This meeting is being recorded.

Jillian: Hello and good afternoon everybody and thank you very much for joining us today for this genomics England webinar about reanalysing the data which they hold from the 100,000 Genomes Project participants. I’m delighted today and to be here and to be talking to you and to be able to bring forward the great news that we have been hearing as a Participant Panel for a while now with what Genomics England are doing with the data that we have all shared with them in the course of the 100,000 Genomes Project. So I'm delighted to be welcoming today my co-chair or the vice chair of the Participant Panel Rebecca Middleton, here to help me ask the questions that you have already sent in and that we will have today. Answering those questions are Chris Wigley who's the Chief Executive of Genomics England. Thank you Chris. And Dr. Ellen Thomas who is Clinical Director and Director of Quality at Genomics England and Dr. Suzi Walker who is Head of Translational Genomics, but we just call her the gene detective because she's doing some incredible work there in the background and we will be hearing a lot more about that in the course of the webinar. So and I know that lots of you listening today and watching today will have questions, please can you take them into the Q&A box? I don't think the chat has been enabled for you. So we need to go through the Q&A. If you put them in during the course of the webinar, we'll hope to try and be able to answer them in the question session at the end. We've got quite a lot that we would like to cover and enough questions have already been submitted that will be in carrying on with the questions that we've got already, but we will have time at the end to ask a few more up today and any questions that we don't get to answer today, we will be able to take and answer afterwards and a summary of the answers and those questions will be available on the Genomics England website in due course and along with the recording of this webinar and a Blog which is going to summarize the key points. And if you don't have time to watch a whole hour in retrospect, then we will be able to share the blog with you which will have the headlines in it. So without further delay, and thank you very much again Chris and Ellen and Suzi for joining us. My first question is for Chris. Perhaps you could start by giving us an overview of where Genomics England have come from to get to where you are today and how you've been working with the NHS in bringing patients into this and what's happened since.

Chris: Thanks Jillian, very happy to do that. I guess if we go right back to the beginning, Genomics England was created as a government company to deliver on the 100,000 Genomes Project in partnership with the NHS and I thought it might be helpful as a first step to just talk through the different phases of that work and who's doing what along the way so if the gods of Technology are with me, I'll hopefully share this this slide. Can you see that?

Jillian: Yes.

Chris: Great. So the first phase of the 100,000 Genomes Project back in kind of 2013-14 when it was just being designed was really in this planning work. So the blue boxes on here are things that the NHS are doing, the pink boxes are things that GEL are doing and the green boxes involve either consultation or activities with patients and participants. So that first phase was really all about the joint planning and design which was kind of co-created with early patient representatives. Into the recruitment phase of the project where patients who had cancer or undiagnosed rare diseases had a conversation with their doctor, saw the materials that explained what the program was about and chose to join in to the project, gave samples and gave consent for how their data was going to be used. Those samples were then sequenced to generate the genomes we tapped into other clinical data sets as well and GEL then spent a lot of effort in sequencing and analysing those results and returning the results to the NHS. So at that time the NHS teams were the Genomic Medicine Centres, for the 13 of those I think, that processed the findings confirmed them, because the confirmation of the finding has to be done by those teams of doctors and clinical scientists, and then returned those primary results back to the participants. That wasn't the end of the story, that was really to some extent the beginning of the story. So those patients who had a positive finding from the first ways that wave of the projects would go into treatment pathways in the NHS and we're now in in this sort of ongoing phase of researching those genomes, those data sets, working with clinical interpretation Partnerships, who are groups of academics, and also working leading work in-house which Ellen and Suzi will talk through in more detail to keep looking at those genomes, keep bringing the latest science and the latest findings to bear on those and then, just as with the primary findings, passing those research findings through to the NHS to kind of confirm and pass back to patients and participants. So that hopefully gives us sense of kind of who's doing what and what we’re up to.

Jillian: Can I just say a few words there Chris sorry about who the results are going to be coming back to when we said “receive results via the doctor for any further onward work”, which doctors are going to be hearing about those?

Chris: Yeah, so we passed the research findings to one of seven Regional genomics Lab hubs where the clinical scientists confirm those. They will then pass them back to the relevant consultant who was leading the work and kind of recruited the patient into the program. Ellen of course is one of those and will say more about that interface in in-house section of the webinar. So if I stop sharing that now so that people can see us. I guess the other piece that's important to mention is that on top of those, you know, the 100,000 Genomes Project has been a real world leader and has laid the foundations for a lot of broader activities now which Genomics England and the NHS are involved in. First and foremost that's the launch of world's first nationwide whole genome sequencing diagnostic service, the NHS genomic medicine service, and as well as that we've done a lot of work through the pandemic on COVID for example, and other research programs. The largest of which is a program to sequence up to 100,000 newborn babies, which will be happening over the next few years. And I think the really important point to make about those is that the more work that we do, the more there's a sort of positive reinforcement loop because there's still so much that we don't understand about the genome and the more data that we have, the better everyone benefits from that. And so the additional work that we're doing is not sort of separate to the work at 100,000, it's really intimately connected to it because that helps us to learn more and pass more diagnoses, more findings back to the original 100,000 genomes participants as well. The final point I guess just to make about the slide that I shared is also Genomics England and the NHS work really closely in partnership, but we each have quite specific roles and the role of the NHS is to work directly with patients and our role is to support them. And so today we'll be talking a lot about the work Genomics England is doing it in support of that but we should also be clear that we're not the people who actually kind of treat patients, you know, that's the NHS. But the work that we're doing and support of that is ongoing as I say.

Jillian: Thank you very much. That's great. Okay, Rebecca has the next question for you?

Rebecca: Chris in lay terms, could you briefly describe the state of play on the science that really is underpinning all the activities that you guys are engaged with right now?

Chris: Yeah, absolutely. As a lay person myself, I always need to put it in simple terms for myself as well. So that's always helpful. So when we talk about genomics, we're talking about our whole genome, all of our DNA and there's a copy of that in every cell of our body. Across that genome, there are there are 3.2 billion base pairs of that we represent with letters. Obviously, they're like little molecules, but we represent them with letters and within those 3.2 billion base pairs of letters, there are 22,000 genes. So one of the analogies that I like is if you think about kind of a piece of string that stretches from London to New York, you've got kind of 22,000 beads along the string which are the genes that make proteins that then then do all of the all of the things in our body and so that's about 2% of the of the DNA. If we look across all humans about 99% of our DNA is the same and so we're looking at where one person's genome is different in some specific places from a kind of quote unquote “normal genome”. Of course, we're all different in lots of different ways so there isn't a kind of single perfect genome but we're looking for where people have little sort of differences or glitches that we can we can try and investigate to see if that's what's causing whatever symptoms it is that someone's being recruited for so. It's worth saying, you know as we talked about at the beginning of the program and continue to talk about, the science is moving really fast here. The technology is moving really fast. And we continue to learn more about the genome and how it how it affects our body and our wellness and sickness and so on. There is still a lot that we don't understand about that. So when we talk about these variants or glitches in our in our DNA, we can classify some of those really confidently. We know that if you have this particular glitch that you will have sickle cell anaemia, for example. There are others that we suspect may be associated with a specific conditional symptom and there are others that we know are doing something but we still don't know what they're doing so they're what we call variants abundance significance and there's still lots and lots and lots of variants abundance significance that, back to the kind of positive feedback loop, the more that we and the more that we learn, the more we can actually classify those and become more confident. The final thing that's worth saying is that in some diseases genetics plays a really big role back to something like anaemia which just caused by one change in our DNA, and in other diseases genetics plays some role, it might change our risk factor or how our body responds to that disease, and in other areas genetics one player role. While genetics and genomics are really powerful tools to help us understand what's happening on our body, they don't give us all the answers for all conditions. And so we're continuing to work with, you know, leading scientists around the world to bring the latest advances into the work that we're doing both with the NHS and on the research side, but it's still not a kind of magic wand that tells us everything about what's happening in someone's body.

Jillian: Thank you for that, time to bring in Ellen now. She’s the NHS clinician among us as well as being a closely involved in the work of Genomics England. Ellen, how have you been using participant data up to now and how are you going to be using it next?

Ellen: Yes, thank you Jillian. So and there are really two sort of broad ways in which the data from 100,000 Genomes Project participants continues, has been used and continues to be used. So the first way which I think is of immediate interest to many participants and has been and will continue to be, is really looking at those three billion DNA letters in the genome that Chris was talking about and trying to target a very specific question to that data. So the specific question is: is there anything that we can see in the genome which explains the reason why this particular patient developed these particular symptoms? That is then a question which if we can answer it, then obviously unlocks, you know, a lot of things which are very helpful in terms of understanding a condition and understanding implications for a family and so on. So that kind of diagnostic question that we target at the data that was very much the question, that was the target of the first round of analysis. So as Chris said we developed an automated bioinformatics pipeline where we use the genomic data and the clinical data from participants. I put those together and tried to reach something which was a potential answer to that very specific question. And then the output of that was sent to NHS clinical scientists who looked at the output of the automated Pipeline and made expert human decisions about which parts of it met the evidence threshold to be useful now to look after families in their healthcare based on what we know about the genome and about that family today. So that human review of the data by these really expert people in the NHS is really crucial and happened for all of the main findings in the 100,000 Genomes Project. As Chris said, you know, that's really only the beginning of the story because we have since carried on looking at the genomes and carried on trying to answer that same question because we know that knowledge moves on and over time, we will understand, we do understand and we will understand more about genomes and how they relate to our symptoms and our healthcare. We are continuing to target that very specific diagnostic question at the genomes. When we find new diagnoses, those are returned to the NHS genomic laboratory hubs via what is called the Diagnostic Discovery pathway and that is a pathway which the NHS is absolutely with us in running that pathway and it's mentioned in the NHS England genomic strategy across the NHS. So that's really helpful for continuing to make sure that this pathway functions and I think as one of your earlier questions was suggesting, the person who originally suggested patients joined the Project might have retired or moved on but the Genomic Medicine Service is still there and it's still receiving these findings and is using standard NHS processes for changes in staff over time to continue to receive that information and do the right do the right things with it. So that's really the first way in which we look at genome data. The second way we look at genome data is in a sort of broader more zoomed out sense is how can we use that data really to understand more at a basic and quite sophisticated level about the way the human genome works, the ways in which the human genome can develop problems and the ways in which those problems can lead to healthcare issues. So that's not targeted at a specific answering a specific question for a specific person, that is more of an advancing science altogether. But while doing that advancing science, sometimes something happens which then means that we do have a new diagnosis for somebody. So if we advance science by findings by researcher, for example finding that there isn't enough evidence to prove that a particular gene causes a particular condition, then the people who were studied as part of that research out of that research will get a diagnosis because their diagnosis is now a known gene rather than an unknown gene. We also have the Diagnostic Discovery pathway available to us so that as well as doing the specific looking for Diagnostic questions, if when we're doing the broader research, we come across diagnostic answers, we have the processes in place to get those back to the NHS for that all important clinical scientists review. So that's really the two ways in which we're looking at the data at the moment.

Jillian: Thank you. Yes, and I think obviously we've heard a lot that about a quarter of the rare disease patients or rare disease families who signed up for the 100K originally have got a diagnosis so far. But I think Rebecca has a question which will be on the lips of the other 75% of them, which is one that a lot of people come to ask us this so I'm sure a lot of people be really interested to hear what you have to say.

Rebecca: Thank you. Yes, I'm one of those many people who didn't get a diagnosis or haven’t received a diagnosis so far. What should I do? Should I have another test? If so what test should I have? What should be my next steps?

Ellen: Yes, thank you Rebecca. So really that question is tricky to answer at a sort of level for everybody because everybody who came into the project came into it with a different type of symptoms, a different situation in their family. They've then had different life events or different choices that they've been making in life and different evolution of the symptoms that they originally came in with. So there isn't really a single answer to the question about what other tests and people should have, it's definitely the case that if things have changed for you or your family, or you have any questions about your health care or your specific situate your specific situation then going back to your NHS team is very much the right way to go about that. Obviously that starts with a GP but also there are a range of experts including clinical geneticists and other sub specialist experts who are available to GPs to consult if they need to. So that specific question for each individual is going to be very much dependent on their own condition and context. I think it is worth saying that even if you didn't have something found on the on the first analysis and then the things that Suzi is going to be talking more about in a minute about how we continuing to target diagnostic questions at the data all the time. So, it doesn't mean that something won't come out of that that for you and obviously it's difficult to predict exactly when that might happen for anyone individual but we are continuing to look and continuing to return those diagnoses. So if you did get a negative result the first time round that was very much a ‘nothing has been found so far.’ It wasn't a ‘nothing has been found and we've stopped looking’.

Jillian: Thank you very much. We've talked a lot already in this webinar about the rare disease arm of the 100,000 Genomes Project but what's the news on the cancer side? What can you tell us about how things have gone with that? Because obviously the people who joined who had cancer already had a diagnosis there. But the question was there anything that could be done to further understand their cancers or to find a treatment or a trial for them?

Ellen: Yes, absolutely. So cancer genomics is quite different in its context from rare disease genomics. So in cancer genomics, what we’re really aiming to do is to look at the tumour that's developed. So we're interested in the tumour’s DNA and what has happened to the genome in the tumour which has driven that tumour to grow and is then driving it to develop. The nature of tumours is that they are not static over time. So they may change over time if they come back for example, or sometimes they're taken out surgically and then we all very much hope that at that point they've gone and they don't continue to change because they've been taken out and cured. So in terms of how we’re using the cancer data, we are very much still looking at it and still drawing lots of research conclusions from it and learning about how you use tumour genome data to how you analyse it better, how you visualize it, how you pull out the useful elements of it. But for the patients that's quite different because for a patient who had cancer during the course of the time frame of the 100,000 Genomes Project, any new information that came out now from looking at their tumour genome is very unlikely to be relevant to them because either they don't have their tumour anymore or they have a different tumour now because it won't stay the same. So if participants who join the cancer projects do develop a new tumour or their cancer relaxes then as part of their standard care, they will be talking to their clinicians about is there a different genomic test that we should be doing now, on the tumour I have now, would that help? Is that a useful thing to do? So genomics is still very much being used now to help understand tumours that are developing that on being diagnosed now, but new information that we learn about tumours that happened five years ago, for example are very unlikely to be of any of any relevance to the ongoing health care for people. So when we're thinking about how we return, how we focus on returning information from our ongoing research into the NHS, that is very much focused on the rare disease context because we know that the germline genome, the genome that we all inherit from our parents and pass on to our children, is relatively static over time. So that something that we sequence five years ago, if we find something new in it now, then that is still there and still relevant now, so that's why this conversation has really been very much focused on rare disease.

Jillian: Thanks very much Ellen. Rebecca, your turn.

Rebecca: Thanks Ellen. Another question from my side. I suppose an obvious question that, as a participant especially those who haven't had any results or have a condition where things are changing, why can't we put participants back through the pipeline? Why can't we look again at their genome because as we've heard from Chris science is moving at a pace?

Ellen: Yeah, I think that's a really important question. So I want to sort of zoom out a little bit in addressing that one. So I'm very aware of that in the past during the main sort of phase of the of the 100,000 Genomes Project, we said to our participants that when everyone in the project had finished receiving the first round of results and the first round of additional findings, we would make sure that all participants benefited from the learning that we had made from the data that they had contributed to the project. So we absolutely 100%, that has never changed that commitment and we're absolutely committed to continuing to do that. I think one of the issues here has been that at the time when we were first saying that, we thought that we knew what the best way of achieving that would be. And we thought that the best way to do that would be to take every participant’s genome if they didn't have an answer from the first time around and put them back into the new version of the automated pipeline and put them back through the whole process. But since then actually we have done probably a lot more learning than we expected to about genomes and about how to interact with genomes and how to interact with that data. And actually we don't believe that that would be the best way of doing things. So our commitment to wanting to go back to participants and make sure that everybody benefits from the learning is absolutely intact and it's because of that we believe that we found a better way of doing it than putting everybody back one by one through the pipeline. So firstly I just wanted to apologise to everybody. I think we were over confident in the way that we explained what we were intending to do. We didn't take account of the amount of learning that we would do through the project. So I think we said that we would take specific technical steps, which now we don't believe are the right technical steps to take based on the learning. So I apologise that we were overconfident on our messaging about that one. But as I say we are completely committed to continuing to look at the data. And the reasons why, so Suzi is going to talk a bit more about what we're doing instead. But the reason why we think broadly that we think that we have a better solution now is that firstly that the pipeline is one way of looking at genome. It's one way of targeting a question at a genome, but it's not the only way to target questions at a genome and by if we if we take the same approach again versus taking a new approach this time. Actually, we think that we can find things and we have already found things that we think we can find more things by using a different approach rather than by using the same approach again. As well as finding the things that we would take by running the same approach again. Then the other thing which I think is really important is that it took us about five years to take every participant's genome, run it through the automated pipeline and then run it through the NHS process which is crucial to making the dating useful. So we spent five years doing that, if we kick that off again now started again, it would realistically take us another five years. It is a it is a big undertaking which would mean that some people will be waiting another five years before they got to the point where their data had been back through the genome. So that would mean there would be another queue and everybody would be in the queue. Whereas with the approach we're taking now where we look at all of the genomes and target questions across all of the genomes together, it means that everybody's at the top of the queue every day. Nobody is waiting five years to start the process of having another look at their data. So that's why we really believe that this is the right approach to take. The final thing is just to say that all of the new diagnoses that we find must go over the NHS because that is where the experts are to say ‘yes, this is appropriate to use in healthcare’. The NHS is where healthcare experts sit and so everything that's going to be used for our healthcare must you know, I would want everything for my healthcare to go via those experts. But what we can do by using the current approach is help giving the healthcare experts a bit of a helping hand by adding in more evidence and information and presenting that back to them to help them with that process just to make it a bit more efficient for the NHS to then process those and return them to patients. So we really feel that the approach we are taking gets the best balance in terms of in terms of sticking to that original commitment to make sure that everybody who joined the project and who donated data to the project is benefiting from that donation that they made.

Jillian: Thank you very much, Ellen. We were wondering about whether there's an analogy that we can share to help people understand the difference between the original one-by-one pipeline approach and the new approach that Suzi is developing with her team. I suppose it's equivalent to if you're trying to find in a football stadium people whose birthday is the third of April for example, how do you find the people as fast as possible? Do you ask them by one or do you just say to the whole stadium ‘put your hand up if that's you’ and I think that's the sort of scale of difference that we're talking about here between the original intended approach and where you're talking about getting to next. I think this is a good opportunity to put in Suzi and who's been patiently waiting to tell us all about the science side of things, thank you very much for joining us today Suzi. The first question we've got for you is can you tell us and what you and the team are doing with participant data to help find these new diagnoses?

Suzi: Thank you Jillian. Slightly to recap and set this up nicely of what we've spoke about before, but everybody has so many millions of genetic variants in their genome and in the case of families with rare conditions, we're often looking for a really small number of those changes that might be related to somebody's health condition. We're looking for one or two genetic changes. So that's a lot of genetic changes in somebody's genome we have to work through to find the really sort of pertinent changes that we're looking for. When we first did this we looked at everybody one by one in their families because that's how we have to look at people when they present and need an exploration of their genome. But now we're in a really fortunate position as Ellen said that we have everybody's genomes in the research environment and in the National Genomic Research Library, and that gives us a huge amount of power to look across everybody's genomes together and then everybody that has really kindly shared their data for research purposes can help to benefit other families across the country to help everybody collectively find more diagnoses. This is what we're doing now, and as Ellen said there are research groups working across the country and across the world to help find new diagnoses. And this may be academic groups looking from universities and other institutions. There are also commercial and Enterprises that are using the data perhaps with the objective of developing new therapies, but they may have specific interests in the specific condition or they may have a specific type of genetic change that they're interested in. And so what we're doing inside Genomics England is really working with those groups, but also independently in our own work to make sure that the new learnings and the new science that's coming through is available to all participants that were recruited to the project and everybody has an opportunity to have a new diagnosis identified. And there are some really key areas where the science has developed and the technology is developed over the last few years that by looking at everybody's genomes together, we're really able to zoom in on the areas where we think there's a really high probability or high potential finding for one of one or more families recruited to the project. And so as Chris said there are over 20,000 genes in the genome. We don't understand yet what all of these genes do. It's a rapidly developing science and we're gaining more and more and knowledge as time goes on. And so it might be that you were recruited to the project at a time where the gene that might underlies are particular condition in your family wasn't well known or wasn't well understood. But we know now through science which genes have been better described, which genes we understand better in 2022 than we did in 2018. And so we can look across everybody in in the cohort and say who has a genetic variant in one of these genes that's been newly understood that might be related to their health condition. Similarly, we know which areas of the genome are technically very difficult to work with and we know perhaps where the family by family type of analysis might have limitations that make things difficult to find in that way. So by knowing the sort of the technical side as well as the scientific side of how the analysis works, we can look at regions of the genome where it might take and somebody to sit and patiently looks through potential findings in that region of the genome to make sure we truly understand them properly because that region of the genome might be tricky to understand. We really do have this deep understanding of our pipelines, we continue to develop these as part of our work with the NHS and that really helps us to find areas where we think we've learned something that might mean that we can find something for a family that was analysed previously.

Jillian: How can the new diagnoses be found? Do you use a magnifying glass? What kind of techniques are you using? Can you tell us a bit more about that?

Chris: You were a tiny bit quiet there Jillian, was that ‘what techniques are Suzi and team using?

Jillian: Yes, how are you going about finding these new diagnoses?

Suzi: Yeah, so we're using different techniques to those that we used in the first analysis. We are selecting genes and regions of the genome where we think there might be a diagnosis. We're not necessarily using the same sets of genes that we used in to look for diagnoses in the first analysis. In the original analysis, nobody's analysis was restricted to a particular set of genes, but we might have used a set of genes to prioritise genetic changes that we think are most relevant to their healthcare. Whereas now we're taking a different approach and looking at genes, looking across everybody at genes that we think could be relevant to the health condition for anybody in the project. To follow your analogy Jillian, we're looking at a gene and saying does anybody think that this gene might be relevant for them, but using their genome to answer that question.

Jillian: The project initially had heard about this concept in gene Panels, can you just unpack a little bit about the difference between what the gene panel could tell somebody and what you've been telling us about what you can do now?

Suzi: Yeah, so in the first analysis we used gene panels to prioritise genetic variants that were found in that family for genes that are known to be associated with the particular condition that was known for that family. That's not to say that only those genes were looked at in the analysis. It's just there was a hypothesis that those genes might be the first ones to look at based on what was known about the family. And in many cases the underlying diagnosis was found in one of the genes that was prioritised using the panels. But in other cases, it can be very difficult to predict which genes should be included on the panels, which are the right panels to use for somebody's condition if it's a very complicated one. And again, we know that new genes have been described since that time. So now, rather than using this panel based approach, we're sort of using the panels in another way. We're asking the panels to show us who's genomes and might have a genetic change in one of those genes known to be associated with a condition. Rather than using a panel and to prioritise variants in any one individual genome.

Jillian: Great, thank you.

Rebecca: Thanks Suzi. If I can jump in, I'm an ultra-rare patient. How can I be sure that you're not going to miss me or miss my genes as a rare disease patient?

Suzi: We're not looking at everybody's genome one by one, we're looking at everybody's genomes all of the time. So on any one particular day, there's a possibility that a diagnosis may be found for anyone individual in the project. We understand that there are people with ultra-rare conditions and in some cases it might take a long time before we can find a diagnosis because the genes underlying that condition may not be well understood today in a way that can be used in healthcare. But by using the genomes all together and looking at everybody in the project together, we might we might be able to accelerate that process by finding that actually there's somebody else in the project that has a genetic change in their genome that's very similar to the genetic change we can find in in your genome perhaps or somebody else's genome. We then can see that the symptoms and the clinical presentation of those individuals is very similar, and then suddenly, we not only help to find a diagnosis for you, but bring the science forward as well at the same time. And in other cases we might see that ultra-rare conditions are actually very similar to a condition that we know very well but might be slightly different from or a slightly different form of a very well-known condition due to the nature of the specific genetic change in your family. And again by having the ability to look at everybody together, we can start to see these complicated scenarios that we all know are hidden in our genomic data.

Rebecca: Thank you.

Jillian: Is there a week for participants to know where they are in the process of all of this? It's really reassuring to hear that you're looking at everybody every day but is there any way of knowing how long before somebody might get an answer?

Suzi: It’s a different way to the way we did it in the first time we looked at everybody's genomes. This isn't something that everybody is going to go through the process, go in the beginning and come out the other side. It's an ongoing thing. And so we can't necessarily tell you where you are in the process other than to tell you that every day everybody's genome is being looked at and every day there is the potential for a new diagnosis to be found for your process for your family. This work will continue, we don't necessarily know when a diagnosis might be found for you, but you can feel reassured that your genomes are constantly being explored and with the aim of trying to find something for your family.

Rebecca: Thank you, and I suppose a question for you Ellen. As kind of participants we're keen to play our role. Is there anything we can do to help this process?

Ellen: Yes, as Suzi was saying this research work looks at all participants all of the time. So it's not something where you need to say, please can you look at me or please can you make sure that I'm included unless you have withdrawn your consent for being an ongoing participant in the program you will be included in it. So it's not something where you need to nominate yourself. We do have ongoing, people are sometimes a bit worried that you know, well, I've got a new diagnosis now compared to where I was when I joined the program but we get refreshes of the data that we get. So for example, if you go into hospital and the hospital will enter a code to say that you've been in hospital and to say what you were in hospital with and that data is collected by NHS digital and is then available with again with your name and your NHS number and everything taken off it in the National genomic research Library alongside your genome data. So we do have that refresh data coming into us so we are able to look at that updated data. So we are we are looking at all the genomes. We are looking at updated data about your health and it doesn't matter whether you know, you don't need your clinician to ask us you don't need to be still in touch with a doctor. It doesn't make any difference whether you are still being seen once a month in an NHS clinic or whether you haven't seen a doctor since the day you joined the project. We are still looking at the data and we’re still feeding it back. So really there isn't anything that you need to do in order to make sure that you are included in this process because you are.

Jillian: Thank you. I'm sure that's enormously reassuring to the whole audience. Thank you Ellen. Coming back to Chris. We've covered a lot of ground in the last 45 minutes and we're wondering what sort of summary could you pull together for us?

Chris: The first thing I would say is thank you, the 100,000 Genomes program really was ground-breaking in terms of the science, the ability to translate that science into clinical treatment not just in this country but in the whole world. I've been really struck since the pandemic has kind of eased back a bit of travelling to other countries and talking to other programs and all of them really hold up to 100,000 Genomes Project as this massively ground-breaking work. Our commitment is to make sure that everyone on the call and everyone who is a participant in the program gets the most benefit for them and their families as they can for being a pioneer and you know coming on that journey with us. On that note the second thing I would say is the journey continues, it's not over. As Suzi and Ellen have said, no one has been forgotten, everyone's on the bus and we want to move forward together and the more work that we do whether it's in COVID, whether it's a newborns and whatever, everyone's in it together and the more the more people there are, the more everyone benefits. I do think it's worth just repeating one of the points I made at the beginning around we may never get to a genetically driven reason for everyone's condition because not everyone's condition may be driven by genomics again. That doesn't mean we've forgotten those people or that then they're not on the journey. It's just that of all of the tools available to medical science this what this one may not be the one that shines light on that and condition. But the more that we do together the more will know and the more we learn the more we can bring those diagnoses back to those patients and those families. We want to keep working on that together kind of hand in hand with patients and participants such as you Jillian and Rebecca, you know convene the Panel group, but also on behalf of all the participants that we serve. That's what gets us out of bed in the morning is trying to do the best that we can for everyone.

Jillian: Thanks very much. Obviosuly there's a lot of people listening in today and more will listen in later. And I think we're all always really interested to know what's happening next. So this is been a great opportunity to hear more about it. And thank you all again for your contributions today. It's really interesting. We've had a number of questions come in in the course of the conversation. I think now is the time to go and have a look at those. Our colleagues Daisy and Yufan have been collating them over the course of the call so hopefully I'll be able to come back and here. I'm just going to read out the question and if you think it's you just dive in and answer, it's probably the easiest way and if nobody wants it, then we'll have to go in think about it again and write down the answer and put you on the website later. Is there a method of updating the clinical data that was originally input when patients were recruited to the 100,000 Genomes Project?

Ellen: The main way in which we are updating the data now is by the mechanism I just touched on briefly a bit earlier. Whereby we have a number of data sets which are held by the NHS and under the terms of their consent that you all gave to join the project, you very kindly agreed for us to be able to refresh the data sets that we held that the NHS holds about you in order to make sure that we can continue to compare your genome against your updated health data. So that is the main way in which we are updating that that information.

Suzi: Just to add a little bit to that, sometimes we might find something in somebody's genome that we think we need more additional data and in some cases we might write to a clinician or a participants clinician and ask them if they can provide us with updated data to help us improve how we look at the genome.

Jillian: Thank you. Next question, which I think is one which a lot of participants may be interested to know about and it's a question about additional findings. Now a lot of people when we signed up initially for the 100,000 Genomes Project, were offered the opportunity to find out about additional findings, which was whether we had a genetic predisposition to certain forms of cancer or other chronic conditions, which could be genetically indicated. I know there's been an extensive amount of work done to try and improve together answers for those people, perhaps this is a question for Ellen. Can you give us a quick update on how things are with the additional findings results please and what should people do if they haven't heard yet?

Ellen: Yeah, absolutely. Thank you Jillian. The additional findings analysis is interesting in terms of its timing because we were literally in March 2020. Just having the final meeting between Genomics England and NHS England to start to finalize the final details of the analysis. And unfortunately, then it did, with other things that NHS England were doing and so on and the NHS was doing, we had to pause for a little while. So we then had about an 18 months pause during the height of the COVID pandemic when we weren't able to get started really an earnest on the additional findings results. So the pipeline started running in summer 2021 and we have been running all the participants who said they wanted to be through the pipeline since then and returning those results to the NHS. As with the main findings, it's really important that they go by the NHS to double check them and check that they are meeting the right standards before they come back to participants and the NHS has then taking the responsibility to contact people and say either nothing was found when we ran your additional findings or we did find something and it's not those are not being returned via the clinician who originally suggested that you joined the project. Because if for example you came in to the project suggested by neurologist, they're not going to necessarily know what to do with the result about an inherited cancer predisposition. So the way that that's working is that the results are being returned centrally by the central hubs in the Genomic Medicine Service and that return of a positive result then comes with a pathway in the NHS. So here is an appointment with somebody who will be able to advise you and tell you more and help to work out what we should do with this result next. So the moment we know that a lot of participants have had their results either positive or negative, the great majority are negative, which is to say nothing has been found. Which is what we were expecting because these are rare conditions and most people don't have them. We know there's a lot of participants have had those results but there are still a lot of participants who are in the process and it's all working and it's still happening, but that they just haven't quite got back to all the participants yet. So what we're suggesting is that if in the New Year, you still haven't heard anything and you were expecting to hear, then if you get in touch with these Service Desk at Genomics England, then we can look into that for you. But at the moment if you haven't heard, that doesn't mean that something's gone wrong or that you've been forgotten. The process is very much still active and running Suzi's been very involved in the additional findings analysis process. So I might just check whether she thinks I've got that right and whether there's anything she would add.

Suzi: No, that's perfect. Well done Ellen.

Jillian: How are variants decided to be significant or not? The variant found in this participant who sent in the question through the 100,000 Genomes Project was classified as a variant of unknown significance, but in other countries the same variant has been classified as significant. We think others in the 100,000 Genomes Project have encountered this issue with the same variant in England or across the UK as well. Why is there a discrepancy between the UK and international?

Ellen: I'll take the first the first element of that. Variant interpretation is the process of looking at specific change that has been found in a person's genome and comparing that to the condition that they have presented with and then piecing together pieces of evidence to say is this just part of the normal natural variation that we all have, much of which is very rare in all of us, or can we really pin down enough evidence to be clear that this specific variant is causing this specific health condition and this is a really important and expert process and internationally there have been a number of efforts to try and standardize the process over time and it has become more standardized over time. But as with all as with all standardization efforts, there are always complexities which make the standardization which mean it's difficult to reach a point where you always get exactly the same answer when you're on a borderline between a variant that you think could w, whether there's enough evidence or not, sometimes there is more evidence. Sometimes one person was looking at a year later and there was some new evidence compared with the person that looked at it a year ago. So there are all sorts of reasons why you can end up with that variant interpretation process, not always coming out with the same answers in two different places and different countries have different approaches which are matched to their own expectations and their own expertise and their own healthcare systems, but one of the ways in which you can really help break through this is by centralising data in one place and that's why for example at Genomics England we have the clinical variant arc. So quite a lot of situations where people from one place in England have looked up a variant in the clinical variant arc which contains all of the data from all of the participants in the project and then they're able to say or somebody else thought this about it and then if they think something different they can get in touch and reach an agreement together. There’s obviously a lot of work still to do in this area. But we do think that we're moving in the right direction in terms of having all the data in the same place such that it really facilitates those conversations.

Suzi: Another thought under the end of that is that, as Ellen said we need to have enough evidence to be able to be confident that that variant is significant in that particular family and obviously that evidence will change over time, new scientific discoveries will be made. So it might be that the time that the initial interpretation was done the evidence was less than it could be now and part of our work will be looking back at variants that have been classified as the US historically or previously and seeing if there is now sufficient evidence to be classified those for those families.

Jillian: Thank you. Okay, we've got lots more questions to come. So we'll try and keep moving through them. Apologies if we don't answer them on screen, but we will answer it afterwards and it will come up on the website. Here's a question relating to the beginning of the project. Why did the 100K Project not want samples from other members of my family when there are five other people that are undiagnosed of similar and different symptoms?

Ellen: The question about which family members have a particular test can be very individual for a very specific context so it's that there is no kind of there's no generic answer to exactly what is the best approach in terms of when you do a test how many people in the family do you look at the same time? So there are sort of general principles about when it's helpful to look for family members at the same time and when it's helpful to look at family members separately. But those principles there are always situations where a particular condition, for example, we know that there are particular conditions when looking at family members together can actually mean that you're more likely to miss things for example. So if things are if a condition is relatively common, you can have the same condition in the family twice by chance, and I know that sounds a bit crazy, but actually it happens more often than you think it does. Then if you look at the whole family together, that can really put you off finding the answer. So there are some situations where it's better to look at lots of people together and there are some situations where it's better to look at one person or a smaller group of people to start with. I would say that would be my general answer to that question.

Jillian: Thank you. Somebody would like to say thank you Suzi and everyone at Genomics England for the work and effort going on into reanalysing the results. It means a huge amount those who have so far had a negative result. Thank you. But here's another question. How are you looking at everyone's genes every day? It was previously indicated that Genomics England was looking at specific genes one at a time, can you explain this in more detail? I'm guessing that question was written on some time ago. So I think we've covered quite a lot of that. But if there's anything else you wanted to add, now would be a good time.

Chris: One reflection I had when I read that question was the way that it could work to look at all the genomes when we're looking at specific genes is kind of back to your football stadium analogy Jillian which is to say, right we've just had some new learnings in the science about people whose birthday is on April the third, so we're looking at all of the genomes to see who's birthday is on April the third and then investigating those in more detail. So even though we might be working through a specific finding or a specific gene kind of each time, we're looking at that finding across the whole base of all the genomics.

Jillian: Yeah, thank you. I think this question's also been answered. But just checking with you Ellen, with being seen by different healthcare professionals in different departments or clinics be reported back by Genomics England, for example, if someone has lost their hearing since they first joined 100K Project, but were discharged by their original health professionals and they're only see Audiology, will that information be included if they were not admitted to a hospital?

Ellen: Yes, thank you. That's a great clarification question because I know I said earlier about if somebody had been into hospital but I was being too specific there. So whenever you have an outpatient appointment or a procedure, so if you have a hearing test or if you have a scan or if you have any kind of consultation with a specialist in hospital, those things will all lead to an entry in the data as well. So if you've been seen by an audiologist and you've had a hearing test that information will be there in the data.

Jillian: Thank you very much. That's great. Next question relates to the Our Future Health genomics program, which we haven't mentioned at all today. Chris, would you maybe answer this question be able to refer to what it's trying to achieve? Someone's asked is it worth joining Our Future Health as a parent of a child participant in the 100K project or would that be duplicating their data in the system?

Chris: Thanks Jillian. Maybe just for those who are less familiar with Our Future Health, this is a big research program, which has been kind of getting prepared for the last couple of years and is just the stage now of starting to recruit the first participants through places like boots and so on in the community and the goal of our future health is to recruit five million people. So a massive cohort, to try and help with understanding the sort of prediction and prevention and early diagnosis of a whole range of different diseases because it's much broader. Sort of five million people. It's also to some extent a bit shallower. So for example, not everyone who joins Our Future Health will get their whole genome sequenced, they'll do a kind of a smaller sample of their genetics of each of the people. This is a really timely question about whether people should join or not and there are very strong and different views about it. UK Biobank recently sent a letter to all of their participants saying that they shouldn't join Our Future Health because of exactly the point that's flagged in the question itself, they're saying actually this risks being duplicative. A lot of people disagreed really strongly with that view. I have to be honest and say I think we haven't come to a kind of formal position on this as Genomics England. But certainly if you're motivated to help with, you know, science and research. I don't think it's a bad thing for people to sign up to Our Future Health indeed. We're trying to make it as easy as possible for colleagues at Genomics England to sign up if they're keen to do so because you know, we're keen to support Our Future Health, we’re keen to explore where they're opportunities to collaborate because there are so many areas of shared interest. So it's a great program. If you're motivated to join up, don't feel like you're going to be messing anything up by doing that but it does prompt me to think actually we probably should articulate some guidance for our participants probably in consultation with them. So let me take that as an action.

Jillian: Thank you very much. That's the completion of the original time slot that we had, Yufan has sent me a message to say that there's still lots of questions coming in. So I think the best way for us to answer all those will be in writing afterwards with the part of the blog and the website answers, which will go on afterwards. Is there anything in closing comment or reflection from each of you please about what you see the role of the reanalysis being over the next year?

Ellen: One of the things I'm really excited about in terms of what Suzi and her team are doing is that it has this sort of very dual purpose. So the first purpose is obviously returning diagnoses to individuals who took part in the project and that's really important. And then the second purpose is really understanding more about how you find diagnoses in genome data and then working out how we can use that experience and that information and those insights in making our ecosystem function better over time, and I think that combination is just feels like a real win-win to me.

Chris: I would just add I think it's great to get these questions in and thank you so much for those people who are submitting the questions. This is the point of these sessions, to try and say things that are relevant to what some people's minds and so I’m unconscious that in in this session, there were some structured sections up front when we wanted to explain what we were doing, but I think we're keen that this is kind of the start of a conversation not the end of a conversation and so we're really happy to come back and do more of these webinars where we maybe have a brief kind of update section up front and then more time just kind of whatever questions are on people's minds, a sort of ask us anything type session because then I'm really keen that we are responsive to what some people's minds not just kind of preaching about whatever's on our minds. And so thanks for asking the questions don't feel like thinking to a vacuum and do you kind of you know dial back in for the next one of these because we will be back.

Suzi: My closing comment is a round of thank yous thank you to all the participants for sharing their genomes and being brave to share them for research as well. You're helping each other. You're helping us do a better job and we're so grateful for that. And also thank you to the academic researchers and the commercial researchers. We're learning from them every day as well and their work is bringing things forward and of course, thank you to all of our NHS friends and colleagues who help us with bringing those findings back to the participants and the patient.

Jillian: Rebecca was there anything that you wanted to conclude with? Or are we going to wrap up there and say thank you very much.

Rebecca: Yes, just thank you. Thank you very much everybody for joining us today and thank you for your time and your questions in the Q&A. Thank you to our speakers and do look out on our website. There will be a Blog about it summarising what we've heard today, there will also be the Q&A so rest assured that all questions will be answered. We'll just get around to it in a written Q&A rather than on the call today. So, thank you everybody.

Jillian: Thank you very much, and have a good afternoon or whenever you happen to be watching this and thank you again for joining us. Bye for now. Thank you.