HGP10
Larry Thompson
National Human Genome Research Institute
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Operator: Good day and welcome to a briefing about the 10th anniversary of the completion of the Human Genome Project. The National Human Genome Research Institute, one of the 27 institutes and centers that make up the National Institutes of Health, is the organizer. The discussion will last up to 60 minutes. There will be one principal speaker who will provide opening remarks then members of the media will be invited to ask questions. To ask questions, you can press the 'star' key and the number '1' on your touchtone phone to enter the queue. You leave the queue by pressing the number or hash key. This call will be recorded, transcribed and available as soon as possible on the website of the National Human Genome Research Institute, www.genome.gov. Now I will turn the program over to moderator Larry Thompson, Chief of Communications at the National Human Genome Research Institute. Please go ahead.

Larry Thompson: Hi there everybody, this is Larry Thompson. I am the Chief of Communications here at Genome as you know. I'm glad that you're going to be participating in what I'm sure will be an interesting discussion. So this call is not embargoed and you are welcome to write about this whenever you feel like it. We have just posted on genome.gov the press release and a graphic that has many of the statistics that you will hear about today, so if you miss a number, don't panic. You will be able to get it in the genome.gov highlights section where it's easily available.

Today's speaker, we're only going to have one, is Dr. Eric Green who's the Director of the Genome Institute. Dr. Green's professional career started about the same time as the Human Genome Project and he has been a participant throughout its run until its completion and he of course now leads the efforts of the use of genome science to advance human health. I'm going to ask him to make a few opening remarks and then we'll move to discussion. Dr. Green?

Dr. Eric Green: Thank you, Larry, and thanks to all of you for joining the conversation this afternoon. Well, this Sunday, April 14th, will precisely mark the 10th anniversary of the completion of the Human Genome Project. I know that in and of itself this genomic odometer moment does not necessarily constitute breaking news but I do think it's worth taking a few minutes to reflect on the overall progress that has been made since the start of the Human Genome Project and then over the last decade since the end of the Human Genome Project, and at the same time, to consider where the field of genomics is going especially as it relates to medical applications and advances. Well, at April 14, 2003, 10 years ago this Sunday, NHGRI and our international partners announced the completion of the Human Genome Project. The project was declared completed because it had successfully achieved its flagship goal, the generation of a highly accurate and publicly available reference sequence of the human genome. Those ordered three billion letters provided the most fundamental knowledge about the human genetic blueprint and gave us a framework of knowledge for pursuing numerous new and exciting genomic studies.

Since that milestone, the genomic era has reached a remarkably mature stage and the fields have expanded in many productive ways, both

anticipated and unanticipated. By way of reflection, let me give you some examples, first in the area of DNA sequencing technologies. As many of you know, when the Human Genome Project started, none of us involved in the project truly knew how we were going to sequence the human genome. So even back then our institute, then actually a center, invested in the development of technologies to improve our ability to map and to sequence genomes. With great improvements in DNA sequencing, we got to a point where we actually could sequence the first human genome as part of the Human Genome Project but of course that took us six to eight years of active sequencing and cost roughly $1 billion to complete the task. While certainly worth the money and worth the wait, we realized that the cost of genome sequencing needed to be reduced to advance the field of genomics in myriad desired ways. But by the end of the Human Genome Project we were already getting better at genome sequencing. In fact, in 2003 if the researchers that had just finished the first reference human genome sequence had immediately proceeded to sequence a second human genome, they estimated it would have taken them about three to four months to complete and cost somewhere between $30 and $50 million. But even that was too slow and too expensive.

A fast forward to today, 10 years later, and DNA sequencing technologies have advanced tremendously, perhaps the most impressive technology development effort in the history of biomedical research. Now the human genome can be sequenced in a day or two and at a cost well below $10,000.00, probably closer to $4,000.00 to $5,000. So in 10 short years we have knocked five zeroes from that $1 billion price tag and will likely knock that last zero off within a year or two or three. So today, sequencing the human genome is in the cost range of a sophisticated medical test like

an MRI and genome sequencing can in principle be affordably added to the medical testing repertoire. Now we just need to understand the appropriate settings to do so and what the resulting information will mean for patients. So towards that end, NHGRI and other research organizations have invested in understanding what information is encoded in the human genome and how it is relevant for health and disease.

So let me move to the second area worth mentioning and that is comparative genomics. As a means to understand how the human genome works, genomics researchers started to focus on sequencing a wide range of other organisms even before the Human Genome Project ended. This included animals used for research and ones at key places on the evolutionary tree of life. We looked at laboratory animals such as mice and rats and worms and flies, but also companion animals such as dogs and cats, agricultural animals such as cows and pigs, and weirdo animals along the way such as the platypus and the possum. Reflecting back, we had generated genome sequences for three vertebrates 10 years ago in 2003. Today, we have genome sequences for more than 112 vertebrates along with 455 non-vertebrate eukaryotes and nearly 9,000 prokaryotes in other words bacteria. Most of those are pathogens. We have truly generated genome sequence data from across the evolutionary tree, and by comparing those genomes we were able to essentially read evolution's notebook and see what parts of the genome nature thought was important enough to keep the same across mice and rats and dogs and other mammals. Those bits of evolutionarily conserved sequences have proven to be surprising once we had learned more about where they were in the genome. What do I mean by that?

Well, for example only about a third of the most highly conserved sequences in our genome codes for protein, constituting about 1.5% of our 3 billion bases and adding up to a total of about 20,000 genes. When the Human Genome Project ended, even 10 years ago we thought our gene inventory was much larger than 20,000. Well, the remaining bits of highly conserved sequences that do not encode for protein, in fact these outnumber the bases that do encode for protein, but in aggregate these reflect the non-coding functional parts of our genome. And figuring out what those non-coding sequences are functionally doing has been and will be a high priority for genomics research.

So this naturally leads me to my third area of highlights and that relates to understanding genome function. So to understand how the human genome works, researchers set out to identify the functional parts of the genome. As one example, the ENCODE project which stands for Encyclopedia of DNA Elements Project was launched by NHGRI and began cataloguing all functional elements in the human genome, and we now know that the human genome is a beehive of activity generating thousands of RNAs that seem to not code for protein but of other biological activity.

Further, our ENCODE data now suggest that upwards of 80% of the human genome is associated with computational or experimental evidence for being functional. Now that 80% claim has been controversial and researchers will argue it out in the coming years as NHGRI continues adding more ENCODE data to the public databases. But reflecting back to a decade ago, we know a tremendous amount more in terms of the functional parts of the human genome. While at the same time there is so much more to learn and understand with respect to the complexities of the

biological information encoded in our genome, and elucidating those complexities remain a high priority for genomics.

Let me now move to the next area of highlights to reflect upon and that's human genomic variation and human genetic disease. Well, even before the human genome project was completed, researchers realized humans were quite alike at the genomic level, something like 99.9% identical at the base-by-base level. But in that 1/10 of 1% difference resided the basis for inherited susceptibility to numerous diseases. So NHGRI helped organize several international projects, the SNP Consortium, the International HapMap Project and the 1000 Genomes Project, to catalogue and characterize human genomic variation. The resulting catalogues of human genomic variance are astonishing in their depth and breadth. When the Human Genome Project ended, we knew about 3.4 million single-nucleotide polymorphisms or SNPs or letters in the genome that some people had and that varied from the reference sequence at a particular base position.

Fast-forward to today, 10 years later, we've now catalogued nearly 54 million SNPs or genomic variance, a sixteen-fold increase in our knowledge about human genomic variations in the intervening 10 years. Now why has this proven valuable? Well, biotech companies have used those variant catalogues to make genotyping chips that can be used to study diseases especially genetically complex diseases where multiple variants contribute to the risk for the disorder. For this, the decade has brought the emergence of the Genome-Wide Association Study or GWAS where researchers compare a large number of individuals with the disease like diabetes with large numbers of individuals without the disease.

Well, 10 years ago there was great skepticism about whether GWAS approaches would work. At that time there were no - that is zero - successful examples of genome-wide association studies, GWAS studies, and zero publications reporting them. Today there have been over 1,400 such publications reporting successful genome-wide association studies. So a decade ago, we only knew about six genomic variants that were statistically associated with a complex genetic disease, six in total. Today that number is nearly 3,000, about a 600-fold increase. But these latest figures reflect progress with the genetically harder complex diseases. Even more impressive progress has been made with rare diseases caused by defects in a single gene. Before the Human Genome Project began we knew the genetic bases for just about 60 of what we knew were thousands and thousands of rare diseases. The Human Genome Project energized efforts to find the genes underlying rare disorders such that when the Human Genome Project ended 10 years ago that number was up from 60 to over 2,200. Today, we now know the genetic defect causing close to 5,000 rare disorders. That is substantial progress, and keep in mind that rare disorders in aggregate afflict more than 25 million Americans even though individually they are rare.

Well, this leads me to my next area of highlight, medical applications of genomics. It is true that we have not cured every disease since the Human Genome Project ended. No one seriously thought that we would. We can say today that genomics is beginning to have meaningful impact on medicine. We are on a very healthy trajectory. Today the FDA requires genetic information on the labels of 106 medications currently on the market. That means that the label tells doctors that there is genomic

information of some sort that should probably be considered when giving that drug to a patient. Before the Human Genome Project started, only four drugs carried such a label.

Perhaps the greatest medical advances that we can anticipate due to genomic advances will be in the area of cancer. In fact, we can already see genomics changing the care of cancer patients right now. Cancer is a genomic disease and the Cancer Genome Atlas Project, a partnership between the National Cancer Institute and our institute, NHGRI, has systematically sequenced hundreds of tumors from patients with over 20 different types of cancer including brain, lung, colon, and breast cancer. As a result, doctors are already linking particular genomic profiles with outcomes and determining treatments based on genomic information. Cancer patients will clearly be one of the big early winners due to genomic applications to medicine. We're clearly not done and we have a long way to go to deliver on the promise of genomic medicine. NHGRI is now supporting a number of large studies to identify clinically relevant genomic variance and also to study how people would use genomic information when they receive it from their doctors.

Well, finally let me say a word about societal implications of genomics. I should start with a story. When NHGRI's founding director, James Watson, held his first press conference after being named to oversee NIH's contribution to the Human Genome Project, he surprised NIH leadership by announcing that he would devote a portion of the funding to study the ethical, legal and social implications of genomic science. He actually had not told then NIH Director James Wyngaarden that he was going to propose that, but that proposal stuck and eventually the Congress

enshrined it in the NHGRI budget. Now 5% of our annual budget is spent on so-called ELSI research, Ethical, Legal, Social Implications Research, and this has been the case since the beginning of the Human Genome Project. Since the intervening time NHGRI has invested some $300 million in ELSI studies, supporting about 500, over 500 research projects or nearly 500 research projects to study the broader ELSI issues of genomics research. The debates fostered through this community helped focus Congressional attention to the need to pass the Genetic Information Nondiscrimination Act of 2008 called GINA, as well as to bring attention to a range of important issues such as privacy and access to genomic data and direct-to-consumer marketing of genetic information. Dr. Watson also observed the public needs to understand genomic science especially as they are asked to make decisions about their own medical care based on genomic tests. So NHGRI has increased its public outreach through National DNA Day celebrations for students, through our genome TV channel on YouTube and other social media, and this summer, through a collaboration with the Smithsonian's National Museum of Natural History which will result in a new exhibition on genomics that will open at the National Museum of Natural History in June.

Finally on a personal note, I should end by pointing out that I've been involved in genomics for roughly 25 years and I was a frontline start-to-finish participant in the Human Genome Project. I have been at NHGRI now for about 18 and a half years holding various leadership positions for most of that time, and I've now been the Director of the Institute for about three and a half years. Well, when I look back at what has been done and how far we've come in genomics over the past 23 years since the beginning of the genome project, and in particular over the past 10 years

since the end of the genome project, I am simply amazed. The joy ride continues for the field and for NHGRI, profoundly excited about these new frontiers that we at NHGRI will be pushing ourselves into as we explore the application of genomics to medical care. Day in and day out I think about where genomics is going and I continually conclude that the field's future is really quite bright. So, thank you for your attention. I'm now happy to answer your questions.

Larry Thompson: So let's start to open the phone. So Lindsay, would you remind everybody how to get in the queue to ask a question, please/?

Operator: Absolutely. At this time if you would like to ask a question, please press the 'star' and '1' on your touchtone phone. You may remove your question from the queue at any time by pressing the number or hash key. Once again, that is 'star' and '1' if you would like to ask a question.

Larry Thompson: Why don't we go ahead and I'll ask you guys to introduce yourselves as you ask the question, but I can see sort of who is in the queue so, Mark, why don't you go first? Tell us who you are and what's your question?

Mark Johnson: Hi, this is Mark Johnson from the Milwaukee Journal Sentinel. Kind of two questions because one is very brief. The first is how complete is the human genome? I was actually, I was at a NimbleGen Roche meeting this week and people were talking about how actually in fact there are still parts of the human genome that are gaps that we haven't filled in. The other thing I wanted to get maybe was your feeling on how much funding you expect to go to genomic research this year and how that compares to what the need is.

Dr. Eric Green: Okay, happy to answer both those, Mark. I hope the weather in Wisconsin is warming up. I know it was cold there about a week or two ago so I hope your spring is improving.

Mark Johnson: A little.

Dr. Eric Green: A little, just a little. Oh, so okay, first question was how complete is the human genome sequence. The short answer is that it gets better every year. By no means do we yet even have truly end-to-end, telomere-to-telomere complete contiguous sequence for every human chromosome. The most significant missing pieces on every chromosome are the centromeres which are just filled with incredibly complicated repetitive sequence that is almost impossible to stitch together using current technologies. Outside of that, there are little bits and pieces where there are little gaps and those just seem to get continually filled in. I actually will point out to you that NHGRI continues to fund efforts to sort of fill those in. I actually, off the top of my head I'll only get it for you. I don't know the number. I mean the ones sounded like 300 of those gaps. I think it's much fewer than that now, but that absolutely is not something that we ignore, but part of it is that some of them are just structurally so complicated that the methods, even the newer methods we have for sequencing DNA cannot tackle them chemically, and it just ends up being a problem. But those are getting fewer and fewer.

In terms of the centromeres and any of these really structurally complicated parts, there is always the hope that new technologies will provide us a way to finally read some of those out, especially single

molecule sequencing that would give you very, very long read lengths so you wouldn't – they're a problem with structurally complicated regions that are highly repetitive as when you break up the DNA, putting that jigsaw puzzle back together when everything looks the same is nearly impossible. But if we actually could get a method that would allow you to read maybe even millions of DNA bases that are all as you pull a strand of DNA through something or other, it's hopeful maybe we'll get more accurate reads of what's really there. But you know it really is still a small, small, small fraction of the total genome, well under 1% or something that we've never seen, in fact like even far less than that, but it's something we would love to have the ability to read through. So that's the first question.

Second question is related to funding levels. The short answer is we don't have enough. Genomics is hot, hot, hot. It's obviously at the end of the day this year even NHGRI, we're taking a sizable cut because of the sequestration and because of additional constraints here in the federal government. So at a time where we would love to see a major ramp-up in our funding because we see these opportunities as incredibly compelling and exciting, we're going the wrong direction by taking a five-plus percent cut in our budget, but it's not just us. That same five-plus percent cut goes all across NIH and I would point out to you that the majority, when you look at all of the funding and research, the NIH research that goes to genomics research, we're a small fraction of it at NHGRI. The reason for that is because all these exciting developments in genomics especially medical applications of genomics means that every institute or at least most of the institutes are doing genomics research now and their theme increases in the proportion of their research portfolio falling out of sort of

the category of genomics research. So to the extent that all of us are cut it means that we're not moving as quickly as I would have liked because even these other institutes are having a slow-down in their genomics research efforts.

Mark Johnson: Thank you.

Larry Thompson: Cool. Let's go on to the next question, Matt?

Matt Jones: Matt with GenomeWeb.

Larry Thompson: Say that again?

Matt Jones: Okay, yes, this is Matt with the GenomeWeb. So a decade ago there was a lot of excitement and over the last decade of course there's still a lot of excitement, a lot of discoveries as you'd laid out there a minute ago. But sometimes there is in the popular press disappointment that things haven't moved fast enough, not enough innovation and sometimes business journalists write about this, too. Why aren't these companies taking off quite as much as they should? Why don't we have personalized medicine everywhere now? I understand that the complexity of the human genome and genomes in general, it became clear that it was a lot more complex than we had perhaps thought 10 years ago. But how do you respond to when people say why aren't things moving faster or why hasn't the genome totally revolutionized medicine yet?

Dr. Eric Green: So here's how I answer it, Matt, and I get asked this question a lot. First thing is let's get some perspective and let's review the history of

biomedical research and basic science discoveries which, based on the genome project, was leading to clinical innovation and changes in the practice of medicine. There's a lot of history there, whether it is the basic biochemical insights that eventually led to the development of drugs like the statins or the germ theory of antibiotics that eventually led to the discovery and use of penicillin. Any of those discoveries, the medical advances come decades, literally decades after the initial major basic science discovery. So the notion that we would revolutionize medicine a decade after the first full human genome sequence was put in front of us was naïve to even believe it. Now, that said, a decade ago and I was there when the champagne bottles were being uncorked and we were having our parties and being immensely proud of having completed the human genome sequence sooner than we ever thought, better than we ever thought, I am quite sure that in that exuberance there are a lot of audaciously celebratory things that were said. Maybe they were even overstated. Maybe we were misinterpreted. I don't think it matters, whether we really said it or whether we were misinterpreted or maybe things were twisted around. I'm quite sure we said we're going to revolutionize medicine. I don't know if it was in the same sentence where we said that's going to all happen in a decade. I don't really remember, I don't really care, but I'm sure our exuberance was misconstrued either intentionally or not intentionally.

But if we get some perspective, it was unrealistic to think that it was going to be game-changing in the first decade. I can defend everything when I would say that if you look over the - first of all, you made one sure that there wasn't enough innovation. That's the one thing that might get me a little bit into a fighting mood because I challenge anybody to come up

with an example of better technical innovation in biomedical research than what has happened in the arena of DNA sequencing technology over the last decade. I mean that has been some of the most innovative, some of the most groundbreaking, some of the most high impact technology development that we've seen in the biological sciences certainly, and actually I think in many of the other sciences. I'm not sure if they've had as much impact as quickly as these have. So I think we get kudos for innovation especially in that round, but I think the biggest thing to say, and if anything I think this is the biggest story to write about right now at the 10-year point. If you look across the full landscape of what was going to be needed, what is going to be needed to really advance genomics and eventually have it play a major role in improving the medical care of patients, I think we have a major progress report on every front, and whether that's on understanding how the human genome works, whether it's technology for doing genome analysis, whether it's for getting catalogues of human genomic variation, whether it's for clearly setting up a circumstance where we're getting now to the molecular basis of a disease.

Now, finally, whether you actually can see it operationalized, beginning to be operationalized for clinical medicine with some of the low-hanging fruit being in cancer and pharmacogenomics and ultra-rare diseases, there is a reason why there is a huge amount of press attention constantly to genomics, and the reason why is because we're hitting doubles and triples by baseball analogy, maybe even some homeruns all the time on multiple fronts. And if the only thing I had for you was better sequencing technologies I couldn't make these claims. If all I had for you were doubling the number of human diseases for which we now know the

molecular basis, well, then maybe I wouldn't have as much to convince or I would have a harder time convincing people. But as I just look across the full landscape of everything we need to do to march this field forward, I think it's impossible to not believe that we're on a very healthy trajectory to really eventually attaining our goal of changing medical practice. I probably don't use the word revolutionize medical practice but I think changing it in a positive way, and I think we have examples already. I think by the end of this decade we'll have more examples and I think we'll continue to march along. But I want to measure this in decades. It's not fair to measure this in years.

Matt Jones: Could I follow up quickly or…?

Dr. Eric Green: Go ahead.

Matt Jones: Thanks. So at the end of your statements you discussed a feeling of amazement that happens all the time as you look back and look forward. I wonder if you have any anecdotal moments or things or studies that came out or revolutionary technologies that happened in the last 10 or even years before that where you just said, "Wow, this is something!" Do you remember any of those that…?

Dr. Eric Green: Well, yes, when I sort of go back in time I mean I think about, well, I think designing one study, there's been a handful of them but I don't want to - But I would say it amazes me but I also think about what amazes my neighbor when I bump into him and I say, "Well, what's the latest?" I think when you talk about now, and again, I'm just pulling out examples. When you talk about the notion and it's not science fiction anymore that

you could take a pregnant woman and you could draw her blood and not only can you detect the DNA of your unborn baby but they even get a complete genome sequence of her unborn baby such as sort of has now been published recently, I mean that's just like, wow! One, it's technically remarkable but then you start to think about, well, we may not be very far away from not having to do amniocentesis or chorionic villus sampling anymore. I mean it's just – I think that's amazing. I mean I have two children, we had amniocentesis for both of them, I am quite sure my wife would have much rather just given a couple of samples of blood instead of having needles stuck to her belly. I just think that's pretty cool and a pretty like wow, won't that change the face of something?

So I mean that technically is sort of is way cool. I think about these stories, sure that you guys have covered, whether it be Nick Volker in Milwaukee, whether that Mark has written about extensively, whether it be the Berry Twins and their story, or whether it be some of these cancer patients, some of which I know of personally where it just seemed like there was no options left. You sequence the individuals, you sequence their tumors, you get insights and new ideas and it's gained – it's life-changing for these people. I mean those moments are very, very captivating. Then I just sometimes I go to genomics meetings and I just look at the pace in aggregate what we're learning, and the idea that we're so casually talking all of a sudden about all this biological richness. For example a lot of our non-coding DNA being functional and I think back 10 years ago we were so ignorant then and now in fact we know a lot more now and just the world has changed around us. So I think those are just a handful of examples but it happens on a regular basis.

Matt Jones: Thank you.

Larry Thompson: So we don't have any other calls or questions in the queue? Does anybody in the group have something they would like to ask Dr. Green? Mark's back in the queue. Go ahead, Mark.

Mark Johnson: Hi, thanks for taking our questions. I did want to ask about the possibility of FDA approval for whole genome or exome sequencing for clinical use. I wondered if you could talk about where that stands now and how long you expect it to take to get past that barrier.

Dr. Eric Green: So that's a complicated question. I admit I am not as much of an expert on all the intricacies. There is certainly not a timeline at present. I do know there's lots of discussions and activity now especially around trying to develop standards for genome sequencing and having materials so that we can have sort of routines and protocols and standards so that we can have a better way of sort of assessing how people are doing a test as straightforward as sequencing the genome, but of course it's not straightforward. Lots of things being discussed, I know the FDA I know I hear some of their presentations from time to time but I don't think there's a defined timetable as far as I am aware.

Mark Johnson: Okay, thank you.

Larry Thompson: Okay, does anybody else have a question they would like to ask Dr. Green? Matt?

Matt Jones: I thought I'd throw a follow-up out there if I could.

Larry Thompson: Go ahead.

Matt Jones: So the NHGRI budget in the present budget the other day reflected what appears to be the continued transition of an execution of a long-term strategic plan which is kind of shifting away from biology and structural towards medical application. Could you just talk broadly about that where it's going, how you're monitoring it, and do you expect that shift to continue in the next three, four or five years?

Dr. Eric Green: Thanks for the question. I wanted to take minor exception to your wording. I just want to make a minor amendment to your question to sort of reflect my thinking. I don't think we are shifting away from basic genomics. I like to think of it that we're extending our studies to encompass critical applications of genomics. So if you go back and we're very deliberate in making sure that wording comes across in that even if you go back and look at our strategic plan from two years ago that we published in Nature, even in figure two which is sort of this classic density plot that shows progress over different time intervals across sort of several activities from way back. If you actually notice, it's not that all the colors shift right where and at the old areas of structure and function and genomes become blank but rather they retain some coloration that we'll still be working in that area. We just sort of extend our scope in the clinical stuff.

So for example, I mean just this past year we've renewed our program of ENCODE to continue to understand the structure of genomes. We are continuing to develop technologies for sequencing DNA. We have

extensive amounts of studies that continue to go on to really understand fundamentals of genome regulation, gene regulation, and we are not letting up by any means. If anything now sort of to realize that big Asteria of our investment is trying to get at the genomic basis of disease which is sort of discovery-oriented work which is really at the interface between basic science and clinical research. But then of course we are launching a number of initiatives that you're probably familiar with that really are at the more clinical side of things in a number of areas including some exploratory projects to do genome sequencing and studies to look at newborn screening and newborn sequencing and so forth.

Obviously, our budget is not going up so of course in order to sort of have a move, a shifting, not moving in a complete shift away from but an expansion, it means we have to sort of redistribute our resource a little and yes, we've done that. The good news of course is that genome sequencing gets cheaper and cheaper so we can get more bang for our dollar of sequencing without having to see our output for total sequencing going down because the prices keep going down. So we have re-sorted some things and we will continue to do that, and we also continue to hope for improved budgets, but it is not easy. So I don't mean to portray for a minute that any of these is easy making such prioritization decisions, but we also do a lot of the things we're doing.

We're doing in partnership with other institutes a lot of these clinical programs we find that we are able to get other institutes to join us because maybe we're doing some exploratory clinical genomics research in the area of cancer and the Cancer Institute has been very generous to join us in some of those efforts. That means our dollars go further and so we try to

be as creative, you know the newborn sequencing initiative that we'll be announcing the new grants for the coming months, that's in partnership with the Child Health Institute. So again, we haven't had to do all this alone and that helps so we can increase the size of our pie. But we do anticipate a continued growth in our clinical research area but by no means are we completely abandoning the basic genomics that has always been our hallmark.

Matt Jones: Excellent. Thanks.

Larry Thompson: Okay, Mark's got another question. We go to Mark.

Mark: Hi. Thanks again. You've made a couple of references to the newborn sequencing initiative. I'm not familiar with that. What is that?

Dr. Eric Green: Sure, happy to talk about it a little although I won't be able to give you the punchline because those grants are just in the process of being reviewed and going to our advisory groups and so forth. The basic premise of it of course which I do like to talk about is in countries, developed countries in particular, but it's only a country like the United States that every individual's first encounter with genetics occurs in a day or two of life. They don't know it at the time but that newborn baby is subjected to a heel stick. A little bit of blood is put on a piece of filter paper called a Guthrie card and that's mailed off to a State laboratory because State laboratories are responsible for that early genetic testing. It depends upon what State that baby is born in, how many genetic tests they're tested for, it's usually on the order of a couple of dozen to a few dozen, and mostly have been disorders for which early intervention can lead to a positive outcome, for

example adjusting the diet of the child who might have some genetic defect making conventional diets bad for them.

One could imagine, and I already hinted at it, I mean the fact that we now know the genomic basis for almost 5,000 rare genetic diseases but we're only testing newborn babies for a few dozen, or that we now know increasingly much more about the genomic basis of drug response and maybe it would be worthwhile even at a newborn period to know what might be medications you wouldn't want to give a baby because they wouldn't be good responders based on their genomic. Would it make sense of instead of just expanding the genetic tests one at a time, at some point it's just going to be more cost-effective to just sequence that baby's genome and what would you do with that data?

Now obviously that immediately raises lots of ethical, legal and social implications. We need to study that. But Alan Guttmacher, the Director of the Child Health Institute, approached me shortly after he became director which was really only shortly after I became director of my institute and said, "You know what? This is something that's so important for the pediatric period and the future's mass society is going to be different. It just seems like we're not going to use this old-fashioned method. At some point we'll be using newer sequencing methods perhaps, but let's get ahead of the curve by doing some research projects to study it," and of course we believe in that that we think these medical decisions and medical routines should be based on data and scientific research first.

So we partner with them and we have an initiative, a request for applications that was issued last year, applications are in and these are all going to be pilots to explore what that future might look like. And embedded within this research, this whole program, is some studies, research studies on the ethical, legal and social implications of that, lots of questions about who should have the information, how it should be handled, what should we be reporting back to parents and eventually to the child when they get to a certain age and so forth. So it is really important, I think it makes just a whole lot of sense and we want to try to get ahead of that curve by doing some research before we started to see this and try to be implemented for example.

Mark Johnson: Do you have money available for it? I mean is there money assigned to the sequencing initiative at this point?

Dr. Eric Green: We wouldn't put out a request for applications if we didn't have money ready to fund those grants. I forgot the exact dollar figures. It was some multiple of millions of dollars. It's not tens of millions of dollars, but I mean initially, but I mean it was a healthy amount to get a handful of investigators working on this and also have several different projects funded so they can interact with each other and form a small consortium and so forth. But yes, there will absolutely be dollars there.

Mark Johnson: Okay, great.

Larry Thompson: Alright. So I don't have anybody else in the queue at the time. Does anybody going once, going twice, have a brain question they'd like to ask

Dr. Green? Lindsay, you want to just remind them one more time how to post a question if they like one?

Operator: Once again, that is 'star' and '1' if you would like to enter the queue.

Larry Thompson: I'm hearing crickets, so I guess what we will do is wrap this up. I'd like to thank everyone for their participation. Of course if you have any other questions, don't hesitate to call the communications office and we'll try to run down an answer for you or connect you with Dr. Green if that's something that's required or he has time to do it. But at this point I think we're done and thank you very much.

Dr. Eric Green: Thank you, everyone.

END