Next-Generation Screening – The Promise and Perils of DNA Sequencing of Newborns at Birth

Roundtable on Genomics and Precision Health

National Academies of Sciences, Engineering, and Medicine

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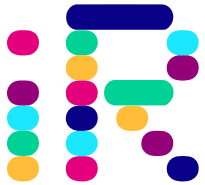
Disclosures

Northwestern Mutual®



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HUDSONALPHA
INSTITUTE FOR BIOTECHNOLOGY

Life insurance company

Molecular lab

Clinical services lab

Objectives

- Discuss how genetic information ascertained at birth could be used across the lifespan and how this could help or hinder efforts to address health disparities.
- Discuss potential legal and ethical issues that should be addressed (e.g., informed consent, data privacy, regulatory landscape).

About Genomics England

Two core, linked functions:

To support an evolution in genomic healthcare

To accelerate genomic research

To do this, we:

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

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

Background

Newborn Genomes Programme

Starting point 2019…

Current UK 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.**

The GENERATION STUDY

Three parts | Ethics committee approved

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

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

How we work

Core in-house team

Expert working groups established, focusing on:

- Conditions the research study should screen for
- Recruitment
- Ethics
- Evaluation
- Education and training

- **NHS Steering Group** – designed to support and develop the research study
- **NHS England Newborn Genomes Programme Clinical Assurance Group** to support our 'choosing conditions' work
- **Co-design** with parents and healthcare professionals
- **Engagement programme** to work with stakeholders – including members of the public
- **Participant panel**

'All in offer'

Parents will be asked for use of their babies' genome & link to clinical data to allow:

1. Return of actionable findings to newborns' families
2. Research on newborn screening
3. Research on broader healthcare questions (within NGRL acceptable uses)
4. Recontact to request follow up data related to newborn screening research or to offer opportunities to participate in other studies.
   - If further studies are related to specific conditions, it would only be possible where the baby has been identified through the screening analysis or has a confirmed diagnosis for that condition.
5. Use of any of the baby's leftover sample for further research

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

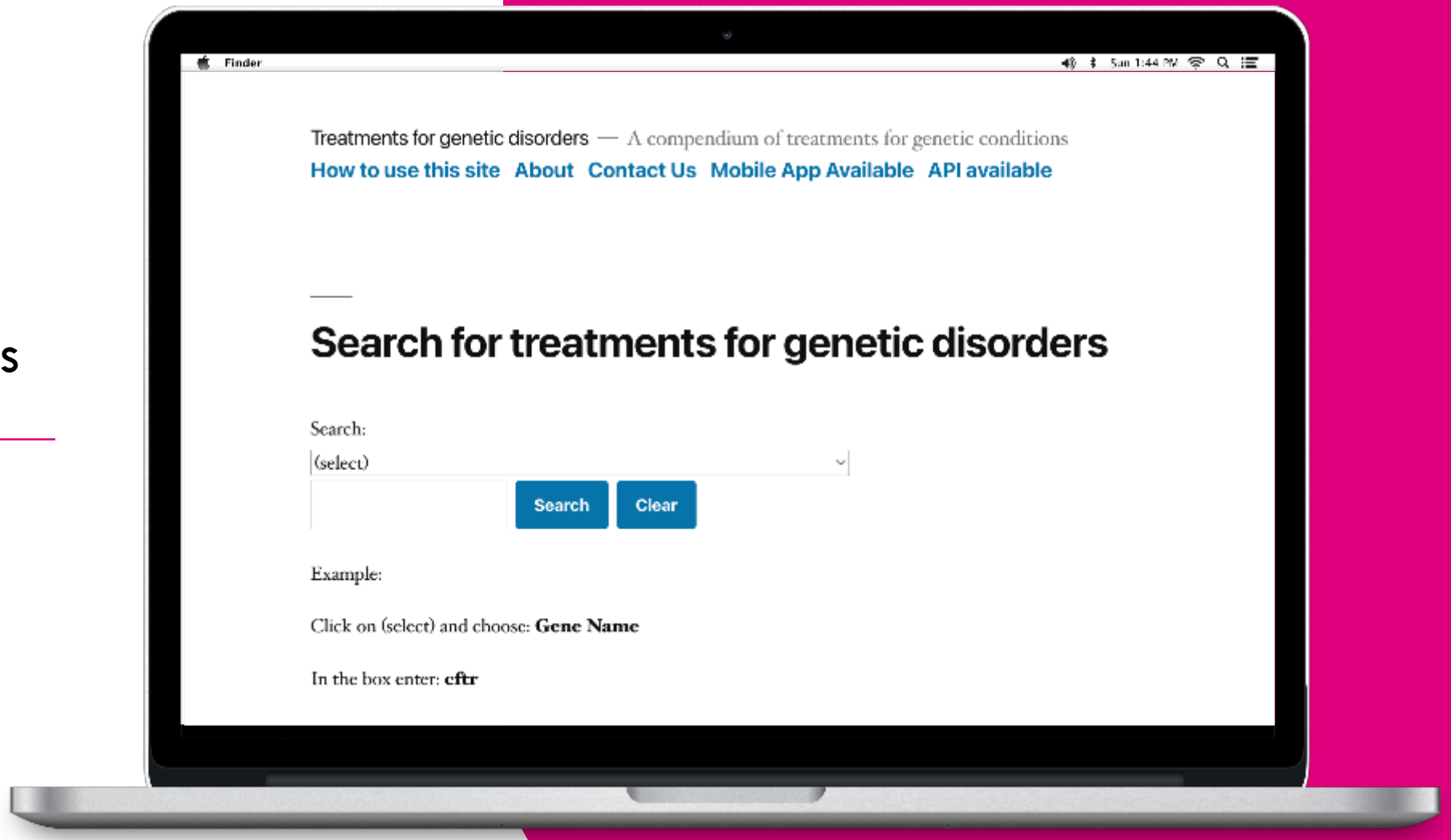
Early or pre-symptomatic intervention for the condition has been shown to lead to substantially improved outcomes in children, compared to intervention after the onset of symptoms.

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

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."

* The above steps may not be needed for each condition, and the order of those steps may vary

Screen-positive babies - expected to be 500 - 1,000.

Each baby needs a structured care and treatment pathway in place

Ensure equity across minority groups – disorders chosen, recruitment & care

Newborn Genomic Screening is starting worldwide

United States

BabySeq2 at Harvard – Massachusetts

BeginNGS at Rady Children's Hosp. - California

GUARDIAN study at Columbia U – New York

ScreenPlus at Albert Einstein – New York

EarlyCheck2 at University of North Carolina - North Carolina

Perkin-Elmer – Commercial laboratory

Middle East

Newborn study – Qatar

Europe

Screen4Care – European Consortium

Baby Detect – Belgium

Generation Study – England

First Steps - Greece

Netherlands

Asia

Australia

BabyScreen+ Murdoch Children's Research Institute

Newborn study at University of Sydney

NewbornsInSA 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

Thank you

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