 136:10,11 176:10 176:13 285:1 <b>portions</b> 39:16 <b>pose</b> 126:22 <b>position</b> 186:16 <b>positive</b> 113:5 193:9 227:16 <b>possibility</b> 185:10 <b>possible</b> 73:8 74:1 80:13,14 81:12 122:9 142:15 147:11,19 149:12 157:18 163:3 185:8 196:12,12 208:16,17 235:18 241:1 262:19	282:5 <b>possibly</b> 36:16 141:7 <b>post</b> 16:15 17:1 107:19 <b>postoperative</b> 225:5 <b>potential</b> 16:19 110:9 124:14 155:21 156:1 188:10 189:10 194:13,14 219:8 237:15 244:8 249:7 250:5,21 251:10 252:7 261:2 305:5 <b>potentially</b> 32:4 104:5 121:3 147:8 209:22 218:10,12 218:14,15 274:10 274:21 275:4 <b>pounding</b> 307:22 <b>power</b> 124:6 <b>powerful</b> 89:1,12 89:20 113:6 124:10 152:21 186:1 <b>practical</b> 58:12 73:13 106:19 142:9 <b>practicalities</b> 180:2 <b>practically</b> 208:15 <b>practice</b> 16:8 25:7 25:7 56:20 120:3 199:19 200:22 248:13 <b>practices</b> 85:16 100:21 214:10 273:17 <b>prader</b> 105:5 <b>pre</b> 3:22 4:1,3,4,5 23:12 56:21 58:10 59:13,14,18 65:6
---	---	---	---

89:9 154:5 <b>precise</b> 131:5 <b>precision</b> 300:9 <b>preclinical</b> 197:22 224:16 <b>precludes</b> 122:11 <b>preconceived</b> 53:11 <b>predicable</b> 30:7 33:7 <b>predicted</b> 214:22 <b>predictors</b> 88:21 <b>predicts</b> 90:3 <b>predominantly</b> 190:15 <b>prefer</b> 286:7 <b>preference</b> 142:20 <b>prejudice</b> 110:4 <b>prenatal</b> 248:14 <b>prepared</b> 316:3 <b>prerogative</b> 276:2 <b>prescribed</b> 307:21 310:9,18 <b>prescribing</b> 172:16 174:1 306:12 307:5 <b>prescription</b> 307:14 <b>presence</b> 54:19 <b>present</b> 3:1 87:9 298:14 <b>presentation</b> 23:6 23:21 107:20 <b>presentations</b> 107:13 <b>president</b> 47:18 67:8 276:7 290:13 296:2 306:19 <b>press</b> 4:9 <b>pressure</b> 249:16 <b>presume</b> 46:3 <b>pretentious</b> 28:16 <b>pretty</b> 46:3 143:21 157:8 173:12	183:13 208:6 209:15 210:5 253:13 262:15 263:19 271:22 281:1 <b>prevailing</b> 306:7 <b>prevalence</b> 69:22 289:14 <b>prevent</b> 283:22 <b>prevention</b> 225:13 <b>prevents</b> 157:13 <b>previous</b> 75:15 77:15 84:15 114:19 194:6 197:6 293:15 <b>previously</b> 166:19 188:1 200:18 203:22 <b>primarily</b> 79:14 <b>primary</b> 97:16,19 <b>principal</b> 10:9 <b>principle</b> 189:18 <b>principles</b> 223:18 <b>printing</b> 151:8 <b>prior</b> 8:9 74:14 115:1 315:5 <b>priorities</b> 117:14 117:15,15 123:1 <b>prioritize</b> 106:16 113:8 <b>priority</b> 10:12 124:6 127:6 <b>privacy</b> 63:9 102:17 103:17 <b>private</b> 147:5 168:7 178:5 179:2 179:20 248:13 253:21 256:15 <b>privilege</b> 186:21 <b>privileged</b> 186:16 <b>proactive</b> 125:11 268:11,13 <b>probability</b> 143:14	<b>probable</b> 151:16 <b>probably</b> 51:3 58:5 103:12 113:9 129:14 136:5,9 164:9 167:1 169:20 170:1,10 173:15 180:6 202:12 228:5 235:16 254:10 267:8 272:11 279:19 299:9 <b>probiotic</b> 310:15 <b>problem</b> 108:16 160:15 161:2 171:1 172:14 229:5 236:7 265:19 288:16 <b>problems</b> 110:3 160:15 169:8 175:12 268:14 <b>procedures</b> 90:20 91:9 <b>proceeding</b> 316:4 <b>proceedings</b> 315:3 315:4,6,8 316:6 <b>process</b> 15:19 18:7 47:10 77:5 93:16 94:6 121:12 122:15 123:11 125:4 136:21 177:20,21 188:12 192:21,22 203:13 215:13,20 216:6 216:13 217:1 224:15 229:3,19 240:13 241:17 260:5 261:8 269:11 271:12 303:18 <b>processes</b> 18:5,8 121:17 229:22 <b>proctor</b> 309:4 <b>produce</b> 259:8	<b>produced</b> 140:14 <b>product</b> 2:3,8 3:3 3:5 6:3,4,10,12 7:1,4,20 12:10 13:8 14:5 15:11 15:14 16:9,20 18:3 24:15 29:7 40:22 116:12 117:9 119:13 120:15 126:14 127:17 128:18 129:3,6 130:6 139:15,17,21,21 140:4 141:10,13 142:6 143:4 144:4 147:15,17 166:11 177:19 198:12,18 230:22 232:14,22 244:16 251:7 285:13 312:21 313:13 <b>production</b> 161:10,15 <b>productive</b> 10:3 <b>products</b> 2:5 9:16 13:7 14:11 16:2 16:21 18:2,16 20:7 29:2,5,17 67:4 118:3 119:10 121:7 122:17 123:4,6,14 124:4 124:18 128:5,16 128:19,21 129:13 129:15,17 131:20 131:20 132:6,16 136:22 140:12 141:1,17 148:7 150:9 161:17 194:7,9 195:5 196:1,11 198:17 199:15 210:20 212:20 251:11 257:21 275:5,13 313:16 314:6
--	---	---	--

<p><b>professional</b> 26:1 37:12 142:22</p> <p><b>professionals</b> 2:12</p> <p><b>professions</b> 250:17</p> <p><b>professor</b> 10:18</p> <p><b>profit</b> 133:9 176:11 246:17</p> <p><b>profitable</b> 282:15</p> <p><b>prognosis</b> 187:17</p> <p><b>program</b> 10:21 16:18 17:5 20:2,3 20:4 40:17 43:1 43:10 44:15 59:4 60:3 74:17 75:4 75:12 82:18,19 83:1 120:19 164:9 177:18 198:15,16 241:8 251:13,15 255:18 292:10 294:21 295:6</p> <p><b>programs</b> 46:12 114:14 127:10 239:14 255:1,2,3 255:16 269:18 293:10</p> <p><b>progress</b> 83:8 93:7 130:22,22 165:17 166:16 184:22 221:20 265:22 266:1</p> <p><b>progressed</b> 298:8</p> <p><b>progression</b> 14:15 23:7 33:17 42:9 60:21 84:8,17 89:10 205:16 287:15 294:15</p> <p><b>progressive</b> 138:11 151:22 152:20</p> <p><b>progressively</b> 190:19</p> <p><b>project</b> 103:4,4,5 266:12 292:12</p>	<p>304:18</p> <p><b>projects</b> 23:18 197:14 229:7 266:22 273:4</p> <p><b>promise</b> 11:18 123:22 125:17 235:16 263:12</p> <p><b>promising</b> 197:20</p> <p><b>promote</b> 20:6 117:18 293:22</p> <p><b>promoting</b> 27:6 74:19</p> <p><b>prompt</b> 65:3</p> <p><b>proof</b> 86:22 227:7</p> <p><b>proper</b> 90:6 133:18 213:22 287:10 305:7</p> <p><b>properly</b> 42:17 49:11 60:19 212:19</p> <p><b>proportion</b> 12:1</p> <p><b>proposition</b> 77:16 85:5,12</p> <p><b>pros</b> 142:21</p> <p><b>prospective</b> 23:11 23:16 34:21 49:21 70:7,14 79:9,18</p> <p><b>prospectively</b> 42:19 268:9</p> <p><b>protect</b> 228:14</p> <p><b>protecting</b> 122:10 214:12</p> <p><b>protections</b> 25:6</p> <p><b>protects</b> 76:4</p> <p><b>protein</b> 296:12,17 296:18,21</p> <p><b>proteinosis</b> 296:3</p> <p><b>proteins</b> 129:21 212:18 296:8</p> <p><b>protocol</b> 58:4 97:2 157:6 161:20 171:9 192:22 216:7</p>	<p><b>protocols</b> 57:15 157:13 161:20 170:12 306:7</p> <p><b>proud</b> 282:9 293:10</p> <p><b>proven</b> 177:4 302:16</p> <p><b>provide</b> 6:15,21 7:8 8:6,21 14:4,8 14:13 16:1 20:21 21:1 25:13 32:20 38:10 44:7,12 59:15 63:12 75:17 76:20 78:2 85:3 85:11 122:2 132:21 133:18 146:1 162:20 181:4 187:17 242:8 255:2 285:9 290:20 291:4 292:16 312:3</p> <p><b>provided</b> 141:2 292:18 308:5</p> <p><b>provider</b> 216:17</p> <p><b>providers</b> 25:13 122:1 216:9 305:15</p> <p><b>provides</b> 32:9 33:6 34:14 35:9 241:12</p> <p><b>providing</b> 15:19 21:7 54:4 179:19 207:3 294:19 306:13</p> <p><b>public</b> 1:7 2:2 5:4 8:5,6,14,17,20 9:4 61:22 115:10 123:21 147:5 148:12 168:7 178:4 179:2,11,20 214:12 253:21 256:14 265:11 274:20 283:3,6,12 283:21 284:17,22 286:5,12,17</p>	<p>306:14 311:5 312:1,7 314:13,20 315:1,21</p> <p><b>publications</b> 83:16</p> <p><b>publicly</b> 113:20</p> <p><b>publish</b> 106:6</p> <p><b>published</b> 301:13 301:16</p> <p><b>publishing</b> 39:18</p> <p><b>puff</b> 182:16</p> <p><b>pull</b> 35:16 236:9 277:6</p> <p><b>pulling</b> 54:1</p> <p><b>pulmonary</b> 12:15 12:20 64:3 169:9 295:22 296:3 298:13</p> <p><b>pulmonologist</b> 191:17</p> <p><b>purchase</b> 4:6</p> <p><b>purchased</b> 4:2</p> <p><b>purpose</b> 20:5 34:10 49:1 63:4 72:15 73:10 74:1 80:1,2 81:5,6 85:15 86:1 98:15</p> <p><b>purposes</b> 7:16 24:6 52:9 63:12 73:13 154:16 176:11 242:16 248:6 250:4,16 285:9 300:2</p> <p><b>pursue</b> 192:15</p> <p><b>pursued</b> 205:20</p> <p><b>push</b> 34:17 137:12</p> <p><b>pushback</b> 110:1 170:19</p> <p><b>pushes</b> 151:21</p> <p><b>pushing</b> 219:7</p> <p><b>put</b> 49:14 62:1 69:6 88:16 102:4 106:6,8 107:16 135:19 138:19</p>
---	---	--	--

139:10 144:7 151:2 173:17 176:10 178:4 206:4,9 221:12 229:15 231:2 244:17 245:13 247:20 248:3 251:15 258:8,8 274:13,15 <b>puts</b> 261:11 276:13 <b>putting</b> 46:12 178:12 179:15 207:17 250:16 275:20	<b>queried</b> 164:11 <b>queries</b> 90:22 164:10 <b>question</b> 31:8,12 43:14 45:14 46:2 47:21 48:14 50:7 60:12 62:13 63:22 64:16,21 65:3,12 66:3 78:8 86:3 98:1 101:8 106:1 112:7,8,15 113:12 155:20 156:6,16 163:12 168:2,12 175:16 176:22 178:10 198:13 201:4 202:8,12 210:8 214:21 219:21 226:16,16 228:7 254:6 256:22 261:15 269:2,5 272:18 273:12 279:19 282:7,8 <b>questioning</b> 208:22 <b>questions</b> 3:20 4:12 5:9,10 7:8 9:19 26:5 27:14 31:11 37:20 45:13 45:16,18 54:22 55:8 59:12,13,18 59:19 63:16 66:1 68:6,8 75:2 101:19,21 105:10 105:20 107:9,21 112:10 155:3 156:3 165:12 175:16 177:11 178:17 180:11,11 181:12,12,13 191:10 198:3 203:16 224:22 225:19 233:1 268:21 273:9	276:3 314:4 <b>quick</b> 53:17 58:8 65:16 178:20 215:2 <b>quicker</b> 259:10 <b>quickly</b> 29:4 56:15 64:1 80:13 104:6 122:9 182:20 183:13 188:16 210:1 226:20 240:5 264:10 <b>quite</b> 34:8 35:13 36:4 121:20 157:18 182:3 184:16 185:13 195:17 205:15 216:4 217:8 221:9 237:1 265:22 274:7 281:11 282:10	<b>range</b> 13:15 31:22 42:16 134:6 <b>rank</b> 115:9 <b>rapid</b> 304:20 <b>rapidly</b> 120:22 173:19 209:3 <b>rare</b> 1:2,3 2:2,3,8 2:10,22 3:3,5 4:16 6:2,5,7,10,12,18 7:4,20 12:4,6 13:1 13:3,7,8,16,17,22 13:22 14:2,3,19 14:20 15:9,11,13 16:22 18:3,16 19:19 20:2,7 21:14 22:1,5,9,10 22:13,18 23:20,21 24:8 29:1 30:16 30:21 31:1 35:4 41:5,10 44:8 45:1 45:2 48:6 50:8 53:7,14 55:11 56:10 57:11 58:21 60:17 66:13 67:10 68:4 70:22 71:1,4 72:21 74:11,16 75:6,8,14,18 76:11,20 77:7 80:16 85:2 90:1 94:18 97:20 101:14 102:7 104:8,15 108:9,16 109:3 116:9,20 117:2,6,9,21 118:7,8,14,17 119:19 120:9,12 121:3 122:22 123:10,20 126:14 126:21 127:3,3,5 127:8,16 129:5,14 130:6,12,19 131:19 134:3,13 134:19 135:4 136:6 138:13,21
<b>q</b>			
<b>qualification</b> 60:2 <b>qualified</b> 159:14 160:2 315:7 <b>qualifying</b> 137:5 <b>qualitative</b> 78:22 <b>qualities</b> 301:18 <b>quality</b> 24:16 25:10 26:2 27:22 28:5 32:16 34:9 35:1,8 36:13,21 37:22 38:12,16 48:2,5 49:12,17 52:20 53:21 64:16 73:21 95:6 113:2 124:13 131:22 132:2,5 174:11 189:2 298:2,15 301:14 306:16 <b>quantifiable</b> 134:16 <b>quantifying</b> 84:19 85:10 <b>quantitation</b> 84:16 <b>quantitative</b> 67:14 75:11 76:17 113:18			
		<b>r</b>	
		<b>r&amp;d</b> 67:8 <b>races</b> 243:18 <b>radar</b> 75:5 100:10 100:16,16 107:17 107:19 <b>radiation</b> 114:18 115:6,13 <b>radiologic</b> 240:21 <b>radiological</b> 24:17 130:2 248:8 <b>radly</b> 304:19 <b>raise</b> 7:9 155:5 162:11 183:14 228:6 286:8 <b>raised</b> 65:1 229:2 301:19 <b>raising</b> 65:13 143:1 <b>ran</b> 10:19 246:2 <b>randomize</b> 15:6 <b>randomized</b> 32:20 162:19 239:2 298:9	

138:22 139:1,2,2 139:6 140:18 141:7,13 142:10 144:17 146:4 148:18,20 149:9 149:18 151:3 156:20 158:14 159:3 163:7,13,14 165:9 166:8 169:15 171:15,17 176:15 178:9,10 182:10 183:7 184:2,3 185:9,17 186:8 187:11 188:3 189:7 193:20 207:6,14 213:12 221:7 222:4 226:18,19 227:11 230:22 232:14,21 233:12 236:2 237:6,7 238:5,9,12,17 240:8 241:20 246:20 248:2 249:21 250:4 251:11 252:2 253:1 257:3 260:14,15 265:2 265:19 266:2 269:8 271:18 273:16 277:13 278:4 282:2,3 284:5,6 285:12 286:20 287:3 288:13,17 289:3,6 289:13 290:18,22 293:1,4,6,8,11,16 293:19 294:1,3,4 294:8,15,16 295:3 295:14,17 296:6 297:8 298:20 299:21,22,22 300:2 301:15 303:1,9,11,12,15	303:16,21 304:13 304:15,17 305:7 305:10,11 312:20 312:22 313:8,10 313:12,17 <b>rarity</b> 260:17 <b>rate</b> 12:20 42:9 265:22 288:7 289:17 <b>rationale</b> 213:6 <b>reach</b> 43:21 104:12 270:4 <b>reached</b> 184:3 214:17 242:8,15 269:17 <b>reaching</b> 111:6 241:5 256:1 <b>reaction</b> 278:11 <b>read</b> 183:11 201:20 242:11 <b>ready</b> 41:2 43:7 91:13 276:16 280:7 <b>real</b> 14:15 15:15 15:15,16,16 16:2 16:6,10,10,14,14 16:18,19 17:4 25:20 27:4,13 28:3 54:2 94:17 122:8 179:9 184:14 185:14 210:2 231:16 <b>realistically</b> 203:13 <b>reality</b> 99:5 113:6 170:17 235:16 <b>realize</b> 42:21 53:9 79:15 93:6 140:3 140:8 219:4 222:22 235:22 268:15 280:3 300:9 <b>realized</b> 90:10 92:15 114:2	183:17 <b>realizes</b> 166:9 <b>really</b> 23:2,4,12,15 24:17,21 25:13,15 25:17,21 26:18 29:4 32:12 33:1 34:9,16,17,17 35:9,20 36:21 37:3 40:3 42:8,13 42:22 43:6,10 46:6 47:9 48:16 48:22 49:9 50:16 52:21 54:4 59:11 63:11 68:5 69:6 69:20 71:15 72:1 73:9,14 77:16 78:13 80:7,9,11 81:6,17,21 82:17 82:21,22 83:1,10 83:10 84:21 85:9 86:7,15,22 88:1 88:22 89:7,12,16 89:20 90:3 92:2,8 92:15 93:19,21 94:6,8 95:16,19 95:21,21 96:3,11 96:11,13,14,22 97:1,7 99:12 101:1 102:10,14 102:18 103:10 108:9 109:7 111:14,17 115:18 116:10 120:20,22 122:18 131:12 134:16,20 135:15 136:1,3 139:7,8 141:10 142:1,2,4 143:2 145:20 149:18 150:5 151:12,15 153:5 153:20 154:8,12 155:22 156:5 157:20 158:3,10 169:3 170:8,8,15	175:5,12 179:2 185:15 186:13,22 192:10,20 193:10 194:16,21 196:17 198:6,7 200:14,15 202:14,15,22 203:1 205:4,7 206:2 207:4,5,13 207:19 208:17 209:18 210:11 214:17 216:1,1,11 216:12,20 217:19 218:6,7,8,10,16 218:18 219:3,4 220:20 221:17,18 222:3,5,16,20 223:10,16,21 224:7,11 229:7 230:6 231:14,15 232:7 235:5 242:14 243:7 248:12 249:2,12 250:1,11 251:16 253:4,18 254:11 255:21 256:7,14 257:2 258:2 260:15 261:13 262:1,17 264:9 265:22 266:18 267:10,12 268:7 268:18 270:1,9,19 270:22 271:1,16 273:12 276:12,19 277:1,8 278:1,4,7 284:14,16 299:13 311:4 312:2 <b>reason</b> 3:16 187:20 209:21 234:2 240:16 283:5 <b>reasonable</b> 95:18 151:14,15 152:6 162:6,16 264:12
--	--	--	--

<p><b>reasons</b> 64:9 89:5 103:20 143:7 153:19 178:1</p> <p><b>rebranded</b> 111:19</p> <p><b>receive</b> 5:19 17:15 45:16 160:3 184:12 191:15 192:17 287:9,22 303:14</p> <p><b>received</b> 10:22 11:4 159:9,10 190:9 193:6 204:8 303:2</p> <p><b>receiving</b> 74:18 110:1 184:10 208:4,19,20</p> <p><b>receptive</b> 191:10</p> <p><b>recessive</b> 183:18</p> <p><b>recipients</b> 144:2</p> <p><b>recognize</b> 174:20 207:11 249:9 251:3 257:7 291:15 311:13</p> <p><b>recognized</b> 10:8 303:4 309:22</p> <p><b>recommend</b> 4:4</p> <p><b>recommendation</b> 44:20</p> <p><b>recommendations</b> 43:20 44:3 57:4 141:11 291:11,19 292:16,17</p> <p><b>reconvene</b> 180:16</p> <p><b>record</b> 12:3 15:20 164:2,5 302:17 315:9 316:5</p> <p><b>recorded</b> 5:7 315:6</p> <p><b>recording</b> 315:8 316:4</p> <p><b>records</b> 23:9 26:21 27:20 35:16 124:22 164:4,15 164:19</p>	<p><b>recovery</b> 297:4</p> <p><b>recruit</b> 156:4</p> <p><b>recruiting</b> 156:7</p> <p><b>recur</b> 298:7</p> <p><b>recycle</b> 212:18</p> <p><b>recycled</b> 212:20 212:21</p> <p><b>recycling</b> 213:3</p> <p><b>red</b> 270:8,12 272:11 285:18</p> <p><b>redesigned</b> 95:4</p> <p><b>reduce</b> 259:10 304:13</p> <p><b>reduced</b> 315:6</p> <p><b>reengineer</b> 133:1</p> <p><b>refer</b> 23:4,15 28:19 275:10,15</p> <p><b>referenced</b> 203:18</p> <p><b>referrals</b> 100:20</p> <p><b>refers</b> 28:17</p> <p><b>refined</b> 138:12 274:16,18</p> <p><b>reflect</b> 11:13,14 204:2</p> <p><b>reflections</b> 215:16</p> <p><b>reflects</b> 57:19</p> <p><b>reform</b> 138:10</p> <p><b>reframe</b> 210:8</p> <p><b>regard</b> 44:3 149:5</p> <p><b>regarding</b> 6:17 20:13 21:2 43:22 67:20 273:22 300:18</p> <p><b>regards</b> 47:21</p> <p><b>regimen</b> 288:22</p> <p><b>regional</b> 110:14 172:2</p> <p><b>regions</b> 103:18</p> <p><b>register</b> 286:4 314:10</p> <p><b>registered</b> 54:21 285:2 314:19</p> <p><b>registers</b> 295:14</p>	<p><b>registration</b> 3:12 3:21 5:11,20 8:10 165:20 247:22 314:15</p> <p><b>registries</b> 25:20 26:5,13,15 34:21 35:7 37:13,20,22 38:9,13,15 44:9 50:1 58:18 75:8 75:22 77:1,2,9 78:9 80:18,21 81:19 85:17 89:20 99:18 107:18 110:14 111:16 125:1 131:10 294:11,13 303:19</p> <p><b>registry</b> 6:9,18 15:10 20:14 21:3 23:15 26:3,20 31:15 33:10 37:14 37:18 44:2 46:18 47:1 54:15 63:2 65:4 66:13 67:21 69:14,17,18,20 70:1,12 75:6 78:22 81:16 82:3 82:4,20 83:11,12 85:15,22 86:11,16 87:1 90:2 94:3 97:11 102:12 104:18 105:11 107:4,8,11 108:4 109:22 110:1 111:8,19,22 112:2 134:11,12 152:12 160:10 169:12 226:21,22 294:21 295:6,12 313:1</p> <p><b>regular</b> 88:11 95:18 262:16</p> <p><b>regulate</b> 123:4 307:4</p> <p><b>regulated</b> 124:17</p>	<p><b>regulates</b> 21:16,17 194:7</p> <p><b>regulation</b> 10:13 236:22 261:16 265:12 308:20</p> <p><b>regulations</b> 103:18,22 154:2 202:15 214:12 260:19 261:1,3,7 307:1</p> <p><b>regulator</b> 52:2</p> <p><b>regulators</b> 56:18 74:5 123:14 194:1 204:6 215:13 241:6 262:14 264:2 280:8</p> <p><b>regulatory</b> 16:16 17:16 18:21 20:15 24:20 27:7,9,13 28:4,7 37:20 40:4 45:9 46:15 52:11 58:11 74:4 83:18 113:21 121:12,21 122:3,4 125:3 133:3 138:10 139:12 146:10 147:1,9 149:7 150:3,7,8,10,11 151:11 157:15 165:18 170:20 181:5 188:20 195:12 201:7,8 202:5,16 203:19 205:8 207:15 236:12 241:10 247:4 251:1 257:19 274:20 275:1 279:9 290:13</p> <p><b>reimbursement</b> 162:14 167:12 301:7,11</p> <p><b>reinforce</b> 117:13</p>
---	---	--	---

<b>reinvent</b> 149:19 <b>reinvented</b> 150:1 <b>reinventing</b> 94:21 <b>reinvigorated</b> 297:14 <b>reiterate</b> 197:7 <b>relapses</b> 144:16 145:3 <b>related</b> 22:14 30:13 105:17 197:10 198:13,20 230:9,10 232:15 315:11 316:7 <b>relates</b> 84:7 126:20 176:2 203:17 <b>relating</b> 260:16 <b>relationship</b> 214:6 280:19 281:5 <b>relationships</b> 111:12 <b>relative</b> 315:13 316:10 <b>relatively</b> 140:18 149:3 161:10,11 238:6 <b>relay</b> 243:18 <b>release</b> 27:22 <b>released</b> 28:2 48:20 179:12 <b>relevance</b> 25:9 28:5 <b>relevant</b> 55:20 60:22 83:10 113:9 123:2 300:3 302:2 302:4 <b>reliability</b> 25:9 28:5 113:3 <b>reliable</b> 30:3,6,6,8 <b>relief</b> 192:3 308:4 <b>relies</b> 229:20 <b>relook</b> 264:14 <b>relying</b> 135:10	<b>remain</b> 7:13 13:17 132:9 286:1,8 298:18 <b>remaining</b> 8:20 <b>remains</b> 13:18 131:8 <b>remapping</b> 112:18 <b>remarkable</b> 120:7 154:16 234:14 265:22 <b>remarks</b> 6:6,15,22 8:19,21 9:10 10:4 21:22 31:5 52:11 126:9 285:19 312:4,6 <b>remember</b> 51:5 64:7 102:22 176:19 216:22 266:12 <b>reminded</b> 193:15 217:20 <b>reminder</b> 285:22 <b>remiss</b> 301:6 <b>remission</b> 145:17 <b>remote</b> 8:2 <b>removed</b> 175:1 <b>removing</b> 217:21 <b>renal</b> 162:8 <b>renewed</b> 187:1 <b>reorganization</b> 24:22 61:19 181:19 <b>repeat</b> 140:15 <b>repeated</b> 287:19 <b>repeatedly</b> 72:3 <b>replaced</b> 142:7 <b>replacing</b> 272:2 300:16 <b>replicate</b> 76:19 <b>report</b> 90:21 91:9 100:4 206:6,7 307:13 <b>reported</b> 1:7 26:8 26:9,9 60:3 62:8	95:6 99:7 124:21 134:22 137:4,8,11 155:10 <b>reporting</b> 133:10 <b>reports</b> 17:20 42:5 42:11 <b>repository</b> 157:21 <b>represent</b> 27:18 78:5 <b>representation</b> 129:3 289:18 <b>representative</b> 39:11,13 264:5 <b>representativeness</b> 36:22 38:17 <b>representatives</b> 37:10 190:2 253:13 312:16 <b>represented</b> 96:19 258:7 <b>representing</b> 7:15 280:16 290:14,16 309:11 <b>represents</b> 13:3 <b>reproducible</b> 98:7 <b>request</b> 18:7 276:10,18 277:7 278:8,9 <b>require</b> 157:15 158:20 188:11 218:20 219:12,13 219:16 230:7 261:18 <b>required</b> 102:11 297:21 <b>requirement</b> 203:3 <b>requirements</b> 17:1 45:9 122:3 133:10 165:19 201:7,8 206:17 292:2,4 <b>requires</b> 32:7 35:18 36:8 287:16	<b>requiring</b> 261:7 <b>research</b> 10:21 13:13 37:8 39:19 46:8 62:11,12 64:12,19 67:7,11 69:12 70:2 71:4 74:12 75:1 82:8 82:18,19 108:10 109:12 111:10 114:5 119:8,11 126:10,11,13 127:1,10 129:12 156:9,10 163:7 174:7,8,14 199:20 225:3,6 226:20 233:13 235:3,4 240:22 242:10,11 250:13 265:3,11 279:19 293:9 297:9 298:7 304:2 <b>researched</b> 204:20 <b>researcher</b> 10:9 155:9,21 277:15 <b>researchers</b> 63:11 63:18 70:4 107:10 116:12 121:6 156:8 175:21 191:7,7 233:22 242:9 255:10 312:16 <b>researching</b> 116:22 <b>residency</b> 11:2 115:13,14 <b>resident</b> 11:2 <b>resistance</b> 191:3 <b>resistant</b> 192:1 193:12 199:4 <b>resource</b> 44:13 50:3 80:22 112:4 124:10 126:18,19 217:1 <b>resources</b> 48:18 50:2 53:10 80:17
--	---	---	---

102:4,5,6,9,11 103:3 299:12 304:10,12 <b>respect</b> 28:3 59:10 60:20 63:9 109:7 248:19 249:20 250:2 261:6 292:3 <b>respectful</b> 9:7 <b>respecting</b> 263:21 <b>respiratory</b> 29:16 159:8 190:17 296:9 <b>respond</b> 53:13 144:21 <b>responding</b> 206:2 304:10 <b>response</b> 16:17 92:9,12 93:1 <b>responsiveness</b> 203:19 <b>rest</b> 148:2 151:21 152:4 <b>restrict</b> 152:16 <b>restricted</b> 63:6 <b>restrictive</b> 160:10 <b>restrooms</b> 3:13 <b>result</b> 181:19 200:17 287:15 310:12,17,19 <b>results</b> 12:16 87:18,20 88:13 227:16 230:8 298:11,16 <b>retriever</b> 245:3 <b>retrospective</b> 23:8 33:11 79:9 <b>retrospectively</b> 42:18 <b>return</b> 108:8 132:15 <b>reversal</b> 225:14 <b>reverse</b> 212:10 <b>review</b> 3:7,8 5:22 17:19 57:14	<b>reviewing</b> 22:10 241:9 300:22 <b>reviews</b> 23:8 33:11 46:15 <b>revisit</b> 125:20 <b>revolution</b> 131:4 221:10 <b>rewarded</b> 235:9 <b>rewards</b> 108:22 <b>rhiannon</b> 252:13 252:14,14 254:1,2 254:14,19 269:6,9 269:15 270:5 <b>rich</b> 67:1 248:16 <b>richards</b> 4:10,14 <b>right</b> 3:15 21:5 48:8,12 50:9 59:12 62:3 68:9 68:22 72:2 77:15 77:18 78:7 80:5 86:9,15 87:8 89:16,19 100:17 105:19 107:12 109:19 114:8 118:10 129:8 132:1,11 136:18 140:7 145:9 147:19 149:20 152:11 153:8,9,10 153:12 154:4 162:9 163:14 164:20 166:22 170:8 171:3 180:21 184:18 191:20 195:13 196:5 198:11 200:17 202:10,20 220:4,9 221:2,5 222:10 231:7 244:2 250:20 256:4,4 257:14 258:6 259:12 272:6,16 273:5 274:6 275:8,9,18	278:15,19 279:2 279:16 281:6 282:10 308:6 <b>rights</b> 246:5 301:20,20 <b>rigid</b> 16:3 <b>rigor</b> 53:20 54:9 79:1,4 <b>rigorous</b> 32:8,21 50:19 90:19 124:11 302:7 <b>rigorously</b> 49:16 55:16,22 <b>rigorousness</b> 50:17 <b>ripple</b> 217:14 <b>risen</b> 11:22 <b>risk</b> 21:20 65:8 136:20 137:10,17 192:9 203:21 204:4,10,13 205:10,22 206:5 206:12 207:5,8,11 207:22 208:5,7,8 208:13 209:16 210:11 211:7 217:17,18,18 218:4,21 289:1,4 <b>risks</b> 205:2,6,6 208:17 211:15 213:15 214:7 218:4 219:15 287:11 310:19 311:3 <b>risky</b> 143:19 242:22 <b>road</b> 90:17 <b>roadblocks</b> 216:15 <b>robust</b> 35:10 36:9 42:22 54:4 90:21 125:2 <b>rock</b> 182:14	<b>rodent</b> 292:9 <b>role</b> 21:1 70:14 81:2 111:10 122:21 163:14 185:1 194:15 216:3 255:13 304:16 <b>roles</b> 10:17 15:17 78:15 114:19 196:17 <b>rolled</b> 17:11 <b>romberg</b> 155:8 <b>romero</b> 67:12 68:21 75:10,11 83:5 97:8 104:13 106:12 111:1 112:14 <b>romero's</b> 86:7 <b>room</b> 2:15 3:11,13 3:18 4:1,7 5:2,8 5:12,14,17 7:7,9 7:13 8:18 9:9 20:17 45:15 65:22 66:10 112:9 116:8 116:18 130:11 140:7 157:9 168:2 168:17 170:10,18 175:16 178:17 180:11,12 190:1,2 197:4 203:9 268:21 282:13 285:7 299:4,10 301:9 302:15 312:10 <b>rooms</b> 3:17 <b>roots</b> 242:6 243:19 284:11 <b>round</b> 253:17 <b>rounds</b> 272:13 <b>route</b> 229:16 <b>routine</b> 15:19 <b>routinely</b> 37:17 <b>rows</b> 286:6
---	---	---	---

<b>rules</b> 8:22 63:17 102:17 104:1 <b>run</b> 81:7 89:21 104:17 168:5 225:18 282:4 <b>running</b> 128:6 180:4 261:5 <b>runs</b> 233:12	<b>saw</b> 12:3 50:6 71:6 71:18 191:5 224:15,16 <b>saying</b> 71:22 89:8 93:20 98:4 130:18 156:18 162:7 178:1 187:5 203:2 216:21 265:21 284:6 <b>says</b> 88:7 218:1 302:3 <b>scale</b> 118:9 140:4 140:5 220:8,18 224:12 <b>scales</b> 99:7 <b>scarce</b> 136:18 <b>scarring</b> 12:17 190:17 266:15 <b>scary</b> 209:12 <b>schedule</b> 128:7 <b>schema</b> 122:4 <b>schmo</b> 267:21 <b>school</b> 10:19 109:6 115:7 144:16 293:18 <b>schools</b> 250:15 <b>science</b> 29:3 46:14 47:13 61:21 67:12 120:22 124:14 125:18 126:6 136:2,3,12,15 148:3,4,5 179:19 242:22 244:15 264:10,13 301:3 <b>sciences</b> 178:3 233:9 <b>scientific</b> 11:17 13:15 47:4,12 79:1,3 126:16 165:18 213:6 242:17 261:14 <b>scientifically</b> 89:2 213:8	<b>scientist</b> 57:9 61:9 144:3 155:7 186:10 193:17 209:19 <b>scientist's</b> 46:12 <b>scientists</b> 40:21 41:10,18 42:1,21 43:5 57:21 69:2 145:20 183:9 234:16 262:15 264:21 265:8 <b>scientist's</b> 242:11 <b>scleroderma</b> 13:1 <b>sclerosis</b> 12:22 <b>scooped</b> 234:21 <b>scope</b> 79:11 81:22 102:21 <b>scratch</b> 107:8 <b>screen</b> 5:3 231:2 <b>scuttle</b> 261:3 <b>search</b> 164:9 <b>seat</b> 66:7 286:8 <b>seats</b> 5:18 <b>second</b> 20:18 65:7 66:8 72:6 73:6,9 86:18 96:14 118:1 132:19 151:6 152:15 184:14 185:4 208:22 243:14 277:7 285:17 292:3 <b>secondhand</b> 64:10 <b>sectional</b> 23:10 <b>sector</b> 48:4 <b>secure</b> 274:12 <b>see</b> 5:12 8:2 16:4 22:16 31:6,8 35:20 40:19 45:1 51:15 58:4 65:10 71:16 72:4 77:3 86:1 97:18 104:21 116:10 119:16,19 120:7 121:19 123:12 126:12	136:8 142:3 148:14 153:11 155:21 157:9 163:2 165:12 171:7 175:15 177:17 185:14 206:18 213:5 218:11,11,12 219:3 220:20 221:14 227:22 236:3 247:21 248:13 250:14 277:18,19,22 283:8 284:11 287:8 304:6 307:15,18 <b>seeing</b> 22:1 35:21 37:3 78:20 96:2 117:8 121:11 130:8 134:1 137:9 137:15 146:8 159:18,21 178:4 192:3 237:12,14 239:16 240:8 241:3,6 307:14 <b>seeking</b> 39:14 288:18 <b>seen</b> 13:6 36:6 64:14 82:22 85:17 85:22 106:8 118:13 120:3,5,13 133:14 146:3 165:15 202:2 234:14,15 240:10 242:21 253:12 <b>sees</b> 189:5 283:7 <b>selected</b> 37:13 <b>selective</b> 42:6 53:8 <b>self</b> 176:4 206:7 300:4 302:13 <b>sell</b> 108:18 <b>selling</b> 108:19 <b>seminars</b> 162:12
<b>s</b>			
<b>sacrifice</b> 109:4 <b>sadly</b> 303:11 <b>safe</b> 14:17 18:1,16 36:11 205:20 245:16 294:7 313:16 314:20 <b>safely</b> 228:11 <b>safer</b> 259:9 <b>safety</b> 15:4 16:16 17:20 21:19 122:10 124:3 151:14,16 152:6 162:20 202:21 205:19 206:4 213:22 228:14 245:16 259:14,16 259:22 <b>sales</b> 243:18 244:18 <b>sample</b> 98:20 157:14 158:20 <b>samples</b> 156:13 157:6,12 188:17 <b>samulski</b> 242:15 <b>san</b> 115:15 <b>sandwiches</b> 4:6 <b>sandy</b> 163:6,6,12 <b>sarcoma</b> 117:1 <b>satisfaction</b> 246:13 <b>satisfy</b> 17:1 201:6 <b>satisfying</b> 202:2 <b>save</b> 86:10 <b>saving</b> 301:21			

<p><b>senate</b> 306:19  <b>send</b> 57:15,15  314:1  <b>sending</b> 113:16  314:18  <b>senior</b> 6:16 19:16  267:6  <b>sense</b> 47:22 77:19  106:3 109:2 220:4  223:22 296:18  <b>sensitive</b> 92:4  <b>sensors</b> 158:19  <b>sent</b> 145:17  <b>sentence</b> 182:9  <b>sentiment</b> 299:9  <b>separates</b> 236:1  <b>september</b> 17:11  <b>sequence</b> 186:18  <b>sequencing</b> 30:14  187:10 304:14,21  305:3,9,14  <b>series</b> 42:5,11  <b>serious</b> 12:15  28:21 130:19  311:13  <b>seriously</b> 281:9  <b>serve</b> 24:3 28:12  55:21 69:4 82:22  87:4 114:21 147:7  250:3 293:10  301:9  <b>served</b> 8:11,19  11:2 115:2,5  <b>serves</b> 52:9  <b>service</b> 115:10  133:19 277:10  <b>services</b> 293:10  <b>serving</b> 181:20  <b>session</b> 6:8,11  15:8 30:12 82:3  181:3 194:6 197:6  268:20 284:16  <b>sessions</b> 123:20  188:2</p>	<p><b>set</b> 37:17 48:10  54:4 55:16,18  67:19 72:5,7 77:2  77:16 84:6 90:15  94:9 97:13,21  98:14 100:5,17,18  101:4 104:9  110:14 112:17  157:20 158:5,10  167:9,15 169:7,16  169:21 170:7,12  211:20 219:19  <b>sets</b> 37:18 72:13  74:6 99:14 103:10  104:4  <b>setting</b> 13:4 97:11  132:15 137:22  171:4  <b>settings</b> 16:3  293:17  <b>settled</b> 91:22  <b>settling</b> 154:5  <b>seven</b> 171:15,17  184:14 287:9  303:10  <b>severe</b> 190:19,20  205:15 289:16  296:10  <b>severely</b> 169:17  <b>severity</b> 84:5  <b>sex</b> 98:19 99:3  <b>shameless</b> 75:4  <b>shannon</b> 107:5  <b>shannon's</b> 107:5  <b>share</b> 8:18 31:17  70:11,16 71:10  72:9 74:9 83:4  86:14 108:22  110:22 111:14  154:20 157:6  189:3 198:18  241:1 248:18  259:21 269:22  273:22 274:11</p>	<p>283:10 294:14  <b>shared</b> 60:22 63:5  81:4,8 89:2  116:19 145:10,14  169:3 212:14  277:12 291:11  293:22 312:18  <b>shares</b> 277:12  294:6  <b>sharing</b> 7:17 8:3  9:8 90:6,9 95:8  104:4 106:9  116:15 155:2  156:22 170:16  196:9 224:4 290:6  <b>sharon</b> 93:11  <b>sheet</b> 301:22  <b>sheila</b> 175:17,17  242:1,2,2 258:14  258:15 271:4  <b>shelf</b> 244:21  <b>sheriffs</b> 307:13  <b>she's</b> 184:17 203:7  297:3,4  <b>shift</b> 13:4 264:14  <b>shifted</b> 217:11  <b>shifting</b> 218:7  <b>ship</b> 138:1 251:13  257:15  <b>shirt</b> 45:20  <b>short</b> 193:6  243:10,10 270:18  276:4 314:12  <b>shortly</b> 10:6  <b>shortness</b> 296:8  <b>shot</b> 184:14 213:6  <b>shoulder</b> 310:11  310:19  <b>shouldn't</b> 197:1  215:8 268:8  <b>show</b> 152:6 175:5  212:8  <b>showed</b> 212:17</p>	<p><b>shower</b> 109:5  <b>showing</b> 153:15  212:15 225:7  245:19  <b>shown</b> 204:20  234:10 288:6  <b>shows</b> 174:14  304:20  <b>shrink</b> 230:13  <b>shuren</b> 129:9,22  130:1 132:12  136:19 143:20  149:15 158:16  165:6 248:5  251:13  <b>shy</b> 111:3  <b>siami</b> 163:6,6,12  <b>sibling</b> 87:14  <b>sick</b> 72:3 296:13  <b>sicker</b> 289:20  <b>sickle</b> 252:15,18  <b>side</b> 25:8 38:22  39:3,4 40:1,1 56:6  98:17 99:9,10  132:18 138:8,8  148:9 152:19  162:15 176:1  207:17 277:6  287:17  <b>sides</b> 98:17  <b>sign</b> 3:12 4:11 8:8  8:9,13,15 86:12  125:21,22  <b>signature</b> 315:20  316:14  <b>signed</b> 286:4  <b>significant</b> 7:19  121:4 126:17,22  227:18 250:18  285:12 287:10,13  289:4,18  <b>significantly</b>  281:2,3</p>
---	--	---	---

<p><b>signs</b> 5:14</p> <p><b>silence</b> 3:9</p> <p><b>silos</b> 257:6,8</p> <p><b>similar</b> 15:5 32:15 33:16 34:2,8 50:10 102:19 111:6 157:3 195:18 204:5 273:19</p> <p><b>similarly</b> 289:11</p> <p><b>simple</b> 82:6,19 177:12 212:2 311:15</p> <p><b>simpler</b> 230:1,1</p> <p><b>simplification</b> 228:21</p> <p><b>simplify</b> 275:21</p> <p><b>simplistic</b> 98:20</p> <p><b>simply</b> 248:3 258:8 274:13</p> <p><b>simultaneously</b> 224:13</p> <p><b>singing</b> 182:15</p> <p><b>single</b> 32:2 34:16 78:2 92:1 98:11 100:1 112:16 143:2 148:11 164:19 189:17 214:3 220:3 229:4 242:12 249:11 271:10 274:15 291:22 292:8,8</p> <p><b>sinks</b> 76:2</p> <p><b>sister</b> 281:5</p> <p><b>sit</b> 231:3</p> <p><b>sites</b> 91:13,14,17 238:21</p> <p><b>sitting</b> 182:4,5 186:9 231:1 244:21 282:17 283:12</p> <p><b>situation</b> 56:9 162:1,4 192:14 214:13 215:7</p>	<p>301:6</p> <p><b>situations</b> 211:4 215:4</p> <p><b>six</b> 29:15 88:9 182:17 262:4 296:22</p> <p><b>size</b> 33:2,6 126:21 147:13 245:14</p> <p><b>skeptical</b> 245:11</p> <p><b>skiing</b> 182:13</p> <p><b>skills</b> 315:10 316:6</p> <p><b>skin</b> 212:5</p> <p><b>skull</b> 183:1</p> <p><b>slide</b> 9:20</p> <p><b>slightly</b> 180:13 210:8 299:6</p> <p><b>slim</b> 173:5</p> <p><b>slot</b> 286:5</p> <p><b>slow</b> 12:19 130:22 184:21 234:16</p> <p><b>slowed</b> 166:21</p> <p><b>slowing</b> 167:1</p> <p><b>sma</b> 29:12,18,20 30:10 73:7 159:5 159:6 164:13 176:2 235:15 271:15 303:1</p> <p><b>small</b> 20:8 33:2 53:9 126:21 129:20 132:14 133:5 136:10 139:17 140:4 146:5,15 149:2 150:16 152:3 160:21 167:3 187:18 194:22 198:9,10 212:5 219:13 224:21 237:10 245:13,13 249:20 250:4 251:18 252:2 262:6 270:21 278:18,19 279:11 279:12</p>	<p><b>smaller</b> 3:17 148:8 229:1,1 239:16,16 281:3</p> <p><b>smart</b> 234:8</p> <p><b>smile</b> 277:18</p> <p><b>smoke</b> 64:11 65:7</p> <p><b>smpokou</b> 182:2 199:13,14 205:3 220:22</p> <p><b>sms</b> 51:8</p> <p><b>snacks</b> 4:6</p> <p><b>social</b> 142:10 174:22 184:3 187:8 270:4</p> <p><b>societies</b> 26:1 37:12 142:22</p> <p><b>society</b> 308:9</p> <p><b>sole</b> 291:20</p> <p><b>solid</b> 237:19</p> <p><b>solution</b> 44:18 161:21</p> <p><b>solutions</b> 3:3 6:2 17:22 113:18 229:14</p> <p><b>solve</b> 99:20</p> <p><b>solved</b> 229:11</p> <p><b>somebody</b> 58:6 108:20 141:19 143:4 153:12 158:7 175:1 215:5</p> <p><b>somebody's</b> 11:9</p> <p><b>someplace</b> 164:21</p> <p><b>somewhat</b> 28:15 167:21</p> <p><b>son</b> 159:7 171:22 183:22</p> <p><b>songs</b> 182:16</p> <p><b>sons</b> 299:21</p> <p><b>sonya</b> 316:2,15</p> <p><b>soon</b> 41:11 201:17 227:5 262:3</p> <p><b>sooner</b> 295:18</p> <p><b>sophisticated</b> 17:21</p>	<p><b>sorry</b> 56:12 72:19 93:18 163:12 184:15 231:5 291:2</p> <p><b>sort</b> 11:16 49:6 53:18 58:14 67:19 68:5 70:14 78:18 78:21 79:22 86:15 88:5,10 95:7 103:13 105:15 106:2 136:20 138:3 144:4 146:3 146:4 167:7 170:22 204:1 215:6,13,17 232:16 237:5,12 237:21 261:8 263:19,20 264:18 266:20 267:6 268:12 269:12 281:4</p> <p><b>sorts</b> 129:21</p> <p><b>sounds</b> 128:14 157:10 266:20</p> <p><b>soup</b> 25:14</p> <p><b>source</b> 78:2 84:7 152:10</p> <p><b>sources</b> 23:9 24:7 25:11,20 26:3 77:12 83:9 84:2 125:3 136:5 310:22</p> <p><b>sovereignty</b> 167:8</p> <p><b>sox</b> 270:8,12 272:11</p> <p><b>space</b> 3:18 13:12 16:22 59:15 102:8 129:14 131:17,19 132:20 137:16 146:9,12 148:7 149:18 150:19 156:21 157:16,18 158:8 160:20 166:2,8 188:20</p>
---	--	---	---

220:9 223:17,17 228:8 232:3 246:10 249:6,8 251:1,2,2 259:18 262:16 275:7 294:20 300:2 <b>speak</b> 5:11 7:10 8:16 31:22 37:5 52:21 59:3 100:10 111:14 185:22 199:17 213:1 239:9 260:13 265:9 269:20,21 280:4 285:3 286:17 291:12 296:1 299:16 <b>speaker</b> 198:3 285:3,4,5 286:11 <b>speakers</b> 8:16 285:2 312:9 <b>speaking</b> 4:12 146:2 155:1 181:2 183:7 277:21 285:14,16 <b>speaks</b> 184:5 <b>special</b> 10:12 19:20 20:7 109:6 162:7 173:6,6 248:7 <b>species</b> 202:17 292:8,8 <b>specific</b> 23:13 50:13 57:4 60:20 106:14 119:20 151:9 171:4,5 190:12,12 194:19 208:8 218:5 221:15,18 233:1 239:4 241:13 251:6,7,7 274:19 295:15 <b>specifically</b> 12:7 79:8 146:14 163:8	<b>specifics</b> 24:9 <b>specified</b> 23:13 89:9 <b>specify</b> 65:6 <b>specimen</b> 158:21 <b>specimens</b> 158:11 <b>spectrum</b> 78:18 81:22 82:9 96:19 120:1 135:19 159:17 210:20 251:21 265:10 272:21 303:20 <b>speed</b> 121:12 122:7,13 <b>spend</b> 22:22 95:20 97:3 108:10 <b>spending</b> 111:11 121:4 155:13 304:22 <b>spent</b> 74:14 116:21 208:21 240:12 <b>sphere</b> 117:9 120:15 <b>spheres</b> 257:5 <b>spikes</b> 1:7 <b>spinal</b> 29:9,10,12 51:6 71:17 120:4 154:10,13 188:15 <b>spinraza</b> 159:13 188:15 <b>spirit</b> 201:11 301:4 <b>spite</b> 151:17 <b>splice</b> 189:14 <b>splicing</b> 188:9 189:19 211:21 212:3,9 <b>spoke</b> 53:3 110:2 168:9 183:9 300:17 <b>spoken</b> 121:15 176:7 195:8	<b>spokespeople</b> 111:13 <b>sponsor</b> 35:16 39:14 186:4 293:11 <b>sponsoring</b> 142:20 <b>sponsors</b> 18:10 43:21 168:5 169:1 170:15,18 274:1 <b>sponsors'</b> 273:20 <b>sport</b> 234:7 <b>sports</b> 270:7 <b>spread</b> 138:4 155:16 156:1 255:20 <b>spreadsheet</b> 82:21 <b>spreadsheets</b> 100:20 <b>spring</b> 62:18,19 <b>spur</b> 135:16 <b>spy</b> 168:13 <b>stability</b> 292:10 <b>stable</b> 169:20 170:4 209:22 <b>staff</b> 5:11,11 6:16 9:15 19:16 58:22 162:12 313:20 314:1,16 <b>stage</b> 19:11 33:17 33:17 67:19 128:6 168:16 180:20 186:9 190:1 230:16 231:1,17 244:3 253:15 <b>stages</b> 143:3 241:11 <b>staggering</b> 174:14 <b>stairs</b> 89:19 <b>stakeholder</b> 26:6 26:19 34:20 37:10 38:11,15 39:1 43:4 44:6 49:9 52:7,16 58:13,17 58:20 59:17,21	121:15 <b>stakeholders</b> 2:10 3:2 4:17 6:1,7 13:19 15:9 17:2 21:12 26:1 30:22 37:12 54:6 59:1 96:15 107:9 108:12 116:11,17 196:14 253:14 257:16 311:12 <b>standard</b> 17:20 25:16 90:20 91:8 122:10,14 124:3 133:4 151:13 152:2 169:2 180:8 213:10 292:1 <b>standardization</b> 75:17 89:1 112:16 112:19 113:2,11 273:13,18,22 <b>standardize</b> 99:22 <b>standardized</b> 88:12 91:1 <b>standardizing</b> 88:20 274:6 <b>standards</b> 98:1,14 98:14,15,16 100:11 112:13 167:4,15 228:10 228:12,13,18 229:1 260:2 292:7 300:13 304:5 <b>standing</b> 170:7 <b>standpoint</b> 39:8,8 189:4 206:13 257:11 275:2 <b>stands</b> 75:5 <b>stars</b> 215:7,9 216:20 <b>start</b> 21:7 27:20 29:14 31:17 41:11 45:19 46:22 47:10 47:14,22 48:10 55:8 61:3 68:9,10
--	--	--	---

68:15 69:17 80:2 82:13,14 86:3 98:3 99:6 104:18 105:1 107:8 113:1 140:9 148:19 160:6 165:21 168:20 179:10 183:14 194:2 209:1,11 233:3 253:6 254:1,13 269:15 270:15 274:4 276:9,20 278:1 284:22 313:22 <b>started</b> 41:14,20 53:19,22 54:13,13 70:4 74:16,17 79:13 80:20,21 81:1,3 90:7 91:7 93:21 98:22 99:1 100:19 103:21 107:8,11 108:4 109:22 135:21 144:22 180:22 183:7,15 193:7 226:22 242:4,6 244:13 253:17 262:21 267:2 270:11 293:14 <b>starting</b> 41:12 53:14 67:18 84:1 87:1 163:2 225:20 225:22 262:11 269:9 <b>starts</b> 40:12 47:5 47:13 265:16 <b>state</b> 7:13,14 226:12 249:1 266:1 306:18 308:10,17 315:21 <b>statement</b> 64:7 282:9 299:9 <b>statements</b> 4:19 250:15	<b>states</b> 91:12 109:16 110:4 149:22 164:2 167:13 263:4 281:18,22 293:12 300:14 305:3 306:20 <b>statins</b> 228:19 <b>statisticians</b> 57:17 <b>statistics</b> 118:21 <b>statutory</b> 58:11 <b>stay</b> 9:16,17 185:6 247:16 314:3 <b>steadfast</b> 298:19 <b>stein</b> 21:5,7,9 31:18,19 41:21 43:16 44:4 48:15 51:17 53:17 55:14 58:8 60:1 61:18 62:20,22 64:20 75:15 <b>stein's</b> 59:10 <b>stems</b> 75:19 <b>step</b> 17:21 32:17 45:14 68:18 80:8 82:18 86:17,18 109:1 121:8 158:14 209:6,6 212:14 222:4 251:16 253:5 270:21 271:22 <b>stephen</b> 114:14 115:17 304:19 <b>stepped</b> 245:22 <b>steps</b> 170:6 182:22 209:6 229:13 <b>steroidal</b> 173:4 <b>stewardship</b> 108:15 <b>stick</b> 65:22 97:6 276:19 <b>stifle</b> 97:14 <b>stipend</b> 286:15	<b>stood</b> 27:17 <b>stop</b> 5:19 78:6 211:3 247:1 252:9 264:15 306:7 308:22 <b>stopped</b> 187:16 298:6 <b>storage</b> 183:12 <b>store</b> 86:13 <b>stored</b> 110:5 <b>stories</b> 238:4 298:1 <b>story</b> 183:15 184:5 189:3 193:6 222:11 274:5 <b>straightforward</b> 208:6 <b>stratakis</b> 225:6 <b>strategic</b> 66:19 <b>strategy</b> 17:13 <b>streamline</b> 17:19 18:6 240:22 241:13 <b>streamlined</b> 137:5 216:7,19 <b>street</b> 175:4 243:2 245:18 308:4 <b>strength</b> 94:15 <b>strengthen</b> 18:4 <b>stress</b> 288:22 <b>stretch</b> 19:12 154:1 <b>strides</b> 12:5 <b>striking</b> 299:3 <b>strong</b> 151:18 212:12 <b>stronger</b> 191:1 271:3 <b>strongest</b> 71:18 <b>strongly</b> 68:18 314:7 <b>struck</b> 196:16 <b>structure</b> 24:22 38:22 49:6 97:21	99:11 100:5 246:21 <b>structured</b> 46:18 <b>structures</b> 150:7 <b>struggling</b> 110:7 142:12 <b>student</b> 145:5 <b>studied</b> 29:13 134:9 162:5 212:7 <b>studies</b> 14:13 15:2 16:12 22:22 23:4 23:5 24:2 25:6 30:10 31:21 35:13 36:16 39:7 41:14 43:6 45:2,5,8 48:20 50:21 51:2 53:5 55:10 56:20 57:13,15,16 58:2 61:16 64:5 67:21 70:2,4,14 72:13 72:18 74:19,20,21 75:22 78:10 79:8 80:2,19 81:1 86:22 98:11 99:18 104:10 125:1 131:10 142:20 188:16 200:18,21 202:17 233:11 246:1 273:20 303:20 313:2,3 <b>study</b> 16:15 17:1 23:14 29:21,22 33:22 40:12,18 41:20 42:18 44:1 44:2 46:18 49:11 51:15 53:15 54:15 58:4 69:15 70:7,8 71:14,21 73:11 79:11,11,14,18 80:16 81:20,21 83:13 90:8,16 91:5,18 92:19,19 93:14,15 97:12 104:18 130:13
--	--	--	--

156:3,5,11 162:7 211:3 225:21 262:7 292:8 295:4 307:19 <b>studying</b> 51:8 212:3 <b>stuff</b> 99:8 144:21 210:3 267:20 <b>subgroup</b> 92:4 <b>subgroups</b> 284:5 <b>subjectively</b> 206:9 <b>submission</b> 17:19 18:9 166:10 <b>submissions</b> 59:13 76:16 <b>submit</b> 5:4 18:10 286:1 314:8,9 <b>submits</b> 98:12 <b>submitted</b> 34:15 57:18 <b>subs</b> 59:18 <b>subsequent</b> 56:1 <b>subset</b> 139:19 149:2 <b>subspecialty</b> 231:21 <b>substantial</b> 34:14 36:7 <b>subtitle</b> 95:5 <b>succeed</b> 97:11 <b>success</b> 13:17 154:20 220:8 237:17 238:3 241:7 273:3 297:11 298:1 <b>successful</b> 135:9 215:4,9,18 245:17 254:16 277:3 <b>successfully</b> 234:9 <b>sudden</b> 98:2 270:12 <b>suddenly</b> 184:13 308:3	<b>suffered</b> 176:21 <b>suffering</b> 64:2 176:21 177:8 <b>sufficient</b> 42:13 211:17,18 213:3 213:12 230:14 301:17 <b>suggestion</b> 110:18 <b>suggestions</b> 110:15 <b>suicide</b> 308:8 <b>sum</b> 97:10 185:13 <b>summarize</b> 233:15 237:5 <b>summer</b> 62:19 <b>sunday</b> 286:2 <b>sunsets</b> 152:7 <b>supplement</b> 39:16 <b>supplemental</b> 192:5 <b>supplementing</b> 39:15 <b>support</b> 2:7 3:5 6:4,10 15:11,13 16:6,7,11,12,21 17:1,8,15,22 18:3 20:6 25:14 27:5 33:9 39:11,12 44:10 75:21 90:17 103:14 104:10 116:19 121:10,14 122:2 123:8 124:14 127:6,16 133:22 169:22 188:18 191:16,19 225:3 243:21 245:6,7 247:5 279:12 287:6 289:5 308:14 309:12 313:15 <b>supported</b> 27:3,9 <b>supporting</b> 1:3 2:3 18:15 22:7 25:19 78:16 129:5 130:6	134:20 211:12 226:21 278:17 302:17 <b>supportive</b> 88:14 301:5 <b>supports</b> 25:1,4 228:4 279:11 <b>suppose</b> 151:19 <b>supposedly</b> 109:15 <b>sure</b> 19:7 33:15 35:7 36:10 45:5 54:18 60:18 62:12 65:5 68:1 73:10 76:2 80:9 83:14 84:15 86:4 90:22 94:20 95:22 97:2 102:3 112:11 113:8 132:2,5,6 154:18 157:9 160:4 165:14 170:18 184:1 190:9 193:4 201:6 203:9 216:6 233:4 248:18 258:5 259:15,21 276:21 <b>surfactant</b> 296:8 298:14 <b>surh</b> 45:21,22 <b>surprising</b> 148:18 <b>survey</b> 109:5 314:12,14,18 <b>surveys</b> 105:13 <b>survival</b> 304:6 <b>survivals</b> 169:4 <b>survive</b> 303:12,13 <b>susan</b> 231:3,4,7,12 231:18 236:15,18 242:1 247:13 252:13 253:11 256:3,10,12 258:14 260:11 264:16 268:19 273:8 276:1	279:16 282:7 284:12 <b>susie</b> 248:19 <b>susie's</b> 272:18 <b>sustainability</b> 67:20 101:12,13 101:22 102:4 112:12 113:13,22 <b>sustainable</b> 103:13 141:1 191:2 243:8,12 <b>swallow</b> 96:9 <b>swallowing</b> 88:15 96:8 <b>swimming</b> 182:13 235:7 246:9 <b>swinging</b> 173:16 <b>switching</b> 301:4 <b>sworn</b> 114:15 315:5 <b>sympathize</b> 282:12 <b>symptom</b> 105:16 287:15 <b>symptoms</b> 87:10 135:11 192:4 <b>syndrome</b> 105:5 107:6 151:5 155:9 164:12 168:20 172:2 309:10,20 310:3 <b>synergistic</b> 258:20 <b>synonymous</b> 78:13 <b>system</b> 27:1,11,15 27:16,20 38:4,8 38:19 79:21 91:3 137:5 138:1 164:15,19 176:8 179:11 195:9 196:21 251:14 258:1,3 274:8 275:9 278:16 279:8,10 308:11
---	--	---	--

<p><b>systematic</b> 92:1</p> <p><b>systemic</b> 12:22</p> <p><b>systems</b> 38:2 79:21 167:15 273:2 279:3 287:6 289:5</p>	<p>316:9</p> <p><b>takes</b> 38:13 80:15 107:18 143:7 224:19 229:12 303:10</p> <p><b>talk</b> 26:14 41:13 41:17 44:16 48:20 51:18 58:18 62:10 67:22 68:16 85:14 85:16 89:17 100:4 116:2 131:9 138:11 146:6 148:18 167:18 213:16 222:12 224:8 232:13 241:12 243:14 252:10 255:10 265:20 309:15</p> <p><b>talked</b> 62:7 101:11 162:3 189:8 200:18 215:4 221:3 227:7 232:16 247:18 253:21 256:14 272:13 275:7 309:16 311:4</p> <p><b>talking</b> 23:2 50:12 53:20 64:5 65:2 74:2 78:8 95:20 124:5 223:6 227:17 231:16 232:4 233:6 236:12,13 253:21 254:14 283:13,15</p> <p><b>talks</b> 50:5 214:6</p> <p><b>talotti</b> 309:4,5,7,9</p> <p><b>tangible</b> 241:7</p> <p><b>taper</b> 173:19</p> <p><b>target</b> 224:7</p> <p><b>targeted</b> 13:10 46:19 59:19 80:12 199:22 205:13</p> <p><b>targeting</b> 37:14 42:4</p>	<p><b>targets</b> 272:5 295:15</p> <p><b>tart</b> 50:9</p> <p><b>task</b> 188:6</p> <p><b>taxpayer</b> 277:16</p> <p><b>team</b> 22:12 67:3 74:16 184:19 185:2 199:14 200:4,6,7 201:12 201:12,13,15 202:13,22 217:11 218:7 234:7,18 236:5,21,21 247:19 253:4 270:8,13 271:3,5 272:7,10,14,14,15 272:17 273:6</p> <p><b>teams</b> 272:22 273:1 274:5</p> <p><b>teamwork</b> 234:16</p> <p><b>team's</b> 201:5</p> <p><b>technical</b> 10:16 17:14,18 18:15 66:14 197:9</p> <p><b>technically</b> 235:17</p> <p><b>technique</b> 139:16</p> <p><b>technologies</b> 25:2 25:2 27:2,12,16 38:5 138:13 148:1 152:22 153:1 165:7 221:11 222:6 236:11 239:22 249:9,19 250:3 252:1 311:8</p> <p><b>technology</b> 17:8 17:12,22 18:5,5 18:13 30:18 144:6 144:8 148:6 158:17 176:3,10 176:13,14 247:3 259:1,2,6,7,7,15 271:8,9,11 274:8</p> <p><b>tedious</b> 95:21</p>	<p><b>teeing</b> 95:11</p> <p><b>teen</b> 254:21</p> <p><b>teens</b> 254:22</p> <p><b>tell</b> 41:3 46:10 51:21 89:18 131:1 135:3 184:5 232:19</p> <p><b>telling</b> 98:3 183:15</p> <p><b>template</b> 219:19</p> <p><b>ten</b> 7:2 42:11 55:13 80:15 93:12 137:17 180:14</p> <p><b>tend</b> 78:17 215:6 268:13 289:15,20</p> <p><b>tended</b> 12:2</p> <p><b>tendinitis</b> 310:11</p> <p><b>tendinosis</b> 310:11</p> <p><b>tenfold</b> 197:17</p> <p><b>tenosynovial</b> 120:2</p> <p><b>tens</b> 228:19</p> <p><b>tensions</b> 260:9</p> <p><b>teresa</b> 66:7</p> <p><b>term</b> 28:16 77:20 78:9 81:16 96:7 100:17 103:1,5,11 191:3 241:15 243:10,12 270:15 270:18</p> <p><b>terminology</b> 80:4 83:4,7 98:18 99:9 99:19 106:3 282:19</p> <p><b>terms</b> 6:13,20 46:4 69:7 86:13,18 100:22 102:16 103:16 112:15 123:5 130:9 138:16 147:21 154:6 206:21 207:3 209:18 232:20,21 248:3 253:15 270:4</p>
<p><b>t</b></p>			
<p><b>t</b> 195:18</p> <p><b>table</b> 5:20 8:10 264:6</p> <p><b>tables</b> 3:13</p> <p><b>tackle</b> 48:14 94:8 223:14</p> <p><b>tackling</b> 106:14 188:5 189:7</p> <p><b>tags</b> 5:12</p> <p><b>tailored</b> 184:11,12 307:7</p> <p><b>take</b> 11:11 19:12 32:2 58:6 66:7 79:5 92:18 95:19 101:1,15 106:1 112:8 128:9 134:15 153:10,16 160:12 166:18 170:5 174:3 182:21 186:11 190:8 198:3 213:21 216:3,17 218:2 225:1 229:3 235:14,19,20 254:22 255:3 257:10 258:9 262:16 264:18 270:2 281:9 283:19 287:9 310:15</p> <p><b>takeaway</b> 67:19</p> <p><b>takeda</b> 244:1</p> <p><b>taken</b> 64:10,13 70:22 108:6 167:21 172:8,13 210:18 246:3 259:13 315:3,12</p>			

<p><b>terrible</b> 96:12 193:8</p> <p><b>terribly</b> 137:9</p> <p><b>terrific</b> 115:19 116:10 125:5 126:11</p> <p><b>test</b> 88:9 130:14 143:11 151:4 183:22</p> <p><b>tested</b> 204:16 264:9</p> <p><b>testifying</b> 315:5</p> <p><b>testing</b> 87:13 88:8 88:10,14 89:14 131:8 197:22,22 224:16,17 228:9 230:5 277:17</p> <p><b>tests</b> 87:19,19 88:15,16 89:14 298:13</p> <p><b>texas</b> 115:3 159:3 303:1</p> <p><b>thank</b> 2:17,18 10:1,3,6 11:7,8,10 19:6,7,9,16,18,21 21:9,10 24:11,13 28:8 31:4 36:17 40:6 43:12 44:19 45:11,22 47:15,19 53:16 63:21 65:14 65:18 66:5,5,10 69:10 70:17,18 74:9,12 75:10 85:13 100:8 101:7 103:7 104:20 105:3 107:1,2 109:8,9 114:9,9 115:17 116:6,8 127:19 128:1,2,9 128:10,11 141:4 156:16 160:7 163:5 171:11,13 175:14 178:16,19 180:5,10,16 185:3</p>	<p>185:21 186:2,6,7 190:6 193:14,21 194:3 199:11,16 203:15 208:2 214:20 219:8 226:14 228:6 230:15,18,20 236:15 237:4 247:12,14,15,19 253:11 256:3 282:6 284:14,15 284:19,21 286:16 290:5,6,7,10,12 292:19,20 293:2,5 294:19 295:18,19 296:1 299:15,18 299:20 302:18,20 305:20,21 308:19 308:21 309:1,6,8 311:21,22 312:4,8 314:20</p> <p><b>thanks</b> 178:15 230:18 233:5 256:21</p> <p><b>that's</b> 182:10 188:9 194:6 196:2 197:3 203:2,3 204:10 205:4 206:15 213:12,20 214:16 216:20 218:19 220:3,20 224:4 225:6 226:12 228:21 229:4,18 230:5 231:4 233:21 234:5,11 236:8 239:11 243:8 246:10 247:7 249:5,18 251:13 254:9 259:7 260:5 261:14,16,20 263:18 267:10 268:7 270:1,19,21 271:9,22 272:3,13</p>	<p>273:15 275:10,19 276:16 277:9 278:15 279:7 281:6 282:14 284:8,12 301:7 311:4,6</p> <p><b>theme</b> 130:5 171:21</p> <p><b>themes</b> 197:10</p> <p><b>theory</b> 56:17</p> <p><b>therapeutic</b> 14:17 85:7 129:20 168:18 176:3 186:22 242:16 244:19 245:15 291:8,22 292:13</p> <p><b>therapeutics</b> 56:15 177:3 196:8 231:19 259:20,22 261:19 291:5,16</p> <p><b>therapies</b> 7:3 13:10,11 28:13,17 28:18,19 29:1 35:4 41:2 46:15 94:3,5 122:8 129:13 131:16 138:16,18 140:8 146:7,13,15 148:4 160:22 161:3,4 171:5 177:12 181:3,5 189:9 191:1 194:9,13,14 194:18 195:17 200:1,12 202:11 203:14 204:3 205:13 217:8 227:17 230:2 232:3 302:9 304:11 311:9 313:10</p> <p><b>therapist</b> 297:3</p> <p><b>therapists'</b> 219:22</p> <p><b>therapy</b> 28:15 29:8,20 30:19,20</p>	<p>32:6 57:12 71:6 72:8 94:17 109:13 119:21 120:3 131:20 140:17 141:20,21 142:7 147:22 149:1,1 154:6,10 160:20 161:5 165:22 175:19,21 176:9 177:15 178:8 180:19 187:18 190:10,10,11 191:4,8,11,14,20 191:22 193:7,10 194:8,10,11 197:20 198:19 199:2 201:9 204:9 204:12,14,15 207:19 210:22 211:16 227:8,10 227:16 242:4,20 244:7,14 245:12 246:20 271:7 296:7 297:16,21 298:7,20 299:1 300:15 301:14</p> <p><b>theresa</b> 66:18 68:14,20 69:9 70:18 78:7 85:13 100:8 101:7 103:7 104:20 105:22 107:1 109:9 110:17 112:6 114:8</p> <p><b>there's</b> 191:19,19 196:4 197:4 198:8 199:1 200:21 203:10 215:5 216:15 218:21 221:14 224:22 226:10 229:8 241:20 248:21 249:4,13 250:1 252:7 254:11</p>
--	---	--	--

255:6,7 258:19,19 258:22 259:5,14 260:2,6,7 269:1 270:17 271:17 272:5,14 273:14 277:2 <b>thermometer</b> 249:15 <b>they're</b> 186:13 194:21 206:6,8 231:10 236:2,2 246:8,9 261:12 267:8 268:5 275:18 278:6 306:4 <b>they've</b> 263:1 <b>thing</b> 46:8 80:1 84:18 89:20 94:13 97:9 107:15 108:13 110:22 111:16,17 112:21 115:20 141:5 144:11 158:2 177:15 178:20 180:6 196:3 197:5 198:4 224:1 227:4 243:6 246:15 255:21 261:7 266:11 268:4 270:7 275:19 276:22 277:7 278:7 281:14,20 282:14 <b>things</b> 28:20 31:20 36:12 40:11 48:18 57:2,20,22 64:4 68:15 72:10,14 74:5 77:14,22 83:16 87:7 88:19 89:4 91:6 97:13 99:5 100:21 106:8 107:12,22 115:20 121:17 130:15 133:18,21 134:5	137:13 139:10,22 139:22 140:3 141:15,16 143:2 143:12 145:15 147:12,13,15,16 147:20,22 152:8 153:4,7,8 154:1,7 157:3,11 158:5,18 160:8 161:9,10,12 164:10,17 166:21 167:1,10,18 168:20 169:16 177:10,12 193:16 195:16 196:2 210:17 220:16 226:13 228:11 234:15,22 240:8 241:1 244:18 251:12 253:9 264:14 266:4 267:14 269:22 276:8 279:22 280:18 282:2,22 299:7 301:9 309:16 311:14 <b>think</b> 11:9 15:13 22:22 23:20 26:13 31:7,20,22 32:17 33:12,13 34:20 36:12,20 40:13 41:22 42:20 43:10 43:15 44:4,17 45:7,12 46:10 47:10,19 49:4 50:7,13,17,19 53:13 54:14 55:14 55:15 56:8,16,20 57:19 59:4,9,20 61:4,7,12,17 62:9 63:6,21 65:2,17 66:13 68:7,11,14 68:18 69:1 72:10 72:16 73:2,21 74:5 78:12,15,17	79:6,9,10 80:4,6,8 80:18 81:5,7 82:2 83:5 86:2,12 88:3 94:6,20 95:3,8,11 96:21 97:12,21 98:16 100:5 102:22 103:6,12 104:1 106:9 109:1 109:2,7 112:6,9 114:7 117:15 118:6 119:18 120:22 121:22 122:11,11,12 129:4 130:10 131:3,9 133:7,17 134:2 136:9 138:15 139:4,13 140:9 141:15 142:15 143:21 144:1,12 145:20 145:21 147:10 149:10,13,16 150:3,12 154:2,9 154:20 156:18,21 156:22 157:19 158:2,6,8 160:7,8 162:3 163:15,20 165:1,2,6 166:14 169:19,20 170:4 172:12 173:13 174:21 177:6,9,11 177:14,22 178:6 179:9 181:21 185:10 187:2,19 189:5 191:13 193:15 195:6,13 196:2,10,12,20,20 197:4 198:6,7,13 199:6,21 200:13 201:11 202:4 203:11,12,17 204:10,18,22 205:8,10 206:7 207:3,22 209:12	210:8,10,17 211:10,11 213:20 214:11,16,21 215:3,6,8 216:2,4 216:5,9,11,14,22 219:21 220:8,13 220:20 221:21 222:2,21 223:19 224:12,13,19 225:17,20 227:19 227:20 228:2,8 229:22 230:16,17 232:2,11,20 233:17 234:13 235:3,5 236:8 237:6,7,11 241:11 241:19,20 243:6 247:8 249:2,5,8 249:12,19,22 250:8,21 251:21 253:12 256:22 257:14 258:8,21 260:7,8,14,22 261:12,22 263:9 263:14,18,21,22 264:1,4,5,11,19 267:9 268:17 270:7,14 272:7 277:3,8,22 280:22 284:12 299:8 313:4 <b>thinking</b> 26:18 42:11 47:22 51:14 87:22 93:22 94:2 121:2 139:8,11 144:7 147:11 149:18 158:4 185:6 190:4 200:15 203:1 212:13 218:8,20 219:4,13,13,16 220:14 224:21,21 228:22 230:7 238:19 262:3
--	--	---	--

264:9 278:1 300:7 313:12 <b>third</b> 109:13 124:6 151:10 267:12 <b>thirdly</b> 186:20 <b>thornton</b> 306:1,2 306:3 308:17,20 308:22 <b>thorough</b> 125:12 <b>thought</b> 46:16 71:7 185:5 193:19 211:15 219:10 221:1 232:12 235:2 236:5 242:21 244:22 250:13 256:5 <b>thoughtful</b> 48:16 154:6 <b>thoughts</b> 59:16 144:2 269:10,22 <b>thousand</b> 54:20 197:18 <b>thousands</b> 30:15 44:22 45:2,4 72:21 94:18 217:13 219:1 228:20 238:22 304:15 308:2 <b>threatening</b> 28:22 144:15 <b>three</b> 8:16 30:2 57:9 74:13 77:9 91:4 117:15 120:16,17 152:5 154:13 156:13 182:8 190:18 218:17,22 265:1 266:15 273:8 276:2,4 285:2 299:21 309:21 <b>threshold</b> 207:12 <b>thrilled</b> 253:18,20 294:16	<b>throw</b> 75:4,9 178:20 214:1 <b>thursday</b> 76:15 <b>tie</b> 152:8 <b>tied</b> 56:22 114:1 <b>tight</b> 142:14 <b>tim</b> 201:14,17 203:6 <b>time</b> 2:20 8:17,20 12:3 14:14 19:19 23:1 31:7 33:19 34:4 35:8,19 41:12,15 43:19 45:13 54:2,9,21 55:19 60:11 70:3 71:11,15,20 79:15 82:13 86:10,11 87:9 90:10 92:2 93:5 94:10 95:21 97:3,6 99:4 109:6 111:11 112:7,16 114:7,21 120:21 121:5 126:4,13 127:2 134:20 140:19 142:2 152:5 180:15 182:14,21 184:1,6 185:15 186:1 187:1,14,19 188:5 190:1,15 193:7 197:14 204:12 205:7 210:2 215:1 221:17,20 224:21 226:15 228:20 237:20 238:8 239:20 241:19 242:20 244:14 245:9,9 250:18 253:18 261:12 274:7 285:6,17,18 285:20 286:7 287:21 289:21 292:19 299:11 310:10 312:7	313:4 <b>timely</b> 303:9 <b>timepoint</b> 153:16 <b>timepoints</b> 79:3 <b>timer</b> 285:18 <b>times</b> 39:6 41:8 59:16 82:22 201:15 207:22 308:2 <b>timing</b> 56:16 261:8 285:15 <b>timothy</b> 182:2 184:4 186:6 211:14 219:10 228:6 <b>tiny</b> 138:3 151:3,3 151:12 <b>tisha</b> 295:20,21,21 <b>tissue</b> 188:17 <b>tissues</b> 28:13,18 <b>titering</b> 260:3,4 <b>tobacco</b> 10:14 <b>today</b> 2:10,17 3:7 3:11 4:10,11 5:8 5:17 8:9 9:1,3,6 9:12,13 10:2 11:11,13 14:6 19:18 20:12,18 21:11 31:17 45:22 54:19,21 66:22 68:3 70:17 100:12 115:19 116:2,7 127:16,20 128:10 144:5 160:2 171:16 181:8 200:13 221:22 222:2 232:6,16 242:19 243:5 246:8 247:5 253:20 285:1 290:14 291:10 293:5 294:6,8,18 294:22 296:1 299:4,17 300:5	303:3 309:10,15 309:17 310:7 312:2,18,18 313:12,14,20 314:7 <b>today's</b> 5:22 9:22 128:11 130:5 <b>today's</b> 312:11 <b>toddlers</b> 137:20 <b>toing</b> 268:4 <b>told</b> 93:12,21 99:3 174:15 182:19 183:4 184:7,21 234:19 250:10 297:20 <b>tolerance</b> 298:3 <b>ton</b> 86:10 <b>tool</b> 76:17 113:7 185:18 189:10 206:21 218:18 <b>toolbox</b> 183:5 185:19 218:18 <b>toolkit</b> 107:17 <b>tools</b> 16:7 17:18 24:5 85:3 103:3 106:10 113:20 134:8 136:6,17 137:3 165:8 183:4 186:11,13,17,22 186:22 187:3 189:15 212:3 220:6 221:10 226:1 <b>tooting</b> 111:4 <b>top</b> 138:6 149:13 300:20 <b>topic</b> 43:14 300:19 <b>topics</b> 248:21 312:13 <b>torjusen</b> 19:17 20:1 24:11 28:8 31:4 36:17 40:6 43:12,18 44:19 45:11 47:15 48:13
--	---	--	--

53:16 54:17 55:2 55:6,12 56:3,11 59:7 60:9,15 61:2 62:20 63:20 65:15 <b>torturing</b> 308:13 <b>total</b> 12:9 82:9 161:15 <b>touch</b> 86:19 <b>touched</b> 40:8 222:17 <b>touches</b> 116:4 <b>tough</b> 97:5 <b>tox</b> 292:8,9 <b>toxic</b> 161:8 <b>toxicity</b> 174:22 <b>toxicology</b> 201:12 202:18,20 206:3 228:9 230:5 <b>track</b> 266:21 281:8 302:16 <b>tracked</b> 14:14 <b>traditional</b> 195:3 202:9 228:3 242:7 <b>traditionally</b> 196:15 234:17 <b>tragic</b> 127:1 <b>trained</b> 114:18 234:17,18 <b>trainee</b> 296:9 <b>training</b> 106:4 <b>trajectories</b> 264:15 <b>trajectory</b> 205:16 207:10 222:8,13 223:17 <b>transaminitis</b> 259:19 <b>transcribed</b> 5:6 <b>transcriber</b> 316:1 <b>transcript</b> 316:3,5 <b>transcriptionist</b> 315:7 <b>transform</b> 234:9	<b>transformative</b> 71:7 <b>transforming</b> 239:11 <b>transition</b> 91:3 128:4 284:17 312:3,6 <b>translation</b> 234:6 234:11 <b>translational</b> 67:8 67:12 178:3 179:18 233:9 235:4 <b>translators</b> 267:6 <b>transparency</b> 7:16 285:9 <b>transparent</b> 83:4 96:1 106:7 108:21 <b>transplant</b> 252:20 297:22 <b>trapnell</b> 297:8,12 <b>trash</b> 213:1 <b>travel</b> 2:16 7:19 73:20 159:4 171:16 285:11 286:15 296:4 300:4 303:3 309:13 <b>traveled</b> 192:16 193:3 <b>travels</b> 314:21 <b>travesty</b> 177:6 <b>treat</b> 20:7 22:19 35:4 117:9 119:21 120:4,11 144:18 145:1 147:14 166:11 190:21 217:19 221:16 237:7,16 238:5 260:15 290:21 294:5 303:3 305:18 <b>treated</b> 110:11 173:15 176:15	184:16 191:6 208:10 218:12 243:20 246:20 247:7 <b>treating</b> 116:22 117:1 172:6 188:22 208:7,8,13 217:18,19 218:17 219:16 220:2,3 263:12 278:6 <b>treatment</b> 2:22 12:6,14 13:3 16:13 24:1 29:9 31:2 32:22 35:21 39:17 64:9 71:16 81:11,13 119:22 120:2 131:22 143:15 145:16,16 148:10 159:11,15 162:13,14 171:19 171:20 172:5,7,19 173:20 185:1,11 188:10 190:22 191:15 192:10,17 194:11 196:22 197:2 199:5 202:21 203:22 206:3 207:3 209:2 213:2 215:22 218:15 244:11,12 266:2 280:10 287:14 289:9 294:5 295:15,18 304:6 309:18 <b>treatments</b> 13:18 15:5 34:7 68:3 71:22 80:12 94:19 110:9 116:20 121:2 123:9,18 124:15 127:7 131:13 136:6,16 136:17 144:19 146:20 159:12 160:3 172:8,13	173:6,9 182:11 185:16 189:11 192:6 195:10,14 215:14 216:14 220:7 243:11,13 243:16,22 287:17 290:3 294:7 304:7 305:5,6,7 311:8 <b>tremendous</b> 13:6 13:12 146:12 173:22 200:5 <b>trend</b> 105:4 <b>trial</b> 14:20 16:11 32:3,11 34:6,16 40:19 41:4 45:4 46:21 47:8 50:15 52:3 54:5 73:14 78:1 84:6,13,22 85:12 89:22 91:13 91:20 92:6 98:13 134:21 152:12 159:21 162:5,15 162:17,18 169:21 170:7 179:6,7 239:2 246:7 261:14 276:16 287:4 288:11 289:1,7 298:9 <b>trials</b> 14:16 15:5 16:4 24:4 25:17 32:20 40:15 41:5 41:16 51:19 56:2 70:2 76:1,6,13,18 77:20 83:13,17 85:4 87:4 90:17 91:10,14 92:11,11 92:17,20 93:2 99:2 109:13 113:19 118:9 124:22 127:10 137:10 157:17,17 159:14,18 160:5 160:17 163:16 164:6 168:5,11,18
--	---	---	---

169:1,22 171:5 178:22 180:4 238:20 239:13 254:5 260:20 280:2 287:12 288:1,2,4,7,10,20 289:19 290:1,3 295:16 298:10,11 304:3,4 305:6 <b>trickled</b> 223:15 <b>trickles</b> 301:1 <b>tried</b> 107:11 145:17 192:11 296:19 <b>trip</b> 193:5 <b>triple</b> 119:21 <b>tropism</b> 275:17,19 <b>trouble</b> 30:4 <b>troubling</b> 301:6 <b>true</b> 114:22 149:3 220:8 234:5 241:6 303:7,20 315:9 316:5 <b>truly</b> 97:10 106:18 154:11,16 187:6 193:21 200:9 205:10 206:12,14 207:13,20 218:10 218:16 250:3 251:17,21 257:10 257:12 258:3,10 272:20 279:10 293:20 <b>trust</b> 37:8 38:10 108:17 290:4 <b>trusted</b> 296:20 <b>truth</b> 265:21 <b>try</b> 43:6 44:12,17 50:19 53:8 58:5 58:10 59:6 64:21 72:12 82:5 94:16 101:15,16 104:7 110:19,22 117:17 130:15 142:10	154:21 160:9 161:14 166:7 170:6,20 172:20 173:9 177:16 192:7 194:16 195:9 201:20 215:1 219:20 220:13 221:17 222:20 223:9,14 227:1 230:14 248:22 259:20,21 262:17 269:13,18 272:20 277:4,6 296:18 <b>trying</b> 25:13 33:22 36:7 37:16 39:21 42:2 49:10 51:4 56:22 74:20 94:9 109:21 110:8,11 110:12 111:7 136:11 137:11 147:4 150:19 156:11 157:3 166:1 170:11,12 175:4 192:10 200:8 204:19 235:10 257:14 270:2 278:15,15 306:10,21 <b>tubes</b> 88:16 <b>tuesday</b> 140:6 <b>tumor</b> 47:18 120:2 120:2 217:21,22 218:1 237:21,22 238:1,2,7 <b>tumors</b> 237:19 238:12 <b>turn</b> 101:9,19 146:17 181:9 186:4 190:8 193:22 199:12 285:8,17,18 <b>turned</b> 184:13	<b>turning</b> 173:11 177:22 <b>turnout</b> 116:7 <b>turns</b> 161:10 280:2 310:1 <b>tweet</b> 9:21 <b>twenty</b> 30:2 233:18 <b>twins</b> 148:16 155:17 <b>two</b> 29:15,17 46:4 57:9,15,15 63:21 66:12 73:11 87:15 91:4 95:15 98:17 103:4 108:21 109:13 142:17 146:21 152:8 153:4 154:13 182:14 183:17,22 190:18 192:7 195:7,14 198:7 202:17,17 203:16 209:4 218:17,22 221:12 223:12 233:15 238:7 255:3,6 262:22 276:4,8 277:2 281:15 286:6 291:15 292:12 298:9 301:9 310:5 <b>tying</b> 26:22 89:13 89:15,19 <b>type</b> 7:22 33:18 79:10 129:5 147:5 154:13 159:6 178:4 188:8,9 189:13,14,16 219:17 256:9 258:12 274:1 <b>types</b> 16:6 34:2 81:19 139:22 162:20 238:10 242:13 257:1 300:22	<b>typewriting</b> 315:7 <b>typical</b> 195:1 <b>typically</b> 46:19 47:3 56:21 58:9 182:12 239:13 <b>u</b> <b>u.s.</b> 11:22 111:16 115:10 137:22 167:5 179:8 192:12 261:17 263:2 264:3 281:8 298:9 306:14,19 306:19 307:2 <b>ucla</b> 296:1 <b>udn</b> 291:4 <b>ultimate</b> 207:5 <b>ultimately</b> 147:15 147:19 275:1 297:16 301:11 <b>ultra</b> 50:8 146:4 149:9 176:14 178:9 226:18,18 227:10 246:19 290:22 <b>umbrella</b> 48:5 104:8 280:14 286:20 <b>unable</b> 192:20 <b>unacceptable</b> 277:10 304:8 <b>unbelievably</b> 143:18 <b>uncertainty</b> 85:6 85:10,11 210:12 210:13,14,18 211:7,11 <b>uncharted</b> 203:22 204:22 <b>undeniably</b> 303:8 <b>underline</b> 36:13 41:22 43:2,10 62:22 <b>underlying</b> 127:2
--	---	---	--

<b>undermine</b> 150:11	<b>undiagnosed</b>	<b>unscientific</b> 307:1	<b>uses</b> 12:12 16:14
<b>underpinnings</b>	291:4 303:18	<b>unsurpassed</b>	16:19 28:3 120:11
238:1	304:1,2,4,7	120:21	271:9,10 275:9
<b>underrecognized</b>	<b>unethical</b> 15:6	<b>untrue</b> 122:14	302:7
105:16	<b>unfortunate</b>	<b>unusual</b> 188:8	<b>usually</b> 16:3 40:13
<b>underscore</b> 90:5	265:21	<b>unwilling</b> 192:20	81:17 102:7 135:9
<b>underserved</b>	<b>unfortunately</b>	<b>upcoming</b> 117:14	144:22 167:8
287:5 289:12	137:16 143:4	124:7	258:16
290:2 303:22	160:11 161:4	<b>update</b> 201:17	<b>utility</b> 49:18,19
<b>understand</b> 2:19	310:3 312:6	<b>uphold</b> 124:2	228:15
14:10,15,22 42:3	<b>uniform</b> 16:3	<b>upside</b> 259:13	<b>utilization</b> 301:13
42:14 43:8 50:16	<b>uniformly</b> 154:12	<b>upstream</b> 235:8	<b>utilize</b> 32:18 63:18
51:5 63:4 76:4	292:1	<b>upwards</b> 254:9	292:5
77:21 83:14 84:10	<b>union</b> 280:5	<b>urge</b> 101:1 104:11	<b>utilized</b> 38:18 39:6
87:16 93:1,20	<b>unique</b> 3:1 14:7	268:15 302:11	<b>utilizes</b> 27:8
94:4 96:13 97:7	27:6 106:21	311:12	<b>utilizing</b> 305:8
100:11 104:14	146:18 148:17,17	<b>urgent</b> 5:10	<b>v</b>
105:13 106:12,16	148:21 149:1	<b>urs</b> 280:17	<b>vaccines</b> 129:13
108:6 111:8 112:3	151:7 262:12	<b>use</b> 9:9,22 15:10	194:7,11 259:8
126:2 141:17	287:5 288:12	16:8 17:7,15 20:3	<b>validate</b> 46:19
148:5,13 149:16	289:11 293:7	27:4,7 32:1,4 33:9	<b>validation</b> 132:14
153:1 202:14	294:13	35:6 36:15 40:3	<b>validity</b> 156:5
277:5 300:21	<b>unite</b> 82:22	40:18 48:2 54:21	<b>valuable</b> 47:11
302:1	<b>united</b> 91:12	61:1,6 63:11	69:20
<b>understandable</b>	109:16 110:4	69:22 78:9 86:6	<b>value</b> 52:14 54:2
96:1	149:22 164:2	88:13 90:1 91:8	59:11 60:20 67:20
<b>understanding</b>	167:12 263:3	92:16 95:1 108:5	77:16 85:4,12
13:15 14:18 49:6	281:18,21 293:12	113:7 118:10	267:22 301:14
78:19 84:21 85:10	306:20	124:20 125:15	<b>valued</b> 267:22
94:7 104:16 105:8	<b>units</b> 87:21,21	126:4,19 132:17	<b>variability</b> 84:2,7
123:9 131:5,12	<b>university</b> 10:19	133:11,11 135:7	84:11 131:12
189:9 191:14	11:1,5,5 71:12	135:13 136:16	<b>variable</b> 15:1 30:7
205:2 209:20	115:2,7,15 191:6	153:1,21 156:4	98:21 205:16
211:5 239:10	192:17	161:5 164:20	<b>variables</b> 37:17
240:18 254:4	<b>unknown</b> 208:14	165:7 172:22	<b>variance</b> 150:21
263:10,15	210:4 305:1	174:10 178:5,8	<b>variant</b> 144:21
<b>understandings</b>	<b>unknowns</b> 213:10	190:12 205:21	<b>variety</b> 3:5 6:5,6
111:9	<b>unleashing</b> 118:4	220:17 225:20	57:12 150:16
<b>understood</b> 14:21	<b>unlimited</b> 102:7	229:17 243:15	160:8 170:1
183:6 306:12	<b>unmet</b> 12:11	244:22 259:5	237:16
<b>undertaken</b> 27:5	119:4 121:4 303:6	286:7 302:4	<b>various</b> 2:9 6:7
253:20	312:21	<b>useful</b> 49:19 51:20	26:6 63:12 130:15
<b>underway</b> 109:13	<b>unprecedented</b>	74:6 82:17 226:1	136:5 181:4 204:5
	121:1		260:19 300:1

310:21 <b>vary</b> 210:15 <b>varying</b> 261:6 <b>vasum</b> 247:13,14 256:5,11,21 272:9 274:4 <b>vcu</b> 191:17 192:19 193:1 <b>vector</b> 176:4 198:19 <b>vectors</b> 147:22 161:6 197:13,16 197:19 <b>vein</b> 190:3 215:16 <b>venues</b> 62:2 300:7 <b>version</b> 164:3 <b>versus</b> 78:1 81:10 83:12,13 174:14 205:5 208:7 217:18 218:4 <b>viability</b> 140:22 <b>viable</b> 140:20 228:2 247:2 <b>vice</b> 67:8 290:13 296:2 <b>victims</b> 307:15 <b>video</b> 106:8 <b>viewing</b> 25:17 <b>views</b> 9:5 <b>vigorous</b> 140:1 <b>viral</b> 161:5 <b>virginia</b> 309:14 <b>virtually</b> 289:6 <b>virus</b> 190:12 245:13 <b>viruses</b> 161:6 <b>vis</b> 259:2,3 <b>visible</b> 301:2 <b>vision</b> 10:16 77:4 77:13 87:2 182:18 283:8,8 <b>visit</b> 73:16 249:13 <b>visits</b> 73:12,22 90:13 91:22	<b>vitarello</b> 182:2,7,8 208:2 217:10 <b>voice</b> 11:11 62:8 123:17 124:9 302:7 <b>voices</b> 61:18 293:19 313:13 <b>volunteers</b> 3:21 309:12 <b>voodoo</b> 210:3 <b>vulnerable</b> 271:14  <b>w</b> <b>wait</b> 197:16 <b>waiting</b> 94:19 141:19 <b>walk</b> 88:9 89:14 89:18 100:18 216:12,12 219:20 243:2,9 <b>walked</b> 263:10 <b>walkers</b> 88:18 <b>walking</b> 88:16 <b>wall</b> 223:8 243:1 245:18 <b>walls</b> 283:21 <b>wang</b> 295:20,21 295:22 <b>want</b> 9:16 10:1 19:7 21:10 32:17 36:9 42:14 43:2 43:13,16,18 45:6 46:17 47:9 51:21 54:12 64:22 65:17 68:12,16 69:6 76:2,19,20 80:9,9 82:7,16 83:15,20 84:12,14,22 85:1 86:3 96:19 97:3,5 97:10,18 100:3,12 101:9,15,18,20 104:17 106:16 107:16 108:2 112:22 114:8 119:14 121:18,18	124:5 125:14 126:1,2,12 127:15 127:19 130:14 132:5 140:15 143:18 149:19,22 153:3 154:21 155:4,18 159:16 164:6 165:2,4 176:21 178:8 179:4,9 185:5 186:7 187:4 197:14 198:2,3,4 199:7 206:18 215:2 219:22 223:8 224:11,12 243:6 244:11 246:11,15 247:19 251:8 261:13 268:7 269:5 271:1 275:2,21 276:9 277:5,6 283:17,17 283:21,21 284:11 291:19 300:22 313:17,21 <b>wanted</b> 19:18,20 19:22 43:20 52:4 57:13 60:10 63:22 100:11 101:3 105:6 122:21 128:9 143:5 164:7 168:16 178:20 185:22 211:21 212:3 220:22 257:16 269:4,9 <b>wants</b> 131:21 150:11 223:1 231:13 268:1 <b>warning</b> 173:18 310:5 <b>warrant</b> 301:18 <b>warriors</b> 306:4 <b>wasn't</b> 182:5 191:2,18,18 193:4 204:17 208:10	242:17 245:7,15 <b>watch</b> 174:13 <b>watching</b> 107:13 <b>waters</b> 203:22 <b>way</b> 15:5 17:17 32:9,21 34:2,3 36:4 43:1 45:20 50:10 58:14 60:7 63:2 83:3,8 88:13 89:11,22 90:20 91:2 92:10 97:14 98:20 99:15 103:5 112:10 113:5,10 125:2 128:3 131:18 132:6 134:20 135:19,21 146:19 147:4 149:14 150:9 151:2 160:11 161:4,6 164:14,16 170:4 175:20 187:20 194:21 196:11 199:17 200:10 201:7 205:10 206:9 210:8 211:22 212:18 219:13,17 219:18 220:10 223:4,5,21,21,21 236:3 237:10 239:12 241:10 248:14 256:4 261:2 263:19,20 266:12 271:1 274:12,13 275:2 282:19 283:5,8,16 286:5 <b>ways</b> 17:14,15 22:19 31:22 33:1 54:15 99:2 108:9 116:4 118:11 121:16 122:15,18 123:17 126:18 127:11 134:6
---	---	---	--

135:2 140:22 142:9 150:4,12,16 163:19 165:5 187:3 189:6 190:4 214:19 228:22 230:6,7 233:15 240:9 280:20 <b>we've</b> 27:3 31:6 33:14 35:12 36:2 36:6 61:22 68:6 69:6 70:7 75:20 76:8,9 82:22 92:18 106:7 110:7 118:13 120:5,13 124:6 133:14,15 137:21 146:3 148:12 150:19 160:8 162:2 167:13 168:22 176:7,15 178:6 <b>weak</b> 29:14 <b>weaknesses</b> 85:21 <b>wearing</b> 5:12 314:17 <b>web</b> 5:20 7:8 69:19 106:7 165:13 175:15,15 175:16 314:17 <b>webcast</b> 2:19 5:7 7:22 9:10 66:11 101:10 112:8,10 312:11 <b>website</b> 100:13,16 106:9 <b>wee</b> 54:22 <b>week</b> 166:5 209:3 293:6 <b>weeks</b> 91:21 159:9 159:10 192:2,2 <b>week's</b> 193:7 <b>weigh</b> 207:5 <b>weighed</b> 210:5 <b>weighing</b> 204:13	<b>welcome</b> 2:2,9 6:14 11:6 66:10 67:15 68:2 117:22 121:13 125:7 286:5 <b>welcoming</b> 115:16 <b>wellness</b> 283:1 <b>went</b> 5:17 9:12 73:20 144:19 145:6 245:5,18 <b>weren't</b> 216:19 <b>we'd</b> 196:20 225:1 <b>we'll</b> 181:12 199:12 206:18 214:21 225:18 226:12 233:1 236:14 244:3 276:5 <b>we're</b> 180:22,22 181:1,21 182:3,4 182:5 188:4 196:2 197:7 202:6 205:14 214:17,22 222:18 223:9 224:13 225:22 227:20 230:11,16 231:8,22 232:13 233:16 235:10 236:12 237:12,14 239:4,16,17,20,21 240:7 241:3,6,8,9 241:11 244:2,5 246:6 247:6,8,10 247:12 252:11 254:8 255:19 256:3 257:14,15 260:10 261:3,17 262:2,3,8 263:20 264:9 266:10,22 267:15 270:1 271:12,13,19,21 276:4 278:15 280:1 282:20 290:17 295:16	298:21 299:8 311:2 312:5,7 <b>we've</b> 181:20 186:2 189:8 195:7 195:20 197:15 210:20 224:5 227:7 232:7 234:2 234:14,15 235:6 247:17 250:22 251:15 256:13 267:10 269:17 275:7 276:10 277:1 291:7,11,12 297:18,22 <b>whatsoever</b> 209:13 307:12 <b>what's</b> 201:18 208:3 240:19 255:17,17 256:7,8 256:12,18 262:12 310:18 <b>wheel</b> 94:22 149:19 <b>wheelchair</b> 182:22 296:11 <b>wheelchairs</b> 88:19 246:8 <b>where's</b> 268:2 <b>whistles</b> 133:9 <b>white</b> 45:20 181:14 208:6,11 210:6 <b>who've</b> 85:20 <b>wholly</b> 301:5 <b>who'd</b> 183:8 <b>who's</b> 186:10 265:17 <b>who've</b> 195:8 265:20 308:13 <b>wi</b> 5:2 <b>wide</b> 13:15 138:3 <b>wider</b> 59:17 <b>wife</b> 115:21	<b>wild</b> 210:3 <b>willi</b> 105:5 <b>willing</b> 14:12 46:7 133:17 156:14 158:8 159:20 161:17,19 191:10 211:8 216:17 269:19 299:11 <b>wilson</b> 28:10,10 40:10 44:21 50:4 50:12,18 51:1 53:2 56:7 57:7 61:4 <b>window</b> 287:14 <b>winds</b> 306:8 <b>winning</b> 270:11,13 270:15 <b>wins</b> 271:15 <b>wish</b> 66:9 <b>wishful</b> 121:2 <b>withdrawn</b> 211:1 <b>witness</b> 117:7 315:4 <b>witnessing</b> 297:4 <b>witten</b> 182:2 194:2 194:3,4 210:7 224:1 225:17 227:19 <b>woman</b> 64:1 65:14 155:7 178:18 179:16,21 180:5 276:6 277:22 279:4,14 282:8 296:10 <b>women</b> 287:5 288:5,6,9,13,18 289:3,5,8,14 <b>wonder</b> 105:12 <b>wonderful</b> 49:14 63:2 128:3 153:7 154:20 169:3 186:13,17 188:4 189:5 247:17,21 249:3 250:14
--	--	---	--

261:1 264:12 280:21 314:21 <b>wonderfully</b> 164:1 220:6 <b>wondering</b> 172:10 225:9 <b>won't</b> 268:18 311:15 <b>woodcock</b> 129:9 129:18,19 130:10 132:8 134:2 142:8 144:10 148:8 153:3 157:19 162:2 167:3 168:9 169:5 170:22 172:12 174:19 179:14,17,22 294:17 300:20 <b>word</b> 108:6 209:5 284:13 <b>words</b> 22:21 80:19 139:15 148:3,10 182:15,20 209:4,5 276:13 282:18 <b>work</b> 19:1,4 20:5 21:13 22:6 24:15 33:13 36:8 37:6 38:9 39:19 42:4 43:6 44:10 45:4 47:14 49:7,8 51:1 68:3 71:6,13 72:12 83:8 86:15 89:7 94:13 117:3 117:12 121:8 123:16 125:5,10 126:19 127:15 134:7 136:4,11 150:4,12 154:5,8 154:8,18 156:12 161:14 162:11 164:16 166:1,12 167:17 168:4 170:6 171:21 174:13 175:3	178:11,13 180:2 186:15 189:11 195:9 203:4,11 211:17,18 213:17 221:8 223:16 224:10 230:6 236:6 237:2 240:9 240:10,22 241:5 241:16 245:21 249:5 250:1 254:20 255:5,22 257:13 258:18 267:19 268:17 272:3,15,17 281:16 283:18 290:9 291:3,17 302:3 304:18 305:12 <b>worked</b> 70:5 105:14 176:6 247:21 254:11 256:18 279:21 308:14 <b>working</b> 13:19 17:17 26:11 28:20 30:22 34:18 37:6 37:9,13,21 38:22 39:4,7 41:1,10,11 44:8 49:21 57:10 57:21 58:1 61:10 61:11 62:1 68:22 72:18 121:10 122:15 123:11 128:22 131:2 135:5 137:21 142:20,22 143:13 153:12 158:8 161:13 164:14 167:8 173:8 176:1 178:14 187:18 212:19 215:11,16 218:20 224:9 235:21 236:17 240:6 241:4,4	244:5 247:6,12 252:17,21 256:7 259:3 266:11 273:5 274:7 283:22 288:8 298:21 302:14 313:15 314:16 <b>works</b> 22:13 31:2 112:14 168:5 177:7 215:18 251:17 256:17 259:2,4 278:9 295:6 <b>workshop</b> 140:7 197:7,8 198:1 <b>workshops</b> 61:22 62:17 <b>world</b> 14:15 15:15 15:15,16,16 16:2 16:6,10,10,14,14 16:18,19 17:5 25:20 27:4,13 28:3 83:6,19 88:12 89:3 110:8 118:14 121:1,6,11 121:19 145:12 158:3 166:5 183:10 184:12 208:18,20 227:1 227:12 235:10 256:1 257:19 274:10,22 275:11 <b>worried</b> 162:18 <b>worse</b> 12:17 71:19 96:2 <b>worth</b> 219:20 <b>wouldn't</b> 203:4 216:19 221:5 225:15 242:18 245:8 <b>would've</b> 204:21 <b>wow</b> 231:8 <b>wrestling</b> 149:6	<b>writing</b> 76:16 88:6 <b>written</b> 144:11 243:3 256:6 292:17 306:11 <b>wrong</b> 107:12,13 154:5 <b>wrote</b> 223:12 300:17
			<b>x</b>
			<b>x</b> 151:5 164:12
			<b>y</b>
			<b>yale</b> 191:6,6 192:16,17 193:3 <b>yeah</b> 36:20 44:21 55:6 70:9 83:5 90:14 97:8 106:5 111:5 112:11 136:9 142:8 149:15 157:19 162:2 163:1 165:14 174:19 220:22 227:19 233:4 256:11,21 275:6 277:21 279:14,15 280:12 280:13 <b>year</b> 22:3,3 24:22 29:8 51:15 61:20 61:22 62:2 88:8 92:2 103:4,4 105:9 115:4 117:14 118:18 119:9 120:9,17 124:7 133:8 137:8 183:22 184:9 190:11 226:19 244:4,6 248:15 262:22 293:12,15 300:7 <b>year's</b> 96:2 <b>years</b> 29:6 31:2 33:20 34:5 36:2 46:14 57:3,9 70:1

70:9 71:2 73:11 74:14,14 76:10 80:15 91:4 93:12 96:6,22 106:4 108:8 119:6,16 135:11 137:19 147:20 152:5 153:14 154:13 155:14 159:7,12 163:8 168:10,14 182:8,18 183:2 184:14 188:22 190:18 199:20 208:12 225:21 229:19,20,21 233:19 234:15 240:11 243:13 245:19 252:5,16 252:19 253:17 254:9 262:22 265:1 266:2,16 270:8 277:1 287:9 297:2 303:10 307:17 309:20,21 310:5 <b>year's</b> 184:6 <b>yellow</b> 285:17 <b>yep</b> 231:3 279:4 <b>yielding</b> 176:9 <b>young</b> 232:1 282:9 296:20 <b>younger</b> 289:16 <b>you'd</b> 238:11 <b>you'll</b> 234:21 285:14 <b>you're</b> 190:11 200:13 207:14 214:13 227:17 232:18 234:20 238:19 275:20 277:20 281:6 283:13,15 284:3 285:10	<b>you've</b> 188:2,14 197:11 204:3 212:16 219:9 229:5 270:15 <b>yu</b> 182:3 184:4,19 185:2 186:6 190:6 208:14 211:14 219:10 228:5,6 <b>yu's</b> 224:20
	<b>z</b>
	<b>zelgensma</b> 29:8 <b>zero</b> 308:1
	<b>à</b>
	<b>à</b> 259:2

Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate.

The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

DISCLAIMER: THE FOREGOING FEDERAL PROCEDURE RULES ARE PROVIDED FOR INFORMATIONAL PURPOSES ONLY.

THE ABOVE RULES ARE CURRENT AS OF APRIL 1, 2019. PLEASE REFER TO THE APPLICABLE FEDERAL RULES OF CIVIL PROCEDURE FOR UP-TO-DATE INFORMATION.

VERITEXT LEGAL SOLUTIONS  
COMPANY CERTIFICATE AND DISCLOSURE STATEMENT

Veritext Legal Solutions represents that the foregoing transcript is a true, correct and complete transcript of the colloquies, questions and answers as submitted by the court reporter. Veritext Legal Solutions further represents that the attached exhibits, if any, are true, correct and complete documents as submitted by the court reporter and/or attorneys in relation to this deposition and that the documents were processed in accordance with our litigation support and production standards.

Veritext Legal Solutions is committed to maintaining the confidentiality of client and witness information, in accordance with the regulations promulgated under the Health Insurance Portability and Accountability Act (HIPAA), as amended with respect to protected health information and the Gramm-Leach-Bliley Act, as amended, with respect to Personally Identifiable Information (PII). Physical transcripts and exhibits are managed under strict facility and personnel access controls. Electronic files of documents are stored in encrypted form and are transmitted in an encrypted fashion to authenticated parties who are permitted to access the material. Our data is hosted in a Tier 4 SSAE 16 certified facility.

Veritext Legal Solutions complies with all federal and State regulations with respect to the provision of court reporting services, and maintains its neutrality and independence regardless of relationship or the financial outcome of any litigation. Veritext requires adherence to the foregoing professional and ethical standards from all of its subcontractors in their independent contractor agreements.

Inquiries about Veritext Legal Solutions' confidentiality and security policies and practices should be directed to Veritext's Client Services Associates indicated on the cover of this document or at [www.veritext.com](http://www.veritext.com).