False-Positive Newborn Screening Result and Future Health Care Use in a State Medicaid Cohort

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KEY WORDS

newborn screening, false-positive results, health care service utilization, infants

ABBREVIATIONS

NBS—newborn screening
ED—emergency department
CPT—Current Procedural Terminology
E&M—evaluation and management
IRR—incidence rate ratio
CI—confidence interval

A portion of this work was presented at the Pediatric Academic Societies Meeting; May 1-4, 2010; Vancouver, British Columbia, Canada.

The views expressed herein do not necessarily represent those of the University of Michigan, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the Michigan Department of Community Health, or 3M.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-2448

doi:10.1542/peds.2010-2448

Accepted for publication Jun 10, 2011

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

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

Funded by the National Institutes of Health (NIH).

WHAT'S KNOWN ON THIS SUBJECT: There has been long-standing concern that parents of children with false-positive results for newborn-screening (NBS) tests overuse health care services because they believe their child to be persistently vulnerable to illness. Previous studies that have explored this issue have yielded conflicting results.

WHAT THIS STUDY ADDS: These analyses revealed that Medicaid-insured term infants with false-positive NBS results did not have more health care visits than infants with normal NBS results. However, preterm infants with false-positive NBS results had more acute outpatient visits than those with normal NBS results.

abstract

OBJECTIVE: To compare health care visit rates between infants with false-positive and those with normal newborn screening (NBS) results.

PATIENTS AND METHODS: We analyzed administrative claims of Medicaid-enrolled infants born in Michigan in 2006 and calculated the average number of outpatient, emergency department, and hospital visits for infants aged 3 to 12 months according to NBS results. We calculated an adjusted incidence rate ratio for each visit category, adjusting for covariates and accounting for interaction effects.

RESULTS: Of the 49 959 infants in the analysis, 818 had a false-positive NBS result. We noted a significant interaction between gestational age and NBS results. We found that preterm, but not term, infants with false-positive results had more acute outpatient visits than their counterparts with normal NBS results. We found no difference in adjusted rates of other visit types (emergency department, inpatient, outpatient well) between infants with false-positive and normal NBS results, regardless of gestational age.

CONCLUSIONS: Increased rates of acute outpatient visits among preterm infants with false-positive NBS screening results may be attributable to underlying chronic illness or parental anxiety. The absence of increased health care utilization among term infants may be unique to this Medicaid population or a subgroup phenomenon that was not detectable in this analysis. *Pediatrics* 2011;128:715–722

Newborn screening (NBS) is a mandatory state-run public health program by which newborns are screened for inherited disorders. In 2005, the American College of Medical Genetics recommended that states expand their NBS panels to screen for 29 disorders. Nearly all states have complied with this recommendation.¹ However, screening for additional rare disorders increases the number of false positive results even when a highly specific test is used.²

There is concern that false-positive results increase parents' anxiety about their child's future health, leading to greater use of health care services.³ A recent study did not find evidence of increased health care visits (outpatient, emergency, inpatient) in children with false-positive NBS results compared with those with normal NBS results.⁴ However, this study may have been subject to recall and selection bias because it involved voluntary participation and assessment of health care use by use of parental report. With that in mind, our objective was to conduct a population-based study by using state Medicaid claims to explore whether infants with false-positive NBS results had greater future health care use than infants with normal NBS results.

PATIENTS AND METHODS

This study was approved by the institutional review boards of the University of Michigan and the Michigan Department of Community Health.

Source Population

The source population for this study was all infants born in Michigan in 2006 who had ≥ 11 months of Medicaid eligibility and no other health insurance.

FIGURE 1
Study population.

Matching Medicaid Claims With NBS Data

The institutional review boards of the University of Michigan and the Michigan Department of Community Health required that the process of matching infants' Medicaid claims with their NBS result be conducted by the Michigan Department of Community Health and that all subsequent data analysis be conducted on a deidentified data set. To improve the validity of the match, a previously validated 3-step linkage process⁵ was used: (1) NBS records were matched to live birth records; (2) Medicaid claims were matched to live birth records; and (3) NBS records were linked to Medicaid claims. Concordant/discordant data were investigated by hand after the final linkage was completed. Disorders included in the Michigan NBS panel are listed in Appendix 1.

Exclusions

We excluded infants from our analysis who met any of the following criteria: died before 12 months of age; eligible for

Medicaid but did not have any claims or encounters; unknown gestational age; true-positive NBS results (Fig 1).

Independent Variables

Gestational Age, Birth Weight

Gestational age and birth weight information were obtained from each infant's NBS card. Internal validity checks between the NBS card and the vital records, for which we used a cut-off of ≥ 37 weeks for term infants, demonstrated excellent concordance (98% concordance). For those infants for whom gestational age was not available from the NBS card, we determined gestational age by using *International Classification of Diseases, Ninth Revision*, codes for gestational age from birth claims. We identified and excluded incompatible combinations of gestational age and birth weight by using a previously published method.⁶

Child Gender

The infant's gender was obtained from the Medicaid beneficiary table.

Birth Date

Because this analysis was conducted on a deidentified data set, we had to estimate each infant's birth date. We did so by subtracting the age in months at the time of service from the date of service to calculate a birth date for each claim. The earliest calculated birth date among an infant's set of claims served as the estimated birth date for that infant.

Utilization Outcomes

We measured health care use by counting the number of visits (represented by submitted claims) for outpatient (well and acute visits), emergency department (ED), and inpatient services. If a child had multiple visits within the same visit category (outpatient well, outpatient acute, ED, inpatient) on a given day, then only 1 visit was counted in the analysis. If an infant had multiple visits in different visit categories on a given day, each visit was counted individually with 1 exception: if an infant had an ED visit with a date of service that was identical to the admission date for an inpatient claim, then we assumed that the infant had been admitted to the hospital from the ED and categorized this visit as an inpatient visit or hospitalization.

We counted only visits from 3 to 12 months of age because infants with false-positive NBS results may use health care services in the first 2 months of life for evaluation of their positive screening result. Because preterm infants often have lengthy hospital stays after birth, we checked to see how many preterm infants were still in the hospital at 2 months of age. Of those preterm infants for whom we had birth admission claims ($n = 4840$), 95% were discharged from the hospital before 2 months of age.

We classified a claim as an outpatient visit for acute care if the claim contained any of the following *Current*

Procedural Terminology (CPT) evaluation and management (E&M) codes: 99201–99205 (new patients); 99211–99215 (established patients); and 99241–99245 (office consultation). We used the following CPT E&M codes to identify outpatient visits for well-child care: 99381–99386 (new patients) and 99391–99397 (established patients).

We analyzed ED visits, observation care visits, and urgent care visits as 1 visit category because all of these visits occur in similar care settings and similar services are provided. We classified a claim as an ED visit if a claim contained either of the following: a revenue code (045x) or a CPT E&M code (99281–99285). We classified a claim as an observation care or urgent care visit if the claim had any of the following codes: 99217–99220, 99234–99236, or G0381–G0383 (CPT codes) or 700 (cast room), 760–762 (specialty room/observation room), or 769 (other treatment/observation room) (revenue codes).

We identified inpatient visits as claims that had a billing revenue code of 100 through 179 or 190 through 219 and 2 of the 3 following elements: admission date; discharge date; length of stay. When an infant was transferred to another hospital during an admission, we counted the infant as having a single hospitalization.

Chronic Illness

Because chronic illness can confound the relationship between NBS result type and health care utilization, we accounted for chronic illness among the study population by using the Clinical Risk Group (CRG) software system developed by 3M (Wallingford, CT). With this software we analyzed administrative claims for visits, procedures, and medication use and assigned children to 9 different health status groups (healthy, significant acute illness, and 7 chronic illness groups). In previously published studies this software was

TABLE 1 Demographics of the Study Population

	Normal, <i>n</i> (%)	False-Positive, <i>n</i> (%)
Gestational age		
≥37 wk (term)	43 968 (86.3)	460 (54.4)
<37 wk (preterm)	5173 (10.1)	358 (42.4)
Gender ^a		
Female	25 033 (49.1)	345 (40.8)
Male	25 919 (50.9)	500 (59.2)
Birth weight ^b		
≥2500 g	45 831 (90.0)	561 (66.4)
<2500 g	4524 (8.9)	271 (32.1)
Missing	597 (1.1)	13 (1.5)
Chronic illness ^a		
No	44 695 (87.7)	538 (63.7)
Yes	6257 (12.3)	307 (36.3)

^a $P < .001$.

^b $P < .05$.

used to assess chronic illness in a cohort of pediatric patients who were covered by Medicaid.^{7,8} For this analysis, we created a dichotomous chronic illness variable: no chronic illness (a CRG status of healthy or significant acute) versus chronic illness (any of 7 CRG chronic illness health status levels). Each individual assigned to a health status level also had a primary chronic disease (PCD) that represented the most significant chronic condition for which the infant was under active treatment. We have provided a list of the top 5 PCDs for infants with false-positive and normal NBS results (Appendix 2).

Statistical Analysis

Our objective for this study was to compare outpatient, ED, and inpatient visits between infants with false-positive NBS results and infants with normal NBS results. We performed χ^2 tests on demographic characteristics stratified according to NBS result type (Table 1). We also calculated the number of infants with false-positive results for various disorders or metabolites, categorized these results either as an endocrine or a metabolic abnormality, and stratified them according to gestational age (Table 2).

TABLE 2 Disorders/Analytes for False-Positive Results

Disorder/Analytes	Term, <i>n</i>	Preterm, <i>n</i>
Endocrine	282	268
Congenital hypothyroidism	233	51
Congenital adrenal hyperplasia	49	217
Metabolic	178	90
Biotinidase	119	34
Propionic acidemia	14	7
3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)	14	0
Acyl-carnitine abnormality	13	41
Argininemia	0	1
Carnitine palmitoyl transferase IA/II deficiency (CPT1A/CPT2)	5	1
Short-chain acyl-CoA dehydrogenase deficiency (SCAD)	5	0
Medium/short-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency (M/SCHAD)	4	0
Carnitine uptake deficiency	1	1
Isovaleric acidemia	1	3
Phenylketonuria (PKU)	1	0
Homocystinuria	0	1
Isolated elevation	0	1
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	1	0

CoA indicates coenzyme A.

We calculated the average and total numbers of visits in each health care visit category according to gestational age (preterm versus term). Using negative binomial regression to account for overdispersion,⁹ we calculated an unadjusted and adjusted incidence rate ratio (IRR) for each visit category. The adjusted model included covariates for gender, birth weight, gestational age, and chronic illness. Prompted by our clinical experience, we explored an interaction effect between gestational age (preterm versus term) and NBS screening result (false-positive versus normal). We then calculated the predicted rates of visits on the basis of the presence of the interaction. By slicing interactions, we tested the difference in visit rates between infants with false-positive and infants with normal NBS results for each gestational age (eg, preterm

and term) in those visit categories in which the interaction was significant.

RESULTS

Study Population

After we applied exclusion criteria to the matched study population, there were 49 141 infants with normal NBS results and 818 with false-positive NBS results. Of the term infants with false-positive results, 282 had an endocrine abnormality and 178 had a metabolic abnormality (Table 2). Infants with false-positive results were more likely to be male, have a birth weight of <2500 g, and have a chronic illness (Table 1).

Health Care Visits

We calculated the visit rates for infants for each type of health care visit category (Table 3). In unadjusted analyses,

there was a statistically significant increase in acute outpatient visits (IRR: 1.36 [95% confidence interval (CI): 1.26–1.46]), emergency visits (IRR: 1.16 [95% CI: 1.05–1.28]), and hospitalizations (IRR: 2.71 [95% CI: 2.14–3.44]) for infants with false-positive NBS results but no difference for outpatient well visits (IRR: 1.02 [95% CI: 0.97–1.07]). After adjustment for gender, birth weight, gestational age, and chronic illness, infants with false-positive NBS results remained more likely to have additional acute outpatient visits (IRR: 1.07 [95% CI: 1.00–1.15]) but not outpatient well visits (IRR: 1.0 [95% CI: 0.96–1.05]), emergency visits (IRR: 0.95 [95% CI: 0.86–1.05]), or hospitalizations (IRR: 1.19 [95% CI: 0.96–1.47]).

However, we noted differences in visit rates across different health care visit categories according to gestational age (Table 3). We then found a significant interaction between gestational age and NBS result type (eg, false-positive or normal) in the adjusted model for outpatient acute visits ($P = .004$) but not for any of the other types of health care visit categories. The adjusted predicted mean rates for acute outpatient visits were highest for preterm infants who received false-positive results even after we adjusted for chronic illness (Fig 2). After adjustment of data for confounders and interaction effects, preterm infants with false-positive NBS results had more acute outpatient visits than preterm infants with normal NBS results ($P = .001$). However, term infants with false-

TABLE 3 Health Care Visit Rates (Unadjusted) of Children According to Newborn Screening Result and Gestational Age

	Preterm		Term		Total	
	Normal	False-Positive	Normal	False-Positive	Normal	False-Positive
Outpatient (acute)	3.8 (19 535)	5.8 (2085)	3.3 (143 361)	3.5 (1593)	3.3 (162 896)	4.5 (3678)
Outpatient (well)	2.3 (12 145)	2.4 (867)	2.3 (103 033)	2.4 (1086)	2.3 (115 178)	2.4 (1953)
Emergency visit ^a	1.3 (6845)	1.6 (558)	1.1 (47 188)	1.1 (486)	1.1 (54 033)	1.3 (1044)
Hospitalization	0.1 (735)	0.3 (108)	0.1 (2722)	0.1 (48)	0.1 (3457)	0.2 (156)

Rates per child (visits).

^a Includes observation visits.

FIGURE 2

Figure 2. Adjusted predicted mean visit rates for children according to NBS result and gestational age.

positive NBS results did not have more acute outpatient visits than term infants with normal NBS results ($P = .64$).

DISCUSSION

Since the early days of NBS, there has been concern that parents of infants with false-positive NBS results overuse health care services because they believe their child to be persistently vulnerable to illness.¹⁰ Previous studies that have used voluntary enrollment of study participants instead of a population-based methodology have yielded conflicting results.^{3,4}

In this study, which represents the largest and only population-based analysis to date, we found that only preterm infants with false-positive NBS results had more acute outpatient visits than their preterm counterparts with normal NBS results. We did not find such a difference among term infants. Furthermore, regardless of prematurity status, we found no difference in outpatient well visits, ED visits, or hospitalizations between infants with false-positive and those with normal NBS results.

There are a number of possible explanations for our findings. First, it is possible that parents of premature infants with false-positive NBS results make more acute outpatient visits be-

cause they are overanxious about both the child's history of prematurity and the false-positive NBS result. However, others might counter that parents of preterm infants deal with so many concerns about their child's tenuous health that parents are unlikely to pay much attention to a false-positive NBS result. Second, it is conceivable that preterm infants with false-positive NBS results have more acute outpatient visits because of their underlying chronic illness. Premature infants are known to have a higher rate of false-positive results because of illness-related stress¹¹ and the use of screening cutoffs based on studies of term infants.^{12,13} So it is possible that, despite our best efforts, we were unable to fully control for the confounding influence of chronic illness on health care use in preterm infants with false-positive results. Nonetheless, additional studies should be performed to examine the psychosocial effects of a false-positive NBS result on parents of preterm infants. Finally, although case reports have identified cases in which infants with false-positive results have been inappropriately diagnosed as disease free,¹⁴ this phenomenon is likely to be uncommon and thus is not likely to account for our study findings.

We did not find any differences between infants with false-positive and those with normal NBS results for other health care visit types (eg, well visits, ED visits, hospitalizations), regardless of prematurity status. There are a number of plausible explanations for this null finding. First, it is possible that the phenomenon of parental anxiety that leads to increased health care use¹⁵ is present only in certain subgroups, such as parents who had difficulty conceiving, those with pregnancy complications, or even first-time parents. These subgroups may be "primed" to become concerned about the lasting significance of their

child's false-positive NBS result. If so, it is unlikely that these subgroups will be identified in an aggregate analysis of a study population.

Alternatively, it may be that there are certain types of false-positive results, such as those for disorders that can be more immediately life-threatening, such as MCADD (medium chain acyl CoA dehydrogenase deficiency). Hearing that their newborn may have a potentially life-threatening illness leave a more powerful and lasting effect on parents' perceptions of their child's health than if they had been told that the disorder was not immediately life threatening.¹⁶ We had neither sufficient numbers of these disorders nor the necessary parental medical and social information to explore either of these hypotheses in the current analysis.

It is conceivable that our findings are unique to a continuously enrolled Medicaid population. Children with private insurance have greater outpatient health care use than children with public insurance.¹⁷ Although some of this discrepancy in use may be because of lack of access to care among the publicly insured, it could also be fueled by the phenomenon of the "worried well." Future studies will need to examine the relationship between false-positive NBS results and health care use in a privately insured population.

There are limitations of this study that should be noted. As evidenced by the fact that every child in our analysis did not have a claim record for their birth admission ($n = 8729$ [17%]), it is likely that our collection of claims did not represent all of the health care visits for the study population. Nonetheless, we have no reason to suspect there would be a differential bias for missing claims according to NBS result. As noted above, we may not have completely controlled for chronic illness,

and so our results may be explained, in part, by residual confounding. Finally, because we examined only health care use in the first 12 months of life, children may not have had enough opportunities to seek acute care for illness. As a result, we might have failed to detect a difference between infants with false-positive and normal NBS results that would become evident in the next few years of life when the ratio of acute to well health care visits rises.

In addition, it is important to recognize that increased health care utilization is only one potential manifestation of parental anxiety about false-positive NBS results. Although we did not find a link between false-positive NBS results and increased health care visits, we cannot rule out that parental anxiety about false-positive results may have been present and could conceivably have been manifested through other actions, such as decisions to forego future childbearing or restriction of the child's activity.¹⁸ Additional studies are needed to explore the presence and

scope of maladaptive parental behaviors that might result from persistent parental anxiety regarding false-positive NBS results.

CONCLUSIONS

We believe that our study findings highlight the potential complexity of the relationship between false-positive NBS results and future health care use. We were unable to find a difference in health care visits between term infants with false-positive results and those with normal NBS results in a Medicaid population. However, because a parent's worry about his/her child's health predicts health care use for that child,¹⁵ it may be that the relationship between false-positive NBS results and health care use exists only in certain subgroups of the population who are prone to being more worried about their child's health. Nonetheless, in this study we have demonstrated that it is important that future studies of the effect of false-positive results on future health care use account for the

potential interaction effect between NBS result and gestational age.

ACKNOWLEDGMENTS

This project was funded by the Robert Wood Johnson Health and Society Scholars Small Grant Award, the Michigan Institute for Clinical and Health Research, and an intramural grant through the department of pediatrics at the University of Michigan. This work was conducted with a research license from 3M corporation and was not funded by the 3M corporation. Dr Tarini was supported by the Clinical Sciences Scholars Program at the University of Michigan and a K23 Mentored Patient-Oriented Research Career Development Award from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (K23HD057994).

We acknowledge Lisa Cohn and Dr John Neff for their helpful comments with data analysis and Dr Piero Rinaldo for his thoughtful comments during the preparation of the manuscript.

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APPENDIX 1 Disorders Included in the Michigan NBS Panel, 2006

Phenylketonuria (PKU)
 Isovaleric acidemia (IVA)
 Benign hyperphenylalaninemia (H-PHE)
 2-Methylbutyryl-CoA dehydrogenase deficiency (2MBG)
 Biotin cofactor biosynthesis (BIOPT [BS])
 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)
 Defects of biotin cofactor regeneration (BIOPT[Reg])
 3-OH 3-CH3 glutaric aciduria (HMG)
 Maple syrup disease (MSUD)
 3-Methylglutaconic aciduria (3MGA)
 Homocystinuria (HCY)
 Beta-ketothiolase deficiency (BKT)
 Hypermethioninemia (MET)
 Glutaric acidemia type I (GA I)
 Citrullinemia (CIT)
 Propionic acidemia (PA)
 Citrullinemia type II (CIT II)
 Methylmalonic acidemia (mutase deficiency) (MUT)
 Argininosuccinic acidemia (ASA)
 Methylmalonic acidemia (MA), also known as cobalamin A or B deficiency (CblA, CblB)
 Tyrosinemia type I (TYR I)
 Methylmalonic acidemia (MA), also known as cobalamin C or D deficiency (CblC, CblD)
 Argininemia (ARG)
 Multiple carboxylase deficiency (MCD)
 Carnitine:acylcarnitine translocase deficiency (CACT)
 2-Methyl 3 hydroxy butyric aciduria (2M3HBA)
 Carnitine palmitoyltransferase II deficiency (CPT II)
 Malonic acidemia (MAL)
 Carnitine uptake defect (CUD)
 Isobutyryl-CoA dehydrogenase deficiency (IBG)
 Carnitine palmitoyltransferase IA deficiency (liver) (CPT 1A)
 Congenital adrenal hyperplasia (CAH)
 Short-chain acyl-CoA dehydrogenase deficiency (SCAD)
 Congenital hypothyroidism (CH)
 Glutaric acidemia type II (GA II)
 Galactosemia (GALT)
 Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
 Biotinidase deficiency (BIOT)
 Long-chain L-3-OH acyl-CoA dehydrogenase deficiency (LCHAD)
 Sickle cell anemia (HbSS)
 Trifunctional protein deficiency (LCHAD/TFP)
 HbS/C disease (HbS/C)
 Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
 HbS/ β -thalassemia (HbS/ β -Th)
 Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT)

CoA indicates coenzyme A.

Data source: Korzeniewski SJ, Young WI, Andruszewski K, Hawkins HC. *Michigan Newborn Screening Program, Annual Report, 2006*. Lansing, MI: Michigan Department of Community Health. Available at: michigan.gov/documents/mdch/Final_NBS_2006_Report_222194_7.pdf.

APPENDIX 2 Top 5 PCD Categories According to NBS Result Type

PCD Category	<i>n</i>
Infants with false-positive NBS results	
Major respiratory anomalies	65
Asthma	48
Other chronic pulmonary diagnoses	29
Blindness, visual loss, and chronic eye diagnoses, major/moderate	23
Chronic endocrine, nutritional, fluid, electrolyte, and immune diagnoses	12
Infants with normal NBS results	
Asthma	2286
Major respiratory anomalies	352
Ventricular and atrial-septal defects	340
Other chronic pulmonary diagnoses	318
Hydrocephalus, encephalopathy, and other brain anomalies	181

TESTING FOR FETAL GENDER: My wife and I have 4 children. Each pregnancy was marked by joy, eager anticipation, and many, many long discussions trying to decide on a name for our child. We had to pick out names for both girls and boys because we had always instructed the obstetrician doing the prenatal ultrasound not to reveal the sex of the fetus. Although our discussions were not quite as bitter as those between Democrats and Republicans in Congress, they did last a long time and were marked by twists, surprises, and compromises. It turns out, however, that couples can save themselves some trouble. As reported in *The New York Times* (Health: August 9, 2011), a recently published systematic review and meta-analysis of noninvasive fetal sex determination testing in ~6500 pregnancies found that properly performed tests had $\geq 95\%$ sensitivity and specificity at 7 weeks' gestation and 99% sensitivity and specificity at 20 weeks' gestation. The review focused on tests that detect and amplify cell-free fetal DNA in maternal blood. The test kits generally use polymerase chain reaction to detect the fetal Y chromosome in a few drops of maternal blood. Detection of the Y chromosome confirms a male infant. Failure to detect the Y chromosome indicates that the fetus is a girl or, possibly, that no fetal DNA was present in the sample. Although the kits have been available for several years, they are not regulated by the US Food and Drug Administration, and some have been plagued by poor specificity. The fetal DNA test kits are likely to be used by parents and physicians worried about sex-linked diseases such as Duchenne muscular dystrophy and those just anxious to know the sex of their child a little earlier. Although not usually an issue in the United States, because the kits can be used to select the sex of offspring, some manufacturers do not sell the kits in India or China, where boys are favored over girls. Although the tests are noninvasive, the total cost can be quite high. The test kit itself may cost \$25, but once shipping and laboratory fees are calculated, the total cost may be closer to \$250. As for us, we were fortunate that we did not have to worry more than usual about gender-linked illnesses, and the surprise of seeing each of our new arrivals greet us in the delivery room regardless of gender was priceless.

Noted by WVR, MD