Received: 9 January 2020 | Revised: 6 March 2020 | Accepted: 25 March 2020

DOI: 10.1002/ajmg.a.61587

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A WILEY

How a baby with classic galactosemia was nearly missed: When the test succeeds but system fails

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Abstract

Newborn screening (NBS) is a well-established state-run public health program which has targeted the early identification of treatable diseases like classic galactosemia (CG) for over a decade. We describe the case of a symptomatic newborn with CG and an abnormal screen report, including positive DNA-based test, who still managed to fall through the cracks in a sub-optimally functioning NBS program, despite decades of screening experience. While much attention is paid to testing technology, this case illustrates basic minimum requirements a newborn screening program must fulfill to reliably identify and treat all affected individuals including minimum reporting requirements, case surveillance and a dedicated short-term follow-up program. In newborn screening, success is systematic.

KEYWORDS

galactosemia, newborn screening, public health, system

1 | INTRODUCTION

For over 50 years, newborns in the United States (US) have received a test after birth for inherited, treatable disorders through their state's newborn screening (NBS) program. This mandatory state-run public health program aims to prevent irreversible harm by identifying affected newborns before symptoms develop. While tests play a key role, success and safety depend upon a functional system. Without it, errors resulting in missed infants, delayed treatment and subsequent disability or death may occur.

A functional NBS system requires operation of multiple components: education of stakeholders, screening, follow-up of out-of-range results, confirmatory testing and diagnosis, medical management, periodic outcome evaluation and system quality assurance (American College of Medical Genetics Newborn Screening Expert Group, 2006). Birthing hospitals, couriers, laboratories, state public health programs, healthcare providers (HCPs), and specialists, scattered across a state and beyond state borders, are responsible for executing these components under the guidance of each state's NBS program. Because many screened disorders require urgent intervention, timely functioning of the system is critical (Grosse, Boyle, Kenneson, Khoury, & Wilfond, 2006). In the 5 days after a newborn's birth a program must collect, transport, and test specimens; inform parents of the results; arrange follow-up evaluation and—if necessary—treat affected children (NewSTEPs Timeliness Report, 2016). The absence or dysfunction of one of these system components can be deadly.

Classic galactosemia (CG), a disorder for which timely identification and intervention is critical, has been screened nationally for decades (Pyhtila, Shaw, Neumann, & Fridovich-Keil, 2015). Newborns with CG are deficient in the galactose-1-phosphate uridyltransferase (GALT) enzyme and cannot metabolize galactose-1-phosphate, a key ingredient in breast milk and cow's milk-based formulas. Affected infants not switched to soy-based formula within the first 5–7 days of life can develop fatal liver failure, sepsis, and coagulopathy (Berry, 1993). In the condition's early stages, affected infants commonly present with lethargy while on an exclusive breast-milk diet.

All US NBS programs include CG but despite decades of screening, analytical methods continue to vary between jurisdictions. Most use GALT enzyme analysis and quantitation of total galactose (Pyhtila, Shaw, Neumann, & Fridovich-Keil, 2014); three programs additionally use second-tier DNA analysis of the GALT gene (Pyhtila et al., 2015). As this illustrates, state variability in testing platforms adds a complicating feature to an already complex system. These nuances can be challenging for HCPs to grasp and further compounded when

newborns cross state lines for care—that is, born in one state but receiving medical care in another—as providers may not have the same level of understanding of results from outside states.

Herein we present a near-miss case of CG illustrating the risks when state-of-the-art testing technology is delivered within a suboptimally-functioning NBS system. The history in this case came from parental recall, chart review and experience of staff at referral institution.

2 | PATIENT PRESENTATION AND DIAGNOSIS

A term male infant born in a Washington, DC (DC) hospital in June 2017 had a newborn screen collected day of life 2 (DOL 2). The specimen was sent to Perkin Elmer, a commercial laboratory that performs testing for DC's NBS program. On DOL 6, a testing report was completed stating "PRESUMPTIVE POSITIVE SCREEN RESULT Galactosemia… RECOMMEND immediate referral to metabolic specialist." (Figure 1) The report listed low GALT enzyme (19.7 μM, normal >40 μM), normal total galactose (11.3 mg/dL, normal <15.0 mg/dL) and targeted DNA analysis reporting two copies (homozygous) of the p.K285N classical galactosemia variant. A newborn with this result—low GALT and homozygous for p.K285N—is essentially diagnosed with CG, that is, a true positive result (Dobrowolski et al., 2012).

On DOL 7, an HCP from the birth hospital phoned informing parents their child had an "abnormal" NBS result. The provider gave parents general results but did not discuss the likelihood of CG or represent urgency of intervention by galactose-restriction. The parents told the birth hospital provider that the newborn was "lethargic" on exclusive breast milk. The NBS report contained no instructions or resources on clinical management, no contact information for the

PATIENT DATA	FILTER PAPER DATA	SUBMITTER DATA
Name:	**Filter Paper:**	Submitter:
AKA Name:	Accession No:	
Birth Date:	Date Collected:	
Sex: **M**	Date Recvd:	
Weight (g): 3760	Transfused:	
Gestation: 40 weeks	Trans Date:	
Med. Rec.	Completed:	
PS ID:	Print Date:	Physician:
Mother:		Phone:
Phone:		Initial Release:

Galactosemia
Uridyltransferase (UT)

Result: PRESUMPTIVE POSITIVE

PRESUMPTIVE POSITIVE SCREEN RESULT FOR Galactosemia.
RECOMMEND immediate referral to a metabolic specialist.

UT activity < 40 μM even in the presence of a normal galactose level is presumptive positive.

Total Galactose (Gal + Gal-1-phosphate combined) = 11.3 mg/dL blood (Normal < 15.0).
Enzyme assay for Uridyltransferase = 19.7 μM (Normal > 40.0).

Galactosemia
Total Galactose

Result: Within Normal Limits

DNA analysis detected 2 copies (homozygous) of the K285N classical galactosemia mutation. The K285N allele has an overall frequency of 8% in people of European descent.
GENETIC COUNSELING IS RECOMMENDED TO EXPLAIN THE IMPLICATIONS OF THESE RESULTS.

Gene analysis for galatose-1-phosphate uridyltransferase deficiency to detect N314D, Q188R, S135L, K285N, and L195P mutations is performed by polymerase chain reaction and melting curve analysis to detect the mutant and wild type form of the gene. Galactosemia is inherited as an autosomal recessive trait.

FIGURE 1 Washington, DC newborn screening laboratory report

NBS program, and no information about where to refer an infant the infant for specialist evaluation. Upon hearing the newborn was "lethargic"—a concerning symptom to any pediatric provider—parents were advised to have him evaluated at the nearest emergency department (ED). The hospital provider did not give instructions on the need for follow-up with a genetic specialist.

Family presented to a community hospital ED in a neighboring state where HCPs obtained the NBS report, initated soy-based formula, performed a physical exam, and ordered laboratory testing including liver function and coagulation studies. It is important to note that the NBS program in this neighboring state did not conduct DNA-based testing. Upon normal initial laboratory results, ED providers deemed the newborn stable and told family the NBS was a "likely false positive." He was discharged and parents allowed to resume breastmilk-feeding without formal referral to genetics. Fortuitously, an ED provider faxed a copy of the NBS result to a metabolic specialist in the Children's National Rare Disease Institute (CNRDI) who was personally known to the ED provider for performing follow-up evaluations of newborns with out-of-range NBS results in the DC region.

On DOL 8, over 48 hr after the abnormal result report generated by NBS laboratory, the fax was received by a CNRDI provider who immediately contacted the family to stop breastmilk-feeding and made arrangements for evaluation. Ultimately, the diagnosis of CG was confirmed DOL 10 during the initial visit to the metabolic specialist. At this visit, the baby presented with normal vitals, except for a 6% decrease from birth weight, a normal physical exam and a quantitative GALT enzyme of 0.3 μM (normal >24).

3 | DISCUSSION

The historic success of NBS programs is indisputable. However, the degree to which this success depends upon a functional NBS system is frequently overlooked. Too often, testing technology receives the credit and not the complete system orchestrating each affected newborn's access to swift and appropriate evaluation. This case illustrates how critical a functional system is to this success.

As with any near-miss safety event, a tendency exists to blame individuals who made errors or failed to perform to expected standards. However, a systems-based approach to healthcare safety—as recommended by the Institute of Medicine's "To Err is Human"—eschews blaming errors on individuals. To improve safety and care outcomes we must focus on the system (Institute of Medicine, 2000). Ultimately, every NBS program should assume the responsiblility of ensuring individuals have the support and guidance needed to execute their roles.

In this case, none of the providers who encountered him recognized this newborn's high risk for CG. There are a number of explanations for this oversight. First, although disappointing, it is not surprising given that most medical training covers little of NBS or genetics. Second, the ED providers were not familiar with the DNA-based testing included in the NBS report, because it was not conducted by their state's NBS program. Finally, these ED providers commonly encountered NBS results with falsely low GALT and normal galactose in the summer months when heat degrades GALT enzymes on dried blood spots causing artificially low GALT levels.

Yet, all HCPs reviewed the essentially diagnostic NBS report, illustrating that an accurate test report alone is insufficient. A functional NBS program is also responsible for providing, at a minimum, critical clinical management resources and local expert and program contact information. For example, it was a missed opportunity that the NBS report did not direct the providers to the nearest pediatric metabolic center which was <10 miles from the family and the child's provider.

Ironically, the DNA-based test—a technological innovation implemented to decrease false positive NBS galactosemia results—was thwarted by a dysfunctional system. This was compounded by the ED provider's experiences with frequent false positives. A lack of appropriate clinical urgency fostered by high rates of false positive results is an ongoing concern among NBS programs (Pyhtila et al., 2015) and potential systems-based countermeasures include diminishing false postives where possible but also attempting to regionally standardize the contents of NBS reports.

The absence of a short-term follow-up program surveilling out-of-range NBS results certainly contributed here. Worryingly, this scenario is obviously reproducible and could be chronic to an unknown degree given unavailable surveillance data. In this case, the DC NBS program did not contact the hospital provider or the parents to ensure the newborn had received appropriate evaluation or treatment. Had the ED providers not applied a relationship-based intervention in reaching out to CNRDI, this family could have continued to breastfeed unaware of the dangerous consequences—despite the NBS result in hand and signs of clinical deterioration (lethargy). In this case, the presence of a system-based follow-up program and local referral information within the NBS report could have reduced the time to intervention. In states with formal follow-up programs, trained personnel make direct contact with HCPs, and, if needed, with families to share results and next steps, facilitate referrals to appropriate local specialists, and follow along to ensure all necessary tasks are completed. They also typically provide and reinforce education about these rare diseases and appropriate diagnostic and management strategies or resources (Therrell et al., 2010).

In order to avoid such outcomes, at a minimum, every state NBS program should have a short-term follow-up program providing case management (Therrell et al., 2010). This entails accountability from test collection through diagnosis and primary responsibility for closing the loop on out-of-range results. This may be most successful when programs contact HCPs and sub-specialists directly to ensure timely repeats or referrals. Many HCPs are unfamiliar with screening conditions and may refer to the wrong specialist or be unaware of the availability of appropriate specialists for each of these rare disorders (Viall et al., 2015).

While NBS is widely considered one of the most successful public health programs of all time (CDC), significant gaps remain. The jurisdiction where a child is born should not determine whether timely identification of their treatable disease is received. For this to be

secured, the appropriate infrastructure and staff must be in place in every NBS program. As states consider adding newer and more complex conditions, evaluation of current and optimal testing, reporting and follow-up methods are paramount. Programs must keep in mind that the true success of newborn screening extends beyond just the test itself. While this baby was lucky, a screening program should rely on a functional system, not luck.

ACKNOWLEDGMENTS

The authors would like to thank Natasha Bonhomme for her thoughtful review of the manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

S. V. designed the study, analyzed the data and drafted the initial manuscript, and reviewed and revised the manuscript. A. C., B. T., and N. A. M. made substantial contributions to the analysis and interpretation of data, and critically revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed in this study.

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How to cite this article: Viall S, Calhoun A, Mew NA, Tarini BA. How a baby with classic galactosemia was nearly missed: When the test succeeds but system fails. *Am J Med Genet Part A*. 2020;1–4. https://doi.org/10.1002/ajmg.a.61587