Newborn Screening by Whole Genome Sequencing

Workshop on Considerations for Returning Individual Genomic Results from Population-Based Surveys: Focus on the National Health and Nutrition Examination Survey

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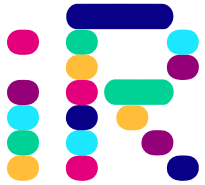
Genomics England

Disclosures

Northwestern Mutual®

Life insurance company



iRepertoire

Molecular lab

HUDSONALPHA
INSTITUTE FOR BIOTECHNOLOGY

Clinical services lab

About Genomics England

Two core, linked functions:

To support genomic in healthcare

To accelerate genomic research

To do this, we:

- **Work with the NHS** to **deliver and improve genomic testing** that helps doctors diagnose, treat, and prevent illnesses like **cancer and rare diseases.**
- Provide the **health data and advanced genomic technology researchers** use to:
  - Make **medical discoveries**
  - **Develop medicines** for patients and their families

Key to both these activities: **turning science into healthcare together**

Background

Newborn Genomes Programme

Starting point 2019…

Current NHS Newborn Blood Spot (NBS) Screening Programme

Newborns can currently be screened for **nine conditions** via a bloodspot test.

There is a 97% uptake of newborns screening in the UK.

> "There is a clear potential for genomics in the testing for many of the conditions currently included in the blood spot test."
>
> Generation Genome

- Sickle cell disease
- Cystic fibrosis
- Congenital hypothyroidism
- Phenylketonuria
- Medium-chain acyl-CoA dehydrogenase deficiency
- Maple syrup urine disease
- Glutaric aciduria type 1
- Homocystinuria

NHS screening currently **only looks for these conditions**, rather than screening the baby's genome.

We are testing a broader approach.

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**

9

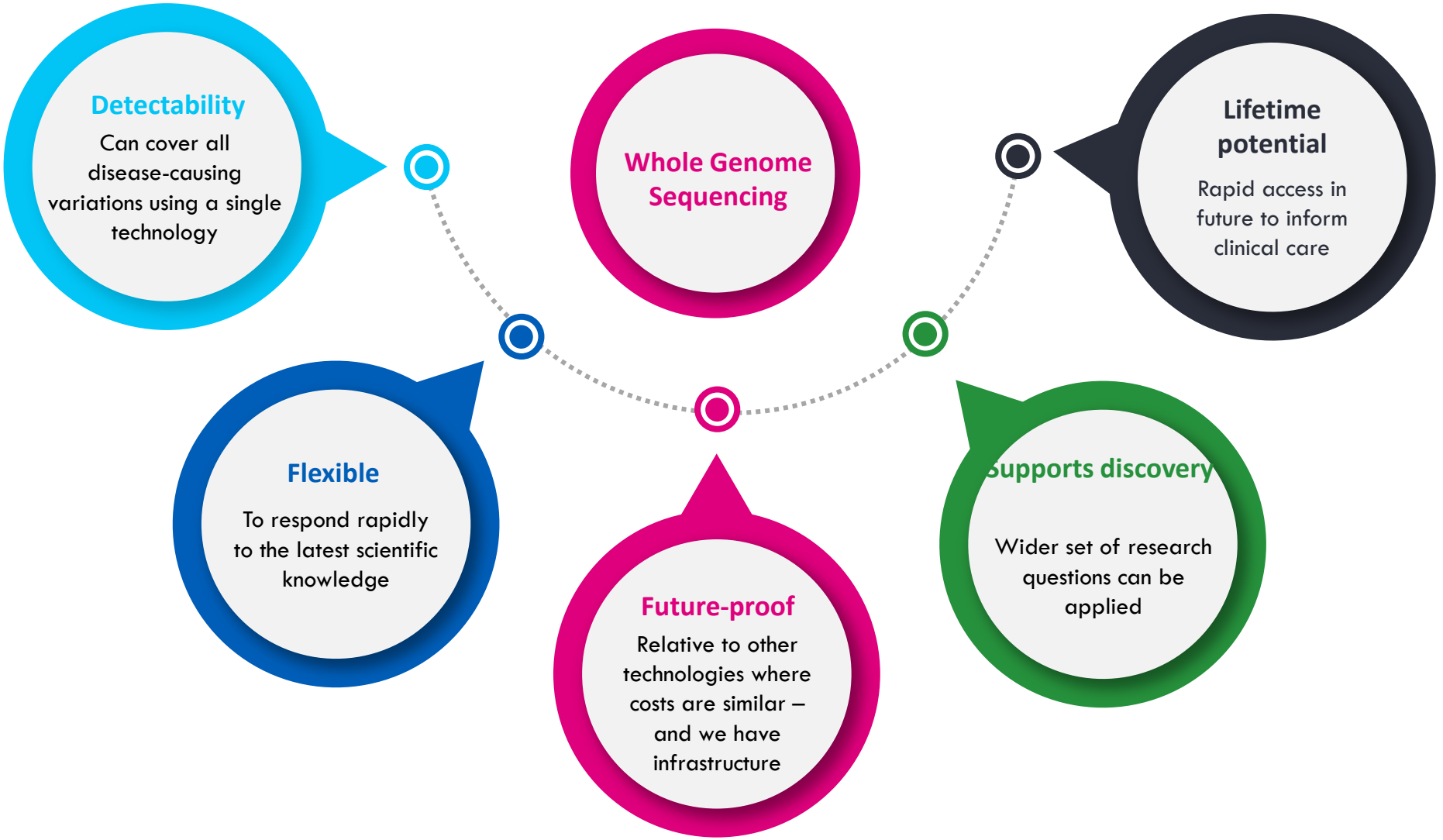
683,191 live births in the United Kingdom in 2020

1 in 190 live births with a treatable disorder*

* https://www.rx-genes.com/about/

Where we are today…

Why whole genome sequencing?



Key numbers

Research pilot beginning **in 2023**

2022 — **2023** — 2024 — 2025

Whole Genome Sequencing to find children born with a rare, treatable genetic disease – where early intervention is crucial

Research pilot will analyse

100,000

newborn genomes for a specific set of childhood-onset, actionable conditions – potentially up to **200,000**

500

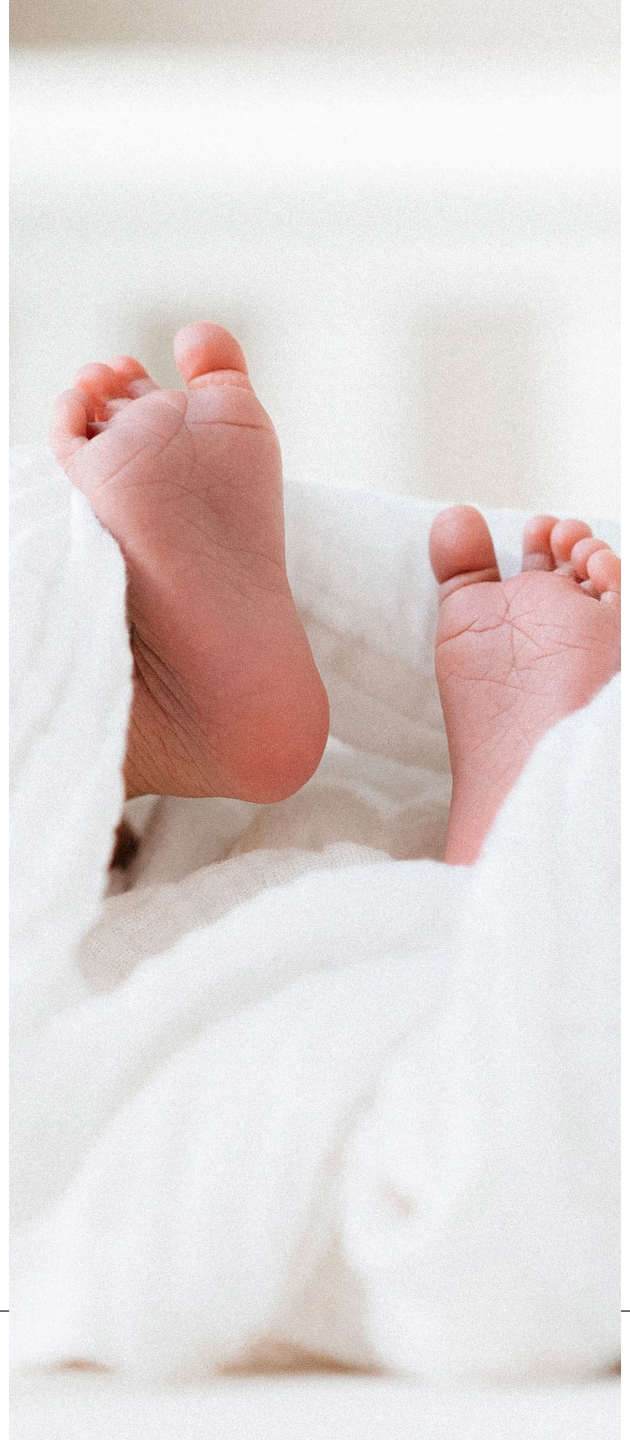
Expecting 500 – 1,000 **positive results**

Choosing disorders for screening and the Wilson and Jungner screening criteria – a starting point….

- The condition sought should be an important health problem
- The natural history of the condition, including development from latent to declared disease, should be adequately understood
- There should be a recognisable latent or early symptomatic stage
- There should be a suitable test or examination
- The test should be acceptable to the population
- There should be an agreed policy on whom to treat as patients
- There should be an accepted treatment for patients with recognised disease
- Facilities for diagnosis and treatment should be available
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in reaction to possible expenditure on medical care as a whole
- Case-finding should be a continuing process and not a “once and for all” project

Conditions Framework workgroup results

- The working group established **four core principles** which each screened-for condition should meet
- The pilot will only screen for a **specific set of conditions, genes, and variants**



Four core principles

A

There is strong evidence that the genetic variant(s) causes the condition and can be reliably detected.

Where appropriate, there may be a confirmatory test that can establish whether the child has the condition.

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.

C

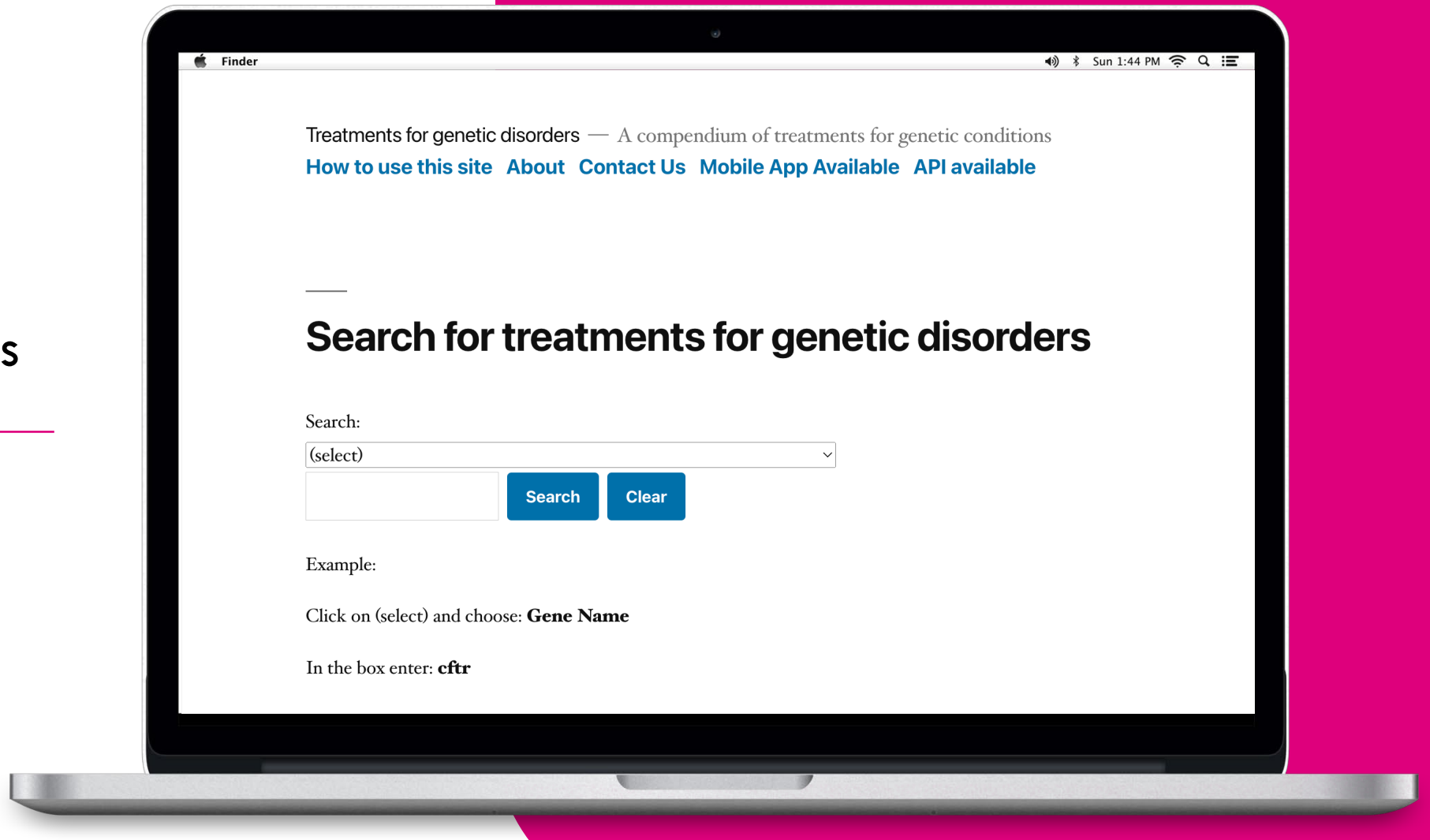
Early or pre-symptomatic intervention for the condition has been shown to lead to substantially improved outcomes in children, compared to intervention after the onset of symptoms.

D

Conditions screened for are only those for which the interventions are equitably accessible for all.

Website with information about treatable disorders

Rx-genes.com



An online compendium of treatable genetic disorders.

Bick D, Bick SL, Dimmock DP, Fowler TA, Caulfield MJ, Scott RH.
Am J Med Genet C Semin Med Genet. 2021 Mar;187(1):48-54.

Treatable rare diseases are numerous

4,684

genes associated with phenotype-causing variants listed in Online Inheritance in Man (OMIM) (9/11/22)

15% (725/4684) of these have a treatment directed against the disease mechanism

19 genes result in 2 or more different diseases

744

disease entities resulting from variants in 725 genes

19

genes associated with adult disorders (e.g., BRCA1)

Program will only include variants with high positive predictive value

Positive predictive value = (sensitivity x prevalence) / [(sensitivity x prevalence) + ((1 – specificity) x (1 – prevalence))]

Example disease

1 in 10,000 live births
Variant with sensitive 99.5% & specific 99.5% = 2% PPV
98 out of 100 times this is a FALSE POSITIVE!

Only pathogenic and like pathogenic variants will be reported

https://www.sciencedirect.com/science/article/pii/S1525157820300386

Establishing a model for consent

'All-in' offer

1. Return of actionable findings to newborns' families
2. Research on newborn screening
3. Research on broader healthcare questions (within NGRL acceptable uses)
4. Opportunity to recontact

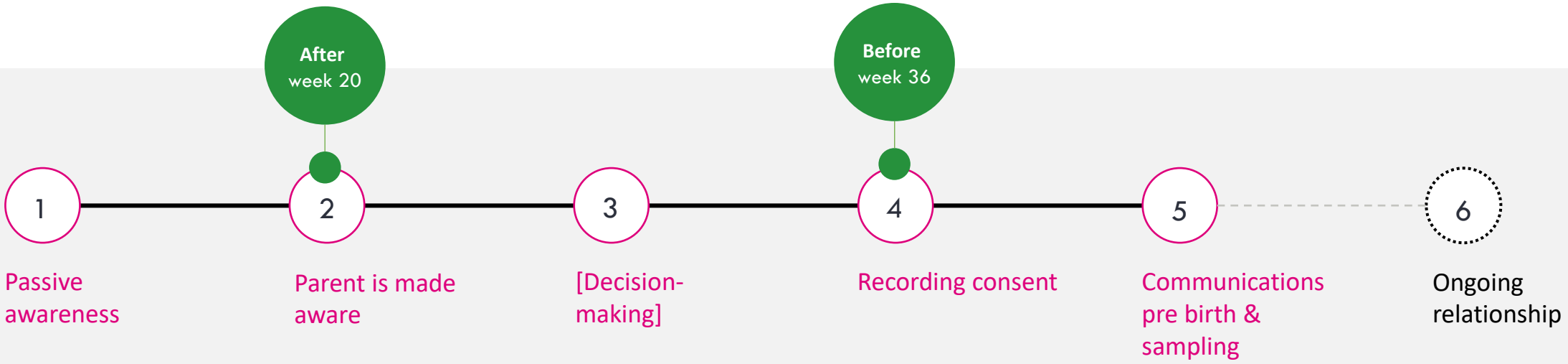
Inputs

- Lessons learned from 100K
- Feedback from Ethics Working Group
- Feedback from parent interviews
- NHS Newborn Steering Group
- Genomics England leadership

Considerations

- Emphasizes that the entire programme is research and the relationship between the study's aims
- Simpler to deliver in the context of NHS care and workforce
- Need to gather ongoing evidence to understand whether families choose not to take part due to broader healthcare research focus
- Ensuring involvement of the child/young adult as they gain autonomy
- Different models should be explored for a future service

Bringing together a timeline for recruitment and consent

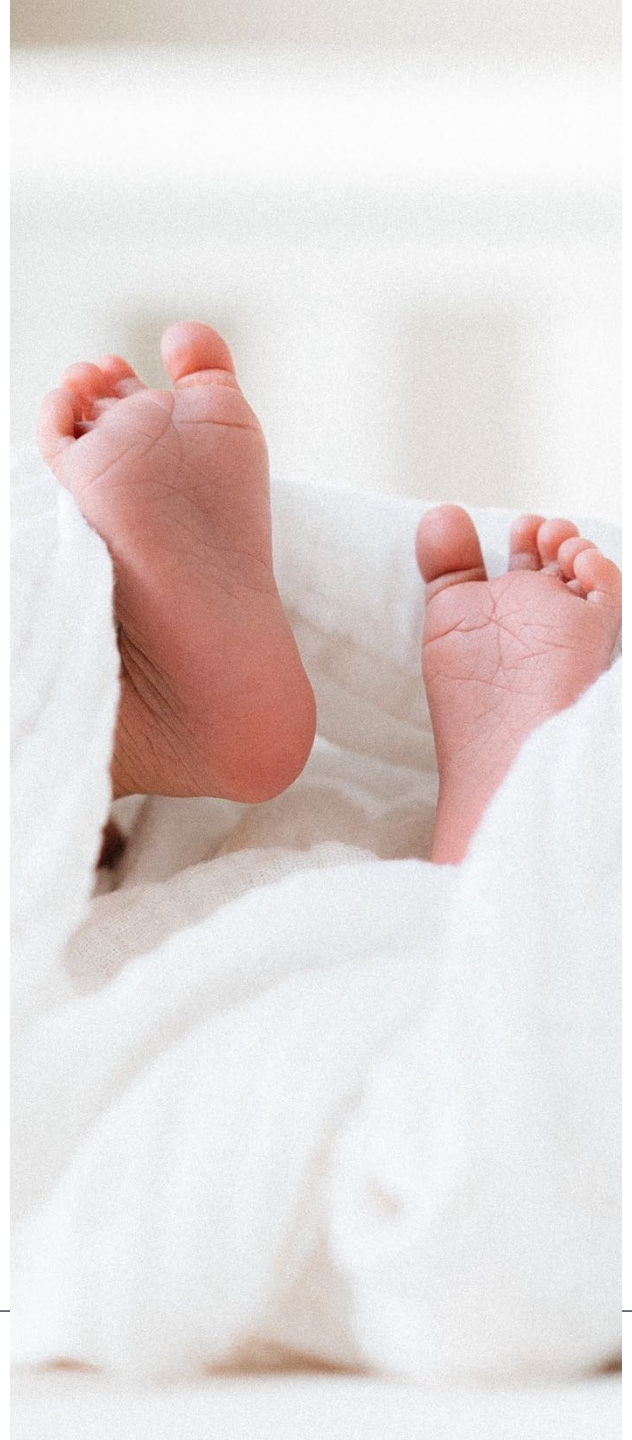


The parent journey has been defined and refined in an iterative way. Inputs so far have included:

- Ethnography with a diverse group of 60+ parents to understand their experiences of pregnancy, of receiving healthcare information, and their decision-making
- Feedback from parents in co-design interviews about when they would like to be deciding whether or not to take part
- Input from the Recruitment Working Group (inc. midwives, obstetrics, parent + patient representatives)
- Learnings from previous studies and published literature*

*https://pubmed.ncbi.nlm.nih.gov/28967862/

Bringing together a timeline for recruitment and consent



Earlier in the pregnancy, you're desperate for your child to survive. It was only once the week 20 scan happened did it really feel like there's a baby rocking up soon."

"I'd like to be told prior because I didn't know about the heel prick test until it had to happen. I'd like to be told so you can get other people's opinions and Google it."

Care and treatment pathways

"Considering existing pressures in healthcare, the programme must understand the services and resources required to support children and families, and education and training needs for the workforce to provide high quality care."

Each baby needs a structured care and treatment pathway in place before we begin.

NHS Newborn Genomes Programme Conditions Review Group – Chair Vin Diwakar,
Medical Director for Transformation in NHS England

Workforce input

Understanding needs of the NHS workforce is crucial to ensure we can adopt an optimal approach and take its concerns into account

- Co-designing with midwives with a focus on recruitment, consent and samples
- Working with clinicians across a range of specialisms to establish how the study would affect clinical care
- Discussing with nurses to understand approaches to care and treatment pathways
- Engaging with genetic counsellors and genetic clinical and laboratory services
- Education and training working group with representation from various NHS workforce groups to establish learning and resource needs
- Liaising with Royal Colleges to understand workforce needs and capacity

Study of sample types

Dried Blood Spots (DBS) - Standard NHS cards

Cord Blood

Heel prick into capillary tube

Saliva via sponge stick

Study Underway: 150 dried blood spot cards, 600 buccal swabs, 400 cord bloods, 150 capillary tubes, 600 maternal buccal swabs (as comparator)

Newborn Genomic Screening is starting worldwide

United States

BabySeq2 at Harvard – Massachusetts

BeginNGS at Rady Children's Hosp. - California

Newborn study at Columbia U – New York

ScreenPlus at Albert Einstein – New York

Newborn study at Geisinger – Pennsylvania

EarlyCheck2 at University of North Carolina - North Carolina

Perkin-Elmer – Commercial laboratory

Middle East

Newborn study – Qatar

Europe

Screen4Care – Consortium

Baby Detect – Belgium

Newborn Genomes Programme – England

Netherlands

Asia

Australia

Murdoch Children's Research Institute

University of Sydney

University of Adelaide

China

Newborn study at Children's Hospital of Zhejiang University

Newborn study at Beijing Children's Hospital

Newborn study by Beijing Genome Institute

Learn more

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Thank you

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The Genomics England newborns core team:

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- **Sally Donovan,** Delivery Manager
- **Frankie Edwards,** Integrated Designer
- **Sofia Garcia Noriega,** Service Designer
- **Liz Gardner,** Mobilisation Operations Lead
- **Kate Harvey,** Engagement Manager
- **Edyta Jaworek,** Product Designer
- **Mathilde Leblond,** Human-Centred Design Researcher
- **Christella Matoko,** Delivery Coordinator
- **Amanda Pichini,** Clinical Lead for Genetic Counselling
- **Jonathan Roberts,** Clinical Content Developer
- **Dr Richard Scott,** Chief Medical Officer (senior sponsor)
- **Sally Shillaker,** Clinical Content Developer
- **Katrina Stone,** Clinical Fellow in Genomics
- **Alice Tuff-Lacey,** Programme Lead
- **Chantal Wood,** Programme Manager
- **Joanna Ziff,** Delivery Manager

A long list of issues to resolve……

How will we find enough positives for rare disorders to give evidence for/against adding a gene to newborn screening?

Do we understand penetrance and expressivity of variants found in an asymptomatic newborn?

Will we reanalyze genome if child develops a phenotype suggesting a genetic disorder?

How long will families be followed to look for false negatives and study outcome of positives?

Will genetic disorders where there is a clinical trial available in the UK be included?

How will we handle an incidental finding? Example finding a hemizygous variant in treatable X-linked disorder a female which would suggest Turner syndrome.

How will we ensure minority communities are well represented in the study?

Will genes and variants be added during the program?