048

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

Nina Gold[1], Julie Yeo[2], Derek Ansel[3], Mei Baker[4], Jorune Balciuniene[5], Jonathan Berg[6], François Boemer[7], Wendy Chung[8], Heidi Cope[9], David Eckstein[10], Nicolas Encina[11], Laurence Faivre[12], Alessandra Ferlini[13], Judit Garcia-Villoria[14], Michael Gelb[15], Jose Manuel Gonzalez De Aledo Castillo[14], Katie Golden-Grant[16], Thomas Minten[17], Richard Parad[18], Nidhi Shah[19], Zornitza Stark[20], Kristen Sund[21], Petros Tsipouras[22], Meekai To[23], Lilian Downie[24]

[1]Massachusetts General Hospital; [2]Massachusetts General Hospital for Children; [3]Worldwide Clinical Trials; [4]University of Wisconsin School of Medicine and Public Health; [5]Revvity Omics; [6]University of North Carolina School of Medicine; [7]University of Liege; [8]Boston Children's Hospital; [9]RTI Health Solutions; [10]National Institutes of Health; [11]International Consortium of Newborn Sequencing; [12]FHU TRANSLAD; [13]University of Ferrara; [14]Hospital Clínic de Barcelona; [15]University of Washington; [16]Illumina Inc; [17]KU Leuven; [18]Brigham and Women's Hospital; [19]Dartmouth Hitchcock Medical Center; [20]Victoria Clinical Genetics Services, Murdoch Children's Research Institute; [21]Nurture Genomics; [22]FirstSteps-BNSI; [23]Genomics England; [24]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, University of Melbourne

Introduction: Over 30 international research and commercial programs are exploring the screening by genomic sequencing in apparently healthy newborns and children (NBSeq). However, the genes that are assessed vary widely across programs, which complicates broader implementation and equitable outcomes of this screening approach. The International Consortium of Newborn Sequencing (ICoNS), founded in 2022, brings together nearly 250 leaders across 16 large-scale global research projects investigating the use of NBSeq. In this study, we used a Delphi methodology to assess the perspectives of ICoNS members regarding criteria for gene selection in future NBSeq public health programs. The results of this Delphi study were used to develop expert consensus criteria for gene selection.

Methods: We developed a set of statements to assess ICoNS members' perspectives regarding the selection of genes for population-wide NBSeq implementation. These statements were divided into nine categories: age of symptom onset and actionability, prevalence and gene-disease validity, penetrance, clinical features, variant calling and interpretation, variant curation and reporting, confirmatory testing, treatment, and parental engagement. The questionnaire was distributed to all ICoNS members. Using a Delphi methodology, three rounds of statements were sent to prospective participants online. Consensus agreement with a statement in Round 1 (43 statements) was defined as concordance of >85% among participants. The results and free text responses collected in Round 1 were used to draft Round 2 of the Delphi questionnaire. In Round 2 (27 statements), the consensus threshold was set to >75% agreement. Statements with sufficient concordance from both rounds were used to develop 10 final statements, which were circulated in Round 3 to confirm consensus. These 10 criteria form the expert consensus guidelines from gene selection from ICoNS.

Results: A total of 94 participants, including clinicians, researchers, and representatives from the pharmaceutical industry, completed Round 1 of the Delphi questionnaire. In this round, 10 statements achieved consensus, 25 statements were approaching consensus (60-85% consensus), and 8 statements produced a divided opinion (<60% agreement). In Round 2, 81 participants completed the questionnaire and 14 statements reached consensus. We found that 7 statements approached consensus and 6 produced a divided opinion. In Round 3, 68 participants completed the questionnaire and all 10 statements had a consensus of at least 72%. These statements included: (1) variants should be associated with a disease for which treatment or surveillance is recommended to begin 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 or function should not be reported, (4) variants should be included in NBSeq, 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 approach for newborn screening by genomic sequencing, (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 classic variants cannot easily be detected on sequencing should be included in newborn screening by genomic sequencing 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, and (10) if only VUS are found in a gene, no variants should be reported.

Conclusion: The results of this study offer a globally-informed, expert perspective on characteristics of genes that should be considered for future population-based NBSeq programs. This process also highlighted several areas of divided opinion for which more evidence is needed to guide NBSeq practices in the future.

https://doi.org/10.1016/j.gimo.2025.102421

049

Estimate of the cost of informed consent in NBS: The ScreenPlus model

Nicole Kelly[1], Katrina Paleologos[2], Megan Clarke[2], Sean Bailey[3], Jaya Ganesh[4], Marjorie Joseph[4], Gabriel Kupchik[5], Rishi Lumba[3], Annemarie Stroustrup[6], Aaron Goldenberg[7], Melissa Wasserstein[2]

[1]Children's Hospital at Montefiore; [2]Albert Einstein College of Medicine; [3]NYU Grossman School of Medicine; [4]Icahn School of Medicine at Mount Sinai; [5]Maimonides Children's Hospital of Brooklyn; [6]Cohen Children's Medical Center; [7]Case Western Reserve University School of Medicine

Introduction: Newborn screening (NBS) is a vital public health tool that enables early detection and management of treatable disorders. While its benefits are well-established, evolving ethical and legal frameworks increasingly emphasize informed consent (IC) in NBS, reflecting societal priorities for parental autonomy and trust. Lawsuits about residual dried blood spot (DBS) practices have highlighted the importance of detailed parental engagement and education, as has the delay in the Newborn Screening Saves Lives Reauthorization Act. The future implementation of sequencing-based NBS similarly emphasizes the need to understand the optimal way to ensure transparency and choice in NBS practices. However, a comprehensive economic analysis of IC implementation costs remains lacking. Barriers include logistical complexities, accommodating linguistic and cultural diversity, and financial uncertainties in scaling consent