Effect of Laboratory Practices on the Incidence Rate of Congenital Hypothyroidism

abstract

OBJECTIVE: Newborn screening (NBS) laboratories in the United States expanded their programs to include primary congenital hypothyroidism (CH) in the 1970s. An increase in the national CH-incidence rate since 1987 has been reported. Our goal was to analyze national data reported by state NBS programs and laboratories from 1991 to 2000 to determine the extent to which changing laboratory methods might have contributed to the reported rise in CH-incidence rate.

METHODS: We used generalized estimating equations to analyze the association between the rate of confirmed cases of CH per 100 000 live births and the initial screening method (thyroxine [T4] or thyrotropin [TSH] assay), the T4- and TSH-assay methods, the screening-test cutoff value used to report abnormal T4- or thyrotropin-assay results, and the performance of a second screen on ≥80% of newborns in the state. We then evaluated the association of CH rate with year after adjusting for any screening methodology or parameter that was significant in the univariate analysis.

RESULTS: During 1991–2000, laboratories that used a TSH assay for initial screening reported a 24% higher incidence rate of CH than those that used a T4 assay. The assay type also affected the incidence rate. Screening for T4 by enzyme immunometric assay (EIA) or fluoroimmunoassay (FIA) methods resulted in 38% and 24% higher incidence rates of CH, respectively, compared with the radioimmunoassay (RIA) method, whereas screening for TSH by the FIA method resulted in a 20% higher incidence rate of CH than did screening with radiochemical methods. During the decade studied, many laboratories changed their T4-assay method from RIA to either FIA or EIA; this particular change seemed to have the greatest impact on the CH-incidence rate.

CONCLUSIONS: Although the use of different laboratory methods and screening practices by NBS laboratories affected the incidence rate of CH, after adjusting for screening methodologies and parameters, an increasing incidence rate still persisted during the decade studied. Thus, there seem to be additional unknown factors that contributed to the reported increase in incidence rate. *Pediatrics* 2010;125:S48–S53

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KEY WORDS

hypothyroidism, incidence rate, newborn screening, diagnosis, laboratory methodology

ABBREVIATIONS

NBS—newborn screening
CH—primary congenital hypothyroidism
T4—thyroxine
TSH—thyrotropin
NNSIS—National Newborn Screening Information System
NNSGRC—National Newborn Screening and Genetics Resource Center
FIA—fluoroimmunoassay
EIA—enzyme immunometric assay
RIA—radioimmunoassay
IRMA—immunoradiometric assay
NSQAP—Newborn Screening Quality Assurance Program
OR—odds ratio
CI—confidence interval

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Newborn screening (NBS) for primary congenital hypothyroidism (CH) began with the work of Dussault and Laberge in the 1970s.[1] They successfully added CH screening to an ongoing NBS program for phenylketonuria in Canada.[2] Shortly thereafter, NBS laboratories in the United States and elsewhere began to expand their NBS programs to include CH, and it is now one of many congenital disorders for which newborns are screened in all US states and territories and in many other countries.[3] Initially, most North American NBS programs measured thyroxine (T4) as the initial screening methodology, whereas screening in other countries often measured the concentration of thyrotropin (TSH). Although elevations of TSH concentration are generally acknowledged as a better disease predictor, T4 concentrations are less subject to physiologic variations shortly after birth; therefore, the T4 method was more popular in the initial screening strategy in NBS systems that were affected by early hospital discharge or early specimen collection. To improve screening sensitivity and specificity, initial T4 screening is usually accompanied by second-tier TSH screening. In this screening algorithm, a proportion of specimens with abnormal T4 results (usually ~10%) are retested to determine their TSH concentrations, and the combined T4 and thyrotropin results are used together to determine the need for patient recall.[4] Both screening strategies (TSH screening alone or T4 screening with second-tier TSH screening) have been shown to provide essentially equivalent case detection.[5]

As part of the 6-part NBS system,[6] program evaluation is a necessary component for ensuring quality and identifying areas for improvement and further study. The Council of Regional Networks for Genetic Services initiated a national NBS data-collection effort in the late 1980s that has evolved into the National Newborn Screening Information System (NNSIS), currently maintained online by the National Newborn Screening and Genetics Resource Center (NNSGRC). Through systematic review of various NNSIS data elements, state NBS programs can monitor their performance over time and compare their outcomes with those of other programs as a self-assessment strategy.[7] Previously, a review of the case-detection data for various NBS disorders revealed a tendency toward an increased CH-incidence rate over time.[8] In 2007, a detailed internal analysis of the CH screening data in New York further revealed this trend in CH-incidence rate for the state (138% increase in incidence rate, from 1 in 3378 in 1978 to 1 in 1414 in 2005) and nationally, excluding New York (73% increase in incidence rate, from 1 in 4098 in 1987 to 1 in 2370 in 2002).[9]

Because decisions about medical services at both the state and national levels typically take into account disease-incidence rates, it is important to understand observed trends, particularly if there is an unexplained increase such as that identified for CH. Many factors may cause an increased incidence, including changing demographic characteristics of the US population and evolving medical management practices. For a summary of factors that potentially affect the CH-incidence rate, see the article by Olney et al.[10]

There currently is no national NBS policy; US NBS programs are state based, and significant differences exist among state NBS laboratories regarding laboratory instrumentation, commercial kits, and diagnostic criteria. In addition, testing techniques have changed over time; in particular, many laboratories have changed from a radiochemical-based assay to a fluoroimmunoassay (FIA) or enzyme immunometric assay (EIA). Furthermore, to detect clinically significant disorders that might be missed by a single NBS test, 8 states have mandated that a second NBS sample be collected from all infants, preferably at 8 to 14 days of age, regardless of the results of the first NBS test, and 3 other states routinely perform a second screening test on >85% of newborns in the state. The number and proportion of newborns who receive an obligatory second newborn screen has increased over time; currently, 22% to 23% of all US newborns receive a mandated or strongly recommended second screening. There is evidence that some cases of CH may not be detected until the second screen, which potentially affects the CH-incidence rate in those states that have adopted routine second screening relative to those that have not.[11–14]

Any changes that occur in the NBS laboratory protocol have the potential for causing a difference in CH-incidence rate because of variations in sensitivity and specificity of the screening test. Therefore, a change in laboratory methodology that modestly affects these parameters may alter the CH-incidence rate over time, particularly if multiple laboratories make similar methodology modifications. As changes in laboratory screening practices for CH have occurred over time, it is reasonable to evaluate whether such changes might be associated with the observed increasing incidence rate of CH. The purpose of this study was to quantify the effect of changing laboratory practices on the incidence rate of CH over the 1991–2000 decade to determine their relative contributions to the observed increase.

METHODS

Data for these analyses were extracted from information reported by state NBS programs to the NNSIS from 1991 to 2000. The 10-year data were com-

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piled by the NNSGRC and submitted to each state NBS program director for correction and validation as confirmed cases of CH. Cases of CH were confirmed through individual state NBS program protocols. Data from all 51 US programs (50 states plus the District of Columbia) were validated. We used the number of births that occurred in state jurisdictions reported to the NNSGRC by the National Center for Health Statistics and assumed that all infants were screened. For each state in each year we reviewed the following data points: the number of confirmed cases of CH; the method for initial screening (T4 assay, TSH assay, or both); the method for T4 screening (radioimmunoassay [RIA], EIA, or FIA); the reported abnormal cutoff value for the T4 assay; the method for TSH screening (RIA or immunoradiometric assay [IRMA] as a combined group, EIA, or FIA); the reported abnormal cutoff value for the TSH assay; whether a second screen was performed on ≥80% of newborns in the state; and the number of live births. State laboratories that did not report exact cutoff values for their screening tests but, rather, reported a percentage for the cutoff (eg, lowest 10%) were excluded from the analyses of the screening-test cutoff values.

Further evaluations of changes in laboratory cutoff values for the T4 and TSH assays were performed by using data from the Newborn Screening Quality Assurance Program (NSQAP) at the Centers for Disease Control and Prevention. The NSQAP has been operating a proficiency testing program for CH since 1978. Dried blood spot quality-control and proficiency-testing materials enriched with varying concentrations of T4 and TSH have been distributed to state NBS laboratories and to private and contract laboratories. Participants tested the specimens and sent back quantitative and qualitative results, in addition to reporting the methods used for testing. The NSQAP began collecting laboratory cutoff information in 1997, whereas the types of methods used were reported for the entire study period.

Because our goal was to determine if changing laboratory methods and diagnostic criteria contributed to the rise in the CH-incidence rate, we first examined trends in the number of confirmed cases of CH versus the number of live births (ie, the incidence rate) by combining data from all state NBS programs and using state as a repeated measure. We performed the following analytic steps: (1) regression analysis of the annual CH-incidence rate; (2) variance of the CH-incidence rate by the initial screening method, also including the T4-assay (RIA, FIA, or EIA) and TSH-assay (RIA/IRMA combined, FIA, or EIA) methods, as relevant; (3) regression analysis of the annual CH-incidence rate versus T4- and TSH-assay cutoff values for an abnormal screening-test result, as relevant; and (4) regression analysis of the annual CH-incidence rate versus whether a second obligatory NBS test was performed on ≥80% of births in the state, as relevant. We then examined the relationship to year after adjusting for laboratory characteristics. These analyses were performed on all reporting states and the District of Columbia, except for New York. Data from New York were excluded from the analyses because of major differences between the number of cases of CH reported annually in the validated NNSIS data and the number of cases of CH reported in the published results from a New York study that showed an increasing CH-incidence rate over time.[9]

Each of these analyses was performed by using SAS 9.2 (SAS Institute, Inc, Cary, NC). In particular, the proc genmod procedure in SAS was used to create a generalized estimating equation analysis,[15,16] with the number of cases of CH as the numerator, the number of occurrent live births as the denominator, a log link, and the negative binomial distribution to account for extra-Poisson variation.

In the analyses with state as a repeated measure, we used an exchangeable correlation matrix. From the results, odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated. Results were statistically significant at $P < .05$.

RESULTS

Table 1 lists the ORs and associated 95% CIs for analysis of year and for laboratory methods in a univariate analysis on all states together (except New York) for the incidence rate of CH among live births. A 4% increase in CH-incidence rate according to year during the 1991–2000 time period was observed (OR: 1.04 [CI: 1.02–1.05]), which is equivalent to a 42% increase in incidence rate from 1991 to 2000.

TABLE 1 ORs and Associated 95% CIs for Analysis of Year and for Laboratory Methods in Univariate Analyses, All States (Except New York)

Covariate	OR (95% CI)
Year	1.04 (1.02–1.05)[a]
Initial screening analyte	
T4	0.76 (0.63–0.92)[a]
T4/TSH	0.89 (0.72–1.10)
TSH	Referent
T4 method	
EIA	1.38 (1.22–1.57)[a]
FIA	1.24 (1.10–1.40)[a]
RIA	Referent
T4 cutoff value	1.05 (1.00–1.10)
TSH method	
EIA	1.16 (0.97–1.38)
FIA	1.20 (1.08–1.34)[a]
RIA/IRMA	Referent
TSH cutoff value	1.00 (0.99–1.01)
Obligatory second screen for ≥80% of the infants	0.94 (0.76–1.18)
Year (only states that use the RIA-for-T4 method)	1.03 (1.01–1.05)[a]
Year (only states that use the EIA or FIA-for-T4 method)	1.04 (1.01–1.08)[a]

[a] Statistically significant ($P < .05$) results.

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Laboratories screen for CH by initially measuring concentrations of T4, TSH, or both. For laboratories in which T4 was the initial screened analyte, the CH-incidence rate was 24% lower than for laboratories in which TSH was the initial analyte (OR: 0.76 [CI: 0.63–0.92]).

The number of available testing methods for T4 and TSH increased from 1991 to 1997 and then declined in 2000 (Table 2). All methods reported were immunoassay based. Although numerous testing methods were reported because of the availability of different commercial kits, testing methods could still be grouped into a radiochemical-based method, FIA, or EIA. However, variability probably exists even within groups, and it was not possible to account for potential within-group variability in the analyses for the T4 or TSH methods.

Laboratories that measured the T4 concentration by using either the EIA or FIA procedure had at least a 24% higher incidence rate of CH than did laboratories that used the RIA procedure (Table 1). As shown in Table 3, the trend over the decade was for state laboratories to shift away from using RIA to using EIA or FIA for the T4 assay. We hypothesized that the increasing CH-incidence rate during the decade could be largely attributable to laboratories changing the T4-assay method from RIA to EIA or FIA. Therefore, we stratified the data set into states and years in which the RIA method was used to measure T4 versus states and years in which EIA or FIA was used to measure T4. We found that the association between year and CH-incidence rate was only slightly attenuated when RIA was used (OR: 1.03 [for RIA] vs 1.04 [for all states combined]; Table 1). There was no attenuation of the association between year and CH-incidence rate when EIA or FIA was the T4-assay method. Although the CH-incidence rate was at least 24% higher for states and years in which the EIA or FIA method was used to assay T4 rather than the RIA method, there was still a significant increase in the CH-incidence rate among states that used EIA or FIA, as well as among those that used RIA.

In the univariate analysis of the procedure for measuring TSH, results were similar to those for T4 (Table 1). Laboratories that used the FIA method had a 20% higher incidence rate of CH than did those that used radiochemical assay methods (OR: 1.20 [CI: 1.08–1.34]). The CH-incidence rate for laboratories that used EIA was also higher than for those that used RIA, but the difference did not reach statistical significance.

Mean cutoff values for the T4 and TSH assays, along with the range of cutoff values for the years 1997–2000, are listed in Table 4. For T4 assays, results are reported as abnormal for values below the cutoff. The mean cutoff value for T4 (serum) decreased from 8.0 μg/dL in 1997 to 6.6 μg/dL in 1998 and remained relatively stable through 2000. The minimum cutoff values for T4 changed little over the 4-year period; the maximum cutoff values were higher for 1997 and 2000 and lower for 1998 and 1999. Although a specific pattern did not emerge, because data are not reported for the earlier part of the decade (1991–1996), at least for the more recent years it seems that, overall, the cutoff values for T4 decreased, which suggests the use of more stringent criteria for identifying screening-test results as abnormal.

For TSH assays, results are reported as abnormal for values above the cutoff. The mean cutoff value for TSH increased from 1997 to 1999 and then remained stable in 2000 (Table 4). The minimum cutoff value for TSH (serum) increased between 1999 and 2000, from 11.0 to 17.4 μIU/mL, while the maximum values remained the same. The upward trend in the TSH cutoff value also suggests more stringent criteria for this screening-test result being considered as abnormal.

Because modest changes were observed by the NSQAP in the cutoff values for the T4 and TSH assays during the latter part of 1991–2000, the possibility of an effect of cutoff values on the

TABLE 2 Methods Reported to the NSQAP for T4 and TSH Assays

Year[a]	T4 Assay, *n*	TSH Assay, *n*
1991	6	6
1993	6	6
1994	4	4
1996	9	11
1997	10	10
1998	9	8
1999	7	8
2000	7	9

[a] Information was missing for 1992 and 1995.

TABLE 3 T4 Assay Methodology as Reported by the State Laboratories for Each Year

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
RIA, *n*	48	46	46	44	41	36	29	25	24	20
Midyear shift from RIA, *n*[a]	0	0	0	2	1	0	1	1	0	1
EIA or FIA, *n*	0	1	1	1	3	4	8	15	15	18
Laboratory did not test for T4, *n*[b]	2	2	2	3	3	6	9	10	10	12
No data, *n*[c]	1	2	2	1	3	5	4	0	2	0

Data are from the annual data reports submitted to the NNSGRC.

[a] The laboratory reported that a shift occurred during the year from RIA to either EIA or FIA.

[b] The screening analyte tested in the laboratory was TSH, so the laboratory did not perform the T4 assay.

[c] The laboratory did not submit data for the annual report on the type of method used.

TABLE 4 Mean Cutoff Values and Ranges for T4 and TSH Reported to the NSQAP

Year	T4 Mean (Range) Cutoff, μg/dL Serum	TSH Mean (Range) Cutoff, μIU/mL Serum
1997	8.0 (5.0–12.8)	27.2 (11.0–50.0)
1998	6.6 (5.0–10.0)	28.4 (11.0–50.0)
1999	6.6 (5.0–10.0)	29.4 (11.0–50.0)
2000	6.9 (5.0–13.0)	29.5 (17.0–50.0)

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incidence rate of detected cases of CH was suggested. Therefore, univariate analyses were performed with regard to the laboratories' cutoff values for an abnormal T4 or TSH concentration in relation to the CH-incidence rate, and when the entire decade was evaluated, there were no significant associations found for the CH-incidence rate in relation to the cutoff value for either analyte (Table 1).

Some NBS laboratories in states that mandate or strongly recommend routine second screening (10 days to 3 weeks of age) have reported varying degrees of cases of CH detected on the second screen after a normal initial screen result, which suggests that states that perform second screens on the majority of newborns might have a higher incidence rate of CH. However, by using univariate analysis comparing states with a single screening test and states in which ≥80% of newborns received a second obligatory NBS test, we found that there was no significant difference in CH-incidence rates (Table 1).

In general, when adjusting for various laboratory method parameters in regression analyses on all states (except New York), there was some attenuation of the association of year with CH-incidence rate (Table 5). In fact, the regression analysis on states that performed the T4 assay, when adjusting for the assay method and the screening-test cutoff value, showed a confidence interval that included 1.00 (OR: 1.02 [CI: 1.00–1.05]), which indicates that there was no significant trend of increase for the incidence rate of CH according to year after accounting for the T4-assay method and cutoff value. However, in states that performed the TSH assay, when adjusting for the assay method and the screening-test cutoff value, we found no attenuation of the CH-incidence rate increase according to year (OR: 1.04 [CI: 1.02–1.06]). Regression analysis on all states with adjustment for initial screening analyte continued to show a significant trend of increase for the incidence rate of CH according to year, but with an attenuated OR of 1.03 (CI: 1.02–1.05).

TABLE 5 ORs and Associated 95% CIs for Analysis of Year After Adjustment for Laboratory Methods Using All States (Except New York)

Adjustment for	OR (95% CI)
Initial screening analyte	1.03 (1.02–1.05)[a]
T4 method and cutoff value	1.02 (1.00–1.05)
TSH method and cutoff value	1.04 (1.02–1.06)[a]

[a] Statistically significant ($P < .05$) results.

DISCUSSION

NBS is a national public health system that has been successful in identifying newborns with specific metabolic, endocrinologic, and hematologic conditions who are at risk for significant morbidity or mortality if treatment is delayed.[3] However, screening laboratory procedures vary across the NBS system, and it is reasonable to assume that differences in screening methodologies or parameters might yield different incidence rates for the screened conditions. Results of the analyses reported here indicate that such differences can be seen with CH screening. During the 1991–2000 decade, laboratories that used a TSH assay as the initial screening method reported a 24% higher incidence rate of CH than laboratories that used a T4 assay for initial screening. The type of assay method also seemed to affect the CH-incidence rate. Screening for T4 by the EIA or FIA methods led to a 38% and 24% higher CH-incidence rate, respectively, when compared with that from the RIA method, whereas screening for TSH by FIA resulted in a 20% higher CH-incidence rate compared with that from radiochemical methods (RIA/IRMA).

Our analyses revealed a 4% increase in CH-incidence rate according to year during 1991–2000, which confirms previous reports.[8,9] There were some indications that shifts in testing methodology that occurred during the decade might be associated with the apparent increasing CH-incidence rate. There was a significant trend during the decade for laboratories to change their T4-screening method from RIA to either FIA or EIA; this particular change in laboratory protocol seemed to have had the greatest impact on the incidence rate of CH. However, laboratories that used RIA or either FIA or EIA still had an increase in the CH-incidence rate, which indicates that factors other than the T4-screening method also contributed to the CH-incidence rate increase. Although some laboratories changed to an initial TSH assay during the decade (2 laboratories in 1991 and 12 in 2000 screened for TSH alone), there was considerably less effect from this methodology change.

Even after taking into account all of the changes in screening methodologies and parameters, an increasing incidence rate of CH still persisted during the decade, particularly among states that performed the TSH assay as the primary screening analyte. Thus, we conclude that additional factors also contributed to the increasing CH-incidence rate, particularly because some states have reported an increase during periods in which no changes in laboratory methodology occurred (see the article by Hinton et al[17]). Other potential factors that could affect the CH-incidence rate include changes in medical management, demographic composition of US births, rate of preterm or low birth weight births, and misclassification or misreporting of transient hypothyroidism as true CH (for discussions of these fac-

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tors, see the articles by Olney et al,[10] Hinton et al,[17] and Parks et al[18]).

The timing of reporting cases of CH to the NNSGRC may have also affected the incidence rate and could continue to do so. With implementation of a Web-based NNSIS reporting system during the past decade, the speed with which case reports have been recorded in the national database has increased; cases today are reported within weeks or months versus years in the 1990s. The implications of timing of case reporting are felt most in differentiating transient from permanent hypothyroidism. Physiologic variations in thyroid hormone production at or near birth sometimes result in "apparent" cases of CH, which typically resolve as the endocrine system matures by 2 to 3 years of age. For this reason, it is common for patients whose CH status is not clear to be taken off treatment at 3 years of age to determine if their hypothyroidism was transient.[4] Given the longer time frame for reporting cases to the NNSGRC in the 1990s, some NBS programs may have subsequently excluded cases of transient hypothyroidism from their overall case counts, whereas others may not have done so. With the shortened time frame for reporting cases of CH, transient cases are less likely to be eliminated from data reported today, which could have resulted in an apparent increasing CH-incidence rate over time. For a discussion of the effects of transient hypothyroidism on the incidence rate of newborns with CH, see the article by Parks et al.[18]

The analyses reported here included only the years 1991–2000, because counts of cases of CH were validated to the NNSGRC for this time period only. Additional analyses of years after 2000 for the effects of laboratory methodology could strengthen the observed associations, although validated data sets for subsequent years are not currently available. The limitations of these analyses are related to the data sets themselves. Although state NBS laboratories are encouraged to provide accurate, complete data, reporting is voluntary; there are only sporadic checks to validate accuracy or ensure completeness. Staff changes in each state program may also have affected the consistency of the reported data. Finally, the data sets were not originally designed or intended for epidemiologic studies, because most data elements were reported in aggregate. The strength of these analyses is that they were derived from nationally representative data on NBS. Although there are significant differences in laboratory practices between state NBS programs, analyses that combine the data from all programs can show suggestive trends that help inform the NBS system of differences that merit further evaluation.

REFERENCES

1. Dussault JH, Laberge C. Thyroxine (T4) determination in dried blood by radioimmunoassay: a screening method for neonatal hypothyroidism. *Union Med Can.* 1973;102(10):2062–2064
2. Dussault JH, Coulomb P, Laberge C, Letarte J, Guyda H, Khoury M. Preliminary report on a mass screening program for neonatal hypothyroidism. *J Pediatr.* 1975;86(5):670–674
3. Therrell BL, Adams J. Newborn screening in North America. *J Inherit Metab Dis.* 2007;30(4):447–465
4. Hollowell JG, Therrell BL, Hannon WH. Congenital hypothyroidism. In: Wald N, Leck I, eds. *Antenatal and Neonatal Screening.* Oxford, United Kingdom: Oxford University Press; 2000:370–397
5. Dussault JH, Morissette J. Higher sensitivity of primary thyrotropin in screening for congenital hypothyroidism: a myth? *J Clin Endocrinol Metab.* 1983;56(4):849–852
6. Therrell BL Jr. U.S. newborn screening policy dilemmas for the twenty-first century. *Mol Genet Metab.* 2001;74(1–2):64–74
7. Therrell BL, Hannon WH. National evaluation of US newborn screening system components. *Ment Retard Dev Disabil Res Rev.* 2006;12(4):236–245
8. Therrell BL. National newborn screening data collection practices. Presented at: Newborn Screening and Genetic Testing Symposium; November 4–7, 2002; Phoenix, AZ
9. Harris KB, Pass KA. Increase in congenital hypothyroidism in New York State and in the United States [published correction appears in *Mol Genet Metab.* 2008;94(1):140]. *Mol Genet Metab.* 2007;91(3):268–277
10. Olney RS, Grosse SD, Vogt RF Jr. Prevalence of congenital hypothyroidism—current trends and future directions: workshop summary. *Pediatrics.* 2010;125(2 suppl):S31–S36
11. LaFranchi SH, Hanna CE, Krainz PL, Skeels MR, Miyahira RS, Sesser DE. Screening for congenital hypothyroidism with specimen collection at two time periods: results of the Northeast Regional Screening Program. *Pediatrics.* 1985;76(5):734–740
12. Levine GD, Therrell BL Jr. Second testing for hypothyroidism. *Pediatrics.* 1986;78(2):375–376
13. Hunter MK, Mandel SH, Sesser DE, et al. Follow-up of newborns with low thyroxine and nonelevated thyroid-stimulating hormone-screening concentrations: results of the 20-year experience in the Northwest Regional Newborn Screening Program. *J Pediatr.* 1998;132(1):70–74
14. Maniatis AK, Taylor L, Letson GW, Bloch CA, Kappy MS, Zeitler P. Congenital hypothyroidism and the second newborn metabolic screening in Colorado, USA. *J Pediatr Endocrinol Metab.* 2006;19(1):31–38
15. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika.* 1986;73(1):13–22
16. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics.* 1986;42(1):121–130
17. Hinton CF, Harris KB, Borgfeld L, et al. Trends in incidence rates of congenital hypothyroidism related to select demographic factors: data from the United States, California, Massachusetts, New York, and Texas. *Pediatrics.* 2010;125(2 suppl):S37–S47
18. Parks JS, Lin M, Grosse SD, et al. The impact of transient hypothyroidism on the increasing rate of congenital hypothyroidism in the United States. *Pediatrics.* 2010;125(2 suppl):S54–S63

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