Establishing risk factors and outcomes for congenital hypothyroidism with gland in situ using population-based data linkage methods: study protocol

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ABSTRACT

Introduction There has been an increase in the birth prevalence of congenital hypothyroidism (CH) since the introduction of newborn screening, both globally and in the UK. This increase can be accounted for by an increase in CH with gland in situ (CH-GIS). It is not known why CH-GIS is becoming more common, nor how it affects the health, development and learning of children over the long term. Our study will use linked administrative health, education and clinical data to determine risk factors for CH-GIS and describe long-term health and education outcomes for affected children.

Methods and analysis We will construct a birth cohort study based on linked, administrative data to determine what factors have contributed to the increase in the birth prevalence of CH-GIS in the UK. We will also set up a follow-up study of cases and controls to determine the health and education outcomes of children with and without CH-GIS. We will use logistic/multinomial regression models to establish risk factors for CH-GIS. Changes in the prevalence of risk factors over time will help to explain the increase in birth prevalence of CH-GIS. Multivariable generalised linear models or Cox proportional hazards regression models will be used to assess the association between type of CH and school performance or health outcomes.

Ethics and dissemination This study has been approved by the London Queen Square Research Ethics Committee and the Health Research Authority’s Confidentiality Advisory Group CAG. Approvals are also being sought from each data provider. Obtaining approvals from CAG, data providers and information governance bodies have caused considerable delays to the project. Our methods and findings will be published in peer-reviewed journals and presented at academic conferences.

INTRODUCTION

An increasing number of children are living with rare diseases as a result of improved drug treatments and neonatal care. Parents of affected children frequently report having to manage uncertainty about their child’s current health status and prognosis,1 2 and a lack of expertise about the condition among health professionals.3 The 2014 UK Strategy for Rare Diseases4 stresses the lack of longitudinal, population-based data to assess the aetiology and health outcomes of rare conditions to support parents, clinicians and commissioners.

Existing data sources for research into the aetiology and long-term outcomes of rare diseases have major weaknesses. Disease registries contain detailed data on specific conditions, yet data collection requires substantial time input from clinicians and parents, leading to high costs and (non-random) loss to follow-up. Treating clinicians keep detailed records of phenotypes and treatments, however, these may not be stored in an easily analysable format. Further, these data sources only contain data on children with a particular
condition, and health or development outcomes cannot easily be compared with control groups. In contrast, administrative health and education data are universally and routinely collected for all children, including those with rare diseases. However, rare conditions are hard to characterise in administrative health databases due to lack of specificity of clinical coding. Further, these databases lack information on prescribed drugs, genotypes and biomarkers, which are important for understanding and eventually predicting the expected health and development trajectories of affected children. Instead, linkage between clinical and routinely collected health, vital statistics and education databases would allow long-term follow-up of children with rare conditions. We propose a follow-up study of cases and controls applying population-based data linkage methodologies to examine risk factors, and long-term health and education outcomes for children with congenital hypothyroidism with gland in situ (CH-GIS; a rare endocrine disorder).

CH and CH-GIS

Newborn screening for CH was introduced in the late 1970s in the UK and many other countries globally. Where screening and early treatment for CH has been introduced, including in the UK, severe neurological impairment due to CH has been eliminated. Approximately 65% of children with CH are born with no, or an underdeveloped or malpositioned, thyroid gland. This is known as thyroid dysgenesis, hypoplasia or ectopic thyroid, respectively. The remaining 35% of children with CH have normally situated and sized glands, but with malfunctions in thyroid hormone synthesis: this is known as CH-GIS. The birth prevalence of CH in the UK has increased from 29/10 000 births in 1982–1984 to 53/10 000 births in 2011–2012. Many other countries report similar rises, which remain even after considering improvements in screening assays. These increases are largely accounted for by a rise in birth prevalence of CH-GIS. Several reasons may explain this observed increase, including improved survival of children born prematurely or with low birth weight, or a change in the ethnic group composition of the population. Variations in dietary iodine intake, and variations in the prevalence of autosomal recessive thyroid hormone defects, may contribute to these observed differences in CH by ethnic group. To date, no study has examined multiple risk factors simultaneously.

Despite the increasing proportion of children diagnosed with CH-GIS, the health and development outcomes for children with this condition are not well understood. While some studies have shown suboptimal school performance even in children with very mildly suppressed thyroid hormone levels in the neonatal period, this needs to be weighed against potential risks of suboptimal educational outcomes that have been associated with overtreatment. Monitoring health and education outcomes for children with CH-GIS is recommended by the European Society for Paediatric Endocrinology. Many studies of outcomes for children with CH involve small cohorts who were born over 30 years ago. Since screening and treatment thresholds have changed substantially during this period, up-to-date studies are urgently required.

Aim

The overall aims of this study are to determine risk factors for CH-GIS and describe long-term health and education outcomes for affected children. We propose to use a clinical database containing clinical and treatment information for children with CH-GIS (to be developed as part of the project), linked to vital statistics and administrative health and education data to meet the research aims. This protocol describes the current study design, and the original design that had to be amended due to requests from data providers and information governance bodies.

Objectives

The objectives of this research study are to:

1. Develop a coherent, structured and catalogued clinical database of children with CH-GIS that can also be used for research.
2. Determine what factors have contributed to the increase in the birth prevalence of CH-GIS in the UK.
3. Determine health and education outcomes of children with CH-GIS compared with children with other forms of CH, and those who do not have CH.
4. Describe how a child’s CH-GIS genotype affects treatment, health and educational outcomes.
5. Determine treatment trajectories for children with CH-GIS.

METHODS AND ANALYSIS

Study design

Objective 2 will be addressed via a population-based cohort study, and objectives 3–5 will be addressed using a follow-up study of cases and controls.

Study population

For the cohort study (objective 2), the study population will include all children born in the North Thames region and screened at the North Thames Newborn screening laboratory between 1 January 2000 and 31 December 2020. This study period will allow us to examine changes in neonatal levels of thyroid stimulating hormone (TSH) concentrations over a 21-year period. We will propose to include all children, apart from where a child has opted out of their National Health Service (NHS) data being used for research.

For the follow-up study (objectives 3–5), the population consists of all children referred to the Great Ormond Street Hospital (GOSH) Endocrinology Clinic after a screen positive newborn bloodspot test result for CH between 2006 and 2020—this is also the population in the database to be established for objective 1. Fifteen controls will be selected per case of CH for the follow-up study.
Data sources

Cohort study data sources

North Thames Newborn Screening database

The population ‘spine’ for the cohort study will be the North Thames Newborn Screening (NBS) database, held at GOSH; North Thames covers the urban areas of West, North and East London and the suburban and rural areas of Essex, Hertfordshire and Bedfordshire. The database covers all babies in North Thames region screened at the GOSH Newborn Screening laboratory; over 99.9% of babies born in North Thames and approximately 20% of all births in England. The NBS database receives a daily feed of birth notifications from the NHS Personal Demographic Service dataset, a national electronic database of NHS patient details, as part of the Fail-safe system, an IT solution for England that reduces the risk of babies missing or having delayed newborn blood spot screening.27 The North Thames NBS database holds data on screening test results, babies’ and mothers’ NHS numbers, sex, dates of birth and sample collection, ethnicity, birth weight and gestational age.

Children in the cohort who have screened positive for CH and been referred to the GOSH endocrinology service will also be linked to diagnosis and follow-up data through a bespoke clinical management and research database created as part of this study (see below).

GOSH CH database

This clinical dataset contains information on 1800 children who have screened positive for CH through the North Thames NBS programme since 2006 and been referred to the Endocrinology Clinic at GOSH. Until 2018, all children with blood-spot TSH concentrations $\geq 6$ mU/L, on first or repeat screening, were referred to this team. From 2018, the screening cut-off was set higher, at $\geq 8$ mU/L.28 Note that GOSH has historically had a lower screening threshold for a positive CH test compared with the national screening programme (which recommended $\geq 10$ mU/L when GOSH used $>6$ mU/L).7

The dataset holds information on final diagnosis and screening outcome (ie, true or false positive on screening), longitudinal data on blood tests at diagnosis and during follow-ups (at 2, 4 and 8 weeks and 6, 9 and 12 months after start of treatment, and as indicated afterwards), thyroid scans, and treatment dose, including starting dose, and changes in dosage during follow-up. The dataset also contains genetic data for ~50 children with CH from whole exome sequencing, targeted Sanger sequencing, and a customised next generation sequencing panel of CH-associated genes.29 The CH clinical and genetic data were originally held in a variety of formats at GOSH, including Microsoft Word and Excel files, but we propose to consolidate the data to develop a clinical database that is also research ready (objective 1).

Birth and death registration data

The Office for National Statistics (ONS) collate data from registry offices on all births and deaths, which are then shared with NHS Digital (NHSD), the NHS data provider for England. The birth registration database contains key sociodemographic information about registration type (sole or joint), and parental ages, occupations and countries of birth. Death registration data contains information about date of death and causes of death. All children from the NBS database will be linked to birth and death registration data.

Follow-up study data sources

The follow-up study of cases and controls will include all children who have been referred to the GOSH Endocrinology Clinic after having tested positive through a blood spot test from the CH database. All children from the CH database will be linked to Hospital Episode Statistics (HES), the National Pupil Database (NPD) and the NHS Business Services Authority (NHBSA) community dispensing data. HES and NPD data are already linked for the Education and Child Health Insights from Linked Data (ECHILD) database.30 Controls will be selected from the HES portion of the ECHILD database; this minimises the risk of patient identification since controls will be selected using pseudonymised data.

Hospital Episode Statistics

HES contains data on all admissions to NHS hospitals,31 including deliveries and births, as well as accident and emergency (A&E) attendances and outpatient bookings. HES datasets are supplied by NHSD.

Department for Education National Pupil Database (NPD)

The NPD holds data on all children in state primary and secondary schools; 93% of all school children in England.32 The NPD contains pupil-level information on school test results (early years foundation stage (EYFS) profiles, key stages (KSs) and phonics) and special educational needs (SEN) provision.

Education and Child Health Insights from Linked Data

The ECHILD database30 is a pseudonymised, linkable collection of HES, NPD, and social care data for a whole population-based cohort of children and young people in England, born between 1 September 1995 and 31 August 2020. ECHILD is held in the ONS Secure Research Service33 (SRS). University College London (UCL) holds a copy of the HES portion of ECHILD in the UCL Data Safe Haven34 (DSH).

NHBSA community dispensing data

The NHBSA dispensing database contains data relating to NHS prescriptions dispensed and submitted to NHS Prescription Services by community pharmacies in England. Note that we will only have NHBSA community dispensing data for cases. NHBSA dispensing data are supplied by NHSD.

Consolidating the CH database

The existing GOSH CH database will be consolidated to develop a clinical database that is also research ready.
Currently, the CH database contains data on patient’s referral to GOSH, final CH diagnosis and treatments and is held in Microsoft Excel format. Longitudinal thyroid testing and thyroid treatment data are available from a separate Microsoft Word document that is updated at each patient appointment. Longitudinal testing and treatment data will be extracted from Microsoft Word documents and the Epic electronic health records software at GOSH, and linked to patients in the existing CH database. The resulting database will be imported to, and managed using, Research Electronic Data Capture (REDCap) electronic data capture tools hosted at GOSH.35 36  REDCap is a secure, web-based software platform designed to support data capture for research studies. Moving forward, the database will be updated and maintained by the clinical team using REDCap.

Data linkage
The suggested data flows for study data are outlined in figure 1.

For the cohort study, the GOSH NBS database will be linked to the CH clinical database deterministically, using NHS number, date of birth and postcode by the GOSH Digital Research Environment (DRE) team. The GOSH DRE team will also link babies who were born to the same mother to create a ‘family’ ID using the mothers’ NHS numbers, and link postcodes to lower super output areas to assign Index of Multiple Deprivation (IMD) deciles.37 The DRE team will submit baby identifiers from the NBS database to NHSD, who will link the NBS data to births and deaths records via a well-established deterministic algorithm using NHS number, name, date of birth and postcode.

For the follow-up study of cases and controls, the cases will be the CH-NBS linked subsample of the NBS cohort. The GOSH DRE team will flag CH cases in the NBS dataset. NHSD will use these flagged identifiers to link CH records to (1) NHSBSA data dispensing data and (2) the ECHILD cohort. Encrypted ECHILD IDs will be returned to the UCL study team who will link the cases to the pseudonymised HES part of the ECHILD data stored on the UCL DSH via the existing encrypted IDs. Controls will be selected from the pseudonymised HES data, matched to cases by sex, month and year of birth and local authority at delivery. Since the NPD variables need to remain in the ONS SRS, variables from the CH

Figure 1 Data flow and linkage diagram. CH, congenital hypothyroidism database; DRE, Digital Research Environment; ECHILD, Education and Child Health Insights from Linked Data; GOSH, Great Ormond Street Hospital; HES, Hospital Episode Statistics; NBS, Newborn Screening database; NHSBSA, NHS Business Services Authority; NPD, National Pupil Database; ONS, Office of National Statistics; SRS, Secure Research Service; UCL DSH, University College London Data Safe Haven.
database and some variables from the HES database will be transferred to the ONS SRS for analysis of education outcomes.

**Data storage and access**
The final linked cohort data will be stored, accessed, and analysed in UCL’s DSH. Data for the follow-up study will also be stored, accessed and analysed via the DSH, with the exception of the linked NPD data, which will be kept in the ONS SRS, according to Department for Education (DfE) regulations. All researchers analysing data for this study will hold the Approved Researcher Status certified by the ONS.

**Outcomes of interest**
The primary outcome of interest from the cohort study (objective 2) is type of CH (ie, no CH, agenesis, ectopic, hypoplastic or CH-GIS). The secondary outcome of interest is neonatal TSH levels from newborn screening. For the follow-up study, the outcomes for objectives 3 and 4 are:

- Age group-specific (<1 year, 1–4 years, 5+ years) A&E attendance and emergency hospital admission rates (from HES)
- EYFS phonics, KS1 and KS2 results (from NPD).
- SEN status (from NPD).
- Dispensing rates of drugs, including for severe ADHD (attention deficit hyperactivity disorder) and asthma (from NHSBSA dispensing data); as we will only have these data for cases, we will describe patterns of prescribing among cases only and this outcome will primarily be explored for objective 4.

For objective 5, the outcome is levothyroxine dose by age (from the CH clinical database or NHSBSA dispensing data).

**Other variables of interest**
We will consider a number of variables as potential explanatory variables for the cohort study of temporal trends in TSH levels and CH-GIS, and as confounding variables for the follow-up study of cases and controls. These variables include sex, birth weight, parity, gestational age, maternal age at delivery, ethnicity, socioeconomic status (measured as parental occupation and IMD, the latter derived from postcode of residence at delivery). Note that there are no routinely collected, population level data on iodine status in pregnant women in England.

Data sources and corresponding variables or outcomes of interest are listed in table 1.

**Statistical analysis**
We will present the distribution of key baby and parental (as recorded on birth registration records) characteristics for the children in the cohort and case–control follow-up studies.

To address objective 2, the aetiology of CH for referred children using the CH database (eg, screening result, CH-GIS, other types of CH) will be established. The NBS database and birth registration data will be used to define known and potential risk factors for CH-GIS available within these datasets, including sex, birth weight, gestational age, multiple birth status, parental country of birth, ethnicity and socioeconomic position (using either parental occupation from the birth registration record.

### Table 1 Data sources and variables or outcomes of interest

<table>
<thead>
<tr>
<th>Study design</th>
<th>Data source</th>
<th>Variables of interest</th>
<th>Years requested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort study</td>
<td>North Thames Newborn Screening database (NBS)</td>
<td>Sex, date of birth, date of sample collection, ethnicity, birth weight, gestational age, screening test results, IMD (derived from postcode of residence at birth)</td>
<td>2000–2020</td>
</tr>
<tr>
<td></td>
<td>GOSH congenital hypothyroidism database (CH)</td>
<td>Final diagnosis, screening outcome, blood tests, thyroid scans, treatment doses, genotype</td>
<td>2006–2020</td>
</tr>
<tr>
<td></td>
<td>Birth and Death Registration data</td>
<td>Date of death, cause of death, registration type, parents’ age, parents’ occupations, parent’s birth countries</td>
<td>2000–2020</td>
</tr>
<tr>
<td>Follow-up study of cases and controls*</td>
<td>National Pupil Database (NPD)</td>
<td>Hospital admissions, A&amp;E attendances, outpatient visits (can be used to derive indicators of co-morbidity)</td>
<td>2006–2020</td>
</tr>
<tr>
<td></td>
<td>Hospital Episode Statistics (HES)</td>
<td>EYFS results, KS results, Phonics tests, SEN status</td>
<td>2006–2020</td>
</tr>
<tr>
<td></td>
<td>NHS Business Services Authority community dispensing data (NHSBSA)†</td>
<td>Free school meal eligibility, Language spoken</td>
<td>2006–2020</td>
</tr>
</tbody>
</table>

*The cases for the follow-up study will consist of the population in the CH database. Controls will be selected from pseudonymised HES data which are part of the Education and Child Health Insights from Linked Data linked database.

†NHSBSA will only be available for CH cases.

A&E, accident and emergency; EYFS, early years foundation stage; IMD, Index of Multiple Deprivation; KS, key stage; NHS, National Health Service; SEN, special educational needs.
or (IMD). We will use linear, quantile, logistic or multinomial regression models to establish independent child, maternal and family risk factors for neonatal TSH levels and CH-GIS as appropriate, and determine how these have changed over time to determine which of these factors explain the increase in CH-GIS birth prevalence. We will explore the impact of changing screening thresholds and instrumentation (the North Thames Screening Programme changed from Autodellia to a Genetic Screening Processor in 2019) during the study period in the regression models.

To determine the health and education outcomes of children with CH-GIS compared with children with other forms of CH, or those who do not have CH (objective 3), data from the follow-up study will be used. Appropriate statistical models, such as proportional hazard regression models, will be used to examine whether children with CH-GIS are more likely to experience the health outcomes of interest compared with other children, while adjusting for other risk factors as defined for objective 2, as well as risk factors that can be defined within HES (such as comorbidities). Death registration data will be used to calculate person-time at risk.

The association between thyroid CH-GIS and school performance will be examined using linked NPD data. Test scores will be standardised within each school year. Multivariable linear regression models will be used to assess the association between type of CH and school performance, adjusting for the risk factors defined for objective 2, and season of birth (eg, summer vs autumn born children). Multivariable logistic regression models will be used to determine if children with CH-GIS are more likely to have SEN status compared with other children. For both objectives 3 and 4, we will also explore the effect of different neonatal TSH levels within each CH diagnostic group.

The analyses for objective 4 will be exploratory at this stage, as the number of children with available genomic data is small (~50). The proportion of children with comorbidities and SEN status will be compared according to CH genotype using χ²-tests, t-tests, and linear and logistic regression models as appropriate. We will compare the proportion of children who are receiving treatment for asthma and severe ADHD according to genotype.

To address objective 5, two data-driven approaches will be used to predict levothyroxine treatment trajectories in children with CH-GIS: mixture cure models and group-based trajectory models. The analysis of the follow-up study of cases and controls will include all cases from the CH database (approximately 1800 children), plus the control sample. To decide on the size of the control sample, we reviewed two similar studies: the Cleft Registry and Audit Network (CRANE) database study; a cohort study investigating differences in academic achievement between children with and without a cleft palate; and a study of health and educational outcomes for children with Downs Syndrome (Dr Maria Peppa, personal communication). The Downs syndrome study used a control sample size of 9 controls per case. The CRANE study revealed that academic attainment of 5-year-old children with an oral cleft was between 0.2 and 0.4 SD lower than the national average. However, for our study, we expect to observe smaller differences in the outcomes of interest (ie, school attainment in children with CH). Assuming a significance level α<0.05, a minimum statistical power of 90%, and allowing for statistical adjustment of multiple confounders (ie, sociodemographic characteristics) some of which are less common (eg, premature birth), a more suitable control group would include 15 controls per case. Thus, the total sample for the follow-up study is 28800 (1800 CH cases and 27000 controls).

ETHICS AND DISSEMINATION

Ethics and information governance

This study has obtained, or is in the process of obtaining, ethical or information governance approvals from the following committees:

- London—Queen Square Research Ethics Committee (REC) (reference number: 20/LO/1216—Outcome: Favourable Opinion)
- The Antenatal and Newborn Screening Programme (ANBN) Research Advisory Committee (RAC) (full approval, reference ANNB_NHS_046)
- Confidentiality Advisory Group (CAG) (conditional support, reference 21/CAG/0071)
- NHS Digital Data Access Request Service (DARS) (reference NIC-365469-00P1Q)—pending
- Department for Education (DiE) (access to NPD via ONS SRS, reference DR211029.01)—pending
- Internal review by The Research Data Access Group at GOSH DRIVE Unit (pending Information Governance Committee at GOSH (approved, reference 19PE26)
- ONS Research Accreditation Panel (RAP)—pending.

Changes to original study design

We originally proposed meeting objectives 3–4 using a cohort study design, creating the cohort using the NBS dataset as the cohort spine, with the entire cohort linked to the requested HES and NPD datasets. We also proposed linking the whole cohort to two further datasets held by Public Health England (PHE): the Newborn Hearing Screening Programme (NHSP) database and National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). Using a cohort design for
objectives 3 and 4 would have allowed us to adjust analyses for comorbidities which are rare in the general population of children, but more common among children with CH and CH-GIS. Further, a cohort design where neonatal TSH levels for all children were linked to health and education outcomes would have allowed an exploration of the impact of mildly repressed thyroid hormone levels in the neonatal period on health and education outcomes.

The study received PHE RAC approval in November 2020, however the original study design was not approved by CAG. Feedback from CAG outlined concerns around the number of controls per case using a complete cohort design (~1200 controls/case). The feedback indicated that CAG recognised the public interest in conducting the study but suggested we apply for research database approval so that the NBS study cohort and linked NHSD data could be established as a database that could be accessed and analysed for other projects. The study was given a deferred outcome, with the protocol to be resubmitted once the concerns were addressed.

When these suggestions were subsequently reviewed by the RAC, we were informed that RAC were not prepared to approve establishing research database, as it would require senior NHS Screening Programme review. We were given two options—either wait for this review to take place (we were not given a time frame, but we deemed it highly unlikely to be within the time frame of the project) or amend the study design. This led to the current study design, using both a cohort and the follow-up study of cases and controls to address the research objectives. These issues caused considerable delays to the project (~6–7 months for an 18-month project). Further, due to the delays expected within PHE to provide linked data from NCARDRS and the NHSP, these datasets will no longer be used in this study.

Through our patient involvement activities (see below), we learnt that parents were interested in healthy growth in children with CH. We therefore explored linking the NBS and the CH database to the National Child Measurement Programme (NCMP) dataset (containing height and weight data for children starting primary and secondary school). We were also given approval by CAG to proceed with this linkage. However, due to the data sharing agreement for NCMP data, in which NHSD and PHE are joint controllers, the data cannot be linked at individual level to other datasets for research purposes.

Project approvals, data permissions and subsequent correspondence with governing bodies and data controllers have resulted in substantial delays (see figure 2). While we acknowledge that some of these steps are necessary for data protection and data governance issues, our experience clearly demonstrates that the process of linking multiple data sets is both complex and time consuming. The multiple applications to different ethics/governance committees and data providers required in England (unlike, for example, in Scotland or Wales), often providing very similar information about the study, cause significant delays to projects with tight funding timelines. Unfortunately, these experiences are not uncommon when applying for linkage to English NHS datasets for research.

**Dissemination plan**

Study outputs will be disseminated through Open Access publications and at academic conferences. Updates for children and families affected by CH will be distributed via the British Thyroid Foundation newsletter. Results will also be available to the wider public via the UCL Institute of Child Health Informatics Group website. Metadata and statistical code used in the analysis will be published on GitHub.
Patient and public involvement
Extensive work has been carried out to discuss the research priorities and methodologies with parents and young people. The following groups have been consulted about this project:
► The Young Person’s Advisory Group (YPAG) and the Parents and Carers Advisory Group (PCAG) at GOSH. The YPAG has been consulted three times at meetings where PH presented the project and explained how the study would involve linking newborn screening data from the laboratory at GOSH, to clinical data held by the endocrinology team at GOSH, plus national hospital admissions and school’s data.
► The British Thyroid Foundation (BTF): PH spoke to several parents whose children have CH as well as young people with CH about this study, after the BTF published the study summary on the BTF website and asked interested parents/young people to contact PH. PH also presented the research project at one of the BTF Children’s Conference and will continue to update parents on the progress of the research via their newsletter and Facebook page.
► The Genetic Alliance: PH has presented the study at a meeting with representatives from rare disease organisations.

The researchers will continue to work with the BTF, YPAG, PCAG and The Genetic Alliance to provide updates on the research progress, interpret findings and support dissemination.

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Contributors
PH, RK and CP conceived the study, developed the study protocol, and developed the methodology. PH, MR and MC drafted the manuscript, and all authors contributed to and reviewed the protocol manuscript.

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Competing interests
RK holds an honorary clinical consultant contract with the ANNB screening programme, now hosted by NHS England and Improvement (formally with Public Health England). RK is also the chair of the ANNB Research Advisory Committee. MRN holds an honorary contract with NHS Digital. No other authors have any competing interests to declare.

Patient and public involvement
 Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not applicable.

Ethics approval
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
No data are available. Not applicable.

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