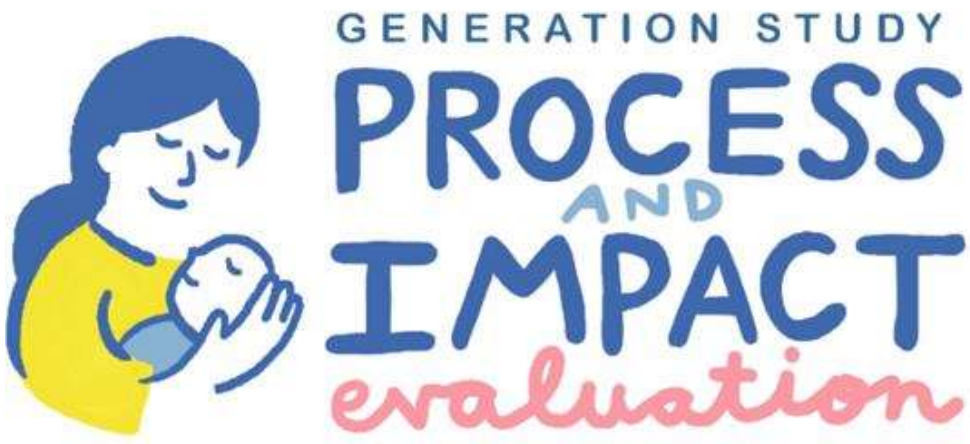
Generation Study

Process and Impact Evaluation

Interim Report executive summary

28 May 2025



EXECUTIVE SUMMARY

BACKGROUND

Genomic newborn screening (gNBS), in which DNA sequencing is used to identify infants at risk of having an inherited or congenital condition before symptoms arise, is being explored across many countries as a method of expanding current newborn screening programmes. The Generation Study, funded by the UK government and run by Genomics England, is a large-scale research initiative aiming to explore the benefits, challenges, and practicalities of offering whole genome sequencing (WGS) to parents of newborns. The UCL-led Process and Impact Evaluation of the Generation Study is providing an independent mixed-methods evaluation of the use of gNBS to assess the feasibility, acceptability, impact, and experiences and attitudes of both parents and healthcare staff, as well as to understand the associated costs and clinical utility. Two advisory groups have been set up to oversee and guide the evaluation: a Study Advisory Group (with members from academic, clinical and PPIE backgrounds) and a Patient and Public Involvement and Engagement Advisory Group (PPIE AG) comprised of five parents and two patient group advocates. Both groups have met three times since the start of the evaluation.

KEY FINDINGS TO DATE

Scoping Study

A scoping exercise was conducted to review the data collection approaches being used in eight gNBS projects around the globe. Data collection tools were reviewed by the evaluation team for consideration in the Study 2 parent survey and interview topic guides.

Study 1 - Identifying goals, challenges and early lessons in implementation

To date, we have conducted interviews with 19 professionals involved with designing the Generation Study and experts in genomics and newborn screening ("designers and experts"), and 38 staff delivering the Generation Study ("early implementers"). Observations of recruitment and consent processes have taken place at four NHS sites. Interviews with professionals involved in returning results to parents are underway.

Designers and experts identified key facilitators and challenges associated with the design and delivery of the Generation Study.

Facilitators perceived by the designers and experts included:

- Designing the study over a long time-period including extensive consultation with key stakeholders and considerable user-design of materials
- Training events to prepare health professionals for recruiting parents and collecting samples
- Setting up of mobilisation workshops with early recruiting sites to share feedback with Genomics England and enable learning and early insights to be passed on
- The flexibility built into the study design whereby sites could direct their own recruitment processes i.e. how, by whom and at what time point parents are first approached about the study

Challenges and concerns perceived by the designers and experts included:

- The initial 18 months proposed to conduct the study was ambitious
- Ethical concerns around parents providing proxy-consent for their babies
- Concerns that parents should not be be asked to consent for both screening and storge of genomic data at the time of consent
- Payment of sites is based on number of recruits which could affect diversity with sites prioritising 'easy recruits'
- Lack of time preparing health professionals who might return condition suspected or condition confirmed results as well as specialist practitioners such as General Practitioners not directly involved in the study
- Biochemical testing was not also being conducted for all recruited babies to enable comparison across methods
- Concerns that gaps in the current understanding of penetrance for many of the conditions being screened for could result in unnecessary anxiety for parents

Common facilitators for delivering the Generation Study noted by staff implementing the study across sites included:

- Having dedicated research staff focused on discussing and consenting parents
- The importance of fostering support and engagement amongst wider clinical teams to spread awareness about the study across the Trust
- Good communication and support from the team at Genomics England to address emerging problems and queries as sites begin recruitment

Perceived barriers and challenges included:

- A need for additional training sessions for new staff, difficulties with staff recruitment and retention in part due to lack of funding and high turnover
- A need for increased administrative support so that research staff could focus on recruitment rather than administrative tasks
- Numerous changes to study documents were excessive and difficult to keep on top of
- Issues accessing the study portal
- Concerns around recruitment being focused on numbers not diversity which could be addressed if there were more staff supporting recruitment
- Whilst study materials had been made in numerous languages, there was still a need for additional languages to be developed

GMSA staff reported mixed experiences of the specialist mapping process, with some indicating that the clinicians they contacted were happy to be involved in the study, while others reported encountering resistance. Some also expressed concerns about the possibility of being unable to contact parents with results, for example if the parents moved out of the country before they received the results.

Staff involved in recruiting parents commented that parents noted that the main reasons parents joined the Generation Study were a desire to take advantage of any additional tests

on offer, feeling that taking part could benefit their child directly through accessing treatment early, and/or for reassurance that their baby did not have one of the conditions being looked for. The most commonly cited reasons for declining to take part were related to how long the data would be stored, what the genomic data would be used for and how taking part might affect their insurance.

Study 2 - Impact, experiences and attitudes of parents

We are conducting a survey and a subset of follow-up interviews with parents who are taking part in the Generation Study. Surveys are being circulated three months following receipt of gNBS results to assess acceptability, experience, attitudes, quality of life and impact (positive and negative).

To date we have designed and piloted the survey that comprises validated health-related and non-health-related quality of life measures (parent-child relationships, parent anxiety, decisional regret, personal utility of genomic results) as well as bespoke questions to assess out-of-pocket expenses and satisfaction with the process of receiving results. The interview topic guide explores decision-making processes, reasons for consenting, concerns around gNBS, emotional and practical impacts of receiving results and general reflections on gNBS. The survey was piloted by sending to the first 19 parents to have received results from the Generation Study. Following minor changes to the survey wording, survey recruitment and follow-up interviews with survey respondents are underway. The revised surveys have been sent to 100 Generation Study participants with a "no condition suspected" result and 8 participants with either a "condition confirmed" or "false positive" result. Follow-up interviews have been conducted with four participants.

Study 3 - Gathering wider professional viewpoints about the Generation Study and gNBS implementation

A survey with staff delivering the Generation Study at early adopter sites and professionals from a range of relevant backgrounds across England has been developed to examine the wider workforces' experiences and attitudes to the use of gNBS. The survey will be disseminated through participating NHS Trusts as well as professional bodies and conferences.

Study 4 - Views of the rare disease community

An online survey (conducted between October-December 2024) and ongoing semi-structured interviews are exploring the views of representatives from rare disease support groups to determine attitudes to gNBS, including positive and negative impacts as well as unintended consequences on parents and the rare disease community more broadly. In total we received 59 eligible survey responses (response rate 20%) and 20 in-depth follow-up interviews have been conducted.

Initial results from the survey indicate variation in the level of knowledge the support organisations have about how the pilot will be carried out, including understanding how conditions were selected. There were varying levels of involvement by support groups in the development of the pilot. Thirty-nine percent of the respondents indicated that their organisation had been involved in consultations on the 'Condition Information Sheets' for

parents of a baby with a suspected condition. Only 7% of respondents felt that they had had a lot of involvement in designing the Generation Study and 20% agreed or agreed strongly that they had had as much involvement as they wanted. About two thirds of respondents (66%) did not know that Genomics England runs a service desk (phone and email helpline) for information about the Generation Study. For 49% it was extremely or very important to the function of their organisation to be well informed about the Generation Study. Just over half the organisations (54%) felt very or somewhat prepared to support someone who contacts them about the Generation Study and 48% felt that responsibility for provision of information should sit equally between NHS England / Genomics England and support organisations. Respondents' assessments of the benefits of gNBS outweighed their view of the potential risks - 85% felt that the benefits greatly outweighed the risks.

Study 5 - Public views

We will conduct a public survey with new mothers not invited into the Generation Study to explore their views around the acceptability of gNBS. Questions will be informed by the survey and interview findings from Study 2.

Study 6 – Health economic evaluation

We are currently conducting several sub-streams of work as part of Study 6 to estimate the costs associated with sequencing newborns in the Generation Study, as well as the health-related and non-health-related outcomes. The results of these analyses will be used as inputs into the decision-model being developed by Genomics England to assess the potential cost-effectiveness of a national gNBS programme.

We have performed a micro-costing study to estimate the total cost per baby for both the gNBS and current newborn screening programmes. The costs of recruitment, consent, sample collection, and registration have been calculated per site and weighted by site-specific recruitment rates to calculate mean and median costs per newborn across the six gNBS sites. The average sequencing cost for gNBS per newborn has also been calculated, as well as the cost of the current newborn bloodspot programme. These findings have been presented to Genomics England, and we are currently updating our estimates based on the feedback we have received. It is important to note that this analysis is based on assumptions from a specific research service model and publicly available laboratory protocols and pricing, which may limit the generalisability of our estimated costs for future national implementation.

Data collection to estimate the impact of gNBS on out-of-pocket and productivity costs is underway as part of Study 2. We will also be using individual-level Hospital Episode Statistics data to quantify secondary care resource use and costs as this data becomes available through Genomics England. Further, we are exploring the use of Clinical Practice Research Datalink (CPRD) data to estimate the primary care costs accrued by children with inherited conditions screened in the newborn screening programme. We will consult with expert clinicians to determine the potential impact of a gNBS programme on these costs.

Data for health-related quality of life and non-health outcomes for babies participating in the Generation Study is also being collected by Study 2. We conducted a literature review to

identify estimates of the outcomes for babies in the existing newborn screening programme as potential inputs to Genomic England's economic model.

Finally, interviews with designers and implementers (Study 1) and healthcare professionals (Study 3) will be used to inform our analysis on the costs of implementing and scaling up gNBS as a national service.

Study 7 – Clinical utility assessment

In the final six months of the evaluation, we will assess the impact of introducing gNBS on health outcomes, using longitudinal healthcare data that are being linked to the Generation Study. In a series of cohort studies, we will compare health service use and mortality for children who received a confirmed diagnosis from gNBS with children with similar conditions who were diagnosed through routine clinical practice, false positives, children in the Generation Study who test negative, and the general population of children in England, while accounting for differential selection into the Generation Study.