Genomics England | Generation Study

The Generation Study

Metbionet annual BMS training day

30 January 2024

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Agenda

1. The Generation Study
2. Ethics, Engagement & Education
3. Choosing Conditions
4. Return of results
5. Evaluation and next steps

The Generation Study

Our research study's focus

Three parts | All subject to ethics committee approval

** Key point: not just how each might be implemented, but whether they should be implemented.**

01

Evaluating the utility and feasibility of screening newborns for a larger number of childhood-onset rare genetic conditions in the NHS using whole genome sequencing

02

Understanding how babies' genomic data could be used for discovery research, focusing on developing new treatments and diagnostics for NHS patients

03

Exploring the potential risks, benefits, and broader implications of storing a baby's genome over their lifetime

Key numbers

Research study beginning **in 2023**

2022 — **2023** — 2024 — 2025

Aiming to find some of the **9** children born each day in the UK with a rare, treatable genetic disease – where early intervention is crucial

1,000

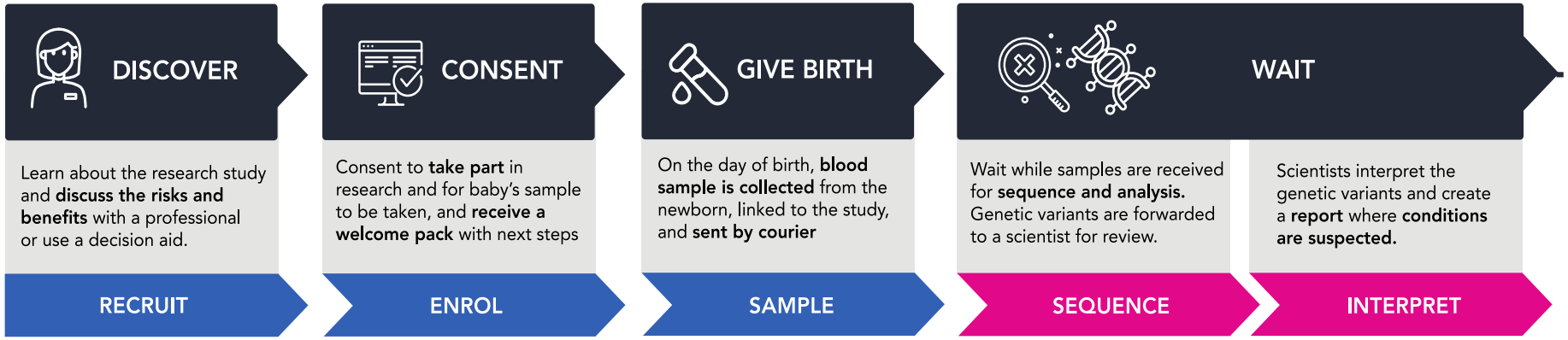
Expecting 1,000 **positive results** during the study

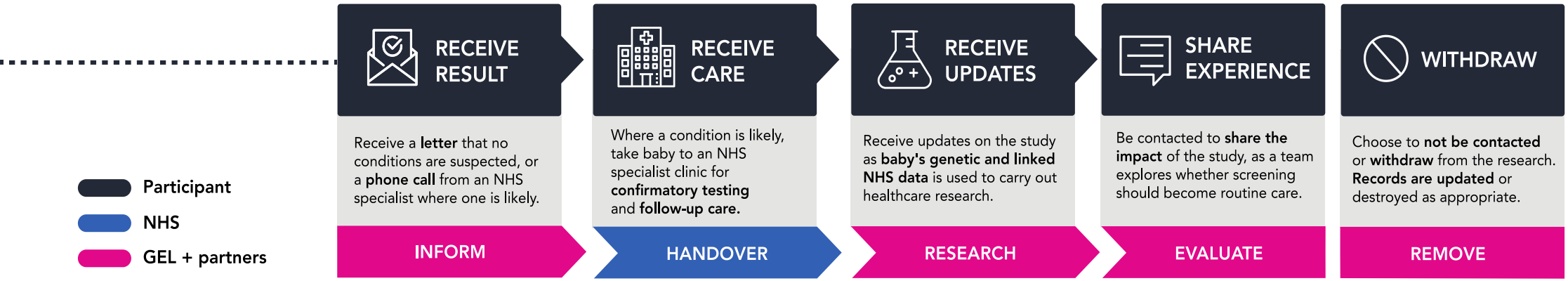
To find these children, we'll analyse

100,000+

newborn genomes for a specific set of childhood-onset, actionable conditions

Participant experience





The locations of our study

NHS sites **throughout England**

Factors we're considering when choosing sites:

- Birth volumes
- The diversity of people who use the hospital
- Maternity department performance

Site opening will be in stages

- Starting with **3-5 trusts**
- Increasing up to **40 trusts**

Barts Health NHS Trust

Birmingham Women's and Children's NHS Foundation Trust

Cambridge University Hospitals NHS Foundation Trust

Chelsea and Westminster Hospital NHS Foundation Trust

University Hospitals Bristol and Weston NHS Foundation

Frimley Health NHS Foundation Trust

Guy's and St Thomas' NHS Foundation Trust

Imperial College Healthcare NHS Trust

Liverpool Women's NHS Foundation Trust

Manchester University NHS Foundation Trust

Oxford University Hospitals NHS Foundation Trust

The Newcastle upon Tyne Hospitals NHS Foundation Trust

University College London Hospitals NHS Foundation Trust

University Hospitals Birmingham NHS Foundation Trust

Ethics, Engagement & Education

Ethical questions and issues

Consent

What is the optimal approach to consent to each of the research study's three parts?

Data

How can information governance support ethical storage, use, access, linkages of newborns' data?

Values

What values should underpin our research study?

Equity

How can design and delivery of the research study be undertaken equitably?

Answering these questions will help us to understand the optimal approach to:

- Pre-symptomatic care and treatment
- Diverse representation in our research study
- Additional findings
- Interpreting and sharing results or diagnoses
- The potential of storing, and reanalysing, a baby's genome over their lifetime
- Treatment and care pathways
- Workforce
- How we frame, describe, and communicate the research study

Engagement projects

Discovery research dialogue

- Deliberation with 112 members of the public – in person and online (north and south)
- Understanding the red lines for, and acceptability of, discovery research with newborns' genomic data
- Discovery research case studies; and working with researchers

Engaging with ethnic minority community leaders

Developing a more comprehensive view of ethnic minorities' attitudes towards:

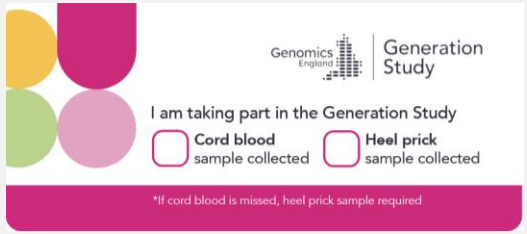
- Consent model;
- Potential barriers to participation (and how we can overcome them)
- Communicating optimally with different communities
- *(in scope: Pakistani; Indian; Black African; Black Caribbean; Gypsy, Roma and Traveller communities)*
- Focusing on community-based, voluntary, and civil society organisations – building ongoing relationships

Pilot Public Standing Group on Ethics

- Involving an informed public group in the NGP (2021 dialogue participants) - 21 members
- 3 meetings: TORs; ethics issue (tbc); evaluation
- After the pilot: decision on whether to continue – subject to resources

Staff training and engagement

- Training will be modular; different roles can just attend the parts they need and access information in different formats
- Materials to be available on demand online, via SOPs, with crib sheets and reminder cards
- GMSAs being funded to provide regional support for ongoing E&T and general wider awareness
- Items to help identify participants and remind staff to take samples:
  - Stickers, magnets, reminder cards and staff room posters, sluice-room reminders, heel prick cards, plus small thank you items
- Educators retreat 6-7 Feb 2024 at Wellcome Genome Campus



Generation Study

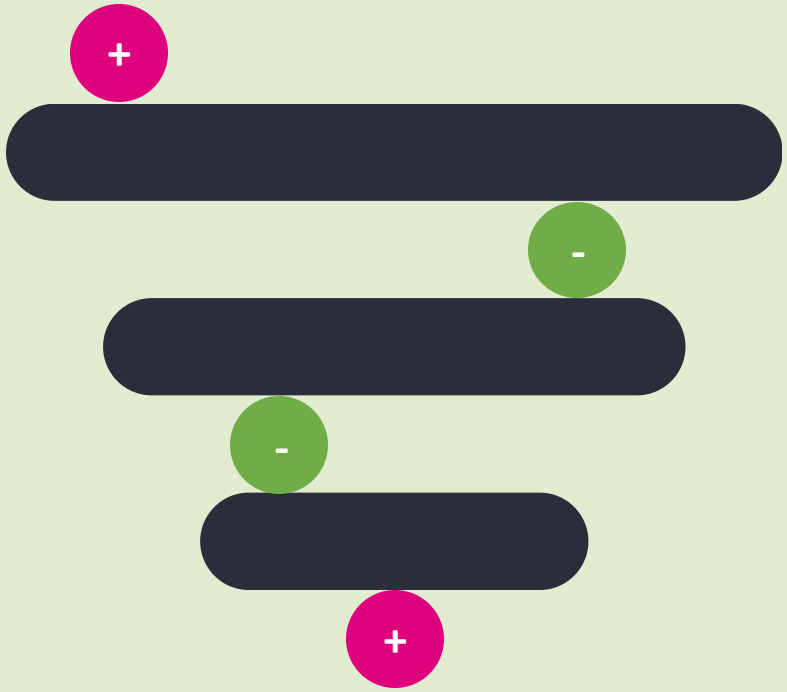
Choosing which conditions to screen for

Choosing which conditions to screen for

The challenge: there are thousands of conditions that could be detected through whole genome sequencing – but we may not want to look for all of them

The programme will only screen for a specific set of conditions, genes, and variants

Principles and criteria for screening already exist – we have developed a bespoke set of principles.



Principles

Overview

Principle A: there is strong evidence that the genetic variant or variants cause the condition and can be reliably detected

Principle B: a high proportion of individuals who have the genetic variant or variant would be expected to have symptoms that would have a debilitating impact on quality of life if left undiagnosed

Principle C: early or pre-symptomatic intervention for the condition has been shown to lead to substantially improved outcomes in children, compared to intervention after the onset of symptoms

Principle D: Conditions screened for are only those for which the interventions are equitably accessible for all

How we're identifying which genes and variants to assess

Rx-genes.com

- Website developed by clinical geneticists
- Catalogues genetic conditions
- Helped us to identify approximately 700 childhood onset, rare conditions that could be treated or have other interventions

Working with paediatric specialists

- Identifying specialists through clinical networks, royal colleges, and professional institutions
- Building relationships with those clinicians, as they'll be 'making the call' to parents where a condition is suspected
- Asking them to review and suggest genes that relate to their specialism

Obtaining input from the NHS and Experts

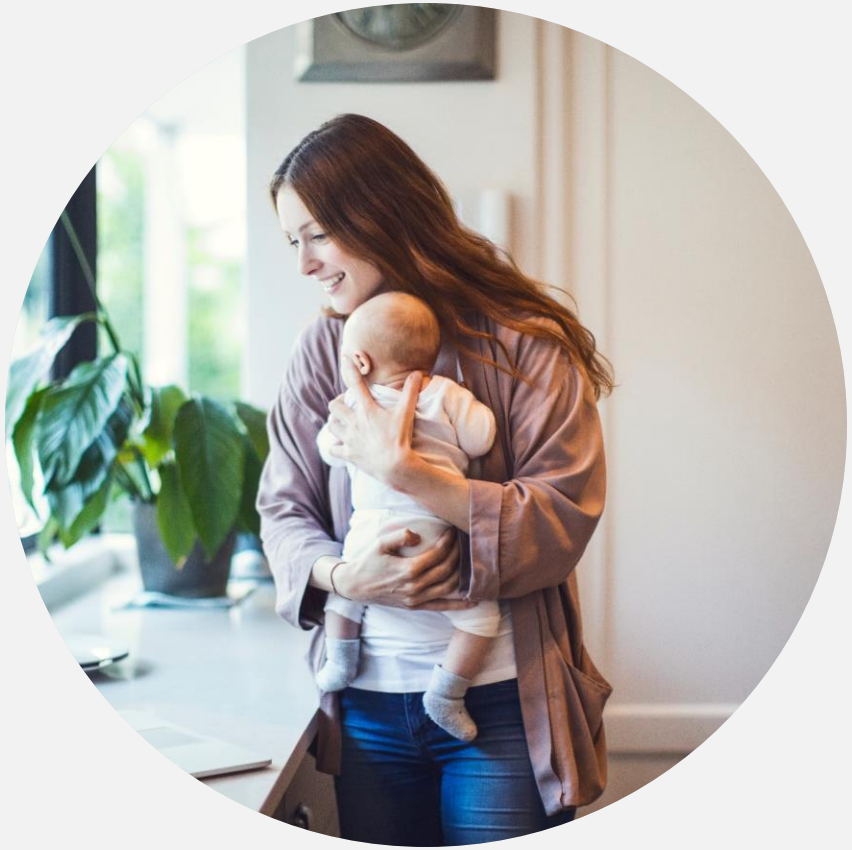
Meeting with National Specialty Advisors and NHS Commissioners

Seeking expert input on:

- Whether a condition meets the four principles
- Availability of treatment
- Establishing networks for returning ‘condition suspected’ results.

NHSE Newborn Genomes Programme Clinical Assurance Group

Role: to ensure that for each condition included, appropriate NHS services and clinical pathways are in place and able to accept children identified through the Generation Study.



To date: 834 genes reviewed 480 selected representing 228 conditions.

- This list is **not set in stone**
- Likely that conditions will be **added,** or **removed,** in response to emerging evidence
- Where changes are made, they will be highlighted in an **amended** published list
- Work will continue to define **variants** and **clinical pathways**

Analysis

- A bespoke bioinformatic pipeline has been developed
- Aims to only prioritise Pathogenic/Likely Pathogenic Variants
- All prioritised variants will be manually reviewed by a clinical scientist
- Handling of an individual gene/condition pair depends on the inheritance pattern and mechanism of disease:
    - Look for known P/LP variants (ClinVar, CVA, purchased list)
    - pLOF prioritisation
    - Custom inclusion list e.g. *RET* related MEN2
    - Special caller e.g. SMA
    - CNVs
    - Exclusion list e.g. Duarte Variant in *GALT,* known artefacts
- This approach aims to maximise specificity.

Confirmatory Testing and Referral Pathways

Confirmatory Testing Pathways

- Condition specific guidance on:
  - Urgency of initial review
  - Confirmatory testing
  - Outline of management
  - Location agnostic

Referral Pathways

- Clinical contact information by GMSA
  - Populated by GMSA and Commissioners
  - Incorporating advice from clinicians for certain conditions.
  - GMSA check that the team are willing and able to receive referrals from the GS.
  - Regional coordinator responsible for maintaining the list.

Return of results

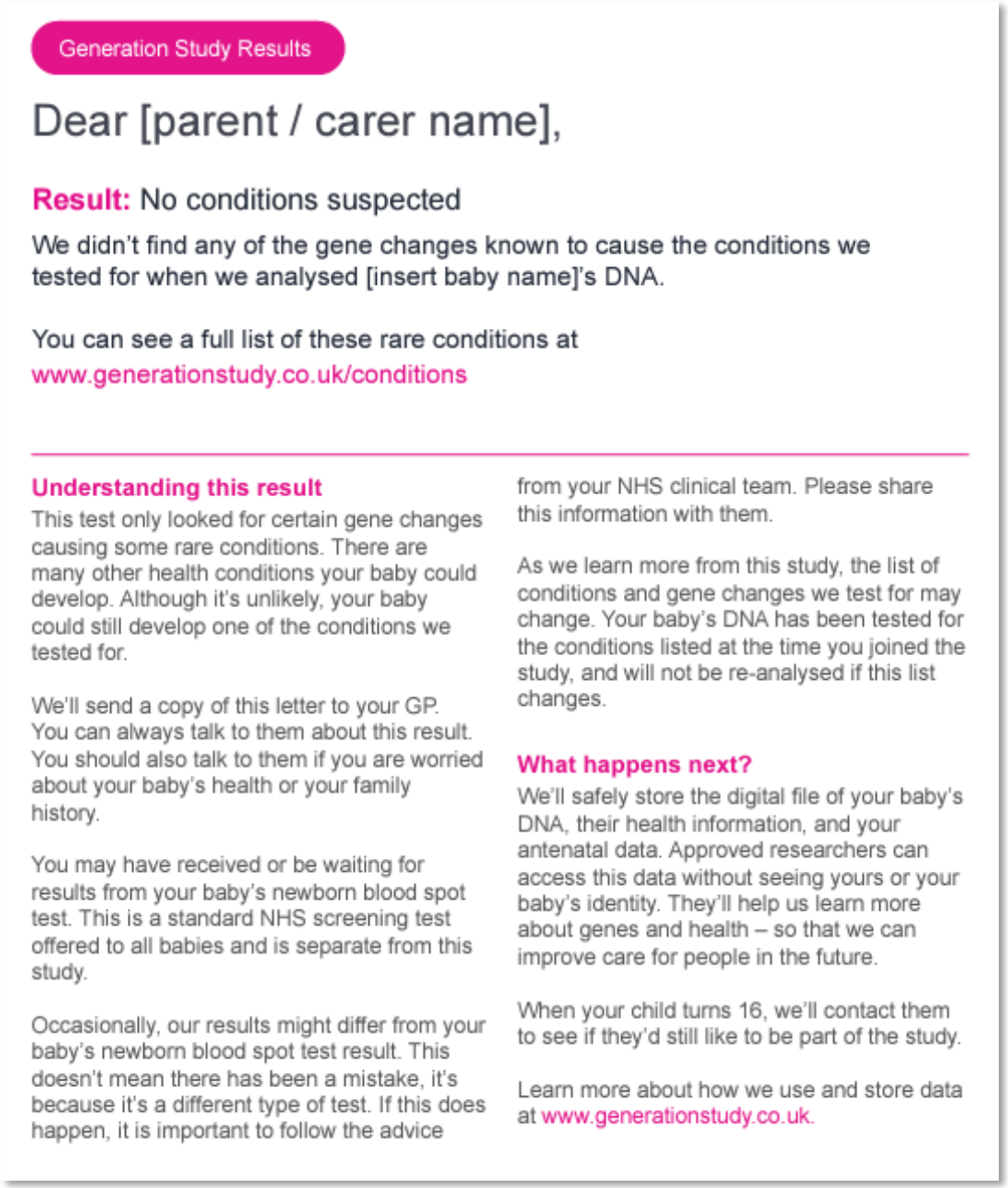
Communicating results

- **Communicating** 'no conditions suspected':

- **~99% of babies**
- How: by email/letter, a few months after birth
- Sent by Genomics England to parents, with a copy also sent to the baby's GP for their record
- Includes information about what to expect in the future as a study participant

Communicating 'sample failure / no results returned':

- How: by email/letter
- Sent by Genomics England to parents
- May occur if samples are not taken or the test could not be completed



Generation Study Results

Dear [parent / carer name],

Result: No conditions suspected

We didn't find any of the gene changes known to cause the conditions we tested for when we analysed [insert baby name]'s DNA.

You can see a full list of these rare conditions at www.generationstudy.co.uk/conditions

Understanding this result

This test only looked for certain gene changes causing some rare conditions. There are many other health conditions your baby could develop. Although it's unlikely, your baby could still develop one of the conditions we tested for.

We'll send a copy of this letter to your GP. You can always talk to them about this result. You should also talk to them if you are worried about your baby's health or your family history.

You may have received or be waiting for results from your baby's newborn blood spot test. This is a standard NHS screening test offered to all babies and is separate from this study.

Occasionally, our results might differ from your baby's newborn blood spot test result. This doesn't mean there has been a mistake, it's because it's a different type of test. If this does happen, it is important to follow the advice from your NHS clinical team. Please share this information with them.

As we learn more from this study, the list of conditions and gene changes we test for may change. Your baby's DNA has been tested for the conditions listed at the time you joined the study, and will not be re-analysed if this list changes.

What happens next?

We'll safely store the digital file of your baby's DNA, their health information, and your antenatal data. Approved researchers can access this data without seeing yours or your baby's identity. They'll help us learn more about genes and health – so that we can improve care for people in the future.

When your child turns 16, we'll contact them to see if they'd still like to be part of the study.

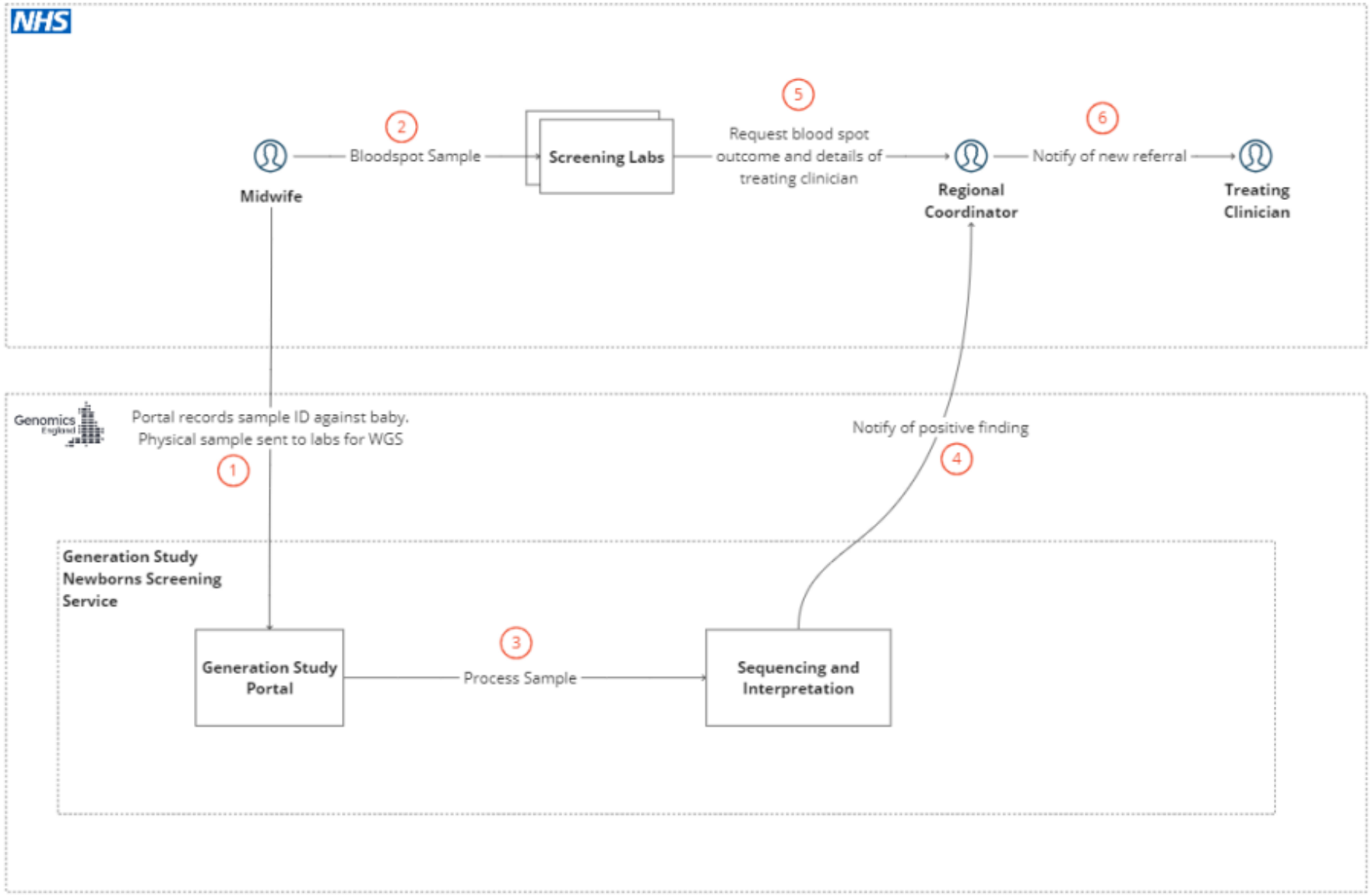
Learn more about how we use and store data at www.generationstudy.co.uk.

Return of ‘condition suspected’ results

Avenues of support:

- NHS Specialist team (consultants, nurse specialists, psychologists, allied health professionals)
- Additional study-funded genetic counselling
- Patient charity organisations
- Genomics England Service Desk

Screening Lab, GEL Interface Data Flow Diagram



Non-Genomic Confirmatory Testing

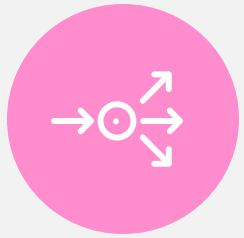
- Principle A "… Where appropriate, there may be a confirmatory test that can establish whether or not the child has the condition"
- Genotype first
- In a baby with this genotype, which biochemical test would provide evidence that the baby has the condition?
- Samples should be processed at usual lab for the test in the region.

Timetable and evaluation

Evaluation framework

Process Evaluation

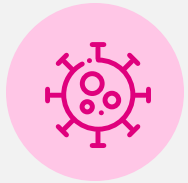
Performance Dashboard



Impact Evaluation

Economic Model

Five core areas



Feasibility & acceptability

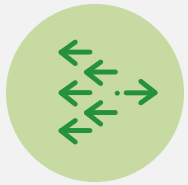
Is the use of WGS as a tool for early diagnosis of rare, childhood-onset, actionable genetic conditions feasible and acceptable?

Uptake & results

What is the clinical utility of genome-led newborn screening as judged by the uplift in screen-identified diagnoses compared to standard of care?

Cost effectiveness

What is the cost effectiveness of genome-led newborn screening compared to standard of care, estimated by a health economic model developed to support the programme?

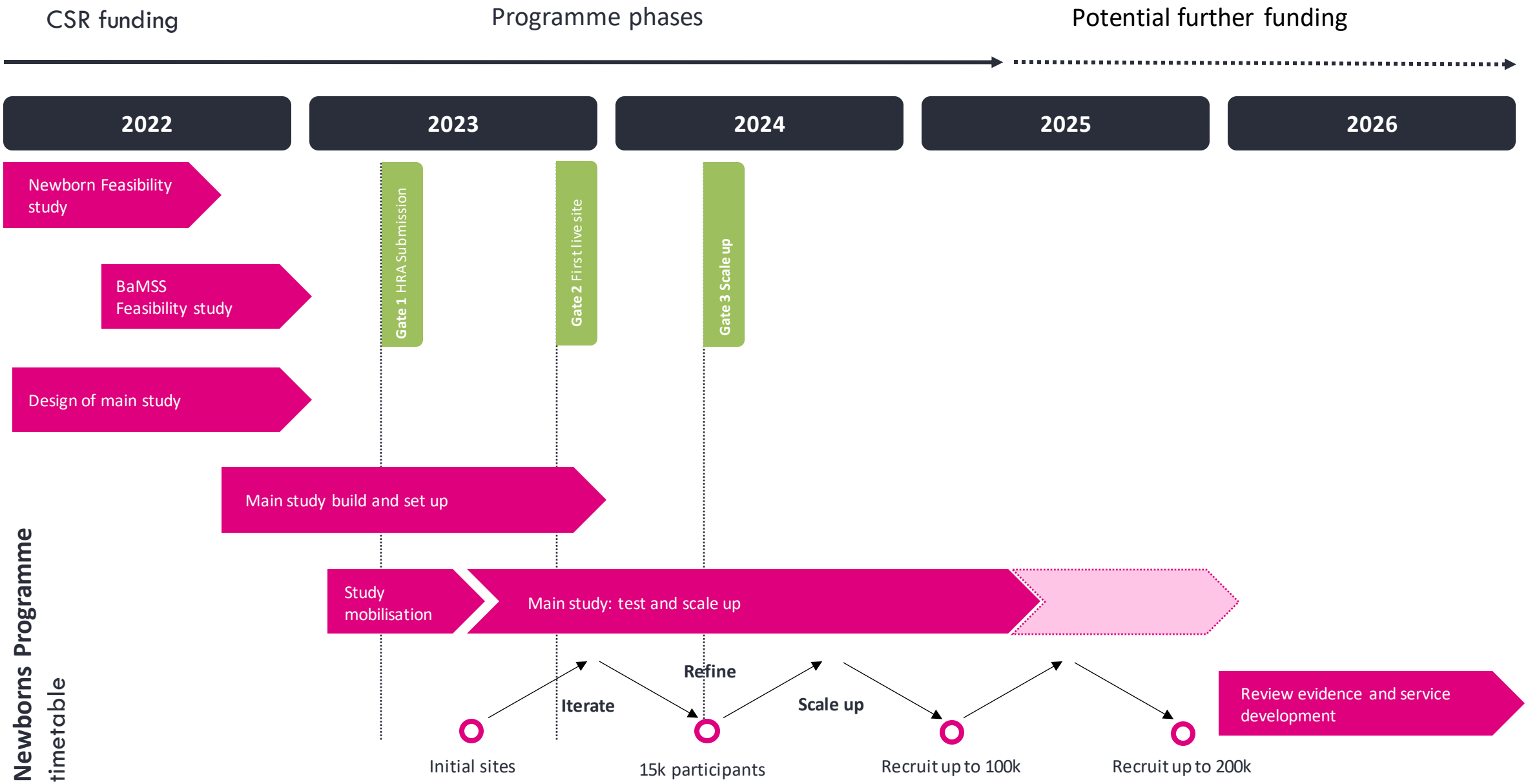


Impacts

What is the impact (both positive and negative) of the programme on stakeholders and the wider system?

Experiences & attitudes

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


CSR funding
Programme phases
Potential further funding
2022
2023
2024
2025
2026
Newborn Feasibility study
BaMSS Feasibility study
Design of main study
Main study build and set up
Study mobilisation
Main study: test and scale up
Gate 1 HRA Submission
Gate 2 First live site
Gate 3 Scale up
Refine
Iterate
Scale up
Initial sites
15k participants
Recruit up to 100k
Recruit up to 200k
Review evidence and service development
Newborns Programme timetable

Research study endpoints

By the end of the Generation Study, we will have:

- Sequenced the genomes of up to 100,000 newborns from across England
- Established an evidence base on what the screening of those babies means for future treatment and research with newborns
- Provided the data needed to evaluate the research study's outcomes, to inform future policy

Questions?

https://www.genomicsengland.co.uk/initiatives/newborns

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Thank you

Visit: www.genomicsengland.co.uk