The Generation Study Protocol

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Note for recruiting sites

The best place to access quick-reference, up to date methodological information is 'Study Guide for Recruiting Sites' and 'Sampling Guide for Recruiting Sites' in the ISF

Contents

Authors & Study Staff:

Alice Tuff-Lacey, Harriet Etheredge, Amanda Pichini, David Bick, Dasha Deen, Sally Donovan, Kate Harvey, Dalia Kasperaviciute, Mathilde Leblond, Geraldine Nash, Will Navaie, Aditi Satija, Sally Shillaker, Afshan Siddiq, Katrina Stone, Chantal Wood, Joanna Ziff, Richard H Scott

Chief investigator: Ellen Thomas

Mobilisation Lead: Liz Gardner, liz.gardner@genomicsengland.co.uk

Sponsors: Genomics England, One Canada Square, Canary Wharf, London, E14 5AA

1. Version Control Table

Version	Author/approved by	Date	Summary
V0.1	Chantal Wood	31 January 2023	First Draft
V0.2	Chantal Wood	12 February 2023	Second Draft
V0.3	Chantal Wood	20 February 2023	Third Draft
V0.4	Chantal Wood	23 February 2023	Fourth Draft
V0.5	Richard Scott	02 March 2023	Fifth Draft for Peer Review
V0.6	Richard Scott	26 March 2023	Sixth Draft responding to Peer Review
V1.0	Richard Scott	29 March 2023	Submitted for REC meeting to be held on 14 April 2023
V2.0	Richard Scott	18 May 2023	Submitted to REC 18 May 2023 following feedback
V2.1	Harriet Etheredge, Dasha Deen	4 July 2023 and 25 July 2023	Study Amendment - Removal of Buccal Swab as a sample - Revision of inclusion / exclusion criteria - Correction of minor typographical errors
V3.0	Richard Scott	28 July 2023	Submitted to REC 28 July under GSAM001
V3.1	Harriet Etheredge, Richard Scott, Ellen Thomas, Alice Tuff-Lacey	28 October 2023	Study amendment - Updated sampling strategy - Removal of baby exclusion if born < 36 weeks gestation (facilitating inclusion of babies born prematurely) - Death of birthing parent pathway updated based on external legal advice - Updated for publication of conditions list - Updated to reflect our approach to unanticipated events - Updated modelling
V4.0	Richard Scott and Ellen Thomas	1 November 2023	Submitted to REC 3 November under GSAM002

V5.0	Ellen Thomas, Harriet Etheredge, Amanda Pichini	3 October 2023	Submitted to REC under GSAM006
V6.0	Harriet Etheredge	17 December 2024	Submitted to REC GSAM008
V7.0	Harriet Etheredge	21 March 2025	Submitted to REC GSAM009
V8.0	Nicola Turner	02 December 2025	- Addition of PBMC sample processing - Clarification around a baby being born at a different hospital than planned - Updated temperature range for sample processing at site - Correction of typos

2. Protocol Synopsis

Background

Genomics in healthcare

Genomics is playing an increasing role in healthcare, with the UK at the forefront of its implementation, building on historical excellence together with recent progress such as the 100,000 Genomes Project and the creation of the NHS Genomic Medicine Service and the National Genomic Research Library. The role of genomics is currently most prominent in diagnostics where it is now part of routine care for rare conditions and cancer. Its role is growing in preventative and predictive care, most notably through pharmacogenomics. Translational research is exploring potential roles in other areas such as polygenic risk scores.

The advent of next generation sequencing, and with it a new era of gene discovery and the routine use of whole genome sequencing in diagnostics, has had enormous impact for individuals with rare conditions. However, rare conditions remain a major cause of mortality and disability in high income countries.

Only ~10% of rare conditions have a treatment. However, there is real promise that, with the right research investment, infrastructure and regulatory frameworks, new precision treatments will change this.

In recent years there has been great interest in the possibility of routine newborn sequencing – particularly whole genome sequencing – to support screening, research and to be stored for future healthcare use. The potential value in these areas has been highlighted as well as the risks and complexities.

Newborn screening

Newborn screening is one of the success stories of modern healthcare, identifying rare conditions that are treatable early in childhood. However, generating the evidence to inform decisions on expansion of newborn screening is hard due to the rarity of the conditions. In the UK, nine conditions are currently screened for, predominantly using biochemical testing. Genomics plays only a small role, as a second tier test. The use of genomics presents the opportunity to look for a broader range (potentially hundreds) of rare conditions that are treatable early in childhood. We refer to this in this protocol as 'genomic newborn screening'.

A number of studies of genomic newborn screening are preparing to launch internationally, but there have been only three relatively small prospective studies that returned findings to participants. While these previous studies have given early insights, there remain many questions to explore in this complex area, from the right analytical approaches and test performance, methods of implementation, impact on outcomes (positive and negative) and workforce, as well as psychosocial implications, public attitudes and ethical questions.

Supporting research

Discovery research, such as is now supported as part of routine genomic care in the NHS through the National Genomic Research Library, has had incredible impact in recent years, particularly on clinical diagnostics. However, there remain many urgent healthcare questions to address. Large scale research in 'unselected' cohorts of newborn babies has the potential to have real impact here, for example to better understand allele frequencies in children born today to improve diagnostics and screening, tracking the natural history of rare conditions or to identify those eligible for novel treatments early in the course of their condition. It also presents the opportunity for research on other analytical techniques for screening (e.g., tandem mass spectrometry and proteomics) and research across broader health questions (e.g., on common childhood disease).

Longer term storage of genomic data for reuse for healthcare

With the advent of next generation sequencing - and of whole genome sequencing in particular - the idea of generating genomic data once and reusing it to support a person's healthcare is increasingly discussed. It is possible to imagine that whole genome data generated at birth initially for newborn screening might be reused later for diagnostic testing, for example in a child who falls critically ill with features suggestive of a rare condition. As well as research to understand the potential costs and impacts of this approach, there are important questions to explore in terms of public attitudes, risks and broader implications of storing an individual's genome over their lifetime.

Development, vision and objectives

Responding to these opportunities and questions, Genomics England was funded by the Department of Health and Social Care to co-design and run a research study on the potential value and costs, risks and benefits of offering whole genome sequencing to all newborn babies.

The Newborn Genomes Programme will be delivered by Genomics England in partnership with the NHS, underpinned by joint governance. The vision of the programme, developed with the Programme's NHS Steering Group is:

1. To evaluate the clinical utility, operational feasibility, acceptability and positive and negative impacts of screening for a larger number of childhood-onset rare genetic conditions in

newborn babies using whole genome sequencing, and providing ongoing patient support and diagnostic and care pathways, through the Generation Study.
2. To support healthcare research and understand how, with consent, genomic and health data could be used for research in the newborn setting to enable new diagnostic discoveries and treatments to be developed
3. To explore the potential risks, benefits, and broader implications of storing an individual's genome over their lifetime (e.g., potential for preventative steps, personalised risk-based screening in later life etc.)

These will aims will be delivered through this protocol and the National Genomics Research Library Protocol. In joining the Generation Study, parents will be consenting to their child joining the research under both protocols.

This protocol focuses on the development of evidence to allow policy makers to decide whether and how whole genome sequencing should be offered to all newborn babies. The National Genomic Research Library Protocol will support broader research across all three aims of the study and be particularly crucial in supporting aims 2 and 3 where the emphasis is more on discovery than evaluation.

While all three of the broader study aims may drive policy and will be the focus of research questions investigated through this protocol, the most immediate policy focus is on newborn screening.

The research questions explored by the study (described in more detail in Section 13 and Appendix A) cover the following broad areas:

1. **Feasibility, acceptability and uptake.** Is genomic newborn screening feasible and acceptable and would it be broadly taken up if offered as part of routine care?
2. **Test performance and clinical utility.** What is the clinical utility of genomic newborn screening as evidenced by the number of screen-identified diagnoses likely to benefit from intervention compared to standard of care alone?
3. **Cost effectiveness and positive and negative impacts.** What is the cost effectiveness of genomic newborn screening compared to standard of care alone?
4. **Experiences and attitudes.** What are families' and stakeholders' experiences and attitudes to genomic newborn screening?

While it is important to emphasise the breadth of research questions necessary to support policy decisions and therefore explored through the study, we have also identified the following primary and secondary outcomes (each linked to one of the areas above).

The primary outcome is:

- To determine the clinical utility of genomic newborn screening as evidenced by the number of screen-identified diagnoses likely to benefit from intervention compared to standard of care alone.

The secondary outcomes are:

- To determine the feasibility and acceptability of genomic newborn screening in the NHS utilising mixed-method approaches to assess study implementation.
- To determine the cost effectiveness of genomic newborn screening compared to standard of care alone, supported by a health economic model developed to support the programme.

- To determine whether families' and stakeholders' experiences and attitudes are supportive of the adoption of genomic newborn screening.
- To determine any differential areas of positive or negative impact of genomic newborn screening related to indices of diversity including ethnicity and socio-economic deprivation.

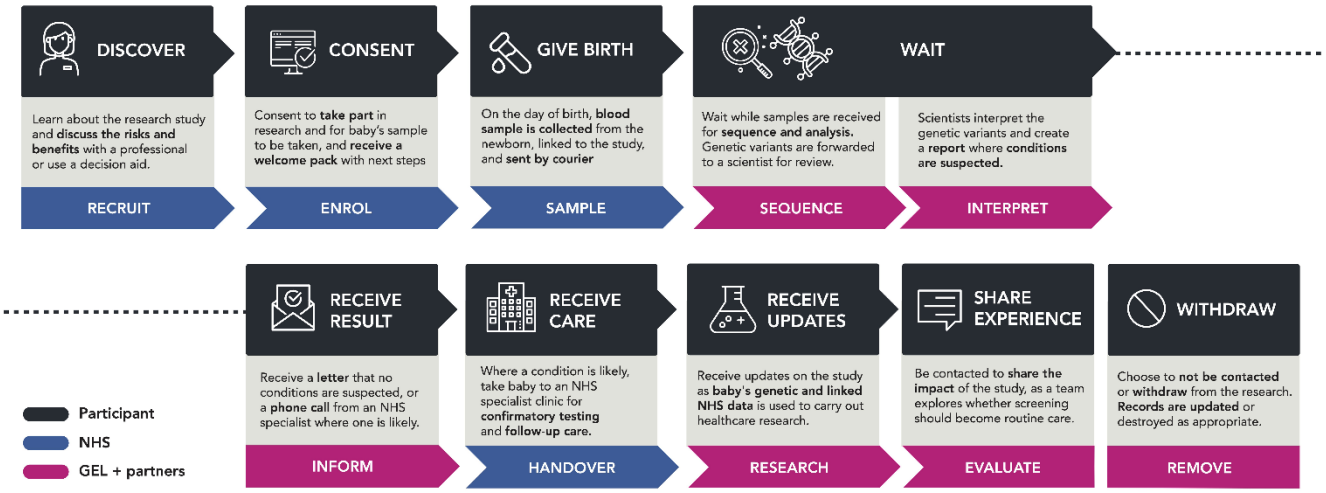
Methodology, delivery and sample size

Methodology and delivery

The Programme will be delivered in partnership with the NHS. The end-to-end patient journey is summarised in Figure 1 below.

Recruitment and sample collection will take place in NHS Trusts. All babies will undergo whole genome sequencing and receive results following analysis for a defined list of rare conditions that are treatable in childhood. Condition selection is governed by a set of agreed principles established by an expert Working Group following expert and public consultation, and under the oversight of an NHS Clinical Assurance Group that ensures relevant expert sign off of conditions, the availability of treatments and the capacity of clinical pathways. Modelling indicates that our approach will achieve a true positive to false positive ratio similar to existing newborn screening services.

Figure 1 - The participant experience



Comparator data will be drawn from age and gender matched children in two groups:

- a population comparator group of babies born at non-participating Trusts during the recruitment period of the study
- a rare conditions comparator group of children diagnosed with the study conditions nationally as identified through specialist clinical services and laboratories over a multi-year period with similar diagnostic genomic testing availability to the study period

Sample size

The sample size calculation based on current estimates of disease frequency and analytical parameters indicates a sample size of approximately 105,000 newborns to address the primary outcome of the study; details of the sample size calculations are provided in Section 6.

Evaluation

Programme evaluation aims to develop holistic evidence to drive future policy decisions. It will be carried out in four workstreams: a performance dashboard, an economic model, process evaluation and impact evaluation. Evaluation will be delivered by Genomics England in partnership with an Evaluation Partner and covered by an additional Evaluation Protocol.

Together, the economic modelling and process and impact evaluation will explore research questions in the four broad areas set out above, each with a primary question and multiple secondary questions exploring both positive and negative impacts. Rather than isolated workstreams, these will be interlinked.

Conclusion

The Generation Study builds on the strong track record that the UK has in genomics, and the recent investments by government, research funders and the NHS in genomic healthcare research and implementation. Delivered in partnership with the NHS, at scale across a national health system, the study is uniquely placed to deliver on its aims to develop evidence for policy makers on whether and how whole genome sequencing should be offered routinely to all newborns while also stimulating vital research and new discoveries.

3. Background

Genomics in healthcare

Genomics – the study of a person's DNA – is playing an increasing role in healthcare. This builds on many decades of foundational discoveries. From Mendel's insights into inheritance, to the elucidation of the structure of DNA by Franklin, Crick and Watson and the invention of the first methods to read the sequence of DNA by Sanger[1,2,3].

More recently, this has been followed by the invention of 'next generation' sequencing technologies that allow sequencing at greater scale and lower cost. This has brought a new era of scientific discovery across a range of health conditions. Paired with the development of supporting analytical and computing capabilities, knowledge bases and laboratory scientific interpretation standard operating procedures, this has widened the range of settings in which genomics is used in routine care[4,5].

With the advent of next generation sequencing, health systems now have a number of techniques at their disposal, with different tests used to address different clinical questions. These range from highly targeted tests, such as those that assay for one or a handful of specific genomic variants in one gene, to panel sequencing, typically looking at tens or hundreds of genes, and exome sequencing, which targets the 1-2% of the genome that codes for genes, to whole genome sequencing.

Analysis for next generation sequencing-based tests, and particularly whole exome sequencing (WES) and whole genome sequencing (WGS) means that there is a practical and conceptually useful separation into three different elements:

1. **The assay.** The generation of raw sequence data from a sample.
2. **The analysis.** The analysis of the data in a given clinical context, using complex analytical algorithms tailored to the clinical context. For example, looking for variation in carefully selected parts of the genome that might be relevant to the clinical context.
3. **The result.** The generation of a result and return of the result to the clinician and patient

The recognition of these distinct elements is useful in deciding how to use genomic testing clinically and, critically, explaining to patients and participants the nature of the analysis that is being performed. The three elements can also happen at different times – the data generated from an assay performed for one purpose could be reused to perform a different analysis, for example to answer a different clinical question.

Diagnostics

In the NHS and other advanced health systems, genomics is now routinely used in diagnostics. It is a mainstay in the diagnosis of rare conditions and in the diagnosis and stratification for treatment in cancer[6,7,8]. The range of diagnostic settings that it is used in is expanding rapidly, with whole genome sequencing playing an increasing role, particularly in complex rare conditions and certain cancers.

Predictive and preventative care

The role of genomics in predictive and preventative care is also increasing. This includes its use in 'pharmacogenomics', the use of genomic testing to tailor the choice or dose of medication to avoid harm (for example by avoiding adverse reactions) and to increase efficacy [9,10]. Testing using polygenic risk scores to identify people at higher risk of common diseases including cardiovascular

disease and certain cancers is the focus of research to understand whether it can be used in routine care to identify those who would benefit from risk lowering treatment or closer surveillance for disease[11]. Highly targeted genomic tests also play a small but increasing role in screening for rare, treatable conditions in newborn babies[12,13,14].

Genomics in newborns

The potential value – as well as the risks and complexities – of routine genomic testing, even whole genome sequencing, being routinely offered to all newborn babies has been increasingly discussed in recent years[15,16,17,18]. Areas of potential utility fall broadly in three areas:

1. **Newborn screening.** For immediate use as part of newborn screening
2. **Supporting research.** To support healthcare research, including to improve newborn screening and to improve diagnosis and support the development of new treatment for rare conditions
3. **Life course use in healthcare.** To be stored for future healthcare use during the life course

Rare conditions

In the UK, a rare condition is defined as affecting fewer than 1 in 2,000 people. There are estimated to be approximately 7,000 rare conditions. This means that while they are individually rare, they are collectively common. It is estimated that 1 in 17 people have a rare condition. They disproportionately affect children, are often medically complex and are a leading cause of mortality and disability in children in high income countries[19], The rarity of the conditions means that they have historically been hard to diagnose.

For many of these conditions, most benefit is derived if they are detected early, with better outcomes in the pre-symptomatic phases. The importance of an early diagnosis was recognised in the UK government's 2022 Rare Disease Framework[20,21,22,23].

Treatments

Fewer than 10% of rare conditions have a treatment available that substantially impacts on outcomes[24,25]. The majority of these are conventional treatments such as ocular surveillance for those at risk of retinoblastoma; dietary changes in metabolic conditions; preventative antibiotics in sickle cell disorder; or dietary management, preventative antibiotics and airway clearance in cystic fibrosis[26,27,28]. In a number of conditions, particularly immunodeficiencies, bone marrow transplant is used and in a number of metabolic disorders enzyme replacement therapies are available[29].

There are promising signs recently that things will improve thanks to a number of classes of therapy that leverage understanding of the molecular cause of rare conditions. This includes an increasing array of small molecule therapies and cell and gene therapies[30]. Perhaps most striking are the oligonucleotide-based therapies that have already achieved approval in conditions such as spinal muscular atrophy. They have even been used in ultra-rare (even n=1) settings[31,32].

This means that there is the potential for a step change in the coming years. However, there are challenges in developing and evidencing new treatments because of the very rarity of the conditions. That means that the promise of this new wave of treatments will only be realised if the right infrastructure to collect evidence on natural history and support trials and the right policy and regulatory frameworks are in place

The impact of genomics in the diagnostic setting

Increasingly, whole exome sequencing (WES) and whole genome sequencing (WGS) have been adopted in complex childhood rare condition settings as part of diagnostics. Despite the higher costs of these tests, they have been shown to be cost effective, reducing the need for repeated rounds of targeted testing and shortening the 'diagnostic odyssey[33],[34]. Given the lack of treatments for the large majority of rare conditions, the diagnostic odyssey often starts what some refer to as a 'treatment odyssey'.

Building on the learnings of the 100,000 Genomes Project – delivered in partnership by Genomics England and NHS – the NHS in England has now commissioned WGS for a range of rare disorders including complex childhood conditions[35],[36].

Several papers demonstrate the clinical utility of WGS for diagnosis of rare conditions. The clinical utility of WGS for rare conditions can be measured in a number of ways.[37] A meta-analysis in 2018 demonstrated the superiority of WGS and WES over microarray with respect to therapeutic management.[38]

The effect of this approach is most powerful in the context of critically ill newborn babies with features suggestive of a rare condition[39]. A recent study of the aetiology of infant mortality demonstrates the utility of WGS in terms of outcome and therapy[40]. In the setting of the acutely ill newborn babies, both WGS and WES show higher rates of changes in management compared to usual care[41]. A systematic review in 2022 found utility of WGS and WES across one or more of five categories of utility in studies of genomics for critically ill babies[42].

While the implementation of diagnostic genomic testing in standard of care and earlier in clinical pathways has had a positive impact, diagnosis can still be too late to avoid irreversible harm in some children where a treatment would have been available[43,44]. This has led to calls to consider the use of genomics as a screening tool for all newborn babies[45].

Newborn screening

Current newborn screening

Newborn screening can be carried out using a variety of approaches including newborn physical examination, newborn hearing screening and newborn blood spot testing.[46]

Since the 1960s screening newborns for treatable disorders by heel prick blood spot testing has proven effective in preventing or dramatically ameliorating the burden of disease for these conditions.[47] Newborn blood spot screening has been deployed successfully worldwide[48] and the rapid development of new technologies has expanded the disorders tested[49].

The number of conditions tested for varies in different countries. In Italy, 40 conditions are looked for. In the United States, the recommended universal screening panel covers 35 conditions. In Australia and New Zealand 25 conditions are screened for and in Germany 19. The UK Newborn Blood Spot Test currently tests for nine conditions[50]:

- sickle cell disorder
- cystic fibrosis
- congenital hypothyroidism

- phenylketonuria
- medium-chain acyl-CoA dehydrogenase deficiency
- maple syrup urine disease
- glutaric aciduria type 1
- homocystinuria and
- isovaleric academia

In the UK, a pilot is ongoing to evaluate the addition of severe combined immune deficiency (SCID) screening[51,52]. Screening for tyrosinaemia has recently been recommended for inclusion by the UK National Screening Committee. Alongside the Newborn Blood Spot Test sit other newborn screening programmes such as hearing screening and newborn physical examination.

Performance of newborn screening programmes including false positive rates

A range of parameters are closely monitored for newborn screening including overall uptake as well as performance metrics such as sensitivity, specificity and observed true and false positive rates. The balance of these different parameters depends partly on the nature of the condition and partly on performance of test(s). The approach chosen also depends on the cost, availability and nature of confirmatory testing and balances the clinical utility of the finding and the impact of the condition if not detected early or before symptoms appear and the negative impacts of false positive findings on the child, the family and the health system.

Uptake of the Newborn Blood Spot Test in the UK is excellent, with >99% of newborns screened each year. The false positive rate for the UK programmes varies. For example, amongst inherited metabolic diseases from 10:1 true positives to false positives (medium-chain acyl-CoA dehydrogenase deficiency) to 1:5 true positives to false positives (isovaleric academia).[53].

Criteria and evidence for inclusion of conditions in newborn screening

The Wilson and Jungner criteria are used as the basis for most decision making frameworks on newborn screening internationally, including in the UK[54]. These focus on knowledge of the condition, its natural history, the existence of a latent or early symptomatic stage and the availability of acceptable and effective tests and treatment. Overall, in the words of Muir Gray, the expectation is of a screening pathway that does "more good than harm, at reasonable cost"[55].

Generating evidence on newborn screening is hard, as in many areas of research on rare conditions. This poses real challenges: the standard of evidence expected for common disease is not attainable in rare conditions. Ensuring the right infrastructure and ongoing monitoring and research after implementation is vital to ensuring that the right balance is achieved. Ideally the delivery and infrastructure would ensure an ongoing flow of evidence after adoption so that policy makers are able to approve screening for new conditions on reasonable evidence while being confident that screening can be changed or even phased out if the evidence suggests it should be.

Screening technologies and pathways now and in the future

While discussion about screening often centers on the initial screening test, screening is best considered a pathway that starts before testing. That said, screening depends on the availability of an effective initial test or tests that can be carried out at scale on available samples. At the moment, biochemical testing is the mainstay of newborn heel prick testing programmes, most notably using tandem mass spectrometry-based approaches. This technique has allowed more rapid expansion of

programmes across a number of inherited metabolic conditions with the capability to look for more than 50 conditions[56]

Genomic testing is used as a first tier test in spinal muscular atrophy in those countries where it has been added to newborn screening[57], [58]. Other than this, genomic testing is currently a second tier. For example in cystic fibrosis screening targeted genetic testing is used as a follow up testing after a positive screen result. With the advent of more precision treatments, it is also now used to determine suitability for specific cystic fibrosis treatments[59]

There are multiple routes by which the expansion of screening is being explored. Many are studies or pilots of screening for individual diseases yet to be adopted in a given country, for example, in the UK, the ongoing pilot on severe combined immunodeficiency (SCID) and the research study on spinal muscular atrophy[60,61]. A number of technologies present themselves for research to explore their value across multiple conditions. This includes the potential to broaden the already successful use of tandem mass spectrometry.

Proteomics, which has advanced considerably in recent years thanks to technological advances also presents opportunities[62,63]. However, genomics is the area with the most focus currently, with a number of programmes internationally investigating genomics-led approaches to newborn screening – see 'International context' later in this section.

Genomic newborn screening – opportunities and challenges

Just as it has revolutionised diagnostics for rare conditions, the use of genomics presents the opportunity to look for a broad range – potentially hundreds – of rare conditions that are treatable early in childhood. In this protocol we refer to this genomics-led approach as 'genomic newborn screening'.

The majority of these would be conditions for which no test suitable for use as a first-line in screening is currently available[64] across immune, haematological, endocrine, neurological, cardiac, respiratory, dermatological and childhood cancer predisposition, and a substantial number of metabolic conditions. For conditions where screening is already available or other tests would be better suited as a first-line screening test, there is the opportunity for genomics to be used later in the screening pathway, either to improve screening accuracy or to help identify the most appropriate treatment[65].

The idea of genomic newborn screening comes with questions and challenges across a range of areas . Many of these are shared with any expansion of newborn screening. Below we highlight the questions and challenges that are distinctive to a genomics-led approach.

Choice of genomic assay – panel, whole exome and whole genome sequencing

Panel testing uses next generation sequencing to target a specific subset of genes or genomic regions and WES targets sequencing to the coding region of the genome where, currently, most known disease-causing variants reside[66]. Both involve 'capturing' the target regions before sequencing[67]. While both have proven highly valuable in diagnostics for rare conditions, as the price of WGS reduces and the capability for whole genome data analysis become more widely accessible, whole genome sequencing is becoming more widely used, particularly where the number of potentially causative genes is high.

Advantages of WGS are seen in a number of areas. Whole genome sequencing has the potential to deliver results more rapidly than WES due to the avoidance of the 'capture' step. While the majority of small variants affecting the coding regions of the genome are captured by WES, WGS can detect non-coding variation and a broader range of types of variation (particularly with the advent of an increasing number of locus-specific callers)[68]. An example of this is Haemophilia A (Factor 8 Deficiency), a treatable rare condition which is typically caused by a gene inversion detectable by WGS but not WES. Using the current short read sequencing technology > 95% of the genome can be evaluated.

Whole genome sequencing also has advantages when considering the ability of the health system as a whole to learn – for example about allele frequencies across the population – and the benefits that can be brought through potential research use and longer term storage of the data for clinical reuse (both discussed later in this section).

Sequencing technology

The majority of diagnostic next generation sequencing is currently carried out using Illumina short read instruments. Its use at ≥30X coverage is well established in the detection of reportable variation in the context of rare conditions and is supported by an end-to-end tool chain for the identification of the range of germline variation required to support analysis, interpretation and reporting in an accredited setting at scale[69,70].

Additional sequencing platforms continue to emerge with promise in particular from long read sequencing, where costs are coming down and the associated tooling is maturing and there is the prospect of their utility at population scale in the future.[71] It is of note that the majority of evidence related to the effectiveness of genomic newborn screening is likely to be independent of the specific sequencing technology.

Analytical approach

A key question – as for any potential screening test – is what the sensitivity, specificity and positive predictive value of genomic newborn screening approaches would be. The analytical approach taken needs to consider the incomplete penetrance observed in some conditions and the lack of population-derived data on penetrance for many. This favours a conservative approach, reporting only variants and genotypes with strong evidence of pathogenicity.

The sensitivity of any approach will depend on the knowledgebases available. These are improving rapidly – in part fueled by large scale research studies such as those exploring the use of genomics in newborns – but are still limited for many rare conditions. There are important questions about the right analytical approach and the best knowledgebases to achieve the best sensitivity.

It is also important to understand what the impact of different analytical approaches are on sensitivity, positive predictive value and total number of true positive findings in different communities. There is likely to be a complex interplay here that will be influenced not just by underrepresentation of non-European ancestry communities in genomic knowledgebases but also by population structure (e.g., the frequency of well known 'founder' variants and the frequency of consanguinity / homozygosity for rare alleles) and the different prevalence of the specific rare conditions tested for. This study will

explore this, aiming to determine any differential areas of positive or negative impact of genomic newborn screening related to indices of diversity including ethnicity and socio-economic deprivation.

Implementation

Implementation of genomic newborn screening requires consideration of the right models of delivery, including on consent, on integration of the screening pathway with existing screening and on return of findings. These will bring with them specific questions on workforce and training as well as the testing infrastructure and the regulatory framework that needs to be followed.

Previous research on genomic newborn screening

There have been few studies of genomic newborn screening. Below we summarise the literature to date including those covering public and professionals' views, condition selection, studies that have looked at potential analytical approaches and finally the prospective studies that have returned findings to families.

Public and professionals' views

Public attitudes towards the use of genomic screening have been assessed by a number of methodologies including formal public dialogues, focus groups and opinion surveys. Typically >70% of participants are supportive when considering the return of conditions similar to those looked for in existing newborn screening[72,73,74,75,76,77]. Evidence from work carried out in preparation for this study and the more nuanced views from participants on discussion of some of the more complex elements of genomics are discussed further in Section 6. Health professionals consistently emphasise the need for caution based on current evidence, often emphasising the need for research before it could be adopted[78,79].

Condition selection

A number of publications have described expert-led decision making frameworks used for the selection of conditions suitable for use in genomic newborn screening [80,81,82,83]. These have typically built on the approaches developed for existing newborn screening although some authors have proposed a broader approach, for example looking for adult onset conditions or for parental carrier status. The condition lists vary considerably with the number of genes proposed for inclusion varying from 388 to 954 genes.

Analytical approach

The NBSeq project studied the potential use of WES sequencing in a cohort of 1,728 children who had received a true or false positive result for an inherited metabolic condition as part of routine newborn screening[84]. The exome-led approach had a specificity of 98.4% and a sensitivity of 88% compared to a specificity of 99.8% and a sensitivity of 99% for routine newborn screening. The authors concluded that it was not suitable as a first tier test for these conditions and highlighted the large number of false positives that this would yield if implemented as a second tier test. Of note, the analytical approach they used included variants of uncertain significance which would be expected to

tend towards lower specificity and positive predictive value than approaches proposed by more recent authors and favoured by studies currently in development.

A second study carried out by the BeginNGS study investigators looked at the performance of a proposed newborn sequencing pipeline focused on 388 genes by analysing whole genome data from 2,208 children who had undergone diagnostic whole genome analysis in the context of critical illness[85]. The pipeline identified 108 of 119 (87%) diagnoses as well as 15 additional findings that were not identified on diagnostic testing. This corresponded to a sensitivity of 88.8%. This same pipeline was also applied to genome data from 457,707 UK Biobank participants (not expected to have a treatable childhood disorder) and was found to have a specificity of 99.7% following root cause analysis.

Prospective studies returning findings

There have only been three prospective studies of genomic newborn screening published that include return of findings to families.

The NC Nexus study used a WES-based approach to look for 466 childhood onset, treatable conditions in 45 children with an inherited metabolic disorder and 61 healthy newborns[86]. The study also included randomisiation to be offered the option of receipt of results for a broader range of childhood conditions, adult onset treatable conditions and/or carrier status to inform reproductive choices. The study identified 5 of 28 children with deafness (18%), 15 of 17 children with inherited metabolic conditions as well as four children with treatable childhood conditions that would have been missed by routine newborn screening.

The most widely cited study is BabySeq, a randomised controlled study of 127 healthy and 32 critically ill newborns[87]. The study used a WES-based approach to look for 954 childhood actionable or childhood onset conditions as well as carrier status, pharmacogenomic variants and five actionable adult conditions. Fifteen of the 159 children randomised to the sequencing arm (9.4%) were found to be at risk of a childhood onset condition. Comparison of findings between WES and conventional newborn screening in BabySeq participants yielded very little overlap in findings. They identified two children in whom routine newborn screening identified a condition and WES did not and fifteen children in whom WES-led screening identified a condition and not routine newborn screening. Parents were approached within 24 hours of giving birth and as a result, enrollment rates were only 10% of all parents approached in BabySeq, with a diverse range of reasons given[88]. It is noteworthy that families in the study were only approached postnatally. As discussed later in this section, the study also found no persistent negative psychosocial impact on families. A second larger, multi-site phase of the BabySeq Project is currently underway in six cities in the US.

Finally, the Guardian study has recently launched in the US, and will enroll 100,000 unselected newborns who will all undergo WGS to assess risk for an initial 250 conditions.[89] The study manually reviews annotated variant data rather than using variant lists and reports the following variants for return to families:

- Autosomal dominant and X-linked condition: likely pathogenic and pathogenic variants only
- Autosomal recessive conditions where there is an orthogonal assay available: two likely pathogenic or pathogenic variants or variants of uncertain significance that are not 'leaning benign' that are paired with a likely pathogenic or pathogenic variant

- Autosomal recessive conditions for which there is no orthogonal assay: two likely pathogenic or pathogenic variants or variants of uncertain significance that are 'leaning pathogenic' that are paired with a likely pathogenic or pathogenic variant.

The Guardian study has recently returned findings to the first 984 participants and has reported and performed follow testing on findings to 42 participants (4.6%) including 27 apparent true positives, 15 apparent false positives and three pending confirmation). Three participants received two positive findings. This gives a true positive to false positive ratio of approximately 2:1. Twenty-one of the positive findings related to Glucose 6 Phosphate Dehydrogenase Deficiency, eleven of the apparent false positives related to a single mis-classified variant in the CFTR (cystic fibrosis) gene. Without these two individual genes, the study has had five apparent true positive findings and three apparent false positive. This also gives a true positive to false positive ratio of approximately 2:1 (personal communication W Cheung).

Macroeconomic considerations

Using WGS 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".[90] 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 for these patients, 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.

Whilst there is an evidence base for the cost-effectiveness of using WGS testing for babies and children who have suspected genetic disorders[91] (i.e. are symptomatic), there is a lack of literature evaluating the cost-effectiveness of using WGS in the general newborn population for screening.

Workforce implications

The implementation of new technologies in healthcare, including genomics, brings significant implications for the healthcare workforce. While healthcare professionals may broadly support the adoption of genomics into healthcare, there is a need for appropriate training, policies, funding and pathway coordination to enable the sustainable uptake of genomic technologies[92]. As a research study embedded in the NHS, with results fed back via clinical care mechanisms, we anticipate that this study will impact hospital and community health services across the country. We have been working with a number of clinical, scientific and operational staff across our NHS Steering Group, Clinical Assurance Group and Working Groups to consider the time, training and resource requirements from the point of recruitment through to ongoing care (see Section 6). This includes working with bodies such as Health Education England and Royal Colleges who consider workforce capacity needs. Our ongoing engagement has shaped how we will work with study sites and regional infrastructures to ensure there are resources in place to support implementation and sustainability, beyond immediate delivery of the study. We will also be monitoring the acceptability of and impact on the health care workforce throughout the study (see Section 16).

Psychosocial implications

There are a number of psychosocial implications to consider when using genomic technologies or introducing population screening programmes, and it is crucial to be able to assess these potential benefits or harms to babies and families[93]. Research with families who receive results from newborn screening highlight a range of psychosocial challenges, which could be further exacerbated by the introduction of genomic technologies like WGS[94] .

Genomic tests and screening tests all have the potential to identify results that are uncertain. While early identification of a genetic condition can remove the 'diagnostic odyssey' that families may otherwise experience, a different kind of odyssey may be created as parents need to adapt to a potential diagnosis in their child with ambiguity about their future[95]. This can be mitigated by focusing on variants where their association with a condition is well established; however, uncertainties will always be present, particularly when a variant is found outside of the context of a personal or family history of the condition[96].

The results of genomic newborn screening also have the potential to impact family relationships, such as parents perceiving their child as medically vulnerable; knowledge of a potential diagnosis consciously or unconsciously affecting how parents bond with their child; or parents placing blame on themselves or their partner as a consequence of passing on a genetic condition.[97] Limited empirical research in this area has primarily focused on evaluating anxiety, distress or empowerment, and suggests that there is no persistent negative psychosocial effects on families who receive newborn genomic screening.[98] Reasons for this may include that there are improved health outcomes for children who are able to access early treatment; or that parents are able to engage in their child's care at the earliest possible stage, providing greater control than if their child were diagnosed later[99].

The complexity and uncertainty of genomic screening results raises issues with regards to consent. Parents are asked to make a decision on behalf of their child, where results have the potential to be life-changing or have health implications beyond the individual (e.g. for their wider family). Evidence suggests that current methods of providing information about newborn screening in the UK is challenging and inadequate, with parents often making a decision based on limited understanding. This may in turn have negative effects on parents' psychological wellbeing after receiving a positive screen result. Maximizing opportunities for information and discussion prior to consent can support with parents' expectations and preparedness for results, and reduce the potential for psychological harm[100,101].

It is important that psychosocial impacts of newborn genomic screening are evaluated longitudinally, to understand if potential harms are only present for a short period of time after receiving a result, or if they persist. These studies can also help to identify potential interventions that can protect against these risks, such as genetic counselling, or other methods of communication and information provision. An important part of this study and it's evaluation is therefore focused on addressing and assessing these psychosocial impacts.

Supporting research

The National Genomic Research Library

The paradigm for a link to be built between the use of genomics in a clinical setting and, with consent, the use of genomic and longitudinal health data in research is one that is now well established in the UK through the National Genomic Research Library, governed under its own protocol[102].

Genomic data from participants choosing to join the National Genomic Research Library is de-identified and made available alongside linked healthcare data in a secure research environment – often now referred to as a 'trusted research environment' model. Researchers can visit that data and perform research in the research environment but may only export summary data. Researchers from academia and the life sciences industry receive accreditation to use the library and then approval for specific research projects from an independent Access Review Committee that includes study participants and ensures that the research fits with the expected healthcare uses set out in the protocol.

The National Genomic Research Library consent also includes the ability to recontact participants for future research opportunities, for example recruitment to clinical trials based on their genomic profile or to inform them about further clinically relevant findings related to the reason they joined the study (for example their rare condition or cancer). This creates the potential for a learning system, where data from the health system drives research, which in turn provides insights that improve healthcare.

The model was first established through the 100,000 Genomes Project, a research study delivered as a partnership between Genomics England and the NHS that explored the value of whole genome sequencing in diagnostic settings in rare disease and cancer. More than 130,000 participants have now joined the National Genomic Research Library with further participants having joined the library through specific research cohort studies including approximately 35,000 participants in the GenOMICC COVID-19 study.[103] It has led to more than 264 peer reviewed papers across a range of areas, from clinical application to new discovery in diagnostics and therapeutics.[104]

Patients receiving WGS in the NHS England Genomic Medicine Service in England are now routinely offered the opportunity to join the National Genomic Research Library. In these diagnostic contexts, patients have shown strong support for taking part in research, with 90% of those approached opting to join the National Genomic Research Library. This mirrors the strong support for participation in research under the right terms seen in the formal public dialogue that was used to inform the consent model used[105].

As well as the benefits that might come from research itself, there are also important questions to ask about the perceptions and preferences of the public, parents and young people on the use of data in healthy newborns for research. This includes questions on what future models might be for offering research participation in the context of genomic newborn screening if it became routinely offered.

The need and the opportunity

There have been enormous advances in recent years in the understanding of genomics in diagnostics, and the development of treatments for rare conditions and in healthcare more broadly, but there are many urgent questions left to address.

The pace of new gene discovery for rare conditions continues with hundreds of new gene associations reported each year[106]. Despite this, only 30-50% of patients with a rare condition receive a diagnosis, even with the best testing. Natural history is poorly understood in most rare conditions. While there is great promise of new therapies, still only 10% of rare conditions have a treatment, lagging far behind the pace of discovery of new conditions[107]. Large scale research in unselected newborns has a potentially pivotal role here, for example to better understand allele frequencies in babies born in the UK today, tracking the natural history of rare conditions.

It also has the potential - alongside children with rare conditions identified through diagnostic pathways - to drive greater evidence on new precision (and conventional) treatments by identifying those eligible who might benefit, early in the course of their condition.

In newborn screening, as well as the potential for expansion through the use of genomics, there are many areas where further evidence could help increase its impact. For example, through greater understanding of natural history of rare conditions. Or through better understanding of the normal values in the newborn population of relatively well established analytical techniques (e.g., through tandem mass spectrometry) or newer techniques (e.g., proteomics).

As with other birth cohorts, there are also broader health-related research questions that could be addressed, for example on common childhood disease, growth and health outcome and potentially, in time, adult health conditions and outcomes[108],[109].

Longer term storage of genomic data for reuse for healthcare

The concept of the lifetime genome

With the advent of next generation sequencing, and of whole genome sequencing in particular, the idea of generating genomic data once and reusing it to support a person's healthcare has become increasingly discussed.

As set out above, this derives in part from the useful distinction of the different elements of genomic testing. First, the generation of raw sequence data (the assay). Second, the analysis of the data in a given clinical context to answer a specific clinical 'question' (the analysis). Third, the generation of a result and the return of the result to the clinician and patient (the output). These three steps can happen at different times with the data generated from the assay potentially being stored and reused later with a different analysis to answer a different clinical question.

It is possible to imagine whole genome data generated at birth initially for newborn screening being reused later for diagnostic tests in a child who falls critically ill with features suggestive of a rare condition. With the increasing role of pharmacogenomics, there may in the future be the facility for systems supporting a clinician prescribing a new medicine to check for relevant genomic variants that would alter the choice or dose of medication[110],[111]. If polygenic risk scores are proven to add value clinically, they could be used when the person reaches adulthood to estimate risk of adult disease [112].

Perhaps later in adulthood the person develops cancer and the sample from birth can be used as a comparison to understand which variants in the cancer's genome are somatic.

Broader questions

Currently, while the potential is clear, research is needed on many of the individual potential clinical uses of genome analysis. There is also uncertainty about how long data from any one individual sequencing technology will remain relevant or clinically useful or whether it may become more cost effective to perform a new sequence each time. There are also important questions to explore in terms of potential and perceived risks and broader implications of storing an individual's genome over their lifetime.

Other similar programmes internationally

Internationally, a number of studies of genomic newborn screening that plan to return findings prospectively to families are in design or in the early stages of delivery (Table 1)[113,114,115,116,117,118,119]. The studies vary in size from 1,000 to 100,000 babies.

The majority are in early development. The proposed approach to variant prioritization has been published for the BeginNGS study and is described in the Analytical approach subsection above. Early data is available from the Guardian Study and is also discussed above, in the subsection on Prospective studies returning findings.

All but one take an observational methodological approach, with BabySeq2 randomising between standard of care alone and standard of care plus genomic newborn screening. All but one are using whole genome sequencing, with Screen4Care (Europe) using a panel-based approach with the number of genes targeted varying from 126 to approximately 600.

Table 1 – Summary of the characteristics of the main studies exploring genomic newborn screening

Study (location)	Number of babies	Design	Sequencing	Number of genes	Variant list
Guardian Study (US)	100,000	Observational	Whole genome	160	No
Baby Detect (Belgium)	40,000	Observational	Whole genome	126	No
Screen4Care (Europe)	18,000	Observational	Panel	To be confirmed	No
EarlyCheck2 (US)	10,000	Observational	Whole genome	~200	No
BeginNGS (US)	>2,000	Observational	Whole genome	~460	Yes
BabySeq2 (US)	>1,000	Randomised	Whole genome	~1,000	No
BabyScreen+ (Australia)	1,000	Observational	Whole genome	~500	No

4. Stimulus and development of this programme

Stimulus, early development and funding

Over the last several years, the following published reports have highlighted much of the evidence outlined in the Section above.

- Annual report of the Chief Medical Officer 2016: Generation Genome[120]
- PHE's report Generation genome and the opportunities for screening programmes[121]
- Genetic Alliance UK's Patient Charter on Newborn[122]
- Genetic Alliance. Fixing the present, building for the future: Newborn Screening for Rare Conditions[123]
- Genomic Analysis in Children Task and Finish Group[124]
- Genome UK: the future of healthcare[125]

They have recognised the potential value in the use of genomics in newborn screening for the UK but identified that some of the complex ethical, societal and operational issues that needed exploring before it can be considered for clinical use.

Following the 2016 Generation Genome report, a group was convened by Genomics England on the request of the Chief Medical Officer, Dame Sally Davis, to examine in further detail the ethical and societal questions around using genomic analysis in children, and to begin to quantify the benefits and risks. This report from this group – the Genomic Analysis in Children Task and Finish Group – outlined the initial conservative analysis suggesting 1 in 260 live births are affected with a condition where identification through genome sequencing has the potential to reduce or avoid harm in early life. The group recommended a high quality, large-scale prospective research study to create a major NHS transformation programme using whole genome sequencing for screening in newborns.

These reports led Genomics England and the UK National Screening Committee to commission public engagement in 2021 examining the implications of genome sequencing in newborn screening with members of the public using specific dialogue methodology.[126] The dialogue, delivered by Hopkins Van Mil, involved 130 members of the public, who gave clear steers on the conditions under which our study should be established.

The engagement concluded that "It would be acceptable to use WGS to identify a wider set of conditions than the current NHS newborn screening programme if (1) the conditions impact the infant in early childhood and (2) there are treatments and interventions to cure, prevent, or slow progression of the conditions." The report pointed to the potential for genomic newborn screening to bring health benefits to the rest of the family and the importance of genetic counselling and mental health assistance for the family receiving a confirmed diagnosis. Further, establishment of a comprehensive genetic database was recommended to ensure that ethnic minorities are not disadvantaged as they are at risk to receiving more uncertain, or less accurate, diagnoses than the rest of the population from newborn screening. The public engagement also acknowledged the research value of the WGS data to deliver improved diagnoses, treatment and care provided that the information was anonymised, and the benefits and risks from the use of WGS data throughout the infant's lifetime.

Genomics England was funded by the UK Government's Department of Health and Social Care to co-design and run a research study in partnership with the NHS on the potential value and costs, risks

and benefits of offering WGS to all newborns. The funding covers sequencing of 100,000 babies during the current government spending period ending April 2025. It also covers associated costs such as staff training, site mobilization, consumables, transport, sample storage and incidentals for participants – such as transport cover for attending follow-up appointments in 'condition suspected' babies.

Partnership with the NHS, expert engagement and ethos of the Generation Study

From the outset, the Newborn Genomes Programme has been a partnership with the NHS. In 2021 an independently chaired NHS Steering Group was established to support development of a shared vision for the programme and to provide advice from experts and key stakeholders in the design of the Programme – see Section 22 (Governance and Programme Management).

Working with the NHS Steering Group, a vision for the Programme was developed[127] and co-design of the programme begun. Expert Working Groups, each with an independent chair, were established to provide advice in particular areas of focus: Ethics, Evaluation, Recruitment, Conditions, and Education and Training.

As well as these areas of individual focus, a cross cutting theme has been to consider the workforce implications and the impact on clinical care pathways both of running the study but also if whole genome sequencing were adopted in routine care. To further support this, we established an NHS Clinical Assurance Group that provides advice to the programme and also reports to governance structures within NHS England to advise on the selection of conditions, with a particular focus on ensuring relevant expert sign off of each condition and pathway, the availability of treatments and the capacity of clinical care pathways. It includes representation from relevant NHSE Clinical Reference Groups, the NHSE Genomics Unit, Specialised Commissioning, NICE and the UK National Screening Committee.

Working with our partners in the NHS and beyond, we have established an ethos for the study that leads us to take a cautious approach, recognising the complexity of the questions the study is engaged with, for example favouring high positive predictive value when considering conditions and variants that will be returned to families.

A model for delivery of the Generation Study has been developed, again as a partnership with the NHS, with recruitment taking place in NHS Trusts and 'condition suspected' results returned by the expert clinical teams who routinely care for children with the condition in question. NHS Genomic Medicine Service Alliances will support the study in particular by enhancing regional engagement and awareness, providing education and training and supporting the return of 'condition suspected' results[128].

Co-design and public involvement

Introduction

This section briefly details our co-design work, and how the insights manifest in the study. This is central to our approach in developing this study. We use the term 'co-design' to encompass both Public and Patient Involvement (PPI) and our wider agenda to design the research study with continued public input, in an iterative manner.

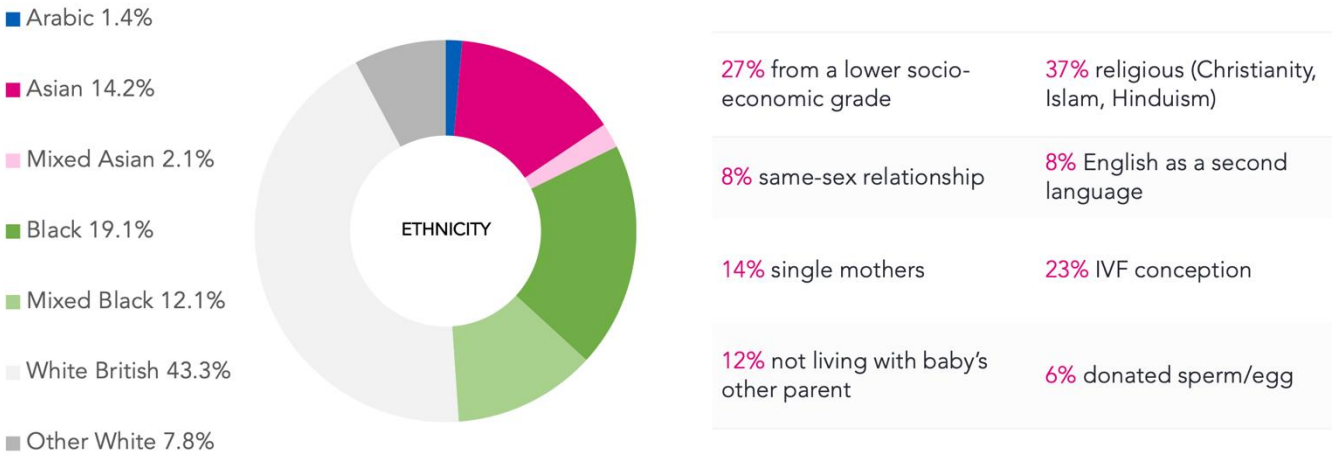
Approach

Between January 2022 and March 2023, 141 parents contributed to the co-design through interviews. All were pregnant or ≤ three months postpartum to avoid recall bias. Each participant was interviewed once, so they were not able to develop expertise in the subject matter. Participants were encouraged to engage with the interviewer in a real-world setting, with their family members present. Sampling ensured broad representation, and views from a range of individuals were elicited, depicted in Figure 2:

- Socio-demographics (age, ethnicity, socio-economic grade, geography)
- Family shape (traditional, single mothers / birthing parents, same-sex couples)
- Stage of pregnancy and post-partum, primiparous/multiparous
- Pregnancy type: natural, IVF, donated sperm/eggs
- Religion, trust in the government/the NHS, non-native English speakers

None of the participants had any prior knowledge of Genomics England or of this study. However, some participants reported a genetic condition within their family (24%), and some had children with confirmed genetic conditions such as sickle cell anemia and β-thalassemia.

Figure 2 – Breakdown of 141 parents involved in co-design



The timeline of our co-design interventions is illustrated in Figure 3

Figure 3 – Co-design timeline

Limitations

As with all such work, our co-design work has some limitations:

- Participants were generally interested in taking part in research. We have aimed to broaden our reach by using an external recruitment agency with expertise in recruiting a broad range of profiles, and by offering cash remuneration to help incentivise participation from a broader range of parents.
- Because most sessions were online, participants had a certain level of digital literacy that may not be common across our study cohort.
- All of the co-design work was carried out in English. However, in the main study, we will provide translations appropriate to the population of our partner sites and test these with lay audiences as we iterate them.
- The qualitative methods utilized in our co-design produce data that are not generalisable. However, qualitative data has the advantage of yielding deep and complex insights into the lived experience of participants, and these have been instrumental in our study design.

Examples of co-design insights

The remainder of this section sets out how the co-design has shaped some aspects of the programme. However, this is not an exhaustive summary of all areas of co-design or the work in each area. Further details are available on request.

Information provision and development of patient information and materials

Providing sufficient information about a study, in a manner that potential participants can understand, and in an accessible format, is an important facilitator of consent. This study introduces significant complexity into the maternity process, and understanding how best to inform potential participants about the study was a particular focus of our PPI.

The results of our PPI demonstrate that parents' attitudes towards their pregnancy changes over time. The first 20 weeks may be a 'danger zone' – the reality of having a baby is yet to sink in. Parents may also feel overwhelmed with new information and leaflets at the Booking appointment (Week 8) and the 12 week scan. After the 20 week scan, things settle and the pregnancy becomes more tangible. To this end, parents will usually be officially approached and invited to consider participation after the 20 week scan – however this approach may happen earlier if a potential participant has heard about the study and registered interest on the Generation Study website. PPI participants wanted to involve others/partners in their decision-making and many wanted time to think about the study, and discuss it with family members, before deciding about participation. Participants also expressed preferences for a range of different learning tyles and information formats.

We have used these insights to develop our Recruitment and Consent strategy as set out in Section 7, we have designed a flexible recruitment process where parents can sign up at the time of invitation, or in the weeks afterwards when they are ready.

As well as building on insights from our PPI work, participant materials have been developed by drawing on relevant guidance and exemplars of good practice, as well as engagement with the public, families living with rare conditions, and clinical, ethical and scientific experts[129,130,131]. Information supporting the recruitment and consent process will be layered; a minimum level of critical information will be made available with access to other more specific and detailed information as required by each parent based on their questions and needs[132].

Participant materials will include:

- **Posters** – placed in participating hospitals that include a QR code and web link, inviting parents to speak to their midwife or hospital team to find out more about whether they can take part.
- **Leaflet** – providing a brief high-level description of the study, and including a QR code, web link, and local contact information should the parents be interested in taking part.
- **Video** – explaining the purpose of the study, what is involved, risks and benefits. The video is intended to be used as an introduction into the study.
- **Participant information sheet** – this will be made available to all parents in hard copy or electronically, and include all relevant information about the study.
- **Decision aid** – using scenarios to help parents (independently or via discussion with a study team member) consider how they may react to particular situations that could arise from their or their child's participation in the study
- **Participant microsite** – this will be made accessible via a QR code or web link on other study materials. It will provide general information about the study, the video and decision aid, information about results, and all details contained in the information sheet (including a link to download or print a PDF version). The site will also contain links to the Genomics England main website should potential participants wish to understand more about Genomics England.
- **Welcome letter** – provided to parents after they have given consent, this will provide information to parents about next steps including sample collection and results.

Whilst there is no uniform guidance for translation and interpretation of materials, a proportionate approach that facilitates understanding is recommended[133]. Information sheets will be made accessible (e.g., for people with visual disabilities) and available in selected languages, based on

non-English languages most commonly spoken across study sites. These will be translated forwards and backwards to ensure accuracy of information. Language line will otherwise be available for support to site study teams to ensure parents have sufficient opportunity to ask questions in their preferred language.

Developing inclusive materials

People from ethnic minority groups may be particularly wary of healthcare research due to being aware of historical research studies which were not ethical[134]. Our co-design suggests that we need to strike a delicate balance between facilitating participation of people from these groups, but ensuring they do not feel targeted in recruitment. Accordingly, our study materials emphasise the goal of *advancing health in all communities*. This phrase underwent many iterations, and in our final round of co-design with ethnic minority participants, it was generally well received. In addition, in our materials, we use photography inclusively, to represent different types of families, depicting a range of ethnicities and family structures.

Sample collection and reaffirmation of consent

In our co-design, we explored parent's views of obtaining samples from their babies. Parents felt that extra hospital visits for sample collection may discourage their participation. Consequently, we will aim to collect samples on Day 0. Understandably, some parents were concerned about the invasiveness of sample collection methods. As set out in Section 8 (Sample Collection), our focus is on non-invasive means of collection with heel prick only where cord blood sampling has failed.

Our co-design participants noted that previously-held sentiments may change after birth, so reiterating consent on Day 0 is desirable. However, they also highlighted that this may not be their priority on the day and it may be disruptive. Reflecting this, as set out in the Recruitment and Consent section, at the time of sample collection on Day 0, consent will be reaffirmed, questions answered and parents given an opportunity to withdraw from the study before any samples are taken. However, the level of interaction will be determined by the experienced study team at each site.

Return of results

Parents expressed a desire to know the timeframe within which they should expect results. Knowing the timeframe was more important to them than speed. Our engagement with parents mirrored what we found in previous reports including broader expectations on returning results and the importance of support when results are returned including reflecting language and accessibility needs and the need for psychological support[135136,137]. These insights have informed our plans on return of results set out in Section 11.

Ongoing Engagement

Alongside and responding to our co-design work, and building on the 2021 public dialogue and experience and insights from other engagement work including, for example, the 2019 public dialogue on genomic medicine, we continue deliberative engagement projects that will support delivery and programme and iteration of our approaches.

Developing principles for conditions to return findings on: deliberative workshops

This exercise, to engage broadly in the development of principles which took place between May and July 2022, is explained in more detail in Section 6.

Engaging with ethnic minority community leaders

Between January and March 2023, we worked with Basis Social, a research and insight consultancy, to develop a comprehensive view of a selection of ethnic minority groups' attitudes towards our study. Using birth data, and an analysis of our previous work with minority groups, we identified five communities to focus on: Pakistani; Indian; Black African; Black Caribbean; and Gypsy, Roma and Traveller. Leaders for each of those communities were identified through their work with community-based and civil society organisations. Basis explored leaders' perceptions and opinions on our research study, focusing particularly on what they felt might be potential barriers to community members' participation, how we might work with both those leaders and their community members to overcome those barriers, and optimal methods of communication.

A report of findings, which will be shared on Genomics England's website, is being produced by Basis Social at the time of writing. We anticipate building on relationships forged with community leaders for this engagement project, and working with them once our study launches – for example, to seek their advice if participation is low among parents in their respective communities. We might also consider undertaking the exercise with further ethnic minority groups, should participation be low in other communities.

Discovery research deliberation

Between January and March 2023, we worked with Hopkins Van Mil (an organisation specialising in public deliberation) to understand the red lines for, and acceptability of, undertaking discovery research using newborns' genomic data. Over 100 members of the public were involved in this deliberation. To inform their deliberations, participants were provided with case studies that focused on a variety of hypothetical, yet realistic, scenarios. They were also introduced to researchers from academia, the NHS, and industry, who described their work, and their hopes for discovery research using newborns' genomic data. At the time of writing, a report with key findings is being produced by Hopkins Van Mil. This will be shared on Genomics England's website. These insights will be used to continue to shape the broader research agenda that the Programme supports, primarily through the National Genomic Research Library protocol.

Pilot Public Standing Group on Ethics

Responding to the desire of participants in the 2021 public dialogue on genome sequencing in newborns to continue to work with Genomics England, interested participants were asked in January 2023 to express their interest in joining a Pilot Public Standing Group on Ethics. Twenty-two individuals volunteered, and subsequently met three times. Their role was to discuss ethical issues

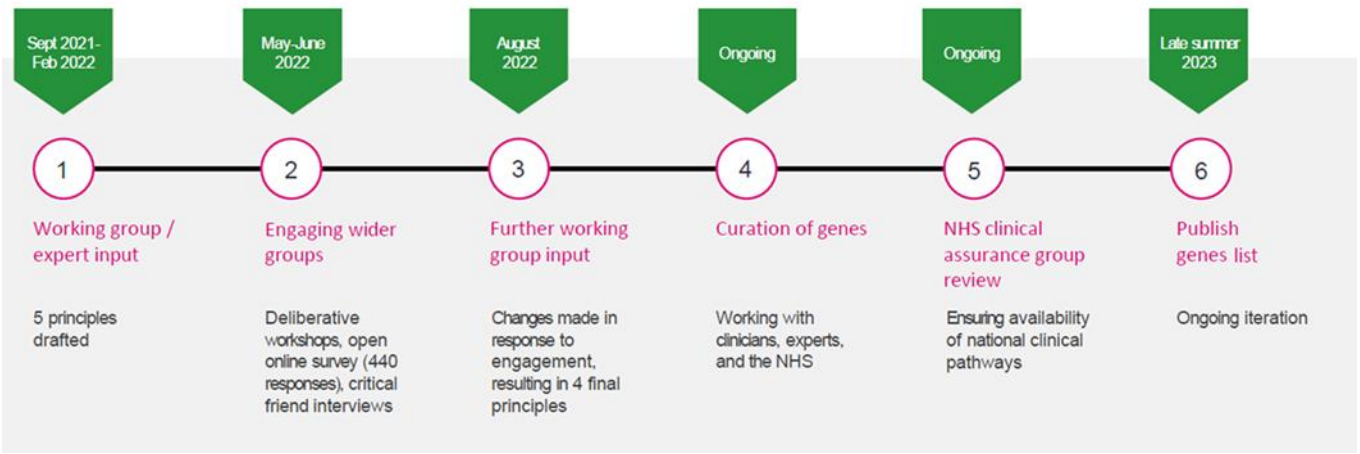
relevant to the study's design, including optimal approaches to communicating our work to both participants and to more general audiences. An evaluation of this pilot group is planned for late spring 2023, after which a decision will be made as to whether it should continue as an established group for a period of a year.

Selecting conditions and the supporting governance

Key to planning this study was deciding which conditions should be included in our screen. An initial condition list was published in October 2023 (https://www.genomicsengland.co.uk/initiatives/newborns/choosing-conditions/conditions-list-generation-study). We are committed to iterating and improving this over time. Any decisions related to the conditions list, both past and future, have been framed by our commitment to robustness, fairness and transparency; whilst recognising that there are challenges to screening led by genome sequencing. In selecting conditions, the Generation Study has taken a more conservative approach than many international comparators, reflecting the cautious approach that we aim to take in the programme overall.

We have taken a stepwise approach to developing criteria for selection of conditions with expert and public input and established governance jointly with the NHS. This is summarised in the figure below.

Figure 4 – Process for selecting conditions



Establishing the principles for selection of conditions

Although there are existing criteria for deciding what to include in national screening programmes,[138] the Generation Study is a research study and the genomic approach provides distinct considerations.

1. **Working group / expert input**

We established an independently-chaired Conditions Working Group with a range of laboratory, clinical and policy expertise as well as patient and participant representation.

A key input was the views from participants in the 2021 public dialogue on the implications of whole genome sequencing for newborn screening that the focus should be on conditions that have an impact in early childhood, and where there are intervention(s) that can cure, prevent or slow

progression. The group also built on existing screening criteria and a review of published literature[139,140,141,142]. The group produced an initial five draft principles.

2. Engaging wider groups

Working with the public participation charity Involve, we brought together a working group including healthcare professionals; clinical scientists; social science and ethics researchers; and members of the public and rare disease communities, to get wider views and input on the draft principles.[143]

3. Further working group input to finalise the four principles

The Conditions Working Group used the feedback from the wider engagement work to iterate and finalise the principles for selecting conditions. This resulted in a set of four principles that will be used in the programme.

The four principles

In order for a variant and condition to be looked for in our study:

- **Principle A.** *There is strong evidence that the genetic variant(s) is pathogenic and can be reliably detected through WGS. Where appropriate, there may be a confirmatory test that can establish whether or not the child has the condition.*

  This principle addresses evidence for clinical validity and analytic validity. However, case control data are rarely available for rare diseases to establish a gene's specificity for a disease and therefore positive predictive value cannot always be established. The confirmatory test describes a non-genomic test (for example, a biochemical test) that would provide clarity on whether the condition is present.

- **Principle B.** *A high proportion of individuals who have the genetic variant(s) would be expected to have symptoms that would have a debilitating impact on quality of life if left undiagnosed.*

  The impact should include considerations such as the testimony of patients and families affected and QALYs where available. This principle is related to gene penetrance, and only conditions with a high penetrance will be included in the study.

- **Principle C.** *Early or pre-symptomatic intervention for the condition leads to substantially improved outcomes in children, compared to intervention after the onset of symptoms.*

  The intervention would normally be initiated in early childhood (by age 5); and could either cure, delay or modify the course of the condition. This principle also focuses us on only including conditions where the intervention would start in childhood, not conditions that might affect the baby when they become an adult. Our view is that if any intervention can wait until the child is old enough to make their own decisions, then they should be given that choice themselves.

- **Principle D.** *Conditions screened for are only those for which the interventions are equitably accessible for all.*

  This entails incorporating input from NHS England and other relevant clinical and commissioning bodies (via the NHS Newborns Conditions Clinical Assurance Group) to ensure that 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 study.

Implications of the principles

We expect that the conditions currently recommended for screening in the NHS Newborn Bloodspot programme would meet these principles. Examples of additional conditions we expect to meet these principles include:

- Hereditary fructose intolerance
- Spinal muscular atrophy
- Hereditary retinoblastoma

There will be a variety of genetic conditions that will not meet these principles and therefore not be looked for in the study. While there is recognised benefit in solely having knowledge of a condition to adapt and prepare for the future, our principles also indicate that we would not look for conditions where there is no intervention available that can be supported by the NHS.

While we recognise that adult-onset conditions could have health relevance for other family members such as the newborns' parents, current clinical guidance suggests avoiding genomic testing in children unless results could impact the healthcare of the child[144]. Therefore, carrier status will not be directly sought, and conditions where the intervention does not start until adulthood (for example, Lynch syndrome or Hereditary Breast and Ovarian Cancer syndrome) will not be looked for.

When a gene is associated with both an adult-onset and a childhood-onset condition, only the childhood-onset condition would be directly sought in the programme. For example, Fanconi anaemia, an autosomal recessive childhood-onset condition which is expected to meet these principles, may be caused by pathogenic variants in the *BRCA2* gene. We would exclude heterozygous *BRCA2* pathogenic variants from our analysis, which are associated with a cancer-predisposing condition where preventative action would not be taken until adulthood.

We acknowledge that the conditions we look for may impact other family members – for example, parents being identified as a carrier for a recessive condition, or having a *BRCA2* gene variant if their child is found to have Fanconi anaemia. We further discuss how we would address the results feedback process in Section 11 below.

The Conditions Working Group recognised that the vast majority of current knowledge on penetrance and expressivity of monogenic conditions has been ascertained from individuals with an existing medical or family history of the condition; it is therefore likely that many conditions will have lower penetrance or milder symptoms than expected when found through screening asymptomatic populations[145]. Developing evidence on penetrance and expressivity will be an important output from the study. The Working Group also emphasised the need for a cautious approach on variant selection and prioritisation, which has been adopted and is described in Section 13 (Project Evaluation and Data Analysis).

The Group also recognised the limited data available in other areas in rare disease, many of which are challenges in screening for rare disease, irrespective of the first line technology used. This includes the limited knowledge about the natural history of the condition or benefits of an intervention. Contributing evidence on this and other areas will also be an important output of the study.

4. Curation of genes

We then worked with Conditions Working Group to establish a standard operating procedure for assessing whether a condition adheres to these four principles We have also developed a standard process for assessing gene analytic validity, variant selection and reporting as shown in the Bioinformatics section of this document.

5. NHS Clinical Assurance Group review

As part of our partnership working with the NHS and the overall governance for the programme (see Section 23, Programme Management and Governance), we established an NHS-chaired NHS Clinical Assurance Group. This group provides advice to the programme and also reports within NHS England to advise on the selection of conditions with a particular focus on ensuring relevant expert sign off of each condition and pathway, the availability of treatments and the capacity of clinical pathways. It includes representation from relevant NHSE Clinical Reference Groups, the NHSE Genomics Unit, Specialised Commissioning, NICE and the UK National Screening Committee.

By working with the NHS Clinical Assurance Group and associated clinical and commissioning experts, a working case definition will be created for each condition looked for in the study.

6. Publication of genes list and iteration

In Summer 2023, before launch of the programme, the initial gene list will be published to allow further feedback.

We recognise that new evidence will emerge as we continue to engage with experts, healthcare professionals, rare disease communities and the public. Where new evidence emerges about pathogenicity or penetrance of a variant, or a new treatment is developed, the gene list will respond to this. We will use the processes, groups and governance set out in this section to oversee any changes.

Preparatory Research on Sample Collection – the Baby and Mum Sample Study (BaMSS)

As WGS is not widely used in newborn babies for screening purposes, Genomics England undertook a REC (IRB) 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 for the Generation Study.

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 findings have been instrumental in the design of the sample collection approach taken for the Newborn Genomes Study – see Section 8 (Sample Collection).

Sample types considered

The study involved assessing three types of samples: cord blood, heel prick collected to dried blood spot card or EDTA tube, and buccal swab.

Cord blood. Obtaining a blood sample from the umbilical cord is non-invasive, however, there is risk that umbilical cord blood can be contaminated with the mother / birthing parent's genetic information rendering it unsuitable for screening for rare diseases. Small-scale studies assessing the

proportion of cord blood samples that might be contaminated enough to prohibit sequencing present contradictory findings[146;147,148,149]. Additionally, the now common practice of delayed cord blood clamping may affect the amount of material it is possible to obtain, and it is important to understand how often it might not be possible to obtain a sample in this way.

Heel prick to dried blood spot card or EDTA tube. WGS based on samples obtained from dried blood spots and capillaries (which could be collected by newborn heel prick) is feasible, but there is limited evidence that samples obtained from dried blood spots or capillary tubes from newborn samples consistently provide high enough quality whole genome sequences[150].

Buccal swab. Buccal sampling is a common and non-invasive method of DNA collection in adults, requiring rigorous mouth cleaning procedures before sampling. However, it is not a preferred method of DNA collection for whole genome sequencing in the NHS Genomic Medicine Service in adults or children due to the presence of mucosal flora. It is unclear how a newborn's cheek cell collection would perform noting the potential difference in levels of mucosal flora but also the likelihood of recent feeding with colostrum, breast milk or infant formula.

Design and delivery

The primary objective of the study was to determine which of a variety of methods produced the most reliable biomaterial sample for WGS in newborn babies. The secondary objectives were to determine the operational and technical feasibility of each sample type.

Over a period of 5 months, 603 mother/birthing parent and baby pairs were recruited from five sites across England. We attempted to obtain two sample types from each neonate :

- Cord blood on Day 0
- Baby buccal swab using Genotek OC175 /ORACollect™ (Day 0)

We collected residual blood from heel prick samples (stored in EDTA tube or dried blood spot cards (DBS)) when heel prick was indicated for other medical purposes to minimise the impact on a baby. A mother / birthing parent's saliva sample was also taken to allow cross-check for maternal contamination of samples.

Sequencing was carried out using Illumina NovaSeq instruments with the expectation that similar data will be generated on other instruments and technologies as the end-to-end platforms (e.g., including bioinformatics as well as sequencing) reach maturity, reach the required performance metrics and are available to the required accredited standards.

Descriptive statistics were used to analyse the key outcomes, and Table 2 illustrates the main findings for each sample type considered in the Study.

Table 2 Main findings from the Baby and Mum Sample Study

Sample Type	Sample size	Expected % of failures*. Note: this does not include failure to collect sample	% Sample DNA contamination > 1%	Average DNA yield from samples that passed QC	Ease of collection reported by NHS staff	Average time collecting sample (min, max)	Failures to collect samples from recruited participants	Operational observations
Cord Blood	392	1%	2.3%	28,648ng	91% easy 1% difficult 8% not reported	4m30s (Min 2min Max 20mins)	Average 20% all birth types *35% emergence C section 10% planned C section 20% spontaneous vaginal*	Collection rates improved over time at all sites. Published hospital guidelines and staff training may improve collection rates. Good sample type with low extraction and pre sequencing QC failures and low contamination Good quality WGS
Heel prick EDTA	82	5%	2.4%	8,868ng	75% easy 11% difficult 14% not reported	6m40s (2 Min, 15 Max)	Not required unless baby was having a sample taken for another purpose	Taken after sample for medical purpose so some difficulty due to low volume. Sequencing failures only occurred when insufficient volume of blood provided. Low extraction and QC failures. Low contamination reported. Good Quality WGS.
Heel prick DBS	127	2%	0%	402ng	63% Easy 5% difficult 32% not reported	7m (3 Min, 15 Max)	Not required unless baby was having a sample taken for another purpose	Taken after sample for medical purpose Processed via crude Lysate extraction therefore no extraction QC's . No contamination reported. Good quality WGS
Buccal Swab	191	25%	11.5%	4,162ng	95% Easy 5% not reported	3m (1 Min, 10 Max)	9% mainly baby discharged before research staff could take sample	Easy and quick to obtain. High extraction and pre sequencing failures. Concerns around extraction protocol being investigated. WGS quality TBC

*Adjusted for identified correctable processing errors

Summary of findings and implications for the Generation Study

Of the two non-invasive sample types – cord blood and buccal swab – cord blood performed considerably better where the sample was taken. Cord blood produced greater DNA yield but sampling was not possible in 20% of births in the study. Sequencing failure rate was approximately one percent and failure due to contamination was 2.3%. Buccal swab had a 20-25% failure rate on sequencing and 12% DNA cross-contamination.

In terms of heel prick, heel prick into EDTA tube (via capillary) performed well with very low sequencing failure rate (one percent) and was straightforward logistically. Heel prick on Day 0 onto dry blood spot and on Day 5 using either method was more challenging logistically and had a higher failure rate on Day 5 (i.e., when taken after the routine newborn screening heel prick sample). Of note, feedback as part of our co-design with families and concern that the programme does not interfere with the existing screening programme and preference for early sampling to achieve more rapid return of results, argues against combination with day 5.

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. 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.

5. Programme Aims, Protocol Scope and Study Questions and Outcomes

Overarching aims of the Newborn Genomes Programme and Protocol Scope

The Newborn Genomes Programme has three overarching aims:

1. To evaluate the clinical utility, operational feasibility, acceptability and positive and negative impacts of screening for a larger number of childhood-onset rare genetic conditions in newborn babies using whole genome sequencing, and providing ongoing patient support and diagnostic and care pathways, through the Generation Study.

2. To support healthcare research and understand how, with consent, genomic and health data could be used for research in the newborn setting to enable new diagnostic discoveries and treatments to be developed

3. To explore the potential risks, benefits, and broader implications of storing an individual's genome over their lifetime (e.g., potential for preventative steps, personalised risk-based screening in later life etc.)

These aims will be delivered jointly through the this protocol and the National Genomics Research Library Protocol[151]. In joining the Generation Study, parents will be consenting to their child joining the research under both protocols – see Section 7 (Recruitment and Consent).

This protocol focuses primarily on the development of evidence to allow policy makers to decide whether and how whole genome sequencing should be offered to all newborn babies.

The National Genomic Research Library Protocol will support broader research across all three aims of the study but be particularly crucial in supporting aims 2 and 3 where the emphasis is more on discovery than evaluation.

Study questions and outcomes

As stated above, the study focuses primarily on the development of evidence to allow policy makers to decide whether and how whole genome sequencing should be offered to all newborn babies. This requires the development of evidence across a broad range of areas that will sit alongside evidence available from other sources.

Working with the programme's Evaluation Working Group we have developed an approach that will. encompass economic modelling as well as process evaluation, impact evaluation across a range of areas and exploring both positive and negative impacts – set out in detail in Section 13 (Project Evaluation and Data Analysis) and Appendix A.

Together, the economic modelling and process and impact evaluation will explore research questions in four broad areas described below. Rather than isolated workstreams, these will be interlinked, for example with process and impact evaluation informing, providing inputs for and responding to the work on the economic model. This also means that modelling of the concepts used in different aspects of the work will take similar approaches.

The broad areas and the linked primary research question are listed below. The full list of research questions that link to these is set out in Appendix A.

1. **Feasibility, acceptability and uptake.** Is genomic newborn screening feasible and acceptable and would it be broadly taken up if offered as part of routine care?
2. **Test performance and clinical utility.** What is the clinical utility of genomic newborn screening as evidenced by the number of screen-identified diagnoses likely to benefit from intervention compared to standard of care alone?
3. **Cost effectiveness and positive and negative impacts.** What is the cost effectiveness of genomic newborn screening compared to standard of care alone?
4. **Experiences and attitudes.** What are families' and stakeholders' experiences and attitudes to genomic newborn screening?

While it is important to emphasise the breadth of research questions necessary to support policy decisions and therefore explored through the study, we have also identified the following primary and secondary outcomes (each linked to one of the areas above).

The primary outcome is:

- To determine the clinical utility of genomic newborn screening as evidenced by the number of screen-identified diagnoses likely to benefit from intervention compared to standard of care alone.

The secondary outcomes are:

- To determine the feasibility and acceptability of genomic newborn screening in the NHS utilising mixed-method approaches to assess study implementation.
- To determine the cost effectiveness of genomic newborn screening compared to standard of care alone, supported by a health economic model developed to support the programme.
- To determine whether families' and stakeholders' experiences and attitudes are supportive of the adoption of genomic newborn screening.
- To determine any differential areas of positive or negative impact of genomic newborn screening related to indices of diversity including ethnicity and socio-economic deprivation.

The exploration of the research questions and realisation of these outcomes – and the assessment of feasibility and acceptability in particular – requires an extensive, multidisciplinary project evaluation drawing on a range of specific expertise in newborn screening and implementation and behavioural science. Therefore, as well as external experts on economic modelling, Genomics England will engage an Evaluation Partner to undertake this work with us.

We will co-create an Evaluation Protocol with our Evaluation Partner with external advice including from the UK National Screening Committee. The Evaluation Protocol will govern and set out the work and analytical plans in detail including any additional participant-facing materials related to this work e.g., on interviews and questionnaires with participating families.

6. Methodology

This is a quantitative, longitudinal birth cohort study. The study has been approved by the Health Research Authority (IRAS number: 324562). We will recruit newborn babies and their mother/birthing parent, from whom we will source data relevant to the pregnancy (at one timepoint) and child (longitudinally). Recruitment will take place from a subset of maternity units across England with the potential to expand to other Nations of the UK in the future. The study began recruitment in April 2024 and the end date for study activities is 30 June 2027.

All babies recruited to the study will receive the study intervention – whole genome-led newborn screening – in addition to standard of care. The study will take an observational, quasi-experimental approach with comparator data drawn from babies born at centers not recruiting to the study.

This approach was developed under the guidance of the programme's Evaluation Working Group. An observational quasi-experimental model is preferred because it permits generation of good comparator data with greater statistical power across a range of research outcomes, with larger comparator data sets available for a number of key datasets e.g., outcome data on children diagnosed with the rare conditions that the study will return findings on. See Section 12 for description of Data Flows and Data Collection and Section 13 for description of Data Analysis and Project Evaluation.

Inclusion and exclusion criteria

- Inclusion criteria
  - Mother / birthing parent aged 16 or over.
  - Mother / birthing parent must have parental responsibility for baby
  - Mother / birthing parent is registered with a GP in England
  - Singleton birth

For those with complicated births or early postnatal periods, for example where admission to NICU is necessary, final sampling decisions will be made on a case-by-case basis at the discretion of the research staff and with the NHS clinical team – as well as consent from the parent(s). Births from an egg or sperm donor are eligible, provided the pregnant person will also have full parental responsibility.

- Exclusion criteria
  - Mother / birthing parent under 16
  - Mother / birthing parent who will not have parental responsibility for the baby (Babies who are being adopted)
  - Mother / birthing parent lacking capacity to provide informed consent for any reason
  - Mother / birthing parent who do not give birth in one of the recruiting hospitals
  - Mother / birthing parent who do not have an NHS number
  - Mother / birthing parent who is serving time in prison

In the initial rollout of the study we will exclude multiple births. We will seek to include these in the study as soon as our core processes are established and we feel the processes are robust enough to support them.

Sample size

Determination of sample size was aligned to the primary outcome of the study, to determine clinical utility of genomic newborn screening, and focusing on one component of it[152] - evidence of the potential incidence range of genetic diseases where early intervention is likely to improve outcomes in newborns in the UK population. As set out in Sections 6 and 13 in more detail, the primary outcome is one of a suite of strands of evidence that the study aims to generate to support policy decisions in this area.

The work carried out by the Genomic Analysis in Children Task and Finish Group estimates that between 1 in 457 and 1 in 686 live births would be affected by a disorder that:

- Is not part of current newborn screening
- Has a treatment available within the first five years of life that impacts substantially on mortality or morbidity

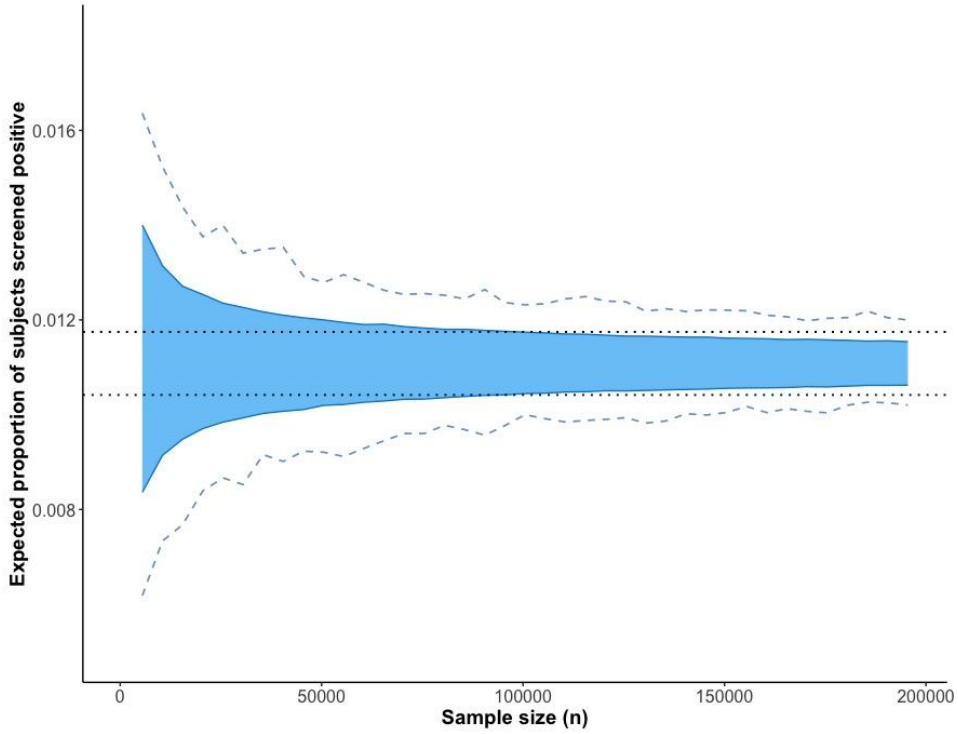
The required number of participants to be 95% certain that the incidence estimate from the study will be between the middle point of an estimate, 1/572 +/- 6% error, is approximately 105,000.

The sample size calculation to estimate this incidence of genetic diseases was based on the normal approximation to the binomial distribution with simple random sampling assumed[153]. For the sample size calculations the proportion of subjects screened positive was assumed to be 0.011, and it was derived from an estimate of the true population incidence, the middle point of the estimate, 1/572, by using the sensitivity of detection of 65% and specificity of detection of 99%[154,155]. Dropout rate was assumed to be 10%. The sensitivity of detection of 65% and specificity of detection of 99% used in calculations is the lower bounds of the estimates obtained during bioinformatics prioritisation algorithm modelling. Expected specificity is discussed in more detail in Section 10. We note that sample size calculations for estimating prevalence in rare conditions are highly sensitive to the assumptions of test performance metrics, in particular the assumption on specificity[156]. Therefore we will update the calculations before the study, when the list of conditions is finalised and sensitivity and specificity modelling for those conditions is complete, as well as monitor and update throughout the study. In addition, throughout the study we will be updating the calculations to monitor that the sample size is sufficient to evaluate expected study-wide true positive rate. See section 13 for more information.

To validate the sample size calculations further and to understand the behaviour of sample size in relation to other parameters, Monte Carlo simulations using a range of true population incidence, sensitivity and specificity were performed. An example of simulation, assuming 65% sensitivity, 99% specificity and 1/572 true incidence is depicted in Figure 5.

Figure 5 – An example of the Monte Carlo simulation of two-sided 95% confidence interval for the proportion of subjects screened positive assuming 99% specificity and 65% sensitivity. For each value in the sample size, the expected proportion of subjects screened positive was computed from a binomial distribution 15 000 times. The final confidence interval is obtained by clipping 95% of the values among the 15 000 (filled area). The dashed lines show the maximum and minimum values of the obtained proportion of subjects screened positive for each sample size. The dotted lines indicate the expected proportion of subjects screened positive +/- 6% error margin.

Figure 5 – An example of the Monte Carlo simulation of two-sided 95% confidence interval for the proportion of subjects screened positive assuming 99% specificity and 65% sensitivity.



Site selection and delivery

The study will be delivered through a select network of NHS Trust sites. The study will start with six trusts over a 4-6 month period to ensure the design of the study is working as expected before it is expanded to the number of trusts required to deliver the full sampling size. Provisional modelling has suggested that this could be up to 25-40 trusts but part of the initial implementation will involve monitoring of the consent and sample rates to identify the final number required.

Our site selection aims to ensure successful delivery of the study with a particular emphasis on ensuring diversity of participation. Criteria to determine which sites to approach to be part of the first six centered on:

- High birth volumes
- High percentage of births in hospital setting
- Level of diversity of patient reported ethnicity compared to national average
- Level of socio-economic deprivation compared to national average
- Previous engagement in the 100,000 Genomes Project, other national genomics research or the Baby and Mum Sample Study
- Track record of maternity research
- Nature of population served – urban vs rural
- Support of Trust leadership to participate in the study factoring in capacity of maternity service to support recruitment

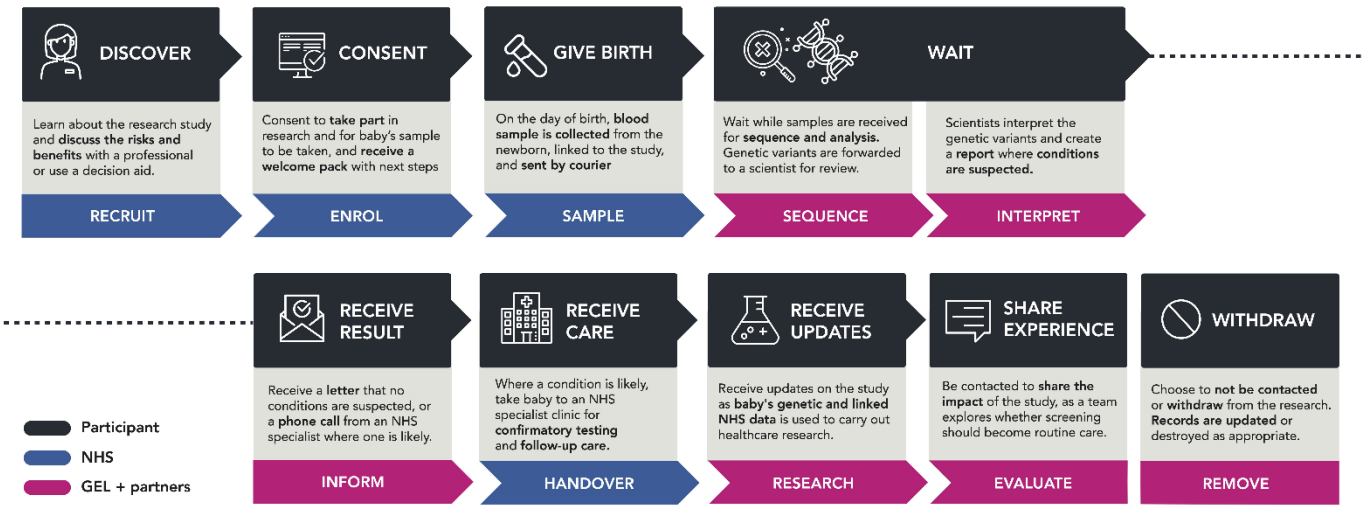
These criteria will be used to identify trusts to participate in the further implementation and scale up but a critical factor will also be ensuring we are gathering evidence in different types of trusts e.g. rural vs city, less genomically aware trusts etc.

Potential participating trusts will be approached consecutively, and invited to take part in the study. Diversity within the sample will be promoted through careful site selection, and aiming for a broadly representative sample of babies born in the country.

End-to-end participant experience

In the following sections, the different elements of delivery of the programme are described. The end-to-end experience form the participants' perspective is shown in Figure 6.

Figure 6 – Participant experience



7. Recruitment and Consent

Introduction

Genomic medicine and research presents important and practical challenges which require careful ethical consideration. These include the complexity and uncertainty of genomic information, implications for the wider family, and the link between research and clinical practice.[157],[158] The study will follow established legal and regulatory standards for seeking informed consent of its participants, or those who would consent on their behalf, in this case, someone with legal parental responsibility providing consent on behalf of the newborn. [159,160]

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 (this Protocol), and to participation in the National Genomic Research Library (the NGRL Governance Framework) for ongoing data linkage and wider research.

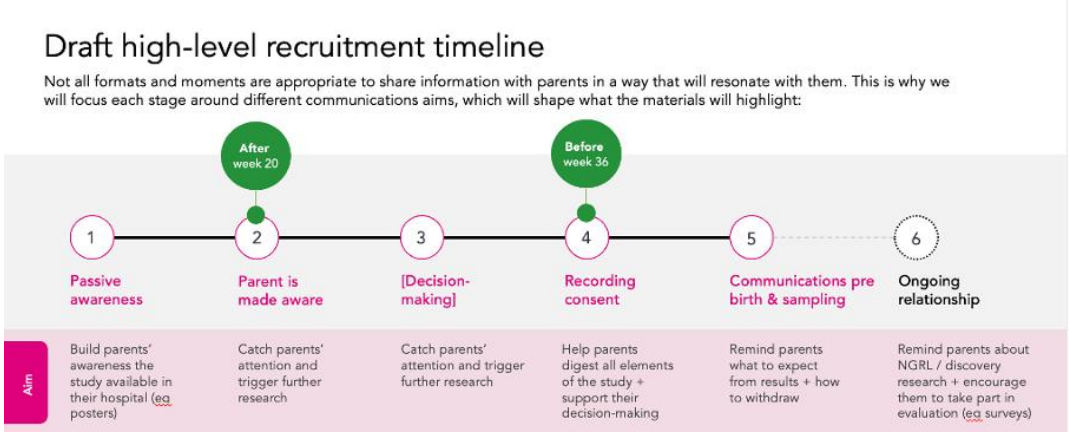
In conventional terms, as was the case with the 100,000 Genomes Project and National Genomic Research Library, a 'broad' consent model is proposed whereby permission is given for future research. The exact nature of this future research may as yet be unknown; however, it will fall within the boundaries of acceptable uses as outlined in the National Genomic Research Library protocol. Further detail about the model of consent for this study and it's ethical underpinnings can be found in Section 17 (Regulation, Ethics and Legal Considerations).

The process of recruitment and consent

Recruitment may take place across a number of settings. Whilst the mainstay of recruitment is study hospitals, mothers/birthing parents may also be approached to participate at smaller antenatal clinics. It is critical that these clinics routinely provide standard NHS care for the recruiting Trust. Study-trained Trust research staff should still perform the consent activities at any outsourced clinic via the research team and trained clinical healthcare professionals at each study site. Samples should still be procured according to the samples collection procedures detailed in Section 8.

The process for recruitment aims to maximise time and opportunities for parents to make an informed decision about their child taking part in the study during pregnancy, given the need to collect, sequence and analyse samples in a timely manner after birth. The exact process may vary in each study site; a general overview of the recruitment and consent process can be found in Figure 7. Further information about how public, patient and professional insights have shaped the recruitment and consent process can be found in Section 4 (Stimulus and development of this programme).

Figure 7 – The process of recruitment and consent



Passive awareness: parents may learn about the study by viewing study materials (e.g., seeing a poster or leaflet, viewing the microsite, or receiving social media communications about the study), through word of mouth or community-specific initiatives led by site study teams. If they are interested in taking part, they will be directed to speak to their study team who can support them with decision making and recording consent. In some cases, potential participants may find out about the study if they are sent a text message using Generation Study wording, or they may see notifications on maternity groups like Badger net.

- **Initial approach:** a member of the site study team may pro-actively approach parents from around 20 weeks' gestation to invite them to participate in the study. This may include when they are attending their 20-week anomaly scan appointment where an approach may be made in the scan waiting room. Site study teams will be aware of study exclusion criteria to minimise approaching parents who would not be eligible to take part. Parents will be given a copy of the study leaflet or patient information sheet (depending on the amount of time available to have an initial discussion about the study), and signposted to the study microsite/digital information sheet. Parents will be asked for permission to be contacted by the site study team to further discuss participation. It should be noted that in some cases potential participants may be approached at a later stage in pregnancy, and in other those in early pregnancy who have heard about the study and expressed interest in participating may provide consent.

- **Time to consider:** parents will be given time to consider participation in the study by reviewing hard-copy and digital resources (see section below), and to ask any questions they have about the study by speaking with a member of their study team. Parents may decide to take part on the same day when they are initially approached about the study, or may want more time to consider. Participant materials and study teams will highlight the importance of discussing participation with others with parental responsibility such as the baby's other parent (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. Drop-in information sessions (run face to face or virtually at site or national level) may also be used to provide further information about the study.

- **Decision making:** prior to delivery, parents will be contacted by the site study team (including by telephone or face to face at hospital appointments) to confirm eligibility, ensure provision of information about the study and answer any questions. More than one conversation may take place, depending on individual parent needs. Some potential participants may be approach in induction of labour wards or in late pregnancy. A specific pathway has been developed to facilitate this – detailed at the end of this section.

- **Recording consent:** if and when the parent agrees to take part in the study, they will review the study consent form with a member of the site study team and their consent decision will be recorded in a secure data capture system along with demographic information. Consent may be recorded in a face to face consultation, or through verbal agreement following a telephone or video consultation. The method of recording consent will depend on processes at the study site, and availability and convenience to the parent. Study staff will confirm the identity of the individual they are speaking to, including name, date of birth and relationship to the unborn child. Once consent has been received, parents will be informed that they will receive a record of their consent along with a letter welcoming them to the study, either by email following the telephone or video consultation, or in hard copy following a face to face appointment. A copy will also be included in the mother / birthing parent's hospital patient record. The duration of storage of these records will be at the discretion of each Trust, and will exceed five years, in line with Good Clinical Practice expectations.

- **Registration and data collection:** participants will be enrolled by the site study team using a Genomics England-provided web-based application. The application will also be used for registering sample details post birth. The users of the application will be authenticated via systems conforming to standards expected for the data held in the system (e.g., NHS Care Identity Service 2 and Role Based Access Control applied). The data collected during enrolment will be limited to that required for capturing consent, demographic details, number of expected babies and language requirements to facilitate return of results. To ensure consistency with NHS data, the application will query the Personal Demographics Service (PDS) Spine when collecting demographic data on the participant. Demographic data on the babies after birth will be received via NEMS notifications and stored in the application.

- **Sample collection:** at the time of sample collection on the day that the baby is born, site study teams will allow time for any further questions and obtain consent to take the study samples, ensuring parents are aware of the opportunity to withdraw from the study.

If parents have questions through the course of reviewing information about the study, they will be given the contact information of the team delivering the study at their hospital. They will also be able to contact Genomics England directly via the Genomics England service desk.

Each point of contact with parents throughout the process of recruitment (e.g., initial invitation to the study, conversations about participation) will be documented locally in hospital site records. Where it is not appropriate to offer the study to parents because they meet one or more exclusion criteria, this will also be recorded at site level.
Some parents may be approached at different points in time – for example, if an anomaly was found on the 20-week scan and parents are in distress, such that it was not appropriate to discuss a research study. In these instances, the site study team will use their expert judgement, and liaise with other clinical colleagues as appropriate, on the suitable timing for asking parents to take part. In all cases, recruitment would only take place where parents can be given time to fully consider their participation and make an informed decision.

Where there is a known history of a genetic or other condition, site study teams will be encouraged to ensure that standard of care processes are not disrupted and that referrals are made to relevant specialists as appropriate.

Study teams will be asked to record locally any information on numbers of participants approached vs consented. We will receive aggregated data on consent numbers as a numerator of those approached in order to determine the uptake rate of the study.

Pathway for recording consent post-partum

The Generation Study does not provide a formal post-partum consent pathway. However, we acknowledge the practicalities associated with conducting a witnessed consent close to birth and do allow for delayed recording of consent in the Generation Study Portal for mothers / birthing parents who deliver after having a verbal consent conversation antenatally (as detailed below).

This situation can arise, for example, when a mother / birthing parent has been advised to take time to reflect on the participation decision after a face to face discussion in late pregnancy, or when registering their interest for participation on the study website close to birth.
Parents should be made aware that participation may not be possible unless:

1. A consent conversation has been completed (to the extent that the 11 consent statements in the consent form have been discussed),
2. The birthing parent has been advised to take time to consider participation (acknowledging that this will vary person to person), and
3. The birthing parent has verbally expressed a willingness to participate. If an initial introduction to the study has been made but a consent conversation covering the main points in the consent form has not been completed by the time the baby is born (as outlined in the point above), the birthing parent would not be eligible to participate in the study. Potential participants should be made aware of this risk upfront.

Process

- A verbal expression of willingness to participate should be recorded in the patient notes to ensure visibility for the wider ward team and in line with usual expectation for clinical research interactions.
- If the baby is delivered whilst the potential participant (who has verbally expressed interest in participating – see point above) is reflecting on their decision, a cord blood sample should still be taken. Ideally, verbal ratification from the participant at the time should be sought before sampling. Otherwise staff should follow-up as soon as reasonably possible with the birthing parent to affirm their choice to consent.
- The sample can be refrigerated as per standard protocol
- Consent should then be formally recorded in the Generation Study Portal. This should include the date that verbal consent was taken, not the date entered into GSP (if different). This should happen as soon after birth as possible, but no longer than 28 days post-partum. If written authorisation cannot be sought within this period, then the sample should be discarded per local policy and the person will not be considered as enrolled into the Generation Study.

If the cord blood sample is missed the heel prick pathway can be followed only after the mother/birthing parent's formal consent is recorded in the Generation Study Portal

8. Sample Collection

Introduction

The Generation Study sampling strategy is based on the results of our feasibility study (see Section 4). This study demonstrated that cord blood was an ideal sample type. One sample of cord blood will be collected from each baby, this may take place in hospital, or at home if it is a home birth. NHS England encourages mothers/birthing parents to deliver at home where it is safe to do so.[161,162]

In some cases, obtaining a cord blood sample may not be possible, for instance where there is an emergency c-section. However, it is important to facilitate the collection of a sample where it is safe for the baby. In these cases a heel prick sample may be taken or, if the baby is admitted, a sample may drawn from an indwelling line.

Importantly, the procurement of any sample other than cord blood is at the discretion of the research teams, in collaboration with clinical teams. Safety of the baby is paramount. Parents should be informed of the risks of sampling in advance, and verbal parental consent for a secondary sample (heel prick or blood from an indwelling line) should be sought. Secondary samples must be procured as close to birth as possible. If this is not possible, recruiting centres will be asked not to carry out heel prick sampling in the home context until after the Newborn Blood Spot test has been taken, to avoid the risk that parents might conflate the Generation Study sample with the Newborn Blood Spot standard of care.

For sites: Please refer to the separate study sampling guide for recruiting sites for details relating to sample collection, local processing and shipping. All NHS staff at recruiting sites handling study samples should adhere to the guidelines in this supporting document.

More detail on each sample type is provided below:

Preferred sample - Cord Blood

- Can be obtained from babies born in hospital and those born at home.
- Should be collected by a trained member of research or clinical staff just after the birth, on Day 0.
- Approximately 3mls should be obtained by needle aspiration and placed in an EDTA tube.
- The sampling of cord blood poses no risk to the mother / birthing parent or the baby.

Secondary sample - Heel Prick

- Can be obtained from babies born in hospital and those born at home, where it has not been possible to collect cord blood
- The sample should be taken as close to Day 0 as possible.
- *Heel prick sampling will be at the discretion of sites and depending on capacity. Heel prick sampling must* ***not take place on the same day as the Newborn Blood Spot test is carried out (usually day 5)***
- Before a heel prick is taken, parents should be informed the cord blood has not been collected. The risks of the heel prick (mainly brief pain for the baby) should be explained.
- Parents should be invited to opt-out of a heel prick, however must be made aware that this would also constitute a withdrawal from the study as we will not have a sample to sequence.
- The blood may be collected into an EDTA capillary tube or an EDTA microtainer.
- The latest a sample can be taken AND registered is 28 days after birth. After 28 days the participant will be automatically withdrawn from the study if no sample has been registered and will be issued communication to reflect this, from Genomics England.

Secondary sample for hospitalised babies – Blood from indwelling line

- Can be obtained from a hospitalised baby with an indwelling line where it has not been possible to collect cord blood
- Sampling will be at the discretion of the research team in collaboration with the treating team
- Before this sample is taken, parents should be informed that cord blood has not been collected.
- Parents should be invited to opt-out of sampling from an indwelling line, however must be made aware that this would also constitute a withdrawal from the study as we will not have a sample to sequence.
- Sample volume should not exceed 1ml
- The blood may be collected into an EDTA capillary tube or an EDTA microtainer.

Baby born at a different hospital than planned

In cases where a consented participant delivers at a different hospital to their planned delivery hospital:

- If the delivery hospital is **not** participating in the study, the cord blood sample will not be taken. The hospital that originally consented the participant may invite the participant back to give a heel prick sample. If a heel prick sample is not obtained within study timelines the participant will be withdrawn or removed from the study.
- If the delivery hospital **is also** participating in the study, the delivery hospital must confirm consent by checking the Generation Study Portal, and/or checking with the hospital that

consented the participant. If consent is confirmed, the delivery hospital may take and dispatch the cord blood sample as normal.

Sample processing at site

All sampling equipment will be provided to the study site by Genomics England. Samples will be refrigerated at 2-8˚C until transported to a central processing facility for DNA extraction. Data collected during sample registration shall be limited to that required for sample identification and collection source (i.e., cord blood or heel prick). Samples will be labelled with barcodes at the time of collection, also supplied by Genomics England and these will be linked to the participant record via a system provided by Genomics England.

9. Sample processing, DNA extraction, Quality Control, Sequencing and Storage

Laboratory arrangements

Sample processing, DNA extraction, quality control, sequencing and storage will be carried out by partner laboratories managed under contract and performing to agreed KPIs and meeting agreed standards and accreditation. This will include ISO15189 accreditation for sample processing, extraction and sequencing laboratories.

Sequencing platform

The study aims to develop 'modular' evidence for policy makers on sequencing as in other areas. For example, separating the evidence on the performance of specific sequencing platforms to detect a particular range of genomic variation from the evidence on the impact of using screening led by the detection of particular classes of genomic variation. This mirrors the 'technology agnostic' approach taken by NHS England in the NHS Genomic Test Directory.

To this end, we expect to perform sequencing using multiple platforms during the course of the study to enable the development of this evidence. Some of this sequencing will generate data used directly during the primary interpretation and return of findings process. Other sequencing will generate comparator data to provide research insights to assist evaluation of the relative performance of different platforms and approaches.

Sequencing used in the primary interpretation and return of findings process will use platforms for which there is validation data, accreditation and operational maturity of the sequencing platform and end-to-end tool chain for the range of germline variation required to drive identification of rare monogenic conditions. This is similar to the approach that Genomics England have taken in other programmes in which results are returned to patients, for example the use of illumina short read sequencing on NovaSeq instruments to depth ≥30X and ≥95% of the autosomal genome covered at ≥15X[163,164].

Through the course of the study, we will continue to evaluate other platforms and their associated tooling as they evolve for their suitability for newborn sequencing use cases and respond accordingly.

Sample transport and tracking

Couriers will be organised by Genomics England for collection and dispatch of samples to the laboratories responsible for sample processing, sequencing and storage. Samples will be tracked using the unique identifier information attached to each sample and a sample tracking tool provided by Genomics England. No identifiable data will be shared with partner laboratories.

All samples arriving in the laboratories will be accessioned appropriately into their designated laboratory information management system for accurate record keeping. The receiving laboratory will share a receipt confirmation with Genomics England and any issues or discrepancies in sample numbers will be resolved by Genomics England in engagement with sites and courier providers/biorepository and whole genome sequencing providers as necessary. Both biorepository and whole genome sequencing providers will need to meet ISO 15189 standards.

Sample processing, DNA extraction and quality control

All samples will need to be processed in the processing lab(s) to achieve contractually agreed KPIs that will include sample processing and DNA extraction timelines, QC metrics and according to agreed standards to achieve rapid both rapid sample processing and to maximise successful, high quality sequencing. Below, for illustrative purposes, we include the approach currently used for Genomics England programmes that use the illumina NovaSeq instruments for germline sequencing. These requirements will be updated as new evidence emerges and match the specific requirements of the sequencing platform being used.

Sample processing and DNA extraction

For blood samples, data generated from the Baby and Mum Sample Study (see Section 4) demonstrates that good DNA yield and quality for sequencing using illumina NovaSeq instruments can be obtained using Perkin Elmer's Chemagic 360 instrument (chemagic 360 Instrument for Nucleic Acid Extraction | PerkinElmer). Previously the same extraction method has been used for other Genomics England projects extensively, for example ~30k blood samples sent from multiple hospital sites using this instrument for COVID19 in at least two different processing labs with equivalent results[165].

For dried blood spot cards, data from the Baby and Mum Sample Study indicates that good sequencing quality on illumina NovaSeq instruments can be achieved via a lysis protocol using Illumina's purification beads, lysis buffer and Proteinase K (see page 40 Illumina DNA PCR-Free Library Prep Reference Guide (1000000086922) in combination with the illumina Tagmentation library preparation method using 6x3mm^2 punches.

On-bead tagmentation allows faster generation of sequence-ready libraries than other methods by simultaneously fragmenting the gDNA and adding the sequencing primers. It also allows the normalisation of the library without ancillary reagents or equipment; this method is ideal for low input samples as requires less DNA than TrueSeq PCR Free Library prep and also less hands-on time.

Extraction of Peripheral Blood Mononuclear Cells

As cord blood sample with a volume of ≥ 3ml arrive at the lab, a sub-set of these samples will be separated, and PBMC's will be extracted from residual blood, with the rest of the sample undergoing

WGS and analysis. If there is any cord-blood remaining after PBMC extraction it will be stored as residual blood.

The PBMC's will be stored and utilised for ongoing research into genes and health, as per the NGRL Governance Framework.

Quality control

Quantification of double stranded DNA is required for most process although not, for example, where a lysis extraction protocol is followed by PCR-Free library preparation. Methods such as picogreen and / or Qubit are recommended.

Purity assessment will also be performed to measure the OD 260/280 ratio. Multiple methods can be used to obtain a DNA purity estimate such as the standard cuvette spectrophotometer or a NanoDropTM Spectrophotometer.

Further measurement of DNA integrity will be performed to ensure the DNA extracted is not degraded, methods such as the Agilent's tapestation – automated gel electrophoresis solution to qualify and quantify nucleic acid samples or Femto Pulse system can both be used to assess DNA integrity.

Sequencing

Sequencing and data transfer

See the 'Laboratory arrangements' section above for a description of the process of selection of sequencing platforms and providers.

The whole genome sequencing provider(s) will deliver sequencing according to the contractually agreed processes and KPIs and meeting agreed standards and accreditation including ISO15189.

As part of the sample tracking process (described above), the provider(s) will receive necessary sample metadata, for example on DNA quality. The provider(s) will share all sample pass/failure data with Genomics England throughout the sample processing and sequencing operational pipeline. Any failures will require a repeat process using the already collected second sample, where available. Decisions on any failures will be made on per case based on alternative sample availability as appropriate. Where alternative sample is not available no further repeat work will be carried out.

The data generated by the sequencing provider(s) will be transferred encrypted to Genomics England via a dedicated link. Genomics England will capture quality metrics for each genome as well as monitor for systematic artefacts by checking for the presence of batch effects at different levels, as applicable to technology, such as plate, run, flowcell, DNA extraction batch or participant recruitment site to ensure that sequence data quality is maintained, any systematic deviations could be quickly identified, and corrective actions taken to aid improvements in processes over time.

Storage and use of residual samples and DNA

Residual blood or PBMCs and residual DNA will be stored for future quality improvement or research purposes, within the Genomics England Central Biorepository. Each set of samples sent to the Genomics England Central Biorepository should be preceded by a sample dispatch message identifying the sample as labelled. It should also include additional relevant sample-specific data such as concentration etc.

Residual samples will remain in storage at the Genomics England Central Biorepository for the duration of this study, and the way these might be used in future research studies is detailed in the NGRL governance framework. The parent providing consent to study participation is made aware of the potential future uses of stored DNA, and the duration of storage, in the Participant Information Sheet. The duration of storage will be until the participant reaches the age of 16, in which case they will be approached to consent independently, or until the residual sample is used up, whichever comes first.

10. Analysis, Interpretation and Reporting Strategy

Overall approach

As we note in Section 3 (Background), there is a range of true positive to false positive ratios observed in existing newborn screening programmes, as well as a range of risk thresholds for families to be called for additional confirmatory tests after first screening results. These thresholds depend on a large number of factors, including the nature and availability of confirmatory testing, clinical utility, impact of the condition if not detected early or before symptoms appear and health economics analyses. One of the objectives of this study will be to explore and define what is an acceptable and optimal of sensitivity and specificity rates for genomic newborn screening.

In line with the overall ethos of the study to take a cautious approach, and recognising the negative impact on children, families and the health system of high positive rates, the aim of our analysis, interpretation and reporting strategy is to achieve high positive predictive value and similar ratios of true positive to false positive findings to those observed in existing newborn screening.

We will take a two stage approach:

1. automated analysis
2. expert manual interpretation and reporting

If genomic newborn screening is to be feasible at population scale, the process must be scalable to and avoid the requirement for lengthy manual expert review of numerous variants. The automated analysis will therefore aim to identify 'candidate' variants that have a high probability of being reported after manual interpretation.

Foundations of our automated analysis

Our approach to genomic newborn screening automated 'bioinformatic' analysis is developed based on the experience from the 100,000 Genomes Programme and NHS Genomic Medicine Service[166],[167]. Genomics England bioinformatics systems for the NHS Genomic Medicine Service are accredited under ISO 13485 and ISO 15189 standards. As a research programme, the Generation

Study will not initially seek UKAS accreditation, but will adopt the same standards and rigour in the development processes as they are for the Genomics England accredited pipelines and systems.

Genome alignment and sequence variation detection

The sequencing provider(s) will deliver the genome data in the format of sequencing reads with associated base quality scores suitable for ingestion into the Genomics England bioinformatics pipeline. Sequencing read alignment and sequence variation detection will be performed using Genomics England bioinformatics pipeline.

The DRAGEN toolset from Illumina for alignment and variant detection was chosen after internal benchmark of multiple alignment and variant detection tools following best practice guidelines[168] , as well as reviewing the data available from external resources, such as the precisionFDA challenge "Truth Challenge V2: Calling Variants from Short and Long Reads in Difficult-to-Map Regions"[169]. The performance was robustly validated both following best practice guidelines for medical whole genome sequencing[170], including comprehensive validation for clinically relevant variants for all variant types that would be reportable in the programme. The results of the validation of performance of mapping and variant detection toolset to be used in the pipeline are available on request. Genomics England will routinely assess the quality of the mapping and variant calling and compare this against alternative algorithms to ensure the data has been processed with the best available pipelines.

Any new tool or version upgrade will be rigorously tested to ensure that the analytical performance is equivalent or improved before being incorporated into the pipeline.

To further ensure the quality of variant detection, Genomic England participates in external quality assurance (EQA) schemes suitable for whole genome sequencing, e.g. "Next Generation Sequencing (NGS) germline" scheme provided by Genomics Quality Assurance (GenQA)[171]. We will be regularly monitoring available EQA schemes for their suitability and enrol as appropriate. We are also working closely with GenQA on establishing bespoke EQA schemes suitable for genomic newborn screening.

It is possible that in the future sequencing providers will be able to deliver already-aligned genomes with variants called according to Genomics England specifications. If this strategy is adopted, the same requirements for quality assurance, meeting ISO 15189 standards for alignment and variant calling, and comprehensive benchmarking and testing will apply for externally provided alignments and variant calls.

Automated variant prioritisation

As stated above, the automated variant prioritisation will be optimised to maximise positive predictive value, aiming to minimise false positive findings while maintaining high sensitivity so that, when combined with the manual interpretation and reporting step, the study achieves a true positive to false positive ratio similar to that observed in existing newborn screening.

It is anticipated that the pipeline will prioritise variants in two categories:

1. Inclusion list variants
2. Highly deleterious (e.g., predicted loss of function) rare variants, where this mechanism is consistent with the relevant gene and condition

Variants that fall into either of these categories will only be passed on to the manual interpretation stage if they fit with the pattern of inheritance of the relevant gene and condition e.g., two variants consistent with homozygosity or compound heterozygosity for autosomal recessive inheritance.

Inclusion list variants

The pipeline will identify variants that are in an "inclusion list" of variants that have high evidence of causing conditions included in the screening in the patients with those conditions, e.g. those that were classified as pathogenic or likely pathogenic in the patients with the conditions from the screening list using ACMG[172] and ACGS[173] criteria. The variant inclusion list will be drawn from external knowledgebases, such as ClinVar[174], publications, and/or external variant curation and interpretation providers through competitive tendering. The quality of the inclusion list will be assessed before it is being used by the prioritisation algorithm.

Highly deleterious rare variants consistent with the disease mechanism

The pipeline will also identify highly deleterious variants compatible with the disease mechanism. For example this will identify rare variants very likely to cause protein loss of function in the genes where protein loss of function is a known disease mechanism and where the variants match the mode of inheritance for the condition.

Variant phasing

We note that because the study will not collect parental samples up front, in some cases it will not be possible to determine whether the variants found in a baby follow the expected mode of inheritance because short read technology does not enable phasing heterozygous variants unless they are in close proximity (within the same fragment). To quantify this we have performed modelling in ~35,000 adult individuals in the National Genomic Research Library largely recruited for reasons other than a rare condition. This analysis showed that this scenario, where candidate high risk compound heterozygous variants in biallelic genes will be indistinguishable from two heterozygous variants *in cis* will be expected only in ~0.1% of participants, and therefore will not cause a major increase in false positive cases. For the cases where it is not possible to distinguish *cis* and *trans* phases, the follow up testing will be arranged to determine the phase using the most appropriate method (e.g. inheritance analysis in a family, or long read sequencing). This, depending on condition and urgency of testing and possible interventions, may be done before or in parallel to other orthogonal testing, such as metabolic testing.

We will continuously monitor and fine tune the performance of automated filtering to incorporate new knowledge about conditions, genes and variants, as well as adapt to sequencing technology and alignment and variant calling specifics (e.g., remove recurrent technical artefacts).

Analytical validity

In addition to genome-wide benchmarking of mapping variant detection and prioritisation toolsets, the analytical validity will be assessed for every gene proposed to be included in condition list (see Selecting conditions and supporting governance in Section 4).

The term analytical validity refers to how well a test predicts the presence or absence of a particular genetic change or a group of changes[175,176]. To assess analytical validity for the testing of the genes

selected for newborn screening, we need to estimate sensitivity and specificity if the test is going to be included in the newborn screening.

Where suitable datasets or samples from the patients with relevant conditions are available, we will use them to directly assess the sensitivity of our approach. Due to extreme rarity of many conditions, we anticipate that for many conditions we will not be able to directly measure sensitivity. In those cases, we will use other metrics that informs us about expected sensitivity of the test. Those metrics reflect "callability" of genomic region and inform how well clinically relevant variants are expected to be detected in a particular gene. The metrics include but are not limited to the assessment of gene coverage by well-aligned sequencing reads, the proportion of known pathogenic and likely pathogenic variants associated with the chosen condition in the gene regions with good coverage and detectability of specific variants that account for the large proportion of cases.

Specificity will be assessed by estimating the frequency of potentially reportable variants in the large cohort of individuals largely without rare diseases. Both internal Genomics England datasets from different project of individuals with appropriate consent, and external datasets e.g., UK Biobank can be used for this assessment as required.

The analytical validity will be reviewed if changes significantly affecting variant detection or prioritisation are introduced into the pipeline (e.g., a change to read alignment algorithm, a change to sequencing technology).

We will continuously monitor variant prioritisation performance to rapidly incorporate leanings from the programme into variant prioritisation algorithm.

Expert manual interpretation and reporting

Our modelling indicates that the cautious approach we are taking means that only a small minority of participants will have any variants prioritised by the pipeline.

Participants with no prioritised variants

For participants where genomic data passes quality checks but no variants are prioritised by automated filtering, a "no conditions suspected" result will be issued without manual review of the data.

Participants with one or more prioritised variant

Accredited clinical scientists working under research governance will review any variants prioritised using a tool provided by Genomics England. This will involve reviewing quality of sequencing data, such as read alignments, coverage to exclude possible technical artefacts, and reviewing available evidence for variant pathogenicity following ACMG/ACGS guidelines. The Clinical Scientist(s) will make a decision whether the results need to be reported. Where this is the case, a 'condition(s) suspected report' will be created and the relevant clinical pathway triggered, which will include confirmatory testing. Where the variant(s) do not merit reporting, a 'no conditions suspected' report will be created. The results will be returned as described in the Section 11.

Modelling to guide the variant prioritisation strategy

To test our assumptions and chosen strategy, we modelled our approach using a dataset of ~35,000 adult individuals in the National Genomic Research Library largely recruited for reasons other than a rare condition. While the list of conditions and genes is not finalised, for the initial analysis we use the gene list available at rx-genes.com (July 2022)[177] . A total of 739 genes with different modes of inheritance (148 autosomal dominant, 484 autosomal recessive, 66 dual modes of inheritance and 41 X-linked) were included in this exploratory analysis. We note that a considerably smaller number of genes are going to satisfy condition selection principles, therefore our initial analysis is overestimating expected numbers of potential false positives and represents the "worst case" scenario e.g., some of the genes in the Rx-genes database are associated with low penetrance or have variable or later onset, and therefore pathogenic variants in those genes are expected to be detected. However, for simplicity and to estimate "the worst case" we included all genes and assumed all individuals that carry variants that would be reportable as pathogenic or likely pathogenic were false positives following the automated process but prior to manual interpretation. Depending on the strictness of criteria used in filtering, we achieved 98-99.5% study-wide specificity from automated filtering outputs.

The specificity further increased after light-touch manual curation of automated outputs e.g., for autosomal recessive genes, the variants in 46% of samples were reclassified as non-reportable during manual review, e.g. because they were obvious technical artefacts or because they were reclassified as variants of unknown significance (such as some predicted loss of function variants in the last exons, or previously reported ClinVar likely pathogenic variants with insufficient evidence).

For autosomal recessive genes, the specificity after manual curation reached 99.8%. The lower specificity for autosomal dominant genes (98.2% before manual curation) was heavily driven by a small number of genes with a large number of pathogenic or likely pathogenic variants in ClinVar, with just two genes accounting for 25% of samples, and 15 genes accounting for 70% of the samples with P/LP variants. Upon inspection, none of those genes are likely to pass conditions framework principles to be included in the programme. Although many of the autosomal dominant genes will not pass conditions selection by failing principles because of low penetrance and/or age of onset, our specificity modelling will feed into analytical validity assessment and the genes that present a risk of materially reducing study-wide specificity will not be included.

We also note, that for a small number of individuals, where relevant phenotype data was available in the National Genomic Research Library, we were able to confirm the presence of the condition, and thus reclassify them as true positives, however we did not include those into the assessment, because the phenotype data was not available for the majority of individuals.

Based on this preliminary analysis, we estimate that the study-wide (i.e. for all genes combined) specificity of 99.5% or higher is achievable. The estimate of 99.5% specificity, assuming 65% sensitivity and study-wide conditions prevalence of 1:575. Reducing the gene list to the ones that satisfy conditions selection framework principles will further increase specificity. Of note, this modelling is based only on automated interpretation of results, and does not account for the effect of manual interpretation. We estimate that the number of children with a finding that would be returned to families would be <1%.

The data available from the Guardian study set out in Section 3 (Background) also provides useful estimation of the likely ratio of true positive to false positive findings at the point of returning findings to families. Analysis of the first 984 participants achieved a true positive to false positive ratio of

approximately 2:1 despite taking more inclusive (less specific) approach in reporting to that proposed in this study by including some variants of unknown significance (personal communication, W Cheung). Similarly to our modelling analysis, their experience show that these numbers are strongly driven by a small number of genes, e.g., 11/14 false positives to date were due to one incorrectly classified variant.

We will repeat study-wide specificity analysis, and perform sensitivity analysis using available genomic datasets of patients with the conditions when the conditions and gene selection is finalised, which will further enable to fine-tune variant prioritisation rules. We will also repeat the assessment of expected true positive findings based on existing knowledge of population prevalence.

11. Returning Results

Introduction

Parents will receive one of three results from the programme: 'No results produced' (where this has not been possible due to sample failure); 'No conditions suspected'; and 'Condition(s) suspected'. As set out above in Section 12, our modelling indicates that only a small minority of participants will have any variants prioritised by the pipeline , meaning that the number of children following the 'Condition(s) suspected' pathway will be <1%.

Preparation for returning results

In preparation for the return of results:

- Parent information and contact details will be obtained when consent takes place. These details will be used to return results. Parents will be advised to keep their details updated with the Newborn Genome Programme.
- Any language or accessibility needs for will be noted. Additional support or resources needed to return results will be considered. This may include translation and interpretations of communications.
- NHS Spine will be used during the return of results process to check whether the baby and mother / birthing parent are alive. If the baby or mother / birthing parent have died, this will be flagged and results will be returned via a non-standard pathway.

Sample failure – no results produced

As is the case when no sample has been taken or fails extraction, we will inform families if we are unable to generate results from the study. The content of the letter will be standard, but it will be personalised with the individual's name. Based on our sampling strategy and data from the Baby and Mum Sample Study, we aim for the sample failure rate to be <1%.

No conditions suspected results

'No conditions suspected' results will be sent to the mother / birthing parent via a letter. This will take place as soon as possible, within the first few months after birth. As well as stating the result, parents will also be reminded about the implications of their ongoing participation in the study, including continued use of samples and data for research and the potential for re-contact with study updates and opportunities for further research. The content of the letter will be standard but personalised with the individual's name. Genomics England will take all reasonable measures to ensure that

parents receive their 'no conditions suspected' results, and the Genomics England service desk will be available for parent queries.

The 'no condition suspected' results letter has been co-designed with parents and user tested. It will be translated into the predominant languages spoken across our study sites, and a letter in the appropriate language will be sent to parents. Participants who would like additional support to understand the letter are encouraged to speak with the local research team, call the service desk or use the study website. A copy of the letter will also be sent to the mother / birthing parent's General Practitioner so that they are aware of their participation in this study and may be a point of contact for future queries relevant to the child or family's health. This is outlined to parents in study information materials and consent, and information obtained through NHS Spine.

If a baby or mother / birthing parent is deceased, Genomics England will liaise with the regional coordinator to decide on the most appropriate way to notify the family of the result. This may include engaging a healthcare professional known to the surviving family (such as a bereavement midwife, the obstetric or neonatal consultant or the family's General Practitioner), and/or altering the wording of the 'no conditions suspected' letter appropriately depending on the family's situation. These decisions will be made on a case-by-case basis.

Condition(s) suspected results

Turnaround time

The target 'sample to answer' turnaround time for 'condition(s) suspected' results for the bulk of the programme 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 within first 9 months of programme starting. The target sample to answer turnaround time at the start of the programme will be 28 days.

This timeline reflects that most conditions will require urgent follow-up testing and treatment. Some babies may already be showing symptoms of the condition at this point and already receiving care.

Personnel

Through extensive consultation with NHS stakeholders, it has been agreed that a network of coordinators will work with clinical teams with expertise in the relevant condition(s) to facilitate the return of 'condition suspected' results and further assessment including non-genomic follow-on testing.

For clinical safety purposes, there will be mechanisms in place within the network to ensure that a result has been communicated to the family and feedback provided to confirm this. The network will also be used to obtaining feedback on the outcome of confirmatory tests (see section 12 – Data Collection).

The following roles will comprise the network:

- **Central coordinator:** Based at Genomics England, the central coordinator will receive 'condition suspected' results from the interpretation team and relay them to the appropriate regional co-ordinator, along with other relevant information and documentation.
- **Regional coordinators:** Based at regional level (mapped to the NHS GMSA regions), the network will include at least one regional coordinator. Regional coordinators will be responsible for maintaining a list of relevant specialists within the region and contacting

specialist teams urgently to inform them of a 'condition suspected' result. They will also follow-up with the relevant specialist team to ensure the result has been provided and to collect data on outcomes of further testing to support evaluation of the study. Regional coordinators will also be involved in liaising with screening laboratories where a result relates to a condition looked for in the NHS blood spot test, as well as patient support networks. They will supporting the specialist teams in providing support to parents through the return of results process.

- **Specialist clinical teams.** Identified through the conditions selection process with the support of the NHS Clinical Assurance Group (see Section 4), clinical teams with expertise in treating the condition in question will be responsible for communicating condition suspected results to the parents and arranging an urgent follow-up appointment to facilitate confirmatory testing. The confirmatory test will be condition-specific so clinical pathways will vary depending on the condition which is suspected. Specialist teams are expected to comprise healthcare professionals, including paediatric consultants and clinical nurse specialists, as well as broader members of multi-disciplinary networks including genetic counsellors, psychologists and allied health professionals.
- **Other healthcare professionals.** Other healthcare professionals may be involved in the return of results process, but this may be condition and/or location specific. Where there are challenges in communicating results to families or seeing them to arrange follow-up tests, a multi-disciplinary approach will be taken between the regional coordinators, specialist teams and Genomics England to address these on a case by case basis.

Process

The process for return of condition(s) suspected results will be as follows

1. **Report generated.** The dissemination of a condition suspected result through the network begins with a 'condition suspected report' is issued to the central coordinator at Genomics England following interpretation.

2. **Report sent to regional coordinator.** The central coordinator will send the report to the appropriate regional coordinator with the parental contact details, a communication checklist and a template results letter. They will confirm receipt of this information.

3. **Regional coordinator contacts specialist clinical team.** The regional coordinator will then contact the local specialist urgently and passes on the suite of information.

4. **Specialist clinical team contacts parents.** The specialist clinical team will then contact the parents, and arranging an urgent appointment including for confirmatory non-genomic testing. The expected timeline for the initial phone call and appointments will be in line with the condition's clinical pathway as agreed and supported by the governance of the NHS Clinical Assurance Group.

5. **Clinical follow-up and ongoing care.** The specialist clinical team will arrange initial confirmatory testing and ongoing follow-up and care in line using the agreed clinical pathway for the condition according the relevant routinely commissioned services and using their expert clinical judgement. Further information about support is outlined below.

   Note: the governance of the process will fall under usual clinical governance for the clinical pathway in question from the time that the family have been contacted by the clinical team.

To ensure that condition suspected results are understood, any specific accessibility or language needs will be noted when consent is given, and this information will be communicated to the network who will use usual local processes to support families' needs.

6. **Tracking return of results.** The regional coordinator will contact the central coordinator at Genomics England to allow central tracking of the result return process. A feedback loop will ensure that Genomics England is notified when the parents have received the result, and the outcome of further confirmatory tests.
   If the parents cannot be contacted, the specialist clinician will be responsible for taking all reasonable steps to make contact. This may involve support from the regional coordinator, the local midwifery team or the family GP.

7. **Study Specific Information.** Parents will also be sent study-specific information as is similarly communicated to participants with a 'no condition suspected' result. This includes the implications of their ongoing participation in the study, including continued use of samples and data for research and the potential for re-contact with study updates and opportunities for further research.
   Study specific information will be sent by the study team separately and at a later date than the initial information about the baby's result. This is to avoid overloading parents with non-essential information when they receive their initial 'condition suspected' result.

Supporting materials

The following supporting materials will be available to facilitate the return of condition(s) suspected results:

- A communication checklist for the clinician contacting the family to deliver the condition suspected result, adapted from Chudleigh et al 2021[178].
- A Template Results Letter for the specialist team to send to the family following contact above, adapted from Chudleigh et al 2021[179].
- Condition-specific information that can be made available to parents (including signposting to relevant support groups). These will be honed with input from specialists and rare disease charities as part of the Communication of Results and Onward Support Working Group.

Follow-up, support for families and ongoing care

As set out above, ongoing care will be under clinical governance and follow the pathways agreed for each condition as agreed and supported by the governance of the NHS Clinical Assurance Group. This includes assurance of the availability and capacity to support each family that receives a 'condition suspected' result.

Based on the results of further confirmatory tests, the specialist team will initiate next steps regarding treatment and management as appropriate, guided by the established treatment pathway and clinical judgement. This will include confirmatory genomic testing using the usual testing approach (as set out in the NHS National Genomic Test Directory)[180].
Other healthcare professionals including health visitors and GPs often provide support for families, and we will be providing wider training and engagement to ensure this can be facilitated. In addition, we are continuing to work with rare disease charities and support groups who provide an important source of support for families living with rare conditions.

Guidance will be provided from Genomics England (co-developed with the Communication of Results and Onward Support Working Group) to outline support needs that should be facilitated, including in complex cases when a case-by-case approach may be needed. Genomics England will ensure that results are transmitted promptly to the specialist clinician via the pathways described above. Feedback mechanisms will be in place so that Genomics England is notified that a family has received the result, and the outcome of further confirmatory tests.

Managing uncertainties and psychosocial impact of results

We are targeting high positive predictive value and focussing on conditions where there is a defined NHS pathway and working case definition agreed through the NHS Clinical Assurance Group. Nevertheless, there are ways in which families may experience distress or uncertainty, as is the case with the current NHS screening programme. These include:

- The psychosocial impact of receiving a condition suspected result or diagnosis of a condition
- Where confirmatory testing indicates that the baby does not have the condition (false positive)
- Where confirmatory test results are uncertain, such that a diagnosis cannot be confirmed or ruled out
- Where the onset and severity of symptoms vary or cannot be specifically predicted for each individual
- Where the timing of the initiation of treatment may vary (from immediately to later in infancy or early childhood)
- The wider familial implications, for example:
    - where parents may be carriers for an autosomal recessive condition, impacting future reproductive decisions;
    - where siblings are also identified to have the condition
    - where parents are identified to have a health risk (e.g., where a child is diagnosed with Fanconi Anaemia and parents are each heterozygous for a *BRCA2* gene variant, putting them at increased risk of adult-onset cancers where preventative screening is available)

The specialist team will ensure that condition-specific and broader support needs are facilitated, including where a false positive result is identified and the child would not require ongoing medical management. This includes genetic counselling to address the psychosocial, lifelong and familial impact of the result, as well as referrals for other family members where there are health implications for them.

Where the baby is already deceased

As set out in the 'Preparation for returning results section' above, the NHS Spine will be used to check that the baby and mother / birthing parent are still alive before disseminating results. If the baby is deceased, the result will be returned to the regional coordinator, who will identify the baby's lead clinician prior to their death (if there was one) and the General Practitioner. Together, they will plan for returning the results to the family, which may also require input from a specialist clinician with experience of the suspected condition. Clinical judgement will be required to assess whether the suspected condition may have played a role in the baby's death or if they died from an unrelated cause. Parental testing should be arranged if clinically indicated and the family should be referred for genetic counselling if they are at risk of having another affected child in the future.

Safeguarding

Where a baby is not brought for their follow-up appointment and safeguarding concerns are raised, clinicians should refer to their local hospital's policy and seek advice from the Trust's pediatric safeguarding lead as appropriate.

Limitations of the return of results strategy

Although we have made every effort to address and prepare for any eventuality in returning condition suspected results, circumstances that have not been anticipated may arise. In these circumstances, decisions will be taken on a case-by-case basis, in collaboration with the results network and aligned with our results return pathways. The best interests of the participating infant will be foregrounded, and necessary expertise called engaged if needed.

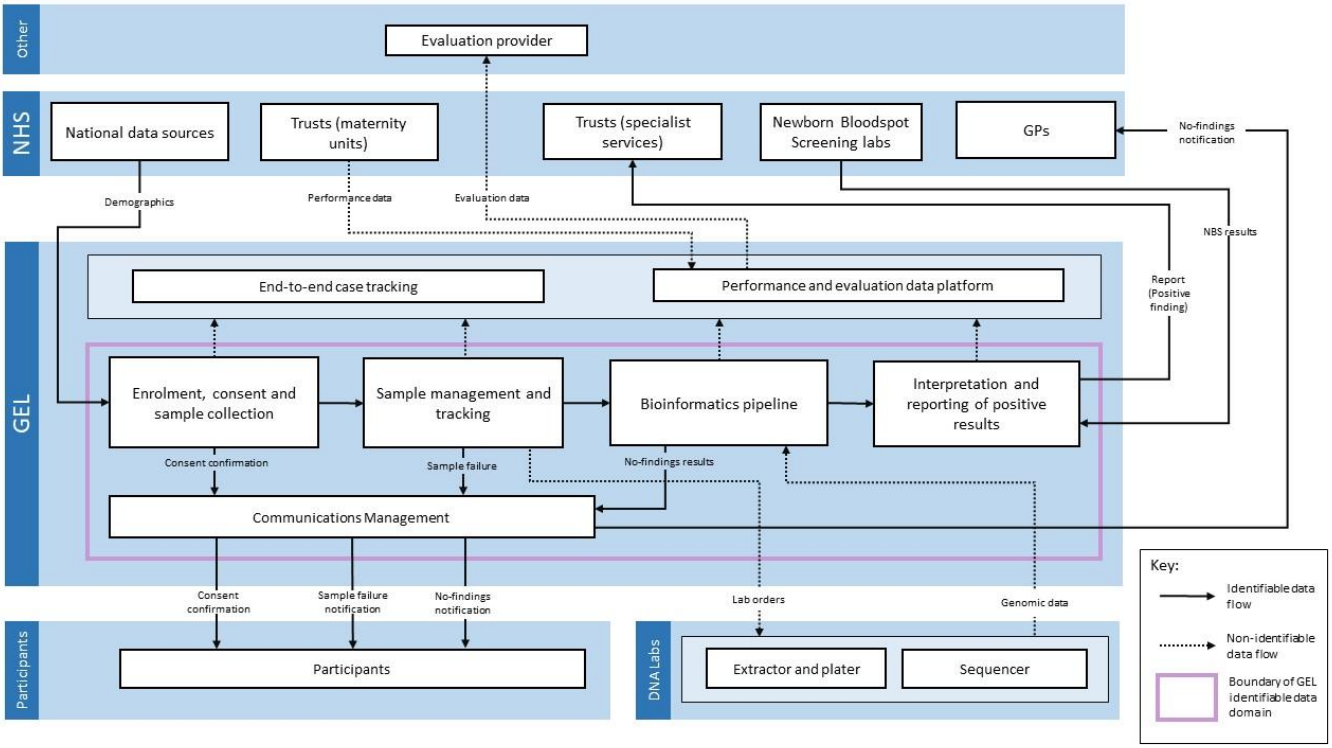
12. Data Flows and Data Collection

Data flows

Figure 8 provides an overview of the data flows to support the Newborn Genomes Programme showing the interfaces between Genomics England systems, participants, NHS users, partner laboratories and others, including evaluation partners. The approach to Data Protection and Cyber Security is summarised in Section 18.

Researcher access to data will be through the National Genomic Research Library as described in the National Genomic Research Library Protocol and is restricted to de-identified data

Figure 8 – Overview of data flows for recruitment, sample management, sequencing, analysis and return of findings



Data collection

Data on participants in the Generation Study

End-to-end tracking

Event driven data on the timing and status at different stages of the end-to-end recruitment-to-results process will be generated and stored for all participants.

Recruitment

The data collected during enrolment will be limited to that required for capturing consent, demographic details including related to ethnicity (in line with current best practice), number of

expected babies and language requirements. It is expected that this data will be collected prior to birth.

The data collected during sample registration will be limited to that required for sample identification and collection source (i.e., cord blood or heel prick).

This will be supplemented by demographic data updates (from the NHS patient demographic service) and information on outcomes of the newborn blood spot test (from Newborn Blood Spot Screening labs and the National Events Management Service)

Samples, sequencing and automated analysis
Data related to the processing of samples, quality control and transport will be collected. Genome data generated by the sequencing provider(s) and outputs of automated bioinformatic analysis will be stored.

Interpretation, reporting and return of results
Data collected during the interpretation and reporting will include decision to report, final variant classification and variant assessment criteria used.

Regional coordinators will oversee collection of data regarding the return of results to parents and the child's ongoing care. This will include the nature, dates and outcomes of confirmatory non-genomic and genomic testing and the clinical assessment of the child's status according to the study's working case definition for each condition- apparent true positive; apparent false positive; uncertain.

Healthcare records
Data will be collected through detailed, manual review of local clinical records in all participants to receive a 'condition(s) suspected' result and a subset of those who receive a 'no condition suspected' result including all those known to have a false negative result. This will include the nature, dates and outcomes of condition-specific investigations and interventions.

Interviews and questionnaires with participating families
Data will be collected through interviews and questionnaires with participating families to explore the positive and negative impacts of the study and genomic newborn screening. These will be governed by and detailed in the Evaluation Protocol.

Interviews and questionnaires with healthcare teams
Data will be collected through interviews and questionnaires with clinical, administrative and laboratory teams involved in the delivery of the core elements of the programme and broader clinical pathways to explore the positive and negative impacts of the study and genomic newborn screening. These will include attitudes to the study and its positive and negative impacts. These will be governed by and detailed in the Evaluation Protocol.

Longitudinal data sources
As set out in and governed by the National Genomic Research Library Protocol, data will be linked longitudinally. For the mother / birthing parent, these data sources will be restricted to those relevant to the pregnancy, birth and newborn period of the participating baby. These data sources will be linked until exclusion or withdrawal.

Data on comparator groups

Comparator data will be drawn from babies born at non-participating Trusts and from aggregate National figures. This will include national and local data described below. Comparator data will be age and gender match – with other matches such as location and ethnicity being considered.

Population comparator group

All children born at selected non-participating Trusts during the recruitment period of the study. Trusts will be selected on the basis of matching characteristics including level of diversity of patient reported ethnicity and socio-economic deprivation and the rural vs urban nature of the area served.

Rare conditions comparator group

All children diagnosed with the study conditions nationally as identified through specialist clinical services and laboratories over a multi-year period with similar diagnostic genomic testing availability to the study period. These children will be matched also according to the condition they are diagnosed with using the condition clustering approach described in the Economic modelling subsection of Section 13.

Sources of comparator data

National data sets

We will source data from the following national data sets:

- Community Service Data Set (e.g., for service usage for Allied Health Professional-led services)
- Hospital Episode Statistics (e.g., for hospital service usage)
- National Child Measurement Programme (e.g., for growth parameters)
- National Congenital Anomaly and Rare Disease Registration Service (e.g., to identify children diagnosed with rare conditions)
- National Neonatal Data Set (e.g., for neonatal service usage)
- NHS Genomic Medicine Service Clinical Variant Ark (e.g., to identify children diagnosed with rare conditions)

Local data sets

Local datasets accessed are expected to include those held by specialist clinical services and laboratories (genomic and non-genomic) and local Trusts. Specifically, data will detail children diagnosed through standard of care with the conditions looked for in the study.

13. Project Evaluation and Data Analysis

Overview

As set out in Section 5 (Objectives and Protocol Scope), project evaluation and data analysis will support the development of evidence across a broad range of areas. This will facilitate policy decisions on whether and how whole genome sequencing should be adopted as part of routine care.

Evaluation of the Generation Study requires an extensive, multidisciplinary project drawing on a diverse range of specific expertise in newborn screening, implementation and behavioural science. Therefore, to will engage an Evaluation Partner to co-create an Evaluation Protocol and undertake the work together, with external input from the UK National Screening Committee. The Evaluation Protocol will stipulate detailed work and analytical plans including any additional participant-facing interactions e.g., interviews and questionnaires with participating families.

Research questions, outcomes and data sources

Here and in Appendix A we set out the research questions, outcomes and expected data sources that have been developed in collaboration with the programme's Evaluation Working Group. These support the study overall and will be inputs to the development of the Evaluation Protocol.

They cover four broad areas exploring both positive and negative impacts. Each area is linked to a primary research question and a series of secondary research questions. The areas and their primary research questions are listed below. The full list of research questions and expected data sources are set out in Appendix A.

1. **Feasibility, acceptability and uptake.** Is genomic newborn screening feasible and acceptable and would it be broadly taken up if offered as part of routine care?
2. **Test performance and clinical utility.** What is the clinical utility of genomic newborn screening as evidenced by the number of screen-identified diagnoses likely to benefit from intervention compared to standard of care alone?
3. **Cost effectiveness and positive and negative impacts.** What is the cost effectiveness of genomic newborn screening compared to standard of care alone?
4. **Experiences and attitudes.** What are families' and stakeholders' experiences and attitudes to genomic newborn screening?

Questions related to equity will be included and assist in determining any differential areas of positive or negative impact of genomic newborn screening vis-a-vis indices of diversity including ethnicity and socio-economic deprivation.

While it is important to emphasise the breadth of research questions necessary to support policy decisions and therefore explored through the study, we have also identified the following primary and secondary outcomes linked to the areas above and the overarching question of equity.

The primary outcome is:

- To determine the clinical utility of genomic newborn screening as evidenced by the number of screen-identified diagnoses likely to benefit from intervention compared to standard of care alone.

The secondary outcomes are:

- To determine the feasibility and acceptability of genomic newborn screening in the NHS utilising mixed-method approaches to assess study implementation.
- To determine the cost effectiveness of genomic newborn screening compared to standard of care alone, supported by a health economic model developed to support the programme.
- To determine families' and stakeholders' experiences and attitudes to the adoption of genomic newborn screening.
- To determine any differential areas of positive or negative impact of genomic newborn screening related to indices of diversity including ethnicity and socio-economic deprivation.

Project Evaluation

Four linked workstreams have been identified for programme evaluation that will together explore the research questions set out above. These are based on recommendations set out in the Treasury's Magenta Book[181]. They include:

- Performance monitoring
- Economic modelling
- Process evaluation
- Impact evaluation

Rather than separate workstreams, these will be interlinked, for example with process and impact evaluation informing, providing inputs for and responding to the work on the economic model. This also means that modelling of the concepts used in different aspects of the work will take similar approaches. For example, as set out in the Economic Modelling section below, reflecting the low prevalence rate of most of the conditions individually, we will develop evidence both on individual conditions and on 'clusters' of conditions, grouping conditions with similar clinical characteristics, clinical pathways and natural histories together.

Genomics England will develop the performance dashboard and economic model internally, with input from external experts including health economists. As described above, process and impact evaluation will be delivered in partnership with an Evaluation Partner ensuring that the programmes of work are integrated, for example the impact evaluation feeding data to and responding to the requirements of the economic modelling work. Each of the evaluation workstreams are briefly discussed below.

Performance monitoring

A performance dashboard will be created to inform decision making and monitor programme delivery, consisting of a set of key performance indicators (KPIs) that are closely aligned with project ambition to inform decision making. This quantitative monitoring data will be collected through a variety of sources including:

- Data from Genomics England core systems
- Data fed back from the NHS as part of monitoring the programme.
- Data fed back to Genomics England by the partner performing the process and impact evaluations (see below)

Genomics England will develop the performance dashboard using appropriate software, such as Tableau. Where appropriate, data will be presented as a time series using data visualisation best

practice and updated regularly (live where possible). In some instances, further analysis or forecasting will be required to ensure the research questions are being answered.

Appropriate governance and accountability mechanisms will be established to monitor delivery, including uptake and results, and to remediate off-track KPIs. Monitoring will be ongoing throughout the programme.

Economic modelling

GEL is developing an economic model internally for the health economic evaluation. The initial proposals for the model were produced through a collaboration between GEL and external experts, with the model itself developed by an external economic modelling team. GEL continues to liaise with the NSC and other expert teams on the model. We include a description of the model below, noting that it will be iterated and populated as data from the Generation Study and other studies are generated and responding to ongoing expert input and best practice.

The model aims to estimate the costs and benefits of genomic newborn screening alongside current newborn bloodspot screening. The model includes a control arm, current blood-spot test, as well as an intervention arm for the addition of genomic newborn screening. Consent rates for both screening tests are incorporated, resulting in a subset of babies receiving neither screening test.

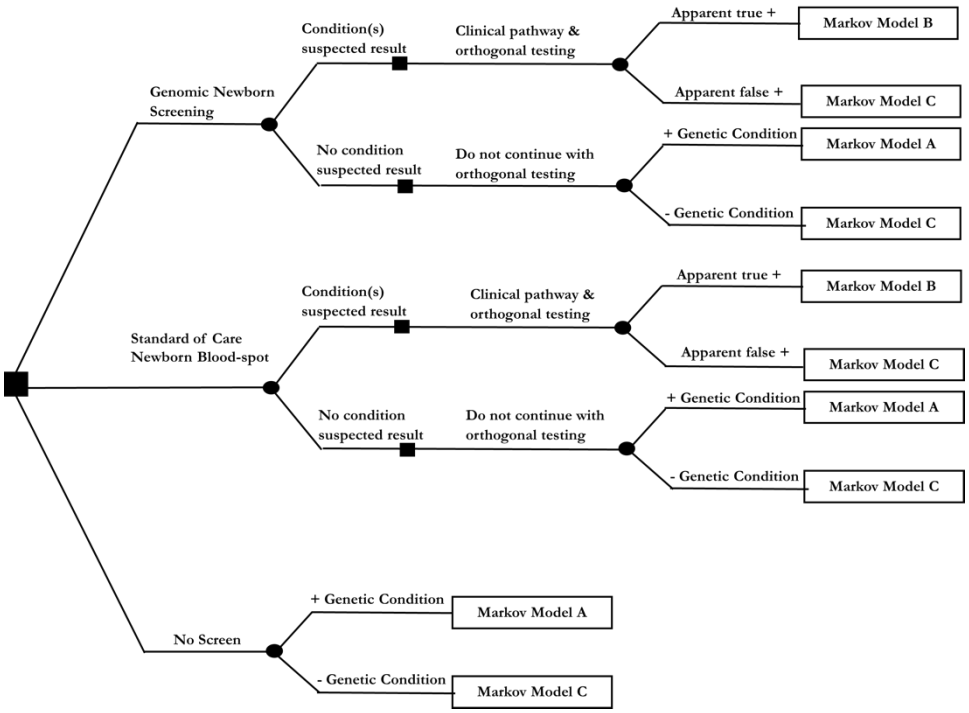
The model takes a clustering approach, grouping conditions with similar clinical characteristics, clinical pathways and natural histories together. In total the model currently contains six clusters of conditions that have similar characteristics each of which is represented by around ten conditions. This subset of ~60 conditions, representing the 200+ conditions that will be screened for by WGS, was chosen based on prevalence, data availability, and also clinical importance. Within each cluster, condition-specific inputs are obtained for costs, utilities, and mortality rates, and a weighted cluster average is then calculated for each variable based on the relative prevalence of the condition within the cluster. The model is run individually for each of the six clusters and then aggregated to reach a population-level estimate, based on the relative prevalence of each cluster within the overall population. This allows for cost-effectiveness to be estimated both for individual clusters and for the overall group of conditions.

The model is structured in two phases. The first phase, a decision tree (shown below), considers the initial screening process and is used to define distinct groups of patients based on the outcome of screening. In the second phase, these groups of patients then progress through one of three distinct Markov models, each simulating a specific post-screening pathway. For the first phase, a weekly-cycle length is used to capture the costs associated with the screening tests, the sequencing process, the interpretation of the screening results and finally the cost of confirmatory diagnostic tests. In the second phase, an annual cycle length is applied to all Markov models, with a half-cycle correction implemented, to capture all the relevant costs and benefits that babies accrue as they are followed for a lifetime time horizon.

The first Markov model (Model A) tracks babies affected with a genetic disease but who have not been detected via WGS or blood-spot (false negative), or who were not detected because of non-participation in the screening programme (i.e., parents declined screening). The second Markov model (Model B) tracks babies with a genetic disease detected by WGS or blood-spot (apparent true positive). The third Markov model (Model C) tracks unaffected babies, this includes babies with

negative WGS or blood-spot results, babies with positive WGS or blood-spot results which was subsequently disproved as negative by a diagnostic test (apparent false positive), and finally unscreened babies that did not participate in either screening program and never develop a genetic condition (unaffected). The model includes the positive predictive value (PPV) and negative predictive value (NPV) for both the blood-spot and WGS screening tests, which determine the number of false negatives and false positives in the population.

Figure 9– Decision tree for the draft health economic model



Babies diagnosed with a genetic condition at birth, through either blood-spot or WGS will enter Markov model B in the "pre-symptomatic" health state, and those who subsequently receive treatment will continue through to the "asymptomatic-treatment" health state. From here, they will transition to one of three subsequent health states: "asymptomatic-complete response", "symptomatic-partial response", "symptomatic-treatment failure". The model also includes a "symptomatic-symptoms management" health state to reflect patients who will benefit from having a diagnosis, even without treatment initiation and those with uncertain condition status. Transition probabilities between health states are based on treatment efficacy rates, specific to each condition in the model. In addition, specific mortality rates are applied to each health state.

Babies diagnosed with a genetic condition at symptom onset, either due to false negative results or babies in the control arm who have conditions not screened for in the blood-spot test, will enter Markov model A. The health states in this model are similar to those in model B, except for the addition of a "symptomatic-diagnostic odyssey" health state, which captures the period of time between symptom-onset and receiving a diagnosis. In addition, in model A the "asymptomatic-treatment" state is replaced by the "symptomatic-treatment", since treatment will only begin after symptom onset and diagnosis. Despite the similarity in health-states between models A and B, the transition probabilities differ for some conditions due to reduced treatment efficacy when treatment

is initiated at symptom onset rather than at birth. As with model B, specific mortality rates are applied to each health state.

Finally, Markov model C captures the progression of unaffected infants (false-positive, true-negative, and unaffected unscreened infants). Only two health states are considered for this model: "unaffected-well" and "death". For false positive patients, harms of a false diagnosis such as anxiety are captured within the first phase of the model, after a confirmatory negative test they are assumed to rejoin the "unaffected" population.

Specific costs and utilities are applied to each health state in the three Markov models, therefore patients accrue costs and quality-adjusted life years (QALYs) as they pass through the model. In terms of costs, the model considers treatment costs, direct medical costs, and direct non-medical costs (e.g., social care costs). Utility values for health states are adjusted to account for adverse events from treatments.

Initial data inputs in the model have been obtained from a wide range of sources. The majority of inputs have been sourced from published literature and publicly available datasets. In cases where there was a lack of data available, expert clinicians have been consulted to provide assumptions for the model. For healthcare resource use costs, an analysis of HES datasets has been conducted to obtain resource use inputs for each condition in the model. The model has been built to allow for live data from the Generation Study to be incorporated once available.

Discounting is applied in the model, and differential discount rates are used for costs and benefits. Costs are discounted at a rate of 3.5%, whereas benefits are discounted at a rate of 1.5%.

The key outputs of the model include costs, life years, and QALYs for the blood-spot and WGS arms of the model. These outputs are used to calculate an Incremental Cost Effectiveness Ratio (ICER) to evaluate the cost-effectiveness of introducing WGS screening for newborns. As well as overall costs, QALYs, and ICER estimates, the model also produces disaggregate ICERs for each of the six clusters of diseases in the model. This generates insights into the drivers of cost-effectiveness, particularly useful due to the large variation in treatment costs between the six disease categories.

The model also includes deterministic sensitivity analysis (DSA) to explore the effects of uncertainty on the model's results. As part of the DSA, model inputs are varied between their upper and lower bounds, resulting in a range of plausible results rather than single point estimates. Scenario analyses are also performed, for example on discount rates, to explore the effect of methodological uncertainty within the model.

Process evaluation

Delivered in collaboration with our Evaluation Partner, and governed by the Evaluation Protocol, process evaluation will focus on the acceptability and feasibility of the programme, taking a mixed methods approach to data collection. It will include evaluation of effective approaches to implementation, uptake and withdrawal rates, consistency of sample taking and DNA quality, turnaround times for the end-to-end process, and whether findings can be returned safely and effectively to participants. It will also focus on participant experiences of participation and will give consideration to demographic factors. Further detail of the questions and data sources that will drive this evaluation can be found in Appendix A.

Impact evaluation

Delivered in collaboration with our Evaluation Partner, impact evaluation will comprise a series of impact reports. These reports will assess the benefits and negative impacts of the programme, focusing specifically on stakeholders, the wider system and experiences and attitudes. It will include an assessment of clinical utility as judged by the number of screen identified diagnoses compared to standard of care as well as the number of false positive and negative findings. It will also consider the benefits and harms on participants including health related outcomes, quality of life impacts and wider impacts on families. In addition, it will focus on monetary and non-monetary impacts on the health system. We will monitor standard of care screening uptake to understand whether babies undergoing heel prick for the study (in the event of failure to collect cord blood, or home birth) proceed to access national newborn screening through the heel prick, or not. We will also explore attitudes and experiences of participants, the public and a range of professional stakeholders. Further detail of the questions and data sources that will drive this evaluation can be found in Appendix A. The Evaluation Protocol will cover those elements of impact evaluation that are not part of this main protocol.

Data analysis

Overview and analysis against the primary study outcome

Data analysis will span the range of research questions and outcomes described above and in Appendix A. As noted above, this will include analysis related to equity across each of the areas to determine any differential positive or negative impact in specific areas or overall linked to diversity including ethnicity and indices of socio-economic deprivation.

Particular and early focus will be given to analysis against the primary study outcome: *'To determine the clinical utility of genomic newborn screening as evidenced by the number of screen-identified diagnoses likely to benefit from intervention compared to standard of care alone'*.

As preparation for the study, formal *a priori* sample size estimation was done using a precision approach with the aim to identify the minimum sample size that would ensure a precise estimate of the incidence of diseases.

For the consequent data analysis we will use a Bayesian approach for data modelling outcomes of interest to better account for extreme-values and zero-numerator problems such as in case of rare genetic conditions. We will formulate a prior probability distribution for apparent false positives and false negatives based on the extensive modelling already conducted and also after collecting expert opinions. We will recalculate the posterior probabilities alongside the progression of the programme thus incorporating and refining parameters of uncertainty

Exposition of the data analysis strategy across the full breadth of the research questions and study outcomes is beyond the scope of this protocol.

Interim Analysis

This interim analysis will allow for decisions and adjustments - for example to recruitment materials, sampling strategy, the stringency of variant prioritisation filtering, adjusting variant inclusion or exclusion lists, adjustments to the conditions/genes list and study continuation.

We expect to perform interim analyses when the first 1,000 participants' data is processed, then at 5,000, 20,000 and 50,000. These points may be adjusted and made more frequent, especially in the initial stages of the study, if deemed necessary e.g., if significant changes to variant prioritisation approach are implemented and the impact of that needs assessment.

The main focus of the interim analysis will be to assess:

- recruitment profile including crude recruitment rates as a proportion of births at recruiting sites and the diversity of recruitment as compared to the diversity of the birthing population at recruiting sites sourced from the Maternity Services Data Set
- apparent true positive and false positive numbers and their ratio overall, for individual genes/conditions and by participant ethnicity so that we can:
    - adjust bioinformatics and interpretation approach to variant reporting, including stringency of variant filtering strategy, thresholds and adjustment to variant inclusion and exclusion lists
    - re-evaluate the sample size calculations required to achieve the primary study outcome. This analysis will re-evaluate sample size required for the incidence estimate, as described in Section 6, using real world study data, as well as sample size required to achieve the expected number of screen-identified true positive diagnoses in the study. The true positives for this analysis will be defined as newborns with pathogenic or likely pathogenic variants identified and reported through genomic screening, and diagnosis confirmed by orthogonal testing (e.g., biochemical tests). The expected number of true positives will be updated when the conditions to be screened list is finalised.

The data on true positives and false positives will be obtained from the results of confirmatory testing for participants with "condition(s) suspected" results. We will also collect data on false negatives from linked longitudinal health data and incorporate it into interim analysis.

Interim analysis will also provide information on study-related harm and adverse events, and recruitment will be halted if the analysis demonstrates unacceptable levels of harm. Such decisions will involve extensive consultation within the study Governance framework.

14. Communications and Ongoing Engagement

Communications

Updates on the Generation Study's progress will be added to the Genomics England website and the study microsite. Responsibility for updating the websites will rest with Genomics England's communications team.

Key milestones in the communications plan will include:

- '**One-year on update**'. We will issue an update on the research study's progress one year after the first baby is enrolled (e.g., in the form of a news item), and each year thereafter.
- **Update on next steps after completion of recruitment.** An announcement that the research study has completed recruitment; and an accompanying account of 'what happens next' with respect to the evaluation of the study.

Throughout the study, the team will respond to enquiries via Genomics England's service desk, or the Newborn Genomes Programme's dedicated inbox. Each month, questions received will be reviewed in order for themes to be identified. Where questions arise frequently, the communications team will work with the Programme's team to make a decision about the optimal communications strategy for addressing these questions openly and clearly. These strategies might include:

- Adding a 'Q&A' entry to the Newborn Genomes Programme's website;
- Writing an article or blog post for the Programme's website; or
- Assessing if the enquiry needs to be addressed more broadly – e.g., through working with specialist academic journals, newspapers, or broadcasters.

Stakeholder engagement

Different communities and individuals have been involved throughout the development and design of the study. This commitment will continue throughout its delivery. This requires ongoing, regular reflection on the progress of the study, and how particular stakeholder groups might offer support, guidance, and feedback throughout the study's life course.

This regular reflection will take the form of a once-monthly team stock-take of issues that have arisen. Key to such reflection will be assessing how working with stakeholders involved to date could help to address such issues. Those stakeholders include parents; people with experience of a rare condition; members of the public, including from ethnically diverse communities and young people, healthcare professions, including doctors, midwives, health visitors, nurses, genetic counsellors, pharmacists and laboratory staff, health researchers, including academic researchers, clinical researchers and researchers from the life sciences industry and policymakers.

There are several methods of engagement and involvement that the Newborn Genomes Programme team will consider using to address issues which arise. These include meetings, interviews, co-production, focus groups, presentations and deliberative workshops.

15. Withdrawal

Parents will be made aware that they can withdraw from the study at any time, by contacting the team at the site who recruited them to the study, or by contacting Genomics England directly via the Genomics England service desk (contact details provided in the Participant Information Sheet).

Withdrawal will be available on one of two levels, in line with Partial ('No further contact') or Full ('No further use') options outlined in the National Genomic Research Library protocol. In the situation of Full Withdrawal:

- Samples that are in-transit or in storage that have not yet been sequenced will be destroyed.
- Data will not be included in future releases in the National Genomic Research Library but, as set out in that protocol, will remain in previous releases.
- Where sequencing and analysis is complete and results have been made available,* genomic data will be retained for the purposes of analytical validity and improvement. These data will

never be made available in the NGRL. Remaining samples will be destroyed. Data will be put beyond reasonable use.
- An audit record of withdrawal will be maintained.

In the situation of Partial Withdrawal:
- Samples and data will be processed as described in this protocol, and data from clinical records will continue to be linked to the baby's genomic and demographic information
- We will no longer contact the family. They will not receive exceptional findings, nor will they receive study updates or invitations to participate in Evaluation research.
- When babies whose parents have partially withdrawn turn 16, they will be actioned as full withdrawals – as we will not be able to contact and obtain consent for ongoing participation.

*Exceptionally, parents may wish to withdraw the baby from the study after analysis of the genome sequence has started, but before screening results are made available. Because of the high threshold for positive predictive value of the screening results generated by the study, and in order to fulfil our duty of care to child participants, parents will be made aware that they will still receive study results should they partially or fully withdraw during this phase. Once screening results have been made available, the parent's wish to withdraw will be actioned. This aspect of the withdrawal process was specifically advised by the Newborns Ethics Working Group in January 2023. It is important to note that if a baby withdrawn during this period has a suspected condition, this case will still be referred into the clinical pathway, for confirmatory testing and ongoing clinical management.

16. Training

Governance and delivery

Research initiatives, new technologies and changes to practice carry implications for education and training. Through the 2021 public dialogue and ongoing engagement with stakeholders from public, patient and healthcare professional groups, it is clear that the safety and effectiveness of this study relies on an engaged and competent workforce. Genomics England has therefore 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 Health Education England (HEE) Genomics Education Programme.

Through this group, and broader work, Genomics England is working with HEE and other stakeholders with experience in education involving genomics, screening and research.

Training will be delivered by providing materials to study site teams, as well as through virtual and in-person contact with study sites. This will include training on encouraging diverse participation so that all eligible parents are approached and given an opportunity to take part. Training will also include ensuring that routine or other required clinical referrals or investigations are not disrupted because of this study.

As well as provide training for specific needs to deliver the study, we recognise that there is a need to provide education at all levels to ensure that healthcare professionals are aware of and equipped with the knowledge required to support genomic medicine.[182] This includes ensuring health care professional groups like midwives, nurses, health visitors and GPs are aware of the programme and

the potential impact of genomic testing in this context. Funding will also be provided to the GMSAs to support this wider training and engagement.

Training approach

A competency framework and supporting resources will be 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. This aims to promote consistency and participant safety, as well as support flexibility in delivery models across sites.

A train-the-trainer approach will also be employed to expand training capacity, as well as support site and regional accountability and sustainability. Training and materials will be provided for those involved in recruiting participants, collecting samples and facilitating return of results. This will ensure that those supporting parents and families in the study will be able to understand the study aims and processes, answer questions and provide appropriate support for families.

17. Regulation, Ethics and Legal Considerations

Regulatory Framework

Definition of project activity

This project constitutes research as defined in the UK Policy Framework for Health and Social Care Research S3.3 as follows:

> *"… research is defined as the attempt to derive generalisable or transferable new … knowledge to answer or refine relevant questions with scientifically sound methods"*[183]

Relevant Approvals

The project requires and has received HRA Approval (insert IRAS ID 324562). The designation of the project is 'Other'. All materials have been reviewed and approved by HRA and East of England - Cambridge Central REC (23/EE/0044). Genomics England has worked closely with HRA to ensure that this project has correct designation and approval. This Approval covers the screening aim of the project. Long term storage and use of data and tissue generated by the project will be governed by Genomics England's approval for the NGRL governance framework, as explained earlier in this document.

National Genomic Research Library Regulation

Genomics England has generic Research Tissue Bank Approval (20/EE/0035) for the use of data and tissue in future research projects. The governance of samples and data can be found in the NGRL governance framework. Any further use of data and samples from the Newborns genome Project will be in line with the BGRL protocol and Conditions of REC Approval.

Good Clinical Practice (GCP) training and human resources

This study does not require GCP trained personnel to conduct recruitment, take samples or handle samples as it is not a clinical trial of an investigational medical product.[184] All recruiting staff will be qualified and appropriately trained in research procedures Genomics England in partnership with Health Education England have developed specific training and learning for genomic research.[185]

Ethics

The ethical implications of genomic newborn screening have been explored by a number of authors. They span the trajectory from choosing conditions through to the way in which uncertainty is conveyed before and after testing, and beyond[186,187,188,189].

To ensure that ethics is at the core of our thinking as we develop and deliver the programme, we established an independently chaired Ethics Working Group to provide advice. This group meets regularly. It has advised on specific elements of the Generation study (for instance the withdrawal strategy) and on the programme overall. To promote ethical rigor across the delivery of the programme, ethics research will form part of the ongoing project evaluation (Section 13). It is also ongoing in our engagement work, for example our Pilot Public Standing Group on Ethics (Section 4).

This framework complements:

- the broader governance at Genomics England including the Genomics England Ethics Advisory Committee and
- our approach to risk management – see Section 22.

Risks and benefits

According to the UK Policy Framework for Health and Social Care Research (S2.1),[190] the benefits proposed by health and social care research – both as direct benefits to participants and wider societal benefit – should outweigh the risks. Risk / benefit analysis should consider the broader implications if a proposed study does not take place, against those associated with actioning the study.

For example, in a recent blog post for the Nuffield Council for Bioethics, Professor Frances Flinter summarised the risks and benefits of the use of using whole genome sequencing to screen newborn babies as follows:

> *"The potential benefits are early diagnosis and treatment for more babies with genetic conditions. The potential harms are false or uncertain results, unnecessary anxiety for parents, and a lack of good follow-up care for babies with a positive screening result."*[191]

Whilst the summary from Prof Flinter is not an exhaustive accounting of the risks and benefits associated with this study, it is a useful prompt to reiterate Genomics England's commitment to transparency and developing balanced evidence. We have acknowledged the limitations of our chosen study design, methodology and delivery pathway throughout – we will continue to hone the study as we move forward. Wherever possible, we have made maximum effort to mitigate risk and manage limitations. Our ongoing endeavours aim to ensure that the study provides evidence on both harms and benefits of the proposed approach and is transparent in how we do this. As set out in this Protocol, we aspire to weave this mindset into the study's fabric including its governance,

extensive planning, engagement and working partnerships with the NHS. See in particular Section 4 and Section 22.

To directly address the risks raised by Prof Flinter. Firstly, while significant efforts have been made to optimise positive predictive value of the results generated through analysis of the WGS, uncertainties remain. In particular, these may relate to the significance for health and disease that can be revealed by genome sequencing, particularly in the absence of a relevant family history. This may cause worry or distress for parents and families. Plans have been made to ensure support can be provided as set out in the Returning Results section. Furthermore, conditions have been selected only if orthogonal testing is available within the NHS. For the majority of families who receive a 'condition suspected' result, this will be definitively confirmed or disproved. For some, however, this may not be the case. We are developing a network to support these families with inconclusive findings. Finally, in terms of uncertain results, our diligent interim analysis will identify these, and this information will be one basis of decision-making for study continuation.

Secondly, the risk of lacking follow-up care has been very carefully considered. It is for this reason that the NHS Clinical Assurance Group was established. This group provides advice to the programme and also reports within NHS England. It considers the selection of conditions with a particular focus on ensuring relevant expert sign off of each condition and pathway, the availability of treatments and the capacity of clinical pathways. It includes representation from relevant NHSE Clinical Reference Groups, the NHSE Genomics Unit, Specialised Commissioning, NICE and the UK National Screening Committee.

Over and above those discussed previously, risks and mitigations are detailed in Table 3, below

Table 3 Risk and Mitigation overview

Risk	**Mitigation(s)**
Risk of therapeutic misconception – the risk that parents may believe that the Generation Study test is clinically validated standard of care.	1. Emphasis in participant-facing materials that this is a research study to determine the risk and benefits of the approach, distinct from and not replacing routine care including antenatal scans, clinical referrals based on medical or family history, and the NHS newborn screening programme. 2. Selection of an 'all in' consent model so that discussion can focus on the core elements of the study including the research-nature of the screening element of the study. See Section 7 (Recruitment and Consent)
Risk of negative impact on NHS newborn blood spot screening programme – the risk that the study will reduce the number of children undergoing routine newborn screening	1. Emphasis of the Generation Study as a research study, distinct from the routine newborn screening in participant-facing materials; 2. Design of sampling strategy to avoid impact

	on routine blood spot collection and use of heel prick sampling only where cord blood not available; 3. Close monitoring of uptake of routine bloodspot at recruitment sites and in recruited children from the outset of the programme.
Risk of re-identification of research participants. The risk that, whilst measures will be in place to keep participants' identity and information confidential, there is an unavoidable, though remote, risk of re-identification through participation	See Section 7 (Recruitment and Consent) 1. Genomics England hosts robust informatics systems, with vigorous security and data protection protocols in place; 2. All Genomics England staff have information governance training including expectations of confidentiality; 3. Identifiable data is only available in the systems in which it is required.
Risk of harm through high false positive rate	See Section 18 (Data Protection and Cyber Security). 1. A conservative approach is being taken for gene/condition selection and in variant prioritisation to favour high positive predictive value (i.e., low false positive rate); 2. Validation of the low risk of the approach using control data in advance of go live; 3. Careful monitoring of early findings from the study, 4. A section on Uncertainties in the Patient Information Sheet clearly stating that the research results produced by the Generation Study may be incorrect, or orthogonal testing may be inconclusive.
Risk that clinical pathways will be unavailable or will not have capacity to support children with 'condition(s) suspected' results	See Section 4 (Stimulus and development of this programme) and Section 10 (Analysis, Interpretation and Reporting Strategy). 1. This is the focus of one of the principles of our condition selection framework: "Conditions screened for are only those for which the interventions are equitably accessible for all." 2. We have established the NHS Clinical Assurance Group to provide assurance on this point. It has senior NHS representation including from Clinical Reference Groups.

See Section 4 (Stimulus and development of this programme)

Additional risks and benefits are associated with the retention and sharing of longitudinal genomic and healthcare data, these are detailed in the NGRL governance framework.

Information provision and consent

A central ethical consideration is the approach to consent and the level of detail required. This detail involves:

- Ensuring that complex scientific concepts are explained in a manner that accounts for people's level of literacy, language and accessibility needs
- Ensuring clarity on the purpose of data and sample storage
- Promoting the autonomy of parents as responsible decision-makers for their children, through the provision of carefully layered, concise information
- Furthering the best-interests of our baby (and later child) participants and recognising their right to an open future.

It is notable that in some countries, standard of care newborn screening currently operates on implicit consent or is mandated. However the Generation Study differs because it is research. Across the planning phase, the team has undertaken extensive work on the information provision process and explicit consent will be sought in all instances. This is detailed in Section 4. Moreover, the process of providing information about the study, and subsequently gaining consent to participate, will be ongoing. Because the study is relatively complex, and has implications for the parents of babies and the babies themselves, information sharing materials have been carefully co-designed, with substantial parent involvement.

Verbal consent and proportionality

As set out in Section 7 (Recruitment and Consent), consent for the study may be recorded in a face to face consultation, or through verbal agreement following a telephone or video consultation. The approach taken will depend on preferences of the study site, and availability and convenience to the parent.

Supporting a verbal, telephonic consent as an alternative to face to face consent involved weighting the imperative of:

- Parents understanding the complexity and implications of the study, against
- The logistical and resource requirements of a solely face-to-face consent process.

It is important that parents have time to fully consider study participation, including to it discuss with others and ask questions. The layered approach to information provision means that parents will be able to take as much time as needed to consider participation. However, inviting parents back to the hospital for a face-to-face consenting appointment may present significant logistical complexity in some cases. A verbal consent process is proportional to the risks associated with parents being given insufficient time to consider participation.

Once verbal consent has been given by the mother / birthing parent, a confirmation copy of the consent form will be sent via email, so that the participant has a record of their consent.

Assent and future consent for young people

Newborns recruited into this study will not be in a position to provide assent to continuing research participation or withdrawal until they reach a level of cognitive capacity consistent with independent decision-making. Assent to ongoing longitudinal research is addressed in the NGRL governance framework and Genomics England has an SOP addressing this issue, which will be followed in the Generation Study.

At approximately 16 years old, 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). 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. This process will be underpinned by the relevant Standard Operating Procedure.

If it is not possible to reach the young person at that time, their data and samples would be removed in line with the process for Full Withdrawal. If the young person in question does not have sufficient cognitive capacity to independently consent to ongoing participation, this will be sought from the legal next of kin, with proportional input from the young person.

Mother / birthing parents or newborns who die

Both the mother / birthing parent (consenting individual) and the baby may be enrolled in the study and later die. The death of a mother/birthing parent, or of a child, will be managed as soon as the Newborns Genome Programme becomes aware of it, as follows:

Mother / birthing parent

In line with the Human Tissue Act 2004 (in England, Wales and Northern Ireland) and HTA Code of Practice on Consent, (v14.0, July 2014) the mother/birth parent's consent remains valid subsequent to their death. This means that the maternity data collected from mothers / birthing parents would continue to be processed in alignment with the study aims and objectives. The spirit of this provision is to is in place to maximise potential for future research.

However, surviving family members may not be supportive of ongoing participation for the mother/birthing parent. In these scenarios, as per the NGRL governance framework, once we become aware of a death, Genomics England will seek engagement with the clinical team, where relevant, to support the ongoing continuation, or withdrawal, of a deceased mother/birthing parent. If an appointed nominee to the deceased mother/birthing parent is in place, this individual may make decisions on behalf of the deceased. These decisions are binding, and cannot be overridden by those in qualifying relationships with respect to the deceased. The Newborn Genomes Programme note our legal obligations in this regard, and will consider all such requests made by representatives.

Ongoing participation of a baby / child following death of mother / birthing parent

If a mother / birthing parent of a baby in the Generation Study dies, the parental consent that had been provided for the child to participate in the Generation Study will no longer be legally valid. Consent must thus be obtained from another individual with legal parental responsibility for the child, as soon as practically possible. The precise pathway for making contact with another individual whom has parental responsibility will be determined on a case-by-case basis, sensitive and empathetic to the experience of the collective family unit. Obtaining a new consent may involve liaison with clinical teams or social workers at various times. Because the death of a mother / birthing parent invalidates the legality of the baby's participation in the |Generation Study, the data pertinent to the baby will not be further processed until consent has been provided by another individual with parental responsibility. If this consent is not provided, the baby will be fully withdrawn from the study. However, if the baby's genomic sequence is being processed by Genomics England at the time a mother / birthing parent dies, the study result will still be returned through the appropriate channels.

Child

If a child in the Newborns Genome Programme dies, the same processes for the demise of a mother/birthing parent will be followed. The child will not automatically be withdrawn from the study, and the mother/birthing parent may be approached to ratify consent or withdraw the child at an appropriate time in the future. These situations would be dependent on input and clinical judgement, as to the manner to best navigate the continued participation of the child without causing harm to the grieving parents, and weighted with the benefit of the child's data remaining in the project for future research.

The consent model

One of the key tensions facing the research team in designing this study was developing a consent model that is ethical, fair and facilitates the measurement of our key outcomes. Following extensive consultation, detailed below, we have decided to implement an "all-in" consent model. This section and Table 4 lays-out the rationale for adopting this model.

All-in consent provides that the parents who decide to enroll their baby agree to the following in relation to this Protocol and the National Genomic Research Library:

- Genome analysis for select variants linked to 200+ rare conditions
- Research on the utility of genome sequencing for newborn screening
- Use of samples, genome and health data for wider healthcare research
- Re-contact, for which reasons include:
    - Sharing news and updates about the study
    - Asking for further samples or information
    - Inviting to take part further research

Further research may include research relevant to evaluation of the study, relevant to a condition the participant is known to have, or opportunities to take part in clinical trials (particularly for those who are identified to have a condition). These reasons for re-contact for further research are further outlined in the NGRL governance framework. This includes incidental findings identified during the course of research, which will only be fed back to participants if there is an exceptional reason for

doing so (and where Genomics England's Science Advisory Committee and/or Ethics Advisory Group may be consulted).

Parents and participants can agree or decline invitations to take part in further research when they are contacted. They may also choose to have no further contact, in line with Partial Withdrawal (see Section 15).

There are two primary reasons we will not be offering parents a tiered consent process:

- Concerns have been raised about creating a therapeutic misconception and inadvertently discouraging parents from participating in the NHS Newborns Blood Spot (NBS) test. The all-in consent model serves to emphasise that this is a research study rather than a clinical service.
- We will not be able to meet our scientific objectives of program evaluation (as reflected in the aims and objectives) without long-term access to the linked clinical data set of each participant, as well as their genome.

Table 4 Key considerations in selecting the consent model

Item	Decision
Clinical screening programmes differ from research screening programmes.	The all-in consent model may not reflect the reality of a clinical newborns screening programme as these would not include data / sample storage and future research. The research team acknowledges this limitation to the model. In order to provide maximum benefit to participants and minimise potential harms, we have set a very high threshold for labelling a screening result as potentially pathogenic. This provides us with little data to evaluate the feasibility of Whole Genome Sequencing for newborns screening at the outset. We contend that outcomes measurement is essential to fulfilling our primary study objective and we have taken the decision to prioritise this over implementation science – which we may phase into the project at a later point. This would trigger an amendment to the study. This decision represents a commitment to extracting maximum value for money in a publicly-funded research project. A contextual point here is that some members of the Newborns Ethics Working Group proposed trialing different consent model across study sites. Offering this complexity of recruitment options is not feasible within the study resources, however the research team remains open to reconsidering the all-in decision based on interim data analysis.
Diversity and Inclusion	Potential participants (especially from minority groups) may find the all-in consent model off-putting and refuse to participate. To this end, we have an ongoing consent dialogue with leaders from ethnic minority communities (explained in the Development of the Newborn Genomes Programme section of this document). Anecdotal evidence suggests that diverse communities may be reluctant to participate in studies requiring that genomic data is made available to researchers for future research.

	Conversely, making the consent model too complicated risks alienating those from minority groups. To recruit from diverse groups, we may need to rely on Language Line interpreters and a simpler model may facilitate robust and informative recruitment conversations under these circumstances. We acknowledge this very real concern and we are committed to promoting diversity and inclusion into our research sample for this study. Our sampling strategy has been carefully crafted to produce a braodly representative cohort of births in England. As part of our interim analysis, we will continuously monitor study uptake amongst our minority populations. If we find this to be significantly below average study uptake, we may need to reconsider the all-in consent model. This would only be done once an amendment to the study was approved by the REC.
Consent conversations and seeking consent	The all-in consent model mitigates the risk of consent conversations being dominated by discussions of the various tiers on offer. In the 100k Genomes project undertaken by Genomics England in partnership with the NHS, feedback from recruiters and participants was that when faced with a choice of consent tiers, people were often less concerned understanding the core offer of the study (genetic testing and diagnosis) and more concerned with understanding the consent tiers (whether to consent to testing only, or to consent to both testing and NGRL participation). This is one of the strengths of the all-in consent offer. Parents of potential newborn participants will have the opportunity to carefully consider the core research offer–ng-- screening and the return of actionable newborn findings. The Newborns Ethics Working Group challenged the research team to design a consent process that facilitates conversation and understanding of all aims of the programme. This way, parents can be clear on what they are signing up for if they wish to participate, and participant expectations match what the study expects to deliver. We argue that we have embraced this challenge as follows: • Through creating a robust set of user-friendly, accessible informative materials that have been user tested • Creating multimedia information sheets and decision aids, all of which have been user tested • Implementing a tiered withdrawal process that is emphasised in the Participant Information Sheet, and making withdrawal from the study very simple • We have consistently emphasised that this is a research study, and findings have not been clinically validated.

Confidentiality

The NHS Constitution for England sets out patient rights to privacy and confidentiality, to be informed about how data are used, and to decide whether their data can be used for research

purposes[192]. The common law duty of confidentiality holds that a person can reasonably expect that their personal information, in this case Confidential Patient Information (CPI), is held in confidence. Where CPI is to be used in research, explicit consent is required in order to have a legal basis for use of the data. Consent should be freely given, fully informed and from an individual with capacity to consent. These elements are reflected in the Generation Study Participant Information Sheet and consent form.

All information collected as part of the Newborns Genome Project will be treated confidentiality. Because the meaningful interpretation of genomic data requires information about an individual's health and medical history, this study proposes to link to a number of clinical data sets. Identifiable clinical, laboratory and the health data flowing from NHS and other organisations into Genomics England will be pseudonymised prior to storage within the Research Environment in line with the National Genomic Research Library Protocol. All study staff will be bound by the inherent duty to confidentiality given their roles as healthcare professionals.

Reimbursement of study expenses

Costs incurred through participation in this study will be minimal. Mothers/birthing parents delivering at home, who wish to travel to the hospital for sampling after the birth of the baby, will be reimbursed transport costs where appropriate. However, these parents will be encouraged to piggy-back their sampling visit onto a standard of care visit, where appropriate.

In the case of screen positive results, parents will be reimbursed for cost incurred in the initial visit for confirmatory testing.

Emerging ethical issues

In addition to the numerous, cross-cutting ethical issues that we have carefully considered in designing this study, there are some the magnitude and significance of which we cannot reliably predict in preparatory phases. We are aware that the following ethical issues may arise. These have implications beyond the ethical conduct of the programme, with wider societal significance and potential to cause psychological harms to participants and families:

- Possibly introducing stigma towards people with identified genetic variants
- Possibly medicalising babies - an aspect we are acutely aware of and will be addressed through honing our pipeline and through our site-based training (Section 16)
- Possibly undermining he notion of a well-baby, and consequently affecting bonding with the newborn.

Based on findings from similar studies, we are confident that these ethical issues should be rare in the Generation Study. For instance, in the BabySeq Study, a randomised control trial demonstrated that receiving genetic findings had no psychological affects for any of the 325 families enrolled[193]. However, we are well-prepared should these issues arise, and they are aspects of the study we will consistently monitor as we progress. The Generation Study boasts a robust ethical governance structure, and we will make use of the expertise this affords us should the need arise.

Unanticipated events and response

A number of situations requiring tailored and ad-hoc intervention may arise. When the Generation Study team becomes aware of these cases, this will be escalated to the appropriate touch-points within the governance structure for decision-making. This may also include escalation to external stakeholders within the governance framework if necessary.

Legal Considerations

There is a wide legal framework that medical research is required to adhere to. For the purposes of clarity in the protocol we have focussed on the law that is most relevant to the methodology.

Human Tissue Act 2004

Under the act, appropriate consent is required for the use of relevant material in research. Cord blood, and whole blood all constitute relevant material and the necessary consent will be in place in all cases. Explicit consent is required for DNA analysis to be undertaken. This is reflected in the consent materials.

HTA License Requirements

Samples for this project are being collected at NHS sites and will not be stored at this site for more than 7 days. There is no requirement for individual sites to be licensed by the HRA. Sample storage will be governed by the National Genomic Research Library Protocol and storage sites will have the required license.

UKGDPR and Data Protection Act 2018

Genomics England Ltd will act as the Data Controller of the project.

The lawful basis for processing personal data will be 'legitimate Interest' and in some cases 'consent'.

Article 5(1) (b) states that data must be:

- collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes.

As the data being processed includes special category data additional assurance for this processing can be found in Article 9 (2)(j): Processing is necessary for '… scientific or historical research purposes'.

The Data Controller has an obligation to ensure that data is processed in line with the purpose(s) for which it was collected. Explicit reference to what data are being collected, what they are being used for, for how long, where and how they are being stored and whom they are shared with are incorporated in the participant literature.

The Genomics England Data Protection Team have reviewed all relevant project materials for compliance, and carried out a Data Protection Impact Assessment.

Statutory Reporting and safeguarding

Although highly unlikely, it is possible that through our ongoing contact with participants, the study team may become aware of welfare issues, child abuse or neglect. Although there is no legislative requirement to report child abuse, there is an expectation that those working with children will do so unless there are exceptional circumstances.

If our team becomes aware of a risk to a child participant, it will be discussed with the CI and referred to the appropriate authority and / or relevant safeguarding partner that may variously consist of:

- The local authority,
- NHS Clinical Commissioning Groups (CCGs)
- Police force[194]

Insurance implications

Under the Code on Genetic Testing and Insurance (October 2018) (the Code) the results of whole-genome sequencing carried out in the research study are not disclosable to personal life insurers. Insurers have the normal expectation that patients will disclose relevant family history, other non-genetic diagnostic test results and GPs' reports when applying for new insurance. Under the Code, the results of other genetic tests do not need to be disclosed unless the test is for Huntington's Disease and the insured sum is over £500,000. The Code is evergreen and is subject to review every three years. We will continue to adhere to the Code throughout.

18. Data Protection and Cyber Security

Genomics England has implemented a multi layered approach to Data Protection and Cyber Security and is committed to keeping secure the data entrusted to us.

All our staff have to complete mandatory training as part of their induction, and this is then refreshed on a yearly basis to ensure their skills remain up to date and relevant. All staff are assigned the minimum permissions necessary to complete their roles and we use a centralised tool to manage this. Where we are processing particularly sensitive information, we have implemented additional controls and measures to keep this data even more secure.

Genomics England has implemented data protection by design and by default. Due diligence checks are carried out and appropriate contracts/data processing agreements are in place with all data processors. Data sharing agreements will be in place for all third parties who will share personal data with us for this project.

All our data is processed within UK Data Centres that meet the highest standards for security and are monitored 24x7x365. We have tools that continuously monitor who is accessing the data and that will then take steps to intervene should there be any unusual activity taking place. We ensure that these data centres have technology that restrict access and any communication across the networks that transmit this data is encrypted. Where it is appropriate to do so we also encrypt the data on the storage giving additional protection.

We keep our data segregated so that Researchers are only able to work on data that has been de-identified and for which they have been through an extensive approval process. Before they access any data they must also undergo data protection training and they are restricted to working within tight controls to ensure they do not remove any of the data we hold. Researchers can apply to export statistical analysis data based on the research they have completed however this is subject to a thorough review and approval process. There are sanctions in place for researchers who attempt to re-identify or remove data.

Genomics England works with partners across Government and the private sector to regularly test our cyber security resilience and defences. We work with our colleagues across Government to ensure we are implementing national guidance and we use external partners to ensure the technology we deploy gives us the greatest depth of defence. We also regularly review our partners to ensure that we have access to the latest technologies and obtain fresh insight on any vulnerabilities that may exist.

19. Publication and Dissemination of Results

Primary study results will be published in academic journals and relevant pre-print platforms. Results will also and be presented at conferences. Results will be made available to our stakeholders within the NHS, especially the National Screening Committee, at regular intervals through publication and presentation. Results will also be published on the Newborns Study Website.

Study progress and results will be communicated to participants through newsletters, these communications will be over-and-above the dissemination of study results.

20. Governance and Programme Management

Genomics England governance

Genomics England is a company set up by the Department of Health and Social Care (DSHC) in 2013, with the Secretary of State for Health and Social Care as the sole shareholder.

Governance and oversight for Genomics England is provided by the following groups:[195]

- **Executive Leadership Team**: The Executive Leadership Team works alongside the Board of Directors to set and influence our strategic direction, while providing leadership both within the organisation and externally, as ambassadors and thought leaders.
- **Genomics England Board:** The Genomics England Board oversees all of our activities, ratifies all major decisions and sets the overall strategy for the organisation. Genomics England has several independent advisory committees that report to the board. These include the Ethics Advisory Committee, Science Advisory Committee, Data Advisory Committee, Access Review Committee, GeCIP Board and the Audit Committee.
- **Participant Panel:** The Participant Panel sits at the heart of Genomics England and is made up of participants from the 100,000 Genomes Project, and parents or carers of people involved in this project. It is expanding to include patients and relatives from the GenOMICC COVID-19 study and NHS patients who give consent for their whole genome sequences and associated health data to be used for research in the Genomics England National Genomic Research Library. The Panel acts as an advisory body to the Genomics England Board, working to ensure that the health data held by Genomics England is being looked after with respect and used in the best interests of our participants.
- **Science Advisory Committee:** Our independent Science Advisory Committee advises the Genomics England Board on scientific aspects of the company's projects. This includes overseeing: disease inclusion criteria; Genomics England Clinical Interpretation Partnership (GeCIP) domain formation; data access request applications; and patient recruitment strategies. The Committee considers the interests of patients, the public, scientists and clinicians engaged in genomic research or genomic medicine.
- **Ethics Advisory Committee:** Our independent Ethics Advisory Committee identifies, defines, examines and responds to ethical issues across our projects. The Committee also helps to ensure projects and services are delivered in the interests of the public and of participants. The Committee provides advice, guidance, review and recommendations on ethical issues, as requested by the Board.
- **GECIP Board:** The Genomics England Clinical Interpretation Partnership (GECIP) consists of groups or 'domains', overseen by the GECIP Board. Each domain covers a different disease or topic. The groups are responsible for interpreting the data to improve clinical care, and also undertake complementary research, including medical, computational and social research.

The GECIP Board oversees the operation of GECIP and includes representatives from GECIP funders and the GECIP domains.

Genomics England-NHS England partnership governance

Genomics England works in close partnership with NHS England in a number of areas including in support of the NHS Genomic Medicine Service (whole genome sequencing service) and also in delivery of NHS embedded research studies including the Newborn Genomes Programme. The Partnership is managed through a monthly Partnership Executive Group meeting, jointly chaired by the Genomics England Chief Executive and the NHS England Chief Scientific Officer. The Partnership Executive Group reports to the NHS England – Genomics England Partnership Board, which is chaired by the Genomics England Chairperson and the NHS England Chairperson.

Newborn Genomes Programme governance

The Newborn Genomes Programme was approved by the Department of Health and Social Care in Spring 2022. Genomics England was funded to deliver the programme with £105m assigned from the Department of Health and Social Care, and overseen by the Office of Life Sciences.

Internally, the programme is supported by a multidisciplinary team, led by the Senior Responsible Officer, Dr Richard Scott, and Programme Director, Alice Tuff-Lacey. Programme Management is co-ordinated by a Programme Manager and team of Delivery Managers.

An internal Programme Board meets every six weeks to review progress, ratify decisions and monitor risks and issues. Risks, actions, issues and decisions are tracked and monitored in accordance with project management best practice. An Integrated Assurance and Approvals Plan (IAAP) is in place setting out key approvals and gates for the programme.

A Study Management Group meets regularly to oversee the operational running of the study, monitoring progress and managing issues.

External oversight and advice is provided by the following independently chaired groups, developed in partnership with the NHS. These groups will be modified during the course of the study to ensure the right support is available at different stages of delivery.

Table 5 External oversight and advisory Groups

Group	**Purpose**
Newborn Genomes Programme NHS Steering Group	To provide advice, strategic partnership and support with the design and delivery of the Newborns Genome Programme.
Newborn Genomes Programme NHS Clinical Assurance Group	Provides advice to the programme and also reports within NHS England to advise on the selection of conditions. Particular focus is on ensuring relevant expert sign off of each condition and pathway, the availability of treatments and the capacity of clinical pathways. Includes representation from relevant NHSE

	Clinical Reference Groups, the NHSE Genomics Unit, Specialised Commissioning, NICE and the UK National Screening Committee.
Newborn Genomes Programme Working Groups on: 1. Ethics 2. Recruitment 3. Education and Training 4. Evaluation 5. Conditions 6. Communication of results and onward support	Provide expert input on specific aspects of the Programme through regular meetings.

Appendix A: Research Questions and Evaluation Data Sources

This appendix sets out the research questions and expected data sources for the study evaluation across the four broad areas that the study will explore:

- Feasibility and acceptability
- Clinical utility, uptake and test performance
- Cost effectiveness and positive and negative impacts
- Experience and attitudes

The data sources are linked to the categories of data that are set out in Section 12 (Data Flows and Data Collection).

This work will inform, provide inputs for and respond to the work on the economic model.

As set out in Section 13 (Project Evaluation and Data Analysis), Genomics England will be working with an Evaluation Partner to deliver the process and impact evaluation for the newborn genomes programme. The Evaluation Protocol will govern and set out the process and impact evaluation in detail and additional participant-facing materials.

Feasibility, acceptability and uptake

Primary question

- Is the use of WGS as a tool for early diagnosis of rare, childhood-onset, actionable genetic conditions feasible and acceptable?

Secondary questions

Screening

- What are the effective approaches to implementation for delivery if WGS were to be adopted in clinical care nationally and could the approaches scale?
- Can information about genomic newborn screening be effectively conveyed and informed choices made in the healthcare setting?
- Can samples be taken consistently in a busy newborn setting and with sufficient quality to support WGS and analysis?
- Can a sufficiently rapid end-to-end turnaround time be achieved from sample to issue of (positive and negative) screening results to families (including confirmatory testing) to inform clinical care?
- Can findings be returned safely and effectively using the approach adopted for the study overall?
- Are the specific clinical pathways established for the disorders included in the study being followed
- Can we sustainably collect data on important outcomes for babies and families, and is the process of collecting this outcome sustainable to families?
- Is WGS as a tool for early diagnosis of rare, childhood-onset, actionable genetic conditions broadly acceptable by families?
- What are the demographic and other factors including personal choice that determine access and uptake? (To include indices of diversity including self-reported ethnicity and indices of socio-economic deprivation).

Supporting research

- Is the offer of participation in the National Genomic Research Library research offer alongside genomic newborn screening acceptable to the large majority of families?
- What proportion of families would chose for their baby to participate in the National Genomic Research Library or other models of research if offered alongside genomic newborn screening in routine care?
- What would the operational requirements be to offer participation in the National Genomic Research Library or other models of research alongside genomic newborn screening?

Longer term storage of genomic data for healthcare

- Is retention of WGS data following genomic screening for longer term use in healthcare acceptable to the large majority of families?
- What proportion of families would want their baby's genome retained after genomic newborn screening for longer term use in healthcare?

Data sources

Feasibility

Through collection of internal management information and with support from Genomics England regional coordinators embedded in NHS trusts, we will monitor the feasibility of delivering WGS in newborns, to include the following:

Data from End-to-end tracking

- Primary and secondary DNA sample collection rate by NHS trust and site by date
- Sample collection failure rate by sample type
- Sample processing failure rate by sample type and stage at failure
- Sample processing and transport time for the end-to-end journey, from sample collection to notification of the treating clinician or delivery of a 'no findings' letter

Data from Interpretation, reporting and return of results

- Time taken from notification of treating clinician to confirmation of diagnosis / ruling out a diagnosis.

Data from Interviews and questionnaires with healthcare teams

- Through interviews and focus groups with midwives, data on their experience of consent, sample taking and reasons for sample collection failure.

Acceptability

Data from End-to-end tracking and Recruitment

- The number of parents approached regarding participation in the study by NHS trust and site by date
- The number of participants consented by NHS trust and site by date.
- Consent rates by demographic factors collected during consent including ethnicity and age
- Numbers of parents that are referred for enrolment but fail on exclusion criteria and reasons why
- Numbers of parents that change their mind during enrolment and where possible reasons why
- Study withdrawal rates and where possible reasons why

Data from Interviews and questionnaires with participating families

- Through interviews and focus groups with midwives, we will also capture data on reasons for participants choosing not to participate in the study and their attitudes to genomic newborn screening, the National Genomic Research Library and longer term storage of genomic data for healthcare if they were offered routinely.

For further detail on qualitative measurement of acceptability, see section 5 on experiences and attitudes.

Test performance and clinical utility

Primary question

- What is the clinical utility of genomic newborn screening as judged by the number of apparent true positive screening diagnoses identified?

Secondary questions

Screening

- How many screen positive and how many would be expected if it were adopted nationally?
- What proportion of apparent false positive and false negative findings are there in the study according to each condition's working case definition?
- What proportion of babies have uncertain status following orthogonal testing according to each condition's working case definition
- What age are looked for conditions clinically diagnosed and treatment started with genomic newborn screening as compared to standard of care alone?
- What is the prevalence of the conditions looked for in the newborn population?
- What is the level of uptake of the programme and what would the level of uptake of genomic newborn screening be if it were adopted nationally?
- What are the demographic and other factors that determine outcome e.g., percentage apparent true positive findings? (To include diversity including self-reported ethnicity and indices of socioeconomic deprivation).

Data sources

Data from End-to-end tracking, Samples, sequencing and automated analysis, Interpretation, reporting and return of results, Healthcare records, Longitudinal data sources and from National and Local data sets on the Rare conditions comparator group

- The number of babies who have a 'condition(s) suspected' finding returned
- The number of babies in whom follow-up orthogonal and/or genomic testing indicates an apparent false positive screen result according to each condition's working case definition
- The number of babies in whom follow-up orthogonal and/or genomic testing indicates an apparent true positive screen result according to each condition's working case definition
- The number of babies in whom follow-up orthogonal and/or genomic testing results in uncertain status according to each condition's working case definition
- The number of babies in whom the study fails to identify a looked for condition (i.e., false negative finding)

- The age of confirmation of clinical diagnosis and commencement of treatment of looked for conditions in participants in the Generation study
- The number of children with a confirmed clinical diagnosis of a looked for condition in children in the comparator groups
- The age of confirmation of clinical diagnosis and commencement of treatment of looked for conditions in children in the comparator groups
- The parameters that influence these factors including ethnicity, gene and variant type

Data from Interviews and questionnaires with participating families and Interviews and questionnaires with healthcare teams

- Broader assessments of clinical utility will be explored through interviews and questionnaires with participating families and healthcare teams. This may include use of existing tools or their adaptation, for example C-GUIDE[196,197]

Cost effectiveness and positive and negative impacts

Primary question

- What is the cost effectiveness of genomic newborn screening compared to standard of care alone?

Secondary questions

Screening

- What is the impact on primary and secondary healthcare resource use including estimates of end-to-end costs – from recruitment, through sample processing, sequencing and interpretation through to clinical care?
- What are the healthcare workforce implications of offering genomic newborn screening?
- What is the impact (both positive and negative) of the programme on children, families, stakeholders and the wider system?
- What are the positive and negative impacts on health-related outcomes including: morbidity, mortality and quality of life?
- What are the positive and negative impacts on non-health-related outcomes including: perceived personal utility and psychosocial wellbeing?
- What is the impact on the wider family and society including: family member case identification, reproductive choices and patient and public values and preferences?
- What is the impact on uptake of existing newborn screening?
- What is the impact on the delivery of existing genomic medicine service in the health system?

Supporting research

- What is the additional cost of supporting linkage of genomic newborn screening to the National Genomic Research Library platform?
- What are the healthcare workforce implications of offering participation in the National Genomic Research Library or other models of research alongside genomic newborn screening?
- How many research studies observational clinical studies and clinical trials are registered with the programme?
- How many children receive a diagnosis as a result of research in the study and in what time frame?

- How many children participate in observational clinical studies through the study?
- How many children receive an intervention, experience a change in clinical management or access alternative healthcare as a result of research in the study?
- What is the broader research impact of the outputs from the discovery research supported by the study e.g., as measured by publications?

Longer term storage of genomic data for healthcare

- What are the end-to-end costs of maintaining genome data ready for healthcare reuse and collecting new genomic data as required?
- How many participating children have or are eligible for genomic testing that could be supported from whole genome data?

Data sources

Healthcare costs

Data from Healthcare records, Longitudinal data sources and Comparator data from National and Local data sets on the Population and Rare conditions comparator group

- We will also assess the downstream cost implications of the additional / fewer healthcare encounters that result from WGS.
- Data for participants will be sourced through linkage to secondary data such as Hospital Episode Statistics, the National Neonatal Dataset and prescription data, whilst comparator data will be identified through specialist clinical services, disease registries, participants in the 100,000 Genomes Project and / or longitudinal birth cohort data.
- Data on costs of healthcare encounters will be sourced through clinical contact and drug pricing data where applicable.

Data from Interviews and questionnaires with healthcare teams

- In addition to the above data, data from End-to-end tracking (e.g., on 'hands on time') and Interviews and questionnaires with healthcare teams will be used to explore the expected workforce implications of offering genomic newborn screening in routine care and of offering participation in the National Genomic Research Library

Data from Healthcare records, Longitudinal data sources and from National and Local data sets on the Population and Rare conditions comparator groups

- For each of the following areas, data from study participants will be compared with data from the both the Population comparator group and the Rare conditions comparator group.

Health care service usage

- We will seek to measure the health encounters (including primary care usage, A&E attendances, outpatient appointments, admissions, allied health professional appointments) for all 'true' positive participants as compared to age matched children in two groups: those with comparable diagnoses in the comparator group.
- Measurement will involve monitoring frequency and duration of health encounters over defined time intervals e.g., every 6 months.
- We will monitor the interventions (including procedures, medication and treatment) received by all 'true' positive participants as compared to age matched children with comparable diagnoses.

- Measurement will involve a suite of indicators which may include i) time from first clinical contact to first intervention, ii) age at first intervention, iii) frequency and duration of interventions over defined time intervals, iv) side effects experienced.

Quality of life, morbidity and mortality

- We will monitor negative and positive impacts on the quality of life parents of study participants as compared to parents of age matched children with comparable diagnoses.
- An appropriate instrument will be employed by our evaluation partner such as FACToR, PUGS or EQ-5D for data collection from parents of participants[198],[199], [200]
- We will seek to measure morbidity for all apparent true positive participants as compared to age matched children with comparable diagnoses in the comparator group.
- Measurement will involve a suite of indicators which may include i) developmental milestones reached, ii) outcomes from specific measurements used in clinical care e.g., Bayley scale / SOGs iii) growth[201]
- We will monitor the mortality of apparent true positive participants as compared to age matched children with comparable diagnoses in the comparator group.
- Measurement will include i) age at death, and ii) cause of death

Wider impacts on families

- Through surveys conducted by our evaluation partner, wider positive and negative impacts on families will be monitored to include impacts on parental mental health, reproductive choices such as prenatal genetic diagnosis and cascade testing in families.

Impacts on the health service (non-monetary)

- Through surveys conducted by our evaluation partner, impacts on workforce pressures will be measured to include impacts on clinicians, GPs, genomic counsellors, midwives, allied health professionals and GLHs.
- Impacts on uptake of the Newborns bloodspot will be measured at local level and National level through linkage to secondary data. Efforts will be made to ensure timely access to and analysis of data. Methods of social media monitoring will also be introduced.
- Impacts on turnaround time for the Genomic Medicine Service will also be monitored.

Experiences and attitudes

Primary question

- What are stakeholders' experiences and attitudes to the use of WGS as a tool for early diagnosis of rare, childhood-onset, actionable genetic conditions?

Secondary questions

Screening

- What are Health Care Professionals' and genomics experts' attitudes to and experiences of delivering genomic newborn screening?
- What are clinicians education and training needs?
- What are the broader public attitudes to genomic newborn screening?
- What is the family experience of joining the study?

- What are parents information and support needs to facilitate decision making, receiving results and ongoing care and support networks?
- What is the family experience of receiving results (screen negative and screen positive) and of the downstream pathways for those with a true or false positive screen?

Discovery research

- What is the family experience of joining the programme from the perspective of the research offer?
- What is the family experience of receiving new research findings or receiving or taking part in new research offers?
- What are the views of participants in the programme of the National Genomic Research Library and other research models?
- What are clinicians' and genomics experts' attitudes to and experiences of participation in the National Genomic Research Library or other models of research being offered alongside genomic newborn screening?
- What are broader public views on participation in the National Genomic Research Library or other models of research being offered alongside newborn WGS for screening?

Longer term storage of genomic data for healthcare

- What are clinicians' and genomics experts' attitudes to longer-term storage of genome data following newborn WGS?
- What are broader public views on longer-term storage of genome data following newborn WGS and on communication and involvement in the reuse of genome data?
- What are the views of participants in the programme on:
    - longer term storage of WGS data for healthcare use
    - their communication preferences with respect to potential data reuse
    - how they would want to offer their input into the reuse of the data
- Are there novel technical approaches – e.g., to data storage or access control – that could be employed and address public views or practical challenges?
- What are the additional clear 'red lines' and norms that need to be established before longer-term storage of genome data following newborn WGS could be adopted in mainstream care?

Data sources

Data from Interviews and questionnaires with participating families

- Through surveys conducted by Genomics England's User Research team, parents experiences and attitudes to participating in the study will be explored.
- Through surveys conducted by our evaluation partner, parents experiences and attitudes of receiving results in the study and of potential future models of delivery will be explored in representative groups of families receiving 'condition(s) suspected' and 'no condition suspected' results.

Data from Interviews and questionnaires with healthcare teams

- Through surveys conducted by our evaluation partner, health care professional experiences and attitudes to WGS in newborns across the three aims of the programme

will be explored to include those of clinicians, GPs, genomic counsellors, midwives, scientists, commissioners and rare disease support groups.

- These will be supplemented, as in other areas by surveys conducted by our evaluation partner, public experiences and attitudes to WGS in newborns across the three aims of the programme will be explored. This will be designed to be complementary to the broader engagement work delivered by Genomics England (see Ongoing engagement in Section 4).

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