

7PROTEUS
Larry Thompson
National Human Genome Research Institute
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Operator: Good morning and welcome to the Proteus Centrum Gene Discovery Press Conference hosted by the National Institutes of Health. This press conference will last for 60 minutes. There will be four primary speakers who will provide brief remarks and then members of the media will be invited to ask questions. To ask questions you can press * and 1 on your touchtone telephone to enter the queue. You leave the queue by pressing the # key. This conference call will be recorded and available by 5:00 pm today on the website of the National Human Genome Research Institute, www.genome.gov. Now, I will turn the program over to moderator Larry Thompson, Chief of Communication at the National Human Genome Research Institute.

Larry Thompson: Good morning, everybody. Thank you very much. I'm Larry Thompson, the Chief of Communications in the Public Liaison Branch at the National Human Genome Research Institute, which is one of the 27 institutes and centers at the National Institutes of Health. I'd like to welcome everyone to what I know will be an interesting telebriefing. Embargoed materials including videos, illustrations, and photos related to this announcement will be available on our website genome.gov/proteus. That information is available right now. It's not available to the public. Generally it's not hooked up to the website, but if you go to that genome.gov/proteus you'll be able to find all the background information available now. We'll start with a brief opening remarks by Dr. Eric Green, who's the Director of the National Human Genome Research Institute and Dr. Leslie Biesecker to my right, who's the Chief and Senior Investigator of the NHGRI Genetic

Disease Research Branch and most senior author on this paper. In addition, we'll have with us by phone from Colorado, Kim Hoag, who's the Founder and Executive Consultant to the Proteus Syndrome Foundation in the United States and from London we have with us Tracey Whitewood-Neal who's the Chairperson of the Proteus Syndrome Foundation in the United Kingdom. During the call we will discuss a paper that will be released at 5:00 pm ET today Wednesday, July 27th in the early online edition of the New England Journal of Medicine. Please note that the contents of this briefing and the contents of the paper are embargoed until that time, 5:00 pm ET today. Now, let me introduce Dr. Eric Green who'll make some opening remarks and provide some context for this gene discovery story. Dr. Green?

Dr. Eric Green: Thank you, Larry and good morning everyone. I'm Eric Green, Director of the National Human Genome Research Institute here at the National Institutes of Health. We're here today to talk about the discovery of the genetic cause of a very rare and profoundly complex disorder called Proteus Syndrome named for the shape shifting sea god from Greek Mythology. Unlike the sea god who could select his form, the bodies of Proteus Syndrome patients change against their will because of a single letter that is altered among the billions of letters that make up their genetic code. This single letter change causes parts of their bodies to grow out of control, becoming misshaped, enlarge, and painful. For many, it is life shortening. Few of us will ever meet someone with Proteus Syndrome. Moreover, few doctors ever see a case in their medical practice since there are fewer than 500 known cases in the developed world. So why does NIH take such an interest in a disease that is that rare? The answers are actually rather simple. First, rare diseases provide important windows into how the human body works and often provides valuable clues about the

causes and possible treatments for more common diseases. The gene involved in Proteus Syndrome for example is also mutated in some forms of cancer. Second, even though these individual types of disorders are uncommon, as a group, rare diseases actually affect a large number of people. One in 25 million Americans suffer from some 6,000 rare diseases and the burden in human suffering is tremendous and fewer than 300 rare diseases have useful treatments at the present time. Relatively few places in the world can afford to study rare diseases. The clinical center here at the National Institutes of Health in Bethesda, Maryland is one of them. In cases like Proteus Syndrome, that can make all the difference. Any [share eyed] clinical brought Proteus Syndrome patients to the NIH clinical center to participate in medical studies and for treatment, often times involving surgery to remove uncontrolled growth. As a result, NIH staff collected tissues for analysis that ultimately led to the current discovery. In addition to a world class research hospital, my NIH colleagues could also turn to the expertise and technologies within the NIH Intramural Sequencing Center where researchers perform genome sequencing of Proteus Syndrome patients and tissues and then analyzed the resulting data. It is the power of the new genome sequencing technologies as well as the unique resources and collaborations common across NIH that make today's announcement possible. As they sequenced the genomes of more and more individuals, the medical value of genome sequencing will grow. Discovery of the genetic cause of diseases like the one today and many others earlier this year will become more frequent and eventually help us in understanding the genetic basis for more common disorders from diabetes to heart disease. We're just starting to capitalize on the new leading edge of this genomic revolution, but like x-ray peering into our bodies in the previous century, the power to routinely and robustly peer into our genomes will prove revolutionary. To tell you what

was done in studying Proteus Syndrome and what has been learned, I'd like to introduce Dr. Leslie Biesecker, a board certified medical geneticist, a human genetics researcher, and Chief of the Genetic Disease Research branch in NHGRI Intramural Research Program. Dr. Biesecker.

Dr. Leslie Biesecker: Thank you, Dr. Green. Today's report in the New England Journal of Medicine is a culmination of a fifteen year long search for the cause of Proteus Syndrome in my research group here at the National Human Genome Research Institute, but much of the credit goes to the Proteus Syndrome Foundations of the US and the UK and physicians in hospitals around the United States and around the world that have referred their patients to our study here in the Bethesda. While the American tax payer funded most of our work, critical financial support also came from the Proteus Syndrome Foundations, both in the United States and the United Kingdom, who's not only provided funding but helped us to recruit and they supported patients from around the world participated in our study. You will hear from Kim Hoag and Tracey Whitewood-Neal shortly about what discover means for members in their communities but first, let me tell you about this disorder. No two patients with Proteus Syndrome are exactly alike. Most of the affected individuals appear healthy at birth, but typically during the child's first year some parts of their bodies begin to grow faster and larger than they should, becoming progressively and sometimes startlingly pronounced with age. Our clinical studies have shown that the overgrowth can affect just about any part of the body, but most commonly affects the skull or arms and legs and a variety of skin lesions including thickening of the soles of the feet. For some patients, neurological impairments can occur and others have suffered fatal blood clots and lung disease. It is, for many patients, a truly devastating condition. Participants in our Proteus Syndrome study came to the NIH

Clinical Center where for some are team performed operations to help stop bones and tissues from overgrowing. While certainly helpful for those patients, these surgeries also provided vital biological materials that we could bank and then later study for genetic changes. These studies proved to be clinically important because the gene mutation that causes Proteus Syndrome rarely appears in blood samples. In the clinic, we must have tissue biopsies to genetically diagnosed the disorder. Not only did we need the tissue samples for our research study, but we also needed genome analysis technologies to mature. With the advent of what is called next generation sequencing, it became affordable to send DNA from biopsied tissue to the NIH Intramural Sequencing Center where our colleagues perform whole exome sequencing on seven patients affected with Proteus Syndrome. Whole exome sequencing analyzes just the protein coding sequence of the genes, allowing us to discover a point of mutation, a single letter misspelling in the three billion letters of the genome DNA in a gene called AKT1. This activates the sporadic tissue growth in patients with Proteus Syndrome. A more standard sequencing strategy then went on that same gene mutation in an additional twenty affected individuals, and I really want to emphasize that all patients so far have exactly the same mutation in the same genome. The AKT1 gene mutation has never been found in unaffected people as our survey of several genomic databases in other populations we study here in NIH. Here's the really surprising part, which is that the mutation is not inherited. Instead it occurs anew in a single cell in each affected individual during embryonic development and the severity of the disease depends on when during embryonic development the mutation arises. Once the mutation happens, the cells that descend from that mutated cell display the uncontrolled growth that characterizes this disorder. This explains why the mutation was difficult to detect. When we take tissue samples from an affected

individual, some of the tissue is affected by the mutation and some of the tissue is essentially normal. The mutation that occurs in this was at some time during embryonic development is called a genetic mosaicism. The consequence is that only some of the body's tissues and bones displayed the overgrowth and other parts of the body are not affected. The affected patients are thus a mixture. Parts of them have the disease and parts of them do not. This makes sense biologically with what we know about this gene. The AKT1 gene mutation creates an oncogene, the kind of mutation that can drive uncontrolled cell division normally associated with cancer. In fact, the AKT1 mutation has been found among a group of mutations that cause cancer to spread. The research on this gene mutation in cancer may turn out to be beneficial for patients with Proteus Syndrome. Work has been done by others to inhibit the activity of mutated AKT1 has shown that it may become possible to treat patients with Proteus Syndrome with a drug originally developed for cancer. There are a number of other potential drugs being developed to inhibit the pathway involving this gene. I can answer questions you may have about the science of the AKT1 gene, but I would also like to mention the Proteus Syndrome has played an important role in our cultural history and art. The most famous person we know with hallmark features of Proteus Syndrome is the 19th century Englishman Joseph Merrick, formerly known as the elephant man, has gained renown during his life and well afterwards due to his profound overgrowth which included a very large skull, an overgrown arm and leg, and numerous other complications. Through the cooperation of professors Martin and [unintelligible] at the Royal London and Barts Hospital where he died in 1890 at the age of 27 years, we have begun a study to test DNA from Merrick's skeleton for the genetic mutation of Proteus Syndrome. We will be testing this DNA in our labs and hope that our tests will answer the more than a century old question of

the cause of his condition. It will not be an easy study since his DNA is quite old and degraded by the way the skeleton was prepared. So at the moment we do not have results to report, but we hope to be able to announce an answer in the coming months. So let me close there and ask Larry to introduce our Proteus Syndrome Foundation representatives that joined us today.

Larry Thompson: Thank you, Dr. Green and Dr. Biesecker. Now to speak on behalf to eh Proteus Syndrome Foundation of the United States and the United Kingdom to represent the families of those with Proteus Syndrome are Kim Hoag and Tracy Whitewood-Neal. I'd ask Kim to go first and make your opening statement. Please go ahead, Kim.

Kim Hoag: Okay. Good morning. Today I would like to give you a brief understanding of what it is like to be a parent that has a child with Proteus Syndrome and what this finding means to our families. This is obviously a syndrome that is shared by only several hundred people in the world and is very scary for the parent to have one of their children. I gave birth to Alex, my first child, in 1990. After one full year, he was finally diagnosed with Proteus Syndrome. I was handed an article with numerous cases of children with horrible, horrible overgrowth. The articles spoke of amputations, disfigurement, and Joseph Merrick, the elephant man. It was positively a nightmare come true and the real kick quick no one knew what caused it. I had so many questions and I had no idea where to turn because no one knew much about Proteus Syndrome in 1990. Imagine getting the flu and no one had ever heard of it or seen it. Just you with the flu not knowing the course it would take. It was very much like being lost in space. In 1990 there was not a clear cut diagnostic criteria for Proteus Syndrome. Most doctors would never even see a child with this syndrome,

so who could be an expert? I myself had to become the professional to the professional, making sure that each of his six or so doctors was aware of what the other doctors were doing, thinking, or guessing. It was a very scary place to be. So in 1992 I started the Proteus Syndrome Foundation in the USA. I did this for several reasons. One of which is in order to pull families together so that a database of Proteus patients could be made in order to make research into Proteus Syndrome a more manageable task. Another reason of course was to save Alex's life. Over the past nineteen years I've had families come to the Proteus Foundation in many different states – scared, worried, ashamed, unsure of how to raise their own child, and always scared of death. Unfortunately, I did not accomplish my goal of saving Alex. In 1999, at the age of nine, he died of a pulmonary embolism. Pulmonary embolisms or DDTs we now know are common to these kids. Back then the pieces hadn't been put together quite yet, so we weren't looking for DDTs. Now, thanks to Dr. Biesecker and his work and the other wonderful doctors at NIH, in 2011 there is a clear diagnostic criteria for Proteus Syndrome, making it easier to diagnose. New Proteus patients are immediately told about the foundation to give them support and guidance and now parents can understand what has caused their child to have this syndrome. This discovery opens a pathway for research in medicine to regulate this growth of these cells. This opportunity was not available before the finding of this gene. The next chapter for the Proteus Syndrome Foundation is to stay committed to the NIH and Dr. Biesecker as we move forward with therapeutic research.

Larry Thompson: Great. Kim, thank you very much. So Tracey, would you like to make your opening statement, please?

Tracey Whitewood-Neal: Of course. For me and the families that I support, this is so much more than a scientific breakthrough. This is personal and this is real. It's the light at the end of the tunnel and that glimmer of hope that we've been waiting for all these years. Many of the families that I've talked to have dared to dream for so many years a cause would finally be found and they would have a chance to actually stop Proteus in its tracks. I actually started the support group in England after meeting Les and meeting Kim and for many of the same reasons that Kim has explained, about the lack of information, the isolation, and the wanting to find answers. Of course this news is so exciting that it could be very easy to forget the fifteen years of dedication, hard work, and commitment put in by so many people - by Les and the team at the NIH, by Kim and the Proteus Syndrome Foundation that she started all those years ago. If you think about it, all these years have been all the presentations we've given to groups and schools and organizations, the documentaries, the meetings, the fund raisers. It's about the families that have travelled from all over the world to take part in the study, the children that we had to watch them going through countless tests and examinations, and it's about the doctors that support this research by sending tissue samples after operations, but it's also about the lives that have been so tragically lost and Kim has just talked about Alex. I never had the pleasure of meeting him, but I have met many children one year and then heard of their passing away the year after. We are so lucky that Kim and the other families that have carried on despite their tremendous loss and I'm very aware of how we must be sensitive to that. Lastly, I must mention my son, Jordan, who has Proteus Syndrome. He is sixteen now and I'm grateful everyday that he's still here with us. He has endured a lot of pain in his life and various operations since he was actually two weeks old. Jordan had his first leg amputated in September 2009 and the other leg in February 2010. That

was a very, very difficult decision for him but he's happy he made that decision and he starts college this year and hopes to go to university to become an architect. He's inspired many people and I'm proud of what he's achieved and I'm proud of the drive and ambition that he has. Now as Kim said, we need to start a new chapter and channel our energies into finding treatment options. Just lastly, it's been an honor and privilege to work with everyone involved. Thank you.

Larry Thompson: Thank you very much, Tracey. So I guess what we'd like to do now is open up the phones to the reporters to ask questions for any of the four members of our panel here. Please give us your name and tell us what your news organization is when you ask your question. Leo, would you remind everybody how they can indicate they'd like to ask a question?

Operator: If you'd like to ask a question, please press the * and 1 keys now on your touchtone telephone. To withdraw from the queue, you may press the # key. Once again, to ask a question please press *1 now on your touchtone telephone. We'll take our first question from the site of Michelle Cortez of Bloomberg News.

Michelle Cortez: Thanks so much for taking the call. I am wondering if you can tell us about the idea that the cancer drugs might afford some type of a treatment. Do you have a study planned to do that? How would you envision that that might actually work? How would it benefit these patients?

Larry Thompson: I'd ask you guys, everybody who's speaking on our side to identify themselves also since we're on the phone.

Michelle Cortez: Right. I'm Michelle Cortez with Bloomberg. Thanks.

Larry Thompson: Thanks, Michelle.

Dr. Leslie Biesecker: So as you're aware, there are a number of steps involved in getting from the discovery of a causative mutation to an effective therapy. We are extremely fortunate that because this mutation has already been known to be a mutation that is involved in some cancers, that a substantial amount of work has already been done studying the effect of this mutation as well as a number of companies have begun programs to screen for small molecules or therapeutics that are active against this protein or even better, the activated form of this protein as this mutation is. So that allows us to leapfrog a number of steps. However, there's still much to do with respect to the fact that Proteus Syndrome isn't cancer. It's an overgrowth disorder, and so it will be a challenge to adapt treatment which are designed for cancers to work for overgrowth because again, these patients are mosaics and part of their body has this mutation and part does not. So the trick will be to have a treatment that balances slowing down the mutation in the overactive cells without excessively swelling or inhibiting the activity of that protein in the normal unaffected cells which would probably have negative connotations for their health.

Larry Thompson: Follow up Michelle? Does that answer your question?

Michelle Cortez: Yes. I guess I'm just wondering how it theoretically it would work. Is the idea that this kind of treatment would stop the cells from dividing and slow down the process? Is that it or would it actually kill those cells?

Dr. Leslie Biesecker: Great question. This protein does a number of different jobs in a number of different cells. So the answer to your question will depend on exactly which cells are involved, so it's a really interesting and challenging

question. Most of what the protein does is slow down apoptosis or programmed cell death, and so the cells don't stop growing or die when they're supposed to. So what we would hope is by inhibiting this protein that we could make that process start up again and so that the cells would stop growing. So the hope would be that by inhibiting the protein, you will see a slow replication or stop it in cells that in fact should have slowed or no replication and mimic the effect of the unmutated protein, but there are other effects and one of the other effects is that this protein is active in platelet activation which as you know, is important for blood clotting which relates to the problem of thrombosis and embolism. So reducing the activity of platelets will be another task that we will want to try and do. So it'll be challenging to inhibit the multiple effects of this mutation in multiple cells.

Larry Thompson: Great. Thank you very much. So we move to the next question please. It looks like Brendan from Nature would like to ask a question?

Operator: Yes. Brendan, from Nature. Your line is open.

Brendan Maher: Hi. This is Brendan Maher from Nature Magazine. I was curious what this discovery means for previous findings that a P10 mutation was associated with Proteus Syndrome and Codon Syndrome and others. Does it kind of clinically delineate further what these different sorters are in some way, shape, or form?

Dr. Leslie Biesecker: Thanks for the question. It's a great question because it turns out that AKT1 is in the same pathway as P10, the P10 gene, and that this explains why mutations that knock out P10 function cause a similar phenotype to mutations that activate AKT1 and that explains why patients with these

two disorders have overlapping but somewhat distinct clinical manifestations, which is what we had concluded from our clinical research work on the patients who've come to NIH. That is that patients with the P10 disorders and there are two names for that disorder. It's either called the P10 tumor hematoma syndrome or the Solamen Syndrome and patients with that phenotype can also have overgrowth but the character of the overgrowth is different than it is in patients with Proteus Syndrome but it does again, explain why there is overlap between these two disorders because the loss of one protein should cause the same effect as the gain of the other protein.

Larry Thompson: Anything else, Brendan?

Brendan Maher: No, not right now. Thanks.

Larry Thompson: Okay. Can we move on to Matt Jones, please?

Operator: Matt Jones of Genome Web, your line is open.

Matt Jones: Thank you. For Dr. Biesecker and Dr. Green. First of all, I'd like to find out if this project was under the Rare and Neglected Disease Program and second, I'd like to hear a little bit more about the genomic analysis and how the process worked and whether or not you knew you were hunting for a single mutation?

Dr. Eric Green: I'll answer the first question and then Les can answer the second. This project was not done under the offices of the Rare and Neglected Disease Program. In fact, it predates that program by probably a good dozen years or so of effort, if I remember the full history, or some large number years, but well over a decade. So no, it's not formally part of that project and it's

not been at all associated with that program at least up to the present time.
Matt, restate the second part of your question about...?

Matt Jones: Oh, how the sequencing was done in the analysis and if you thought or suspected that you were looking for a single mutation.

Dr. Leslie Biesecker: Okay. Matt, thank you for that. Actually, I would say that all bets were off as far as what kind of a genomic aberration could cause this disorder. That is to say it could have been a point mutation, it could have been a large genomic aberration such as a copy number variant or a structural genomic variant, it could've been a change in the imprinting or methylation or histone modification of a gene. There was just no way to know in advance and therefore we worked through a number of possibilities. One of many of which was a point mutation and because exome sequencing has become affordable now and with the support of the Proteus Syndrome Foundations, it became a [tractable] problem to sequence exomes of a number of patients and then compare the affected tissues to the unaffected tissues within the same patient and as well our study included a pair of monozygotic twins, and in those twins, one of the monozygotic twins has Proteus Syndrome and the other one does not and again, leading to this mosaicism hypothesis. So this is a different kind of a sequencing study. Most sequencing studies, you compare affected patients to unaffected patients, but here our primary comparison was comparing within patients. The tissues that have the trait to those tissues that don't have the trait, so it's kind of in between what you do for inherited diseases and what you do for cancer sequencing. Does that answer your question?

Matt Jones: Yes, thanks so much.

Dr. Eric Green: As I started to say Les that the degree of genetic homogeneity that you have found was not expected necessarily. Going into it, you had no idea what you were going to find.

Dr. Leslie Biesecker: Exactly. As in many traits we study, some of our traits can be caused by mutations in multiple genes in addition to multiple mutations in the same gene. Again, all bets were off. We just had no idea. Once you know what the mutation is and understand the biological pathway then it makes sense that it is a single gene because in general, it's more specific - the mutation that leads to activating a gene than it is that mutations that lead to loss of function of a gene. The latter are typically much more heterogeneous.

Larry Thompson: I just have a question that's occurring to me. Were you surprised that it was a single letter that was being changed? I mean, this has a hugely powerful effect for switching to single letter in the genome and we know though there are snips all over the genome that have no effects like this. So why is this letter change having a profound effect?

Dr. Leslie Biesecker: There's a huge variation in the correlation between genomic variation and health and disease. As you say, all of us have thousands of variations in our genome. Some of which cause little and many of which cause absolutely no consequences, but a few mutations in a few genes can have overwhelming and profound effects on our phenotype and our physiology and this is one and it's in a key protein that is important for regulating growth and activation of multiple pathways and so this is one of those few that just has a huge effect because it is a key player in physiology of growth and development.

Larry Thompson: Very interesting. So we move on to the next question. I think Brendan has a follow up?

Operator: Yes. We have a follow up question from Brendan Maher of Nature Magazine. Go ahead.

Brendan Maher: Yes. Getting onto the idea that this one mutation seemed to affect so many in your sample group or almost all in your sample group, is there any ideas to the biology of why this one gene seems to be mutated in this one specific spot? Why that's potentially tolerated in the cell in the embryo and why it causes this disease?

Dr. Leslie Biesecker: Okay. Thanks, Brendan. In general, activating mutations are much more limited in their spectrum because again, there are fewer ways to turn on a protein than there are to turn it off. What we would predict is that loss of function mutations in this gene would be more variable and scattered throughout the gene, but they would be predicted to cause a phenotype in an individual that is, in many ways the opposite of Proteus Syndrome, would probably cause undergrowth of cells in early apoptosis, etc. may actually cause early embryonic severe fetal growth restriction or fetal loss and cause a completely different disorder that we haven't even recognized yet. The mutation spectrum, the limited mutation spectrum, that we see in patients with Proteus Syndrome exactly mirrors what we see when the researchers who've done the previous work on sequencing cancers for this gene. This gene is most commonly mutated in breast cancer. It's not a high fraction. I think it's about 5% of breast cancers, but when you look at those cancers, it's almost all this single mutation, exact same mutation in those cancers as well. So I think that mutations can probably occur throughout this gene. It's just that this one mutation is the kind of

mutation that can cause this kind of an effect in the cell, and so that's what we have found because nature has filtered out these other effects and left us with patients with Proteus Syndrome or these cancers and so that's what we see when we look at it from that side.

Larry Thompson: The thing that's so interesting about it though to me was the severity of the disease in Proteus is dependent on when during embryonic development the mutation occurs. The mutation is spontaneous and so is there a way to linearly project how severe it's going to be based on when or do you guys have an insight into that?

Dr. Leslie Biesecker: So we obviously don't have the ability to go back and determine when and where this mutation occurred in the affected patients. That'll be work that we need to do in animal models to try and model that phenomenon and see if we can understand that better, but once you understand and have proven the mosaicism hypothesis, you can predict that the earlier the mutation is, the more diverse will be the tissues that are affected because those cells will go on to potentially contribute to more and more diverse organs and tissues in the developing body and conversely, the later the mutation occurs, you would expect the disease would be more mild and it would be more restricted to smaller areas of the body. In fact, there are rare patients reported in the literature who have just a quarter size lesion on their foot that looks like it's Proteus Syndrome, but they don't have any other manifestations of that disorder. So one would predict, and we are going to start working on this, predict that those patients have a very late mutation, limited to just one tiny part of the body, but it's the same mutation and the same disease process, just later and lesser than it is in patients with Proteus Syndrome. The converse of this is that it's a mosaic disorder and there are no cases known in the world of patients who have

this disorder who have either an affected child or who have an affected brother and sister. The hypothesis for that, which is now supported by this work, is that this is such a key growth regulating gene that if you have this mutation in all cells, because you inherited it from a parent, that that would be an early fetal or embryonic lethal disorder and therefore we do not see any such affected patients clinically because all those pregnancies are lost.

Larry Thompson: That's really interesting stuff. Do we have any other questions in the queue? Leo, would you ask the group/ invite the group one more time please if anyone has a question left?

Operator: Please press *1 if you'd like to ask a question.

Larry Thompson: If not, we can bring this briefing to a close for now and certainly anybody who has any other questions can call the media office here at the Genome Institute on the number that's on the release that went around and you can go to genome.gov/proteus to see the paper itself and other background materials that are available to help you guys tell the story. I would especially like to thank our two colleagues from the Proteus Foundations in the United States, Kim, and Tracy in the UK. Your participation of this was really quite wonderful and we are grateful for you taking the time. Is there any closing remarks anybody has or would like to add? I think in that case we'll bring this briefing to a close and I'll thank you all for your participation. Thank you very much.

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