

# Follow-up Testing Among Children With Elevated Screening Blood Lead Levels

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**I**N 1997, THE CENTERS FOR DISEASE Control and Prevention (CDC) changed the recommendation for childhood lead poisoning prevention from near-universal testing of all children to targeted testing based on the risk of lead exposure.<sup>1,2</sup> This change was motivated by the decrease in the prevalence of lead poisoning because of the success of primary prevention strategies, such as the removal of lead from paint and gasoline.<sup>3</sup> The CDC directed states to develop plans for lead testing according to local risk.<sup>1</sup> Testing was also recommended for children according to the results from a standardized risk-assessment questionnaire and for those enrolled in public-assistance programs (eg, Medicaid; the Supplemental Food Program for Women, Infants, and Children).<sup>1</sup>

An expected benefit of switching to risk-based lead testing, also referred to as lead screening, was to allow greater health care resources to be directed to individuals at greatest risk for lead poisoning. In 1997 and again in 2002, the CDC outlined the role of child health care providers after an elevated screening blood lead level ( $\geq 10$   $\mu\text{g}/\text{dL}$  [0.48  $\mu\text{mol}/\text{L}$ ): all elevated screening blood lead test results require diagnostic confirmation, and because capillary sampling has been associated with false elevations, only venous blood should be

**See also p 2274 and Patient Page.**

**Context** Follow-up testing after an abnormal screening blood lead level is a key component of lead poisoning prevention.

**Objectives** To measure the proportion of children with elevated screening lead levels who have follow-up testing and to determine factors associated with such care.

**Design, Setting, and Participants** Retrospective, observational cohort study of 3682 Michigan Medicaid-enrolled children aged 6 years or younger who had a screening blood lead level of at least 10  $\mu\text{g}/\text{dL}$  (0.48  $\mu\text{mol}/\text{L}$ ) between January 1, 2002, and June 30, 2003.

**Main Outcome Measure** Testing within 180 days of an elevated screening lead level.

**Results** Follow-up testing was received by 53.9% (95% confidence interval [CI], 52.2%-55.5%) of the children. In multivariate analysis adjusting for age, screening blood lead level results, and local health department catchment area, the relative risk of follow-up testing was lower for Hispanic or nonwhite children than for white children (0.91; 95% CI, 0.87-0.94), for children living in urban compared with rural areas (0.92; 95% CI, 0.89-0.96), and for children living in high- compared with low-risk lead areas (0.94; 95% CI, 0.92-0.96). Among children who did not have follow-up testing, 58.6% (95% CI, 56.3%-61.0%) had at least 1 medical encounter in the 6-month period after the elevated screening blood lead level, including encounters for evaluation and management (39.3%; 95% CI, 36.9%-41.6%) or preventive care (13.2%; 95% CI, 11.6%-14.8%).

**Conclusions** The rate of follow-up testing after an abnormal screening blood lead level was low, and children with increased likelihood of lead poisoning were less likely to receive follow-up testing. At least half of the children had a missed opportunity for follow-up testing. The observed disparities of care may increase the burden of cognitive impairment among at-risk children.

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used for confirmation.<sup>1,4</sup> The urgency for confirmatory testing varies according to the initial level, from 3 months for levels 10 to 19  $\mu\text{g}/\text{dL}$  (0.48-0.82  $\mu\text{mol}/\text{L}$ ) to emergently for children with levels of at least 70  $\mu\text{g}/\text{dL}$  (3.38  $\mu\text{mol}/\text{L}$ ). Once the level is confirmed, repeated testing is recommended, with a frequency ranging from as soon as possible for those with levels of at least 45  $\mu\text{g}/\text{dL}$  (2.17  $\mu\text{mol}/\text{L}$ ) to 3 months for those with levels from 10 to 14  $\mu\text{g}/\text{dL}$  (0.48-0.67  $\mu\text{mol}/\text{L}$ ) to ensure that the blood lead level is not increasing and, if applicable, is responding to intervention.<sup>4</sup> Of note, any repeated testing that occurs af-

ter a 6-month break is considered to be a screening test, regardless of the previous lead level, and would therefore require confirmatory testing and subsequent repeated testing as necessary.

Lead poisoning prevention is a collaborative effort between primary care clinicians and public health agencies.

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Primary care clinicians should ensure that children are appropriately screened for lead poisoning as part of routine preventive care and then receive follow-up testing and care as necessary. State and local public health departments provide and coordinate services for children identified with lead poisoning (eg, environmental investigation, lead abatement). In some communities, public health departments also offer blood lead testing, usually for children who do not have a regular source of medical care.

Because of the harm of even modest elevations in blood lead level,<sup>5</sup> significant efforts have been made to improve screening among at-risk children. However, screening is effective only with appropriate follow-up care. No previous population-based study has evaluated the care that children receive after having an elevated screening blood lead level.

To begin to understand the care provided to children after an elevated screening blood lead level, we chose to focus on one component of care: follow-up blood lead testing. We based our study in Michigan because this state has a reporting mechanism for all blood lead levels, regardless of result, and compared with other states, Michigan has a high number of children with lead poisoning.<sup>6</sup> We chose to study Medicaid-enrolled children because they are at high risk for lead poisoning<sup>7</sup> and because demographic and health care use data are available for these children.

## METHODS

### Study Design

We performed a retrospective cohort study of children aged 6 years and younger who had an elevated blood lead level ( $\geq 10$   $\mu\text{g/dL}$  [0.48  $\mu\text{mol/L}$ ]) between January 1, 2002, and June 30, 2003, in Michigan and who were continuously enrolled in Michigan Medicaid during the 180-day period after the elevated blood lead level. Because we were interested in newly identified cases of lead poisoning, we excluded children who had an elevated blood lead level reported in 2001.

For each child, we identified the first elevated blood lead level during this 18-month period. We then identified any other blood lead testing during the subsequent 180 days. We chose 180 days because blood lead testing after a 6-month break is considered to be a new screening test and because follow-up blood testing, regardless of the initial blood lead level, should occur earlier.<sup>1</sup> All medical encounters during this 180-day period were identified to determine missed opportunities for follow-up testing.

This study was approved by the University of Michigan Medical School institutional review board, which waived informed consent for this retrospective study.

### Data Sources

Demographic, enrollment, and encounter data were obtained from Medicaid program administrative files and were linked to blood lead results collected by the Michigan Department of Community Health (MDCH). Each laboratory in Michigan has been required since 1997 to report all blood lead results to the MDCH. The laboratories supply identifying information about each individual tested (eg, name, address, birth date, Medicaid number), collection date, blood lead level result, and the method of specimen sampling (eg, venous, capillary). These data are entered into an electronic file that is subsequently linked through a complex algorithm to other data sets maintained by the state, including the Medicaid program files.

Bull Services conducted an internal study in 2002 commissioned by MDCH that found the linkage process across all data sets to be more than 99% accurate, with 0.4% false matches and 0.3% false nonmatches (written communication, Tom Rothan, June 2004). This study was undertaken to test the accuracy of the match for purposes of overall calibration of the Unique Client Identifier system. Bull Services Inc believes the study was accurate for that purpose. It was based on a sampling of data and reflected the data sets at the

time of the study [2002]. The results of the study were not intended as a guarantee or warranty of accuracy for any selected matching process using Unique Client Identifier at that time or in the future).

### Outcomes Measured

The main outcome measures of this study were the proportion of children who had at least 1 follow-up test during the 180 days after an elevated screening blood lead level and the number of missed opportunities among those children who did not have any other follow-up testing. We determined missed opportunities by using claims data, classifying encounter types according to *Current Procedural Terminology* code.<sup>8</sup> Medical encounters were classified as visits for evaluation and management (99201-5, 99211-5, 99354-5), preventive care (99381-3, 99391-3), emergency care (99281-5), consultation (99241-5), and inpatient care (99221-3, 99231-6, 99251-5, 99261-3, 99291-9, 99346-7). We also evaluated the relationship between the screening blood lead level and the first follow-up test result.

### Independent Variables

Certain demographic factors are associated with the risk of lead poisoning, including age, race or ethnicity, urban or rural status, and local risk of lead exposure.<sup>7,9</sup> We hypothesized that children with increased likelihood of having elevated blood lead levels (eg, younger children, nonwhite children, children living in urban areas or in communities with a high risk of lead exposure) would also have a greater likelihood of follow-up testing after an elevated screening level. We also hypothesized that there would be differences in follow-up testing rates across local public health department catchment areas. Although there is variation in the proportion of children with elevated blood lead levels across the catchment areas, all local public health departments in Michigan share responsibility with private practitioners in coordinating services for children with

lead poisoning. Finally, we hypothesized that follow-up would be greater among children who had an initial capillary sample or who had higher initial blood lead levels.

In our analysis, we dichotomized race or ethnicity as non-Hispanic white and Hispanic or nonwhite according to classification by parents on Medicaid enrollment forms. Address in the calendar year of the screening test was used to classify urban or rural status, lead-exposure risk, and health department catchment area.

Urban residence was classified according to metropolitan statistical areas (MSAs), as defined by the US Census Bureau.<sup>10</sup> Each MSA is formed around an urbanized area of 50 000 or more inhabitants and includes adjacent communities if they are economically or socially integrated to the urbanized area. Each MSA is composed of 1 or more counties. In Michigan, 26 of the 83 counties are classified as being in an MSA.

Children were considered to have a high risk of lead exposure according to Michigan's targeted screening plan, which categorizes ZIP code areas by the incidence of lead poisoning, the stock of older houses, and the proportion of children living in poverty.<sup>11</sup> In cases of incomplete address information, we used the ZIP code from the following or preceding calendar year in our data set for risk classification. We performed a sensitivity analysis to test the validity of this assumption by reanalyzing the data, omitting children with missing ZIP code data.

There are 45 local health departments in Michigan. To evaluate the effect of health department, we compared the rates of follow-up testing in the 2 local health departments that had the largest number of children with elevated screening blood lead levels with that of the other local health departments.

Other independent variables were the blood sample type (ie, capillary, venous) and the value of the screening blood lead level. We categorized blood lead level to reflect recommended treatment: 10 to 19  $\mu\text{g}/\text{dL}$  (0.48-0.92  $\mu\text{mol}/\text{L}$ ) (fol-

low-up lead monitoring and education), 20 to 44  $\mu\text{g}/\text{dL}$  (0.97-2.13  $\mu\text{mol}/\text{L}$ ) (as per lower levels plus environmental investigation and abatement, and neurodevelopmental monitoring), and at least 45  $\mu\text{g}/\text{dL}$  (2.17  $\mu\text{mol}/\text{L}$ ) (as per lower levels plus chelation therapy).<sup>1,4</sup> Throughout, to convert blood lead levels to  $\mu\text{mol}/\text{L}$ , multiply values by 0.0483.

### Statistical Analysis

Confidence intervals (CIs) were based on a normal distribution for continuous variables and on a binomial distribution for categorical variables. We used 3 measures to evaluate the association between each independent variable and likelihood of follow-up testing: the proportion of children at each level of the variable that had follow-up testing, the unadjusted relative risk (RR) of follow-up testing, and the adjusted RR of follow-up testing. Modified Poisson regression was used to determine the adjusted RRs and their CIs.<sup>12</sup> Variables were also compared with Pearson  $\chi^2$  test for categorical variables or *t* test for continuous variables. Observations with missing data were excluded from bivariate and regression analyses. All reported *P* values and CIs are 2-sided. *P* < .05 was considered to indicate statistical significance. Stata 8.2 software (Stata-Corp, College Station, Tex) was used for all analyses.

## RESULTS

### Study Population and Demographic Characteristics

There were 5175 Medicaid-enrolled children who had a blood lead level of at least 10  $\mu\text{g}/\text{dL}$  (0.48  $\mu\text{mol}/\text{L}$ ) between January 1, 2002, and June 30, 2003. Of these, 3682 (71.2%) did not have an elevated blood lead level during 2001 and were therefore included in this analysis.

The demographic characteristics of these children are listed in TABLE 1. For all but 148 of the children (96.0%), we used ZIP code data from the calendar year of the screening test. For the remainder, we used ZIP code data for the other year during the study period.

One- and 2-year-old children accounted for slightly more than half of the children with elevated blood lead levels. Most children were Hispanic or nonwhite, lived in urban areas, and had high risk of lead exposure.

Race and ethnicity and risk of lead exposure were clustered by urban or rural residence. Compared with rural areas, urban areas had a greater proportion of Hispanic or nonwhite children (88.8% vs 21.0%; *P* < .001) and a greater proportion of children with high risk of lead exposure (96.1% vs 84.9%; *P* < .001).

Most of the children lived within districts served by either of 2 local public health departments, both serving urban areas but on opposite sides of the state. One served the area in which 67.0% of the children lived, and the other served the area in which 14.0% of the children lived.

### Screening Blood Lead Level

The screening test was based on a capillary sample for 1543 (41.9%) of the children, a venous sample for 2138 (58.1%) of the children, and unknown for 1 child. The mean blood lead level did not vary according to blood sample type (capillary, 14.7  $\mu\text{g}/\text{dL}$ ; venous, 14.4  $\mu\text{g}/\text{dL}$ ; *P* = .11). TABLE 2 lists the categorized distribution of blood lead levels stratified by blood sample type; differences in the distribution were not statistically significant (*P* = .39).

### Follow-up Testing

Overall, 53.9% (95% CI, 52.2%-55.5%) had follow-up testing within 180 days of their elevated blood lead screening test, with a mean of 68.5 days (95% CI, 66.3-70.6 days). The mean number of days before the first follow-up test was shorter for capillary (51.5 days; 95% CI, 48.5-54.4 days) than for venous screening tests (83.7 days; 95% CI, 80.8-86.6 days) and for higher screening blood lead levels (10-19  $\mu\text{g}/\text{dL}$ : 73.2 days [95% CI, 70.8-75.6 days]; 20-44  $\mu\text{g}/\text{dL}$ : 49.2 days [95% CI, 44.4-54.1 days];  $\geq 45$   $\mu\text{g}/\text{dL}$ : 10.0 days [95% CI, 5.9-14.0 days]).

Most follow-up tests were done with venous samples (*n* = 1789; 90.2%), in-

cluding 88.4% of the screening tests that used capillary samples (n=829). Mean follow-up blood lead levels were 3.6 µg/dL (95% CI, 3.0-4.2 µg/dL) lower than the screening blood lead level. The mean change was greater for capillary (6.6 µg/dL; 95% CI, 6.0-7.1 µg/dL) compared with venous screening tests (3.0 µg/dL; 95% CI, 2.6-3.3 µg/dL).

On follow-up testing, 47.5% (95% CI, 45.2%-50.0%) of the children still had elevated blood lead levels. Children with screening tests using venous blood compared with capillary blood were more likely to have an elevated lead level on follow-up testing (60.1% vs 33.4%;  $P < .001$ ). Regardless of blood sample type, higher screening levels were associated with a greater likelihood of an elevated follow-up blood lead level (10-14 µg/dL: 32.8%; 15-19 µg/dL: 64.6%;  $\geq 20$  µg/dL: 77.8%;  $P < .001$ ).

### Predictors of Follow-up Testing

Table 1 lists the proportion, unadjusted RR, and adjusted RR of follow-up testing by each of the independent variables. Although higher screening levels were associated with increased rates of follow-up testing, not all children in the highest category, at least 45 µg/dL, had follow-up testing. Children who had screening with capillary blood or who had a higher screening blood lead level had a greater likelihood of follow-up testing.

The likelihood of follow-up testing decreased with increasing age after 2 years ( $P < .001$ ). The likelihood of follow-up testing was lower for Hispanic or nonwhite children ( $P < .001$ ), for children with urban residence ( $P < .001$ ), and for children with high lead-exposure risk ( $P = .003$ ). Children living within the area served by the first local public health department had a lower likelihood of follow-up testing than those served by other health departments ( $P < .001$ ). In contrast, children served by the second local public health department had a greater likelihood of follow-up testing than other health departments ( $P < .001$ ) (Table 1). The association between follow-up and

**Table 1.** Characteristics of the Study Population and the Associated Likelihood of Follow-up Testing (N = 3682)

Characteristic	Distribution, No. (%)	Proportion (95% CI)	Likelihood of Follow-up Testing	
			Relative Risk	
			Unadjusted (95% CI)	Adjusted (95% CI)*
Age, y				
<1	130 (3.5)	58 (49-67)	0.98 (0.85-1.15)	0.95 (0.92-0.99)
1	1280 (34.8)	59 (57-62)	1.00	1.00
2	827 (22.5)	57 (53-60)	0.96 (0.89-1.03)	1.02 (1.01-1.03)
3	634 (17.2)	53 (49-57)	0.90 (0.82-0.98)	0.96 (0.95-0.97)
4	552 (15.0)	45 (41-50)	0.76 (0.69-0.84)	0.85 (0.81-0.89)
5	204 (5.5)	37 (31-44)	0.63 (0.52-0.75)	0.71 (0.71-0.71)†
6	55 (1.5)	22 (12-35)	0.37 (0.22-0.61)	0.43 (0.42-0.43)†
Race/ethnicity‡				
Non-Hispanic white	479 (13.0)	66 (61-70)	1.00	1.00
Hispanic or nonwhite	3178 (86.3)	52 (50-54)	0.79 (0.74-0.85)	0.91 (0.87-0.94)
Residence				
Rural	100 (2.7)	67 (57-76)	1.00	1.00
Urban	3582 (97.3)	53 (52-55)	0.80 (0.69-0.92)	0.92 (0.89-0.96)
Lead exposure risk‡				
Low	156 (4.2)	65 (57-73)	1.00	1.00
High	3525 (95.7)	53 (52-55)	0.82 (0.72-0.92)	0.94 (0.92-0.96)
Local public health department area				
1	2466 (67)	48 (46-50)	0.81 (0.76-0.88)	0.88 (0.86-0.89)
2	517 (14)	75 (71-78)	1.26 (1.17-1.37)	1.20 (1.17-1.22)
All others	699 (19)	59 (55-63)	1.00	1.00
Initial blood sample type‡				
Venous	2138 (58.1)	49 (47-51)	1.00	1.00
Capillary	1543 (41.9)	61 (58-63)	1.24 (1.17-1.32)	1.11 (1.05-1.16)
Initial blood lead level, µg/dL				
10-19	3205 (87.1)	51 (49-53)	1.00	1.00
20-44	445 (12.1)	71 (67-75)	1.39 (1.30-1.49)	1.36 (1.34-1.39)
$\geq 45$	32 (0.9)	94 (79-99)	1.84 (1.67-2.02)	1.82 (1.81-1.82)†

SI conversion factor: To convert blood lead levels to µmol/L, multiply values by 0.0483.

\*Adjusted for age, screening blood lead level results, and local public health department catchment area.

†Narrow confidence interval (CI) because of rounding.

‡Missing data: race/ethnicity (n = 25), lead exposure risk (n = 1), and initial blood sample type (n = 1).

these demographic factors persisted after multivariate adjustment.

### Sensitivity Analysis

Omitting cases with missing ZIP code data in the year of testing had no significant effect on the overall rate of follow-up testing, the proportion of children in low- or high-risk areas for lead exposure who had follow-up testing, the unadjusted risk of follow-up testing by lead-exposure risk, or any of the adjusted RRs for follow-up testing.

### Missed Opportunities for Follow-up Testing

Among individuals who did not have follow-up testing, 58.6% (95% CI,

**Table 2.** Distribution of Screening Blood Lead Levels by Blood Sample Type

Level, µg/dL	Capillary, No. (%) (n = 1543)*	Venous, No. (%) (n = 2138)*
10-19	1331 (86.3)	1873 (87.6)
20-44	196 (12.7)	249 (11.7)
$\geq 45$	16 (1.0)	16 (0.8)

SI conversion factor: To convert blood lead levels to µmol/L, multiply values by 0.0483.

\*The blood sample type for 1 observation, with a level of 18 µg/dL, was unknown. Differences in the distribution by blood sample type were not statistically significant ( $P = .39$ ).

56.3%-61.0%) had at least 1 medical encounter during the 180 days after the elevated screening blood lead level, with a mean of 2.3 (95% CI, 2.1-2.4) encounters among those who had any

subsequent encounters. The most common type of medical encounter was for evaluation and management (39.3%; 95% CI, 36.9%-41.6%); however, 13.2% (95% CI, 11.6%-14.8%) had at least 1 preventive care visit, and 26.7% (95% CI, 24.6%-28.8%) had an emergency department visit. Outpatient consultations (2.6%; 95% CI, 1.9%-3.4%) and hospitalizations (2.4%; 95% CI, 1.7%-3.1%) were rare. Among individuals who did not have follow-up testing, 11.4% (95% CI, 10.0%-12.9%) had an emergency department visit as their only medical encounter in the 180 days after the initial elevated blood lead level.

## COMMENT

This is the first population-based study, to our knowledge, of follow-up after an elevated screening blood lead level. Although we cannot comment on other interventions that these children may have received for their elevated blood lead level, follow-up testing is the cornerstone of lead poisoning management and an essential component of secondary prevention.<sup>1,4</sup> We found that nearly half of the children in this study had no follow-up testing 6 months after an elevated screening blood lead level result. Furthermore, those children with the greatest risk of lead poisoning according to demographic factors, including nonwhite children, those living in urban areas or in communities with a high risk of lead exposure, and those living in the local public health department catchment area with the greatest number of elevated screening blood lead levels, were the least likely to have follow-up testing. Multivariate modeling demonstrated that these effects are independent; the more demographic risk factors a child had, the less likely the child was to receive follow-up testing. These findings suggest a lack of connection between federal efforts to eliminate childhood lead poisoning<sup>13</sup> and current lead screening practices.

The lack of follow-up testing is likely to have a significant clinical effect. Even modestly elevated blood lead levels have been associated with intellectual impairment.<sup>5</sup> Nearly half of the individu-

als with follow-up testing had persistently elevated blood lead levels. We suspect that the proportion of children with persistently elevated levels may be even higher in those without follow-up testing because of their greater risk of lead poisoning. The differential pattern of follow-up testing may further disadvantage minority children.

Our study has several limitations. We are unable to determine the cause of the low rate of follow-up testing or its inequitable pattern. Our findings could be biased by inaccuracies in the Medicaid enrollment files, including classification of race and ethnicity. We classified children's residence according to a single address and did not consider the effect of changing residences. Our classification of urban or rural status does not allow us to understand neighborhood-level effects. Finally, we are unable to specify the site of screening or follow-up testing.

Under the current system, primary care providers are responsible for follow-up testing as part of the care provided within the medical home, with local health departments primarily coordinating treatment for children with confirmed lead poisoning. Loss of medical follow-up does not itself account for the low rate of follow-up testing. More than half of the children with no follow-up testing had medical encounters in the 6 months after their elevated screening blood lead level result. However, at least 10% of these encounters were outside of the primary care setting, where there may be no knowledge of the elevated screening level and follow-up lead testing is unlikely to occur. To minimize loss to follow-up because of poor information sharing, New York City has recently integrated blood lead test results into their immunization registry.<sup>14</sup> A similar approach has been proposed in Michigan.<sup>15</sup>

Information-related barriers are unlikely to solely account for the observed disparities. We suspect that elevated screening blood lead levels in children perceived to be at low risk may attract extra attention. In contrast, care may be less aggressive in high-risk

populations if lead poisoning is not considered unusual or if resources for optimal care (eg, environmental investigation, lead abatement) are insufficient. Inadequate guideline adherence is not unique to childhood lead poisoning prevention.<sup>16-18</sup> Future research is needed to understand the specific barriers to optimal care for children with elevated screening blood lead levels and to clearly define the responsibilities of public and private health care practitioners.

Childhood lead poisoning is common, affecting 2% of US children aged 1 through 5 years.<sup>6</sup> Furthermore, Medicaid-enrolled children have a 3-fold greater risk.<sup>7</sup> Current federal plans call for the elimination of childhood lead poisoning by 2010,<sup>13</sup> primarily through secondary prevention.<sup>1,4</sup> In this first population-based study of the outcomes of screening, we found that half of Medicaid-enrolled children with an elevated blood lead level have no follow-up testing, and those children at greatest risk of having an elevated blood lead level are less likely to receive follow-up testing. Because each state handles lead poisoning prevention differently, we do not know whether these results are generalizable to other states. We hope that our findings lead other states to perform similar assessments. To maximize cognitive development in these children, it is crucial to improve follow-up and to understand and develop interventions to overcome these unexpected disparities in care.

**Author Contributions:** Dr Kemper had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Kemper, Cohn, Fant, Dombkowski.

**Acquisition of data:** Kemper, Cohn, Dombkowski.

**Analysis and interpretation of data:** Kemper, Cohn, Fant, Dombkowski, Hudson.

**Drafting of the manuscript:** Kemper.

**Critical revision of the manuscript for important intellectual content:** Cohn, Fant, Dombkowski, Hudson.

**Statistical analysis:** Kemper, Dombkowski.

**Obtained funding:** Kemper.

**Administrative, technical, or material support:** Cohn.

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