Prevalence and Course of Strabismus in the First Year of Life for Infants With Prethreshold Retinopathy of Prematurity

Findings From the Early Treatment for Retinopathy of Prematurity Study

Deborah K. VanderVeen, MD; David K. Coats, MD; Velma Dobson, PhD; Douglas Fredrick, MD; Robert A. Gordon, MD; Robert J. Hardy, PhD; Daniel E. Neely, MD; Earl A. Palmer, MD; Scott M. Steidl, MD; Betty Tung, MS; William V. Good, MD; for the Early Treatment for Retinopathy of Prematurity Cooperative Group

Objective: To present strabismus data for premature infants with prethreshold retinopathy of prematurity (ROP) enrolled in the Early Treatment for Retinopathy of Prematurity study.

Design: The prevalence of strabismus was tabulated for all of the infants with high-risk prethreshold disease who participated in the randomized trial of the Early Treatment for Retinopathy of Prematurity study and were examined at 6 and/or 9 months' corrected age as well as for all of the infants with low-risk prethreshold disease who were examined at 6 months' corrected age.

Main Outcome Measures: Presence or absence of strabismus at 6 and 9 months' corrected age.

Results: The prevalence of strabismus at 6 months was higher for infants with high-risk prethreshold ROP than for those with low-risk prethreshold ROP (20.3% vs 9.6%, respectively; \(P<.001\)). Risk factors associated with the development of strabismus at 9 months include abnormal fixation behavior, presence of amblyopia, and outborn birth status (ie, born outside of a study-affiliated hospital). At 9 months, 30% of infants with high-risk prethreshold ROP had strabismus, although only 42% showed strabismus at 6 months. Thirty percent of infants with strabismus at 6 months showed normal alignment at 9 months.

Conclusions: Infants with high-risk prethreshold ROP show significant variability in the presence vs absence of strabismus in the first year of life; thus, conservative management is recommended.

Application to Clinical Practice: Ophthalmologists managing strabismus in infants who have high-risk prethreshold ROP should be aware of the significant variability in ocular alignment during the first year of life.

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Strabismus has been reported to develop in the first year of life in 14.7% of preterm infants with birth weights less than 1251 g. The rate of strabismus is higher for preterm infants who had more severe acute-phase retinopathy of prematurity (ROP) and also for infants with neurodevelopmental abnormalities. Strabismus can cause abnormal binocularity and amblyopia, necessitating amblyopia therapy, spectacle wear, and/or surgical procedures. Additionally, there may be psychosocial consequences from the cosmetic effect of misaligned eyes.

This article reports strabismus data that were collected prospectively from 730 premature infants with birth weights less than 1251 g who were enrolled in the Early Treatment for Retinopathy of Prematurity study. All of the 730 infants developed prethreshold ROP during the neonatal period; 401 of them developed high-risk prethreshold ROP and were enrolled in the randomized trial of early treatment for ROP. Data were examined to compare the prevalence and type of strabismus at 6 and 9 months' corrected age for infants who developed high-risk prethreshold ROP and were enrolled in the randomized trial of early treatment for ROP as well as the prevalence and characteristics of strabismus at 6 months' corrected age in infants with low- vs high-risk prethreshold ROP. Analyses were conducted to determine whether presence of strabismus...
was correlated with demographic variables, visual acuity measures, ocular structural outcomes, and anisometropic refractive status.

### METHODS

Infants with birth weights less than 1251 g and birth dates between October 1, 2000, and September 30, 2002, were screened at 26 participating centers. All of the centers had the Early Treatment for Retinopathy of Prematurity study protocol reviewed and approved by their human ethics committees. Infants who developed prethreshold ROP and whose parents had consented to enrollment in the natural history portion of the Early Treatment for Retinopathy of Prematurity study were followed up to at least 6 months’ corrected age (age from estimated due date). High-risk prethreshold ROP was determined by the RM-ROP2 model based on results of examinations by 2 independent study-certified ophthalmologists. Infants who developed high-risk prethreshold ROP were eligible for the randomized trial of early treatment vs conventional management with treatment at threshold if threshold ROP was reached. All of the randomized infants were also examined at 9 months’ corrected age to evaluate structural and visual outcomes. All of the examinations were performed by study-certified ophthalmologists. The details of these examinations and determination of eligibility for randomization have been published previously.\(^\text{9,11}\)

At the 6- and 9-month examinations, visual acuity indicators (including fixation behavior and presence or absence of nystagmus), ocular alignment and motility status, cycloplegic refraction, and structural outcomes were recorded. Standard clinical methods to assess visual acuity as well as ocular motility and alignment were used, and observations were made while the patient was fully awake. Normal fixation was defined as central, steady, and maintained (CSM). Ocular alignment was classified as normal, abnormal, or unable to assess. If strabismus was present, it was classified as intermittent or constant and by the direction of the deviation (esotropia, exotropia, hypertropia, or any combination thereof). Some infants showed more than 1 direction of strabismus during a given examination. The magnitude of the deviation was not recorded. Children were deemed unable to assess if they were somnolent or in instances where findings were suspicious but inconclusive.

If significant refractive error or amblyopia was found at the 6-month examination, spectacle correction and/or amblyopia therapy was instituted. Amblyopia was defined as abnormal, unmaintainable fixation behavior in 1 eye in the absence of an unfavorable structural outcome (ie, retinal fold or detachment involving the macula, or retrolental mass) to satisfactorily explain poor fixation in 1 or both eyes. Amblyopia treatment was also instituted despite the presence of an unfavorable structural outcome at the discretion of the examining ophthalmologist.

At the 9-month examination, grating visual acuity was measured with Teller visual acuity cards, and results were designated as favorable or unfavorable.\(^\text{12}\) The favorable group included eyes with visual acuity scores in the normal (≥3.70 cycles per degree) and below normal (1.85 to <3.70 cycles per degree) categories, and the unfavorable group included eyes with lower visual acuity scores. All of the infants were tested with spectacle correction for significant refractive errors and, if amblyopia was suspected, after at least 4 weeks of amblyopia therapy.

Statistical tests were first performed using univariate analyses for each variable, and P values are given in the text. Then, multiple logistic regression analysis including all of the variables was performed to examine the association of factors with strabismus. The P values for the final model are included in this article.

Data for 96.8% of the 316 surviving infants with low-risk prethreshold ROP and for 94.8% of the 386 surviving randomized infants with high-risk prethreshold ROP were available for comparison at the 6-month examination. Data for 98.2% of the 379 surviving infants with high-risk prethreshold ROP were available at the 9-month examination.

Table 1 indicates the prevalence of strabismus at the 6-month examination for infants with low-risk prethreshold ROP and at 6 and 9 months for infants with high-risk prethreshold ROP. Strabismus was more likely to be present at 6 months in the high-risk prethreshold group compared with the low-risk prethreshold group (20.3% vs 9.6%, respectively; \(P<.001\)). Within each risk group, there were no statistically significant differences at 6 months in the prevalence of strabismus based on birth weight, gestational age at birth, race, sex, inborn (ie, born in a study-affiliated hospital) or outborn birth status, or single vs multiple birth status.

For infants with high-risk prethreshold ROP, strabismus was more common at the 9-month examination than at the 6-month examination (30.0% vs 20.3%, respectively; \(P=.002\)). At 9 months, the prevalence of strabismus was again not related to gestational age at birth, race, sex, or single vs multiple birth status. Although the prevalence of strabismus appears to be less for infants with a birth weight greater than 1000 g (6.3%) than for infants with a birth weight less than 750 g (30.4%) and between 750 and 1000 g (32.4%), this was not statistically significant after adjusting for other risk factors. Strabismus was more common in outborn infants than in those who were inborn (44.4% vs 26.4%, respectively; \(P=.003\)), even after adjusting for other baseline variables.

Strabismus was compared in the randomized infants who were seen at both the 6- and 9-month examinations to evaluate the short-term evolution of strabismus in infants with high-risk prethreshold ROP. A total of 357 infants with high-risk prethreshold ROP were seen at both the 6- and 9-month examinations, representing 94.2% of the cohort expected for this comparison. Strabismus was present in 107 (30.3%) of the 354 infants who could be assessed at 9 months compared with 66 (20.1%) of the 329 infants who could be assessed at 6 months. Of the 263 infants with normal alignment at 6 months, 45 (17.1%) had strabismus at the 9-month examination. Of the 66 infants with strabismus at 6 months, 20 (30.3%) showed normal alignment at the 9-month examination. The majority (68.2%) of the 66 infants with strabismus at 6 months continued to have strabismus at 9 months, and only 1 of these infants, an infant with intermittent strabismus, showed a change in the direction of the deviation. Seventeen (60.7%) of 28 infants who were classified as unable to assess at 6 months had strabismus during the 9-month examination. Inability to assess alignment at 6 months was associated with the inability to determine or the presence of abnormal fixation in 1 or both eyes, as only 1 infant among the 28 was CSM in both eyes. Of the 107 infants...
with strabismus at 9 months, only 42.1% had strabismus at the 6-month examination. Three infants underwent surgical intervention for strabismus between the 6- and 9-month examinations, but each of these infants continued to have strabismus at 9 months.

Esotropia was the most common form of strabismus at both the 6- and 9-month examinations. At the 6-month examination, 51 (75.0%) of the 68 infants with strabismus were esotropic, and at the 9-month examination, 79 (71.8%) of the 110 infants with strabismus were esotropic. Some infants (2 infants at 6 months and 2 infants at 9 months) showed more than 1 type of strabismus. One of these infants had Duane syndrome. More infants showed constant strabismus at the 9-month examination (62.7%) compared with the 6-month examination (44.1%).

Abnormal fixation behavior in 1 or both eyes was highly predictive of strabismus. In the 237 infants in whom fixation was CSM in both eyes, only 21 infants (8.9%) had strabismus, but in the 105 infants in whom fixation was not CSM in 1 or both eyes, 77 (73.3%) had strabismus (P<.001). There was little difference in the prevalence of strabismus between those infants with poor fixation in 1 eye only compared with poor fixation in both eyes (72.6% vs 80.0%, respectively). In the 291 infants with grating visual acuity that was classified as favorable in both eyes, 59 (20.3%) had strabismus whereas in the 75 infants with grating visual acuity that was classified as unfavorable in 1 or both eyes, 50 (66.7%) had strabismus (P<.001). Additionally, more infants who were diagnosed with amblyopia by the examining ophthalmologist at the 9-month examination (80.8%) had strabismus than those who were not diagnosed with amblyopia at either the 6- or 9-month examination (26.1%) (P<.001).

The prevalence of strabismus at 9 months was higher for randomized infants with an unfavorable structural outcome in 1 or both eyes compared with infants with a favorable structural outcome in both eyes (67.9% vs 22.8%, respectively; P<.001).

To compare the presence of anisometropic refractive status and strabismus, we calculated spherical equivalents for each eye, and we chose 2.00 diopters (D) of difference between eyes as significant anisometropia. There was a higher rate of strabismus for infants with anisometropia greater than 2.00 D than for those with less than 2.00 D of anisometropia (38.5% vs 21.0%, respectively; P<.001).

In the final regression analysis of data (Table 2), the 3 significant factors were fixation behavior (P<.001), amblyopia (P=.02), and inborn or outborn birth status (P=.007). Abnormal fixation behavior (not CSM) in 1 or both eyes was associated with a 15.3-time greater risk of strabismus, and the presence of amblyopia was associated with a 4.2-time greater risk of strabismus. Being inborn was protective, and it was associated with a 65% reduction in the odds of having strabismus.

### Table 1. Prevalence of Strabismus at 6 and 9 Months

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Infants in Low-Risk Prethreshold ROP Group</th>
<th>Infants in High-Risk Prethreshold ROP Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 mo</td>
<td>9 mo</td>
</tr>
<tr>
<td></td>
<td>Total, No.</td>
<td>Total, No.</td>
</tr>
<tr>
<td></td>
<td>Strabismus, No. (%)</td>
<td>Strabismus, No. (%)</td>
</tr>
<tr>
<td></td>
<td>UA, No.*</td>
<td>UA, No.*</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;750</td>
<td>149</td>
<td>240</td>
</tr>
<tr>
<td>750-999</td>
<td>123</td>
<td>109</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤27</td>
<td>244</td>
<td>323</td>
</tr>
<tr>
<td>&gt;27</td>
<td>62</td>
<td>43</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>153</td>
<td>233</td>
</tr>
<tr>
<td>Black</td>
<td>91</td>
<td>69</td>
</tr>
<tr>
<td>Hispanic</td>
<td>39</td>
<td>50</td>
</tr>
<tr>
<td>Other</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>174</td>
<td>198</td>
</tr>
<tr>
<td>Female</td>
<td>132</td>
<td>168</td>
</tr>
<tr>
<td>Inborn†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>270</td>
<td>291</td>
</tr>
<tr>
<td>No</td>
<td>36</td>
<td>75</td>
</tr>
<tr>
<td>Single vs multiple birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>201</td>
<td>258</td>
</tr>
<tr>
<td>Multiple</td>
<td>105</td>
<td>108</td>
</tr>
</tbody>
</table>

Abbreviations: ROP, retinopathy of prematurity; UA, unable to assess.
* Those infants who were deemed unable to assess were not included in the percentage calculations.
† Born in study-affiliated hospital.
Premature infants have a higher rate of strabismus than full-term infants.\textsuperscript{1,13-21} Previous investigators have noted that as the severity of acute-phase ROP increases, the incidence of strabismus increases.\textsuperscript{1,13,18,22-24} All of the infants in this study had prethreshold ROP, and there was a significantly higher prevalence of strabismus in infants randomized for high-risk prethreshold ROP than in infants who had low-risk prethreshold ROP when examined at 6 months’ corrected age (20.3% vs 9.6%, respectively; \(P<.001\)). At 9 months’ corrected age, 30.0% of the infants who had high-risk prethreshold ROP and were participants in the randomized trial had strabismus. Even among the subgroup of infants who had a favorable ocular structural outcome in both eyes at 9 months, 22.8% had strabismus.

Even though low birth weight and gestational age are correlated with a higher rate of severe ROP and/or neurologic insult,\textsuperscript{3,4,9} among this sample of infants with a birth weight less than 1251 g, there was no difference between prevalence of strabismus and gestational age or weight at birth. Outborn birth status was associated with a higher prevalence of strabismus at 9 months, although outborn birth status did not appear to be a significant factor at 6 months. Infants who were outborn and transferred to a referral center may represent infants who were the sickest and thus were at higher risk of developing more morbidity associated with their prematurity, but we could not explain why there was a difference at the 6- vs 9-month examinations regarding presence of strabismus.

Not surprisingly, infants with an abnormal visual acuity measure in 1 or both eyes were more likely to have strabismus than infants with normal visual acuity measures in both eyes. In the final analysis, there was a stronger association for abnormal fixation behavior in 1 or both eyes and presence of strabismus (\(P<.001\)) than for an unfavorable grating visual acuity result in 1 or both eyes and presence of strabismus (\(P=.46\)). Grating visual acuity tests may underestimate the presence of low vision, especially in patients with macular or cerebral visual impairment, and the range of normal grating visual acuity results in infancy includes values that correspond to low vision if measured in older children or adults.\textsuperscript{25-28} The diagnosis of amblyopia was found to be highly correlated with the presence of strabismus, although no correlation with the cause of amblyopia was made. We could not evaluate whether amblyopia contributed to the development of strabismus or the strabismus contributed to the development of amblyopia for this group of infants. Anisometropia appeared to be predictive of strabismus, as did an unfavorable structural outcome in 1 or both eyes. However, when all of the other variables such as amblyopia were factored in, neither was a significant risk factor in itself as shown in the final model in Table 2.

Importantly, this cohort provides insight into the evolution of strabismus in the first year of life for infants with high-risk prethreshold ROP. For full-term infants with normal neurologic status, ocular alignment status can usually be classified by 6 months of age.\textsuperscript{12} Infants in this study were not examined for strabismus until 6 months’ corrected age, and while the presence of strabismus or the inability to assess the alignment at 6 months was predictive of strabismus at 9 months, those with strabismus at 6 months showed a 30.3% rate of spontaneous resolution by the 9-month examination. Additionally, of those with strabismus at 9 months, 42.1% had shown normal alignment at 6 months. This suggests that stability of ocular alignment is delayed, whether owing to ocular or developmental abnormalities. Study-certified pediatric ophthalmologists performed the strabismus evaluations, thus reducing the likelihood of missing small-angle strabismus or misclassifying pseudostrabismus. Phillips et al\textsuperscript{10} reported the diagnosis of strabismus at a mean age of 8.5 months in a cohort of premature infants with birth weights less than 1500 g, and Page et al\textsuperscript{15} noted that strabismus was seen with increasing frequency through the second year of life in a cohort of infants with birth weights less than 1251 g. Longer-term studies\textsuperscript{2,20,30} show strabismus in up to 39% of premature infants with birth weights less than 1501 g who were followed up until 5 to 10 years of age.

The impact of abnormal developmental status on the incidence of strabismus is important, and neurodevelopmental data will be collected in the long-term follow-up of this cohort. Infants with high-risk prethreshold ROP may represent infants with a higher rate of coexisting neurologic morbidity and developmental delays, thus impacting the higher prevalence of strabismus and the instability of ocular alignment. The incidence of strabismus is about 30% for premature infants diagnosed with cerebral palsy or periventricular leukomalacia\textsuperscript{1,2,11,12,31,32} or with evidence of grade III or IV intraventricular hemorrhage,\textsuperscript{3} and it is increased for infants with ultrasound evidence of cerebral damage.\textsuperscript{4}

### Table 2. Multivariate Analysis to Determine Independent Variables That Increase the Odds of Developing Strabismus at 9 Months in Randomized Infants

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight per 100 g</td>
<td>0.90 (0.71-1.16)</td>
<td>.42</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>0.96 (0.76-1.22)</td>
<td>.75</td>
</tr>
<tr>
<td>Race (black = 1, others = 0)</td>
<td>1.43 (0.61-3.34)</td>
<td>.41</td>
</tr>
<tr>
<td>Sex (male = 1, female = 0)</td>
<td>0.83 (0.43-1.62)</td>
<td>.59</td>
</tr>
<tr>
<td>Inborn (inborn = 1, outborn = 0)</td>
<td>0.35 (0.16-0.74)</td>
<td>.007</td>
</tr>
<tr>
<td>Single vs multiple birth (single = 1, multiple = 0)</td>
<td>0.56 (0.27-1.16)</td>
<td>.12</td>
</tr>
<tr>
<td>Anisometropia ≥2 diopters (no = 0, yes = 1)</td>
<td>1.13 (0.56-2.29)</td>
<td>.74</td>
</tr>
<tr>
<td>Fixation (both eyes normal [CSM] = 0, other = 1)</td>
<td>15.27 (7.02-33.21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visual acuity (both eyes favorable = 0, other = 1)</td>
<td>1.47 (0.53-4.10)</td>
<td>.46</td>
</tr>
<tr>
<td>Structure (both eyes favorable = 0, other = 1)</td>
<td>1.42 (0.46-4.42)</td>
<td>.54</td>
</tr>
<tr>
<td>Amblyopia (no = 0, ever diagnosed = 1)</td>
<td>4.22 (1.26-14.07)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CSM, central, steady, and maintained; OR, odds ratio.
This article confirms that the prevalence of strabismus in the first year of life is higher for infants with high-risk prethreshold ROP compared with previously published rates for all of the preterm infants with birth weights less than 1251 g. Almost one third of these infants show strabismus by a corrected age of 9 months, and most are esotropic. There is a strong association between out-born birth status, abnormal fixation, or amblyopia and the presence of strabismus. Since a significant number of premature infants show improvement or variability in their strabismus through the first year of life, conservative management is recommended.

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Author Affiliations: Children's Hospital Boston, Harvard Medical School, Boston, Mass (Dr VanderVeen); Texas Children's Hospital, Baylor College of Medicine (Dr Coats) and School of Public Health, University of Texas Health Science Center (Dr Hardy and Ms Tung), Houston; Department of Ophthalmology and Vision Science, University of Arizona, Tucson (Dr Dobson); Department of Ophthalmology, University of California (Dr Frederick) and Smith-Kettlewell Eye Research Institute (Dr Good), San Francisco; Department of Ophthalmology, Tulane University Medical Center, New Orleans, La (Dr Gordon); Department of Ophthalmology, Indiana University, Indianapolis (Dr Neely); Casey Eye Institute, Oregon Health & Science University, Portland (Dr Palmer); and Department of Ophthalmology, University of Maryland School of Medicine, Baltimore (Dr Steidl).

Correspondence: Deborah K. VanderVeen, MD, Department of Ophthalmology, Children's Hospital Boston, 300 Longwood Ave, Fegan 4, Boston, MA 02115 (deborah.vanderveen@childrens.harvard.edu).

Author Contributions: Dr Hardy 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.

Group Information: The Early Treatment for Retinopathy of Prematurity Cooperative Group members are listed on page 771.

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REFERENCES


Clinical Centers, Investigators, and Clinic Coordinators

Lucille Packard Children's Hospital, Stanford University, Palo Alto, Calif: Ashima Madan, MD; Michael Gaynon, MD (coprincipal investigator); M. Bethany Ball, BS; Patricia N. Hartsell, RN, BA; Dottie Ingullo, RN (study center coordinators); Deborah Alcorn, MD; William V. Good, MD; Donna Ornitz, MD; David Stevenson, MD (coinvestigators). *California Pacific Medical Center, Oakland* Children's Hospital, *University of California, San Francisco* Medical Center, San Francisco: William V. Good, MD (principal investigator); Monica Hubbard, MS, PNP; Jason Lee, MD (study center coordinators); Daniel Brenton, MD; Susan Day, MD; David Durand, MD; Douglas Fredrick, MD; Roderic H. Phipps, MD; Daniel Schwartz, MD; Terri Slage, MD; Gordon Smith, MD (coinvestigators). *University of Illinois at Chicago Hospital and Medical Center*: Michael Shapiro, MD (principal investigator); Yesenia Garcia; Maria Genio; Jeffrey Parker; Bernadine Rupar (study center coordinators); Herbert Becker, MD; Rama Bhat, MD; Jeffrey N. Bloom, MD; Jessica V. Corsino, MD; Lawrence Kaufman, MD; Wico Waikwan Lai, MD; Jose Pulido, MD, MS; Tonse N. K. Raju, MD; Arvid K. Shukla, MD; Benjamin Ticho, MD; Dharmapuri Vidyasagar, MD (coinvestigators). *Indiana University School of Medicine, James Whitcomb Riley Hospital for Children, Indiana University Hospital, Wishard Memorial Hospital, Methodist Hospital, Community Hospitals of Indianapolis, Indianapolis*: James Lemons, MD (principal investigator); Daniel Neely, MD (coprincipal investigator); Dee Dee Appel, RN; Elizabeth A. Hynes, RN; Leslie Wright, RN (study center coordinators); David Plager, MD; Naval Sondhi, MD; Derek Sprunger, MD (coinvestigators). *Tulane University Medical Center, Medical Center of Louisiana at New Orleans*: Robert A. Gordon, MD (principal investigator); Deborah S. Neff, LPN (study center coordinator); Douglas B. Babel, OD, MD; James G. Diamond, MD; William L. Gill, MD (coinvestigators). *University of Maryland Medical Systems, Mercy Medical Center, Franklin Square Hospital, Baltimore*: Ira H. Gewolb, MD (principal investigator); Kelly A. Hutcheson, MD (coprincipal investigator); Loni Huynh, COA; Rani Kalsi, BA, COA; Xiaonong Liu; L. Jennifer Smell, RN (study center coordinators); Susan J. Dulkarian, MD; Michael J. Elman, MD; Eric Jones, MD; Mark W. Frelan, MD; Scott M. Steidl, MD, DMA (coinvestigators). *Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Greater Baltimore Medical Center, St Joseph Medical Center, Baltimore*: Michael X. Repka, MD (principal investigator); Jennifer A. Shepard, NNP; Pamela Donahue, PhD (study center coordinators); Susan W. Aucott, MD; Tuvia Blechman, MD; Mary Louise Collins, MD; Maureen M. Gilmore, MD; James T. Han, MD; Ananth Vijay Mudgil, MD; Quan Dong Nguyen, MD; Cameron F. Parsa, MD; Dante Pieramici, MD; David Plotsky, MD; Jeffrey J. Pomerance, MD (coinvestigators). *New England Medical Center, Children's Hospital, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Lowell General Hospital, Lawrence General Hospital, Winchester Hospital, Newton-Wellesley Hospital, South Shore Hospital, Melrose-Wakefield Hospital, Beverly Hospital, Boston, Mass*: Cynthia H. Cole, MD, MPH (principal investigator); Deborah VanderVeen, MD (coprincipal investigator); Lacy Berman; Christy Faherty, RN, BSN; Caitlin Hurley, BS; Terri Mansfield, RN; Brenda MacKinnon, RNC; Marianne Moore, RN (study center coordinators); Caroline Baun, MD, FRCSC; Amita Bhatt, MD; Mark Dacey, MD; Jay Duker, MD; Janine Eagle, MD; Anthony Fraioli, MD; Paul Greenberg, MD; Mark Hughes, MD; Robert Lacy, MD; O'ine McCabe, MD; Robert Peterson, MD; Elias Reichel, MD; Adam Rogers, MD; William Stinson, MD; Mitchell Strominger, MD (coinvestigators). *William Beaumont Hospital, Children's Hospital of Michigan, St John's Hospital, Detroit, Mich*: John Baker, MD (principal investigator); Kristi Cumming, MSN; Michelle Kulak, RN; Pat Manatre, RN (study center coordinators); Daniel Batton, MD; Mary Bedard, MD; Antonio Capone, MD; Renato Casabar, MD; Edward O'Malley, MD; Rajesh Rao, MD; John Roarty, MD; Michael Trease, MD; George Williams, MD (coinvestigators). *Fairview University Medical Center, Children's Hospital, Hennepin County Medical Center, Minneapolis, Minn*: Stephen P. Christiansen, MD (principal investigator); Sally Cook, BA; Ann Holleschau, BA; Molly Maxwell, RN, Marla Mills, RN, MSN; Carol Miller, RN; Kristin Reberus, RN, NNP; Nancy Trower, RN, NNP (study center coordinators); Steven Bennett, MD; David Brasel, MD; Robert Couser, MD; Sundeep Dev, MD; Allison Jensen, MD; Richard Lussky, MD; George Miller, MD; Robert Mittra, MD; Timothy Olsen, MD; Robert Ramsey, MD; William Rosen, MD; Edwin Ryan, MD; Shelley Springer, MD; Eric Steuer, MD; C. Gail Summers, MD; David Williams, MD (coinvestigators). *Cardinal Glennon Children's Hospital, St Mary's Health Center, St Louis, Mo*: Bradley V. Davitt, MD (principal investigator); Julie Breuer, RN; Linda Breuer, LPN (study center coordinators); Oscar Cruz, MD; Stephen Feman, MD; William Keenan, MD; Greg Mantsch, MD (coinvestigators). *Duke University Medical Center, University of North Carolina Hospital, Durham and Chapel Hill*: Sharon Freedman, MD (principal investigator); David Wallace, MD (coprincipal investigator); Eileen Camp, RN; Sharon Clark, RN; Lori Hutchins, RN, Lora Lake, RN (study center coordinators); Edward Buckley, MD; Laura Enyedi, MD; Ricki Goldstein, MD; Maurice Landers III, MD; Diane Marshall, MD; Travis Meredith, MD; Kean Oh, MD; Joan Roberts, MD (coinvestigators). *Women's and Children's Hospital of Buffalo, Sisters of Charity Hospital, Buffalo, NY*: James D. Reynolds, MD (principal investigator); Dawn C. Gordon, RNC; Barbara Kuppel, RN, BSN (study center coordinators); George P. Albert, MD;
Clinical Centers, Investigators, and Clinic Coordinators (cont)

Steven Awner, MD; Rita Ryan, MD (coinvestigators). Stony Brook University Hospital, Stony Brook, NY; Westchester Medical Center, Valhalla, NY: Pamela Ann Weber, MD (principal investigator); Adriann Combs, RNC; Natalie Dweck, RN (study center coordinators); Howard Charles, MD; Tina Chou, MD; Joseph DeCristofaro, MD; Corina Gerontis, MD; Marc Horowitz, MD; Richard Koty, MD; Edmund LaGamma, MD; Maury Marmor, MD (coinvestigators). New York Presbyterian Hospital (Columbia and Cornell campuses), New York: John Flynn, MD (principal investigator); Thomas Lee, MD (coprincipal investigator); Osode Coki, RNC, BSN (study center coordinator); Michael Chiang, MD; Steven Kane, MD; Alfred Krauss, MD; Robert Lopez, MD; Richard Polin, MD (coinvestigators). University of Rochester Medical Center, Rochester, NY; Crouse-Irving Memorial Hospital, Syracuse, NY: Dale L. Phelps, MD (principal investigator); Steven J. Gross, MD; David Hakanson, MD (principal investigators); Marcia Dodge, RN; Cassandra Horihan, MS; Pamela Parker, BA; Jane Phillips (study center coordinators); Dennis Asselin, MD; Shi-Hwa W. Chang, MD; Ernest Guillett, MD; Robert Hampton, MD; Gary Markowitz, MD; Walter Merriam, MD; Leon-Paul Noel, MD; Robert Olsen, MD; Suzanne Pesce, MD; Steven Rose, MD; Bryan Rutledge, MD; Richard Simon, MD; Sam Spalding, MD; Donald Tingley, MD; Paul Torrisi, MD; Robert Vanderlinde, MD (coinvestigators). Columbus Children's Hospital, Ohio State University Hospital, Mount Carmel Medical Center, Grant Medical Center, Riverside Methodist Hospital, Mount Carmel East Hospital, St Ann's Hospital, Columbus: Gary L. Rogers, MD (principal investigator); Don Bremer, MD (co-principal investigator); Rae Fellows, MD; Sharon Klamfoth, LPN; Brenda Mann, RNC (study center coordinators); Leandro Cordero, MD; Richard Hertle, MD; Alan Letson, MD; Richard McClead, MD; Mary Lou McGregor, MD; Patrick Wall, MD (coinvestigators). Children's Hospital of Oklahoma, Oklahoma City: R. Michael Siatkowski, MD (principal investigator); Karen E. Corff, MS, ARNP; Melissa Fuhr, RN (study center coordinators); Reagan H. Bradford, MD; Robert E. Leonard, MD; Mark H. Scott, MD (coinvestigators). Doernbecher Children's Hospital at Oregon Health and Science University, Legacy Emanuel Children's Hospital, Providence St Vincent's Hospital, Portland: David T. Wheeler, MD (principal investigator); Karen Davis, RN; Nancy Dolphin, RN; Sharon Dunham, RN (study center coordinators); Aazy Aaby, MD; Shawn Goodman, MD; Andreas Lauer, MD; Valerie Newman, MD; Earl A. Palmer, MD; De-Anne Pillers, MD, PhD; Joseph Robertson, MD; Ann Stout, MD; Tim Stout, MD; Andrea Tongue, MD (coinvestigators). The Children's Hospital of Philadelphia, The Hospital of the University of Pennsylvania, Pennsylvania Hospital, Philadelphia: Graham E. Quinn, MD, MSCE (principal investigator); Jamie G. Koh, RN, MSN, CCRC; Marianne E. Letterio, RN, BSN; Molly McDaniel, BA (study center coordinators); Soraya Abbasi, MD; Jane C. Edmond, MD; Brian J. Forbes, MD, PhD; Albert M. Maguire, MD; Monte D. Mills, MD; Eric A. Pierce, MD; Terri L. Young, MD (coinvestigators). Magee-Women's Hospital, Pittsburgh, Pa: Kenneth Cheng, MD (principal investigator); Judith Jones, RNC, BSN (study center coordinator); Robert Bergren, MD; Beverly Brozanski, MD; Bernard Doft, MD; Mitchell Fineman, MD; Louis Lobes, MD; Karl Olsen, MD (coinvestigators). Medical University of South Carolina, Charleston: Richard A. Saunders, MD (principal investigator); Lisa Langdale, RN (study center coordinator); Amy Hutchinson, MD; M. Millicent Petersem, MD; Dilip Purohit, MD (coinvestigators). Baylor College of Medicine, Texas Children's Hospital, Texas Woman's Hospital, Ben Taub General Hospital, Houston: David K. Coats, MD (principal investigator); Laura Gonzalez; Nataliya Kazymyrko, MD; Alma Sanchez, COT; Michele Steward, COT (study center coordinators); Kathryn Brady-McCreery, MD; Joseph Garcia-Prats, MD; Eric Holz, MD; Scott Jarriel, MD; Karen Johnson, MD; George Mandy, MD; Evelyn A. Paysee, MD; A. Melinda Rainey, MD; Kimberly G. Yen, MD (coinvestigators). University Hospital, Christus Santa Rosa Children's Hospital, San Antonio, Tex: W. A. J. van Heuven, MD (principal investigator); Alice K. Gong, MD (coprincipal investigator); Melanie H. Drummond, RN (study center coordinator); Timothy Paul Cleland, MD; James C. MacDonald, MD; Lina M. Marouf, MD; Juan Elian Rubio, MD (coinvestigators). University of Utah Health Science Center, Primary Children's Medical Center, Salt Lake City: Robert Hoffman, MD (principal investigator); Susan Bracken, RN (study center coordinator); Paul Bernstein, MD; David Dries, MD; Jerald King, MD; Richard Olson, MD; Michael Teske, MD; Kimberly Yen, MD (coinvestigators).

National Eye Institute, Bethesda, Md

Maryann Redford, DDS, MPH (program officer; June 2001 to present); Richard L. Mowery, PhD (October 2000 to May 2001); Donald F. Everett, MA (September 1999 to September 2000).

Study Headquarters

Smith-Kettlewell Eye Research Institute, San Francisco, Calif: William V. Good, MD (principal investigator); Michelle Quintos, BA (project coordinator).
Coordinating Center
School of Public Health, Coordinating Center for Clinical Trials, University of Texas Health Science Center, Houston: Robert J. Hardy, PhD (principal investigator); Betty Tung, MS (project manager); Gordon Tsai, MS (coordinating center staff).

Vision Testing Center
University of Arizona, School of Medicine, Tucson: Velma Dobson, PhD (principal investigator); Graham E. Quinn, MD (coinvestigator); Kathleen M. Mohan, MA; Meigan B. Baldwin, BA (vision testers); Suzanne M. Delaney, PhD (vision testing center coordinator).

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