Newborn Genomes Programme – Generation Study

Frequently-asked questions for healthcare professionals

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Context

The Newborn Genomes Programme's team has met with a wide range of healthcare professionals. The role of these individuals is integral to the delivery of the Programme's Generation Study.

This document aims to address questions that have emerged from healthcare professionals about the design and operation of the Generation Study. We anticipate further questions will arise as the Study develops; this is therefore a 'living document' which will be updated every two months so that further responses can be included.

This document is aimed at healthcare professionals who work in NHS settings, including:

- Clinical scientists and technologists working for one of the seven NHS Genomic Laboratory Hubs (GLHs)
- Staff in NHS clinical laboratories (e.g. screening or biochemical laboratories)
- Geneticists, genetic counsellors and genomic practitioners working in regional Clinical Genomic services or other mainstream services.
- Clinicians who agree to call families to communicate a 'condition suspected' result, including consultant paediatric specialists or clinical nurse specialists.

The Generation Study protocol is available via the Genomics England website.

Questions are divided into several categories:

1. Questions on the conditions being screened for

1.1 How have the conditions that you will screen for been selected?

We are committed to making this decision in a robust, transparent, and fair way. The Generation Study will only screen for a specific set of conditions, genes, and variants, according to four principles which were developed specifically for the study, to focus on serious conditions that have an intervention available in early childhood in the NHS.

Over the past several months, we have been engaging with a range of NHS specialists, commissioners and members of the rare conditions community to progress this work. Clinicians in our team have applied the four principles to approximately 900 genes and associated conditions.

Working with the NHS England Genomics Unit, we have established a Clinical Assurance Group which includes representation from organisations including NHS England, Clinical Reference Groups, NHS Genomic services, the UK National Screening Committee, NICE, Royal Colleges and other professional bodies. The aim of this group is to provide assurance to the Programme and the NHS on the availability and capacity of the downstream clinical pathways for each condition. To provide this assurance, we have been working with the national specialty advisors, clinical leads and commissioning leads from Clinical Reference Groups across paediatric specialist areas.

This process has led to an initial list which includes **223 conditions caused by genetic changes in over 500 different genes.** You can read more about this process on our website.

1.2. Will the list of conditions change, and if so how/when?

It is likely that conditions will be added or removed, in response to emerging research. Where new research is published, we will re-examine conditions against the principles described above.

We won't go back to analyse samples retrospectively, so if we add any new conditions these will only be screened for prospectively for incoming participants. Babies will only be screened for the conditions included in our list (and detailed on our website) at the time of consent.

There will be a process by which any specialist can nominate new conditions for inclusion in the list, or submit concerns about the choice of a particular condition. Any such changes would be determined via the NHS Clinical Reference Groups and the NHS Clinical Assurance Group.

2. Questions on feeding back results

2.1. Will consent to join the study be required from both biological parents or just one? What if there is discrepancy in parental views?

Only the mother / birthing parent would be required to consent, as they would be agreeing to their de-identified antenatal data being included as well. Our REC-approved protocol, participant materials and study teams will highlight the importance of discussing participation with others with parental responsibility (where available), as well as family members or other individuals helping to make decisions about their baby. Although only one person with legal parental responsibility would consent to their baby taking part in the study, where parents have different opinions about agreeing to take part, it will be recommended that they do not participate. This is to emphasise the importance that both parents have a say in the interests of familial decision-making and in the context of genomics.

2.2 How will the communication of results of the newborn screening back to parents be handled?

Where genome sequencing indicates that a baby is suspected to have one of the conditions screened for, families will be called by a clinician who has knowledge of the study, and of the suspected condition. Our team is working with clinicians and NHS Genomic Medicine Service Alliances (GMSAs) to establish a network of paediatric clinical teams who will take on this role. We will also provide funding for roles to support coordination of returning results.

2.3. How long will it take for results to be fed back to families?

Our aim is for results to be returned within two weeks. It might be the case that this takes a little longer at the start of the study, which is why we're starting conservatively through working with only a small number of Trusts when we begin our study.

2.4. Who is responsible for feeding back 'no condition suspected' results?

Genomics England will inform parents by email or letter when no conditions are suspected from the study. A similar letter will also be sent to each participants' GP so they are aware of this result and baby's involvement in the study. This is expected to be sent within the first few months after birth. The content of the letter will be standardised and will include a clear statement on the possibility of 'false negative' results, and the need to follow up with any concerns about medical or family history as per standard clinical practice. It has been co-designed with parents and GPs, and we are working to address accessibility needs (such as translations into the predominant languages spoken across study sites).

2.5. Will the study tell newborns' families if they are a carrier of a particular condition – i.e. to inform reproductive choices?

Carrier status will not be directly sought when the genome sequence is initially analysed. It is possible that carrier status is identified incidentally (for example if two variants are identified and end up being on the same allele), but we expect this situation to be very rare.

Although there are some good arguments to suggest that identifying carriers means that we could go back to the newborns' parents and arrange cascade testing, there are also concerns about this interfering with the child's autonomy and generating a much higher volume of results than the current health system may be able to manage.

However, one aspect of the programme is to explore the broader implications of storing an individual's genome over a longer term. Analysis for carrier status is one potential area which could be explored in the future. Whether this is something that the Programme should explore will need to be considered carefully, e.g. by working with participants, members of the public, and our Ethics Working Group.

2.6. Will all babies who have a 'condition suspected' result is returned be referred to Clinical Genomic Services?

Where a 'condition suspected' result is returned, families will be called by a clinician who is expert in the rare condition that the result is linked to. Whether and when babies have onward referrals to Clinical Genomic services will depend on the judgement of that expert clinician and multidisciplinary team. Factors that might be key to those decisions include whether further family testing is appropriate for the condition; to discuss reproductive options; or to provide psychosocial support in adapting to the result. Genetic counselling support will be integral to any decision and ongoing care, and we recognize that some genetic counsellors are embedded within or linked to mainstream specialist services.

3. Questions on processes

3.1. What sample(s) will you collect from the baby and how was this decided?

One sample of cord blood will be collected from each baby. In the case of home births, or where obtaining cord blood has been impossible, a heel prick into an EDTA tube may be taken. The Generation Study sampling strategy is based on the results of our feasibility study.

As whole genome sequencing (WGS) is not widely used in newborn babies for screening purposes, Genomics England undertook a REC approved feasibility study (the Baby and Mum Sample Study, IRAS project ID: 318588, REC reference: 22/EE/0203) to determine which of a variety of methods produced the most feasible and reliable biomaterial sample for WGS in newborn babies. Feasibility and reliability considered not only an assessment of DNA yield and contaminant levels for sequencing purposes, but also the ease of sample collection within the NHS maternity services, the barriers to and facilitators of collecting different samples types and the relative human resource requirement for each sample type. The study involved assessing three types of samples: cord blood, heel prick collected to dried blood spot card or EDTA tube, and buccal swab.

Detailed results can be found in the Generation Study protocol. To summarise, of the two non-invasive sample types – cord blood and buccal swab – cord blood performed considerably better where the sample was taken. The cross-contamination of DNA, coupled with the sequencing failure rates seen with buccal samples mean that we could not support its use in the Generation Study. Heel prick data indicate that it would be a good back up sample type in cases where cord sampling is not possible, and for home births.

Based on these results, and in the interests of minimising invasive sampling and minimising the possibility of confusion where a heel prick in the Generation Study may be perceived as also taking part in the routine Newborns Blood Spot screen, cord blood was selected as the primary sample type.

3.2. Why are you not sequencing the parents?

We know that sequencing parents could help with interpretation of any results. However, this would require collecting up to 3 times more samples which involves significant complexity including operational requirements to take and store these samples – and we expect only ~1% of babies to have a suspected condition. We have therefore made the decision to not obtain samples from parents up-front during the Study. We would typically suggest that parents are tested for the variants identified after a baby is found to have a condition-suspected result.

3.3. Will the study include multiple sequencing methods allowing rapid data generation for emergency cases, or will all the sequencing be done in the same way?

Our study will focus on newborns who aren't preselected because they have a medical or family history of a condition. Only one method of sequencing (short-read sequencing) and reporting will be used. If the babies who take part in our study develop a phenotype, we would expect that clinicians will use accepted practice to diagnose and treat them.
Rapid genome sequencing for acutely unwell babies with a likely monogenic disease is a separate pathway that is run by Exeter Clinical Laboratory. There will be no immediate overlap with our study.

3.4. Will testing be via the Genomics Laboratory Hubs (GLHs)?

Throughout the development of our study, we have been cognisant of the need to avoid delays to routine WGS analysis.

Study samples will not be processed by the GLHs. In order to minimise detrimental effects on standard clinical services, Genomics England will pay external providers to transport samples, prepare samples, extract DNA, and sequence DNA.

3.5. Will the process of analysis and interpretation be mostly automatic, with minimal input from scientists?

Yes, we are working towards a process that would minimise clinical scientist input as much as possible, because of the type of analysis we would be doing, and given resource constraints in the scientist workforce. This means it won't be the same situation as currently exists in the NHS Genomic Medicine Service, where GLHs review a prioritised list of variants and issue a report to the referring clinician.

We are working with NHS England and representatives from the NHS Genomic Laboratory Hubs (GLHs) to agree a model for interpretation and reporting that does not impact routine clinical care. This includes an Interpretation and Reporting Working Group to advise on processes, and a central team that would be involved in reviewing variants before reporting.

3.6. Will you be reporting on variants of uncertain significance (VUSs)?

No, we are not returning VUSs (variants of uncertain significance). We will only be reporting variants that are pathogenic or likely pathogenic. This is expected to reduce the number of false positives.

4. Questions on the expected volume of screen positive results

4.1. How many babies with a 'condition suspected' result should each Genomic Medicine Service Alliance (GMSA) expect to encounter each year?

The total number of 'condition suspected' babies in the lifetime of the research study is expected to be 500-1,000 over the course of the study. This figure includes false positives.

The NHS Trusts recruiting to the study will be distributed throughout England, with approximately 2-4 Trusts recruiting in each of the seven GMSAs.

On average, we expect that each GMSA region could encounter 24-48 'condition suspected' results per year that require a confirmatory test, spread across all the NHS Trusts in its region. In reality, NHS Trusts will start recruiting at different times, so the number of results will be a little higher for GMSAs with large, city-based Trusts opening in wave one, compared to GMSAs with fewer or smaller NHS Trusts opening a little later.

Once false positives have been excluded, there will be around 10-20 babies per GMSA each year presenting for care or surveillance earlier than they would otherwise have done. Again, these cases would be distributed across several services at different NHS Trusts, and linked to the Clinical Genomic Services in that region.

Before we go live in a region we will have identified all the specialists who will be potentially receiving referrals from each of the sites, and we are not expecting that any one specialist will receive more than a few confirmed cases referred to them because of this study. In most cases, these cases would still have presented to those specialists at a later date, had they not taken part in the study.

Each Regional Clinical Genomics Service will have between zero and two recruiting Trusts in its area by the time all sites are recruiting.

Whilst the number of cases that the study will identify is small in comparison to the large screening size, it is expected that earlier intervention in these babies and children may have a transformational improvement in their outcomes.

4.2. How many 'false positive' results are you expecting?

The true positive to false positive ratio is estimated to be around 1:2.6 (in other words, that 28% of 'condition suspected' screening results will be true positives). We will further refine this calculation when the gene list is finalised.

By only choosing variants that are pathogenic or likely pathogenic we will reduce the number of false positive results. We are also focusing our 'known variant list' on variants that result in onset of the condition in childhood. Additionally, variants will be manually reviewed before results are returned with a view to minimising false positives.

When we find two pathogenic or likely pathogenic variants for a recessive disorder in a newborn this raises the question of whether the variants are in cis (on a chromosome together) or in trans (on different chromosomes). Finding two variants in cis means the child is an unaffected carrier. This would be a false positive. We have examined the question of recessive conditions and phase resolution. Genomics England has 35,000 genomes from adults without known rare genetic conditions. These came from a large COVID study, cancer patients and unaffected parents of children with rare diseases. 481 recessive disorders were sought in these cases. In 14 samples two pathogenic or likely pathogenic variants were found. In 7 of these samples the DNA sequence data showed that the two variants were in cis. In 7 samples we could not tell whether they were in cis or trans. Therefore, in the worst-case scenario 14 of 35,000 genomes have two variants in cis. This suggests that it is unlikely we will find a newborn with two pathogenic variants where they are in cis. It is much more likely the two variants are in trans and the child is suspected to have that condition.

5. Questions on resources

5.1. Given the amount of pressure that NHS is currently under, including Clinical Genomic services, will this study affect the waiting times for other NHS patients who are already waiting for genetic testing results?

Where this study indicates that a participating baby has a condition, it is likely that they will present with that condition at a later date (i.e. if they were not participating in our study, the condition would still present in early childhood). If babies with a potential genetic condition are found earlier, our study could mean that the burden of diagnostic odysseys will be mitigated through identifying babies with pathogenic variants in the gene that cause the condition sooner, before phenotypic expression occurs. This will be one of the key things that is assessed when the study is evaluated.

It is important to note that the question of turnaround times for diagnostic analysis is separate. Our study will include a defined list of genes and variants that newborns will be tested for. This is a different process to the current diagnostic approach, which looks for any variants that might be connected to the child's phenotype, and requires further review by clinicians and clinical scientists in NHS Genomic Laboratory Hubs.

Our analysis of babies' genomes will therefore be able to be streamlined to focus on those genes and variants only, which means that a shorter turnaround time for results can be realised. The target 'sample to answer' turnaround time for condition suspected results for the bulk of the study is 14 days or less, i.e. the time from taking the sample on Day 0 to the time that parents are contacted about the result. We aim to achieve this within first 9 months of the study starting. The target sample to answer turnaround time at the start of the programme will be 28 days.

5.2. Why are we focusing on testing newborns when children with a phenotype with a potential diagnosis are waiting over 12 months (or sometimes much longer) for diagnostic whole genome sequencing?

It is our aim that our study will contribute to understanding the optimal approach to diagnosing and treating rare genetic conditions in babies and young children. Depending on our findings, our study might mean that, in the future, diagnostic WGS may face less of a burden – i.e. by identifying babies with a gene or variant sooner, before they develop a phenotype.

5.3. Will there be additional funding for midwives' time in guiding families through the consent process?

Yes, research funding will be available at site and NHS GMSA levels to support roles that are integral to the delivery of our study. Those roles will be informed through us working closely with the NHS Trusts that we will partner with to run the study.

5.4. Will there be additional funding or support provided to the specialists receiving these referrals?

We are providing funding to each regional NHS GMSA, to enable them to appoint additional staff to support the study and facilitate the onward referral of families with a 'condition suspected' finding to the relevant NHS care pathway.

The total number of babies with a suspected condition in the lifetime of the research study is expected to be relatively small (500 to 1,000 across the country, including false positives.) Based on the limited number of results spread across different specialist groups around the country, we expect there would only be a small number of cases that any one specialist paediatric team would be providing care for. For the true positive cases, most of these would have presented to those specialists at a later date, had they not taken part in the study.

We will only include conditions for which there is a system in place in the NHS to provide all of the ongoing care and support that the child and family will need. We know that creating an equitable and fair system for everybody is a key condition for public support for the Newborn Genomes Programme. This means working with groups including representatives with expertise in the specific conditions and from relevant clinical, commissioning, and other bodies, to ensure that children and their families will not be left to deal with the consequences of a rare disease diagnosis on their own.

Using whole genome sequencing as a newborn screening tool could allow for significantly earlier diagnosis and treatment for children with rare genetic diseases, shortening what can otherwise be a lengthy 'diagnostic odyssey'.

Earlier treatment can lead to more favourable outcomes, leading to a reduction in healthcare usage over a patient's lifetime. As well as a reduction in costs to the NHS, diagnosing severe treatable conditions at birth also generates benefits for patients and their families, such as an improvement in quality of life through a complete or partial reduction in symptoms. Therefore, when weighing up the costs of genomic newborn screening against the long-term savings to the NHS and benefits generated for patients and their families may be a cost-effective intervention.

5.5. Are clinical genomic services prepared for the additional workload? For example, particularly where conditions are included for which ongoing monitoring is required.

We have had a number of discussions with the British Society for Genetic Medicine and its associated member bodies, as well as the Genomic Clinical Reference Group, to explain the scope and aims of our study. We are anticipating that should a condition-suspected result be found, parents will be contacted and managed by specialist paediatric teams. Further support or cascade testing may involve input from Clinical Genomic services and genetic counsellors in mainstream services. We will continue to engage with these services and professional bodies to understand what the impact might be and how this can be best addressed and monitored. This is also something that the NHS Clinical Assurance Group will be considering, understanding the capacity and capability of the NHS to support condition suspected results.

The funding that we are providing to each regional GMSA can be used to increase dedicated genetic counselling capacity. This can enable access to genetic counselling in relation to the research result in a more responsive manner, before the families enter Clinical Genomic services as part of routine care.

5.6. What happens if a baby is diagnosed in Exeter, but the nearest specialist is in Newcastle?

This is clearly an important issue, and one that we are currently discussing with our partners in the NHS and the GMSAs, as well as through the NHS Newborn Clinical Assurance Group. We recognise that the questions about logistics, access to care and the practicalities of delivering it are just as important as the scientific and clinical challenges. We want to make sure this is all addressed before we begin study, and so, for example, we have already spoken to over 150 specialist clinicians throughout the UK to establish what current systems are in place, and what would need to be done in future to treat or support a baby with a particular condition and their family. It's worth noting that this is an issue already when babies are diagnosed with these conditions now – and ensuring comprehensive provision is at the heart of one of the four principles which underpin our 'choosing conditions' work: i.e., that the Newborn Genomes Programme will only screen for conditions for which "interventions are equitably accessible for all as standard of care within the NHS."

We also hope that, through the study, we can gain a better understanding of the impact on treatment pathways (and the pathways' associated logistics). In the case of screen positive results, Genomics England will offer parents reimbursement of costs incurred in the initial visit for confirmatory testing.

6. Questions on data for future research

6.1. How will access to data for future research purposes by managed?

Parents who consent to the Generation Study on behalf of their child would agree to participation in the screening and evaluation aspects of the study (the Generation Study protocol), and to participation in the National Genomic

Research Library (the NGRL protocol). Genomics England has generic Research Tissue Bank Approval (20/EE/0035) for the use of data and tissue in future research projects. Further information is available on the Genomics England website.

6.2. Babies' data will be added to the National Genomic Research Library. But who will be responsible for asking contacting those individuals as they grow up, to seek their consent for their data to remain in the library?

On reaching the age of 16, all existing participants will be asked to give their own consent to remain in the programme (unless it is deemed by their medical team that they do not have the capacity to do so at that time). If it is not possible to reach the young person at that time, their data and samples would be removed in line with Genomics England's process for Full Withdrawal.

Information will be made available on an age-appropriate basis for children and young people. We will continue to engage with participants and young people about the most appropriate ways to support this process, and how this can be facilitated centrally via Genomics England.

7. Other questions / future considerations

7.1. What education and training will be offered to support this study?

Genomics England has established an Education and Training Working Group as part of our programme governance and partnership with the NHS. The Working Group is chaired by the Director of the NHS National Genomics Education team. Through this group, and broader work, Genomics England is working with HEE and other stakeholders with experience in education involving genomics, screening and research.

This Working Group's objectives are aligned to the Clinical Pathway Initiative, which is a standard approach to identifying workforce development and education needs aligned to patient pathways across the NHS Genomic Medicine Service. This aims to promote consistency and participant safety, as well as support flexibility in delivery models across sites. Supporting resources and training are being co-developed with individuals representing healthcare professional groups that will be involved across the study, as well as parents and families living with rare conditions. A 'train-the-trainer' approach will also be employed to expand training capacity, as well as support site and regional accountability and sustainability. We have been discussing workforce and training requirements through our ongoing stakeholder engagement and as part of our dialogue with NHS Trusts.

7.2. Have there been any discussions on how the whole genome sequencing of newborn babies could operate alongside the current blood spot test, or would whole genome sequencing ultimately replace the need for the heel prick test, which currently only screens for nine conditions?

This won't replace standard of care. Babies who are enrolled in the Generation Study will continue to be offered the current NHS standard of care heel prick test. We are working very closely with the UK National Screening Committee who are providing expertise and advice to the programme.

The research will sit alongside the NHS Newborn Screening Programme (heel prick test) to explore its potential additional benefits in screening. It is anticipated that should the evidence demonstrate sufficient value of whole genome sequencing to be recommended to ministers and policymakers for full implementation, it would be adopted alongside rather than instead of the current newborn screening test.

7.3. If this is implemented nationwide in the future, does that mean that SCID screening will phase out or do you think they will go hand in hand?

The Newborn Genomes Programme's study will run alongside established screening programmes and other research or pilot programmes. The study will not replace those programmes. The evidence generated by the study will be used by the National Screening Committee to inform their future policies with respect to newborn screening.

7.4. What are the insurance implications?

In October 2018, the Government and the Association of British Insurers (ABI) published the Code on Genetic Testing and Insurance; this is a shared agreement between the two parties on the use of genetic testing in underwriting insurance policies. Both the government and the ABI recognise that genetic testing is a valuable tool in informing the diagnosis, prevention and treatment of ill health and people should not be discouraged from accessing its benefits because of concerns this might compromise their ability to access insurance cover.

The code commits insurance companies to not require or pressure any applicant to undertake a predictive or diagnostic genetic test to obtain insurance. Insurers will not treat any applicant differently if they have had a predictive genetic test, except for conditions relevant under the code for polices above the financial limits set by the code. To date, only the result of a predictive genetic test for Huntington's disease (which will not be looked for in the Study) when buying life insurance above the financial limit of £500,000 needs to be disclosed. Additionally, any results of genetic testing carried out for the purposes of research, including for Huntington's, do not have to be declared to insurance companies.

The code will be reviewed every three years to ensure it aligns with the latest legislation and guidelines. Our public dialogue participants also told us that one of their concerns about using whole genome sequencing in newborn screening was that it might increase discrimination in several ways. Genomics England will ensure strong governance systems and safeguards are in place to protect participants' privacy and avoid discrimination.