nature portfolio

Corresponding author(s): Heidi Cope

Last updated by author(s): Jun 23, 2025

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Custom code developed for data preprocessing and modeling is available from the corresponding author (H.C., hcope@rti.org) to suitably qualified researchers through any requests that comply with ethical standards. The code is not publicly available due to institutional privacy policies but will be shared for academic purposes under a data use agreement.
Data analysis	SAS Institute Inc. (2020). SAS Enterprise Guide 8.3.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data described in this manuscript, including the gene list, screen-positive genotypes and phenotypes, are provided in supplementary files. De-identified data that support the results reported in this article will be made available to suitably qualified researchers through any requests that comply with ethical standards to the

corresponding author (H.C., hcope@rti.org). Data must be requested within 12 months after the paper has been published, and the proposed use of the data must be IRB approved. Upon approval, deidentified data will be provided by the corresponding author to the applicants within 2 months. Sequencing data files are not publicly available for privacy, ethical, and data protection reasons.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The sex of participating newborns is reported. The consenting parent provided the newborn's sex at the time of consent. No analyses were done using sex as a variable.
Reporting on race, ethnicity, or other socially relevant groupings	The race/ethnicity of participating newborns is reported. The consenting parent provided the newborn's race/ethnicity at the time of consent. These data were collected to assess if we were enrolling a representative cohort of newborns in comparison to state demographics. The following categories used were: American Indian or Alaska Native; Asian; Black, African American or African; Hispanic, Latino or Spanish; Middle Eastern or North African; Native Hawaiian or Pacific Islander; White or Unknown. If parents selected more than one they were classified as Two or more groups. These categories were modeled off the All of Us research program.
Population characteristics	The studied population are newborns up to 31 days old who had standard newborn screening performed by the North Carolina State Laboratory of Public Health, lived in North Carolina or South Carolina, and had residual dried blood spots samples available.
Recruitment	The primary recruitment methods were letters addressed from the North Carolina State Laboratory of Public Health informing birthing parents about the voluntary, free Early Check program and in-person recruitment on the labor and delivery floor at UNC Hospital. Parents provided electronic consent through a web-based portal. Since genomic newborn screening is a complex subject, parents with higher education may have been more likely to enroll. Letters addressed from the State may have caused parents who are less trusting in government not to enroll their baby. The consent portal was in English and Spanish. Thus, parents who speak other languages would have had difficultly enrolling. Parents who are less electronically savvy or who don't have an email address would also have had difficulty enrolling.
Ethics oversight	The study protocol was reviewed and approved by the UNC Institutional Review Board (IRB; #18-0009).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical method was used to predetermine sample size. Our laboratory partners, GeneDx and Illumina, contributed whole genome sequencing for up to 2,000 newborns. Thus, sample size was determined by available funding.
Data exclusions	2,125 newborns were enrolled in Early Check but demographic data are only presented on the 1,979 newborns who were successfully sequenced.
Replication	This is an implementation focused program, thus findings are not replicated. Our methods are well described so other genomic newborn screening programs can replicate our processes.
Randomization	Randomization did not occur. All enrolled newborns received the same intervention (newborn screening via whole genome sequencing).
Blinding	Blinding was not relevant to this study. All enrolled newborns received the same intervention (newborn screening via whole genome sequencing) and individual results were returned.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Registration on Clinicaltrials.gov (NCT03655223).
Study protocol	The study protocol is not publicly available. Our methods are published within the manuscript.
Data collection	For this pilot, the goal was to recruit a representative sample of 2,000 participants across the state. Eligible participants were newborns up to 31 days old who had undergone standard NBS in North Carolina and lived in North Carolina or South Carolina. The online Early Check consent portal was opened for enrollment on September 28th, 2023, enabling English- and Spanish-speaking birthing parents or legal guardians to enroll their newborns after birth. Between September 28, 2023, and June 10, 2024, a total of 2,125 newborns were enrolled. Recruitment letters were mailed to mothers of 42,434 newborns statewide. During the same period, 816 postpartum mothers were approached at UNC Hospital.
Outcomes	Study aims for the first participants reported here include: 1. Characterize study enrollment and panel selection choices 2. Assess feasibility of using state-collected NBS cards for gNBS 3. Return screen positive results and measure workforce efforts 4. Characterize screen-positive outcomes 5. Compare gNBS to standard NBS results 6. Develop nomenclature to categorize gNBS molecular diagnoses and report on related interpretation challenges These outcomes were described using descriptive statistics. A rubric was developed to describe the molecular interpretation of screen-positive results, depending on the inheritance pattern, variant classification, and confirmation status (Table 1). Results were also classified as true positive, possible true positive/possible false positive, false positive, or false negative after a series of evaluations, as shown in Figure 1. True positive results included “Definite” molecular diagnoses that were either penetrant or non-penetrant. “Probable,” “Likely,” and “Possible” molecular diagnoses were also considered true positives if clinical correlation was consistent with the diagnosis (e.g., the individual was penetrant for a phenotypic feature of the condition). Categories of false positive/false negatives include “Technical,” “Allelic,” “Classification,” and “Phenotypic.” Basic statistics were calculated to determine the percentage of enrolled participants with positive screening results and classification into screen-positive result categories.

Plants

Seed stocks	No plants were used in this research.
Novel plant genotypes	No plants were used in this research.
Authentication	No plants were used in this research.