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NewbornsInSA multi-omic newborn screening: protocol for a prospective cohort study

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ABSTRACT

Introduction Newborn bloodspot screening (NBS) is freely and universally available to babies born in Australia, with nearly 300 000 newborns screened each year. The NBS programme screens for approximately 30 conditions; however, there are hundreds of childhood conditions that could be treated if identified earlier and asymptomatically. Contemporary screening platforms have relied on mass spectrometry-based technologies, limiting surveillance to conditions with validated biomarkers detectable within the neonatal period. Advancements in metabolic techniques and genomics have expanded the range of conditions that could be detected. The NewbornsInSA research study will develop, validate and evaluate a novel multi-omic model of newborn screening, integrating metabolomic and genomic newborn screening as complementary methodologies.

Methods Parents can opt in to additional NBS through NewbornsInSA during pregnancy or shortly after birth. One thousand prospectively recruited families will be offered genomic NBS by whole-genome sequencing, including analysis of a virtual gene panel of over 600 genes, and concurrent metabolomic screening. Clinically actionable pathogenic or likely pathogenic genetic variants will be reported to parents and whole genome sequencing data will be available on request for diagnostic reanalysis, if required later in life.

Acceptability of the NewbornsInSA programme will be evaluated through stakeholder engagement activities with healthcare professionals, members of the public and patient advocacy groups. Family experiences will be assessed using online surveys. The diagnostic yield, accuracy and the costs and consequences of the multi-omic NBS model will be assessed by comparison to standard-of-care NBS.

NewbornsInSA will investigate the acceptability, feasibility and cost-effectiveness of a multi-omic newborn screening model in a prospectively recruited South Australian population. We hypothesise that this approach will increase the number of conditions identified, reduce the time to diagnosis and facilitate earlier care with better outcomes for newborns with genetic conditions.

Ethics and dissemination This research study has been ethically approved by the Women's and Children's Health Network Human Research Ethics Committee (2022/HRE00258 and 2023/HRE00236). Findings will be disseminated through peer-reviewed publication and conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study performs genomic newborn screening of actionable genetic conditions in a prospective cohort with return of results to parents and healthcare professionals.
⇒ Metabolomic profiling using mass spectrometry is integrated with genomic screening as complementary tools.
⇒ Surveys with parents who participate will reveal family perspectives, enablers and barriers of participation, along with acceptability of the programme.
⇒ This research study is embedded in South Australia's public health service, thereby proving insight into the feasibility of such a programme in a standard healthcare setting.
⇒ Determination of the diagnostic accuracy of the multi-omic screening methods would require longitudinal follow-up of participants beyond the study period.

INTRODUCTION

First established in the 1960s, Australian newborn bloodspot screening (NBS) programmes now detect 1 in 800 babies each year with serious but treatable health conditions.[1 2] The detection of these conditions within the first week of life, when asymptomatic, is an important opportunity for earlier targeted treatment, resulting in better health outcomes.[3–5] The treatment of these infants prior to clinical presentation reduces morbidity and mortality caused by these conditions.[6] The NBS programme has strong public acceptance, with over 99% uptake.[3 7 8] NBS programmes have been

named by the Centre for Disease Control and Prevention in the United States as one of the top 10 great public health achievements.[9]

It is not uncommon for caregivers of infants and children with rare disease to experience a complex and extended journey seeking answers and treatments for their child. This has been termed a 'diagnostic odyssey' and leads to treatment delays for the child.[10–12] Families often navigate multiple healthcare services over months or even years before a diagnosis is established.[13–15] This prolonged diagnostic journey places a burden on the health system, imposes an emotional and financial strain on parents and leads to increased and potentially unnecessary or invasive investigations and missed opportunities for early intervention in the infant. Population-based screening programmes can mitigate the diagnostic odyssey for certain conditions by enabling earlier detection.[16] Further, early diagnosis of genetic disease can inform families of their risk of conceiving another child affected by the same condition, providing parents with informed reproductive choices.[17]

Newborn screening has historically used biochemical and metabolic technologies.[3] Genetic-based tests have been recently integrated into routine NBS as first or second-tier tests, including screening for cystic fibrosis, spinal muscular atrophy and severe combined immunodeficiency.[3 18–21] Emerging personalised medicines, increases in availability of treatments for childhood conditions and greater affordability of genomic sequencing have resulted in an exploration of the benefits of genomic technologies to complement NBS programmes.[22–24]

Genomic newborn screening by whole genome sequencing (WGS) has the potential to identify hundreds of conditions in a single test from a single dried bloodspot (DBS) sample. There is widespread global interest in investigating the application of genomics in NBS,[7 23 25–31] which in combination with traditional metabolic techniques has the potential to reduce the morbidity and mortality associated with rare childhood diseases. The method can be streamlined in the laboratory and refined at the variant analysis phase through a virtual gene panel where new target genes can be readily included.

While holding great promise, these new genomic approaches also bring challenges associated with analytical interpretation, ethical considerations, public acceptability and value for money.[8 23 25 26 32 33] Offering genomic NBS (gNBS) at population scale may be costly with an undetermined diagnostic yield and accuracy. Further, lack of consensus on conditions for inclusion or reportable variants, informed consent, health service readiness to support increased demand for counselling services, and the potential increase in patients requiring surveillance may be barriers to implementation. Navigating data storage capacity and privacy, insurance implications and the consequences associated with false positive findings are also important considerations for the integration of genomics in NBS. The feasibility of gNBS is currently being investigated by national research efforts including the Genomic Screening Consortium for Australian Newborns, comprised of a series of gNBS research studies exploring the feasibility, social, ethical and legal issues of gNBS in Australia.[34]

The NewbornsInSA research study is investigating a multi-omic approach, integrating metabolomic and genomic techniques to expand NBS screening.[32 35] The feasibility of the approach will be explored through novel metabolomic screening, prospective sequencing of newborns' DNA, and evaluated through health economic cost-effectiveness modelling. The study will also explore stakeholder perspectives and acceptability of this approach with the aim to inform future programmes.

METHODS AND ANALYSIS

The objective of the NewbornsInSA research study is to assess the feasibility and acceptability of an integrated multi-omic newborn screening model by conducting screening of a prospectively recruited South Australian cohort (figure 1). The study has four primary aims:

1. Validate metabolomic profiling for use in newborn screening.
2. Perform metabolomic profiling on an unselected, prospectively recruited newborn cohort in South Australia.
3. Screen newborns identified to be at increased risk of genetic disease using whole-genome sequencing.
4. Evaluate the effectiveness (clinical, cost, implementation) of the model against current NBS standard-of-care.

NewbornsInSA is led by SA Pathology, South Australia's state-wide public pathology service screening 18 000 South Australian newborns each year, the Women's and Children's Hospital, Adelaide's principal tertiary metropolitan children's hospital delivering approx. 4600 babies per year, and the University of Adelaide. Our funding through the National Health Medical Research Council's Medical Research Futures Fund supports multiple research positions, including a genetic counsellor, genomic analyst, metabolic scientists and project manager.

Retrospective validation study (Aim 1)

The retrospective validation study uses archived bloodspots to address the following objectives:

1. Validate a metabolomic screening method to discriminate between normal and abnormal bloodspots.
2. Validate genomic newborn screening using WGS on DBSs.

Untargeted metabolomics of retrospective DBS using ZenoTOF 7600 Quadruple Time of Flight (TOF) and Triple TOF 5600 mass spectrometers can detect tens of thousands of lipids and hydrophobic and hydrophilic metabolites. The retrospective study will use DBS cards from newborns born between January 2019 and May 2024. This will include a discovery cohort to develop a novel metabolomic screening algorithm and a validation cohort to evaluate and optimise the model (figure 2).

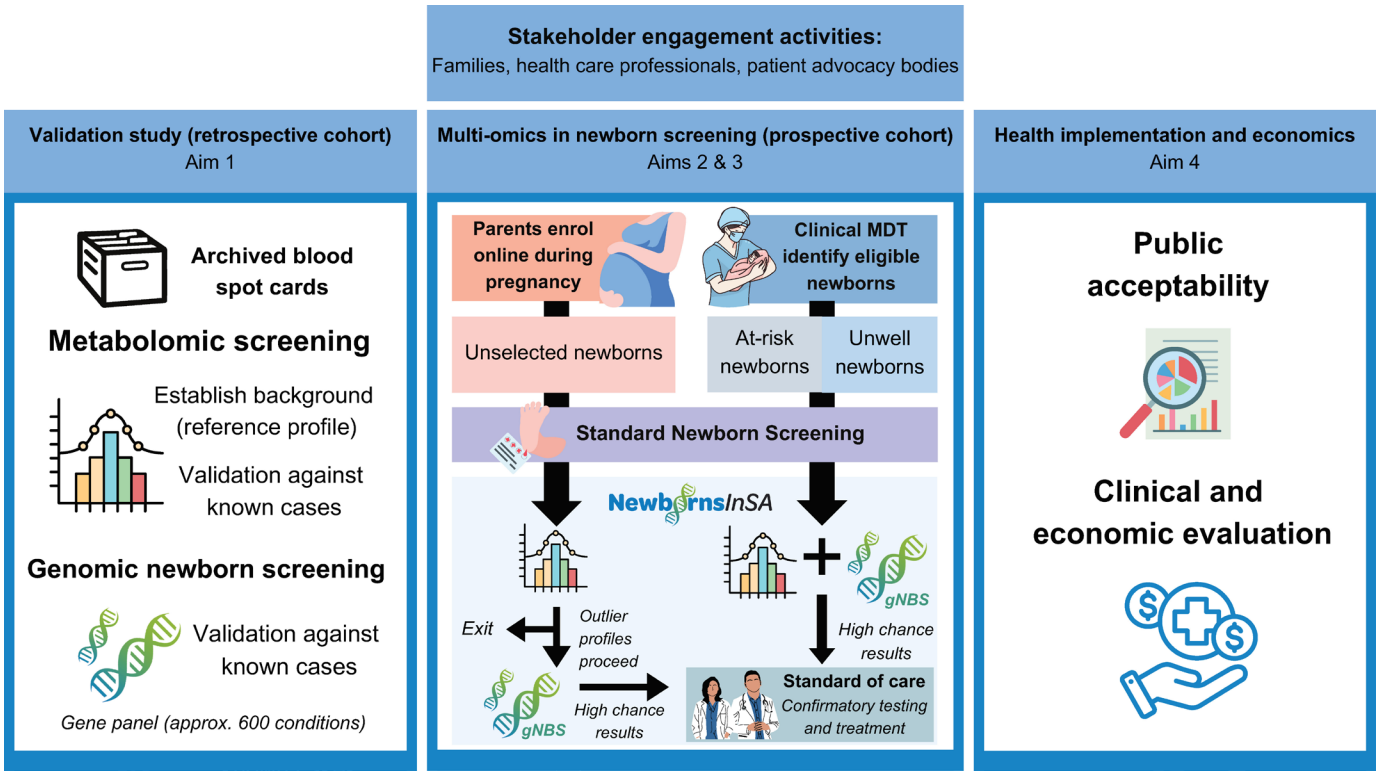

Figure 1 NewbornsInSA study design. gNBS, genomic newborn bloodspot screening; MDT, multi-disciplinary team.

Over 2000 retrospective DBS cards from healthy full-term newborns without a record of health conditions, and 200 DBS with known diagnoses will form the discovery cohort. The profiles from healthy newborns form a 'reference profile'. The validation cohort will comprise approximately 500 healthy full-term newborns and 80 newborns with a known genetic condition. Metabolomic profiling will be performed in the SA Pathology Neonatal Screening Centre at the Women's and Children's Hospital, a clinically accredited public pathology laboratory which performs state-wide NBS.

A statistical approach will be applied to untargeted metabolomic data to develop a semi-targeted algorithm for identifying outlier DBS profiles. This approach will combine sparse principal component analysis (sPCA-DA), linear, multivariate analysis and lasso logistic regressions to identify a selection of informative features that differentiate reference profiles from outliers. These selected features will inform the development of a semi-targeted metabolomic screening method, optimised for high throughput analysis using a triple quadrupole mass spectrometer. The statistical algorithm will be cross-validated using an independent set of bloodspots from additional cases (the validation cohort), analysed by both untargeted and targeted metabolomic methods.

Development of genomic newborn screening technical workflows and analyses

Genomic newborn screening in NewbornsInSA focuses on the detection of pathogenic and likely pathogenic variants within a predefined gene list (as per American College of Medical Genetics and Genomics (ACMG)

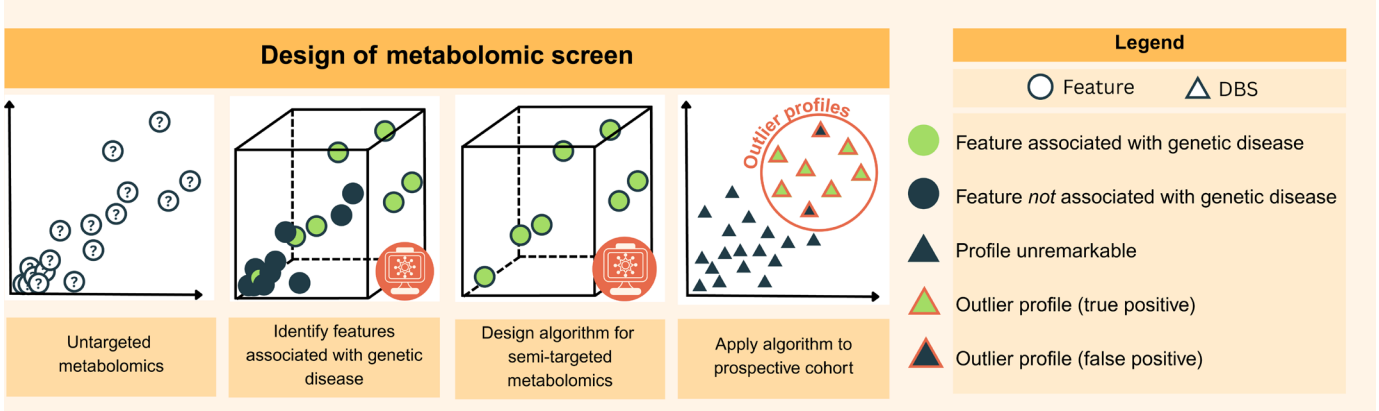

Figure 2 Overview of the development of novel metabolomic screen methodology. DBS, dried blood spot.

guidelines).[36] A gene/condition list including 605 genes curated as part of the BabyScreen+study (publicly available on Panel App Australia) and additional genes proposed by local clinical teams and stakeholders will be adopted. Gene selection will be guided by fundamental screening principles, including disease severity, disease onset (childhood), type and availability of treatment/intervention, ability for detection using WGS and strong gene-disease associations.

To validate the gNBS assay, 50 retrospective bloodspots with a prior genetic diagnosis of a NewbornsInSA target condition, known positives from outside our gene list and cases without genetic disease will be selected. Variant curation will be performed using the in-house VariantGrid software and Illumina's Emedgene software with a custom-built gene panel and presets which filter and prioritise variants by inheritance and population frequency. The genomic analyst will validate this method by performing a blinded analysis of genomes from retrospective bloodspots. These samples will facilitate optimisation of the gene panel and presets to minimise the likelihood of incidental or non-target findings, reduce the number of variants to be curated by the genome analyst, and semi-automate the analysis of low-chance variants. This research study is performed within SA Pathology Genetics and Molecular Pathology, a clinically accredited public pathology laboratory which performs state-wide genetic testing services. The genomic newborn screening assay will be validated to the ISO 15189 standards of the National Association of Testing Authority (NATA) and the National Pathology Accreditation Advisory Council and will be provided as a clinically accredited test.

Prospective research study (Aims 2 and 3)

In the prospective study (participant enrolment from May 2024 to September 2026), families will be offered metabolomics with or without genomic screening in addition to standard-of-care newborn screening. Consent is opt-in using a combination of recruitment by clinicians and e-consent through an online platform. Our research team includes senior clinicians across six paediatric clinical subspecialties (clinical genetics, metabolic medicine, immunology, haematology, oncology and neurology) and the newborn screening department. Participants are supported by a dedicated genetic counsellor and hence the team is well placed to coordinate care pathways for participants identified with a high-chance screening result.

Up to 40 000 newborns may be enrolled in the prospective arm of this research study. All enrolled newborns will have metabolomic profiling, with a subset of 1000 newborns offered gNBS. Newborns will be offered first tier gNBS if they are clinically at risk or unwell or have an outlier metabolomic screen through the study. This research design was chosen in an attempt to offer gNBS to an 'at-increased-risk' population, potentially increasing diagnostic yield and thus providing more opportunity to assess the cost consequences of gNBS and early genetic diagnosis against standard-of-care. During the development of the first tier metabolic screen, all enrolled newborns will be offered first tier gNBS.

Participant recruitment

Social media advertisements, information pamphlets, and direct engagement with healthcare professionals will serve as key strategies for informing and recruiting parents to the study (figure 3, online supplemental files 1 and 2). Eligible participants may self-enrol online during pregnancy or up to 14 days after birth. The NewbornsInSA research screen is performed in parallel with standard-of-care NBS, using the same bloodspot. This allows the study to leverage existing clinical workflows, minimises impact on healthcare services and reduces burden on families by eliminating the need for additional sample collection. The genomic sequence data will be available on request for diagnostic reanalysis, offering the potential for rapid testing that may benefit families years later.

Inclusion criteria for enrolment (all required):

- Enrolling parent is ≥18 years.
- Baby is ≤14 days old or antenatally recruited.
- Baby is born in South Australia.
- Parents opt in to routine NBS and return study consent forms.

Inclusion criteria for gNBS (one or more required):

- Baby has a clinical abnormality or risk factor.
- Outlier metabolomic profile.
- Receives positive NBS screen.
- Selected for first tier gNBS.

Consent of unwell/at-risk cohort (n=300)

This cohort will be referred to the study team by healthcare professionals and through clinical case discussions. See online supplemental table 1 for the clinical eligibility criteria for this cohort. These newborns will be predominantly identified within our major hospitals providing obstetric and paediatric care, including referrals from a level 6 neonatal intensive care unit, neonatal special care units, maternal-fetal medicine settings and through referral from other clinical specialities. Newborns who screen positive in the standard NBS programme will also be referred to the study. Our study's clinical multidisciplinary team (MDT) will review and approve the eligibility of all referrals. This team comprises consultants from paediatric subspecialties including clinical genetics, metabolic medicine, immunology, haematology, oncology and neurology. The study genetic counsellor will invite and consent participants for concurrent metabolomic screening and gNBS. Parents of newborns enrolled in the unwell/at-risk cohort will be given the option to participate in trio gNBS by providing their own DNA sample to assist in variant prioritisation and classification. This also enhances diagnostic utility where reanalysis of the genome is requested for diagnostic testing. Standard of care pathways continue in parallel with participation in this study.

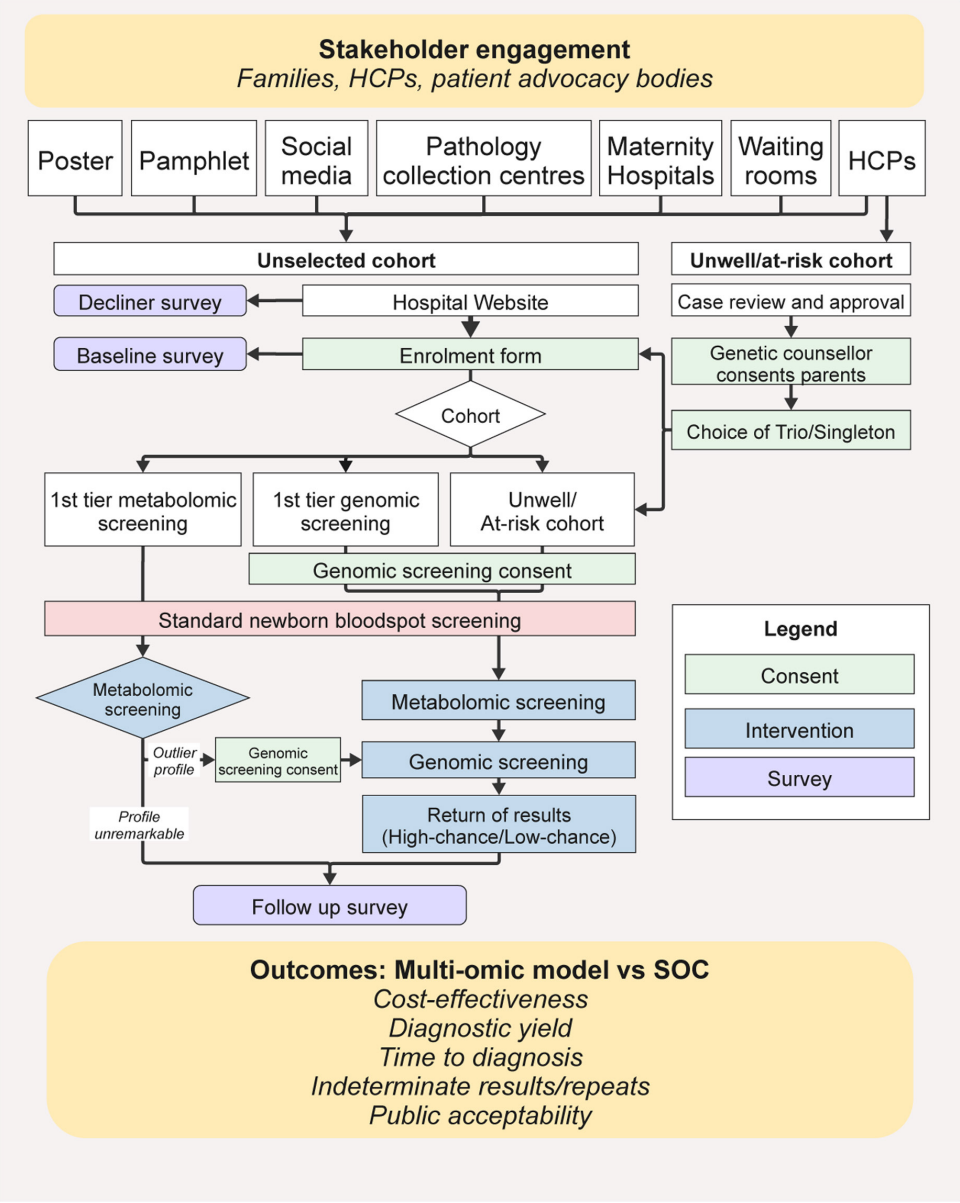

Figure 3 NewbornsInSA prospective study recruitment pathway. HCPs, healthcare professionals; SOC, standard of care.

Consent of unselected cohort (n<40 000)

This cohort will be recruited through online self-enrolment. The study will be advertised through social media, posters and pamphlets in waiting rooms, and antenatal education sessions. Participants consent through Research Electronic Data Capture (REDCap) e-consent forms and have access to a genetic counsellor for questions. First-tier gNBS will be offered in the first phase of the study during optimisation of the metabolomic screening algorithm. Once fully established, metabolomic screening of DBS will be offered as a first-tier screen and only newborns with metabolomic outlier profiles will be offered second-tier gNBS. Families who are eligible for gNBS will be invited to provide consent for singleton gNBS. The study will identify the number of families who enrol in the study but decline gNBS consent or withdraw from the study after initial enrolment. Surveys are offered to these families to capture their concerns and reasons for declining participation.

Return of results

Parents of infants who undergo gNBS will receive the results of their baby's risk of developing one of the conditions included in this study as either a 'low-chance' or 'high-chance' report. High-chance reports will include pathogenic or likely pathogenic variants (as per ACMG guidelines[36]) where variants are supportive of disease in a predictive setting and where follow-up care is supported by local clinicians. Variants of uncertain significance will not be reported in this study. Other clinical information, such as standard NBS tests and hearing screening results, will be consulted in the context of reporting to upgrade or downgrade

relevant variant classifications. The family will receive a lay-language, family-facing report while clinical reports will be entered into the statewide laboratory information system and electronic medical record. During the consent process, families are advised of the possibility of incidental findings. Incidental findings will be discussed at a clinical MDT and reported back to families if medically actionable and deemed relevant for the family.

A high-chance result will be delivered to families through a genetic counsellor, clinical geneticist or medical specialist, as appropriate. Clinical teams will initiate a referral process to the relevant speciality team for confirmatory or diagnostic testing (such as biochemical or imaging) and clinical management. Referral pathways will be facilitated by specialist paediatric clinicians within our study team, including coordination by the state-wide Paediatric and Reproductive Genetics Unit. Rare Voices Australia, the peak advocacy group for rare disease patient groups in Australia, is a research partner in this study and will provide both input into the study and is a valuable support network for many families.

Participants will not receive a result regarding their metabolomic screen as this method is still in an early stage of research and does not yet yield a validated standalone screening outcome. Instead, newborn metabolomic profiles will contribute to the development and optimisation of the screening algorithm, serving to enhance the future utility of the application of these metabolomic approaches in NBS.

Reanalysis

As this study includes WGS performed within a clinical diagnostic service with NATA accreditation, the genome sequence will be available for diagnostic reanalysis later in life. Genomic reanalysis of a stored newborn genome has the potential to fast-track diagnosis and to provide a cheaper alternative to ordering new genomic testing for new clinical questions.[37 38] SA Pathology has established accredited pathways for the reanalysis of genome data. Where clinically indicated and using a new clinical request and consent process, reanalysis for diagnostic purposes will occur under the routine clinical framework.

Data management

Genomic data will be stored as per SA Pathology's clinically accredited procedures and ISO 15189 requirements and housed on secure SA Health servers. Genomic data files are stored for a minimum of 10 years. Metabolomic data will also be stored within SA Pathology's infrastructure.

Research data including enrolment information, clinical follow-up and survey responses (excluding genomic data) will be entered into REDCap[39] and housed by the Central Adelaide Local Health Network of SA Health (South Australian Public Health Service). Patient information and consent forms capture permissions for de-identified data sharing with ethically approved studies, nationally and internationally.

Patient and public involvement

Patients and public contribute to the design and implementation of this research programme through consultation in focus groups and surveys. Families and members of the general public self-enrol in this research programme.

Stakeholder engagement

Acceptability and feasibility of the NewbornsInSA study are primary outcomes of this research study. These are being explored in the context of the South Australian population and health system through stakeholder engagement activities, the public uptake of the prospective research study, and through participant surveys.

Families

The perspectives of parents and expectant parents will be explored. These families are key in designing the recruitment and consent strategies, and in determining the acceptability of the programme. Focus groups will be run with members of the general public to explore the clarity and information content of recruitment materials. Families who enrol will be invited to complete baseline and posttest surveys. Key themes of interest include anxiety, decisional regret, barriers and enablers of participation and acceptability of gNBS, as well as clarity of the information provided about the programme. The surveys include the 6-item State-Trait Anxiety Inventory, Edinburgh Postnatal Depression Scale, Decisional Regret Scale, Decisional Conflict Scale and measures of health beliefs including self-efficacy, perceived barriers, risk and severity. Decliner surveys will be designed to capture barriers to gNBS and will be available to families who choose to opt out of research screening. The survey will be publicly available on the study website.

Healthcare professionals

The research will be introduced to specialist clinical departments and presented at hospital-wide meetings to engage teams with the study. Clinical teams will be invited to suggest genes and monogenic conditions which they believe could improve patient outcomes if identified earlier through gNBS. They will also have the opportunity to identify barriers to providing care for babies who receive high-chance results within their department, for example, concerns regarding provision of long-term surveillance, or uncertainty with respect to monitoring and treatment pathways for asymptomatic patients. Perceptions of the study among doctors, midwives, nurses and allied health staff will also be captured through a survey. The survey will be distributed via hospital communication networks to reach a range of clinicians across departments and community of practice teams and further disseminated through snowball sampling.

Patient advocacy bodies

Three patient advocacy groups are partners in this research study: Rare Voices Australia, Immune Deficiency Foundation of Australia and Sanfilippo's Children Foundation. They will review our research materials, such as

posters, pamphlets and consent information for appropriate use of language, clarity of information provided and any potential ethical concerns about the proposed approaches.

Implementation and economic evaluation (Aim 4)

Prospective pilot evaluation and cost-consequences study

The outcomes of the prospective pilot will be analysed to determine the yield of conditions identified and economic modelling to estimate the costs and consequences of the different screening strategies relative to standard NBS.

Primary outcomes of the research include:

- Patient outcomes and changes in management (where collected).
- Changes to public uptake of standard NBS.
- Diagnostic yield of different screening strategies.
- Performance of different screening strategies (true positives, false positives and positive predictive value).
- Time to diagnosis.
- Number of indeterminate or repeat tests.
- Cost per accurate diagnosis.
- Cost-consequence analysis.

The economic analysis will evaluate the outcomes from the prospective cohorts and identify costs, savings or expenditures to the healthcare system. This will be compared with estimated expenditure in standard of care pathways, including standard newborn screening and typical diagnostic pathways. In addition, parents of newborns who receive high-chance results will be asked about short-term household financial impacts they may have experienced as a result of the diagnosis.

Where appropriate, data will be analysed descriptively and through linear and logistic regression analytical methods for continuous and binary data, respectively. Qualitative data will be analysed through inductive content analysis on participant responses.

Limitations

The number of conditions that are available for inclusion in the retrospective validation study is limited to diagnoses made in the South Australian health system. Further, only recent DBS cards can be included in metabolomic validation studies to account for the potential degradation of metabolites on DBS cards over time. These factors have limited the number and diversity of rare diseases that are available for this arm of the study. Thus, not all conditions of interest can be modelled in the validation study. As unaffected and affected cases are identified during the prospective study, ongoing optimisation of the algorithm may continue to improve the accuracy of the metabolomic screen.

Determination of the false negative rate and sensitivity and specificity of the screening strategies would require longitudinal tracking of participants' health outcomes beyond the study period and is thus out of scope for this study.

Referral of at-risk newborns from clinicians is reliant on the availability and capacity of healthcare professionals to facilitate enrolment. The study genetic counsellor will support consent and recruitment of this cohort.

The study will adopt a self-directed opt-in approach which will require a moderate level of literacy skills. It is understood that people who participate in research typically belong to higher socioeconomic status groups, potentially leading to an inequitable opportunity for participation. The combination of in-person and social media recruitment strategy offers state-wide recruitment from the community and a variety of clinical settings. Supportive educational materials will be available to increase the accessibility of study enrolment.

The research funding supports 1000 participants to receive gNBS, which is only a fraction of the total birth rate in South Australia of 18 000 per annum. Workforce capacity and scalability of gNBS approaches are important considerations, and while critical to implementation of gNBS programmes, operational modelling of this is beyond the scope of the current study.

ETHICS AND DISSEMINATION

This study has been approved by the Women's and Children's Hospital Human Research Ethics Committee (2022/HRE00258 and 2023/HRE00236). A waiver of consent was obtained for the use of archived DBS cards in the retrospective validation study. Families opt in to the prospective research study through provision of informed consent. The findings of this research study will be disseminated through peer-reviewed journal publications and scientific conferences.

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Competing interests None declared.

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.

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