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A protocol for whole-exome sequencing in newborns with congenital deafness: a prospective population-based cohort

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ABSTRACT

Introduction The aetiology of congenital hearing loss is heterogeneous, and in many infants a genetic cause is suspected. Parents face a diagnostic odyssey when searching for a cause of their infant's hearing loss. Through the Melbourne Genomics Health Alliance, a prospective cohort of infants will be offered whole-exome sequencing (WES) with targeted analysis in conjunction with chromosome microarray to determine the genetic causes of congenital hearing loss. Parents will also be offered the opportunity to receive additional results from their infant's WES.

Methods Eligible infants will be identified through the Victorian Infant Hearing Screening Program and offered an appointment in a paediatrician-run clinic, a genetics assessment and enrolment in the Victorian Childhood Hearing Impairment Longitudinal Databank. If parents consent to WES, genes causing deafness will be analysed and they can choose to obtain additional findings. For the additional results component, a modified laboratory protocol has been designed for reporting of results in the absence of a relevant phenotype. Parents' experience of being offered WES will be evaluated using surveys.

Discussion This project will provide descriptive analysis of the genetic aetiology of congenital hearing loss in this cohort and may provide data on genotype–phenotype correlations. Additionally, choices regarding additional findings will be analysed. Participants will represent a diverse cross section of the population, increasing the ability to generalise results beyond the study group. Evaluation surveys will allow analysis of preferences around counselling, usefulness of a decision aid and adequacy of information provision.

What is already known in this topic?

- 50% of congenital bilateral moderate or worse hearing loss is presumed to have a genetic aetiology.
- Many individuals do not receive a genetic diagnosis due to the heterogeneous nature of the disease and the expense of iterative gene testing.
- A majority of individuals, including parents, are interested in receiving additional genomic information when they have next-generation sequencing performed as a diagnostic test.

What this study hopes to add?

- Descriptive evidence of what proportion of congenital hearing loss is due to a genetic aetiology and what the genetic causes are in this cohort.
- A streamlined approach for information delivery and comprehensive care for parents who have a newborn diagnosed with hearing loss.
- An opportunity to investigate if, why and how people want additional findings when they have genomic sequencing in their children.

Strengths and limitations of this study

- Strengths are that this is a population based study with the potential to provide actionable results for families, that the study is integrated into a pre-existing framework, and that it will also provide evidence around the scope of results that should be returned for genomic sequencing.
- Limitations are genomic testing may not identify all genetic causes of hearing loss.

INTRODUCTION

Congenital hearing loss affects 0.1% of the Australian population. Universal newborn hearing screening has lowered the mean age of detection of moderate to profound hearing loss to around 2 months of age[1 2] and early identification of hearing loss allows early amplification (hearing aids and cochlear implants) and early intervention[3] to improve cognitive and communication development.

Although the aetiology of congenital hearing loss is heterogeneous, a significant proportion has a genetic basis.[4] Several hundred genes have been identified as playing a role in hearing and all modes of inheritance

are described: autosomal dominant, recessive, x-linked and mitochondrial.[5] Congenital hearing loss is most commonly an isolated finding; however, in 30% there is an associated syndrome diagnosis.[5] Syndromic associations may not be evident until later childhood or adulthood, for example in Usher syndrome, which results in retinitis pigmentosa and visual loss starting in the later childhood years.

Despite the high frequency of an underlying genetic aetiology, few families receive a genetic diagnosis because of the iterative nature of single gene testing and the significant expense and time required to engage in this process. Whole-exome sequencing (WES) allows simultaneous and rapid analysis of human genes, therefore detection of all exome tractable mutations in genes known to be associated with deafness should be possible for these patients. Benefits of receiving an early genetic diagnosis include provision of prognostic information, streamlined care, accurate recurrence risk advice, and where appropriate, screening for associated health conditions.

Through the Melbourne Genomic Health Alliance (the Alliance), WES will be offered in a clinical context to a 2-year prospective population-based cohort of patients diagnosed in the newborn period with hearing loss. Established as a collaboration in 2013, the members of the Alliance are 10 healthcare, education and medical research institutions committed to incorporating genomics into healthcare to benefit patients.[6] This project is part of the Alliance's broader programme of work to develop an evidence base to inform the cost-effective use of genomics in clinical practice and to build workforce capability in Victoria, Australia.[6] Alliance processes, procedures, and systems are technically agnostic, that is, they are designed to be modifiable as utility in routine clinical practice is demonstrated for other '-omic' technologies. WES with targeted analysis, the first of these technologies, is ready for clinical application. Congenital hearing loss is an ideal candidate condition to further this work because of its extensive genetic heterogeneity, and a population-based cohort is readily identifiable.

In line with international research on the implementation of genomic sequencing[7 8] this cohort of infants will be used to investigate parents' preferences around receipt of additional genomic information about their newborn. This will help inform the scope of genomic sequencing results provided to families and may provide baseline data to inform studies of genomic sequencing in healthy newborns.

Studies of the return of results from genomic sequencing have indicated that the majority of individuals express a desire for additional genetic information.[8–10] Hypothetical preferences for return of additional information indicate that a large proportion (>80%) of survey respondents from the Melbourne Genomics demonstration project want this information for preventable conditions (C. Gaff, unpublished data, 2017). We will contribute to this pool of research, with this study having the benefit of recruiting a population sample with diversity of ethnicity, language, socioeconomic status and education level.

STUDY AIMS AND HYPOTHESIS

The primary aims of the Melbourne Genomics Congenital Deafness project are to understand the reasons parents choose to have genetic testing for their infant and to describe the genetic aetiologies that cause congenital hearing loss in this cohort. A secondary aim is to investigate the feasibility and acceptability of genomic screening of newborns for other health conditions that occur in childhood. This component of the study is titled 'Baby Beyond Hearing'.

The study hypotheses are that: (1) the majority of parents will choose to have WES for their child because accurate genetic diagnosis at an early age will benefit families (understanding the cause, recurrence risk and prognosis information) and health systems (limiting the need for further investigation and tailoring screening as indicated by the genetic diagnosis), (2) up to 50% of children born with moderate or worse bilateral permanent hearing loss will have a genetic cause identifiable by a combination of WES and microarray and (3) parents will want to receive additional genetic information from the WES data about their children.

METHODS/DESIGN

The state of Victoria, Australia, has a unique infrastructure of three major platforms that jointly enable this study to be conducted at the population level, as follows:

Victorian Infant Hearing Screening Program (VIHSP): identification and recruitment

The VIHSP is a well-established state-wide newborn hearing screening programme delivered in all birthing hospitals via a single provider, the Royal Children's Hospital, Melbourne. The programme commenced in 2005 and by 2012 established state-wide coverage of approximately 80 000 births annually. All newborns are offered automated auditory brainstem response (AABR) testing. Those who do not pass the first screening test are referred for a repeat AABR, with a second positive screen result leading to a referral to audiology for confirmatory diagnosis.[2] Based on VIHSP data from previous years, it is estimated that 140 patients will meet the criteria for entry into the study over this 2-year period.[11] There are no similar studies or empirical data on which to predicte uptake and therefore sample size.

Victorian Childhood Hearing Impairment Longitudinal Databank (VicCHILD): recruitment, programme evaluation, long-term outcomes

VicCHILD is a longitudinal databank for Victorian children diagnosed with hearing loss. This programme follows children and families over time to: (1) help researchers and health professionals gain a better

understanding of the causes and outcomes of childhood hearing loss, (2) understand why some children do well while others face greater difficulties and (3) improve intervention and treatment and ultimately the lives of children with permanent hearing loss and their families. Over the 2-year period prior to this project commencing VicCHILD identified that of babies born with congenital hearing loss, 40% of their parents were born overseas with the majority of these being of Asian ethnicity and 20% of families identified a primary language other than English. Families came from a range of socioeconomic backgrounds. This provides an insight into the diversity of the cohort that will be recruited in this project.

Paediatrician clinics: recruitment, phenotyping, long-term outcomes

Two clinical services exist in Victoria, specifically catering to infants diagnosed with hearing loss through VIHSP. These are run through two of the major tertiary hospitals in the state. The Paediatric Hearing Loss Investigation Clinic (PHLIC) through Monash Children's Hospital and the Caring for Hearing Impaired Children (CHIC) clinic through the Royal Children's Hospital.

Eligibility criteria

Infants born between January 2016 and December 2017 (inclusive) in Victoria and diagnosed, following two positive AABR screens delivered by VIHSP, with bilateral permanent hearing loss greater than 40 dB over three frequencies (moderate, severe or profound hearing loss). These criteria include infants classified as having sensorineural, mixed conductive and sensorineural and auditory neuropathy. These infants may have isolated hearing loss or suspected syndromic hearing loss.

Exclusion criteria

Unilateral hearing loss of any degree or mild hearing loss or better in the best ear or hearing loss that is confirmed as conductive and temporary.

RECRUITMENT PROCEDURES

Recruitment procedures are depicted in figure 1.

Opt-out letter

Infants who fulfil the eligibility criteria will be identified by VIHSP and sent an 'opt-out' letter, which briefly outlines the paediatrician-run clinics, VicCHILD and the Melbourne Genomics Congenital Deafness project. Parents will be given the option of doing nothing and therefore being contacted over telephone, sending an 'opt-out' notification back to VIHSP (via prepaid post, email or fax) or deferring contact by several months.

Telephone call

A genetic counsellor or genetic doctor will telephone parents who do not opt-out and provide standardised information using a guideline. Parents will be offered an appointment in CHIC or PHLIC clinic. They will be able to book a genetic counselling appointment to discuss genetic testing on the same day or at an alternate time according to their preference.

Information about VicCHILD will also be provided and parents will be given the opportunity to meet with a VicCHILD staff member on the day of their appointment.

Interpreter services will be available for families from a non-English speaking background. If the family is not contactable over telephone, alternative attempts will be made such as via email or by review of the medical record (if one exists) for an alternative contact number.

At the phone call, parents indicate which of the three initiatives (VicCHILD, Melbourne Genomics and paediatrician clinics) they wish to pursue. For patients who book an appointment for genetic counselling, an information pack will be sent in the post, including a questionnaire and a decision aid. Both parents are encouraged to attend the appointment to facilitate joint decision-making.

BASELINE QUESTIONNAIRE

The questionnaire was designed in collaboration with the paediatricians providing the CHIC and PHLIC clinics and the VicCHILD research team. The questionnaire enables parents to complete a single document that provides the necessary information for: (1) the clinical appointment, (2) inclusion in VicCHILD and (3) data collection for the Melbourne Genomics Congenital Deafness project. Parents can opt to share this information with all three initiatives or exclude any in which they do not wish to participate.

The questionnaire asks about pregnancy, delivery, family history, the child's hearing loss diagnosis, investigations, treatments and service use to date, general health and development (ASQ)[12] as assessed by the parent, demographic information, quality of life (PEDS QL 3.0)[13] and parental mental health.[14] Parents can complete the questionnaire in paper form or online.

DECISION AID

A decision aid has been developed specifically for this study to provide families with information about testing prior to their appointment. The decision aid was modelled on a tool designed by the Public Health Genetics team at the Murdoch Children's Research Institute for couples to use when deciding what investigations to have during pregnancy.[15] The decision aid helps to ensure parents are giving true informed consent for genomic testing, and will also be used to evaluate what resources are required to integrate genomic sequencing into standard clinical practice.[16] The decision aid is designed to help families consider if they would like their child to have WES, and also how much information they would like to receive from the test. The document contains two worksheets where parents can explore their own personal views on: (1) having genetic testing and (2) how much information they are interested in receiving from this testing.

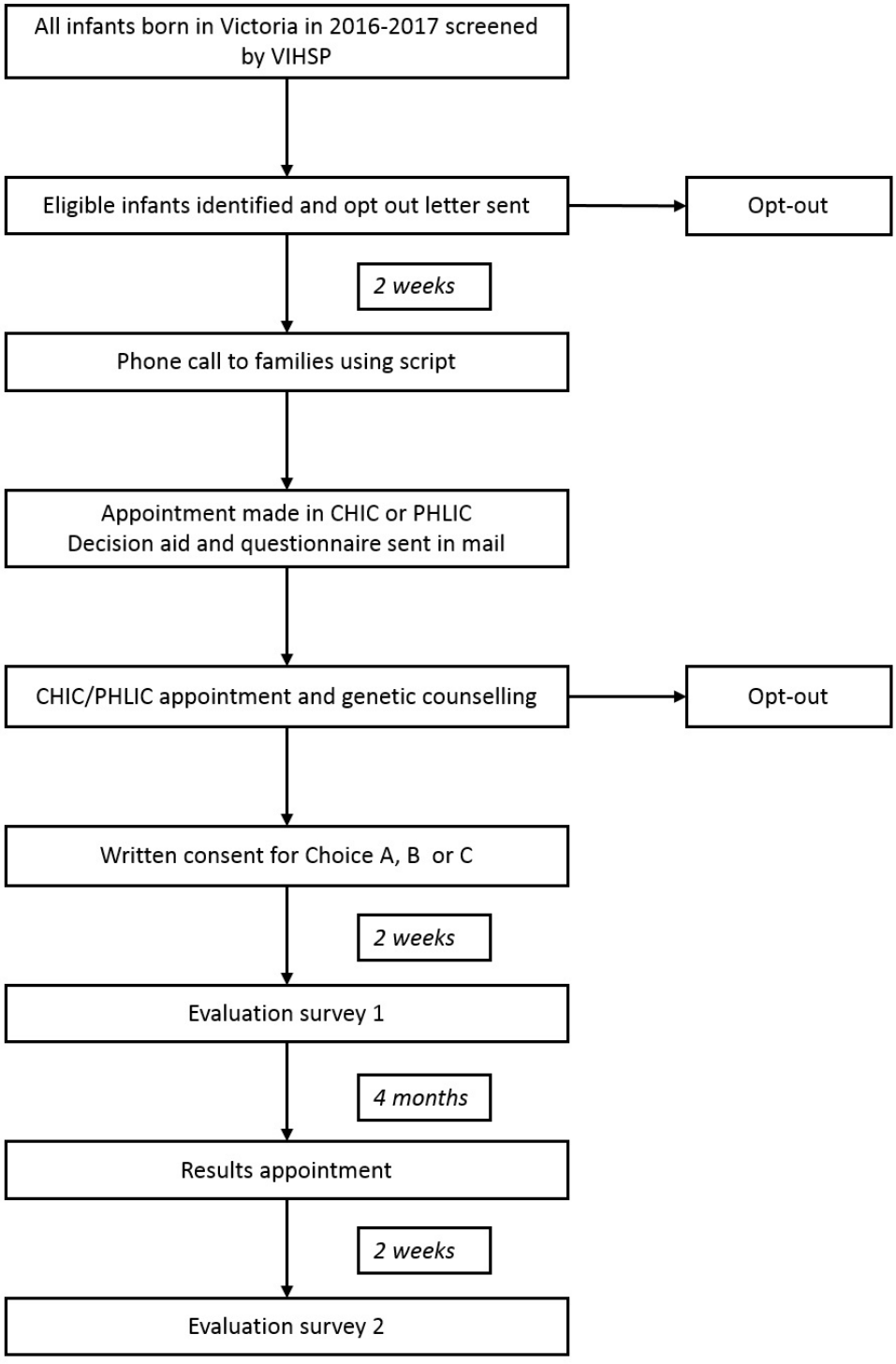

Figure 1 Flowchart of recruitment and testing. CHIC, Caring for Hearing Impaired Children; PHLIC, Paediatric Hearing Loss Investigation Clinic; VIHSP, Victorian Infant Hearing Screening Program.

Infants whose parents consent to investigate the cause of hearing loss will be offered options regarding additional gene analysis (table 1).

Parents are asked to bring the decision aid to the appointment where a genetic counsellor will go through their preferences and use the document as a talking point for exploring their decisions around genetic testing.

CLINIC APPOINTMENT

A paediatrician with special interest in hearing loss and either a doctor with training in genetics or a genetic counsellor will conduct the clinic appointment. During the first hour of the appointment, the patient will have a full clinical and developmental assessment and non-genetic investigations and referrals will be ordered as

Table 1 The three choices offered to parents regarding which genes will be analysed and reported following whole-exome sequence

Choice A	Choice B	Choice C
Only genes that are known to cause hearing loss will be examined. We estimate that we will identify a genetic cause for hearing loss in about half of the infants that we test.	Choice B is the same as Choice A *plus* We will analyse additional genes that cause diseases that: 1. affect children 2. have a known treatment or intervention that will improve the child's health.	Choice C is the same as Choice B *plus* We will analyse additional genes that cause diseases that: 1. affect children 2. may not have a clear treatment pathway or intervention to improve the child's health.

indicated. During the second hour of the appointment, a genetic counsellor will discuss WES with the parents in more detail, using the completed decision aid as a basis for discussion.

Talking points for genetic counsellors will be created in addition to a training session facilitated by an educator and experienced genetic counsellors to upskill counsellors in obtaining consent for additional findings. This ensures that the information and counselling provided is standardised across sites and between clinicians. If the family wishes to participate in the research, clinical grade WES and chromosome microarray will be ordered and a venous blood sample will be taken from the child on the day. Families will also have the option of having more time to consider the testing with follow-up from the genetic counsellor.

Written consent will be required to participate in the study from one parent; however, counsellors will ensure that both parents are aware of the nature of the testing and in agreeance regarding the scope of results to be returned.

Appointments to disclose results will be scheduled when reports are issued for the WES. These may be with a geneticist or paediatrician and genetic counsellor.

Gene lists

Gene lists are designed to allow rapid interpretation of test data as well as filtering of unwanted information such as variants in genes known to cause adult-onset untreatable disease (online supplementary appendix 1).

Choice A contains all of the genes known to cause hearing loss. It was constructed by comparing and merging gene lists from two pre-existing clinical diagnostic panels: OtoSCOPE[17] and OtoGenome,[18] and several research gene lists sourced from Genomics England (the PanelApp Congenital Hearing Impairment (profound/severe) panel v1.8),[19] the Avraham laboratory,[20] the Gasparini laboratory[21] and the Rehm laboratory.[22] Additional genes were added to the list based on recently reported findings in the literature. The list is separated into two tiers. Tier 1 comprises 141 genes for which there is validated evidence that mutations are causative in human patients with hearing loss. Tier 2 contains a further 241 genes with good evidence from a range of sources for their involvement in hearing loss, substantively based on evidence from animal models.

Choice B was adapted from a gene list created, and generously shared, by the NC NEXUS group. This list is based on a metric they devised and used to 'score' gene/disease pairs.[23] These conditions all have treatment or intervention available.

Choice C was devised using a set of criteria that were agreed by the investigative team. These include:

- definitive gene disease association (as defined by the BabySeq group[10]);
- onset of symptoms prior to age 16 the majority of the time;
- validation method available to confirm diagnosis at the time of testing.

All of the diseases associated with genes in choice C have a validation method available such as a biochemical test, X-ray or a one-off clinical examination in order to provide additional certainty around a presymptomatic diagnosis.

LABORATORY PROTOCOL

Exome sequencing, variant detection, variant filtering and interpretation will be performed in a clinically accredited laboratory using similar methods to those previously described in other patient cohorts of the Melbourne Genomics Health Alliance.[24]

Whole-exome sequencing

DNA will be extracted from peripheral blood, and exome sequencing will be performed using SureSelect Clinical Research Exome V.1 (Agilent) on either a HiSeq4000 or NextSeq500 (Illumina) with a targeted average sequencing depth of 100×.

Bioinformatic analysis and variant filtering

Data analysis and variant calling will be performed using Cpipe.[25] Variants will be assessed using LOVDplus.[26] Variants will be prioritised based on the clinician's assessment using information such as likely mode of inheritance (assumed to be autosomal recessive unless family

history indicates otherwise) and any phenotypic information available such as MRI brain findings or dysmorphic features on examination. We predict a large proportion of patients will have no family history and no additional phenotypic information apart from hearing loss and in this instance all variants detected will be curated.

Variant interpretation

The methodology around the interpretation of the additional findings gene lists focuses on the shift in principle from using WES as a diagnostic tool to use of WES as a screening tool. In a diagnostic situation, a high level of sensitivity is required from the test to capture all possible causes of a patient's phenotype. In a 'screening' or 'predictive' analysis, a high level of specificity is required to ensure there is adequate evidence and understanding of the outcome of a gene variant to return results to patients who will often be asymptomatic at that time.

The standard diagnostic laboratory variant interpretation protocol was adapted for this cohort due to the novel situation of offering analysis of genes outside of the patient's current phenotype.

Choice A, tier 1 genes will be analysed in accordance with the laboratory's National Association of Testing Authorities accredited procedures which are aligned with American College of Medical Genetics guidelines,[27] resulting in a clinical report. Choice A, tier 2 genes will be analysed by a research group only in patients who do not receive a clinical result from tier 1.

Choice B and C genes will be analysed by the same clinically accredited diagnostic laboratory for patients who consented to the analysis, but only variants in class 4 or 5[28] will be reported to families for these genes. Variants of uncertain significance, as well as carrier-only variants, will not be reported. In order for this process to be streamlined, any missense variant identified in the genes of interest will first be searched for in the literature. If the variant is not previously described in published literature or in ClinVar, no further curation will be performed. This is on the basis that missense variants cannot be classified any higher than class 3 without supporting case reports. Truncating and nonsense variants are curated in the same way as variants in choice A.

Criteria for classification will be based on the principles outlined in the American College of Medical Genetics and Genomics standards for interpretation of sequence variants.[27] Variant classifications will be reviewed in a multidisciplinary team meeting attended by clinical geneticists and other medical subspecialists, genetic counsellors, molecular geneticists and bioinformaticians.

EVALUATION SURVEYS

Evaluation surveys have been designed and can be completed online or on paper. Patients will complete the first survey 2 weeks after they consent for genomic testing and a second survey 2 weeks following their results appointment (see figure 1). The surveys include data captured for Melbourne Genomics across all patient groups as well as data that is specific to children within the Melbourne Genomics Congenital Deafness project.

The first survey includes questions about the parents' experience of the consent process including the decision aid and the genetic counselling appointment. The Decisional Conflict Scale and Decisional Regret Scales[29] are included in survey 1 and 2, respectively, to evaluate parental decision-making around which gene list they selected for analysis. The first survey includes closed and open questions exploring families' reasons for wanting to have genomic sequencing for their child. Knowledge questions and a question on the likelihood of the test finding the cause of the hearing loss are included to gauge understanding. Validated measures to assess potential predictors of uptake of the expanded analysis are included: tolerance of uncertainty,[30] State-Trait Anxiety scale,[31] medical literacy[32] and information-seeking preferences.[33 34] The Perceived Personal Control scale[35] is included as a measurement of patient empowerment in both surveys.

The second survey includes study-specific questions assessing the parents' understanding of the genomic results, impact these will have on them and their family and what they have valued about having the test done for their child.

ANALYSIS OF DATA

The majority of data analysis will be descriptive in nature due to the small sample size, which is estimated to be approximately 100. The primary outcome measures reported will be uptake of testing, the detection rate of causative/pathogenic variants and identification of carrier status. Detailed sociodemographic characteristics of the participants (eg, socioeconomic status, age of parents, language and cultural background, education) and variable aspects of the process and outcomes will be presented, followed by comparisons between groups of interest. Examples of these include:

1. information delivery methods (phone call, face-to-face consultation and written information) and parental responses to the offer of testing and their knowledge about testing in relation to these various modalities;
2. psychosocial measures of parents who accept versus decline testing and the scope of results chosen by those who participate;
3. differences in uptake between parents of children who require cochlear implant, those who are systemically unwell or have a broader phenotype (not isolated hearing loss) or whose infant was born prematurely for example.

Multivariable statistical analysis may be performed, but this will be dependent on sample size for each group, for example, accept testing versus decline testing and no additional findings versus additional findings.

Audiological and general phenotype data will be correlated with genotype and a summary of these findings will be presented.

DISCUSSION

This project is novel in offering genomic sequencing to infants with congenital hearing loss in conjunction with comprehensive developmental and general health assessments and long-term follow-up.

The primary strengths of the study are that it is a population-based study, has the potential to provide actionable results for families at an early stage and is integrated into a pre-existing framework, making the process streamlined for patients and care providers. It will also provide new and important evidence around the scope of results that should be returned for genomic sequencing. The limitations of the study are concordant with the limitations of all WES. These relate to sequencing gaps which may result in a pathogenic variant not being detected, as well as the technology's inability to detect some types of DNA changes such as copy number variation, and the possible detection of a variant in a gene that is not yet known to have an association with hearing loss. Evidence suggests a significant proportion of congenital hearing loss (15%–20%) is due to copy number variants[36] and for this reason, all patients will simultaneously have a chromosome microarray.

Genomic results will add to the knowledge around the genetic aetiology of congenital hearing loss and will provide important data on genotype–phenotype correlations. The use of genomic sequencing means that families who do not receive a molecular diagnosis initially can participate in research around genes related to hearing loss and enable gene discovery in this area by having their child's WES data reanalysed.

Descriptive analyses of parents' interest in gaining additional results from genomic sequencing will provide novel information that will help to determine the clinical utility of an offer to provide sequencing results beyond those directly related to the child's phenotype, that is, deafness in this case. The study will assess previously described concepts, for example, what has been described as 'inflicted ought' where parents have a desire to do what they believe is the best thing for the child despite the individuals not necessarily seeking similar predictive information for themselves.[37] It will also provide important data on parents' decisions when faced with the reality of testing. Previous studies have found that parent preferences when offered theoretical versus actual testing can produce quite disparate results. In the BabySeq study, a large proportion of parents indicated in preparatory research that they would be interested in genomic sequencing for their newborn;[10] however, in reality the uptake for the study has been very low.[38]

Evaluation surveys will produce data for further descriptive analysis of preferences around counselling, use of a decision aid and the information provided. Together, these results will add substantially to the development of strategies and policies related to implementation of genomic sequencing in the newborn period.

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Competing interests None declared.

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