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Newborn screening should be considered in immigrant populations

— Michael H. Duyzend, MD, PhD

The newborn screen (NBS), a public health program to screen infants for treatable conditions not clinically evident in the newborn period, has reduced mortality and morbidity in jurisdictions where it is mandatory. Beginning in the 1960s with phenylketonuria (PKU), early diagnosis and treatment has prevented thousands of individuals from developing profound intellectual disability. Despite the ability for early detection, missed or underdiagnosed cases exist in both industrialized nations, where NBS is mandatory in infancy, and in lesser developed countries.

In this volume of *The Journal*, van Wegberg et al explore the occurrence of late PKU diagnosis with the hypothesis that organizational issues are more important than technical failures of the NBS. In a web-based survey of 77 metabolic centers in 36 countries, the authors identified 259 cases of missed PKU in individuals ranging from infants to adults (**Figure**). Although the majority of the cases were in regions with no or limited NBS, or born prior to NBS, 52/259 (∼20%) of cases were found in immigrants from nations without or with limited NBS. This ratio increased to 52/114 (∼46%) when removing cases from regions with no/limited NBS or born prior to the implementation of NBS.

This observational study likely underestimates the number of undiagnosed PKU cases due to imperfect ascertainment. Even so, the data suggest that PKU is missed even in regions where NBS is mandatory and available, and immigrant populations share the burden of missed cases. The authors highlight that symptoms can be masked by features such as history of trauma. Although there is no universal requirement for

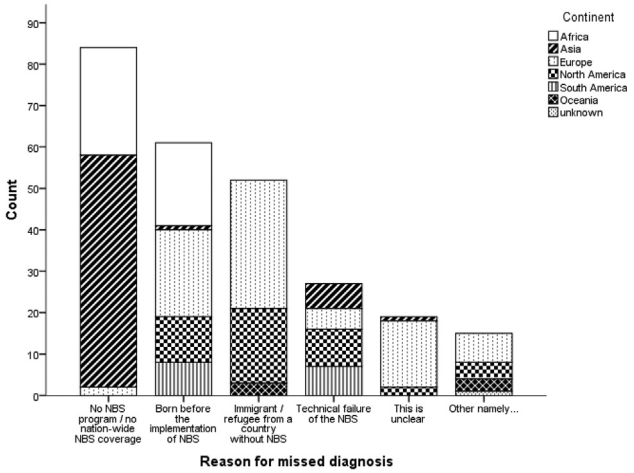

Figure. Reason for missed/late diagnosis per continent (total n = 258).

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NBS in immigrant populations in industrialized nations, NBS should be strongly considered.

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Neurologic complications of common respiratory tract virus infections

— Sarah S. Long, MD

Three studies published in this volume of *The Journal* remind us that although common and familiar to parents and healthcare providers, respiratory tract viruses can lead to neurologic complications. Antoon et al used the Pediatric Health Information system (PHIS) of administrative data to capture 29 676 hospitalizations of children 2 months to <18 years of age with a discharge diagnosis of influenza during influenza seasons of 2015 through 2020 from 49 children's hospitals. Searching for coded concurrent neurologic complications, they found 2246 cases, with febrile seizures occurring in 5% of hospitalizations for influenza, encephalopathy in 1.7%, and non-febrile seizures in 1.2%. With the large denominator and numerator afforded by these methods, they arrived at the likely most reliable recent neurologic complication rate for influenza of 7.6% in hospitalized cases. Compared with those with influenza but without neurologic complications, children with neurologic complications were more likely to have underlying chronic neurologic conditions, had longer lengths of hospital stay, higher intensive care unit admission, and higher death rates and costs. These gross epidemiologic data make a nice pairing with the more granular data reported by Frankl et al from a single children's hospital of complications of 1217 influenza hospitalizations between 2010 and 2017. They found a neurologic complication rate of 10.8%. Pre-existing neurologic condition, age ≤5 years and lack of influenza vaccination had adjusted increased odds ratios for neurologic complication(s).

The subject of the third study by Saravanos et al from Australia is the neurologic complications associated with hospitalizations of children with respiratory syncytial virus (RSV) infection, using a systematic review and aggregated case series methodology. With an estimated 3 million annual hospitalizations globally for RSV, one does not have to go further to make a case for RSV's negative impact on children's health. But this study goes further to search the medical literature to ferret out neurologic complications among RSV hospitalizations. *Excluding* febrile seizures and isolated apnea, they found 155 cases of severe acute neurologic syndromes among 87 unique studies from 26 countries (with 5 of the cases added from their own prospective study of etiologic agents of encephalitis/encephalopathy. Seizures were the most frequent neurologic feature, reported in 85%, followed by reduced level of consciousness and encephalitis, which in at least 25 cases was documented due to inappropriate secretion of antidiuretic hormone. Surprisingly, in 12 cases, RSV was detected by PCR in the CSF. Among 122 children with outcomes reported, recovery was reported in 66% of children, partial recovery in 27%, and death in 7%.

These studies highlight the benefits and limitations both of "big data" and granular clinical data. These studies, however, document that common respiratory viruses are worth preventing not only to reduce the predictable burden of respiratory illnesses, hospitalizations, and deaths but also to avoid serious neurologic complications.

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A better way to detect iron deficiency?

— William S. Ferguson, MD

Approximately 10% of US children under 3 years of age will experience some degree of iron deficiency that, even in the absence of overt anemia, has the potential for causing long-term cognitive defects. Clinicians are not only faced with conflicting guidance on screening for iron deficiency but also lack a straightforward method for doing so. About three-quarters of children with iron deficiency will have nominally normal hemoglobin levels and, because of the relatively long life of erythrocytes, changes in the traditional red cell indices associated with iron deficiency anemia are relatively late findings. Compared with conventional CBCs, biochemical

markers of iron deficiency require venous blood samples, have interpretation issues (eg, elevations of serum ferritin by inflammation), and are relatively expensive.

Modern CBC analyzers determine size and hemoglobin content for each cell in an analytic sample and provide information for specific sub-populations of cells. Examples relevant to iron deficiency include reticulocyte hemoglobin content and, more recently, the proportion of red cells with very low cell volumes (<60 fL; "Micro-R") or hemoglobin content (<17 pg; "HYPO-He"). These cells represent <1% of erythrocytes in normal adults but increase in situations of iron-limited erythropoiesis.

In this volume of *The Journal*, Bahr et al report reference ranges for Mirco-R and HYPO-He derived from a large sample of CBCs from young infants (<90 days old). Like many hematologic parameters, these were significantly different from normal adult values. Of equal importance, elevations of Micro-R and/or HYPO-He were seen more consistently than were decreases of MCV or MCH in infants with biochemical evidence for iron deficiency, suggesting that in both children and adults these new indices may be useful early indicators of clinically relevant iron deficiency.

The FDA has not yet approved use of these measurements for diagnosing iron deficiency; they are currently limited to certain analyzer models, and normal ranges have yet to be determined for the majority of children. However, if these findings can be replicated and expanded to older children (with appropriate reference ranges), it may mean that information directly obtained from routine CBCs may provide a cost- and resource-effective way to screen for early iron deficiency.

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Genomic medicine in a community hospital setting

— Michael H. Duyzend, MD, PhD

Clinical rapid genome sequencing (rGS), the sequencing and interpretation of variation in a patient's genome within ~1 week, has helped to establish diagnoses and direct patient care in numerous studies, but has largely been restricted to an academic setting. In this volume of *The Journal*, Beuschel et al demonstrate that rGS is not only available in a community hospital but also directly affects patient care in this setting. In their retrospective analysis of 24 patients where a genetic diagnosis was suspected, or there was no clear explanatory cause of illness, medical management was altered in 67% of subjects as a result of rGS.

The authors propose a general template for rGS. Specifically, providers prioritize patients, samples are shipped to an outside laboratory for sequencing and initial variant interpretation, and the local team provides final interpretation and implements results.

Interpreting sequencing results is somewhat analogous to interpreting an MR scan; clinical context and expert knowledge is required. Indeed, the American College of Medical Genetics and Genomics (ACMG) has pathogenicity criteria including the Variant of Uncertain Significance (VUS), where there is not yet sufficient overall evidence to deem a variant clinically significant. Assessment of clinical presentation by a genetic medicine expert in the context of a VUS, therefore, is crucial important.

Despite studies showing overall cost-effectiveness of sequencing, the service remains expensive. Even as such, the authors demonstrate the value of rGS in a community setting and propose a path forward that will likely become standard practice and increasingly economical.

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Is the care of children with trisomy 18 changing?

— Paul G. Fisher, MD

The management of children with trisomy 18 has been extensively studied and reported in *The Journal of Pediatrics* and many other publications. The American Academy of Pediatrics has practice guidelines for Down syndrome. But far fewer data have been reported on the care of children with another aneuploidy, trisomy 18 (Edwards syndrome). Historically for many pediatricians this diagnosis alone has been the harbinger of a plan for comfort care only.

Are the patterns of care for children affected by trisomy 18 changing? In this volume of *The Journal*, Fick et al report over 10 000 hospitalizations of these children from 1997 to 2016 using the Kids' Inpatient Database. The investigators observed that the number of children admitted annually with trisomy 18 during the study period increased, and specifically that gastrostomy tube placement increased 12-fold, tracheostomy increased 11-fold, and cardiac interventions rose 5-fold. Although their data are limited to only hospitalized children and do not include all patients with trisomy 18 or capture population incidence, the authors nevertheless have identified an increasing trend of invasive procedures being performed in these children. The findings may speak to changing views about how we manage these children but also how many interventions we perform in any condition when care is still largely palliative. Although the authors attempt to extrapolate some data on survival in trisomy 18 from the inpatient database, further investigation will be needed. Survival, quality of life, and allocation of health care resources need to be explored in the setting of possibly changing societal values regarding how we manage children with trisomy 18.

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