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Letter from Professor Mark Caulfield – this is not your result

Dear [Participant],

Re: The 100,000 Genomes Project results and you
I am writing to you as the interim Chief Executive of Genomics England and Chief Scientist of the 100,000 Genomes Project. I wanted to let you know personally how we are analysing the genomes from the project.

Thank you for taking part in the 100,000 Genomes Project
Firstly, I really wanted to thank you for joining this ground-breaking programme, which will not only bring new insights to rare disease and cancer, but has also enabled the formation of the new Genomic Medicine Service. Although we may have sequenced the 100,000th genome, this does not mean the project is complete. In fact, it may just be the beginning of our search for answers for you. If you have had, or receive results that are negative, I want you to know that my team and I do not see this as the end of your story.

The analyses we have already returned to the NHS
To date, we have returned 62,000 genomic analyses to the NHS. In rare disease, 1 in 5 of the reports contains a potential diagnosis; and in cancer, about half contain a potential trial opportunity for the participant or the opportunity to receive a medicine in the NHS. Your NHS team then check those results and feed back to you. This may take a while.

We will revisit all participants without a finding
We aim to have returned *initial* analysis to the NHS for almost everyone by the end of July 2019. By listening to our participants I have understood how much a diagnostic

answer means for you and the stress caused by the very long time some of you have been trying to get an answer. We have also heard about the impact of a negative result and the disappointment when nothing is identified for you and your family. At the outset of the 100,000 Genomes Project, I built in a commitment to reanalyse our participants' genomes focused on those who have not got an answer yet. In the middle of 2019 we will improve further our ability to read your genome. This is important because our research shows that this will enhance the prospects of finding an answer for you. Once we have improved our ability to read through your genome, in the second half of 2019 we will revisit everyone who is yet to receive a result. I will write with updates on our progress.

Our approach to analysing your genome

You are part of a cutting-edge science project and much of the genome is still a mystery. One of our first tasks was to build ways of automatically sequencing and analysing the genome. When you are looking for a needle in a haystack, having a good place to start is vital.

Where we started the search for your diagnosis

We had to start by using the best scientific knowledge from more than 500 specialists across the entire world. This enabled us to "crowdsource" expertise and knowledge that was both public and held in hospitals, enabling us to build the most advanced gene panels. These use the information provided by your healthcare teams, which helps us to know where to start the analysis. These gene panels are more extensive than those you may have already had in the NHS and we are constantly updating these with new findings by our PanelApp team.

We look first for all those gene changes that are known to be a possible cause of your main condition, and then we move on to look at other parts of your genome. For some conditions, such as intellectual disability, we have been able to find results for 40% of affected participants by using our gene panels. For other problems this approach has not yet provided answers. This tells us that much more research is needed and we are doing this now.

Extending analysis across the entire genome

Since the start of the project, we have been testing ways of analysing the wider genome and have been using approaches that analyse repetitive regions of the genome that were previously considered to be unreadable with this technology. We are now reporting several of these new features to the NHS and are continually investigating new approaches to analyse your genome. These approaches are often

entirely new and first we have to assess the reliability of these techniques. As soon as we have confidence these approaches work, we will add new insights and findings into the reports that go back to the NHS.

Our aim to maximise the opportunities to get you a result

This is long, careful work. We have about 3,000 researchers from 24 countries who have volunteered to look at your data with the aim of driving up the value for healthcare. Today several hundred are already working on the data alongside in some cases our commercial partners' research teams. Already, more than 60 participants will receive an answer because of the work these researchers and industry have done together. The virtuous circle where researchers work closely with the NHS and industry to accelerate the production of new answers from data where your direct identity has been removed is now beginning to work well. Although I cannot promise quick answers, or even give you a specific timeframe, I can tell you that we will keep on looking.

By placing your data alongside others in the programme, this is really beginning to help us get even more answers for participants. We have several examples of where information from a family has helped us to see patterns in the genomes of other participants, giving new insights and diagnoses.

I give you my absolute commitment that my team's highest priority is to try to get valuable findings for all the participants we can. Alongside this, we will bring live the new Genomic Medicine Service for the NHS, which you helped to create and are very much a part of. In this respect, you are the pioneers who have helped us achieve this, and as such you have witnessed the journey (in many cases slower than we would like) that we have taken to build the most advanced genomic healthcare we can for our nation. Without you and your family, we would not have achieved this in the NHS and in some cases your generosity has helped others to get an answer. You are the founders of this new NHS service and have my guarantee that we will keep working as hard and as fast as we can, to achieve answers for as many of you as possible, using the latest reliable approaches.

I was recently interviewed by our Participant Panel Chair Jillian Hastings Ward on this subject, you can find that interview through our website (www.genomicsengland.co.uk), and on YouTube and Facebook.

If you wish to send in questions you can contact us through the website: www.genomicsengland.co.uk/contact-us

We can also reply on Twitter @GenomicsEngland or Facebook.

If you wish to check where you are in the programme, please complete the form on our website: www.genomicsengland.co.uk/trackmysample

With my best wishes,

Professor Mark Caulfield MD FRCP FESC FBHS FMedSci
Chief Executive and Chief Scientist Genomics England