

Evidence-Based Screening Criteria for Retinopathy of Prematurity

Natural History Data From the CRYO-ROP and LIGHT-ROP Studies

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Background: The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) demonstrated the efficacy of treatment for threshold ROP and indicated the need for worldwide ROP screening. Previous guidelines for ROP screening have been largely based on clinical impression; we can now develop evidence-based screening recommendations.

Objective: To define the appropriate ages and retinal ophthalmoscopic signs that determine when to commence and conclude acute phase ROP screening.

Design: Analysis of data from 2 prospective randomized controlled trials: CRYO-ROP (January 1, 1986, to November 30, 1987) and Light Reduction in ROP (LIGHT-ROP) (July 1, 1995, to March 31, 1997).

Setting: Neonatal intensive care units in 23 study centers in the United States for CRYO-ROP and 3 centers for LIGHT-ROP.

Patients: Eyes were examined sequentially in 4099 in-

fants with birth weight less than 1251 g (CRYO-ROP study) and in 361 infants with birth weight less than 1251 g and gestational age less than 31 weeks (LIGHT-ROP study).

Results: In 99% of infants, retinal conditions indicating a risk of poor outcome were not observed before 31 weeks' postmenstrual age or 4 weeks' chronologic age. Signs indicating that the risk of visual loss from ROP was minimal or had passed were the infant's attainment of 45 weeks' postmenstrual age without the development of prethreshold ROP or worse, progression of retinal vascularization into zone III without previous zone II ROP, and full vascularization.

Conclusions: The initial eye examination should be conducted by 31 weeks' postmenstrual age or 4 weeks' chronologic age, whichever is later. Acute phase ROP screening can be discontinued when any of the 3 signs is present, indicating that the risk of visual loss from ROP is minimal or passed.

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IN 1988, THE MULTICENTER TRIAL of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) demonstrated the efficacy of treating threshold ROP.¹ This trial emphasized the need for a reliable, evidence-based screening protocol to ensure appropriate standards of care.

An ideal screening program should detect serious disease in a consistent, clinically effective, safe, and cost-effective manner, implying the avoidance of extraneous examinations.^{2,3} Minimizing examinations is especially important in the screening of low-birth-weight preterm infants because ophthalmic examinations are distressing and have a small risk of harm to these tiny infants.⁴⁻⁶ Furthermore, unnecessary examinations add to the expense and complexity of the care of the preterm infant and may inconvenience

families when examinations continue after hospital discharge.

Several published guidelines are now available for ROP screening. In general, however, these guidelines were developed by committee consensus using published material, or single-center data, and can vary considerably. The United Kingdom guidelines recommend beginning ROP screening at 6 to 7 weeks' chronologic (postnatal) age (CA).⁷ The American Academy of Pediatrics, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology recommend beginning screening at 4 to 6 weeks' CA or 31 to 33 weeks' postmenstrual age (PMA), that is, the age of the fetus or newborn calculated from the date of the onset of the mother's last menstrual period.⁸ The Canadian Association of Pediatric Ophthalmol-

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mologists ad hoc committee recommends beginning acute ROP screening at 4 to 6 weeks' CA.⁹ Nurseries have used these published policy statements in the development of their own screening guidelines, in the absence of substantive validation.¹⁰

The large multicenter database from the CRYO-ROP study affords a unique opportunity for establishing evidence-based screening guidelines. This database, accumulated between January 1, 1986, and November 30, 1987, includes the results of sequential eye examinations of 4099 infants with birth weight less than 1251 g, representing approximately 15% of all deliveries in that birth weight range in the United States during this period.^{11,12} Since that time, numerous changes and improvements in the medical care of very low-birth-weight infants have occurred. Therefore, one could question whether a database collected in 1986 and 1987 is relevant to ROP screening today.

The Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) study¹³ gathered data from sequential eye examinations of 361 surviving infants with birth weight less than 1251 g and gestational age (GA) less than 31 weeks who were born between July 1, 1995, and March 31, 1997. As in the CRYO-ROP study, infants were examined by study-certified ophthalmologists according to a rigorous protocol that was prospectively designed to detect and follow acute phase ROP throughout its natural course.

Comparison of data from these 2 clinical trials provides an opportunity to evaluate the current applicability of the CRYO-ROP data for the development of evidence-based screening. Furthermore, the LIGHT-ROP study provides information on the timing of full vascularization of the nasal and temporal retina, which was not specifically gathered in the CRYO-ROP study.

The purposes of the present article are to use the database from the CRYO-ROP study to define appropriate ages and retinal ophthalmoscopic signs for the initiation and conclusion of acute phase ROP screening and to compare these results with data from the more recently conducted LIGHT-ROP study. Analysis of the time course of normal retinal vascularization and the natural history of ROP provides information on when to begin acute phase ROP screening and when acute phase examinations can be safely concluded.

METHODS

PARTICIPANTS

The CRYO-ROP study enrolled 4099 infants with birth weight less than 1251 g in its natural history cohort. All infants were admitted to a participating hospital at 1 of the 23 study centers and survived to at least age 28 days. All infants underwent an initial eye examination between 4 and 7 weeks of age. Eye examinations were conducted serially every 2 weeks or at least weekly if prethreshold disease was present. Acute phase ROP was classified by an ophthalmologist with specific training in the international classification of ROP.¹⁴ As reported previously, prethreshold ROP was defined as any stage of ROP in zone I, stage 2 ROP with plus disease in zone II, or any stage 3 ROP in zone II. Threshold ROP was defined as at least 5 contiguous or 8 cumulative clock-hours of stage 3 ROP in zone I

or II with plus disease.¹ Gestational age at birth was determined by the neonatologist caring for the infant. That physician made a best estimate, taking into consideration menstrual history; obstetrical dating, including early ultrasonography; and neonatal physical assessments.¹¹

The LIGHT-ROP study enrolled 361 infants with birth weight less than 1251 g and GA less than 31 weeks who were born at a participating hospital at 1 of the 3 study centers and who also survived for at least 28 days and were followed up to outcome. The examination schedule and disease classification were identical to those in the CRYO-ROP study except that the first examination for these 361 infants was conducted at 4 to 9 weeks' CA.¹⁵ Infants were followed until full peripheral retinal vascularization was documented. In the LIGHT-ROP study, GA was determined by a more rigorous process following a hierarchy of criteria in which GA was based on *in vitro* fertilization, ultrasounds performed before 20 weeks of gestation, or physical assessment performed by trained personnel using the New Ballard Score.¹⁶

PROCEDURE

An ROP screening protocol can be devised based on the onset of conditions that may indicate a risk of poor ophthalmic outcome and conditions that may indicate that the risk for serious ROP is minimal or has passed. We define serious ROP as the presence of any of the following 4 disease conditions that indicate a risk of poor outcome: (1) prethreshold ROP, (2) threshold ROP, (3) any stage of ROP with plus disease, and (4) stage 3 ROP with plus disease. The third category is largely a subcategory of prethreshold ROP, but it was selected to be examined separately because data from the CRYO-ROP study demonstrated that plus disease substantially increases the risk of poor outcome in eyes with ROP.¹⁷ The fourth category (stage 3 ROP with plus disease) is a subset of eyes from the prethreshold and threshold categories that are at risk of poor outcome,¹⁷ and it also represents a substantial proportion of eyes that have been identified for treatment in the Early Treatment for ROP trial.¹⁸ Study data from the 2699 participants in the CRYO-ROP study who developed ROP were examined to determine the distribution of PMAs and CAs at which the 4 previously mentioned events occurred. There were no eyes in the CRYO-ROP study or in the LIGHT-ROP study that showed any of the 4 serious ROP disease conditions at the first examination. Thus, the onset of serious ROP was captured in our data for every patient.

The conditions that indicate that the risk of a poor retinal outcome is minimal are (1) vascularization into zone III without previous ROP in zone I or II and (2) full retinal vascularization. Data from the 1400 infants in the study who never developed ROP were analyzed to determine the PMA and CA at which retinal vessels were first observed to end in zone III. Data from the 474 infants who did not develop stage 1 or 2 ROP until the retinal blood vessels had reached zone III were analyzed to determine the PMA and CA at which retinal vessels had reached zone III by the time ROP was first observed. The protocol for the CRYO-ROP study did not include documentation of the age at which full temporal vascularization occurred.

For comparison, data from the 202 infants with ROP in the LIGHT-ROP study were analyzed to determine the PMA and CA at which prethreshold ROP occurred. The other categories of serious ROP indicating a risk of poor outcome (mentioned previously) occurred too infrequently to allow meaningful analysis in this smaller population. Study data from the 110 infants in the LIGHT-ROP study who never developed ROP were analyzed to determine the age at which retinal vessels were observed to end in zone III and to determine the age at which full temporal vascularization was observed.

Table 1. Postmenstrual and Chronologic Age of the Onset of ROP Conditions That May Indicate a Risk of Poor Ophthalmic Outcome: CRYO-ROP Patients*

ROP	Patients, No.	Postmenstrual Age, wk					Chronologic Age, wk				
		1%	5%	Median	95%	99%	1%	5%	Median	95%	99%
Prethreshold	731	30.9 (31.7)	32.4	36.1	41.5	45.0 (45.0)	4.7 (4.9)	6.2	9.6	14.8	17.4 (18.7)
ROP with plus	417	31.9 (31.9)	32.9	36.4	42.0	44.0 (44.7)	4.9 (4.9)	6.6	10.0	15.3	17.3 (17.3)
Stage 3 plus	360	32.3 (32.3)	33.1	36.7	41.8	45.0 (46.3)	6.1 (6.3)	6.9	10.3	14.7	17.3 (17.3)
Confirmed threshold†	245	32.6 (32.6)	33.9	37.3	42.3	45.9 (45.9)	6.7 (6.7)	7.9	11.0	15.1	17.9 (17.9)

*ROP indicates retinopathy of prematurity; CRYO-ROP, Cryotherapy for Retinopathy of Prematurity study. Findings are given for the first eye (fellow eye).

†Confirmed threshold required 2 separate examinations performed within 72 hours of each other. If threshold ROP was observed and then confirmed by a second examiner, the eye was considered to have "confirmed threshold," and the timing of this onset relates to the time of the confirming examination.

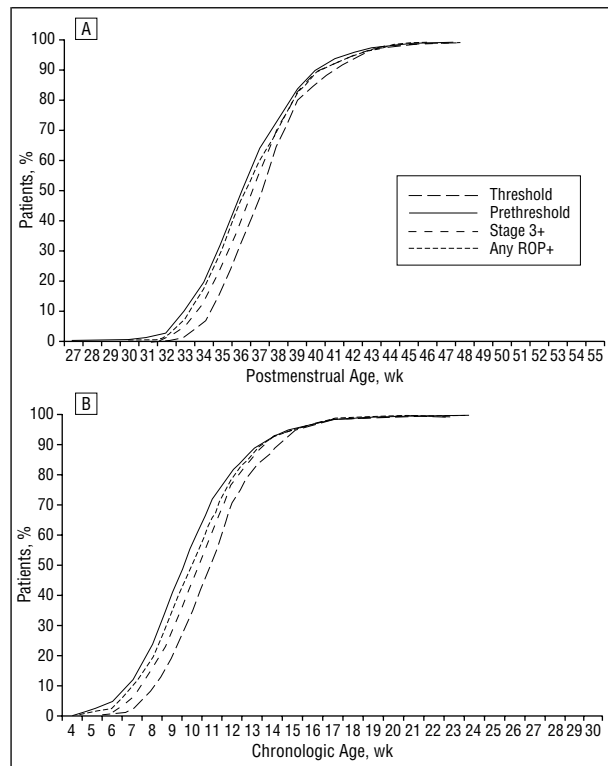


Figure 1. Timing of the onset of threshold, prethreshold, stage 3 plus, and any retinopathy of prematurity (ROP) with plus disease by postmenstrual (A) and chronologic (B) age.

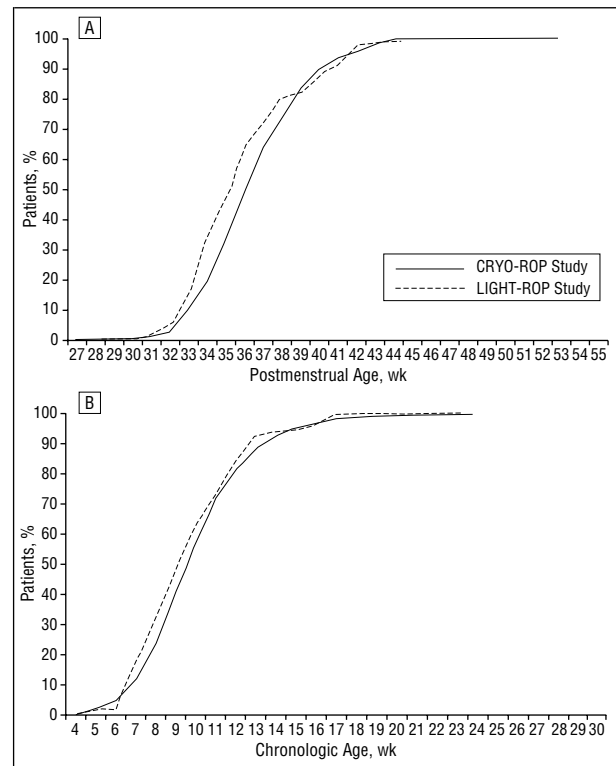


Figure 2. Timing of the onset of prethreshold retinopathy of prematurity for Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) (<31 weeks) and Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) study participants by postmenstrual (A) and chronologic (B) age.

RESULTS

OCCURRENCE OF RETINAL CONDITIONS INDICATING A RISK OF POOR OUTCOME

Data on the distribution of the onset of the initial occurrence of serious ROP conditions indicating a risk of poor outcome by PMA and CA are given in **Table 1**. Because ROP does not always develop or progress in both eyes of a patient simultaneously, Table 1 incorporates the timing of onset in the first eye observed to reach a given condition and the fellow eye.

In 99% of CRYO-ROP eyes, no prethreshold or worse ROP was observed to develop before 30.9 weeks' PMA or 4.7 weeks' CA. Table 1 also shows that 99% of eyes that develop serious ROP will have done so by 46.3 weeks' PMA

or 18.7 weeks' CA. Thus, in 99% of all eyes, the time window for the development of prethreshold or worse ROP was 30.9 to 46.3 weeks' PMA and 4.7 to 18.7 weeks' CA.

Cumulative frequency distributions of the initial observed occurrence of each of the serious ROP conditions for CRYO-ROP patients are presented in **Figure 1** for data based on PMA and CA. These figures are an expansion of the results given in Table 1. The onset of prethreshold ROP occurs at the earliest ages, followed by the onset of ROP with plus disease, stage 3 plus ROP, and, finally, threshold ROP.

Because of the smaller number of patients in the LIGHT-ROP study, only prethreshold ROP occurred with sufficient frequency to allow comparison with CRYO-ROP data. **Figure 2** presents a comparison of cumulative distributions representing the age of initial observa-

Table 2. Postmenstrual and Chronologic Age of the Onset of Conditions That May Indicate That Risk of Serious ROP Is Minimal*

ROP	Patients, No.	Postmenstrual Age, wk					Chronologic Age, wk				
		1%	5%	Median	95%	99%	1%	5%	Median	95%	99%
CRYO-ROP Patients											
Zone III, vascularization, no ROP†	1298	30.4	31.7	35.6	41.9	45.9	3.9	4.0	6.1	12.7	16.3
Zone III, ROP stage 1 or 2‡	474	30.3	32.1	35.3	40.4	43.9	4.0	4.1	6.9	11.9	15.9
LIGHT-ROP Patients											
Zone III, vascularization, No ROP	105	31.3	31.6	34.3	40.1	41.1	4.1	4.1	6.1	12.1	13.7
Full vascularization, no ROP§	105	31.4	32.1	35.7	42.0	42.6	4.1	4.3	7.9	14.3	15.0

*ROP indicates retinopathy of prematurity; CRYO-ROP, Cryotherapy for Retinopathy of Prematurity study; and LIGHT-ROP, Light Reduction in Retinopathy of Prematurity study. Data are given for the first eye. Serious ROP is defined as prethreshold ROP, any ROP with plus disease, stage 3 plus ROP, and threshold ROP.

†Eyes with no ROP and vessels reaching zone III.

‡Eyes with worst disease of stage 1 or 2 first observed in zone III, that is, temporal stage 1 or 2 first observed in the presence of full nasal vascularization.

§These eyes never had ROP.

tion of prethreshold ROP in CRYO-ROP and LIGHT-ROP study participants, plotted by PMA and CA. For this comparison, data plotted for CRYO-ROP study participants include results from only those whose GA was less than 31 weeks ($n=714$), that is, CRYO-ROP participants who would have met the criteria for inclusion in the LIGHT-ROP study. As shown in Figure 2, cumulative distributions for the age of occurrence of prethreshold ROP were nearly identical for the 2 studies, despite being separated in time by nearly a decade.

OCCURRENCE OF CONDITIONS INDICATING THAT THE RISK FOR DEVELOPMENT OF SERIOUS ROP IS MINIMAL

Retinal conditions that indicate a minimal risk of subsequent development of serious ROP include signs of retinal vascular maturation: full retinal vascularization, vascularization into zone III, and mild stage 1 or 2 ROP first developing in zone III.

Table 2 gives the age of first observation of retinal vascularization into zone III for the 1298 CRYO-ROP patients without ROP in whom retinal vascularization into zone III was documented. In 102 of the 1400 CRYO-ROP patients with no ROP, data were not available concerning when retinal vessels reached zone III. Table 2 also gives the timing of first observation of stage 1 or 2 ROP in zone III in the 474 CRYO-ROP patients in whom ROP was first seen in zone III.

Table 2 gives the age of first observation of retinal vascularization into zone III for the 105 LIGHT-ROP patients without ROP in whom retinal vascularization into zone III was documented. In 5 of the 110 LIGHT-ROP patients with no ROP, data were not available concerning when retinal vessels reached zone III. Table 2 also gives the timing of first observation of full retinal vascularization. The latter information was not collected as part of the CRYO-ROP protocol.

Figure 3 presents an expansion of the similar category of data in Table 2, showing a comparison of cumulative distributions of the onset of retinal vessels ending in zone III for no ROP eyes, plotted by PMA and CA for CRYO-ROP and LIGHT-ROP data. Comparing only infants with GA less than 31 weeks, data from the 2 stud-

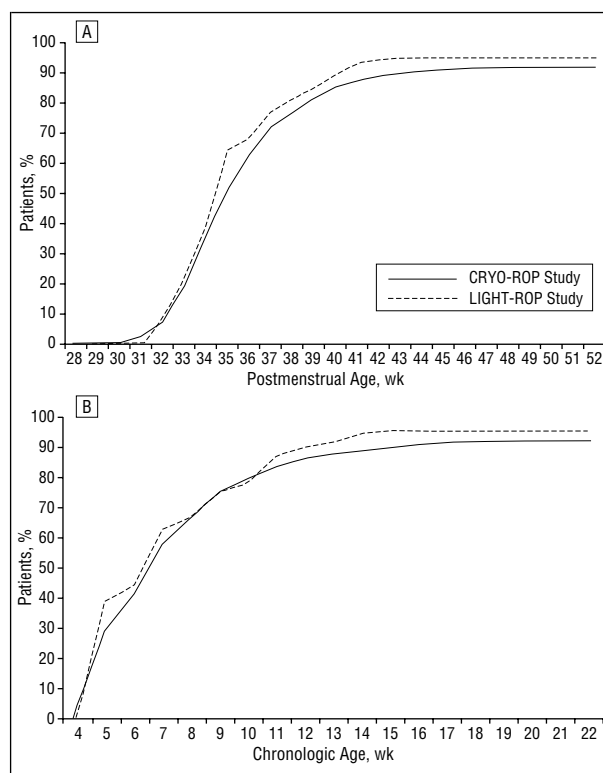


Figure 3. Vessels vascularized to zone III for no retinopathy of prematurity infants in the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) (<31 weeks) and Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) studies by postmenstrual (A) and chronologic (B) age.

ies demonstrated nearly identical timing of retinal vascularization into zone III in eyes with no ROP.

EXAMINER RELIABILITY

In the CRYO-ROP study, there were 2 situations in which examiner variability could be assessed. First, diagnosis of threshold ROP required confirmation by a second certified study examiner within 3 days. If the second examination detected less-than-threshold ROP, then 1 of the 2 examinations had to be in error, probably in borderline conditions. This situation occurred in 12% of eyes initially described as threshold (**Table 3**).

Table 3. Consistency of Examiner Observations of Retinal Vascular Status*

Retinal Status	First Examination, No. of Eyes	Consistent Finding on Next Examination, No. (%) of Eyes
Threshold (CRYO-ROP)	278	245 (88)
No ROP/zone III vessels (CRYO-ROP)	561†	538 (96)
No ROP/zone III vessels (LIGHT-ROP)	56†	54 (96)

*CRYO-ROP indicates Cryotherapy for Retinopathy of Prematurity study; LIGHT-ROP, Light Reduction in Retinopathy of Prematurity study.

†Study protocol did not require a confirming examination for these categories. Therefore, only about half of the patients in these categories in Table 2 received a subsequent examination that could be assessed for consistency.

Table 4. Timing of the Initial Eye Examination Designed to Detect at Least 99% of Serious ROP*

Gestational Age at Birth, wk	Age at Initial Examination, wk	
	Postmenstrual	Chronologic
22†	31	9
23†	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

*ROP indicates retinopathy of prematurity.

†This guideline should be considered tentative rather than evidence based for 22- to 23-week infants owing to the small number of survivors in these gestational age categories.

The other situation involved the observation of zone III vascularization without ROP. If a subsequent examination observed zone II vascularization without ROP, then 1 of the 2 examinations had to be in error. This situation occurred in 4% of eyes in the CRYO-ROP study and in 4% in the LIGHT-ROP study (Table 3).

COMMENT

Screening for acute phase ROP must identify eyes that have a high probability of requiring treatment and must do so at or before a time when that intervention is most likely to be effective. Screening should also be efficient in optimizing the number and frequency of examinations. The results of the present analysis, based on data from 4099 infants in the CRYO-ROP study and supported by data from 361 infants in the LIGHT-ROP study, indicate appropriate ages for the initiation of acute phase ROP screening examinations and help define appropriate ages and ophthalmoscopic retinal signs for their conclusion.

Onset of prethreshold ROP, threshold ROP, any ROP with plus disease, or stage 3 plus ROP occurred in 99% of infants at or after 31 weeks' PMA and after 4 weeks' CA (Table 1 and Figure 1). This curve depicts the timing of the most serious forms of ROP. Table 1 also indicates that the latest observed onset of prethreshold ROP, threshold ROP, any ROP with plus disease, or stage 3 plus ROP occurred in 99% of infants by 46 weeks' PMA and 19 weeks' CA.

Prethreshold ROP almost always precedes threshold ROP. If prethreshold ROP is going to develop, it will be evident by 45 weeks' PMA in at least 99% of patients (Table 1). Thus, an eye that does not have prethreshold ROP at 45 weeks' PMA is not at risk for threshold ROP.

Table 4 represents the recommended schedule for timing of the initial eye examination based on PMA and CA to detect prethreshold ROP. We anticipate that use of this schedule will reduce, not increase, the number of screening examinations. The onset of ROP in infants in the CRYO-ROP study correlated better with PMA than with postnatal age. This knowledge has been used previously in developing an initial eye examination schedule based on PMA and CA.^{15,19} Such a protocol incorporating these dual criteria applies to the full range of the degree of prematurity. Using this method, the initial eye examination should be conducted at 31 weeks' PMA for infants with a GA of less than 27 weeks and at 4 weeks' CA for infants with a GA of 27 weeks or greater. However, because of the small number of survivors with a GA of less than 24 weeks, this recommendation has been extrapolated for 22- and 23-week infants and should be interpreted with caution.

Termination of acute phase ROP screening can occur when the risk for developing serious ROP has passed. As already stated, prethreshold ROP precedes the development of threshold ROP, and 99% of prethreshold ROP has developed by 45 weeks' PMA for the nursery populations studied herein. Thus, acute phase ROP screening can conclude by at least 45 weeks' PMA as long as prethreshold or worse acute ROP is not present. This value is an extreme and is based only on age rather than on retinal findings. It is far more likely that the child's ROP will progress to serious ROP at an earlier age or that retinal maturity or ROP regression will occur earlier than 45 weeks' PMA. Typically, ROP regression begins by 39 weeks' PMA, and 90% of cases show involution by 44 weeks' PMA.²⁰

Retinal maturity may also indicate that the risk of serious ROP is minimal and may permit earlier termination of screening. We used progression of retinal vascularization to the nasal ora (zone III) and temporal ora (full vascularization) as observable signs of retinal maturity. Data from the CRYO-ROP study indicate that no patient without ROP in whom retinal vascularization reached zone III and only 1 patient (0.2%) in whom ROP was first observed in zone III ever developed serious ROP.²¹ The CRYO-ROP study outcomes reported for eyes with zone III ROP do not include eyes that had earlier been judged to have ROP in zone I or II. However, Repka and co-workers²⁰ analyzed this same group of patients from the 5 natural history CRYO-ROP centers, that is, zone II ROP

eyes that later became zone III ROP eyes. Two (1%) of 200 eyes had an unfavorable anatomic result, indicating that it is possible, although unlikely, to have an unfavorable outcome within this group.

Finally, full retinal vascularization precludes the development of ROP. Therefore, the attainment of either zone III vascularization before or simultaneous with ROP development or full vascularization are retinal signs that reasonably indicate that acute phase ROP screening can be safely concluded. The natural history data we presented concerning the onset of zone III vascularization or full retinal vascularization can aid the examiner in determining how typical or atypical an individual infant's retinal findings are compared with the norm.

In summary, the following are guidelines for conclusion of acute phase ROP screening:

1. Zone III retinal vascularization attained without previous zone I or II ROP assuming no examiner error. If there is doubt about the zone or if the PMA is unexpectedly young, confirmatory examinations may be warranted.
2. Full retinal vascularization.
3. PMA of 45 weeks and no prethreshold ROP or worse present.

Regression of ROP, although a favorable sign affecting the frequency of acute examinations, was not a subject of this study.

Table 4 and the 3 guidelines listed previously, based on CRYO-ROP data and, when possible, confirmed by LIGHT-ROP data, provide evidence-based guidelines for initiating and concluding acute phase ROP screening. The screening program we suggest, based on these findings, should detect at least 99% of serious ROP in a period permitting treatment.

The usefulness of ROP screening depends on the accuracy with which the examiner can judge retinal status. Data presented in Table 3 indicate that even experienced examiners specially trained and participating in rigorous protocols can disagree on whether threshold ROP is present. In 12% of patients in the CRYO-ROP study in whom an examiner judged that threshold ROP was present, a second examiner did not confirm that status. Although consistency of examiner observations of zone III retinal status was better than that for judging the presence of threshold ROP, there was a discrepancy rate of 4%. Therefore, examiners should be aware of the possibility of underassessing and overassessing disease or progress of peripheral vascularization. When a statistically unlikely assessment is made, for example, full vascularization or zone III vascularization in a very young patient, then one should suspect observational error and consider reexamination at an appropriate later date. As recommended in the original article of the international classification, it is preferable and safer to err on the side of the lower, more posterior zone.¹⁴

This screening protocol also depends on the accurate determination of GA at birth. Gestational age in the CRYO-ROP study depended heavily on the physical examination findings and the mother's dates because early ultrasounds were rarely used in 1986 and 1987. Since then, early ultrasound to obtain accurate dating information has

become widespread, and it was used during the LIGHT-ROP study. This may account for the small differences observed in figures comparing LIGHT-ROP and CRYO-ROP PMA data. It is also possible that examiners in the LIGHT-ROP study recognized ROP stages slightly sooner because the study design emphasized the early stages of ROP more than did the CRYO-ROP study design. Regardless, neonatologists who participate in ROP screening protocols must appreciate the importance of accurate GA assessments to the appropriateness of these guidelines.

These screening guidelines are based on data from infants with birth weight less than or equal to 1250 g. Infants with birth weight greater than 1250 g still have a risk of developing serious ROP. Because the CRYO-ROP and LIGHT-ROP studies did not include any of these heavier-birth-weight infants, guidelines for screening of these infants must be provided by other studies.

Some other important issues were not presented in this article. One is the frequency of ophthalmologic examinations between the initial and final acute phase ROP examinations. Published recommendations for repeat examination intervals suggest approximately biweekly examinations for patients with immature vascularization or stage 1 or 2 ROP in zone II. Examinations should occur at least weekly for more serious conditions, including stage 3 ROP, zone I ROP, plus disease, or incomplete vascularization in zone I.^{8,9} Another issue beyond the scope of this study is regression of acute ROP. Disease regression or involution is part of the natural history of ROP and can be an important indicator of whether screening examinations can be safely discontinued.²⁰

One final caveat relates to these data being representative of tertiary care centers in the United States. These findings may not be uniformly generalizable on a worldwide basis. The standard of neonatal care varies widely around the world, as does ophthalmologic technology, and these can have an impact on the design and implementation of screening protocols.

In conclusion, we presented evidence-based guidelines for screening examinations for acute phase ROP. Following the recommendations contained in Table 4 and the 3 guidelines listed earlier should allow at least 99% of very low-birth-weight patients to be appropriately evaluated and any serious ROP to be discovered at a point sufficiently early to allow for treatment according to current or evolving standards. Each nursery or examiner will have to determine how to apply these data based on local experience and whether local circumstances warrant modification of our proposed guidelines.

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