Participant Webinar on Reanalysis Q&A (23rd November 2022)

1. If I didn’t receive a diagnosis from 100,000 Genomes Project main findings, should I have another test, and if so, what test should I have, when and how?

There is no simple answer to this question, because every patient is different, as are their family and their context. If something has changed for you or your family, or you have questions about your healthcare, you need to discuss this with your NHS team to see what your options are. If nothing was found in the first analysis of your data, a new diagnosis could still be found through ongoing research work using the data we hold for you.

1. What about patients who joined the Project because they had cancer?

For participants who joined the Project with cancer, analysis was performed looking at each patient’s tumour to understand what is driving it to grow and develop. Tumours change over time, or they are surgically removed (and hopefully don’t come back), so the information found in a tumour genome is most useful at the time the sample of the tumour is collected, and becomes less relevant for how that patient should be cared for over time. It is a view of what is happening in that tumour at that time, so if a patient develops a new tumour, or their cancer relapses, they can discuss with their healthcare team whether a new genomic test on the new tumour might be helpful.

That said, the tumour data donated to the Project is still being used very actively for research; this is more focused on improving our understanding of cancer genomics and how we can treat cancer patients better in future at a broad level and is unlikely to generate new, useful information for individual participants in the 100,000 Genomes Project. The current work looking for new findings for 100,000 Genomes Project participants’ data is therefore primarily focused on the rare disease part of the Project.

1. Are you going to be looking at all the genomes again with the latest version of the bioinformatics pipeline?

Everyone has around 5 million genetic variants in their genome and most of these aren’t causing any health concerns. In the first analysis for primary findings, we were able to identify diagnoses for around 20-25% of families, and it took around 5 years to complete for all 35,000 families. We said that when everyone in the Project had received their primary findings, we would make sure that all participants benefited from the learning they helped to generate. Previously, we said that the best way to do this would be to use the latest version of the automated pipeline for every family’s genomes, if they didn’t have a diagnosis from the original analysis. Since then, we have learned a lot about different ways to look at genomes, and we don’t believe that this is the best way to make sure all participants will benefit.

We are sorry that we were over-confident about predicting what would be the most effective way to look at the data again in future. We are completely committed to the spirit of the original promise, which is to make sure that participants benefit from the learnings made during the Project. This commitment is what has led us to change to a better plan.

The pipeline provides one way to analyse a genome. By using different approaches in ongoing analyses, we can find new and different things, as well as finding the diagnoses that running the pipeline again would find. Re-running the pipeline for each family would be a huge undertaking and would take years to complete. This would include technical and operational work at Genomics England and review of the findings for every family by NHS clinical scientists, and so means some families might wait another 5 years to go through the full process. Using different approaches can help accelerate the number of new diagnoses being found for participants. All the new diagnoses found are still reviewed by NHS clinical scientists before being used in healthcare. Genomics England and other researchers analysing participants’ data can also pass on evidence to the NHS scientists to help them do their work efficiently.

1. What is happening now to help find new diagnoses for participants in the rare disease programme?

We need to be able to run an initial analysis, as we did when we first looked for primary findings, for each family as they visit their specialist and are identified as needing a test. We aim to find as many potential diagnoses as possible in this analysis, but biology and the genome are very complicated so we know that it isn’t possible to find everything using this approach. Compared with where we were in 2013, we now understand much better which types of diagnosis are tricky to find.

We now have the massive advantage of having the data for all participants in the National Genomic Research Library (NGRL) together, so we can work on all the genomes at the same time, and do not have to look at the data one family at a time. There are lots of research teams from academia, industry and healthcare working in the NGRL, using the genomic and clinical data participants have shared. There are research projects using the data in different ways that will help find new diagnoses now and in the future, such as the development of new tools that help identify diagnoses from the 5 million variants in a family’s genome, or the finding of genes that are associated with different conditions. These research approaches are frequently not dependent on gene panels so the number and choice of panels used in your primary analysis will not be as influential.

At Genomics England, we’re using the knowledge we have learned through the Project and from working with researchers using the NGRL to make sure that all participants are included in these ongoing analyses and can benefit from new scientific insights that have come about since the Project began. We’re including all participants who have given consent to share their data, so you don’t need to have an active relationship with your clinician to benefit.

There are around 20,000 genes in the genome and we still don’t understand what they all do, and what conditions might be linked to which individual genes. Since the Project began, lots of genes have been newly linked to different conditions so we are looking to see if there could be participants in the 100,000 Genomes Project with diagnoses in these genes, that may not have been found before. We also know a lot more now about the types of genetic changes that are difficult to find in an automated, family-by-family analysis and we are specifically looking at these areas to look for new findings.

We are also looking at variants of unknown significance (VUS) found in the primary analysis to see if there is new evidence now that would change the classification of these variants. This new evidence might also come from looking at all the genomes together in the NGRL.

1. How are you choosing whose data you analyse?

We are not analysing individual families one by one, but rather we are looking at all the genomes of everyone in the NGRL together. We are looking at the genetic variants found in different genes, focusing on the genes that are known to be associated with health conditions, to try to find the largest number of diagnoses in the shortest amount of time. This means everyone’s genome is being looked at all the time.

1. How can participants know where they are in this process?

The research work in the NGRL is ongoing and we are planning improvements to the research tools available, to encourage more people worldwide to use the de-identified data our participants have generously donated. The work we are doing is an ongoing process and we will continue to look at all the genomes to try to find new diagnoses. The data for all participants is being analysed regularly, so individual families cannot be given a specific “stage” in the process as was the case in the primary or additional findings analyses. Every family is included in all the work, every day.

1. Is there anything participants can do to help?

This research work looks at all participants all of the time, so no one needs to ask to be included in it. Unless you have withdrawn from the Project, you will be included. It doesn’t matter whether you’re still seeing the doctor who suggested you join the Project – the results we find are being returned to the NHS Genomic Medicine Service, who may contact you with new information, or to ask for new samples, or to see you again in the clinic to discuss a new result.

1. How are you looking at everyone’s genes every day? It was previously indicated that Genomics England is looking at specific genes one at a time, can you please explain this in more detail?

We look at all the genetic changes in a particular gene to identify the changes that are likely to be a new diagnosis for the family, or families, who have those variants. We are focusing on genes that are known to be associated with health conditions and we incorporate the latest knowledge about the genes we analyse. There are around 2,000 genes that have a known relationship with a medical condition (such that they are useful in healthcare now), and 35,000 families in the Project – so looking gene by gene helps us to identify clinically useful findings more rapidly.

1. Is other research happening to try to find answers for participants still waiting for answers, such as those with a negative diagnosis from the 100,000 Genomes Project?

Yes, there are lots of different research avenues being followed. There are lots of research projects using the data in the NGRL, some of which are expanding our broader understanding of genomics. These projects might be describing how genes that are not currently well understood can be linked with health conditions or helping to understand the impact of genetic variants that we currently cannot confidently predict. Other work that Genomics England is helping to support includes looking at other types of sample or analysis, often known as ‘omics’ analysis because the different types of test are known as transcriptomics, proteomics, metabolomics etc. These are all different ways to look at the way the genome works in different conditions, and we and our research partners are investigating how they can contribute to rare disease diagnosis. As with the other types of analysis discussed here, if we find answers for individual participants while doing this, the new findings will be returned to NHS centres.

1. Is there a method of updating the clinical data that was originally input when patients were recruited to 100,000 Genomes Project?

In the NGRL, researchers can see your genome data, the original health data provided by your NHS team when you joined the Project, and additional data that we collect from NHS Digital. This includes all the ‘codes’ which track your healthcare in hospitals across England and we receive an update every 3 months. This means that if you have an operation, or an outpatient appointment, or a test or investigation, the information that this happened will be included in your record in the NGRL. As with other data sharing that participants provided their consent for, this information is de-identified, so without your name, date of birth, NHS number etc.

1. Would being seen by different healthcare professionals in different departments/clinics be reported back to Genomics England? For example, if someone has lost their hearing since they first joined the 100,000 Genomes Project, but were discharged by their original healthcare professionals and now only see an audiology department.

Yes, Genomics England will receive information about outpatient appointments, hospital investigations and inpatient stays from NHS Digital, regardless of which team you are seen by. The information includes potentially relevant developments (such as being seen in an audiology clinic and having a hearing test) and also less relevant information (like being seen in A&E after a road accident) - but researchers are very used to using the information which is relevant to their genomic research.

1. Why did they not want samples from other members of my family when there are 5 other people that are undiagnosed that have similar and different symptoms?

Sometimes it can be very helpful to sequence samples from multiple members of the same family. Sometimes it isn’t so helpful and can even make the analysis more difficult. This is quite individual to the family, the condition and the context, so it was up to NHS teams to make that judgement for each individual family who joined the Project. If something is found for a family, additional samples can be collected for family members later to test who else in the family also carries the same genetic change.

1. How are variants decided to be significant or not? The variant found for me through the 100,000 Genomes Project was classified as a variant of unknown significance (VUS) but in other countries the same variant has been classified as significant. Others in the 100k have encountered this issue with the same variant in England/the UK too. Why is there a discrepancy between England vs internationally?

It is often very difficult to be confident that a specific variant is the cause of an individual person’s health condition. This is because all of us have hundreds of thousands of variants which have never (or almost never) been seen before in anyone who has had genomic sequencing. If we are going to use genomic variants to inform your healthcare, we need to be very confident that the evidence for the variant causing the disorder is really strong. The international genomics community has worked on standardising the ‘rules’ about how you collect and assess evidence for each genomic variant. However, this still isn’t completely finished, and some countries have chosen to adjust the international system for their own system. The UK has been a leading contributor to this conversation.

In addition, the evidence for a variant varies over time. For example, more sequence data becomes available to compare internationally each year, which may change our understanding of an individual variant, or a researcher might do an experiment to test the impact of a variant on the gene in a lab. Also, different information may be available for one lab compared with another lab (e.g. they may have previously seen more patients with a particular condition and so know more about that gene), which may also mean they assess a variant differently. This is why it is really important to bring genomic data and knowledge together as much as we possibly can, for example in the Genomics England Clinical Variant Ark, where all diagnoses made via the Genomics England pipeline can be seen by all NHS clinical scientists. In our analysis work, we are also looking at variants that have previously been classified as a VUS to see if there is new evidence to allow the NHS clinical scientists to change that classification.

1. Why would a VUS not be reported in 100,000 Genomes Project primary findings, if it was picked up in initial genetic tests? For example, a variant was found which was why I was recruited to the Project, however my primary results from the Project didn’t mention this VUS at all. Does that mean the initial results were wrong, or was it not reported in the results because it is unknown?

What was reported back to participants was the decision of the local NHS teams – Genomics England ran an automated pipeline and then expert clinical scientists in the NHS reviewed the results and decided whether there was anything new or important to each family’s healthcare. If a variant had already been found before, that might not have been included in the result. It could also be that the evidence supporting the variant has changed in the time between the initial test was performed and the analysis in the Project.

1. Can you please explain why a research student was able to discover a variation in a child’s genome but this was not found through the 100,000 Genomes Project? Would this still be looked at as part of the ongoing project?

Some types of variation in the genome are relatively straightforward to identify from a technical perspective. Others are really complex and hard to find. Sometimes a researcher can spend time focusing on a specific type of variant, or a specific region of the genome, which means they are able to make very helpful individualised insights. We are trying to find as many additional diagnoses as possible, and adapting our methods to try to identify the variants that are more difficult to identify. In other scenarios, it could also be that a variant was found in the 100,000 Genomes Project, but there was not enough evidence available to understand what the impact of the variant could be and the relevance to the clinical presentation in the family. A researcher may now have done additional experiments to investigate the functional consequences of a specific genetic variant so that the variant can be linked to the family’s health condition.

1. How will whole genome sequencing affect future diagnostic work (e.g. in leukaemia)?

Some medical conditions can now be investigated using whole genome sequencing in the current NHS Genomic Medicine Service. Others are better served by different technologies. The NHS continues to review the insights from new research from the Project and other sources, to make decisions about future developments in diagnostic testing, both for which genes should be looked at and the best technologies to use.

1. Is there an update on additional findings?

The final additional findings analysis results have just been returned to NHS centres. Our NHS colleagues are processing these results and sending letters to participants. Most people will receive a letter saying that nothing was found in the analysis that was performed. Only a small number of participants will have a genetic variant identified and will be offered an appointment with the appropriate NHS specialist to provide further advice. If you are expecting to receive an additional findings result, and you have not heard by by January 2023, the fastest way to get in touch is to raise a ticket with the [Genomics England Service Desk](https://jiraservicedesk.extge.co.uk/plugins/servlet/desk). If you cannot access the portal, you can email [ge-servicedesk@genomicsengland.co.uk](mailto:ge-servicedesk@genomicsengland.co.uk) or call 0808 281 9535.

1. If you found something unrelated to a participant’s suspected condition, would the family be told?

The 100,000 Genomes Project is a research project, and the ‘rules’ about how a research project works are laid down in the research protocol. For the NGRL, the protocol says that the Project will focus on trying to understand the condition which led to participants joining in the first place. There is also scope for us to return results outside that in ‘exceptional circumstances’. We at Genomics England are still working through how we better define those exceptional circumstances, working with our Participant Panel and Ethics Advisory Committee, as well as colleagues within the NHS. The results we have returned to the NHS so far have been those which are related to the participant’s suspected condition.

1. Is it worth joining the Our Future Health genomics study as a parent of a child participant in the 100,000 Genomes Project or would this be duplicating my data in the system?

The Our Future Health project is looking at ways in which genomic data can be used to help organise population-level healthcare, particularly related to common conditions such as type 2 diabetes and blood pressure. This doesn’t really overlap with the current priorities for Genomics England and the work being carried out using the data in the NGRL, which are focused on rare diseases and cancer. Genomics England and Our Future Health share the goal of using genomics to support better healthcare, and the teams talk to each other regularly to share experience, support and learning. If you are interested in signing up to take part in Our Future Health, that shouldn’t cause any problems with overlaps in the datasets – you can find more information on [their website](https://ourfuturehealth.org.uk/).