11. Gray W, Resmini A, Baker KD, Holbrook E, Morgan PJ, Ryan J, et al. Concerns, barriers, and recommendations to improve transition from pediatric to adult IBD care: perspectives of patients, parents, and health professionals. Inflamm Bowel Dis 2015;21:1641-51.

12. White PH, Cooley WC. Transitions Clinical Report Authoring Group; American Academy of Pediatrics; American Academy of Family Physicians; American College of Physicians. Supporting the health care transition from adolescence to adulthood in the medical home. Pediatrics 2018;142:e20182587.

The Harms of Carrier Status Identification: A Cautionary Warning Against Newborn Sequencing

Two articles by Farrell et al in this volume of *The Journal* explore the potential psychosocial complications of carrier status notification for sickle cell hemoglobinopathy (SCH) and cystic fibrosis (CF) after newborn screening (NBS). Both articles stem from the Wisconsin Project on Improvement of Communication and Process Outcomes after Newborn Screening. In the first, qualitative telephone interviews with parents were conducted after NBS carrier status was disclosed by a primary care provider to evaluate for effectiveness of results communication, misconception of the child's risk for disease, and parental anxiety.[1] The second assessed parents' perceptions of child vulnerability after being informed of carrier result for SCH or CF, and both groups were compared with a control group using an adapted version of the Vulnerable Baby Scale.[2] Notably, the data collected by Farrell et al in both studies was gathered between 2008 and 2012, and the findings reported in these 2 articles have been corroborated in other studies for these same diseases: (1) parental misunderstanding of carrier status for children with SCH or CF, even in a state that offers genetic counseling; (2) parental anxiety or stress from receiving incidental information; and (3) increased parental assessment of child vulnerability after carrier identification.[3-6] And yet, despite reaffirming the potential harms of carrier status identification in NBS, Farrell et al expect it to expand, concluding that they "suspect that genome sequencing on blood spots will be routine within the coming generation, regardless of ELSI [ethical, legal, and social implications] concerns." Below, we explore why the data from Farrell et al further strengthen the ethical, legal, and social concerns and reject the inevitability of universal adoption of genomic sequencing into NBS programs.

See related articles, p 37 and p 44

NBS has traditionally focused on conditions and disorders, like CF and SCH, that present early in infancy for which early diagnosis can prevent morbidity or mortality. Although most screening currently uses tandem mass spectrometry, the appeal of whole genome sequencing is the potential to screen and diagnose even more conditions using a single platform. However, genomic sequencing without phenotypic information still misses many cases of conditions that are currently identified in NBS. In 2014, Bhattacharjee et al attempted to identify the conditions included in state NBS panels.[7] They wrote: "It is typically assumed that, at least for monogenic disorders, the genotype-phenotype relationship would be simple." Instead the authors found their "ability to pinpoint the clinical phenotype of an individual on the basis of 'genotype' alone is still in its infancy; in our case, only 27 of 36 NBS disease cases were classified correctly without phenotype information."[7]

But imagine that sequencing was better able to identify the conditions included in state NBS panels and could be implemented as the primary platform for NBS. Screening for more conditions would also mean identifying many more carriers. Although broad professional consensus in the US in the early 1990s led to the decision to disclose carrier status when identified in NBS, all US professional statements argue against routine carrier identification in children.[8-11] In BabySeq, a study exploring genomic sequencing of both infants in the neonatal intensive care unit and healthy infants, the researchers demonstrated that >90% of infants screened had ≥1 carrier status variant, with an average of 2 carrier status variants and a range from 0 to 7.[12] This finding is lower than data from Bell et al, who found the average participant (noninfant) on whom genomic sequencing was performed was a carrier for 2.8 conditions (range, 0-7).[13] Primary care physicians are already ill-equipped to discuss NBS carrier results with parents.[14,15] The identification of more carrier status variants in infants through sequencing will only exacerbate these issues; more information about newborns is not always better, particularly when the information is nonactionable for the health of the infant. Farrell et al have demonstrated the possibility of harm to parents and their children from returning these ancillary results—particularly to parents of lower health literacy.[1,2] The failure to effectively counsel a significant number of parents about carrier status

CF	Cystic fibrosis
IRT	Immunoreactive trypsinogen
NBS	Newborn screening
SCH	Sickle cell hemoglobinopathy

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for SCH and CF questions our readiness to implement a platform technology that identifies significantly more carriers.

Methodology matters: CF screening using immunoreactive trypsinogen (IRT) with reflex DNA methodology rather than IRT/IRT is more likely to miss minority infants.[16] Today, all US programs use IRT/DNA with few using an expanded DNA panel, which could improve equity for Black and Hispanic children with less common CF DNA variants.[17] As a public health program, NBS should be designed to decrease health care disparities.[18] Incorporating whole genome sequencing into NBS may exacerbate healthcare disparities and should be avoided until we have more diverse racial and ethnic genomic data for conditions included in state NBS panels and a pediatric workforce prepared to counsel families about the actionable and nonactionable findings.[18-21] ■

Wadsworth A. Williams II, MA
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Lainie Friedman Ross, MD, PhD
Department of Pediatrics
MacLean Center for Clinical Medical Ethics
Institute for Translational Medicine
University of Chicago
Chicago, Illinois

Reprint requests: Lainie Friedman Ross, MD, PhD, University of Chicago Department of Pediatrics, 5841 S Maryland Ave MC 6082, Chicago IL 60637. E-mail: Lross@uchicago.edu

References

1. Farrell MH, La Pean Kirschner A, Tluczek PMF. Experience with parent follow-up for communication outcomes after newborn screening identifies carrier status. J Pediatr 2020;224:37-43.e2.
2. Farrell MH, Sims A, La Pean Kirschner A, Farrell BT. Vulnerable child syndrome and newborn screening carrier results for cystic fibrosis or sickle cell. J Pediatr 2020;224:44-50.e1.
3. Creary S, Adan I, Stanek J, O'Brien SH, Chisolm DJ, Jeffries T, et al. Sickle cell trait knowledge and health literacy in caregivers who receive in-person sickle cell trait education. Mol Genet Genomic Med 2017;5:692-9.
4. Ciske DJ, Haavisto A, Laxova A, Rock LZM, Farrell PM. Genetic counseling and neonatal screening for cystic fibrosis: An assessment of the communication process. Pediatrics 2001;107:699-705.
5. Ulph F, Cullinan T, Qureshi N, Kai J. Parents' responses to receiving sickle cell or cystic fibrosis carrier results for their child following newborn screening. Eur J Hum Genet 2015;23:459-65.
6. Tluczek A, Levy H, Rock MJ, Ondoma C, Brown RL. Impact of intermediate cystic fibrosis classification on parents' perceptions of child vulnerability and protectiveness. J Fam Nurs 2019;25:287-313.
7. Bhattacharjee A, Sokolsky T, Wyman SK, Reese MG, Puffenberger E, Strauss K, et al. Development of DNA confirmatory and high-risk diagnostic testing for newborns using targeted next-generation DNA sequencing. Genet Med 2014;17:337-47.
8. Institute of Medicine (US) Committee on Assessing Genetic Risks. In: Andrews LB, Fullarton JE, Holtzman NA, Motulsky AG, eds. *Assessing Genetic Risks: Implications for Health and Social Policy*. Washington (DC): National Academies Press (US); 1994.
9. Ross LF, Saal HM, Anderson RR, David KL. Ethical and policy issues in genetic testing and screening of children. Pediatrics 2013;131:620-2.
10. Ross LF, Saal HM, David KL, Anderson RR. Technical report: ethical and policy issues in genetic testing and screening of children. Genet Med 2013;15:234-45.
11. Botkin JR, Belmont JW, Berg JS, Berkman BE, Bombard Y, Holm IA, et al. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet 2015;97:6-21.
12. Van Noy GE, Genetti CA, McGuire AL, Green RC, Beggs AH, Holm IA. Challenging the current recommendations for carrier testing in children. Pediatrics 2019;143:S27-32.
13. Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Ganusova EE, Mudge J, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. Sci Transl Med 2011;3.
14. Stark AP, Lang CW, Ross LF. A pilot study to evaluate knowledge and attitudes of Illinois pediatricians toward newborn screening for sickle cell disease and cystic fibrosis. Am J Perinatol 2011;28:169-76.
15. Farrell MH, Christopher SA. Frequency of high-quality communication behaviors used by primary care providers of heterozygous infants after newborn screening. Patient Educ Couns 2014;90:226-32.
16. Ross LF. Newborn screening for cystic fibrosis: a lesson in public health disparities. J Pediatr 2008;153:308-13.
17. El Hajj H, Bish DR, Bish EK. Equity in genetic newborn screening. Nav Res Logist 2019;1-21.
18. Brosco JP, Grosse SD, Ross LF. Universal state newborn screening programs can reduce health disparities. JAMA Pediatr 2015;169:7-8.
19. Harding B, Webber C, Ruhland L, Dalgarno N, Armour CM, Birtwhistle R, et al. Primary care providers' lived experiences of genetics in practice. J Community Genet 2019;10:85-93.
20. Department of Health and Human Services. Genetics education and training. Rep Secr Advis Committte Genet Heal Soc 2011;1-65.
21. Hyland K, Dasgupta S. Medical genetics and genomics education and its impact on genomic literacy of the clinical workforce. Genet Med 2019;21:1259-60.