NEWBORN
Larry Thompson
National Human Genome Research Institute
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Operator: Good morning and welcome to the Genomics Sequencing and Newborn Screening Disorder Research Program Briefing hosted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Human Genomic Research Institute. Both institutes at the National Institute of Health. This press conference will last for 60 minutes. Four principal speakers will provide brief remarks and then members of the media may ask questions. To ask a question, press * and the number 1 on your touchtone phone to enter the queue. You may leave the queue by pressing the # or hash key. This call will be recorded, transcribed, and available soon after 1:00 pm Easter today on the website of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Human Genome Research Institute. Now, I would turn the program over to Moderator, Larry Thompson, Chief of Communications at the National Human Genome Research Institute.

Larry Thompson: Thank you, Misty. Good morning, everyone. Welcome to what I know will be a very interesting discussion this morning. My name is Larry Thompson. I'm the Communications Director of the National Human Genome Research Institute and I will do the air traffic control for today's briefing. I want to remind everyone that the contents of this briefing are embargoed until 10:00 am ET today basically until the end of this meeting. If you need a copy of the press release, please call the NICHD or NHGRI communications offices. You can easily find our numbers on our websites

and we will post the press release and the related materials on our websites also at 10:00 today.

Today's briefing focuses on the first grants awarded under the Genomics Sequencing and Newborn Screening Disorder Research Program research program co-sponsored by these two institutes, NICHD and NHGRI. Typically, we do not hold a telebriefing about grants announcements but in this case we felt a conversation was appropriate because some of the media and some in the media and elsewhere already have been asking questions about genomic sequencing for newborns and its implications. The institute's leadership felt it was appropriate at this time to provide some context about the research program and discuss what we hope to learn from it. We'll start with opening remarks from the directors of the sponsoring institute, Dr. Alan Guttmacher from NICHD and Dr. Eric Green from NHGRI. Their bios are on their respective websites. You'll also hear from Dr. Tina Urv, Program Director of NICHD's Intellectual and Developmental Disabilities branch and Dr. Anastasia Wise, a Program Director in NHGRI's Division of Genomic Medicine. They oversee the grants for their respective institutes and will discuss a bit about the grantee's research goals. Each speaker will make opening remarks about three to five minutes and then we will take your questions. When we go to questions, I'll remind you all to identify yourselves or I'll ask our operator to do that for us and I'll remind our speakers here in the room to do the same since you can't see our faces and may not know what we sound like. Now, I'd like to ask Dr. Guttmacher to make this opening statement. Dr. Guttmacher?

Alan Guttmacher: Thank you, Larry and hello to everyone on the line. As you've heard from Larry, my name is Alan Guttmacher and I am the Director of the Eunice

Kennedy Shriver National Institute of Child Health and Human Development here at the NIH. Hospitals take a drop of blood from the heel of just about every one of the 4 million babies born in the United States each year. That blood drop is then tested for pre-symptomatic evidence of a number of diseases, almost all of them rare genetic disorders. The strategy is compelling. Early identification of the newborn period of certain metabolic or endocrine disorders allows parents and doctors to offer immediate treatment to intervention that can protect the baby from disability and even premature death. The classic example for newborn screening is a metabolic disorder called phenylketonuria or PKU. In PKU, the baby is born with a pair of mutations that prevents him or her from metabolizing the immunoacid phenylalanine. Consequently, phenylalanine, which is in high amounts in virtually everyone's diet, builds up to harmful levels in these babies and can cause neurologic damage, intellectual disability, and other serious health problems. By knowing the baby has the disease early, parents can modify the baby's diet to remove phenylalanine and prevent damage however, if one waits until symptoms appear, the damage is irreversible, so prevention is the only truly effective solution.

Newborn screening is one of the most successful public health programs in our country. We have been screening newborns in the US since the 1960s and studies show that newborn screening prevents more than 12,500 debilitating disorders in children in our country every year, saving millions in lifelong medical costs as well. Newborn screening however does have limitations. Because it is States that administer and regulate newborn screening, laboratories test for different things and different States. Currently, recommendations are the States screen for 31 disorders. These are all well defined disorders for which we have good screening and

follow up diagnostic tests and effective therapies, but 31 is only a small fraction of the many inherited disorders that exist. In the future, it may be possible to screen for more disorders and therefore benefit more children. I happen to be a Pediatrician and Medical Geneticist by training and was the Founding Medical Director in the State of Vermont's Newborn Screening Program. I also used to be the Deputy Director of the National Human Genome Research Institute and so have had the privilege of watching the evolution of genome sequencing technology as well as newborn screening over many years. In discussions with my colleague, Eric Green and others, it seemed a natural collaboration for our two institutes to begin thinking together about a more comprehensive approach to newborn screening to applications of genome sequencing. We can see the potential value of looking at an infant's genome to examine all of the genes or perhaps a particularly informative subset of them at the beginning of life rather than one of the time we're looking solely at biomarkers, which are often only surrogates for genetic mutations. When we began talking about a possible collaboration, it quickly became clear that we needed to understand many things before genome sequencing could be considered truly useful tool for newborn screening. For example, we'd like to better understand even the disorder that we already screened for newborn screening programs and find ways to improve therapies for them. We'd like to see if genomic sequencing can shed light in other disorders that we don't screen for currently and we'd like to see how genomic data might inform clinical care for newborns more generally. We also recognized that there were many ethical, social, and legal questions that the use of genome sequencing technology on newborns may raise. For example, how do we protect the baby's privacy and what are the appropriate consent processes? Where will the baby genome data be stored and who will have access to it? What condition should be included

in the test and what criteria will be used to determine a positive result? What should be the follow up for positive sequencing screening results? What should doctors tell parents about what was found? How much will all of this cost? What will be its overall impact on healthcare and other spending? These are obviously complicated questions and we, as a society, need to consider them thoughtfully before we hope implementing any sort of newborn sequencing program in a wide scale. That is why I am so pleased that NICHD and NHGRI have partnered to bring the respective expertise of our two institutes and of our research and patient communities to this problem and to fund carefully selected studies to begin finding answers to these questions. Back to you, Larry.

Larry Thompson: Thank you very much Dr. Guttmacher. I'd like to now ask NHGRI's Director, Dr. Green to make his opening remarks. Dr. Green?

Eric Green: Thank you, Larry and good morning everyone. I want to start by echoing Alan's satisfaction with this collaboration between our two institutes. In these tight budgetary times, it clearly makes sense for us to look for opportunities to combine our resources in pursuing major research projects aiming to answer important public health questions. Well, as we celebrated the 10th anniversary of the completion of the human genome project, NHGRI finds itself moving more and more into research that involved applying genomics to a wide range of diseases and clinical areas for which other NIH Institutes have subject matter expertise. For example, our collaboration with the National Cancer Institute in overseeing the cancer genome atlas project is an excellent example of such a strategic partnership. Our collaboration with NICHD that we're discussing today falls into the same category. NHGRI brings genome technology expertise and NICHD brings deep expertise in newborn genetic screening. The

public and particularly our children will certainly benefit from our working together.

Now as many of you know, genome sequencing technology have advanced dramatically over the past decade to the point where the prospect of incorporating complete information about an individual's genome sequence into his or her medical record is under serious discussion and careful study. The same time, the cost of collecting genome sequence data are falling below the costs of conducting some individual genetic tests. Thus that might soon make more sense and might be more cost effective to conduct a comprehensive analysis of the patient's entire genome than to perform one of tests of individual genes. This situation might be very relevant at the newborn stage. Recognizing these trends, NHGRI and NICHD held a workshop almost two years ago to identify elements of a research agenda that could inform the possible application of new genomic sequencing technologies to newborn screening and child health. The fruits of that workshop are the awards that we announced today, which focus on a laudable goal improving the healthcare of newborns. I do want to note something about the scale of this research program. Our two institutes expect to commit roughly $25 million over five years to the proposed projects, but we can really only commit to one year at a time pending congressional appropriation. Our ability to identify funds for the project stem from our belief that there are a number of important and challenging questions to answer such as: Is genomic sequencing of newborns an appropriate application of genome sequencing technologies and if it is, what are the situation in which it works best? What is the best way to deliver or present genome sequence information to parents and clinicians? Is complete genome sequence information too much information for either parents or clinicians and what

type of information do they want to receive? Now fortunately, we already know a great deal about newborn genetic screening and how the information can be used as Dr. Guttmacher has described. So we were optimistic that we will be able to answer many of these research questions.

Another issue is understanding cost. The proposed research aims to inform a screening program, which means it'll be associated with many negative results. Current newborn genetic screening cost about $100.00 per patient. Whole genome sequencing on the other hand now costs about $5,000.00 but whole exome sequencing now is down to about $1,000.00 or less. Will the additional information for more complete genome sequencing be worth the cost? We're continuing to support research to advance DNA sequencing technologies to bring down the costs further and it also reduce the time involved and to improve accuracy, but it may still be a bit too expensive in the short run for use in population wide screening program. Whereas traditional newborn screening only tests for a couple of dozen genetic diseases, genome sequencing has the potential to test for many of the nearly 7,000 - 8,000 inheritable diseases. So it could be tremendously powerful perhaps saving many millions of dollars in healthcare costs. So it may be worth it. That's something we hope to examine.

The program we're talking about today however is not just looking at genomic sequencing as a replacement of or in addition to the existing newborn genetic screening programs. Some of the projects are examining conditions for which doctors do not currently screen. Because of sensitivities inherent and research involving children, we also developed this research program in a careful and measured way. For example, every project we are funding has a component focused on the ethical, legal, and

social aspects of using genomic sequencing in newborn care. NHGRI has a long history and deep expertise in studying such issues. Clinical studies under this program will also have a data safety monitoring board that is responsible for protecting patients. The monitors will review protocols, provide advice, and make sure that any adverse events are quickly and appropriately addressed. The individual projects funded by these grants will also train clinicians to interpret the genomic sequencing reports and ensure that genetic counselors are available. Because there are concerns about sharing newborns' genome sequence data, our institutes are not requiring applicants to deposit these data into databases like dbGaP which archive study results related to the interaction of genotypes and phenotypes. These pilot projects are focused on improving the care of the infants in this program and that primarily means inherited diseases that tend to be rare but that need immediate intervention to prevent childhood disease. So for example, these studies are not looking at an infant's risk of developing Alzheimer's disease in their 80s. If researchers encounter incidental findings, they will only analyze the genes related to the symptom that the children may present. The program is also not looking at all at economic questions such as whether insurers will cover these costs in the future. That falls outside this program. There's been considerable and important discussion at NIH between our two institutes and also in the public about doing genomic sequencing of newborns that is an important discussion to foster and to advance and we believe that the pilot studies that we're announcing today will be an important contribution to that discussion. I am happy about our partnership with NICHD and excited to see these studies get underway. Thank you for your attention. I'll send it back to Larry.

Larry Thompson: Thank you, Dr. Green. Four research groups will receive $5 million a year, $5 million a year hopefully for the next five years under this program. I would now like to ask the program directors from the two institutes to describe the bigger scientific questions that these four groups will examine and how they will go about it. First, Dr. Tina Urv, NICHD's Program Director on this collaboration will describe the projects led by Dr. Robert Nussbaum at the University of California San Francisco and Dr. Cynthia Powell at the University of North Carolina at Chapel Hill and then I will ask NHGRI's Program Director, Anastasia Wise, to describe the work by Dr. Robert Green's group at the Brigham and Women's Hospital in Boston and Dr. Steven Kingsmore's group at Children's Mercy Hospital in Kansas City, Missouri. Dr. Urv?

Tina Urv: Thank you, Larry. Good morning to everyone. Each core research project that we will describe for you bring together teams of research from different types foe expertise. These teams will work together to answer questions that Dr. Green just outlined for us. Each of the research projects consist of three parts: Genomic sequence and analysis, research related to patient care, and the ethical, legal, and social implications of using genomic information in the newborn period. The projects that will be funded in no specific order are: Sequencing of the newborn spot DNA to improve and expand newborn screening. The principle investigator of this project is Robert Nussbaum M.D. of the University of California San Francisco. Dr. Nussbaum and his team will explore the potential to exome sequencing as method of newborn screening. Exome sequencing is a strategy used to selectively sequence exomes, the short stretches of DNA within our genomes that code for proteins. They will compare the results from current newborn screening methods to those from exome sequencing from metabolic and immunologic disorders. Dr. Nussbaum's team will

also use the results from exome sequencing to try to predict which children with specific metabolic disorders, fatty acid oxidation disorders, and severe combined immune deficiency are the greatest risk of becoming severely ill. This project also explores to that variation that predict responses to drug used in childhood such as Codeine and some seizure medications. At the same time, the research team also intends to develop a participant protection framework for conducting genomic sequencing during infancy and will explore legal issues related to using genomic analysis in newborn screening programs. Together, these studies have the potential to provide public health benefits for newborns and research based information for policy makers.

The next study is NC NEXUS North Carolina newborn exome sequencing and newborn screening disorders. The principle investigators for this project are: Dr. Cynthia Powell and Jonathan Berg at the University of North Carolina Chapel Hill. There are many challenges that must be met in order to implement genomic sequencing technology in such a diverse newborn population. Dr. Powell and Berg's key research teams will explore the usefulness of exome sequencing as a diagnostic tool to enrich the utility of current newborn screening. They will sequence the exomes of healthy infants and infants with known conditions such as PKUs, cystic fibrosis, and other disorders involving metabolism along with other conditions where children could potentially benefit from being identified early. This group will also develop strategies to guide doctors, laboratories, and families in decisions regarding findings some ways that will respect the child and protect his or her future rights while also respecting the rights of the parents. The research will attempt to develop a tool to help doctors and parents understand what the results of exome sequencing mean and examine the extra challenges that the doctors face as

this new technology is used. This group also plays a professional emphasis on the including multicultural families. Thank you.

Larry Thompson: Thank you, Dr. Urv. Dr. Wise?

Anastasia Wise: Thanks, Larry. Dr. Robert Green at Brigham & Women's Hospital and Dr. Alan Beggs at Boston Children's Hospital aim to create and safely test new methods for using the information obtained from genomic sequencing in the care for sick and healthy newborns. They will test the new approach to the newborn screening in which genomic data is available as a resource for parents and doctors throughout infancy and childhood to inform infant's healthcare. In Project I, they will perform genomic sequencing in a laboratory that meets the legally required testing standards called CLIA and develop electronic reports to return clinically important genomic sequencing results to doctors in a manager that is clear and easy to understand. In Project II, they will explore how doctors act on these repots in both healthy and sick newborns as compared to current newborn screening results and if this influences their clinical care. In Project III, they will examine the impact on parents of receiving these genomic sequencing results as compared to receiving current newborn screening results in once again, both healthy and sick newborns. They will look at the results of stress, usefulness of the results, and behavioral changes. These studies will inform the greater community on the reliability, effective, and scalable approaches to interpret genomic sequencing results in the context of newborn screening and the care of both healthy and sick newborns. They will also investigate the benefits and risks of newborn genomic sequencing, particularly concerned about parental and doctor confusion and anxiety before newborn genomic sequencing is introduced into clinical care.

Dr. Steven Kingsmore's group at Children's Mercy Hospital aims to examine whether incorporating rapid genomic sequencing results into the care of sick newborns improves their diagnosis or clinical management. Many newborns require care in the neonatal intensive care unit or NICU. This group of sick newborns has a high rate of disability and death. Given the severity of illness, these newborns may have the most to gain from a fast genetic diagnosis through the use of genomic sequencing. In Project I, the researchers will work to reduce the turnaround time for conducting genomic sequencing and receiving the results while also maintaining the ability of their method to make the correct diagnosis. In Project II, they will explore the methods, increase the number of diagnosis, decrease the time it takes to reach a diagnosis, or change the clinical care of these sick newborns. In Project III they will study what doctors and parents think the benefits and risks are of genomic sequencing and if these perceptions change after receiving the newborn's genomic sequencing results. Having rapid genomic sequencing results available may allow for earlier treatment of the sick newborns in the study and will provide results and genetic counseling for their families. The data generated in these studies may also potentially benefit future newborns through the identification of genes associated with newborn diseases and the development of improved diagnostic tests. Thanks.

Larry Thompson: Thank you very much, Dr. Wise. I would now like to open the phone to questions. Let's make sure we use the system. I'll ask the operator to remind us all how to use the system to ask a question. Actually, I'll ask her to introduce each of you as you ask a question and we'll go from there. So Misty, would you please remind everyone how to get in the queue?

Operator: Absolutely. At this time if you would like to ask a question, please press the * and 1 keys on your touchtone phone. Once again, if you would like to ask a question, please press * and 1 on your touchtone phone. We'll take our first question from Peter Aldhous with New Scientist. Please go ahead.

Peter Aldhous: Hi. Thank you. I'd like to ask a little bit about how incidental findings are going to be managed. I think it was mentioned by Eric Green in the context of one of the projects. So the American College of Genetics and Genomics is coming out with some guidelines for clinical - that was clinical sequencing rather than research, which is what we're talking about here which left 50 something genetic variants that's relating to 20 something serious conditions which might be actionable, that they should always be returned to the families that are having their genome sequenced. One of the projects, it sounded as if wasn't going to follow those recommendations. I know they have been somewhat controversial. Some people feel they're premature. Given Robert Green is the primary author of those recommendations, I'd be interested to know what his project is going to do and indeed the others because this does seem, at least for clinical sequencing - and I know we're talking about research here - to be a pretty much cutting edge controversy at the moment.

Anastasia Wise: Hi. This is Anastasia Wise. In general, handling incidental findings and how to return these results is one of the questions that these awards are meant to address. So each of the awards is handling incidental findings in a little bit different way. Some of the grants are going to be looking at specifically filtering the results from the genomic sequencing in order to only analyze and look at genes that may be related to the phenotypes and symptoms that these children are presenting in the NICU. Other

applications are specifically addressing the question of what types of incidental findings or results beyond those that are medically actionable at this current time parents would like to receive. So there is a wide range in the types of incidental findings that these programs are addressing and that is one of the questions that they're looking to investigate further.

Eric Green: This is Eric Green. The other thing I would add to this is the recognition that we have a lot to learn about many things before there could be a definitive way of saying how incidental findings should be handled. I think the recent recommendations that came out that involve - as you said, Robert Green, actually involved somebody else from an [unintelligible] I think was sort of a Version 1.0 based on the evidence and information they had at the time, but I think very much that process also revealed a number of questions that need to be answered. Certainly NHGRI is heavily involved in studying that. We have an entire consortium of investigators that are studying incidental findings and then the grants we're announcing today will bring another component associated with that specifically dealing with the newborn period, but I really think we should recognize any recommendations that exist are very much a point to additional questions and additional research studies that we're going to continue to foster to better inform those practice guidelines.

Peter Aldhous: Thank you.

Larry Thompson: On the other team? It's okay? Anybody else? Everybody's good? All right. Let's move on to the next question please.

Operator: Absolutely. Next, we'll take a question from Mark Johnson with Milwaukee Journal Sentinel. Please go ahead.

Mark Johnson: I wondered if you have any estimate for how many newborns will have their genomes tested as a result of these research programs. Then maybe if you could tell me whether any of their genomes tested to date? I'm assuming some newborns have but anybody know?

Eric Green: Looking stuff up. I can jump in. I think in some of these investigators have reported sort of anecdotal examples, clinical examples where they have actually used this as sort of demonstration examples, but the scale is very small.

Anastasia Wise: It's a couple of thousand newborns that'll end up being sequenced as part of this program.

Tina Urv: Right and as part of a public health program, they have not though. As part of the large public health program, this hasn't happened before however babies in the NICU might have…

Eric Green: Exactly. That was what I was about to say I was thinking of.

Mark Johnson: So anecdotally, it's happened from time to time but not…?

Eric Green: Yes. I actually believe one of the PI Kingsmore - I remember hearing talks from him where he's given actual examples where they've jumped in a NICU situation [unintelligible]. I don't know what those numbers are, but I'm sure they're handfuls, not even dozens.

Alan Guttmacher: Right. They're handfuls and I believe there may be some rare exception to this, but they've almost, if not all been, done on kinds for some indication

because they are in the NICU, they're having health problems, tried to ferret that out rather a more or less healthy population of newborns.

Eric Green: Certainly not in the screening context.

Alan Guttmacher: Right.

Mark Johnson: Okay. Thank you.

Larry Thompson: All right. I actually don't have any other questions in the queue right at the moment. So Misty, would you please remind everybody how to ask a question?

Operator: Absolutely. If you'd like to ask a question, please press the * and 1 keys on your touchtone phone.

Larry Thompson: Okay. That's more like it.

Operator: We'll take our next question from Jocelyn Kaiser with Science Magazine. Please go ahead.

Jocelyn Kaiser: Hi. Yes, I just wanted to ask looking ahead where this might be headed. There have been people who've said that we've been able to sequence a fetus' genome. So could there be a time not too far away where you would do the exome of a fetus and then what will the consequences be at that point? You might be able to terminate depending on what is found.

Eric Green: This is Eric. Let me answer from a technical point of view and I'll yield to my colleagues from Child Health Institute to sort of think about, but sort of the operational aspect for me. Certainly, I actually think some very exciting studies that have come out over the past year including by some NHGRI grantees in the technology development arena as well as others have demonstrated that not only that you can use fetal DNA, but it's even the way it's being recovered, and that it's being taken out of material blood as opposed to more invasive procedures to get fetal DNA. So the idea of just taking a blood draw from a pregnant woman and being able to sequence all the DNA [precedent] serum and being able to discriminate any maternal DNA from fetal DNA and in fact, there's at least one paper I know where they were able to do a complete genome assembly of that unborn baby. That's a technical advance that's pretty remarkable. I also know that the commercial sector is getting involved in this and there's really several companies I know setting up to do various types of prenatal diagnosis using maternal blood as the starting material as opposed to amniocentesis or chorionic villus sampling. From a technical point of view, all the things in play for prenatal diagnosis might be technically feasible using sequencing approaches of fetal DNA floating around in maternal serum. That's at a technical level. Now, how that gets operationalized, I think you raise an immediate number of questions. Alan, do you want to…?

Alan Guttmacher: I think it's important in terms of context really because of course prenatal genetic casting is almost as old in area of medicine as in newborn screening. It developed less than a decade after newborn screening went into effect. So prenatal genetic testing is something that's been around for decades. Of course, what we're thinking about in terms of technology is just that newborn screening may move from sort of a genetic based

screening or at least an analyte based screening to a genomic screening, one could imagine that technically prenatal genetic screening could become prenatal genomic screening for some of the reasons that Eric just sketched. That again, would bring with it a whole hosts of clinical, ethical, and other kinds of issues obviously that are peculiar to the prenatal setting just as is the case with prenatal genetic testing.

Jocelyn Kaiser: Okay.

Larry Thompson: Okay, Jocelyn?

Jocelyn Kaiser: Yes.

Larry Thompson: Okay. Let's go on to Lauran please.

Operator: Absolutely. Lauran Neergaard with the Associated Press. Please go ahead.

Lauran Neergaard: Hi. Thanks for taking the question. I have a more philosophical question. I'm wondering what prompted all of this starting with your workshop two years ago. Are there calls from the community to push in this direction or is it more a weariness that maybe the technology is going to get ahead of us and we'll sort of find ourselves accidentally doing the genomics before we're ready?

Alan Guttmacher: This is Alan Guttmacher. I'll take the first cut at that philosophic question. I'll try to give a philosophic answer I guess and Eric may want to chime in too. I think both of our institutes have clearly historically and certainly do now see part of our role of anticipating where science and medicine are

going and trying whenever possible to have research that can inform clinical care, that can inform society's uptake of various kinds of medical technologies, etc. and from our experience both in newborn screening primarily through NICHD and in genome technology primary through NHGRI, we could each see that this was something that was looming over the horizon. I think it's a little bit difficult to predict exactly what year would this become cost and otherwise effective, but we could see that was the case. So we really want to take advantage of this window of opportunity to answer key research questions about the technology, about the clinical implications, about the ethical and social implications of all this while we had a chance to do it so that if it turns out that this is really something that is effective, is worth doing, that we would answer those questions through a little bit about how to make it most effective, etc. before the technology really got there or on the other hand if it proves that really is not something that is worth doing, do we know that and we prove that in rigorous research rather than having to just sort of, "Well gee, let's try something and see what happens."

Eric Green: What I would add to that is I think many people have a vision or envision a possibility that one day an individual will have their genome - many individuals maybe routinely will have their genomes sequenced and have their complete genomic information available in electronic health records that will be accessed routinely by healthcare providers. If you start to imagine that vision, then the issue simply starts to become at what stage in life will that genome sequence be obtained and whether it's in adulthood or in childhood or in this case as a newborn are open questions and it's just a logical thing to then ask, "Will that capability meet this well known, well established, well respected genetic screening program that takes place in countries like United States in the newborn period?" and it's not hard to

imagine that they meet but of course there's many questions and I think that's the kinds of questions that these studies aim to start to address.

Larry Thompson: Does that give you a sufficient philosophical answer, Lauran?

Lauran Neergaard: It does. Thank you.

Larry Thompson: Do you have any follow up?

Lauran Neergaard: Actually, on sort of a separate issue. Are these results going to be posted to each child's individual medical record so that their own pediatrician can use them?

Tina Urv: It depends on the study. I believe that…

Larry Thompson: Let them know who's speaking.

Tina Urv: This is Tina Urv. I think that if they are working with the families and the physicians, yes, that information would go to the families but it's up to the parents to choose what information they choose to receive.

Anastasia Wise: This is another one of those - sorry, this is Anastasia Wise - issues where depending upon the grant they're addressing, this in a little bit different way but many of the studies are planning on returning results both to parents and clinicians.

Lauran Neergaard: But are they planning to return only the results that they've analyzed as a result of the study or do they have the entire genome sequence available

should the doctor at a later date decide to turn to it because the child developed symptoms of something?

Anastasia Wise: So that does also depend on the study. Some of the studies are planning on making the results available for future clinical use where if the individual, the child has been tested does end up developing conditions they could come back and provide them with a report based upon new symptoms that have developed and redo the analysis.

Tina Urv: So the question you're asking is one of the reasons we're doing this study, is to find out what the best way to do that would be and how the parents feel and what they're thinking and what results they would like and also working with the physicians as to how much they understand or don't understand.

Lauran Neergaard: Okay. Thank you.

Larry Thompson: Okay. Let's go on to the next question please.

Operator: Absolutely. We'll move next to Maggie Fox with NBC please go ahead.

Maggie Fox: Hey, good morning. Can you give us a little rundown on some of the genetic conditions that might be turning up in these screening tests?

Alan Guttmacher: This is Alan Guttmacher. If one of the sequencing the genome, there are hundreds or potentially even thousands of conditions that could show up, all of them quite rare. So in a sample of a couple of thousand newborns, it's hard to say exactly which one or ones will show up but there's huge hosts of them that are [unintelligible] will show up in these kids.

Eric Green: But for some of these studies there are also going to be [unintelligible] - they're also going to be focusing on things that are part of the newborn screening panel and to see whether complete sequencing as opposed to the way they're testing for it now gives more informative clinical information.

Alan Guttmacher: Right. So that would focus on the 31 that are part of most States' screening programs currently.

Tina Urv: So it's more to refine the information that they currently have and get a better understanding for the disorders rather than opening a whole box of multiple disorders because this is just a pilot study.

Maggie Fox: You guys aren't identifying yourselves.

Tina Urv: Oh, I'm sorry. This was Tina Urv.

Larry Thompson: That was Tina that was just speaking.

Eric Green: This is Eric Green again, and the other point I would make and I think my colleagues would agree with me is again, and we always say this in genomics - everything's moving so fast that even if the four of us gave you dozens of conditions which are the obvious ones, we have to recognize that over the next one to four years there's going to be a lot of additional genomic information that will become available and then all of a sudden might be very relevant for these various studies whether it's related to pharmacogenmics, whether it's related to rare genetic diseases and so forth, and all that information will be available to these study

investigators and their creative capabilities I'm sure will integrate that new information into their studies.

Larry Thompson: I would just add that we were talking earlier this year about the total number of rare diseases for which we now know the genetic genomic causes. So that's on the order of 7,000…

Eric Green: For which we know, just shy of 5,000.

Larry Thompson: So there's like 7,000 genetic disease.

Eric Green: 7,000 - 8,000. Yes.

Larry Thompson: 7,000 inherited disease and we know 4,000 - 5,000 of their molecular causes. So conceivably any of those could become - once you have the sequence in front of you, you can look for any of those.

Eric Green: This is Eric Green. Not to be too shy about NHGRI's research portfolio but in fact, we have a new program that we just started about a couple of years ago, that was maybe a year and a half ago at this point, our centers in dealing in genomics which are three centers that are now industrialized in process of trying to identify the genetic basis of these remaining 2,000 - 3,000 rare genetic disease for which we don't yet know the defective gene and they are churning out many successful examples that are filling out the literature now. So again, while this program gets underway, we're going to literally see an acceleration of discovery about rare genetic diseases and every one of those become relevant potentially looked at in this study.

Tina Urv: This is Tina Urv…

Maggie Fox: Who just said that please?

Eric Green: Eric Green. Eric Green just said that.

Maggie Fox: Okay. Can you guys please - I'm going to go to Wikipedia and look up genetic disease, but if you would please just name a few? I know you think it's useless but the average reader wants some. I can make them up or you can tell them to me, which do you want?

Tina Urv: One of the things I wanted to add before we hop to that question is the purpose of these grants isn't…

Maggie Fox: Sorry, who is…?

Tina Urv: This is Tina Urv again. It's not a contest to identify the most disorders but really, refine what we know about specific disorders. So I think that's why perhaps we're a little slow on giving you a list of disorders because most of these projects are really targeting things and Alan…

Alan Guttmacher: Okay. [Crosstalk] things like phenylketonuria or PKU we've already mentioned but also Maple Syrup Urine disease if you'd like another metabolic disorder. Cystic fibrosis. So there are really lots of different conditions, some of which there are various kinds of fatty chain oxidation defects, immuno deficiencies of various sorts.

Tina Urv: They can pick up some of the disorders that cause intellectual and developmental disabilities like Rett Syndrome or a Fragile X Syndrome, spinal muscular atrophy might be able to be picked up. Some of the

disorders that can be identified but aren't quite ready for a screening program because treatments as such aren't available at this time.

Maggie Fox: So those last three: Rett Syndrome, Fragile X, spinal muscular atrophy, those are not currently screened for?

Tina Urv: No.

Maggie Fox: Thank you. Who was that please? I'm so sorry.

Tina Urv: This is Tina Urv.

Maggie Fox: Thank you.

Larry Thompson: Okay. Maggie, we'll move on to the next question. You can always get back in the queue if you have further questions. Can we go to the next question please?

Operator: Absolutely. Next we'll go to Julia Karow with the GenomeWeb. Please go ahead.

Julia Karow: Yes. So to your knowledge, is this the first program trying to use genome sequencing in a newborn screening setting or are there similar problems in other countries and if so, do you collaborate with those?

Larry Thompson: We're looking at a table.

Alan Guttmacher: This is Alan Guttmacher. I'm not aware of any and looking around the table, I don't think any of us are aware of any.

Tina Urv: Not in a public health environment. This is Tina Urv.

Anastasia Wise: There are some groups that, on a limited basis, are doing genomic sequencing of newborns that have a particular condition for either research use of the condition or in more of a NICU setting where it's an unidentified condition they're trying to find out what the child has but as Tina mentioned, not really in the public health context of newborn screening.

Larry Thompson: Okay, Julia?

Julia Karow: Yes, thank you very much.

Larry Thompson: Okay. Let's go to the next question please.

Operator: We'll take a follow up from Mark Johnson with Milwaukee Journal Sentinel. Please go ahead.

Mark Johnson: Hi. Just wanted to check whether - has there been a policy for what you will do with children who are involved in these studies when you come across actionable diseases? Is there a set procedure for what'll happen? Related to that, I wondered what will be done in cases where you identify mutations of unknown significance.

Anastasia Wise: This is Anastasia Wise. So regarding both medically actionable findings and some of these other incidental findings, all of these awards are handling them in slightly different ways. This is one of the questions that these awards are really intended to address is what clinically useful

information can we get from genomic sequencing and how to apply it in these different situations. So some of the applications are going to be addressing the question of asking the parents do they want to receive more than just the medically actionable findings? Other groups are looking at returning potentially medically actionable results or only analyzing the medically actionable results and returning those to the parents. So we have a wide range of different responses that these applications are going to be addressing.

Mark Johnson: Okay. Thank you.

Larry Thompson: Anybody else? No? All right. Let's go to the next question please.

Operator: We'll take a follow up from Peter Aldhous with New Scientist. Please go ahead.

Peter Aldhous: Hi. I wonder if you could talk a little bit about how you're going to deal with issues with the accuracy if current whole genome or [unintelligible] complete technology. So I know a little bit about this from having my own exome done. The whole exome genome technologies are not up to the high fidelity yet Sanger Sequencing which means you're going to have both false positives and false negatives. Now, false positives are fairly easy to follow up by doing some limited Sanger Sequencing on the area. False negatives are rather more difficult and I know [unintelligible] some of the clinics are already in this area, the biggest worry. Actually, seem to be inherently problematical when we're talking about screening potentially the legal liabilities there if you're being screened and the screening is missing the important things. So I presume this is something

that needs researching and maybe you can tell us how those projects are going to address those issues.

Eric Green: So let me take a first pass. This is Eric Green and then I'm going to turn it over to Anastasia Wise to give a specific discussion about these grants because I want to contextualize this by completely agreeing with you and acknowledging that there are many things still need to be refined about a current method, these exciting powerful methods for genome sequencing, but they're not quite at a clinical grade shall we say and there's many studies that NHGRI is performing, both at a technological level to refine the methods that we're actually using also at an analytical level to see what can be sort of solved at a software level to sort of make them more accurate, and then developing routines for validating to make thins truly clinical grade. So this program falls into a larger set of studies that all are looking at the same kinds of problems and we regard this as an area that NHGRI very much wants to help solve because to truly make genome sequencing part of clinical care, we have to make the accuracy and the fidelity much higher and I speak of somebody who's actually was trained in clinical pathology, I fully recognize the importance of a clinical grade diagnostics and it's not quite there yet but I think these studies and these investigators are very motivated to help contribute to advance the field. So Anastasia, why don't you give some specific examples?

Anastasia Wise: So that is one of the questions that these applications are really aimed to address and all of these programs in their Project I are looking at genomic sequencing and the technology and many of them are doing studies of sensitivity and specificity looking at the current newborn screening program and whether they can replicate these types of results using genomic sequencing. They also do have a number of different ways that

they're validating some of the results and doing follow up testing before they return these results to the patients either doing CLIA certified genome sequencing to begin with or doing some sort of follow up to be able to return the results to the patients and their clinicians.

Peter Aldhous: Can I just clarify on that? So are you saying that many of these studies will do the conventional newborn screening and then check that the genome sequencing is actually delivering the same results? That's part of what they're doing?

Anastasia Wise: So some of them are looking at comparing known newborn screening results either doing the testing or getting the results from the database and then comparing that to doing genomic sequencing on those same samples.

Alan Guttmacher: This is Alan Guttmacher. I might add two points. One regarding this last one. Of course all of these children will have the standard newborn screening performed outside of the study as part of their regular care. The second point, Peter, is you're right that there's clearly implications for false negatives though since these are State administered systems, various States have laws that shield the newborn screening programs from suit over false negatives, but that is very - but there's also a significant impact of false positives. When one's thinking about this as a public health screening program if there's - in other situations might be a very fine low false positive rate, that may be, in newborn screening setting, excessive. That is the cost of follow up for those false positives may be such that the whole system becomes economically not feasible. So as Dr. Green was mentioning before, getting the technology better for any clinical application's important but in fact, newborn screening and this is one of the reasons why we're quite interested in this, in these studies, the false

positive rate becomes even more important than in almost any other situation.

Tina Urv: This is Tina Urv. One of the projects specifically addresses this and that's [NUS] Found Project in California focuses on that question.

Peter Aldhous: Okay and will that project or others be doing follow up Sanger Sequencing on anything they find to confirm?

Eric Green: Well, I think the projects will be doing backup.

Anastasia Wise: Some of the programs are looking at doing some form of confirmatory sequencing before we're turning the results. It depends on whether or not they're doing CLIA certified sequencing to begin with. This is Anastasia Wise.

Larry Thompson: All right. Thank you, Peter. Let's go to the next question. This is the last question that's in the queue, so we have a few more minutes after this question. If you have a question, get in the queue now. If not, we'll be wrapping up at the top of the hour, but go ahead Jocelyn.

Jocelyn Kaiser: A basic question and I think I've heard this number before, but I just want to check it with you. What is the rate of genetic disorders in newborns? I'm thinking it's something like 1% of all newborns are born with a genetic disorder. Is that the right number?

Alan Guttmacher: This is Alan Guttmacher. It depends how one defines genetic disorder. Clearly, current newborn screening looking for these 31 various disorders almost all of which are genetic is well, well less than 1%. If you look at -

all individuals will have any disorder or any Mendelian disorder then the number obviously gets higher. If you look at all individuals who have genes that put them in increased risk for disease then you're talking about the human population. So at some place between well less than 1% and 100%. [Laughter]

Jocelyn Kaiser: Right, but I'm thinking Mendelian disease.

Alan Guttmacher: So if we look at the 7,000 - off the top of my head, I would think it's still somewhat less than 1% but not a lot less than 1%.

Jocelyn Kaiser: Okay. Thanks.

Alan Guttmacher: We know that the rare disease prevalence in the population is fairly large. If you take all the rare diseases and you add them up, we're talking 25 million Americans suffering from an inherited disease of some sort, something like that.

Larry Thompson: Right. So all right. Let's go to the last question. Mark?

Mark Johnson: Yes. I just wanted to check the figures that you gave out earlier on the cost. Current newborn screen - $100.00. $1,000.00 for exome screening and is it $5,000.00 now for genome?

Eric Green: This is Eric. Let me answer the other two but I would say that I routinely get emails from companies that are offering whole exome sequencing for $1,000.00. I've seen it for $600.00, $700.00, $800.00. So when I think our grantees pretty routinely come in less than $1,000.00 for a whole exome sequencing. For a whole genome sequencing, those numbers is

really heavily depends on a number of factors about like the definition of quality is, about they're doing complete, separate, half the type, and so forth. The number that we generally are seeing these days are sort of in the $3,000.00 - $5,000.00 range kind of thing but again, I put big error bars on it because you really got to look under the hood whether - it's not quite $1,000.00 but it's definitely south of $10,000.00. I actually think it's south of $5,000.00.

Alan Guttmacher: The genetics for the newborn screening - this is Alan Guttmacher - in terms of newborn screening, the $100.00 is really an order of magnitude kind of answer. It depends what you put into the cost. If you talk about just the technology for doing it, it's significantly less than that and it also depends upon the State. Some States actually bear some of the costs of that in various parts of the State government, etc., etc. but $100.00 would be more like the sort of soup to nuts including follow up and other kinds of things for false positives including in fact follow up in terms of medically necessary foods for certain kids who screen positive, etc. The testing itself would be more in the order of a quarter of that.

Mark Johnson: Wow. Also do we know what the accuracy rate is for whole genome sequencing since that was raised? Is there any general figure on…?

Eric Green: This is Eric Green. Again, I'd put this into the broader context of it really depends on where it's being applied. We have many research projects are looking at it. One thing I would certainly tell you, to be realistic, is especially for whole genome sequencing, again, it's all about definition. We still can't fully assemble and entire human genome end to end across human centromeres all repeat [unintelligible] and so forth. So what do you do with the stuff you really can't quite sequence? Does that all count

towards your error rate? If the answer is yes, then that really skews your number. I think we probably have better numbers about whole exome sequencing but even then, there's a lot more refinement that's needed to make a clinical grade.

Larry Thompson: All right. Mark, thank you very much. That's the last question that's in the queue at this time. I think since we're almost at the top of the hour, I think we'll bring this to a conclusion. I'd like to thank my colleagues here for their willingness to speak about this important project and thank the members of the media for their interest. If you all have additional questions after this conference closes, by all means, call the respective press offices and we'll do our best to connect you with the appropriate expert and get your questions answered. The release and the related material will be going up on our respective institute websites - right, it should be at the top of the hour and I'd like to thank everyone for your participation and take care. Thank you very much.

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