Answering a Question Older Than Most Pediatricians: What to Do About Duarte Variant Galactosemia

Shawn E. McCandless, MD

In their article "Developmental Outcomes in Duarte Galactosemia" in this issue of *Pediatrics*, Carlock et al[1] report the results of a landmark study in which it was demonstrated that Duarte variant galactosemia (DG) is not associated with an increased risk of developmental abnormalities and does not require dietary treatment. The field has been waiting 50 years for this study, since newborn screening (NBS) for galactosemia began.[2] This work can be used to impact clinical care and NBS program planning. It can also be used to teach us important lessons about the public funding of research into clinical outcomes and the importance of data-driven clinical decision-making.

The study was well designed and robustly powered to answer the questions asked, and the results clearly reveal through careful neuropsychological testing that no significant developmental differences are seen in children with this biochemically mild variant of galactosemia, compared with controls. The immediate implication of this for health care providers is obvious; dietary therapy, which always includes stopping breastfeeding, is not indicated for infants shown to have DG. Equally important, from a public health perspective, the authors provide clear and compelling evidence that NBS for DG is not useful, nor is it desirable. Thus, those states that have not adjusted their NBS cutoffs to minimize the identification of infants with DG should feel confident in doing so now. Many states have already found that with careful selection of cutoff values, identification of DG and other mild variants can be significantly reduced without missing cases of classic galactosemia.

At present, in most places, the diagnostic evaluation of an abnormal NBS for galactosemia can take more than a week to result. The risk of sepsis, hepatic injury, kernicterus, and even death in infants with classic galactosemia leads most providers to respond to an abnormal NBS result by stopping breastfeeding to use a galactose-free formula. The addition of a DNA mutation screen in the NBS laboratory for the Duarte allele, or better yet, also including the several most common classic galactosemia mutations, could further reduce the number of infants unnecessarily treated. Although the presence of the Duarte allele does not completely eliminate the risk of 2 severe mutations, it would provide reassurance, allowing health care providers to better assess the need to stop breastfeeding without excessive risk to the infant. Most NBS laboratories are now equipped to perform some level of DNA analysis on all samples to test for severe combined immunodeficiency, so this addition should not create an undue burden on the laboratory.

The authors of this work provide an important lesson when considering new conditions for addition to NBS panels; unexpected variants are always found, and reporting them may not be free of harm to the child or family.

Section of Genetics and Metabolism, Department of Pediatrics, School of Medicine, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado

DOI: https://doi.org/10.1542/peds.2018-3292

Accepted for publication Oct 17, 2018

Address correspondence to Shawn E. McCandless, MD, Department of Pediatrics, University of Colorado Denver AMC, 13121 E 17th Ave, L-28 Fourth Floor, MS 8400, Aurora, CO 80045. E-mail: shawn.mccandless@ucdenver.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The author has indicated he has no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2018-2516.

To cite: McCandless SE. Answering a Question Older Than Most Pediatricians: What to Do About Duarte Variant Galactosemia. *Pediatrics*. 2019; 143(1):e20183292

This has been true through the entire 55 years of NBS, beginning with the recognition of mild hyperphenylalaninemia. Knowing this, it is no longer acceptable that the health care community take 50 years to sort out whether milder cases identified by NBS need treatment. Programs adding new conditions should feel a sense of obligation to take part in follow-up studies to understand the natural history of the milder variants identified, and the addition of new disorders to NBS panels should be accompanied by prospective studies designed to determine if treatment of the milder variants is beneficial. Children's health care providers must demand this so that we never again spend 50 years exposing infants to unneeded treatments that may not be harmless.

In a more general sense, the results of this study, funded by the Patient-Centered Outcomes Research Institute, validate the concept of public funding specifically targeted to answer simple, but critical, clinical questions. The question asked and answered here is of fundamental importance to providing high-quality and high-value health care, but it does not have an associated reward that would lead the pharmaceutical or insurance industries to fund nor does it deliver the innovative discovery potential desirable for funding through federal research agencies or large philanthropic organizations. Answering this question required a unique funding mechanism. This approach to funding is a greatly needed contribution to clinical science.

Finally, it is intriguing that in 50 years, competent and thoughtful clinicians routinely came to different conclusions about the need for intervention for DG on the basis of their "experience." Experience should not be confused with fact. Experience is one way of understanding based on limited exposure to data, filtered by many potential intellectual biases, both recognized and unrecognized, and tempered by the emotional milieu associated with the events. As such, experience should not, and cannot, replace data and critical analysis as the basis for clinical decision-making. Carlock et al[1] have shown how it should be done in this important article.

ABBREVIATIONS

DG: Duarte variant galactosemia
NBS: newborn screening

REFERENCES

1. Carlock G, Fischer ST, Lynch ME, et al. Developmental outcomes in Duarte galactosemia. *Pediatrics*. 2019;143(1):e20182516
2. Beutler E, Irwin HR, Blumenfeld CM, Goldenburg EW, Day RW. Field test of galactosemia screening methods in newborn infants. *JAMA*. 1967;199(7):501–503

Answering a Question Older Than Most Pediatricians: What to Do About Duarte Variant Galactosemia

Shawn E. McCandless

Pediatrics 2019;143;
DOI: 10.1542/peds.2018-3292 originally published online December 28, 2018;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Answering a Question Older Than Most Pediatricians: What to Do About Duarte Variant Galactosemia

Shawn E. McCandless

Pediatrics 2019;143;
DOI: 10.1542/peds.2018-3292 originally published online December 28, 2018;