Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scores as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

BMJ Open

Prospective cohort study of genomic newborn screening: BabyScreen+ study protocol

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Keywords:	GENETICS, PAEDIATRICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Prospective cohort study of genomic newborn screening: BabyScreen+ study protocol

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ABSTRACT

Introduction: Newborn bloodspot screening (NBS) is a highly successful public health program that utilises biochemical and other assays to screen for severe but treatable childhood-onset conditions. Introducing genomic sequencing into NBS programs increases the range of detectable conditions but raises practical and ethical issues. Evidence from prospectively ascertained cohorts is required to guide policy and future implementation. This study aims to develop, implement, and evaluate a genomic NBS (gNBS) pilot program.

Methods and analysis: The BabyScreen+ study will pilot gNBS in three phases. In the pre-implementation phase, study materials, including education resources, decision support and data collection tools, will be designed. Focus groups and key informant interviews will also be undertaken to inform delivery of the study and future gNBS programs. During the implementation phase, we will prospectively recruit birth parents in Victoria, Australia, to screen 1000 newborns for over 600 severe, treatable, childhood-onset conditions. Clinically accredited whole genome sequencing will be performed following stdNBS using the same sample. High chance results will be returned by genetic healthcare professionals, with follow-on genetic and other confirmatory testing and referral to specialist services as required. The post-implementation phase will evaluate the feasibility of gNBS as the primary aim, and assess ethical, implementation, psychosocial, and health economic factors to inform future service delivery.

Ethics and dissemination: This project received ethics approval from the Royal Children's Hospital Melbourne Research Ethics Committee: HREC/91500/RCHM-2023, HREC/90929/RCHM-2022 and HREC/91392/RCHM-2022. Findings will be disseminated to policy makers, and through peer-reviewed journals and conferences.

Word count: 2715

Keywords: Genomic newborn screening, rare disease, genomics, implementation

ARTICLE SUMMARY

Strengths and limitations of this study

- A prospective feasibility study to offer genomic newborn screening to birth parents during pregnancy.
- The study includes a multidisciplinary evaluation approach ascertaining perspectives from public, health professionals and participating parents.
- The study will utilise online recruitment tools to facilitate education and consent to allow scaling up for a future screening program.
- Interpreter-assisted recruitment is available for people who use a language other than English.
- Recruitment will encompass birth parents in the private and public healthcare system, however, may not be representative of the wider population as this is a pilot study.

INTRODUCTION

Newborn bloodspot screening (NBS) is a well-established and highly successful public health intervention that has enabled the early diagnosis and prompt treatment of many severe childhood conditions.(1) Traditionally, NBS programs select conditions for inclusion using the classic Wilson and Jungner screening principles,(2) and employ targeted biochemical and other assays that can be delivered at scale with rapid turnaround times and at a relatively low cost. Wide variability exists between, and even within, countries in the number of conditions included, ranging from nine in the United Kingdom to 80 in California, USA.(3) Currently in Australia, NBS programs are funded by state and territory governments and screen for around 27 conditions.

In the last decade, the use of genomic sequencing in the research and clinical setting has transformed rare disease diagnosis.(3) At the same time, increased understanding of the underlying molecular mechanisms of disease has accelerated the development of precision treatments.(4) The gap between the number of rare diseases now considered 'treatable' and those included in NBS programs is expanding rapidly. Integrating genomic sequencing into NBS programs would enable screening for a much broader range of conditions, while also providing the flexibility to quickly add more conditions at low incremental cost.

The concept of performing genomic sequencing in all children at birth, termed genomic newborn screening (gNBS), has been extensively debated. Empirical evidence to guide decision-making is starting to emerge,(5-9) addressing important questions of test design, diagnostic performance, and clinical utility, as well as parental and healthcare professionals' (HCP) views and concerns.(10) However, evidence from prospective cohorts is limited, with the most extensively evaluated cohort, the BabySeq study,(11) having recruited 159 infants.

Many concerns have been raised, including reduced sensitivity of genomic testing for some of the metabolic conditions screened via standard NBS (stdNBS),(7) and the appropriate timing and means of parental education to ensure informed consent.(12) None of the studies to date have fully addressed the key questions of acceptability, feasibility, scalability, and cost-effectiveness of gNBS. Most have focussed on the clinical, legal, insurance, and social contexts in the USA,(1, 6, 7, 9, 11, 12) which have limited applicability to the Australian and other public healthcare systems.

Our prospective cohort study, BabyScreen+, will address many of these questions in an Australian context to inform a future population-scale gNBS program. We will perform gNBS for a cohort of 1000 Victorian newborns using whole genome sequencing (WGS) that will increase the range of conditions screened in stdNBS to over 600 treatable, childhood-onset conditions. Insights from our research will be used to design laboratory processes that can deliver clinically accredited gNBS in an appropriate timeframe and at population scale. In addition, our study will inform the design of pre- and post-test processes, including education, decision support, informed consent, and results management, aimed at facilitating understanding and acceptance of gNBS for parents, HCP, and the Australian public.

METHODS AND ANALYSIS

Study design

The BabyScreen+ study will involve three phases, as outlined in Figure 1**.** Following the design and implementation of education and consent materials, research data collection tools, and laboratory pathways, we will offer and evaluate the feasibility of gNBS. Clinically accredited gNBS will be performed for over 600 treatable, childhood-onset conditions following stdNBS. Evaluation will focus on the health economic, implementation science, psychosocial, and ethical aspects of gNBS.

Study aims

The overall aim of this study is to design and deliver a gNBS program to screen 1000 prospectively recruited newborns and assess feasibility.

Secondary aims are to evaluate:

- Public preferences and perspectives for the delivery of gNBS
- Ethical issues
- Performance of gNBS alongside stdNBS, comparing diagnostic performance, and clinical utility
- Parental screening experience and psychosocial outcomes
- Cost-effectiveness and cost-benefit of gNBS relative to stdNBS
- Implementation of gNBS, including acceptability to HCP, parents, and the public
- Value and ethical implications of using genomic data generated at birth as a lifelong healthcare resource

Study timetable and sites

The pre-implementation phase of the study commenced in July 2022 (Figure 1). Staged recruitment into the implementation phase of the study began on 20 July 2023 at three sites, including a private obstetrics practice and two public hospitals. The post-implementation phase will commence at the completion of recruitment, and the study will be completed by 31 May 2027.

Pre-implementation phase

The pre-implementation phase comprises the design, development, and testing of study processes and materials. These include HCP education materials; the online enrolment, decision support, education, and consent platform; evaluation data collection tools; the list of genes for inclusion in screening; and laboratory protocols. Key informant interviews,

focus groups, and discrete choice experiments will be undertaken to assess public and HCP views on study processes and acceptability of gNBS.

Condition and gene selection

The overarching condition selection principles that are used in stdNBS were maintained when considering which genes and conditions to include in this study.(2) Included conditions:

- have a well-established gene-disease association and the majority of known clinically relevant variants are ascertainable by WGS
- are considered severe (i.e., causing mortality or considerable morbidity/disability in the majority of affected children if untreated),
- have early-onset of disease or significantly benefit from early intervention (<5 years of age in the majority), and
- have an available treatment (e.g., drugs/supplements, enzyme replacement therapy, organ or bone marrow transplant, diet modification, gene therapy) or other intervention that significantly alters the natural progression of the condition. Interventions must be accessible to study participants in Victoria, Australia.

We included all conditions that are currently screened in stdNBS in Australia. The gene selection process and panel content has been informed by prior local and international gNBS projects.(13, 14) Genes included in the study are publicly available for review and comment on PanelApp Australia (BabyScreen+ newborn screening panel: https://panelapp.agha.umccr.org/panels/3931/) and on the study website along with a plain language description of the gene selection process and screening approach.

Key informant interviews

The implementation phase will be informed by interviews with key stakeholders involved in the current delivery of stdNBS. These include laboratory staff, HCP offering stdNBS, other antenatal HCP, and paediatric physicians. Data collection and analysis will be guided by the Action, Actor, Context, Target, Time (AACTT) framework(15) to capture views on who should do what and when. Interviews will explore opinions on offering gNBS; education and consent; sample collection and testing; and result management.

Eliciting public preferences and perspectives

Public preferences and values will be sought through a multi-phase mixed-methods design involving focus groups and discrete choice experiment surveys (DCEs) with members of the Australian public. Focus groups will explore public preferences and perspectives for 1) implementation of gNBS, 2) risks and benefits of gNBS, and 3) use of data generated by gNBS as a lifetime resource and will involve qualitative exploration through facilitated discussion to elicit characteristics of gNBS delivery. Outcomes from the focus groups will be used to inform the implementation phase of the study. The DCE surveys will elicit public preferences, values, and priorities for gNBS to support the economic evaluation and implementation of gNBS in Australia.

Implementation phase

HCP engagement

We will invite HCP from selected public and private healthcare settings to offer the study to their patients. HCP participation is voluntary and will not be incentivised. HCP who wish to

be involved will receive education and support from the study team regarding gNBS and study processes.

Participant eligibility and recruitment

Pregnant individuals will be invited to take part at in the third trimester. At one public hospital, recruitment will also occur via advertisement on a digital pregnancy care platform. To be eligible to participate, birth parents must be due to give birth in Victoria, Australia, within the study timeframe, and participate in the state-based stdNBS. They must be aged 16 years or over, or have a legal representative capable of providing informed consent on their behalf. Enrolment must be completed by two weeks after their baby is born, to ensure that results are returned in a clinically meaningful timeframe.

Enrolment and Consent

After receiving a study invitation, birth parents will complete enrolment and consent for the study online. Figure 2 provides a detailed outline of the participation process.

Birth parents will first be asked to provide consent for the research component of the study via REDCap.(16, 17) This encompasses collection of personal and health related data and survey responses. Participants who use a language other than English will be assisted to enrol and take part by a research genetic counsellor and an interpreter.

Birth parents who consent to research will receive education and decision support, as well as provide informed consent to clinical gNBS for their baby, via the online Genetics Adviser platform. Genetics Adviser is a patient-centred interactive online tool that provides

educational, decisional, and counselling support to patients undergoing genetic testing, along with managing consent capture and return of results (https://www.geneticsadviser.com/). Genetics Adviser has been extensively evaluated and improved by iterative co-design and has been shown to improve participant knowledge and decisional confidence.(18-21) The study will use a locally deployed version of the platform, adapted in collaboration with the Genetics Adviser team.

A 'check-in' module in Genetics Adviser will automatically remind birth parents about the study four weeks prior to their estimated due date via email and SMS. Participants will be invited to log back into Genetics Adviser via email and SMS, where they will receive a brief refresher on gNBS, explore how they are currently feeling, and have the option to review their gNBS consent.

Genetic counselling is available at any time, if requested. Consent to research participation can be withdrawn at any time. Consent to clinical gNBS can be withdrawn at any time prior to result reporting.

Sample testing

Sample collection will be performed by the pregnancy service provider as part of stdNBS undertaken by Victorian Clinical Genetics Services (VCGS). Following completion of stdNBS, four 3mm punches will be taken from a single dried blood spot and processed using clinically accredited protocols and procedures at VCGS. Following DNA extraction, PCR-free genome sequencing libraries will be created using the PCR-free DNA prep kit (Illumina) and sequenced to an average depth of 30x on NovaSeq 6000 of X Plus instruments (Illumina).

For samples with insufficient quantity or quality of DNA, the study team will contact the participant to arrange sample recollection.

Genome data analysis and interpretation will be performed using validated and clinically accredited, cloud-based analysis pipelines and procedures, including the Dragen and eMedgene (Illumina) analysis tools. Interpretation will be restricted to genes on the BabyScreen+ gNBS panel, and only variants that are classified as likely pathogenic or pathogenic will be considered for reporting. We will not report carrier status, adult-onset conditions, or variants of uncertain significance. All variants that are considered for reporting will be discussed by a team of clinical specialists, genetic pathologists, and medical scientists.

Screening results

Results will be returned within four weeks of sample collection. There will be two categories of result:

1) A low chance result, where no reportable variants are identified, or
2) A high chance result, where one or more reportable variants are identified.

For low chance results, birth parents will be informed via the online Genetics Adviser platform following notification of result availability via email and SMS. Genetic counselling follow-up will be available on request.

For high chance results, birth parents will receive a phone call from a genetics HCP to discuss the result, arrange an appointment and any required additional testing (including

confirmation of reported variants), as well as referral to specialist services. Further genetic counselling support will also be available.

Post-implementation phase

The study will move to the post-implementation phase after recruitment, with a focus on evaluation and data analysis. See Figure 1 and Figure 2 for details on the data collection tools, timepoints, and evaluation focus areas.

Evaluation

Feasibility will be evaluated through a set of key performance indicators gathered from laboratory data. This includes data on the percentage of study samples that:

- Are successfully identified from stdNBS samples
- Require a recollect due to insufficient DNA
- Fail sequencing
- Are processed within the expected turn-around time
- Have a concordant high chance result from stdNBS and gNBS

Views on acceptability and participant experiences will be collected during the first two phases of the study. Participant, public and HCP views will be captured through key informant interviews, focus groups, surveys, and discrete choice experiments (see Figures 1 and 2 and Table 1). Participants will complete compulsory surveys at enrolment (T1) and after consent (T2), followed by optional surveys at 3-months post-result (T3) and ~12-months post-result (T4). Participants will also be invited to take part in interviews before and after receiving their gNBS results. Participants who decline gNBS will be asked to

complete a modified T2 survey and invited to take part in an interview. Refer to Table 1 for survey and interview measures.

Table 1: Survey and interview measures used to ascertain parental experiences and preferences throughout the study

Measure	Description	T1	T2	Pre-result int	T3	Post-result int	T4	Decliner int
Details of pregnancy and demographics	Estimated due date, intended birth hospital, sex of baby (if known), twin/triplet pregnancy details (if applicable), education, income, language, marital status, number of children, prior experience with genomic testing, family history, ancestry.	X						
Acceptability E-scale *[gNBS accepter]*	Seven-item scale to determine the acceptability and usability of computerised health-related programs(22).		X					
Information in Genetics Adviser *[gNBS accepter]*	Three study-specific questions to assess the perceived bias of Genetics Adviser content and review/influence of the study gene list.		X					
Knowledge of gNBS *[gNBS accepter]*	Eight study-specific True/False questions to determine participants' understanding of gNBS.		X		X		X	
Difficulty and deliberation of decision *[gNBS accepter]*	Three study-specific questions to assess the level of difficulty making a decision, length of deliberation and sources of information used		X					

	when consenting to gNBS.							
Reasons for accepting or declining *[gNBS accepter]*	One study-specific question addressing reasons for consenting to gNBS. Participants are asked to rate a selection of reasons on a 5-point Likert scale and asked to comment if there are other reasons not listed.		X					
Willingness to pay *[gNBS accepter]*	Dynamic triple-bounded dichotomous choice contingent valuation, also known as a 'bidding game', to assess the value participants place on gNBS.		X		X		X	
State trait anxiety index (STAI-AD) *[gNBS accepter]*	26-item scale measuring state and trait anxiety. *Copyright © 1968, 1977 by Charles D. Spielberger. All rights reserved in all media. Published by Mind Garden,Inc.* *www.mindgarden.com* Note: Only the 6 questions that form the STAI-6 short form(23) are repeated at each timepoint.		X		X		X	
Reasons for declining *[gNBS decliner]*	One study-specific question exploring the reasons for declining. Participants are presented with 11 reasons and asked to rate how much each one influenced their decision on a scale of 1 (did not influence) to 5 (strongly influenced).		X					
Result recall	One study-specific question to determine if participants recall their baby's result correctly.				X		X	

Decision regret scale	Five-item scale to measure regret after a health care decision(24).				X		X	
Health system utilisation	One study-specific question to determine health system utilisation post-result.				X		X	
Result dissemination *[high chance result only]*	One study-specific question for people to determine who participants have shared their result with and why.				X			
Genomics Outcome Scale *[high chance result only]*	Six-item scale based on the Genetic Counselling Outcome Scale-24 adapted to assess outcomes of genetic counselling and patient empowerment.(25)				X			
Service delivery preferences	10 study-specific questions assessing opinions on if, how, and when gNBS should be offered, and what conditions should be screened.				X			
Experience of gNBS	Questions on prior knowledge of genetic or genomic testing and experiences taking part in the study.			X		X		X
Expectations of results	Questions on expected result and how they plan to use the result.			X				
Receiving results, understanding, and making meaning	Questions on result including knowledge of outcomes and how they plan to use the result.					X		
Attitudes and perceptions	Questions on if, how, and when gNBS should be offered, and what conditions should be screened.			X		X		X
Decision making	Questions on reasons for declining gNBS.							X

Data re-use	Study-specific questions around preferences for additional analyses of gNBS data.						X	
Future gNBS decision	One study-specific question asking preference for gNBS for future children						X	

T1, survey at enrolment; T2, survey post-consent; T3, 3-months post result survey; T4, 12-months post result survey; int, interviews; STAI-6, Six-item State-Trait Anxiety Inventory; STAI-AD, State-Trait Anxiety Inventory for Adults; gNBS, genomic newborn screening.

Health economic analyses will be performed from the perspective of the Australian healthcare system, using a lifetime horizon, and based on the outcomes of cost per additional diagnosis, cost per quality-adjusted life-year gained, and net benefit. A budget impact analysis will be conducted to provide policy-relevant insights into the affordability and sustainability of implementing gNBS.

Potential barriers and enablers to implementation of gNBS will be identified to generate strategies to support successful delivery and inform future studies. These will be ascertained through theory-informed interviews. This will include capturing the experiences of professionals including HCP involved in the delivery of gNBS, and those impacted by the implementation of gNBS, including perinatal HCP and paediatric physicians. In addition, process mapping will be undertaken with laboratory staff and study team members at intervals throughout the study to understand adaptations required to deliver gNBS at scale and within clinically meaningful timeframes.

Data analysis

Personal identifying information, clinical, and evaluation data will be collected using recording devices, and electronic data collection forms in the online Genetics Adviser platform(21) and REDCap,(16, 17) both hosted at the Murdoch Children's Research Institute, Melbourne, Australia.

Findings from interviews and surveys will be used to provide qualitative and statistical information on the associations between a particular behaviour and opinions or attitudes about the program. Qualitative data will be either deductively analysed where a theoretical framework has been employed e.g., AACTT(15) or analysed using inductive content analysis(26) or thematic analysis to generate rich descriptions responding to the research aims e.g., acceptability of testing. Economic evaluation and discrete choice experiments will be conducted according to best practice recommendations.(27-29) Quotes from participants will be used to illustrate qualitative findings in scientific presentations and other publications. Statistical analysis will utilise appropriate methods and tests depending on the nature of the data and its normality. Probability values of <0.05 will be considered statistically significant, and confidence intervals will be calculated where possible.

Patient and public involvement

The pre-implementation phase of the study involved extensive consultation with the public via focus groups and discrete choice experiment surveys. These have informed the design of the implementation phase. Condition selection has been done in conjunction with patient

support groups. The study also uses Genetics Adviser, a decision support platform with extensive public input into design and development.(18-21)

ETHICS AND DISSEMINATION

This study is governed and administered by the Murdoch Children's Research Institute (MCRI), Melbourne, Australia. All genetic testing is performed by VCGS, Melbourne, Australia, a wholly owned not-for-profit subsidiary of MCRI. VCGS is clinically accredited (NATA/RCPA) to ISO15189;2012 to carry out genetic and genomic testing. The project has received ethics approval from the Royal Children's Hospital Melbourne Human Research Ethics Committee (main BabyScreen+ protocol: HREC/91500/RCHM-2023; key informant interviews: HREC/90929/RCHM-2022; and focus groups and DCE: HREC/91392/RCHM-2022). Findings from this study will be published in peer-reviewed scientific journal articles and presented at appropriate clinical and research conferences. The findings will also be disseminated to policy makers including the Standing Committee on Screening. All participants have provided informed consent to be involved in this study.

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AUTHOR CONTRIBUTIONS

All authors contributed to the design of the protocol, including its concept and the critical review and final approval of the manuscript. Sebastian Lunke, Sophie Bouffler and Zornitza Stark drafted the manuscript. Simon Sadedin, Stefanie Eggers, Sebastian Hollizeck, Crystle Lee, Meaghan Wall, Ronda Greaves, Paul De Fazio and Sebastian Lunke contributed to the design of the laboratory processes. David Amor, Lilian Downie, Alison Archibald, John Christodoulou, Alison Yeung, Zornitza Stark and Sebastian Lunke contributed to the design of the gene list. Yvonne Bombard, Marc Clausen, Jade Caruana, Alison Archibald, Lilian Downie, Clara Gaff, Sophie Bouffler, Nitzan Lang, Anaita Kanga-Parabia and Zornitza Stark contributed to the design of participant and HCP education materials. Danya Vears, Fiona Lynch and Christopher Gyngell contributed to the design of the ethical evaluation. Erin Tutty, Anaita Kanga-Parabia, Alison Archibald and Stephanie Best contributed to the design of the psychosocial and implementation evaluation. Riccarda Peters and Ilias Goranitis contributed to the design of the health economic evaluation.

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COMPETING INTERESTS

YB and MC are cofounders of the Genetics Adviser. The other authors declare no relevant disclosures.

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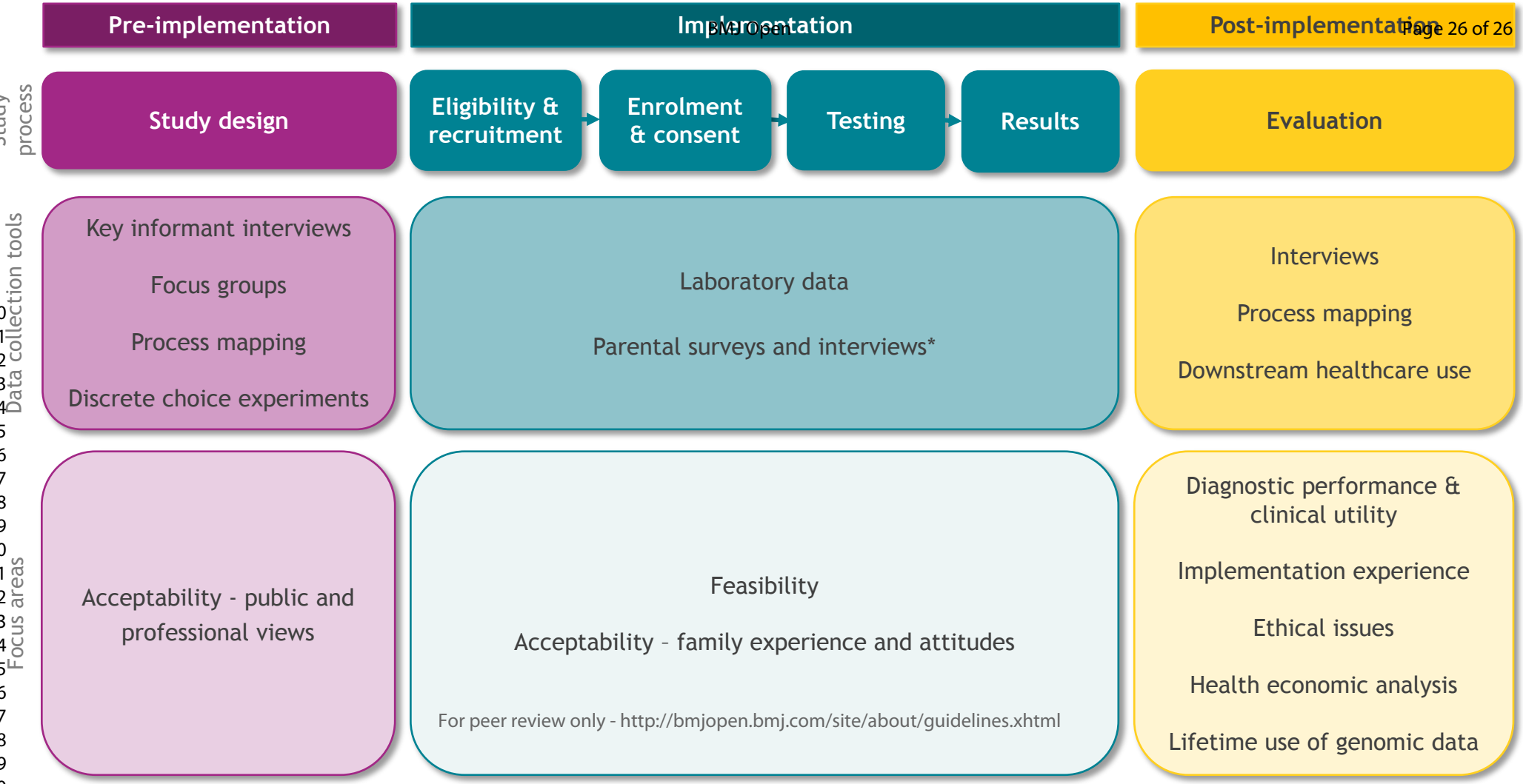
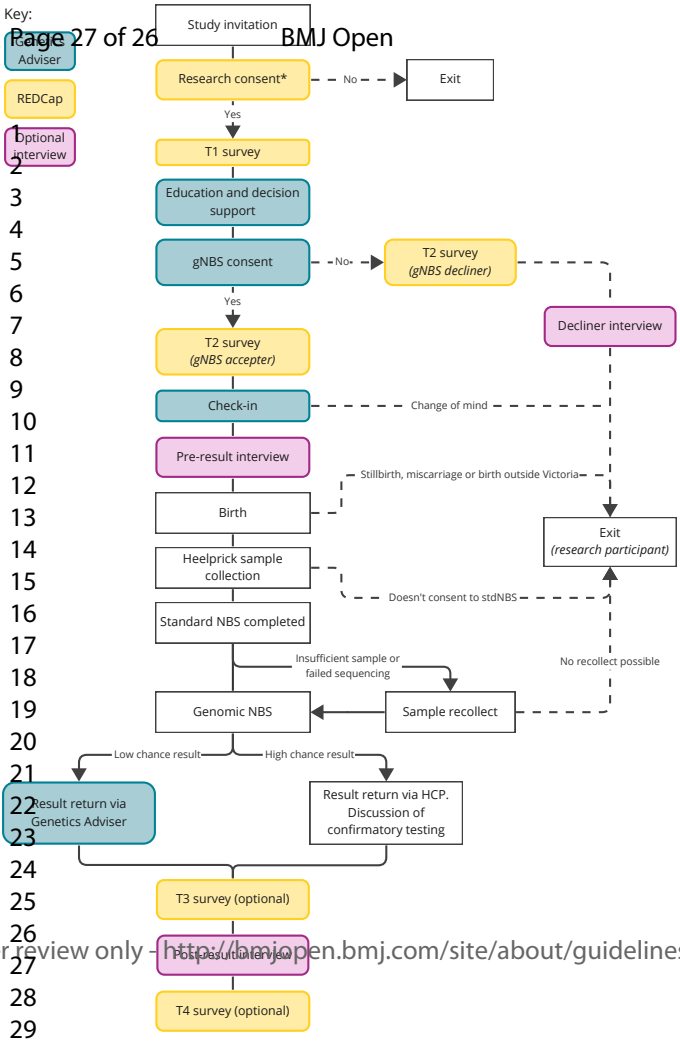
Figure 1: The three phases of the BabyScreen+ study including data collection tools and research focus areas. *refer to Table 1 for survey and interview measures.

Figure 2: Participation process for birth parents. Solid lines represent the expected end-to-end study pathway (offer to result and final surveys), dashed lines represent anticipated study exit pathways. *Participants not able to complete enrolment in English will be supported by a genetic counsellor and an interpreter. HCP, healthcare professional; NBS, newborn bloodspot screening; T1-T4, survey timepoints/identifiers.





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Prospective cohort study of genomic newborn screening: BabyScreen+ pilot study protocol

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ABSTRACT

Introduction: Newborn bloodspot screening (NBS) is a highly successful public health program that utilises biochemical and other assays to screen for severe but treatable childhood-onset conditions. Introducing genomic sequencing into NBS programs increases the range of detectable conditions but raises practical and ethical issues. Evidence from prospectively ascertained cohorts is required to guide policy and future implementation. This study aims to develop, implement, and evaluate a genomic NBS (gNBS) pilot program.

Methods and analysis: The BabyScreen+ study will pilot gNBS in three phases. In the pre-implementation phase, study materials, including education resources, decision support and data collection tools, will be designed. Focus groups and key informant interviews will also be undertaken to inform delivery of the study and future gNBS programs. During the implementation phase, we will prospectively recruit birth parents in Victoria, Australia, to screen 1000 newborns for over 600 severe, treatable, childhood-onset conditions. Clinically accredited whole genome sequencing will be performed following standard NBS using the same sample. High chance results will be returned by genetic healthcare professionals, with follow-on genetic and other confirmatory testing and referral to specialist services as required. The post-implementation phase will evaluate the feasibility of gNBS as the primary aim, and assess ethical, implementation, psychosocial, and health economic factors to inform future service delivery.

Ethics and dissemination: This project received ethics approval from the Royal Children's Hospital Melbourne Research Ethics Committee: HREC/91500/RCHM-2023, HREC/90929/RCHM-2022 and HREC/91392/RCHM-2022. Findings will be disseminated to policy makers, and through peer-reviewed journals and conferences.

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Keywords: Genomic newborn screening, rare disease, genomics, implementation

ARTICLE SUMMARY

Strengths and limitations of this study

- A prospective feasibility study to offer genomic newborn screening to birth parents during pregnancy.
- The study includes a multidisciplinary evaluation approach ascertaining perspectives from public, health professionals and participating parents.
- The study will utilise online recruitment tools to facilitate education and consent to allow scaling up for a future screening program. Interpreter-assisted recruitment is available for people who use a language other than English.
- Recruitment will encompass birth parents in the private and public healthcare system, however, may not be representative of the wider population as this is a pilot study.
- As this is a pilot study, we are unable to fully assess the value of stored genomic data for lifelong healthcare use.

INTRODUCTION

Newborn bloodspot screening (NBS) is a well-established and highly successful public health intervention that has enabled the early diagnosis and prompt treatment of many severe childhood conditions.(1) Traditionally, NBS programs select conditions for inclusion using the classic Wilson and Jungner screening principles,(2) and employ targeted biochemical and other assays that can be delivered at scale with rapid turnaround times and at a relatively low cost. Wide variability exists between, and even within, countries in the number of conditions included, ranging from nine in the United Kingdom to 80 in California, USA.(1, 3-

5) Currently in Australia, NBS programs are funded by state and territory governments and screen for around 27 conditions.(6)

In the last decade, the use of genomic sequencing in the research and clinical setting has transformed rare disease diagnosis.(3) At the same time, increased understanding of the underlying molecular mechanisms of disease has accelerated the development of precision treatments.(7) The gap between the number of rare diseases now considered 'treatable'(8) and those included in NBS programs is expanding rapidly. Integrating genomic sequencing into NBS programs would enable screening for a much broader range of conditions, while also providing the flexibility to quickly add more conditions at low incremental cost.

The concept of performing genomic sequencing in all children at birth, termed genomic newborn screening (gNBS), has been extensively debated. Empirical evidence to guide decision-making is starting to emerge,(9-13) addressing important questions of test design, diagnostic performance, and clinical utility, as well as parental and healthcare professionals' (HCP) views and concerns.(14-18) However, evidence from prospective cohorts is limited, with the most extensively evaluated cohort, the BabySeq study,(19) having recruited 159 infants.

Many concerns have been raised, including reduced sensitivity of genomic testing for some of the metabolic conditions screened via standard NBS (stdNBS),(11) and the appropriate timing and means of parental education to ensure informed consent.(20) None of the studies to date have fully addressed the key questions of acceptability, feasibility, scalability, and cost-effectiveness of gNBS. Most have focussed on the clinical, legal, insurance, and

social contexts in the USA,(1, 10, 11, 13, 19, 20) which have limited applicability to the Australian and other public healthcare systems. Several large-scale newborn genomic screening studies are currently launching worldwide to address these gaps in knowledge.(3, 21, 22)

Our prospective cohort study, BabyScreen+, will address many of these questions in an Australian context to inform a future population-scale gNBS program. We will perform gNBS for a cohort of 1000 Victorian newborns using whole genome sequencing (WGS) that will increase the range of conditions screened in stdNBS to over 600 treatable, childhood-onset conditions. Insights from our research will be used to design laboratory processes that can deliver clinically accredited gNBS in an appropriate timeframe and at population scale. In addition, our study will inform the design of pre- and post-test processes, including education, decision support, informed consent, and results management, aimed at facilitating understanding and acceptance of gNBS for parents, HCP, and the Australian public.

METHODS AND ANALYSIS

Study design

The BabyScreen+ study will involve three phases, as outlined in Figure 1**.** Following the design and implementation of education and consent materials, research data collection tools, and laboratory pathways, we will offer and evaluate the feasibility of gNBS. Clinically accredited gNBS will be performed for over 600 treatable, childhood-onset conditions following stdNBS. Evaluation will focus on the health economic, implementation science, psychosocial, and ethical aspects of gNBS.

Study aims

The overall aim of this study is to design and deliver a gNBS program to screen 1000 prospectively recruited newborns and assess feasibility.

Secondary aims are to evaluate:

- Public preferences and perspectives for the delivery of gNBS
- Ethical issues
- Performance of gNBS alongside stdNBS, comparing diagnostic performance, and clinical utility
- Parental screening experience and psychosocial outcomes
- Cost-effectiveness and cost-benefit of gNBS relative to stdNBS
- Implementation of gNBS, including acceptability to HCP, parents, and the public
- Value and ethical implications of using genomic data generated at birth as a lifelong healthcare resource

Study timetable and sites

The pre-implementation phase of the study commenced in July 2022 (Figure 1). Staged recruitment into the implementation phase of the study began on 20 July 2023 at three sites, including a private obstetrics practice and two public hospitals. The post-implementation phase will commence at the completion of recruitment, and the study will be completed by 31 May 2027.

Pre-implementation phase

The pre-implementation phase comprises the design, development, and testing of study processes and materials. These include HCP education materials; the online enrolment, decision support, education, and consent platform; evaluation data collection tools; the list of genes for inclusion in screening; and laboratory protocols. Key informant interviews, focus groups, and discrete choice experiments will be undertaken to assess public and HCP views on study processes and acceptability of gNBS.

Condition and gene selection

The overarching condition selection principles that are used in stdNBS were maintained when considering which genes and conditions to include in this study.(2) Included conditions:

- have a well-established gene-disease association and the majority of known clinically relevant variants are ascertainable by WGS
- are considered severe (i.e., causing mortality or considerable morbidity/disability in the majority of affected children if untreated),
- have early-onset of disease or significantly benefit from early intervention (<5 years of age in the majority), and
- have an available treatment (e.g., drugs/supplements, enzyme replacement therapy, organ or bone marrow transplant, diet modification, gene therapy) or other intervention that significantly alters the natural progression of the condition. Interventions must be accessible to study participants in Victoria, Australia.

We included all conditions that are currently screened in stdNBS in Australia. The gene selection process and panel content has been informed by prior local and international

gNBS projects.(21, 23) Genes included in the study are publicly available for review and comment on PanelApp Australia (BabyScreen+ newborn screening panel: https://panelapp.agha.umccr.org/panels/3931/; Supplementary Table 1) and on the study website along with a plain language description of the gene selection process and screening approach.

Key informant interviews

The implementation phase will be informed by interviews with key stakeholders involved in the current delivery of stdNBS. These include laboratory staff, HCP offering stdNBS, other antenatal HCP, and paediatric physicians. Data collection and analysis will be guided by the Action, Actor, Context, Target, Time (AACTT) framework(24) to capture views on who should do what and when. Interviews will explore opinions on offering gNBS; education and consent; sample collection and testing; and result management.

Eliciting public preferences and perspectives

Public preferences and values will be sought through a multi-phase mixed-methods design involving focus groups and discrete choice experiment surveys (DCEs) with members of the Australian public. Focus groups will explore public preferences and perspectives for 1) implementation of gNBS, 2) risks and benefits of gNBS, and 3) use of data generated by gNBS as a lifetime resource and will involve qualitative exploration through facilitated discussion to elicit characteristics of gNBS delivery. Outcomes from the focus groups will be used to inform the implementation phase of the study. The DCE surveys will elicit public preferences, values, and priorities for gNBS to support the economic evaluation and implementation of gNBS in Australia.

Implementation phase

HCP engagement

We will invite HCP from selected public and private healthcare settings to offer the study to their patients. HCP participation is voluntary and will not be incentivised. HCP who wish to be involved will receive education and support from the study team regarding gNBS and study processes.

Participant eligibility and recruitment

Pregnant individuals will be invited to take part in the third trimester. At one public hospital, recruitment will also occur via advertisement on a digital pregnancy care platform. To be eligible to participate, birth parents must be due to give birth in Victoria, Australia, within the study timeframe, and participate in the state-based stdNBS. They must be aged 16 years or over, or have a legal representative capable of providing informed consent on their behalf. Enrolment must be completed by two weeks after their baby is born. This timeframe allows for exceptional circumstances, e.g., premature delivery, where enrolment is not completed before birth. However, in the majority of cases we expect enrolment to be completed during pregnancy. The study team will follow up incomplete enrolments two weeks before the expected due date to ensure that results can be returned in a clinically meaningful timeframe.

Enrolment and Consent

After receiving a study invitation, birth parents will complete enrolment and consent for the study online. gNBS and all required pre- and post-test support will be offered at no cost to birth parents. Figure 2 provides a detailed outline of the participation process.

Birth parents will first be asked to provide consent for the research component of the study via Research Electronic Data Capture (REDCap).(25, 26) This encompasses collection of personal and health related data and survey responses. Participants who use a language other than English will be assisted to enrol and take part by a research genetic counsellor and an interpreter.

Birth parents who consent to research will receive education and decision support, as well as provide informed consent to clinical gNBS for their baby, via the online Genetics Adviser platform. Genetics Adviser is a patient-centred interactive online tool that provides educational, decisional, and counselling support to patients undergoing genetic testing, along with managing consent capture and return of results (https://www.geneticsadviser.com/). Genetics Adviser has been extensively evaluated and improved by iterative co-design and has been shown to improve participant knowledge and decisional confidence.(27-30) The study will use a locally deployed version of the platform, adapted in collaboration with the Genetics Adviser team.

A 'check-in' module in Genetics Adviser will automatically remind birth parents about the study four weeks prior to their estimated due date via email and SMS. Participants will be invited to log back into Genetics Adviser via email and SMS, where they will receive a brief

refresher on gNBS, explore how they are currently feeling, and have the option to review their gNBS consent.

Genetic counselling is available at any time, if requested. Consent to research participation can be withdrawn at any time. Consent to clinical gNBS can be withdrawn at any time prior to result reporting.

Sample testing

Sample collection will be performed by the pregnancy service provider as part of stdNBS undertaken by Victorian Clinical Genetics Services (VCGS). StdNBS is expected to take up to two weeks. In order to comply with local requirements for access to NBS cards and avoid interference with stdNBS, BabyScreen+ will only have access to the sample once the routine process is complete. Following completion of stdNBS, four 3mm punches will be taken from a single dried blood spot and processed using clinically accredited protocols and procedures at VCGS. DNA will be extracted using the Omega Biotek Mag-Bind DNA Blood and Tissue kit. Following DNA extraction, PCR-free genome sequencing libraries will be created using the PCR-free DNA prep kit (Illumina) and sequenced using a 2x150 base paired end read configuration to an average depth of 30x on NovaSeq 6000 of X Plus instruments (Illumina). The target timeframe for return of results following handover of the punches from the stdNBS laboratory is two weeks. Considering the two blocks of two weeks, results will be returned within four weeks of sample collection. For samples with insufficient quantity or quality of DNA, the study team will contact the participant to arrange sample recollection.

Genome data analysis and interpretation will be performed using validated and clinically accredited, cloud-based analysis pipelines and procedures, using the Dragen and eMedgene (Illumina) analysis tools, with custom in-house filtering configuration. Interpretation will be restricted to genes on the BabyScreen+ gNBS panel, and only variants that are classified as likely pathogenic or pathogenic will be considered for reporting. We will not report carrier status, adult-onset conditions, or variants of uncertain significance. All variants that are considered for reporting will be discussed by a team of clinical specialists, genetic pathologists, and medical scientists.

Screening results

There will be two categories of result:

1) A low chance result, where no reportable variants are identified, or
2) A high chance result, where one or more reportable variants are identified.

For low chance results, birth parents will be informed via the online Genetics Adviser platform following notification of result availability via email and SMS. Genetic counselling follow-up will be available on request.

For high chance results, birth parents will receive a phone call from a genetics HCP to discuss the result, arrange an appointment and any required additional testing (including confirmation of reported variants), as well as referral to specialist services. Further genetic counselling support will also be available.

Post-implementation phase

The study will move to the post-implementation phase after recruitment, with a focus on evaluation and data analysis. See Figure 1 and Figure 2 for details on the data collection tools, timepoints, and evaluation focus areas.

Evaluation

Feasibility will be evaluated through a set of key performance indicators gathered from laboratory data. This includes data on the percentage of study samples that:

- Are successfully identified from stdNBS samples
- Require a recollect due to insufficient DNA
- Fail sequencing
- Are processed within the expected turn-around time
- Have a concordant high chance result from stdNBS and gNBS

Performance of gNBS will be further evaluated against stdNBS where a genetic diagnosis is confirmed. We will collect data on subsequent clinical management, including the timing of commencement of therapies and downstream healthcare utilisation. Where possible, we will compare this against historical controls from VCGS and the Royal Children's Hospital (RCH) (patients diagnosed with the same disorder in the last 10 years). Cost-effectiveness and cost-benefit analyses will be conducted to evaluate whether the additional cost of gNBS relative to stdNBS is outweighed by longer-term cost-savings and improvements in diagnostic, clinical, and personal outcomes for children and families. Clinical and laboratory data from RCH and VCGS will be accessed and examined to establish if and for what purpose

genomic data generated at birth has been accessed and/or re-analysed within five years post-result.

Views on acceptability and participant experiences will be collected during the first two phases of the study. Participant, public and HCP views will be captured through key informant interviews, focus groups, surveys, and discrete choice experiments (see Figures 1 and 2 and Table 1). Participants will complete compulsory surveys at enrolment (T1) and after consent (T2), followed by optional surveys at 3-months post-result (T3) and ~12-months post-result (T4). Participants will also be invited to take part in interviews before and after receiving their gNBS results. Participants who decline gNBS will be asked to complete a modified T2 survey and invited to take part in an interview. Refer to Table 1 for survey and interview measures.

Table 1: Survey and interview measures used to ascertain parental experiences and preferences throughout the study

Measure	**Description**	**T1**	**T2**	**Pre-result int**	**T3**	**Post-result int**	**T4**	**Decliner int**
Details of pregnancy and demographics	Estimated due date, intended birth hospital, sex of baby (if known), twin/triplet pregnancy details (if applicable), education, income, language, marital status, number of children, prior experience with genomic testing, family history, ancestry.	X						
Acceptability E-scale	Seven-item scale to determine the acceptability and		X					

[gNBS accepter]	usability of computerised health-related programs(31).							
Information in Genetics Adviser *[gNBS accepter]*	Three study-specific questions to assess the perceived bias of Genetics Adviser content and review/influence of the study gene list.		X					
Knowledge of gNBS *[gNBS accepter]*	Eight study-specific True/False questions to determine participants' understanding of gNBS.		X		X		X	
Difficulty and deliberation of decision *[gNBS accepter]*	Three study-specific questions to assess the level of difficulty making a decision, length of deliberation and sources of information used when consenting to gNBS.		X					
Reasons for accepting or declining *[gNBS accepter]*	One study-specific question addressing reasons for consenting to gNBS. Participants are asked to rate a selection of reasons on a 5-point Likert scale and asked to comment if there are other reasons not listed.		X					
Willingness to pay *[gNBS accepter]*	Dynamic triple-bounded dichotomous choice contingent valuation, also known as a 'bidding game', to assess the value participants place on gNBS.		X		X		X	
State trait anxiety index (STAI-AD) *[gNBS accepter]*	26-item scale measuring state and trait anxiety. *Copyright © 1968, 1977 by Charles D. Spielberger. All rights reserved in all media. Published by Mind Garden,Inc.* *www.mindgarden.com*		X		X		X	

	Note: Only the 6 questions that form the STAI-6 short form(32) are repeated at each timepoint.							
Reasons for declining *[gNBS decliner]*	One study-specific question exploring the reasons for declining. Participants are presented with 11 reasons and asked to rate how much each one influenced their decision on a scale of 1 (did not influence) to 5 (strongly influenced).		X					
Result recall	One study-specific question to determine if participants recall their baby's result correctly.				X		X	
Decision regret scale	Five-item scale to measure regret after a health care decision(33).				X		X	
Health system utilisation	One study-specific question to determine health system utilisation post-result.				X		X	
Result dissemination *[high chance result only]*	One study-specific question for people to determine who participants have shared their result with and why.				X			
Genomics Outcome Scale *[high chance result only]*	Six-item scale based on the Genetic Counselling Outcome Scale-24 adapted to assess outcomes of genetic counselling and patient empowerment.(34)				X			
Service delivery preferences	10 study-specific questions assessing opinions on if, how, and when gNBS should be offered, and what conditions should be screened.				X			

Experience of gNBS	Questions on prior knowledge of genetic or genomic testing and experiences taking part in the study.			X		X		X
Expectations of results	Questions on expected result and how they plan to use the result.			X				
Receiving results, understanding, and making meaning	Questions on result including knowledge of outcomes and how they plan to use the result.					X		
Attitudes and perceptions	Questions on if, how, and when gNBS should be offered, and what conditions should be screened.			X		X		X
Decision making	Questions on reasons for declining gNBS.							X
Data re-use	Study-specific questions around preferences for additional analyses of gNBS data.						X	
Future gNBS decision	One study-specific question asking preference for gNBS for future children						X	

T1, survey at enrolment; T2, survey post-consent; T3, 3-months post result survey; T4, 12-months post result survey; int, interviews; STAI-6, Six-item State-Trait Anxiety Inventory; STAI-AD, State-Trait Anxiety Inventory for Adults; gNBS, genomic newborn screening.

Health economic analyses will be performed from the perspective of the Australian healthcare system, using a lifetime horizon, and based on the outcomes of cost per additional diagnosis, cost per quality-adjusted life-year gained, and net benefit. A budget impact analysis will be conducted to provide policy-relevant insights into the affordability and sustainability of implementing gNBS.

Potential barriers and enablers to implementation of gNBS will be identified to generate strategies to support successful delivery and inform future studies. These will be ascertained through theory-informed interviews. This will include capturing the experiences of professionals including HCP involved in the delivery of gNBS, and those impacted by the implementation of gNBS, including perinatal HCP and paediatric physicians. In addition, process mapping will be undertaken with laboratory staff and study team members at intervals throughout the study to understand adaptations required to deliver gNBS at scale and within clinically meaningful timeframes.

Data analysis

Personal identifying information, clinical, and evaluation data will be collected using recording devices, and electronic data collection forms in the online Genetics Adviser platform(30) and REDCap,(25, 26) both hosted at the Murdoch Children's Research Institute, Melbourne, Australia.

Findings from interviews and surveys will be used to provide qualitative and statistical information on the associations between a particular behaviour and opinions or attitudes about the program. Qualitative data will be either deductively analysed where a theoretical framework has been employed e.g., AACTT(24) or analysed using inductive content analysis(35) or thematic analysis to generate rich descriptions responding to the research aims e.g., acceptability of testing. Economic evaluation and discrete choice experiments will be conducted according to best practice recommendations.(36-38) Quotes from participants will be used to illustrate qualitative findings in scientific presentations and other publications. Statistical analysis will utilise appropriate methods and tests depending on the

nature of the data and its normality. Probability values of <0.05 will be considered statistically significant, and confidence intervals will be calculated where possible.

Patient and public involvement

The pre-implementation phase of the study involved extensive consultation with the public via focus groups and discrete choice experiment surveys. These have informed the design of the implementation phase. Condition selection has been done in conjunction with patient support groups. The study also uses Genetics Adviser, a decision support platform with extensive public input into design and development.(27-30)

ETHICS AND DISSEMINATION

This study is governed and administered by the Murdoch Children's Research Institute (MCRI), Melbourne, Australia. All genetic testing is performed by VCGS, Melbourne, Australia, a wholly owned not-for-profit subsidiary of MCRI. VCGS is clinically accredited (NATA/RCPA) to ISO15189;2012 to carry out genetic and genomic testing. The project has received ethics approval from the Royal Children's Hospital Melbourne Human Research Ethics Committee (main BabyScreen+ protocol: HREC/91500/RCHM-2023; key informant interviews: HREC/90929/RCHM-2022; and focus groups and DCE: HREC/91392/RCHM-2022). Findings from this study will be published in peer-reviewed scientific journal articles and presented at appropriate clinical and research conferences. The findings will also be disseminated to policy makers including the Standing Committee on Screening. All participants have provided informed consent to be involved in this study.

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AUTHOR CONTRIBUTIONS

All authors contributed to the design of the protocol, including its concept and the critical review and final approval of the manuscript. Sebastian Lunke, Sophie Bouffler and Zornitza Stark drafted the manuscript. Simon Sadedin, Stefanie Eggers, Sebastian Hollizeck, Crystle Lee, Meaghan Wall, Ronda Greaves, Paul De Fazio and Sebastian Lunke contributed to the design of the laboratory processes. David Amor, Lilian Downie, Alison Archibald, John Christodoulou, Alison Yeung, Zornitza Stark and Sebastian Lunke contributed to the design of the gene list. Yvonne Bombard, Marc Clausen, Jade Caruana, Alison Archibald, Lilian Downie, Clara Gaff, Sophie Bouffler, Nitzan Lang, Anaita Kanga-Parabia and Zornitza Stark contributed to the design of participant and HCP education materials. Danya Vears, Fiona Lynch and Christopher Gyngell contributed to the design of the ethical evaluation. Erin Tutty, Anaita Kanga-Parabia, Alison Archibald and Stephanie Best contributed to the design of the psychosocial and implementation evaluation. Riccarda Peters and Ilias Goranitis contributed to the design of the health economic evaluation.

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COMPETING INTERESTS

YB and MC are cofounders of the Genetics Adviser. The other authors declare no relevant disclosures.

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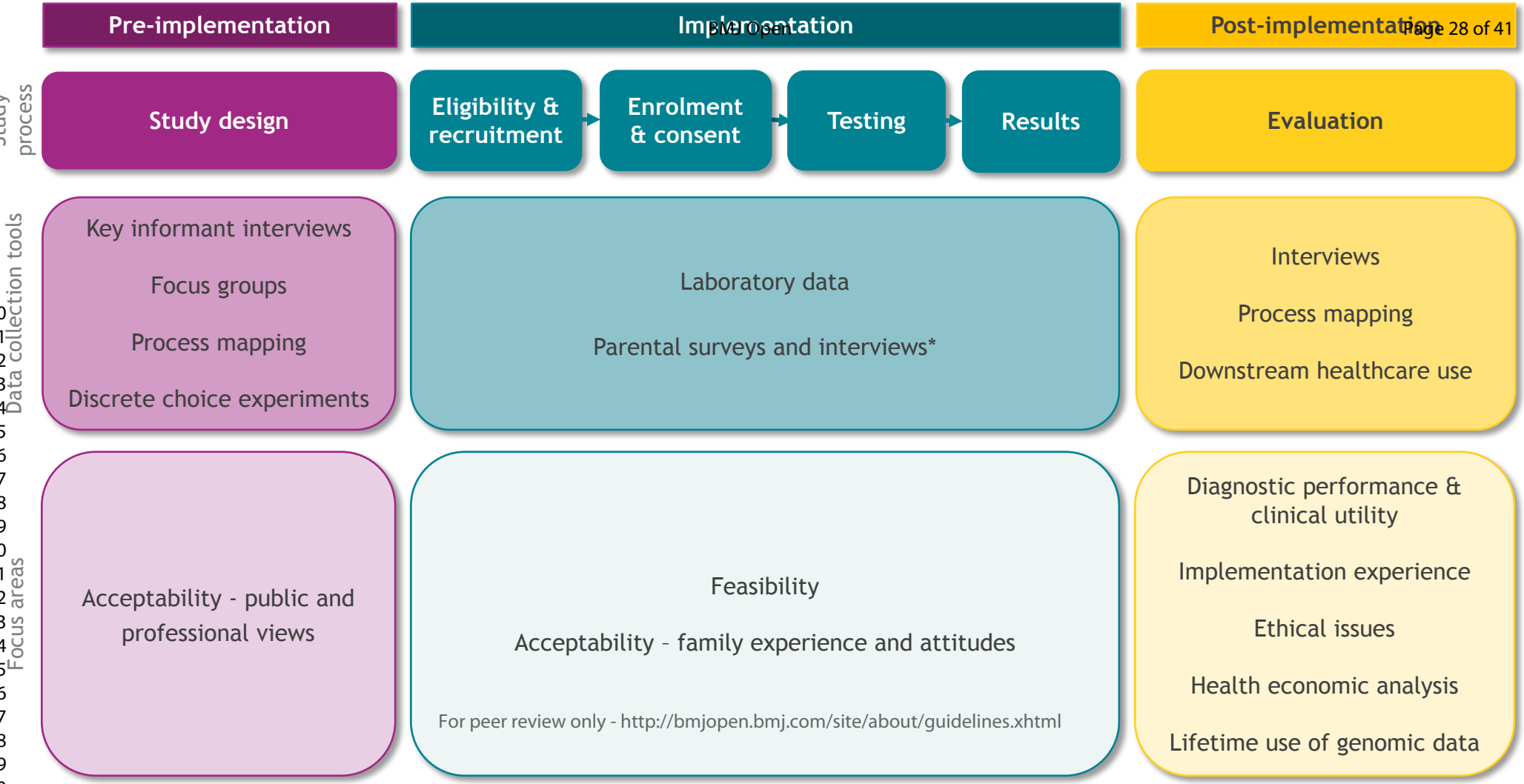
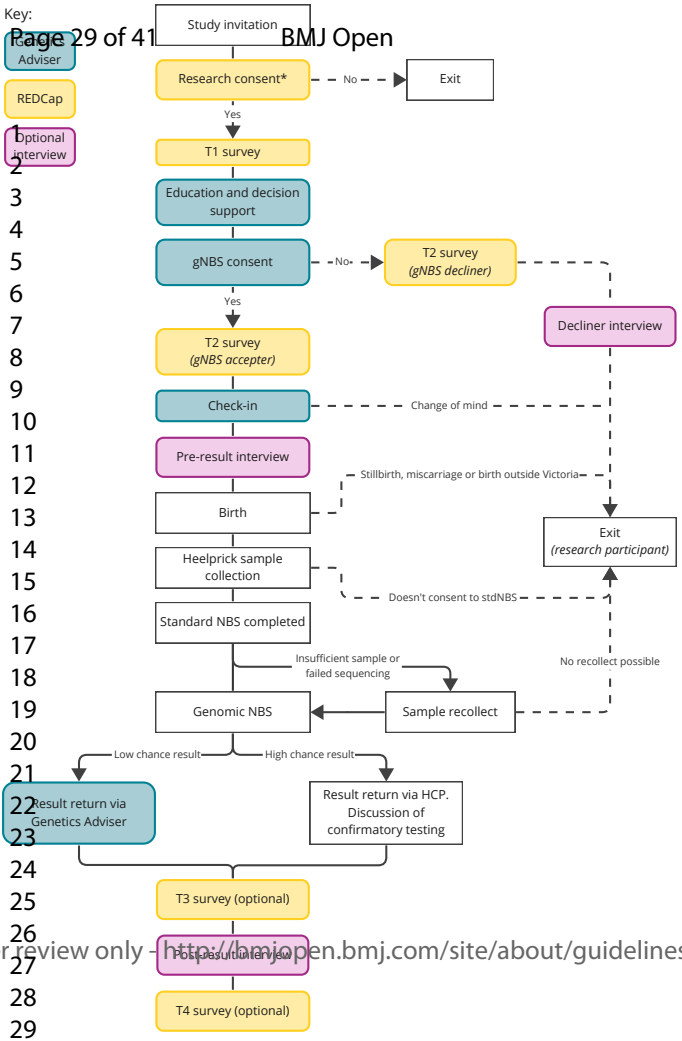
Figure 1: The three phases of the BabyScreen+ study including data collection tools and research focus areas. *refer to Table 1 for survey and interview measures.

Figure 2: Participation process for birth parents. Solid lines represent the expected end-to-end study pathway (offer to result and final surveys), dashed lines represent anticipated study exit pathways. *Participants not able to complete enrolment in English will be supported by a genetic counsellor and an interpreter. HCP, healthcare professional; NBS, newborn bloodspot screening; T1-T4, survey timepoints/identifiers.





Supplementary Table 1: BabyScreen+ gene panel

Gene Name	Model_Of_Inheritance	Phenotypes
AAAS	BIALLELIC	Achalasia-addisonianism-alacrimia syndrome, MIM#231550
ABCC6	BIALLELIC	Arterial calcification, generalized, of infancy, 2, #MIM614473
ABCC8	BOTH monoallelic and biallelic	Hyperinsulinemic hypoglycemia, familial, MIM#256450
ABCD1	X-LINKED: hemizygous mutation in males	Adrenoleukodystrophy, MIM# 300100
ABCD4	BIALLELIC	Methylmalonic aciduria and homocystinuria, cblJ type MIM#614857
ABCG5	BIALLELIC	Sitosterolaemia 2, MIM# 618666
ACAD9	BIALLELIC	Mitochondrial complex I deficiency, nuclear type 20, MIM#611126
ACADM	BIALLELIC	Medium chain acyl CoA dehydrogenase deficiency, MIM#201450
ACADVL	BIALLELIC	VLCAD deficiency, MIM#201475
ACAT1	BIALLELIC	Alpha-methylacetoacetic aciduria, MIM#203750
ACTA2	BOTH monoallelic and biallelic	Aortic aneurysm, familial thoracic 6, MIM# 611788
ACVRL1	MONOALLELIC	Telangiectasia, hereditary hemorrhagic, type 2, MIM#600376
ADA	BIALLELIC	Severe combined immunodeficiency due to ADA deficiency, MIM# 102700, MONDO:0007064
ADA2	BIALLELIC	Vasculitis, autoinflammation, immunodeficiency, and haematologic defects syndrome, MIM# 615688
ADAMTS13	BIALLELIC	Thrombotic thrombocytopenic purpura, familial, MIM#274150
ADGRV1	BIALLELIC	Usher syndrome, type 2C, MIM# 605472
AGL	BIALLELIC	Glycogen storage disease IIIa, MIM#232400
AGRN	BIALLELIC	Myasthenic syndrome, congenital, 8, with pre- and postsynaptic defects, MIM# 615120
AGXT	BIALLELIC	Hyperoxaluria, primary, type 1, MIM# 259900, MONDO:0009823
AHCY	BIALLELIC	Hypermethioninemia with deficiency of S-adenosylhomocysteine hydrolase, MIM#613752
AICDA	BIALLELIC	Immunodeficiency with hyper-IgM, type 2, MIM#605258
AIRE	BIALLELIC	Autoimmune polyendocrinopathy syndrome , type I, with or without reversible metaphyseal dysplasia, MIM#240300
AK2	BIALLELIC	Reticular dysgenesis, MIM# 267500;MONDO:0009973
AKR1D1	BIALLELIC	Bile acid synthesis defect, congenital, 2
ALDH4A1	BIALLELIC	Hyperprolinemia, type II MIM#239510
ALDH7A1	BIALLELIC	Epilepsy, pyridoxine-dependent, MIM#266100
ALDOB	BIALLELIC	Fructose intolerance, hereditary, MIM# 229600
ALPL	BIALLELIC	Hypophosphatasia, childhood OMIM#241510;Hypophosphatasia, infantile OMIM#241500
AMACR	BIALLELIC	Bile acid synthesis defect, congenital, 4, MIM# 214950
AMN	BIALLELIC	Megaloblastic anemia-1, Norwegian type, MIM#618882
AP3B1	BIALLELIC	Hermansky-Pudlak syndrome 2, MIM# 608233 MONDO:0011997
AQP2	BOTH monoallelic and biallelic	Diabetes insipidus, nephrogenic, 2, MIM#125800
ARG1	BIALLELIC	Arginase deficiency, MIM#207800
ARPC1B	BIALLELIC	Immunodeficiency 71 with inflammatory disease and congenital thrombocytopenia, MIM#617718
ARSA	BIALLELIC	Metachromatic leukodystrophy, MIM# 250100
ARSB	BIALLELIC	Mucopolysaccharidosis VI (MPS6, MIM# 253200
ASL	BIALLELIC	Argininosuccinic aciduria, MIM#207900
ASS1	BIALLELIC	Citrullinaemia, MIM#215700
ATP6V0A4	BIALLELIC	Distal renal tubular acidosis 3, with or without sensorineural hearing loss, MIM3602722
ATP6V1B1	BIALLELIC	Distal renal tubular acidosis 2 with progressive sensorineural hearing loss, MIM# 267300
ATP7A	X-LINKED: hemizygous mutation in males	Menkes disease, MIM# 309400
ATP7B	BIALLELIC	Wilson disease MIM#277900
AVP	MONOALLELIC	Diabetes insipidus, neurohypophyseal MIM#125700
AVPR2	X-LINKED: hemizygous mutation in males	Diabetes insipidus, nephrogenic, MIM#304800
BCHE	BIALLELIC	Butyrylcholinesterase deficiency, MIM#617936
BCKDHA	BIALLELIC	Maple syrup urine disease, type Ia, MIM# 248600
BCKDHB	BIALLELIC	Maple syrup urine disease, type Ib, MIM# 248600
BCKDK	BIALLELIC	Branched-chain keto acid dehydrogenase kinase deficiency, MIM#614923
BLNK	BIALLELIC	Agammaglobulinaemia 4, MIM#613502

BMP1	BIALLELIC	Osteogenesis imperfecta, type XIII , MIM#614856
BRCA1	BIALLELIC	Fanconi anemia, complementation group S, MIM# 617883
BRCA2	BIALLELIC	Fanconi anaemia, complementation group D1, MIM# 605724
BRIP1	BIALLELIC	Fanconi anaemia, complementation group J, MIM#609054
BSCL2	BIALLELIC	Lipodystrophy, congenital generalized, type 2, MIM# 269700;Berardinelli-Seip lipodystrophy
BSND	BIALLELIC	Bartter syndrome, type 4a, MIM# 602522
BTD	BIALLELIC	Biotinidase deficiency, MIM#253260
BTK	X-LINKED: hemizygous mutation in males	Agammaglobulinemia, X-linked 1, MIM#300755
C17orf62	BIALLELIC	Chronic granulomatous disease 5, autosomal recessive, MIM# 618935
C2	BIALLELIC	C2 deficiency, MIM#217000
C3	BIALLELIC	C3 deficiency, MIM#613779
C5	BIALLELIC	C5 deficiency, MIM#609536
C6	BIALLELIC	C6 deficiency, MIM#612446
C7	BIALLELIC	C7 deficiency, MIM#610102
C8B	BIALLELIC	C8 deficiency, type II, MIM#613789
C9	BIALLELIC	C9 deficiency, MIM#613825
CA12	BIALLELIC	Hyperchlorhidrosis, isolated MIM#143860
CA2	BIALLELIC	Osteopetrosis, autosomal recessive 3, with renal tubular acidosis, MIM#259730
CA5A	BIALLELIC	Hyperammonaemia due to carbonic anhydrase VA deficiency, MIM#615751
CABP2	BIALLELIC	Deafness, autosomal recessive 93, MIM# 614899
CACNA1S	MONOALLELIC	Malignant hyperthermia susceptibility 5, MIM# 601887
CAD	BIALLELIC	Developmental and epileptic encephalopathy 50, MIM#616457
CALM3	MONOALLELIC	Long QT syndrome 16, MIM#618782
CARD11	BOTH monoallelic and biallelic	Immunodeficiency 11A, autosomal recessive, MIM# 615206;Immunodeficiency 11B with atopic dermatitis, autosomal dominant, MIM# 617638
CASR	BOTH monoallelic and biallelic	Hypocalcemia, autosomal dominant MIM#601198;Hyperparathyroidism, neonatal MIM#239200
CAV1	BIALLELIC	Lipodystrophy, congenital generalized, type 3, MIM#612526
CAVIN1	BIALLELIC	Lipodystrophy, congenital generalized, type 4, MIM# 613327
CD19	BIALLELIC	Immunodeficiency, common variable, 3, MIM#613493
CD247	BIALLELIC	Immunodeficiency 25, MIM# 610163
CD27	BIALLELIC	CD27-deficiency MIM# 615122
CD3D	BIALLELIC	Immunodeficiency 19, MIM#615617
CD3E	BIALLELIC	Immunodeficiency 18, MIM#615615
CD3G	BIALLELIC	Immunodeficiency 17;CD3 gamma deficient MIM# 615607
CD40	BIALLELIC	Immunodeficiency with hyper-IgM, type 3, MIM#606843
CD40LG	X-LINKED: hemizygous mutation in males	Immunodeficiency, X-linked, with hyper-IgM MIM# 308230
CD55	BIALLELIC	Complement hyperactivation, angiopathic thrombosis, and protein-losing enteropathy, MIM# 226300
CD70	BIALLELIC	Lymphoproliferative syndrome 3, MIM# 618261
CD79A	BIALLELIC	Agammaglobulinaemia 3, MIM#613501
CD79B	BIALLELIC	Agammaglobulinaemia 6, MIM#612692
CDC14A	BIALLELIC	Deafness, autosomal recessive 32, with or without immotile sperm, MIM# 608653
CDCA7	BIALLELIC	Immunodeficiency-centromeric instability-facial anomalies syndrome 3, MIM# 616910
CDCA8	BOTH monoallelic and biallelic	Congenital hypothyroidism, MONDO:0018612, CDCA8-related
CDH23	BIALLELIC	Usher syndrome, type 1D (MIM# 601067);Deafness, autosomal recessive 12 (MIM # 601386);Usher syndrome, type 1D/F digenic (MIM #601067)
CDKN1C	MONOALLELIC, imprinted	IMAGe syndrome, MIM# 614732
CEBPE	BIALLELIC	Specific granule deficiency, MIM# 245480
CFD	BIALLELIC	Complement factor D deficiency, MIM#613912
CFH	BIALLELIC	Complement factor H deficiency, MIM# 609814
CFI	BIALLELIC	Complement factor I deficiency MIM#610984
CFP	X-LINKED: hemizygous mutation in males	Properdin deficiency, X-linked, MIM#312060
CFTR	BIALLELIC	Cystic fibrosis, MIM#219700
CHAT	BIALLELIC	Congenital myasthenic syndrome, MIM#254210

CHRNA1	BIALLELIC	Myasthenic syndrome, congenital, 1A, slow-channel, MIM# 601462;Myasthenic syndrome, congenital, 1B, fast-channel , MIM#608930
CHRNB1	BIALLELIC	Myasthenic syndrome, congenital, 2C, associated with acetylcholine receptor deficiency, MIM# 616314;Congenital myasthenic syndrome
CHRND	BIALLELIC	Myasthenic syndrome, congenital, 3B, fast-channel, MIM#616322;Myasthenic syndrome, congenital, 3C, associated with acetylcholine receptor deficiency, MIM#616323;Myasthenic syndrome, congenital, 3A, slow-channel, MIM#616321;Multiple pterygium syndrome, lethal type, MIM# 253290;MONDO:0009668
CHRNE	BIALLELIC	Myasthenic syndrome, congenital, 4B, fast-channel, 616324;Myasthenic syndrome, congenital, 4C, associated with acetylcholine receptor deficiency, 608931;Myasthenic syndrome, slow-channel congenital, 601462;Myasthenic syndrome, congenital, 4A, slow-channel, 605809
CIB2	BIALLELIC	Deafness, autosomal recessive 48, MIM# 609439
CIITA	BIALLELIC	Bare Lymphocyte Syndrome, type II, complementation group A MIM# 209920
CLCN7	BIALLELIC	Osteopetrosis, autosomal recessive 4, MIM# 611490
CLDN14	BIALLELIC	Deafness, autosomal recessive 29, MIM# 614035
CLPP	BIALLELIC	Perrault syndrome 3, MIM# 614129
COCH	BIALLELIC	Deafness, autosomal recessive 110, MIM# 618094
COL11A1	MONOALLELIC	Stickler syndrome, type II, MIM# 604841
COL11A2	BIALLELIC	Deafness, autosomal recessive 53, MIM# 609706
COL13A1	BIALLELIC	Myasthenic syndrome, congenital, 19, MIM#616720
COL1A1	MONOALLELIC	Osteogenesis imperfecta, type I, MIM#166200
COL1A2	MONOALLELIC	Osteogenesis imperfecta, type II , MIM#166210
COL2A1	MONOALLELIC	Stickler syndrome, type I, MIM# 108300
COL4A3	BIALLELIC	Alport syndrome 2, autosomal recessive, MIM# 203780
COL4A4	BIALLELIC	Alport syndrome 2, autosomal recessive MIM#203780
COL4A5	X-LINKED: hemizygous mutation in males	Alport syndrome 1, X-linked, MIM# 301050
COL9A1	BIALLELIC	Stickler syndrome, type IV, MIM#614134
COL9A2	BIALLELIC	Stickler syndrome, type V, MIM# 614284
COL9A3	BIALLELIC	Stickler syndrome, type VI, MIM# 620022
COLQ	BIALLELIC	Congenital myasthenic syndrome, MIM#603034
COQ2	BIALLELIC	Coenzyme Q10 deficiency, primary, 1, MIM#607426
COQ4	BIALLELIC	Coenzyme Q10 deficiency, primary, 7, MIM#616276
COQ6	BIALLELIC	Coenzyme Q10 deficiency, primary, 6, MIM#614650
COQ8A	BIALLELIC	Coenzyme Q10 deficiency, primary, 4, MIM#612016
CORO1A	BIALLELIC	Immunodeficiency 8 MIM# 615401
CPS1	BIALLELIC	Carbamoylphosphate synthetase I deficiency, MIM#237300
CPT1A	BIALLELIC	Carnitine palmitoyltransferase I deficiency, MIM#255120
CPT2	BIALLELIC	CPT II deficiency, infantile 600649;CPT II deficiency, lethal neonatal 608836;CPT II deficiency, myopathic, stress-induced 255110
CRTAP	BIALLELIC	Osteogenesis imperfecta, type VII, MIM# MIM#610682
CSF3R	BIALLELIC	Neutropenia, severe congenital, 7, autosomal recessive, MIM#617014
CTNS	BIALLELIC	Cystinosis, nephropathic MIM#219800
CTPS1	BIALLELIC	Immunodeficiency 24, MIM#615897
CUBN	BIALLELIC	Megaloblastic anaemia-1, Finnish type, MIM#261100
CUL3	MONOALLELIC	Pseudohypoaldosteronism, type IIE 614496
CXCR4	MONOALLELIC	WHIM syndrome 1, MIM#193670
CYB561	BIALLELIC	Orthostatic hypotension 2, MIM#618182
CYBA	BIALLELIC	Chronic granulomatous disease, MIM#233690
CYBB	X-LINKED: hemizygous mutation in males	Chronic granulomatous disease, MIM#306400
CYP11A1	BIALLELIC	Adrenal insufficiency, congenital, with 46XY sex reversal, partial or complete, MIM#613743
CYP11B1	BIALLELIC	Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency, MIM#202010
CYP11B2	BIALLELIC	Hypoaldosteronism, congenital, due to CMO I deficiency, MIM#203400;Hypoaldosteronism, congenital, due to CMO II deficiency, MIM#610600
CYP17A1	BIALLELIC	17,20-lyase deficiency, isolated, MIM#202110
CYP21A2	BIALLELIC	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency, MIM#201910

CYP27A1	BIALLELIC	Cerebrotendinous xanthomatosis, MIM# 213700
CYP27B1	BIALLELIC	Vitamin D-dependent rickets, type I MIM#264700
CYP2R1	BIALLELIC	Rickets due to defect in vitamin D 25-hydroxylation deficiency MIM#600081
CYP7B1	BIALLELIC	Bile acid synthesis defect, congenital, 3, MIM# 613812
DBT	BIALLELIC	Maple syrup urine disease, MIM#248600
DCLRE1C	BIALLELIC	Severe combined immunodeficiency, Athabascan type MIM# 602450;Omenn syndrome, MIM# 603554
DDC	BIALLELIC	Aromatic L-amino acid decarboxylase deficiency, MIM#608643
DFNB59	BIALLELIC	Deafness, autosomal recessive 59, MIM# 610220
DGAT1	BIALLELIC	Diarrhea 7, protein-losing enteropathy type , MIM#615863
DHCR7	BIALLELIC	Smith-Lemli-Opitz syndrome, MIM#270400
DHFR	BIALLELIC	Megaloblastic anaemia due to dihydrofolate reductase deficiency, MIM# 613839
DICER1	MONOALLELIC	DICER1 syndrome, MONDO:0017288
DLAT	BIALLELIC	Pyruvate dehydrogenase E2 deficiency, MIM#245348
DMP1	BIALLELIC	Hypophosphatemic rickets MIM#241520
DNAJC12	BIALLELIC	Hyperphenylalaninemia, mild, non-BH4-deficient, MIM#617384
DNAJC21	BIALLELIC	Bone marrow failure syndrome 3, MIM#617052
DNASE2	BIALLELIC	Autoinflammatory-pancytopenia syndrome, MIM# 619858
DNMT3B	BIALLELIC	Immunodeficiency-centromeric instability-facial anomalies syndrome 1, MIM# 242860
DOCK2	BIALLELIC	Immunodeficiency 40 MIM# 616433
DOCK8	BIALLELIC	Hyper-IgE syndrome, MIM#243700
DOK7	BIALLELIC	Congenital myasthenic syndrome, MIM# 254300
DPAGT1	BIALLELIC	Congenital disorder of glycosylation, type Ij, MIM# 608093;DPAGT1-CDG MONDO:0011964;Myasthenic syndrome, congenital, 13, with tubular aggregates, MIM# 614750
DUOX2	BIALLELIC	Thyroid dyshormonogenesis 6, MIM# 607200
DUOXA2	BIALLELIC	Thyroid dyshormonogenesis 5, MIM# 274900
ECHS1	BIALLELIC	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency MIM# 616277
EDN3	BIALLELIC	Waardenburg syndrome, type 4B, MIM# 613265
EDNRB	BOTH monoallelic and biallelic	Waardenburg syndrome, type 4A, MIM# 277580
EFL1	BIALLELIC	Shwachman-Diamond syndrome 2, MIM#617941
EIF2AK3	BIALLELIC	Wolcott-Rallison syndrome, MIM#226980
ELANE	MONOALLELIC	Neutropenia, congenital, MIM#202700
ENG	MONOALLELIC	Telangiectasia, hereditary hemorrhagic, type 1 MIM#187300
ENPP1	BIALLELIC	Arterial calcification, generalized, of infancy, 1, MIM# 208000;Hypophosphatemic rickets, autosomal recessive, 2, MIM# 613312
EPS8	BIALLELIC	Autosomal recessive nonsyndromic hearing loss 102, MIM#600205, MONDO:0014428
ERCC4	BIALLELIC	Fanconi anemia, complementation group Q, MIM# 615272
ESPN	BIALLELIC	Deafness, autosomal recessive 36, MIM# 609006
ESRRB	BIALLELIC	Deafness, autosomal recessive 35, MIM#608565
ETFA	BIALLELIC	Glutaric acidaemia IIA, MIM#231680
ETFB	BIALLELIC	Glutaric acidemia IIB, MIM#231680
ETFDH	BIALLELIC	Glutaric acidemia IIC, MIM#231680
ETHE1	BIALLELIC	Ethylmalonic encephalopathy, MIM#602473
F10	BIALLELIC	Factor X deficiency, MIM#227600
F13A1	BIALLELIC	Factor XIIIA deficiency, MIM#613225
F13B	BIALLELIC	Factor XIIIB deficiency, MIM#613235
F7	BIALLELIC	Factor VII deficiency MIM# 227500
F9	X-LINKED: hemizygous mutation in males	Haemophilia B, MIM#306900
FAH	BIALLELIC	Tyrosinaemia, type I, MIM#276700
FAM111A	MONOALLELIC	Kenny-Caffey syndrome, type 2, MIM# 127000
FANCA	BIALLELIC	Fanconi anaemia, complementation group A, MIM# 227650;MONDO:0009215
FANCB	X-LINKED: hemizygous mutation in males	Fanconi anaemia, complementation group B, MIM# 300514
FANCC	BIALLELIC	Fanconi anemia, complementation group C, MIM# 227645;MONDO:0009213
FANCD2	BIALLELIC	Fanconi anaemia, complementation group D2, MIM# 227646;MONDO:0009214
FANCG	BIALLELIC	Fanconi anaemia, MIM#614082

FANCI	BIALLELIC	Fanconi anaemia, MIM#609053
FBN1	MONOALLELIC	Marfan syndrome, MIM# 154700
FBP1	BIALLELIC	Fructose-1,6-bisphosphatase deficiency MIM# 229700
FCHO1	BIALLELIC	Immunodeficiency 76, MIM# 619164
FECH	BIALLELIC	Protoporphyria, erythropoietic, 1, MIM#177000
FERMT3	BIALLELIC	Leukocyte adhesion deficiency, type III, MIM#612840
FGA	BIALLELIC	Afibrinogenemia, congenital (MIM#202400)
FGB	BIALLELIC	Afibrinogenaemia, congenital, MIM# 202400
FGF23	BOTH monoallelic and biallelic	autosomal dominant hypophosphatemic rickets MONDO:0008660;familial hyperphosphatemic tumoral calcinosis/hyperphosphatemic hyperostosis syndrome MONDO:0100251
FGF3	BIALLELIC	Deafness, congenital with inner ear agenesis, microtia, and microdontia, MIM# 610706
FGFR3	MONOALLELIC	Achondroplasia MONDO:0007037
FGG	BIALLELIC	Afibrinogenemia, congenital, MIM# 202400
FH	BIALLELIC	Fumurase deficiency MIM# 606812
FKBP10	BIALLELIC	Osteogenesis imperfecta, type XI, OMIM:610968
FLAD1	BIALLELIC	Lipid storage myopathy due to flavin adenine dinucleotide synthetase deficiency, MIM#255100
FOLR1	BIALLELIC	Neurodegeneration due to cerebral folate transport deficiency, MIM# 613068
FOXA2	MONOALLELIC	Hyperinsulinism MONDO:0002177
FOXE1	BIALLELIC	Bamforth-Lazarus syndrome MIM# 241850
FOXN1	BOTH monoallelic and biallelic	T-cell immunodeficiency, congenital alopecia, and nail dystrophy, autosomal recessive MIM# 601705;T-cell lymphopenia, infantile, with or without nail dystrophy, autosomal dominant, MIM#t 618806
FOXP3	X-LINKED: hemizygous mutation in males	IPEX syndrome, MIM#304790
FUCA1	BIALLELIC	Fucosidosis, MIM# 230000
G6PC	BIALLELIC	Glycogen storage disease Ia, MIM#232200
G6PC3	BIALLELIC	Neutropaenia, congenital, MIM#612541
G6PD	X-LINKED: hemizygous mutation in males	Glucose-6-phosphate dehydrogenase deficiency, MIM#300908
GAA	BIALLELIC	Glycogen storage disease II, Pompe disease, MIM# 232300
GALC	BIALLELIC	Krabbe disease, MIM#245200
GALE	BIALLELIC	Galactose epimerase deficiency, MIM#230350
GALK1	BIALLELIC	Galactokinase deficiency with cataracts, MIM#230200
GALM	BIALLELIC	Galactosemia IV MIM#618881
GALNS	BIALLELIC	Mucopolysaccharidosis IVA, MIM#253000
GALNT3	BIALLELIC	Tumoral calcinosis, hyperphosphatemic, familial, 1, MIM# 211900
GALT	BIALLELIC	Galactosaemia, MIM#230400
GAMT	BIALLELIC	Cerebral creatine deficiency syndrome 2, MIM#612736
GATA2	MONOALLELIC	Immunodeficiency 21 MIM# 614172;Emberger syndrome MIM# 614038
GATA3	MONOALLELIC	Hypoparathyroidism, sensorineural deafness, and renal dysplasia, MIM# 146255
GATA4	MONOALLELIC	Neonatal diabetes mellitus, MONDO:0016391, GATA4-related
GATM	BIALLELIC	Cerebral creatine deficiency syndrome 3 MIM#612718
GBA	BIALLELIC	Gaucher disease type 1, MIM#230800
GCDH	BIALLELIC	Glutaric aciduria, type I, MIM#231670
GCH1	BOTH monoallelic and biallelic	Hyperphenylalaninemia, BH4-deficient, B, MIM# 233910;Dystonia, DOPA-responsive, with or without hyperphenylalaninemia, MIM# 128230
GCK	BOTH monoallelic and biallelic	Hyperinsulinemic hypoglycemia, familial, MIM#602485
GCM2	BOTH monoallelic and biallelic	Hyperparathyroidism 4, OMIM #617343;Hypoparathyroidism, familial isolated 2, OMIM #618883
GFI1	MONOALLELIC	Neutropenia, severe congenital 2, autosomal dominant, MIM# 613107
GGCX	BIALLELIC	Vitamin K-dependent clotting factors, combined deficiency of, 1 MIM# 277450
GH1	BOTH monoallelic and biallelic	Growth hormone deficiency, isolated, type IA, MIM# 262400;Growth hormone deficiency, isolated, type II, MIM# 173100;Kowarski syndrome, MIM# 262650
GHR	BOTH monoallelic and biallelic	Growth hormone insensitivity, partial, MIM# 604271;Laron dwarfism, MIM# 262500
GHRHR	BIALLELIC	Growth hormone deficiency, isolated, type IV, MIM# 618157
GIF	BIALLELIC	Intrinsic factor deficiency, MIM#261000

GIPC3	BIALLELIC	Deafness, autosomal recessive 15, MIM# 601869
GJB2	BIALLELIC	Deafness, autosomal recessive 1A, MIM# 220290
GLA	X-LINKED: hemizygous mutation in males	Fabry disease (MIM# 301500)
GLIS3	BIALLELIC	Diabetes mellitus, neonatal, with congenital hypothyroidism MIM#610199
GLRA1	BOTH monoallelic and biallelic	Hyperekplexia, hereditary 1, autosomal dominant or recessive, MIM#149400
GLUD1	MONOALLELIC	Hyperinsulinism, MIM#606762
GNAS	MONOALLELIC	Pseudopseudohypoparathyroidism MIM#612463;Pseudohypoparathyroidism MIM#612462, MIM#603233, MIM#103580
GOT2	BIALLELIC	Developmental and epileptic encephalopathy 82, MIM#618721
GPIHBP1	BIALLELIC	Hyperlipoproteinemia, type 1D MIM#615947;familial chylomicronemia syndrome
GREB1L	MONOALLELIC	Deafness, autosomal dominant 80MIM#619274
GRHPR	BIALLELIC	Hyperoxaluria, primary, type II, MIM# 260000
GRXCR1	BIALLELIC	Deafness, autosomal recessive 25, MIM#613285
GUSB	BIALLELIC	Mucopolysaccharidosis VII, MIM#253220
GYS2	BIALLELIC	Glycogen storage disease 0, liver (MIM#240600)
HADH	BIALLELIC	3-hydroxyacyl-CoA dehydrogenase deficiency, MIM# 231530
HADHA	BIALLELIC	Mitochondrial trifunctional protein deficiency, MIM#609015;LCHAD deficiency, MIM#609016
HADHB	BIALLELIC	Mitochondrial trifunctional protein deficiency, MIM#609015
HAX1	BIALLELIC	Neutropenia, severe congenital 3, autosomal recessive, MIM# 610738;Kostmann syndrome MONDO:0012548
HBB	BIALLELIC	Sickle cell anaemia, MIM# 603903
HELLS	BIALLELIC	Immunodeficiency-centromeric instability-facial anomalies syndrome 4, MIM# 616911
HESX1	BOTH monoallelic and biallelic	Pituitary hormone deficiency, combined, 5, MIM# 182230
HGF	BIALLELIC	Deafness, autosomal recessive 39, MIM# 608265
HIBCH	BIALLELIC	3-hydroxyisobutryl-CoA hydrolase deficiency MIM#250620
HK1	MONOALLELIC	Hyperinsulinism MONDO:0002177, HK1-related
HLCS	BIALLELIC	Holocarboxylase synthetase deficiency, MIM#253270
HMGCL	BIALLELIC	3-hydroxy-3-methylglutaric aciduria, MIM#246450
HOGA1	BIALLELIC	Hyperoxaluria, primary, type III MIM#613616
HSD11B2	BIALLELIC	Apparent mineralocorticoid excess, MIM# 218030;MONDO:0009025
HSD3B2	BIALLELIC	Adrenal hyperplasia, congenital, due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency MIM# 201810
HSD3B7	BIALLELIC	Bile acid synthesis defect, congenital, 1 MIM#607765
ICOS	BIALLELIC	Immunodeficiency, common variable, 1 MIM# 607594
IDS	X-LINKED: hemizygous mutation in males	Mucopolysaccharidosis II (MPS2, Hunter syndrome) 309900
IDUA	BIALLELIC	Mucopolysaccharidosis type 1, MONDO:0001586
IFITM5	MONOALLELIC	Osteogenesis imperfecta, type V MIM#610967
IGF1	BIALLELIC	Insulin-like growth factor I deficiency, MIM# 608747
IGHM	BIALLELIC	Agammaglobulinaemia 1, MIM#601495
IGLL1	BIALLELIC	Agammaglobulinaemia 2, MIM#613500
IGSF1	X-LINKED: hemizygous mutation in males	Hypothyroidism, central, and testicular enlargement, MIM# 300888
IKBKB	BIALLELIC	Immunodeficiency 15B, MIM#615592
IKZF1	MONOALLELIC	Immunodeficiency, common variable, 13 MIM# 616873
IL10	BIALLELIC	Autoinflammatory syndrome, MONDO:0019751, IL10-related
IL10RA	BIALLELIC	Inflammatory bowel disease 28, early onset, autosomal recessive, MIM# 613148
IL10RB	BIALLELIC	Inflammatory bowel disease 25, early onset, autosomal recessive, MIM#612567
IL1RN	BIALLELIC	Interleukin 1 receptor antagonist deficiency, MIM# 612852
IL21R	BIALLELIC	Immunodeficiency 56, MIM# 615207
IL2RA	BIALLELIC	Immunodeficiency 41 with lymphoproliferation and autoimmunity, MIM# 606367
IL2RB	BIALLELIC	Immunodeficiency 63 with lymphoproliferation and autoimmunity, MIM#618495
IL2RG	X-LINKED: hemizygous mutation in males	Severe combined immunodeficiency, X-linked, MIM#312863
IL36RN	BIALLELIC	Psoriasis 14, pustular, MIM# 614204
IL7R	BIALLELIC	Severe combined immunodeficiency, T-cell negative, B-cell/natural killer cell-positive type MIM#608971

ILDR1	BIALLELIC	Deafness, autosomal recessive 42, MIM# 609646
INS	BOTH monoallelic and biallelic	Diabetes mellitus, insulin-dependent, 2, MIM# 125852;Diabetes mellitus, permanent neonatal 4, MIM# 618858;Maturity-onset diabetes of the young, type 10, MIM# 613370
IRAK4	BIALLELIC	Immunodeficiency 67, MIM#607676
IRF8	BIALLELIC	Immunodeficiency 32B, monocyte and dendritic cell deficiency, autosomal recessive, MIM# 226990
IRS4	X-LINKED: hemizygous mutation in males	Hypothyroidism, congenital, nongoitrous, 9, MIM# 301035
ITGA2B	BIALLELIC	Glanzmann thrombasthaenia 1, MIM# 273800
ITGB2	BIALLELIC	Leukocyte adhesion deficiency, MIM#116920
ITGB3	BIALLELIC	Glanzmann thrombasthenia 2, MIM#619267
ITK	BIALLELIC	Lymphoproliferative syndrome 1, MIM#613011
IVD	BIALLELIC	Isovaleric acidemia, MIM#243500
IYD	BIALLELIC	Thyroid dyshormonogenesis 4, MIM# 274800
JAGN1	BIALLELIC	Neutropenia, severe congenital, 6, autosomal recessive, MIM# 616022
JAK3	BIALLELIC	SCID, autosomal recessive, T-negative/B-positive type, MIM#600802
KCNH2	MONOALLELIC	Long QT syndrome 2, MIM# 613688
KCNJ1	BIALLELIC	Bartter syndrome, type 2, 241200
KCNJ11	BOTH monoallelic and biallelic	Diabetes mellitus, transient neonatal, 3 610582;Diabetes, permanent neonatal, with or without neurologic features 606176;Hyperinsulinemic hypoglycemia, familial, 2 601820
KCNJ2	MONOALLELIC	Andersen syndrome MIM#170390
KCNQ1	BOTH monoallelic and biallelic	Jervell and Lange-Nielsen syndrome MIM#220400;Long QT syndrome 1, MIM# 192500
KDELR2	BIALLELIC	Osteogenesis imperfecta 21, MIM# 619131
KLHL3	BOTH monoallelic and biallelic	Pseudohypoaldosteronism, type IID, MIM# 614495
LAMA2	BIALLELIC	Muscular dystrophy, congenital, merosin deficient or partially deficient, MIM# 607855
LAT	BIALLELIC	Immunodeficiency 52, MIM# 617514
LDLR	BIALLELIC	Hypercholesterolemia, familial, 1, MIM# 143890
LEP	BIALLELIC	Obesity, morbid, due to leptin deficiency (MIM#614962)
LEPR	BIALLELIC	Obesity, morbid, due to leptin receptor deficiency (MIM#614963)
LHFPL5	BIALLELIC	Deafness, autosomal recessive 67, MIM# 610265
LHX3	BIALLELIC	Pituitary hormone deficiency, combined, MIM#221750
LHX4	MONOALLELIC	Pituitary hormone deficiency, combined, 4, MIM#262700
LIG1	BIALLELIC	Immunodeficiency 96, MIM#619774
LIG4	BIALLELIC	LIG4 syndrome, MIM# 606593
LIPA	BIALLELIC	Wolman syndrome, MIM#278000
LMBRD1	BIALLELIC	Methylmalonic aciduria and homocystinuria, MIM#277380
LOXHD1	BIALLELIC	Deafness, autosomal recessive 77, MIM# 613079
LPL	BIALLELIC	Lipoprotein lipase deficiency, MIM# 238600
LRBA	BIALLELIC	Immunodeficiency, common variable, 8, with autoimmunity MIM# 614700
LRP5	BIALLELIC	Osteoporosis-pseudoglioma syndrome, MIM# 259770
LRTOMT	BIALLELIC	Deafness, autosomal recessive 63, MIM# 611451
LYST	BIALLELIC	Chediak-Higashi syndrome, MIM#214500
MAFB	MONOALLELIC	Multicentric carpotarsal osteolysis syndrome (MIM#166300)
MAGT1	X-LINKED: hemizygous mutation in males	Immunodeficiency, X-linked, with magnesium defect, Epstein-Barr virus infection and neoplasia (MIM# 300853)
MALT1	BIALLELIC	Immunodeficiency 12 MIM# 615468
MAN2B1	BIALLELIC	Mannosidosis, alpha-, types I and II, MIM# 248500
MARVELD2	BIALLELIC	Deafness, autosomal recessive 49, MIM# 610153
MC2R	BIALLELIC	Glucocorticoid deficiency, due to ACTH unresponsiveness, MIM#202200
MCEE	BIALLELIC	Methylmalonyl-CoA epimerase deficiency MIM#251120
MEFV	BIALLELIC	Familial Mediterranean fever MIM# 249100
MESD	BIALLELIC	Osteogenesis imperfecta, type XX, MIM#618644
MITF	BOTH monoallelic and biallelic	Waardenburg syndrome, type 2A, MIM# 193510;Deafness
MLH1	BIALLELIC	Mismatch repair cancer syndrome 1, MIM# 276300
MLYCD	BIALLELIC	Malonyl-CoA decarboxylase deficiency, MIM# 248360
MMAA	BIALLELIC	Methylmalonic aciduria, vitamin B12-responsive, MIM#251100
MMAB	BIALLELIC	Methylmalonic aciduria, vitamin B12-responsive, due to defect in synthesis of adenosylcobalamin, cblB complementation type, MIM#251110

MMACHC	BIALLELIC	Methylmalonic aciduria and homocystinuria, cblC type, MIM#277400
MMADHC	BIALLELIC	Methylmalonic aciduria and homocystinuria, cblD type, MIM#277410
MNX1	BIALLELIC	Permanent neonatal diabetes mellitus, MONDO:0100164, MNX1-related
MOCS1	BIALLELIC	Molybdenum cofactor deficiency, MIM#252150
MPI	BIALLELIC	Congenital disorder of glycosylation, type Ib, MIM# 602579
MPL	BIALLELIC	Thrombocytopenia, congenital amegakaryocytic, MIM# 604498
MRAP	BIALLELIC	Glucocorticoid deficiency 2, MIM#607398
MSH2	BIALLELIC	Mismatch repair cancer syndrome 2, MIM# 619096
MSH6	BIALLELIC	Mismatch repair cancer syndrome 3, MIM# 619097
MTHFD1	BIALLELIC	Combined immunodeficiency and megaloblastic anemia with or without hyperhomocysteinaemia MIM # 617780
MTR	BIALLELIC	Homocystinuria-megaloblastic anaemia, cblG complementation type, MIM# 250940
MT-RNR1	MITOCHONDRIAL	Aminoglycoside sensitivity
MTRR	BIALLELIC	Methylmalonic aciduria and homocystinuria, MIM#236270
MTTP	BIALLELIC	Abetalipoproteinemia, MIM# 200100
MUSK	BIALLELIC	Congenital myasthenic syndrome, MIM#616325
MUT	BIALLELIC	Methylmalonic aciduria, mut(0) type, MIM#251000
MVK	BIALLELIC	Mevalonic aciduria, MIM# 610377
MYD88	BIALLELIC	Immunodeficiency 68, MIM# 612260
MYH7	BIALLELIC	Cardiomyopathy, hypertrophic, 1, MIM# 192600
MYO15A	BIALLELIC	Deafness, autosomal recessive 3, MIM# 600316
MYO3A	BIALLELIC	Deafness, autosomal recessive 30, MIM:607101
MYO6	BIALLELIC	Deafness, autosomal recessive 37, MIM# 607821
MYO7A	BIALLELIC	Deafness, autosomal recessive 2, 600060;Usher syndrome, type 1B, MIM# 276900
MYSM1	BIALLELIC	Bone marrow failure syndrome 4, MIM#618116
NAGLU	BIALLELIC	Mucopolysaccharidosis type IIIB (Sanfilippo B), MIM# 252920
NAGS	BIALLELIC	N-acetylglutamate synthetase deficiency, MIM#237310
NCF2	BIALLELIC	Chronic granulomatous disease, MIM#233710
NCF4	BIALLELIC	Granulomatous disease, chronic, autosomal recessive, cytochrome b-positive, type III MIM#613960
NEUROG3	BIALLELIC	Diarrhoea 4, malabsorptive, congenital, MIM# 610370
NFKBIA	MONOALLELIC	Ectodermal dysplasia and immunodeficiency 2 MIM# 612132
NHEJ1	BIALLELIC	Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation, MIM#611291
NIPAL4	BIALLELIC	Ichthyosis, congenital, autosomal recessive 6, MIM# 612281
NKX2-1	MONOALLELIC	Choreoathetosis, hypothyroidism, and neonatal respiratory distress MIM#610978
NKX2-5	MONOALLELIC	Atrial septal defect 7, with or without AV conduction defects, MIM#108900
NNT	BIALLELIC	Glucocorticoid deficiency 4, with or without mineralocorticoid deficiency, MIM#614736
NPC1	BIALLELIC	Niemann-Pick disease type C1, MIM#257220
NPC2	BIALLELIC	Niemann-Pick disease type C2, MIM#607625
NR0B1	X-LINKED: hemizygous mutation in males	Adrenal hypoplasia, congenital (MIM# 300200)
NR3C2	MONOALLELIC	Pseudohypoaldosteronism type I, autosomal dominant, MIM#177735
NR5A1	MONOALLELIC	Adrenocortical insufficiency, (MIM#612964)
OAS1	MONOALLELIC	Immunodeficiency 100 with pulmonary alveolar proteinosis and hypogammaglobulinaemia, MIM#618042
OAT	BIALLELIC	Gyrate atrophy of choroid and retina with or without ornithinemia MIM#258870
ORAI1	BIALLELIC	Immunodeficiency 9, MIM# 612782
OTC	X-LINKED: hemizygous mutation in males	Ornithine transcarbamylase deficiency, MIM#311250
OTOA	BIALLELIC	Deafness, autosomal recessive 22, MIM#607039
OTOF	BIALLELIC	Deafness, autosomal recessive 9, MIM#601071
OTOG	BIALLELIC	Deafness, autosomal recessive 18B - MIM#614945
OTOGL	BIALLELIC	Deafness, autosomal recessive 84B, MIM# 614944
OTULIN	BIALLELIC	Autoinflammation, panniculitis, and dermatosis syndrome, MIM# 617099
OTX2	MONOALLELIC	Pituitary hormone deficiency, combined, 6, MIM# 613986
OXCT1	BIALLELIC	Succinyl CoA:3-oxoacid CoA transferase deficiency, MIM#245050
P3H1	BIALLELIC	Osteogenesis imperfecta, type VIII, (MIM# 610915)

PAH	BIALLELIC	Phenylketonuria, MIM#261600
PALB2	BIALLELIC	Fanconi anemia, complementation group N, MIM# 610832
PAX3	MONOALLELIC	Waardenburg syndrome, type 1, OMIM 193500
PAX8	MONOALLELIC	Hypothyroidism, congenital, due to thyroid dysgenesis or hypoplasia, MIM#218700
PC	BIALLELIC	Pyruvate carboxylase deficiency, MIM# 266150
PCBD1	BIALLELIC	Hyperphenylalaninemia, BH4-deficient, D, MIM#264070
PCCA	BIALLELIC	Propionic acidaemia, MIM#606054
PCCB	BIALLELIC	Propionicacidaemia, MIM#606054
PCDH15	BIALLELIC	Usher syndrome, type 1F 602083, Deafness, autosomal recessive 23 609533
PCSK9	MONOALLELIC	Hypercholesterolaemia, familial, 3, MIM# 603776
PDHA1	X-LINKED: hemizygous mutation in males	Pyruvate dehydrogenase E1-alpha deficiency, MIM# 312170
PDHB	BIALLELIC	Pyruvate dehydrogenase E1-beta deficiency, MIM#614111
PDHX	BIALLELIC	Lactic acidaemia due to PDX1 deficiency, MIM# 245349
PDP1	BIALLELIC	Pyruvate dehydrogenase phosphatase deficiency, MIM# 608782
PDX1	BIALLELIC	Pancreatic agenesis, MIM# # 260370
PDZD7	BIALLELIC	Deafness, autosomal recessive 57, MIM# 618003;Usher syndrome, type IIC, GPR98/PDZD7 digenic, MIM# 605472
PGM1	BIALLELIC	Congenital disorder of glycosylation, type It, MIM#614921
PGM3	BIALLELIC	Immunodeficiency 23, MIM#615816
PHEX	X-LINKED: hemizygous mutation in males	Hypophosphatemic rickets, X-linked dominant, MIM#307800
PHGDH	BIALLELIC	Phosphoglycerate dehydrogenase deficiency, MIM#601815
PHKA2	X-LINKED: hemizygous mutation in males	Glycogen storage disease, type IXa1 and a2, MIM# 306000
PHKB	BIALLELIC	Phosphorylase kinase deficiency of liver and muscle, autosomal recessive 261750;Glycogen storage disease IXb, MONDO:0009868
PHKG2	BIALLELIC	Glycogen storage disease IXc, MIM# 613027
PIK3CD	BOTH monoallelic and biallelic	Immunodeficiency 14B, autosomal recessive, MIM# 619281;Immunodeficiency 14A, autosomal dominant, MIM# 615513
PIK3R1	BOTH monoallelic and biallelic	Agammaglobulinemia 7, autosomal recessive, MIM# 615214;Immunodeficiency 36, MIM#616005
PKLR	BIALLELIC	Pyruvate kinase deficiency, MIM#266200
PLG	BIALLELIC	Plasminogen deficiency, type I, MIM# 217090
PLPBP	BIALLELIC	Epilepsy, early-onset, vitamin B6-dependent, MIM#617290
PLS3	X-LINKED: hemizygous mutation in males	Bone mineral density QTL18, osteoporosis - MIM#300910
PNP	BIALLELIC	Immunodeficiency due to purine nucleoside phosphorylase deficiency MIM#613179
PNPO	BIALLELIC	Pyridoxamine 5'-phosphate oxidase deficiency, MIM# 610090
POLE	BIALLELIC	IMAGE-I syndrome, MIM#618336
POMC	BIALLELIC	Obesity, adrenal insufficiency, and red hair due to POMC deficiency MIM#609734
POR	BIALLELIC	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis, MIM#201750;Disordered steroidogenesis due to cytochrome P450 oxidoreductase, MIM# 613571
POU1F1	BOTH monoallelic and biallelic	Pituitary hormone deficiency, combined, 1 MIM# 613038
POU3F4	X-LINKED: hemizygous mutation in males	Deafness, X-linked 2, MIM#304400
PPOX	BIALLELIC	Variegate porphyria, childhood-onset, MIM# 620483
PRDX1	Other	Methylmalonic aciduria and homocystinuria, cblC type, digenic MIM#277400
PRF1	BIALLELIC	Haemophagocytic lymphohistiocytosis, familial, 2, MIM#603553
PRKAR1A	MONOALLELIC	Carney complex, type 1, MIM# 160980
PRKDC	BIALLELIC	Immunodeficiency 26, with or without neurologic abnormalities, MIM#615966
PROP1	BIALLELIC	Pituitary hormone deficiency, combined, 2, MIM#262600
PSTPIP1	MONOALLELIC	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne, MIM# 604416
PTCH1	MONOALLELIC	Basal cell nevus syndrome, MIM# 109400
PTF1A	BIALLELIC	Pancreatic and cerebellar agenesis, MIM#609069;Pancreatic agenesis 2, MIM#615935
PTPRC	BIALLELIC	Severe combined immunodeficiency, T cell-negative, B-cell/natural killer-cell positive MIM# 608971
PTPRQ	BOTH monoallelic and biallelic	Deafness, autosomal recessive 84A, MIM# 613391;Deafness, autosomal dominant 73, MIM# 617663
PTS	BIALLELIC	Hyperphenylalaninemia, BH4-deficient, A, MIM#261640
PYGL	BIALLELIC	Glycogen storage disease VI, MIM# 232700

QDPR	BIALLELIC	Dihydropteridine reductase deficiency, MIM#261630
RAB27A	BIALLELIC	Griscelli syndrome, MIM#607624
RAC2	MONOALLELIC	Immunodeficiency 73B with defective neutrophil chemotaxis and lymphopenia MIM# 618986
RAG1	BIALLELIC	Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity MIM# 609889;Combined cellular and humoral immune defects with granulomas MIM# 233650;Omenn syndrome MIM# 603554;Severe combined immunodeficiency, B cell-negative MIM# 601457
RAG2	BIALLELIC	Omenn syndrome MIM# 603554;Severe combined immunodeficiency, B cell-negative MIM# 601457;Combined cellular and humoral immune defects with granulomas MIM# 233650
RAPSN	BIALLELIC	Myasthenic syndrome, congenital, 11, associated with acetylcholine receptor deficiency (MIM#616326)
RASGRP1	BIALLELIC	Immunodeficiency 64 (MIM#618534)
RB1	MONOALLELIC	Retinoblastoma, MIM# 180200
RDX	BIALLELIC	Deafness, autosomal recessive 24, MIM# 611022
REST	MONOALLELIC	{Wilms tumor 6, susceptibility to}, MIM# 616806
RET	MONOALLELIC	Multiple endocrine neoplasia IIB;Multiple endocrine neoplasia IIA
RFX5	BIALLELIC	Bare lymphocyte syndrome, type II, complementation group C MIM# 209920;Bare lymphocyte syndrome, type II, complementation group E MIM# 209920
RFXANK	BIALLELIC	MHC class II deficiency, complementation group B, MIM#209920
RFXAP	BIALLELIC	Bare lymphocyte syndrome, type II, complementation group D MIM# 209920
RMRP	BIALLELIC	Cartilage-hair hypoplasia MIM#250250
RNPC3	BIALLELIC	Pituitary hormone deficiency, combined or isolated, 7, MIM# 618160
RPE65	BIALLELIC	Leber congenital amaurosis 2 MIM#204100;Retinitis pigmentosa 20 MIM#613794
RPL11	MONOALLELIC	Diamond-Blackfan anaemia, MIM#612562
RPL15	MONOALLELIC	Diamond-Blackfan anaemia 12 , MIM#615550
RPL35A	MONOALLELIC	Diamond-Blackfan anaemia 5, MIM#612528
RPL5	MONOALLELIC	Diamond-Blackfan anaemia, MIM#612561
RPS10	MONOALLELIC	Diamond-Blackfan anaemia 9, MIM#613308
RPS17	MONOALLELIC	Diamond-Blackfan anaemia, MIM#612527
RPS19	MONOALLELIC	Diamond-Blackfan anaemia, MIM#105650
RPS24	MONOALLELIC	Diamond-Blackfan anaemia, MIM#610629
RPS26	MONOALLELIC	Diamond-Blackfan anaemia, MM#613309
RPS7	MONOALLELIC	Diamond-Blackfan anaemia 8, MIM#612563
RUNX1	MONOALLELIC	Platelet disorder, familial, with associated myeloid malignancy, MIM# 601399
RYR1	MONOALLELIC	{Malignant hyperthermia susceptibility 1} MIM#145600
RYR2	MONOALLELIC	Arrhythmogenic right ventricular dysplasia 2;Ventricular tachycardia, catecholaminergic polymorphic
S1PR2	BIALLELIC	Deafness, autosomal recessive 68, MIM# 610419
SAMD9	MONOALLELIC	MIRAGE syndrome, MIM#617053
SAMD9L	MONOALLELIC	Ataxia-pancytopenia syndrome, MIM# 159550
SAR1B	BIALLELIC	Chylomicron retention disease, MIM# 246700
SBDS	BIALLELIC	Shwachman-Diamond syndrome, MIM# 260400
SCNN1A	BIALLELIC	Pseudohypoaldosteronism, type I, MIM# 264350
SCNN1B	BIALLELIC	Pseudohypoaldosteronism, type I MIM# 264350
SCNN1G	BIALLELIC	Pseudohypoaldosteronism, type I, MIM#264350
SERPINF1	BIALLELIC	Osteogenesis imperfecta, type VI, MIM# 613982
SERPINH1	BIALLELIC	Osteogenesis imperfecta, type X, MIM#613848
SGPL1	BIALLELIC	Nephrotic syndrome, type 14 MIM#617575
SH2D1A	X-LINKED: hemizygous mutation in males	Lymphoproliferative syndrome, X-linked, 1, MIM# 308240
SI	BIALLELIC	Sucrase-isomaltase deficiency, congenital, MIM#222900
SLC12A1	BIALLELIC	Bartter syndrome, type 1, MIM# 601678
SLC18A2	BIALLELIC	Parkinsonism-dystonia, infantile, 2, MIM# 618049
SLC18A3	BIALLELIC	Myasthenic syndrome, congenital, 21, presynaptic, MIM#617239
SLC19A2	BIALLELIC	Thiamine-responsive megaloblastic anemia syndrome, MIM# 249270
SLC19A3	BIALLELIC	Thiamine metabolism dysfunction syndrome 2 (biotin- or thiamine-responsive encephalopathy type 2), MIM# 607483

SLC22A5	BIALLELIC	Carnitine deficiency, systemic primary, MIM# 212140, MONDO:0008919
SLC25A13	BIALLELIC	Citrullinemia, type II, neonatal-onset, MIM# 605814
SLC25A15	BIALLELIC	Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome, MIM#238970
SLC25A19	BIALLELIC	Thiamine metabolism dysfunction syndrome 4 (progressive polyneuropathy type), MIM#613710
SLC25A20	BIALLELIC	Carnitine-acylcarnitine translocase deficiency, MIM#212138
SLC25A38	BIALLELIC	Anemia, sideroblastic, 2, pyridoxine-refractory, MIM# 205950
SLC26A3	BIALLELIC	Diarrhoea 1, secretory chloride, congenital, MIM# 214700
SLC26A4	BIALLELIC	Deafness, autosomal recessive 4, with enlarged vestibular aqueduct 600791;Pendred syndrome 274600
SLC26A7	BIALLELIC	Congenital hypothyroidism, MONDO:0018612, SLC26A7-related
SLC2A1	BOTH monoallelic and biallelic	GLUT1 deficiency syndrome 2, childhood onset, 612126;{Epilepsy, idiopathic generalized, susceptibility to, 12}, MIM#614847;GLUT1 deficiency syndrome 1, infantile onset, severe, 606777
SLC30A10	BIALLELIC	Hypermanganesemia with dystonia 1, MIM# 613280
SLC34A3	BIALLELIC	Hypophosphatemic rickets with hypercalciuria, MIM#241530
SLC35A2	X-LINKED: hemizygous mutation in males	Congenital disorder of glycosylation, type IIm, MIM #300896
SLC37A4	BOTH monoallelic and biallelic	Glycogen storage disease Ib, MIM# 232220;Glycogen storage disease Ic, MIM# 232240;Congenital disorder of glycosylation, type IIw, MIM# 619525
SLC39A4	BIALLELIC	Acrodermatitis enteropathica, MIM# 201100
SLC39A7	BIALLELIC	Agammaglobulinaemia 9, autosomal recessive, MIM# 619693
SLC39A8	BIALLELIC	Congenital disorder of glycosylation, type IIn , MIM#16721
SLC46A1	BIALLELIC	Folate malabsorption, hereditary, MIM# 229050
SLC4A1	BIALLELIC	Distal renal tubular acidosis 4 with haemolytic anaemia MIM# 611590
SLC52A2	BIALLELIC	Brown-Vialetto-Van Laere syndrome 2, MIM# 614707
SLC52A3	BIALLELIC	Brown-Vialetto-Van Laere syndrome 1, MIM# 211530
SLC5A1	BIALLELIC	Glucose/galactose malabsorption, MIM# 606824
SLC5A5	BIALLELIC	Thyroid dyshormonogenesis 1, MIM# 274400
SLC5A6	BIALLELIC	Neurodegeneration, infantile-onset, biotin-responsive, MIM# 618973
SLC5A7	BIALLELIC	Myasthenic syndrome, congenital, 20, presynaptic, MIM# 617143
SLC7A7	BIALLELIC	Lysinuric protein intolerance, MIM# 222700
SLITRK6	BIALLELIC	Deafness and myopia MIM#221200
SLX4	BIALLELIC	Fanconi anaemia, complementation group P, MIM# 613951
SMAD2	MONOALLELIC	Loeys-Dietz syndrome 6, MIM# 619656
SMAD3	MONOALLELIC	Loeys-Dietz syndrome 3, MIM# 613795
SMARCD2	BIALLELIC	Specific granule deficiency 2 MIM#617475
SMN1	BIALLELIC	Spinal muscular atrophy type 1, MIM#253300
SMPD1	BIALLELIC	Niemann-Pick disease, type A, MIM# 257200;Niemann-Pick disease, type B, MIM# 607616
SNX10	BIALLELIC	Osteopetrosis, autosomal recessive 8 MIM#615085
SP110	BIALLELIC	Hepatic veno-occlusive disease with immunodeficiency MIM#235550
SPR	BIALLELIC	Dystonia, dopa-responsive, due to sepiapterin reductase deficiency, MIM# 612716
SRP54	MONOALLELIC	Neutropenia, severe congenital, 8, autosomal dominant, MIM# 618752
STAR	BIALLELIC	Congenital lipoid adrenal hyperplasia, MIM#201710
STAT1	BIALLELIC	Immunodeficiency 31B, mycobacterial and viral infections, autosomal recessive MIM#613796
STAT3	MONOALLELIC	Autoimmune disease, multisystem, infantile-onset, 1 MIM# 615952
STIM1	BIALLELIC	Immunodeficiency 10 MIM612783
STK4	BIALLELIC	T-cell immunodeficiency, recurrent infections, autoimmunity, and cardiac malformations MIM#614868
STX11	BIALLELIC	Haemophagocytic lymphohistiocytosis, familial, 4, MIM#603552
STX16	MONOALLELIC, imprinted	Pseudohypoparathyroidism, type IB MIM#603233
STXBP2	BIALLELIC	Hemophagocytic lymphohistiocytosis, familial, 5, MIM# 613101
SYT2	BIALLELIC	Myasthenic syndrome, congenital, 7B, presynaptic, autosomal recessive MIM#619461
TANGO2	BIALLELIC	Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration, MIM# 616878
TAT	BIALLELIC	Tyrosinemia, type II, MIM#276600
TBL1X	X-LINKED: hemizygous mutation in males	Hypothyroidism, congenital, nongoitrous, 8 MIM#301033

TBX19	BIALLELIC	Adrenocorticotropic hormone deficiency, MIM#201400
TCF3	BOTH monoallelic and biallelic	Agammaglobulinaemia 8, autosomal dominant, MIM# 616941;Agammaglobulinaemia 8B, autosomal recessive, MIM# 619824
TCIRG1	BIALLELIC	Osteopetrosis, autosomal recessive 1, MIM# 259700
TCN2	BIALLELIC	Transcobalamin II deficiency MIM# 275350
TECTA	BOTH monoallelic and biallelic	Deafness, autosomal recessive 21 603629;Deafness, autosomal dominant 8/12 601543
TF	BIALLELIC	Atransferrinemia MIM#209300
TG	BIALLELIC	Thyroid dyshormonogenesis 3, MIM# 274700
TGFB2	MONOALLELIC	Loeys-Dietz syndrome 4, MIM#614816
TGFB3	MONOALLELIC	Loeys-Dietz syndrome 5 , MIM#615582
TGFBR1	MONOALLELIC	Loeys-Dietz syndrome 1, MIM# 609192
TGFBR2	MONOALLELIC	Loeys-Dietz syndrome 2, MIM# 610168
TH	BIALLELIC	Tyrosine hydroxylase deficiency, MIM#605407
THRA	MONOALLELIC	Hypothyroidism, congenital, nongoitrous, 6, MIM# 614450
TK2	BIALLELIC	Mitochondrial DNA depletion syndrome 2 (myopathic type), 609560
TMC1	BIALLELIC	Deafness, autosomal recessive 7 MIM#600974
TMEM38B	BIALLELIC	Osteogenesis imperfecta, type XIV , MIM#615066
TMIE	BIALLELIC	Deafness, autosomal recessive 6 MIM#600971
TMPRSS3	BIALLELIC	deafness, autosomal recessive MIM#601072
TNFRSF11A	BIALLELIC	Osteopetrosis, autosomal recessive 7 - MIM# 612301
TP53	MONOALLELIC	Li-Fraumeni syndrome MIM#151623
TPK1	BIALLELIC	Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type) MIM#614458
TPO	BIALLELIC	Thyroid dyshormonogenesis 2A MIM#274500
TPP1	BIALLELIC	Ceroid lipofuscinosis, neuronal, 2 MIM#204500 (Batten disease)
TPRN	BIALLELIC	Deafness, autosomal recessive 79, MIM# 613307
TRHR	BIALLELIC	Hypothyroidism, congenital, nongoitrous, 7, MIM# 618573
TRIM28	MONOALLELIC	Wilms tumour, MONDO:0006058, TRIM28-related
TRIOBP	BIALLELIC	Deafness, autosomal recessive 28, MIM#609823
TRMU	BIALLELIC	Liver failure, transient infantile MIM# 613070
TRPM6	BIALLELIC	Hypomagnesemia 1, intestinal MIM#602014
TSHB	BIALLELIC	Hypothyroidism, congenital, nongoitrous 4, MIM#275100
TSHR	BOTH monoallelic and biallelic	Hypothyroidism, congenital, nongoitrous, 1 - MIM#275200
TTPA	BIALLELIC	Ataxia with isolated vitamin E deficiency MIM#277460
TUBB1	MONOALLELIC	Congenital hypothyroidism, MONDO:0018612, TUBB1-related;Macrothrombocytopenia, autosomal dominant, TUBB1-related, OMIM # 613112
UBE2T	BIALLELIC	Fanconi anaemia, complementation group T, MIM# 616435
UGT1A1	BIALLELIC	Crigler-Najjar syndrome, type I, MIM#218800
UMPS	BIALLELIC	Orotic aciduriaMIM#258900
UNC13D	BIALLELIC	Haemophagocytic lymphohistiocytosis, familial, 3, MIM#608898
UROS	BIALLELIC	Porphyria, congenital erythropoietic MIM#263700
USH1C	BIALLELIC	Usher syndrome type 1 MIM#276904
USH1G	BIALLELIC	Usher syndrome type 1 MIM#606943
USH2A	BIALLELIC	Usher Syndrome Type II MIM#276901
VAMP1	BIALLELIC	Myasthenic syndrome, congenital, 25, MIM# 618323
VDR	BIALLELIC	Rickets, vitamin D-resistant, type IIA MIM#277440
VHL	MONOALLELIC	von Hippel-Lindau syndrome MIM#193300
VKORC1	BIALLELIC	Vitamin K-dependent clotting factors, combined deficiency of, 2 MIM#607473
VPS45	BIALLELIC	Neutropenia, severe congenital, 5, autosomal recessive, MIM#615285
WAS	X-LINKED: hemizygous mutation in males	Neutropenia, severe congenital, X-linked , MIM#300299;Thrombocytopaenia, X-linked, MIM# 313900;Wiskott-Aldrich syndrome, MIM# 301000
WDR1	BIALLELIC	Periodic fever, immunodeficiency, and thrombocytopenia syndrome MIM#150550
WDR72	BIALLELIC	Amelogenesis imperfecta, type IIA3, MIM# 613211;Distal RTA MONDO:0015827
WHRN	BIALLELIC	Usher syndrome, type 2D, MIM# 611383;Deafness, autosomal recessive 31, MIM# 607084
WIPF1	BIALLELIC	Wiskott-Aldrich syndrome 2 MIM#614493
WNK1	MONOALLELIC	Pseudohypoaldosteronism 2C (PHA2C), MIM#614492

WNK4	MONOALLELIC	Pseudohypoaldosteronism, type IIB MIM#614491
WT1	MONOALLELIC	Wilms tumor, type 1, MIM#194070
XIAP	X-LINKED: hemizygous mutation in males	Lymphoproliferative syndrome, X-linked, 2, MIM# 300635
XPA	BIALLELIC	Xeroderma pigmentosum, group A MIM#278700
XPC	BIALLELIC	Xeroderma pigmentosum, group C MIM#278720
ZAP70	BIALLELIC	Immunodeficiency MIM#176947