The development and validation of the Clinician-reported Genetic testing Utility InDEx for Newborn Screening (C-GUIDE NBS): An international initiative

Author name(s):
Robin Z. Hayeems,[1,2] Salma Shickh,[1] Stephanie Luca,[1] Elise Poole,[1] Bowen Xiao,[1] Amanda Pichini,[3] Joanna Ziff,[3] Katrina Stone,[4] Zornitza Stark,[5,6] Lilian Downie,[5,7] Jade Caruana,[5] Holly Peay,[7,8] Heidi Cope,[7] Casey Okoniewski,[7] Wendy J. Ungar,[1,2] Pranesh Chakraborty,[9] David Bick[3]

Author institutional affiliations:
[1]The Hospital for Sick Children,
[2]University of Toronto,
[3]Genomics England
[4]St. George's University Hospitals NHS Foundation Trust,
[5]Murdoch Children's Research Institute,
[6]University of Melbourne, 7Victorian Clinical Genetics Services,
[7]RTI International,
[8]Faegre Drinker Consulting,
[9]Children's Hospital of Eastern Ontario

Introduction
As the use of genomic newborn screening (gNBS) gains traction worldwide, evidence of clinical utility is required to guide policy and funding decisions. To this end, we aimed to develop and validate the Clinician-reported Genetic testing Utility InDEx for Newborn Screening (C-GUIDE NBS), a novel clinician-reported outcome measure.

Methods
Interviews were conducted with clinicians involved in gNBS to assess the relevance, comprehensibility, and comprehensiveness of preliminary C-GUIDE NBS items. We quantified the number of items clinicians accepted, modified, or rejected to inform a revised version. Interviewees completed content validity questionnaires to rate the relevance and clarity of each item on a 4-point Likert scale. Scores between 0 and 1 were calculated; scores <0.8 prompted further revision. We finalized C-GUIDE NBS using a 3-step international Delphi consensus process, including item consensus and stability scoring. Using a cross-sectional survey design and in partnership with the Generation Study (UK), Early Check (USA), and BabyScreen+ (Australia), construct validity testing is underway.

Results
Interviewees (n=22) indicated that eight of the preliminary 11 items were acceptable for inclusion, two required modifications, and one was rejected. On the revised 10-item tool, four items were further revised for the consensus process. With 26 expert panelists, item consensus and stability were achieved for a final 7-item tool. To support validity testing, C-

GUIDE ratings have been completed for 28 confirmed diagnostic cases to date. Examples of cases that received high utility scores included glycogen storage disease and familial hemophagocytic lymphohistiocytosis.

Discussion and Conclusion
C-GUIDE NBS is a rigorously developed, expert-informed tool that provides a novel strategy for measuring the clinical utility of gNBS. Following validation, C-GUIDE NBS will be available for licensed use. Evidence of clinical utility garnered from the use of this tool can inform laboratory, clinical, and policy decisions related to the use of gNBS.