UDN
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Operator: Good morning and welcome to the NIH Undiagnosed Diseases Network Telebriefing, hosted by the National Institutes of Health. This event will last for 60 minutes. There will be five principal speakers who will have brief remarks, and then members of the media will be invited to ask questions. This call will be recorded and made available soon after 2:00 PM Eastern Time today on the website of the National Human Genome Research Institute, genome.gov. Now, we turn the program over to moderator Jeannine Mjoseth, Acting Chief of the Communications and Public Liaison branch at the National Human Genome Research Institute.

Jeannine Mjoseth: Good morning, everybody. This is Jeannine Mjoseth speaking from the National Human Genome Research Institute, one of the 27 institutes and centers of the National Institutes of Health. I'd like to welcome everyone to our telebriefing and grant announcement. For the NIH press release about our announcement today, please visit the News Room section at genome.gov. The press offices at each of the clinical sites we're about to announce are also ready to hear from your news organizations about their plans. At today's conference, five speakers will address different aspects of the Undiagnosed Diseases Network, or UDN. They include Dr. Eric Green, Director of the National Human Genome Research Institute; Dr. James Anderson, Director of the NIH Division of Program Coordination, Planning, and Strategic Initiatives, who oversees the NIH Common Fund; Dr. William Gahl, NHGRI Clinical Director and Director of the NIH Undiagnosed Diseases Program. He is the principal investigator of the UDN clinical site at the NIH Clinical Center; Louise Benge from Brodhead, Kentucky, who along with her four siblings received a

diagnosis from the NIH Undiagnosed Diseases Program in 2009; Dr. Anastasia Wise, a Program Director at NHGRI and co-coordinator of the UDN working group that oversees the development and implementation of the UDN. Each speaker will make brief opening remarks, and then I will return to moderate a question and answer session with our speakers. Dr. Green?

Eric Green: Good morning, everyone, and thanks for joining. I'm Eric Green, Director of the National Human Genome Research Institute, part of the National Institutes of Health. The first diseases to yield to the power of genomics have been rare diseases, usually caused by mutations in a single gene. Now when I say "yield," I mean that researchers have been able to identify individual gene mutations that cause diseases and those discoveries have, in some instances, led to new therapeutic approaches. For instance, NIH researchers have recently described the genetics of adenosine deaminase type 2 deficiency, which can cause strokes and affects physical, cognitive, and emotional function in children and adults by identifying harmful genomic variants that lead to this very rare condition and describing the biochemistry of the disease, clinical researchers have modified treatment and are testing new therapies to prevent strokes in these patients. Another example is propionic acidemia, a sometimes fatal disorder affecting about one in 35,000 newborns. Today, we better understand the condition and researchers have developed treatments involving a low-protein diet and the drug Carbaglu, approved by the FDA in 2010. Now, similarly in methylmalonic acidemia, combined liver and kidney transplantation has extended the lives of affected children. So you can see that real advances are being made in the treatment of rare diseases following the discovery of their genomic bases. Now, knowledge about rare diseases can also lead to insight about the more common and more genomically complex diseases that involve similar genes and biological pathways. Well, meanwhile,

recently advances in genomic technologies, in particular genome sequencing technologies and computational methods have greatly improved our ability to identify the genomic bases of rare disorders. Today, researchers have discovered the genomic bases of more than 5,000 rare genetic disorders, but we are still in the hunt for the cause of an additional 2,000 to 3,000 single gene, also called "Mendelian" disorders. Now, the Undiagnosed Diseases Network that we are announcing today will focus on the rarest of disorders, often those that affect fewer than 50 people in the entire world. They are so rare that they may never have been discovered or doctors may never have encountered them. We're very excited and hopeful for the success of this new program that will harness the power of a national network of experts to solve ultra-rare medical problems. The new clinical network will extend the NIH Undiagnosed Diseases Program, created as a trans-NIH program and administered by my institute, the National Human Genome Research Institute, since 2008. You will hear more about that later from Dr. Bill Gahl, Director of that program. Now in 2012, the NIH decided to build upon the experience and expertise of the NIH Intramural Undiagnosed Diseases Program to advance research into the diagnosis of very rare disorders. Through coordination and collaboration, this new Undiagnosed Diseases Network of clinical sites will share data and approaches to improve diagnoses and disseminate these advances widely. So now it's my pleasure to introduce Dr. Jim Anderson, who will announce the new clinical sites in the Undiagnosed Diseases Network. Jim?

James Anderson: Thank you, Eric. Good morning, everyone. My name is Jim Anderson. I'm the Director of the NIH Division of Program Coordination, Planning, and Strategic Initiatives, which oversees the NIH Common Fund in the Office of the NIH Director. Chances are that you or someone you know is living with a rare disease. Rare diseases are defined by the 1983 Orphan

Drug Act as medical conditions affecting fewer than 200,000 people in the United States population. Individually, these may be quite rare conditions, but collectively, nearly three million Americans or almost one in 10 people are dealing with effects of such a condition. This population represents an important constituency of patients needing diagnoses. The Undiagnosed Diseases Network is one of more than 30 programs sponsored by the NIH Common Fund. The UDN is unique among common fund programs in that it's the only one focusing on the diagnosis of rare disease. However, it fits very nicely into our mission because like other programs we've funded, it addresses broad biomedical research challenges with the potential to fundamentally transform a field of research. The seven UDN clinical sites will do this by accelerating discovery and innovation in the way we diagnose and treat patients with previously undiagnosed diseases. We anticipate that the UDN will create a new paradigm in medical diagnostics that will improve our understanding of rare disorders and also generate insight into human biochemistry and physiology of common diseases. As you've heard, the seed of this network is the pilot intramural research program called the "NIH Undiagnosed Diseases Program," or UDP. The UDP clinical site located in the NIH Clinical Center, which is the world's largest research hospital, will work with new clinical sites to improve approaches to inquiries, evaluation of medical records, and detailed assessment of phenotypes, environment and genotypes in patients and families selected for diagnostic investigation. So now, I'm very pleased to announce the six new clinical sites that will extend the geographic reach and the scientific expertise of this network around the country. The NIH Common Fund has awarded four-year grants of approximately $7.2 million each to the following institutions, and these are in alphabetical order: Baylor College of Medicine in Houston, Texas with the principal investigator Dr. Brendan Lee; the Harvard Teaching Hospitals including Brigham and Women's,

Mass General, and Boston Children's Hospital with the principal investigator Dr. Joseph Loscalzo; Duke University in Durham, North Carolina with co-principal investigators Vandana Shashi and David Goldstein; Stanford Medicine in Stanford California with co-principal investigators Drs. Euan Ashley, Jonathan Bernstein, and Paul Graham Fisher; the University of California, Los Angeles with principal investigators Dr. Eric Vilain, Katrina Dipple, Stanley Nelson, and Christina Palmer; and the sixth is Vanderbilt University Medical Center in Nashville with co-principal investigators Drs. John Phillips III and John Newman. Overall, the NIH Common Fund has committed more than $120 million over five years in this large scale multi-part effort in addition to funding for the seven clinical sites. This includes funding for the UDN Coordinating Center, the gene function studies, and the UDN core laboratories. We are looking forward to myriad discoveries from our medical colleges on the country as they seek to solve medical mysteries. These discoveries hold the potential to improve the lives of individual patients and to have overall knowledge of both rare and common disease. Now, I'll hand it off to Dr. Bill Gahl.

William Gahl: Well, thanks, Jim. We launched the NIH Undiagnosed Diseases Program in May of 2008 in part because the NIH Office of Rare Disease Research, or ORDR, received so many calls from patients who lack diagnoses. Once NHGRI, ORDR, and the NIH Clinical Center established the Undiagnosed Diseases Program, rare disease communities spread the word, and there's never been a shortage of referrals to the program. In the past six years, the UDP has logged nearly 10,000 inquiries from patients or their primary care providers, seeking answers to questions that no one else have been able to answer. It takes eight to 12 weeks for the UDP to evaluate an application, and the waiting list for admission to the program is two to six months. Of the 3,200 people who have submitted applications to the

program, we've selected 750 individuals to spend a week at the NIH Clinical Center. There they receive an exhaustive evaluation from a multidisciplinary healthcare team who tries to analyze their symptoms and diagnose their health problems. We see about 130 patients per year of whom about 60% are adults and about 40% are children. We've resolved between 25% and 50% of cases with either a clinical, molecular, or biochemical diagnosis, and we're pursuing strong leads in approximately 60 additional cases. However, we closed a full quarter of cases without reaching a diagnosis. So you can see that this is a difficult work in which we sometimes fail, but we persist in our efforts on behalf of undiagnosed patients and their families whose medical odyssey would continue otherwise fraught with delayed treatment, endlessly repeated tests, and increasing weariness of physicians who are struggling to identify and treat these disorders. That scenario is bleak and frustrating for patients and clinicians alike. We have performed genetic analysis for approximately 1,600 patients and family members, and we've conducted about 900 exome sequencing analyses. Exome analysis looks at the 1% to 2% of the entire human genome that codes for proteins, where we might find variants within genes that may affect the function of the gene and cause a disorder. As the cause of genotyping and DNA sequencing continues to fall and the accuracy of these methods increases, genomic approach has become more attractive as potentially standard means to diagnose rare disorders. What kinds of cases are we seeing? Well, more than half of the individuals admitted to the NIH Undiagnosed Diseases Program suffer from undiagnosed neurological conditions. With the advent of genomic technologies accompanied by MRIs and CT scans, and evermore sophisticated testing platforms for blood and tissue analyses, the opportunity to identify the causes of rare diseases, unusual presentations of more common conditions, and the discovery of new disorders have never been greater. We've succeeded in diagnosing numerous cases for

people who spent many years without a name for their disorder. We described a rare arterial calcification condition in the New England Journal of Medicine, and we diagnosed the second and third cases in the world of CDG IIb, a congenital disorder or glycosylation, also published in the New England Journal of Medicine. We've diagnosed rare disorders including adducted thumb-clubfoot syndrome, adenylosuccinate lyase deficiency, fatty acid 2-hydroxylase deficiency, ichthyosis follicularis with atrichia and photophobia syndrome, and choreoacanthocytosis. Yes, those are all human diseases. But lists and statistics are inadequate to convey the impact to a patient who receives a diagnosis after years of tests and doctor visits. For that perspective, I'd like to ask Louise Benge, who is calling in from Brodhead, Kentucky to say a few words. Her case came to our attention in the first full year of operation of the NIH Undiagnosed Diseases Program. Louise, will you tell us a little bit about your experience as a patient with an undiagnosed disease?

Louise Benge: Good morning. My name is Louise Benge, and I'm from Brodhead, Kentucky. As a kid, I loved playing Kick the Can, Ghost in the Graveyard, and all the running games. By the time I turned 16, I'd started having pain in my hands that was so bad I had to go to the doctor who told me it was arthritis. Every test for arthritis after that came back negative. By the time I was in my 20s, the pain in my legs was so bad that I had trouble sleeping and lots of trouble walking. My doctor didn't know the cause, but suggested arterial vascular surgery could help. He also said that I would need to repeat the surgery every five years, so I declined the surgery and my pain continued. I wasn't the only one in my family to have this problem. Each of my brothers and sisters eventually started to have the same leg pain and like me, the doctors couldn't explain why. The pain slowed me down quite a bit and has affected my life for a long time. The job that I had required a lot of data entry even with the pain that I had

in my hands. It hurts to stand and walk, but I keep up with the activities in my family. Finally, in 2009, my family physician referred my sister and I to NIH Undiagnosed Diseases Program. My whole family, including my parents and brothers, came to the NIH Clinical Center for a week of intensive testing and evaluation. NIH doctors found that our problem was due to ACDC, a rare genetic disorder that allows calcium to build up in the arteries below the waist and in the hands. It blocks blood flow and makes walking and other movements painful, as I have explained. The one silver lining is that the ACDC doesn't affect the arteries of the heart. ACDC is an inherited recessive disorder. Each member of my family inherited two copies of the mutation, one from each of our parents. Today, I take medications to thin my blood and to help deal with the pain. I am really impressed with everyone connected to the National Institutes of Health. I'm excited that they found out what was causing our problem and pray someday soon they will be able to do something to help me, Paula, Elizabeth, Daryl, and Doug. Even if they can't help us, maybe someday they will be able to help someone else who has this problem.

Anastasia Wise: Thank you, Louise. Hi, I'm Anastasia Wise and I'm a co-coordinator for the Undiagnosed Diseases Network and a Program Director in the Division of Genomic Medicine at NHGRI. The working group for the Undiagnosed Diseases Network has been actively planning for this day since 2012. We are excited to have these new clinical sites added to the network. You've heard a lot about the new UDN clinical sites today, but I'd like to tell you a little bit more about the other components of the UDN initiative. We had issued awards to fund functional studies of suspicious genes discovered during the evaluation of UDP cases. We've also inaugurated a one-year fellowship at the NIH Undiagnosed Diseases Program to train young investigators in the clinical characterization, basic science, and genomics of undiagnosed diseases. In January of this year,

we announced the $9 million four-year awards to Harvard Medical School to establish the UDN Coordinating Center. The Coordinating Center's main charge is to assist in supporting the UDN, and it will play an important role in facilitating collaboration amongst laboratory and clinical researchers across the seven clinical sites, and in sharing data and approaches generated from the cases and patients that are seen as part of the UDN as widely as possible throughout the scientific community. In collaboration with the UDN Steering Committee, the Coordinating Center will also help develop and share common protocols for collecting data and selecting, evaluating, and diagnosing patients. These efforts will enable cross-site analyses of patients on other collaborations. Principal investigator, Isaac Kohane, Professor of Pediatrics at Harvard Medical School and Boston Children's Hospital, is leading this effort at the UDN Coordinating Center. It is also important to know that for the present time, physicians who wish to refer their patients to the UDN will need to submit their applications to the NIH Clinical Center. Application instructions are detailed at the website rarediseases.info.nih.gov/undiagnosed. This site references the required case summary letter and includes the forwarding address for medical records. A toll-free telephone number is also provided for colleagues with inquiries about the application process. While the NIH clinical sites will continue to enroll 130 to 150 patients a year, patients will be seen at the new UDN clinical sites at an incremental fashion at first. The new clinical sites will enroll progressively more patients until they achieve a capacity of about 50 patients per year by the summer of 2017. Additionally, while each of the UDN clinical sites may have variations in handling health insurance coverage for clinical testing and care, no patient will be turned away from participation in the UDN based on a lack of health insurance coverage. Jeannine?

Jeannine Mjoseth: This is Jeannine Mjoseth again and at this time, I would like to open this briefing to reporter questions. Please remember to tell us who you are and the name of your organization when you ask your question. I remind our speakers to briefly identify yourselves before responding.

Operator: As a reminder, it is star and one if you'd like to enter the question queue.

Jeannine Mjoseth: Hi, Maggie. Go ahead and ask your question.

Maggie Fox: Hi! It's Maggie Fox at NBC News. A lot of these rare diseases have names that are a big mouthful. I'm hoping you can provide the names in writing. But can we go into a little bit more detail about what some of the rare diseases are, and also I'd like to hear a little bit more about this patient, Elise, who's been so nice to share her story with us. Thanks.

William Gahl: Yes, this is Bill Gahl, and I can tell you a little bit about Louise's case, because that is one of those mouthfuls. It is a disorder of calcification of the large arteries just especially below the waist. So we would call them the femoral and popliteal arteries as the one coming of the waist and then going down through the knees, and the calcification there is incredibly great and blood doesn't flow through that. So you have to have other smaller vessels be made in order to get any blood flow to the feet, and then the feet hurt a lot because there's insufficient blood flow there. So it turns out that this is due to a particular absence of a protein, which is called CD73, and that protein is an enzyme that normally functions to prevent that calcification in the cells of those vessels, and when you don't have that protein, you get the calcification as a sort of a default, and that's what happened to this family, Louise and her four siblings. So that's a new discovery and it really wasn't known before this that that protein, CD73, was so critical in preventing the calcification of these vessels. So that

would be just an example, but we could describe some of the other disorders that are also mouthfuls in terms of pronunciation. [Pause] Did you want to do that offline or what? [Pause] Maggie?

Jeannine Mjoseth: Sorry. We can provide the names of the diseases that Dr. Gahl mentioned earlier and the correct spellings. Did you want to ask Louise any questions?

Maggie Fox: I did. I also wanted to ask whether this discovery can shed light on calcification in general, which of course we know underlies a lot of common cases of heart disease.

William Gahl: Well, in this particular case, it turns out that the coronary arteries – or the heart disease is not really – they're not really involved, but the vascular biologists, now knowing the role of this particular protein, CD73, now recognize that an entire pathway is geared towards preventing that calcification, and there may be implications for more common diseases like atherosclerosis. Even more so, it turns out that there's a kidney disease which is Monckeberg's medial sclerosis – another mouthful – that causes calcification of certain arteries and that may very well have to do with this particular pathway, and so that's being investigated. And that's fairly common for patients who have big-time kidney disease.

Jeannine Mjoseth: Thanks. What is your question for Louise, Maggie?

Maggie Fox: Well, Louise, can you tell me about your experience at the Clinical Center and just how many doctors have you gone to through your life?

Louise Benge: Well, I have a primary care physician here in Mount Vernon that I have seen – oh, goodness – for years, and I've seen several vascular doctors.

I've seen some neurological doctors. When I went to NIH, they sent us through every doctor imaginable: heart doctors, arthritis specialists, vascular specialists; just all kinds of doctors that – just about every doctor out there, we've seen and they've run a lot of tests and did a lot of blood work and a lot of CT scans, MRIs, EKGs, different things – ABS, which is a test that we do on a treadmill to see how long we can walk with that and then how long it takes for blood flow to get back to the feet, which is we don't have much blood flow at all. They have been really good about helping us, trying their best to figure out something for us to be able to get our life back without having all this pain. Right now we are taking a drug called etidronate that we take for two weeks, and then we're off for 10 weeks, and then we go back on it; and we go back to NIH every six months for them to do more CTs and more EKGs and more blood work, and things – tests like that to try to see if the drug is helping.

Maggie Fox: Thank you so much.

Louise Benge: You're welcome.

Jeannine Mjoseth: Okay. I'd like to move on to Murrey Jacobson, PBS NewsHour.

Murrey Jacobson: Yes. Hi, can you hear me?

Jeannine Mjoseth: Yes, we can.

Murrey Jacobson: Hi, sorry about that. Thanks very much for doing this. I have a couple of questions and I'd also ask, too, if there's a way to maybe email any of those opening statements for some of these diseases or names, as Maggie was alluding to. That would be tremendously helpful. I guess a couple of questions here. The centers that are named, they're obviously all major

names in medical research. But the ones that are chosen here, are they all notable for their work on specific rare disorders or diseases? How were they or why were they selected? Are their programs that advanced? I guess one thing that I'd like to know a little bit more about is I understand that there would be more coordination and all, but help us – or help me, I guess, understand more about why a program like this would be substantially different from UCLA, for example, being in touch with NIH anyway, or Vanderbilt being in touch with NIH anyway. Is this sharing of data just not happening unless you create a more formalized partnership collaboration like this?

Anastasia Wise: Okay. So this is Anastasia Wise and to start off with your question about why these particular sites were selected, we selected all these sites to have broad general expertise, so that all of these sites are able to see a patient with any clinical specialty. That said, each of the centers do have areas of expertise and we would expect to send a patient who might fit into that particular area to one of those sites when they're coming into the UDN. So for example, one of the specialties that I do get interested in is related to [Unintelligible] type conditions, and regarding the collaboration for the UDN and why we're looking for this Undiagnosed Diseases Network, one of the things that each of these clinical sites is offering is a one-week evaluation for these patients. These are patients that have been to a number of doctors and remain undiagnosed. We're going to bring them into this program. They'll receive this one-week very extensive clinical evaluation similar to what Bill Gahl explained for the patients and what they have seen so far in the Undiagnosed Diseases Program at the NIH. Then there's also going to be a series of these core laboratories which each of the UDN clinical sites will have access to, which will provide things such as sequencing, so that they will be able to receive exome or genome sequencing for all of these patients as well.

William Gahl: Yes, this is Bill Gahl. Let me just add one thing. I think you got at the issue of the fact that there's ad hoc collaborations now between the NIH and many centers around the country, but this network is going to create formalized automatic collaborations, because the data sharing is going to be essentially universal. That data sharing will involve both the description of the patients, what we would call "phenotyping," and also the genomic information, namely the exome or genomic sequence data, so that investigators in the program, and we hope eventually other investigators as well, can have access to that, because one of the main issues, especially with genetic diagnosis, especially with new disorders is that any individual who has one of these really rare disorders that might be new disease will have many different variants in the genes or potential mutations, and we don't know for sure which of those variants is causing the disease, but if we find a second patient who has a variant in the same gene and has the same clinical characteristics, then that pretty much nails it as the cause is that gene and the variants in that gene causing that disease. So we need a broader base, a database of information, and this type of database and network will provide that for our investigators to discover new diseases.

Murrey Jacobson: Thank you. If I could just ask one more quick follow-up, and then I'll hop off here. I'm particularly interested, just from years of looking at this Huntington's disease, which by the numbers probably qualifies here now they are more at risk than just the pure number. Now, it's already dealt with in different institutes, I think, at NIH. Would that all now come under this program, for example?

William Gahl: I would say not at all. It's an already diagnosed disorder.

Murrey Jacobson: Oh, I see. It's not undiagnosed. I'm sorry. Right. I understand about the numbers. Sorry. Thank you.

William Gahl: Sure.

Jeannine Mjoseth: Okay, thank you. I'd like to move next to Carolyn Johnson with the Boston Globe.

Carolyn Johnson: Hi, thanks for taking my question. I was wondering if maybe Bill Gahl could go over the numbers again a little slower, of just how many patients have been seen, what the success rate has been, and what you mean by the different numbers. I mean I guess you said several, like 25% haven't been solved, but then Louise says 25% have been solved. So what about the other 50% there, like what are the actual numbers, and also how long does a typical case take to close?

William Gahl: So to start at the beginning, we've had about 10,000 inquiries, but mainly most of those individuals actually don't complete an application process; only about 1/3 of them do. Then of that 3,200, 3,300 or so, we have accepted only about 20% to 25%, so maybe about 750 of those. Of those 750 we think we've got a decent diagnosis in maybe 1/4, 40% or something, but that really depends upon how you define diagnosis. You could put a name on a disease or you could find a gene, but not be absolutely certain that the variant in that gene is causing that particular disease. So it's rough. When we say that we have not made a diagnosis in 25%, the actual wordage that I've used was that we have closed the case. Essentially many of those individuals have died, but the remainder we're still working on, and sometimes we are solving cases that occurred back in 2009 or so. So we're still working on almost all of them. I think there are very few that we've given up on.

Carolyn Johnson: Okay. So your solve rate is about 25%?

William Gahl: Yes, you can say 25%. You could say 15%. You could say 40%, [Laughter] depending upon how you define it.

Carolyn Johnson: Right.

William Gahl: If you have to write something down, go ahead and use 25%.

Carolyn Johnson: Of those that you have found some kind of likely molecular explanation, how many have led to a different treatment or improvement in health?

William Gahl: Well, I would say that that's a very loaded question there. I would say that specific focus treatments have been sort of few and far between, because these are essentially incredibly rare diseases that people haven't worked on, and some of them are absolutely new diseases. I could give you some examples; for example, Louise is being treated with a bisphosphonate right now and that may be beneficial. Out of our program has emanated a new protocol to treat patients who have redox problems and mitochondrial diseases with a drug called EPI-743, which is an investigational drug. We had a woman who had some tumors that were both fibrosis or scarring and inflammatory, and we checked her cells in culture and they responded to hydroxychloroquine, which is Plaquenil, and that has stopped the growth of her tumors. We have several patients whom we did the spinal taps on and they had deficiencies of neurotransmitters, and we've treated those individuals with neurotransmitters and they're now able to essentially get up out of chairs in only a few seconds instead of minutes. So these things have changed the people's lives, and especially their activities of daily living. I think we

should also not underestimate the value of carrying a diagnosis, because individuals who lack a diagnosis are actually a little bit suspect in terms of their complaints not being trusted by their families, their friends, their employers, employees, and even their doctors, and how difficult it is for them to go through life with that element of desperation. If we can take away that element of desperation and have some diagnosis for them, even though it's a bad diagnosis, they're incredibly grateful and it changes their lives and the lives of their families. There's also the genetic counseling issues involved where other family members may be affected. So I think that cures and treatments are one thing, but changing quality of life is another thing that this program has offered to an enormous number of people.

Carolyn Johnson: Great. Thank you so much.

Jeannine Mjoseth: Okay. Next I'd like to move to Delthia Ricks with Newsday.

Delthia Ricks: Oh, yes, just a quick question. You mentioned a glycosylation disorder, and I'm just curious if you can tell me what it is and define it, because that process is so common throughout the body and affecting so many cells. If you could just explain it, I believe, Dr. Gahl.

William Gahl: Sure. This is one of a large number of congenital disorders of glycosylation, which essentially means that you can't put sugars on the proteins where they belong. There may be some glycolipids involved, too, but it's mainly glycoproteins. There are two ways that we put sugars onto glycoproteins; one is through linkages that are involving oxygen; one involves nitrogen. So they're O linked or they're N linked. Okay. So this particular disease has to do with putting of tree of sugars onto the N – the nitrogen's in a particular amino acid on a protein. In this case, the sugars

are put on, but they can't be broken down and built back up into the right sequence of sugars. As a consequence, a whole group of these glycoproteins or sugar proteins are not made properly and the consequences are incredibly wide ranging; for example, these individuals have a small brain's development – poor development, dysmorphic or abnormal shape faces, cognitive delays, and hormonal issues as well. So they're extremely rare. When we say that it's the second and third case in the world, it means that the medical profession doesn't know a whole heck of a lot about these particular diseases. But as a group, they're called "congenital disorders of glycosylation," because the sugars are not made properly and put onto proteins properly. Is that close?

Delthia Ricks: That's interesting and it's very close, but I wanted to know also, does it have anything to do with congenital problems involving the endoplasmic reticulum or the Golgi bodies, because isn't that where all of that happens?

William Gahl: Yes, I wasn't going to go into it, but since you're so sophisticated, [Laughter] I guess I'm going to have to. [Laughter] But [Unintelligible] movement of these glycoproteins from the endoplasmic reticulum to the Golgi and actually, that movement is facilitated by having glucoses put on as the terminal sugars on that tree, and congenital disorder of glycosylation type 2B is a defect in the cleavage of the terminal – the last glucose from that in the Golgi. So there you go.

Delthia Ricks: Thank you [Laughter] very much.

James Anderson: Professor Gahl has told us he'll be giving a take home exam on that topic. [Laughter]

William Gahl: Yes. I'd give a tutorial. [Laughter]

Delthia Ricks: Thank you.

Jeannine Mjoseth: All right. We're going to move next to Mark Johnson with the Milwaukee Journal.

Mark Johnson: Hi, thanks so much for taking our questions. I had kind of two questions. One was just a brief one related to Louise. I was hoping you could explain what the treatment that she's receiving is actually doing and to what extent it's sort of addressing her symptoms. The other thing that I was interested in was whether all of these different clinical operations are going to have a uniform method for sort of revisiting cases, because one of the things that seems to happen a lot with genomic data is that we're finding out new information about SNPs and genetic variations week to week to week. I wondered whether there's a process when you don't necessarily find a diagnosis right away, whether there's a process for sort of reevaluating after six months or a year or so when there are more papers out, more information about SNPs, that kind of thing.

Male: Do you want to [Unintelligible]?

William Gahl: That's Louise.

Male: In front of you.

William Gahl: So, Louise, I think that Mr. Johnson actually addressed the question to you about the treatment. Would you like to answer it or do you want me to chime in?

Louise Benge: I can tell him what the medicine is and what they're hoping it will do.

Mark Johnson: Okay, that'll be great. Thank you.

Louise Benge: Okay. The medicine we're taking right now is called "etidronate," which is a bisphosphonate that they're hoping will dissolve some of the calcium in our arteries to get rid of some problems or at least hopefully will stop the progression of the disease and maybe help us to be able to better continue to live a more better life. Dr. Gahl might be able to – well, will be able to give you a better answer if that's not sufficient. [Laughter]

William Gahl: So actually, Mark, I can mention just a couple of things. Remember, I mentioned that there's a deficiency of CD73, and that CD73 will normally inhibit the calcification process. It does so by inhibiting the production of alkaline phosphatase inside those vessel cells. Well, the bisphosphonate etidronate does inhibit that alkaline phosphatase, and therefore inhibits the calcification at least in a cell system in vitro, namely fibroblast from the patients. So that's the thinking behind it, but of course, it's an investigational treatment.

Mark Johnson: Okay. Great.

Anastasia Wise: This is Anastasia Wise and I can answer your question about the uniform method for revisiting cases. We are planning on developing a network-wide UDN protocol for doing things like analysis of this, the sequence data, though all the clinical sites will also be able to perform their own analyses. As part of that network-wide sequencing protocol, we are planning on having a plan for being able to revisit the analyses of that data at certain points in the future. We haven't decided yet if that will be a certain time point or if it will be when we have a new analysis method to

try out, but we are definitely considering continuing to evaluate this data as time goes on.

Mark Johnson: Thank you.

Eric Green: [Unintelligible] this is Eric Green, and I should add to this, because I think that question and some of the earlier things you heard about when Bill Gahl was explaining how some cases are sort of never closed in many ways that they remain active, that's important. People probably appreciate it, but I should just reiterate that all of this is taking place in the context where every single week, every month, every year, we increase our understanding of all the functional elements in the human genome, which means we can better understand what the variants and the genome that one sees in these patients, which of those are relevant and which ones are not. So the idea, as you imply, of returning and reanalyzing the patient's genome sequence, whether it's their entire genome or whether it's just their exome, and doing that in a somewhat regular basis and comparing it to the latest knowledge that come out about the genome sequence makes complete sense, and while you may have a case that you can't quite figure out among all the patient's genomic variants at the moment, which one might be relevant, six months later it might become much clearer which ones might be relevant because of increased knowledge that we've gained in those six months.

Mark Johnson: Thank you very much.

Jeannine Mjoseth: Okay, I'd like to move on to Kelly Servick with Science Magazine.

Kelly Servick: Hi, thanks a lot of taking my question. I just wanted to follow up about the data that's collected from patients at these different sites, how will that

be centralized, and also how could it be accessed by researchers who are outside those sites? I know you mentioned that was something you hoped to do in the future. Do you have a timeline for that?

Anastasia Wise: So this is Anastasia Wise, and that's one of the functions for the UDN Coordinating Center. They're going to collect the standardized data from all of the UDN clinical sites, and be able to provide that data to public repositories, such as things like dbGaP, as well as organize both the data as well as the protocols from doing these types of patient evaluation for dissemination to the scientific community at large.

Kelly Servick: In terms of the sort of defined [scale] data, is that something that other people will be able to look at if they have more specific questions about something they're researching?

Anastasia Wise: So things like specific information about the phenotype of the patients or things like that…

Kelly Servick: Or genomic data, yes.

Anastasia Wise: Okay. So, all the genomic data will be deposited into public repositories along with information in general about the phenotype. There will also be ways to be able to access more specific information, but we're still working out some of those methods with the Coordinating Center as to what data is going to be standardized across [the area].

Kelly Servick: Great. Thanks a lot.

Jeannine Mjoseth: Okay, the next question, please, from Sandra Ackerman with the American Scientist.

Sandra Ackerman: Yes. Hi! Thank you. I have two questions, both very much logistical. They're unrelated to each other, but they both deal with practical matters. One has to do with whether finally getting a diagnosis for a previously undiagnosed condition makes a difference in the family of the patient in terms of finally getting some kind of medical coverage. Does it change their – I know these days, medical coverage is changing anyway, but are these people who have not been able to get healthcare coverage for their condition because it was not officially named anything before and they now are? My other question is whether this is entirely a United States contained initiative or whether at some point there will be some coordinating or data sharing with other European or other international organizations.

William Gahl: Well, this is Bill Gahl. Let me answer your second question first. We're actually trying to, let's say, involve people from other continents and in fact, there's a common fund sponsored international meeting at the end of September in Rome of investigators in Europe, in the United States, in Canada, and maybe a couple of other places to help establish such a database that – so we hope that this will be throughout the world at some point, and that that shared information will only expand our ability to make diagnoses and make new discoveries. As far as the coverage issues goes, we don't require health insurance here at the NIH and we don't get too involved in that. So I'll just give you my sort of personal perspective on that. When a patient sees a doctor and has coverage for not just because it's a standard through the employer or private – or whatever, the doctor has to write down some sort of a code to get paid. So she or he puts something down and the consequence of that is that the patients who come to us don't actually lack a diagnosis. They actually have many, many more diagnoses than they need, and they're pretty much mostly

incorrect but they allow for reimbursement. So the system actually solves itself that way, and I don't think that there's very much of an influence on insurance coverage based upon having a really definitive diagnosis. I don't think that the ability to get medical care changes very much just because they have a diagnosis.

James Anderson: Most of the billing is done for a specific procedure or for a type of examination, and it doesn't matter what the disease was.

William Gahl: Yes.

Sandra Ackerman: Okay. Thank you.

Operator: As a reminder, if you would like to ask a question, please press the star and number one on your telephone at this time. [Pause]

Jeannine Mjoseth: Okay. Well, if there are no more questions, I'd like to thank you for joining us for this telebriefing. You will find the materials related to this announcement at genome.gov by contacting the NHGRI Office of Communications referenced in the media advisory and press release. You may have also seen news releases from the respective medical centers. We will link from our site to those releases or you may reach out to [press] offices individually. This concludes our call.

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