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The Generation Study

Submission date 30/05/2023	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 29/06/2023	**Overall study status** Ongoing	
Last Edited 26/06/2026	**Condition category** Genetic Diseases	

Plain English summary of protocol

Background and study aims
Each year in England, about 3,000 babies are born with one of about 200 genetic conditions that are treatable in early childhood. Nine of these conditions are currently looked for in the NHS newborn bloodspot test. But there are many more conditions where earlier diagnosis and treatment could help. This study investigates the genomes of newborn babies to see if we can find and treat rare genetic conditions early. A genome is a person's entire genetic sequence – the body's instruction manual. The study team want to see if, by testing babies' genomes, any standard treatment and management of the rare conditions can be initiated earlier.

Who can participate?
Pregnant/expectant mother or birthing parent, aged 16 or over who have parental responsibility for the baby

What does the study involve?
Parents will be asked if they want to take part while they are pregnant. If they consent, a sample of blood from the umbilical cord will be taken from the baby after they are born. In some rare cases, a heel prick may be required. These samples will have DNA extracted that will be analysed by scientists to look for around 200 rare genetic conditions that can be treated early in childhood. Results will then be sent to parents. If a condition is suspected, the baby will be referred to the NHS for confirmation testing and management. We think only 1% of newborns will be suspected to have a condition. We'll safely store the samples, genome sequence, antenatal data and regular updates from the baby's healthcare record in our ethically approved database, the National Genomic Research Library (NGRL). Approved researchers will study this data to learn more about genes and health – without knowing the identity of the baby. When the child is 16 years old we will contact them and they can choose whether they wish to stay in the NGRL.

What are the possible benefits and risks of participating?
The benefits of participating are that the baby will be tested for 200+ rare genetic conditions. It is rare but possible that this will identify a condition early. The baby can then get early treatment, which could help reduce their symptoms or stop them from becoming ill. Taking part also helps researchers learn more about the link between genes and health. Their work could help develop new treatments. It could also help predict or diagnose conditions more quickly in the future.

The risks from participating are that a sample from the baby's heel will be collected with a tiny needle if it has not been possible to collect a sample from the umbilical cord. This could cause them temporary discomfort. The baby could get an incorrect result. This study is for research and is not a diagnosis. This means there is a small chance we could get the baby's result wrong. Parents could feel uncertain about the results. It might be stressful to wait for results. If it is suspected that the baby has a condition, the participants need to have follow-up appointments with the NHS. This could take some time. Because these conditions are rare, there might not be a lot of information available. Parents and babies could be identified through the data. In rare circumstances, a researcher could match parent or baby names with their data. We have safeguards in place which make this very unlikely.

Where is the study run from?
Genomics England (UK). The study will take place in 25-40 NHS hospitals in England, and where the hospital supports it, this will include homebirths.

When is the study starting and how long is it expected to run for?
June 2022 to December 2040

Who is funding the study?
Department of Health and Social Care (DHSC) National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
Generation Study Team, generationstudy@genomicsengland.co.uk

Contact information

Type(s)
Scientific

Contact name
Dr . Generation Study Team

Contact details
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London
United Kingdom
E14 5AB
-
generationstudy@genomicsengland.co.uk

Type(s)
Principal investigator

Contact name
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E14 5AB
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Additional identifiers

Integrated Research Application System (IRAS)
324562

Central Portfolio Management System (CPMS)
56000

Study information

Scientific Title
The Generation Study

Study objectives
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.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 23/05/2023, East of England - Cambridge Central (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)2071048384, 02071048286; cambridgecentral.rec@hra.nhs.uk), ref: 23/EE/0044

Primary study design
Interventional

Study design
Non-randomized interventional study design type

Study type(s)
Screening

Health condition(s) or problem(s) studied
Rare genetic conditions

Interventions
This is a quantitative, longitudinal birth cohort study in which newborn babies and their birthing parents will be recruited. The study aims to gather data relevant to both the pregnancy (at one timepoint) and the child (longitudinally). Initially, 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.

All babies enrolled in the study will undergo the study intervention, which involves whole genome-led newborn screening for approximately 200 treatable childhood conditions, in addition to receiving standard care through the Newborn Blood Spot Test. The study will follow a quasi-experimental approach, comparing data from babies born at centers not participating in the study.

The primary objective is to evaluate the utility, clinical effectiveness, and cost-effectiveness of implementing early standard care for managing rare conditions. Posters introducing the study will be placed in secondary care settings to create awareness. Parents will be approached during routine antenatal appointments at 20 weeks of pregnancy. They will receive a copy of the study leaflet or patient information sheet, have the opportunity to ask questions, and be directed to the study microsite or digital information sheet. Parents will also be asked for permission to be contacted by the site study team for further discussion and can choose to provide consent at this stage.

Before reaching 36 weeks of pregnancy, parents will be contacted by the site study team, which may occur through phone calls or face-to-face meetings during hospital appointments. The purpose of these interactions is to confirm eligibility, provide additional study information, and address any concerns or inquiries. Depending on the needs of individual parents, multiple conversations may take place. Consent can be obtained through face-to-face consultations or verbal agreements following telephone or video consultations.

On the day the baby is born, the site study teams will allow time, whenever possible, for any additional questions and obtain consent to collect study samples. Parents will be made aware of their right to withdraw from the study. The collected samples will be sent for DNA extraction and subsequently undergo whole genome sequencing. All relevant service providers will be accredited, ensuring the use of accredited laboratories. The genomic data will then enter the Genomics England bio pipeline for automated analysis, with a specific focus on the approximately 200 treatable childhood conditions.

In cases where potentially reportable variants are identified, clinical scientists will review the variants and determine whether they should be reported. Based on this analysis, two types of results will be generated: a 'no condition suspected' result, which will be communicated to participants by Genomics England, and a 'condition suspected' result, which will be relayed to participants through NHS care providers. The latter will initiate the clinical confirmation and management pathway for the baby. In instances where the analysis is unsuccessful due to sample failure, parents will receive a letter explaining the lack of results and providing information on what to expect.

The data generated by the study will be stored in the National Genomic Research Library (NGRL) and linked to ongoing healthcare records. This enables the utilization of the data for future approved research purposes. The NGRL possesses generic REC RTB approval (20EE0035).

Particular and early focus will be given to analysis against the primary 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 the case of rare genetic conditions. The team 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. The exposition of the data analysis strategy across the full breadth of the research questions and study outcomes is beyond the scope of this protocol.

Intervention Type
Other

Primary outcome(s)
Clinical utility of genomic newborn screening measured using the number of screen-identified diagnoses likely to benefit from the intervention compared to the standard of care alone. The primary outcome measure will have two timepoints as follows:
1. Firstly in Spring / Summer 2024, or if recruitment is slower than expected, following recruitment of 20,000 babies
2. Secondly at the end of 2025, or if recruitment is slower than expected, 6 months after recruitment of the 100,000th baby. The 6-month time lag is essential due to the length of time taken for babies to receive a diagnostic outcome following a screen-positive result. Given that some babies will still not have a confirmed diagnosis at that point, the intention is to continue intermittent monitoring over a longer time period.

Key secondary outcome(s)
1. Feasibility of genomic newborn screening in the NHS measured using mixed-method approaches to assess study implementation during the study including:
1.1. Primary and secondary DNA sample collection rate by NHS trust and site by date
1.2. Sample collection failure rate by sample type
1.3. Sample processing failure rate by sample type and stage at failure
1.4. 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
1.5. The time taken from notification of treating clinician to the confirmation of diagnosis / ruling out a diagnosis
1.6. Interviews and focus groups with midwives will capture data on their experience of consent, sample taking and reasons for sample collection failure

2. Acceptability of genomic newborn screening in the NHS measured using mixed-method approaches to assess study implementation during the study including:
2.1. The number of parents approached regarding participation in the study by NHS trust and site by date
2.2. The number of participants consented by NHS trust and site by date
2.3. Consent rates by demographic factors collected during consent including ethnicity, age and socio-economic deprivation.
2.4. Numbers of parents that are referred for enrolment but fail on exclusion criteria and reasons why
2.5. Numbers of parents that change their mind during enrolment and where possible reasons why
2.6. Study withdrawal rates and where possible reasons why
2.7. Interviews and focus groups with midwives will capture data on reasons for participants choosing not to participate in the study

3. Cost-effectiveness of genomic newborn screening compared to standard of care alone, supported by a health economic model developed to support the programme and monitoring

the true downstream cost implications of the additional / fewer healthcare encounters that result from WGS, including:
3.1. Costs associated with A&E attendances, outpatient appointments, admissions, allied health professional appointments, procedures, medication and treatment for all ‘true’ positive participants as compared to age-matched children with comparable diagnoses
3.2. 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.
3.3. False negatives will be used as a comparator group
3.4. Data on costs of healthcare encounters will be sourced through clinical contact and drug pricing data where applicable.

4. Are families’ and stakeholders’ experiences and attitudes during the study supportive of the adoption of genomic newborn screening?
4.1. Attitudes and experiences to WGS in newborns:
4.1.1. Through surveys conducted by our evaluation partner, healthcare professional experiences and attitudes to WGS in newborns will be monitored to include those of clinicians, GPs, genomic counsellors, midwives, scientists, commissioners and rare disease support groups.
4.1.2. Through surveys conducted by our evaluation partner, public experiences and attitudes to WGS in newborns will be monitored
4.2. Attitudes and experiences to participation:
4.2.1. Through surveys conducted by Genomics England’s User Research team, parents' experiences and attitudes to participating in the newborn genomes programme will be monitored.
4.2.2. Through surveys conducted by our evaluation partner, parents' experiences and attitudes of receiving results in the newborn genomes programme will be monitored by ‘true’ positive, false positive, false negative etc.

5. Differential areas of the positive or negative impact of genomic newborn screening related to indices of diversity including ethnicity and socio-economic deprivation will be monitored during the study including.
5.1. Health-related outcomes:
5.1.1. Diagnostic Odyssey
5.1.2. Health encounters
5.1.3. Interventions
5.1.4. Morbidity
5.1.5. Mortality
5.2. Quality of life impacts
5.3. Wider impacts on families
5.4. Impacts on the health service (non-monetary)

Completion date
01/12/2040

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 05/12/2023:

1. Mother / birthing parent over the age of 16 years
2. Mother / birthing parent must have parental responsibility for the baby
3. Singleton birth

For those with complicated births or early postnatal periods, for example where admission to NICU is necessary, final sampling decision will be made on a case-by-case basis at the discretion of the research staff and with the NHS clinical team.

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Previous participant inclusion criteria as of 07/11/2023 to 05/12/2023:

1. Mother / birthing parent aged 16 and over
2. Mother / birthing parent must have parental responsibility for the baby
3. Singleton birth
4. Babies born after 36 weeks, for whom a cord blood sample can be obtained*
5. Babies born at home are included if an individual with legal parental responsibility is willing to bring the baby back to the study site for sample collection

*For those with complicated births or early postnatal periods, for example where admission to NICU is necessary, final sampling decision will be made on a case-by-case basis with input from the NHS clinical team.

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Previous participant inclusion criteria:

1. Mother / birthing parent over the age of 16
2. Mother / birthing parent must have parental responsibility for the baby
3. Singleton birth
4. Babies born after 36 weeks, for whom a cord blood sample can be obtained*
5. Babies born at home are included if an individual with legal parental responsibility is willing to bring the baby back to the study site for sample collection

*For those with complicated births or early postnatal periods, for example where admission to NICU is necessary, final sampling decision will be made on a case-by-case basis with input from the NHS clinical team.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 Years

Upper age limit

120 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current participant exclusion criteria as of 05/12/2023:

1. Mother / birthing parent under 16
2. Mother / birthing parent who will not have parental responsibility for the baby (Babies who are being adopted)
3. Mother / birthing parent lacking the capacity to provide informed consent for any reason
4. Mother / birthing parent who does not give birth in one of the recruiting hospitals
5. Mother / birthing parent who does not have an NHS number
6. Mother / birthing parent who is serving time in prison

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Previous participant exclusion criteria:

1. Mother / birthing parent under 16
2. Mother / birthing parent who will not have parental responsibility for the baby (Babies who are being adopted)
3. Mother / birthing parent who does not have a fixed UK address where they reside (prisoners, people in long-term care, people requiring refuge, people of no fixed abode)
4. Mother / birthing parent lacking the capacity to provide informed consent for any reason
5. Mother / birthing parent who does not give birth in one of the recruiting hospitals
6. Mother / birthing parent who does not have an NHS number

Date of first enrolment
15/03/2024

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Royal London Hospital
80 Newark Street
London

England
E1 2ES

Study participating centre
Chelsea & Westminster Hospital
369 Fulham Road
London
England
SW10 9NH

Study participating centre
Birmingham Women's NHS Foundation Trust
Steelhouse Lane
Birmingham
England
B4 6NH

Study participating centre
University Hospitals Bristol and Weston NHS Foundation Trust
Trust Headquarters
Marlborough Street
Bristol
England
BS1 3NU

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
England
NE7 7DN

Study participating centre
St Thomas' Hospital
Westminster Bridge Road
London
England
SE1 7EH

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2GW

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House
Oxford Road
Manchester
England
M13 9WL

Study participating centre
St Marys Hospital
The Bays
South Wharf Road
London
England
W2 1BL

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
England
OX3 9DU

Study participating centre
Frimley Park Hospital
Portsmouth Road
Frimley
Camberley
England
GU16 7UJ

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
England
NW1 2PG

Study participating centre
Liverpool Womens Hospital
Crown Street
Liverpool
England
L8 7SS

Study participating centre
Queens Medical Centre
Derby Road
Nottingham
England
NG7 2UH

Study participating centre
Wexham Park Hospital
Wexham Street
Wexham
Slough
England
SL2 4HL

Study participating centre
Queen Charlotte's and Chelsea Hospital
Du Cane Road
London

England
W12 0HS

Study participating centre
Liverpool Women's Hospital
Crown Street
Liverpool
England
L8 7SS

Study participating centre
Saint Mary's Hospital
Oxford Road
Manchester
England
M13 9WL

Study participating centre
The Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
England
TS1 4LP

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
England
NG5 1PB

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
England
OX3 9DU

Study participating centre
Horton Hospital (branch)
Horton General Hospital NHS Trust
81a Oxford Road
Banbury
England
OX16 9AL

Study participating centre
University College Hospital Elizabeth Garrett Anderson Wing
235 Euston Road
London
England
NW1 2BU

Study participating centre
Heartlands Hospital
Bordesley Green East
Bordesley Green
Birmingham
England
B9 5SS

Study participating centre
Good Hope Hospital
Rectory Road
Sutton Coldfield
England
B75 7RR

Sponsor information

Organisation
Genomics England

ROR
https://ror.org/04rxxfz69

Funder(s)

Funder type
Government

Funder Name
Department of Health and Social Care

Alternative Name(s)
Department of Health & Social Care, DH

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Liz Gardner, ge-servicedesk@genomicsengland.co.uk. These data will be stored in a secure trusted research environment (TRE) called the National Genomics Research Library (NGRL). Genomic data and linked secondary data will be available from NHSE and other sources. The time of availability is not known at this time. Data will be stored for 16 years or until withdrawal, at which point, re-consent of data storage is planned. Data are accessible on application and are accessible to researchers (academic or commercial) with an approved use case. The type of analyses for which data are available is to be decided – this will depend on the applications of the researchers. Consent from participants was obtained. All data will be anonymised.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			20/09/2023	No	No
Participant information sheet	version 2.0	19/05/2023	16/06/2023	No	Yes
Protocol file	version 2.0	19/05/2023	16/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes