When should genomic and exome sequencing be implemented in newborns? A call for an update to newborn screening guidelines

To the Editor:

In 2006, Watson et al. recommended, during their participation in an American College of Medical Genetics (ACMG) Newborn Screening Expert Group, a uniform panel of conditions for inclusion in state newborn screening programs.[1,2] The experts conducted 3949 evaluations for 84 conditions and categorized them based on their clinical characteristics; analytical test features; and diagnosis, treatment, and management of the acute or chronic condition. The conditions were ranked based on a quantified expert opinion analysis. Medium-chain acyl-CoA dehydrogenase deficiency, congenital hypothyroidism, and phenylketonuria were the highest ranked conditions and lysosomal storage diseases, Pompe disease, and Krabbe disease were ranked the lowest. Since then, modern medicine has evolved rapidly and the clinical integration of genomic information has increased. We therefore question if the moment has arrived to discuss and update the ACMG's list of uniform conditions to substantially reflect relevant evidence over the past decade. This is to help ensure that use of genome and exome sequencing (GS and ES) in newborns is based on (1) clinical utility or actionability and (2) disease prevalence and penetrance among the general newborn population.

ES and GS should be implemented in ways that consider their clinical utility or actionability in newborns. For instance, Stark showed that early ES could have benefitted a child with normal features at birth before clinical signs of Kabuki syndrome (e.g., microcephaly and developmental delay) manifested by age 18 months.[3] Kabuki syndrome was not considered or included among the 84 conditions in the 2006 ACMG recommendations. Since 2006, evidence supporting the clinical actionability of genetic testing for Kabuki syndrome (secondary complication prevention, treatment or intervention, and surveillance and guidelines) has surfaced.[4] In another example, Choi et al. identified via ES a novel pathogenic variant in a 4-day-old newborn with carbamoyl phosphate synthetase 1 deficiency (CPS1D) who showed no phenotypic abnormalities at birth but later presented treatable symptoms of hypothermia, poor feeding, lethargy, and respiratory depression.[5] The 2006 ACMG expert panel, however, placed CPS1D at the 17th percentile.[1,2]

Since some state-directed newborn screening programs have incorporated testing for immunodeficiency based on the ACMG's 2006 guidance, Pavey et al. explored the clinical utility of GS in population screening for immunodeficiency-related conditions in newborns.[6] They analyzed clinical and GS data from an ethnically and racially diverse cohort of 1349 newborn–parent trios in California. Results showed that 396 trios, or 29% of their newborn cohort, carried a single pathogenic or likely pathogenic variant in an immunodeficiency-related gene(s). A manual review of all the variants identified only one affected newborn with a high probability of a true immunodeficiency called complement component 9 (C9) deficiency. Pavey et al. recommended that the child undergo clinical confirmation of the disease and receive unconjugated and conjugated forms of the pneumococcal and meningococcal vaccinations, including serogroup B.[6] The ACMG placed severe combined immunodeficiency at the 33rd percentile, yet C9, being a true immunodeficiency, was not discussed or included in the 2006 recommendations.[1,2]

Use of ES and GS in newborns should also consider disease prevalence or penetrance within the population. Kabuki syndrome has an estimated prevalence of 1 in 32,000 in Japan and among the general population, although estimates of 1 in 86,000 have been reported for Australia and New Zealand.[4,7] Choi et al. explained that estimating the prevalence and incidence of CPS1D in the Korean population is very difficult because, to their knowledge, their reported CPS1D case was the first reported case in Korea.[5] CPS1D is a rare condition with an estimated prevalence of 1 in 800,000 newborns in Japan (unknown incidence among the general population). Although reportedly rarer than Kabuki syndrome, ACMG experts appear to prioritize testing for CPS1D versus Kabuki syndrome in the 2006 ACMG guidelines. Also, C9 deficiency is reported as high among Korean and Japanese populations but was not among the conditions considered in the 2006 ACMG guidelines.[1,2,8,9]

In 2019, Milko et al. developed a tool that can be used to carefully select conditions for inclusion in ES and GS newborn screening.[10] They created an age-based semiquantitative metric (ASQM) that can classify gene–disease pairs into categories based on age-based factors and facilitate decision-making about incorporating genomic sequencing into newborn care. Their result was a curation of 822 gene–disease pairs, through which 466 were classified as having childhood onset and high actionability based on expert committee scores against five core characteristics of clinical actionability (severity, likelihood, efficacy of the intervention, burden of the intervention, and knowledge base),[11] and 755 categorized gene–disease pairs.[10] Milko

Submitted 25 September 2019; accepted: 12 November 2019
Published online: 26 November 2019

et al. suggested that the ASQM could assist parents and physicians in making informed decisions about the disclosure and actionability of newborn ES or GS test results.[10] Tools like the ASQM provide more structured risk stratification in newborns, but would benefit from the incorporation of genome- or exome-wide reanalysis to more accurately infer gene–disease risk based on genomic data collected over time and to rule out false positive results obtained from other sources of biomarker testing.

We highly recommend that the ACMG consider evidence since 2006 and consider updating 2006 recommendations on newborn screening. Such updates are necessary for the inclusion of underrecognized genetic conditions and a stronger tier classification system for conditions that are based on clinical utility or actionability and disease prevalence and penetrance based on the latest evidence. We believe this consideration is necessary to ensure that newborns and their families receive maximum clinical benefits from genetic testing as part of newborn screening.

DISCLOSURE

CYL is supported in part by an Ebert Career Development Award at Harvard Pilgrim Health Care Institute. RMH-S is supported as an employee of the Future of Privacy Forum. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Rachele M. Hendricks-Sturrup, DHSc, MSc[1] *and Christine Y. Lu, MSc, PhD*[1]

[1]Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA, USA. Correspondence: Rachele M. Hendricks-Sturrup (rachele_hendricks-sturrup@harvardpilgrim.org)

REFERENCES

1. Watson MS, Mann MY, Lloyd-Puryear MA, et al. Newborn screening: toward a uniform screening panel and system–executive summary. Pediatrics. 2006;117 5 Pt 2:S296–307.
2. Watson MS, Lloyd-Puryear MA, Mann MY, et al. ACMG Newborn Screening Expert Group: newborn screening: screening panel and system. Genet Med. 2006;8:S12–252.
3. Stark Z, Tan TY, Chong B, et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. Genet Med. 2016;18:1090–1096.
4. Adam MP, Banka S, Bjornsson HT. Kabuki Syndrome Medical Advisory Board, et al. Kabuki syndrome: international consensus diagnostic criteria. J Med Genet. 2019;56:89–95.
5. Choi R, Park H-D, Yang M, et al. Novel pathogenic variant (c.580C>T) in the CPS1 gene in a newborn with carbamoyl phosphate synthetase 1 deficiency identified by whole exome sequencing. Ann Lab Med. 2017;37:58–62.
6. Pavey AR, Bodian DL, Vilboux T, et al. Utilization of genomic sequencing for population screening of immunodeficiencies in the newborn. Genet Med. 2017;19:1367–1375.
7. White SM, Thompson EM, Kidd A, et al. Growth, behavior, and clinical findings in 27 patients with Kabuki (Niikawa-Kuroki) syndrome. Am J Med Genet A. 2004;127A:118–127.
8. Fukumori Y, Yoshimura K, Ohnoki S, et al. A high incidence of C9 deficiency among healthy blood donors in Osaka, Japan. Int Immunol. 1989;1:85–89.
9. Kang HJ, Kim HS, Lee YK, et al. High incidence of complement C9 deficiency in Koreans. Ann Clin Lab Sci. 2005;35:144–148.
10. Milko LV, O'Daniel JM, DeCristo DM, et al. An age-based framework for evaluating genome-scale sequencing results in newborn screening. J Pediatr. 2019;209:68–76.
11. Berg JS, Foreman AK, O'Daniel JM, et al. A semiquantitative metric for evaluating clinical actionability of incidental or secondary findings from genome-scale sequencing. Genet Med. 2016;18:467–475.

Advance online publication 26 November 2019. doi:10.1038/s41436-019-0707-7