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Operationalizing the Wilson-Jungner principles for the genomics era: Consensus recommendations from the International Consortium on Newborn Sequencing

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Operationalizing the Wilson-Jungner principles for the genomics era: Consensus recommendations from the International Consortium on Newborn Sequencing

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Abstract

Purpose

For decades, the selection of disorders included in newborn screening (NBS) programs has been guided by principles published by Wilson and Jungner in 1968. As research explores the expansion of conditions included in NBS through genomic sequencing, there is a critical need for updated recommendations to address the opportunities and complexities of genomic data.

Methods

The International Consortium on Newborn Sequencing includes leaders from over 16 research projects investigating genomic NBS across the UK, Europe, USA, and Oceania. Consortium members were invited to participate in a modified Delphi study aggregating opinion on the selection of conditions for genomic NBS through three rounds of online questionnaires, with feedback provided to participants between rounds.

Results

In Round 1, 94 participants completed the questionnaire and 10 of 43 statements reached consensus. In Round 2, 81 participants completed the questionnaire and 14 of 27 statements reached consensus. In Round 3, 68 participants completed the questionnaire and all ten statements reached 72% or more consensus.

Conclusion

The ten consensus recommendations developed in this study can guide future research and public health programs performing genomic NBS. This process also identified key areas of participant discordance, highlighting important topics for future research.

Key Words: Newborn Screening, Gene selection, Genomic sequencing, Delphi Technique

Introduction

Newborn screening (NBS), introduced in the 1960s, is a successful public health intervention that identifies infants at risk for treatable disorders.[1] For nearly six decades, selection of disorders included in NBS programs has been guided by ten principles published by James Wilson and Gunnar Jungner in 1968, which emphasize the inclusion of infant-onset, treatable disorders (Supplementary Table 1).[2] Based on these principles, the United States Health Resources and Services Administration's Recommended Uniform Screening Panel suggests that 38 core and 26 secondary conditions be screened by each state NBS program, and other countries have similar lists.[3] As of 2025, over 800 genetic disorders have treatments and are potential candidates for early detection.[4] Many such disorders cannot be identified through biochemical testing, which has led to growing interest in using genomic sequencing to expand NBS.[1] Genetic information has already been incorporated into population NBS as a first-tier screening test in several jurisdictions[5,6] and several international research studies have explored the feasibility of expanding genomic newborn screening (gNBS) to include hundreds or thousands of other disorders,[7–16] with more studies underway.[17–20] Parents,[21] rare disease specialists,[22] primary care physicians,[23] genetic counselors,[22,24] and the public[25] support the implementation of gNBS for wider detection of disorders similar to those already screened which are largely metabolic and endocrine, severe and treatable. A proportion also supports inclusion of conditions where treatment is limited or supportive. The majority value accuracy of the test over actionability.[26]

Over 30 newborn and pediatric research programs and companies offering gNBS have been developed. While the Wilson-Jungner principles have been utilized as a guide for implementing these studies,[27] they are not applicable to complex genomic information, prompting a need for additional principles to be developed.[28] For instance, some genes can lead to multiple phenotypes, or a spectrum of severity, age of onset, or penetrance making it unclear if they

should be included for screening.[29] Among gNBS programs, there has been tension between maximizing the capabilities of genomic sequencing by screening for thousands of conditions, versus a conservative approach to align with the public health NBS context. This has resulted in limited concordance on which genes and variants should be analyzed and reported.[30–32] As gNBS moves from a research investigation to a public health approach, updated guidelines are needed to identify appropriate disorders for population screening.

The International Consortium on Newborn Sequencing (ICoNS) is a professional organization founded in 2022. It aims to aggregate data from gNBS studies to best implement their findings. The ICoNS gene list subcommittee, which developed this study, was created with the aim of defining principles of gene and variant selection for public health gNBS. The aim of this study was to define principles to guide gene selection for genomic newborn screening in a population health screening context. Other pertinent issues related to gNBS such as universality, equity, accessibility, cost, follow up, consent and data storage were outside the scope of this work and are under active investigation by other subcommittees within ICoNS.

Materials and methods

Study design

The Delphi method provides a transparent process by which a group of experts can reach consensus.[33] It involves iterative rounds of anonymized questionnaires with aggregated results presented between rounds to enable individuals to reflect on collective opinion and refine their own position. Methodology was informed by the Recommendations for the Conducting and REporting of DElphi Studies (CREDES)[34]. Modifications were incorporated to accommodate the participation of a large group of experts and stakeholders located in a broad geographical area. The study was conducted online and included variation in the participants for each round, in contrast to the traditional selection of a fixed group of experts.

Participants

ICoNS membership is available to any individual that identifies as a stakeholder in gNBS. Members are required to disclose their position, expertise and interest in gNBS and financial or conflicting interests at the time of application. Membership falls into the categories of:

- Clinicians involved in genomics or newborn screening. These include clinical geneticists, genetic counselors and physicians. This group includes leaders from each of the large projects investigating gNBS across the UK, Europe, the USA and Oceania (Figure 1).
- Scientists working in both genomics and in traditional newborn screening methods.
- Researchers, including academics from multiple disciplines (medicine, health economics, implementation science, etc.) with an interest or position in a genomic newborn sequencing study.
- Industry, which includes those employed by companies with an interest in genomics, newborn screening or precision medical therapies. This group includes those with financial and commercial interest in gNBS. The consortium actively chose to be inclusive of this group as some are already offering direct to consumer gNBS. This was seen to be mutually beneficial as those with a commercial interest may provide expertise on scaling and automation required to provide population level screening. The consortium membership in return can provide ethical and evidence-based guidance on implementation.

At the time the first Delphi questionnaire was circulated (June 25, 2024), ICoNS had 234 registered members across 28 countries. By the second Delphi questionnaire, the consortium had expanded to 256 members across 28 countries and 27 U.S. states (August 8, 2024) and grew to 270 members across 32 countries and 28 U.S. states by the final Delphi questionnaire

(September 16, 2024). The breakdown of membership is 85% clinicians, scientists and researchers and 15% from industry.

The gene list subcommittee was established in February 2024 and comprises 25 members from 8 countries. The group met monthly via Zoom (March 19, 2024; April 23, 2024; May 28, 2024; July 23, 2024; August 27, 2024) to plan and design the study. The composition of this group was by self-nomination and by invitation with an aim to ensure representation across the different stakeholder groups.

[Place Figure 1]

Questionnaire development

A literature review of criteria for gNBS public health and research programs was completed (Supplementary Table 2). These criteria, along with topics generated by the gene list subcommittee, were utilized to develop a set of 43 statements pertaining to the following categories: age of symptom onset and age of actionability (7 statements), prevalence and gene-disease validity (3 statements), penetrance (5 statements), clinical features of disease (5 statements), variant reporting (8 statements), variant calling and technical interpretation (5 statements), non-genetic confirmatory testing (5 statements), treatment (4 statements), and parental engagement (1 statement). Three to four gene list subcommittee members were tasked with refining statements within each category. The final set of 43 statements were developed into a questionnaire using an online survey tool (REDCap) (Supplementary Note 1).[35,36]

For most statements, participants were offered only “agree” or “disagree” response options to encourage clear answers. For some statements, checkboxes that allowed for multiple selections, a slider with continuous variables, or radio buttons were offered. All questions required a response to continue to the next section. An optional area for free text responses

was included at the end of each category, allowing participants to provide comments, suggestions, or clarifications on their responses.

Per the modified Delphi model, results of the Round 1 questionnaire were collated and presented back to ICoNS members via an online presentation and email. Statements that reached the consensus threshold were integrated into the statements presented in the Round 3 questionnaire (Figure 2). All other statements and free-text responses were utilized to refine, remove, or add questions for the Round 2 questionnaire (Supplementary Note 2). Statements from the Round 2 questionnaire that reached consensus were combined with those from Round 1 and presented as a Round 3 questionnaire (Supplementary Note 3).

[Place Figure 2]

Distribution of questionnaire

The questionnaire was sent by email to all ICoNS members. Participants were asked to consider the statements in the context of public health gNBS, not research programs. Participants were not asked to disclose any identifying data, making all responses anonymous. For this reason, approval from the Institutional Review Board was not required. The questionnaire was piloted before distribution with four individuals who had expertise in medical genetics. These responses were not included in the analysis.

Definition of consensus

There is variation in the literature about what proportion of responses constitutes consensus from the Delphi process.[37] For this process, consensus was defined as ≥85% participant agreement for Round 1, ≥75% for Round 2 and ≥70% for Round 3. Approaching consensus was defined as ≥60% and divided opinion as 41-59% agreement. The threshold for consensus was

set very high in the initial round in order to efficiently identify areas of high agreement or disagreement and focus on more contentious topics to get the highest value out of the process.

Results

Round 1 questionnaire

In Round 1, 94 completed questionnaires were received (40.2% response rate). Ten statements reached consensus, 25 statements were approaching consensus (60-85% consensus) and the remaining 8 statements demonstrated divided opinion below 60% agreement (Figure 3). The statements with the highest consensus included: “Age of symptom onset is an important factor in gene list selection” (96% of participants agreed [n=91]) and “Genes where most disease causing variants are inherited and highly penetrant (for example, deleterious variants in *FBN1* (HGNC:3603), which typically lead to Marfan syndrome (MIM:154700)) should be included” (95% of participants agreed [n=89]) (Supplementary Table 3).

Some statements that were approaching consensus were accompanied by free text responses that allowed the statement to be refined, for example: “Some disorders for which there is not a confirmatory, non-genetic test should be included” (81% of participants agreed [n=70]) with free text statements such as: “*If there is no confirmatory test but you are quite certain about gene-disease validity and a life-saving treatment needs to be administered quickly, confirmatory testing may not be necessary.”* Eight statements that were either approaching consensus or divided were removed based on feedback from free text responses, or due to overlap with other recirculated statements. Two new statements were added after reviewing the free text responses: “Variants associated with disorders that manifest symptoms and require treatment or surveillance only in adulthood (for example, hereditary breast and ovarian cancer): A. Should be reported because a positive result may improve the health of a parent. B. Should be reported

because they are relevant to the child's future health. C. Should not be reported." and "Variants in genes such as *BRCA1* (HGNC:1100), which can cause an autosomal recessive childhood disorder, should only be reported when homozygous or biallelic, even if the monoallelic disease has implications for health."

The most discordant results were in the category of penetrance. For example, "All likely pathogenic and pathogenic variants should be included in newborn screening programs even if the penetrance is not known" (53% of participants agreed [n=50]) and "Low penetrance genotypes may be included for diseases in which the treatment is inexpensive, readily available, and of minimal risk to the well-being of the patient (such as *MYH7* (HGNC:7577) -related cardiomyopathy where echocardiogram surveillance may be recommended)" (57% of participants agreed [n=54]). Seven out of eight of the divided statements were recirculated in the Round 2 questionnaire, and one statement, "All likely pathogenic and pathogenic variants should be included in newborn screening programs even if the penetrance is not known," was removed due to overlap with other recirculated statements.

A total of 59 participants submitted 238 free text responses, which included rationales for the answers selected by participants, feedback on the quality of the question and its wording, and suggestions for future questions. Themes that emerged from the free text responses in the Round 1 questionnaire included the importance of considering the questions for a public health screening context, limited data about penetrance, and the nuances for each gene-disease pair that increase the challenge of creating universal guidelines.

The statement that generated the highest number of free text comments was: "Parents should be given an opportunity to choose which genes are screened in their child." In total, 54 participants (64%) disagreed with this statement. Free text comments in response to this statement included: "*an option for parents to choose would create havoc"* and "*parents can not*

be expected to make decisions about what genes to screen." Multiple free text responses suggested utilizing categories of disease to provide parents' a more informed choice. These responses included: "*if there is choice it should not be on the gene level but perhaps they can opt in for 'less actionable' conditions as a group*" and "*parents can make choices in classes of genes in relation to disease severity and treatment options*."

[Place Figure 3]

Round 2 questionnaire

In Round 2, 81 participants completed the questionnaire (31.6% response rate). Of 27 statements, 14 reached consensus, 7 were approaching consensus and the remaining 6 demonstrated divided opinion (Supplementary Table 4). There were 159 free text responses from 42 participants.

Several statements that were approaching consensus in Round 1 achieved consensus in Round 2. These included: "If there are well-established genotype-phenotype correlations between variants in a gene and the onset of disease (for example, in lysosomal acid lipase deficiency (MIM:620151)), only variants associated with the childhood onset form of the condition should be included" (75% of participants agreed [n=60]), "Different sets of genes or variants should be queried at various ages throughout a person's lifespan" (80% of participants agreed [n=64]), "If meeting all other inclusion criteria, highly prevalent monogenic disorders (such as familial hypercholesterolemia (MIM:143890), G6PD deficiency (MIM:300908)) should be included in genomic newborn screening, even though it would result in increased follow-up burden for healthcare providers" (87% of participants agreed [n=69]), and "Moderate penetrance genotypes may be reported if there is non-genetic confirmatory testing for the disease available. (For example, variants in *HFE* (HGNC:4886), which may cause hemochromatosis

(MIM:235200), can be adjudicated with laboratory tests such as a serum ferritin and transferrin saturation)" (89% of participants agreed [n=66]).

Among the eight statements with divided opinion from Round 1 that were recirculated in Round 2, one reached consensus in Round 2: "Variants associated with mild differences in body structure and/or function should be included (for example, variants in *UGT1A1* (HGNC:12530) related to Gilbert syndrome (MIM:143500))" (40% of participants agreed in Round 1 [n=38], this fell to 14% agreement in round 2). To summarize, 86% [n=64] of participants thought screening for mild conditions should not be included. Six statements with divided opinion in Round 1 had responses that were approaching consensus in Round 2. Only one statement that demonstrated divided opinion in Round 1 continued to demonstrate divided opinion in Round 2: "For genes associated with recessive disorders, if a single pathogenic or likely pathogenic variant is identified, the gene should also be queried for variants of uncertain significance and these should be reported" (50% of participants agreed in Round 1 [n=45], 42% of participants agreed in Round 2 [n=31]) (Table 1).

[Place Table 1]

Free text responses in Round 2 highlighted additional themes, some of which were not observed in Round 1. For example, several participants noted that healthcare resources should not be a significant factor in determining which conditions to screen, as each country's healthcare system will adapt over time and re-allocate care as needed, *"[W]e should not let the burden of healthcare providers stop us from doing the right thing for NBS. Such burden can be short term (i.e. in the long term, care burden for G6PD patients would decrease), and there are other ways to address resource issues if well anticipated."*

A total of 24 statements reached consensus across Rounds 1 and 2. Two additional statements were within 1% of consensus in Round 2. Statements which were beyond the scope of gene list

curation (n=5), for example those regarding the reanalysis of genomic data across the lifespan, were not included in the Round 3 questionnaire. Statements that contained repetitive information or granular detail were refined, for example those relating to carrier status for recessive conditions and adult-onset symptoms in individuals with heterozygous variants in autosomal recessive disease genes were combined into one statement.

Round 3 questionnaire

The remaining 19 statements that had achieved consensus in the prior two rounds were combined and edited by the subcommittee leaders to produce ten final statements, which were circulated as the Round 3 questionnaire (Table 2). Examples of combined statements include those relating to non-confirmatory genetic testing and penetrance (Supplementary Table 4) where 4 statements reached consensus and were readily combined into a single statement "Variants with incomplete penetrance should only be reported if there is a non-genetic confirmatory test expected to be positive before initiation of treatment, or if the disease surveillance or management presents minimal risk."Statements that had not achieved consensus by Round 2 were not included in Round 3. In Round 3, 68 participants completed the questionnaire (25.2% response rate) and all statements reached 72% or greater levels of consensus. Statements were compared to the Wilson and Juenger principles (Table 3).

[Place Table 2]

[Place Table 3]

Discussion

This study presents ten statements based on expert consensus that provide detail and guidance on the selection of conditions and reporting of variants for gNBS programs, which may be used to guide future global public health programs. Although the Wilson-Jungner principles[2] have historically provided a framework by which to choose disorders for NBS, the growing number of

targeted therapies for genetic disorders and the complexities of genomic information provide an opportunity to consider a new, more nuanced set of recommendations.[4,27] Studies have demonstrated that gNBS has the potential to improve detection rates of genetic disease in apparently healthy infants,[38] without causing undue psychosocial harm or damage to infant-parent bonding.[39] However, selection of appropriate genes, conditions, and variants will be critical to the successful implementation of gNBS as a public health approach. Successful implementation will depend not solely on detection rate, but on overall health benefit for individuals and families. Participants' consensus centered around several key themes. Participants indicated that gNBS, like NBS performed through biochemical methods, should continue to focus on severe diseases that are urgent and treatable with intervention in early childhood. This reflects findings from another recent Delphi focussed on treatability in the context of gNBS which concluded that the expected benefit/burden ratio of early treatment should be positive and result in a significant health outcome.[40] Importantly, emphasis was placed not on the time when symptoms were expected to emerge, but when surveillance or treatment for the disorder might begin; for example, Alport syndrome (MIM: 301050, 203780, 620536, 104200) typically leads to adult-onset kidney failure and hearing loss, but anti-hypertensive medications are recommended for use in early childhood to prevent disease progression.[41] Also aligned with Wilson and Jungner, who stated that uncommon disorders could be screened so long as “very serious consequences [were expected] if [the disease was] not discovered and treated very early in life,” these guidelines emphasize that the prevalence of the disease is not relevant, particularly when many conditions can be screened simultaneously.[2] However, in contrast to the Wilson-Jungner principles, which states that there “should be a suitable test or examination” to confirm the presence of disease, participants indicated that a non-molecular diagnostic test does not necessarily need to be available following a positive gNBS result and prior to treatment initiation if the associated treatment is low-risk or inexpensive. This suggestion that genetic information is in some cases sufficient to guide care

would allow expansion of gNBS to a wider range of disorders, including hereditary cancer predisposition syndromes affecting young children or neurodevelopmental disorders that may not be symptomatic in infancy.

This premise needs to be balanced with the potential harm of medicalizing a healthy infant and the burden that anticipatory care can place on families. This is recognized by the consensus that mild conditions, even if they can be readily detected, should still be excluded from newborn screening programs. It also provides the basis for the suggestions for future research in which penetrance and expression data are going to be key to responsible reporting of variants in future programs.

Participants demonstrated divided opinions on a range of topics, which are important areas for future research. Several of the categories are specific to genomic information, for example the reporting of variants of uncertain significance (VUS) when found in the context of a biallelic pathogenic (P) or likely pathogenic (LP) variant. Ongoing gNBS studies approach this challenge differently; for example, in the GUARDIAN study,[12] when infants with a single P or LP variant in a gene associated with autosomal recessive inheritance are identified, their samples are also evaluated for some VUS in the same gene, and second-tier non-molecular orthogonal testing is performed when available. The downstream sensitivity and specificity of this approach, compared with the reporting of P or LP variants alone, is an important area of investigation. One long-term challenge highlighted by this study is the lack of accurate data regarding disease penetrance and expressivity. Because individuals with most genetic conditions have historically been identified after the onset of symptoms, the individual risk to develop phenotypic manifestations often remains unknown based solely on the variants identified. Currently, studies of individuals at risk for genetic disease from biobanks and large datasets may provide insights into penetrance; however, most of these biobanks are exclusively composed of adults.[29,42–44] Furthermore, given the large number of different combinations of alleles for biallelic conditions,

there may not be empirical data to guide a particular combination observed for the first time in gNBS. The medical outcomes of infants from gNBS pilot studies will provide additional longitudinal information in this area.[38]

All elements of gNBS introduction such as health economics, the impact on care pathways and evolution of precision planning and the impact on individual families require significantly larger studies to generate evidence. These studies are underway and funding bodies have recognized the need for this data to implement responsible and acceptable gNBS programs. These guidelines are timely to provide guidance on how to select conditions and variants to report in this context.

Limitations to this study include a modification of the classic Delphi process. This was chosen to maximize participation from a large group of experts and stakeholders. Typically, in a Delphi model, the same participants are selected for their expertise and invited in each round. The group chose to modify this and distribute questionnaires to all ICoNS participants for each round. This meant the group was dynamic, as the membership grew over the course of the study and perhaps in line with this the participation rate was lower than expected for a standard Delphi methodology. The diversity of membership, including those from industry, is viewed as a strength by the study team but could be viewed as a conflict of interest. Being inclusive of the entire membership, provided representation from a wide range of skills and perspectives but not necessarily all relevant parties. Given gNBS is a new area of research, and the implications are relevant to the whole population, preference was given to include as many voices as possible rather than a smaller group of potential experts.

gNBS holds great promise to improve the health of newborns and children, but is a new frontier that requires an updated version of the guidelines that have been used in population screening in the past. The ten recommendations developed in this study can guide further efforts in this

area, including more granular guidance and approaches to building consensus on national and international scale.

Data Availability: The published article includes all datasets generated or analyzed during this study.

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Author Contributions: Conceptualization: D.A., M.B., J.B., J.S.B., F.B., W.K.C., H.L.C., L.D., D.J.E., N.E., L.F., A.F., J.G., M.H.G., N.B.G., J.M.G., K.G., R.B.P., N.S., Z.S., K.L.S., P.T., M.T., J.Y. Data curation: L.D., N.B.G., R.H., J.Y. Formal analysis: L.D., N.B.G., J.Y. Funding acquisition: N.E. Investigation: D.A., M.B., J.B., J.S.B., F.B., W.K.C., H.L.C., L.D., D.J.E., N.E., L.F., A.F., J.G., M.H.G., N.B.G., J.M.G., K.G., R.B.P., N.S., Z.S., K.L.S., P.T., M.T., J.Y. Methodology: D.A., M.B., J.B., J.S.B., F.B., W.K.C., H.L.C., L.D., D.J.E., N.E., L.F., A.F., J.G., M.H.G., N.B.G., J.M.G., K.G., R.B.P., N.S., Z.S., K.L.S., P.T., M.T., J.Y. Supervision: D.B., N.B.G., R.C.G. Visualization: N.B.G., T.M., J.Y. Writing-original draft: L.D., N.B.G., J.Y. Writing-review & editing: All authors.

Ethics Declaration: This study involved responses from 94 participants who completed the questionnaire, and 10 of 43 statements reached consensus. As no individualized or patient-specific data were used, Institutional Review Board (IRB) or Research Ethics Committee (REC) approval were not required.

Conflict of Interest: D.A. is a board member for Gene People. W.K.C is on the board of directors for Prime Medicine. R.C.G. receives compensation for advising the following companies: Allelica, Atria, Fabric, Genomic Life and Juniper Genomics; and is co-founder of Genome Medical and Nurture Genomics. K.S. is a consultant at Nurture Genomics. P.T. is on the board of directors for PlumCare RWE, Inc.

Supplemental Information:

Supplement A: International Consortium on Newborn Sequencing (ICoNS) authors
Supplementary Table 1. Wilson and Jungner Principles for Screening
Supplementary Table 2. Gene list criteria in literature review of NBS and gNBS research programs.
Supplementary Note 1. PDF of Round 1 Questionnaire
Supplementary Note 2. PDF of Round 2 Questionnaire
Supplementary Note 3. PDF of Round 3 Questionnaire
Supplementary Table 3. Statements circulated in Delphi Round 1 (n = 43)
Supplementary Table 4. Statements circulated in Delphi Round 2 (n = 27).
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Figures

Figure 1. Map of global gNBS research programs represented in ICoNS. Countries of research programs are indicated in parentheses. Intended enrollment sizes are indicated where available. Shading on map refers to the locations of individual ICoNS members.

Figure 2. Delphi process for updating gene and disorder selection criteria for population-wide genomic newborn screening. Statements related to gNBS gene and disorder selection criteria were distributed through three rounds of questionnaires. Consensus statements from the first two rounds were compiled to produce ten consensus guidelines.

Figure 3. Summary of consensus levels across Delphi rounds. 43 statements were distributed in the Round 1 Questionnaire across 10 different categories related to gNBS. 27 statements were circulated in the Round 2 Questionnaire.

Table 2. International Consortium on Newborn Sequencing (ICoNS) consensus guidelines for gene selection in genomic newborn screening programs.

Consensus statements
1. Variants should be associated with a disease for which treatment or surveillance should be initiated before age 5.
2. Disorders should have a treatment that greatly improves the severity of disease.
3. Variants associated with mild differences in body structure and/or function should not be reported.
4. Variants should be included, even if the associated disorder is unlikely to escape detection by a clinical team.
5. Sequencing of the infant's sample alone is a sufficient sequencing approach for genomic newborn screening.
6. Variants with incomplete penetrance should only be reported if there is a non-genetic confirmatory test expected to be positive before initiation of treatment, or if the disease surveillance or management presents minimal risk.
7. Genes in which the well described variants cannot easily be detected on sequencing should be included in genomic newborn screening, because other variants may be ascertained.
8. Disease prevalence should not be a criteria for variant reporting in a population.
9. Carrier status of recessive disorders should not be reported.
10. If only variants of uncertain significance are found in a gene, no variants should be reported.

Table 3. International Consortium on Newborn Sequencing (ICoNS) consensus guidelines for gene selection in genomic newborn screening programs as compared with the original Wilson-Jungner principles.

ICoNS consensus statements	Corresponding Wilson-Jungner principle(s)	Implications for gNBS
1. Variants associated with *mild* differences in body structure and/or function should not be reported. 2. Disease prevalence should not be a criteria for variant reporting in a population. 3. Carrier status of recessive disorders should not be reported.	1. The condition should be an important health problem.	Wilson and Jungner wrote that rare disorders like PKU are suitable for screening due to the severe consequences of delayed treatment.[1] ICoNS members agreed that the prevalence of a genetic condition should not determine its inclusion in gNBS. ICoNS members also agreed that genetic variants linked to mild conditions, such as Gilbert syndrome, and reproductive risks without personal medical implications, like carrier status for AR disorders, should be excluded. Importantly, ICoNS reached consensus that AD variants associated with adult-onset disorders in genes that are also linked to AR childhood-onset disorders (e.g., *BRCA1*, which causes both AD HBOC and AR Fanconi anemia) should not be reported on gNBS.
4. Disorders should have a treatment that greatly improves the severity of disease.	2. There should be an accepted treatment for patients with recognized disease. 3. Facilities for diagnosis and treatment should be available.	ICoNS members agreed that there should be a treatment available, and that a non-genomic confirmatory test is not required for a gene to be suitable for screening. ICoNS members did not reach consensus on whether a condition should be included in gNBS if the appropriate treatment is unavailable in the country in which screening is being performed.
	4. There should be a recognizable latent or early symptomatic stage.	A latent or early symptomatic stage was not considered necessary for many genetic disorders to be included in gNBS.
5. Sequencing of the infant's	5. There should be a suitable test	ICoNS members agreed that

sample alone (e.g., no parental DNA samples needed) is a sufficient sequencing approach for genomic newborn screening. 6. Genes in which the well described variants cannot easily be detected on sequencing should be included in genomic newborn screening, because other variants may be ascertained.	or examination. 6. The test should be acceptable to the population.	sequencing the infant's sample alone, rather than duo or trio sequencing with parents, is sufficient and practical. For some conditions, such as hemophilia A, technologies like ES may fail to detect common genetic changes underlying the disease (e.g., inversions). Despite this limitation, ICoNS members agreed that these genes should still be included in gNBS to identify individuals with other P or LP variants.
	7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.	The natural history of most genetic disorders is poorly understood, particularly because they are individually rare and early research often focuses on the most severely affected individuals.
7. Variants should be associated with a disease for which treatment or surveillance should be initiated before age 5. 8. Variants with incomplete penetrance should only be reported if there is a non-genetic confirmatory test expected to be positive before initiation of treatment, or if the disease surveillance or management presents minimal risk. 9. If only variants of uncertain significance are found in a gene, no variants should be reported. 10. Variants should be included, even if the associated disorder is unlikely to escape detection by a clinical team.	8. There should be an agreed policy on whom to treat as patients.	ICoNS members agreed that the existence of an orthogonal, non-molecular confirmatory test was unnecessary for inclusion in gNBS, except in cases where the variant or disorder is known to have incomplete penetrance. They emphasized that as long as at least one variant in a gene is a P or LP (e.g., not two VUS in a gene with AR inheritance) and is associated with a condition requiring treatment or surveillance before age 5, it should be included. Additionally, ICoNS members agreed that variants linked to disorders such as achondroplasia, which present with physical findings at birth, should still be included.
	9. The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole.	A separate ICoNS subcommittee is dedicated to assessing the economic considerations related to gNBS.
	10. Case finding should be a continuing process and not a "once and for all" process.	ICoNS members did reach consensus on the statement, "Different sets of genes or

		variants should be queried at various ages throughout a person's lifespan," but this area was considered beyond the scope of gene selection for gNBS.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ES, exome sequencing; gNBS, genomic newborn screening; HBOC, hereditary breast and ovarian cancer; ICoNS, International Consortium of Newborn Sequencing; PKU, phenylketonuria; P, pathogenic; LP, likely pathogenic

Table 2. International Consortium on Newborn Sequencing (ICoNS) consensus guidelines for gene selection in genomic newborn screening programs.

Consensus statements
1. Variants should be associated with a disease for which treatment or surveillance should be initiated before age 5.
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5. Sequencing of the infant's sample alone is a sufficient sequencing approach for genomic newborn screening.
6. Variants with incomplete penetrance should only be reported if there is a non-genetic confirmatory test expected to be positive before initiation of treatment, or if the disease surveillance or management presents minimal risk.
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4. Disorders should have a treatment that greatly improves the severity of disease.	2. There should be an accepted treatment for patients with recognized disease. 3. Facilities for diagnosis and treatment should be available.	ICoNS members agreed that there should be a treatment available, and that a non-genomic confirmatory test is not required for a gene to be suitable for screening. ICoNS members did not reach consensus on whether a condition should be included in gNBS if the appropriate treatment is unavailable in the country in which screening is being performed.
	4. There should be a recognizable latent or early symptomatic stage.	A latent or early symptomatic stage was not considered necessary for many genetic disorders to be included in gNBS.
5. Sequencing of the infant's	5. There should be a suitable test	ICoNS members agreed that

sample alone (e.g., no parental DNA samples needed) is a sufficient sequencing approach for genomic newborn screening. 6. Genes in which the well described variants cannot easily be detected on sequencing should be included in genomic newborn screening, because other variants may be ascertained.	or examination. 6. The test should be acceptable to the population.	sequencing the infant's sample alone, rather than duo or trio sequencing with parents, is sufficient and practical. For some conditions, such as hemophilia A, technologies like ES may fail to detect common genetic changes underlying the disease (e.g., inversions). Despite this limitation, ICoNS members agreed that these genes should still be included in gNBS to identify individuals with other P or LP variants.
	7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.	The natural history of most genetic disorders is poorly understood, particularly because they are individually rare and early research often focuses on the most severely affected individuals.
7. Variants should be associated with a disease for which treatment or surveillance should be initiated before age 5. 8. Variants with incomplete penetrance should only be reported if there is a non-genetic confirmatory test expected to be positive before initiation of treatment, or if the disease surveillance or management presents minimal risk. 9. If only variants of uncertain significance are found in a gene, no variants should be reported. 10. Variants should be included, even if the associated disorder is unlikely to escape detection by a clinical team.	8. There should be an agreed policy on whom to treat as patients.	ICoNS members agreed that the existence of an orthogonal, non-molecular confirmatory test was unnecessary for inclusion in gNBS, except in cases where the variant or disorder is known to have incomplete penetrance. They emphasized that as long as at least one variant in a gene is a P or LP (e.g., not two VUS in a gene with AR inheritance) and is associated with a condition requiring treatment or surveillance before age 5, it should be included. Additionally, ICoNS members agreed that variants linked to disorders such as achondroplasia, which present with physical findings at birth, should still be included.
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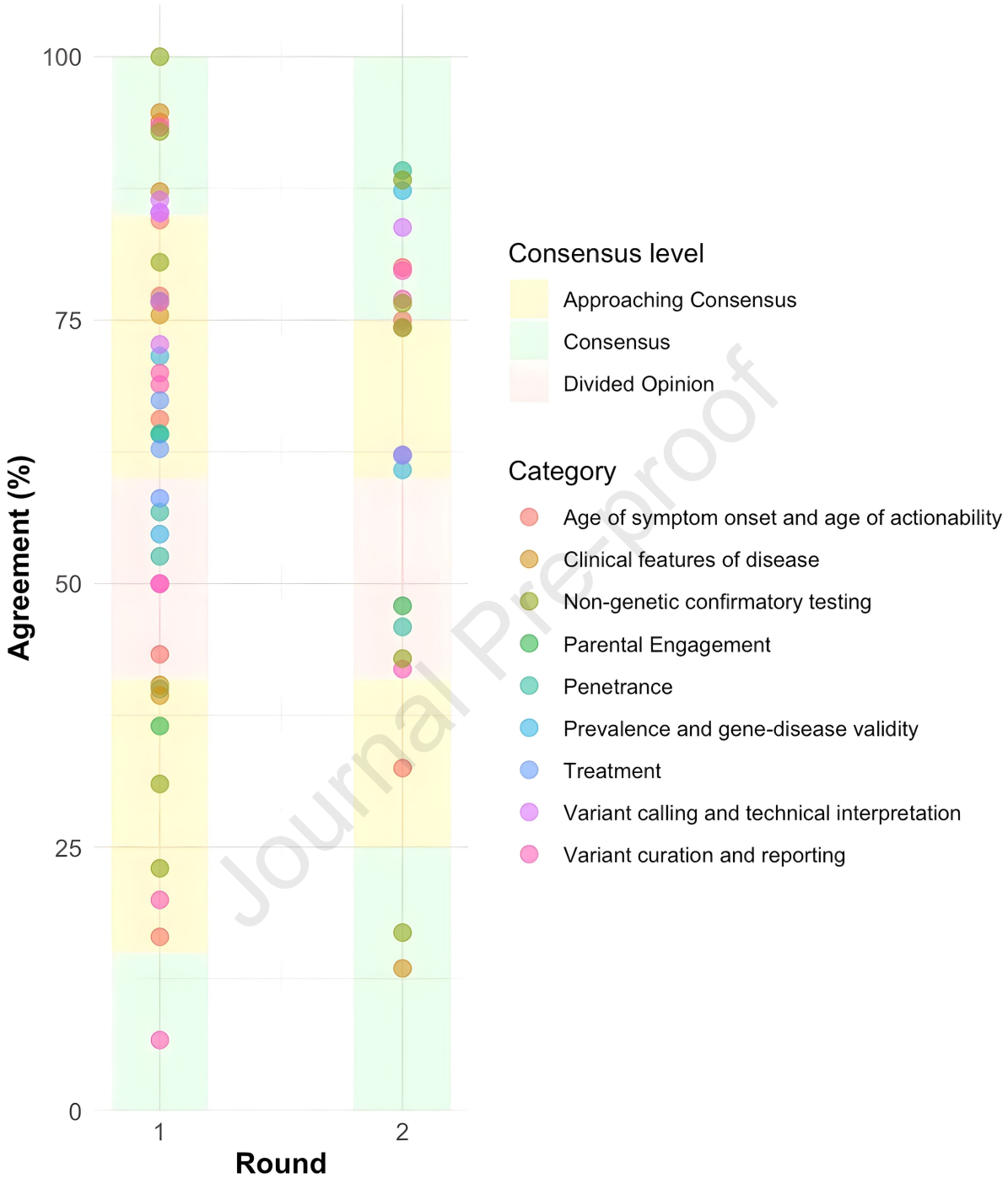
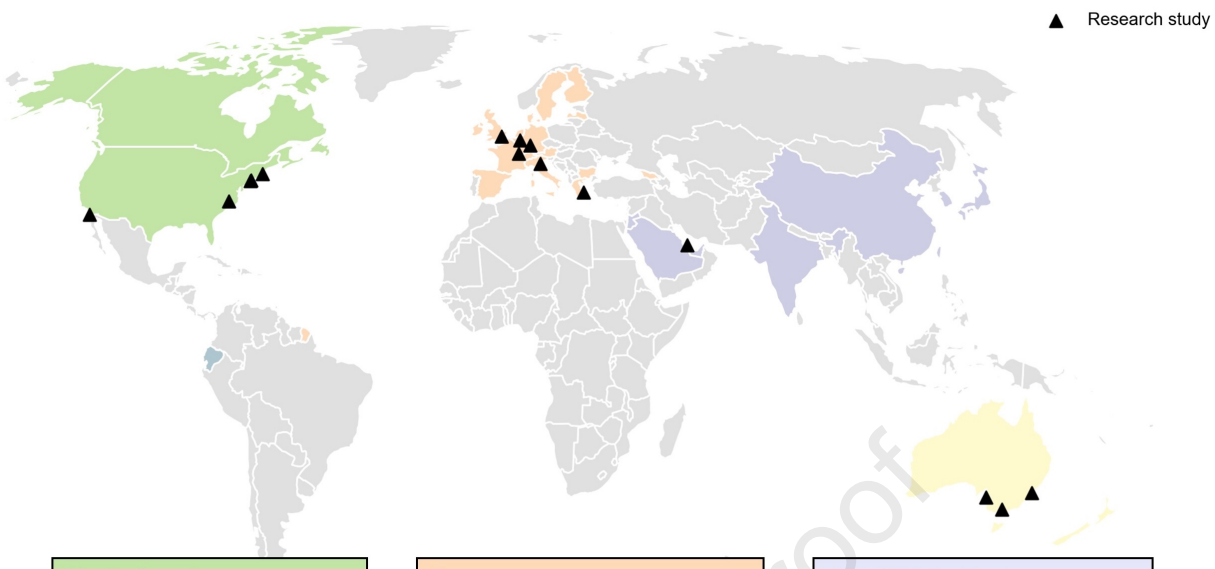
Table 1. Statements across Delphi rounds with divided opinion responses (<60% consensus).

Statement	Round	Suggested areas of future research
Age of symptom onset and age of actionability		
If the earliest reported case of a predominantly adult disorder is in childhood, then the associated disease gene should be included. (For example, PMID: 36313796 describes four cases of children who were diagnosed with Lynch syndrome-associated colorectal cancers age 14–17 years of age.)	Round 1	Review of literature for disorders with a large range of ages of onset
Prevalence and gene-disease validity		
If meeting all other criteria for inclusion, genes with gene-disease validity of moderate or higher based on ClinGen gene-disease validity scoring criteria should be included on genomic newborn screening.	Round 1	Additional curation of gene-disease relationships
Penetrance		
All likely pathogenic and pathogenic variants should be included in newborn screening programs even if the penetrance is not known.	Round 1	Studies of biobanks and large data sets and longitudinal follow-up of infants with positive gNBS results
Low penetrance genotypes may be included for diseases in which the treatment is inexpensive, readily available, and of minimal risk to the well-being of the patient (such as MYH7 related cardiomyopathy where echocardiogram surveillance may be recommended).	Round 1	
Only variants with well established penetrance estimates should be reported in newborn screening programs.	Round 2	
Clinical features of disease		
Genes associated with phenotypes that cause mild differences in body structure and/or function should be included, for example non classical congenital adrenal hyperplasia.	Round 1	Development of a health instrument to measure the severity of genetic disease
Variant curation and reporting		
For genes associated with recessive disorders, if a single pathogenic or likely pathogenic variant is identified, then the gene should also be queried for variants of uncertain significance and these should be reported.	Round 1	Studies of biobanks and large data sets to assess sensitivity and specificity of including

For genes associated with recessive disorders, if a single pathogenic or likely pathogenic variant is identified, then the gene should also be queried for variants of uncertain significance and these should be reported.	Round 2	variants of uncertain significance
Heterozygous variants associated with X-linked disorders should be reported when found in female infants when they are known to be associated with any phenotype, even if that phenotype is more mild or later onset (i.e. G6PD deficiency).	Round 1	Deep phenotyping of females with variants associated with X-linked disorders
Treatment		
Monogenic disorders should only be selected for inclusion in genomic newborn screening if the appropriate treatment is available in the country in which screening is being performed.	Round 1	Global assessment of availability of targeted therapies for genetic disorders
Non-genetic confirmatory testing		
A monogenic condition should be eligible for genomic newborn screening as long as a non-genetic confirmatory test is expected to become abnormal before treatment is initiated.	Round 2	Studies of penetrance and development of additional biomarkers of disease
Parental engagement		
Parents should be given an opportunity to choose if their child is screened for certain types of disorders (for example, treatable or non-treatable).	Round 2	Qualitative research with parents and people with genetic conditions

Abbreviations: gNBS, genomic newborn screening; G6PD, Glucose-6-phosphate dehydrogenase





North America
▲ BabySeq (MA), 10,000
▲ BeginNGS (CA), 2,000
▲ Early Check (NC), 10,000
▲ GUARDIAN (NY), 100,000
▲ ScreenPlus (NY), 100,000

Europe
▲ BabyDetect (BEL), 6,000
▲ FirstSteps (GRE), 100,000
▲ Generation (ENG), 103,000
▲ Screen4Care (EU), 25,000
▲ PERIGENOMED (FRA), 20,000
▲ New_Lives (GER)

Asia/Middle East
▲ Qataf Blooms (QAT), 4,000

Oceania
▲ BabyScreen+ (AUS), 1,000
▲ NewbornsInSA (AUS), 40,000
▲ TRAIL (AUS), 100