SEQUENCE
Larry Thompson
National Human Genome Research Institute
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Operator: Good morning, and welcome to this media briefing hosted by the National Human Genome Research Institute at the National Institutes of Health. This press conference will last for 60 minutes. There will be two principal speakers who will provide brief remarks and then members of the media will be invited to ask questions. To ask questions, you can press star and one on your touchtone phone to enter the queue. You may leave the queue at any time by pressing the pound key. This call will be recorded, transcribed and available after 5:00 PM Eastern today, if not sooner, on the website of the National Human Genome Research Institute, www.genome.gov. Now I would like to turn the program over to our moderator, Larry Thompson, Chief of Communications at the National Human Genome Research Institute. Go ahead.

Larry Thompson: Good morning, everybody. It's Larry Thompson speaking. I'd like to welcome you to what I suspect would be a fairly interesting briefing. If you do not have the embargoed press release already, you can send a quick email to Jeff Spencer at spencer, S-P-E-N-C-E-R-G, @mail.nih.gov or call him at 301-402-0911 which is the Genome Institute's communication line and he will send it to you right away, and it will be posted on Genome.gov at noon right after this briefing is over. Our subject today is the funding plan for NHGRI's flagship initiative, the Genome Sequencing Program. It used to be called the Large-Scale Sequencing Program when it provided the foundation for the Human Genome Project and it principally worked with three large sequencing centers at the Broad Institute in Cambridge, Mass., the Genome Institute at Washington University in St. Louis and the

Human Genome Sequencing Center at the Baylor College of Medicine. Today, NHGRI's leader will describe how this program is evolving. We will start with brief opening remarks by Dr. Eric Green, Director of the National Human Genome Research Institute, and Dr. Mark Guyer, NHGRI's new deputy director and acting director of the Institute's Division of Extramural Research, which as you probably know, is the division that gives the grants. In addition, we have directors of the four components of the Genome Sequencing Program with us to answer questions. They are Dr. Adam Felsenfeld, Program Director for the Genome Sequencing Program, Dr. Lu Wang, Program Director for the Mendelian Disorders Genome Centers Program, Dr. Brad Ozenberger, Program Director for the Genome Medicine, who will oversee the initiative with Dr. Jean McEwen, a program director at NHGRI's Ethical, Legal and Social Implications Program, but Dr. McEwen is not with us today. She had a conflict and wasn't able to come, and Dr. Heidi Sofia, who will oversee the development of new informatics tools for high-throughput sequence data analysis. We'll hear about each of the new program areas in a moment but first, let me introduce Dr. Green, who has some opening remarks. Dr. Green?

Dr. Eric Green: Thank you, Larry, and welcome, everyone. Thanks for joining. When envisioned and then when executed, the core rationale and long-term promise of the Human Genome Project was to improve human health. In the decade since the draft human genome sequence gave us out first peek into our own genetic and genomic makeup, we've learned a tremendous amount about how the genome works and how alterations in it can cause disease, and we continue to believe that this growing body of knowledge will ultimately transform the practice of medicine. At the same time, genomics sometimes gets criticized for not yet curing enough diseases and as such, some claim that the Human Genome Project was a

disappointment. I would point out that it took approximately 66 years from the first human-powered flight in 1903 by the Wright Brothers, to humans then landing on the moon in 1969, and it took about 80 years to manufacture the first antibiotic, penicillin, following Louis Pasteur's development of the germ theory of disease in the mid-1800s. I think it is important to maintain the very real perspective that it takes considerable time and continual systematic effort to deliver results from that first scientific triumph. We believe that genomics is on such a steady course of progress en route to the delivery of medically-important advances, and we are here to talk with you about NHGRI's new plans that will contribute to this momentum. Empowered by powerful, new DNA sequencing technologies and the plummeting cost for sequencing the human genome, there have been numerous examples of genomics being used to unravel the genetic basis of disease especially for rare disorders. Most of you have read about some of these success stories over the last year or two including the news piece that won last year's Pulitzer Prize for explanatory reporting. Closer to our home at the NIH, many of us have been watching the remarkable application of new genome sequencing technologies for studying truly mysterious illnesses in the NIH Undiagnosed Diseases Program, and also the large-scale genomic studies of now roughly 1,000 individuals in NHGRI's ClinSeq study, an effort designed to begin exploring how to apply genomics to medical care. These two intramural-based programs, like several others that have been launched elsewhere in recent years, have made rapid advances for using the analyses of human genome sequences in medical settings. The bottom line is that there have been some remarkable medical successes for genomics, but genome sequencing has yet to find its way into standard medical practice. We continue to believe that this is coming, but before it can, we still have a tremendous amount to learn and to develop through

genomics research. In the new strategic plan for genomics that NHGRI published in Nature earlier this year, we described a research agenda framed by a defined progression from basic genomic research to the use of genomics in medical care. To help realize that new strategic vision, NHGRI has developed a new spending plan for its flagship Genome Sequencing Program to sharpen its focus on medical applications. NHGRI will continue to use its Genome Sequencing Program to conduct a considerable amount of basic research into the biology of the human genome because that understanding will be fundamental to developing health applications. At the same time, the breathtaking advances in DNA sequencing technologies that have occurred over the last eight years have allowed us, indeed have catalyzed us to direct some of those resources for studying issues that need to be addressed and bottlenecks that need to be eliminated for genomic medicine to be realized. I refer to our Genome Sequencing Program as our flagship program in part because of its scale, but more importantly, because of its impressive track record of accomplishments starting with its contribution to the Human Genome Project. For that reason, we are committing a projected $412 million over the next four years to this program because we still have much to learn about how genomes work and genomic variance contribute to phenotypes. About three quarters or about 77% of the funding will go to three large-scale sequencing centers where their efforts will primarily focus on two of the research domains on our strategic plan, understanding the biology of genomes and understanding the biology of disease. The remaining roughly one quarter, about 23% of the funds, will be directed towards three important new areas, the first two of which are more medically-oriented. The first new area will focus on Mendelian diseases, which are mostly rare disorders caused by mutations in the protein coating part of a gene and which are inherited just like other traits of the pea plants originally

described in Mendel's garden. While these are rare diseases afflicting fewer than 200,000 people each, together they affect an estimated 25 million Americans, making this an important public health problem. To accelerate progress in this area, NHGRI is launching a new Mendelian Disorders Genome Centers Program. In a second new area, we will create the Clinical Sequence and Exploratory Research Projects Program to help establish how best to use genome sequencing for medical care. This program will fund multidisciplinary research teams of doctors and other healthcare professionals including also ethicists, genomic scientists, patients and families to help establish how best to use genomic information in patient care. This program will also study psychosocial and ethical questions related to using genomic information in a clinical study. Finally, as the price of genome sequencing has plummeted, we have come to appreciate that the new bottleneck is data analysis. As small labs use the new DNA sequencing instruments, they quickly discover that assimilating and understanding the generated data could be very challenging. NHGRI is creating a new program to develop well-documented and well-supported computer software that can be used by researchers outside of large sequencing centers to analyze genome sequence data. Our goal is to empower all types of researchers and health care professionals to use genomic information in their research and eventually in patient care. We laid out the new vision for our Genome Sequencing Program nearly a year ago in a series of requests for applications, the formal process for announcing available NIH funding. The applicants underwent a very competitive decision making process in which peer review played an important role. Those receiving funding really do represent the best researchers, proposing the best possible ideas in these areas. So I'm expecting a very productive four years ahead as we continue to push the field of genomics towards advancing human health. I would now like to

ask Mark Guyer, Deputy Director of NHGRI, to provide additional details about the funding plan for our new Genome Sequencing Program.

Dr. Mark Guyer: Thank you, Eric, and good morning, everyone. As I think you all appreciate, since the completion of the Human Genome Project less than ten years ago, genomics has become an essential component across the board of the biomedical research agenda. As a simple illustration, the NHGRI research portfolio has broadened remarkably during this time and we now have something like two dozen named initiatives underway, each of which is using genomics to address one of the first three areas, three domains of our recent strategic plan. For example, 1000 Genomes project is directed primarily towards understanding the structure of genomes, the ENCODE and modENCODE Projects towards understanding the biology of genomes, and The Cancer Genome Atlas towards understanding the biology of disease. By applying our understanding of the structure of the human genome and how it works, we're confident that we will come to understand what happens when the genomic machinery stops working right or when the information in the genome is not being interpreted correctly and how these problems cause disease and eventually how to intervene to counteract the problems. Throughout its history, NHGRI has taken a very ambitious and aggressive approach through the use of high-throughput, cost-effective programs to generate data resources and develop new technologies that can be used by many investigators in many fields to solve the problems that stand in the way of that understanding. Our announcement today represents a continuation of that approach. As described in the strategic plan, we still have much to learn about how the human genome is organized and how it works in health and in illness. We believe the Large-Scale approach has continued to present exciting, new opportunities which is why the largest component of the program continues to support large-scale sequencing. Accordingly, we're

announcing today that NHGRI will invest $319 million of the $412 million in this four-year spending plan to fund three sequencing centers. One is the Broad Institute in Cambridge, Massachusetts, which will receive $35.9 million in the first year. Second is the Genome Institute at Washington University in St. Louis, which will receive $28.4 million in the first year, and the third is the Human Genome Sequencing Center at the Baylor College of Medicine in Houston which will receive $21.3 million in the first year. I want to emphasize that I framed the funding levels in terms of the first year awards. Beyond that first year, we plan to continue a practice that we've actually been pursuing for several years now which is to gradually reduce the base funding for these three centers each year over the four years of the program. It's probably not that well-known but the remarkable increases in sequence production that these three groups have achieved over the last several years have come about even though their funding levels were being slowly decreased. We believe that the cost of sequencing will continue to decline and that will allow the NHGRI program to continue its high level of productivity at even lower costs. Doing this allows NHGRI to continue to redirect money from the large-scale sequencing effort into other new scientific priorities as they arrive. Dr. Adam Felsenfeld, who is here, will be overseeing this component of the Genome Sequencing Program and he's here to answer any questions that you may have when I'm finished. In the evolving design of the overall sequencing program, NHGRI recognized the opportunity to sharpen its focus on medical applications at this time and as Eric said, we're going to do this in two ways. First, we will mobilize an intense, focused effort on the most obvious of genetic disorders, the more than 6,000 so-called Mendelian diseases. Second, we will begin a new component designed to learn how to use genomic sequence information in actual medical care by launching a research program to study all of the

issues that need to be addressed in order for sequencing to become a routine component of medical care. The Mendelian Centers will actively use genomic sequencing to search for the cause of as many conditions as they can. NHGRI is partnering with the National Heart, Lung and Blood Institute in this effort to invest $48 million over four years to the following groups. One is the Center for Mendelian Genomics at the University of Washington in Seattle. The second is the Center for Mendelian Disorders at Yale University in New Haven, and the third is a partnership between the Baylor College of Medicine in Houston and the Johns Hopkins University in Baltimore which will form the Baylor-Johns Hopkins Center for Medical Genetics. These three groups will function together as an interactive consortium with the University of Washington group providing the portal into the program for researchers, clinicians and the public. Dr. Lu Wang at NHGRI will be the program manager for this effort and she is here to answer your questions. The other medically-focused initiative that we're starting is called the Clinical Sequencing Exploratory Research Project. NHGRI will contribute $40 million over the four years to this effort, and the National Cancer Institute will contribute about another $8 million over that time to co-support research on questions related to cancer. The grantees in this program are the Baylor College of Medicine in Houston, Brigham and Women's Hospital in Boston, Children's Hospital of Philadelphia, the University of North Carolina at Chapel Hill and the University of Washington in Seattle. We're actually working on the possibility of funding one more group next month. Dr. Brad Ozenberger is the program director for NHGRI's Genomic Medicine Program and he will oversee this effort along with Dr. Jean McEwan, a program director from NHGRI's Ethical, Legal and Social Implications Program. Finally, the fourth initiative focuses on making genome analysis software readily accessible for researchers who are not in the major

sequencing centers. NHGRI will invest $20 million over four years to further develop existing software and make it more available to the broad scope of researchers. These funds will not be distributed until early in 2012. Dr. Heidi Sofia will be the program director for this project and she is here to answer questions. So let me stop there and we will be happy to answer your questions. Larry?

Larry Thompson: Great. Thanks a lot, Mark. So what I'd like to do now is open the phones to questions. Clint, I have lost the conference [watch] so I can't see who's in the queue so you're going to have to sort of do air traffic control for me. Clint will either introduce you or if he doesn't, please tell us who you are and who you're representing, and feel free to direct your questions to any one of the program managers as well as Drs. Green and Guyer. I'd like to remind my colleagues to go identify yourselves when you start speaking since the reporters can't see us and might not recognize our voices. So Clint, you want to get this started and whoever's in the queue, why don't you give us the first question?

Operator: Absolutely. To ask a question, press star and one on your touchtone phone. You can remove yourself from the question queue at any time by pressing the pound key. Again, star and one to ask a question. Looks like our first question comes from the side of Eric Britt with Chemical and Engineering News. Go ahead, your line is open.

Britt Erickson: Hi. This is Britt Erickson. I have a question regarding whether there are any private companies that are in the space currently trying to move genomics into clinical care and whether NIH will be stepping on their toes per se.

Dr. Eric Green: This is Eric Green. I'm happy to take the first pass at that. There absolutely are private companies that are developing technologies and beginning to apply them for clinical research problems. We think this is terrific. In fact, I would contend that the private sector's investment in DNA sequencing technologies deserves a tremendous amount of the credit for what has happened in genomics over the last eight years. I believe that what we are going to be funding now, if anything, will empower and advance the field in a fashion that will actually benefit the private sectors' investments in these areas and future investments as well.

Britt Erickson: Thank you.

Larry Thompson: Next question?

Operator: Our next question comes from the side of Mark Johnson with the Milwaukee Journal Sentinel. Go ahead. Your line is open.

Mark Johnson: Hi. Thanks for taking our questions. My question is if I could get some idea of what kind of an increase this $460 million plan represents over sort of existing expenditures in medical genomics?

Dr. Eric Green: This is Eric. Investments at NHGRI in medical genomics or [crosstalk]…?

Mark Johnson: Right. Yes. Compared to how much we're spending in some of these areas previous to this.

Dr. Adam Felsenfeld: Yes. This is Adam Felsenfeld. Actually the entire four programs that Eric and Mark went over, are roughly the same amount as what we were spending previously in all of large-scale sequencing.

Dr. Mark Guyer: This is Mark. So when I talked about slowly decreasing the amount of money in the large-scale centers, in this case, all the money that we generated in that way was put into these new programs. So the overall

amount has stayed the same. Over the long-term, this represents a decrease – I can't remember how many years ago it was now but certainly about twelve years ago, [it's affixed] about half per year of what were spending then. So it has been a ramp down in spending but a very considerable ramp up in productivity.

Mark Johnson: Thank you.

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

Operator: Our next question comes from the side of Hannah Waters with nature Medicine. Go ahead. Your line is open.

Hannah Waters: Hello. Under the umbrella of each of these programs, under these new centers, are there any programs that are going to be targeted specifically towards drug development?

Dr. Eric Green: This is Eric. I'm happy to – the short answer to that is not in a highly focused way. Certainly you could look under the umbrella of a couple of these programs that are very much geared towards "discovery work" as we refer to it. In other words, discovering variance associated with rare diseases or discovering variance that are relevant for drug response and so forth, and any discovery become father for possible drug development but certainly that's more downstream than what we are directly funding. Adam, you want to add to that?

Dr. Adam Felsenfeld: Yes, I just want to add to that that we always – as the discovery research develops useful resources, we rely on feedback from different [communities] included those interested in developing pharmaceuticals about what's most useful and we take that into account in how we focus the kinds of projects we do along the way.

Dr. Eric Green: I would really emphasize that the fact that NHGRI is in a very focused way developing a sequencing program aiming at for example, Mendelian disorders but also our investments in cancer and our investments in untangling the complexities of more common genetic diseases really will, we believe, accelerate opportunities in therapeutic development and I think some of the broader initiatives that NIH is now pursuing is a direct result of genomic advances and the anticipated genomic advances over the next decade.

Dr. Mark Guyer: This is Mark. I want to try and elaborate a bit on what Adam said and point out or emphasize that the actual scientific agenda for the sequencing program is very dynamic with the sequencing projects that are undertaken, constantly being churned, new projects admitted, existing projects finished and the choice of projects is based on input from not only NHGRI, probably that's a minority but from the sequencing investigators themselves, the wider research community and many others.

Dr. Lu Wang: This is Lu Wang. Just focusing on the Mendelian initiative a little bit, the three centers that we are funding plan to join the International Rare Diseases Consortium soon, which will be this year. We know that a number of pharmaceutical companies are planning to join this consortium too so there will be constant dialogues within the consortium and the priority as to which rare diseases our centers will focus on will be decided [upon] a number of factors including the need from the drug developers.

Larry Thompson: Great.

Dr. Lu Wang: There has already been success in the past on how the discovered where variance have suggested [pathobiology] which led to rapid drug repurposing.

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

Operator: Again it's star and one to ask a question. Our next question comes from the side of Matt Jones with GenomeWeb. Go ahead. Your line is open.

Matt Jones: Hi, thanks. This is for Brad about the Clinical Sequencing Exploratory Research Project. I'm going to try later to get more information about the specific projects that are funded here but I'm wondering if you could maybe characterize what kinds of applications you got and maybe give some examples of a couple of these projects. I'm wondering if they're mostly pharmacogenomics or stratified medicine, what are you looking at funding here and how did you decide which ones were going to win?

Dr. Brad Ozenberger: Yes, this is Brad Ozenberger. It was interesting, we had a very good response in a wide variety of projects proposed in response to the RFA and they really fell into two categories, cancer, because in cancer right now it's an area where genomics can make rapid progress we believe and the investigators believe, and then others in more complex genetics, cardiovascular disease and so on. [What was] I going to say?

Dr. Adam Felsenfeld: Maybe in pharmacogenomics?

Dr. Brad Ozenberger: Not in pharmacogenomics. I was going to point out though that this is not a disease discovery, a gene association discovery project per se. In our history, the large-scale centers have been adept at producing [TCGs and As] and putting them together and pushing the technology and discovery. Whereas this program is really the next step of where the actual sequencing technology and even the disease area is less important than exploring the methods of bringing genomic sequencing into the clinic workflow to the benefit of individual patients. So it's really a different [slant] on the process than some of our previous programs.

Dr. Eric Green: This is Eric Green. As a result, when you do get more information about the individual grantees and the particular things they're working on, I would caution you not to over-interpret those specific disease areas as being anything that we are really emphasizing greater than other areas. As with what Brad said, we should really amplify. We were far more interested in projects that were going to address barriers to clinical implementation of genome sequencing. Within that context, those barriers would come up in lots of different disease areas and it was more important to us and I think for the reviewers who reviewed these applications to find those applications that were most likely to be successful at advancing that aspect of this challenging area.

Dr. Mark Guyer: You asked about how the projects were chosen. They were basically chosen by peer review primarily by the results of peer review and then a certain contribution of making sure that the program overall was balanced among disease areas.

Matt Jones: May I follow up briefly?

Dr. Eric Green: Sure.

Matt Jones: Because Jean isn't there, I'm wondering if someone can comment on what the ethical and psychosocial elements are, what kind of things you might be looking at.

Dr. Brad Ozenberger: This is absolutely essentially for this program. So as Eric said earlier, this is a really multidisciplinary research and as we begin to see the application of genomic sequencing into the clinic, there will come many ethical questions about return of results. If you find that there is an

incidental finding, something that was unanticipated, not at this specific research question or medical question, is that return, under what condition is that returned when you have genetic variance of great uncertainty. How do you decide, how does the physician decide whether to use that information in determining treatment for the patient and so on. Then even beyond the physician's perspective is the patient's perspective. How will there actually be studies in these programs putting patients and physicians in control groups and test groups and trying to understand people's responses to receiving results and different types of results. I want to emphasize, this is beyond genotyping. It's beyond the few genetic tests that are out there in pharmacogenomics and other areas where you're just looking at very specific genomic variance. Here, we're doing entire genome sequencing or at least entire exome sequencing. So instead of looking at dozens of sites in the genome, we may be looking at three billion sites. So it's how to deal with all that unknown information and how to act.

Dr. Eric Green: One of the things I'd like to emphasize, that sort of architectural feature of this program is that those components of these clinical exploratory sequencing efforts that are in the psychosocial ethical areas, we will be facilitating their interactions with other research projects that we support under the umbrella of our ethical legal and social implications program. Those connections, we anticipate to be very fruitful because it will bring together investigators some that are more directly engaged with larger projects that are really doing clinical genomic sequencing, others that are doing scholarly work but may not have quite those connections and so we're going to be facilitating almost a network of investigators that we think are going to be very important for moving that aspect of the field forward.

Matt Jones: Great. Thank you.

Larry Thompson: Okay. Can we move on to the next question, Clint?

Operator: Yes our next question comes from the side of Sandra Porter with Science Blogs. Go ahead, your line is open.

Sandra Porter: Hi! In my world, it seems that there is a lot of fear about the unknown sorts of things that will be uncovered by DNA sequencing, both in the area of insurance and then privacy. I was wondering if NIH is going to be involved in any kind of systemic educational initiative to increase demand and make people realize or highlight some of the benefits to this technology.

Dr. Eric Green: This is Eric, Sandra. That's certainly a terrific question. I'd be the first to tell you that the funding plan that we're describing today about our genome sequencing program probably doesn't have a lot in that area. But what I would refer you to would be this strategic plan that we published in nature earlier this year where we in fact describe in addition to these research domains that are important for advancing genomics, also a series that we called crosscutting elements. One of which is training and education and you hit the nail on the head that we regard sort of education at all levels. You referred more to the general public and perceptions around genetic discoveries and genomic discoveries as being a concern when education would certainly be one way to help to start to address that. We absolutely regard that as an important priority. Actually just tell you that just last week or was it the week before, I can't remember. The last couple of weeks we've even had a workshop here at NIH to try to better

understand the concept of genomic literacy and to think a little bit about sort of the foundation that we're working with as the means to move forward in thinking about genetic and genomic education program and figuring out what we can do as an institute to facilitate this. This is very much on our consciousness. We are working on this but the money we're describing here for these grants don't directly address that. We're trying to address that in other parts of the institute.

Sandra Porter: Thanks!

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

Operator: The next question comes from the side of Jocelyn Kaiser with Science Magazine. Your line is open, go ahead.

Jocelyn Kaiser: Hi! I had a question about the Mendelian Centers. I was wondering if you had some sort of rough target or hope for how many diseases they may get through in the next four years.

Dr. Lu Wang: Ultimately, how many disorders the centers will be able to solve would depend on sample availability and advances that will be made in the next four years in technology. For the initial period, our centers have already in hand, more than 12,000 samples for several hundred disorders. So it is feasible at this point to say that several hundred disorders will be studied and a big portion of them will be solved. By solved, I mean the causal genetic variants discovered. The program will continually adjust its goal. Our goal is to solve as many disorders as possible depending on the advances of technology and availability of sample. Hopefully, additional funds from other [NH] Institute.

Jocelyn Kaiser: Okay. Thanks.

Dr. Eric Green: I do want to point out one detail which I think is important here which is that different disorders in order to understand them, they require sequencing different numbers of sample. So it can be hard to answer the question in terms of the number of diseases, little easier to understand the number of sample that could be sequenced.

Jocelyn Kaiser: Okay.

Larry Thompson: Is that okay, Jocelyn?

Jocelyn Kaiser: Yes, that's good. Thanks.

Larry Thompson: Okay. Clint, let's move on to the next question please.

Operator: The next question comes from the side of Carolyn Johnson with the Boston Globe. Go ahead, your line is open.

Carolyn Johnson: Hi! Thanks! I have two questions. One is whether the clinical sequencing projects are going to include an analysis of the cost of the sequencing and the healthcare costs that are incurred because of it to see – to look at the cost aspect. The second one is whether the sequencing centers, the large sequencing centers - whether the funding is going to underwrite, continue kind of big sequencing projects or will also include functional investigation of genes identified through those projects.

Dr. Brad Ozenberger: This is Brad. On the first question about cost and cost effectiveness – I can say yes, that will be addressed by a few of the projects, not all. It is a specific research aim to explore and understand better the cost models for bringing sequencing into the clinic.

Dr. Eric Green: I want to add one thing to that and that is the recognition that understanding the economics of healthcare is incredibly complicated. So thinking about how genomics might influence or affect that is turning out to be incredibly complicated, we are realizing. As the institute is looking more and more towards the implementation of genomic medicine, we realize we are getting into some areas that us genome scientists are far from familiar with. So while I think the clinical exploratory sequencing might start to touch on that, we should all recognize that is a very big complicated area. We are learning more and more about it and we're taking this very seriously for example, we now have established a working group, a sub advisory group if you will of our advisory council that is focusing exclusively on genomic medicine and in fact we're having regular meetings being sponsored and organized by that working group. One is actually taking place yesterday and today, here in Bethesda. In fact, some of these issues around the economics of healthcare and how genomics is going to affect that are topics for discussion – again, the recognition is really complicated. I'm sure with time, we're going to see interest in trying to understand this better. We will have to think about how such studies are going to really get done. I'm not sure NHGRI is going to be doing this alone. I think we need more expertise brought in than what we can bring.

Carolyn Johnson: Okay.

Dr. Adam Felsenfeld: If I understood your question correctly, you were asking about sort of maybe the handoff or the stopping point of where the large scale centers - of what the large scale centers do. Really, it's a complicated answer because once the data are generated, you have to make sure that they're relevant. So these sequencing studies are often done in the context of a larger consortium with many investigators not just large scale sequencers but also those interested in the functions of the variants that we find. Very often, there are actions to be made there and not only do they result in very nice and important science but they provide clinical feedback to the sequencing operation to make sure that it's on track. At the same time, NHGRI is broadly interested in developing any kinds of resources and knowledge that could in general improve the ability to make these connections between variants and what those variants mean. That goes on at NHGRI in addition to outside but in other programs as well. For example, encode and others that we do and that we're thinking about doing that help build resources that could make these connections for everyone.

Dr. Mark Guyer: I want to add one more thing to that and that is even though we have been trumpeting the fact that thousands of genomes are being sequenced and will continue to be sequenced, the truth is that the power of the studies that are necessary to really understand the genomic basis of common disease, those studies need to be powered by thousands and thousands and very large sample sizes far beyond what has been possible. So the challenge to the large scale sequencing centers over the next four years is going to be to figure out the best way to take advantage of their unique sequencing capability to do things, to understand things that no other approach can do.

Dr. Adam Felsenfeld: I also want to add that this goes on – we always talk about large scale sequencing and data production because that's where a lot of the details are but all of these projects need to be integrated from the design, what kind of samples, what kind of populations, what the statistical power is done through the sequencing and the best way to do the sequencing because there are tradeoffs there with cost and quality depending on how you design the project, what kind of information you need. Through the analysis, which can – as new kinds of projects and opportunities are tackled, whatever larger kinds of projects for example for complex disease, the entire analysis considerations can change and often have to be rebuilt or adapted from what was there before. So the large scale centers along with their collaborators across the community have to put together all of these things to make this work.

Carolyn Johnson: Great. Thanks!

Larry Thompson: Let's go on to the next question if there is one.

Operator: Yes, there is. The next question comes from the side of – correct me if I'm wrong, Uduak Thomas with GenomeWeb. Go ahead, your line is open.

Uduak Thomas: Thank you. You are right actually. My question is for Dr. Sophia. I was wondering if you could provide a bit more details about the informatics bit. So I'm thinking in terms of either plans to improve existing software as well as any new software development plans and what areas those will target. The final part, your plans to make the software available to the larger community.

Dr. Heidi Sofia: Well in this program, we have a large bucket. So basically, we wanted to capture a lot of things of value, we wanted to capture the value of a lot of previous investment that's been going on in a lot of different parts of this field. So you have to appreciate that the territory that's being covered here is extremely wide, that to get the value out of genome sequence information takes many different steps and stages and has a lot of complexities. So while the goal of this investment is to simplify that, we don't hope to cover every possible part because that's just not feasible at this time. So what we did is we selected very high quality representatives from a lot of different types of areas in this work flow or processing pipeline, of going from very raw sequence information, coming off the machines, all the way to information that's clinically relevant. So basically, this encompasses existing software that has been prototyped or developed with a lot of dependencies because it's embedded in a particular center or a particular group that has a lot of expertise. It's the process of pulling out those efforts in a form that can be distributed and it's more widely accessible to a much broader community that really represents the sphere of advancing genome science as it's developing today.

Male: And availability?

Dr. Heidi Sofia: As far as availability, there is the expectation with each of these programs that the software is made available. It's well documented. It's posted in the standard ways but with a special effort to outreach the community so that people can truly take advantage of this.

Uduak Thomas: Alright. Thank you.

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

Operator: The next question comes from the side of John Lauerman with Bloomberg News. Go ahead, your line is open.

John Lauerman: Hi! Thanks for taking my question. I have a few questions. First of all, kind of a housekeeping thing. The press release says 416 million, you keep saying 412 million on the phone. Which one is it?

Larry Thompson: We're working on that. Give your next question.

John Lauerman: The next question is, so you've been talking about the dropping price of sequencing, is there any way that you can quantify that? Do you have any idea how much you're paying per sequence and is this based on what you anticipate it dropping - the cost, dropping to over the next year or so or is it because of decreases that you are already seeing?

Dr. Eric Green: Okay. Let me start with the second question then we'll double back to the first and then you'll give us our third. This is Eric. If you happen to be near a web browser in terms of sequencing cost, that data that we have which we actually think is probably the best data that's out there.

John Lauerman: I think I know that. I've seen what you've already posted on this issue.

Dr. Eric Green: [Crosstalk] Genome.gov.

John Lauerman: Yes, I've seen that.

Dr. Eric Green: That is [pretty darn] good because that's coming from the three large centers, actually the same three centers we're talking about today, that's

being funded again and this is based on quarterly progress reports. We've seen a steady decline, there are lots of metrics I can give you but over the last decade, it's dropped by about 5,000 fold. Is there something beyond that…?

John Lauerman: I was just wondering if there is something more recent or again, is this like a projection? Is there any kind of a projection that you have?

Dr. Eric Green: The reason is it gets updated every three months. So the last update was probably just a couple of months.

Female: There is one soon.

Dr. Eric Green: There is one coming very soon in a matter of weeks. In terms of projections, I sometimes get asked about projections and I don't think there is anything we're discussing today that is based on any precise assumptions about the cost of sequencing except that it's going to go lower because it just seems so much more [unintelligible] in every practitioner in the field you talk to says that they continue to believe that they're going to see sequencing cost go down.

Dr. Brad Ozenberger: In a research setting though, we think we crossed the threshold this year where analysis costs more than the actually sequence production. So if you're just talking about sequence production, it's only that graph, what that graph is about, there is going to be diminishing return in the final product when you roll in the analysis cost.

John Lauerman: Okay. Go ahead.

Dr. Lu Wang: I just wanted to add that when we estimate sequencing cost based on the data submitted from the large scale sequencing centers, we are based on the production cost. Then the centers and the field continue to explore the potential of new sequencing technologies. So we'll have yet to see what miracle will happen.

John Lauerman: [Laughter] Okay. I wanted to talk with you a little bit about practitioners. We're talking about educating the public. I've been hearing this term genomic competency for practitioners, for actual doctors, is that something you'll be addressing?

Dr. Eric Green: Sure. Let me, first of all, tell you that apologies about the flipping around between 416 and 412, the correct one is in the press release. So 416.

John Lauerman: It's 416. Okay. Great.

Dr. Eric Green: So going to the third question which leads to the question one, is there anything that we're announcing today associated with our sequencing program that will relate to competencies or practitioners of genomic medicine is that a…?

John Lauerman: Yes.

Dr. Eric Green: So I would say, I don't think directly. I'm looking at my colleagues to see if they agree with me; I don't think there's anything directly. I would tell you though that I do believe that if successful, the clinical sequencing exploratory efforts will reveal – we expect them to reveal barriers and issues associated with uptake of genomic information to clinical care. With that, might come additional insights about competencies and

additional insights about what is going to be needed for preparing a healthcare profession and I see that very broadly, not just doctors but the whole healthcare profession, all healthcare professionals or what might be sort of a new infusion of issues surrounding genomics. I think it will inform it but this is not – don't look to this program to specifically develop such competencies for healthcare professionals.

John Lauerman: Okay. Thanks very much.

Dr. Mark Guyer: I would just add that the awareness of the need for that is something that was directly, again – directly addressed in a strategic event where the culmination of those activities is actually delivery of genomically informed healthcare, medical care. The strategic plan discusses many of the issues that we're aware of right now.

Larry Thompson: Okay. Next question, please.

Operator: The next question comes from the side of Mark Johnson with the Milwaukee Journal Sentinel. Go ahead, your line is open.

Mark Johnson: Hi! Thanks for taking this second question. I want to make sure I'm understanding this correctly. From your previous answer, the announcement today represents the broadening of the program but not necessarily an increase in funding. Is that correct?

Dr. Brad Ozenberger: It is repurposing to meet genomic strategy.

Dr. Eric Green: The way I would contextualize that is that if you look what we previously called our large scale sequencing program which we're now calling our

genome sequencing program, if you look it's essentially not a growth in terms of total dollars, it is certainly a broadening of the research agenda with an expansion. We're going to continue a lot of the stuff we've been doing. But we're going to expand at the front ebb more and more into clinical application and we fully anticipate a continued tremendous increase in the amount of data being generated because with the same amount of dollars and the dropping cost of DNA sequencing, you just simply get a lot more for even less.

Mark Johnson: Okay. The other thing I wanted to ask – I wondered if you could talk a little bit more about – you mentioned that you were especially interested in projects that were going to address barriers to clinical sequencing. You've mentioned ethical questions. What other barriers were you considering?

Dr. Brad Ozenberger: I'll relate it to the previous question regarding educating practitioners. The other main component is the informatics analysis projects within this clinical sequencing exploratory project. A physician seeing patients has minutes to consult with the patient and make decisions. So we're really looking at streamlining, automating processes as we can to bring the genomic data and what's clinically useful to physicians. It's a real challenge. It's a huge amount of work to be done in this area. We had another meeting workshop in NHGRI recently on a database of clinical variance that has utility. So yes, a lot of pieces have to come in place. The part of these programs will certainly be the informatics to go from DNA sequencers and analysis right into the clinic.

Dr. Adam Felsenfeld: I just want to add to something that Brad said before in this vein, which is that the considerations are a little bit different for different diseases. Are they made – they may turn out to be depending on what action one could

take given knowledge about the variants and how easy that is or hard that is to come by.

Larry Thompson: Okay. Next question please.

Operator: There are no more questions at this time.

Larry Thompson: Okay. Going once, going twice, is there anybody with one last burning question before we bring this to a conclusion? Okay. So we seem to be out of questions. I'd like to bring this briefing to a close and thank everyone for participating. An audio file for this briefing will get posted on genome.gov as quickly as we can and the transcript will follow in a few days. As always, if you guys have any follow-up questions, you can always call the Communications Office at 301-402-0911 and we'll try to get you an answer. So thank you all and farewell.

Operator: This concludes today's teleconference. You may now disconnect.

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